Elucidating the Genetic Association Between Clozapine Use and Cardiometabolic Dysfunction in Treatment-Resistant Schizophrenia

by

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Bachelor of Health and Medical Sciences (Advanced)

Graduate Diploma (Biostatistics)

A Thesis Submitted for the Degree of

Master of Research (Pharmaceutical Science)

Clinical and Health Sciences | Australian Centre for Precision Health | University of South Australia



University of South Australia

November 2025

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ABBREVIATIONS

AD	Anxiety Disorder
ADHD	Attention-Deficit/Hyperactivity Disorder
AIWG	Antipsychotic-Induced Weight Gain
ALZ	Alzheimer's Disease
AN	Anorexia Nervosa
ASD	Autism Spectrum Disorder
BD	Bipolar Disorder
BDNF	Brain-Derived Neurotrophic Factor
β	Beta Coefficient
BG	Blood Glucose
BMI	Body Mass Index
cFDR	Conditional False Discovery Rate
CI	Confidence Interval
CRP	C-Reactive Protein
CVD	Cardiovascular Disease
DAG	Directive Acyclic Graph
DBP	Diastolic Blood Pressure
DEP	Depression
FDR	False Discovery Rate
FG	Fasting Glucose
FGA	First-Generation Antipsychotic
FI	Fasting Insulin
GGT	Gamma Glutamyl Transpeptidase
GWAS	Genome-Wide Association Study
HbA1c	Glycated Haemoglobin
HDL	High-Density Lipoprotein
HF	Heart Failure
HPC	High-Performance Computing
HT	Hypertension
IV	Instrumental Variable
IVW	Inverse Variance Weighted
LD	Linkage Disequilibrium
LDL	Low-Density Lipoprotein

LDSC	Linkage Disequilibrium Score Regression
MD	Mood Disorders
MDD	Major Depressive Disorder
MetS	Metabolic Syndrome
MR	Mendelian Randomization
MR-STROBE	Strengthening the Reporting of Observational Studies in Epidemiology Using Mendelian Randomization
MVMR	Multivariable Mendelian Randomization
OCD	Obsessive-Compulsive Disorder
OR	Odds Ratio
OSF	Centre for Open Science
PD	Psychotic/Psychiatric Disorder
PheWAS	Phenome-Wide Association Study
PP.H_4	Posterior Probability Under Hypothesis 4 in Bayesian Colocalization Analyses
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO	International Prospective Register of Systematic Reviews
PRS	Polygenic Risk Score
PWCoCo	Pairwise Conditional Colocalization
RCT	Randomized Controlled Trial
RDW	Red Cell Distribution Width
SBP	Systolic Blood Pressure
SCZ	Schizophrenia
SE	Standard Error
SGA	Second Generation Antipsychotic
SNP	Single Nucleotide Polymorphism
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
TG	Triglycerides
TRS	Treatment Resistant Schizophrenia
TWAS	Transcriptome-Wide Association Study
WC	Waist Circumference
WHR	Waist-Hip Ratio

EXECUTIVE SUMMARY

Clozapine is the gold-standard antipsychotic medication for treatment-resistant schizophrenia, yet its therapeutic benefits are often compromised by severe cardiometabolic adverse effects. This thesis investigated the genetic associations between cardiometabolic abnormalities and clozapine use in patients with treatment-resistant schizophrenia through a two-stage methodological approach.

First, a systematic review of genomic studies identified substantial shared genetic architecture between psychiatric disorders and metabolic traits, highlighting critical knowledge gaps regarding medication-specific effects versus disease-related factors. Building on these findings, an innovative multi-layered approach integrating Mendelian randomization, phenome-wide association, and colocalization techniques examined causal relationships between clozapine plasma traits and cardiometabolic outcomes. Additionally, it identified potential biomarkers implicated at clozapine metabolising loci.

The genomic analyses revealed distinct metabolite-specific effects: clozapine plasma levels showed positive associations with type 2 diabetes mellitus and systolic blood pressure, while the clozapine-norclozapine ratio demonstrated significant associations with diastolic blood pressure and type 2 diabetes mellitus, and notably, a protective effect against metabolic syndrome. This paradoxical finding suggests complex underlying biological mechanisms. Furthermore, 16 biomarkers demonstrated strong evidence of causality to metabolic outcomes, with gamma-glutamyl transferase, red blood cell distribution width, 25-hydroxyvitamin D, and total testosterone emerging as noteworthy examples.

These genomic associations can have significant clinical implications, supporting a potential shift from reactive monitoring to predictive, pathway-specific approaches in managing clozapine-induced metabolic dysfunction. The identified biomarkers offer possibilities for enhanced patient monitoring strategies, risk stratification prior to clozapine initiation, and targeted interventions based on individual biomarker profiles.

This research provides further evidence for the genetic architecture underlying clozapine-induced metabolic effects and identifies specific biological pathways and biomarkers. These findings provide a potential foundation for investigating personalized approaches to monitor and manage metabolic complications in people with treatment resistant schizophrenia, potentially improving both physical health outcomes and quality of life in this vulnerable population.

DISSEMINATION

MANUSCRIPTS SUBMITTED FOR PUBLICATION:

Shepherd, R, Stacey, D, Janetzki J, Clark, S, Hyppönen, E, Suppiah, V **'Disentangling the Relationship Between Psychiatric Disorders, Metabolic Syndrome, and Antipsychotics: A Systematic Review of Genomic Studies'** [Accepted].

- Registered - Centre for Open Science (Registration DOI: https://doi.org/10.17605/OSF.IO/X3SG7)
- Registered - International Prospective Register of Systematic Reviews (ID = CRD42024574593)
- Accepted for publication - Elsevier, Schizophrenia Research

Shepherd, R, Suppiah, V, Mulugeta, A, Clark, S, Hyppönen, E, Stacey, D **'Genetic Epidemiological Pipeline Identifies Candidate Markers of Clozapine-Induced Metabolic Dysfunction Revealing Potential Avenues for Precision Clozapine Prescription'** [Under Review].

CONFERENCE PROCEEDINGS:

POSTER PRESENTATION: ASCEPT, APFP, AND APSA JOINT CONGRESS, 'Elucidating Psychiatric Disorder, Antipsychotic, and Metabolic Syndrome Genetic Connection in GWAS'. Melbourne Convention and Exhibition Centre, Australia, 1st - 4th December 2024.

ORAL PRESENTATION: SOCIETY FOR MENTAL HEALTH RESEARCH, 45TH CONFERENCE, 'GENOMIC INVESTIGATION OF CLOZAPINE-INDUCED METABOLIC DYSFUNCTION'. Adelaide Convention Centre, Australia, 19th - 21st November 2025.

AWARDS:

SHEER SCIENCE RESEARCH GRANT, UNIVERSITY OF SOUTH AUSTRALIA. Awarded 1st August 2024, University of South Australia, Scholarships and Grants Ceremony.

ASCEPT, APFP, AND APSA JOINT CONGRESS: ASCEPT SPECIAL INTEREST GROUP (PHARMACOGENOMICS), BEST STUDENT POSTER, 'Elucidating Psychiatric Disorder, Antipsychotic, and Metabolic Syndrome Genetic Connection in GWAS'. Melbourne Convention and Exhibition Centre, Australia, 1st - 4th December 2024.

DECLARATION OF AUTHENTICITY

I declare that:

This thesis presents work carried out by myself and does not incorporate without acknowledgement any material previously submitted for a degree or diploma in any university; to the best of my knowledge it does not contain any materials previously published or written by another person except where due reference is made in the text; and all substantive contributions by others to the work presented, including jointly authored publications, is clearly acknowledged.

Rory Justin Shepherd

Signed:



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Date:

12th November 2025

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ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to all those who have contributed to the completion of this thesis and supported me throughout my research journey so far.

First and foremost, I am deeply grateful to my primary supervisor, Dr Vijay Suppiah, for being an exceptional advisor throughout this entire project. Your guidance, expertise, and support have been instrumental in shaping both this research and my development as an early career researcher. Additionally, I extend my upmost appreciation to my co-supervisor, Dr David Stacey. Your expertise was invaluable to this work. The genetic epidemiology aspects formed a substantial segment of this project, and your guidance through these complex concepts was essential. I would also like to thank all my other co-supervisors and contributors for their valuable input and support in various aspects of this project. Your diverse perspectives and expertise have enriched this work considerably. Additionally, thank you to the Australian Centre for Precision Health and the University of South Australia for the opportunity to conduct this research as well as the Australian Government Research Training Program Scholarship and the Sheer Science Research Grant for support through funding.

Beyond the academic realm, I am extremely grateful to my friends and family, who have made the completion of this project possible through their unwavering support. Thank you for always taking interest in my research interests. Most importantly, I owe a special thanks to my mother, Tracy, who has been my greatest supporter throughout my studies. Your encouragement, understanding, and belief in me have been the basis upon which this achievement stands. I am also deeply grateful to my father, Justin, whose influence played a large role in my choice to pursue academia. Though words cannot fully capture the impact you have had on my path, this work stands as evidence to the values you both instilled in me.

To all who have contributed, thank you for being part of this achievement.

CHAPTER 1 - INTRODUCTION AND RESEARCH OBJECTIVES

1.1. Background

1.1.1. Schizophrenia and Treatment Landscape

Schizophrenia (SCZ) is a severe neuropsychiatric disorder characterized by symptoms across three main clusters: positive (delusions, hallucinations), negative (alogia, avolition), cognitive (verbal learning and memory irregularities), as well as episodes of psychosis (Bowie & Harvey 2006; Tandon et al. 2013). The aetiology involves neurotransmitter imbalances affecting dopamine, glutamate, GABA, and serotonin systems, with genetics contributing 60-80% of disease liability (Hilker et al. 2018; Sullivan, Kendler & Neale 2003). To a lesser extent environmental factors have also been associated with the development of SCZ (Aoki et al. 2022; Bouter et al. 2025; Perry et al. 2022b). Episodes of psychosis significantly affect perception of reality, requiring urgent treatment and contributing to reduced life expectancy (Tandon et al. 2013; Zhang, L et al. 2022). Patients with SCZ have a shorter life expectancy compared to the general population, with an increased risk of cardiometabolic disease being a main factor contributing to this disparity (Hennekens et al. 2005; Olfson et al. 2015).

Antipsychotics are the mainstay of pharmacotherapy for psychiatric disorders (PDs) including SCZ. They can be classified into two categories: first-generation antipsychotics (FGAs) and second-generation antipsychotics (SGAs) (Hirsch et al. 2017; Newcomer 2005). While FGAs are effective in managing positive symptoms, they are associated with an increased risk of extrapyramidal adverse effects, including tardive dyskinesia, parkinsonism, and akathisia due to their higher affinity for D2 receptors (Grinchii & Dremencov 2020; Kaar et al. 2020). In contrast, SGAs, including risperidone, olanzapine, quetiapine, and aripiprazole, are often preferred as first-line treatments because of their decreased risk of these adverse effects resulting from lower affinity for dopamine D2 receptors (Hirsch et al. 2017). However, SGAs have their own unique complications. Many SGAs are associated with a higher risk of cardiometabolic adverse effects, characterised by weight gain, dyslipidaemia, and glucose intolerance (Hirsch et al. 2017; Newcomer 2005). The severity of these adverse effects varies among SGAs, with olanzapine, risperidone, and quetiapine having the highest risk, and ziprasidone, lurasidone, and aripiprazole having the lowest risk (Citrome et al. 2012; Melkersson & Dahl 2004; Solmi et al. 2017).

Approximately 30% of patients with SCZ experience treatment-resistant schizophrenia (TRS), characterized by persistent positive symptoms despite adequate trials of at least two different antipsychotics. Clozapine, whilst the most effective SGA for managing symptoms, is often reserved as a last-line treatment for SCZ as its use is limited by the potential for severe adverse effects, including agranulocytosis, cardiomyopathy, and cardiometabolic abnormalities (Dean & Kane 2012; Kaar et al. 2020; Melkersson & Dahl 2004; Newcomer 2005; Song, ZL et al. 2022).

1.1.2. Clozapine Efficacy and Cardiometabolic Risk

The cardiometabolic side effects of clozapine can lead to metabolic syndrome (MetS) which results in a higher risk of type 2 diabetes mellitus (T2DM), cardiovascular disease, dyslipidaemia, decreased high density lipoprotein (HDL) and premature mortality (Alberti et al. 2005; Kappel et al. 2024; Mitchell et al. 2013). MetS is a complex disorder that encompasses a collection of specific phenotypic traits including obesity, increased blood pressure, increased fasting glucose, large waist circumference, high triglyceride (TG) levels, and decreased HDL-C levels (Alberti et al. 2005). The widely accepted pathophysiological mechanisms of MetS include a group of processes that lead to insulin resistance, chronic inflammation, and neurohormonal activation because of increased visceral adiposity (Fahed et al. 2022). Increased visceral adiposity may occur primarily due to genetic and lifestyle factors including overeating and lack of physical exercise. Insulin resistance is understood to be a crucial driver of this process characterized by a reduced ability to mediate glucose uptake into cells and an increased concentration of circulating free fatty acids. This can lead to a detrimental metabolic cascade resulting in the onset of T2DM and hypertension (HT) (Brown & Walker 2016). Adipose tissue also responds to insulin resistance by releasing adipokines which mediate insulin sensitivity beyond their normal role of storing energy (Cho & Lee 2022). Dysregulation of these adipokines contributes to the pathogenesis of MetS. Chronic inflammation, depicted by elevated levels of inflammatory indicators such as IL-6 (interleukin-6) and TNFα (tumour necrosis factor-α), further provokes MetS-related complications by promoting insulin resistance (Boden & Shulman 2002; Dragoi et al. 2020; Shao et al. 2024) (Figure 1.1). Another concerning adverse effect of treatment with clozapine for TRS is agranulocytosis which is defined by dangerously low neutrophil count. This occurs in approximately 1% of patients and can be fatal if not detected early (Dean & Kane 2012). To mitigate this risk, regular white blood cell and absolute neutrophil counts are monitored for patients prescribed clozapine (Herzig et al. 2016).

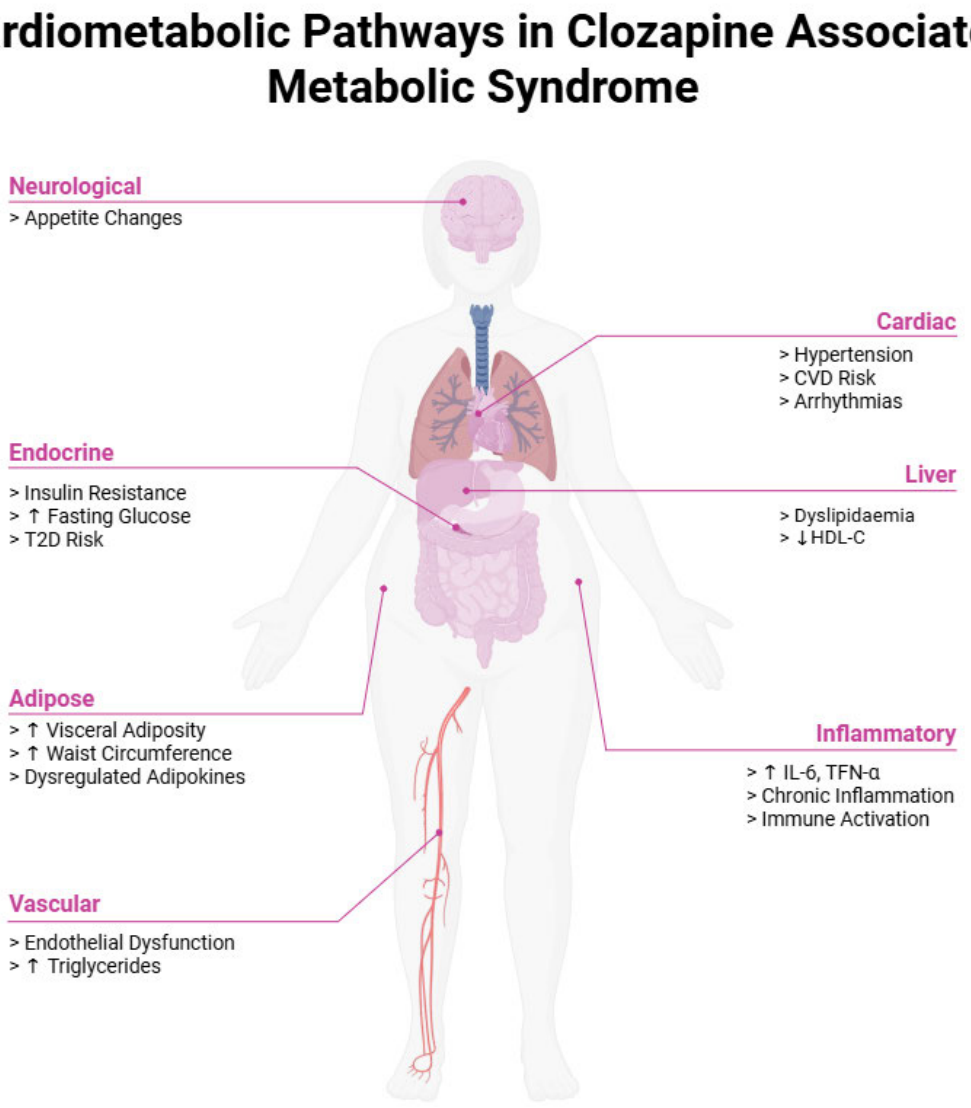


Figure 1.1 - Cardiometabolic Pathways in Clozapine Associated Metabolic Syndrome.
Visual representation of the anatomical regions and pathways associated with the pathogenesis of MetS in patients taking clozapine for TRS. Figure generated with BioRender.com.

A large proportion of clozapine-treated patients develop MetS, with some studies reporting rates as high as 32.5% (Lamberti et al. 2006; Vancampfort et al. 2015). Additionally, the use of clozapine may further exacerbate the treatment-naive threat of cardiometabolic complications in patients with SCZ. This creates a clinical paradox where the most effective treatment for severe mental illness (clozapine response rate of 50 - 60% in TRS cases) carries the greatest risk of life-threatening physical health consequences (Vancampfort et al. 2015). This clinical dilemma highlights the need for a precision health approach to clozapine prescribing that could potentially optimize the therapeutic effects whilst also minimizing adverse cardiometabolic effects. However, developing such approaches requires a stronger understanding of how clozapine influences cardiometabolic outcomes at a biological level, including genetic factors that influence one's susceptibility to these complications.

1.1.3. Current Approaches in Understanding Clozapine-Induced Cardiometabolic Dysfunction

Traditional approaches to understanding and managing clozapine-induced cardiometabolic dysfunction have relied predominantly on observational studies (Lamberti et al. 2006; Mitchell et al. 2013; Vancampfort et al. 2015) and clinical monitoring protocols (Cooper et al. 2016; Nielsen et al. 2013). These approaches, while valuable for documenting associations and establishing monitoring guidelines, face limitations in distinguishing medication-specific genetic effects from disease-related factors and in identifying the specific biological pathways mediating metabolic complications. While observational studies consistently demonstrate strong associations between clozapine treatment and metabolic dysfunction, and recent causal inference methods have made progress in addressing confounding (Burgess, Foley & Zuber 2018), there remains a critical gap in understanding the genetic mechanisms that determine individual susceptibility to clozapine-induced metabolic effects. These limitations have important clinical implications, as they restrict the development of genetically informed prevention strategies and limit understanding of which patients are at highest genetic risk.

Furthermore, traditional pharmacoepidemiologic approaches in clozapine research face unique methodological challenges. The relatively small population receiving clozapine, the complexity of polypharmacy in psychiatric patients, and the variability in treatment timelines all complicate longitudinal studies (Huhn et al. 2019; Kane et al. 1988; McEvoy et al. 2006). Additionally, the necessity of clozapine treatment in TRS makes randomized controlled trials (RCTs) comparing clozapine to placebo ethically problematic, limiting the available evidence for causal inference. However, clozapine has been extensively compared to other SGAs in large cohort studies and meta-analyses, demonstrating consistently the superior efficacy for treatment-resistant cases but confirming substantially higher rates of metabolic complications (Samara et al. 2016; Siskind et al. 2016; Tiihonen et al. 2017; Whiskey et al. 2021).

1.1.4. Genetic Approaches in Psychopharmacology

Approaches utilizing genetic data represent a powerful tool for causal inference. Mendelian randomization (MR) provides a framework for investigating these relationships to infer causality by utilizing genetic variants as instrumental variables (IVs), mimicking RCTs. In the context of clozapine research, MR can leverage genetic variants affecting clozapine pharmacokinetics as instruments, single nucleotide polymorphisms (SNPs), to examine causal effects on metabolic outcomes. The fundamental principle underlying genetic approaches is

that genetic variants are randomly allocated at conception, creating natural experiments that can help establish causality (Figure 1.2). The application of MR to clozapine research offers unique advantages for understanding drug-specific causal pathways. Unlike the use of general SCZ liability as an exposure, clozapine plasma variants provide drug-specific genetic instruments that can isolate the effects of altered drug exposure on metabolic outcomes and avoid potential confounding commonly encountered in observational studies. This approach is particularly valuable given the clozapine pronounced metabolic adverse effects and the clinical necessity of understanding these effects in the specific population requiring this medication.

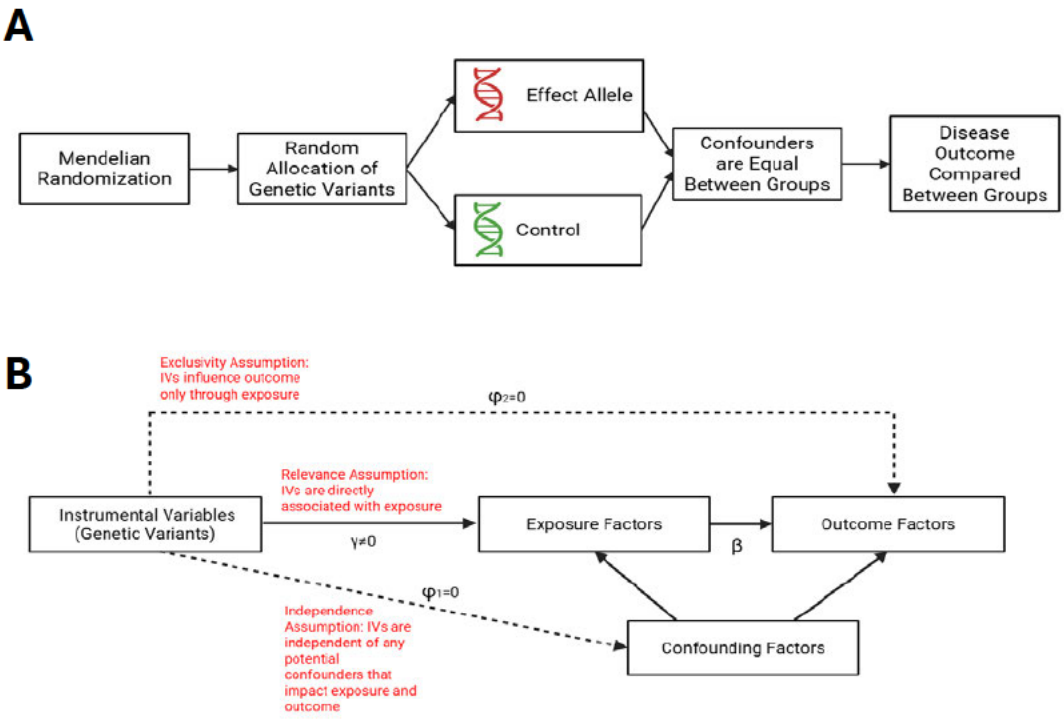


Figure 1.2 - Outline of Mendelian Randomization as an Epidemiological Technique to Infer Causal Relationships. (A) Overview of MR study design showing how random allocation of genetic variants at conception mimics a randomized controlled trial, with equal distribution of confounders between effect allele and control groups enabling unbiased outcome comparisons. (B) Directed acyclic graph illustrating the three core assumptions underlying valid MR analysis: (1) Relevance assumption ($\gamma \neq 0$) - instrumental variables (genetic variants) must be strongly associated with the exposure factor; (2) Independence assumption ($\varphi_1 = 0$) - genetic variants must be independent of confounding factors that influence both exposure and outcome; and (3) Exclusivity assumption ($\varphi_2 = 0$) - genetic variants must affect the outcome only through the exposure pathway. The causal effect of exposure on outcome estimated through the β pathway.

The genetic evidence for connections between PDs and metabolic dysfunction provides important context for understanding clozapine-specific effects. Studies investigating the genetic basis of PDs and MetS have provided another line of evidence for a relationship between these conditions and may be better suited to assist in understanding the link between SCZ and MetS. Genome-wide association studies (GWAS) have identified shared genetic variants associated with both PDs and MetS, suggesting a common genetic aetiology (Bulik-Sullivan et al. 2015; Calabrese 2019; Giambartolomei et al. 2014; Marees et al. 2018; Sanderson et al. 2022; Santoro et al. 2016; Zeng et al. 2015).

In addition to GWAS, phenome-wide association studies (PheWAS) have emerged as a complementary approach to investigate the complex relationships between genetic variants and a wide range of phenotypes (Denny, Bastarache & Roden 2016; Pendergrass & Ritchie 2015). PheWAS utilize large-scale phenotypic data to systematically explore the associations between genetic variants and multiple phenotypes simultaneously (Bush, Oetjens & Crawford 2016). This approach has the potential to uncover pleiotropic effects of genetic variants, where a single variant may influence multiple unrelated traits or diseases, or alternatively reveal causal chains of events where genetic effects cascade through intermediate phenotypes to influence downstream outcomes (Verma et al. 2018). PheWAS can also identify novel associations between genetic variants and phenotypes with no prior assumption of connection, leading to the generation of new hypotheses and identification of shared biological architecture (Hebbring 2014). By combining the results of GWAS and PheWAS, researchers can gain a more comprehensive understanding of the complex interplay between genetic factors and phenotypes (Polimanti, Kranzler & Gelernter 2016). This integrative approach has the potential to uncover novel insights into the shared genetic architecture of these conditions, identify new targets for treatment, and inform the development of personalized treatment strategies. Statistical colocalization methods enable further determination of whether PDs and metabolic trait associations share the same causal genetic variants, distinguishing true biological relationships from coincidental associations due to linkage disequilibrium (LD), the non-random association of alleles at different loci.

1.1.5. Evidence for Genetic Links Between Schizophrenia and Cardiometabolic Dysfunction

Previous studies have demonstrated linked shared pathways between PDs, such as SCZ, and MetS (Belbasis et al. 2018; Stringer et al. 2014). Multiple studies investigating shared genetic aetiology have reported a higher prevalence of MetS in patients with SCZ compared to the general population. A meta-analysis by Vancampfort et al. (2015) found that the pooled MetS prevalence in people with severe mental illness, including SCZ, was 32.6%, with a significantly increased risk compared to population controls (OR: 1.58; 95% CI: [1.35 - 1.86]; $P < 1.00 \times 10^{-3}$) (Vancampfort et al. 2015). Recent studies by Aoki et al. (2022) and Gao et al. (2024) had reported significant genetic correlations between SCZ and several MetS traits, such as body mass index (BMI), lipid levels, blood glucose (BG), and blood pressure (Aoki et al. 2022; Gao et al. 2024). Three studies discovered SNPs and specific genomic regions shared between SCZ and BMI, including loci involved in neurotransmitter signalling, metabolic regulation, and inflammatory pathways that demonstrated pleiotropic effects across both psychiatric and cardiometabolic phenotypes (Cheng et al. 2023; Lv et al. 2022; Yu et al. 2023). Andreassen et al. (2013) and He et al. (2022) identified shared genetic variants and pathways between SCZ and cardiovascular disease risk factors, with some related to inflammation and the immune system (Andreassen et al. 2013; He et al. 2022). One study proposed that genes of the prolactin pathway may be implicated in the comorbidity of SCZ and MetS (Postolache et al. 2019). Other studies have focused on the genetic overlap between SCZ and specific MetS components or related traits. Al-Soufi et al. (2022) found associations between polygenic risk scores (PRS) for educational attainment, BMI, age at first birth, and smoking in both SCZ patients and controls (Al-Soufi et al. 2022). MR studies have been used to investigate causal relationships linking SCZ and MetS. Evidence from one MR study indicated that inflammation could be a shared process with insulin resistance and SCZ (Perry et al. 2021a). Another MR study indicated that liability to SCZ may causally increase heart failure (HF) risk (Veeneman et al. 2022).

While these studies had demonstrated important genetic connections between SCZ and metabolic dysfunction, they primarily reflect disorder-related mechanisms and do not distinguish between disease liability and medication-induced effects. Understanding how these broader genetic relationships interact with medication-specific effects remains a critical knowledge gap, as metabolic complications vary across different antipsychotic medications (Huhn et al. 2019; Tiihonen et al. 2017).

1.1.6. Clozapine Pharmacogenomics and Population Differences

Recent advances in clozapine pharmacogenomics have transformed understanding of the genetic factors influencing drug metabolism, efficacy, and adverse effects. Pardinas et al. (2023) conducted the first comprehensive genome-wide analysis using 10,353 clozapine plasma concentration measurements from 2,989 individuals with TRS, identifying four genome-wide significant loci affecting clozapine pharmacokinetics. The rs2472297 (located between *CYP1A1* and *CYP1A2*) variant showed the largest effect, with minor allele carriers requiring approximately 50 mg/day lower clozapine doses, representing clinically meaningful effect sizes for personalized dosing applications (Pardinas et al. 2023). Individual genetic variants explained 1.15 - 9.48% of pharmacokinetic variance, with the study identifying both coding and regulatory variants in cytochrome P450 and UDP-glucuronosyltransferase genes. Notably, the research revealed evidence for genetic interactions between clozapine, caffeine, and tobacco metabolism pathways, suggesting complex pharmacological relationships that extend beyond traditional drug-metabolizing enzymes. These findings have important implications for clinical practice, as genetic variants affecting clozapine clearance could guide initial dosing strategies and reduce the time needed to achieve effective therapeutic plasma concentrations (Kappel et al. 2024; Li et al. 2022; Pardinas et al. 2023; Ying et al. 2023).

Rare variant contributions have emerged as additional important factors in clozapine metabolism variability. Kappel et al. (2024) employed whole-exome sequencing in 2,062 patients taking clozapine, identifying significant associations between rare damaging variants in pharmacokinetically relevant genes and lower clozapine concentrations. These rare variants in genes such as *CYP1A2* and *CYP2D6* were associated with altered drug clearance and reduced steady-state plasma levels compared to individuals carrying only common variants. Specifically, individuals carrying one damaging allele had clozapine concentrations approximately 35 mg/day lower than non-carriers. Among the genes studied, *CYP1A2* showed the strongest gene-based association with altered clozapine metabolism. This research highlighted the importance of rare genetic variation in explaining individual differences in drug response that are not captured by common variant analyses (Kappel et al. 2024).

Adverse effects may be also influenced by genetic factors, as evidenced by the associations between PRSs for BMI, T2DM, and SCZ with antipsychotic-induced weight gain (AIWG) (Franz et al. 2024; Yoshida et al. 2023). GWASs have also identified specific loci associated with AIWG, within genes such as *PEPD* (peptidase D) and *PTPRD* (protein tyrosine

phosphatase receptor type D), which may be involved in lipid pathway dysfunction (Liao, Y et al. 2024b; Ter Hark et al. 2020).

Pharmacogenetic metabolic adverse effect studies have revealed specific genetic predictors of clozapine-induced weight gain and metabolic dysfunction. Franz et al. (2024) demonstrated that PRS for BMI, SCZ, and T2DM significantly predict AIWG, with the study identifying three novel variants achieving genome-wide significance for weight gain associations: rs10968576 near the *LINGO2* gene, rs11030104 near the *BDNF* gene, and rs4712652 in the *PRL* (prolactin) gene region (Franz et al. 2024; Yoshida et al. 2023). These findings suggest that genetic liability to metabolic dysfunction may predispose individuals to metabolic adverse effects of clozapine, independent of its pharmacokinetic properties (Gunes et al. 2009; Hernandez et al. 2024; Kang, SH et al. 2014; Pardinas et al. 2023).

Furthermore, clozapine is only effective in up to 50 - 60% of people with TRS, an occurrence known as clozapine resistance (Carswell et al. 2023; Siskind, Siskind & Kisely 2017; Ying et al. 2023). Genetic factors may contribute to both clozapine response and side effect profiles, as evidenced by the associations between variants in cytochrome P450 enzymes, dopaminergic, and serotonergic genes with clozapine metabolism and treatment outcomes (Kappel et al. 2024; Li et al. 2022; Pardinas et al. 2023; Ying et al. 2023). Genetic risk for clozapine related agranulocytosis, such as variants in *HLA-DQB1* (major histocompatibility complex, class II, DQ beta 1) and *HLA-B* (human leukocyte antigen B) genes, had been identified, but their predictive power is currently insufficient for routine genetic testing (Dean & Kane 2012; Numata et al. 2018).

While these genetic findings provide important insights into individual susceptibility to clozapine-induced metabolic dysfunction, genetic factors do not operate in isolation. Lifestyle factors including diet, physical activity, and smoking likely interact with genetic predisposition to modulate individual risk. Although research specifically examining gene-environment interactions in clozapine-treated populations remains limited, understanding these relationships holds important clinical implications. Patients identified as genetically high-risk for metabolic complications might benefit from lifestyle interventions alongside pharmacological treatment and enhanced metabolic monitoring, potentially mitigating adverse outcomes while preserving clozapine's therapeutic benefits (Musci, Augustinavicius & Volk 2019; Roerig, Steffen & Mitchell 2011).

Although the aforementioned studies have successfully investigated the genetic factors associated with clozapine response and adverse effects, a significant gap remains in understanding the complex interplay between genetics, clozapine metabolism, and the development of metabolic abnormalities in TRS patients. The majority of pharmacogenetic studies on clozapine have focused on candidate gene approaches, with limited genome-wide investigations (Numata et al. 2018; Pardinas et al. 2019). However, candidate gene studies have demonstrated poor reproducibility and limited reliability, largely due to inadequate statistical power, publication bias, and the complexity of polygenic traits (Border et al. 2019). To address this, novel approaches combining GWAS data and PheWAS techniques can be employed to develop a comprehensive genetic panel for predicting clozapine-induced metabolic risk using variants that are associated with metabolism, response, and adverse cardiometabolic effects of clozapine. Furthermore, statistical methods such as MR and colocalization analysis can be employed to investigate the causal links between genetic risk factors, clozapine pharmacokinetics, and MetS in TRS patients (Burgess et al. 2015; Perry et al. 2021b; Reed et al. 2017; Stahl et al. 2019). The elucidation of causal relationships could have significant implications for personalized treatment approaches in TRS. By identifying patients at higher risk for adverse metabolic outcomes, clinicians could implement targeted monitoring and intervention strategies to minimize adverse effects and improve treatment adherence. Additionally, understanding the genetic basis of clozapine resistance could guide the development of novel therapeutic strategies for patients who do not respond adequately to clozapine.

1.2. Research Problem

Despite substantial advances in clozapine pharmacogenomics, critical knowledge gaps remain that limit the understanding of the relationship between clozapine metabolism and cardiometabolic outcomes. Limited integration of clozapine-specific pathways represents a major gap in current research investigating psychiatric-metabolic relationships. Most existing studies examining SCZ-metabolic associations use general SCZ liability as a proxy rather than examining clozapine-specific genetic instruments. This limitation is problematic given the unique pharmacological profile of clozapine and pronounced metabolic adverse effects that may operate through distinct mechanisms from other antipsychotics. Incomplete causal inference regarding the relationship between clozapine metabolism and metabolic outcomes represents another fundamental gap. While observational studies consistently demonstrate associations between clozapine treatment and metabolic dysfunction, the causal pathways underlying these relationships remain poorly understood. Traditional epidemiological

approaches cannot distinguish between direct pharmacological effects of altered clozapine exposure and indirect effects mediated through improved psychiatric symptoms or lifestyle changes. Phenotypic scope limitations in current clozapine research focus primarily on major adverse outcomes such as weight gain and T2DM, while neglecting other potentially relevant phenotypes that may provide mechanistic insights. To date, the application of systematic phenome-wide approaches to clozapine related variants has not been undertaken, representing a missed opportunity to understand the full spectrum of biological effects associated with altered clozapine exposure.

Understanding the genetic basis of clozapine-induced metabolic dysfunction is essential for several reasons:

- Potential development of predictive genetic markers, allowing for personalized risk assessment before initiating clozapine treatment.
- Identification of implicated biomarkers could provide insights into the mechanisms of clozapine-induced metabolic changes, potentially leading to novel therapeutic targets.
- Information regarding the potential avenues for development of preventive strategies or treatments to mitigate the metabolic risks associated with clozapine use.

Given the critical importance of clozapine in the management of TRS and the significant impact of MetS on patient health and quality of life, there is an urgent need to elucidate the genetic factors contributing to these adverse effects.

1.3. Research Objectives

The primary objective of this research is to investigate the genetic association between cardiometabolic abnormalities and clozapine use in TRS. This overarching aim will be addressed through the following specific aims:

(1) Synthesize genomic evidence for the relationships between PDs, antipsychotic use, and cardiometabolic traits, with particular focus on identifying knowledge gaps regarding medication-specific effects versus disease related-factors and methodological limitations.

(2) To employ an integrated genetic epidemiological pipeline combining MR, PheWAS, and colocalization analyses to investigate evidence for the potential causal relationships between clozapine plasma traits and cardiometabolic outcomes and identify candidate biomarkers potentially influenced by clozapine-metabolising genetic loci.

1.4. Study Significance

This research has the potential to make significant contributions to the field of psychiatric pharmacogenetics and personalized medicine in several ways:

(1) Improved Risk Stratification: By identifying genetic markers associated with clozapine-induced MetS, this study could lead to the development of genetic screening tools to assess individual patient risk before initiating clozapine treatment.

(2) Mechanistic Insights: Identification of genetic loci associated with clozapine-induced MetS may provide insights into the biological mechanisms underlying these adverse effects, potentially revealing new therapeutic targets.

(3) Personalized Treatment Approaches: Understanding the genetic basis of susceptibility to metabolic adverse effects could inform personalized treatment strategies, potentially involving tailored dosing regimens or early interventions for high-risk patients.

(4) Improved Patient Outcomes: By contributing to strategies for mitigating metabolic risks, this research could ultimately lead to improved long-term health outcomes and quality of life for patients with TRS.

(5) Advancement of Pharmacogenomics: This work will contribute to the growing body of knowledge in psychiatric pharmacogenomics, potentially informing future research and clinical applications in this field.

1.5. Study Overview and Pipeline

To successfully investigate the extent of the connection between clozapine pharmacokinetics and cardiometabolic abnormalities in patients with SCZ, a two-step study pipeline was designed. First, a systematic review of genomic studies (Chapter 3) investigating the connection between PDs, antipsychotic use, and cardiometabolic abnormalities was undertaken to assess knowledge and methodological gaps in this area. Secondly, a multi-layered genetic epidemiological study (Chater 4) was designed and undertaken based on the knowledge and methodological gaps identified in the systematic review to investigate the specific effects of clozapine use on the development of cardiometabolic abnormalities and MetS using a collection of genetic epidemiological techniques.

The systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) updated guidelines 2020. The genomic study incorporated several genomic techniques sequentially to investigate the direct connection between clozapine metabolism and metabolic traits and identify potential secondary pathways connecting these two sets of traits. Knowledge and methodological shortcomings identified in the review guided the design of the genomic investigation between clozapine and cardiometabolic dysfunction.

A multi-layered approach was employed to investigate the relationship between clozapine and cardiometabolic abnormalities. MR as a primary tool allowed for the inference of potential causal pathways linking clozapine to metabolic outcomes. This was used in conjunction with PheWAS and colocalization allowing for thorough investigation of potential implicated biomarkers in the relationship, whereby PheWAS generated a list of candidate phenotypes which were then pruned by statistical colocalization. Using the new list of colocalized biomarkers, MR was again employed to assess if there was evidence of causal relationships to cardiometabolic traits indicating a potential relation to the clozapine-metabolic relationship. The study pipeline has been outlined in Figure 1.3.

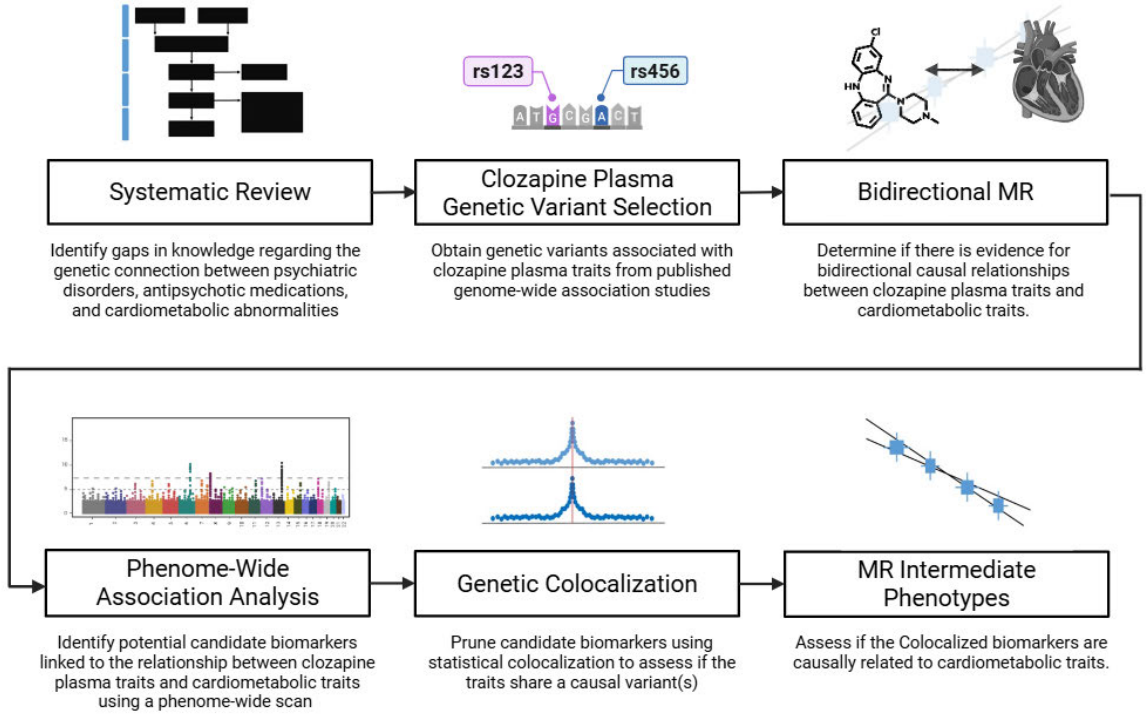


Figure 1.3 - Flowchart of the Study Pipeline Indicating a Multi-layered Approach to Investigate the Genetic Relationship Between Clozapine and poor Metabolic Outcomes in Treatment Resistant Schizophrenia.
Systematic review identifies gaps in knowledge and limitations in methodology. A combination of Mendelian randomization, phenome-wide association, and colocalization analyses then allow for investigation into the genetic relationships between clozapine and cardiometabolic traits potentially outlining direct causal relationships and intermediate biological pathways.

1.6. Thesis Structure

The structure of the thesis is as follows:

- Chapter 2 presents the research protocol for a systematic review of the genetic connection between PDs, antipsychotics, and cardiometabolic dysfunction which is then presented in the subsequent chapter. This research protocol was registered to PROSPERO and OSF.
- Chapter 3 presents a comprehensive systematic review of existing literature investigating the genetic connections between PDs, antipsychotic treatment, and cardiometabolic abnormalities. This chapter outlines the methods for conducting the review, including the search strategy, inclusion and exclusion criteria, as well as quality assessment, data synthesis, and visualization approaches. This chapter comprehensively establishes the knowledge and methodological gaps in genomic understanding of psychiatric-metabolic relationships, particularly the challenge of distinguishing medication-specific effects from disease-related factors, thereby providing the foundation for the subsequent genomic investigation.
- Chapter 4 presents a multi-layered genetic epidemiological study investigating the specific potential causal pathways linking clozapine plasma levels and cardiometabolic abnormalities. This chapter provides a nuanced approach in understanding the biological network of traits connecting clozapine plasma levels to cardiometabolic dysfunction in TRS. This study design is guided by gaps identified in the systematic review.
- Chapter 5 is a general discussion synthesizing results from both studies to address the original aims regarding the relationship between clozapine and cardiometabolic abnormalities in patients with TRS. This chapter also discusses the overall strengths and limitations of the work, the potential clinical and translational implications and future avenues for research.

Appendix A contains the statements of authorships for the two works submitted for publication. Appendix B and C contain supplementary material for chapters 3 and 4 respectively, including additional methodology, tables, and figures too large to include in the main text. Appendix D contains information about the computational environment and code descriptions. Formatting of published or submitted works has been modified for this thesis, but no other specific contents were altered from the submitted material. Section 3.6 was not included in the accepted systematic review but rather serves as a narrative bridge between chapter 3 and 4.

CHAPTER 2 - SYSTEMATIC REVIEW RESEARCH PROTOCOL

This systematic review protocol for “Disentangling the Relationship Between Psychiatric Disorders, Metabolic Syndrome, and Antipsychotics: A Systematic Review of Genomic Studies” was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on August 12, 2024 (ID: CRD42024574593). The research protocol was also registered with the Centre for Open Science (OSF) (Registration DOI: https://doi.org/10.17605/OSF.IO/X3SG7).

2.1. Introduction

2.1.1. Background

MetS is a cluster of interconnected metabolic abnormalities, including central obesity, lipid imbalance, HT, and insulin resistance. These disturbances significantly increase the risk of developing T2DM and CVD (Peterson et al. 2011; van Walree et al. 2022). The pathophysiology of MetS is multifactorial, involving complex interactions between genetic susceptibility and environmental factors (Cherny, Williams & Livshits 2022; Moreira et al. 2019; Penninx & Lange 2018).

In recent years, there has been increasing interest in exploring the intersection between PDs and MetS. Individuals with PDs, including SCZ, BD, and MDD, exhibit a higher occurrence of MetS compared to the general population (Zhang, M et al. 2021). The underlying mechanisms linking PDs and MetS are multifaceted, involving shared genetic susceptibility, neuroendocrine dysregulation, unhealthy lifestyle behaviours, and side effects of psychotropic medications (Penninx & Lange 2018; Vancampfort et al. 2015; Woldekidan et al. 2021).

Psychotropic medications, specifically antipsychotics, are known to prompt metabolic disturbances and weight gain, thereby contributing to the development of MetS in vulnerable individuals (Moreira et al. 2019; Wysokiński & Kołszewska 2011). Genetic factors play a crucial role in mediating the susceptibility to antipsychotic-induced metabolic side effects, highlighting the complex interplay between genetics, environment, and medication exposure in the pathogenesis of MetS (Yumru et al. 2007).

The use of GWAS has become increasingly prevalent in investigating the complex connection of traits across thousands of common genetic variants (Bulik-Sullivan et al. 2015; Bycroft et al. 2018; Robinson, JR et al. 2018). Despite the growing body of literature documenting the

association between PDs, antipsychotics, and MetS, several gaps and challenges remain in our understanding of this complex relationship (Morris et al. 2020; van Walree et al. 2022).

2.1.2. Rationale and Objectives

This systematic review aims to synthesize the current evidence on the genetic connections between PDs, AIWG, and MetS, focusing on GWAS and related analytical approaches. Specifically, this review aims to:

- Systematically identify and synthesize the current literature investigating the genetic connections between PDS, AIWG, and MetS using GWAS.
- Examine the extent and nature of the genetic overlap and shared aetiology among specific PDs, antipsychotic treatment, and metabolic phenotypes.
- Characterize the most studied metabolic phenotypes in relation to PDs and antipsychotic treatment and identify any gaps or understudied areas in the current literature.
- Summarize the key findings regarding the identification of shared genetic loci, biological pathways, and causal relationships linking PDs, AIWG, and MetS.
- Assess the strength and consistency of the evidence supporting the genetic connections between PDs, antipsychotics, and metabolic abnormalities, considering the methodological quality and limitations of the included studies.
- Discuss the potential clinical implications of the current body of literature, such as informing strategies for risk assessment, prevention, and management of metabolic complications in individuals with PDs receiving antipsychotic treatment.
- Identify gaps in the current understanding of the genetic basis of the relationship between PDs, antipsychotics, and MetS, and provide recommendations for future research directions to address these gaps.

2.2. Methods

2.2.1. Search Strategy

A systematic literature search will be conducted in accordance with the PRISMA guidelines. We will search PubMed, Scopus, and Web of Science databases for studies published between January 2005 and August 2025 to coincide with the emergence of large-scale GWAS, which marked a shift from candidate gene approaches. The search strategy will include a combination of keywords and MeSH terms related to PDs, antipsychotics, MetS, and GWAS.

2.2.2. Inclusion and Exclusion Criteria

Studies will be included if they meet the following criteria: **(1)** involve human participants with PDs and MetS or related metabolic comorbidities; **(2)** use GWAS data to investigate genetic overlap, shared aetiology, or causal relationships between PDs, AIWG, and MetS or related metabolic traits; **(3)** report findings related to shared genetic loci, biological pathways, genetic correlations, causal relationships, or PRSs linking the conditions of interest. We will exclude animal studies, non-peer-reviewed articles, and studies not using GWAS data or advanced statistical techniques to investigate the genetic relationships of interest. The full inclusion and exclusion criteria are presented in Supplementary Table 3.9 (Patnala, Clements & Batra 2013).

2.2.3. Study Selection

Two researchers will independently screen titles and abstracts against the inclusion and exclusion criteria. Full-text articles of potentially eligible studies will be retrieved and independently assessed by two researchers. Any discrepancies will be resolved through discussion or consultation with a third researcher.

2.2.4. Data Extraction

Data will be extracted from the included studies using a standardized form. The following information will be extracted and organized into several tables to outline key information about each study:

1. General Study Characteristics:
    - Lead author and year of publication
    - Sample size
    - Ethnicity of the study population
    - Study design and main statistical analyses performed
2. Investigated PDs:
    - Specific PD(s) studied
    - Diagnostic criteria or data source used for psychiatric diagnoses
3. Antipsychotics Investigated:
    - Names of specific antipsychotic medications studied
    - This information will be extracted for studies focusing on antipsychotic-induced metabolic effects
4. Metabolic Phenotypes Examined:
    - Specific metabolic traits or outcomes investigated
    - Diagnostic criteria or measurement methods used for metabolic phenotypes
5. Main Findings and Key Statistical Results:
    - Primary outcomes and main conclusions of each study
    - Key statistical results, including effect sizes, odds ratios, p-values, and confidence intervals where applicable
6. Quality Assessment Results:
    - Ratings for population stratification, multiple testing correction, and replication
    - Overall risk assessment for selection, comparability, and outcome/exposure domains
7. Mendelian Randomization Specific Study Characteristics:
    - One-sample or two-sample design
    - Individual-level or summary-level data
    - Number of genetic instruments used
    - Instrument inclusion criteria
    - Exposure and outcome traits
    - Sensitivity analyses performed
    - MR methods used
    - Tests for weak instruments and heterogeneity
    - Use of leave-one-out analysis

2.2.5. Quality Assessment

The methodological quality of the included studies will be assessed using a customized quality assessment scale for observational studies in the context of GWAS. This customized scale was used to adequately addresses the unique methodological considerations in GWAS-based studies with a high level of heterogeneity in study design by capturing key methodological information regarding these studies. This scale will assess three critical aspects: 'selection,' 'comparability,' and 'outcome/exposure.' Each study will be classified into one of three risk categories - 'low risk,' 'high risk,' or 'unclear risk' - based on pre-defined criteria, this is outlined in Supplementary Table 3.10 (Belbasis et al. 2015; Little et al. 2009; Manolio 2010).

2.2.6. Data Synthesis

Due to the expected heterogeneity of the included studies in terms of PDs, metabolic phenotypes, and genetic methods employed, a narrative synthesis approach will be adopted. The extracted data will be organized into tables and summarized according to the following themes: study characteristics and quality assessment, PDs and metabolic phenotypes investigated, shared genetic loci and biological pathways, causal relationships and genetic correlations, and AIWG and metabolic side effects (Ioannidis et al. 2008; Zeggini & Ioannidis 2009).

2.2.7. Data Visualisation for Mendelian Randomization Studies

For MR studies, we will visualise the data using a forest plot for each individually reported significant trait pair to demonstrate overlap between studies in effect size and direction of association without performing explicit meta-analysis due to error that could arise due to overlapping sample sizes leading to potentially inflated results.

2.3. Discussion

This systematic review will provide a comprehensive synthesis of the current evidence on the genetic connections between PDs, AIWG, and MetS. By identifying shared genetic loci, biological pathways, and potential causal relationships, this review aims to enhance our understanding of the complex genetic interplay between psychiatric and metabolic health. The findings will have implications for risk assessment, prevention strategies, and personalized treatment approaches in psychiatric care.

CHAPTER 3 - SYSTEMATIC REVIEW OF GENOMIC STUDIES

Disentangling the Relationship Between Psychiatric Disorders, Metabolic Syndrome, and Antipsychotics: A Systematic Review of Genomic Studies

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3.1. Abstract

Psychiatric disorders are often comorbid with MetS, suggesting shared genetic architecture. This systematic review investigated the genetic connections between psychiatric disorders, antipsychotic use, and MetS through genome-wide association studies and related genetic approaches. We systematically searched PubMed, Scopus, and Web of Science for relevant studies published between January 2005 and August 2025. Seventy-seven studies were included in the systematic review upon meeting the inclusion criteria. Substantial shared genetic architecture was found between psychiatric disorders and metabolic traits, particularly involving major depressive disorder (MDD), SCZ, and BMI. Key implicated pathways included lipid metabolism, glucose homeostasis, and inflammatory processes. Mendelian randomization studies provided evidence for causal relationships, notably a unidirectional effect of MDD on MetS, and bidirectional relationships between SCZ and BMI. Antipsychotic-induced weight gain showed a more specific genetic basis compared to broader psychiatric disorder-related MetS. Future research should focus on diverse populations, refined phenotype definitions, and translating genetic insights into clinical practice. The integration of pharmacogenomic scores with clinical data shows promise for personalizing treatment strategies in psychiatry.

3.2. Introduction

Many people with psychiatric disorders go on to develop MetS which is a cluster of metabolic dysfunctions including abdominal obesity, increased blood sugars, triglycerides, and blood pressure as well as low high density lipoprotein (HDL) (Afshin et al. 2017; Brown & Walker 2016; Esposito & Giugliano 2004; Firmann et al. 2008; Joy & Hegele 2008; McCracken, Monaghan & Sreenivasan 2018; Palaniappan et al. 2010; Penninx & Lange 2018; Saklayen 2018; Stancakova & Laakso 2014; Swarup et al. 2024; Tylutka et al. 2023; van Walree et al. 2022; Wang, Y et al. 2006; Wildman 2008; Zhu et al. 2020). This comorbidity significantly increases the risk of T2DM and cardiovascular disease (CVD), leading to exacerbating

psychiatric symptoms and premature death (Huangfu et al. 2023b; Swarup et al. 2024). The precise nature of the relationship between psychiatric disorders and MetS is not fully understood. A better understanding could enable the development of more effective prevention strategies and targeted treatments for both psychiatric illnesses and MetS (McCracken, Monaghan & Sreenivasan 2018; Penninx & Lange 2018). MetS has complex underpinnings, characterised by insulin resistance, impaired glucose intake, and dysregulated lipid metabolism (McCracken, Monaghan & Sreenivasan 2018). Visceral adiposity also contributes to MetS through the release of pro-inflammatory adipokines, cytokines, and free fatty acids, promoting chronic low-grade inflammation (Cherny, Williams & Livshits 2022; Swarup et al. 2024). Antipsychotic medications, especially SGAs such as risperidone, olanzapine, and clozapine, are also known to induce metabolic disturbances, particularly weight gain (Newcomer 2005; Teff & Kim 2011; Yumru et al. 2007). Among SGAs, clozapine, the gold standard for the treatment of SCZ, is associated with the highest risk of significant weight gain and MetS, with up to 32.5% of patients experiencing MetS (Dayabandara et al. 2017). Although the precise underlying mechanisms are not fully understood, genetic factors have been known to play a crucial role in mediating susceptibility to antipsychotic-induced metabolic adverse effects. This highlights the complex interplay between genetics, environment, and medication exposure in the pathogenesis of MetS (Chacko, Boyd & Murphy 2018; Richards-Belle et al. 2023; Sjaarda et al. 2023).

The relationship between PDs and MetS appears to be mediated through several shared biological mechanisms, with inflammation emerging as a central component (Osimo et al. 2018; Tylutka et al. 2023). Chronic low-grade inflammation is implicated in both conditions - serving as both a potential cause and consequence of metabolic disturbances in psychiatric disorders, while also playing a crucial role in antipsychotic-induced metabolic effects (Leung et al. 2023; Sernoskie et al. 2022).

Traditional observational epidemiological studies have documented associations between psychiatric disorders and MetS but face inherent limitations in establishing causality due to confounding factors and reverse causation. These methodological challenges make it difficult to disentangle whether psychiatric disorders directly contribute to MetS, whether MetS exacerbates psychiatric symptoms, or whether shared underlying factors drive both conditions. Genetic approaches, particularly those utilizing genome-wide association study (GWAS) data, offer unique advantages for addressing these limitations. Because genetic variants are randomly allocated at conception, they are generally not susceptible to reverse causation or the same confounding factors as traditional observational studies. This makes genetic methods

particularly valuable for exploring potential causal relationships and identifying shared biological mechanisms between complex traits (Abou Kassm et al. 2022; Moreira et al. 2019; Penninx & Lange 2018).

Prior work has demonstrated the value of extending GWAS findings through functional mapping, particularly in mood disorders, highlighting potential biological mechanisms that could be targeted therapeutically (Abou Kassm et al. 2022; Moreira et al. 2019; Penninx & Lange 2018). Moreover, studies conducting secondary analyses using GWAS summary statistics have begun to disentangle the complex and multi-faceted relationship between MetS and psychiatric disorders by enabling the identification of shared genetic loci, estimation of genetic correlations [e.g., LD score regression (LDSC)], and exploration of potential causal relationships [Mendelian randomization (MR)] (Amare et al. 2017; Azam & Azizan 2018; Brauer et al. 2021; Cano-Gamez & Trynka 2020; Denny, Bastarache & Roden 2016; Kieling et al. 2024; Selzam et al. 2019; Udler et al. 2018; van Walree et al. 2022).

This systematic review aimed to investigate the relationship between MetS, antipsychotic medications, and PDs from the genomics literature. Specifically, this review will address three key research questions in the context of Figure 3.1: **(1)** What is the extent and nature of genetic overlap between PDs, antipsychotic treatment, and metabolic phenotypes? **(2)** What evidence exists for causal relationships between PDs, antipsychotic use, and MetS or related metabolic abnormalities? **(3)** What are the key gaps in the current literature in understanding the genetic basis of the relationship between PDs, antipsychotics, and MetS? Recent advances in genetic methodologies and the availability of large-scale biobank data make this systematic examination particularly timely, offering unprecedented opportunities to disentangle these complex relationships. This synthesis of current knowledge could pave the way for research investigating potential personalized approaches and managing both psychiatric and metabolic health in affected individuals.

3.3. Methods

This systematic review adhered to the PRISMA updated guidelines 2020 (Page et al. 2021a) and was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on August 12, 2024 (ID = CRD42024574593). No amendments were made to the original protocol published in PROSPERO. The research protocol was also registered with the Centre for Open Science (OSF) (Registration DOI: https://doi.org/10.17605/OSF.IO/X3SG7).

A database search was conducted in PubMed, Scopus, and Web of Science for relevant studies published in English between January 2005 and August 2025, to coincide with the emergence of largescale GWAS methodology and major psychiatric genetics consortia. The search strategy included a combination of keywords and MeSH terms related to psychiatric disorders, antipsychotics, MetS, and GWASs (complete search string information and retrieval strategy is provided in Appendix B, Supplementary Methods).

Studies were included if they: (1) had human participants with psychiatric disorders and MetS or related metabolic comorbidities; (2) used genome-wide approaches (such as GWAS data) to investigate genetic overlap, shared aetiology, or relationships between psychiatric disorders, antipsychotic-induced weight gain (AIWG), and metabolic traits (candidate gene studies were excluded); and (3) reported findings related to shared genetic loci, biological pathways, genetic correlations, causal relationships, or polygenic risk scores (PRS) linking the conditions of interest. Animal studies, non-peer-reviewed articles, and studies not using GWAS data or genetic-focused statistical techniques were excluded. Figure 1 outlines the screening process. After removing duplicate papers, titles and abstracts were screened by two independent researchers and discrepancies were resolved by a third researcher. This process was repeated for full texts.

Due to the heterogeneity in study designs, psychiatric disorders, metabolic phenotypes, and genetic methods employed, meta-analysis and assessment of publication bias or certainty was not conducted. Instead, a narrative synthesis approach was adopted. The extracted data were organised into themes: study characteristics, quality assessment, psychiatric disorders, pharmaceuticals, metabolic phenotypes, primary outcomes/results, and estimates from MR analyses. The methodological quality of included studies was assessed using a customized quality assessment scale for genetic studies, focusing on three domains: selection, comparability, and outcome/exposure. Each study was classified as 'low risk', 'high risk', or 'unclear risk' of bias for each domain (Appendix B, Supplementary Methods)

To provide a structured framework for our narrative synthesis, Figure 3.1 was developed illustrating the potential relationships between PDs, antipsychotic use, and metabolic outcomes. This guided analysis and interpretation of the extracted data, allowed for a systematic evaluation of evidence for direct associations (Path A), shared risk factors (Path B), and medication-mediated effects (Path C).

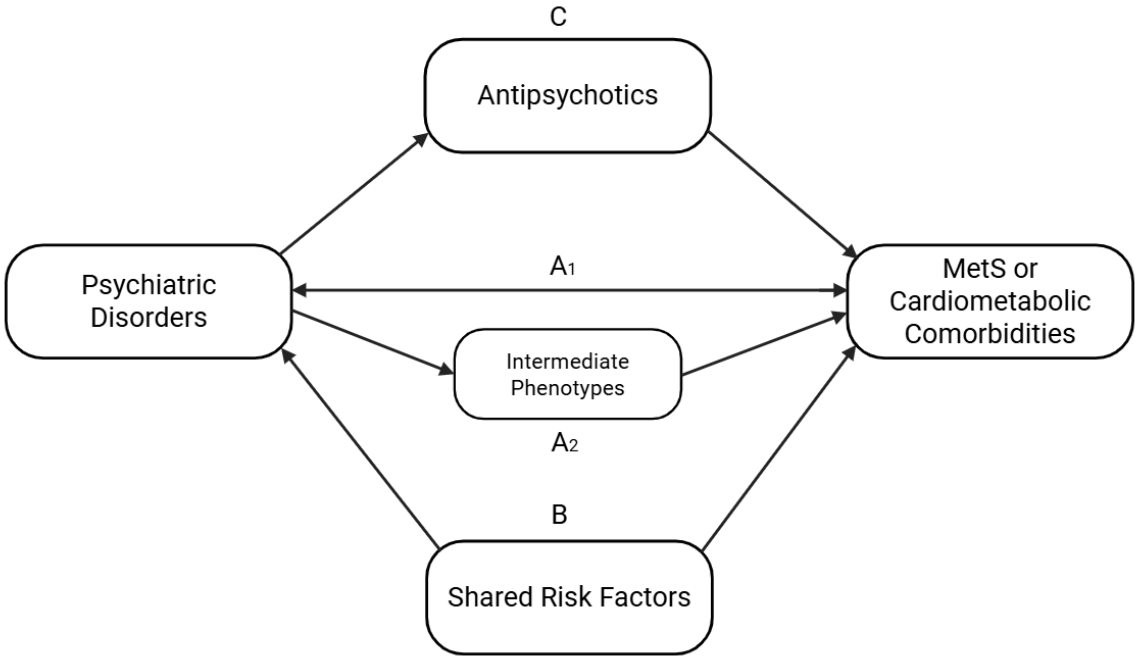


Figure 3.1 - Systematic Review Analytical Framework.

Analytical framework depicting three potential pathways to thoroughly examine the genetic connection between PDs and cardiometabolic abnormalities: (A) direct/bidirectional relationships between PDs and metabolic outcomes, (B) shared risk factors influencing both conditions, and (C) antipsychotic-mediated effects on metabolic outcomes.

3.4. Results

3.4.1. Study Characteristics

The systematic review identified 77 studies that met the inclusion criteria (Figure 3.2) (Adkins et al. 2011; Andreassen et al. 2013; Aoki et al. 2022; Athanasiu et al. 2012; Avinun & Hariri 2019; Badini et al. 2022; Bahrami et al. 2020; Bala et al. 2025; Baltramonaityte et al. 2023; Brandl et al. 2016; Breton & Kaufmann 2025; Byg et al. 2023; Chen, F et al. 2024; Chen, M et al. 2025; Chen, W et al. 2023b; Duncan et al. 2018; El Rouby et al. 2025; Franz et al. 2024; Gao et al. 2024; Giannakopoulou et al. 2021; Guo et al. 2024; Hartwig et al. 2016; He, M et al. 2023; He et al. 2022; He, R et al. 2023; Hou et al. 2025; Huangfu et al. 2023a; Hung et al. 2015; Kang, J et al. 2024; Kappelmann et al. 2021a; Liao et al. 2023; Liao, YD et al. 2024; Liu, H et al. 2020b; Liu, HY et al. 2025; Lukas et al. 2025; Luo, Ruan & Liu 2024; Lv et al. 2022; Ma et al. 2025; Maina et al. 2023; Malhotra et al. 2012; Milaneschi et al. 2017; Muntane et al. 2023; O'Connell et al. 2023; O'Loughlin et al. 2023; Perry et al. 2022b; Perry et al. 2021a; Pickrell et al. 2016; Pisanu et al. 2024; Prieto et al. 2016; Reponen et al. 2023; Rodevand et al. 2021;

Rodevand et al. 2023; Saadullah Khani et al. 2023; Sewell et al. 2021; Sjaarda et al. 2023; So et al. 2019; Song, Y et al. 2025; Speed et al. 2019; Ter Hark et al. 2020; Torgersen et al. 2022; van den Broek et al. 2018; Veeneman et al. 2022; Viinikainen et al. 2024; Wang, LH et al. 2025; Winham et al. 2014; Wong et al. 2019; Xu, Z et al. 2024; Yoshida et al. 2023; Yu et al. 2023; Yu et al. 2024; Zammarchi, Conversano & Pisanu 2022; Zhang, H et al. 2024; Zhang, M et al. 2021; Zhang, X & Li 2024; Zhang, Z & Song 2024; Zheng, X et al. 2023; Zhou et al. 2025), with sample sizes ranging from 139 to over 2.5 million participants. European ancestry populations predominated with limited representation from East Asian and African American populations (Appendix B, Supplementary Table 3.1). Study designs included MR analyses, LDSC analyses, and PRS analyses. SCZ, MDD, and BD were most frequently investigated, while other disorders including ADHD and ASD were underrepresented (Appendix B, Supplementary Table 3.2). Medication status varied considerably: PD studies typically included mixed medicated/unmedicated samples, while pharmacogenomic studies focused specifically on treatment-exposed populations. This distinction particularly affects SCZ studies, where most participants received concurrent antipsychotic treatment. BMI was the most studied metabolic phenotype, followed by lipid profiles and T2DM, with additional investigations of blood pressure, WHR, and inflammatory markers (Appendix B, Supplementary Table 3.4). Fourteen studies specifically examined antipsychotic-induced metabolic effects (Appendix B, Supplementary Table 3.3). Study characteristics are summarized in Table 3.1. The methodological quality of included studies was generally high, with the majority demonstrating low risk of bias across the assessed domains. For the selection domain, 61 studies were assessed as low risk of bias, indicating well-defined and representative samples. In terms of comparability, 55 studies were rated as low risk, suggesting adequate control for potential confounding factors. For the outcome/exposure domain, 68 studies were assessed as low risk, indicating reliable and valid assessment methods (Appendix B, Supplementary Table 3.6) (Belbasis et al. 2018; Little et al. 2009; Manolio 2010; Page et al. 2021b; Patnala, Clements & Batra 2013; Wickham 2016).

Table 3.1 - Summary of study characteristics from 77 publications investigating genetic relationships between psychiatric disorders, metabolic abnormalities, and antipsychotic medications.
Studies were published between 2005 and 2025. The table presents the distribution of analytical methods, population ancestry, sample sizes, PDs investigated, metabolic phenotypes examined, and studies with antipsychotic-specific focus. Multiple categories per study were possible for study design, PDs, and metabolic phenotypes, therefore percentages may exceed 100%.

Study Characteristics	n (%)	Details
Study Design		
Genetic correlation/LDSC	28 (36.4)	Primary method for assessing shared genetic architecture
MR	37 (48.1)	Causal inference between traits
GWAS/PRS analyses	25 (32.5)	Discovery of novel loci or risk prediction
Mixed/Multiple methods	42 (54.5)	Studies using ≥2 analytical approaches
Population Ancestry		
European only	72 (93.5)	Predominant ancestry group
Multi-ancestry	5 (6.5)	Including East Asian, African, Hispanic
Sample Size Range		
<1,000	8 (10.4)	Primarily pharmacogenomic studies
1,000-10,000	14 (18.2)	Medium-sized clinical cohorts and replication samples
>10,000	55 (71.4)	Large consortium-based analyses
Psychiatric Disorders		
SCZ	35 (45.5)	Most frequently studied
MDD/Depressive Symptoms	34 (44.2)	Second most common, includes clinical and subclinical depression
BD	21 (27.3)	Often studied with other major psychiatric disorders
Other (ADHD, AN, ASD, etc.)	18 (23.4)	Underrepresented conditions
Metabolic Phenotypes		
BMI/Obesity	61 (79.2)	Primary metabolic outcome
Lipid profiles	32 (41.6)	HDL, LDL, TG, cholesterol
T2D	20 (26.0)	Common complication of metabolic dysfunction
Cardiovascular traits	24 (31.2)	BP, CAD, HF
Inflammatory markers	12 (15.6)	CRP, cytokines
Antipsychotics Focus		
Clozapine, Olanzapine, Quetiapine, Risperidone, etc.	14 (18.2)	Studies examining medication effects, AIWG

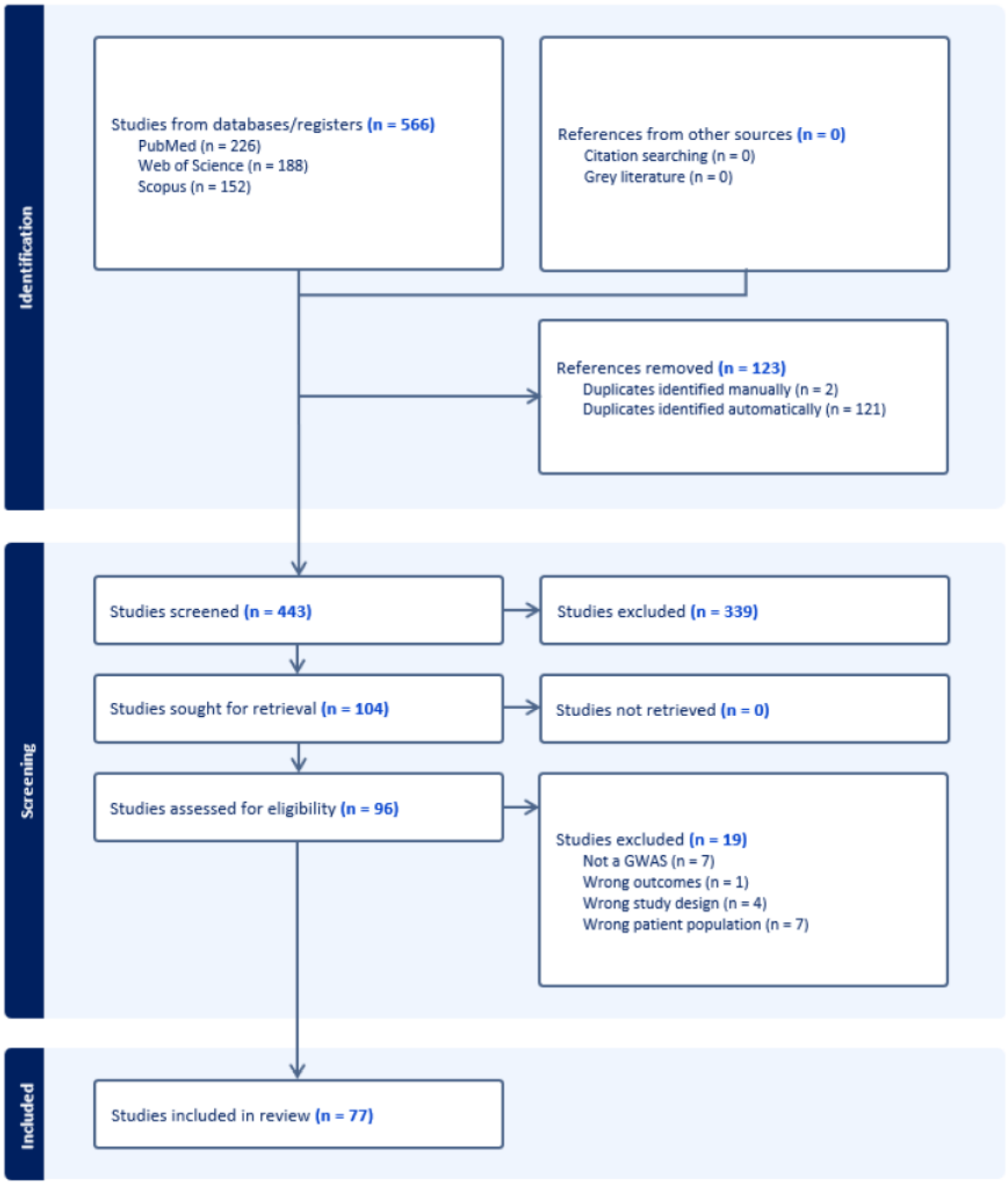


Figure 3.2 - PRISMA Systematic Screening Process Performed Through Covidence.

Flowchart demonstrates three stages of the screening process. Identification: Systematic literature search of PubMed, Covidence, and Web of Science according to an inclusion/exclusion criterion. All duplicates were automatically removed. Screening: Involved multiple researchers initially screening titles and abstracts to identify studies that can be removed. Second screening stage was a full text screening. All studies that passed screening were taken to review. Included: Final list of studies to be included in the review (n = 77), data extraction performed on all studies which passed the screening process.

3.4.2. Shared Genetic Architecture

3.4.2.1. Genetic Correlations

Genetic correlation analyses provided insights into potential direct or intermediated relationships (Path A) and shared risk factors (Path B) (Appendix B, Supplementary Table 3.5). The strength of genetic correlations varied considerably across PDs, ranging from weak to moderate, suggesting disorder-specific patterns of genetic overlap with metabolic traits. Aoki et al. (2022) reported genetic correlations between SCZ and several metabolic traits in both European and East Asian populations. In Europeans, SCZ was shown to be positively correlated with BMI ($r_g = 0.10$, SE = 0.02, $P < 1.00 \times 10^{-3}$) and C-reactive protein (CRP) ($r_g = 0.08$, SE = 0.03, $P = 4.00 \times 10^{-3}$), while in East Asians, these correlations were negative (BMI: $r_g = -0.21$, SE = 0.06, $P < 1.00 \times 10^{-3}$; CRP: $r_g = -0.05$, SE = 0.07, $P = 4.50 \times 10^{-1}$).

Milaneschi et al. (2017) found that MDD cases with increased appetite/weight showed stronger genetic correlations with obesity-related traits (e.g., BMI $r_g = 0.53$, SE = 0.16, $P = 1.00 \times 10^{-3}$). Bahrami et al. (2020) reported a negative genetic correlation between BD and BMI ($r_g = -0.06$, SE = 0.02, $P = 2.00 \times 10^{-3}$), contrasting with the positive correlation observed for MDD ($r_g = 0.12$, SE = 0.03, $P < 1.00 \times 10^{-3}$). Additionally, Duncan et al. (2018) reported genetic correlations between SCZ and other PDs (BD: $r_g = 0.83$, MDD: $r_g = 0.47$) as well as a negative correlation with serum citrate ($r_g = -0.21$), suggesting metabolic implications. The studies examining genetic correlations generally demonstrated high methodological quality, with most rated as low risk of bias in our quality assessment (Appendix B, Supplementary Table 3.6).

3.4.2.2. Shared Genetic Loci and Biological Pathways

Several studies identified shared genetic loci between PDs and metabolic traits, elucidating the genetic architecture and shared risk factors of path B (Appendix B, Supplementary Table 3.5).

Andreassen et al. (2013) found 25 loci associated with SCZ, with 10 loci showing associations with both SCZ and lipid-related traits. He et al. (2022) reported 144 variants shared between SCZ and BMI, with 78 being novel discoveries. Key genes and biological pathways implicated in this shared architecture included: **(1)** Lipid Metabolism: Lv et al. (2022) highlighted the involvement of propionyl-CoA carboxylase subunit beta (*PCCB*), a gene involved in fatty acid metabolism, as a potential mediator between SCZ and MetS ($P < 5.00 \times 10^{-2}$, cFDR). In addition, Pickrell et al. (2016) identified many genetic variants affecting multiple traits such as

BMI and TG. **(2)** Glucose Homeostasis and Insulin Signalling: Perry et al. (2021) found evidence supporting inflammation as a common cause for insulin resistance and SCZ (OR: 2.95, 95% CI: [1.38 - 6.34], $P = 5.00 \times 10^{-3}$). The identification of shared genetic loci involved in glucose homeostasis and insulin signalling provides a potential mechanistic link between insulin resistance and PDs, particularly SCZ. This connection may be mediated through the effects of insulin on dopaminergic signalling in the brain. Insulin receptors are expressed on dopaminergic neurons, and insulin signalling can modulate dopamine release and reuptake, potentially influencing both metabolic regulation and cognitive processes (Kenny 2011; Volkow, Wang & Baler 2011). **(3)** Neurotransmitter Systems: Several studies implicated dopaminergic and serotonergic pathways in the shared genetic basis of psychiatric and metabolic traits. For instance, So et al. (2019) identified these pathways as top shared pathways between SCZ, BD, and cardiometabolic traits ($P < 1.00 \times 10^{-5}$). The implication of dopaminergic pathways in the shared genetic basis of psychiatric and metabolic traits suggests a potential role for reward circuits in this relationship. Dopamine signalling is crucial for both mood regulation and appetite control, potentially explaining the observed genetic overlap between PDs and metabolic traits (Baik 2021; Volkow, Wang & Baler 2011). Dopamine signalling is also responsible for movement processes, potentially leading to sedentary behaviour. **(4)** Inflammatory Pathways: The genetic evidence strongly supports inflammation as a central mechanism linking PDs and metabolic traits. Kappelmann et al. (2021) found extensive genetic overlap between BMI, CRP levels, and depressive symptoms (genetic correlation range: 0.152 - 0.362, $P < 1.00 \times 10^{-3}$), with inflammation appearing to be both a cause and consequence of this relationship. This was particularly evident in depression subtypes - Badini et al. (2022) reported that depression with atypical features, characterized by increased appetite/weight, had higher PRS for BMI and CRP (OR: 1.11), suggesting a specific inflammatory-metabolic endophenotype. Sewell et al. (2021) extended these findings, demonstrating varying associations between psychiatric-related PRSs and peripheral inflammatory markers, with distinct inflammatory dysfunction patterns in MDD and SCZ. The genetic architecture of antipsychotic-induced metabolic effects also showed significant overlap with inflammatory pathways, particularly for medications like clozapine where inflammation can create a self-reinforcing cycle by affecting drug metabolism and metabolic outcomes. **(5)** Brain-Derived Neurotrophic Factor (*BDNF*) and Related Pathways: Perry et al. (2022) identified shared genetic aetiology between SCZ and cardiometabolic traits involving *BDNF* and related pathways ($PP > 0.80$).

Additionally, Liu et al. (2020) identified 21 potential pleiotropic genes underlying the comorbidity of SCZ and cardiometabolic diseases. Winham et al. (2014) found that a Transcription factor 7-like 2 (*TCF7L2*) variant associated with BD risk was BMI-dependent ($P = 2.85 \times 10^{-8}$), suggesting potential shared genetic risk between BD and T2DM. Wong et al. (2019) reported shared genetic bases between depression and cardiometabolic traits varying by depression subtype. Liao et al. (2023) demonstrated polygenic overlap between MDD and obesity traits, with active depression exacerbating the effects of BMI genetics on central obesity measures. Torgersen et al. (2022) revealed extensive polygenic overlap between depression, coronary artery disease, and cardiovascular risk factors. Rødevand et al. conducted two studies and found extensive polygenic overlap between BD, SCZ, and cardiovascular disease risk factors, particularly smoking and BMI. Byg et al. (2023) reported that genetic liability to BD may reduce BMI, predominantly driven by reduced fat mass ($P = 4.00 \times 10^{-3}$).

3.4.3. Evidence from Mendelian Randomization Studies

MR can potentially disentangle Path A from Path B by assessing possible causal relationships between PDs and MetS. Multiple studies found MR evidence for a causal effect of MDD on various metabolic outcomes (Appendix B, Supplementary Table 3.7). Zhang et al. (2021) reported that MDD had impacts on MetS (OR: 1.22, 95% CI: [1.09 - 1.37], $P = 5.59 \times 10^{-4}$) and its components, including waist circumference (OR: 1.08, 95% CI: [1.03 - 1.14], $P = 3.00 \times 10^{-3}$) and TG (OR: 1.11, 95% CI: [1.06 - 1.16], $P = 9.35 \times 10^{-6}$). These findings were corroborated by Zheng et al. (2023), who found similar estimates of MDD on MetS (OR: 1.22, 95% CI: [1.13 - 1.32], $P < 1.00 \times 10^{-3}$). However, the evidence was more mixed for SCZ. Yu et al. (2023) reported that SCZ may increase BMI (OR: 1.02, 95% CI: [1.01 - 1.03], $P = 1.15 \times 10^{-6}$), while Khani et al. (2023) reported only weak associations with low density lipoprotein (LDL) ($\beta = 0.01$, 95% CI: [0.001 - 0.02]) and total cholesterol ($\beta = 0.013$, 95% CI: [0.002 - 0.025]), which lost significance after correction for multiple testing.

Pathway-specific MR analyses have provided mechanistic insights into the causal relationships between PDs and metabolic outcomes. Bala et al. (2024) demonstrated that T2DM variants acting through obesity-mediated insulin resistance and body fat pathways showed the strongest associations with MDD (OR = 1.06, 95%CI: [1.04 - 1.09]). This study revealed that MDD strongly predicted insulin resistance as measured by TG-to-HDL cholesterol ratio ($\beta = 0.11$, 95%CI: [0.075 - 0.14]), with BMI partially mediating the bidirectional relationship between MDD and T2DM (25.86% mediation, $P = 0.027$).

Consistent MR evidence was found for a BMI influence on MDD risk. Van den Broek et al. (2018) reported an effect of BMI on depressive symptoms ($\beta = 0.05$, SE = 0.02, $P = 1.20 \times 10^{-2}$). Chen et al. (2023) found MR evidence of association between BMI and several PDs, including ADHD (OR: 1.94, 95% CI: [1.77 - 2.13], $P < 1.00 \times 10^{-3}$), ASD (OR: 1.16, 95% CI: [1.06 - 1.27], $P = 1.00 \times 10^{-3}$), and MDD (OR: 1.12, 95% CI: [1.08 - 1.15], $P < 1.00 \times 10^{-3}$). Hartwig et al. (2016) found no consistent MR evidence for an effect of BMI on BD or SCZ risk, with borderline evidence for an effect on MDD. Guo et al. (2024) identified multiple lifestyle factors with causal relationships to MDD.

Some studies examined bidirectional relationships between PDs and metabolic traits. Yu et al. (2023) found evidence for a bidirectional relationship between SCZ and BMI, although the effect sizes were small (SCZ → BMI: OR = 1.02, 95% CI: [1.01 - 1.03], $P = 1.15 \times 10^{-6}$; BMI → SCZ: OR = 1.06, 95% CI: [0.99 - 1.17], $P = 1.20 \times 10^{-2}$). Gao et al. (2024) provided evidence for bidirectional relationships between ADHD and obesity-related traits (ADHD → MetS: OR = 1.59, 95% CI: [1.45 - 1.74], $P < 1.00 \times 10^{-3}$; MetS → ADHD: OR = 1.03, 95% CI: [1.02 - 1.04], $P < 1.00 \times 10^{-3}$). Zammarchi et al. (2022) reported MR evidence for an association between MDD and insomnia, further suggesting a shared genetic basis between PDs, sleep traits, and cardiometabolic traits.

Varying degrees of consistency and variability across different trait relationships were seen in the MR studies. Figure 3.3 provides a visual representation of the MR results focusing primarily on psychiatric-cardiometabolic trait relationships.

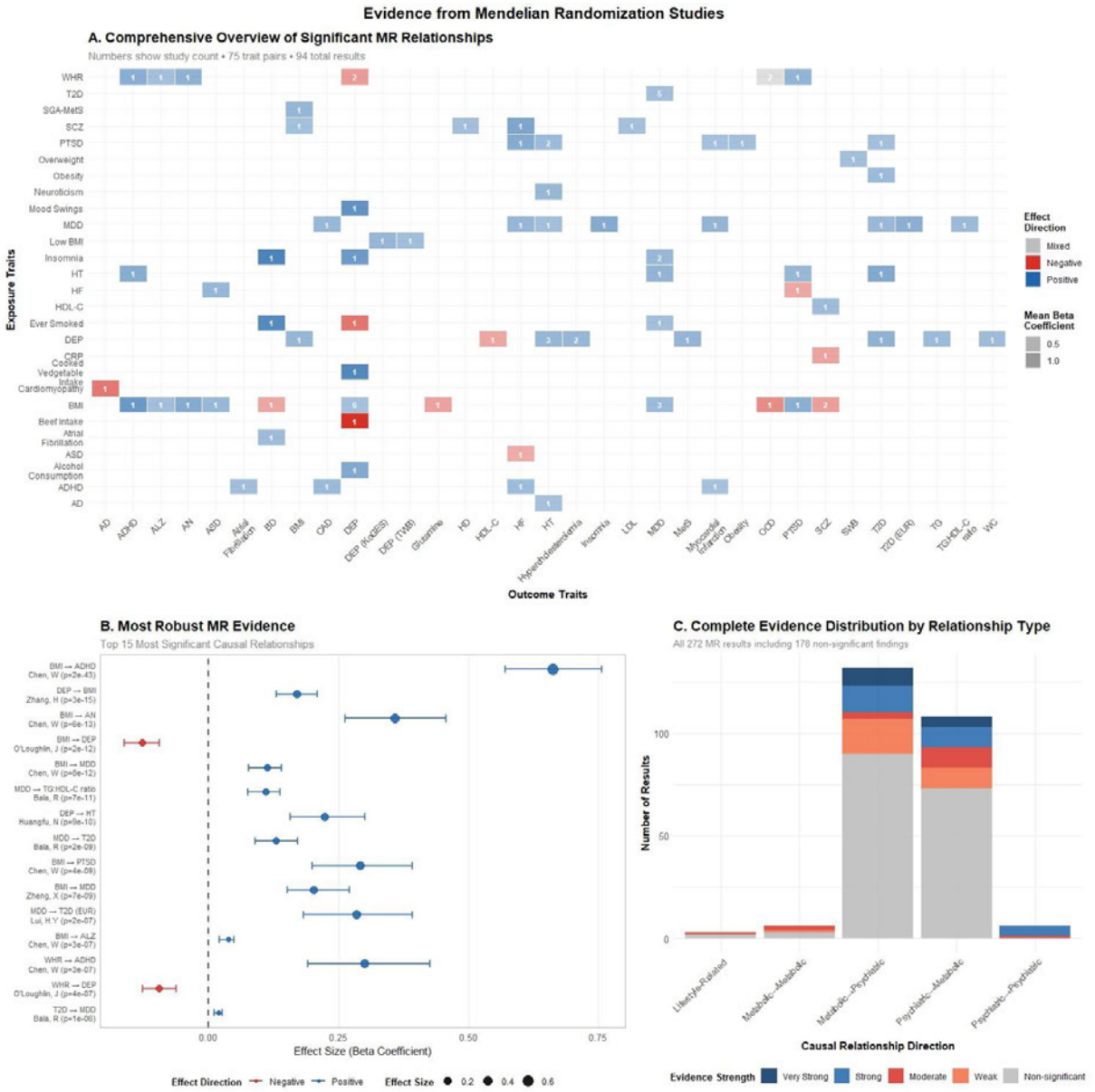


Figure 3.3 - Evidence from Mendelian Randomization Studies.

(A) presents a heatmap overview of all statistically significant ($P < 0.05$) MR relationships identified. Tiles represent unique exposure-outcome trait pairs, with colours indicating effect direction and transparency reflecting effect magnitude (absolute beta coefficient). Numbers within tiles show study count per trait pair. A total of 75 unique trait pairs from 94 significant results are displayed. **(B)** displays a forest plot of the 15 most robust causal relationships by statistical significance. Effect sizes are presented as beta coefficients on a logarithmic scale, with 95% confidence intervals. For studies originally reporting odds ratios, both point estimates and confidence intervals were log-transformed to enable comparison with studies reporting beta coefficients. Point size reflects effect magnitude, and colours indicate causal direction consistent with Panel A. **(C)** shows the complete evidence distribution across all 272 MR results from the systematic review, including both significant and non-significant findings. Results are categorized by relationship direction and evidence strength categories are defined as very strong ($P < 1 \times 10^{-6}$), strong ($P < 0.001$), moderate ($P < 0.01$), weak ($P < 0.05$), and non-significant ($P \geq 0.05$) which is represented by colour.

3.4.4. Antipsychotics and Metabolic Traits

Genetic factors related to antipsychotic-induced metabolic effects were specifically investigated in Path C. Fourteen studies examined genetic factors related to antipsychotic-induced weight gain and other metabolic side effects. (Appendix B, Supplementary Table 3.3). These studies differed importantly from disorder-focused genetic studies in their sample characteristics and phenotype definitions. While disorder-focused studies typically included mixed samples of medicated and unmedicated individuals, pharmacogenomic studies specifically recruited treatment-exposed populations with carefully defined medication histories. This distinction is crucial for interpreting genetic associations, as metabolic phenotypes in disorder-focused studies may be confounded by concurrent or previous antipsychotic treatment.

Several studies identified novel genes and loci associated with AIWG. Liao et al. (2024) performed a GWAS in a Han Chinese population, revealing several novel genetic associations with AIWG: Peptidase D (*PEPD*) (rs10422861, $P = 1.37 \times 10^{-9}$) and protein tyrosine phosphatase receptor type D (*PTPRD*) (rs3824417, $P = 3.35 \times 10^{-9}$). A genetic correlation between AIWG and BMI was observed ($r_g = 0.13$, SE = 0.04, $P = 1.00 \times 10^{-3}$), and the study estimated the SNP-based heritability of AIWG to be 0.12. This relatively high SNP-based heritability suggests that a substantial portion of the variability in AIWG could be attributed to common genetic variants, highlighting the potential for pharmacogenomic approaches in managing AIWG (Wray et al. 2013; Yang et al. 2010). Adkins et al. (2011) identified several genetic loci associated with antipsychotic-induced metabolic side effects in SCZ patients. They found SNPs in Meis Homeobox 2 (*MEIS2*) (rs1568679, $q = 4.00 \times 10^{-3}$, where q represents the false discovery rate-adjusted p-value) associated with risperidone-induced changes in WHR, and variants in Protein Kinase CAMP-Dependent Type II Regulatory Subunit Beta (*PRKAR2B*) (rs13224682, $q < 1.00 \times 10^{-1}$) linked to clozapine-induced changes in TG levels. Additional loci in G protein-coupled receptor 98 (*GPR98*), formin homology 2 domain containing 3 (*FHOD3*), ring finger protein 144A (RNF144A), Astrotactin 2 (*ASTN2*), SRY-box transcription factor 5 (*SOX5*), and Activating Transcription Factor 7 Interacting Protein 2 (*ATF7IP2*) were also identified as potentially relevant ($q < 1.00 \times 10^{-1}$). The significance threshold of $q < 1.00 \times 10^{-9}$ was relatively permissive, these initial insights need rigorous testing in future studies. Sjaarda et al. (2023) identified four novel loci associated with AIWG in a Swiss longitudinal study. The most significant SNP, rs7736552 ($P = 2.54 \times 10^{-9}$), was in the intron of the solute carrier family 25-member 17 (*SLC25A17*) gene. This locus was replicated in psychiatric cohorts but not in healthy populations samples. Athanasiu et al. (2012) found genomic regions near matrix

metallopeptidase 16 (*MMP16*) associated with antipsychotic-induced metabolic effects. SNPs rs7838490 and rs6989402 near *MMP16* were significantly associated with BMI changes ($P = 6.10 \times 10^{-8}$ and $P = 1.50 \times 10^{-7}$, respectively). Lastly, Muntané et al. (2023) demonstrated that genetic factors played a key role in determining BMI increase in first-episode psychosis. They identified 449 loci shared between SCZ and BMI and showed that PRS improved BMI prediction in this population. Ter Hark et al. (2020) focused specifically on amisulpride-induced weight gain, identifying rs78310016*G ($\beta = 1.05$, $P = 3.66 \times 10^{-8}$) as a significant genetic risk factor. Carriers of the risk allele had nearly four times the odds of clinically meaningful weight gain (OR 3.98, 95% CI: [2.13-7.44]). Early foundational studies established key genetic loci for AIWG. Malhotra et al. (2012) identified rs489693 near the melanocortin 4 receptor (*MC4R*) gene as genome-wide significantly associated with severe AIWG (meta-analysis $P = 5.59 \times 10^{-12}$), with recessive effects showing extreme weight gain in homozygotes. Brandl et al. (2016) found rs9346455 upstream of opioid growth factor receptor-like 1 (*OGFRL1*) significantly associated with AIWG ($P = 1.09 \times 10^{-7}$). These studies provided initial evidence for distinct genetic mechanisms underlying medication-induced versus disorder-related metabolic effects.

Multi-ancestry pharmacogenomic investigations have provided novel insights into antipsychotic-induced metabolic effects across diverse populations. El Rouby et al. (2024) conducted the first genome-wide study of SGA-induced MetS, identifying ancestry-specific genetic loci including a chromosome 11 signal in European populations (rs61900075, $\beta = -0.27$, $P = 1.6 \times 10^{-}$) and chromosome 2 *NPPC-DIS3L2* signals in African populations. Importantly, this study demonstrated that BMI causally contributes to SGA-induced MetS (OR: 1.2, 95%CI: [1.1-1.4], $P = 2.0 \times 10^{-3}$), establishing a mechanistic link between genetic predisposition to obesity and antipsychotic-induced metabolic complications.

The potential for integrating genetic information with clinical data to improve risk prediction for AIWG was demonstrated in several studies. Franz et al. (2024) explored the utility of PRS in predicting AIWG. They found that PRSs for BMI ($\beta = 3.78$, $P = 4.10 \times 10^{-3}$), SCZ ($\beta = 5.38$, $P = 2.10 \times 10^{-2}$), and T2DM ($\beta = 13.4$, $P = 4.60 \times 10^{-2}$) were all significantly associated with AIWG. The addition of these PRSs to prediction models increased the explained variation by 6.5%. This finding underscored the potential of integrating genetic information with clinical data to improve risk prediction for AIWG. Yoshida et al. (2023) provided preliminary evidence for shared genetic risks between metabolic traits, autoimmunity, SCZ, and AIWG. They found nominal associations between PRSs for BMI ($R^2 = 0.074$, $P = 1.10 \times 10^{-2}$), coronary artery disease, LDL cholesterol, type 1 diabetes (T1D), and SCZ with AIWG. O'Connell et al. (2023)

leveraged genetic overlap between BMI and TRS to improve genetic discovery. They identified two novel loci [mitogen-activated protein kinase kinase 1 (*MAP2K1*), Zinc Finger DBF-Type Containing 2 (*ZDBF2*)] associated with TRS, which was often treated with clozapine, an antipsychotic known for its significant metabolic side effects (Kappel et al. 2024; Pardinas et al. 2023; Ying et al. 2023). Table 3.2 provides the key genetic findings by each pathway investigated.

Table 3.2 - Summary of principal genetic findings organized according to the three-pathway framework examining relationships between psychiatric disorders and metabolic abnormalities.
Path A/B encompasses shared genetic architecture and causal relationships between psychiatric and metabolic traits. Path C presents findings specific to antipsychotic-induced metabolic effects. Effect sizes are presented as genetic correlations (r_g), ORs with 95% confidence intervals, p-values, and heritability estimates (h^2) where applicable. Representative studies are listed by first author and year.

Pathway and Finding Category	Key Results	Representative Studies
Path A/B: Shared Genetic Architecture		
Genetic correlations (r_g)	• SCZ-BMI: 0.10 to 0.12 (European), -0.21 (East Asian) • MDD-BMI: 0.12 to 0.19 (European), -0.19 (East Asian) • BD-BMI: -0.06 to 0.02; MDD-CRP: 0.15 to 0.36	Aoki 2022, Bahrami 2020, Chen 2024, Kappelmann 2021
Shared genetic loci	• 144 variants shared SCZ-BMI (78 novel) • 63 loci SCZ-BMI, 32 loci MDD-BMI • 21 pleiotropic genes SCZ-cardiometabolic	He 2022, Bahrami 2020, Liu 2020
Key pathways identified	• Lipid metabolism (PCCB); Insulin signalling/glucose homeostasis • Dopaminergic/serotonergic systems; Inflammatory pathways • BDNF	Lv 2022, Perry 2021, So 2019, Perry 2022
Path A: Causal Relationships (MR Evidence)		
Psychiatric → Metabolic	• MDD → MetS: OR 1.22 (95%CI: 1.09-1.37) • MDD → T2D: OR 1.14 (95%CI: 1.09-1.19) • SCZ → BMI: OR 1.02 (95%CI: 1.01-1.03) • ADHD → MetS: OR 1.59 (95%CI: 1.45-1.74)	Zhang 2021, Bala 2024, Yu 2023, Gao 2024
Metabolic → Psychiatric	• BMI → MDD: OR 1.12-1.13 per SD • BMI → ADHD: OR 1.94 (95%CI: 1.77-2.13) • T2D → MDD: OR 1.02 (95%CI: 1.01-1.03)	Chen 2023, van den Broek 2018, Bala 2024
Path C: Antipsychotic-Induced Effects		
Novel AIWG loci	• PEPD (rs10422861, $p=1.37 \times 10^{-9}$) • PTPRD (rs3824417, $p=3.35 \times 10^{-9}$) • MC4R (rs489693, $p=5.59 \times 10^{-12}$) • OGFRL1 (rs9346455, $p=1.09 \times 10^{-7}$)	Liao 2024, Malhotra 2012, Brandl 2016
Ancestry-specific findings	• European: chromosome 11 (rs61900075) • African: chromosome 2 (NPPC-DIS3L2)	El Rouby 2024
SNP-heritability	• AIWG $h^2 = 0.12$-0.13 • Genetic correlation with BMI: $r_g = 0.13$	Liao 2024
PRS applications	• BMI, SCZ, T2D PRS predict AIWG • Combined PRS increased variance explained by 6.5%	Franz 2024, Yoshida 2023

3.5. Discussion

3.5.1. Interpretation and Comparison of Findings

3.5.1.1. Path A and B: Shared Genetic Architecture

The genetic correlation studies consistently demonstrated overlap between psychiatric disorders and metabolic phenotypes. These correlations aligned with the growing body of evidence suggesting shared biological underpinnings of psychiatric and metabolic dysfunction (Milaneschi et al. 2017). However, genetic correlations alone cannot distinguish between direct or mediated relationships (Path A) and shared risk factors (Path B). There was also a notable scarcity of research on conditions such as ADHD and eating disorders like AN. This gap was particularly significant given that ADHD has been associated with increased risk of obesity (Fanelli et al. 2022; Gao et al. 2024; Mick et al. 2011) while AN tends to shows opposite effect (Chen, W et al. 2023b; Fanelli et al. 2022; Gao et al. 2024).

The findings suggest a complex bidirectional relationship between metabolic dysfunction and psychiatric symptoms, mediated by shared genetic factors influencing multiple biological pathways. These pathways demonstrate notable ethnic differences in their effects (e.g. European populations show positive correlations between SCZ and inflammatory markers, East Asian populations show negative), suggesting population-specific mechanisms. Several key biological systems are implicated in this shared architecture: **(1)** Lipid Metabolism: Altered lipid homeostasis appears to be a common factor affecting both neural function and metabolic processes through its role in neurotransmitter function and synaptic plasticity (Cheon 2023; Liao, Y et al. 2024a; Perry et al. 2022b; Valles & Barrantes 2022; Zorkina et al. 2024). **(2)** Glucose Homeostasis and Insulin Signalling: The connection between insulin resistance and SCZ appears to be mediated through effects on dopaminergic signalling, where insulin receptors on dopaminergic neurons modulate dopamine release and reuptake (Ying et al. 2023). This interaction influences both metabolic regulation and psychiatric outcomes through effects on reward processing and motivation (Baik 2021; Figlewicz & Benoit 2009; Stouffer et al. 2015). Dopamine receptor variants affect both food reward processing and metabolic regulation (Gorwood et al. 2012; Moyer et al. 2011), consistent with the shared genetic architecture observed (Akingbuwa et al. 2020; Al-Janabi et al. 2009; de Bartolomeis et al. 2023). **(3)** Inflammatory Pathways: The genetic evidence strongly supports the "inflammatory hypothesis" of PDs (Bergmann, Gyntelberg & Faber 2014; Ellulu et al. 2017; Esposito & Giugliano 2004;

Kappelmann et al. 2021b; Reddy et al. 2019), with shared genetic architecture in inflammatory pathways suggesting inflammation as a key mechanistic link (Mehdi et al. 2023; Osimo et al. 2018). The overlap in inflammation-related genes contributes to both psychiatric vulnerability and metabolic dysfunction, though these relationships show population-specific variations that warrant further investigation.

3.5.1.2. Disentangling Path A from B: Evidence from Mendelian Randomization Studies

MR studies paint a more complex picture than the genetic correlation analyses alone, highlighting the importance of causal inference in understanding complex traits (Davies et al. 2018). Interestingly, the relationship between SCZ and metabolic traits showed mixed results across studies depending on the study populations' ethnicity. These divergent findings further highlighted the complexity of these relationships and the potential influence of population-specific factors.

Potential causal pathways were also identified: **(1)** Behavioural changes: Psychiatric symptoms may lead to altered diet, reduced physical activity, and increased substance use, contributing to metabolic dysfunction (Baik 2021; Kenny 2011); **(2)** Neuroendocrine dysregulation: PDs, particularly stress and anxiety related disorders, are associated with dysregulation of the hypothalamic-pituitary-adrenal axis, which can influence metabolic processes (Smith, SM & Vale 2006); **(3)** Inflammatory processes: Many PDs are associated with low-grade inflammation, which is also implicated in the development of MetS (Esposito & Giugliano 2004; Reddy et al. 2019; Tylutka et al. 2023).

Conversely, for metabolic traits influencing psychiatric outcomes, proposed mechanisms included: **(1)** Neuroinflammation: Obesity and MetS can lead to systemic inflammation, potentially affecting brain function and contributing to psychiatric symptoms (Ellulu et al. 2017; Esposito & Giugliano 2004; Khanna et al. 2022); **(2)** Alterations in neurotransmitter function: Metabolic dysfunction can influence the signalling of neurotransmitters implicated in PDs (de Bartolomeis et al. 2023; Xu, H & Yang 2022); **(3)** Psychosocial factors: The experience of having a chronic metabolic condition may contribute to the development of psychiatric symptoms through stress and lifestyle changes (Bergmann, Gyntelberg & Faber 2014; Ho et al. 2018).

3.5.1.3. Path C: Role of Antipsychotic Medications

The findings from pharmacogenomic studies added complexity to Path C of our framework. The genetic basis of AIWG showed distinct patterns compared to broader PD-related MetS (Liu, H et al. 2020a), with novel loci like *PEPD* and *PTPRD* highlighting specific mechanisms such as lipid pathway dysfunction. The early identification of *MC4R* variants demonstrated overlap between general obesity mechanisms and medication-induced metabolic effects, while *OGFRL1* associations suggested novel pathways specific to antipsychotic response. While the relatively high SNP-based heritability of AIWG suggests substantial genetic influence (Arranz et al. 2019; Brandl et al. 2016; MacNeil & Muller 2016; Zhang, JP, Lencz & Malhotra 2010), environmental factors and gene-environment interactions likely play crucial roles (Bousman, C. A. & Hopwood 2016; Newcomer 2005; Yoshida & Muller 2020). Path C demonstrated how antipsychotics might modify the relationships identified in Path A and B. However, sample characteristics created significant challenges, particularly regarding medication status. Most studies, especially in SCZ, included participants already receiving antipsychotic treatment, making it difficult to identify treatment-naive results (Sullivan & Geschwind 2019).

Future research should prioritize better phenotype definition and sample selection, including medication-naive cohorts where possible. Integration of genetic data with longitudinal clinical monitoring, as demonstrated by Franz et al. (2024), could help distinguish disorder-related from treatment-induced effects. This approach, combined with careful documentation of medication history and long-term treatment response, would enable more precise risk prediction models and better understanding of gene-treatment interactions.

3.5.2. Clinical and Translational Implications and Personalized Medicine Approaches

The substantial genetic overlap and potential causal relationships identified between PDs and metabolic traits support an integrated care approach, aligning with recent calls for holistic treatment models in psychiatry (M et al. 2011). However, translating these genetic insights into clinical practice faces significant implementation barriers that must be addressed alongside the scientific advances (Fernandes et al. 2017; van Dellen 2024; Zanardi et al. 2021).

The most immediate translational opportunity lies in pharmacogenomic approaches to antipsychotic-induced metabolic effects. Studies identifying novel loci like *PEPD* and *PTPRD* (Liao, Y et al. 2024a) provide a foundation for genetic risk prediction, while the integration of

PRSs for PDs, BMI, and antipsychotic response shows promise. Franz et al. (2024) demonstrated that combining these scores with clinical parameters increased predictive performance by 6.5%, though the overall explained variance remains modest. The identification of ancestry-specific loci, including chromosome 11 signals in European populations and chromosome 2 *NPPC-DIS3L2* signals in African populations, highlights the critical need for diverse population studies before clinical implementation (El Rouby et al. 2025). While current polygenic scores explain limited phenotypic variance, their clinical utility may emerge through integration with comprehensive clinical monitoring parameters (Bousman, C. A. & Hopwood 2016; Chen, W et al. 2023a; Cohen, Edmondson & Kronish 2015; Khani et al. 2023; Levine et al. 2021; Newcomer 2005; Vancampfort et al. 2015; Yoshida & Muller 2020). However, cost-effectiveness analyses and health technology assessments remain largely absent from the literature, creating uncertainty about practical implementation feasibility (Perry et al. 2022a).

The distinction between antipsychotic-induced and PD-related metabolic syndrome suggests potential for tailored treatment approaches, aligning with precision psychiatry principles (Chen, W et al. 2023a; Cohen, Edmondson & Kronish 2015; Khani et al. 2023; Levine et al. 2021; Vancampfort et al. 2015). The involvement of BDNF-related pathways in both schizophrenia and cardiometabolic traits points to interventions that could simultaneously address psychiatric symptoms and metabolic disturbances, though functional validation remains needed (Visscher et al. 2017; Wray et al. 2018). However, this progression faces substantial implementation barriers including healthcare system integration challenges, ethical considerations around psychiatric genetic risk prediction, and the need for clinician education about genetic testing applications. Several challenges must be addressed before realizing translational potential. The complex, polygenic nature of psychiatric and metabolic traits means individual genetic variants typically have small effect sizes, necessitating sophisticated statistical approaches to translate findings into clinically meaningful information (Martin et al. 2019; Peterson et al. 2019). The predominance of European ancestry participants limits immediate applicability to diverse populations, requiring large-scale studies in underrepresented groups to elucidate population-specific factors (Amente et al. 2024; Hasin, Seldin & Lusis 2017; Sathyanarayanan et al. 2023). Future clinical applications will likely require multi-omics integration (combining genetic information with neuroimaging, proteomics, and detailed clinical phenotyping) to identify robust biomarkers and treatment targets (Ioannidis et al. 2008; Zeggini & Ioannidis 2009). This integration demands standardized methodologies and reporting practices to facilitate robust meta-analyses, alongside comprehensive environmental assessments for understanding gene-environment interactions (Mullins et al. 2016).

To address these implementation challenges, future research should prioritize: **(1)** large-scale studies in ancestrally diverse populations to elucidate population-specific genetic architectures and ensure equitable benefit from genetic discoveries; **(2)** longitudinal designs tracking both psychiatric symptoms and metabolic parameters; **(3)** comprehensive environmental assessments for gene-environment interactions; **(4)** expanded pharmacogenomic studies incorporating wider genetic variant ranges and pharmacokinetic/pharmacodynamic measures (Arranz, Salazar & Hernandez 2021); **(5)** functional validation studies of identified genetic loci to elucidate biological mechanisms and identify therapeutic targets (Visscher et al. 2017; Visscher et al. 2021); and **(6)** standardized methodologies enabling robust meta-analyses . While the genetic evidence supports shared biological mechanisms underlying psychiatric-metabolic comorbidities, the path to clinical implementation requires addressing substantial methodological, economic, and practical barriers. The integration of genetic insights with established clinical assessment tools offers the most realistic near-term opportunity for improving patient care, with more sophisticated precision medicine applications emerging as these foundational challenges are resolved (Figure 3.5).

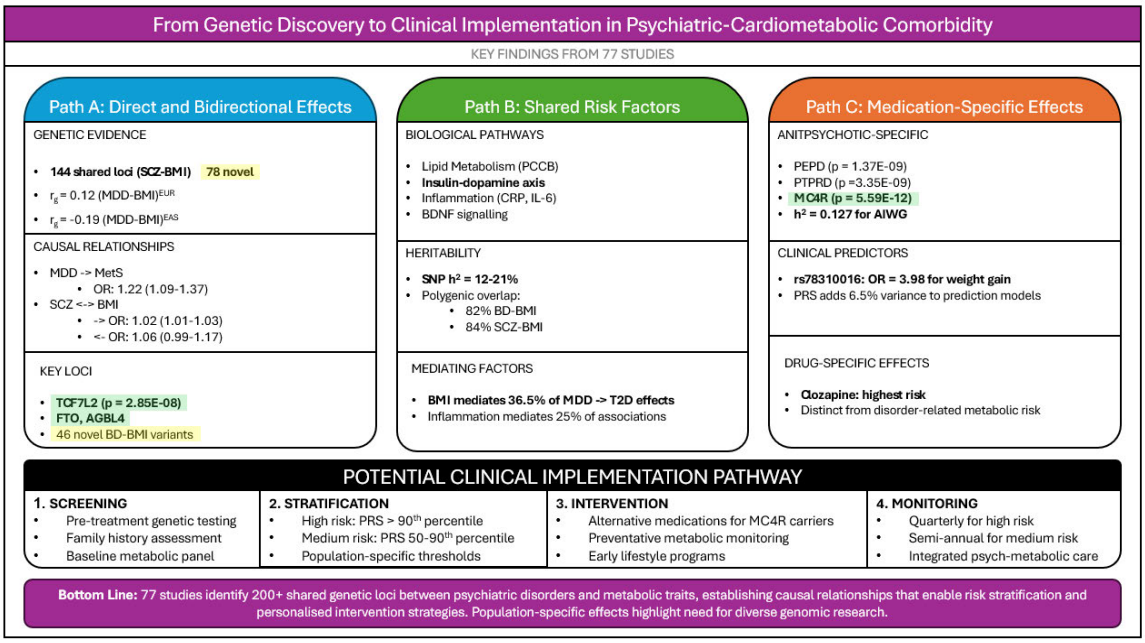


Figure 3.4 - Graphical Executive Summary - From Genetic Discovery to Clinical Implementation in Psychiatric-Metabolic Comorbidity.

The graphical summary highlights key findings from the systematic review of 77 publications focusing on the genetic connection between PDs, antipsychotic use, and cardiometabolic abnormalities. The summary is organised into three pathways; (A) Direct and bidirectional effects of PDs on metabolic traits; (B) Shared risk factors and other biological pathways mediating the connection between PDs and metabolic comorbidities; and (C) Impact of antipsychotic medications on the development of metabolic complications in patients with PDs. Yellow highlight represents novel findings, and green highlights represent replicated findings (≥ 3 studies). A potential clinical intervention pathway is also provided highlighting key considerations of translating genetic research into actionable clinical protocols for patients with PDs.

3.5.3. Limitations and Methodological Considerations

The predominant focus on European ancestry populations severely limits generalizability, particularly concerning given documented population-specific genetic architectures. For instance, BMI-depression correlations are positive in Europeans but negative in East Asians, highlighting the critical need for ancestry-diverse research to elucidate population-specific mechanisms underlying psychiatric-metabolic relationships.

Our three-pathway framework revealed important methodological insights while exposing key limitations. Genetic correlation analyses efficiently identified shared architecture but could not distinguish direct causal effects from pleiotropy (Cano-Gamez & Trynka 2020; Prieto et al. 2016; Visscher et al. 2021), necessitating complementary MR studies. However, MR analyses faced constraints from limited genetic instruments for some exposures and reliance on key assumptions (valid instruments, no pleiotropy, no confounding) that may not hold in complex biological systems (Kraft, Chen & Lindstrom 2020; Sanderson et al. 2022).

Path A investigations were often confounded by medication effects, as most PD studies included treated participants; Path C studies struggled to separate medication-specific effects from underlying disorder-related metabolic risk. The MR results revealed substantial effect size and precision variability stemming from differences in study populations, phenotype definitions, and analytical methods.

Substantial heterogeneity in study designs, sample sizes (139 to > 2.5 million), PDs investigated, and analytical methods precluded formal meta-analysis. While this heterogeneity reflected the field's methodological diversity, it limited direct statistical comparisons across studies. Sample overlap between large consortium studies (particularly PGC and UK Biobank data) could not be formally assessed due to potential lack of independence in findings. Our search was restricted to English-language peer-reviewed literature from three major databases, potentially missing relevant studies in other languages, grey literature, or emerging preprint repositories. While our customized quality assessment tool addressed genetic study-specific methodological issues, standardized tools for genetic systematic reviews remain underdeveloped in the field. The assessment categories (low/high/unclear risk) may not capture the full spectrum of bias risk present in genetic association studies, where factors like population stratification, linkage disequilibrium patterns, and statistical power vary substantially across studies.

This review focused on common genetic variants and statistical associations without functional validation studies that could elucidate biological mechanisms. While genetic associations were identified across all three pathways, functional analyses would be crucial for understanding how these variants exert effects on both psychiatric and metabolic outcomes. Publication bias may have inflated effect estimates, as studies with significant findings are preferentially published. The rapidly evolving nature of psychiatric genetics means early studies employed smaller sample sizes and older analytical methods compared to recent large-scale consortium efforts, creating inherent methodological inconsistencies across the 20-year study period. This temporal heterogeneity, combined with varying GWAS statistical power and phenotype definitions, affects the comparability of genetic associations and may inflate apparent replication rates. The substantial methodological heterogeneity necessarily limits confidence in synthesized conclusions, particularly where effect directions or magnitudes varied across studies using different populations or analytical approaches.

We did not identify studies via our search that specifically examined the gut microbiota-immune-brain axis using genome-wide approaches (Cheung et al. 2019; Cryan et al. 2019; Ezenabor, Adeyemi & Adeyemi 2024). Emerging evidence suggests this pathway may represent an important mechanism connecting psychiatric disorders and metabolic dysfunction, with recent genetic studies identifying microbiome-related genes (such as *LCT* and *FUT2*) that may influence both psychiatric and metabolic phenotypes (Goodrich et al. 2016; Kurilshikov et al. 2021). Future research integrating GWAS data with microbiome profiles may provide valuable insights into this mechanism and its contribution to the psychiatric disorder-MetS relationship (Valles-Colomer et al. 2019).

Recent methodological developments have enhanced psychiatric-metabolic genetic research robustness. Trans-ethnic MR approaches demonstrated improved statistical power and accuracy in underrepresented populations, while machine learning prediction models for treatment-resistant depression achieved high performance while revealing shared genetic architecture with metabolic traits. These advances highlight the potential for integrating diverse analytical approaches (Burgess, Foley & Zuber 2018; Kraft, Chen & Lindstrom 2020; Perry et al. 2022a). The framework's integration of multiple genetic methodologies provided complementary insights but revealed the need for: **(1)** standardized methodologies enabling robust meta-analyses, **(2)** longitudinal designs with comprehensive medication history documentation, **(3)** functional validation of identified genetic loci, **(4)** large-scale studies in diverse populations, and **(5)** multi-omics integration to identify robust biomarkers and treatment targets. Future research combining framework-based approaches with functional genomic analyses could

validate associations and provide mechanistic understanding essential for clinical translation (Martin et al. 2019).

3.6. Bridging Systematic Review Findings to Genomic Investigation

The systematic review identified four critical methodological limitations that constrain current understanding of clozapine-induced metabolic dysfunction, each representing a fundamental gap that must be addressed to advance the field.

Firstly, most studies investigated general SCZ liability rather than medication-specific pathways, despite the unique pharmacological profile of clozapine and pronounced metabolic effects. This limitation is particularly problematic given that findings from general psychiatric liability studies may not accurately reflect the specific biological mechanisms underlying the metabolic effects of clozapine. Secondly, traditional observational and candidate gene approaches have dominated the literature, preventing establishment of clear causal relationships between clozapine exposure and metabolic outcomes. These methodological approaches cannot distinguish direct pharmacological effects from confounding factors such as lifestyle changes, treatment adherence, concurrent medications, or improved psychiatric symptoms following treatment initiation. Thirdly, current research has exhibited restricted phenotypic scope, focusing predominantly on major adverse outcomes such as BMI and T2D while neglecting alternative biological pathways that could provide crucial mechanistic insights. Finally, the field lacks systematic approaches for identifying and validating potential biomarkers that could inform clinical monitoring and intervention strategies, representing a missed opportunity for translational impact.

To directly address these identified limitations, Chapter 4 presents a comprehensive multi-layered genomic investigation employing three integrated methodological innovations. To overcome limited medication-specificity, genetic variants affecting clozapine plasma levels will be utilized as drug-specific instrumental variables. This will enable investigation of pharmacological effects directly attributable to altered clozapine exposure rather than general PD liability. To establish causal relationships, MR analyses will be employed, leveraging the random allocation of genetic variants at conception to mimic randomized controlled trials. This approach overcomes the confounding limitations of observational studies while avoiding the ethical constraints of placebo-controlled trials in TRS populations who require clozapine therapy. PheWAS will be employed to examine the full spectrum of biological effects associated with clozapine metabolism variants and validated using statistical colocalization and

MR. This comprehensive approach enables the identification of strong biomarkers and novel associations beyond traditional metabolic outcomes, potentially revealing previously unrecognized biological pathways linking clozapine pharmacokinetics to metabolic dysfunction.

These statistical methodologies will be implemented through a three-stage analytical pipeline designed to validate findings across multiple lines of genetic evidence. The investigation will: **(1)** use bidirectional MR to establish causal relationships between clozapine plasma traits and cardiometabolic outcomes; **(2)** systematically identify candidate biomarkers through PheWAS of clozapine metabolism variants, followed by statistical colocalization to distinguish true biological relationships from linkage disequilibrium artifacts; and **(3)** conduct secondary MR analysis of validated biomarkers against cardiometabolic outcomes to elucidate potential biological pathways mediating the metabolic effects of clozapine. This integrated framework will provide several methodological advantages over existing approaches, including enhanced causal validity compared to observational studies, systematic discovery of intermediate biological pathways, and validation of shared genetic architecture through multiple complementary analytical methods. This approach will address the limitations identified in the systematic review while providing a robust foundation for understanding the complex biological mechanisms underlying clozapine-induced cardiometabolic dysfunction in TRS.

CHAPTER 4 - GENETIC EPIDEMIOLOGICAL ANALYSIS OF CLOZAPINE-INDUCED METABOLIC DYSFUNCTION

Genetic Epidemiological Pipeline Identifies Candidate Markers of Clozapine-Induced Metabolic Dysfunction Revealing Potential Avenues for Precision Clozapine Prescription

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4.1. Abstract

Clozapine is the gold-standard for treatment-resistant schizophrenia despite its severe metabolic complications, including MetS and T2DM risk. A better understanding of the genetic factors influencing clozapine pharmacokinetics and their relationship to metabolic risk could help inform precision medicine approaches to clozapine prescribing. Using a series of genetic-epidemiological approaches, we aimed to identify candidate biomarkers associated with clozapine-induced metabolic dysfunction. We first used two-sample MR leveraging genome-wide association summary data to investigate evidence of causal relationships between clozapine metabolism and cardiometabolic traits. These analyses indicated that higher plasma clozapine levels and a higher clozapine-norclozapine ratio were both associated with a higher risk of T2DM and higher blood pressure. We then applied a Phenome-scan-colocalization-MR pipeline to identify traits influenced by clozapine-metabolism loci that might serve as biomarkers of cardiometabolic risk. This pipeline identified 28 colocalizing candidate biomarkers associated with clozapine metabolising genetic loci. Subsequent MR highlighted associations for 16 of these 28 biomarker candidates with cardiometabolic outcomes, which included haematological markers and excretory traits (e.g. gamma-glutamyl transferase, red cell distribution width, and urea). These findings may inform the development of biomarker-guided monitoring approaches for risk stratification and early intervention, enabling a shift from reactive monitoring to predictive approaches in managing clozapine-induced metabolic dysfunction with appropriate clinical validation. These findings may also help to mitigate the risk of metabolic dysfunction associated with other antipsychotic medications.

4.2. Introduction

Clozapine is the gold-standard medication for TRS, which comprises ~30% of all people with SCZ. However, its therapeutic potential is severely constrained by adverse effects, particularly impacting the cardiometabolic system (Hurley et al. 2023; Myles et al. 2018; Pandey & Kalita 2022; Smith, J et al. 2020; Yuen et al. 2021). Between 10 - 60% of all clozapine-treated patients develop MetS, which is a cluster of interconnected cardiometabolic abnormalities including increased blood pressure and glucose levels, abnormal cholesterol, and excess abdominal fat (Brown & Walker 2016; Stancakova & Laakso 2014). These metabolic side effects are major contributors to the substantial mortality gap in SCZ, where patients experience a 15-20-year reduction in life expectancy compared to the general population (Grover et al. 2016; Hurley et al. 2023; Lamberti et al. 2006; Quek et al. 2022; van der Weide et al. 2017; Walker et al. 1997). Therefore, a precision medicine approach to safe clozapine prescribing has the potential to improve cardiometabolic outcomes, through early identification of high-risk patients and targeted co-administration of protective medications such as metformin or GLP-1 antagonists (Per et al. 2025).

Genetic variants in serotonin receptors (*HTR2C*), leptin (*LEP*), and melanocortin 4 receptor (*MC4R*) genes have been linked to clozapine-induced weight gain and metabolic dysfunction via candidate gene studies (Gunes et al. 2009; Hernandez et al. 2024; Kang, SH et al. 2014; Pardinas et al. 2023). These findings suggest that individual genetic differences may modulate susceptibility to clozapine's cardiometabolic effects. Individual differences in clozapine pharmacokinetics have been suggested as a key mechanism underlying this genetic variation, with plasma drug levels potentially serving as biomarkers for metabolic risk (Lesche et al. 2020; Menus et al. 2020; Numata et al. 2018). Clozapine is primarily metabolized in the liver by the cytochrome P450 enzyme complex, with *CYP1A2* playing a predominant role in converting clozapine to its major metabolite, N-desmethylclozapine (norclozapine) (Bousman, Chad A. 2023; Erickson-Ridout, Sun & Lazarus 2012; Olsson et al. 2015; Pardinas et al. 2023). Secondary metabolic pathways involve *CYP2D6* and *CYP3A4* (Spina, Hiemke & de Leon 2016). Recent genome-wide association studies (GWAS) have identified genetic variants in these enzymes that influence clozapine metabolism and plasma concentrations (Okhuijsen-Pfeifer et al. 2022; Pardinas et al. 2023). Loci in *UGT1A* and *UGT2B* gene clusters that impact clozapine and norclozapine levels have also been identified (Pardinas et al. 2023). Overall, 4 key independent loci (*CYP1A2*, *CYP2D6*/*CYP2C19*, *UGT1A*, and *UGT2B* gene clusters) have been highlighted as associated with clozapine pharmacokinetics, providing robust genetic instruments for investigating relationships between drug exposure and metabolic outcomes

(Doude van Troostwijk et al. 2003; Erickson-Ridout, Sun & Lazarus 2012; Kohlrausch 2013; Manu et al. 2015; Menus et al. 2020; Pardinas et al. 2023).

In this study, we leveraged summary data from GWAS of plasma clozapine and norclozapine levels to determine whether individual differences in drug exposure alter the risk of metabolic disturbances. We then applied a series of genetic epidemiological methods (phenome-scan, statistical colocalization, and MR analyses) to identify biomarkers influenced by clozapine-metabolizing genetic loci that could inform precision medicine approaches to clozapine prescribing (Richardson et al. 2020; Wu et al. 2018). The key strength of this approach lies in its ability to overcome traditional confounding factors that limit observational studies in clozapine-treated populations, providing more reliable evidence for potential causal relationships while identifying measurable biomarkers for potential clinical use (Emdin, Khera & Kathiresan 2017; Huhn et al. 2020).

4.3. Methods

4.3.1. Study Design and Overview

This study followed the STROBE-MR reporting guidelines for transparent MR studies and employed a multi-layered genomic approach to investigate potential causal relationships between plasma clozapine levels and cardiometabolic outcomes. This approach addresses key limitations of traditional observational studies in clozapine-treated patients, including small sample sizes, treatment-related confounding, and difficulty establishing temporal relationships between biomarker changes and metabolic dysfunction. By using inherited genetic variants as instrumental variables, our design has enabled the use of large population-based datasets to identify potential biomarkers and causal relationships without confounding seen in clinical studies.

The analytical pipeline integrated direct genetic associations and potential biomarkers through a pipeline of genetic epidemiological methods, including PheWAS, colocalization, and MR (Figure 4.1). Our approach relied on three core MR assumptions: **(1)** genetic variants are strongly associated with clozapine plasma levels (relevance); **(2)** genetic variants are not associated with confounders (independence); **(3)** genetic variants affect outcomes only through clozapine exposure (exclusion restriction) (Appendix C, Supplementary Figures 4.1). Drug-metabolizing loci used for biomarker identification are highly pleiotropic, which may violate assumption 3, but this does not invalidate discovery as traits sharing genetic architecture with

clozapine pharmacokinetics may be informative, regardless of causal pathway (Burgess et al. 2019; Stacey et al. 2022).

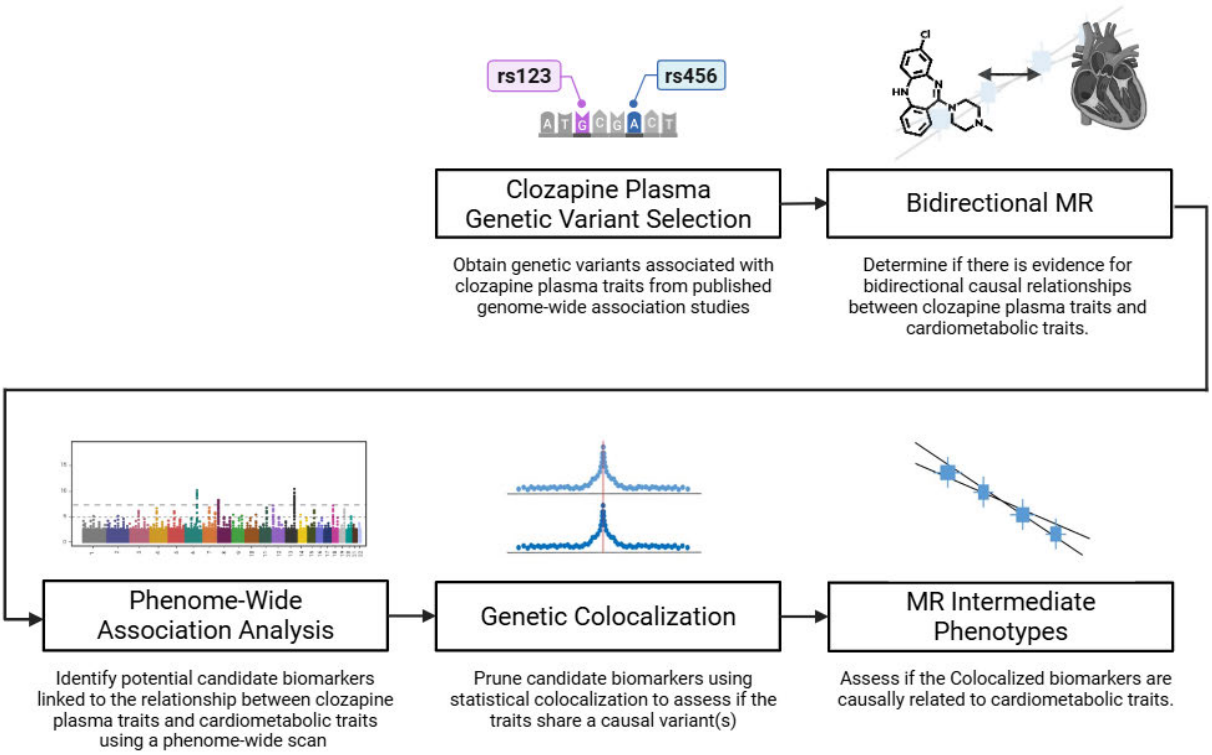


Figure 4.1 - Multi-layered Analytical Framework for Investigating Clozapine-Induced Metabolic Dysfunction. Schematic representation of the four-stage analytical pipeline used in this study. The framework begins with bidirectional MR to examine direct causal relationships between clozapine plasma traits and cardiometabolic outcomes. This is followed by a PheWAS to identify candidate biomarkers, genetic colocalization to filter these candidates for shared genetic architecture, and finally targeted MR to assess potential causal effects of these biomarkers on metabolic outcomes.

4.3.2. Data Sources

Variant-level summary statistics for clozapine plasma levels were derived from the CLOZUK2 (Walters Group Data Repository, Centre for Neuropsychiatric Genetics and Genomics) GWAS (n = 4,495), which provided statistics for plasma concentrations of clozapine, norclozapine, and the ratio of the two from a UK patient monitoring system (Pardinas et al. 2023). All datasets are European in ancestry to minimize population stratification bias. Large-scale clozapine pharmacokinetic GWAS datasets from non-European populations remain extremely limited or absent, highlighting a critical disparity in available pharmacogenomic data that restricts the generalizability of findings to diverse populations despite documented ancestry-specific differences in clozapine metabolism (Pardinas et al. 2023).

Cardiometabolic GWAS represent population-based cohorts with minimal overlap with clozapine-treated populations, reducing sample overlap bias. Cardiometabolic outcomes were obtained from large-scale European GWAS studies through the OpenGWAS and GWAS Catalog platforms, including BMI, blood pressure, HbA1c, lipid traits, T2DM, and MetS (Table 4.1). Summary statistics for the identified candidate biomarkers were obtained based on PheWAS hits with the largest sample size and European ancestry.

Table 4.1 - Metabolic Outcome Traits with Their Respective Data Sources Obtained from OpenGWAS and GWAS Catalog.

Metabolic Trait	Study ID	Year	Sample Size	nSNPs	Ethnicity
Metabolic Syndrome	GCST009602	2019	291,107	9,463,307	European
Type 2 Diabetes Mellitus	ieu-a-1090	2016	120,286	8,404,296	European
Body Mass Index	ukb-b-19953	2018	461,460	9,851,867	European
Systolic Blood Pressure	ieu-b-38	2018	757,601	7,088,083	European
Diastolic Blood Pressure	ieu-b-39	2018	757,601	7,160,619	European
HDL Cholesterol	ieu-a-299	2013	187,167	2,447,442	European
LDL Cholesterol	ieu-a-300	2013	173,082	2,437,752	European
HbA1c	ieu-b-103	2010	46,368	2,529,804	European
Triglycerides	ieu-b-111	2020	441,016	12,321,875	European

4.3.3. Bidirectional Mendelian Randomization

To investigate genetic evidence for causal relationships between clozapine plasma levels and cardiometabolic outcomes, two-sample MR analyses were performed bidirectionally. Genetic instruments for clozapine pharmacokinetic traits were selected using a threshold of $P < 1.00 \times 10^{-5}$ to ensure adequate instrument availability while maintaining biological relevance to drug metabolism pathways where genome-wide significant variants were insufficient. This threshold yielded 47 instrumental variables compared to only 9 at genome-wide significance, while maintaining robust instrument strength for reliable causal inference (Table 4.2).

Table 4.2 - Genetic Instrumental Variables for Clozapine Pharmacokinetics Used in LD-Aware MR (Clozapine Plasma Effects on Cardiometabolic Outcomes).
All instrumental variables were selected using $P < 1.00 \times 10^{-5}$ followed by LD-clumping ($r^2 < 0.1$, 10 Mb windows). F-statistics > 10 indicate strong instruments with minimal weak instrument bias. Variants listed under multiple exposures serve as instruments for those respective phenotypes.

SNP (GRCh37)	Chr	Position	EA	OA	EAF	Beta	SE	P-value	F-Statistic
Clozapine Plasma									
rs3732218	2	234,627,304	A	G	0.1	-0.217	0.031	3.30×10^{-12}	48.5
rs6791266	3	1,446,510	G	A	0.21	-0.114	0.024	2.10×10^{-6}	22.5
rs6791077	3	140,176,199	C	T	0.23	-0.101	0.022	3.90×10^{-6}	21.3
rs75860583	3	165,859,297	T	G	8.00×10^{-2}	-0.155	0.034	5.60×10^{-6}	20.6
rs2100040	5	65,134,980	A	G	0.25	0.101	0.022	3.70×10^{-6}	21.4
rs2389763	7	17,307,847	C	T	0.57	-0.096	0.019	4.30×10^{-7}	25.6
rs34872991	7	42,222,857	A	G	0.11	0.146	3.00×10^{-2}	1.10×10^{-6}	23.7
rs1057868	7	75,615,006	T	C	0.27	-0.094	0.021	9.00×10^{-6}	19.7
rs56282157	7	37,411,377	G	T	8.00×10^{-2}	-0.161	0.036	9.80×10^{-6}	19.5
rs11020316	11	93,146,805	C	T	0.28	-0.096	0.021	6.90×10^{-6}	20.2
rs56133064	12	124,747,789	G	A	8.00×10^{-2}	0.155	0.034	3.50×10^{-6}	21.5
rs73055220	12	17,655,750	C	T	0.14	-0.126	0.027	4.60×10^{-6}	21
rs2151870	13	72,813,751	C	T	0.21	-0.108	0.023	3.80×10^{-6}	21.4
rs1956171	14	94,677,145	T	C	0.28	-0.101	0.021	1.90×10^{-6}	22.7
rs854311	14	25,218,824	A	C	8.00×10^{-2}	-0.161	0.036	5.70×10^{-6}	20.6
rs2472297	15	75,027,880	T	C	0.24	-0.15	0.023	4.40×10^{-11}	43.4
rs62087495	18	9,398,708	T	C	8.00×10^{-2}	0.165	0.035	2.80×10^{-6}	22
Norclozapine Plasma									
rs4663325	2	234,616,357	T	C	0.12	-0.203	0.028	8.10×10^{-13}	51.3
rs11123265	2	115,736,492	C	T	0.27	0.101	0.021	1.30×10^{-6}	23.4
rs77755140	3	165,859,270	A	G	8.00×10^{-2}	-0.153	0.033	4.50×10^{-6}	21
rs6791266	3	1,446,510	G	A	0.21	-0.107	0.024	5.90×10^{-6}	20.5
rs2926036	4	69,682,629	G	A	0.86	0.292	0.027	3.20×10^{-28}	121.4
rs79870297	4	186,614,953	T	C	0.22	-0.109	0.023	1.40×10^{-6}	23.2
rs79204178	4	20,753,714	C	T	0.1	0.143	3.00×10^{-2}	2.50×10^{-6}	22.1
rs112400791	5	175,991,431	T	C	6.00×10^{-2}	-0.167	0.037	6.70×10^{-6}	20.3
rs77634225	7	42,227,050	C	T	7.00×10^{-2}	-0.164	0.036	5.80×10^{-6}	20.6
rs12779195	10	77,631,585	C	T	0.49	-0.083	0.019	7.40×10^{-6}	20.1
rs34633304	11	11,419,070	A	G	0.13	0.133	0.028	2.70×10^{-6}	22
rs12286285	11	107,399,326	G	A	0.31	-0.088	0.019	5.80×10^{-6}	20.5
rs854311	14	25,218,824	A	C	8.00×10^{-2}	-0.178	0.034	1.50×10^{-7}	27.5
rs1956168	14	94,680,291	A	G	0.28	-0.093	2.00×10^{-2}	4.30×10^{-6}	21.1
rs2472297	15	75,027,880	T	C	0.24	-0.135	0.022	2.10×10^{-9}	35.9
rs12918756	16	49,574,239	T	G	0.18	-0.113	0.024	2.70×10^{-6}	22
rs902589	18	63,842,961	T	C	0.87	-0.134	0.029	3.70×10^{-6}	21.4
rs4805573	19	30,995,755	T	C	0.1	0.141	0.032	8.20×10^{-6}	19.9
Clozapine-Norclozapine Plasma Ratio									
rs896809	2	19,976,506	T	C	0.28	0.094	0.021	7.30×10^{-6}	20.1
rs835309	4	69,682,855	G	T	0.87	-0.619	0.023	2.10×10^{-153}	696.1
rs6830368	4	69,911,097	G	A	0.49	0.163	0.019	1.90×10^{-18}	76.8
rs4272075	4	70,269,936	A	G	0.72	-0.14	2.00×10^{-2}	3.90×10^{-12}	48.2
rs115163219	4	70,366,972	A	G	5.00×10^{-2}	0.279	0.044	1.50×10^{-10}	41.1
rs3777760	6	12,150,811	A	G	0.31	0.089	2.00×10^{-2}	8.70×10^{-6}	19.8
rs41301394	7	75,612,803	T	C	0.27	-0.115	0.021	4.80×10^{-8}	29.8
rs62530100	9	7,652,916	A	G	0.1	0.143	3.00×10^{-2}	1.60×10^{-6}	23.1
rs1926711	10	96,484,777	A	G	0.17	0.232	0.024	4.70×10^{-22}	93.2
rs61832289	10	11,207,045	A	G	0.13	-0.128	0.028	6.60×10^{-6}	20.3
rs7103488	11	124,020,568	T	C	0.15	-0.124	0.027	5.20×10^{-6}	20.8
rs75929054	14	23,812,891	C	T	6.00×10^{-2}	0.177	0.039	5.10×10^{-6}	20.8

Instrumental variables were validated through LD clumping ($r^2 < 0.001$) and strength assessment. All 47 variants exceeded the conventional $F > 10$ threshold for strong instruments, with 91.5% demonstrating $F > 20$, indicating minimal risk of weak instrument bias (Burgess, Small & Thompson 2017; Liu, J et al. 2023; Pierce, Ahsan & Vanderweele 2011; Sanderson, Spiller & Bowden 2021). Our genetic instruments captured steady-state plasma concentrations reflecting integrated pharmacokinetic processes rather than isolated metabolic activity. For reverse MR analyses, genetic instruments were selected at genome-wide significance for cardiometabolic traits (exposure) and tested against clozapine plasma traits as outcomes.

The primary analysis used inverse variance weighted (IVW) MR method, complemented by sensitivity analyses including MR-Egger regression to evaluate the presence of directional pleiotropy, weighted median estimation, and heterogeneity assessment using Q-statistics and I^2 values (Bowden et al. 2016; Brion, Shakhbazov & Visscher 2013; Verbanck et al. 2018; Winkler et al. 2014). Forest plots and scatterplots were generated to visualize the results (Emdin, Khera & Kathiresan 2017; Sanderson et al. 2022; Wickham 2016). Leave-one-out plots were also generated to test if the MR estimate was sensitive to a particular variant.

4.3.4. Phenome-Wide Association Analysis

To identify candidate biomarkers for clozapine induced metabolic dysfunction, a PheWAS was conducted using the OpenGWAS platform (Hemani et al. 2018). Ten lead variants previously identified at genome-wide significance as associated with clozapine pharmacokinetics (Table 4.3) were used as the basis for this analysis. The variants selected as leads are located on chromosomes 2, 4, 10, and 15 with a spread of mapped genes including *CYP1A, CYP2C, UTG1A,* and *UTG2B* genes. The PheWAS queried these variants against thousands of phenotypes available in OpenGWAS, with a genome-wide significance threshold applied to identify potentially relevant traits. The resulting associations were categorized into functional groups to identify key biological systems potentially involved in the clozapine-metabolic relationship (Bastarache, Denny & Roden 2022; Dennis et al. 2021; Denny, Bastarache & Roden 2016; Machiela & Chanock 2015; Zheng, J et al. 2020).

Table 4.3 - Lead Variants Used in the PheWAS-Colocalization-MR Pipeline to Identify Potential Biomarkers. Variants describe the biological pathways connecting clozapine plasma traits to cardiometabolic abnormalities around key loci (*CYP* and *UGT* regions).

SNP (GRCh37)	P-Value	Chr	Position	Mapped Gene(s)	Clozapine Associated Trait	Study Accession
rs2011425	8.00×10^{-9}	2	233718962	*UGT1A4*	Norclozapine	GCST007686
rs3732218	3.00×10^{-12}	2	233718658	*UGT1A9, UGT1A6, UGT1A8, UGT1A5, UGT1A7, UGT1A10*	Clozapine, Norclozapine	GCST90239836
rs10000284	4.00×10^{-20}	4	68803465	*UGT2B10*	Norclozapine	GCST010564
rs10023464	2.00×10^{-91}	4	68794020	*UGT2B10, UGT2B15*	Ratio	GCST007684
rs11725502	5.00×10^{-15}	4	68815224	*UGT2B10*	Norclozapine	GCST007686
rs7668556	4.00×10^{-13}	4	69164555	*UGT2B11, SPOPLP1*	Ratio	GCST007684
rs835309	2.00×10^{-153}	4	68817137	*UGT2B10*	Ratio	GCST90239838
rs12767583	1.00×10^{-16}	10	94787706	*CYP2C19*	Ratio	GCST010563
rs1926711	5.00×10^{-22}	10	94725020	*CYP2C18*	Ratio	GCST90239838
rs2472297	4.00×10^{-10}	15	74735539	*CYP1A1, CYP1A2*	Clozapine	GCST007685

4.3.5. Statistical Colocalization

To distinguish true shared genetic effects from those attributable to LD, colocalization analyses were performed on the biomarkers identified through PheWAS. The Pairwise Conditional and Colocalization (PWCoCo) method was employed with the 1000 Genomes European reference panel (Liu, B et al. 2019). This method employs a Bayesian framework to calculate posterior probabilities for five hypotheses where the following hypotheses were implemented:

H_0: No association with either trait
H_1: Association with trait 1 only
H_2: Association with trait 2 only
H_3: Association with both traits, different causal variants
H_4: Association with both traits, shared causal variant

For each identified phenotype, ± 500kb windows around lead variants were analysed, and a posterior probability threshold of $PP.H_4 > 0.8$ was applied to signal robust colocalization indicating a shared causal variant between the traits (Foley et al. 2021; Giambartolomei et al. 2014; Robinson, JW et al. 2022; Wallace 2020).

4.3.6. Mendelian Randomization of Intermediate Phenotypes

The phenotypes that demonstrated robust genetic colocalization with clozapine plasma traits were then used as exposures in a series of MR analyses against cardiometabolic outcomes bidirectionally. For these analyses, genetic instruments were selected at genome-wide significance. These analyses followed the same methodological approach as the primary MR analyses, including similar sensitivity analyses and visualization methods. This final analytical step aimed to quantify the potential causal effects of these candidates on metabolic outcomes, thereby identifying potential biological pathways that may be implicated in the relationship (Emdin, Khera & Kathiresan 2017; Sanderson et al. 2022; Wickham 2016).

Detailed directed acyclic graphs depicting the assumptions and relationships for each MR analysis stage are provided in (Appendix C, Supplementary Figures 4.1). Additional statistical and procedural details are available in the Appendix C, Supplementary Methods and Appendix D.

4.3.7. Genetic Correlation Analysis

To characterize the genetic architecture of candidate biomarkers and inform analytical strategy, we performed linkage disequilibrium score regression (LDSC) using the GenomicSEM R package (version 0.0.5). GWAS summary statistics for all 16 candidate biomarkers were first standardized using the munge function, which filtered SNPs to the HapMap3 reference panel, aligned alleles to the 1000 Genomes Phase 3 European population, and applied quality control filters (MAF > 0.01, INFO > 0.90). Genetic correlations (r_g) were computed for all pairwise combinations using the ldsc function with pre-computed LD scores derived from the 1000 Genomes Phase 3 European reference panel (503 individuals, ~1.2M HapMap3 SNPs). Hierarchical clustering using complete linkage was applied to the genetic correlation distance matrix (1 - $|r_g|$). A height threshold of 0.85 was selected to define distinct biomarker clusters. Biomarkers with moderate/strong genetic correlations ($|r_g| > 0.15$) clustering together were considered as sharing substantial genetic architecture, justifying joint analysis in multivariable frameworks.

4.3.8. Multivariable Mendelian Randomization

Based on genetic correlation results, we performed focused multivariable MR (MVMR) on biomarkers demonstrating moderate/strong genetic correlations. MVMR extends conventional univariable MR by simultaneously estimating the independent causal effects of multiple correlated exposures on an outcome. We used the MVMR R package to implement inverse-variance weighted (IVW) MVMR, selecting genetic instruments that were genome-wide significant. Instrument strength was assessed using conditional F-statistics, with $F > 10$ indicating strong instruments.

4.4. Results

4.4.1. Clozapine Plasma Traits are Associated with Cardiometabolic Outcomes

To determine whether individual differences in clozapine plasma levels influence the risk of metabolic outcomes, we conducted two-sample MR using plasma levels of clozapine, norclozapine, and their ratio as exposures against cardiometabolic outcomes. All genetic instruments demonstrated robust strength, indicating minimal weak instrument bias and supporting reliable causal inference (Table 4.2).

Using IVW MR as the main analysis with a Bonferroni adjusted p-value threshold of ($P = 0.05/27 = 1.85 \times 10^{-3}$), we found that clozapine plasma levels were strongly associated with T2DM (OR = 1.62, SE = 0.036, $P = 5.05 \times 10^{-41}$) and systolic blood pressure ($\beta = 0.331$, SE = 0.054, $P = 7.63 \times 10^{-10}$). We also found some evidence for a protective association with MetS (OR = 0.99, SE = 0.005, $P = 2.99 \times 10^{-2}$), though this did not survive correction for multiple testing.

While norclozapine levels did not reveal any significant associations in primary IVW-MR analyses, the clozapine-norclozapine ratio was associated with diastolic blood pressure ($\beta = 0.210$, SE = 0.023, $P = 1.30 \times 10^{-19}$) and T2DM (OR = 1.74, SE = 0.165, $P = 7.92 \times 10^{-4}$). A higher clozapine-norclozapine ratio was also associated with lower risk of MetS ($\beta = -0.018$, SE = 0.005, $P = 1.48 \times 10^{-4}$) (Figure 4.2).

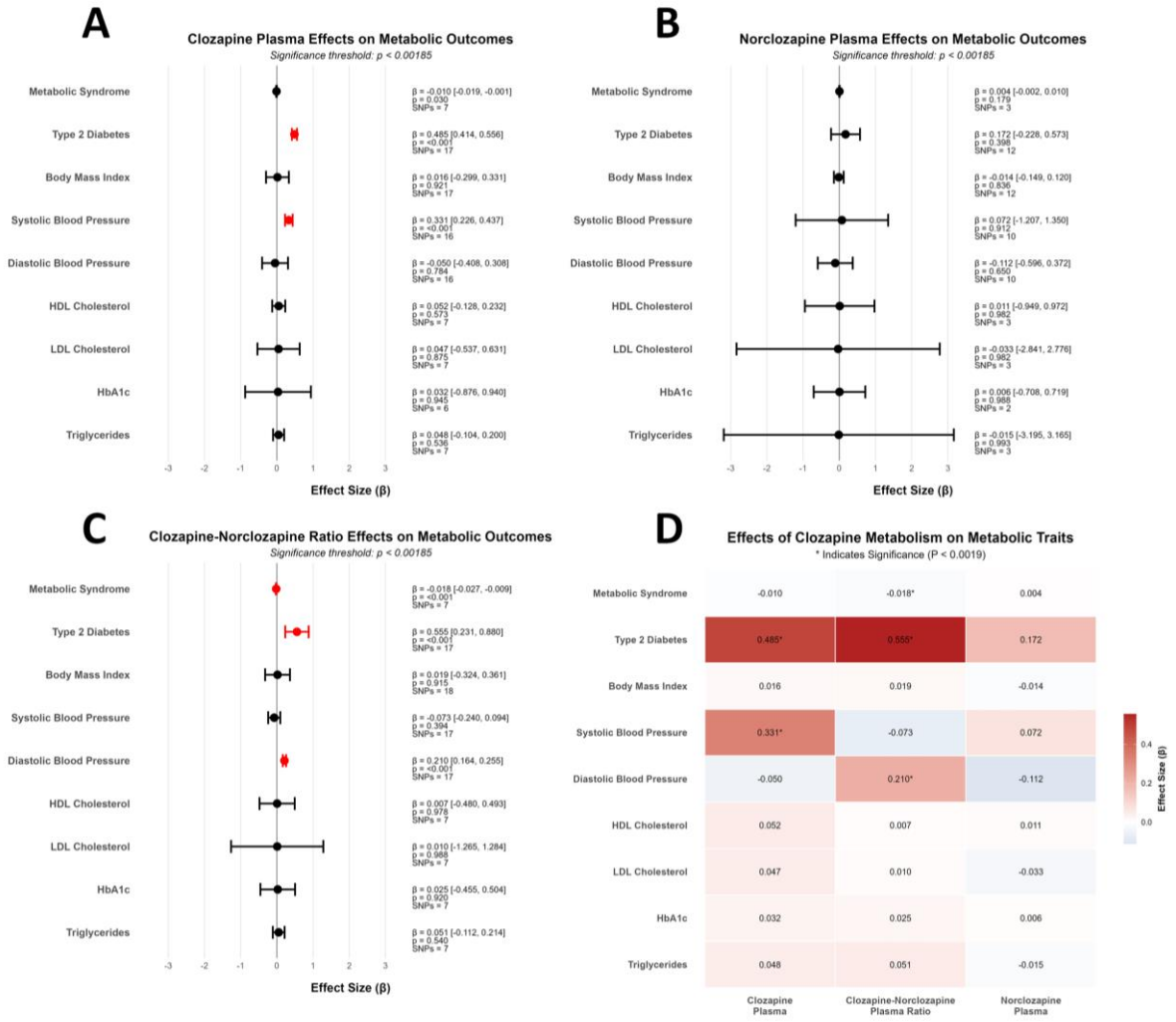


Figure 4.2 - Direct Effects of Clozapine Plasma Levels on Cardiometabolic Outcomes.

Forest plots showing causal effect estimates (β), 95% confidence intervals, number of instrumental variables, and P-values from inverse-variance weighted MR analyses. Results are presented for (A) Clozapine plasma level, (B) Norclozapine plasma level, and (C) Clozapine-Norclozapine plasma ratio against multiple metabolic outcomes including MetS, T2DM, BMI, blood pressure, and lipid parameters. Red points indicate statistically significant associations after multiple testing correction ($P < 1.85 \times 10^{-3}$). (D) Heatmap summary of the clozapine-cardiometabolic MR analyses. The colour represent directionality (positive: red, negative: blue) of the association with an asterisk indicating significance after multiple testing correction ($P < 1.85 \times 10^{-3}$).

These findings remained consistent across multiple sensitivity analyses, with little evidence of directional pleiotropy for most analyses (MR-Egger intercept $P > 0.2$). For the clozapine plasma-T2DM relationship (MR-Egger intercept $P = 3.10 \times 10^{-3}$), the association remained significant and directionally consistent in pleiotropy-robust weighted median analysis ($\beta = 0.521$, $P = 4.56 \times 10^{-3}$). For MetS analyses of the clozapine-norclozapine ratio (MR-Egger intercept $P = 1.83 \times 10^{-5}$), the association was attenuated and lost significance in weighted median analysis ($\beta = -0.006$, $P = 0.80$), suggesting this relationship may be influenced by

pleiotropy. (Appendix C, Supplementary Table 4.1; Supplementary Figures 4.2). We found limited evidence of reverse causation with the only exception being potential causal effects of T2DM on blood plasma levels of both clozapine ($\beta = 0.098$, SE = 0.032, $P = 1.91 \times 10^{-3}$) and norclozapine ($\beta = 0.090$, SE = 0.031, $P = 3.46 \times 10^{-3}$). However, these associations did not withstand multiple testing correction (Appendix C, Supplementary Table 4.2; Supplementary Figures 4.2).

To ensure that observed associations between clozapine pharmacokinetic traits and metabolic outcomes reflect medication effects rather than disease liability, we verified that genetic variants associated with clozapine pharmacokinetics showed no association with SCZ risk. LD-clumping identified 9 independent variants across the three pharmacokinetic traits, spanning 6 genomic regions (chromosomes 2, 4, 7, 10, and 15). All 9 lead variants were present in the SCZ GWAS dataset (excluding one where a proxy SNP was used). None of the 9 variants showed even nominal significance in the SCZ dataset (all $P > 0.05$), demonstrating strong evidence against horizontal pleiotropy through disease liability pathways. A proxy SNP rs12570829 was used for rs1926711 (10.1 kb distant, same genomic region, $R^2 = 0.992$) (Table 4.3; Figure 4.3).

Table 4.4 - Assessment of Pleiotropy: Schizophrenia GWAS Associations for Clozapine Pharmacokinetic Variants.
(*) Indicates that a proxy SNP was used due to missing lead variant in the schizophrenia dataset.

Variant (GRCh37)	Chromosome : Position	Associated Trait	Clozapine Plasma Trait P-Value	SCZ P-Value
rs4663325	2 : 234,616,357	Norclozapine	8.10×10^{-13}	0.583
rs3732218	2 : 234,627,304	Clozapine	3.30×10^{-12}	0.991
rs2926036	4 : 69,682,629	Norclozapine	3.20×10^{-28}	0.841
rs835309	4 : 69,682,855	Ratio	2.10×10^{-153}	0.358
rs6830368	4 : 69,911,097	Ratio	1.90×10^{-18}	0.968
rs13353587	4 : 70,312,793	Ratio	4.72×10^{-40}	0.137
rs41301394	7 : 75,612,803	Ratio	4.80×10^{-08}	0.722
rs12570829*	10 : 96,474,651	Ratio	4.70×10^{-22}	0.135
rs2472297	15 : 75,027,880	Clozapine, Norclozapine	4.40×10^{-11}	0.125

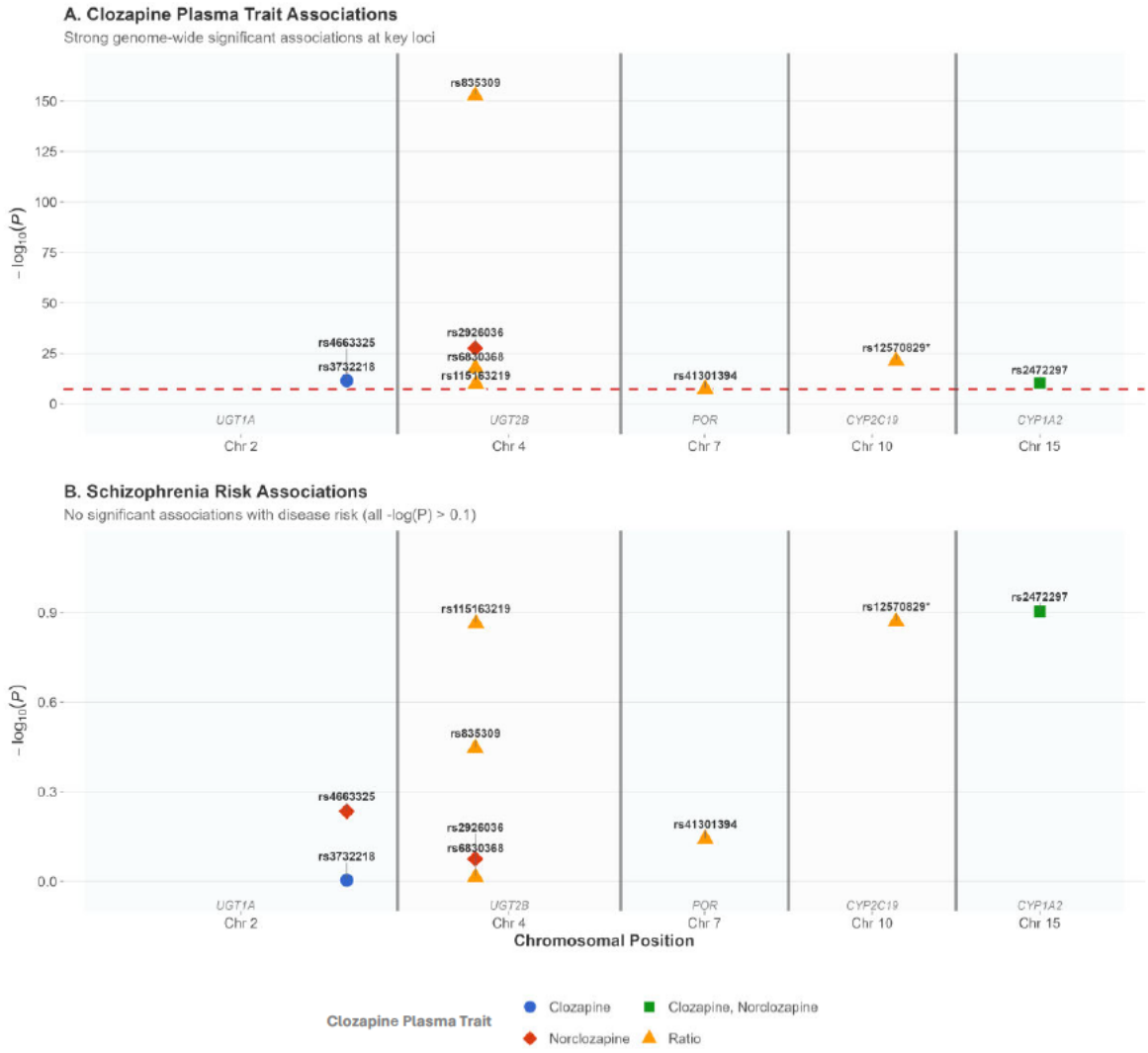


Figure 4.3 - Assessment of Horizontal Pleiotropy Between Schizophrenia and Clozapine Pharmacokinetics. SCZ GWAS associations for clozapine pharmacokinetic lead variants. (A) Clozapine plasma trait associated -log(P) from the CLOZUK dataset, all variants significant at a genome-wide level. (B) Corresponding PGC SCZ dataset variant -log(P), no variants reach even nominal significance (P = 0.05). Variant details: rs4663325 and rs3732218 (*UGT1A* cluster), rs2926036, rs835309, rs6830368 and rs115163219 (*UGT2B* cluster), rs41301394 (*POR*), rs12570829* (*CYP2C19*), rs2472297 (*CYP1A2*). Red line: genome-wide significance ($P = 5.00 \times 10^{-8}$). *rs12570829 used as a proxy SNP for rs1926711which was not present in the PGC SCZ dataset.

4.4.2. Phenome-wide Association Identified Candidate Traits Influenced by Clozapine-Metabolising Genetic Loci

Given the evidence that individual differences in clozapine plasma levels influence cardiometabolic outcomes, we sought to identify measurable candidate traits influenced by clozapine-metabolizing genetic loci that could potentially be evaluated for risk stratification in people with SCZ. To this end, a previously established genetic epidemiological pipeline beginning with a PheWAS with a significance threshold of $P < 5.00 \times 10^{-8}$ (Table 4.2) was employed (Stacey et al. 2022). This approach yielded 391 significant associations across 203 unique studies, representing 98 distinct candidate biomarker traits. These hits clustered into several biological categories, including liver function markers, renal markers, body composition measurements, and dietary factors (Figure 4.4; Appendix C, Supplementary Table 4.3; Supplementary Figures 4.3).

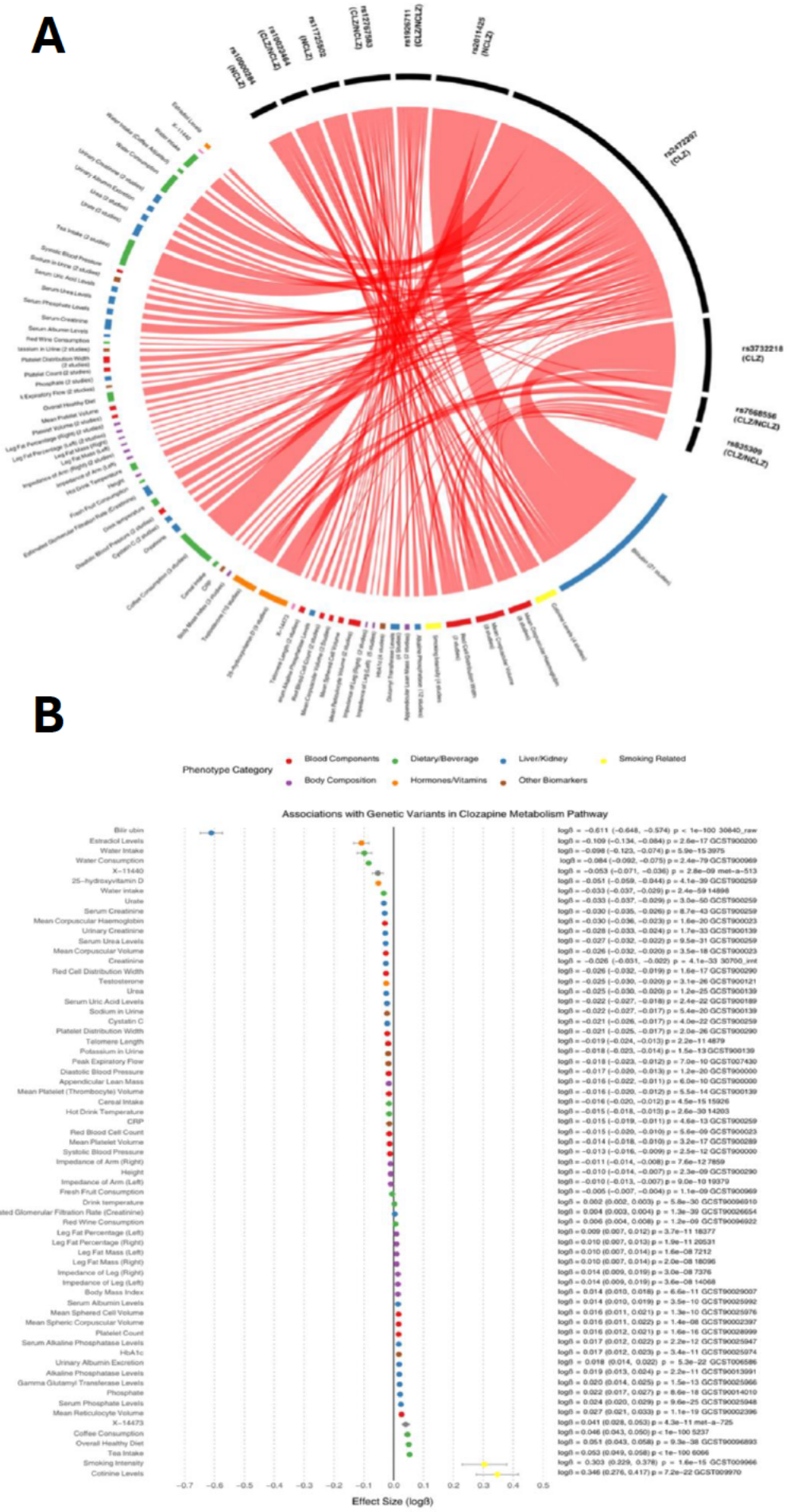

A
rs10980694 (NCL2)
rs1980984 (CLZ/NCL2)
rs1172503 (NCL2)
rs12767993 (CLZ/NCL2)
rs1805711 (CLZ/NCL2)
rs2011425 (NCL2)
rs2472297 (CLZ)
rs3732218 (CLZ)
rs7568556 (CLZ/NCL2)
rs825309 (CLZ/NCL2)
B
Phenotype Category
Blood Components
Dietary/Beverage
Liver/Kidney
Smoking Related
Body Composition
Hormones/Vitamins
Other Biomarkers
Associations with Genetic Variants in Clozapine Metabolism Pathway
Bilirubin
Estradiol Levels
Water Intake
Water Consumption
X−11440
25−hydroxyvitamin D
Water Intake
Urate
Serum Creatinine
Mean Corpuscular Haemoglobin
Urinary Creatinine
Serum Urea Levels
Mean Corpuscular Volume
Creatinine
Red Cell Distribution Width
Testosterone
Urea
Serum Uric Acid Levels
Sodium in Urine
Cystatin C
Platelet Distribution Width
Telomere Length
Potassium in Urine
Peak Expiratory Flow
Diastolic Blood Pressure
Appendicular Lean Mass
Mean Platelet (Thrombocyte) Volume
Cereal Intake
Hot Drink Temperature
CRP
Red Blood Cell Count
Mean Platelet Volume
Systolic Blood Pressure
Impedance of Arm (Right)
Height
Impedance of Arm (Left)
Fresh Fruit Consumption
Drink temperature
Estimated Glomerular Filtration Rate (Creatinine)
Red Wine Consumption
Leg Fat Percentage (Left)
Leg Fat Percentage (Right)
Leg Fat Mass (Left)
Leg Fat Mass (Right)
Impedance of Leg (Right)
Impedance of Leg (Left)
Body Mass Index
Serum Albumin Levels
Mean Sphered Cell Volume
Mean Spheric Corpuscular Volume
Platelet Count
Serum Alkaline Phosphatase Levels
HbA1c
Urinary Albumin Excretion
Alkaline Phosphatase Levels
Gamma Glutamyl Transferase Levels
Phosphate
Serum Phosphate Levels
Mean Reticulocyte Volume
X−14473
Coffee Consumption
Overall Healthy Diet
Tea Intake
Smoking Intensity
Cotinine Levels
−0.7 −0.6 −0.5 −0.4 −0.3 −0.2 −0.1 0.0 0.1 0.2 0.3 0.4 0.5
Effect Size (log(β)
log(β = −0.611 (−0.648, −0.574) p < 1e−100 30840_raw
log(β = −0.109 (−0.134, −0.084) p = 2.6e−17 GCST900200
log(β = −0.098 (−0.123, −0.074) p = 5.9e−15 3975
log(β = −0.084 (−0.092, −0.075) p = 2.4e−79 GCST900969
log(β = −0.053 (−0.071, −0.036) p = 2.8e−09 met−a−513
log(β = −0.051 (−0.059, −0.044) p = 4.1e−39 GCST900259
log(β = −0.033 (−0.037, −0.029) p = 2.4e−59 14898
log(β = −0.033 (−0.037, −0.029) p = 3.0e−50 GCST900259
log(β = −0.030 (−0.035, −0.026) p = 8.7e−43 GCST900259
log(β = −0.030 (−0.036, −0.023) p = 1.6e−20 GCST900023
log(β = −0.028 (−0.033, −0.024) p = 1.7e−33 GCST900139
log(β = −0.027 (−0.032, −0.022) p = 9.5e−31 GCST900259
log(β = −0.026 (−0.032, −0.020) p = 3.5e−18 GCST900023
log(β = −0.026 (−0.031, −0.022) p = 4.1e−33 30700_irnt
log(β = −0.026 (−0.032, −0.019) p = 1.6e−17 GCST900290
log(β = −0.025 (−0.030, −0.020) p = 3.1e−26 GCST900121
log(β = −0.025 (−0.030, −0.020) p = 1.2e−25 GCST900139
log(β = −0.022 (−0.027, −0.018) p = 2.4e−22 GCST900189
log(β = −0.022 (−0.027, −0.017) p = 5.4e−20 GCST900139
log(β = −0.021 (−0.026, −0.017) p = 4.0e−22 GCST900259
log(β = −0.021 (−0.025, −0.017) p = 2.0e−26 GCST900290
log(β = −0.019 (−0.024, −0.013) p = 2.2e−11 4879
log(β = −0.018 (−0.023, −0.014) p = 1.5e−13 GCST900139
log(β = −0.018 (−0.023, −0.012) p = 7.0e−10 GCST007430
log(β = −0.017 (−0.020, −0.013) p = 1.2e−20 GCST900000
log(β = −0.016 (−0.022, −0.011) p = 6.0e−10 GCST900000
log(β = −0.016 (−0.020, −0.012) p = 5.5e−14 GCST900139
log(β = −0.016 (−0.020, −0.012) p = 4.5e−15 15926
log(β = −0.015 (−0.018, −0.013) p = 2.6e−30 14203
log(β = −0.015 (−0.019, −0.011) p = 4.6e−13 GCST900259
log(β = −0.015 (−0.020, −0.010) p = 5.6e−09 GCST900023
log(β = −0.014 (−0.018, −0.010) p = 3.2e−17 GCST900289
log(β = −0.013 (−0.016, −0.009) p = 2.5e−12 GCST900000
log(β = −0.011 (−0.014, −0.008) p = 7.6e−12 7859
log(β = −0.010 (−0.014, −0.007) p = 2.3e−09 GCST900290
log(β = −0.010 (−0.013, −0.007) p = 9.0e−10 19379
log(β = −0.005 (−0.007, −0.004) p = 1.1e−09 GCST900969
log(β = 0.002 (0.002, 0.003) p = 5.8e−30 GCST90096910
log(β = 0.004 (0.003, 0.004) p = 1.3e−39 GCST90026654
log(β = 0.006 (0.004, 0.006) p = 1.2e−09 GCST90096922
log(β = 0.009 (0.007, 0.012) p = 3.7e−11 18377
log(β = 0.010 (0.007, 0.013) p = 1.9e−11 20531
log(β = 0.010 (0.007, 0.014) p = 1.6e−08 7212
log(β = 0.010 (0.007, 0.014) p = 2.0e−08 18096
log(β = 0.014 (0.009, 0.019) p = 3.0e−08 7376
log(β = 0.014 (0.009, 0.019) p = 3.6e−08 14068
log(β = 0.014 (0.010, 0.018) p = 6.6e−11 GCST90029007
log(β = 0.014 (0.010, 0.019) p = 3.5e−10 GCST90025992
log(β = 0.016 (0.011, 0.021) p = 1.3e−10 GCST90025976
log(β = 0.016 (0.011, 0.022) p = 1.4e−08 GCST90002397
log(β = 0.016 (0.012, 0.021) p = 1.6e−16 GCST90028999
log(β = 0.017 (0.012, 0.022) p = 2.2e−12 GCST90025947
log(β = 0.017 (0.012, 0.023) p = 3.4e−11 GCST90025974
log(β = 0.018 (0.014, 0.022) p = 5.3e−22 GCST006586
log(β = 0.019 (0.013, 0.024) p = 2.2e−11 GCST90013991
log(β = 0.020 (0.014, 0.025) p = 1.5e−13 GCST90025966
log(β = 0.022 (0.017, 0.027) p = 8.6e−18 GCST90014010
log(β = 0.024 (0.020, 0.029) p = 9.6e−25 GCST90025948
log(β = 0.027 (0.021, 0.033) p = 1.1e−19 GCST90002396
log(β = 0.041 (0.028, 0.053) p = 4.3e−11 met−a−725
log(β = 0.046 (0.043, 0.050) p < 1e−100 5237
log(β = 0.051 (0.043, 0.058) p = 9.3e−38 GCST90096893
log(β = 0.053 (0.049, 0.058) p < 1e−100 6066
log(β = 0.303 (0.229, 0.376) p = 1.6e−15 GCST009966
log(β = 0.346 (0.276, 0.417) p = 7.2e−22 GCST009970

Figure 4.4 - Phenome-Wide Analysis Results Identifying Candidate Intermediate Phenotypes Modulating the Relationship Between Clozapine Metabolism and Cardiometabolic Outcomes.

Graphical representation of the results from the PheWAS analysis run through OpenGWAS. (A) Circular plot of the associated phenotypes relating to a specific lead variant used for the analysis. All connections had a genome-wide significance ($P < 1.85 \times 10^{-3}$), when multiple studies reported the same trait, number of studies is displayed. Identified phenotypes are colour-coded by trait category. (B) Forest plot of the same identified phenotypes also colour-coded by trait category. Forest plot shows causal effect estimates (log(β)) with 95% confidence intervals, specific P-value, and associated study ID for each identified trait. When multiple studies reported the same trait, the most significant hit was used.

The lead variant rs2472297 near *CYP1A1*/*CYP1A2* emerged as the predominant driver of associations, demonstrating strong connections to caffeine metabolism and various metabolic traits. Similarly, rs3732218 (located within *UGT1A8*) demonstrated strong associations with bilirubin, while rs10000284 showed connections to smoking and nicotine metabolism. These PheWAS results provided an initial set of candidate biomarker traits influenced by clozapine-metabolizing genetic loci.

4.4.3. Colocalization Confirms Shared Genetic Architecture Between Clozapine Pharmacokinetics and Candidate Biomarkers

The PheWAS results could potentially include traits that do not share the same genetic aetiology with clozapine pharmacokinetic traits and are therefore confounded by LD. To identify and remove these spurious associations, we conducted pairwise colocalization analyses using PWCoCo, which combines conditional analyses with colocalization to address the single causal variant assumption limitation (Appendix C, Supplementary Methods).

From the 98 candidate biomarker traits identified in the PheWAS, we uncovered robust evidence of colocalization ($PP.H_4 > 0.80$) with clozapine plasma traits for 28 phenotypes (28.6%) including renal, inflammatory, liver, and haematological markers (Appendix C, Supplementary Table 4.4; Supplementary Figures 4.4). The network visualization of colocalizing biomarker traits (Figure 4.5) illustrates the wide variety of traits impacted by the clozapine metabolising loci. The clustering of colocalization signals among functionally related traits (renal markers, body composition measures, liver function tests) suggests that these variants operate through coherent biological pathways. Notably, several phenotypes colocalized at multiple independent loci, providing particularly strong evidence for shared genetic architecture with clozapine pharmacokinetic traits. For example, bilirubin showed colocalization across the independent loci with the clozapine-norclozapine ratio ($PP.H_4 = 0.927$

- 1.000), while total testosterone colocalized at two independent loci ($PP.H_4$ = 0.901 - 0.957), and 25-hydroxyvitamin D demonstrated both conditional and unconditional colocalization signals across multiple analyses ($PP.H_4$ = 0.939 - 1.000) (Appendix C, Supplementary Figures 4.4, Supplementary Table 4.4).

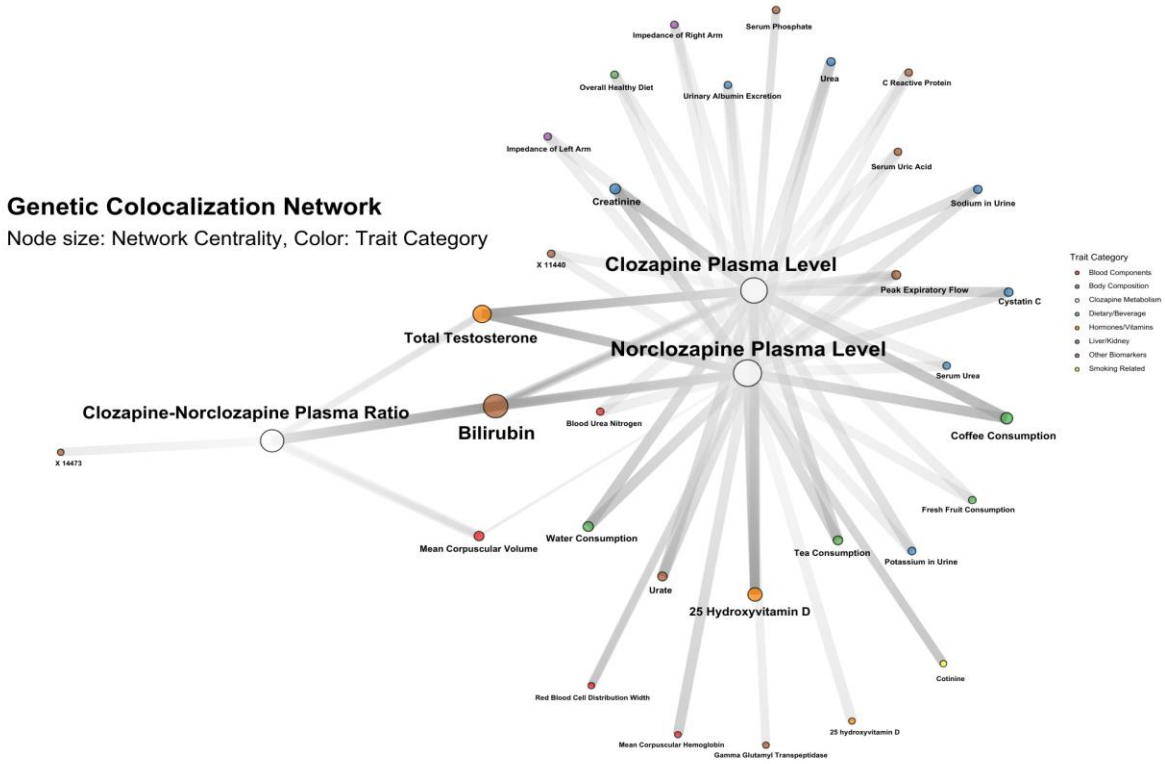


Figure 4.5 - Genetic Colocalization Network of Clozapine Metabolism and Candidate Phenotypes Visualization of Phenotypes Demonstrating Robust Genetic Colocalization with Clozapine Metabolism Traits.
Nodes represent phenotypes color-coded by trait category as shown in the legend, with node size indicating network centrality. The three clozapine metabolism traits (clozapine plasma level, norclozapine plasma level, and clozapine-norclozapine ratio) are positioned at the core of the network, with connecting lines representing robust genetic colocalization ($PP.H_4 > 0.80$).

The colocalization analysis effectively prioritized the list of candidate biomarker traits to a set with strong evidence of shared genetic architecture with clozapine pharmacokinetics, establishing a foundation for subsequent MR.

4.4.4. Bidirectional Mendelian Randomization Identifies 16 Key Biomarkers with Evidence of Causality to Cardiometabolic Outcomes

To determine which of the colocalized phenotypes might causally influence metabolic outcomes, we conducted MR analyses using these phenotypes individually as exposures against 9 cardiometabolic outcomes. From the 28 colocalized phenotypes, 16 demonstrated evidence consistent with causal effects ($P = 0.05/9 = 5.56 \times 10^{-3}$, correction for 9 cardiometabolic outcomes) on at least one cardiometabolic outcome, suggesting their potential utility as candidate clinical biomarkers.

Gamma glutamyl transferase (GGT) showed particularly strong effects on glucose homeostasis, with substantial impacts on T2DM risk (OR = 0.072, SE = 0.126, $P = 2.13 \times 10^{-97}$), along with effects on blood pressure and LDL cholesterol which were directionally consistent with T2DM. Red blood cell distribution width (RDW) emerged as a crucial biomarker of cardiovascular effects, with remarkably strong associations with both diastolic ($\beta = 0.653$, SE = 0.010, $P < 1.00 \times 10^{-300}$) and systolic blood pressure ($\beta = 1.181$, SE = 0.031, $P < 1.00 \times 10^{-300}$), as well as associations with LDL cholesterol and T2DM. Additionally, 25-hydroxyvitamin D demonstrated effects on T2DM and TG (T2DM: OR = 1.680, SE = 0.151, $P < 6.07 \times 10^{-4}$; TG: $\beta = 0.507$, SE = 0.162, $P < 1.74 \times 10^{-3}$) and total testosterone exhibited significant influence on BMI ($\beta = 0.047$, SE = 0.014, $P < 9.86 \times 10^{-4}$) (Figure 4.6; Appendix C, Supplementary Table 4.5; Supplementary Figures 4.5).

Several other colocalizing phenotypes also demonstrated strong causal effects on metabolic outcomes. Body composition measures showed strong associations with MetS (left arm impedance: $\beta = 0.721$, SE = 0.031, $P = 1.41 \times 10^{-118}$; right arm impedance: $\beta = 0.717$, SE = 0.032, $P = 1.0\ 2 \times 10^{-110}$). Renal function markers, particularly blood urea nitrogen, showed significant associations with MetS and blood pressure. Coffee consumption demonstrated negative associations with both BMI ($\beta = -0.754$, SE = 0.191, $P = 7.83 \times 10^{-5}$) and T2DM risk (OR = 0.223 per SD increase in coffee intake, $P = 1.28 \times 10^{-4}$), consistent with established protective effects of coffee consumption on metabolic outcomes. (Figure 4.6 A; Appendix C, Supplementary Table 4.5; Supplementary Figures 4.5).

To assess bidirectionality, we conducted reverse MR analyses using cardiometabolic traits as exposures against the 28 colocalized candidate phenotypes. After Bonferroni correction for multiple testing ($P = 0.05/28 = 1.79 \times 10^{-3}$), reverse associations were identified across several key biomarker traits. Vitamin D and RDW both demonstrated reverse effects, suggesting complex feedback mechanisms rather than simple unidirectional pathways. Bioelectrical impedance also had noteworthy relationships with BMI and MetS (Appendix C, Supplementary Table 4.6; Supplementary Figures 4.5.4).

4.4.5. Genetic Correlation Analyses Highlight a Cluster of Renal System Markers

To identify opportunities for reducing redundancy among candidate biomarkers, we examined their genetic relationships using LD score regression and hierarchical clustering analyses. Overall, MR analyses prioritised 16 candidate biomarkers associated with metabolic dysfunction. We therefore sought to determine which of these candidates are independent and whether there could be opportunities to remove redundancy. We first conducted LD score regression analyses, which revealed that most candidate biomarkers were genetically independent, with weak or negligible genetic correlations ($|r_g| < 0.15$) (Figure 4.6 B). Hierarchical clustering identified 2 distinct clusters, with 11 candidate markers failing to cluster. This is consistent with substantial genetic independence across most traits (Figure 4.6 C).

Notably, three biomarkers formed a 'renal function cluster' (Cluster 2) consisting of serum creatinine, urinary sodium excretion, and urinary albumin excretion. These markers demonstrated moderate-to-strong genetic correlations, with the strongest correlation observed between creatinine and urinary albumin ($r_g = 0.59$, $P = 8.2\times10^{-117}$), followed by creatinine and urinary sodium ($r_g = 0.56$, $P = 0.023$), and finally urinary sodium and urinary albumin ($r_g = 0.37$, $P = 0.035$). The only other multi-biomarker cluster identified was Cluster 1, comprising bilateral bioimpedance measurements of the left and right arms, which showed near-perfect genetic correlation ($r_g = 0.96$, $P = 5.0\times10^{-239}$), as expected for measurements of the same physiological parameter (Appendix C, Supplementary Table 4.7 and 4.8).

4.4.6. Multivariable Mendelian Randomization Analysis Reveals Independent Causal Effects of Renal Biomarkers

To further explore potential relationships between the 16 candidate biomarkers, we conducted multivariable MR analyses (MVMR). We first conducted exploratory MVMR using all 16 candidates as exposures across 9 cardiometabolic outcomes, but this resulted in very weak instruments ($F<10$). The findings should therefore be treated with caution (Appendix C, Supplementary Table 4.10; Supplementary Figures 4.6).

We then conducted targeted MVMR analyses focused on the 'renal function' cluster we identified in LDSC analyses. Despite the substantial genetic correlations observed, all three renal markers showed independent associations with multiple cardiometabolic outcomes (Figure 6D; Supplementary Table 8). For body mass index, a genetic propensity to higher creatinine levels was associated with lower BMI ($\beta = -0.26$, $P = 3.5\times10^{-23}$), while higher urinary sodium ($\beta = 0.41$, $P = 1.4\times10^{-152}$) and urinary albumin ($\beta = 0.40$, $P = 2.3\times10^{-39}$) were associated with higher BMI (Figure 4.6 D; Appendix C, Supplementary Table 4.9).

Similar patterns of independent effects were observed for blood pressure, with all three markers showing associations with both DBP (creatinine: $\beta = -0.05$, $P = 5.2\times10^{-14}$; urinary sodium: $\beta = 0.03$, $P = 9.1\times10^{-13}$; urinary albumin: $\beta = 0.03$, $P = 1.7\times10^{-51}$) and SBP. For MetS, urinary albumin ($\beta = 0.26$, $P = 0.04$) and urinary sodium ($\beta = 0.14$, $P = 0.03$) were nominally associated. Notably, creatinine and urinary albumin/sodium demonstrated opposing directions of effect on BMI and blood pressure despite their positive genetic correlations, a pattern consistent with the clinical use of urinary albumin-to-creatinine ratio (UACR) as a marker of kidney damage (American Diabetes Association Professional Practice 2025; Tang et al. 2022; Tangri et al. 2025). These results indicate that the renal function markers, despite their genetic correlation, each provide independent and complementary information about cardiometabolic risk, suggesting that composite measures such as ratios may be particularly informative for monitoring metabolic health in people undergoing clozapine treatment.

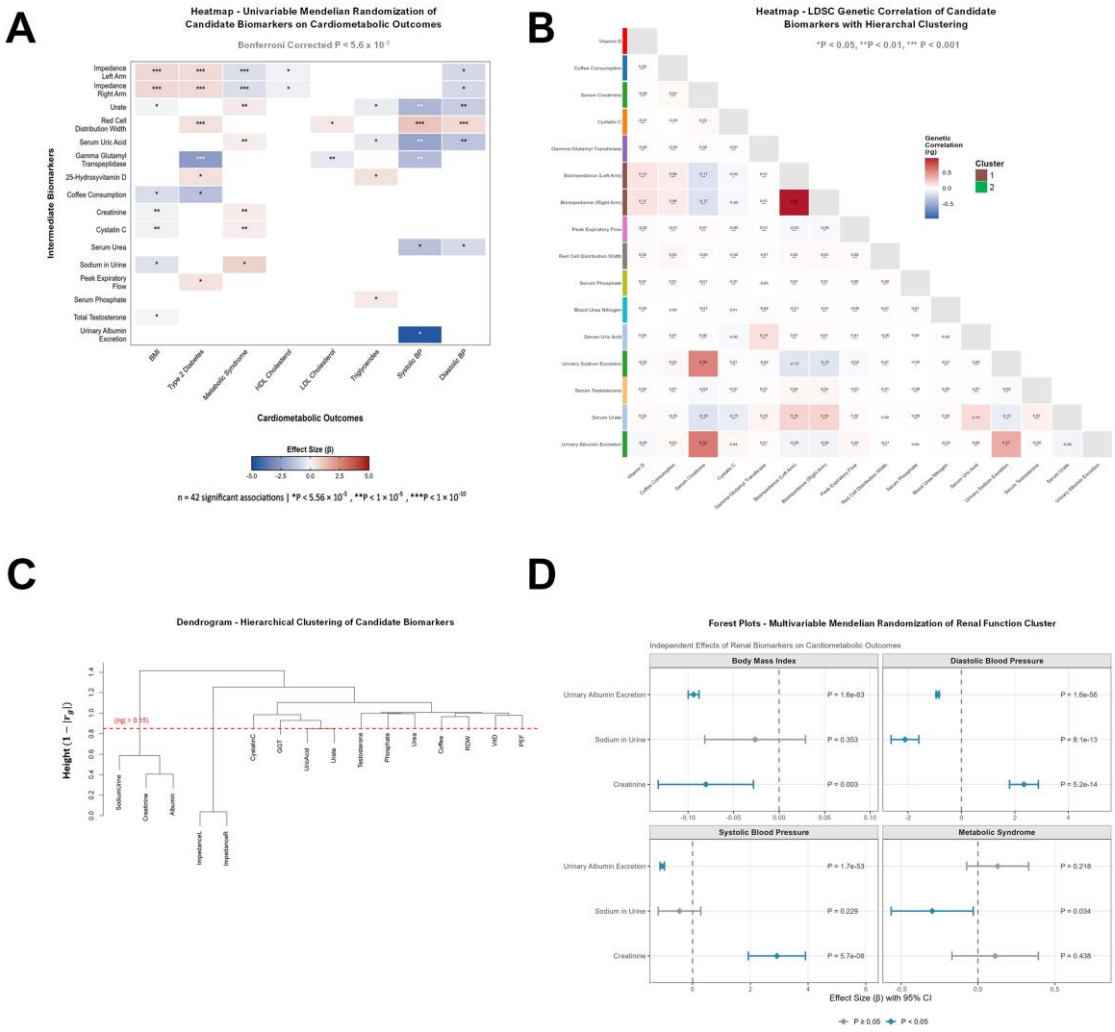


Figure 4.6 - Genetic Architecture and Multivariable Causal Analysis of Biomarkers on Cardiometabolic Outcomes. (A) Heatmap of univariable Mendelian randomization effect estimates for 16 candidate biomarkers across 8 cardiometabolic outcomes. Effect sizes (β) shown with significance indicated by asterisks (*P < 5.56×10^{-3}, **P < 1×10^{-5}, ***P < 1×10^{-10}). Bonferroni-corrected significance threshold: P < 5.56×10^{-3}. (B) Genetic correlations between candidate biomarkers estimated by linkage disequilibrium score regression (LDSC). Genetic correlation coefficients (r_g) indicated by cell colour and significance levels indicated in each cell indicated by asterisks (***P < 0.001, **P < 0.01, *P < 0.05). Biomarkers ordered by hierarchical clustering (complete linkage, distance = 1 - $|r_g|$, height threshold = 0.85) (C) Hierarchical clustering dendrogram of 16 candidate biomarkers based on genetic correlation distance (1 - $|r_g|$). (D) Forest plots showing multivariable Mendelian randomization results for Cluster 3 renal biomarkers against key cardiometabolic outcomes. Effect estimates (β) with 95% confidence intervals shown. Blue markers indicate P < 0.05 and grey markers indicate P > 0.05. Each biomarker shows independent causal effects despite genetic correlation.

4.5. Discussion

This study presented a comprehensive genetic investigation of clozapine-induced metabolic dysfunction using established genetic epidemiological methods. We systematically investigated the complex relationships between clozapine plasma traits and cardiometabolic outcomes, identifying evidence of causal relationships and 16 candidate biomarkers potentially useful for identifying patients at risk of clozapine-induced metabolic dysfunction.

This study has addressed methodological challenges that limit research into clozapine-induced metabolic dysfunction. Traditional approaches to identifying biomarkers of cardiometabolic risk in clozapine-treated patients face significant constraints due to the relatively small population receiving this medication, polypharmacy, and inconsistent treatment timelines complicating longitudinal studies. Furthermore, existing studies have established only correlational relationships that cannot definitively determine whether changes in biomarkers precede metabolic disturbance or represent consequences of existing dysfunction. To circumvent these limitations, we leveraged genetic loci robustly associated with clozapine plasma levels, which enabled us to utilize GWAS summary data from the general population to establish potential causal relationships and identify candidate biomarkers. Our approach is inherently exploratory and hypothesis-generating, applying established methods to identify candidate biomarkers that require prospective validation in clinical cohorts before translation to practice.

4.5.1. Evidence of Causal Effects

Our analysis revealed strong evidence for causal effects of clozapine plasma levels on T2D (OR=1.62, $P=5.05\times10^{-41}$), while a nominal protective association with MetS (OR=0.99, P=0.030) did not survive multiple testing correction. This paradox requires careful interpretation. First, the MetS effect size is extremely small (OR=0.99) and unlikely to represent a clinically meaningful protective effect. Second, this pattern could reflect collider bias: MetS is diagnosed based on clustering of multiple risk factors including diabetes. Because clozapine has strong effects on T2DM (one component of MetS) but potentially weaker or null effects on other components, the composite MetS outcome may produce spurious associations that don't reflect the true causal effect on MetS as a whole. In statistical terms, analysing a composite outcome when the exposure has heterogeneous effects on its components can induce bias. Third, while MR-Egger intercept testing did not detect significant directional pleiotropy (P=0.250), the association was attenuated and lost significance in weighted median analysis

(P=0.80), suggesting it may not represent a genuine causal effect. Therefore, the nominal MetS association should not be considered evidence of a true protective effect. The strong T2D association likely reflects the effect of clozapine through well-established diabetogenic mechanisms including insulin resistance and impaired glucose metabolism.

The analysis of plasma clozapine, norclozapine and their ratio revealed metabolite-specific effects on metabolic outcomes (Newcomer 2005). While primary IVW analysis for norclozapine showed non-significant associations with BMI and metabolic outcomes, sensitivity analyses revealed significant negative associations with LDL cholesterol and TG, contrasting with positive effects observed for clozapine plasma. These opposing directions between parent compound and metabolite align with pharmacological precedence where metabolites possess distinct biological activity. For instance, acetaldehyde rather than alcohol itself appears to drive cancer associations (Salaspuro 2011; Seitz & Stickel 2010). The clozapine-norclozapine ratio analyses revealed significant associations with diastolic blood pressure and T2DM, with a nominally significant association with MetS that showed evidence of pleiotropy and did not survive correction for multiple testing. This potentially suggests that relative concentrations of parent compound and metabolite have distinct cardiovascular implications.

These genetic findings partially align with clinical meta-analysis data showing positive correlations between clozapine serum levels and TG and norclozapine levels with both TG and total cholesterol (Tan et al. 2021). However, the opposing genetic effects between clozapine and norclozapine on lipid metabolism suggest complex regulatory mechanisms that may not be captured in observational clinical correlations (Brooks, Goldman & Li 2009; Seitz & Stickel 2010).

4.5.2. Downstream Effects of Clozapine Metabolising Loci

PheWAS-colocalization-MR analyses revealed a network of biological pathways that provided a detailed genetic picture regarding clozapine's influences on metabolic outcomes. The identification of these candidate biomarkers is key, as it helps establish a hierarchical organization of metabolic effects, moving beyond simple correlations.

Body composition measures serve as positive controls that validate our primary findings rather than representing independent biomarkers. Bioelectrical impedance measurements showed consistent effects across both arms, which is strongly supported by reverse MR showing

evidence that BMI and MetS causally influence impedance measurements. These findings confirm the expected relationships between clozapine exposure and body composition changes. The strong association demonstrating higher RDW and increased blood pressure indicated that haematological changes may potentially play a role in clozapine's cardiovascular effects (Leung et al. 2023). However, reverse MR analyses revealed significant reverse relationships with TG and MetS, suggesting complex feedback loops rather than simple unidirectional relationships. Similarly, GGT's impact on glucose homeostasis is clinically significant as GGT elevation indicates hepatic toxicity, which may be related to inflammatory processes (Thakur et al. 2024).

The effects of 25-hydroxyvitamin D on T2DM and TG revealed vitamin D pathways' role in energy regulation during clozapine treatment, though bidirectional analyses showed some reverse causation, indicating complex vitamin D-metabolic feedback mechanisms. Higher total testosterone associated with lower BMI demonstrated that endocrine disruption represents a potential mechanism, with reverse MR confirming bidirectional testosterone-metabolic relationships. This finding has important clinical implications as males have been reported to be more likely to develop metabolic abnormalities such as high cholesterol or TG, HT, and cardiovascular risk (Alberich et al. 2019). This suggests sex-specific biomarker profiles may be clinically useful for risk stratification.

Notably, many of the excretory traits identified in the analyses demonstrated significant associations with blood pressure parameters. Markers of renal function such as urinary albumin excretion, serum urea, and creatinine all showed robust associations with both systolic and diastolic blood pressure. This pattern is biologically plausible given the fundamental role of excretory systems, particularly the kidneys, in blood pressure homeostasis through regulation of fluid volume and electrolyte balance (Suzumoto et al. 2023). However, these findings warrant further investigation as they contradict the typical understanding derived from observational studies that increased urate, uric acid, and urea, lead to increased blood pressure (Lanaspa, Andres-Hernando & Kuwabara 2020; Sanchez-Lozada et al. 2020; Sedaghat et al. 2014). This apparent contradiction highlights a distinction between observational correlations and causal inference. While observational studies consistently demonstrate that people with high blood pressure tend to have elevated uric acid and urea levels, our MR analyses suggest these associations may not reflect causal relationships (Lanaspa, Andres-Hernando & Kuwabara 2020; Sanchez-Lozada et al. 2020; Sedaghat et al. 2014). Instead, this could represent compensatory physiological responses to existing blood pressure dysfunction rather than causal drivers of HT. This pattern of contradictory findings is well-documented in genetic epidemiology, exemplified by studies of C-reactive protein and SCZ where observational

associations do not align with causal estimates from genetic instruments (Prins et al. 2016; Wang, Z et al. 2017). These discrepancies underscore the value of MR in distinguishing candidate causal estimates from confounded observational associations (Sanderson et al. 2022).

LD score regression demonstrated that most biomarkers were genetically independent, with only three forming a coherent renal function cluster characterized by moderate-to-strong genetic correlations. This genetic clustering provided strong justification for focused multivariable MR analysis of these markers, as their shared genetic architecture necessitates joint modelling to obtain valid estimates of independent causal effects. Importantly, this data-driven clustering approach addresses potential concerns about selective biomarker inclusion. The naive MVMR sensitivity analysis, while expected to suffer from weak instrument bias when including all 16 biomarkers simultaneously, provides potential validation: the renal markers retained very small p-values, while other biomarkers showed substantial attenuation. This differential behaviour strongly suggests that the Cluster 2 findings reflect true causal effects rather than statistical artifacts or selective reporting. Moreover, the genetic architecture revealed by LDSC analysis justified our focused approach over exploratory inclusion of all biomarkers.

By identifying these specific biological pathways, our analysis has provided clarity regarding the potential mechanisms of clozapine-induced metabolic dysfunction. This disentanglement not only advances the theoretical understanding but has potential implications for clinical monitoring and intervention strategies, allowing for more targeted approaches in managing cardiometabolic risks in clozapine-treated patients.

4.5.3. Clinical Implications and Future Directions

The identified candidate biomarkers offer potential tools for risk stratification and early intervention, but translation to clinical practice requires extensive validation. Prospective studies in cohorts of TRS patients initiating clozapine treatment are essential to determine whether these candidate biomarkers can accurately predict metabolic disturbances and, crucially, whether monitoring these biomarkers leads to improved clinical outcomes through early intervention.

The strong associations between liver function markers and metabolic outcomes suggest that enhanced monitoring protocols focusing on GGT and other hepatic markers could enable earlier intervention, though this hypothesis requires clinical validation. Similarly, endocrine and

nutritional assessment, particularly vitamin D and testosterone levels, represents a candidate approach for targeted supplementation strategies that requires testing in clinical trials (Hypponen & Boucher 2018). The identification of excretory system markers as potential mediators of blood pressure effects suggests value in monitoring renal function parameters, though the clinical utility remains to be established.

The opposing causal effects observed for genetically correlated renal markers in MVMR analyses suggest that composite measures may provide more informative risk assessment than individual biomarkers considered in isolation. Specifically, the UACR, an established clinical marker of kidney damage in diabetes and chronic kidney disease (American Diabetes Association Professional Practice 2025; Tang et al. 2022; Tangri et al. 2025), exemplifies how ratios can capture meaningful pathophysiological relationships that individual components cannot reveal independently. Our findings that creatinine associates with lower BMI while urinary albumin and sodium associate with higher BMI, despite their positive genetic correlations, parallel the clinical observation that UACR integrates information about both glomerular filtration and tubular damage. This pattern suggests that monitoring composite renal measures, rather than relying on any single marker, may enable more nuanced assessment of clozapine-induced cardiometabolic risk. Future validation studies should therefore evaluate whether ratios such as UACR, or novel composite measures derived from these genetically correlated markers, provide superior predictive performance compared to individual biomarkers for identifying patients at risk of metabolic dysfunction during clozapine treatment.

These findings also suggest potential for patient stratification prior to clozapine initiation that requires further investigation. Genetic testing for variants in the *CYP1A2* region, particularly rs2472297 which has demonstrated the strongest and most widespread associations with metabolic traits in our analyses, could potentially identify patients predisposed to altered clozapine metabolism and higher metabolic risk before treatment begins (Doude van Troostwijk et al. 2003; Mihara et al. 2000; Viikki et al. 2014). However, the limited SNP-based heritability of several key biomarkers (h^2 range: 0.05–0.49; Supplementary Table 8) suggests that genetic prediction alone may have modest clinical utility, particularly for urinary markers like albumin excretion ($h^2 = 0.08$) and sodium ($h^2 = 0.10$) where direct biomarker measurement is likely more informative for risk stratification. The clinical value of genetic testing would need to be demonstrated through studies showing that genetic information leads to improved outcomes through more intensive monitoring or early co-administration of protective medications such as metformin or GLP-1 antagonists for high-risk patients (Per et al. 2025). This pharmacogenomic approach could be supplemented by screening of key clozapine

metabolizing genes to identify rare loss-of-function variants, though the clinical utility remains to be established (Zhou & Lauschke 2022).

Several high-priority research areas have emerged from these findings. Large-scale pharmacogenetic studies focusing specifically on clozapine metabolism are needed to better characterize metabolite-specific effects and strengthen genetic instruments. These studies should particularly focus on understanding the mechanisms underlying the paradoxical effects on T2DM versus overall MetS. Functional studies exploring the biological interactions between clozapine plasma traits and the candidate biomarkers could provide valuable insights into the mechanisms of metabolic dysfunction.

Most critically, prospective clinical validation studies are needed to determine whether the identified genetic variants and candidate biomarkers can predict metabolic dysfunction in real-world clinical settings and whether this information can guide interventions that improve patient outcomes. Such studies should evaluate the incremental value of genetic and biomarker information beyond standard clinical risk factors.

By targeting specific biological pathways and leveraging candidate biomarkers, clinicians could potentially identify at-risk patients earlier and implement pathway-specific interventions before significant metabolic dysfunction occurs, though this approach requires clinical validation. This represents a potential advancement over current monitoring protocols, which primarily focus on detecting complications after they have developed, leading to potential safer prescribing of clozapine.

4.5.4. Strengths and Limitations

One of the difficulties in studying clozapine-induced metabolic effects is confounding by clinical variables like medication adherence, dosage variation, polypharmacy, and treatment duration. However, our MR approach minimizes these issues because the outcome datasets were derived from generally healthy populations, allowing isolation of genetic effects from treatment-related confounders (Khasawneh, Al-Mahayri & Ali 2022; Pierce, Ahsan & Vanderweele 2011). While MR-Egger regression and other sensitivity analyses suggested minimal directional pleiotropy, residual horizontal pleiotropy remains a potential limitation, particularly for analyses with fewer genetic instruments. This concern is heightened given that genetic variants in cytochrome P450 genes (particularly *CYP1A2*) index broad pharmacokinetic pathways affecting multiple medications and endogenous compounds beyond clozapine,

meaning observed associations may partially reflect these broader metabolic effects rather than exclusively clozapine-specific mechanisms. Additionally, the focus on European ancestry populations due to data availability limits generalizability across diverse ancestral groups. Genetic architecture and metabolic responses to clozapine may differ across populations (Ju et al. 2022).

These considerations should be viewed within the context of the study's overall methodological robustness and the convergent evidence observed across multiple analytical approaches, which collectively strengthen confidence in the suggested possible causal pathways while acknowledging the inherent limitations of genetic epidemiological methods in fully characterizing complex pharmacological relationships.

4.6. Conclusions

This study employed a comprehensive genetic epidemiological approach to identify candidate biomarkers for clozapine-induced metabolic dysfunction, leveraging the strengths of MR to overcome confounding inherent in observational studies of clozapine-treated populations. Our findings indicate that genetically predicted higher plasma clozapine levels and clozapine-norclozapine ratio are associated with increased risk of T2DM and elevated blood pressure, supporting a causal role for clozapine pharmacokinetics in metabolic dysfunction. Through phenome-wide scanning, colocalization, and subsequent MR analyses, we identified 16 candidate biomarkers spanning hepatic, renal, haematological, and endocrine systems that show evidence of associations with cardiometabolic outcomes. Notably, genetic correlation analyses revealed substantial independence among most candidate biomarkers, apart from a renal function cluster comprising creatinine, urinary sodium, and urinary albumin. MVMR demonstrated that these renal markers exert independent causal effects on metabolic outcomes despite their genetic correlations, suggesting that composite measures such as urinary albumin-to-creatinine ratio may provide superior risk assessment. While these findings require extensive clinical validation before implementation, they provide a rational foundation for developing biomarker-guided monitoring strategies that could enable earlier identification and intervention for patients at high risk of clozapine-induced metabolic complications, potentially improving the benefit-risk profile of this essential medication for TRS.

CHAPTER 5 - GENERAL DISCUSSION

5.1. Integration of Findings from Systematic Review and Genomic Investigation

This thesis employed a two-stage approach to investigate the genetic associations between clozapine use in TRS and cardiometabolic dysfunction. The systematic review (Chapter 3) identified critical knowledge and methodological gaps in the current literature, which subsequently guided the design and implementation of the genetic epidemiological investigation (Chapter 4). This integrated approach has yielded several complementary insights that collectively advance the understanding of clozapine-induced metabolic dysfunction.

The systematic review revealed extensive shared genetic architecture between PDs and metabolic traits, with key biological pathways including lipid metabolism, glucose homeostasis, and inflammatory processes (Cheon 2023; Liao, Y et al. 2024a; Perry et al. 2022b; Valles & Barrantes 2022; Zorkina et al. 2024). Particularly noteworthy was the identification of AIWG as having a more specific genetic basis compared to broader PD-related MetS. This finding provided a critical foundation for the investigation of clozapine, suggesting that medication-specific effects could be separated from those attributable to the core disorder with appropriate methodological considerations (Arranz et al. 2019; Brandl et al. 2016; MacNeil & Muller 2016; Sullivan & Geschwind 2019; Zhang, JP, Lencz & Malhotra 2010).

Building on this foundation, the investigation employed a multi-layered approach integrating MR, PheWAS, and colocalization techniques to examine the potential causal relationships between clozapine plasma levels and cardiometabolic outcomes (Bastarache, Denny & Roden 2022; Denny, Bastarache & Roden 2016; Emdin, Khera & Kathiresan 2017; Giambartolomei et al. 2014; Stacey et al. 2022). This methodological framework directly addressed the knowledge gap identified in the systematic review regarding the need for more sophisticated approaches to disentangle medication-specific effects from disease-related factors (Burgess et al. 2019; Stacey et al. 2022). The findings from this integrated approach represent a significant advancement in pharmacogenomics, particularly in understanding drug-gene interactions in psychiatric medications. Unlike traditional pharmacogenomic studies that focus on single drug-gene relationships, this work has demonstrated the multi-pathway nature of medication effects where observable outcomes represent only a fraction of the underlying biological complexity. This has broader implications for precision psychiatry, suggesting that effective personalized approaches should require integration of multiple biological systems rather than the over-reliance on single genetic markers (Sharew et al. 2024).

The results presented in Chapter 4 has revealed several key findings: **(1)** Metabolite-specific effects: The MR analyses demonstrated distinct effects of clozapine plasma levels versus the clozapine-norclozapine ratio on cardiometabolic outcomes. This metabolite specificity extends beyond the general concepts of antipsychotic-induced metabolic effects identified in the systematic review, providing a deeper understanding of the metabolic impact of clozapine; **(2)** Paradoxical metabolic effects: The finding of increased T2D risk but decreased MetS risk represents one of the most intriguing results of this work. This apparent paradox aligns with evidence that clozapine-induced glucose dysregulation occurs independently of weight gain and other metabolic parameters, suggesting direct glucotoxicity effects through distinct pharmacological mechanisms (Koller & Doraiswamy 2002; Yuen et al. 2021). Temporal dynamics may also contribute, with hyperglycaemia sometimes preceding other metabolic changes (Newcomer 2005). While the genetic approach provides evidence for these differential effects, the biological mechanisms underlying this paradox remain speculative and represent a critical area for future functional studies. This finding challenges the conventional understanding of MetS as a unified syndrome and suggests that monitoring strategies for clozapine-treated patients may need to move beyond traditional MetS frameworks to capture medication-specific metabolic risks (Carlsson et al. 2009; Kassi et al. 2011; Shen et al. 2003); and **(3)** Potential biological pathways: The identification of 16 biomarkers linked to clozapine plasma levels with strong evidence of causality to cardiometabolic outcomes has provided specific biological mechanisms that could potentially be impacted by clozapine use. These findings extend the broader biological pathways identified in the systematic review, offering more detailed insights into the potential molecular mechanisms surrounding clozapine specifically.

The integration of findings across both studies has demonstrated a progression from identifying patterns of genetic overlap between PDs and metabolic traits to elucidation of specific causal mechanisms linking clozapine plasma levels to cardiometabolic outcomes. This progression has highlighted the value of the two-stage study pipeline, where review findings identifying the knowledge and methodological gaps guided the design of the subsequent study.

5.2. Methodological Strengths and Limitations

The primary methodological strength lies in the complementary nature of the two studies. The systematic review provided a comprehensive assessment of the current literature, identifying knowledge gaps and methodological limitations that informed the design of the subsequent investigation. This approach ensured that the genomic study directly addressed some limitations in previous research, particularly the challenge of distinguishing medication-specific effects from those related to the underlying disorder. This was done by ensuring that there was no significant overlap between the genetic variants used as instruments from the clozapine datasets and a SCZ dataset (Table 4.4; Figure 4.3).

The analytical pipeline used represents a methodological innovation in pharmacogenomic research. By integrating MR, PheWAS, and colocalization techniques, this approach overcame several limitations of traditional observational studies, including confounding, reverse causation, and false associations due to LD. The combination of these methods allowed for both the assessment of potential causal relationships and the identification of potential biomarkers. Thus, providing a more comprehensive understanding than would be possible through any single method alone. The bidirectional MR analyses further strengthened causal inference by examining potential reverse causation. The finding of minimal evidence for reverse causation increases confidence in the primary causal direction from clozapine metabolism to metabolic outcomes. Additionally, the use of multiple sensitivity analyses, including MR-Egger regression, weighted median estimation, and heterogeneity assessment, provided a robust evaluation of potential biases in the MR analyses. The colocalization step was particularly valuable in distinguishing true shared genetic effects from those caused by LD. This refinement represented a significant advance over approaches that rely solely on genetic correlation or PheWAS without addressing the effects of LD.

Despite the strengths, several methodological limitations must be acknowledged, with varying degrees of impact on the validity and generalizability of the findings of this work. The predominance of European ancestry populations in both the systematic review and genomic investigation represents a fundamental limitation affecting global applicability of these findings. This constraint is multifaceted: genetic architecture of both clozapine metabolism and metabolic traits shows substantial variation across populations, with *CYP2D6* poor metaboliser phenotypes ranging from 1% in East Asians to 7-10% in Europeans. The systematic review revealed population-specific patterns, with European populations showing positive correlations between SCZ and inflammatory markers while East Asian populations demonstrated negative

correlations (Aoki et al. 2022). Furthermore, allele frequencies for clozapine-metabolizing variants differ markedly across ancestries, and the CLOZUK2 dataset lacks representation from non-European populations which may have distinct pharmacogenomic profiles. This limitation is particularly concerning given higher clozapine prescribing rates in certain non-European countries and documented ethnic differences in both clozapine dosing requirements and metabolic risk profiles. The reliance on exclusively European datasets may not capture population-specific genetic variants or gene-gene interactions relevant to clozapine metabolism in other ancestries (Martin et al. 2019; Smith, GD & Ebrahim 2004; VanderWeele et al. 2014).

While the MR approach provided strengths in causal inference, it relied on several key assumptions that may not be fully satisfied (Sanderson et al. 2022). Although sensitivity analyses suggested minimal directional pleiotropy for most analyses, residual horizontal pleiotropy remains a potential concern, particularly for analyses with fewer genetic instruments (Verbanck et al. 2018). The validity of MR findings also depends on the strength of genetic instruments, which varied across analyses, although these were above the widely accepted threshold for reliable causal inference (Pierce, Ahsan & Vanderweele 2011). Two additional limitations warrant consideration: the identification of intermediate phenotypes through the PheWAS-colocalization-MR pipeline, while methodologically robust, does not establish that these phenotypes necessarily mediate the relationship between clozapine plasma traits and cardiometabolic outcomes. The traits that made it through the entire pipeline represent strong candidate mediators but until tested independently, the observed associations could represent parallel pathways. Finally, the reliance on existing GWAS datasets, particularly the relatively modest sample size of the CLOZUK2 dataset (n = 4,495) compared to outcome datasets, potentially limited statistical power and may not capture all relevant biological pathways, particularly those specific to non-European populations (Pierce, Ahsan & Vanderweele 2011; VanderWeele et al. 2014). Despite these limitations, the research has addressed fundamental methodological challenges that have typically limited research in this field. Leveraging of genetic loci robustly associated with clozapine plasma enabled the utilization GWAS summary data from the general population.

The multi-layered analytical approach employed in this thesis, while methodologically robust, represents one of several possible strategies for investigating pharmacogenomic relationships. The sequential usage of MR, PheWAS, colocalization, and targeted MR first inferred causal relationships between clozapine and cardiometabolic traits, then identified a collection of biomarkers potentially implicated in the relationship. These biomarkers were then pruned

through colocalization and targeted MR with cardiometabolic traits as outcomes. Despite this providing robust identification of biomarkers, different analytical approaches may have expanded phenotype discovery. For instance, beginning with comprehensive PheWAS expanding from the loci selected (Table 4.3), followed by colocalization, and then applying MR to both direct and potential indirect pathways. This approach might have identified additional biomarkers but would have substantially increased multiple testing burden and computational requirements. The chosen approach prioritized statistical power and interpretability over extensive phenotype discovery.

The exclusive focus on genetic variants could have potentially overlooked epigenetic modifications that may significantly influence clozapine metabolism and metabolic outcomes. DNA methylation patterns, particularly in *CYP1A2* and related metabolic genes can vary with age, environmental exposures, and disease states (Habano et al. 2015). The addition of epigenetic data might have provided additional insights and explained some of the residual variation in metabolic outcomes. While the MR approach minimizes the potential effects of confounding, it potentially overlooks important gene-environment interactions that could modify the relationships identified. For example, smoking status significantly affects *CYP1A2* activity and could modify the genetic effects on clozapine metabolism. Coffee consumption, dietary factors, and co-medications represent additional environmental modulators that could interact with genetic variants to influence outcomes (Gee et al. 2017; Wagner et al. 2020). Additionally, the cross-sectional nature of GWAS data obscures the temporal relationships between genetic effects, metabolic changes, and clinical outcomes. Longitudinal genetic analysis, while methodologically complex, might reveal that genetic effects on metabolism vary over treatment duration or interact with treatment adherence patterns.

While Bonferroni correction was applied throughout the MR analyses, this approach can be overly conservative and may have reduced sensitivity to detect genuine associations (García-Pérez 2023; Perneger 1998). Alternative approaches such as cFDR correction or empirical Bayes methods might have identified additional significant relationships while maintaining appropriate Type I error control (Greenland & Robins 1991; Smeland et al. 2020). The interpretation of effect sizes in MR studies requires careful consideration of the biological meaning of genetic associations. While statistically significant, some of the identified effects may represent associations that, while causally valid, have limited clinical significance at the individual patient level. The translation from population-level genetic effects to individual clinical decision-making requires additional validation studies.

5.3. Clinical Implications and Translational Potential

The findings from this thesis have several significant clinical implications that could potentially inform the future monitoring and management of clozapine-induced metabolic dysfunction in patients with TRS.

A key clinical implication is the potential for more targeted monitoring strategies based on the identified metabolite-specific effects. The evidence that clozapine plasma levels and the clozapine-norclozapine ratio have distinct and sometimes opposing effects on cardiometabolic outcomes suggests that monitoring both parameters could provide more robust risk assessment (Costa-Dookhan et al. 2020; de Leon & Diaz 2003; Dufresne & Ellison 2015; Lally et al. 2013; Rajkumar et al. 2017). Recent advances in therapeutic drug monitoring have emphasized the importance of metabolite ratios in optimizing psychopharmacological treatment. The finding of increased T2DM risk but decreased MetS risk has important implications. It suggests that clinicians should invest specific attention to markers of glucose metabolism regardless of their MetS classification (Kassi et al. 2011; Konuthula, Tan & Burnet 2023; Oda 2012). This distinction could help identify at-risk patients who might otherwise be overlooked in conventional monitoring protocols. This finding also raises important questions about whether alternative explanations, such as differential medication adherence or lifestyle factors among patients who develop MetS versus T2DM, might contribute to the observed paradox.

The identified biomarkers represent candidates for validation in future monitoring studies. Current monitoring guidelines for patients taking clozapine focus primarily on detecting complications after they've developed. The findings suggest potential for an expanded monitoring protocol that incorporates biomarkers provided that adequate validation research is undertaken to confirm these biomarker's utility as intervention points: **(1)** Liver function markers: The strong association between GGT and metabolic outcomes, particularly T2DM, suggests that routine liver function monitoring could be leveraged for risk assessment (Fraser et al. 2007; Koenig & Seneff 2015; Kunutsor, Apekey & Seddoh 2015); **(2)** Haematological parameters: The strong association between RDW and DBP/SBP indicates that this routinely collected parameter could be used for cardiovascular risk stratification; **(3)** Nutritional and endocrine assessment: The identification of 25-hydroxyvitamin D and total testosterone as potential mediators suggests value in monitoring these parameters, with potential for targeted supplementation strategies in patients who are deficient (Lally et al. 2016; Leucht et al. 2013); and **(4)** Renal markers: The association between renal function markers and metabolic outcomes

demonstrates the importance of monitoring urinary biomarkers such as albumin and creatinine for cardiovascular risk assessment (Figure 5.1) (Mitchell et al. 2013; Solmi et al. 2017).

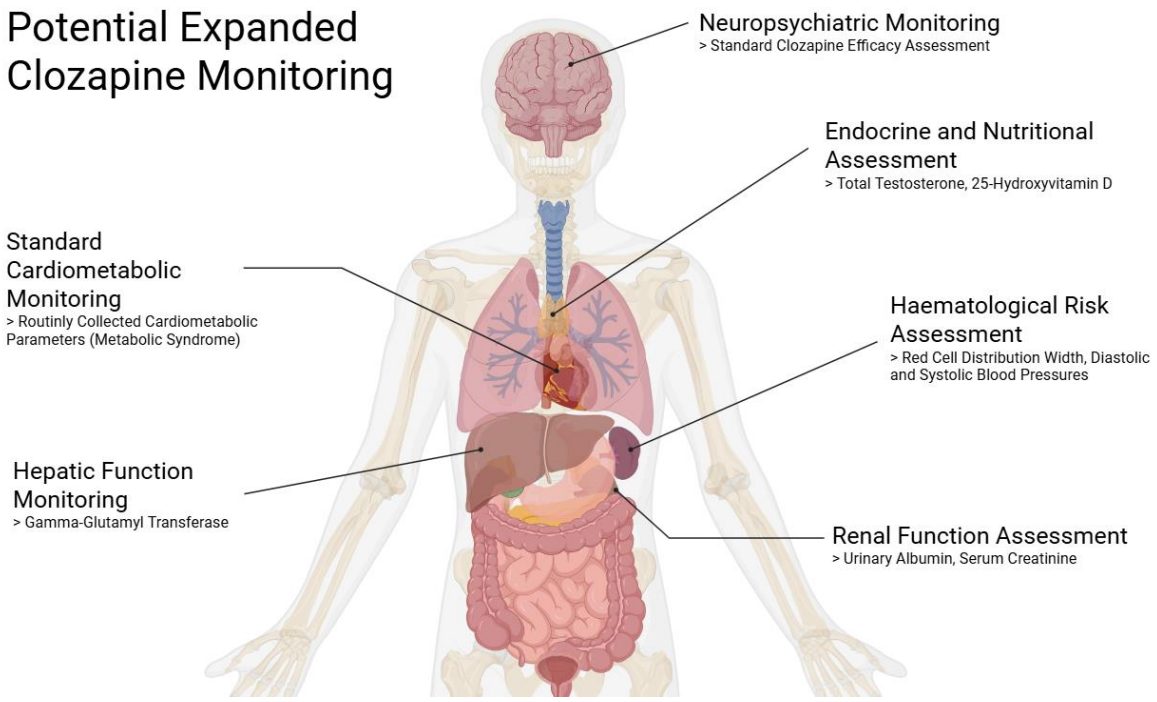


Figure 5.1 - Potential Expanded Clozapine Monitoring Protocol.

Illustration of potential biomarker-based monitoring strategies beyond standard cardiometabolic surveillance. Key additions include hepatic function monitoring (GGT for metabolic risk), haematological assessment (RDW for cardiovascular risk), endocrine/nutritional evaluation (testosterone, 25-hydroxyvitamin D for targeted supplementation), and renal function assessment (albumin, creatinine for cardiovascular stratification). Functional validation research is required before theses biomarkers are fit for clinical use. Figure generated with BioRender.com.

Beyond enhanced monitoring, the findings support the potential for patient stratification prior to clozapine initiation. Genetic testing for variants in the *CYP1A2* region, could identify patients predisposed to altered clozapine metabolism and higher metabolic risk before treatment begins. This pharmacogenomic approach could inform personalized monitoring schedules and early intervention for high-risk patients (Ghotbi et al. 2007; Spina & de Leon 2015).

Several additional considerations merit attention in clinical translation. Firstly, the ethical implications of genetic testing in psychiatric populations require careful consideration, particularly regarding informed consent and potential for genetic discrimination. Secondly, the findings' specificity of the findings to clozapine raises questions about generalizability to other understanding whether similar metabolite-specific effects exist for other antipsychotics could inform broader precision psychiatry approaches. Thirdly, the economic implications extend

beyond monitoring costs to include potential healthcare savings from preventing severe metabolic complications, which could be substantial healthcare costs associated with TRS and ongoing management of cardiometabolic effects.

Despite these promising implications, several challenges must be addressed to translate these findings into clinical practice. Firstly, the implementation of expanded monitoring protocols must balance comprehensiveness with feasibility and cost. While comprehensive metabolic monitoring guidelines exist for clozapine, there is limited literature on expanded biomarker panels beyond standard cardiometabolic parameters. Secondly, the clinical utility of the identified biomarkers requires validation in future studies. While the genetic evidence provides support for causal relationships, the predictive value of these biomarkers for individual patients needs to be established in diverse clinical populations. Thirdly, the development of potential clinical tools integrating genetic information with biomarker data would be necessary to make these findings accessible to clinicians which could be feasible using machine learning techniques (Cearns et al. 2022). Finally, the potential benefits of enhanced monitoring and personalized approaches must be balanced against maintaining access to clozapine for all patients who could benefit. Overly burdensome monitoring requirements could create additional barriers to clozapine prescription, potentially denying patients access to what remains the most effective treatment for TRS (Clark et al. 2025).

Despite these challenges, the findings present potential for a more nuanced approach to managing clozapine. Clinicians could potentially identify at-risk patients earlier and implement targeted treatment and monitoring before significant metabolic dysfunction occurs, ultimately improving long-term physical health outcomes in this vulnerable population. Progressing to this approach from the current practice will require much greater expansion of our current understanding through future research.

5.4. Future Research Directions

This thesis identified several critical research priorities that could shape future translational impact.

The most urgent priority is functional validation of the identified biological mechanisms. Future studies should investigate how genetic variants in the identified regions affect clozapine metabolism and downstream metabolic outcomes. Particular attention should be paid to understanding the mechanisms underlying the paradoxical effects on T2DM versus overall

MetS, as well as the specific biological interactions between clozapine metabolism and the identified candidate phenotypes. Simultaneously, validation studies in prospective clinical cohorts are essential to confirm whether monitoring the identified biomarkers could improve early detection and management of clozapine-induced metabolic complications in a real-world setting.

Expansion to diverse ethnic populations represents a critical medium-term priority, given that current findings are limited to European ancestry populations. These studies should actively recruit participants from diverse ancestral backgrounds to identify population-specific genetic factors and validate current findings across different genetic contexts (Lynch & Ho 2020; Omeranovic et al. 2025). Large-scale pharmacogenetic studies focusing specifically on clozapine should be conducted, collecting comprehensive data on clozapine and norclozapine levels, detailed metabolic monitoring, and genetic information (Hong & Park 2012). Longitudinal designs would be particularly valuable for examining relationships between genetic factors, drug metabolism, and development of metabolic complications. During this timeframe, predictive model development should also be prioritized, integrating genetic information, baseline clinical characteristics, biomarker data, and treatment parameters using machine learning approaches to identify complex patterns and interactions.

The ultimate goal involves translating findings into routine clinical practice. This includes cost-effectiveness analyses of expanded monitoring protocols, development of clinical decision support tools, and large-scale intervention trials testing pathway-specific treatments. Investigation of intervention strategies targeting identified biological pathways could move beyond risk prediction to active management. Additionally, comparative studies with other SGA would determine whether similar metabolite-specific effects exist more broadly, informing comprehensive precision psychiatry approaches in the treatment of SCZ (Martin et al. 2019; Smith, GD & Ebrahim 2004). Finally, the integration of machine learning frameworks that can integrate genetic, clinical, environmental, and treatment response data further could push clozapine prescription towards a truly personalized approach. Machine learning algorithms might identify complex interaction patterns that are not apparent through traditional statistical approaches. Predictive models incorporating genetic, biomarker, and clinical data might improve risk stratification accuracy beyond what is achievable through individual markers. Such models could enable more precise individualization of treatment approaches, greatly contributing to the precision-medicine approach.

5.5. Positioning Within the Broader Research Landscape

This thesis has addressed several critical gaps in the psychiatric pharmacogenomics literature while advancing methodological approaches that have broader implications for precision psychiatry research.

The field of psychiatric pharmacogenomics is typically challenged with disentangling medication-induced effects from those attributable to underlying PDs. While extensive research has documented shared genetic architecture between PDs and metabolic traits, relatively few studies have focused specifically on medication-induced effects. This thesis has directly addressed this gap by focusing specifically on clozapine metabolism, thereby isolating medication-specific genetic factors from broader PD-related metabolic associations.

Previous research in this area had relied predominantly on genetic correlation analyses and observational studies, which cannot establish causality. The systematic review identified this as a major limitation, with most studies unable to distinguish between direct causal effects and shared genetic risk factors. This work has circumnavigated this by employing the multilayered genetic epidemiological pipeline, leveraging genetic loci robustly associated with clozapine plasma levels. This enabled utilization of GWAS summary data from the general population to establish potential causal relationships and identify candidate biomarkers for metabolic disturbance. This represents one of the first comprehensive applications of these integrated genetic methods to psychiatric pharmacogenomics.

Despite clozapine being the gold-standard treatment for TRS and having the highest risk of metabolic complications among the SGAs, dedicated genetic research on clozapine-induced metabolic effects has been limited to date. The systematic review identified few studies specifically examining AIWG genetics, with most focusing on broader antipsychotic classes rather than clozapine specifically. Current approaches in managing clozapine-induced cardiometabolic complications are predominantly reactive, focusing on management of the adverse effects after they have developed. This thesis has provided the scientific foundation for a shift toward predictive, personalized approaches by identifying genetic factors and biomarkers that could enable early risk stratification and targeted intervention. The identification of 16 biomarkers across diverse biological systems represents a significant advancement in understanding the complexity of medication effects, although they need to be validated using an orthogonal approach (e.g., ideally a prospective longitudinal study). This multi-pathway perspective aligns with the broader evolution in precision medicine toward

recognizing the polygenic nature of drug response and adverse effect profile, and the need for comprehensive approaches to personalization.

The analytical pipeline developed in this thesis provides a replicable framework that could be applied to other antipsychotics and alternative psychiatric medications (e.g. antidepressants and antiepileptics), potentially accelerating the development of personalized approaches across psychopharmacotherapy. The demonstration that medication-specific effects can be successfully isolated and characterized using this approach has implications well beyond clozapine. The identification of specific genetic variants and biomarkers that predict treatment outcomes represents a potential for a shift toward personalised prescribing practices that could transform psychiatric care. The findings suggest that metabolic complications are not merely side effects but integral components of the biological response to psychiatric medications. This perspective challenges traditional distinctions between therapeutic effects and adverse effects, suggesting more integrated approaches to understanding medication mechanisms. The identification of specific biological pathways mediating metabolic effects suggests new targets for drug development. Future psychiatric medications might be designed to minimize metabolic effects or co-administered with agents that prevent metabolic complications.

This work positions itself at the intersection of several evolving fields, psychiatric pharmacogenomics, precision psychiatry, and complex trait genetics, while addressing fundamental methodological challenges that have limited progress in understanding medication-induced effects. The work not only advances understanding of clozapine specifically but also provides methodological and conceptual foundations that could accelerate progress across psychiatric pharmacogenomics more broadly. The analytical pipeline employed in this research represents a methodological contribution that could be applied to other pharmacogenomic questions. The integration of MR, PheWAS, and colocalization techniques provides a framework for investigating complex relationships between genetic variants, drug metabolism, and clinical outcomes across therapeutic areas. The identification of multiple biomarkers implicated in the relationship between clozapine plasma phenotypes and metabolic outcomes illustrates the complex, multi-pathway nature of pharmacogenomic relationships. This complexity challenges simple single-gene approaches to pharmacogenomics and supports more comprehensive approaches. The findings contribute to understanding the genetic architecture of drug response, demonstrating that pharmacogenomic effects operate through multiple biological pathways with varying effect sizes and clinical significance.

5.6. Reflection on Research Aims

This thesis aimed to investigate the genetic association between clozapine use and cardiometabolic abnormalities in TRS through two specific objectives: **(1)** To systematically review and synthesize genomic evidence investigating the genetic relationships between PDs, antipsychotic use, and cardiometabolic traits, with particular focus on identifying knowledge gaps regarding medication-specific effects versus disease related-factors and methodological limitations; **(2)** To employ an integrated genetic epidemiological pipeline combining MR, PheWAS, and colocalization analyses to investigate causal relationships between clozapine plasma traits and cardiometabolic outcomes and identify candidate biomarkers influenced by clozapine-metabolising genetic loci.

The first objective was comprehensively addressed through the systematic review presented in Chapter 3. This review synthesized findings from 56 studies utilizing genome-wide approaches to investigate the genetic relationships between PDs, antipsychotic use, and metabolic traits. The review successfully identified several critical knowledge gaps, particularly the challenge of distinguishing medication-specific effects from disease-related factors in metabolic complications. Additionally, methodological limitations in establishing causal relationships were highlighted, including the predominance of genetic correlation studies that could not distinguish between direct causal effects and shared risk factors, and the heterogeneity in metabolic phenotype definitions across studies.

The second objective was addressed through the multi-layered genomic investigation presented in Chapter 4. This study directly addressed the knowledge gaps identified in the systematic review by employing an integrated genetic epidemiological pipeline that investigated causal relationships between clozapine plasma traits and cardiometabolic outcomes using MR and identified candidate biomarkers influenced by clozapine-metabolizing genetic loci through phenome-wide association studies combined with colocalization analyses. The genomic investigation successfully identified causal relationships between clozapine plasma levels and cardiometabolic outcomes, as well as 16 biomarkers with strong evidence of causality to metabolic outcomes. Additionally, through the analytical pipeline, the study revealed potential biological pathways involved in clozapine-induced metabolic dysfunction. These findings represent a significant advancement in understanding the specific mechanisms linking clozapine to metabolic dysfunction, directly addressing the core research objectives.

5.7. Conclusions

This thesis has made significant contributions to psychiatric pharmacogenomics by demonstrating that clozapine-induced metabolic dysfunction involves complex, metabolite-specific effects through multiple potential biological pathways. The magnitude of this contribution lies in providing the first comprehensive genetic evidence for causal relationships between clozapine plasma levels and cardiometabolic outcomes, while identifying candidate biomarkers for future clinical investigation.

Several key conclusions emerge from this research:

1. Clozapine plasma levels exhibit evidence of distinct metabolite-specific effects with cardiometabolic outcomes, with the paradoxical finding of increased T2DM risk alongside protective effects against MetS, challenging conventional MetS understandings.
2. Sixteen biomarkers demonstrate evidence of causality to metabolic outcomes, revealing potential that clozapine-induced cardiometabolic dysfunction may involve multiple biological systems operating in parallel rather than through a single dominant pathway.
3. The identified genetic associations and candidate phenotypes suggest potential biomarkers that, following validation, could enable earlier detection and intervention before significant cardiometabolic dysfunction develops, potentially transforming current reactive clozapine monitoring to predictive, personalized approaches.
4. The combination of PheWAS, colocalization, and MR provides a powerful, replicable framework for investigating medication-specific effects while overcoming traditional observational study limitations, with broad applicability to other psychiatric medications.
5. These findings provide the genetic and biological foundations necessary for the potential development of personalized approaches to clozapine treatment, potentially contributing to safer prescribing with appropriate validation.

These conclusions have significant implications for both clinical practice and future research. The findings support a shift from reactive monitoring to predictive, pathway-specific approaches in managing clozapine-induced cardiometabolic dysfunction. By targeting specific biological pathways and leveraging readily available biomarkers following appropriate validation, clinicians could potentially identify at-risk patients earlier and implement targeted treatments, potentially improving long-term outcomes in this patient population. Future

research should focus on validating these findings in diverse populations, conducting dedicated pharmacogenetic studies with comprehensive metabolic phenotyping, exploring the functional biology underlying the identified associations, and developing and testing predictive models and intervention strategies based on these insights.

This work has made a significant contribution to the understanding of clozapine-induced metabolic dysfunction, and genetic psychiatry more broadly, by elucidating the genetic architecture underlying these effects and identifying potential biomarkers implicated in the relationship. While important questions remain, these findings provide a foundation for more personalized approaches to monitoring and managing metabolic complications in patients with TRS, potentially improving both physical health outcomes and quality of life in this challenging clinical population.

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Appendix A - Statements of Authorship

Disentangling the Relationship Between Psychiatric Disorders, Metabolic Syndrome, and Antipsychotics: A Systematic Review of Genomic Studies

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Statement of Authorship

Title of Paper	Disentangling the Relationship Between Psychiatric Disorders, Metabolic Syndrome, and Antipsychotics: A Systematic Review of Genomic Studies
Publication Status	☐ Published ■ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details Relevant reference details	Protocol: Registered with the International Prospective Register of Systematic Reviews (PROSPERO) on August 12, 2024 (ID: CRD42024574593) and Centre for Open Science (OSF) (https://doi.org/10.17605/OSF.IO/X3SG7). Systematic review manuscript submitted for publication.
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Chapter 4 - Genetic Epidemiological Analysis of Clozapine-Induced Cardiometabolic Dysfunction

Genetic Epidemiological Pipeline Identifies Candidate Markers of Clozapine-Induced Metabolic Dysfunction Revealing Potential Avenues for Precision Clozapine Prescription

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Statement of Authorship

Title of Paper	Genetic Epidemiological Pipeline Identifies Candidate Markers of Clozapine-Induced Metabolic Dysfunction Revealing Potential Avenues for Precision Clozapine Prescription
Publication Status	☐ Published ☐ Accepted for Publication ■ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details Relevant reference details	Manuscript submitted for Publication.
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Contribution to the Paper Brief description of your work in this publication	Conceptualization, data preparation, data analyses, data visualisation, manuscript preparation – writing and editing.
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Signature *Signatures will be redacted by the Library at the time of publication*	Elina Hypponen Digitally signed by Elina Hypponen Date: 2025.11.06 19:22:03 +10'30'	6th Nov 2025 Date
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Appendix B - Supplementary Material for Chapter 3

Supplementary Methods

Search Strategy

A systematic literature search was conducted in accordance with the PRISMA guidelines. PubMed, Scopus, and Web of Science were searched for studies published between January 2005 and August 2025. The 2005 cutoff was chosen to coincide with the emergence of large-scale GWAS, which marked a shift from candidate gene approaches, enabling the detection of robust, replicable genetic associations with adequate statistical power, as earlier candidate gene studies have demonstrated limited reproducibility. The search strategy included a combination of keywords and MeSH terms related to PDs, antipsychotics, MetS, and GWAS (Supplementary Table 3.8).

Inclusion and Exclusion Criteria

Studies were included if they met the following criteria: **(1)** involved human participants with PDs and MetS or related metabolic comorbidities; **(2)** used GWAS data to investigate genetic overlap, shared aetiology, or causal relationships between PDs, AIWG, and MetS or related metabolic traits; **(3)** reported findings related to shared genetic loci, biological pathways, genetic correlations, causal relationships, or PRSs linking the conditions of interest (Patnala, Clements & Batra 2013). Animal studies, non-peer-reviewed articles, and studies not using GWAS data or genetic-focused statistical techniques to investigate the genetic relationships of interest. After removing duplicated, titles and abstracts were screened by two researchers and discrepancies were resolved by a third researcher. This process was repeated for full texts (Supplementary Table 3.9)

Quality Assessment

The methodological quality of the included studies was assessed using a customized quality assessment scale for observational studies in the context of GWAS. This customized scale was used to adequately addresses the unique methodological considerations in GWAS-based studies with a high level of heterogeneity in study design by capturing key methodological information regarding these studies. This scale assessed using three critical aspects: 'selection,' 'comparability,' and 'outcome/exposure.' Each study was classified into one of three risk

categories - 'low risk,' 'high risk,' or 'unclear risk' - based on pre-defined criteria (Belbasis et al. 2018; Little et al. 2009; Manolio 2010).

Three researchers conducted the assessment process (RS, DS, and VS), with each study being independently reviewed by two of these researchers to ensure minimal bias. Discrepancies between reviewers were resolved through discussion to maintain a rigorous and objective evaluation of the quality of each study (Supplementary Table 3.10).

Data Synthesis Approach

Due to the heterogeneity of the included studies in terms of PDs, metabolic phenotypes, and genetic methods employed, a narrative synthesis approach was adopted with support from statistical visualisation of MR results.

Visualisation of Mendelian Randomization Results

We extracted data from eligible studies, including effect estimates (beta coefficients or odds ratios), standard errors/confidence intervals, and p-values. Only results from the inverse-variance weighted (IVW) method were included. Visualisations were created using ggplot2 in R (Wickham 2016).

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Supplementary Table 3.1 - Study Characteristics

Key information about the characteristics of the studies investigated for this review including year of publication, sample size, ethnicity of the sample used, and the main statistical analyses performed. Study characteristics were extracted for all studies.

PMID	*Lead Author*	*Sample Size*	*Ethnicity*	*Study Design*
20195266	Adkins, D. E	738	European, American, African American	GWAS, SNP-BMI interactions
23375658	Andreassen, O. A	21,856	European	cFDR leveraging pleiotropy between SCZ and CVD risk factors
35536160	Aoki, R	East Asian: 24,504 cases, 42,770 controls; European: 33,640 cases, 43,456 controls	East Asian, European	LDSC, MR
22417934	Athanasiu, L	594	European	Linear regression with SNP effect, max BMI, SNP×BMI interaction
31445318	Avinun, R	Discovery: 524; Replication: 5,930	European	Linear regression, mediation analyses
32624019	Badini, I	30,069	European	PRS, SNP-based heritability using GCTA-GREML and GCTB
31913414	Bahrami, S	SCZ: 82,315; BD: 51,710; MD: 480,359; BMI: 795,640	European	QQ plots, LDSC, cFDR
40595333	Bala, R	T2DM: >2.5 million (>500,000 cases); MDD: 371,184 cases/978,703 controls; Various glycaemic biomarkers: 85-168 variants; UKB: up to 374,900 individuals	European (primary), with analyses in East Asian, South Asian, African, Hispanic	Bidirectional two-sample and one-sample MR
37390107	Baltramonaityte, V	562,507 effective sample size	European	Genomic SEM, LDSC
39971893	Breton, É	AN: from GWAS (16,992 cases, 55,525 controls); BMI: from GWAS (~700,000); Age at menarche: from GWAS (182,416)	European	Conjunctional FDR analysis, GWAS
36377279	Byg, L. M	Bipolar disorder: 41,917 cases, 371,549 controls; BMI: 359,983	European	Two-sample MR (IVW, weighted median, MR-Egger)
38549512	Chen, F	SCZ: 130,644; ADHD: varies by trait; CVD traits: 46,952 to 1,320,016	European	LDSC, MR, FUMA, functional enrichment
40122258	Chen, M	BMI: 323,298; DEP: 286,052 (18,503 cases, 267,549 controls)	East Asian	LDSC, cross-trait meta-analysis, colocalization analysis, MR
37474010	Chen, W	Obesity traits: 694,649; Psychiatric disorders: 9,725 to 807,553	European	Two-sample MR (IVW, MR-Egger, weighted median, weighted mode)
29294133	Duncan, L. E	Schizophrenia: 74,626; Other traits: 5,422 to 232,101	European	LDSC
40259522	El Rouby, N	BioVU: 8,783 European, 1,471 African; BioMe: 465 European, 1,022 Hispanic, 547 African; Total meta-analysis: European N=9,248, African N=2,018	Multi-ancestry (European, African, Hispanic)	GWAS, Mendelian randomization
38042056	Franz, M	200	European	Multiple linear regression with 10-fold cross-validation
38245519	Gao, X	MetS GWAS: 461,920; Outcome GWAS: 9,725 to 807,553	European	LDSC, UVMR, MVMR (IVW, weighted median, MR-Egger)
34586374	Giannakopoulou, O	194,548 participants, 178,777 controls	East Asian	GWAS meta-analysis, LDSC, MVMR, MR
38487581	Guo, S	215,644 to 461,053	European	UVMR, MVMR (IVW, MR-Egger, weighted median, simple mode, weighted mode)
27601421	Hartwig, F. P	Bipolar disorder: 7,481 cases, 9,250 controls; Schizophrenia: 34,241 cases, 45,604 controls; Major depressive disorder: 9,240 cases, 9,519 controls	European	Two-sample MR (IVW, MR-Egger, weighted median)
37900287	He, M	Smoking: 280,508 cases, 180,558 controls; Sleep: 462,341; BMI: 336,107; Major depressive disorder: 8,276 cases, 209,308 controls; bipolar disorder: 20,352 cases, 31,358 controls	European	UVMR, MVMR, sensitivity analyses
36008755	He, Q	SCZ: 105,318; BMI: 236,231; WHR: 348,501; T2DM: 159,208; FG: 58,047; FIN: 51,750; HDL:	European	cFDR, conjFDR, HESS, MR

		99,900; LDL: 95,454; TC: 100,184; TG: 96,598		
36510667	He, R	Glutamine: 24,462; BMI: 339,224; MDD: 381,455; Depressive symptoms: 442,840 to 449,019	European	Linear regression, logistic regression, ROC analysis
39689714	Hou, L	Varies by GWAS (e.g., DEP: 2,113,907; MetS: 291,107; HT: 55,917 cases, 162,837 controls)	European, East Asian, African, Hispanic/Latino	Trans-ethnic MR (TEMR)
36923957	Huangfu, N	FinnGen: 42,857 cases, 162,837 controls; UK Biobank: 54,358 cases, 408,652 controls	European	Multiplicative random-effects IVW, weighted median, MR-Egger
25903154	Hung, C. F	Discovery: 2,521 (1,895 cases, 626 controls); Replication 1: 1,679 (822 cases, 857 controls); Replication 2: 2,993 (1,296 cases, 1,697 controls)	European	Linear regression, logistic regression, ROC analysis
38745458	Kang, J	Training data: VUMC N=106,789, MGB N=78,620; GWAS: N=154,433 across 4 biobanks (VUMC, MGB, GHS, MVP)	European	Machine learning prediction models, GWAS
33079133	Kappelmann, N	CRP: 204,402; Depressive symptoms: up to 117,907; MDD: 500,199 (170,756 cases), up to 230,214 (45,396 cases); BMI: up to 322,154; Height: up to 253,280; Insomnia: up to 386,533	European	LDSC, MR
37091807	Khani, N. S	SCZ: 53,386 cases, 77,258 controls; Cardiometabolic traits: 21,244 to 757,601	European	MR
36206878	Liao, S. F	106,604	East Asian	Linear/logistic regression, PRS
38336841	Liao, Y	Discovery: 1,936; Validation: 534; External validation: 630	European, East Asian, African	MR
32425817	Liu, H	Summary-level GWAS data from large consortia	European	FUMA, Sherlock, SMR, UTMOST, FOCUS, DEPICT, GSA-SNP2, MAGMA
40659072	Liu, H.-Y	DEP: varies by ancestry (36,818-170,756 cases); T2DM: varies by ancestry (16,832-242,283 cases)	Multi-ancestry (European, African, East Asian, South Asian, Hispanic/Latin American)	Two-sample bidirectional MR analysis
39755697	Lukas, E	PTSD: 1,222.9 (1,085.7 effective); Atrial fibrillation: 537.4 (482.3 effective); CAD: 1,165.7 (984.2 effective); Hypertension: 458.6 (313.8 effective); HF: 977.3 (930.0 effective)	European	LDSC, Genomic SEM, Two-sample MR, MVMR
39284855	Luo, X	Overweight: 158,855; Class 1 obesity: 98,697; Class 2 obesity: 72,546; Depressive symptoms: 161,460; SWB: 298,420	European	Two-sample MR
36399892	Lv, H	SCZ: 320,404; MetS: 291,107	European	LDSC, GNOVA, condFDR, TWAS
40056998	Ma, H	BD: 158,036 cases; BMI: 681,275	European	LDSC, cross-trait meta-analysis, MR, colocalization analysis
37494602	Maina, J. G	T2DM: 19,344 cases, 463,641 controls; MDD: 5,262 cases, 86,275 controls; Depressive symptoms: 153,079	European	MR, MTAG, eQTL analysis
29049554	Milaneschi, Y	MDD: 6,998 cases, 16,116 controls; Atypical depression: 1,446 cases, 16,116 controls; Obesity-related traits: up to 330,611	European	Genomic relationship matrix, linear/logistic mixed models
36852609	Muntane, G	Training: 224; Validation: 157	European	PRS, Pleiotropy analysis
37146461	O'Connell, K. S	TRS: 10,501 cases, 20,325 controls; BMI GWAS: 795,640 and 28,681; SCZ GWAS: 53,386 cases, 77,258 controls	European-American, African American	cFDR, PGS
36726144	O'Loughlin, J	15,771 cases, 178,777 controls, 100,377 participants	East Asian	MR, NLMR
35156041	Perry, B. I	SCZ: 40,675 cases, 64,643 controls	European	LDSC, GNOVA, Colocalization
33711016	Perry, B. I	MAGIC: up to 108,557; DIAGRAM: up to 435,387; GLGC: up to 173,082; GIANT: up to 339,224	European	Two-sample UVMR and MVMR
27182965	Pickrell, J. K	~5,000 to ~300,000 (varying by GWAS)	European	Pairwise GWAS, model of effect-size distribution, causal inference method

39299147	Pisanu, C	BD: 19,924 cases, 30,547 controls; SZ: 50,807 cases, 71,993 controls; MDD: 32,408 cases, 38,522 controls; BMI: 434,794 women, 374,756 men; WHRadjBMI: 379,501 women, 315,284 men	European	LDSC, MiXeR, conjFDR, cross-trait GWAS meta-analysis
27529678	Prieto, M. L	7,316	Caucasian	Logistic regression, ANCOVA
37145175	Reponen, E. J	SCZ: 699 (541 fasting); BD: 391 (331 fasting); HC: 822 (165 fasting)	European	ANCOVA, Linear regression
37145175	Reponen, E. J	699 SCZ (541 fasting); 391 BD (331 fasting); 822 HC (165 fasting)	European	Cross-sectional study with PRS
34301917	Rodevand, L	SCZ: 53,386 cases, 77,258 controls; CVD risk factors: 159,208 to 1,320,016	European	MiXeR, cFDR
37752828	Rodevand, L	BD: 51,710; CVD phenotypes: 159,208 to 795,640	European	MiXeR, cFDR, genomic SEM
34107350	Sewell, M. D. E	MDD: 367,329; SCZ: 366,465; BD: 366,383	European	Generalized Linear Regression
37173452	Sjaarda, J	1,135	European	GWAS Linear Regression
30045777	So, H. C	SCZ: 82,315; BD: 40,255; Cardiometabolic traits: up to ~700,000	European	MR (IVW, MR-Egger), LDSC, PRS
39190819	Song, Y	DEP: 15,771 cases, 178,777 controls; SCZ: 22,778 cases, 35,362 controls; 96 additional phenotypes from BBJ	East Asian	Multi-trait GWAS (MTAG), genetic correlation analysis
31383844	Speed, M. S	UK Biobank (anthropometric traits): ~332,000; PGC (depression): 480,000 (main GWAS), 173,005 (sub-GWAS)	European	Linear regression, IVW, weighted median regression
32126890	Ter Hark, S. E	339	European	Linear Regression
35560157	Torgersen, K	Depression: 450,619 (121,198 cases, 329,421 controls); CAD: 502,713; CVD risk factors: 204,402 to 776,078	European	cFDR, MR, MiXeR
29666151	van den Broek, N	BMI: 339,224; Subjective well-being: 204,966; Depressive symptoms: 161,460	European	MR
34730178	Veeneman, R. R	SCZ: 130,644; HF: 977,323; CAD: 332,477; Other CVD traits: 46,952 to 757,601	European	LDSC, bidirectional MR, MVMR
38394117	Viinikainen, J	1,523	European	Linear regression, MR
40187433	Wang, L.H	15,125 White British MDD patients	White British	GWAS, PRS analysis
24322204	Winham, S. J	388 cases, 1020 controls	European	Logistic regression with SNP effect, max BMI, SNP×BMI interaction; joint 2 df LR test
30521077	Wong, B. C	Varied by trait, up to ~339,000	European, Chinese	PRS, LDSC
38123074	Xu, Z	Observational: Depression -> hypertension: 434,582; Hypertension -> depression: 467,615; Genetic: Depression: 660,418 cases, 1,453,489 controls; Hypertension: 55,917 cases, 162,837 controls	European	Cox models, LDSC, bidirectional MR, MVMR
37106021	Yoshida, K	CATIE: 151; CAMH-Toronto: 138	European	Regression models using PRS
37202504	Yu, Y	SCZ: up to 76,755 cases, 243,649 controls; BMI: UK Biobank data	European	LDSC, HESS, partitioned LDSC, cross-trait GWAS meta-analysis, colocalization analysis, MR, functional analysis, heritability enrichment
39301319	Yu, Y	PTSD: 406,822 (3,005 cases, 403,817 controls); T2DM: 70,127 (12,931 cases, 57,196 controls)	European	Two-sample MR
(eISSN 1999-4893)	Zammarchi, G	Varied by trait, from ~5,900 for TS to ~339,000 for BMI	European	LDSC, k-means clustering, two-sample MR, partitioned LDSC, HESS
39394142	Zhang, H	DEP: >1.3 million (371,184 with DEP); BMI: 806,834	European	Comprehensive genetic analysis (LDSC, MR, cross-trait meta-analysis, SMR)
34903730	Zhang, M	Depression: 2,113,907 (660,418 cases, 1,453,489 controls); MetS: 291,107 (59,677 cases, 231,430 controls); Other MetS components: 281,416 to 462,166	European	Two-sample MR using multiple methods (IVW, MR-Egger, weighted median, MR-PRESSO, MR-RAPS)

38439019	Zhang, X	MDD: 135,458 cases, 344,901 controls; HT: 54,358 cases, 408,652 controls	European	Two-sample MR
38788001	Zhang, Z	DEP: 500,199 (170,756 cases, 329,443 controls); Hypercholesterolemia: 206,067 (8,808 cases, 197,259 controls)	European	Bidirectional 2-sample MR
37535610	Zheng, X	MDD: 59,851 cases, 113,154 controls; Exposures: GWAS sample sizes ranging from 9 to 262 SNPs	European	UVMR and MVMR using multiple methods (IVW, MR-Egger, weighted median, simple mode, weighted mode)
40338309	Zhou, Y	BMI: 806,834; MDD: 45,591/97,674; SWB: 204,966; SA-ISGC: 26,590/492,022; SA-iPSYCH: 6,024/44,240; Early/Adult body size: 453,169	European	Bidirectional two-sample MR

Supplementary Table 3.2 - Investigated Psychiatric Disorders

Information surrounding the disorders investigated in each study. All studies reported at least one disorder investigated.

Lead Author	*Psychiatric Disorder(s)*	*Diagnostic Criteria/Data Source*
Adkins, D. E	SCZ	DSM-IV
Andreassen, O. A	SCZ	Psychiatric Interviews, Systematic Phenotypic Quality Control
Aoki, R	SCZ	NR
Athanasiu, L	SCZ, BD, Psychosis	DSM-IV
Avinun, R	DEP	CES-D
Badini, I	MDD	DSM-V
Bahrami, S	SCZ, BD, MD	Source GWAS Data
Bala, R	MDD, Treatment resistant depression (TRD), GP derived depression	MDD: Als et al. GWAS; TRD: UK Biobank GP records (non-response to antidepressants); GP depression: UK Biobank electronic health records
Baltramonaityte, V	MDD	NR
Breton, É	AN	GWAS summary statistics from Watson et al. 2019
Byg, L. M	BD	DSM-IV, ICD-9, or ICD-10
Chen, F	ADHD, AD, ASD, AN, BD, MDD, PTSD, SCZ	Psychiatric Genomics Consortium (PGC)
Chen, M	DEP	Multi-ancestry GWAS, structured clinical interviews, medical records, symptoms questionnaires, self-reported surveys
Chen, W	ADHD, AN, AD, ASD, BD, MDD, OCD, PTSD, SCZ, ALZ	NR
Duncan, L. E	SCZ	NR
El Rouby, N	SGA-treated PDs (SCZ, BD, autism, others)	EHR data, prescription records for SGA medications
Franz, M	SCZ	NR
Gao, X	ADHD, AN, AD, ASD, BD, MDD, OCD, PTSD, SCZ, ALZ	NR
Giannakopoulou, O	MDD	Health Records, Self-reported Questionnaires, Structured Interviews
Guo, S	MDD	NR
Hartwig, F. P	BD, SCZ, MDD	DSM-IV, ICD-9, ICD-10
He, M	MDD, BD	NR
He, Q	SCZ	NR
He, R	MDD	Schedules for Clinical Assessment in Neuropsychiatry Interview
Hou, L	MDD, BD, SCZ	Source GWAS Data
Huangfu, N	AD, ADHD, ASD, MDD, OCD, PTSD, SCZ	Source GWAS Data
Hung, C. F	MDD	Schedules for Clinical Assessment in Neuropsychiatry Interview
Kang, J	MDD, TRD	ICD-9 and ICD-10 codes, ECT CPT codes (90870), excluded bipolar, schizophrenia, psychotic disorders
Kappelmann, N	MDD	NR
Khani, N. S	SCZ	DSM-IV
Liao, S. F	MDD	Self-reported
Liao, Y	SCZ	DSM-IV
Liu, H	SCZ	NR
Liu, H.-Y	MDD	Structured clinical interviews, medical records, symptoms questionnaires, self-reported surveys; PGC data; UK Biobank
Lukas, E	PTSD	Clinician administered, self-report, DSM-4 Posttraumatic Stress Disorder Checklist, electronic health records
Luo, X	Depressive symptoms	GWAS summary statistics
Lv, H	SCZ	NR
Ma, H	BD	Multi-ancestry GWAS meta-analysis, majority European ancestry
Maina, J. G	MDD	PHQ-9, ICD-10 codes
Milaneschi, Y	MDD	DSM-IV

Muntane, G	Psychosis	ICD-10
O'Connell, K. S	SCZ	Clozapine Use
O'Loughlin, J	MDD	DSM-V, Self-reported
Perry, B. I	SCZ	NR
Perry, B. I	SCZ	NR
Pickrell, J. K	SCZ, BD	NR
Pisanu, C	BD, MDD, SZ	PGC and iPSYCH GWAS data, psychiatric interviews, systematic phenotypic quality control
Prieto, M. L	SCZ, BD	DSM-V
Reponen, E. J	SCZ, BD	DSM-V
Reponen, E. J	SCZ, BD	SCID-1 (DSM-IV); SCZ spectrum: schizophrenia, schizoaffective, schizophreniform, psychotic disorder NOS; BD spectrum: bipolar I, II, BD NOS
Rodevand, L	BD	Source GWAS Data
Rodevand, L	SCZ	Source GWAS Data
Sewell, M. D. E	MDD, SCZ, BD	Source GWAS Data
Sjaarda, J	BD, MDD, PDs	ICD-10
So, H. C	SCZ, BD	NR
Song, Y	MDD, SCZ	GWAS summary statistics from largest East Asian cohorts
Speed, M. S	MDD	DSM or ICD
Ter Hark, S. E	SCZ	NR
Torgersen, K	MDD	NR
van den Broek, N	MDD	Self-reporting, clinical assessment, medical records
Veeneman, R. R	SCZ	DSM-IV
Viinikainen, J	MDD	Beck's Depression Inventory
Wang, L.H	MDD, Treatment-resistant depression (TRD)	Primary care records, hospitalization records
Winham, S. J	BD	DSM-IV
Wong, B. C	MDD, Neuroticism	DSM-IV
Xu, Z	MDD	ICD-10
Yoshida, K	SCZ	DSM-V
Yu, Y	SCZ	Source GWAS Data
Yu, Y	PTSD	Post-traumatic Stress Disorder Checklist (PCL), FinnGen diagnostic criteria
Zammarchi, G	SCZ, MDD, BD, ADHD, ASD, PTSD, OCD, TS, AN	Source GWAS Data
Zhang, H	DEP	Meta-analysis of six datasets by Thomas D et al. 2023
Zhang, M	MDD	NR
Zhang, X	MDD	GWAS meta-analysis
Zhang, Z	DEP	GWAS meta-analysis summary statistics, Howard et al dataset
Zheng, X	MDD	Source GWAS Data
Zhou, Y	MDD, SWB, SA	MDD: DSM-V; SWB: surveys; SA-ISGC: European data; SA-iPSYCH: Danish birth cohort

Supplementary Table 3.3 - Antipsychotics Investigated

Information on which studies investigated antipsychotics, and which drugs were specifically reported within each study.

Lead Author	*Antipsychotic*
Adkins, D. E	Olanzapine, Perphenazine, Quetiapine, Risperidone, Ziprasidone, Clozapine
Athanasiu, L	Various, Grouped by Side Effect Potential Into 3 Groups
El Rouby, N	SGA - grouped together rather than analysed separately
Facal, F	Clozapine (for TRS definition)
Franz, M	Quetiapine, Haloperidol, Olanzapine, Risperidone, Amisulpride, Aripiprazole
Liao, Y	Olanzapine, Risperidone, Quetiapine, Aripiprazole, Ziprasidone
Muntane, G	Aripiprazole, Clozapine, Trifluoperazine, Haloperidol, Olanzapine, Paliperidone, Quetiapine, Risperidone, Ziprasidone, Amisulpride
O'Connell, K. S	Clozapine
Sjaarda, J	Amisulpride, Aripiprazole, Clozapine, Olanzapine, Quetiapine, Risperidone, Valproate
Ter Hark, S. E	Amisulpride
Wang, L.H	Antipsychotics (augmentation therapy), Clozapine, Olanzapine, Quetiapine, Risperidone, Aripiprazole
Yoshida, K	Clozapine, Olanzapine, Quetiapine, Risperidone

Supplementary Table 3.4 - Metabolic Phenotypes Examined

Information regarding the metabolic phenotypes investigated by each study. Every study investigated at least one metabolic phenotype.

Lead Author	*Metabolic Phenotypes*	*Diagnostic Criteria/Data Source*
Adkins, D. E	BMI, WC, TG, BGL, HbA1c, BP, HR	Standard Clinical Measurements
Andreassen, O. A	SBP, DBP, LDL, HDL, TG, T2DM, BMI, WHR	Standard Clinical and Laboratory Measurements
Aoki, R	BMI, CRP, HDL-C, FG, TG, SBP	GWAS Summary Statistics
Athanasiu, L	BMI, WC, TG, BGL, HbA1c, CRP, BP, HR	Standard Clinical Measurements
Avinun, R	BMI	Calculated from measured height and weight
Badini, I	BMI, Leptin, CRP	GWAS Summary Statistics
Bahrami, S	BMI	GWAS Summary Statistics
Bala, R	T2DM, FG, HbA1c, Insulin fold change, Insulin sensitivity index, TG:HDL-C ratio	T2DM: Suzuki et al. GWAS with 8 mechanistic pathway clusters; Glycaemic biomarkers: MAGIC consortium (individuals without T2DM); TG:HDL-C ratio: proxy for insulin resistance
Baltramonaityte, V	CAD, T2DM	NR
Breton, É	BMI, age at menarche	GWAS summary statistics from GIANT and ReproGen consortia
Byg, L. M	BMI	NR
Chen, F	Atrial fibrillation, CAD, cardiomyopathy, HF, HT, myocardial infarction	Large genomic consortia GWAS
Chen, M	BMI, underweight	Korean Biobank and Biobank Japan GWAS data
Chen, W	BMI, WHR	NR
Duncan, L. E	Serum citrate	Nuclear Magnetic Resonance
El Rouby, N	MetS, BMI, BP, FG, HDL, TG	National Cholesterol Education Program (NCEP) Adult Treatment Panel III criteria, EHR clinical measurements
Franz, M	AIWG	Percentage Weight Change from Baseline to Five Weeks
Gao, X	MetS	Genetic Single MetS Factor Derived from Genomic Structural Equation Modelling, Capturing Shared Genetic Variance Among 5 Metabolic Components
Giannakopoulou, O	CAD, BMI, T2DM	N/A
Guo, S	BMI	NR
Hartwig, F. P	BMI	Calculated from Height and Weight
He, M	BMI	NR
He, Q	BMI, TG	NR
He, R	BMI, Circulating Glutamine Levels	Calculated from Weight and Height (BMI), Nuclear magnetic resonance metabolomics (Circulating Glutamine Levels)
Hou, L	BMI, MetS, HT, T2DM, WC, Triglycerides, HDL-C, FG	GWAS Summary Statistics
Huangfu, N	HT	ICD-8 codes 401-404, ICD-9 codes 4,019X, 4039A, ICD-10 code I10
Hung, C. F	BMI, Obesity	Calculated from Height and Weight
Kang, J	Treatment-resistant depression (TRD), BMI	ECT receipt as surrogate for TRD, GWAS summary statistics for BMI
Kappelmann, N	BMI, CPR-L	NR
Khani, N. S	BMI, WHR, HbA1c, FG, INS, HDL, LDL, TG, cholesterol, BP	NR
Liao, S. F	BMI, BF Rate, WHR	Physical Measurements
Liao, Y	BMI, LDL-C, HDL-C, TG, FG	Standard Clinical and Laboratory Measurements
Liu, H	BMI, CAD, T2DM, HDL, LDL, TC, TG	NR
Liu, H.-Y	T2DM, BMI (mediator), smoking (mediator), alcohol consumption (mediator), physical activity (mediator), sleep duration (mediator)	Multi-ancestry GWAS meta-analysis, physician diagnosis of T2DM, Electronic Health Records
Lukas, E	Atrial fibrillation, CAD, HT, HF	Clinical diagnosis for heart failure (any aetiology); Paroxysmal or permanent atrial fibrillation, atrial flutter for AF; See original Supplementary Table 32 for CAD; UKB for hypertension
Luo, X	BMI categories (overweight ≥25, class 1 obesity ≥30, class 2 obesity ≥35), Subjective well-being	GIANT Consortium GWAS, SSGAC GWAS
Lv, H	MetS	National Cholesterol Education Program

Ma, H	BMI	GWAS Summary Statistics from GIANT consortium and UK Biobank
Maina, J. G	T2DM, BMI	GWAS Summary Statistics
Milaneschi, Y	BMI, CPR-L, Leptin	NR
Muntane, G	BMI	Calculated from Height and Weight
O'Connell, K. S	BMI	GWAS Summary Statistics
O'Loughlin, J	BMI, WHR	Calculated from Weight and Height, Waist Measurements
Perry, B. I	INS, FG, HbA1c, GT, T2DM, lipids, BMI, CAD, CRP	GWAS Summary Statistics
Perry, B. I	INS, HDL, TG, LDL, BGL, HbA1c, leptin, BMI, GT, T2DM	GWAS Summary Statistics
Pickrell, J. K	BMI, WHR, FG, T2DM, LDL, HDL, TG, Cholesterol	GWAS Summary Statistics
Pisanu, C	BMI, WHRadjBMI	GIANT consortium and UK Biobank GWAS summary statistics
Prieto, M. L	EHR-derived Phenotypes	ICD-9
Reponen, E. J	BMI, CRP, MPO, Adiponectin, Leptin/Adiponectin Ratio, HDL-C	Physical exam (BMI), Fasting Plasma Levels (Other Biomarkers)
Reponen, E. J	BMI, CRP, MPO, Adiponectin, Leptin/adiponectin ratio, TC/HDL, TG/HDL, HOMA2-IR	Standard clinical measurements; BMI from height/weight; fasting plasma levels for biomarkers
Rodevand, L	BMI, WHR, T2DM, Cholesterol, LDL, HDL, TG, SBP, DBP, CAD	GWAS Summary Statistics
Rodevand, L	BMI, WHR, Smoking Initiation, Daily Cigarettes, TG, HDL, LDL, cholesterol, SBP, DBP, T2DM, CAD	GWAS Summary Statistics
Sewell, M. D. E	58 markers across inflammatory/immune, haematological, bone, cardiovascular, hormone, liver, renal and diabetes categories	Blood Samples
Sjaarda, J	BMI	Calculated from Weight and Height
So, H. C	LDL, HDL, TC, TG, BMI, FG, INS, WHR, T2DM, CAD, Leptin, Adiponectin, SBP, DBP, BF%, SAT, PAT, SAT, VATHU, VAT/SAT-R	GWAS Summary Statistics
Song, Y	BMI, weight, HDL cholesterol, total cholesterol, T2DM, various biomarkers	GWAS summary statistics from BioBank Japan
Speed, M. S	BF%, BFM, Height	Bioelectrical impedance analysis
Ter Hark, S. E	AIWG	BMI change
Torgersen, K	BMI, SBP, DBP, TG, T2DM, CRP	GWAS Summary Statistics
van den Broek, N	BMI	Calculated from Weight and Height
Veeneman, R. R	HF, CAD, SBP, DBP, HFV, QTIs, Early Repolarization, Dilated Cardiomyopathy ECG Patterns	GWAS Summary Statistics
Viinikainen, J	BMI	Young Finns Study
Wang, L.H	BMI	Calculated from height and weight
Winham, S. J	BMI	Calculated from Weight and Height
Wong, B. C	BMI, WHR, FG, INS, IR, BF%, TG, Adiponectin, Leptin, SBP, DBP, CAD, T2DM	GWAS Summary Statistics
Xu, Z	HT	ICD-10
Yoshida, K	AIWG	Percentage Change in Weight
Yu, Y	BMI	GWAS Summary Statistics
Yu, Y	T2DM, Obesity, HT, Hyperlipidaemia	GWAS summary statistics, various databases
Zammarchi, G	BMI, T2DM, CAD, CRP	GWAS Summary Statistics
Zhang, H	BMI	GIANT consortium meta-analysis: BMI calculated as weight(kg)/height(m^2)
Zhang, M	BMI	GWAS Summary Statistics
Zhang, X	HT	UK Biobank GWAS (54,358 cases, 408,652 controls)
Zhang, Z	Hypercholesterolemia	FinnGen data (ICD-10 diagnostic criteria), UK Biobank data
Zheng, X	MetS, WC, HT, FG, TG, HDL, Cholesterol	GWAS Summary Statistics
Zhou, Y	BMI, Early life body size, Adult body size	BMI from height/weight; Early life body size: questionnaire at age 10; Adult body size: baseline measurement

Supplementary Table 3.5 - Main Findings and Key Statistical Result

The main finding and main statistical result extracted from each study.

Lead Author	*Study Design*	*Main Findings*	*Key Statistical Result*
Adkins, D. E	GWAS/SNP Analysis	Identified SNPs in MEIS2, PRKAR2B, GPR98, FHOD3, RNF144A, ASTN2, SOX5, ATF7IP2, and intergenic regions associated with antipsychotic-induced metabolic side effects	rs1568679 (MEIS2) q=0.004 for risperidone effect on waist/hip; rs13224682 (PRKAR2B) for clozapine effect on TG; other loci q<0.1
Andreassen, O. A	Mixed Methods	Identified 25 SCZ susceptibility loci leveraging CVD risk factors, 10 loci associated with both SCZ and CVD factors (mainly lipids), suggesting shared pathobiology	25 loci at cFDR<0.01
Aoki, R	Genetic Correlation/LDCS	Genetic correlation between SCZ and BMI, CRP, HDL-C, blood sugar, triglycerides, SBP	rg = 0.10 (BMI), 0.08 (CRP), 0.07 (HDL-C, BGL), 0.05 (TG, SBP); q-values < 0.05
Athanasiu, L	GWAS/SNP Analysis	Identified genomic regions near MMP16 associated with antipsychotic-induced metabolic effects	rs7838490 and rs6989402 (MMP16) P=6.1x10-8 and 1.5x10-7 for BMI; rs11615274 P=3.4x10-7 for HDL-C
Avinun, R	PRS	Higher BMI PRS predicted higher ELS, which predicted higher depressive symptoms; lower alcohol use PRS predicted higher depressive symptoms via ELS	Indirect effects: BMI PRS->ELS->Depression = 0.21; Alcohol PRS->ELS->Depression = -0.12
Badini, I	PRS	Depression with atypical features (↑WS) had higher PRS for BMI, CRP, MDD and lower PRS for alcohol use v. other MDD; CAD and TG PRS associated with ↑ WS v. controls; SNP-h2 higher in ↑WS than ↓WS	OR 1.20 BMI, 1.11 CRP, 1.10 MDD, 0.88 alcohol use; SNP-h2 ~14-21% ↑WS, 12-16% ↓WS
Bahrami, S	Mixed Methods	Extensive polygenic overlap between BMI and SCZ, BD, and MD; mixed association directions suggest complex interplay of metabolism-related pathways	rg -0.11 (BMI-SCZ), -0.06 (BMI-BD), 0.12 (BMI-MD); 63, 17, 32 loci at conjFDR<0.01 for BMI-SCZ, BMI-BD, BMI-MD
Bala, R	Bidirectional two-sample and one-sample MR with pathway-specific analysis	Bidirectional causal association between MDD and T2DM. T2DM variants acting via obesity-mediated insulin resistance and body fat pathways showed strongest associations with MDD. MDD strongly predicted insulin resistance (TG:HDL-C ratio). BMI partially mediates the relationship.	MDD→T2DM: OR=1.14 (95%CI: 1.09, 1.19); T2DM→MDD: OR=1.02 (95%CI: 1.01, 1.03); T2DM obesity pathway→MDD: OR=1.06 (95%CI: 1.04, 1.09); MDD→TG:HDL-C: β=0.11 (95%CI: 0.075, 0.14)
Baltramonaityte, V	Mixed Methods	Identified shared genetic influences and potential biological mechanisms underlying psycho-cardiometabolic multimorbidity	rg=0.39 (CAD-T2DM), 0.13 (CAD-depression), 0.15 (depression-T2DM); OR per SD = 1.91 (95% CI 1.74-2.10) for multimorbidity PRS
Breton, É	Conjunctional FDR and evolutionary analysis	Found 22 loci overlapping between AN and BMI, 9 loci between AN and age at menarche. Evidence for recent evolutionary selection at AN-associated loci. Chronobiology genes prominently involved	22 loci AN-BMI overlap, 9 loci AN-menarche overlap; Negative NSS scores suggesting evolutionary selection; ARNTL identified as key chronobiology gene
Byg, L. M	Mendelian Randomization	Genetic liability to BD reduces BMI, predominantly driven by reduced fat mass; no evidence of BMI causally influencing BD risk	Egger slope −0.195, p=0.004 for BD liability on BMI
Chen, F	Integrative analysis	Extensive genetic correlations between neuropsychiatric disorders and CVD; 19 significant causal relationships in MR; shared genetic pathways	18 pairwise traits with significant genetic overlaps; ADHD-Heart failure rg=0.375, P=2.80E-30; 13 shared independent significant SNPs
Chen, M	Mixed Methods	Significant negative genetic correlation between BMI and depression in East Asians, 26 shared risk SNPs including FTO and AGBL4, causal effect of lower BMI on depression	rg = −0.19, P = 0.002 (BMI-depression); MR OR = 1.14, 95% CI: 1.02-1.28, P = 0.021 (lower BMI → depression)
Chen, W	Mendelian Randomization	Significant causal associations between obesity and ADHD, AN, PTSD, MDD, ALZ; bidirectional relationships for some disorders	ORs ranging 0.74 to 2.35 for obesity-psychiatric disorder associations; bidirectional ORs 1.02 to 1.66
Duncan, L. E	Genetic Correlation/LDCS	Genetic correlations between SCZ and BD, MDD, AN, ASD; negative genetic correlation between SCZ and serum citrate	rg=0.83 (SCZ-BD), 0.47 (SCZ-MDD), 0.19 (SCZ-AN, SCZ-ASD); rg=−0.21 (SCZ-serum citrate)
El Rouby, N	GWAS/MR	Novel genetic loci for SGA-induced MetS; European ancestry: chromosome 11 signal; African ancestry: chromosome 2 NPPC-DIS3L2 signals; BMI causally associated with SGA-MetS	European: rs61900075, β=−0.27, p=1.6E−8; African: multiple signals p<2.5×10−8; MR BMI→SGA-MetS: OR=1.2, 95% CI: 1.1-1.4, p=0.002

Franz, M	PRS	PRS for BMI, SCZ, and T2DM significantly associated with AIWG; addition of PRS increased model's explained variation	β = 3.78 (p=0.0041) BMI PRS, β = 5.38 (p=0.021) SCZ PRS, β = 13.4 (p=0.046) T2DM PRS; +6.5% variation explained
Gao, X	Mendelian Randomization	Significant causal associations between MetS and ADHD, AN, MDD; bidirectional relationships for some disorders	rg=0.33 (MetS-ADHD), 0.35 (MetS-AN), 0.15 (MetS-MDD), −0.10 (MetS-SCZ); OR per SD: ADHD 1.59, AN 1.42, MDD 1.23 for MetS
Giannakopoulou, O	GWAS/SNP Analysis	Novel loci at 1q24.1 and 7p21.2 in East Asian cohorts; limited evidence for transferability of depression loci from European to East Asian populations	rs4656484 at 1q24.1: OR=0.94; rs10240457 at 7p21.2: OR=1.08
Guo, S	Mendelian Randomization	Multiple lifestyle factors have causal relationships with depression in univariable and multivariable analyses	ORs ranging 0.33 to 5.19 for lifestyle factors on depression
Hartwig, F. P	Mendelian Randomization	No consistent evidence for causal effect of BMI on BD or SCZ risk; weak evidence for effect on MDD	OR 0.88 to 1.23 for BMI on BD; 0.93 to 1.41 for BMI on SCZ; 1.15 to 1.40 for BMI on MDD
He, M	Mendelian Randomization	Causal effect of smoking, sleep, and BMI on MDD and BD	Smoking on MDD OR 1.03; insomnia on MDD OR 1.04; BMI on MDD OR 1.01; smoking on BD OR 2.46; insomnia on BD OR 2.73
He, Q	Mixed Methods	Moderate to high genetic overlap between SCZ and BMI/TG, with bidirectional associations; novel shared SNPs and genes identified	144 variants shared SCZ-BMI, 55% novel; 15 variants shared SCZ-TG, 40% novel; mixed effect directions
He, R	Mendelian Randomization	Higher BMI was causally associated with lower glutamine levels; both obesity and downregulation of glutamine were causally linked to depression	Glutamine on MDD/symptoms -0.036 to -0.013; BMI on glutamine -0.103; BMI on MDD/symptoms 0.017 to 0.050
Hou, L	Trans-ethnic MR using multiple methods (IVW, MR-Egger, weighted median)	TEMR improved statistical power and estimation accuracy of MR in underrepresented populations. Found 17 causal relationships not identified by other MR methods, including causal effects of smoking, sleep, BMI on MDD and BD.	ORs ranging 0.33 to 5.19 for lifestyle factors on depression; TEMR showed 15-50% improvement in precision when rg ≥ 0.4
Huangfu, N	Mendelian Randomization	Genetic liability to depression causally related to hypertension	OR 1.25 (95% CI 1.17-1.35) for depression on hypertension; OR 1.16 (95% CI 1.02-1.33) for neuroticism on hypertension
Hung, C. F	PRS	GRS based on 32 SNPs was a highly significant predictor of obesity in people with MDD but accounted for only a modest amount of variance	GRS explained +1.27% BMI variance (P<0.001); AUC 0.69 to 0.71 adding GRS
Kang, J	Machine Learning/GWAS	ECT-based TRD prediction models validated across sites; two genome-wide significant loci; shared genetic architecture with metabolic traits	Model performance: AUROC 0.90-0.91; Heritability 2-4.2%; Chr16 FTO locus: p=4.3E−11; Chr22 MCHR1 locus: p=1.82E−8; rg with BMI: -0.33 to -0.65
Kappelmann, N	Genetic Correlation/LDCS	Extensive genetic overlap between BMI, CRP levels, and depressive symptoms; mixed association directions suggest complex interplay of metabolism-related pathways	rg 0.152-0.362 CRP-depressive symptoms; IL-6 on suicidality 0.035 (SE 0.010); BMI on depressive symptoms 0.028 to 0.121
Khani, N. S	Mendelian Randomization	Did not find strong evidence that SCZ causally influences most cardiometabolic traits; dyslipidaemia and obesity in SCZ likely driven by other factors rather than SCZ itself	β=0.013 (95% CI 0.001-0.024) SCZ on LDL; β=0.013 (95% CI 0.002-0.025) SCZ on TC; not significant after correction
Liao, S. F	PRS	Demonstrated polygenic overlap between MDD and obesity traits; active depression exacerbated effects of BMI genetics on central obesity measures	BMI PRS explained 9.06% BMI variance; MDD PRS explained 0.017% obesity traits variance; interaction effects observed
Liao, Y	GWAS/SNP Analysis	Identified novel genetic loci (PEPD, PTPRD) associated with AIWG; results highlight lipid pathway dysfunction as potential mechanism	rs10422861 (PEPD) P=1.37E-9, rs3824417 (PTPRD) P=3.35E-9 for AIWG; rg = 0.13 with BMI; h2 = 0.127
Liu, H	Bioinformatics/Pathway Analysis	Identified potential pleiotropic genes and pathways underlying comorbidity of SCZ and cardiometabolic diseases through integrated analysis	21 potential pleiotropic genes meeting various thresholds
Liu, H.-Y	Mendelian Randomization	Causal effect of depression on T2DM in Europeans only, stronger in females, BMI and smoking mediate 25.86% and 24.67% respectively	OR = 1.33, 95% CI: 1.20-1.48, P = 1.59E-7 (depression→T2DM in Europeans); BMI mediation: 25.86%, P = 0.027; Smoking mediation: 24.67%, P = 5.53E-04
Lukas, E	LDSC, Genomic SEM, Two-sample MR, MVMR	Significant genetic correlations between PTSD and CAD, HT, and HF (rg = 0.21-0.32), but not with AF. Mendelian randomization indicated PTSD causally increases CAD, HF, and to lesser degree	rg = 0.21 (PTSD-HT), 0.26 (PTSD-CAD), 0.32 (PTSD-HF); MR OR = 1.53 (95% CI 1.19-1.96, p=0.001) PTSD on CAD; OR = 1.44 (95% CI 1.08-1.92, p=0.012) PTSD

		HT. Insomnia, smoking, alcohol dependence, waist-to-hip ratio, and inflammation partly mediated associations	on HF; OR = 1.25 (95% CI 1.05-1.49, p=0.012) PTSD on HT
Luo, X	Two-sample MR	Overweight and class 1 obesity causally associated with increased depressive symptoms; class 2 obesity causally associated with reduced SWB	Overweight → depressive symptoms: IVW β=0.033, P=0.010; Class 1 obesity → depressive symptoms: IVW β=0.033, P<0.001; Class 2 obesity → SWB: IVW β=-0.033, P<0.001
Lv, H	Genetic Correlation/LDCS	Revealed genetic overlap and shared loci between SCZ and MetS, suggesting shared biological mechanisms; highlighted PCCB and KCTD13 as potential mediators	rg=0.09 SCZ-MetS; 22 loci at conjFDR < 0.05
Ma, H	Mixed Methods	Found genetic correlation between BD and BMI, identified 46 shared risk SNPs including 3 novel variants, causal effect of BD on BMI but not reverse	rg = −0.06, P = 1.48E-05 (BD-BMI genetic correlation); MR OR = 0.95, P = 1.78E-04 (BD→BMI); 46 genome-wide significant shared SNPs
Maina, J. G	Bioinformatics/Pathway Analysis	Causal role of depression on T2DM, mediated by BMI; shared genetic basis involving insulin secretion and inflammation	7 shared loci; OR 1.26 depression on T2DM; 36.5% mediated by BMI
Milaneschi, Y	Genetic Correlation/LDCS	MDD cases with increased appetite/weight showed distinct genetic overlap with obesity and metabolic dysregulation traits, suggesting shared pathophysiology	BMI rg=0.53 (SE=0.16) MDD with increased appetite/weight; CRP OR=1.08, Leptin OR=1.09
Muntane, G	PRS	Genetic factors play a key role in determining BMI increase in first episode psychosis, with shared genetic architecture with SCZ	449 loci shared SCZ-BMI; negative rg; improved BMI prediction with PRS
O'Connell, K. S	Mixed Methods	Improved genetic discovery and polygenic prediction of TRS by leveraging genetic overlap with BMI	2 novel loci (MAP2K1, ZDBF2) for TRS at cFDR<0.01; cross-trait PRS enrichment improved TRS prediction
O'Loughlin, J	Mendelian Randomization	Higher BMI causally associated with lower depression in East Asians, influenced by sociocultural factors	Higher BMI associated with lower odds of depression
Perry, B. I	Mixed Methods	Shared genetic etiology between SCZ and cardiometabolic traits, involving BDNF and related pathways	85 regions of locus-level correlation; 10 colocalized loci; weak rg -0.07 to -0.09 (SCZ-T2DM/BMI)
Perry, B. I	Mixed Methods	Evidence supports inflammation as a common cause for insulin resistance and SCZ, potentially explaining their frequent co-occurrence	Fasting insulin OR 2.95; HDL OR 0.55; p=0.035 (Holm-Bonferroni) in inflammation-related insulin resistance
Pickrell, J. K	Mixed Methods	Many genetic variants affect multiple traits; some represent causal relationships between traits	Relative likelihood >100 for causal vs. non-causal BMI-TG, LDL-CAD
Pisanu, C	Mixed Methods	Sex-specific genetic overlap between severe mental disorders and metabolic traits; identified sex-specific druggable genes and shared loci	24 and 91 shared loci between BD/SZ and BMI in women; 13 and 208 shared loci in men; mixed directions of effect; sex-specific druggable genes identified
Prieto, M. L	PRS	Inverse association between BD PRS and BMI; no other significant PRS associations with other medical phenotypes	BD PRS-BMI coefficient -0.297, p=0.03 (Bonferroni)
Reponen, E. J	PRS	Found negative correlation between BMI and BD PRS and SCZ PRS; no significant associations for other CVD biomarkers	BD PRS-BMI coefficient -0.297, p=0.03; SCZ PRS-BMI coefficient -0.237, p=0.29 (Bonferroni)
Reponen, E. J	Cross-sectional polygenic risk score analysis	BD PGRS significantly negatively associated with BMI after multiple testing correction; SCZ PGRS nominally negatively associated with BMI	BD PGRS-BMI: coefficient -0.297, p=0.03 (Bonferroni); SCZ PGRS-BMI: coefficient -0.237, p=0.29 (after correction)
Rodevand, L	Mixed Methods	Extensive polygenic overlap between BD and CVD phenotypes; mixed effect directions may reflect variation in CVD genetic risk across BD subgroups	Polygenic overlap 82% (BD-BMI), 20-22% (BD-SBP/DBP), 11% (BD-CAD); 129 loci at conjFDR<0.05
Rodevand, L	Mixed Methods	SCZ has polygenic overlap with CVD risk factors, particularly smoking and BMI; mixed effect directions of shared loci suggest differences in CVD genetic liability across SCZ subgroups	~90% SCZ-smoking, ~84% SCZ-BMI polygenic overlap (MiXeR); 825 loci at conjFDR<0.05
Sewell, M. D. E	Mixed Methods	Varying associations between disorder PRS and peripheral markers; inflammatory dysfunction implicated in MDD and SCZ; many associations influenced by lifestyle factors	38, 32, 20 associations at p<0.05 for MDD, SCZ, BD PRS; 13, 14, 10 after lifestyle adjustment
Sjaarda, J	GWAS/SNP Analysis	Identified 4 novel loci associated with psychotropic-induced weight gain; one replicated in psychiatric but not general population	rs7736552, rs11074029, rs117496040, rs7647863 at p<5E-8 for AIWG
So, H. C	Bioinformatics/Pathway Analysis	Extensive genetic overlap between SCZ, BP, and cardiometabolic traits, with many shared loci and pathways; provides insight into shared biological mechanisms	Several genome-wide significant loci; top pathways include insulin secretion, VEGF, aldosterone

Song, Y	MTAG and genetic correlation	Identified novel pleiotropic loci between depression/SCZ and metabolic traits in East Asians. Found genetic correlations between depression and obesity-related traits, SCZ and lipid markers	1 novel locus (1q25.2) shared between depression and SCZ; 10 novel loci for depression, 4 for SCZ; rg=0.46 between depression and SCZ
Speed, M. S	Mendelian Randomization	Higher fat mass and shorter height may causally increase depression risk, but not fat-free mass	Beta 0.17-0.34 for fat mass measures on depression
Ter Hark, S. E	GWAS/SNP Analysis	rs78310016 and potentially HMGCS1 involved in amisulpride-induced weight gain; genetic variants may help predict weight gain risk	rs78310016 β=1.05, p=3.66E-8; OR 3.98 for clinically meaningful weight gain
Torgersen, K	Mixed Methods	Extensive polygenic overlap of depression with CAD and CVD risk factors; many shared loci	79 shared loci depression-CAD/CVD risk factors
van den Broek, N	Mendelian Randomization	Higher BMI likely causes increased depression risk, but depression does not cause high BMI	Beta 0.17 BMI to depression, non-significant depression to BMI
Veeneman, R. R	Mendelian Randomization	SCZ liability has causal effects on heart failure and ECG patterns, not mediated by behavioural factors; weak evidence blood pressure affects SCZ	SCZ on heart failure OR 1.27, p=0.027; suggestive effects on ECG partially mediated by BMI/lipids
Viinikainen, J	Mendelian Randomization	Higher BMI may causally increase depression risk in females; statistical power and instrument strength impact ability to detect effects	MR beta 0.302, p=0.007 BMI on depression in females; beta -0.070, p=0.520 in males
Wang, L.H	GWAS, SNP-heritability estimation, PRS analysis	TRD had significant genetic influence (h^2g 21-24%), particularly HOSP-TRD (28-31%). Different TRD endpoints enriched with various psychiatric genetic liability spectra. BD PRS increased likelihood of ECT, lithium, valproate by 1.27-1.80 fold.	h^2g 0.21-0.24 for TRD, 0.28-0.31 for HOSP-TRD; OR 1.20-1.80 for various PRS associations
Winham, S. J	GWAS/SNP Analysis	TCF7L2 variant associated with BD risk is BMI-dependent; potential shared genetic risk between BD and T2DM	rs12772424 (TCF7L2) p=2.85E-8 for BMI-dependent BD risk
Wong, B. C	Mixed Methods	Shared genetic bases between depression and cardiometabolic traits varying by depression subtype; some biological pathways identified	Polygenic associations varied by depression subtype; several pathways identified
Xu, Z	Mixed Methods	Positive genetic correlation between depression and hypertension rg=0.15, p=5.75e-10 MR suggested depression has a causal effect on hypertension (OR=1.27) but not the reverse	rg=0.15, p=5.75E-10 depression-hypertension; MR OR 1.27 depression on hypertension
Yoshida, K	PRS	Preliminary evidence for shared genetic risks between metabolic traits, autoimmunity, SCZ, and AIWG	Nominal PRS associations for BMI (R2=0.074, p=0.011), CAD, LDL-C, T1D, SCZ with AIWG
Yu, Y	Mendelian Randomization	Depression is likely a causal risk factor for hypertension; reverse is less clear	rg 0.12 SCZ-BMI; MR OR 1.22 SCZ on BMI; 34 genes, 18 cell types affecting SCZ-BMI in brain
Yu, Y	Two-sample MR	PTSD increases genetic susceptibility to T2DM, with obesity (9.51%) and hypertension (2.09%) as mediators	OR = 1.036 (95% CI: 1.008-1.064, P = 0.011) for PTSD on T2DM
Zammarchi, G	Mixed Methods	Shared genetic bases between some psychiatric disorders, sleep traits, and cardiometabolic traits; MDD has causal effect on insomnia	MR OR 1.97-2.29 MDD on insomnia; top shared genes show enriched interactions
Zhang, H	Multi-method genetic analysis	Positive genetic correlation between DEP and BMI (rg=0.19). Bidirectional causal association found. 16 shared genetic loci identified (5 novel). NEGR1 identified as key shared functional gene	rg=0.19 (P=4.07E-26); MR DEP→BMI: β=0.21 (SE=0.05, P=4.10E-6); MR BMI→DEP: β=0.17 (SE=0.02, P=3.29E-15)
Zhang, M	Mendelian Randomization	MDD has causal impacts on MetS and its components, but not vice versa	ORs ~1.1-2.3 for 19 risk factors on MDD, e.g., OR 1.39 smoking, 0.69 education, 1.42 neuroticism
Zhang, X	Two-sample MR	MDD causally increased risk of hypertension	IVW: OR=1.000573, 95%CI 1.0000732-1.001074, P=0.0246392; WM: OR=1.000499, P=0.0416871; MR-Egger: OR=1.004436, P=0.5932928
Zhang, Z	Bidirectional 2-sample MR	Depression causes 31% increased risk of hypercholesterolemia; no reverse causation found	OR = 1.31 (95% CI: 1.10-1.57, P = 0.002) for depression on hypercholesterolemia
Zheng, X	Mendelian Randomization	MDD has causal impacts on MetS and its components, but reverse direction not supported	MR OR 1.22 MDD on MetS, 1.08 on WC, 1.03 on hypertension, 1.11 on TG, 0.93 on HDL
Zhou, Y	Bidirectional two-sample MR with univariable and multivariable approaches	Genetically predicted BMI significantly associated with increased risk of MDD, SA-ISGC, SA-iPSYCH. Adult body size directly linked to increased risks; early-life body size showed no direct effect	BMI→MDD: OR=1.13 (95%CI=1.06-1.22, p=6.1E-4 BMI→SA-ISGC: OR=1.17 (95%CI=1.08-1.27, p=1.9E-4); BMI→SA-iPSYCH: OR=1.31 (95%CI=1.12-1.54, p=6.2E-4)

Supplementary Table 3.6 - Quality Assessment Results

Quality assessment using a customized quality assessment scale performed by a total of three researchers to reduce potential bias. Headings with an asterisk (*) are all values revealed by the customized quality assessment scale. Quality assessment was performed for every study.

Lead Author	*Population Stratification*	*Multiple Testing Correction*	*Replication*	**Selection*	**Comparability*	**Outcome /Exposure*
Adkins, D. E	No	Yes	No	Unclear Risk	Unclear Risk	Low Risk
Andreassen, O. A	Yes	Yes	No	Low Risk	Unclear Risk	Low Risk
Aoki, R	No	Yes	No	Low Risk	Low Risk	Low Risk
Athanasiu, L	No	No	No	Unclear Risk	Unclear Risk	Unclear
Avinun, R	No	No	Yes	Low Risk	Low Risk	Low Risk
Badini, I	Yes	Yes	No	Low Risk	Low Risk	Low Risk
Bahrami, S	Yes	Yes	No	Low Risk	Low Risk	Low Risk
Bala, R	Yes	No	Yes	Low Risk	Low Risk	Low Risk
Baltramonaityte, V	Yes	Yes	No	Low Risk	Low Risk	Low Risk
Breton, É	Yes	Yes	No	Low Risk	Low Risk	Low Risk
Byg, L. M	Yes	Yes	No	Low Risk	Unclear Risk	Low Risk
Chen, F	Yes	Yes	No	Low Risk	Low Risk	Low Risk
Chen, M	Yes	Yes	No	Low Risk	Low Risk	Low Risk
Chen, W	Yes	No	No	Low Risk	Low Risk	Low Risk
Duncan, L. E	Yes	Yes	No	Low Risk	Low Risk	Low Risk
El Rouby, N	Yes	Yes	Yes	Low Risk	Low Risk	Low Risk
Franz, M	No	No	No	Unclear Risk	Low Risk	Low Risk
Gao, X	Yes	Yes	Yes	Low Risk	Low Risk	Low Risk
Giannakopoulou, O	Yes	Yes	No	Low Risk	Low Risk	Low Risk
Guo, S	Yes	Yes	No	Unclear Risk	Low Risk	Low Risk
Hartwig, F. P	Yes	Yes	No	Low Risk	Low Risk	Low Risk
He, M	Yes	Yes	No	Low Risk	Unclear Risk	Low Risk
He, Q	Yes	Yes	No	Low Risk	Unclear Risk	Low Risk
He, R	Yes	Yes	No	Low Risk	Low Risk	Low Risk
Hou, L	Yes	Yes	No	Low Risk	Low Risk	Low Risk
Huangfu, N	Yes	Yes	Yes	Low Risk	Unclear Risk	Low Risk
Hung, C. F	No	Yes	Yes	High Risk	Low Risk	Low Risk
Kang, J	Yes	Yes	Yes	Low Risk	Low Risk	Low Risk
Kappelmann, N	Yes	Yes	No	Low Risk	Low Risk	Low Risk
Khani, N. S	Yes	Yes	No	Low Risk	Low Risk	Low Risk
Liao, S. F	No	No	No	Low Risk	Unclear Risk	Low Risk
Liao, Y	No	Yes	Yes	Low Risk	Unclear Risk	Low Risk
Liu, H	Yes	Yes	No	Low Risk	Unclear Risk	Low Risk
Liu, H.-Y	Yes	Yes	No	Low Risk	Low Risk	Low Risk
Lukas, E	Yes	Yes	No	Low Risk	Low Risk	Low Risk
Luo, X	Yes	Yes	No	Low Risk	Low Risk	Low Risk
Lv, H	Yes	Yes	No	Low Risk	Low Risk	Low Risk
Ma, H	Yes	Yes	No	Low Risk	Low Risk	Low Risk
Maina, J. G	Yes	No	No	Low Risk	Low Risk	Low Risk
Milaneschi, Y	Yes	Yes	No	Low Risk	Low Risk	Low Risk
Muntane, G	No	No	Yes	Unclear Risk	Unclear Risk	Low Risk

O'Connell, K. S	No	No	No	Low Risk	Unclear Risk	Low Risk
O'Loughlin, J	Yes	Yes	No	Low Risk	Low Risk	Low Risk
Perry, B. I	Yes	Yes	No	Low Risk	Low Risk	Low Risk
Perry, B. I	Yes	Yes	No	Low Risk	Low Risk	Low Risk
Pickrell, J. K	Yes	Yes	No	Low Risk	Low Risk	Low Risk
Pisanu, C	Yes	Yes	No	Low Risk	Low Risk	Low Risk
Prieto, M. L	No	Yes	No	Unclear Risk	Unclear Risk	Unclear Risk
Reponen, E. J	No	Yes	No	Low Risk	Unclear Risk	Low Risk
Reponen, E. J	Yes	Yes	No	Low Risk	Unclear Risk	Low Risk
Rodevand, L	Yes	Yes	No	Low Risk	Low Risk	Low Risk
Rodevand, L	Yes	Yes	No	Low Risk	Low Risk	Low Risk
Sewell, M. D. E	Yes	No	No	Low Risk	Low Risk	Unclear Risk
Sjaarda, J	No	Yes	No	Unclear Risk	Unclear Risk	Low Risk
So, H. C	Yes	Yes	No	Low Risk	Unclear Risk	Low Risk
Song, Y	Yes	Yes	No	Low Risk	Low Risk	Low Risk
Speed, M. S	Yes	Yes	No	Low Risk	Low Risk	Low Risk
Ter Hark, S. E	No	No	No	Low Risk	Unclear Risk	Low Risk
Torgersen, K	Yes	Yes	No	Low Risk	Low Risk	Low Risk
van den Broek, N	Yes	Yes	No	Low Risk	Low Risk	Low Risk
Veeneman, R. R	Yes	Yes	No	Low Risk	Unclear Risk	Low Risk
Viinikainen, J	No	Yes	No	Low Risk	Low Risk	Low Risk
Wang, L.H	Yes	Yes	No	Low Risk	Low Risk	Low Risk
Winham, S. J	No	No	No	Low Risk	Low Risk	Low Risk
Wong, B. C	Yes	Yes	No	Low Risk	Low Risk	Low Risk
Xu, Z	Yes	Yes	No	Unclear Risk	Low Risk	Low Risk
Yoshida, K	No	Yes	No	Unclear Risk	Unclear Risk	Low Risk
Yu, Y	Yes	Yes	No	Low Risk	Unclear Risk	Low Risk
Yu, Y	Yes	Yes	No	Low Risk	Low Risk	Low Risk
Zammarchi, G	Yes	Yes	No	Low Risk	Unclear Risk	Low Risk
Zhang, H	Yes	Yes	No	Low Risk	Low Risk	Low Risk
Zhang, M	Yes	Yes	No	Low Risk	Unclear Risk	Low Risk
Zhang, X	No	No	No	Low Risk	Low Risk	Low Risk
Zhang, Z	Yes	Yes	Yes	Low Risk	Low Risk	Low Risk
Zheng, X	Yes	Yes	No	Low Risk	Unclear Risk	Low Risk
Zhou, Y	Yes	Yes	No	Low Risk	Low Risk	Low Risk

Supplementary Table 3.7 - Mendelian Randomization Specific Study Characteristics

Characteristics unique to the studies that underwent Mendelian Randomization as a statistical method for understanding the genetic connection between psychiatric disorders and metabolic comorbidities. Out of the 56 total studies, 23 employed Mendelian randomization as a technique.

Study	*One-Sample or Two-Sample*	*Individual Level or Summary Level*	*Number of Instruments*	*Instrument Inclusion Criteria*	*Ethnicity*	*Exposure List*	*Outcome List*	*Sensitivity Analysis?*	*MR Methods*	*Test for Weak Instruments*	*Evidence of Heterogeneity*	*Use of Leave-One-Out Analysis*
Aoki, R	Two-Sample	Summary	NR	p < 5E-8	East Asian, European	MetS Traits	SCZ	Yes	MR-Egger, IVW, MR-PRESSO, WM	F-Statistic	NR	NR
Bala, R	Both Two-Sample and One-Sample	Both Summary Level and Individual Level	T2DM: 1289; MDD: 293; Glycaemic traits: 5-168	P < 5E-8	European, East Asian, South Asian, African, Hispanic	T2DM (8 pathway clusters), MDD, Fasting glucose, HbA1c, Insulin fold change, ISI, TG:HDL-C ratio	MDD, T2DM, TRD, GP depression, Glycaemic biomarkers	Yes	IVW, MR-Egger, Weighted median, Penalised weighted median, MR-Horse, MRlap	F-statistics ≥23 (mean F-statistic: T2DM=90, MDD=41)	MR-Egger pleiotropy test	Not explicitly mentioned
Byg, L. M	Two-Sample	Summary	53 (BD), 517 (BMI)	p < 5E-8	European	BD, BMI	BD, BMI	Yes	MR-Egger, WM, IVW	F-Statistic	Cochran's Q	Yes
Chen, F	Two-Sample	Summary Level	Varies by exposure	P < 5E-8	European	8 neuropsychiatric disorders	6 cardiovascular diseases	Yes	IVW, MR-Egger, weighted median	F Statistic > 10	Cochran's Q test	Yes
Chen, M	Two-Sample	Summary Level	26 shared SNPs identified	P < 5E-8 for shared SNPs	East Asian	BMI, Depression	BMI, Depression	Yes	Not specified for MR methods	NR	NR	NR
Chen, W	Two-Sample	Summary	46-235	p < 5E-8	European	BMI, WHR, WHRadjBMI	10 Psychiatric Disorders	Yes	MR-Egger, WM, MR-PRESSO, IVW	F-Statistic	Cochran's Q, MR-PRESSO	Yes
El Rouby, N	Two-Sample	Summary	11-297 per trait	P < 5E-8, r^2 < 0.01, F > 10	Multi-ancestry	BMI, fasting glucose, blood pressure, HDL, triglycerides	SGA-MetS	Yes	IVW, MR-Egger, weighted median	F-Statistic	Cochran's Q	Yes
Gao, X	Two-Sample	Summary	53-517	p < 5E-8	European	MetS	10 Psychiatric Disorders	Yes	UVMR	F-Statistic	Cochran's Q, MR-PRESSO	Yes
Guo, S	Two-Sample	Summary	11-297	p < 5E-8	European	8 Lifestyle Factors	MDD	Yes	MR-Egger, WM, IVW, SM, Wmode	F-Statistic	Cochran's Q	Yes
Hartwig, F. P	Two-Sample	Summary	97 (BMI)	p < 5E-8	European	BMI	BP, SCZ, MDD	Yes	MR-Egger, Weighted Median, IVW	F-Statistic	Cochran's Q	Yes
He, M	Two-Sample	Summary	78 (Smoking), 39 (Sleep), 302 (BMI)	p < 5E-8	European	Smoking, Sleep, BMI	MDD, BD	Yes	MR-Egger, Weighted median, MR-PRESSO, IVM	F-Statistic	Cochran's Q	Yes
He, R	Two-Sample	Summary	144 (BMI), 15 (TG)	Conjunctional FDR < 0.05	European	BMI, TG	SCZ	Yes	MR-Egger, Weighted	NR	NR	No

									median, IVW				
Hou, L	Two-Sample	Summary Level	11-297 (varies by exposure)	p < 5E-8	European, East Asian, African, Hispanic/Latino	8 Lifestyle Factors, MetS, BMI, Smoking, Sleep	MDD, BD, Hypertension, T2DM, MetS components	Yes	TEMR, IVW, MR-Egger, Weighted median, MR-PRESSO	F-Statistic	Cochran's Q, MR-PRESSO	Yes
Huangfu, N	Two-Sample	Summary	Varies by exposure (2-109)	p < 5E-8	European	Mental Health Disorders	Hypertension	Yes	Weighted median, MR-Egger, MR-PRESSO, IVW	NR	Cochran's Q	NR
Kappelmann, N	Two-Sample	Summary	Varies by exposure (5-297)	p < 5E-8	European	CRP Levels, IL-6 signalling, BMI	DEP, Depressive Symptoms	Yes	Weighted median, MR-Egger, MR-PRESSO, IVW	F-Statistic	Cochran's Q	Yes
Khani, N. S	Two-Sample	Summary	Up to 185 (SCZ), varies for cardiometabolic traits (e.g. 105 for HDL, 71 for LDL)	p < 5E-8	European	SCZ, Cardiometabolic Traits	SCZ, Cardiometabolic Traits	Yes	MR-Egger, Weighted median, Weighted mode, IVW	NR	Cochran's Q	Yes
Liu, H.-Y	Two-Sample	Summary Level	10-402 independent SNPs	P < 5E-8 (5E-6 for non-European/sex-stratified)	Multi-ancestry	Depression, T2DM	T2DM, Depression	Yes	IVW, weighted median, MR-Egger	F-Statistic > 10	Cochran's Q	Yes
Lukas, E	Two-Sample	Summary	46 (PTSD), varies by CVD outcome (29-42 SNPs)	P < 5E-8, independent (r^2 = 0.01)	European	PTSD, Atrial fibrillation, Coronary artery disease, Hypertension, Heart failure	PTSD, Atrial fibrillation, Coronary artery disease, Hypertension, Heart failure	Yes	IVW, MR-Egger, Weighted median, Weighted mode, MR-PRESSO	F-Statistic >10	Cochran's Q	Not explicitly mentioned
Luo, X	Two-Sample	Summary Level	13 (overweight), 16 (class 1 obesity), 9 (class 2 obesity) for depressive symptoms; 10, 12, 8 respectively for SWB	P < 5E-8, LD r^2 < 0.001	European	Overweight, Class 1 obesity, Class 2 obesity	Depressive symptoms, Subjective well-being	Yes	IVW, RAPS, MR-Egger, cML-MA	F-statistics > 10	Cochran's Q test, P > 0.05	Yes
Ma, H	Two-Sample	Summary Level	Varies by analysis	P < 5E-8, LD clumping r^2 > 0.01	European (majority)	BD, BMI	BD, BMI	Yes	IVW, MR-Egger, weighted median, simple mode, weighted mode, GSMR	F-Statistic > 10	Cochran's Q	Yes
Maina, J. G	Two-Sample	Summary	78-180	p < 5E-8	European	BMI	SCZ, SWB, DEP	Yes	MR-Egger, Weighted Median, IVW	F-Statistic	Cochran's Q	Yes
O'Loughlin, J	Two-Sample	Summary	78-181	p < 5E-8	Asian	BMI, SWB, DEP	BMI, SWB, DEP	Yes	MR-Egger, Weighted Median, IVW	F-Statistic	Cochran's Q	Yes
Perry, B. I	Two-Sample	Summary	9-81	p < 5E-8	European	Cardiometabolic Traits	SCZ	Yes	MR-Egger, Weighted Median, MR-PRESSO, IVW	F-Statistic	Cochran's Q, MR-PRESSO	Yes
So, H. C	Two-Sample	Summary	3-517	p < 5E-8	European	Cardiometabolic Traits, SCZ, BD	Cardiometabolic Traits, SCZ, BD	Yes	MR-Egger, Weight	NR	Cochran's Q	Yes

									ed Median , IVW			
van den Broek, N	Two-Sample	Summary	NR	p < 5E-8	European	BMI, MDD	BMI, MDD	Yes	MR-Egger, Weighted Median , IVW	NR	NR	Yes
Veenemaan, R. R	Two-Sample	Summary	185 (SCZ), 237 (SBP), 158 (DBP), 12 (HF), 9 (HRV), 68 (QT), 9 (ERP), 34 (DCM)	p < 5E-8	European	SCZ, SBP, DBP, HF, HRV, QT, ERP, DCM	SCZ, SBP, DBP, HF, HRV, QT, ERP, DCM	Yes	MR-Egger, Weighted Median , MR-PRESSO, IVW	F-Statistic	Cochran's Q	Yes
Viinikainen, J	Two-Sample	Summary	70 (DEP), 69 (Insomnia)	p < 5E-8	European	DEP, Insomnia	DEP, Insomnia	Yes	MR-Egger, Maximum likelihood, MR-PRESSO, IVW	F-Statistic	Cochran's Q	Yes
Xu, Z	Two-Sample	Summary	89 (DEP), 129 (Hypertension)	P < 5E-8	European	DEP, Hypertension	Hypertension, DEP	Yes	MR-Egger, Weighted Median , MR-PRESSO, IVW	F-Statistic	Cochran's Q	Yes
Yu, Y	Two-Sample	Summary	270 (SCZ), 870 (BMI)	P < 5E-8	European	SCZ, BMI	SCZ, BMI	Yes	MR-Egger, Weighted Median , MR-PRESSO, IVW	F-Statistic	Cochran's Q	Yes
Yu, Y	Two-Sample	Summary Level	94 (PTSD)	p < 5E-8	European	PTSD	T2DM, Obesity, Hypertension, Hyperlipidaemia, Alcohol consumption, Smoking status	Yes	IVW, MR-Egger, Weighted median , Weighted mode	F-Statistic	Cochran's Q test	Yes
Zammarchi, G	Two-Sample	Summary	39 (MDD to Insomnia), 12 (Insomnia to MDD)	P < 5E-8	European	MDD, Insomnia	Insomnia, MDD	Yes	MR-Egger, Weighted Median , MR-PRESSO, IVW	F-Statistic	Cochran's Q	Yes
Zhang, H	Two-Sample	Summary	DEP and BMI specific instruments	P < 5E-8	European	Depression, BMI	BMI, Depression	Yes	IVW, MR-Egger, Weighted median , MR-PRESSO, GSMR	F-statistics >10	Cochran's Q test	Yes
Zhang, M	Two-Sample	Summary	97 (DEP), 79 (MetS), 30 (Waist circumference), 10 (Hypertension), 118 (FBG), 26 (Triglycerides), 60 (HDL-C)	P < 5E-8	European	DEP, MetS, Waist circumference, Hypertension, FBG, Triglycerides, HDL-C	MetS, Waist circumference, Hypertension, FBG, Triglycerides, HDL-C, DEP	Yes	MR-Egger, Weighted Median , MR-PRESSO, IVW	F-Statistic	Cochran's Q	Yes
Zhang, X	Two-Sample	Summary Level	28 (from 44 original)	P < P < 5E-8, LD r^2 < 0.01	European	Major depressive disorder	Hypertension	Yes	IVW, weighted median , MR-Egger	F-statistics > 10	Cochran's Q test, P < 0.05 (significant heterogeneity)	Yes
Zhang, Z	Two-Sample	Summary Level	40 (depression)	p < 5E-8	European	Depression	Hypercholesterolemia	Yes	IVW, MR-Egger, Weighted median , Weighted mode	F-Statistic	Cochran's Q test	Yes
Zheng, X	Two-Sample	Summary	97 (DEP)	P < 5E-8	European	Smoking, Sleep, BMI, Education, Income,	DEP	Yes	MR-Egger, Weighted	F-Statistic	Cochran's Q	Yes

						Physical activity, Neuroticism, Feeling guilty			median, MR-PRESSO, MR-RAPS, IVW				
Zhou, Y	Two-Sample	Summary Level	BMI: 97; MDD: varies; Early life: 305; Adult: 557	P < 5E-8 for BMI; P < 5E-8 for psychiatric traits; $p<5\times10^{-8}$ for body size	European	BMI, Early life body size, Adult body size, MDD, SWB, SA	MDD, SWB, SA-ISGC, SA-iPSYCH, BMI	Yes	IVW, Weighted median, MR-Egger, MR-PRESSO, GSMR	F-statistic >10	Cochran's Q test	Yes	

Supplementary Table 3.8 - Systematic Review Search Strings

Details of the search strings curated to search PubMed, Scopus, and Web of Science for relevant studies. Keywords were chosen in relation to common terminology used in genetic and GWAS studies as well as studies focusing on psychiatric disorders, antipsychotics, and MetS and/or metabolic comorbidities.

Database	*Search String*
PubMed	("Genome-Wide Association Study"[MeSH] OR "GWAS"[All Fields] OR "Genome Wide Association"[All Fields]) AND ("MetS"[MeSH] OR "Cardiometabolic Traits"[All Fields] OR "Metabolic Abnormalities"[All Fields] OR "BMI"[All Fields] OR "Body Mass Index"[MeSH] OR "High Blood Pressure"[All Fields] OR "Hypertension"[MeSH]) AND ("Mental Disorders"[MeSH] OR "Psychiatric Disorder"[All Fields] OR "Mental Illness"[All Fields] OR "Schizophrenia"[MeSH] OR "Bipolar Disorder"[MeSH] OR "Depression"[MeSH] OR "Antipsychotic Agents"[MeSH] OR "Psychotropic Drugs"[MeSH])
Scopus	(ABS ("Genome-Wide Association Study" OR "GWAS" OR "Genome-Wide Association") AND ABS ("MetS" OR "Cardiometabolic Traits" OR "Metabolic Abnormalities" OR "BMI" OR "Body Mass Index" OR "High Blood Pressure" OR "Hypertension") AND ABS ("Mental Disorders" OR "Psychiatric Disorder" OR "Mental Illness" OR "Schizophrenia" OR "Bipolar Disorder" OR "Depression" OR "Antipsychotic Agents" OR "Psychotropic Drugs"))
Web of Science	("Genome-Wide Association Study" OR "GWAS" OR "Genome-Wide Association") (Abstract) and ("MetS" OR "Cardiometabolic Traits" OR "Metabolic Abnormalities" OR "BMI" OR "Body Mass Index" OR "High Blood Pressure" OR "Hypertension") (Abstract) and ("Mental Disorders" OR "Psychiatric Disorder" OR "Mental Illness" OR "Schizophrenia" OR "Bipolar Disorder" OR "Depression" OR "Antipsychotic Agents" OR "Psychotropic Drugs") (All Fields)

Supplementary Table 3.9 - Systematic Review Inclusion and Exclusion Criteria

Details of the inclusion and exclusion criteria used for selecting studies from the collection of studies found using search strings outlined in Table S1 from PubMed, Scopus, and Web of Science.

	Inclusion Criteria	*Exclusion Criteria*
Population	>Studies involving human participants with psychiatric disorders AND MetS or related metabolic comorbidities >Studies involving participants treated with antipsychotic medications AND effect on MetS or related metabolic comorbidities	>Animal studies >Studies not involving participants with psychiatric disorders or MetS/related comorbidities
Intervention/Exposure	>Studies using genome-wide association study (GWAS) data to investigate genetic overlap, shared aetiology, or causal relationships between psychiatric disorders, antipsychotic-induced weight gain, and MetS or related metabolic traits	>Studies not using GWAS data or advanced statistical techniques to investigate the genetic relationships between psychiatric disorders, antipsychotics, and metabolic traits
Comparator/Context	>Studies comparing genetic associations, shared aetiology, or causal relationships between psychiatric disorders, antipsychotic-induced weight gain, and MetS or related metabolic traits	>Studies not comparing genetic associations, shared aetiology, or causal relationships between the conditions of interest
Outcome	>Studies reporting findings related to shared genetic loci, biological pathways, genetic correlations, causal relationships, or polygenic risk scores linking psychiatric disorders, antipsychotic-induced weight gain, and MetS or related metabolic traits	>Studies not reporting genetic findings related to the associations or causal relationships between the conditions of interest
Study Characteristics	>Peer-reviewed original research articles published in English between January 2005 and March 2024	>Non-peer-reviewed articles, commentaries, editorials, or conference abstracts >Studies published before January 2005

Supplementary Table 3.10 - Systematic Review Quality Assessment Table

Customized quality assessment scale used for assessment of the selected studies. This scale allows studies to be assessed based on selection, comparability, and outcome/exposure. Each study is classified as low, high, or unclear risk based on these methodological aspects, with specific consideration for the unique characteristics of genomic studies.

Low Risk	Selection:	The study has a well-defined, representative sample with clear inclusion/exclusion criteria and minimal risk of selection bias.
	Comparability:	The study adequately controls for potential confounding factors through appropriate study design, matching, or statistical adjustment.
	Outcome/Exposure:	The assessment of the outcome or exposure uses standardized methods with appropriate quality control. For genetic data, this includes established genotyping platforms with adequate quality filters (e.g., call rates >95%, Hardy-Weinberg equilibrium testing). For phenotypes, this includes validated instruments, clinical diagnoses, or measurements following standardized protocols.
High Risk	Selection:	The study uses a highly selected convenience sample without clear rationale. Note: Large-scale biobanks (e.g., UKB) are not automatically classified as high risk despite potential selection bias, particularly when genetic associations studied are unlikely to be substantially affected by selection factors.
	Comparability:	The study fails to adequately control for potential confounding factors, leading to a high risk of bias in the results.
	Outcome/Exposure:	The assessment of the outcome or exposure uses non-standardized methods, lacks appropriate quality control measures, or shows inconsistent application across participants. This includes genetic data without standard quality filters or phenotype data with unstandardized, unvalidated measures, or substantial missing data without appropriate handling.
Unclear Risk	Selection:	The study provides does not information on the sample selection process, inclusion/exclusion criteria, or potential selection bias to make a clear judgment.
	Comparability:	The study provides insufficient information on the control of confounding factors or the adequacy of the comparability between groups.
	Outcome/Exposure:	The study provides insufficient information on the assessment methods, quality control measures, or completeness of data collection, preventing clear evaluation of reliability or validity.

Appendix C - Supplementary Material for Chapter 4

Supplementary Methods

Study Design and Analytical Framework

This study employed a multi-layered genomic approach, integrating Mendelian randomization with phenome-wide association studies and colocalization techniques to investigate potential causal relationships between clozapine plasma levels and cardiometabolic outcomes. The analytical framework consisted of two main pathways of interconnected analysis; **(1)** Bidirectional Causal Investigation: Examining direct effects of clozapine plasma levels on metabolic outcomes; **(2.1)** Phenome-Wide Analysis: PheWAS approach to identify candidate biomarkers associated with clozapine-induced metabolic dysfunction based on a selection of lead variants; **(2.2)** Colocalization Analysis: Prune the list of candidate biomarkers using pairwise conditional colocalization (PWCoCo) to identify if they share causal variants with clozapine plasma levels; and **(2.3)** Causal Investigation of colocalized biomarkers: With the list of colocalized biomarkers, determine if these are causally related to cardiometabolic outcomes indicating potential biomarkers linked to metabolic risk as a result of clozapine use.

Figure 4.1 provides a visual representation of this pipeline, while the directed acyclic graphs (DAGs) (Supplementary Figures 4.1) in the supplementary figures depict the assumptions and relationships for each MR analysis component.

Data Sources and Instrument Selection

Clozapine Plasma Traits Dataset

Genetic instruments for clozapine plasma levels were derived from summary statistics from the CLOZUK2 GWAS (Walters Group Data Repository, Centre for Neuropsychiatric Genetics and Genomics; n = 4,495), which provided variant-level data for clozapine plasma concentration, N-desmethylclozapine (norclozapine) plasma concentration, and clozapine-norclozapine plasma ratio. Population from a United Kingdom study.

Cardiometabolic Datasets

Cardiometabolic outcome data were obtained from large-scale European GWAS through the OpenGWAS platform (https://www.ebi.ac.uk/gwas/) and GWAS Catalog (https://gwas.mrcieu.ac.uk/), including:

- Metabolic syndrome (GCST009602; n = 291,107)
- Type 2 diabetes (ieu-a-1090; n = 120,286)
- Body mass index (ukb-b-19953; n = 461,460)
- Systolic blood pressure (ieu-b-38; n = 757,601)
- Diastolic blood pressure (ieu-b-39; n = 757,601)
- HDL cholesterol (ieu-a-299; n = 187,167)
- LDL cholesterol (ieu-a-300; n = 173,082)
- HbA1c (ieu-b-103; n = 46,368)
- Triglycerides (ieu-b-111; n = 441,016)

Genetic Instrument Selection

For MR analyses using clozapine plasma instruments, clumping was done using the following parameters to ensure independence; clumping r^2 threshold: 0.001, clumping window: 10,000 kb, and significance threshold: $P < 1.00 \times 10^{-5}$. Standard quality control procedures were applied to the genetic data using PLINK v1.9. This included filtering variants based on minor allele frequency (MAF > 0.01), genotype missingness (< 5%), imputation quality scores (INFO > 0.8), and Hardy-Weinberg equilibrium ($P > 1.00 \times 10^{-6}$). These QC steps ensured that only high-quality genetic variants ($F \approx 20$) were used as instruments in the MR analyses.

A systematic approach was implemented to select genetic instruments for clozapine plasma traits to be used in the PheWAS-colocalization analysis: **(1)** Initial SNP (single nucleotide polymorphism or genetic variant) collection: 92 SNPs for clozapine metabolism were collected from Open Targets (https://genetics.opentargets.org/) and GWAS Catalog (https://www.ebi.ac.uk/gwas/); **(2)** Significance thresholding: Applied a P-value threshold of 5.00×10^{-8}, reducing the list to 28 SNPs; **(3)** Duplicate removal: After removing duplicates, 16 SNPs remained; **(4)** Linkage disequilibrium (LD) assessment: LD relationships between SNPs on the same chromosome were assessed using LDmatrix by the National Institutes of Health (NIH) (https://ldlink.nih.gov/?tab=ldmatrix); and **(5)** Final selection: After careful consideration of LD patterns, particularly for the complex locus on chromosome 4 with multiple

partially independent signals and implicated gene clusters previously identified with clozapine plasma traits, 10 lead SNPs were retained as genetic instruments.

Primary Causality Analysis

Direct MR Analysis

For the primary analysis examining direct effects of clozapine plasma traits on metabolic outcomes, we performed LD-aware inverse variance weighted (IVW) Mendelian randomization using the selected genetic instruments.

The analysis was conducted using the TwoSampleMR package (v0.5.6) in R (v4.3.3), with custom modifications to incorporate LD information. For each clozapine plasma trait (clozapine plasma, norclozapine plasma, and clozapine-norclozapine plasma ratio) against each metabolic outcome, we: **(1)** Harmonized exposure and outcome data to ensure consistent effect allele alignment; **(2)** Incorporated LD matrices derived from the 1000 Genomes European reference panel; **(3)** Computed LD-aware IVW estimates using the following formula:

$$\hat{\beta}_{IVW} = (X' \, \Omega^{-1} X)^{-1} \, \mathrm{X}' \, \Omega^{-1} \, \mathrm{Y}$$

Where, X is the matrix of SNP-exposure effects ($\hat{\beta}_X$) with dimensions $n \times 1$ (n SNPs), Y is the vector of SNP-outcome effects ($\hat{\beta}_y$) with dimensions $n \times 1$, Ω is the LD-adjusted variance-covariance matrix with dimensions $n \times n$, where $\Omega = \sum Y \times R$ ($\sum Y$ is a diagonal matrix of outcome variances (SE_Y^2) and R is the genetic correlation matrix); and **(4)** Calculated F-statistics to assess instrument strength using:

$$F_j = \left(\frac{\beta_{X_j}}{SE_{X_j}}\right)^2$$

$$\bar{F} = \left(\frac{1}{n}\right) \sum_{j=1}^{n} F_j$$

To assess the robustness of our findings, we conducted several sensitivity analyses. MR-Egger regression to evaluate directional pleiotropy. This method allows for the estimation of a non-zero intercept that can indicate the average pleiotropic effect:

$$\beta_Y = \beta_0 + \beta_{Egger} \times \beta_X + \varepsilon$$

Where β_0 is the intercept term, representing the average pleiotropic effect. β_{Egger} is the slope coefficient, representing the causal effect adjusted for directional pleiotropy. The intercept term (β_0) provides a test for directional pleiotropy. Weighted median estimation was also used to assess consistency.

$$\hat{\beta}_{WMed} = Median_{w_j}(\beta_j)$$

Where $\beta_j = \frac{(\beta_{Y_j})}{(\beta_{X_j})}$ which is the Wald ratio estimate for the j^{th} SNP. $w_j \propto \frac{1}{Var(\frac{\beta_{Y_j}}{\beta_{X_j}})}$ are weights which are inversely proportional to the variance of the Wald ratio. This approach provides consistent estimates when up to 50% of the information comes from invalid instruments. Heterogeneity assessment using Q-statistics and I^2 values were calculated by:

$$Q = \sum_{j=1}^{n} w_j (\frac{(\beta_{Y_j})}{(\beta_{X_j})} - \hat{\beta}_{IVW})^2$$

$$I^2 = \max [0,100\% \times \frac{Q - df}{Q}]$$

where Q is Cochran's Q statistic and df is the degrees of freedom. Leave-one-out analysis to identify influential outliers that might drive the overall effect was also run generating plots available in the Appendix C Supplementary Figures (Wickham 2016).

Reverse Causation Analysis

To investigate potential bidirectional relationships, we conducted reverse MR analyses using metabolic traits as exposures and clozapine plasma phenotypes as outcomes. Metabolic trait instruments extracted using Plink1.9 at a genome-wide significance p-value threshold. The same analytical approach and sensitivity analyses were applied.

Phenome-Wide Association Analysis

To identify potential biomarkers linked to the clozapine-metabolic relationship, we conducted a phenome-wide association study using the R integrated API for OpenGWAS. For each of the 10 lead SNPs identified for clozapine plasma traits, we: **(1)** Queried the OpenGWAS database; and **(2)** Prioritized biomarkers based on significance, consistency across SNPs, and biological relevance to metabolic outcomes (Bastarache, Denny & Roden 2022; Denny, Bastarache & Roden 2016).

Colocalization Analysis

To evaluate whether the genetic signals for clozapine plasma levels and identified biomarkers via the PheWAS analysis share causal variants, we performed colocalization analysis using PWCoCo (Pairwise Colocalization with Conditioning). PWCoCo implements colocalization analyses from coloc.abf (colocalization R package) for colocalization evidence. A limitation of the coloc.abf method is where the loci being assessed for colocalization evidence must contain only one causal variant (single variant assumption). PWCoCo allows for this assumption to hold as the conditional analyses will identify and then systematically condition upon each independent signal within a region. These regions are then assessed for colocalization evidence using each pairwise combination of conditionally independent signal. This was done using the following pipeline: **(1)** Data preparation: Summary statistics were extracted for each lead SNP and its associated traits within a ± 500kb window. Allele frequencies were calculated using the appropriate chromosomal reference datasets from 1000 Genomes; **(2)** Reference dataset preparation: Chromosome-specific reference files were merged using PLINK v1.9; and **(3)** Colocalization implementation: PWCoCo analysis was performed using the merged reference dataset, applying a Bayesian framework to calculate posterior probabilities for five hypotheses in a high-performance computing suite where the following hypotheses were implemented:

H_0: No association with either trait
H_1: Association with trait 1 only
H_2: Association with trait 2 only
H_3: Association with both traits, different causal variants
H_4: Association with both traits, shared causal variant

Estimates were calculated by PWCoCo using the following model: Posterior probability of hypothesis PP.H_4:

$$PP(H_4) = \frac{P(D|H_4) \times prior_4}{\sum_{j=0}^{4} P(D|H_i) \times prior_i}$$

Where $P(D \mid H_i)$ is the likelihood of the data under hypothesis i, $prior_i$ is the prior probability assigned to hypothesis i. The bayes factor calculation for comparing H_4 to H_3 is:

$$BF_{4,3} = \frac{(P(D|\ H_4))}{(P(D|\ H_3))}$$

Where a high bayes factor supports the hypothesis of a shared causal variant; **(4)** Conditional analysis: PWCoCo was further used to evaluate conditional relationships, allowing us to identify independent biological pathways by adjusting for other colocalized traits:

$$PP(H_4|Z) = \frac{P(D \mid H_4, Z) \times prior_4}{\sum_{j=0}^{4} P(D \mid H_i, Z) \times prior_i}$$

Where Z represent the conditioning variable (another trait) and $P(D|H_i, Z)$ is the likelihood of the data under hypothesis i after conditioning on Z. The likelihood calculation under conditioning is:

$$P(D|H_4, Z) = \int P(D|\beta, Z) \times P(\beta|H_4) d\beta$$

Where β represents the effect sizes of variants, $P(D|\beta, Z)$ is the likelihood of the data given effect sizes β after conditioning on Z, and $P(\beta|H_4)$ is the prior distribution of the effect sizes under H_4; and **(5)** Threshold application: We applied a PP.H_4 > 0.80 threshold for robust colocalization, indicating strong evidence for a shared causal variant.

To visualise the colocalization results, we generated stacked regional association plots for each exposure-outcome relationship. These plots display the regional association patterns for clozapine metabolism traits, association patterns for colocalized phenotypes, LD structure, and position of genes and variants within the region. Stacked association plots were generated using geni.plots (v0.1.2) in R and provide a visualisation of the colocalization patterns seen by this analysis.

For candidate biomarkers identified through the PheWAS-colocalization pipeline ($PP.H_4 > 0.8$), we conducted MR analyses to estimate their causal effects on metabolic outcomes: **(1)** Instrument Selection: For each unconditional phenotype, genetic instruments were selected using the R integrated API 'tophits' function at genome-wide significance; **(2)** Data harmonization and quality control: Instruments were harmonized with outcome data and screened for duplicate variants and missing values; **(3)** MR estimation: IVW analysis (non-LD-aware) was performed using the TwoSampleMR package:

$$\hat{\beta}_{IVW} = \frac{\sum_{j=1}^{n} \beta_{Y_j} \times \beta_{X_j} \times w_j}{\sum_{j=1}^{n} \beta_{X_j}^2 \times w_j}$$

Where β_Y, j is the effect of SNP j on the outcome, β_X, j is the effect of SNP j on the exposure, and $w_j \propto \frac{1}{Var(\frac{\beta_Y, j}{\beta_X, j})}$ are the weights (inverse variance of the Wald ratio). Sensitivity analyses (MR-Egger, weighted median) were conducted as described in section 3.1. Weighted mode was also conducted as an additional sensitivity analysis:

$$\hat{\beta}_{WMode} = argmax_{\beta}[\sum_{j=1}^{n} K_h(\beta - \beta_j) \times w_j]$$

Where $\beta_j = \frac{(\beta_{Y_j})}{(\beta_{X_j})}$ which is the Wald ratio estimate for the j^{th} SNP, K_h is the kernel function with bandwidth h, $w_j \propto \frac{1}{Var(\frac{\beta_{Y_j}}{\beta_{X_j}})}$ are the weights inversely proportional to the squared standard error of the Wald ratio. This estimator is robust to horizontal pleiotropy when up to 50% of the genetic variants are invalid instruments, as it identifies the most common (modal) causal effect estimate among all genetic variants; and **(4)** Result visualization: Forest plots, scatter plots, and leave-one-out plots were generated to visualize the effect estimates (Emdin, Khera & Kathiresan 2017; Sanderson et al. 2022; Wickham 2016).

The same analysis techniques were used with metabolic traits as exposures and intermediate phenotypes as outcomes to assess bidirectionality.

Linkage Disequilibrium Score Regression Analysis

To characterize the genetic architecture of candidate biomarkers and inform multivariable analysis strategy, we performed linkage disequilibrium score regression (LDSC) using the GenomicSEM R package (v0.0.5). LDSC estimates genetic correlation (r_g) between trait pairs by regressing the product of z-scores on LD scores, providing estimates of shared genetic architecture that are robust to confounding from population stratification.

GWAS summary statistics for all 16 candidate biomarkers were standardized using the munge function, which filtered SNPs to the HapMap3 reference panel (~1.2M SNPs), aligned alleles to the 1000 Genomes Phase 3 European reference, and applied quality control filters (MAF > 0.01, INFO > 0.90 when available). Duplicate SNPs and variants in the MHC region (chr6:25–34 Mb) were excluded. Palindromic SNPs (A/T, G/C) were removed to prevent strand mismatches.

Genetic correlations were estimated for all 120 pairwise combinations using the ldsc function with pre-computed LD scores from the 1000 Genomes Phase 3 European reference panel (503 individuals, distributed with GenomicSEM package). Standard errors were computed using block jackknife with 200 genome-wide blocks. For binary traits, liability-scale genetic correlations were estimated by providing sample and population prevalence. The LDSC intercept was examined for each trait to assess potential confounding from population stratification.

Hierarchical clustering was performed using the hclust function in R with complete linkage on the genetic correlation distance matrix ($D = 1 - |r_g|$). A height threshold of 0.85 was selected based on dendrogram structure and biological interpretability, corresponding to a minimum absolute genetic correlation of $|r_g| = 0.15$ for cluster membership. This threshold was validated by varying between 0.75 and 0.95.

Multivariable Mendelian Randomization

Multivariable Mendelian randomization (MVMR) extends standard MR by simultaneously estimating independent causal effects of multiple correlated exposures on an outcome. For genetic variant j and exposures X_1, X_2, ..., X_K, the MVMR model assumes:

$$\Gamma Y_j = \beta_1 \Gamma X_{1j} + \beta_2 \Gamma X_{2j} + \ldots + \beta_K \Gamma X_{Kj} + \varepsilon_j,$$

where Γ terms represent genetic associations and β coefficients represent conditional causal effects. MVMR requires three assumptions: (1) genetic variants are associated with at least one exposure (relevance), (2) variants are independent of confounders (independence), and (3) variants affect the outcome only through the modeled exposures (exclusion restriction).

For the focused Cluster, genetic instruments were selected by identifying SNPs reaching genome-wide significance ($P < 5\times10^{-8}$) for at least one exposure, followed by LD clumping ($r^2 < 0.001$, 10,000 kb window) using 1000 Genomes European reference. Variants were harmonized across all GWAS, with palindromic SNPs excluded when MAF was 0.40–0.60. IVW MVMR was implemented using the MVMR R package (v0.4), which estimates causal effects by regressing variant-outcome associations on variant-exposure associations, weighted by inverse variances:

$$(\Gamma X' W \Gamma X) - 1 \Gamma X' W \Gamma Y$$

Instrument strength was assessed using conditional F-statistics for each exposure, computed as the squared t-statistic from regressing each exposure's GWAS effects on other exposures' GWAS effects, weighted by inverse variances. $F > 10$ indicates strong instruments. Cochran's Q statistic was computed to assess heterogeneity in variant-specific estimates, with significant Q potentially indicating pleiotropy violations.

As a sensitivity analysis, naive MVMR was performed including all biomarkers simultaneously across nine outcomes. Instruments were selected using the same approach (genome-wide significant for ≥ 1 biomarker, LD clumping $r^2 < 0.001$). As anticipated for high-dimensional MVMR, this resulted in weak instruments due to multicollinearity. However, this analysis served to validate that focused Cluster findings were robust and not artifacts of selective biomarker inclusion.

All analyses were conducted in R version 4.3.0 using GenomicSEM (v0.0.5) for genetic correlations and MVMR (v0.4) for multivariable MR. Hierarchical clustering used the hclust function (stats package) and visualization used ggplot2 (v3.4.2).

Software and Implementation Details

All analyses were conducted using R (v4.3.3) with the following key packages: TwoSampleMR (v0.6.8) for MR analysis and data harmonization, ieugwasr (v1.0.1) for accessing OpenGWAS data and PheWAS analysis, ggplot2 (v3.5.1) for visualization, data.table (v1.16.1) for data manipulation, dplyr (v1.1.4) for data transformation, circlize (v0.3.16) for circular representation of PheWAS and colocalization results, and geni.plots (v0.1.2) for colocalization visualization. PWCoCo colocalization analysis was performed on a high-performance computing system using custom scripts. PLINK v1.9 was used for handling genetic data, particularly for LD calculations, file formatting, and genetic instrument clumping. A 1000 Genomes Reference Data set was also used. Genetic correlation analyses were performed using the GenomicSEM R package (version 0.0.5) in R version 4.3.0. All MVMR analyses were conducted using the MVMR R package (version 0.4). Hierarchical clustering and visualization were performed in R using the hclust function (stats package) and ggplot2 (version 3.5.1) for figure generation.

Statistical Analysis and Interpretation

Significance Thresholds and Bonferroni P-Value Adjustment

To account for multiple-testing (controlling for increased risk of type I error), Bonferroni adjustment was made on P-values by dividing the overall significance threshold by the number of tests being run. This adjustment results in a stricter significance level for each individual test, reducing the overall probability of a false positive.

- Forward clozapine plasma on cardiometabolic traits ($P = \frac{0.05}{27} = 1.85 \times 10^{-3}$)
- Reverse clozapine plasma on cardiometabolic traits ($P = \frac{0.05}{27} = 1.85 \times 10^{-3}$)
- Forward candidate biomarkers on cardiometabolic traits ($P = \frac{0.05}{9} = 5.56 \times 10^{-3}$)
- Reverse candidate biomarkers on cardiometabolic traits ($P = \frac{0.05}{28} = 1.79 \times 10^{-3}$)

Causal Inference Framework

Interpretation of results follows the principles of Mendelian randomization as a causal inference method, requiring the following assumptions: **(1)** The genetic variants are robustly associated with the exposure; **(2)** The genetic variants affect the outcome only through the exposure; and **(3)** The genetic variants are not associated with confounders.

The multi-layered approach employed in this study was specifically designed to address potential violations of these assumptions through sensitivity analyses, colocalization methods, and adjusting for potential confounders.

Interpretation Considerations and Limitations

Several methodological aspects require caution when interpreting results from this multi-layered analysis: **(1)** while our colocalization approach identified significant shared genetic signals between clozapine plasma traits and identified biomarkers, these statistical associations do not definitively prove biological causality or fully elucidate the molecular mechanisms involved. The identified colocalized biomarkers represent promising candidates for further experimental validation; **(2)** despite our comprehensive approach to addressing pleiotropy through sensitivity analyses and adjusting for confounding factors, residual horizontal pleiotropy may still influence some findings. While MR-Egger intercepts suggested minimal directional pleiotropy, this test has limited power, especially when using smaller numbers of genetic instruments; and **(3)** our analysis focused primarily on individuals of European ancestry due to data availability, limiting the generalizability of our findings to other populations. Genetic architecture and metabolic responses to clozapine may differ across ancestral groups, highlighting the need for future studies with diverse population representation.

Supplementary Tables

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Supplementary Table 4.1 - Clozapine Plasma Traits Effects on Metabolic Outcomes (LD-aware MR)

Exposure	*Outcome*	*MR Method*	*nSNP*	*Beta*	*SE*	*P-Value*	*F Stat (Mean)*	*F Stat (Min)*	*Q Stat*	*Q P-Value*	*I^2*	*Egger Intercept*	*SE Egger Intercept*	*Egger Intercept P-Value*
Clozapine Plasma	DBP	IVW (LD-corrected)	16	-0.05003198	0.182494314	0.783964448	24.57485479	19.54228913	NA	NA	NA	NA	NA	NA
Clozapine Plasma	DBP	MR Egger (LD-corrected)	16	0.003690956	NA	NA	24.57485479	19.54228913	0.907051593	0.999999873	0	-0.026913615	0.028485597	0.344753421
Clozapine Plasma	DBP	Weighted median (LD-corrected)	16	-0.183184565	0.180608128	0.310456157	24.57485479	19.54228913	NA	NA	NA	NA	NA	NA
Clozapine Plasma	SBP	IVW (LD-corrected)	16	0.331239776	0.05383875	7.63E-10	24.57485479	19.54228913	NA	NA	NA	NA	NA	NA
Clozapine Plasma	SBP	MR Egger (LD-corrected)	16	0.031877396	NA	NA	24.57485479	19.54228913	0.540915994	0.999999997	0	-0.037510006	0.055144737	0.496371451
Clozapine Plasma	SBP	Weighted median (LD-corrected)	16	0.330551405	0.01666986	1.66E-87	24.57485479	19.54228913	NA	NA	NA	NA	NA	NA
Clozapine Plasma	HbA1c	IVW (LD-corrected)	6	0.032215382	0.463197658	0.944551861	29.59310964	20.20769488	NA	NA	NA	NA	NA	NA
Clozapine Plasma	HbA1c	MR Egger (LD-corrected)	6	0.020119763	NA	NA	29.59310964	20.20769488	4.73E-05	1	0	-0.001810285	0.289051973	0.995003012
Clozapine Plasma	HbA1c	Weighted median (LD-corrected)	6	0.031248784	0.003569804	2.07E-18	29.59310964	20.20769488	NA	NA	NA	NA	NA	NA
Clozapine Plasma	HDL	IVW (LD-corrected)	7	0.051786991	0.091792518	0.572635434	28.58390925	20.20769488	NA	NA	NA	NA	NA	NA
Clozapine Plasma	HDL	MR Egger (LD-corrected)	7	0.03079577	NA	NA	28.58390925	20.20769488	0.002079172	1	0	-0.002288648	0.051314906	0.964426086
Clozapine Plasma	HDL	Weighted median (LD-corrected)	7	0.053374952	0.005431462	8.62E-23	28.58390925	20.20769488	NA	NA	NA	NA	NA	NA
Clozapine Plasma	LDL	IVW (LD-corrected)	7	0.046831807	0.298085749	0.875159333	28.58390925	20.20769488	NA	NA	NA	NA	NA	NA
Clozapine Plasma	LDL	MR Egger (LD-corrected)	7	0.032472843	NA	NA	28.58390925	20.20769488	0.000330753	1	0	-0.002608471	0.155301335	0.986599206
Clozapine Plasma	LDL	Weighted median (LD-corrected)	7	0.044602785	0.006578338	1.20E-11	28.58390925	20.20769488	NA	NA	NA	NA	NA	NA
Clozapine Plasma	Triglycerides	IVW (LD-corrected)	7	0.048083776	0.077618243	0.535593182	28.58390925	20.20769488	NA	NA	NA	NA	NA	NA
Clozapine Plasma	Triglycerides	MR Egger (LD-corrected)	7	0.019682168	NA	NA	28.58390925	20.20769488	0.000181811	1	0	-0.003250201	0.287063885	0.990966368
Clozapine Plasma	Triglycerides	Weighted median (LD-corrected)	7	0.04803685	0.003920202	1.61E-34	28.58390925	20.20769488	NA	NA	NA	NA	NA	NA
Clozapine Plasma	T2DM	IVW (LD-corrected)	17	0.485407043	0.036188229	5.05E-41	24.45449315	19.54228913	NA	NA	NA	NA	NA	NA
Clozapine Plasma	T2DM	MR Egger (LD-corrected)	17	-0.090308044	NA	NA	24.45449315	19.54228913	14.73386012	0.544210571	0	-0.06150953	0.020794407	0.003096578
Clozapine Plasma	T2DM	Weighted median (LD-corrected)	17	0.520664097	0.183545631	0.004558226	24.45449315	19.54228913	NA	NA	NA	NA	NA	NA
Clozapine Plasma	BMI	IVW (LD-corrected)	17	0.01604503	0.160931507	0.920581719	24.45449315	19.54228913	NA	NA	NA	NA	NA	NA
Clozapine Plasma	BMI	MR Egger (LD-corrected)	17	0.004042266	NA	NA	24.45449315	19.54228913	0.002684616	1	0	-0.002743244	0.0530733	0.958777437
Clozapine Plasma	BMI	Weighted median (LD-corrected)	17	0.016491121	0.01259765	0.190512923	24.45449315	19.54228913	NA	NA	NA	NA	NA	NA
Clozapine Plasma	MetS	IVW (LD-corrected)	7	-0.009837229	0.004530063	0.02989013	28.58390925	20.20769488	NA	NA	NA	NA	NA	NA
Clozapine Plasma	MetS	MR Egger (LD-corrected)	7	-0.029117219	NA	NA	28.58390925	20.20769488	34.63794399	5.06E-06	82.67795571	-0.002460813	0.002139193	0.250001272
Clozapine Plasma	MetS	Weighted median (LD-corrected)	7	-0.00130527	0.019885487	0.947664995	28.58390925	20.20769488	NA	NA	NA	NA	NA	NA
Cloz-Norcloz Plasma Ratio	DBP	IVW (LD-corrected)	17	0.209895676	0.023167129	1.30E-19	30.2245365	19.89666534	NA	NA	NA	NA	NA	NA

Cloz-Norcloz Plasma Ratio	DBP	MR Egger (LD-corrected)	17	0.030628848	NA	NA	30.2245365	19.89666534	0.678287536	0.999999997	0	-0.020532052	0.028197883	0.734049618
Cloz-Norcloz Plasma Ratio	DBP	Weighted median (LD-corrected)	17	0.21086976	0.064991118	0.001176184	30.2245365	19.89666534	NA	NA	NA	NA	NA	NA
Cloz-Norcloz Plasma Ratio	SBP	IVW (LD-corrected)	17	-0.072733882	0.085258125	0.393602711	30.2245365	19.89666534	NA	NA	NA	NA	NA	NA
Cloz-Norcloz Plasma Ratio	SBP	MR Egger (LD-corrected)	17	-0.048317557	NA	NA	30.2245365	19.89666534	19.3061321	0.253108204	17.12477718	-0.047688421	0.010899572	0.829708588
Cloz-Norcloz Plasma Ratio	SBP	Weighted median (LD-corrected)	17	0.366154603	0.376780965	0.331151559	30.2245365	19.89666534	NA	NA	NA	NA	NA	NA
Cloz-Norcloz Plasma Ratio	HbA1c	IVW (LD-corrected)	7	0.024560281	0.244487354	0.919982119	27.46053471	19.89666534	NA	NA	NA	NA	NA	NA
Cloz-Norcloz Plasma Ratio	HbA1c	MR Egger (LD-corrected)	7	0.005545249	NA	NA	27.46053471	19.89666534	0.012450472	0.99999996	0	-0.005012107	0.047522723	0.971036355
Cloz-Norcloz Plasma Ratio	HbA1c	Weighted median (LD-corrected)	7	0.029103868	0.030405884	0.338476998	27.46053471	19.89666534	NA	NA	NA	NA	NA	NA
Cloz-Norcloz Plasma Ratio	HDL	IVW (LD-corrected)	7	0.006951815	0.248225862	0.977657362	27.37530277	19.89666534	NA	NA	NA	NA	NA	NA
Cloz-Norcloz Plasma Ratio	HDL	MR Egger (LD-corrected)	7	0.006465766	NA	NA	27.37530277	19.89666534	0.035265261	0.999999098	0	-0.006465105	0.035022899	0.979269478
Cloz-Norcloz Plasma Ratio	HDL	Weighted median (LD-corrected)	7	-0.052730474	0.046521644	0.257020671	27.37530277	19.89666534	NA	NA	NA	NA	NA	NA
Cloz-Norcloz Plasma Ratio	LDL	IVW (LD-corrected)	7	0.009614707	0.650172269	0.988201363	27.37530277	19.89666534	NA	NA	NA	NA	NA	NA
Cloz-Norcloz Plasma Ratio	LDL	MR Egger (LD-corrected)	7	-0.004078833	NA	NA	27.37530277	19.89666534	0.007475178	0.999999991	0	-0.006700166	0.079696218	0.979623741
Cloz-Norcloz Plasma Ratio	LDL	Weighted median (LD-corrected)	7	0.056917023	0.050793979	0.262480887	27.37530277	19.89666534	NA	NA	NA	NA	NA	NA
Cloz-Norcloz Plasma Ratio	Triglycerides	IVW (LD-corrected)	7	0.050978759	0.083163708	0.539881064	27.37530277	19.89666534	NA	NA	NA	NA	NA	NA
Cloz-Norcloz Plasma Ratio	Triglycerides	MR Egger (LD-corrected)	7	-0.006783066	NA	NA	27.37530277	19.89666534	0.004604597	0.999999998	0	-0.006231228	0.094180159	0.983222166
Cloz-Norcloz Plasma Ratio	Triglycerides	Weighted median (LD-corrected)	7	0.051318627	0.028709611	0.073855602	27.37530277	19.89666534	NA	NA	NA	NA	NA	NA
Cloz-Norcloz Plasma Ratio	T2DM	IVW (LD-corrected)	17	0.555227286	0.165464658	0.000792033	30.13758144	19.89666534	NA	NA	NA	NA	NA	NA
Cloz-Norcloz Plasma Ratio	T2DM	MR Egger (LD-corrected)	17	0.121371711	NA	NA	30.13758144	19.89666534	6.42198589	0.982862674	0	-0.09947558	0.042730855	0.226642222
Cloz-Norcloz Plasma Ratio	T2DM	Weighted median (LD-corrected)	17	0.542614494	0.315478967	0.085437817	30.13758144	19.89666534	NA	NA	NA	NA	NA	NA
Cloz-Norcloz Plasma Ratio	BMI	IVW (LD-corrected)	18	0.018595983	0.174904762	0.915327971	29.68585626	19.89666534	NA	NA	NA	NA	NA	NA
Cloz-Norcloz Plasma Ratio	BMI	MR Egger (LD-corrected)	18	0.001273302	NA	NA	29.68585626	19.89666534	0.003168193	1	0	-0.002794265	0.051660515	0.976547964
Cloz-Norcloz Plasma Ratio	BMI	Weighted median (LD-corrected)	18	0.023628265	0.00657974	0.000329331	29.68585626	19.89666534	NA	NA	NA	NA	NA	NA
Cloz-Norcloz Plasma Ratio	MetS	IVW (LD-corrected)	7	-0.017993681	0.004743145	0.000148468	27.37530277	19.89666534	NA	NA	NA	NA	NA	NA
Cloz-Norcloz Plasma Ratio	MetS	MR Egger (LD-corrected)	7	-0.012164309	NA	NA	27.37530277	19.89666534	56.25375939	2.59E-10	89.33404618	0.001331815	0.000641924	1.83E-05
Cloz-Norcloz Plasma Ratio	MetS	Weighted median (LD-corrected)	7	-0.006439093	0.025688364	0.802075557	27.37530277	19.89666534	NA	NA	NA	NA	NA	NA
Norclozapine Plasma	DBP	IVW (LD-corrected)	10	-0.111882181	0.246840666	0.650363922	99.70394317	20.10514773	NA	NA	NA	NA	NA	NA
Norclozapine Plasma	DBP	MR Egger (LD-corrected)	10	-0.031648831	NA	NA	99.70394317	20.10514773	0.128975247	0.99999992	0	-0.026842823	0.079009059	0.466526898
Norclozapine Plasma	DBP	Weighted median (LD-corrected)	10	-0.136976649	0.105632138	0.19472317	99.70394317	20.10514773	NA	NA	NA	NA	NA	NA
Norclozapine Plasma	SBP	IVW (LD-corrected)	10	0.071693847	0.652322679	0.912484325	99.70394317	20.10514773	NA	NA	NA	NA	NA	NA
Norclozapine Plasma	SBP	MR Egger (LD-corrected)	10	0.000203746	NA	NA	99.70394317	20.10514773	0.047812973	0.999999999	0	-0.04786301	0.222540679	1.21E-05

Norclozapine Plasma	SBP	Weighted median (LD-corrected)	10	0.248617239	0.238729024	0.29768055	99.70394317	20.10514773	NA	NA	NA	NA	NA	NA
Norclozapine Plasma	HbA1c	IVW (LD-corrected)	2	0.005663635	0.363887411	0.987582026	358.120146	20.10514773	NA	NA	NA	NA	NA	NA
Norclozapine Plasma	HbA1c	MR Egger (LD-corrected)	2	0.002665231	NA	NA	358.120146	20.10514773	0.001318309	0.971036355	0	-0.004151356	0.114335584	0.916004796
Norclozapine Plasma	HbA1c	Weighted median (LD-corrected)	2	-0.041353291	0.021424171	0.053580009	358.120146	20.10514773	NA	NA	NA	NA	NA	NA
Norclozapine Plasma	HDL	IVW (LD-corrected)	3	0.011113608	0.490017785	0.981905521	245.3419288	19.7854944	NA	NA	NA	NA	NA	NA
Norclozapine Plasma	HDL	MR Egger (LD-corrected)	3	0.003821647	NA	NA	245.3419288	19.7854944	0.000675429	0.999662343	0	-0.005935779	0.228432911	0.853545528
Norclozapine Plasma	HDL	Weighted median (LD-corrected)	3	-0.059379084	0.034756546	0.087556806	245.3419288	19.7854944	NA	NA	NA	NA	NA	NA
Norclozapine Plasma	LDL	IVW (LD-corrected)	3	-0.03262356	1.433046901	0.981837589	245.3419288	19.7854944	NA	NA	NA	NA	NA	NA
Norclozapine Plasma	LDL	MR Egger (LD-corrected)	3	0.004928147	NA	NA	245.3419288	19.7854944	0.000654138	0.999672984	0	-0.00591299	0.231513069	0.93299973
Norclozapine Plasma	LDL	Weighted median (LD-corrected)	3	-0.0606238	0.015737798	0.000117102	245.3419288	19.7854944	NA	NA	NA	NA	NA	NA
Norclozapine Plasma	Triglycerides	IVW (LD-corrected)	3	-0.014706882	1.622377521	0.992767261	245.3419288	19.7854944	NA	NA	NA	NA	NA	NA
Norclozapine Plasma	Triglycerides	MR Egger (LD-corrected)	3	0.004048142	NA	NA	245.3419288	19.7854944	0.000443975	0.999778037	0	-0.005561429	0.264459116	0.947248169
Norclozapine Plasma	Triglycerides	Weighted median (LD-corrected)	3	-0.055010485	0.012322127	8.03E-06	245.3419288	19.7854944	NA	NA	NA	NA	NA	NA
Norclozapine Plasma	T2DM	IVW (LD-corrected)	12	0.172450271	0.204148862	0.398262692	92.50154795	19.7854944	NA	NA	NA	NA	NA	NA
Norclozapine Plasma	T2DM	MR Egger (LD-corrected)	12	-0.044859341	NA	NA	92.50154795	19.7854944	1.57853218	0.99951256	0	-0.048530873	0.040139552	0.019914403
Norclozapine Plasma	T2DM	Weighted median (LD-corrected)	12	0.299195531	0.19319662	0.121463906	92.50154795	19.7854944	NA	NA	NA	NA	NA	NA
Norclozapine Plasma	BMI	IVW (LD-corrected)	12	-0.014171573	0.068597334	0.836329501	92.50154795	19.7854944	NA	NA	NA	NA	NA	NA
Norclozapine Plasma	BMI	MR Egger (LD-corrected)	12	-0.00823656	NA	NA	92.50154795	19.7854944	0.002781623	1	0	-0.001543774	0.052514678	0.956864267
Norclozapine Plasma	BMI	Weighted median (LD-corrected)	12	-0.015341564	0.006003113	0.010600442	92.50154795	19.7854944	NA	NA	NA	NA	NA	NA
Norclozapine Plasma	MetS	IVW (LD-corrected)	3	0.004184411	0.003112573	0.17883274	245.3419288	19.7854944	NA	NA	NA	NA	NA	NA
Norclozapine Plasma	MetS	MR Egger (LD-corrected)	3	0.00259982	NA	NA	245.3419288	19.7854944	41.95910882	7.74E-10	95.23345453	-0.003642965	0.000850198	0.038012163
Norclozapine Plasma	MetS	Weighted median (LD-corrected)	3	0.008361582	0.047264524	0.859578838	245.3419288	19.7854944	NA	NA	NA	NA	NA	NA

Supplementary Table 4.2 - Metabolic Traits Effects on Clozapine Plasma Traits (LD-aware MR)

Exposure	Outcome	MR Method	nSNP	Beta	SE	P-Value	F Stat (Mean)	F Stat (Min)	Q Stat	Q Stat P-Value	I^2	Egger Intercept	Egger Intercept SE
BMI	Clozapine Plasma	IVW (LD-corrected)	197	0.024477	0.079719	0.758815	74.81586599	30.16352643	206.246	0.293811898	4.96783414	NA	NA
BMI	Clozapine Plasma	MR Egger (LD-corrected)	197	-0.02521	0.081513	0.757133	74.81586599	30.16352643	NA	NA	NA	0.004706978	0.001611232
BMI	Clozapine Plasma	Weighted median (LD-corrected)	197	0.16288	0.18403	0.37612	74.81586599	30.16352643	NA	NA	NA	NA	NA
BMI	Clozapine-Norclozapine Plasma Ratio	IVW (LD-corrected)	197	0.085945	0.07868	0.274688	74.81586599	30.16352643	204.2862	0.327682007	4.05617301	NA	NA
BMI	Clozapine-Norclozapine Plasma Ratio	MR Egger (LD-corrected)	197	0.03938	0.080436	0.624426	74.81586599	30.16352643	NA	NA	NA	0.004430439	0.001590106
BMI	Clozapine-Norclozapine Plasma Ratio	Weighted median (LD-corrected)	197	0.049855	0.100623	0.620273	74.81586599	30.16352643	NA	NA	NA	NA	NA
BMI	Norclozapine Plasma	IVW (LD-corrected)	197	-0.01275	0.077875	0.869931	74.81586599	30.16352643	189.8365	0.610591524	0	NA	NA
BMI	Norclozapine Plasma	MR Egger (LD-corrected)	197	-0.0398	0.079585	0.616999	74.81586599	30.16352643	NA	NA	NA	0.002589294	0.001571017
BMI	Norclozapine Plasma	Weighted median (LD-corrected)	197	0.197715	0.154472	0.200566	74.81586599	30.16352643	NA	NA	NA	NA	NA
DBP	Clozapine Plasma	IVW (LD-corrected)	199	-0.00422	0.008445	0.617155	86.27207084	29.70012014	231.3126	0.052459443	14.4015589	NA	NA
DBP	Clozapine Plasma	MR Egger (LD-corrected)	199	-0.0029	0.008484	0.732063	86.27207084	29.70012014	NA	NA	NA	-0.002555204	0.001576822
DBP	Clozapine Plasma	Weighted median (LD-corrected)	199	0.012989	0.019083	0.496069	86.27207084	29.70012014	NA	NA	NA	NA	NA
DBP	Clozapine Plasma	IVW (LD-corrected)	208	-0.00493	0.004858	0.309985	81.18791338	29.93981381	215.5616	0.327157379	3.97176983	NA	NA
DBP	Clozapine Plasma	MR Egger (LD-corrected)	208	-0.00407	0.004896	0.405452	81.18791338	29.93981381	NA	NA	NA	-0.002162276	0.00153186
DBP	Clozapine Plasma	Weighted median (LD-corrected)	208	-0.00741	0.009599	0.439852	81.18791338	29.93981381	NA	NA	NA	NA	NA
DBP	Clozapine-Norclozapine Plasma Ratio	IVW (LD-corrected)	199	-0.00062	0.008326	0.941087	86.27207084	29.70012014	236.4494	0.03197096	16.261157	NA	NA
DBP	Clozapine-Norclozapine Plasma Ratio	MR Egger (LD-corrected)	199	0.0011	0.00836	0.895321	86.27207084	29.70012014	NA	NA	NA	-0.003566948	0.001553752
DBP	Clozapine-Norclozapine Plasma Ratio	Weighted median (LD-corrected)	199	0.003516	0.020803	0.865778	86.27207084	29.70012014	NA	NA	NA	NA	NA
DBP	Clozapine-Norclozapine Plasma Ratio	IVW (LD-corrected)	208	-0.00158	0.004804	0.742439	81.18791338	29.93981381	260.318	0.007018692	20.4818756	NA	NA
DBP	Clozapine-Norclozapine Plasma Ratio	MR Egger (LD-corrected)	208	-0.00121	0.00484	0.803111	81.18791338	29.93981381	NA	NA	NA	-0.000955196	0.001513637
DBP	Clozapine-Norclozapine Plasma Ratio	Weighted median (LD-corrected)	208	-0.00427	0.010928	0.696009	81.18791338	29.93981381	NA	NA	NA	NA	NA
DBP	Norclozapine Plasma	IVW (LD-corrected)	199	-0.00389	0.008251	0.637593	86.27207084	29.70012014	225.619	0.08670963	12.2414196	NA	NA
DBP	Norclozapine Plasma	MR Egger (LD-corrected)	199	-0.00357	0.008291	0.667068	86.27207084	29.70012014	NA	NA	NA	-0.000604849	0.001538041
DBP	Norclozapine Plasma	Weighted median (LD-corrected)	199	0.008857	0.009467	0.349539	86.27207084	29.70012014	NA	NA	NA	NA	NA
DBP	Norclozapine Plasma	IVW (LD-corrected)	208	-0.00359	0.004744	0.448747	81.18791338	29.93981381	212.4906	0.38201339	2.58390517	NA	NA
DBP	Norclozapine Plasma	MR Egger (LD-corrected)	208	-0.00291	0.004782	0.542745	81.18791338	29.93981381	NA	NA	NA	-0.00167587	0.001493296

DBP	Norclozapine Plasma		Weighted median (LD-corrected)	208	0.004182	0.007293	0.566381	81.18791338	29.93981381	NA	NA	NA	NA	NA
HbA1c	Clozapine Plasma		IVW (LD-corrected)	9	-0.4197	0.228753	0.066543	64.04395192	32.76199546	11.65395	0.167324195	31.3537705	NA	NA
HbA1c	Clozapine Plasma		MR Egger (LD-corrected)	9	-0.34262	0.248722	0.168354	64.04395192	32.76199546	NA	NA	NA	-0.006519644	0.008258518
HbA1c	Clozapine Plasma		Weighted median (LD-corrected)	9	-0.40714	0.332598	0.220905	64.04395192	32.76199546	NA	NA	NA	NA	NA
HbA1c	Clozapine-Norclozapine Ratio	Plasma	IVW (LD-corrected)	9	-0.1125	0.228982	0.623209	64.04395192	32.76199546	7.630542	0.470365606	0	NA	NA
HbA1c	Clozapine-Norclozapine Ratio	Plasma	MR Egger (LD-corrected)	9	-0.08345	0.251217	0.739738	64.04395192	32.76199546	NA	NA	NA	-0.002329644	0.008287859
HbA1c	Clozapine-Norclozapine Ratio	Plasma	Weighted median (LD-corrected)	9	-0.1399	0.276986	0.613506	64.04395192	32.76199546	NA	NA	NA	NA	NA
HbA1c	Norclozapine Plasma		IVW (LD-corrected)	9	-0.36972	0.222713	0.096899	64.04395192	32.76199546	9.297436	0.317829332	13.9547713	NA	NA
HbA1c	Norclozapine Plasma		MR Egger (LD-corrected)	9	-0.30893	0.242712	0.203082	64.04395192	32.76199546	NA	NA	NA	-0.005073462	0.008051437
HbA1c	Norclozapine Plasma		Weighted median (LD-corrected)	9	-0.37308	0.234686	0.111905	64.04395192	32.76199546	NA	NA	NA	NA	NA
HDL	Clozapine Plasma		IVW (LD-corrected)	68	0.071737	0.06348	0.258447	109.135486	29.94521605	95.04062	0.013745147	29.5038284	NA	NA
HDL	Clozapine Plasma		MR Egger (LD-corrected)	68	0.058567	0.063789	0.358542	109.135486	29.94521605	NA	NA	NA	0.005684641	0.002704565
HDL	Clozapine Plasma		Weighted median (LD-corrected)	68	0.034167	0.154566	0.82505	109.135486	29.94521605	NA	NA	NA	NA	NA
HDL	Clozapine-Norclozapine Ratio	Plasma	IVW (LD-corrected)	68	-0.00986	0.06256	0.874707	109.135486	29.94521605	92.49277	0.021271958	27.5619019	NA	NA
HDL	Clozapine-Norclozapine Ratio	Plasma	MR Egger (LD-corrected)	68	-0.01223	0.062872	0.845806	109.135486	29.94521605	NA	NA	NA	0.001007767	0.002669846
HDL	Clozapine-Norclozapine Ratio	Plasma	Weighted median (LD-corrected)	68	-0.02729	0.144818	0.850504	109.135486	29.94521605	NA	NA	NA	NA	NA
HDL	Norclozapine Plasma		IVW (LD-corrected)	68	0.075679	0.062087	0.222875	109.135486	29.94521605	81.57155	0.108552444	17.8635236	NA	NA
HDL	Norclozapine Plasma		MR Egger (LD-corrected)	68	0.064236	0.062397	0.303259	109.135486	29.94521605	NA	NA	NA	0.00486521	0.002640481
HDL	Norclozapine Plasma		Weighted median (LD-corrected)	68	0.115013	0.120934	0.341585	109.135486	29.94521605	NA	NA	NA	NA	NA
LDL	Clozapine Plasma		IVW (LD-corrected)	49	-0.0105	0.059621	0.86021	146.5344204	27.78540649	44.39234	0.621458782	0	NA	NA
LDL	Clozapine Plasma		MR Egger (LD-corrected)	49	-0.01075	0.05974	0.857178	146.5344204	27.78540649	NA	NA	NA	0.000219475	0.003286443
LDL	Clozapine Plasma		Weighted median (LD-corrected)	49	0.011048	NA	NA	146.5344204	27.78540649	NA	NA	NA	NA	NA
LDL	Clozapine-Norclozapine Ratio	Plasma	IVW (LD-corrected)	49	0.065675	0.059199	0.267257	146.5344204	27.78540649	36.70715	0.882641803	0	NA	NA
LDL	Clozapine-Norclozapine Ratio	Plasma	MR Egger (LD-corrected)	49	0.067449	0.05933	0.255603	146.5344204	27.78540649	NA	NA	NA	-0.001467843	0.003265063
LDL	Clozapine-Norclozapine Ratio	Plasma	Weighted median (LD-corrected)	49	0.019317	NA	NA	146.5344204	27.78540649	NA	NA	NA	NA	NA
LDL	Norclozapine Plasma		IVW (LD-corrected)	49	-0.03941	0.058083	0.497501	146.5344204	27.78540649	45.46696	0.577228764	0	NA	NA
LDL	Norclozapine Plasma		MR Egger (LD-corrected)	49	-0.04113	0.058205	0.479831	146.5344204	27.78540649	NA	NA	NA	0.001466115	0.003206126
LDL	Norclozapine Plasma		Weighted median (LD-corrected)	49	-0.01655	NA	NA	146.5344204	27.78540649	NA	NA	NA	NA	NA

MetS	Clozapine Plasma		IVW (LD-corrected)	46	0.09794	0.051366	0.056558	71.18298489	29.88623736	64.94621	0.027324019	30.7118884	NA	NA
MetS	Clozapine Plasma		MR Egger (LD-corrected)	46	0.101284	0.05191	0.051038	71.18298489	29.88623736	NA	NA	NA	-0.001487207	0.003332259
MetS	Clozapine Plasma		Weighted median (LD-corrected)	46	0.101008	0.147845	0.494477	71.18298489	29.88623736	NA	NA	NA	NA	NA
MetS	Clozapine-Norclozapine Ratio	Plasma	IVW (LD-corrected)	46	0.045688	0.050801	0.368458	71.18298489	29.88623736	66.69867	0.019441642	32.5323848	NA	NA
MetS	Clozapine-Norclozapine Ratio	Plasma	MR Egger (LD-corrected)	46	0.052547	0.051347	0.306136	71.18298489	29.88623736	NA	NA	NA	-0.003022468	0.003293545
MetS	Clozapine-Norclozapine Ratio	Plasma	Weighted median (LD-corrected)	46	0.043075	0.122641	0.725419	71.18298489	29.88623736	NA	NA	NA	NA	NA
MetS	Norclozapine Plasma		IVW (LD-corrected)	46	0.077473	0.050088	0.121928	71.18298489	29.88623736	56.72625	0.112856453	20.671651	NA	NA
MetS	Norclozapine Plasma		MR Egger (LD-corrected)	46	0.077346	0.050613	0.126464	71.18298489	29.88623736	NA	NA	NA	5.66E-05	0.003251502
MetS	Norclozapine Plasma		Weighted median (LD-corrected)	46	0.042081	0.112748	0.708976	71.18298489	29.88623736	NA	NA	NA	NA	NA
T2DM	Clozapine Plasma		IVW (LD-corrected)	80	0.098123	0.031608	0.001907	87.28145992	29.94180028	80.204	0.441051016	1.50117264	NA	NA
T2DM	Clozapine Plasma		MR Egger (LD-corrected)	80	0.095899	0.031816	0.002577	87.28145992	29.94180028	NA	NA	NA	0.001536923	0.002510703
T2DM	Clozapine Plasma		Weighted median (LD-corrected)	80	0.128375	0.075088	0.087328	87.28145992	29.94180028	NA	NA	NA	NA	NA
T2DM	Clozapine-Norclozapine Ratio	Plasma	IVW (LD-corrected)	80	0.020266	0.031079	0.514361	87.28145992	29.94180028	85.7519	0.282553734	7.87376257	NA	NA
T2DM	Clozapine-Norclozapine Ratio	Plasma	MR Egger (LD-corrected)	80	0.02078	0.031281	0.506512	87.28145992	29.94180028	NA	NA	NA	-0.000358627	0.00247704
T2DM	Clozapine-Norclozapine Ratio	Plasma	Weighted median (LD-corrected)	80	-0.00491	0.073378	0.946697	87.28145992	29.94180028	NA	NA	NA	NA	NA
T2DM	Norclozapine Plasma		IVW (LD-corrected)	80	0.090127	0.030828	0.003461	87.28145992	29.94180028	81.91159	0.389065155	3.55455586	NA	NA
T2DM	Norclozapine Plasma		MR Egger (LD-corrected)	80	0.088002	0.031032	0.00457	87.28145992	29.94180028	NA	NA	NA	0.001464794	0.002443687
T2DM	Norclozapine Plasma		Weighted median (LD-corrected)	80	0.13558	0.06238	0.029746	87.28145992	29.94180028	NA	NA	NA	NA	NA
Triglycerides	Clozapine Plasma		IVW (LD-corrected)	47	-0.04891	0.061265	0.424695	179.9328287	30.90051903	62.45077	0.053409409	26.3419789	NA	NA
Triglycerides	Clozapine Plasma		MR Egger (LD-corrected)	47	-0.03001	0.063037	0.634069	179.9328287	30.90051903	NA	NA	NA	0.004118315	0.003232938
Triglycerides	Clozapine Plasma		Weighted median (LD-corrected)	47	-0.07882	NA	NA	179.9328287	30.90051903	NA	NA	NA	NA	NA
Triglycerides	Clozapine-Norclozapine Ratio	Plasma	IVW (LD-corrected)	47	0.04709	0.060934	0.439632	179.9328287	30.90051903	62.46858	0.05324476	26.362984	NA	NA
Triglycerides	Clozapine-Norclozapine Ratio	Plasma	MR Egger (LD-corrected)	47	0.074806	0.062724	0.233018	179.9328287	30.90051903	NA	NA	NA	0.005953173	0.003195804
Triglycerides	Clozapine-Norclozapine Ratio	Plasma	Weighted median (LD-corrected)	47	0.112365	NA	NA	179.9328287	30.90051903	NA	NA	NA	NA	NA
Triglycerides	Norclozapine Plasma		IVW (LD-corrected)	47	-0.06964	0.059239	0.23978	179.9328287	30.90051903	59.43859	0.088181572	22.6092	NA	NA
Triglycerides	Norclozapine Plasma		MR Egger (LD-corrected)	47	-0.06798	0.060953	0.26474	179.9328287	30.90051903	NA	NA	NA	0.000364841	0.003155712
Triglycerides	Norclozapine Plasma		Weighted median (LD-corrected)	47	-0.07878	NA	NA	179.9328287	30.90051903	NA	NA	NA	NA	NA

Supplementary Table 4.3 - PheWAS Results

Chr	Pos	Beta	SE	P	n	ID	rsID	EA	NEA	EAF	Trait	Query SNP	Ethnicity	Window Start	Window End
2	2.35E+08	-0.04636	0.00361	9.66E-38	NA	ieu-b-4812	rs1337113701	G	T	0.07939	25-Hydroxyvitamin D	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.04674	0.00373	5.07E-36	417580	ebi-a-GCST90000614	rs2011425	G	T	0.077893	25-Hydroxyvitamin D	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.04664	0.003672	5.80E-37	417580	ebi-a-GCST90000615	rs2011425	G	T	0.077923	25-Hydroxyvitamin D	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.04656	0.003674	8.28E-37	417580	ebi-a-GCST90000616	rs2011425	G	T	0.077893	25-Hydroxyvitamin D	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.04382	0.00368	1.09E-32	417580	ebi-a-GCST90000617	rs2011425	G	T	0.077923	25-Hydroxyvitamin D	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.04783	0.003761	4.66E-37	496946	ebi-a-GCST90000618	rs2011425	G	T	0.079578	25-Hydroxyvitamin D	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.04589	0.00456	8.13E-24	329247	ukb-d-30890_irnt	rs2011425	G	T	0.079392	25-Hydroxyvitamin D	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.99468	0.095686	2.63E-25	329247	ukb-d-30890_raw	rs2011425	G	T	0.079392	25-Hydroxyvitamin D	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.05149	0.003958	4.10E-39	418691	ebi-a-GCST90025967	rs2011425	G	T	0.079601	25-Hydroxyvitamin D	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.0458	0.00419	8.16E-28	373045	ebi-a-GCST90014016	rs2011425	G	T	NA	25-Hydroxyvitamin D	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.04404	0.003543	1.81E-35	NA	ieu-b-4812	rs3732218	A	G	0.081658	25-Hydroxyvitamin D	rs3732218	EUR	233627304	235627304
2	2.35E+08	-0.04647	0.003639	2.37E-37	417580	ebi-a-GCST90000614	rs3732218	A	G	0.081652	25-Hydroxyvitamin D	rs3732218	EUR	233627304	235627304
2	2.35E+08	-0.04647	0.003582	1.76E-38	417580	ebi-a-GCST90000615	rs3732218	A	G	0.081687	25-Hydroxyvitamin D	rs3732218	EUR	233627304	235627304
2	2.35E+08	-0.04628	0.003583	3.67E-38	417580	ebi-a-GCST90000616	rs3732218	A	G	0.081652	25-Hydroxyvitamin D	rs3732218	EUR	233627304	235627304
2	2.35E+08	-0.04374	0.00359	3.78E-34	417580	ebi-a-GCST90000617	rs3732218	A	G	0.081687	25-Hydroxyvitamin D	rs3732218	EUR	233627304	235627304
2	2.35E+08	-0.04718	0.00368	1.26E-37	496946	ebi-a-GCST90000618	rs3732218	A	G	0.082928	25-Hydroxyvitamin D	rs3732218	EUR	233627304	235627304
2	2.35E+08	-0.04527	0.004479	5.11E-24	329247	ukb-d-30890_irnt	rs3732218	A	G	0.081597	25-Hydroxyvitamin D	rs3732218	EUR	233627304	235627304
2	2.35E+08	-0.97746	0.093973	2.46E-25	329247	ukb-d-30890_raw	rs3732218	A	G	0.081597	25-Hydroxyvitamin D	rs3732218	EUR	233627304	235627304
2	2.35E+08	-0.04424	0.004114	5.61E-27	373045	ebi-a-GCST90014016	rs3732218	A	G	NA	25-Hydroxyvitamin D	rs3732218	EUR	233627304	235627304
2	2.35E+08	-0.06692	0.002903	1.90E-120	436055	ebi-a-GCST90025973	rs2011425	G	T	0.079614	Bilirubin Levels	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.04655	0.006033	1.20E-14	NA	ieu-b-4868	rs1337113701	G	T	0.080217	Bioavailable Testosterone	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.03534	0.00611	7.30E-09	NA	ieu-b-4869	rs1337113701	G	T	0.079462	Bioavailable Testosterone	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.02569	0.004701	3.30E-08	188507	ebi-a-GCST90012102	rs2011425	G	T	0.07945	Bioavailable Testosterone	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.05025	0.005656	6.40E-20	178782	ebi-a-GCST90012103	rs2011425	G	T	0.079615	Bioavailable Testosterone	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.03766	0.003714	8.90E-25	382988	ebi-a-GCST90012104	rs2011425	G	T	0.079474	Bioavailable Testosterone	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.04533	0.005924	2.00E-14	NA	ieu-b-4868	rs3732218	A	G	0.08243	Bioavailable Testosterone	rs3732218	EUR	233627304	235627304
2	2.35E+08	-0.03414	0.006004	1.30E-08	NA	ieu-b-4869	rs3732218	A	G	0.081613	Bioavailable Testosterone	rs3732218	EUR	233627304	235627304
2	2.35E+08	-0.02521	0.004619	3.10E-08	188507	ebi-a-GCST90012102	rs3732218	A	G	0.081646	Bioavailable Testosterone	rs3732218	EUR	233627304	235627304
2	2.35E+08	-0.04819	0.005553	3.10E-19	178782	ebi-a-GCST90012103	rs3732218	A	G	0.081856	Bioavailable Testosterone	rs3732218	EUR	233627304	235627304
2	2.35E+08	-0.0368	0.003647	1.10E-24	382988	ebi-a-GCST90012104	rs3732218	A	G	0.081698	Bioavailable Testosterone	rs3732218	EUR	233627304	235627304
2	2.35E+08	-0.09581	0.004659	6.62E-94	292933	ukb-d-30660_irnt	rs2011425	G	T	0.079128	Direct Bilirubin	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.10485	0.004051	1.48E-147	292933	ukb-d-30660_raw	rs2011425	G	T	0.079128	Direct Bilirubin	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.2908	0.03446	3.23E-17	NA	ukb-e-30660_AFR	rs2011425	G	T	0.90436	Direct Bilirubin	rs2011425	AFR	233627608	235627608
2	2.35E+08	-0.2136	0.02143	2.09E-23	NA	ukb-e-30660_CSA	rs2011425	G	T	0.8081	Direct Bilirubin	rs2011425	Mixed	233627608	235627608
2	2.35E+08	-0.08554	0.003526	1.60E-134	372420	ebi-a-GCST90025983	rs2011425	G	T	0.079238	Direct Bilirubin	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.09642	0.004326	4.99E-110	332739	ebi-a-GCST90013997	rs2011425	G	T	NA	Direct Bilirubin	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.406	0.03625	4.07E-29	NA	ukb-e-recode1_AFR	rs2011425	G	T	0.90444	Direct Bilirubin	rs2011425	AFR	233627608	235627608
2	2.35E+08	-0.252	0.02271	1.31E-28	NA	ukb-e-recode1_CSA	rs2011425	G	T	0.8077	Direct Bilirubin	rs2011425	Mixed	233627608	235627608
2	2.35E+08	-0.09998	0.004577	1.05E-105	292933	ukb-d-30660_irnt	rs3732218	A	G	0.081285	Direct Bilirubin	rs3732218	EUR	233627304	235627304
2	2.35E+08	-0.10708	0.003979	2.55E-159	292933	ukb-d-30660_raw	rs3732218	A	G	0.081285	Direct Bilirubin	rs3732218	EUR	233627304	235627304
2	2.35E+08	-0.2583	0.03357	1.42E-14	NA	ukb-e-30660_AFR	rs3732218	A	G	0.8997	Direct Bilirubin	rs3732218	AFR	233627304	235627304
2	2.35E+08	-0.2114	0.02135	3.97E-23	NA	ukb-e-30660_CSA	rs3732218	A	G	0.8082	Direct Bilirubin	rs3732218	Mixed	233627304	235627304
2	2.35E+08	-0.10042	0.004249	1.69E-123	332739	ebi-a-GCST90013997	rs3732218	A	G	NA	Direct Bilirubin	rs3732218	EUR	233627304	235627304
2	2.35E+08	-0.3614	0.03531	1.37E-24	NA	ukb-e-recode1_AFR	rs3732218	A	G	0.8998	Direct Bilirubin	rs3732218	AFR	233627304	235627304
2	2.35E+08	-0.2516	0.02263	1.02E-28	NA	ukb-e-recode1_CSA	rs3732218	A	G	0.8079	Direct Bilirubin	rs3732218	Mixed	233627304	235627304
2	2.35E+08	-0.0253	0.002844	5.73E-19	312102	ukb-d-30850_irnt	rs2011425	G	T	0.079206	Testosterone	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.09949	0.012601	2.91E-15	312102	ukb-d-30850_raw	rs2011425	G	T	0.079206	Testosterone	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.02433	0.002793	3.02E-18	312102	ukb-d-30850_irnt	rs3732218	A	G	0.081417	Testosterone	rs3732218	EUR	233627304	235627304
2	2.35E+08	-0.09791	0.012377	2.57E-15	312102	ukb-d-30850_raw	rs3732218	A	G	0.081417	Testosterone	rs3732218	EUR	233627304	235627304
2	2.35E+08	-0.02576	0.002705	1.67E-21	353805	ebi-a-GCST90014013	rs2011425	G	T	NA	Testosterone Levels	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.02491	0.002655	6.56E-21	353805	ebi-a-GCST90014013	rs3732218	A	G	NA	Testosterone Levels	rs3732218	EUR	233627304	235627304
2	2.35E+08	0.05749	0.006589	2.63E-18	NA	bbj-a-53	rs2011425	G	T	0.1331	Total Bilirubin	rs2011425	EAS	233627608	235627608
2	2.35E+08	-0.08307	0.004277	5.83E-84	342829	ukb-d-30840_irnt	rs2011425	G	T	0.079476	Total Bilirubin	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.59643	0.019265	3.66E-210	342829	ukb-d-30840_raw	rs2011425	G	T	0.079476	Total Bilirubin	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.3826	0.03204	7.32E-33	NA	ukb-e-30840_AFR	rs2011425	G	T	0.8972	Total Bilirubin	rs2011425	AFR	233627608	235627608
2	2.35E+08	-0.2218	0.01952	6.63E-30	NA	ukb-e-30840_CSA	rs2011425	G	T	0.802	Total Bilirubin	rs2011425	Mixed	233627608	235627608
2	2.35E+08	0.044991	0.005492	2.60E-16	124341	ebi-a-GCST90018753	rs2011425	G	T	0.132742	Total Bilirubin	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.0347	0.0034	8.07E-25	342829	ebi-a-GCST90018973	rs2011425	G	T	0.093653	Total Bilirubin	rs2011425	EUR	233627608	235627608

2	2.35E+08	-0.08572	0.003929	1.68E-105	388303	ebi-a-GCST90013872	rs2011425	G	T	NA	Total Bilirubin	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.08603	0.003936	6.44E-106	388303	ebi-a-GCST90014012	rs2011425	G	T	NA	Total Bilirubin	rs2011425	EUR	233627608	235627608
2	2.35E+08	0.0355	0.006279	1.58E-08	NA	bbj-a-53	rs3732218	A	G	0.1325	Total Bilirubin	rs3732218	EAS	233627304	235627304
2	2.35E+08	-0.08738	0.004201	4.74E-96	342829	ukb-d-30840_irnt	rs3732218	A	G	0.08168	Total Bilirubin	rs3732218	EUR	233627304	235627304
2	2.35E+08	-0.61094	0.018918	1.86E-228	342829	ukb-d-30840_raw	rs3732218	A	G	0.08168	Total Bilirubin	rs3732218	EUR	233627304	235627304
2	2.35E+08	-0.3424	0.03137	9.91E-28	NA	ukb-e-30840_AFR	rs3732218	A	G	0.8932	Total Bilirubin	rs3732218	AFR	233627304	235627304
2	2.35E+08	-0.2193	0.01947	1.98E-29	NA	ukb-e-30840_CSA	rs3732218	A	G	0.8026	Total Bilirubin	rs3732218	Mixed	233627304	235627304
2	2.35E+08	0.031648	0.005413	5.00E-09	124341	ebi-a-GCST90018753	rs3732218	A	G	0.131559	Total Bilirubin	rs3732218	EUR	233627304	235627304
2	2.35E+08	-0.0426	0.0033	8.64E-38	342829	ebi-a-GCST90018973	rs3732218	A	G	0.094956	Total Bilirubin	rs3732218	EUR	233627304	235627304
2	2.35E+08	-0.08998	0.003858	2.56E-120	388303	ebi-a-GCST90013872	rs3732218	A	G	NA	Total Bilirubin	rs3732218	EUR	233627304	235627304
2	2.35E+08	-0.09024	0.003864	1.21E-120	388303	ebi-a-GCST90014012	rs3732218	A	G	NA	Total Bilirubin	rs3732218	EUR	233627304	235627304
2	2.35E+08	-0.03206	0.005844	4.10E-08	NA	ieu-b-4864	rs1337113701	G	T	0.07939	Total Testosterone	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.046	0.005735	1.00E-15	NA	ieu-b-4865	rs1337113701	G	T	0.080366	Total Testosterone	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.03349	0.005199	6.60E-11	230454	ebi-a-GCST90012112	rs2011425	G	T	0.079396	Total Testosterone	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.04834	0.005631	1.90E-18	194453	ebi-a-GCST90012113	rs2011425	G	T	0.07973	Total Testosterone	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.02498	0.002389	3.10E-26	425097	ebi-a-GCST90012114	rs2011425	G	T	0.079563	Total Testosterone	rs2011425	EUR	233627608	235627608
2	2.35E+08	-0.04567	0.00563	5.00E-16	NA	ieu-b-4865	rs3732218	A	G	0.082622	Total Testosterone	rs3732218	EUR	233627304	235627304
2	2.35E+08	-0.03203	0.005108	1.40E-10	230454	ebi-a-GCST90012112	rs3732218	A	G	0.081552	Total Testosterone	rs3732218	EUR	233627304	235627304
2	2.35E+08	-0.04713	0.005527	2.50E-18	194453	ebi-a-GCST90012113	rs3732218	A	G	0.082015	Total Testosterone	rs3732218	EUR	233627304	235627304
2	2.35E+08	-0.02446	0.002346	3.80E-26	425097	ebi-a-GCST90012114	rs3732218	A	G	0.081777	Total Testosterone	rs3732218	EUR	233627304	235627304
2	2.35E+08	-0.0532	0.0089	2.77E-09	7250	met-a-513	rs3732218	A	G	0.0805	X-11440	rs3732218	EUR	233627304	235627304
4	70030273	-0.02102	0.001939	2.18E-27	NA	ieu-b-4812	rs7668556	G	A	0.529883	25-Hydroxyvitamin D	rs7668556	EUR	69030273	71030273
4	70030273	-0.02462	0.002	8.04E-35	417580	ebi-a-GCST90000614	rs7668556	G	A	0.531216	25-Hydroxyvitamin D	rs7668556	EUR	69030273	71030273
4	70030273	-0.02436	0.001969	3.92E-35	417580	ebi-a-GCST90000615	rs7668556	G	A	0.531156	25-Hydroxyvitamin D	rs7668556	EUR	69030273	71030273
4	70030273	-0.02479	0.00197	2.56E-36	417580	ebi-a-GCST90000616	rs7668556	G	A	0.531216	25-Hydroxyvitamin D	rs7668556	EUR	69030273	71030273
4	70030273	-0.02251	0.001974	3.88E-30	417580	ebi-a-GCST90000617	rs7668556	G	A	0.531156	25-Hydroxyvitamin D	rs7668556	EUR	69030273	71030273
4	70030273	-0.02349	0.002042	1.26E-30	496946	ebi-a-GCST90000618	rs7668556	G	A	0.531408	25-Hydroxyvitamin D	rs7668556	EUR	69030273	71030273
4	70030273	-0.02481	0.002452	4.61E-24	329247	ukb-d-30890_irnt	rs7668556	G	A	0.52896	25-Hydroxyvitamin D	rs7668556	EUR	69030273	71030273
4	70030273	-0.53574	0.051451	2.19E-25	329247	ukb-d-30890_raw	rs7668556	G	A	0.52896	25-Hydroxyvitamin D	rs7668556	EUR	69030273	71030273
4	70030273	-0.02466	0.002267	1.44E-27	373045	ebi-a-GCST90014016	rs7668556	G	A	NA	25-Hydroxyvitamin D	rs7668556	EUR	69030273	71030273
4	70030273	-0.01211	0.002	8.50E-10	382988	ebi-a-GCST90012104	rs7668556	G	A	0.530497	Bioavailable Testosterone	rs7668556	EUR	69030273	71030273
4	69669183	0.346195	0.035995	7.17E-22	5185	ebi-a-GCST009970	rs10000284	C	T	0.079997	Cotinine	rs10000284	EUR	68669183	70669183
4	69659738	0.324022	0.034764	1.23E-20	5185	ebi-a-GCST009970	rs10023464	T	C	0.085986	Cotinine	rs10023464	EUR	68659738	70659738
4	69680942	0.348836	0.036823	2.89E-21	5185	ebi-a-GCST009970	rs11725502	T	A	0.077045	Cotinine	rs11725502	EUR	68680942	70680942
4	69682855	-0.34433	0.035959	1.08E-21	5185	ebi-a-GCST009970	rs835309	G	T	0.920031	Cotinine	rs835309	EUR	68682855	70682855
4	69669183	0.345179	0.03663	4.65E-21	5185	ebi-a-GCST009965	rs10000284	C	T	0.079997	Cotinine levels smokers	rs10000284	EUR	68669183	70669183
4	69659738	0.319984	0.035451	1.89E-19	5185	ebi-a-GCST009965	rs10023464	T	C	0.085986	Cotinine levels smokers	rs10023464	EUR	68659738	70659738
4	69680942	0.349734	0.03748	1.11E-20	5185	ebi-a-GCST009965	rs11725502	T	A	0.077045	Cotinine levels smokers	rs11725502	EUR	68680942	70680942
4	69682855	-0.34445	0.036591	5.11E-21	5185	ebi-a-GCST009965	rs835309	G	T	0.920031	Cotinine levels smokers	rs835309	EUR	68682855	70682855
4	69669183	-0.0261	0.004118	2.34E-10	292933	ukb-d-30660_irnt	rs10000284	C	T	0.10247	Direct Bilirubin	rs10000284	EUR	68669183	70669183
4	69669183	-0.02332	0.003427	1.01E-11	332739	ebi-a-GCST90013997	rs10000284	C	T	NA	Direct Bilirubin	rs10000284	EUR	68669183	70669183
4	69659738	-0.02543	0.00411	6.10E-10	292933	ukb-d-30660_irnt	rs10023464	T	C	0.10312	Direct Bilirubin	rs10023464	EUR	68659738	70659738
4	69659738	-0.02307	0.00342	1.54E-11	332739	ebi-a-GCST90013997	rs10023464	T	C	NA	Direct Bilirubin	rs10023464	EUR	68659738	70659738
4	69680942	-0.02561	0.004189	9.79E-10	292933	ukb-d-30660_irnt	rs11725502	T	A	0.10009	Direct Bilirubin	rs11725502	EUR	68680942	70680942
4	69680942	-0.02263	0.003485	8.45E-11	332739	ebi-a-GCST90013997	rs11725502	T	A	NA	Direct Bilirubin	rs11725502	EUR	68680942	70680942
4	69682855	0.025585	0.004118	5.23E-10	292933	ukb-d-30660_irnt	rs835309	G	T	0.89765	Direct Bilirubin	rs835309	EUR	68682855	70682855
4	69682855	0.022998	0.003427	1.93E-11	332739	ebi-a-GCST90013997	rs835309	G	T	NA	Direct Bilirubin	rs835309	EUR	68682855	70682855
4	69669183	0.153862	0.020525	6.58E-14	3956	eqtl-a-ENSG00000249763	rs10000284	C	T	0.092262	ENSG00000249763	rs10000284	EUR	68669183	70669183
4	69659738	0.136709	0.020519	2.69E-11	3691	eqtl-a-ENSG00000249763	rs10023464	T	C	0.092413	ENSG00000249763	rs10023464	EUR	68659738	70659738
4	69680942	0.158225	0.021782	3.75E-13	3871	eqtl-a-ENSG00000249763	rs11725502	T	A	0.080937	ENSG00000249763	rs11725502	EUR	68680942	70680942
4	70030273	-0.17388	0.011876	1.53E-48	10239	eqtl-a-ENSG00000249763	rs7668556	G	A	0.551021	ENSG00000249763	rs7668556	EUR	69030273	71030273
4	69682855	-0.15593	0.021015	1.17E-13	3956	eqtl-a-ENSG00000249763	rs835309	G	T	0.912433	ENSG00000249763	rs835309	EUR	68682855	70682855
4	70030273	-0.09092	0.011942	2.67E-14	5493	eqtl-a-ENSG00000250696	rs7668556	G	A	0.551021	ENSG00000250696	rs7668556	EUR	69030273	71030273
4	70030273	-0.00695	0.000847	1.90E-16	206927	ebi-a-GCST90012105	rs7668556	G	A	0.530887	Estradiol Levels	rs7668556	EUR	69030273	71030273
4	70030273	-0.10877	0.012853	2.62E-17	147690	ebi-a-GCST90020091	rs7668556	G	A	0.530151	Estradiol Levels	rs7668556	EUR	69030273	71030273
4	70030273	-0.0133	0.002	1.21E-11	344104	ebi-a-GCST90018954	rs7668556	G	A	0.599685	Gamma glutamyl transpeptidase	rs7668556	EUR	69030273	71030273
4	70030273	-0.01216	0.002223	4.47E-08	344104	ukb-d-30730_irnt	rs7668556	G	A	0.52935	Gamma Glutamyltransferase Levels	rs7668556	EUR	69030273	71030273
4	70030273	-0.01305	0.001953	2.37E-11	389672	ebi-a-GCST90014004	rs7668556	G	A	NA	Gamma glutamyltransferase levels	rs7668556	EUR	69030273	71030273
4	69669183	-0.02136	0.003885	3.81E-08	350472	ukb-d-30050_irnt	rs10000284	C	T	0.102974	Mean Corpuscular Haemoglobin	rs10000284	EUR	68669183	70669183
4	69680942	-0.0216	0.003951	4.54E-08	350472	ukb-d-30050_irnt	rs11725502	T	A	0.100603	Mean Corpuscular Haemoglobin	rs11725502	EUR	68680942	70680942
4	69682855	0.021215	0.003885	4.73E-08	350472	ukb-d-30050_irnt	rs835309	G	T	0.897145	Mean Corpuscular Haemoglobin	rs835309	EUR	68682855	70682855
4	69669183	-0.03341	0.005865	1.22E-08	172332	ebi-a-GCST004630	rs10000284	C	T	0.1032	Mean Corpuscular Haemoglobin	rs10000284	EUR	68669183	70669183

4	69669183	-0.02932	0.003196	4.76E-20	486823	ebi-a-GCST90002322	rs10000284	C	T	0.101608	Mean Corpuscular Haemoglobin	rs10000284	EUR	68669183	70669183
4	69669183	-0.0312	0.003432	9.80E-20	408112	ebi-a-GCST90002390	rs10000284	C	T	0.102406	Mean Corpuscular Haemoglobin	rs10000284	EUR	68669183	70669183
4	69669183	-0.02628	0.003082	2.90E-19	572863	ebi-a-GCST90028995	rs10000284	C	T	0.10228	Mean Corpuscular Haemoglobin	rs10000284	EUR	68669183	70669183
4	69659738	-0.0336	0.005866	1.02E-08	172332	ebi-a-GCST004630	rs10023464	T	C	0.1017	Mean Corpuscular Haemoglobin	rs10023464	EUR	68659738	70659738
4	69659738	-0.02969	0.003195	1.63E-20	486823	ebi-a-GCST90002322	rs10023464	T	C	0.102344	Mean Corpuscular Haemoglobin	rs10023464	EUR	68659738	70659738
4	69659738	-0.03101	0.003423	1.30E-19	408112	ebi-a-GCST90002390	rs10023464	T	C	0.103188	Mean Corpuscular Haemoglobin	rs10023464	EUR	68659738	70659738
4	69659738	-0.0189	0.0028	7.05E-12	350472	ebi-a-GCST90018964	rs10023464	T	C	0.158403	Mean Corpuscular Haemoglobin	rs10023464	EUR	68659738	70659738
4	69659738	-0.02582	0.003075	7.00E-19	572863	ebi-a-GCST90028995	rs10023464	T	C	0.103017	Mean Corpuscular Haemoglobin	rs10023464	EUR	68659738	70659738
4	69680942	-0.0329	0.005864	2.01E-08	172332	ebi-a-GCST004630	rs11725502	T	A	0.1009	Mean Corpuscular Haemoglobin	rs11725502	EUR	68680942	70680942
4	69680942	-0.02977	0.003248	5.22E-20	486823	ebi-a-GCST90002322	rs11725502	T	A	0.099109	Mean Corpuscular Haemoglobin	rs11725502	EUR	68680942	70680942
4	69680942	-0.03173	0.003492	1.00E-19	408112	ebi-a-GCST90002390	rs11725502	T	A	0.099867	Mean Corpuscular Haemoglobin	rs11725502	EUR	68680942	70680942
4	69680942	-0.0216	0.004	4.54E-08	350472	ebi-a-GCST90018964	rs11725502	T	A	0.100603	Mean Corpuscular Haemoglobin	rs11725502	EUR	68680942	70680942
4	69680942	-0.02658	0.003137	3.30E-19	572863	ebi-a-GCST90028995	rs11725502	T	A	0.099726	Mean Corpuscular Haemoglobin	rs11725502	EUR	68680942	70680942
4	70030273	0.012219	0.001932	2.61E-10	486823	ebi-a-GCST90002322	rs7668556	G	A	0.534333	Mean Corpuscular Haemoglobin	rs7668556	EUR	69030273	71030273
4	70030273	0.012318	0.002086	3.50E-09	408112	ebi-a-GCST90002390	rs7668556	G	A	0.531746	Mean Corpuscular Haemoglobin	rs7668556	EUR	69030273	71030273
4	70030273	0.011565	0.001873	1.20E-09	572863	ebi-a-GCST90028995	rs7668556	G	A	0.53231	Mean Corpuscular Haemoglobin	rs7668556	EUR	69030273	71030273
4	69682855	0.032665	0.005845	2.29E-08	172332	ebi-a-GCST004630	rs835309	G	T	0.898	Mean Corpuscular Haemoglobin	rs835309	EUR	68682855	70682855
4	69682855	0.029438	0.003192	3.12E-20	486823	ebi-a-GCST90002322	rs835309	G	T	0.89842	Mean Corpuscular Haemoglobin	rs835309	EUR	68682855	70682855
4	69682855	0.031033	0.00343	1.50E-19	408112	ebi-a-GCST90002390	rs835309	G	T	0.897602	Mean Corpuscular Haemoglobin	rs835309	EUR	68682855	70682855
4	69682855	0.025957	0.003079	4.90E-19	572863	ebi-a-GCST90028995	rs835309	G	T	0.89764	Mean Corpuscular Haemoglobin	rs835309	EUR	68682855	70682855
4	69669183	-0.02619	0.003021	4.53E-18	544127	ebi-a-GCST90002334	rs10000284	C	T	0.101832	Mean Corpuscular Volume	rs10000284	EUR	68669183	70669183
4	69669183	-0.02746	0.003396	6.10E-16	408112	ebi-a-GCST90002392	rs10000284	C	T	0.102408	Mean Corpuscular Volume	rs10000284	EUR	68669183	70669183
4	69669183	-0.02048	0.003352	1.00E-09	396624	ebi-a-GCST90013979	rs10000284	C	T	NA	Mean Corpuscular Volume	rs10000284	EUR	68669183	70669183
4	69659738	-0.02628	0.003021	3.52E-18	544127	ebi-a-GCST90002334	rs10023464	T	C	0.101803	Mean Corpuscular Volume	rs10023464	EUR	68659738	70659738
4	69659738	-0.02725	0.003388	8.70E-16	408112	ebi-a-GCST90002392	rs10023464	T	C	0.10319	Mean Corpuscular Volume	rs10023464	EUR	68659738	70659738
4	69659738	-0.02007	0.003345	1.98E-09	396624	ebi-a-GCST90013979	rs10023464	T	C	NA	Mean Corpuscular Volume	rs10023464	EUR	68659738	70659738
4	69680942	-0.02663	0.003068	4.15E-18	544127	ebi-a-GCST90002334	rs11725502	T	A	0.098463	Mean Corpuscular Volume	rs11725502	EUR	68680942	70680942
4	69680942	-0.02802	0.003456	5.20E-16	408112	ebi-a-GCST90002392	rs11725502	T	A	0.099869	Mean Corpuscular Volume	rs11725502	EUR	68680942	70680942
4	69680942	-0.0205	0.003408	1.80E-09	396624	ebi-a-GCST90013979	rs11725502	T	A	NA	Mean Corpuscular Volume	rs11725502	EUR	68680942	70680942
4	70030273	0.013142	0.001822	5.71E-13	544127	ebi-a-GCST90002334	rs7668556	G	A	0.53683	Mean Corpuscular Volume	rs7668556	EUR	69030273	71030273
4	70030273	0.011838	0.002064	9.80E-09	408112	ebi-a-GCST90002392	rs7668556	G	A	0.531735	Mean Corpuscular Volume	rs7668556	EUR	69030273	71030273
4	69682855	0.026109	0.003017	5.22E-18	544127	ebi-a-GCST90002334	rs835309	G	T	0.898518	Mean Corpuscular Volume	rs835309	EUR	68682855	70682855
4	69682855	0.027144	0.003394	1.30E-15	408112	ebi-a-GCST90002392	rs835309	G	T	0.897599	Mean Corpuscular Volume	rs835309	EUR	68682855	70682855
4	69682855	0.020236	0.003352	1.57E-09	396624	ebi-a-GCST90013979	rs835309	G	T	NA	Mean Corpuscular Volume	rs835309	EUR	68682855	70682855
4	69669183	0.023776	0.003901	1.10E-09	350473	ukb-d-30070_irnt	rs10000284	C	T	0.102973	Red Cell Distribution Width	rs10000284	EUR	68669183	70669183
4	69669183	0.022991	0.003129	2.11E-13	531774	ebi-a-GCST90002369	rs10000284	C	T	0.102247	Red Cell Distribution Width	rs10000284	EUR	68669183	70669183
4	69669183	0.026987	0.003512	1.50E-14	408112	ebi-a-GCST90002404	rs10000284	C	T	0.102439	Red Cell Distribution Width	rs10000284	EUR	68669183	70669183
4	69669183	0.025041	0.003247	7.90E-17	514929	ebi-a-GCST90029001	rs10000284	C	T	0.102311	Red Cell Distribution Width	rs10000284	EUR	68669183	70669183
4	69659738	0.023944	0.003894	7.79E-10	350473	ukb-d-30070_irnt	rs10023464	T	C	0.103608	Red Cell Distribution Width	rs10023464	EUR	68659738	70659738
4	69659738	0.023714	0.003129	3.61E-14	531774	ebi-a-GCST90002369	rs10023464	T	C	0.102114	Red Cell Distribution Width	rs10023464	EUR	68659738	70659738
4	69659738	0.027197	0.003504	8.30E-15	408112	ebi-a-GCST90002404	rs10023464	T	C	0.103223	Red Cell Distribution Width	rs10023464	EUR	68659738	70659738
4	69659738	0.025113	0.003239	6.00E-17	514929	ebi-a-GCST90029001	rs10023464	T	C	0.103047	Red Cell Distribution Width	rs10023464	EUR	68659738	70659738
4	69680942	0.024419	0.003967	7.51E-10	350473	ukb-d-30070_irnt	rs11725502	T	A	0.100602	Red Cell Distribution Width	rs11725502	EUR	68680942	70680942
4	69680942	0.023786	0.003178	7.44E-14	531774	ebi-a-GCST90002369	rs11725502	T	A	0.098866	Red Cell Distribution Width	rs11725502	EUR	68680942	70680942
4	69680942	0.027556	0.003574	1.30E-14	408112	ebi-a-GCST90002404	rs11725502	T	A	0.099898	Red Cell Distribution Width	rs11725502	EUR	68680942	70680942
4	69680942	0.025718	0.003304	6.60E-17	514929	ebi-a-GCST90029001	rs11725502	T	A	0.099754	Red Cell Distribution Width	rs11725502	EUR	68680942	70680942
4	69682855	-0.02426	0.003901	5.02E-10	350473	ukb-d-30070_irnt	rs835309	G	T	0.897145	Red Cell Distribution Width	rs835309	EUR	68682855	70682855
4	69682855	-0.02345	0.003125	6.45E-14	531774	ebi-a-GCST90002369	rs835309	G	T	0.898116	Red Cell Distribution Width	rs835309	EUR	68682855	70682855
4	69682855	-0.02755	0.00351	4.20E-15	408112	ebi-a-GCST90002404	rs835309	G	T	0.897568	Red Cell Distribution Width	rs835309	EUR	68682855	70682855
4	69682855	-0.02569	0.003244	1.60E-17	514929	ebi-a-GCST90029001	rs835309	G	T	0.897611	Red Cell Distribution Width	rs835309	EUR	68682855	70682855
4	69669183	0.30326	0.038037	1.63E-15	4772	ebi-a-GCST009966	rs10000284	C	T	0.079481	Cotinine Levels/Cigarettes per Day	rs10000284	EUR	68669183	70669183
4	69659738	0.280343	0.036714	2.35E-14	4772	ebi-a-GCST009966	rs10023464	T	C	0.085454	Cotinine Levels/Cigarettes per Day	rs10023464	EUR	68659738	70659738
4	69680942	0.301806	0.038948	9.71E-15	4772	ebi-a-GCST009966	rs11725502	T	A	0.076431	Cotinine Levels/Cigarettes per Day	rs11725502	EUR	68680942	70680942
4	69682855	-0.30292	0.038032	1.74E-15	4772	ebi-a-GCST009966	rs835309	G	T	0.920698	Cotinine Levels/Cigarettes per Day	rs835309	EUR	68682855	70682855
4	70030273	-0.01168	0.001528	2.10E-14	312102	ukb-d-30850_irnt	rs7668556	G	A	0.52886	Testosterone	rs7668556	EUR	69030273	71030273
4	70030273	-0.03816	0.00677	1.75E-08	312102	ukb-d-30850_raw	rs7668556	G	A	0.52886	Testosterone	rs7668556	EUR	69030273	71030273
4	70030273	-0.01124	0.00145	9.13E-15	353805	ebi-a-GCST90014013	rs7668556	G	A	NA	Testosterone Levels	rs7668556	EUR	69030273	71030273
4	69669183	-0.02741	0.00378	4.13E-13	342829	ukb-d-30840_irnt	rs10000284	C	T	0.10301	Total Bilirubin	rs10000284	EUR	68669183	70669183
4	69669183	-0.11192	0.017039	5.09E-11	342829	ukb-d-30840_raw	rs10000284	C	T	0.10301	Total Bilirubin	rs10000284	EUR	68669183	70669183
4	69669183	-0.0263	0.0033	3.98E-15	342829	ebi-a-GCST90018973	rs10000284	C	T	0.095971	Total Bilirubin	rs10000284	EUR	68669183	70669183
4	69669183	-0.02484	0.002933	2.41E-17	388303	ebi-a-GCST90013872	rs10000284	C	T	NA	Total Bilirubin	rs10000284	EUR	68669183	70669183
4	69669183	-0.0248	0.002953	4.59E-17	388303	ebi-a-GCST90014012	rs10000284	C	T	NA	Total Bilirubin	rs10000284	EUR	68669183	70669183

4	69659738	-0.02673	0.003773	1.39E-12	342829	ukb-d-30840_irnt	rs10023464	T	C	0.10364	Total Bilirubin	rs10023464	EUR	68659738	70659738
4	69659738	-0.10976	0.017007	1.09E-10	342829	ukb-d-30840_raw	rs10023464	T	C	0.10364	Total Bilirubin	rs10023464	EUR	68659738	70659738
4	69659738	-0.0197	0.0028	1.32E-12	342829	ebi-a-GCST90018973	rs10023464	T	C	0.158256	Total Bilirubin	rs10023464	EUR	68659738	70659738
4	69659738	-0.02455	0.002927	4.96E-17	388303	ebi-a-GCST90013872	rs10023464	T	C	NA	Total Bilirubin	rs10023464	EUR	68659738	70659738
4	69659738	-0.0245	0.002947	9.49E-17	388303	ebi-a-GCST90014012	rs10023464	T	C	NA	Total Bilirubin	rs10023464	EUR	68659738	70659738
4	69680942	-0.02773	0.003844	5.44E-13	342829	ukb-d-30840_irnt	rs11725502	T	A	0.10064	Total Bilirubin	rs11725502	EUR	68680942	70680942
4	69680942	-0.11124	0.017328	1.37E-10	342829	ukb-d-30840_raw	rs11725502	T	A	0.10064	Total Bilirubin	rs11725502	EUR	68680942	70680942
4	69680942	-0.0277	0.0038	5.43E-13	342829	ebi-a-GCST90018973	rs11725502	T	A	0.10064	Total Bilirubin	rs11725502	EUR	68680942	70680942
4	69680942	-0.02495	0.002982	5.96E-17	388303	ebi-a-GCST90013872	rs11725502	T	A	NA	Total Bilirubin	rs11725502	EUR	68680942	70680942
4	69680942	-0.02488	0.003003	1.17E-16	388303	ebi-a-GCST90014012	rs11725502	T	A	NA	Total Bilirubin	rs11725502	EUR	68680942	70680942
4	69682855	0.02709	0.00378	7.69E-13	342829	ukb-d-30840_irnt	rs835309	G	T	0.8971	Total Bilirubin	rs835309	EUR	68682855	70682855
4	69682855	0.10966	0.017039	1.23E-10	342829	ukb-d-30840_raw	rs835309	G	T	0.8971	Total Bilirubin	rs835309	EUR	68682855	70682855
4	69682855	0.0259	0.0033	7.85E-15	342829	ebi-a-GCST90018973	rs835309	G	T	0.90422	Total Bilirubin	rs835309	EUR	68682855	70682855
4	69682855	0.024619	0.002933	4.68E-17	388303	ebi-a-GCST90013872	rs835309	G	T	NA	Total Bilirubin	rs835309	EUR	68682855	70682855
4	69682855	0.02457	0.002953	8.81E-17	388303	ebi-a-GCST90014012	rs835309	G	T	NA	Total Bilirubin	rs835309	EUR	68682855	70682855
4	70030273	-0.02097	0.003148	2.70E-11	NA	ieu-b-4864	rs7668556	G	A	0.530847	Total Testosterone	rs7668556	EUR	69030273	71030273
4	70030273	-0.0183	0.003099	3.50E-09	NA	ieu-b-4865	rs7668556	G	A	0.533614	Total Testosterone	rs7668556	EUR	69030273	71030273
4	70030273	-0.02134	0.002808	5.40E-14	230454	ebi-a-GCST90012112	rs7668556	G	A	0.530193	Total Testosterone	rs7668556	EUR	69030273	71030273
4	70030273	-0.01981	0.003037	6.00E-11	194453	ebi-a-GCST90012113	rs7668556	G	A	0.531311	Total Testosterone	rs7668556	EUR	69030273	71030273
4	70030273	-0.01176	0.001288	1.50E-19	425097	ebi-a-GCST90012114	rs7668556	G	A	0.530689	Total Testosterone	rs7668556	EUR	69030273	71030273
10	96547463	0.018622	0.002782	2.18E-11	389883	ebi-a-GCST90013991	rs12767583	T	C	NA	Alkaline Phosphatase Levels	rs12767583	EUR	95547463	97547463
10	96484777	0.018062	0.00275	5.10E-11	389883	ebi-a-GCST90013991	rs1926711	A	G	NA	Alkaline Phosphatase Levels	rs1926711	EUR	95484777	97484777
10	96547463	-0.0164	0.0027	5.96E-10	450243	ebi-a-GCST90000025	rs12767583	T	C	0.1492	Appendicular Lean Mass	rs12767583	EUR	95547463	97547463
10	96484777	-0.0149	0.0026	1.41E-08	450243	ebi-a-GCST90000025	rs1926711	A	G	0.1534	Appendicular Lean Mass	rs1926711	EUR	95484777	97484777
10	96547463	-0.0214	0.002556	5.20E-18	436055	ebi-a-GCST90025973	rs12767583	T	C	0.14912	Bilirubin Levels	rs12767583	EUR	95547463	97547463
10	96547463	-0.01931	0.003512	3.83E-08	292933	ukb-d-30660_irnt	rs12767583	T	C	0.14876	Direct Bilirubin	rs12767583	EUR	95547463	97547463
10	96547463	-0.01808	0.002949	1.70E-11	372420	ebi-a-GCST90025983	rs12767583	T	C	0.148524	Direct Bilirubin	rs12767583	EUR	95547463	97547463
10	96547463	-0.0177	0.002925	1.45E-09	332739	ebi-a-GCST90013997	rs12767583	T	C	NA	Direct Bilirubin	rs12767583	EUR	95547463	97547463
10	96484777	-0.01989	0.003471	1.01E-08	292933	ukb-d-30660_irnt	rs1926711	A	G	0.15305	Direct Bilirubin	rs1926711	EUR	95484777	97484777
10	96484777	-0.01791	0.002891	5.87E-10	332739	ebi-a-GCST90013997	rs1926711	A	G	NA	Direct Bilirubin	rs1926711	EUR	95484777	97484777
10	96547463	-0.12693	0.016114	3.35E-15	9188	eqtl-a-ENSG00000108239	rs12767583	T	C	0.162097	ENSG00000108239	rs12767583	EUR	95547463	97547463
10	96484777	-0.12689	0.015937	1.70E-15	9188	eqtl-a-ENSG00000108239	rs1926711	A	G	0.166598	ENSG00000108239	rs1926711	EUR	95484777	97484777
10	96547463	0.276319	0.015981	5.58E-67	31086	eqtl-a-ENSG00000119969	rs12767583	T	C	0.162097	ENSG00000119969	rs12767583	EUR	95547463	97547463
10	96484777	0.27673	0.015802	1.16E-68	31470	eqtl-a-ENSG00000119969	rs1926711	A	G	0.166598	ENSG00000119969	rs1926711	EUR	95484777	97484777
10	96547463	-0.19527	0.016066	5.42E-34	31086	eqtl-a-ENSG00000173145	rs12767583	T	C	0.162097	ENSG00000173145	rs12767583	EUR	95547463	97547463
10	96484777	-0.18419	0.015897	4.85E-31	31470	eqtl-a-ENSG00000173145	rs1926711	A	G	0.166598	ENSG00000173145	rs1926711	EUR	95484777	97484777
10	96547463	0.019709	0.002755	1.50E-13	437651	ebi-a-GCST90025966	rs12767583	T	C	0.149132	Gamma Glutamyl Transferase Levels	rs12767583	EUR	95547463	97547463
10	96547463	0.0143	0.0024	2.39E-09	344104	ebi-a-GCST90018954	rs12767583	T	C	0.192329	Gamma glutamyl transpeptidase	rs12767583	EUR	95547463	97547463
10	96484777	0.0145	0.0023	3.08E-10	344104	ebi-a-GCST90018954	rs1926711	A	G	0.228646	Gamma glutamyl transpeptidase	rs1926711	EUR	95484777	97484777
10	96547463	0.016736	0.002737	9.65E-10	389672	ebi-a-GCST90014004	rs12767583	T	C	NA	Gamma Glutamyltransferase Levels	rs12767583	EUR	95547463	97547463
10	96484777	0.015472	0.002705	1.07E-08	389672	ebi-a-GCST90014004	rs1926711	A	G	NA	Gamma Glutamyltransferase Levels	rs1926711	EUR	95484777	97484777
10	96547463	0.018993	0.003223	3.78E-09	344182	ukb-d-30750_irnt	rs12767583	T	C	0.14941	Glycated Haemoglobin	rs12767583	EUR	95547463	97547463
10	96484777	0.01937	0.003186	1.21E-09	344182	ukb-d-30750_irnt	rs1926711	A	G	0.15362	Glycated Haemoglobin	rs1926711	EUR	95484777	97484777
10	96484777	0.11688	0.021257	3.83E-08	344182	ukb-d-30750_raw	rs1926711	A	G	0.15362	Glycated Haemoglobin	rs1926711	EUR	95484777	97484777
10	96547463	0.017493	0.002858	9.34E-10	389889	ebi-a-GCST90014006	rs12767583	T	C	NA	Glycated Haemoglobin HbA1c Levels	rs12767583	EUR	95547463	97547463
10	96484777	0.017766	0.002825	3.20E-10	389889	ebi-a-GCST90014006	rs1926711	A	G	NA	Glycated Haemoglobin HbA1c Levels	rs1926711	EUR	95484777	97484777
10	96547463	0.017312	0.002719	3.40E-11	437749	ebi-a-GCST90025974	rs12767583	T	C	0.149057	Haemoglobin A1c Levels	rs12767583	EUR	95547463	97547463
10	96547463	0.014044	0.002549	3.60E-08	454857	ukb-b-14068	rs12767583	T	C	0.149125	Impedance of Leg (Left)	rs12767583	EUR	95547463	97547463
10	96547463	0.014012	0.002528	3.00E-08	454863	ukb-b-7376	rs12767583	T	C	0.149124	Impedance of Leg (Left)	rs12767583	EUR	95547463	97547463
10	96547463	0.014696	0.00254	7.44E-09	544127	ebi-a-GCST90002334	rs12767583	T	C	0.149218	Mean Corpuscular Volume	rs12767583	EUR	95547463	97547463
10	96547463	0.013862	0.002595	6.30E-09	444035	ebi-a-GCST90025963	rs12767583	T	C	0.149074	Mean Corpuscular Volume	rs12767583	EUR	95547463	97547463
10	96484777	0.01464	0.002515	6.02E-09	544127	ebi-a-GCST90002334	rs1926711	A	G	0.153611	Mean Corpuscular Volume	rs1926711	EUR	95484777	97484777
10	96547463	0.024477	0.002989	2.60E-16	408112	ebi-a-GCST90002396	rs12767583	T	C	0.149413	Mean Reticulocyte Volume	rs12767583	EUR	95547463	97547463
10	96547463	0.022653	0.002742	1.30E-17	436944	ebi-a-GCST90025975	rs12767583	T	C	0.14897	Mean Reticulocyte Volume	rs12767583	EUR	95547463	97547463
10	96547463	0.021717	0.003355	9.66E-11	344728	ukb-d-30260_irnt	rs12767583	T	C	0.149202	Mean Reticulocyte Volume	rs12767583	EUR	95547463	97547463
10	96484777	0.026828	0.002955	1.10E-19	408112	ebi-a-GCST90002396	rs1926711	A	G	0.153669	Mean Reticulocyte Volume	rs1926711	EUR	95484777	97484777
10	96484777	0.023564	0.003317	1.21E-12	344728	ukb-d-30260_irnt	rs1926711	A	G	0.153446	Mean Reticulocyte Volume	rs1926711	EUR	95484777	97484777
10	96547463	0.016185	0.002653	1.30E-10	437736	ebi-a-GCST90025976	rs12767583	T	C	0.148929	Mean Reticulocyte Volume	rs12767583	EUR	95547463	97547463
10	96547463	0.016445	0.002749	2.70E-10	535537	ebi-a-GCST90028997	rs12767583	T	C	0.149023	Mean Reticulocyte Volume	rs12767583	EUR	95547463	97547463
10	96484777	0.016344	0.002717	2.00E-10	535537	ebi-a-GCST90028997	rs1926711	A	G	0.153285	Mean Reticulocyte Volume	rs1926711	EUR	95484777	97484777
10	96547463	0.016208	0.002912	2.60E-08	408112	ebi-a-GCST90002397	rs12767583	T	C	0.149354	Mean spheric corpuscular volume	rs12767583	EUR	95547463	97547463
10	96484777	0.016322	0.002878	1.40E-08	408112	ebi-a-GCST90002397	rs1926711	A	G	0.153625	Mean spheric corpuscular volume	rs1926711	EUR	95484777	97484777

10	96547463	-0.01501	0.002588	6.85E-09	545203	ebi-a-GCST90002363	rs12767583	T	C	0.149199	Red Blood Cell Count	rs12767583	EUR	95547463	97547463
10	96547463	-0.01417	0.002682	6.30E-09	445305	ebi-a-GCST90025964	rs12767583	T	C	0.149097	Red Blood Cell Count	rs12767583	EUR	95547463	97547463
10	96547463	-0.01417	0.002704	7.60E-09	526540	ebi-a-GCST90029002	rs12767583	T	C	0.14917	Red Blood Cell Count	rs12767583	EUR	95547463	97547463
10	96484777	-0.01495	0.002562	5.58E-09	545203	ebi-a-GCST90002363	rs1926711	A	G	0.153583	Red Blood Cell Count	rs1926711	EUR	95484777	97484777
10	96484777	-0.01401	0.002673	8.90E-09	526540	ebi-a-GCST90029002	rs1926711	A	G	0.153435	Red Blood Cell Count	rs1926711	EUR	95484777	97484777
10	96547463	0.019774	0.003326	2.77E-09	350473	ukb-d-30070_irnt	rs12767583	T	C	0.149357	Red Cell Distribution Width	rs12767583	EUR	95547463	97547463
10	96547463	0.016147	0.002636	9.26E-10	531774	ebi-a-GCST90002369	rs12767583	T	C	0.149166	Red Cell Distribution Width	rs12767583	EUR	95547463	97547463
10	96547463	0.017473	0.002984	4.80E-09	408112	ebi-a-GCST90002404	rs12767583	T	C	0.149504	Red Cell Distribution Width	rs12767583	EUR	95547463	97547463
10	96547463	0.017817	0.002762	2.50E-11	441263	ebi-a-GCST90025988	rs12767583	T	C	0.149079	Red Cell Distribution Width	rs12767583	EUR	95547463	97547463
10	96547463	0.018651	0.002758	2.50E-12	514929	ebi-a-GCST90029001	rs12767583	T	C	0.149189	Red Cell Distribution Width	rs12767583	EUR	95547463	97547463
10	96484777	0.0232	0.003288	1.72E-12	350473	ukb-d-30070_irnt	rs1926711	A	G	0.153608	Red Cell Distribution Width	rs1926711	EUR	95484777	97484777
10	96484777	0.019072	0.002607	2.69E-13	531774	ebi-a-GCST90002369	rs1926711	A	G	0.153544	Red Cell Distribution Width	rs1926711	EUR	95484777	97484777
10	96484777	0.02041	0.00295	4.60E-12	408112	ebi-a-GCST90002404	rs1926711	A	G	0.153769	Red Cell Distribution Width	rs1926711	EUR	95484777	97484777
10	96484777	0.021299	0.002726	3.90E-16	514929	ebi-a-GCST90029001	rs1926711	A	G	0.153449	Red Cell Distribution Width	rs1926711	EUR	95484777	97484777
10	96547463	0.016849	0.002657	2.20E-12	437896	ebi-a-GCST90025947	rs12767583	T	C	0.149152	Serum Alkaline Phosphatase Levels	rs12767583	EUR	95547463	97547463
10	96547463	-0.01854	0.002769	2.20E-11	472174	ieu-b-4879	rs12767583	T	C	0.154478	Telomere Length	rs12767583	EUR	95547463	97547463
10	96484777	-0.0178	0.002726	6.60E-11	472174	ieu-b-4879	rs758646836	A	G	0.161331	Telomere Length	rs1926711	EUR	95484777	97484777
10	96547463	-0.02424	0.003222	5.31E-14	342829	ukb-d-30840_irnt	rs12767583	T	C	0.14945	Total Bilirubin	rs12767583	EUR	95547463	97547463
10	96547463	-0.09508	0.014523	5.89E-11	342829	ukb-d-30840_raw	rs12767583	T	C	0.14945	Total Bilirubin	rs12767583	EUR	95547463	97547463
10	96547463	-0.0185	0.0025	3.19E-13	342829	ebi-a-GCST90018973	rs12767583	T	C	0.190246	Total Bilirubin	rs12767583	EUR	95547463	97547463
10	96547463	-0.01986	0.002505	2.23E-15	388303	ebi-a-GCST90013872	rs12767583	T	C	NA	Total Bilirubin	rs12767583	EUR	95547463	97547463
10	96547463	-0.01964	0.002522	6.96E-15	388303	ebi-a-GCST90014012	rs12767583	T	C	NA	Total Bilirubin	rs12767583	EUR	95547463	97547463
10	96484777	-0.02366	0.003185	1.12E-13	342829	ukb-d-30840_irnt	rs1926711	A	G	0.15368	Total Bilirubin	rs1926711	EUR	95484777	97484777
10	96484777	-0.09627	0.014358	2.02E-11	342829	ukb-d-30840_raw	rs1926711	A	G	0.15368	Total Bilirubin	rs1926711	EUR	95484777	97484777
10	96484777	-0.0185	0.0024	4.35E-14	342829	ebi-a-GCST90018973	rs1926711	A	G	0.225109	Total Bilirubin	rs1926711	EUR	95484777	97484777
10	96484777	-0.01937	0.002476	5.17E-15	388303	ebi-a-GCST90013872	rs1926711	A	G	NA	Total Bilirubin	rs1926711	EUR	95484777	97484777
10	96484777	-0.01913	0.002493	1.66E-14	388303	ebi-a-GCST90014012	rs1926711	A	G	NA	Total Bilirubin	rs1926711	EUR	95484777	97484777
10	96547463	0.0406	0.0062	4.34E-11	6486	met-a-725	rs12767583	T	C	0.1543	X-14473	rs12767583	EUR	95547463	97547463
15	75027880	0.013988	0.00208	1.40E-12	436055	ebi-a-GCST90025973	rs2472297	T	C	0.262586	Bilirubin Levels	rs2472297	EUR	74027880	76027880
15	75027880	-0.0251	0.0026	3.97E-22	344052	ebi-a-GCST90018948	rs2472297	T	C	0.26649	Blood Urea Nitrogen Levels	rs2472297	EUR	74027880	76027880
15	75027880	-0.005	6.00E-04	5.78E-16	173149	ebi-a-GCST90103632	rs2472297	T	C	0.2591	Blood Urea Nitrogen Levels	rs2472297	EUR	74027880	76027880
15	75027880	0.009221	0.001557	3.20E-09	NA	ieu-b-5118	rs2472297	T	C	0.26172	Body Mass Index	rs2472297	EUR	74027880	76027880
15	75027880	0.014059	0.002188	8.40E-11	457756	ebi-a-GCST90025994	rs2472297	T	C	0.262581	Body Mass Index	rs2472297	EUR	74027880	76027880
15	75027880	0.014183	0.002188	6.60E-11	532396	ebi-a-GCST90029007	rs2472297	T	C	0.262425	Body Mass Index	rs2472297	EUR	74027880	76027880
15	75027880	0.0122	0.0019	1.40E-10	786480	ieu-b-40	rs2472297	T	C	0.2496	Body Mass Index	rs2472297	EUR	74027880	76027880
15	75027880	0.013257	0.002246	3.60E-09	461460	ukb-b-19953	rs2472297	T	C	0.261612	Body Mass Index	rs2472297	EUR	74027880	76027880
15	75027880	0.01339	0.002263	3.30E-09	454884	ukb-b-2303	rs2472297	T	C	0.26163	Body Mass Index	rs2472297	EUR	74027880	76027880
15	75027880	0.014287	0.002329	8.62E-10	407609	ebi-a-GCST90013870	rs2472297	T	C	NA	Body Mass Index	rs2472297	EUR	74027880	76027880
15	75027880	0.014179	0.00233	1.16E-09	407609	ebi-a-GCST90013974	rs2472297	T	C	NA	Body Mass Index	rs2472297	EUR	74027880	76027880
15	75027880	-0.01585	0.002022	4.50E-15	441640	ukb-b-15926	rs2472297	T	C	0.261458	Cereal Intake	rs2472297	EUR	74027880	76027880
15	75027880	0.017741	0.00288	7.30E-10	64949	ukb-b-9508	rs2472297	T	C	0.25771	Coffee Consumed	rs2472297	EUR	74027880	76027880
15	75027880	0.046471	0.001827	1.10E-142	428860	ukb-b-5237	rs2472297	T	C	0.262883	Coffee Intake	rs2472297	EUR	74027880	76027880
15	75027880	-0.01501	0.002277	4.60E-13	436939	ebi-a-GCST90025959	rs2472297	T	C	0.262546	C-Reactive Protein Levels	rs2472297	EUR	74027880	76027880
15	75027880	-0.02623	0.002188	4.15E-33	344104	ukb-d-30700_irnt	rs2472297	T	C	0.26651	Creatinine	rs2472297	EUR	74027880	76027880
15	75027880	-0.38844	0.042336	4.53E-20	344104	ukb-d-30700_raw	rs2472297	T	C	0.26651	Creatinine	rs2472297	EUR	74027880	76027880
15	75027880	-0.01866	0.002459	3.26E-14	344264	ukb-d-30720_irnt	rs2472297	T	C	0.2665	Cystatin C	rs2472297	EUR	74027880	76027880
15	75027880	-0.0028	0.000439	1.69E-10	344264	ukb-d-30720_raw	rs2472297	T	C	0.2665	Cystatin C	rs2472297	EUR	74027880	76027880
15	75027880	-0.02138	0.0022	4.00E-22	437846	ebi-a-GCST90025945	rs2472297	T	C	0.262579	Cystatin C	rs2472297	EUR	74027880	76027880
15	75027880	-0.01594	0.002121	5.77E-14	389834	ebi-a-GCST90014003	rs2472297	T	C	NA	Cystatin C	rs2472297	EUR	74027880	76027880
15	75027880	0.01402	0.001685	8.62E-17	62072	ebi-a-GCST90096908	rs2472297	T	C	NA	Decaffeinated Coffee Consumption	rs2472297	EUR	74027880	76027880
15	75027880	-0.01673	0.001803	1.69E-20	810865	ebi-a-GCST90000059	rs2472297	T	C	0.2604	Diastolic Blood Pressure	rs2472297	EUR	74027880	76027880
15	75027880	-0.01666	0.001788	1.21E-20	810865	ebi-a-GCST90000063	rs2472297	T	C	0.257	Diastolic Blood Pressure	rs2472297	EUR	74027880	76027880
15	75027880	-0.1321	0.0201	5.39E-11	724537	ieu-b-39	rs2472297	T	C	0.261	Diastolic Blood Pressure	rs2472297	EUR	74027880	76027880
15	75027880	0.002353	0.000207	5.84E-30	444097	ebi-a-GCST90096910	rs2472297	T	C	NA	Drink Temperature	rs2472297	EUR	74027880	76027880
15	75027880	-0.09836	0.0126	5.90E-15	64949	ukb-b-3975	rs2472297	T	C	0.25771	Drinking Water Intake	rs2472297	EUR	74027880	76027880
15	75027880	-0.07735	0.014003	3.32E-08	31185	eqtl-a-ENSG00000067221	rs2472297	T	C	0.235925	ENSG00000067221	rs2472297	EUR	74027880	76027880
15	75027880	-0.22109	0.013894	5.17E-57	31185	eqtl-a-ENSG00000103653	rs2472297	T	C	0.235925	ENSG00000103653	rs2472297	EUR	74027880	76027880
15	75027880	0.093351	0.013996	2.57E-11	31185	eqtl-a-ENSG00000138629	rs2472297	T	C	0.235925	ENSG00000138629	rs2472297	EUR	74027880	76027880
15	75027880	0.0812	0.014001	6.66E-09	30971	eqtl-a-ENSG00000140365	rs2472297	T	C	0.235925	ENSG00000140365	rs2472297	EUR	74027880	76027880
15	75027880	-0.27429	0.013827	1.41E-87	30971	eqtl-a-ENSG00000140400	rs2472297	T	C	0.235925	ENSG00000140400	rs2472297	EUR	74027880	76027880
15	75027880	-0.25348	0.013855	9.00E-75	31185	eqtl-a-ENSG00000140474	rs2472297	T	C	0.235925	ENSG00000140474	rs2472297	EUR	74027880	76027880
15	75027880	0.272187	0.01383	3.11E-86	31185	eqtl-a-ENSG00000140497	rs2472297	T	C	0.235925	ENSG00000140497	rs2472297	EUR	74027880	76027880

15	75027880	-0.10915	0.013988	6.04E-15	26110	eqtl-a-ENSG00000169371	rs2472297	T	C	0.235925	ENSG00000169371	rs2472297	EUR	74027880	76027880
15	75027880	0.087079	0.013999	4.96E-10	31185	eqtl-a-ENSG00000177971	rs2472297	T	C	0.235925	ENSG00000177971	rs2472297	EUR	74027880	76027880
15	75027880	0.187867	0.013929	1.85E-41	31185	eqtl-a-ENSG00000178802	rs2472297	T	C	0.235925	ENSG00000178802	rs2472297	EUR	74027880	76027880
15	75027880	-0.08065	0.014002	8.42E-09	4868	eqtl-a-ENSG00000227288	rs2472297	T	C	0.235925	ENSG00000227288	rs2472297	EUR	74027880	76027880
15	75027880	0.003762	0.000286	1.32E-39	1159871	ebi-a-GCST90026654	rs2472297	T	C	0.2552	Glomerular Filtration Rate (Creatinine)	rs2472297	EUR	74027880	76027880
15	75027880	0.0039	3.00E-04	6.17E-35	165726	ebi-a-GCST90103633	rs2472297	T	C	0.2613	Glomerular Filtration Rate (Creatinine)	rs2472297	EUR	74027880	76027880
15	75027880	0.0038	3.00E-04	1.94E-33	1004040	ebi-a-GCST90103634	rs2472297	T	C	0.2614	Glomerular Filtration Rate (Creatinine)	rs2472297	EUR	74027880	76027880
15	75027880	0.0031	5.00E-04	4.51E-09	460826	ebi-a-GCST90103635	rs2472297	T	C	0.2572	Glomerular Filtration Rate (Cystatin-C)	rs2472297	EUR	74027880	76027880
15	75027880	0.050494	0.007604	3.10E-11	64949	ukb-b-748	rs2472297	T	C	0.25771	Filtered Coffee Intake	rs2472297	EUR	74027880	76027880
15	75027880	-0.00535	0.000877	1.09E-09	433186	ebi-a-GCST90096912	rs2472297	T	C	NA	Fresh Fruit Consumption	rs2472297	EUR	74027880	76027880
15	75027880	0.011104	0.001252	7.38E-19	283449	ukb-d-1508_3	rs2472297	T	C	0.269937	Ground Coffee Consumption	rs2472297	EUR	74027880	76027880
15	75027880	0.018267	0.001407	1.51E-38	72276	ebi-a-GCST90096913	rs2472297	T	C	NA	Ground coffee consumption	rs2472297	EUR	74027880	76027880
15	75027880	-0.01028	0.001784	3.10E-09	458235	ebi-a-GCST90025949	rs2472297	T	C	0.262577	Height	rs2472297	EUR	74027880	76027880
15	75027880	-0.01032	0.001783	2.30E-09	673878	ebi-a-GCST90029008	rs2472297	T	C	0.26242	Height	rs2472297	EUR	74027880	76027880
15	75027880	-0.01539	0.001345	2.60E-30	457873	ukb-b-14203	rs2472297	T	C	0.261771	Hot Drink Temperature	rs2472297	EUR	74027880	76027880
15	75027880	-0.00981	0.001601	9.00E-10	454850	ukb-b-19379	rs2472297	T	C	0.261628	Impedance of Arm (Left)	rs2472297	EUR	74027880	76027880
15	75027880	-0.01118	0.001928	6.78E-09	331279	ukb-a-272	rs2472297	T	C	0.266644	Impedance of Arm (Right)	rs2472297	EUR	74027880	76027880
15	75027880	-0.01092	0.001595	7.60E-12	454826	ukb-b-7859	rs2472297	T	C	0.261628	Impedance of Arm (Right)	rs2472297	EUR	74027880	76027880
15	75027880	0.020452	0.000991	1.08E-94	180764	ebi-a-GCST90096914	rs2472297	T	C	NA	Instant Coffee Consumption	rs2472297	EUR	74027880	76027880
15	75027880	0.073119	0.012472	4.60E-09	64949	ukb-b-930	rs2472297	T	C	0.25771	Instant Coffee Consumption	rs2472297	EUR	74027880	76027880
15	75027880	0.010169	0.001799	1.60E-08	454823	ukb-b-7212	rs2472297	T	C	0.261624	Leg Fat Mass (Left)	rs2472297	EUR	74027880	76027880
15	75027880	0.010216	0.00182	2.00E-08	454846	ukb-b-18096	rs2472297	T	C	0.261629	Leg Fat Mass (Left)	rs2472297	EUR	74027880	76027880
15	75027880	0.010148	0.001715	3.25E-09	331278	ukb-a-278	rs2472297	T	C	0.266644	Leg Fat Percentage (Left)	rs2472297	EUR	74027880	76027880
15	75027880	0.009465	0.001431	3.70E-11	454826	ukb-b-18377	rs2472297	T	C	0.261627	Leg Fat Percentage (Left)	rs2472297	EUR	74027880	76027880
15	75027880	0.010068	0.001737	6.74E-09	331296	ukb-a-274	rs2472297	T	C	0.266644	Leg Fat Percentage (Right)	rs2472297	EUR	74027880	76027880
15	75027880	0.009736	0.001449	1.90E-11	454854	ukb-b-20531	rs2472297	T	C	0.261628	Leg Fat Percentage (Right)	rs2472297	EUR	74027880	76027880
15	75027880	0.01223	0.002121	8.27E-09	544127	ebi-a-GCST90002334	rs2472297	T	C	0.258502	Mean Corpuscular Volume	rs2472297	EUR	74027880	76027880
15	75027880	0.009746	0.002109	8.90E-09	444035	ebi-a-GCST90025963	rs2472297	T	C	0.262678	Mean Corpuscular Volume	rs2472297	EUR	74027880	76027880
15	75027880	-0.01632	0.002695	1.41E-09	350470	ukb-d-30100_irnt	rs2472297	T	C	0.266596	Mean Platelet Thrombocyte Volume	rs2472297	EUR	74027880	76027880
15	75027880	-0.01608	0.002138	5.48E-14	396616	ebi-a-GCST90013981	rs2472297	T	C	NA	Mean Platelet Thrombocyte Volume	rs2472297	EUR	74027880	76027880
15	75027880	-0.01465	0.002196	2.58E-11	460935	ebi-a-GCST90002346	rs2472297	T	C	0.262905	Mean Platelet Volume	rs2472297	EUR	74027880	76027880
15	75027880	-0.01413	0.002335	1.50E-09	408112	ebi-a-GCST90002395	rs2472297	T	C	0.263703	Mean Platelet Volume	rs2472297	EUR	74027880	76027880
15	75027880	-0.0136	0.002011	4.00E-17	445364	ebi-a-GCST90025960	rs2472297	T	C	0.262668	Mean Platelet Volume	rs2472297	EUR	74027880	76027880
15	75027880	-0.01391	0.002012	3.20E-17	694866	ebi-a-GCST90028996	rs2472297	T	C	0.262515	Mean Platelet Volume	rs2472297	EUR	74027880	76027880
15	75027880	0.010778	0.002226	3.90E-08	436944	ebi-a-GCST90025975	rs2472297	T	C	0.262698	Mean Reticulocyte Volume	rs2472297	EUR	74027880	76027880
15	75027880	0.050613	0.003941	9.26E-38	258758	ebi-a-GCST90096893	rs2472297	T	C	NA	Overall Healthy Diet	rs2472297	EUR	74027880	76027880
15	75027880	-0.0176	0.0029	7.00E-10	321047	ebi-a-GCST007430	rs2472297	T	C	0.264	Peak Expiratory Flow (PEF)	rs2472297	EUR	74027880	76027880
15	75027880	-0.01205	0.002083	7.20E-09	421986	ukb-b-12019	rs2472297	T	C	0.261532	Peak Expiratory Flow (PEF)	rs2472297	EUR	74027880	76027880
15	75027880	-0.01139	0.002075	3.98E-08	374599	ebi-a-GCST90013995	rs2472297	T	C	NA	Peak Expiratory Flow (PEF)	rs2472297	EUR	74027880	76027880
15	75027880	0.021282	0.002747	9.49E-15	314658	ukb-d-30810_irnt	rs2472297	T	C	0.26642	Phosphate	rs2472297	EUR	74027880	76027880
15	75027880	0.003423	0.000441	8.66E-15	314658	ukb-d-30810_raw	rs2472297	T	C	0.26642	Phosphate	rs2472297	EUR	74027880	76027880
15	75027880	0.021624	0.002517	8.56E-18	357302	ebi-a-GCST90014010	rs2472297	T	C	NA	Phosphate	rs2472297	EUR	74027880	76027880
15	75027880	0.014749	0.002142	5.96E-12	542827	ebi-a-GCST90002357	rs2472297	T	C	0.258073	Platelet Count	rs2472297	EUR	74027880	76027880
15	75027880	0.015701	0.002399	5.90E-11	408112	ebi-a-GCST90002402	rs2472297	T	C	0.26374	Platelet Count	rs2472297	EUR	74027880	76027880
15	75027880	0.0143	0.0026	4.42E-08	350474	ebi-a-GCST90018969	rs2472297	T	C	0.266596	Platelet Count	rs2472297	EUR	74027880	76027880
15	75027880	0.015031	0.002119	1.20E-14	444866	ebi-a-GCST90025951	rs2472297	T	C	0.262661	Platelet Count	rs2472297	EUR	74027880	76027880
15	75027880	0.01639	0.002141	1.60E-16	600968	ebi-a-GCST90028999	rs2472297	T	C	0.262505	Platelet Count	rs2472297	EUR	74027880	76027880
15	75027880	0.01428	0.002609	4.42E-08	350474	ukb-d-30080_irnt	rs2472297	T	C	0.266596	Platelet Count	rs2472297	EUR	74027880	76027880
15	75027880	0.016206	0.002224	3.18E-13	396621	ebi-a-GCST90013980	rs2472297	T	C	NA	Platelet Count	rs2472297	EUR	74027880	76027880
15	75027880	-0.02418	0.002448	5.20E-23	408112	ebi-a-GCST90002401	rs2472297	T	C	0.263713	Platelet Distribution Width	rs2472297	EUR	74027880	76027880
15	75027880	-0.02119	0.002192	2.00E-26	572201	ebi-a-GCST90029000	rs2472297	T	C	0.262487	Platelet Distribution Width	rs2472297	EUR	74027880	76027880
15	75027880	-0.02297	0.002668	7.36E-18	350470	ukb-d-30110_irnt	rs2472297	T	C	0.266596	Platelet Distribution Width	rs2472297	EUR	74027880	76027880
15	75027880	-0.01556	0.002753	1.59E-08	326816	ukb-a-334	rs2472297	T	C	0.266644	Potassium in Urine	rs2472297	EUR	74027880	76027880
15	75027880	-0.01846	0.0025	1.51E-13	395995	ebi-a-GCST90013988	rs2472297	T	C	NA	Potassium in Urine	rs2472297	EUR	74027880	76027880
15	75027880	0.006266	0.00103	1.18E-09	211628	ebi-a-GCST90096922	rs2472297	T	C	NA	Red Wine Consumption	rs2472297	EUR	74027880	76027880
15	75027880	0.014479	0.002437	3.50E-10	400938	ebi-a-GCST90025992	rs2472297	T	C	0.262478	Serum Albumin Levels	rs2472297	EUR	74027880	76027880
15	75027880	-0.01203	0.002168	4.40E-09	437896	ebi-a-GCST90025947	rs2472297	T	C	0.262579	Serum Alkaline Phosphatase Levels	rs2472297	EUR	74027880	76027880
15	75027880	-0.03045	0.002261	8.70E-43	437660	ebi-a-GCST90025946	rs2472297	T	C	0.262585	Serum Creatinine	rs2472297	EUR	74027880	76027880
15	75027880	-0.02425	0.001951	1.81E-35	389678	ebi-a-GCST90014001	rs2472297	T	C	NA	Serum Creatinine	rs2472297	EUR	74027880	76027880
15	75027880	-0.0262	0.0022	4.08E-33	344104	ebi-a-GCST90018979	rs2472297	T	C	0.26651	Serum Creatinine	rs2472297	EUR	74027880	76027880
15	75027880	0.02436	0.00244	9.60E-25	400159	ebi-a-GCST90025948	rs2472297	T	C	0.262471	Serum Phosphate Levels	rs2472297	EUR	74027880	76027880
15	75027880	-0.02706	0.00236	9.50E-31	437580	ebi-a-GCST90025991	rs2472297	T	C	0.262581	Serum Urea Levels	rs2472297	EUR	74027880	76027880

15	75027880	-0.0223	0.0023	2.42E-22	343836	ebi-a-GCST90018977	rs2472297	T	C	0.26649	Serum Uric Acid Levels	rs2472297	EUR	74027880	76027880
15	75027880	-0.02029	0.00267	2.98E-14	326831	ukb-a-335	rs2472297	T	C	0.266644	Sodium in Urine	rs2472297	EUR	74027880	76027880
15	75027880	-0.02215	0.002419	5.38E-20	396020	ebi-a-GCST90013989	rs2472297	T	C	NA	Sodium in Urine	rs2472297	EUR	74027880	76027880
15	75027880	10.2075	1.04443	1.50E-22	64949	ukb-b-3291	rs2472297	T	C	0.25771	Standard Tea Intake	rs2472297	EUR	74027880	76027880
15	75027880	-0.01251	0.0018	3.63E-12	810865	ebi-a-GCST90000062	rs2472297	T	C	0.2604	Systolic Blood Pressure	rs2472297	EUR	74027880	76027880
15	75027880	-0.01251	0.001786	2.48E-12	810865	ebi-a-GCST90000066	rs2472297	T	C	0.2571	Systolic Blood Pressure	rs2472297	EUR	74027880	76027880
15	75027880	0.017197	0.001363	1.65E-36	434171	ebi-a-GCST90096926	rs2472297	T	C	NA	Tea Consumption	rs2472297	EUR	74027880	76027880
15	75027880	0.053345	0.002401	2.30E-109	447485	ukb-b-6066	rs2472297	T	C	0.262049	Tea Consumption	rs2472297	EUR	74027880	76027880
15	75027880	0.012504	0.002012	5.17E-10	388303	ebi-a-GCST90013872	rs2472297	T	C	NA	Total Bilirubin	rs2472297	EUR	74027880	76027880
15	75027880	0.012546	0.002026	5.95E-10	388303	ebi-a-GCST90014012	rs2472297	T	C	NA	Total Bilirubin	rs2472297	EUR	74027880	76027880
15	75027880	-0.02232	0.002295	2.44E-22	343836	ukb-d-30880_irnt	rs2472297	T	C	0.26649	Urate	rs2472297	EUR	74027880	76027880
15	75027880	-1.8062	0.18521	1.82E-22	343836	ukb-d-30880_raw	rs2472297	T	C	0.26649	Urate	rs2472297	EUR	74027880	76027880
15	75027880	-0.03295	0.00222	3.00E-50	437354	ebi-a-GCST90025965	rs2472297	T	C	0.262583	Urate	rs2472297	EUR	74027880	76027880
15	75027880	-0.0209	0.002006	2.10E-25	389404	ebi-a-GCST90014015	rs2472297	T	C	NA	Urate	rs2472297	EUR	74027880	76027880
15	75027880	-0.02506	0.002591	3.99E-22	344052	ukb-d-30670_irnt	rs2472297	T	C	0.26649	Urea	rs2472297	EUR	74027880	76027880
15	75027880	-0.03348	0.003633	3.12E-20	344052	ukb-d-30670_raw	rs2472297	T	C	0.26649	Urea	rs2472297	EUR	74027880	76027880
15	75027880	-0.0249	0.002379	1.23E-25	389608	ebi-a-GCST90013998	rs2472297	T	C	NA	Urea Levels	rs2472297	EUR	74027880	76027880
15	75027880	0.018124	0.00188	5.31E-22	382500	ebi-a-GCST006586	rs2472297	T	C	0.267268	Urinary Albumin Excretion	rs2472297	EUR	74027880	76027880
15	75027880	-0.02715	0.002597	1.42E-25	327525	ukb-a-333	rs2472297	T	C	0.266644	Urinary Creatinine	rs2472297	EUR	74027880	76027880
15	75027880	-0.02842	0.002356	1.66E-33	396837	ebi-a-GCST90013987	rs2472297	T	C	NA	Urinary Creatinine	rs2472297	EUR	74027880	76027880
15	75027880	-0.08378	0.004442	2.45E-79	445799	ebi-a-GCST90096929	rs2472297	T	C	NA	Water Consumption	rs2472297	EUR	74027880	76027880
15	75027880	-0.04809	0.004639	3.50E-25	400642	ebi-a-GCST90096928	rs2472297	T	C	NA	Water Consumption	rs2472297	EUR	74027880	76027880
15	75027880	-0.03342	0.002057	2.40E-59	427588	ukb-b-14898	rs2472297	T	C	0.26061	Water Intake	rs2472297	EUR	74027880	76027880

Supplementary Table 4.4 - Colocalization Results

Exposure	*Outcome*	*SNP1*	*SNP2*	*PP.H4*	*Conditional Status*	*LogABF*
Norclozapine Plasma Level	25 hydroxyvitamin D	rs1824264	rs4466107	0.999562	Conditional Both	28.4326
Norclozapine Plasma Level	25 Hydroxyvitamin D	rs1824264	rs114024927	0.957364	Conditional Both	26.2375
Clozapine Plasma Level	25 Hydroxyvitamin D	Unconditioned	Unconditioned	0.964721	Unconditional	87.8816
Clozapine Plasma Level	25 Hydroxyvitamin D	Unconditioned	Unconditioned	0.9906	Unconditional	86.8581
Norclozapine Plasma Level	25 Hydroxyvitamin D	Unconditioned	Unconditioned	0.964099	Unconditional	89.3327
Norclozapine Plasma Level	25 Hydroxyvitamin D	Unconditioned	Unconditioned	0.990584	Unconditional	88.3373
Clozapine Plasma Level	25 Hydroxyvitamin D	Unconditioned	Unconditioned	0.939667	Unconditional	92.2257
Clozapine Plasma Level	25 Hydroxyvitamin D	Unconditioned	Unconditioned	0.939667	Unconditional	92.2257
Norclozapine Plasma Level	25 Hydroxyvitamin D	Unconditioned	Unconditioned	0.942417	Unconditional	93.7584
Norclozapine Plasma Level	25 Hydroxyvitamin D	Unconditioned	Unconditioned	0.942417	Unconditional	93.7584
Norclozapine Plasma Level	25 Hydroxyvitamin D	Unconditioned	Unconditioned	0.961088	Unconditional	63.3093
Norclozapine Plasma Level	25 Hydroxyvitamin D	Unconditioned	Unconditioned	0.961088	Unconditional	63.3093
Clozapine Plasma Level	25 Hydroxyvitamin D	Unconditioned	Unconditioned	0.962933	Unconditional	61.8826
Clozapine Plasma Level	25 Hydroxyvitamin D	Unconditioned	Unconditioned	0.962933	Unconditional	61.8826
Norclozapine Plasma Level	25 Hydroxyvitamin D	Unconditioned	Unconditioned	0.998486	Unconditional	88.2741
Clozapine Plasma Level	25 Hydroxyvitamin D	Unconditioned	Unconditioned	0.998514	Unconditional	87.0637
Norclozapine Plasma Level	25 Hydroxyvitamin D	Unconditioned	Unconditioned	0.967552	Unconditional	70.2313
Norclozapine Plasma Level	25 Hydroxyvitamin D	Unconditioned	Unconditioned	0.967552	Unconditional	70.2313
Clozapine Plasma Level	25 Hydroxyvitamin D	Unconditioned	Unconditioned	0.968536	Unconditional	68.7752
Clozapine Plasma Level	25 Hydroxyvitamin D	Unconditioned	Unconditioned	0.968536	Unconditional	68.7752
Clozapine-Norclozapine Plasma Ratio	Bilirubin	rs11726899	rs293435	0.92734	Conditional Both	123.232
Clozapine-Norclozapine Plasma Ratio	Bilirubin	rs11726899	rs293435	0.927342	Conditional Both	123.223
Clozapine-Norclozapine Plasma Ratio	Bilirubin	rs11726899	rs293435	0.927342	Conditional Both	123.223
Clozapine-Norclozapine Plasma Ratio	Bilirubin	rs835309	rs293435	0.957796	Conditional Both	13.7865
Clozapine-Norclozapine Plasma Ratio	Bilirubin	rs835309	rs293435	0.957801	Conditional Both	13.7889
Clozapine-Norclozapine Plasma Ratio	Bilirubin	rs835309	rs293435	0.957801	Conditional Both	13.789
Clozapine-Norclozapine Plasma Ratio	Bilirubin	rs835309	rs2670430	0.989571	Conditional Both	19.6749
Clozapine-Norclozapine Plasma Ratio	Bilirubin	rs835309	rs2670430	0.989571	Conditional Both	19.6751
Clozapine-Norclozapine Plasma Ratio	Bilirubin	rs835309	rs2670430	0.989571	Conditional Both	19.6727
Clozapine-Norclozapine Plasma Ratio	Bilirubin	rs72846859	rs2670430	0.999718	Conditional Both	31.5329
Clozapine-Norclozapine Plasma Ratio	Bilirubin	rs72846859	rs2670430	0.999718	Conditional Both	31.5331
Clozapine-Norclozapine Plasma Ratio	Bilirubin	rs72846859	rs2670430	0.999718	Conditional Both	31.5318
Clozapine Plasma Level	Bilirubin	rs3732218*	rs887829	0.969434	Conditional Both	1394.23
Clozapine Plasma Level	Bilirubin	rs3732218*	rs10180090	0.852145	Conditional Both	1155.23
Clozapine Plasma Level	Bilirubin	rs3732218*	rs10180090	0.854293	Conditional Both	1129.24
Clozapine Plasma Level	Bilirubin	rs3732218*	rs887829	0.968581	Conditional Both	234.689
Clozapine Plasma Level	Bilirubin	rs3732218*	rs7567229	0.854093	Conditional Both	12745
Clozapine Plasma Level	Bilirubin	rs3732218*	rs7567229	0.854093	Conditional Both	12745
Clozapine Plasma Level	Bilirubin	rs3732218*	rs2284294	0.889816	Conditional Both	33.021
Clozapine Plasma Level	Bilirubin	rs3732218*	rs2284294	0.889816	Conditional Both	33.021
Norclozapine Plasma Level	Bilirubin	rs4663325*	rs17863787	0.808566	Conditional Both	666.838
Norclozapine Plasma Level	Bilirubin	rs4663325*	rs17863787	0.809381	Conditional Both	707.713
Norclozapine Plasma Level	Bilirubin	rs4663325*	rs10180090	0.895005	Conditional Both	1129.59
Norclozapine Plasma Level	Bilirubin	rs4663325*	rs10180090	0.895471	Conditional Both	1155.58
Norclozapine Plasma Level	Bilirubin	rs2926036	rs2670430	0.985766	Conditional Both	63.405
Norclozapine Plasma Level	Bilirubin	rs2926036	rs2670430	0.985766	Conditional Both	63.4053
Norclozapine Plasma Level	Bilirubin	rs2926036	rs2670430	0.985766	Conditional Both	63.4085

Norclozapine Plasma Level	Bilirubin	rs4663325*	rs17863787	0.8105	Conditional Both	302.017
Norclozapine Plasma Level	Bilirubin	rs4663325*	rs17863787	0.8105	Conditional Both	302.017
Norclozapine Plasma Level	Bilirubin	rs4663325*	rs7567229	0.896151	Conditional Both	12745.3
Norclozapine Plasma Level	Bilirubin	rs4663325*	rs7567229	0.896151	Conditional Both	12745.3
Norclozapine Plasma Level	Bilirubin	rs4663325*	rs2284294	0.937328	Conditional Both	33.6031
Norclozapine Plasma Level	Bilirubin	rs4663325*	rs2284294	0.937328	Conditional Both	33.6031
Clozapine-Norclozapine Plasma Ratio	Bilirubin	Unconditioned	Unconditioned	0.991493	Unconditional	62.3425
Norclozapine Plasma Level	Bilirubin	Unconditioned	Unconditioned	0.999963	Unconditional	22.6255
Clozapine Plasma Level	Bilirubin	Unconditioned	Unconditioned	0.999965	Unconditional	26.302
Clozapine-Norclozapine Plasma Ratio	Bilirubin	Unconditioned	Unconditioned	0.847452	Unconditional	46.1441
Clozapine-Norclozapine Plasma Ratio	Bilirubin	Unconditioned	Unconditioned	0.847464	Unconditional	46.1452
Norclozapine Plasma Level	Bilirubin	Unconditioned	Unconditioned	0.82273	Unconditional	68.8938
Norclozapine Plasma Level	Bilirubin	Unconditioned	Unconditioned	0.82273	Unconditional	68.8939
Norclozapine Plasma Level	Bilirubin	Unconditioned	Unconditioned	0.822731	Unconditional	68.8942
Norclozapine Plasma Level	Bilirubin	Unconditioned	Unconditioned	0.822731	Unconditional	68.8944
Clozapine-Norclozapine Plasma Ratio	Bilirubin	Unconditioned	Unconditioned	0.846334	Unconditional	347.183
Clozapine-Norclozapine Plasma Ratio	Bilirubin	Unconditioned	Unconditioned	0.846334	Unconditional	347.187
Clozapine-Norclozapine Plasma Ratio	Bilirubin	Unconditioned	Unconditioned	0.846334	Unconditional	347.175
Clozapine-Norclozapine Plasma Ratio	Bilirubin	Unconditioned	Unconditioned	0.846334	Unconditional	347.173
Clozapine-Norclozapine Plasma Ratio	Bilirubin	Unconditioned	Unconditioned	0.862011	Unconditional	58.1654
Clozapine-Norclozapine Plasma Ratio	Bilirubin	Unconditioned	Unconditioned	0.918877	Unconditional	57.1685
Clozapine-Norclozapine Plasma Ratio	Bilirubin	Unconditioned	Unconditioned	0.945142	Unconditional	58.4516
Norclozapine Plasma Level	Bilirubin	Unconditioned	Unconditioned	0.973565	Unconditional	73.1564
Norclozapine Plasma Level	Bilirubin	Unconditioned	Unconditioned	0.973565	Unconditional	73.1562
Norclozapine Plasma Level	Bilirubin	Unconditioned	Unconditioned	0.984126	Unconditional	72.8209
Norclozapine Plasma Level	Bilirubin	Unconditioned	Unconditioned	0.99165	Unconditional	71.8527
Clozapine-Norclozapine Plasma Ratio	Bilirubin	Unconditioned	Unconditioned	0.992387	Unconditional	352.125
Clozapine-Norclozapine Plasma Ratio	Bilirubin	Unconditioned	Unconditioned	0.998647	Unconditional	350.946
Norclozapine Plasma Level	Blood Urea Nitrogen	Unconditioned	Unconditioned	0.999998	Unconditional	47.1006
Clozapine Plasma Level	Blood Urea Nitrogen	Unconditioned	Unconditioned	1	Unconditional	50.7767
Norclozapine Plasma Level	Coffee Consumption	Unconditioned	Unconditioned	0.999995	Unconditional	19.9061
Clozapine Plasma Level	Coffee Consumption	Unconditioned	Unconditioned	0.999997	Unconditional	23.5822
Norclozapine Plasma Level	Coffee Consumption	Unconditioned	Unconditioned	0.999998	Unconditional	323.301
Clozapine Plasma Level	Coffee Consumption	Unconditioned	Unconditioned	1	Unconditional	326.977
Norclozapine Plasma Level	Coffee Consumption	Unconditioned	Unconditioned	0.993917	Unconditional	22.9852
Clozapine Plasma Level	Coffee Consumption	Unconditioned	Unconditioned	0.993918	Unconditional	26.6595
Norclozapine Plasma Level	Coffee Consumption	Unconditioned	Unconditioned	0.999998	Unconditional	85.0531
Clozapine Plasma Level	Coffee Consumption	Unconditioned	Unconditioned	1	Unconditional	88.7291
Norclozapine Plasma Level	Coffee Consumption	Unconditioned	Unconditioned	0.999998	Unconditional	213.419
Clozapine Plasma Level	Coffee Consumption	Unconditioned	Unconditioned	1	Unconditional	217.095
Norclozapine Plasma Level	Coffee Consumption	Unconditioned	Unconditioned	0.999988	Unconditional	18.1233
Clozapine Plasma Level	Coffee Consumption	Unconditioned	Unconditioned	0.99999	Unconditional	21.7994
Norclozapine Plasma Level	Cotinine in Current Smokers	Unconditioned	Unconditioned	0.957686	Unconditional	86.6263
Norclozapine Plasma Level	Cotinine in Current Smokers	Unconditioned	Unconditioned	0.957686	Unconditional	86.6263
Norclozapine Plasma Level	Cotinine in Current Smokers	Unconditioned	Unconditioned	0.957687	Unconditional	86.6268
Norclozapine Plasma Level	Cotinine in Current Smokers	Unconditioned	Unconditioned	0.967169	Unconditional	85.913
Norclozapine Plasma Level	Creatinine	Unconditioned	Unconditioned	0.999998	Unconditional	71.9653
Clozapine Plasma Level	Creatinine	Unconditioned	Unconditioned	1	Unconditional	75.6414
Norclozapine Plasma Level	Creatinine	Unconditioned	Unconditioned	0.999998	Unconditional	54.7763
Clozapine Plasma Level	Creatinine	Unconditioned	Unconditioned	1	Unconditional	58.4524

Norclozapine Plasma Level	Creatinine	Unconditioned	Unconditioned	0.999998	Unconditional	90.6127
Clozapine Plasma Level	Creatinine	Unconditioned	Unconditioned	1	Unconditional	94.2892
Clozapine Plasma Level	Creatinine	Unconditioned	Unconditioned	1	Unconditional	80.9571
Norclozapine Plasma Level	Creatinine	Unconditioned	Unconditioned	0.999998	Unconditional	71.1569
Clozapine Plasma Level	Creatinine	Unconditioned	Unconditioned	1	Unconditional	74.833
Norclozapine Plasma Level	C Reactive Protein	Unconditioned	Unconditioned	0.999998	Unconditional	21.7447
Clozapine Plasma Level	C Reactive Protein	Unconditioned	Unconditioned	1	Unconditional	25.4212
Norclozapine Plasma Level	Cystatin C	Unconditioned	Unconditioned	0.999998	Unconditional	28.9065
Clozapine Plasma Level	Cystatin C	Unconditioned	Unconditioned	1	Unconditional	32.5826
Norclozapine Plasma Level	Cystatin C	Unconditioned	Unconditioned	0.999998	Unconditional	47.2486
Clozapine Plasma Level	Cystatin C	Unconditioned	Unconditioned	1	Unconditional	50.9251
Clozapine Plasma Level	Cystatin C	Unconditioned	Unconditioned	0.990486	Unconditional	31.9614
Norclozapine Plasma Level	Fresh Fruit Consumption	Unconditioned	Unconditioned	0.999987	Unconditional	18.5819
Clozapine Plasma Level	Fresh Fruit Consumption	Unconditioned	Unconditioned	0.999989	Unconditional	22.258
Norclozapine Plasma Level	Gamma Glutamyl Transpeptidase	rs2926036	rs113185623	0.95701	Conditional Both	55.5757
Norclozapine Plasma Level	Impedance of Left Arm	Unconditioned	Unconditioned	0.999854	Unconditional	18.7517
Clozapine Plasma Level	Impedance of Left Arm	Unconditioned	Unconditioned	0.999856	Unconditional	22.4278
Norclozapine Plasma Level	Impedance of Right Arm	Unconditioned	Unconditioned	0.986011	Unconditional	16.9526
Clozapine Plasma Level	Impedance of Right Arm	Unconditioned	Unconditioned	0.986041	Unconditional	20.6286
Norclozapine Plasma Level	Mean Corpuscular Haemoglobin	rs2926036	rs294776	0.994891	Conditional Both	62.8769
Norclozapine Plasma Level	Mean Corpuscular Haemoglobin	rs2926036	rs294776	0.994891	Conditional Both	62.8607
Norclozapine Plasma Level	Mean Corpuscular Haemoglobin	rs2926036	rs294776	0.994891	Conditional Both	62.8664
Clozapine-Norclozapine Plasma Ratio	Mean Corpuscular Volume	rs835309	rs11726946	0.898953	Conditional Both	40.0267
Clozapine-Norclozapine Plasma Ratio	Mean Corpuscular Volume	rs72846859	rs72846859	0.999998	Conditional Both	61.7142
Norclozapine Plasma Level	Mean Corpuscular Volume	rs1824264	rs62298399	0.836111	Conditional Both	15.6027
Norclozapine Plasma Level	Overall Healthy Diet	Unconditioned	Unconditioned	0.999998	Unconditional	82.7179
Clozapine Plasma Level	Overall Healthy Diet	Unconditioned	Unconditioned	1	Unconditional	86.3939
Norclozapine Plasma Level	Peak Expiratory Flow	Unconditioned	Unconditioned	0.999873	Unconditional	16.7618
Clozapine Plasma Level	Peak Expiratory Flow	Unconditioned	Unconditioned	0.999875	Unconditional	20.4378
Clozapine Plasma Level	Peak Expiratory Flow	Unconditioned	Unconditioned	0.999774	Unconditional	18.8317
Norclozapine Plasma Level	Peak Expiratory Flow	Unconditioned	Unconditioned	0.892823	Unconditional	37.1155
Clozapine Plasma Level	Peak Expiratory Flow	Unconditioned	Unconditioned	0.893014	Unconditional	40.7914
Norclozapine Plasma Level	Potassium in Urine	Unconditioned	Unconditioned	0.999834	Unconditional	16.1192
Clozapine Plasma Level	Potassium in Urine	Unconditioned	Unconditioned	0.999836	Unconditional	19.7952
Clozapine Plasma Level	Potassium in Urine	Unconditioned	Unconditioned	0.999991	Unconditional	30.9988
Norclozapine Plasma Level	Red Blood Cell Distribution Width	rs1824264	rs10020490	0.937493	Conditional Both	13.4812
Norclozapine Plasma Level	Red Blood Cell Distribution Width	rs1824264	rs10020490	0.937618	Conditional Both	13.482
Norclozapine Plasma Level	Red Blood Cell Distribution Width	rs1824264	rs10020490	0.937688	Conditional Both	13.4821
Norclozapine Plasma Level	Red Blood Cell Distribution Width	rs2926036	rs10020490	0.979931	Conditional Both	63.2371
Norclozapine Plasma Level	Serum Phosphate	Unconditioned	Unconditioned	0.946806	Unconditional	49.9442
Clozapine Plasma Level	Serum Phosphate	Unconditioned	Unconditioned	0.946901	Unconditional	53.6206
Norclozapine Plasma Level	Serum Urea	Unconditioned	Unconditioned	0.999998	Unconditional	65.7065
Clozapine Plasma Level	Serum Urea	Unconditioned	Unconditioned	1	Unconditional	69.383
Norclozapine Plasma Level	Serum Uric Acid	Unconditioned	Unconditioned	0.999998	Unconditional	47.2079
Clozapine Plasma Level	Serum Uric Acid	Unconditioned	Unconditioned	1	Unconditional	50.884
Norclozapine Plasma Level	Sodium in Urine	Unconditioned	Unconditioned	0.999985	Unconditional	29.0183
Clozapine Plasma Level	Sodium in Urine	Unconditioned	Unconditioned	0.999987	Unconditional	32.6943
Norclozapine Plasma Level	Sodium in Urine	Unconditioned	Unconditioned	0.999997	Unconditional	41.9587
Clozapine Plasma Level	Sodium in Urine	Unconditioned	Unconditioned	0.999999	Unconditional	45.6347
Norclozapine Plasma Level	Tea Consumption	Unconditioned	Unconditioned	0.999998	Unconditional	48.6422

Clozapine Plasma Level	Tea Consumption	Unconditioned	Unconditioned	1	Unconditional	52.3182
Norclozapine Plasma Level	Tea Consumption	Unconditioned	Unconditioned	0.999998	Unconditional	79.613
Clozapine Plasma Level	Tea Consumption	Unconditioned	Unconditioned	1	Unconditional	83.289
Norclozapine Plasma Level	Tea Consumption	Unconditioned	Unconditioned	0.999998	Unconditional	246.759
Clozapine Plasma Level	Tea Consumption	Unconditioned	Unconditioned	1	Unconditional	250.435
Clozapine-Norclozapine Plasma Ratio	Total Testosterone	rs12646327	rs7438942	0.901361	Conditional Both	56.5107
Clozapine-Norclozapine Plasma Ratio	Total Testosterone	rs835309	rs9994887	0.95699	Conditional Both	10.3865
Norclozapine Plasma Level	Total Testosterone	Unconditioned	Unconditioned	0.966643	Unconditional	39.3702
Clozapine Plasma Level	Total Testosterone	Unconditioned	Unconditioned	0.969384	Unconditional	37.9852
Clozapine Plasma Level	Total Testosterone	Unconditioned	Unconditioned	0.983943	Unconditional	35.8764
Norclozapine Plasma Level	Total Testosterone	Unconditioned	Unconditioned	0.984377	Unconditional	37.3405
Norclozapine Plasma Level	Total Testosterone	Unconditioned	Unconditioned	0.95724	Unconditional	45.4847
Clozapine Plasma Level	Total Testosterone	Unconditioned	Unconditioned	0.957861	Unconditional	44.0121
Norclozapine Plasma Level	Total Testosterone	Unconditioned	Unconditioned	0.9679	Unconditional	24.8059
Clozapine Plasma Level	Total Testosterone	Unconditioned	Unconditioned	0.970804	Unconditional	23.4109
Norclozapine Plasma Level	Total Testosterone	Unconditioned	Unconditioned	0.960195	Unconditional	48.5317
Norclozapine Plasma Level	Total Testosterone	Unconditioned	Unconditioned	0.960195	Unconditional	48.5317
Clozapine Plasma Level	Total Testosterone	Unconditioned	Unconditioned	0.960916	Unconditional	47.0756
Clozapine Plasma Level	Total Testosterone	Unconditioned	Unconditioned	0.960916	Unconditional	47.0756
Clozapine Plasma Level	Total Testosterone	Unconditioned	Unconditioned	0.967799	Unconditional	52.7835
Clozapine Plasma Level	Total Testosterone	Unconditioned	Unconditioned	0.967799	Unconditional	52.7835
Norclozapine Plasma Level	Total Testosterone	Unconditioned	Unconditioned	0.964927	Unconditional	24.2381
Clozapine Plasma Level	Total Testosterone	Unconditioned	Unconditioned	0.967653	Unconditional	22.8486
Norclozapine Plasma Level	Total Testosterone	Unconditioned	Unconditioned	0.976717	Unconditional	43.8151
Clozapine Plasma Level	Total Testosterone	Unconditioned	Unconditioned	0.979196	Unconditional	42.4074
Norclozapine Plasma Level	Total Testosterone	Unconditioned	Unconditioned	0.965848	Unconditional	29.3186
Clozapine Plasma Level	Total Testosterone	Unconditioned	Unconditioned	0.967461	Unconditional	27.8788
Norclozapine Plasma Level	Total Testosterone	Unconditioned	Unconditioned	0.968346	Unconditional	61.2868
Clozapine Plasma Level	Total Testosterone	Unconditioned	Unconditioned	0.972234	Unconditional	59.9247
Norclozapine Plasma Level	Urate	Unconditioned	Unconditioned	0.999998	Unconditional	47.3742
Clozapine Plasma Level	Urate	Unconditioned	Unconditioned	1	Unconditional	51.0502
Norclozapine Plasma Level	Urate	Unconditioned	Unconditioned	0.999998	Unconditional	110.067
Clozapine Plasma Level	Urate	Unconditioned	Unconditioned	1	Unconditional	113.743
Norclozapine Plasma Level	Urate	Unconditioned	Unconditioned	0.999998	Unconditional	54.291
Clozapine Plasma Level	Urate	Unconditioned	Unconditioned	1	Unconditional	57.9671
Norclozapine Plasma Level	Urea	Unconditioned	Unconditioned	0.999998	Unconditional	46.8845
Clozapine Plasma Level	Urea	Unconditioned	Unconditioned	1	Unconditional	50.5606
Norclozapine Plasma Level	Urea	Unconditioned	Unconditioned	0.999998	Unconditional	54.8205
Clozapine Plasma Level	Urea	Unconditioned	Unconditioned	1	Unconditional	58.4965
Norclozapine Plasma Level	Urinary Albumin Excretion	Unconditioned	Unconditioned	0.999718	Unconditional	46.5503
Clozapine Plasma Level	Urinary Albumin Excretion	Unconditioned	Unconditioned	0.99972	Unconditional	50.2262
Norclozapine Plasma Level	Water Consumption	Unconditioned	Unconditioned	0.999989	Unconditional	31.3833
Clozapine Plasma Level	Water Consumption	Unconditioned	Unconditioned	0.999991	Unconditional	35.0593
Norclozapine Plasma Level	Water Consumption	Unconditioned	Unconditioned	0.999998	Unconditional	177.792
Clozapine Plasma Level	Water Consumption	Unconditioned	Unconditioned	1	Unconditional	181.468
Norclozapine Plasma Level	Water Consumption	Unconditioned	Unconditioned	0.999998	Unconditional	53.7716
Clozapine Plasma Level	Water Consumption	Unconditioned	Unconditioned	1	Unconditional	57.4477
Norclozapine Plasma Level	Water Consumption	Unconditioned	Unconditioned	0.999998	Unconditional	131.942
Clozapine Plasma Level	Water Consumption	Unconditioned	Unconditioned	1	Unconditional	135.618
Norclozapine Plasma Level	X 11440	Unconditioned	Unconditioned	0.978314	Unconditional	28.3318

Clozapine Plasma Level	X 11440	Unconditioned	Unconditioned	0.980717	Unconditional	26.9575
Clozapine-Norclozapine Plasma Ratio	X 14473	Unconditioned	Unconditioned	0.96687	Unconditional	52.7449

Supplementary Table 4.5 - Candidate Biomarkers Effects on Metabolic Outcomes (MR)

Exposure	Outcome	Method	nSNP	Beta	SE	P-Value	F Stat (Mean)	F Stat (Min)	Q Stat	Q Stat P-Value	I^2	Egger Intercept	Egger Intercept SE	Egger Intercept P-Value
25 Hydroxyvitamin D	BMI	Inverse variance weighted	137	0.103993336	0.052213763	0.046405698	34.67841116	25.34654566	1706.203832	2.25E-269	91.64575751	NA	NA	NA
25 Hydroxyvitamin D	BMI	MR Egger	137	-0.159249318	0.11530005	0.169507695	34.67841116	25.34654566	NA	NA	NA	0.004514481	0.001771773	0.011953965
25 Hydroxyvitamin D	BMI	Weighted median	137	-0.031659972	0.027104762	0.242782795	34.67841116	25.34654566	NA	NA	NA	NA	NA	NA
25 Hydroxyvitamin D	BMI	Weighted mode	137	-0.060948569	0.034339123	0.078151183	34.67841116	25.34654566	NA	NA	NA	NA	NA	NA
25 Hydroxyvitamin D	DBP	Inverse variance weighted	131	-0.1152133	0.350407041	0.742308016	33.56019072	25.34654566	864.5737759	8.23E-109	84.96139558	NA	NA	NA
25 Hydroxyvitamin D	DBP	MR Egger	131	-0.006015681	0.854221308	0.994391985	33.56019072	25.34654566	NA	NA	NA	-0.00177927	0.012684004	0.888660188
25 Hydroxyvitamin D	DBP	Weighted median	131	0.185027612	0.239922524	0.44058997	33.56019072	25.34654566	NA	NA	NA	NA	NA	NA
25 Hydroxyvitamin D	DBP	Weighted mode	131	-0.276479397	0.410619467	0.50193731	33.56019072	25.34654566	NA	NA	NA	NA	NA	NA
25 Hydroxyvitamin D	HbA1c	Inverse variance weighted	49	-0.019118651	0.050674081	0.705960639	37.9073573	25.38609467	70.88992905	0.017487869	31.76601192	NA	NA	NA
25 Hydroxyvitamin D	HbA1c	MR Egger	49	-0.085370497	0.121178728	0.484597438	37.9073573	25.38609467	NA	NA	NA	0.00106545	0.001767676	0.549578777
25 Hydroxyvitamin D	HbA1c	Weighted median	49	-0.027007972	0.070901377	0.703260318	37.9073573	25.38609467	NA	NA	NA	NA	NA	NA
25 Hydroxyvitamin D	HbA1c	Weighted mode	49	-0.027632604	0.084335752	0.744601194	37.9073573	25.38609467	NA	NA	NA	NA	NA	NA
25 Hydroxyvitamin D	HDL	Inverse variance weighted	57	0.320818416	0.318714678	0.314126701	37.41855666	25.38609467	2210.857957	0	97.45592582	NA	NA	NA
25 Hydroxyvitamin D	HDL	MR Egger	57	-0.041904625	0.804874649	0.9586667	37.41855666	25.38609467	NA	NA	NA	0.005706688	0.011613074	0.625097502
25 Hydroxyvitamin D	HDL	Weighted median	57	-0.226420226	0.094295503	0.016342413	37.41855666	25.38609467	NA	NA	NA	NA	NA	NA
25 Hydroxyvitamin D	HDL	Weighted mode	57	-0.284811066	0.115471099	0.016729982	37.41855666	25.38609467	NA	NA	NA	NA	NA	NA
25 Hydroxyvitamin D	LDL	Inverse variance weighted	57	0.426050726	0.239819166	0.075642317	37.41855666	25.38609467	1071.181276	1.15E-187	94.58780238	NA	NA	NA
25 Hydroxyvitamin D	LDL	MR Egger	57	1.188658975	0.597050168	0.051470853	37.41855666	25.38609467	NA	NA	NA	-0.011998106	0.008615938	0.169360971
25 Hydroxyvitamin D	LDL	Weighted median	57	0.096959666	0.106288407	0.361646699	37.41855666	25.38609467	NA	NA	NA	NA	NA	NA
25 Hydroxyvitamin D	LDL	Weighted mode	57	0.062157187	0.118024834	0.600520065	37.41855666	25.38609467	NA	NA	NA	NA	NA	NA
25 Hydroxyvitamin D	MetS	Inverse variance weighted	145	-0.255984581	0.129644857	0.048324208	46.11739519	25.34654566	1432.829967	4.98E-211	89.58209319	NA	NA	NA
25 Hydroxyvitamin D	MetS	MR Egger	145	0.15972319	0.222133388	0.473288527	46.11739519	25.34654566	NA	NA	NA	-0.008914392	0.003896395	0.02361244
25 Hydroxyvitamin D	MetS	Weighted median	145	0.074407631	0.078472597	0.3430282	46.11739519	25.34654566	NA	NA	NA	NA	NA	NA
25 Hydroxyvitamin D	MetS	Weighted mode	145	0.059093764	0.076472926	0.440942195	46.11739519	25.34654566	NA	NA	NA	NA	NA	NA
25 Hydroxyvitamin D	SBP	Inverse variance weighted	130	-0.204435757	0.590120668	0.729019259	33.60329102	25.34654566	796.953668	8.81E-97	83.77954487	NA	NA	NA
25 Hydroxyvitamin D	SBP	MR Egger	130	0.474735543	1.440526227	0.742273374	33.60329102	25.34654566	NA	NA	NA	-0.011033482	0.021336014	0.605958208
25 Hydroxyvitamin D	SBP	Weighted median	130	-0.674058761	0.469836128	0.151381787	33.60329102	25.34654566	NA	NA	NA	NA	NA	NA
25 Hydroxyvitamin D	SBP	Weighted mode	130	-0.759993778	0.707757764	0.28491463	33.60329102	25.34654566	NA	NA	NA	NA	NA	NA
25 Hydroxyvitamin D	T2DM	Inverse variance weighted	78	0.519202583	0.151440558	0.000607094	30.93213602	25.34654566	267.0708	8.52E-23	70.86524817	NA	NA	NA
25 Hydroxyvitamin D	T2DM	MR Egger	78	-0.047783523	0.651836525	0.941755216	30.93213602	25.34654566	NA	NA	NA	0.007553761	0.008445942	0.373949938
25 Hydroxyvitamin D	T2DM	Weighted median	78	0.251290799	0.146177695	0.085600246	30.93213602	25.34654566	NA	NA	NA	NA	NA	NA
25 Hydroxyvitamin D	T2DM	Weighted mode	78	-0.035319757	0.374381632	0.925082885	30.93213602	25.34654566	NA	NA	NA	NA	NA	NA
25 Hydroxyvitamin D	Triglycerides	Inverse variance weighted	57	0.507973804	0.162259502	0.001744342	37.41855666	25.38609467	608.1197225	9.81E-94	90.72449483	NA	NA	NA
25 Hydroxyvitamin D	Triglycerides	MR Egger	57	0.273874274	0.404956931	0.501681462	37.41855666	25.38609467	NA	NA	NA	0.003706728	0.005868757	0.530262415
25 Hydroxyvitamin D	Triglycerides	Weighted median	57	0.195157303	0.085104519	0.021839454	37.41855666	25.38609467	NA	NA	NA	NA	NA	NA
25 Hydroxyvitamin D	Triglycerides	Weighted mode	57	0.138355931	0.100120758	0.172493251	37.41855666	25.38609467	NA	NA	NA	NA	NA	NA
Bilirubin	BMI	Inverse variance weighted	178	0.003665217	0.008352429	0.660791607	802.2960849	20.17688058	1143.91634	4.44E-141	84.46552148	NA	NA	NA
Bilirubin	BMI	MR Egger	178	0.000482838	0.009187099	0.958145189	802.2960849	20.17688058	NA	NA	NA	0.000414428	0.000496231	0.404765612
Bilirubin	BMI	Weighted median	178	-0.002423884	0.00359587	0.500263993	802.2960849	20.17688058	NA	NA	NA	NA	NA	NA
Bilirubin	BMI	Weighted mode	178	-0.00386357	0.004263361	0.366048063	802.2960849	20.17688058	NA	NA	NA	NA	NA	NA
Bilirubin	DBP	Inverse variance weighted	162	-0.084176161	0.122870368	0.493292777	876.9567602	20.17688058	2891.537746	0	94.2856024	NA	NA	NA
Bilirubin	DBP	MR Egger	162	0.027625453	0.133315005	0.836102024	876.9567602	20.17688058	NA	NA	NA	-0.015196594	0.007408421	0.041872265
Bilirubin	DBP	Weighted median	162	0.01289218	0.032738097	0.693730557	876.9567602	20.17688058	NA	NA	NA	NA	NA	NA
Bilirubin	DBP	Weighted mode	162	0.035404752	0.038924924	0.364411549	876.9567602	20.17688058	NA	NA	NA	NA	NA	NA
Bilirubin	HbA1c	Inverse variance weighted	108	0.031406833	0.014765305	0.033414296	1232.623302	24.97340002	683.468133	8.12E-85	81.6472861	NA	NA	NA
Bilirubin	HbA1c	MR Egger	108	0.007472438	0.014801862	0.614725479	1232.623302	24.97340002	NA	NA	NA	0.004185009	0.000979297	4.22E-05
Bilirubin	HbA1c	Weighted median	108	0.00366164	0.006310735	0.561763531	1232.623302	24.97340002	NA	NA	NA	NA	NA	NA
Bilirubin	HbA1c	Weighted mode	108	0.001550965	0.006331156	0.806946175	1232.623302	24.97340002	NA	NA	NA	NA	NA	NA
Bilirubin	HDL	Inverse variance weighted	119	0.00121459	0.019959544	0.951476615	1128.368769	24.10435168	1324.247646	5.33E-203	91.08264537	NA	NA	NA
Bilirubin	HDL	MR Egger	119	-0.001185921	0.021624931	0.956359108	1128.368769	24.10435168	NA	NA	NA	0.000489963	0.00166004	0.768401467
Bilirubin	HDL	Weighted median	119	0.000340031	0.006192758	0.956211849	1128.368769	24.10435168	NA	NA	NA	NA	NA	NA
Bilirubin	HDL	Weighted mode	119	-0.003138741	0.007624531	0.681332901	1128.368769	24.10435168	NA	NA	NA	NA	NA	NA
Bilirubin	LDL	Inverse variance weighted	119	0.041753194	0.023243568	0.072441537	1128.368769	24.10435168	1531.242606	2.70E-244	92.28483715	NA	NA	NA
Bilirubin	LDL	MR Egger	119	0.045260081	0.025183638	0.074883187	1128.368769	24.10435168	NA	NA	NA	-0.000714891	0.001933606	0.712260062
Bilirubin	LDL	Weighted median	119	0.033143211	0.006708166	7.78E-07	1128.368769	24.10435168	NA	NA	NA	NA	NA	NA
Bilirubin	LDL	Weighted mode	119	0.040747366	0.008819883	9.87E-06	1128.368769	24.10435168	NA	NA	NA	NA	NA	NA

Bilirubin	MetS	Inverse variance weighted	180	0.003029865	0.030603873	0.921136156	793.8811768	20.17688058	1415.383119	4.79E-191	87.34481673	NA	NA	NA
Bilirubin	MetS	MR Egger	180	0.007863083	0.03373566	0.815967648	793.8811768	20.17688058	NA	NA	NA	-0.000623141	0.001808973	0.73089796
Bilirubin	MetS	Weighted median	180	0.001541057	0.012139212	0.898981018	793.8811768	20.17688058	NA	NA	NA	NA	NA	NA
Bilirubin	MetS	Weighted mode	180	0.010001101	0.013915723	0.473268583	793.8811768	20.17688058	NA	NA	NA	NA	NA	NA
Bilirubin	SBP	Inverse variance weighted	160	-0.004890872	0.166843223	0.976614019	887.2866916	20.17688058	1743.30605	2.00E-264	90.81271206	NA	NA	NA
Bilirubin	SBP	MR Egger	160	0.075209923	0.18265672	0.681076627	887.2866916	20.17688058	NA	NA	NA	-0.01097042	0.010206764	0.284094589
Bilirubin	SBP	Weighted median	160	0.06458442	0.05508561	0.241021561	887.2866916	20.17688058	NA	NA	NA	NA	NA	NA
Bilirubin	SBP	Weighted mode	160	0.094106867	0.07038376	0.183114872	887.2866916	20.17688058	NA	NA	NA	NA	NA	NA
Bilirubin	T2DM	Inverse variance weighted	131	-0.036258042	0.025887891	0.161339953	1018.751737	24.10435168	582.5759649	1.64E-58	77.68113835	NA	NA	NA
Bilirubin	T2DM	MR Egger	131	-0.037909994	0.028076944	0.179310274	1018.751737	24.10435168	NA	NA	NA	0.00027428	0.001765456	0.876780898
Bilirubin	T2DM	Weighted median	131	-0.037855404	0.012911607	0.003369066	1018.751737	24.10435168	NA	NA	NA	NA	NA	NA
Bilirubin	T2DM	Weighted mode	131	-0.029255564	0.014898432	0.051702876	1018.751737	24.10435168	NA	NA	NA	NA	NA	NA
Bilirubin	Triglycerides	Inverse variance weighted	119	0.020589536	0.021821933	0.345412506	1128.368769	24.10435168	1675.314448	2.56E-273	92.95483325	NA	NA	NA
Bilirubin	Triglycerides	MR Egger	119	0.022090828	0.023650869	0.352207583	1128.368769	24.10435168	NA	NA	NA	-0.000306975	0.001819858	0.866339042
Bilirubin	Triglycerides	Weighted median	119	0.017165316	0.006201034	0.005637766	1128.368769	24.10435168	NA	NA	NA	NA	NA	NA
Bilirubin	Triglycerides	Weighted mode	119	0.005216254	0.008289446	0.530392304	1128.368769	24.10435168	NA	NA	NA	NA	NA	NA
Blood Urea Nitrogen	BMI	Inverse variance weighted	147	-0.013027087	0.035775255	0.715755854	92.09978006	29.34027778	2540.65961	0	94.24773896	NA	NA	NA
Blood Urea Nitrogen	BMI	MR Egger	147	0.013685723	0.078929354	0.862585092	92.09978006	29.34027778	NA	NA	NA	-0.000668227	0.00175863	0.704523642
Blood Urea Nitrogen	BMI	Weighted median	147	0.032624373	0.017388782	0.060631457	92.09978006	29.34027778	NA	NA	NA	NA	NA	NA
Blood Urea Nitrogen	BMI	Weighted mode	147	0.034150949	0.023197391	0.143122169	92.09978006	29.34027778	NA	NA	NA	NA	NA	NA
Blood Urea Nitrogen	DBP	Inverse variance weighted	133	-0.596996268	0.315697454	0.058619109	92.05290471	29.34027778	2084.72933	0	93.66412813	NA	NA	NA
Blood Urea Nitrogen	DBP	MR Egger	133	-0.422816943	0.675826377	0.532646399	92.05290471	29.34027778	NA	NA	NA	-0.004408484	0.01510949	0.770924626
Blood Urea Nitrogen	DBP	Weighted median	133	-0.386291956	0.185912835	0.03772666	92.05290471	29.34027778	NA	NA	NA	NA	NA	NA
Blood Urea Nitrogen	DBP	Weighted mode	133	0.04623162	0.276624361	0.867525252	92.05290471	29.34027778	NA	NA	NA	NA	NA	NA
Blood Urea Nitrogen	HbA1c	Inverse variance weighted	53	-0.041267602	0.027436721	0.132555345	104.7602194	29.46938776	64.1309602	0.120570988	17.56564206	NA	NA	NA
Blood Urea Nitrogen	HbA1c	MR Egger	53	-0.099886932	0.069288874	0.155527489	104.7602194	29.46938776	NA	NA	NA	0.00141178	0.001531928	0.361091692
Blood Urea Nitrogen	HbA1c	Weighted median	53	-0.064982801	0.038623867	0.092481229	104.7602194	29.46938776	NA	NA	NA	NA	NA	NA
Blood Urea Nitrogen	HbA1c	Weighted mode	53	-0.117768366	0.061714115	0.061881517	104.7602194	29.46938776	NA	NA	NA	NA	NA	NA
Blood Urea Nitrogen	HDL	Inverse variance weighted	60	-0.080431795	0.050186699	0.109011593	105.9010754	29.46938776	188.8130831	1.69E-15	68.26141381	NA	NA	NA
Blood Urea Nitrogen	HDL	MR Egger	60	-0.190613702	0.125897102	0.135445556	105.9010754	29.46938776	NA	NA	NA	0.002811681	0.002945989	0.343837261
Blood Urea Nitrogen	HDL	Weighted median	60	-0.088796376	0.048750376	0.068538467	105.9010754	29.46938776	NA	NA	NA	NA	NA	NA
Blood Urea Nitrogen	HDL	Weighted mode	60	-0.072692543	0.059574115	0.227242534	105.9010754	29.46938776	NA	NA	NA	NA	NA	NA
Blood Urea Nitrogen	LDL	Inverse variance weighted	60	-0.054952976	0.065871091	0.404139964	105.9010754	29.46938776	278.5259167	3.19E-30	78.7024156	NA	NA	NA
Blood Urea Nitrogen	LDL	MR Egger	60	-0.140197273	0.165954431	0.401697345	105.9010754	29.46938776	NA	NA	NA	0.002176495	0.003884861	0.577466366
Blood Urea Nitrogen	LDL	Weighted median	60	-0.087642761	0.054515252	0.107906561	105.9010754	29.46938776	NA	NA	NA	NA	NA	NA
Blood Urea Nitrogen	LDL	Weighted mode	60	-0.066783953	0.056694025	0.243537517	105.9010754	29.46938776	NA	NA	NA	NA	NA	NA
Blood Urea Nitrogen	MetS	Inverse variance weighted	166	0.114168986	0.053786582	0.033784912	87.74668517	29.34027778	642.6133461	1.51E-57	74.19930139	NA	NA	NA
Blood Urea Nitrogen	MetS	MR Egger	166	0.018036616	0.120570658	0.881268956	87.74668517	29.34027778	NA	NA	NA	0.002334032	0.002619547	0.374231201
Blood Urea Nitrogen	MetS	Weighted median	166	0.012523082	0.047654709	0.792714047	87.74668517	29.34027778	NA	NA	NA	NA	NA	NA
Blood Urea Nitrogen	MetS	Weighted mode	166	-0.027277625	0.063762418	0.669353855	87.74668517	29.34027778	NA	NA	NA	NA	NA	NA
Blood Urea Nitrogen	SBP	Inverse variance weighted	132	-1.060887622	0.521569845	0.041948781	92.48078502	29.34027778	1860.469027	3.17E-303	92.93576774	NA	NA	NA
Blood Urea Nitrogen	SBP	MR Egger	132	-0.419680835	1.114261551	0.707051632	92.48078502	29.34027778	NA	NA	NA	-0.016253858	0.0249444	0.5158073
Blood Urea Nitrogen	SBP	Weighted median	132	-0.281861267	0.344700808	0.413529478	92.48078502	29.34027778	NA	NA	NA	NA	NA	NA
Blood Urea Nitrogen	SBP	Weighted mode	132	0.379626901	0.396385401	0.339967288	92.48078502	29.34027778	NA	NA	NA	NA	NA	NA
Blood Urea Nitrogen	T2DM	Inverse variance weighted	105	-0.007444152	0.10274214	0.942240046	95.98305123	29.34027778	721.8315372	3.62E-93	85.56656824	NA	NA	NA
Blood Urea Nitrogen	T2DM	MR Egger	105	0.080227123	0.22929467	0.727138257	95.98305123	29.34027778	NA	NA	NA	-0.002161571	0.005049036	0.669460869
Blood Urea Nitrogen	T2DM	Weighted median	105	0.151404565	0.072054784	0.035619696	95.98305123	29.34027778	NA	NA	NA	NA	NA	NA
Blood Urea Nitrogen	T2DM	Weighted mode	105	0.142000308	0.081859394	0.085759173	95.98305123	29.34027778	NA	NA	NA	NA	NA	NA
Blood Urea Nitrogen	Triglycerides	Inverse variance weighted	60	-0.167179707	0.134210232	0.212890917	105.9010754	29.46938776	1421.267087	2.83E-258	95.73901253	NA	NA	NA
Blood Urea Nitrogen	Triglycerides	MR Egger	60	0.212392687	0.334362732	0.527785491	105.9010754	29.46938776	NA	NA	NA	-0.00970321	0.00783544	0.220566147
Blood Urea Nitrogen	Triglycerides	Weighted median	60	0	0.048039778	1	105.9010754	29.46938776	NA	NA	NA	NA	NA	NA
Blood Urea Nitrogen	Triglycerides	Weighted mode	60	-0.019161684	0.059973264	0.750473114	105.9010754	29.46938776	NA	NA	NA	NA	NA	NA
Coffee Consumption	BMI	Inverse variance weighted	35	-0.754114731	0.190935701	7.83E-05	77.65577496	30.10111407	2241.580155	0	98.4393995	NA	NA	NA
Coffee Consumption	BMI	MR Egger	35	-0.436905332	0.376916381	0.254711269	77.65577496	30.10111407	NA	NA	NA	-0.006085646	0.006233169	0.336002935
Coffee Consumption	BMI	Weighted median	35	-0.275461608	0.039253149	2.26E-12	77.65577496	30.10111407	NA	NA	NA	NA	NA	NA
Coffee Consumption	BMI	Weighted mode	35	-0.28364509	0.032763685	4.09E-10	77.65577496	30.10111407	NA	NA	NA	NA	NA	NA
Coffee Consumption	DBP	Inverse variance weighted	33	1.333832387	0.502119516	0.007897889	80.39895466	30.10111407	181.6837392	7.64E-23	82.38582876	NA	NA	NA
Coffee Consumption	DBP	MR Egger	33	1.372646756	1.003064539	0.181006934	80.39895466	30.10111407	NA	NA	NA	-0.000743883	0.016552062	0.964441773
Coffee Consumption	DBP	Weighted median	33	1.449674741	0.499951742	0.003736042	80.39895466	30.10111407	NA	NA	NA	NA	NA	NA
Coffee Consumption	DBP	Weighted mode	33	2.252178366	0.802675413	0.008468936	80.39895466	30.10111407	NA	NA	NA	NA	NA	NA
Coffee Consumption	HbA1c	Inverse variance weighted	19	-0.088714689	0.056982853	0.119502209	104.8183811	30.13711083	20.93896213	0.282503664	8.366967875	NA	NA	NA
Coffee Consumption	HbA1c	MR Egger	19	0.004935649	0.105112524	0.96309562	104.8183811	30.13711083	NA	NA	NA	-0.001925683	0.001818738	0.304503367

Coffee Consumption	HbA1c	Weighted median	19	-0.061418945	0.067945339	0.36602382	104.8183811	30.13711083	NA	NA	NA	NA	NA	NA
Coffee Consumption	HbA1c	Weighted mode	19	-0.042584367	0.071915128	0.561116962	104.8183811	30.13711083	NA	NA	NA	NA	NA	NA
Coffee Consumption	HDL	Inverse variance weighted	19	0.187501621	0.14783727	0.204691774	105.7807462	30.13711083	118.9348808	6.67E-17	84.62948775	NA	NA	NA
Coffee Consumption	HDL	MR Egger	19	0.066262088	0.279628825	0.815516321	105.7807462	30.13711083	NA	NA	NA	0.002716106	0.005273298	0.613138006
Coffee Consumption	HDL	Weighted median	19	-0.075422537	0.105117375	0.473060823	105.7807462	30.13711083	NA	NA	NA	NA	NA	NA
Coffee Consumption	HDL	Weighted mode	19	0.024859282	0.092539505	0.791265838	105.7807462	30.13711083	NA	NA	NA	NA	NA	NA
Coffee Consumption	LDL	Inverse variance weighted	19	-0.037320755	0.113977658	0.74333571	105.7807462	30.13711083	61.10783332	1.35E-06	70.01780679	NA	NA	NA
Coffee Consumption	LDL	MR Egger	19	-0.137081809	0.21515944	0.532535403	105.7807462	30.13711083	NA	NA	NA	0.002247103	0.004078171	0.588797586
Coffee Consumption	LDL	Weighted median	19	-0.107497275	0.084004499	0.20066441	105.7807462	30.13711083	NA	NA	NA	NA	NA	NA
Coffee Consumption	LDL	Weighted mode	19	-0.120000367	0.073347688	0.119194472	105.7807462	30.13711083	NA	NA	NA	NA	NA	NA
Coffee Consumption	MetS	Inverse variance weighted	35	0.555176333	0.28840138	0.054227763	77.65577496	30.10111407	468.8270678	6.69E-78	92.74524107	NA	NA	NA
Coffee Consumption	MetS	MR Egger	35	0.500880424	0.577180896	0.391768243	77.65577496	30.10111407	NA	NA	NA	0.001041515	0.009542498	0.913748594
Coffee Consumption	MetS	Weighted median	35	0.502490762	0.1741525	0.003909798	77.65577496	30.10111407	NA	NA	NA	NA	NA	NA
Coffee Consumption	MetS	Weighted mode	35	0.411652207	0.130631722	0.003384086	77.65577496	30.10111407	NA	NA	NA	NA	NA	NA
Coffee Consumption	SBP	Inverse variance weighted	33	1.894895288	0.923238013	0.04012643	80.39895466	30.10111407	202.1476983	1.34E-26	83.63976235	NA	NA	NA
Coffee Consumption	SBP	MR Egger	33	0.302109595	1.815108295	0.868890282	80.39895466	30.10111407	NA	NA	NA	0.030489796	0.029921469	0.316092909
Coffee Consumption	SBP	Weighted median	33	2.253615035	0.839504814	0.007264761	80.39895466	30.10111407	NA	NA	NA	NA	NA	NA
Coffee Consumption	SBP	Weighted mode	33	0.818271724	1.316480195	0.538634298	80.39895466	30.10111407	NA	NA	NA	NA	NA	NA
Coffee Consumption	T2DM	Inverse variance weighted	26	-1.499028693	0.391292132	0.000127639	67.23356478	30.10111407	287.5274308	1.89E-46	91.29737353	NA	NA	NA
Coffee Consumption	T2DM	MR Egger	26	-1.627770038	0.963735728	0.104167637	67.23356478	30.10111407	NA	NA	NA	0.002065033	0.014070079	0.884541285
Coffee Consumption	T2DM	Weighted median	26	-0.465767644	0.191253343	0.014877646	67.23356478	30.10111407	NA	NA	NA	NA	NA	NA
Coffee Consumption	T2DM	Weighted mode	26	-0.368687688	0.19018085	0.063917036	67.23356478	30.10111407	NA	NA	NA	NA	NA	NA
Coffee Consumption	Triglycerides	Inverse variance weighted	19	0.356367227	0.473144958	0.451336794	105.7807462	30.13711083	1309.548899	3.66E-267	98.57048803	NA	NA	NA
Coffee Consumption	Triglycerides	MR Egger	19	-0.25325005	0.879951933	0.776979011	105.7807462	30.13711083	NA	NA	NA	0.013837656	0.016778778	0.420957026
Coffee Consumption	Triglycerides	Weighted median	19	0.002732782	0.108455681	0.97989765	105.7807462	30.13711083	NA	NA	NA	NA	NA	NA
Coffee Consumption	Triglycerides	Weighted mode	19	0.042685031	0.090947012	0.644462036	105.7807462	30.13711083	NA	NA	NA	NA	NA	NA
Cotinine in Current Smokers	BMI	Inverse variance weighted	3	0.013795375	0.018114668	0.446323688	84.00410838	45.7566758	18.02269014	0.000122018	0	NA	NA	NA
Cotinine in Current Smokers	BMI	MR Egger	3	-0.055530927	0.017421599	0.193534387	84.00410838	45.7566758	NA	NA	NA	0.016203452	0.003819836	0.14738711
Cotinine in Current Smokers	BMI	Weighted median	3	0.008046579	0.007464746	0.281058678	84.00410838	45.7566758	NA	NA	NA	NA	NA	NA
Cotinine in Current Smokers	BMI	Weighted mode	3	0.004732161	0.00821063	0.62259944	84.00410838	45.7566758	NA	NA	NA	NA	NA	NA
Cotinine in Current Smokers	DBP	Inverse variance weighted	3	-0.102026622	0.116250476	0.380136528	84.00410838	45.7566758	8.968563312	0.011284991	0	NA	NA	NA
Cotinine in Current Smokers	DBP	MR Egger	3	0.327373472	0.1666289	0.299727895	84.00410838	45.7566758	NA	NA	NA	-0.100085319	0.03654652	0.222887229
Cotinine in Current Smokers	DBP	Weighted median	3	-0.101234183	0.074595633	0.174747523	84.00410838	45.7566758	NA	NA	NA	NA	NA	NA
Cotinine in Current Smokers	DBP	Weighted mode	3	-0.139033347	0.113092487	0.343934801	84.00410838	45.7566758	NA	NA	NA	NA	NA	NA
Cotinine in Current Smokers	MetS	Inverse variance weighted	3	0.01223212	0.019873264	0.53822038	84.00410838	45.7566758	0.658190664	0.719574415	0	NA	NA	NA
Cotinine in Current Smokers	MetS	MR Egger	3	0.037347905	0.057344229	0.63248974	84.00410838	45.7566758	NA	NA	NA	-0.005870532	0.012572915	0.721902664
Cotinine in Current Smokers	MetS	Weighted median	3	0.015543012	0.021544036	0.470630767	84.00410838	45.7566758	NA	NA	NA	NA	NA	NA
Cotinine in Current Smokers	MetS	Weighted mode	3	0.017915722	0.025777102	0.558930862	84.00410838	45.7566758	NA	NA	NA	NA	NA	NA
Cotinine in Current Smokers	SBP	Inverse variance weighted	3	-0.105392107	0.143398716	0.462364763	84.00410838	45.7566758	4.479310681	0.106495203	0	NA	NA	NA
Cotinine in Current Smokers	SBP	MR Egger	3	0.328178516	0.389131233	0.553966522	84.00410838	45.7566758	NA	NA	NA	-0.100755511	0.085157846	0.446713985
Cotinine in Current Smokers	SBP	Weighted median	3	-0.263900374	0.124856476	0.034546895	84.00410838	45.7566758	NA	NA	NA	NA	NA	NA
Cotinine in Current Smokers	SBP	Weighted mode	3	-0.268341754	0.19852724	0.309061401	84.00410838	45.7566758	NA	NA	NA	NA	NA	NA
Creatinine	BMI	Inverse variance weighted	305	-0.139379856	0.025816816	6.71E-08	89.03212516	29.78522205	4990.828485	0	93.31111212	NA	NA	NA
Creatinine	BMI	MR Egger	305	0.118821967	0.053396596	0.026798882	89.03212516	29.78522205	NA	NA	NA	-0.006159673	0.001129639	1.03E-07
Creatinine	BMI	Weighted median	305	-0.023739105	0.013335905	0.075061308	89.03212516	29.78522205	NA	NA	NA	NA	NA	NA
Creatinine	BMI	Weighted mode	305	0.003036082	0.016223849	0.851678087	89.03212516	29.78522205	NA	NA	NA	NA	NA	NA

Creatinine	DBP	Inverse variance weighted	270	-0.612355014	0.245960368	0.012786926	91.84761123	29.78522205	4693.553036	0	94.19217503	NA	NA	NA
Creatinine	DBP	MR Egger	270	-1.504671363	0.531349958	0.004979935	91.84761123	29.78522205	NA	NA	NA	0.021324918	0.01127059	0.059557452
Creatinine	DBP	Weighted median	270	-0.184186907	0.144773972	0.203288673	91.84761123	29.78522205	NA	NA	NA	NA	NA	NA
Creatinine	DBP	Weighted mode	270	0.279313315	0.301354269	0.354829888	91.84761123	29.78522205	NA	NA	NA	NA	NA	NA
Creatinine	HbA1c	Inverse variance weighted	138	0.017114854	0.018512317	0.355219939	101.9546904	29.78522205	189.0242571	0.002157044	27.27255193	NA	NA	NA
Creatinine	HbA1c	MR Egger	138	0.041455698	0.040089011	0.302928791	101.9546904	29.78522205	NA	NA	NA	-0.00059883	0.000874349	0.494581204
Creatinine	HbA1c	Weighted median	138	0.003471012	0.026069092	0.894077415	101.9546904	29.78522205	NA	NA	NA	NA	NA	NA
Creatinine	HbA1c	Weighted mode	138	-3.90E-05	0.044876487	0.999307693	101.9546904	29.78522205	NA	NA	NA	NA	NA	NA
Creatinine	HDL	Inverse variance weighted	149	0.123342739	0.048308961	0.010673629	97.68811398	29.78522205	887.3193596	9.62E-106	83.27644911	NA	NA	NA
Creatinine	HDL	MR Egger	149	0.18321473	0.107547812	0.090575427	97.68811398	29.78522205	NA	NA	NA	-0.001459406	0.002340943	0.533970331
Creatinine	HDL	Weighted median	149	0.129598604	0.038388861	0.000735632	97.68811398	29.78522205	NA	NA	NA	NA	NA	NA
Creatinine	HDL	Weighted mode	149	0.082337303	0.09494248	0.387217961	97.68811398	29.78522205	NA	NA	NA	NA	NA	NA
Creatinine	LDL	Inverse variance weighted	149	0.092643929	0.052640819	0.078420411	97.68811398	29.78522205	900.5850253	3.73E-108	83.52716309	NA	NA	NA
Creatinine	LDL	MR Egger	149	0.030974921	0.116892979	0.791391993	97.68811398	29.78522205	NA	NA	NA	0.001507912	0.002550568	0.555290292
Creatinine	LDL	Weighted median	149	0.019055873	0.04120666	0.643761197	97.68811398	29.78522205	NA	NA	NA	NA	NA	NA
Creatinine	LDL	Weighted mode	149	0.001886593	0.083829739	0.982075389	97.68811398	29.78522205	NA	NA	NA	NA	NA	NA
Creatinine	MetS	Inverse variance weighted	339	0.222894161	0.044266525	4.77E-07	95.53130673	29.78522205	1792.859104	2.49E-196	80.69998664	NA	NA	NA
Creatinine	MetS	MR Egger	339	0.005003485	0.088631662	0.955014737	95.53130673	29.78522205	NA	NA	NA	0.005504291	0.001946266	0.004962165
Creatinine	MetS	Weighted median	339	0.183881276	0.037656722	1.04E-06	95.53130673	29.78522205	NA	NA	NA	NA	NA	NA
Creatinine	MetS	Weighted mode	339	0.061189629	0.045868699	0.183096383	95.53130673	29.78522205	NA	NA	NA	NA	NA	NA
Creatinine	SBP	Inverse variance weighted	269	-0.375415462	0.375618813	0.317572573	91.68078949	29.78522205	3585.580131	0	92.46399821	NA	NA	NA
Creatinine	SBP	MR Egger	269	-1.452600372	0.817073172	0.076573279	91.68078949	29.78522205	NA	NA	NA	0.025659948	0.017295457	0.139088277
Creatinine	SBP	Weighted median	269	0.122009106	0.251894812	0.62812664	91.68078949	29.78522205	NA	NA	NA	NA	NA	NA
Creatinine	SBP	Weighted mode	269	1.102738546	0.585137752	0.060568748	91.68078949	29.78522205	NA	NA	NA	NA	NA	NA
Creatinine	T2DM	Inverse variance weighted	212	-0.1416831	0.064021973	0.026894983	94.55797341	29.78522205	1025.135399	4.36E-107	78.70769503	NA	NA	NA
Creatinine	T2DM	MR Egger	212	0.209789335	0.145060323	0.149605973	94.55797341	29.78522205	NA	NA	NA	-0.008174445	0.003037908	0.007701633
Creatinine	T2DM	Weighted median	212	0.01903149	0.057953404	0.742614568	94.55797341	29.78522205	NA	NA	NA	NA	NA	NA
Creatinine	T2DM	Weighted mode	212	0.047507354	0.089216337	0.594942729	94.55797341	29.78522205	NA	NA	NA	NA	NA	NA
Creatinine	Triglycerides	Inverse variance weighted	149	0.052116285	0.076120927	0.493564045	97.68811398	29.78522205	2316.178847	0	93.54722339	NA	NA	NA
Creatinine	Triglycerides	MR Egger	149	-0.129374084	0.16889263	0.444896372	97.68811398	29.78522205	NA	NA	NA	0.00442382	0.003676323	0.230784028
Creatinine	Triglycerides	Weighted median	149	-0.138177211	0.036112123	0.000130063	97.68811398	29.78522205	NA	NA	NA	NA	NA	NA
Creatinine	Triglycerides	Weighted mode	149	-0.124241723	0.035527726	0.000621366	97.68811398	29.78522205	NA	NA	NA	NA	NA	NA
CRP	BMI	Inverse variance weighted	224	-0.001332476	0.012279745	0.913591106	246.355641	24.48283305	1868.050764	2.59E-257	87.59492526	NA	NA	NA
CRP	BMI	MR Egger	224	-0.031343912	0.015791214	0.048387208	246.355641	24.48283305	NA	NA	NA	0.001757584	0.000596085	0.003534156
CRP	BMI	Weighted median	224	-0.00503253	0.008494987	0.553574944	246.355641	24.48283305	NA	NA	NA	NA	NA	NA
CRP	BMI	Weighted mode	224	-0.022423385	0.006006168	0.000239858	246.355641	24.48283305	NA	NA	NA	NA	NA	NA
CRP	DBP	Inverse variance weighted	201	-0.051819231	0.120268695	0.66656859	266.324831	24.48283305	1989.310598	7.44E-292	89.9202978	NA	NA	NA
CRP	DBP	MR Egger	201	0.019719322	0.156385772	0.899784748	266.324831	24.48283305	NA	NA	NA	-0.004322959	0.006029746	0.47425248
CRP	DBP	Weighted median	201	-0.058092674	0.074500939	0.435533567	266.324831	24.48283305	NA	NA	NA	NA	NA	NA
CRP	DBP	Weighted mode	201	0.012145828	0.052367138	0.81682481	266.324831	24.48283305	NA	NA	NA	NA	NA	NA
CRP	HbA1c	Inverse variance weighted	121	0.01090069	0.013164904	0.407664039	283.6377623	24.48283305	225.0447613	2.13E-08	46.14854881	NA	NA	NA
CRP	HbA1c	MR Egger	121	-0.001362973	0.017335385	0.937463966	283.6377623	24.48283305	NA	NA	NA	0.000732247	0.000674101	0.279560796
CRP	HbA1c	Weighted median	121	-0.009921977	0.014883856	0.505010556	283.6377623	24.48283305	NA	NA	NA	NA	NA	NA
CRP	HbA1c	Weighted mode	121	-0.002183905	0.011620128	0.851239924	283.6377623	24.48283305	NA	NA	NA	NA	NA	NA
CRP	HDL	Inverse variance weighted	130	-0.034031829	0.039942986	0.394208465	267.3442928	24.48283305	1831.075992	1.93E-298	92.82070377	NA	NA	NA
CRP	HDL	MR Egger	130	0.016818974	0.051360413	0.743847697	267.3442928	24.48283305	NA	NA	NA	-0.003434609	0.002199093	0.120797135
CRP	HDL	Weighted median	130	0.052639827	0.021919716	0.016328764	267.3442928	24.48283305	NA	NA	NA	NA	NA	NA
CRP	HDL	Weighted mode	130	0.044677196	0.013562511	0.001274445	267.3442928	24.48283305	NA	NA	NA	NA	NA	NA
CRP	LDL	Inverse variance weighted	130	0.02873375	0.049586025	0.562270233	267.3442928	24.48283305	2441.070435	0	94.66707647	NA	NA	NA
CRP	LDL	MR Egger	130	-0.015145812	0.064026443	0.813379729	267.3442928	24.48283305	NA	NA	NA	0.002985443	0.002758548	0.281175262
CRP	LDL	Weighted median	130	-0.007393921	0.01983342	0.709296481	267.3442928	24.48283305	NA	NA	NA	NA	NA	NA
CRP	LDL	Weighted mode	130	0.046709796	0.017873462	0.010031099	267.3442928	24.48283305	NA	NA	NA	NA	NA	NA
CRP	MetS	Inverse variance weighted	224	-0.07885416	0.03447603	0.022183164	245.9246686	24.48283305	1360.64364	2.56E-162	83.60167826	NA	NA	NA
CRP	MetS	MR Egger	224	-0.088985655	0.045094158	0.049698513	245.9246686	24.48283305	NA	NA	NA	0.000593221	0.001697194	0.727022447
CRP	MetS	Weighted median	224	-0.060780513	0.032803406	0.063900705	245.9246686	24.48283305	NA	NA	NA	NA	NA	NA
CRP	MetS	Weighted mode	224	-0.068512242	0.020623149	0.001043956	245.9246686	24.48283305	NA	NA	NA	NA	NA	NA
CRP	SBP	Inverse variance weighted	199	0.000503121	0.189775249	0.997884697	261.169586	24.48283305	1578.224513	1.98E-213	87.41420124	NA	NA	NA
CRP	SBP	MR Egger	199	0.125732808	0.247013965	0.611314192	261.169586	24.48283305	NA	NA	NA	-0.007467763	0.009416209	0.428688032
CRP	SBP	Weighted median	199	0.180436718	0.131634293	0.170455247	261.169586	24.48283305	NA	NA	NA	NA	NA	NA
CRP	SBP	Weighted mode	199	0.129910383	0.094914826	0.172642407	261.169586	24.48283305	NA	NA	NA	NA	NA	NA
CRP	T2DM	Inverse variance weighted	155	0.050633984	0.038908325	0.193133095	241.1590029	24.48283305	607.1493651	4.58E-55	73.99881018	NA	NA	NA
CRP	T2DM	MR Egger	155	0.117489865	0.05147945	0.023851776	241.1590029	24.48283305	NA	NA	NA	-0.0036526	0.001863728	0.051831997

CRP	T2DM	Weighted median	155	0.005734982	0.035434396	0.871425645	241.1590029	24.48283305	NA	NA	NA	NA	NA	NA
CRP	T2DM	Weighted mode	155	0.031860453	0.027804944	0.253632318	241.1590029	24.48283305	NA	NA	NA	NA	NA	NA
CRP	Triglycerides	Inverse variance weighted	130	-0.058434497	0.041602274	0.160140666	267.3442928	24.48283305	2101.044666	0	93.81793257	NA	NA	NA
CRP	Triglycerides	MR Egger	130	-0.090450377	0.053811376	0.095225198	267.3442928	24.48283305	NA	NA	NA	0.002165718	0.002307203	0.349664548
CRP	Triglycerides	Weighted median	130	0.001927819	0.01523244	0.899288605	267.3442928	24.48283305	NA	NA	NA	NA	NA	NA
CRP	Triglycerides	Weighted mode	130	0.014223467	0.012287082	0.249168119	267.3442928	24.48283305	NA	NA	NA	NA	NA	NA
Cystatin C	BMI	Inverse variance weighted	305	-0.139379856	0.025816816	6.71E-08	89.03212516	29.78522205	4990.828485	0	93.31111212	NA	NA	NA
Cystatin C	BMI	MR Egger	305	0.118821967	0.053396596	0.026798882	89.03212516	29.78522205	NA	NA	NA	-0.006159673	0.001129639	1.03E-07
Cystatin C	BMI	Weighted median	305	-0.023739105	0.013782068	0.084985643	89.03212516	29.78522205	NA	NA	NA	NA	NA	NA
Cystatin C	BMI	Weighted mode	305	0.003036082	0.016479127	0.853949566	89.03212516	29.78522205	NA	NA	NA	NA	NA	NA
Cystatin C	DBP	Inverse variance weighted	270	-0.612355014	0.245960368	0.012786926	91.84761123	29.78522205	4693.553036	0	94.19217503	NA	NA	NA
Cystatin C	DBP	MR Egger	270	-1.504671363	0.531349958	0.004979935	91.84761123	29.78522205	NA	NA	NA	0.021324918	0.01127059	0.059557452
Cystatin C	DBP	Weighted median	270	-0.184186907	0.139641363	0.187169237	91.84761123	29.78522205	NA	NA	NA	NA	NA	NA
Cystatin C	DBP	Weighted mode	270	0.279313315	0.298529303	0.350302303	91.84761123	29.78522205	NA	NA	NA	NA	NA	NA
Cystatin C	HbA1c	Inverse variance weighted	138	0.017114854	0.018512317	0.355219939	101.9546904	29.78522205	189.0242571	0.002157044	27.27255193	NA	NA	NA
Cystatin C	HbA1c	MR Egger	138	0.041455698	0.040089011	0.302928791	101.9546904	29.78522205	NA	NA	NA	-0.00059883	0.000874349	0.494581204
Cystatin C	HbA1c	Weighted median	138	0.003471012	0.027119312	0.898156563	101.9546904	29.78522205	NA	NA	NA	NA	NA	NA
Cystatin C	HbA1c	Weighted mode	138	-3.90E-05	0.046069661	0.999325623	101.9546904	29.78522205	NA	NA	NA	NA	NA	NA
Cystatin C	HDL	Inverse variance weighted	149	0.123342739	0.048308961	0.010673629	97.68811398	29.78522205	887.3193596	9.62E-106	83.27644911	NA	NA	NA
Cystatin C	HDL	MR Egger	149	0.18321473	0.107547812	0.090575427	97.68811398	29.78522205	NA	NA	NA	-0.001459406	0.002340943	0.533970331
Cystatin C	HDL	Weighted median	149	0.129598604	0.040138699	0.001243241	97.68811398	29.78522205	NA	NA	NA	NA	NA	NA
Cystatin C	HDL	Weighted mode	149	0.082337303	0.099736282	0.410388057	97.68811398	29.78522205	NA	NA	NA	NA	NA	NA
Cystatin C	LDL	Inverse variance weighted	149	0.092643929	0.052640819	0.078420411	97.68811398	29.78522205	900.5850253	3.73E-108	83.52716309	NA	NA	NA
Cystatin C	LDL	MR Egger	149	0.030974921	0.116892979	0.791391993	97.68811398	29.78522205	NA	NA	NA	0.001507912	0.002550568	0.555290292
Cystatin C	LDL	Weighted median	149	0.019055873	0.042816005	0.65627332	97.68811398	29.78522205	NA	NA	NA	NA	NA	NA
Cystatin C	LDL	Weighted mode	149	0.001886593	0.087046163	0.982737611	97.68811398	29.78522205	NA	NA	NA	NA	NA	NA
Cystatin C	MetS	Inverse variance weighted	339	0.222894161	0.044266525	4.77E-07	95.53130673	29.78522205	1792.859104	2.49E-196	80.69998664	NA	NA	NA
Cystatin C	MetS	MR Egger	339	0.005003485	0.088631662	0.955014737	95.53130673	29.78522205	NA	NA	NA	0.005504291	0.001946266	0.004962165
Cystatin C	MetS	Weighted median	339	0.183881276	0.038594018	1.89E-06	95.53130673	29.78522205	NA	NA	NA	NA	NA	NA
Cystatin C	MetS	Weighted mode	339	0.061189629	0.047289741	0.196572939	95.53130673	29.78522205	NA	NA	NA	NA	NA	NA
Cystatin C	SBP	Inverse variance weighted	269	-0.375415462	0.375618813	0.317572573	91.68078949	29.78522205	3585.580131	0	92.46399821	NA	NA	NA
Cystatin C	SBP	MR Egger	269	-1.452600372	0.817073172	0.076573279	91.68078949	29.78522205	NA	NA	NA	0.025659948	0.017295457	0.139088277
Cystatin C	SBP	Weighted median	269	0.122009106	0.246763186	0.620996854	91.68078949	29.78522205	NA	NA	NA	NA	NA	NA
Cystatin C	SBP	Weighted mode	269	1.102738546	0.505884355	0.030141004	91.68078949	29.78522205	NA	NA	NA	NA	NA	NA
Cystatin C	T2DM	Inverse variance weighted	212	-0.1416831	0.064021973	0.026894983	94.55797341	29.78522205	1025.135399	4.36E-107	78.70769503	NA	NA	NA
Cystatin C	T2DM	MR Egger	212	0.209789335	0.145060323	0.149605973	94.55797341	29.78522205	NA	NA	NA	-0.008174445	0.003037908	0.007701633
Cystatin C	T2DM	Weighted median	212	0.01903149	0.05750924	0.740697929	94.55797341	29.78522205	NA	NA	NA	NA	NA	NA
Cystatin C	T2DM	Weighted mode	212	0.047507354	0.087829641	0.589144714	94.55797341	29.78522205	NA	NA	NA	NA	NA	NA
Cystatin C	Triglycerides	Inverse variance weighted	149	0.052116285	0.076120927	0.493564045	97.68811398	29.78522205	2316.178847	0	93.54722339	NA	NA	NA
Cystatin C	Triglycerides	MR Egger	149	-0.129374084	0.16889263	0.444896372	97.68811398	29.78522205	NA	NA	NA	0.00442382	0.003676323	0.230784028
Cystatin C	Triglycerides	Weighted median	149	-0.138177211	0.035762948	0.000111684	97.68811398	29.78522205	NA	NA	NA	NA	NA	NA
Cystatin C	Triglycerides	Weighted mode	149	-0.124241723	0.035603279	0.000637515	97.68811398	29.78522205	NA	NA	NA	NA	NA	NA
Fresh Fruit Consumption	BMI	Inverse variance weighted	47	-0.021555111	0.279504751	0.938528924	49.18711786	29.86280136	1277.835979	1.61E-237	96.39367838	NA	NA	NA
Fresh Fruit Consumption	BMI	MR Egger	47	-0.309173295	1.048844613	0.769521345	49.18711786	29.86280136	NA	NA	NA	0.00175622	0.006167926	0.77715405
Fresh Fruit Consumption	BMI	Weighted median	47	0.119490343	0.125878087	0.342491179	49.18711786	29.86280136	NA	NA	NA	NA	NA	NA
Fresh Fruit Consumption	BMI	Weighted mode	47	0.283929821	0.13871719	0.046413282	49.18711786	29.86280136	NA	NA	NA	NA	NA	NA
Fresh Fruit Consumption	DBP	Inverse variance weighted	41	0.70145255	1.510442212	0.642359679	50.80845309	29.86280136	377.4138309	1.76E-56	89.31917819	NA	NA	NA
Fresh Fruit Consumption	DBP	MR Egger	41	3.615614253	5.507969518	0.515400172	50.80845309	29.86280136	NA	NA	NA	-0.018234357	0.033119109	0.585069228
Fresh Fruit Consumption	DBP	Weighted median	41	1.813135055	0.919289073	0.048572736	50.80845309	29.86280136	NA	NA	NA	NA	NA	NA
Fresh Fruit Consumption	DBP	Weighted mode	41	2.602776297	1.093494165	0.022156014	50.80845309	29.86280136	NA	NA	NA	NA	NA	NA
Fresh Fruit Consumption	HbA1c	Inverse variance weighted	23	-0.173539574	0.128120884	0.175577321	55.23834917	30.19651482	14.23694669	0.892856559	0	NA	NA	NA
Fresh Fruit Consumption	HbA1c	MR Egger	23	0.236098056	0.426979573	0.586136874	55.23834917	30.19651482	NA	NA	NA	-0.002701344	0.002685955	0.325994509

Fresh Fruit Consumption	HbA1c	Weighted median	23	-0.178921233	0.172708097	0.300213909	55.23834917	30.19651482	NA	NA	NA	NA	NA	NA
Fresh Fruit Consumption	HbA1c	Weighted mode	23	-0.107848959	0.254855292	0.676274085	55.23834917	30.19651482	NA	NA	NA	NA	NA	NA
Fresh Fruit Consumption	HDL	Inverse variance weighted	24	0.13833968	0.222917337	0.534871162	56.62790153	30.19651482	46.157426	0.002859139	50.15995714	NA	NA	NA
Fresh Fruit Consumption	HDL	MR Egger	24	0.192200247	0.820551349	0.816970159	56.62790153	30.19651482	NA	NA	NA	-0.000350347	0.005127441	0.946141894
Fresh Fruit Consumption	HDL	Weighted median	24	0.321977287	0.239452901	0.178742412	56.62790153	30.19651482	NA	NA	NA	NA	NA	NA
Fresh Fruit Consumption	HDL	Weighted mode	24	0.301132429	0.288279496	0.307069945	56.62790153	30.19651482	NA	NA	NA	NA	NA	NA
Fresh Fruit Consumption	LDL	Inverse variance weighted	24	-0.316204701	0.349004201	0.364925396	56.62790153	30.19651482	96.01053197	6.82E-11	74.85310455	NA	NA	NA
Fresh Fruit Consumption	LDL	MR Egger	24	0.952272052	1.261810011	0.458439789	56.62790153	30.19651482	NA	NA	NA	-0.008235703	0.007874142	0.306955439
Fresh Fruit Consumption	LDL	Weighted median	24	0.045607028	0.242376868	0.850746711	56.62790153	30.19651482	NA	NA	NA	NA	NA	NA
Fresh Fruit Consumption	LDL	Weighted mode	24	0.026481377	0.296921096	0.929705706	56.62790153	30.19651482	NA	NA	NA	NA	NA	NA
Fresh Fruit Consumption	MetS	Inverse variance weighted	47	0.161488067	0.450985016	0.720284519	49.18711786	29.86280136	305.2817727	5.83E-40	84.90164331	NA	NA	NA
Fresh Fruit Consumption	MetS	MR Egger	47	0.651479852	1.69111523	0.70187695	49.18711786	29.86280136	NA	NA	NA	-0.002992833	0.009947446	0.764903635
Fresh Fruit Consumption	MetS	Weighted median	47	-0.036463106	0.343091226	0.915361656	49.18711786	29.86280136	NA	NA	NA	NA	NA	NA
Fresh Fruit Consumption	MetS	Weighted mode	47	-0.201648247	0.466663844	0.667683235	49.18711786	29.86280136	NA	NA	NA	NA	NA	NA
Fresh Fruit Consumption	SBP	Inverse variance weighted	41	-0.053948648	2.577131685	0.983298622	50.65877936	29.86280136	362.6908463	1.31E-53	88.35024012	NA	NA	NA
Fresh Fruit Consumption	SBP	MR Egger	41	12.96583871	9.144990498	0.164187764	50.65877936	29.86280136	NA	NA	NA	-0.081229595	0.054811125	0.146378322
Fresh Fruit Consumption	SBP	Weighted median	41	4.325543095	1.526800837	0.00461024	50.65877936	29.86280136	NA	NA	NA	NA	NA	NA
Fresh Fruit Consumption	SBP	Weighted mode	41	4.8317768	1.730109956	0.007978744	50.65877936	29.86280136	NA	NA	NA	NA	NA	NA
Fresh Fruit Consumption	T2DM	Inverse variance weighted	41	-0.597806724	0.421510425	0.156118091	48.83751158	29.86280136	142.7117064	1.87E-13	70.94147395	NA	NA	NA
Fresh Fruit Consumption	T2DM	MR Egger	41	-2.320894678	1.499140023	0.129663473	48.83751158	29.86280136	NA	NA	NA	0.010551497	0.00881384	0.238473983
Fresh Fruit Consumption	T2DM	Weighted median	41	-0.988025003	0.395912924	0.0125758	48.83751158	29.86280136	NA	NA	NA	NA	NA	NA
Fresh Fruit Consumption	T2DM	Weighted mode	41	-0.580835171	0.625382914	0.3585808	48.83751158	29.86280136	NA	NA	NA	NA	NA	NA
Fresh Fruit Consumption	Triglycerides	Inverse variance weighted	24	-0.412389298	0.230292419	0.073338198	56.62790153	30.19651482	51.69146837	0.000549964	51.73374594	NA	NA	NA
Fresh Fruit Consumption	Triglycerides	MR Egger	24	0.65631046	0.814606464	0.429051394	56.62790153	30.19651482	NA	NA	NA	-0.006953557	0.005092066	0.185875582
Fresh Fruit Consumption	Triglycerides	Weighted median	24	-0.488717581	0.269980981	0.070265921	56.62790153	30.19651482	NA	NA	NA	NA	NA	NA
Fresh Fruit Consumption	Triglycerides	Weighted mode	24	-0.883705792	0.539759578	0.115195247	56.62790153	30.19651482	NA	NA	NA	NA	NA	NA
Gamma Glutamyl Transpeptidase	BMI	Inverse variance weighted	166	-0.091593883	0.125400558	0.465139308	133.9428039	29.5936	0.018114061	1	0	NA	NA	NA
Gamma Glutamyl Transpeptidase	BMI	MR Egger	166	-0.072453506	0.211262239	0.73207128	133.9428039	29.5936	NA	NA	NA	-0.001020121	0.009061464	0.91050287
Gamma Glutamyl Transpeptidase	BMI	Weighted median	166	-0.090911541	0.143754158	0.527119119	133.9428039	29.5936	NA	NA	NA	NA	NA	NA
Gamma Glutamyl Transpeptidase	BMI	Weighted mode	166	-0.090144826	2.331491342	0.969205001	133.9428039	29.5936	NA	NA	NA	NA	NA	NA
Gamma Glutamyl Transpeptidase	DBP	Inverse variance weighted	148	-1.151665608	0.559179701	0.039440373	122.7369432	30.1804198	0.534430696	1	0	NA	NA	NA

Gamma Glutamyl Transpeptidase	DBP	MR Egger	148	-0.318286803	1.390212727	0.819229511	122.7369432	30.1804198	NA	NA	NA	-0.015197806	0.02321118	0.513651003
Gamma Glutamyl Transpeptidase	DBP	Weighted median	148	-1.148102722	0.735332844	0.118444147	122.7369432	30.1804198	NA	NA	NA	NA	NA	NA
Gamma Glutamyl Transpeptidase	DBP	Weighted mode	148	-0.772455875	2.695716479	0.774860848	122.7369432	30.1804198	NA	NA	NA	NA	NA	NA
Gamma Glutamyl Transpeptidase	HbA1C	Inverse variance weighted	75	-0.111671355	0.061991006	0.071637934	114.6089411	30.4704	0.223779317	1	0	NA	NA	NA
Gamma Glutamyl Transpeptidase	HbA1C	MR Egger	75	0.05312572	0.39420823	0.893168071	114.6089411	30.4704	NA	NA	NA	-0.006675823	0.015770435	0.6733118
Gamma Glutamyl Transpeptidase	HbA1C	Weighted median	75	-0.109605443	0.063638284	0.085011699	114.6089411	30.4704	NA	NA	NA	NA	NA	NA
Gamma Glutamyl Transpeptidase	HbA1C	Weighted mode	75	-0.109494731	0.281390729	0.698304944	114.6089411	30.4704	NA	NA	NA	NA	NA	NA
Gamma Glutamyl Transpeptidase	HDL	Inverse variance weighted	83	-0.263262344	0.353437216	0.456354477	115.7431691	29.5936	0.108669636	1	0	NA	NA	NA
Gamma Glutamyl Transpeptidase	HDL	MR Egger	83	-0.088141702	0.748406705	0.906539504	115.7431691	29.5936	NA	NA	NA	-0.00443871	0.016720962	0.79133124
Gamma Glutamyl Transpeptidase	HDL	Weighted median	83	-0.336669668	0.459518187	0.463767056	115.7431691	29.5936	NA	NA	NA	NA	NA	NA
Gamma Glutamyl Transpeptidase	HDL	Weighted mode	83	-0.344257869	1.802685784	0.849021585	115.7431691	29.5936	NA	NA	NA	NA	NA	NA
Gamma Glutamyl Transpeptidase	LDL	Inverse variance weighted	83	-0.420694777	0.077727241	6.22E-08	115.7431691	29.5936	0.310928217	1	0	NA	NA	NA
Gamma Glutamyl Transpeptidase	LDL	MR Egger	83	-0.196864154	0.530465802	0.711520299	115.7431691	29.5936	NA	NA	NA	-0.003317841	0.007778225	0.670835021
Gamma Glutamyl Transpeptidase	LDL	Weighted median	83	-0.423381285	0.094131843	6.87E-06	115.7431691	29.5936	NA	NA	NA	NA	NA	NA
Gamma Glutamyl Transpeptidase	LDL	Weighted mode	83	-0.429388466	3.590833479	0.905109099	115.7431691	29.5936	NA	NA	NA	NA	NA	NA
Gamma Glutamyl Transpeptidase	MetS	Inverse variance weighted	75	0.020162487	0.025557884	0.430173387	143.4054503	30.4704	1314.08475	3.45E-226	94.36863084	NA	NA	NA
Gamma Glutamyl Transpeptidase	MetS	MR Egger	75	0.019137498	0.042043604	0.650329128	143.4054503	30.4704	NA	NA	NA	3.41E-05	0.001105731	0.975491371
Gamma Glutamyl Transpeptidase	MetS	Weighted median	75	0.002449855	0.011715064	0.834354479	143.4054503	30.4704	NA	NA	NA	NA	NA	NA
Gamma Glutamyl Transpeptidase	MetS	Weighted mode	75	0.010195158	0.008999313	0.260921167	143.4054503	30.4704	NA	NA	NA	NA	NA	NA
Gamma Glutamyl Transpeptidase	SBP	Inverse variance weighted	146	-1.651862829	0.362719556	5.26E-06	123.1501115	30.1804198	1.9670405	1	0	NA	NA	NA
Gamma Glutamyl Transpeptidase	SBP	MR Egger	146	-1.025562638	0.667648356	0.126712591	123.1501115	30.1804198	NA	NA	NA	-0.017323924	0.015504548	0.265707739
Gamma Glutamyl Transpeptidase	SBP	Weighted median	146	-1.592282604	0.506429279	0.001665779	123.1501115	30.1804198	NA	NA	NA	NA	NA	NA
Gamma Glutamyl Transpeptidase	SBP	Weighted mode	146	-1.584192998	2.109306295	0.453840156	123.1501115	30.1804198	NA	NA	NA	NA	NA	NA
Gamma Glutamyl Transpeptidase	T2DM	Inverse variance weighted	169	-2.628947505	0.125522903	2.13E-97	132.0769146	29.5936	109.1265542	0.999869768	0	NA	NA	NA
Gamma Glutamyl Transpeptidase	T2DM	MR Egger	169	-3.016967133	0.487334121	4.48E-09	132.0769146	29.5936	NA	NA	NA	0.00690068	0.008374498	0.411108495
Gamma Glutamyl Transpeptidase	T2DM	Weighted median	169	-2.29250887	0.274565717	6.85E-17	132.0769146	29.5936	NA	NA	NA	NA	NA	NA
Gamma Glutamyl Transpeptidase	T2DM	Weighted mode	169	-2.160720302	0.255507288	1.28E-14	132.0769146	29.5936	NA	NA	NA	NA	NA	NA
Gamma Glutamyl Transpeptidase	Triglycerides	Inverse variance weighted	83	-0.232574298	0.30817418	0.450438266	115.7431691	29.5936	0.128224688	1	0	NA	NA	NA
Gamma Glutamyl Transpeptidase	Triglycerides	MR Egger	83	-0.152676624	0.468747071	0.745482069	115.7431691	29.5936	NA	NA	NA	-0.003866535	0.01709277	0.821608864
Gamma Glutamyl Transpeptidase	Triglycerides	Weighted median	83	-0.209585408	0.386878521	0.58800148	115.7431691	29.5936	NA	NA	NA	NA	NA	NA
Gamma Glutamyl Transpeptidase	Triglycerides	Weighted mode	83	-0.205724556	2.771569377	0.941010746	115.7431691	29.5936	NA	NA	NA	NA	NA	NA

Impedance of Left Arm	BMI	Inverse variance weighted	406	0.720600476	0.031125777	1.41E-118	66.70360883	29.73931538	5409.413083	0	92.51248477	NA	NA	NA
Impedance of Left Arm	BMI	MR Egger	406	0.706882336	0.08444284	9.45E-16	66.70360883	29.73931538	NA	NA	NA	0.000195972	0.001121166	0.861329829
Impedance of Left Arm	BMI	Weighted median	406	0.467601622	0.020995103	6.91E-110	66.70360883	29.73931538	NA	NA	NA	NA	NA	NA
Impedance of Left Arm	BMI	Weighted mode	406	0.353487837	0.055734	6.05E-10	66.70360883	29.73931538	NA	NA	NA	NA	NA	NA
Impedance of Left Arm	DBP	Inverse variance weighted	372	-0.86530781	0.280343826	0.002024633	67.17515693	29.73931538	4764.282095	0	92.18915214	NA	NA	NA
Impedance of Left Arm	DBP	MR Egger	372	-1.623289217	0.76681554	0.034933333	67.17515693	29.73931538	NA	NA	NA	0.010791628	0.010161905	0.288942424
Impedance of Left Arm	DBP	Weighted median	372	-0.700041041	0.170229405	3.92E-05	67.17515693	29.73931538	NA	NA	NA	NA	NA	NA
Impedance of Left Arm	DBP	Weighted mode	372	-0.56708091	0.350434577	0.10646459	67.17515693	29.73931538	NA	NA	NA	NA	NA	NA
Impedance of Left Arm	HbA1c	Inverse variance weighted	176	0.036661379	0.027959684	0.189782444	71.77259765	29.82825126	274.5076928	2.25E-06	36.24758269	NA	NA	NA
Impedance of Left Arm	HbA1c	MR Egger	176	0.031105997	0.081571995	0.703422275	71.77259765	29.82825126	NA	NA	NA	7.87E-05	0.001085696	0.942268818
Impedance of Left Arm	HbA1c	Weighted median	176	0.017682027	0.035925585	0.622588715	71.77259765	29.82825126	NA	NA	NA	NA	NA	NA
Impedance of Left Arm	HbA1c	Weighted mode	176	0.056954265	0.071228053	0.425024045	71.77259765	29.82825126	NA	NA	NA	NA	NA	NA
Impedance of Left Arm	HDL	Inverse variance weighted	191	-0.135516867	0.048472487	0.005177973	75.11137713	29.82666148	697.0540433	5.09E-59	72.50604421	NA	NA	NA
Impedance of Left Arm	HDL	MR Egger	191	-0.289092631	0.129349838	0.026590368	75.11137713	29.82666148	NA	NA	NA	0.002334414	0.001823394	0.202023781
Impedance of Left Arm	HDL	Weighted median	191	-0.037905641	0.051602349	0.462600193	75.11137713	29.82666148	NA	NA	NA	NA	NA	NA
Impedance of Left Arm	HDL	Weighted mode	191	0.129298559	0.240934698	0.592134478	75.11137713	29.82666148	NA	NA	NA	NA	NA	NA
Impedance of Left Arm	LDL	Inverse variance weighted	191	0.01080631	0.047284185	0.819226757	75.11137713	29.82666148	567.8713638	2.68E-39	66.43166568	NA	NA	NA
Impedance of Left Arm	LDL	MR Egger	191	0.103086174	0.126246523	0.415215565	75.11137713	29.82666148	NA	NA	NA	-0.001404776	0.001781672	0.431415726
Impedance of Left Arm	LDL	Weighted median	191	0.026206807	0.050072169	0.600709346	75.11137713	29.82666148	NA	NA	NA	NA	NA	NA
Impedance of Left Arm	LDL	Weighted mode	191	0.059930956	0.065303594	0.359924612	75.11137713	29.82666148	NA	NA	NA	NA	NA	NA
Impedance of Left Arm	MetS	Inverse variance weighted	406	-0.654860519	0.059187169	1.87E-28	66.70360883	29.73931538	1790.985571	4.91E-173	77.34137785	NA	NA	NA
Impedance of Left Arm	MetS	MR Egger	406	-0.520575863	0.160465506	0.001275947	66.70360883	29.73931538	NA	NA	NA	-0.001917811	0.002130051	0.368465446
Impedance of Left Arm	MetS	Weighted median	406	-0.492225411	0.055207736	4.84E-19	66.70360883	29.73931538	NA	NA	NA	NA	NA	NA
Impedance of Left Arm	MetS	Weighted mode	406	-0.090892495	0.15720177	0.563457183	66.70360883	29.73931538	NA	NA	NA	NA	NA	NA
Impedance of Left Arm	SBP	Inverse variance weighted	371	-1.143328218	0.466344588	0.014219061	67.24130083	29.73931538	4333.857982	0	91.43504791	NA	NA	NA
Impedance of Left Arm	SBP	MR Egger	371	-2.437844288	1.275150424	0.056674909	67.24130083	29.73931538	NA	NA	NA	0.018425473	0.016893188	0.276114728
Impedance of Left Arm	SBP	Weighted median	371	-0.719269124	0.288094818	0.012537607	67.24130083	29.73931538	NA	NA	NA	NA	NA	NA
Impedance of Left Arm	SBP	Weighted mode	371	-0.410840458	0.607031974	0.498954479	67.24130083	29.73931538	NA	NA	NA	NA	NA	NA
Impedance of Left Arm	T2DM	Inverse variance weighted	314	0.622356426	0.090341132	5.62E-12	66.27818888	29.73931538	1780.175851	2.42E-203	81.94020694	NA	NA	NA
Impedance of Left Arm	T2DM	MR Egger	314	1.340431859	0.262405182	5.67E-07	66.27818888	29.73931538	NA	NA	NA	-0.009918386	0.003408213	0.003872446
Impedance of Left Arm	T2DM	Weighted median	314	0.423818609	0.074561148	1.31E-08	66.27818888	29.73931538	NA	NA	NA	NA	NA	NA
Impedance of Left Arm	T2DM	Weighted mode	314	0.020109558	0.281503525	0.943096179	66.27818888	29.73931538	NA	NA	NA	NA	NA	NA
Impedance of Left Arm	Triglycerides	Inverse variance weighted	191	0.049285894	0.078818493	0.531768431	75.11137713	29.82666148	1935.691327	2.21E-286	90.18399688	NA	NA	NA
Impedance of Left Arm	Triglycerides	MR Egger	191	0.066189616	0.210801402	0.753874629	75.11137713	29.82666148	NA	NA	NA	-0.000256931	0.00297045	0.931163912
Impedance of Left Arm	Triglycerides	Weighted median	191	0.117289413	0.048790909	0.016220349	75.11137713	29.82666148	NA	NA	NA	NA	NA	NA
Impedance of Left Arm	Triglycerides	Weighted mode	191	0.115092163	0.131184968	0.381416826	75.11137713	29.82666148	NA	NA	NA	NA	NA	NA
Impedance of Right Arm	BMI	Inverse variance weighted	402	0.717000309	0.032069647	1.02E-110	66.65358101	29.74046345	5585.353726	0	92.81872001	NA	NA	NA
Impedance of Right Arm	BMI	MR Egger	402	0.691417264	0.08717412	2.19E-14	66.65358101	29.74046345	NA	NA	NA	0.000365259	0.001157132	0.752426374
Impedance of Right Arm	BMI	Weighted median	402	0.444772976	0.02014254	4.78E-108	66.65358101	29.74046345	NA	NA	NA	NA	NA	NA
Impedance of Right Arm	BMI	Weighted mode	402	0.347127759	0.051752274	6.76E-11	66.65358101	29.74046345	NA	NA	NA	NA	NA	NA
Impedance of Right Arm	DBP	Inverse variance weighted	369	-0.849777389	0.27863099	0.002289703	66.74811856	29.74046345	4568.231852	0	91.88078391	NA	NA	NA
Impedance of Right Arm	DBP	MR Egger	369	-2.053258107	0.759762267	0.007201708	66.74811856	29.74046345	NA	NA	NA	0.017065952	0.01002714	0.089606704
Impedance of Right Arm	DBP	Weighted median	369	-0.884695848	0.171152777	2.35E-07	66.74811856	29.74046345	NA	NA	NA	NA	NA	NA
Impedance of Right Arm	DBP	Weighted mode	369	-0.716367854	0.325513534	0.028375636	66.74811856	29.74046345	NA	NA	NA	NA	NA	NA
Impedance of Right Arm	HbA1c	Inverse variance weighted	180	0.022102388	0.026128938	0.397610264	73.15161666	29.78926876	254.4857622	0.000178422	29.62010331	NA	NA	NA
Impedance of Right Arm	HbA1c	MR Egger	180	0.044823672	0.074474279	0.548027966	73.15161666	29.78926876	NA	NA	NA	-0.000323457	0.000992461	0.744872466
Impedance of Right Arm	HbA1c	Weighted median	180	0.030296951	0.037956325	0.424751187	73.15161666	29.78926876	NA	NA	NA	NA	NA	NA
Impedance of Right Arm	HbA1c	Weighted mode	180	0.10211882	0.074013066	0.169387627	73.15161666	29.78926876	NA	NA	NA	NA	NA	NA
Impedance of Right Arm	HDL	Inverse variance weighted	194	-0.178679622	0.047045635	0.000145865	74.37086527	29.78926876	684.8996517	2.93E-56	71.5535877	NA	NA	NA

Impedance of Right Arm	HDL	MR Egger	194	-0.340821605	0.129034062	0.008938404	74.37086527	29.78926876	NA	NA	NA	0.002444014	0.001811674	0.178913986
Impedance of Right Arm	HDL	Weighted median	194	-0.052395061	0.050930279	0.30359221	74.37086527	29.78926876	NA	NA	NA	NA	NA	NA
Impedance of Right Arm	HDL	Weighted mode	194	0.052842708	0.252245965	0.834287626	74.37086527	29.78926876	NA	NA	NA	NA	NA	NA
Impedance of Right Arm	LDL	Inverse variance weighted	194	0.015009109	0.046630283	0.747547607	74.37086527	29.78926876	575.6365947	1.04E-39	66.47097281	NA	NA	NA
Impedance of Right Arm	LDL	MR Egger	194	0.006270834	0.128575071	0.961151876	74.37086527	29.78926876	NA	NA	NA	0.000131858	0.001807361	0.94191697
Impedance of Right Arm	LDL	Weighted median	194	0.02764338	0.051078365	0.588372859	74.37086527	29.78926876	NA	NA	NA	NA	NA	NA
Impedance of Right Arm	LDL	Weighted mode	194	0.071599163	0.063345474	0.259754042	74.37086527	29.78926876	NA	NA	NA	NA	NA	NA
Impedance of Right Arm	MetS	Inverse variance weighted	401	-0.658411547	0.061038805	3.98E-27	66.782178	29.74046345	1846.075063	5.22E-184	78.09923219	NA	NA	NA
Impedance of Right Arm	MetS	MR Egger	401	-0.338912408	0.165737033	0.041522281	66.782178	29.74046345	NA	NA	NA	-0.004554858	0.00219812	0.038892248
Impedance of Right Arm	MetS	Weighted median	401	-0.490481468	0.055462764	9.28E-19	66.782178	29.74046345	NA	NA	NA	NA	NA	NA
Impedance of Right Arm	MetS	Weighted mode	401	-0.128938238	0.137018247	0.347257591	66.782178	29.74046345	NA	NA	NA	NA	NA	NA
Impedance of Right Arm	SBP	Inverse variance weighted	368	-0.891512917	0.473374337	0.059657713	66.83107649	29.74046345	4335.396344	0	91.48244573	NA	NA	NA
Impedance of Right Arm	SBP	MR Egger	368	-2.700064706	1.291637116	0.037269536	66.83107649	29.74046345	NA	NA	NA	0.025639569	0.017041801	0.133312412
Impedance of Right Arm	SBP	Weighted median	368	-0.559497523	0.306058605	0.067538572	66.83107649	29.74046345	NA	NA	NA	NA	NA	NA
Impedance of Right Arm	SBP	Weighted mode	368	-0.250136427	0.60796739	0.680996932	66.83107649	29.74046345	NA	NA	NA	NA	NA	NA
Impedance of Right Arm	T2DM	Inverse variance weighted	310	0.666807854	0.091327966	2.85E-13	66.66903015	29.78926876	1776.246545	3.72E-204	82.43654752	NA	NA	NA
Impedance of Right Arm	T2DM	MR Egger	310	1.103335299	0.269540607	5.44E-05	66.66903015	29.78926876	NA	NA	NA	-0.005996133	0.003484825	0.086320301
Impedance of Right Arm	T2DM	Weighted median	310	0.424306777	0.075263016	1.72E-08	66.66903015	29.78926876	NA	NA	NA	NA	NA	NA
Impedance of Right Arm	T2DM	Weighted mode	310	-0.0007193	0.256090217	0.997760738	66.66903015	29.78926876	NA	NA	NA	NA	NA	NA
Impedance of Right Arm	Triglycerides	Inverse variance weighted	194	0.071442528	0.077525002	0.356767644	74.37086527	29.78926876	1954.717921	1.34E-288	90.12508312	NA	NA	NA
Impedance of Right Arm	Triglycerides	MR Egger	194	0.103879097	0.213419871	0.627000716	74.37086527	29.78926876	NA	NA	NA	-0.000488783	0.002995167	0.870539928
Impedance of Right Arm	Triglycerides	Weighted median	194	0.138419518	0.04639081	0.002847205	74.37086527	29.78926876	NA	NA	NA	NA	NA	NA
Impedance of Right Arm	Triglycerides	Weighted mode	194	0.14561006	0.111112374	0.191592345	74.37086527	29.78926876	NA	NA	NA	NA	NA	NA
Overall Healthy Diet	BMI	Inverse variance weighted	15	-0.169189367	0.112109371	0.131261571	53.68053088	30.8877901	440.4316125	3.74E-85	96.7382461	NA	NA	NA
Overall Healthy Diet	BMI	MR Egger	15	-0.390615524	0.396908747	0.34300719	53.68053088	30.8877901	NA	NA	NA	0.006240319	0.010707302	0.569993298
Overall Healthy Diet	BMI	Weighted median	15	-0.255358614	0.034491043	1.33E-13	53.68053088	30.8877901	NA	NA	NA	NA	NA	NA
Overall Healthy Diet	BMI	Weighted mode	15	-0.250479756	0.03442674	4.06E-06	53.68053088	30.8877901	NA	NA	NA	NA	NA	NA
Overall Healthy Diet	DBP	Inverse variance weighted	13	0.243731091	0.65403042	0.70940138	56.73574237	30.8877901	150.8414866	3.83E-26	91.24407077	NA	NA	NA
Overall Healthy Diet	DBP	MR Egger	13	2.463142365	2.20768643	0.288325908	56.73574237	30.8877901	NA	NA	NA	-0.06404224	0.060870091	0.315311195
Overall Healthy Diet	DBP	Weighted median	13	-0.714078731	0.332300009	0.031642509	56.73574237	30.8877901	NA	NA	NA	NA	NA	NA
Overall Healthy Diet	DBP	Weighted mode	13	-0.833709684	0.378073768	0.047693883	56.73574237	30.8877901	NA	NA	NA	NA	NA	NA
Overall Healthy Diet	HbA1c	Inverse variance weighted	8	-0.012847613	0.047198348	0.785464609	63.76905335	30.8877901	3.167216562	0.86911439	0	NA	NA	NA
Overall Healthy Diet	HbA1c	MR Egger	8	-0.019608051	0.14315887	0.895537266	63.76905335	30.8877901	NA	NA	NA	0.000200465	0.004007702	0.961730018
Overall Healthy Diet	HbA1c	Weighted median	8	-0.029107195	0.061607411	0.636596655	63.76905335	30.8877901	NA	NA	NA	NA	NA	NA
Overall Healthy Diet	HbA1c	Weighted mode	8	-0.042714716	0.076984061	0.596271681	63.76905335	30.8877901	NA	NA	NA	NA	NA	NA
Overall Healthy Diet	HDL	Inverse variance weighted	10	-0.056821255	0.108281345	0.599753018	60.16360273	30.8877901	40.36658233	6.52E-06	73.4559718	NA	NA	NA
Overall Healthy Diet	HDL	MR Egger	10	0.300143419	0.307685558	0.35788896	60.16360273	30.8877901	NA	NA	NA	-0.01112922	0.009014039	0.251991807
Overall Healthy Diet	HDL	Weighted median	10	-0.065894307	0.078647834	0.402120531	60.16360273	30.8877901	NA	NA	NA	NA	NA	NA
Overall Healthy Diet	HDL	Weighted mode	10	-0.064722792	0.098962357	0.529457509	60.16360273	30.8877901	NA	NA	NA	NA	NA	NA

Overall Healthy Diet	LDL	Inverse variance weighted	10	-0.049654216	0.125672903	0.692764086	60.16360273	30.8877901	47.40161158	3.30E-07	80.55494913	NA	NA	NA
Overall Healthy Diet	LDL	MR Egger	10	-0.208765073	0.385273153	0.602674047	60.16360273	30.8877901	NA	NA	NA	0.004963432	0.011294342	0.671956019
Overall Healthy Diet	LDL	Weighted median	10	-0.105299291	0.074204065	0.155884394	60.16360273	30.8877901	NA	NA	NA	NA	NA	NA
Overall Healthy Diet	LDL	Weighted mode	10	-0.114038628	0.074821649	0.161809979	60.16360273	30.8877901	NA	NA	NA	NA	NA	NA
Overall Healthy Diet	MetS	Inverse variance weighted	16	0.086273103	0.240501898	0.719803749	53.16005779	30.8877901	210.3669686	1.65E-36	92.85687362	NA	NA	NA
Overall Healthy Diet	MetS	MR Egger	16	0.219549905	0.878956048	0.806381591	53.16005779	30.8877901	NA	NA	NA	-0.003761725	0.023794474	0.876641663
Overall Healthy Diet	MetS	Weighted median	16	0.081014313	0.140637173	0.564580091	53.16005779	30.8877901	NA	NA	NA	NA	NA	NA
Overall Healthy Diet	MetS	Weighted mode	16	0.124841679	0.217090449	0.573770978	53.16005779	30.8877901	NA	NA	NA	NA	NA	NA
Overall Healthy Diet	SBP	Inverse variance weighted	13	0.131301449	1.130408982	0.907530546	56.73574237	30.8877901	148.4734744	1.16E-25	91.6779758	NA	NA	NA
Overall Healthy Diet	SBP	MR Egger	13	2.284435691	3.944639546	0.574173219	56.73574237	30.8877901	NA	NA	NA	-0.062072635	0.108660174	0.579311346
Overall Healthy Diet	SBP	Weighted median	13	-1.434949877	0.543058412	0.008233316	56.73574237	30.8877901	NA	NA	NA	NA	NA	NA
Overall Healthy Diet	SBP	Weighted mode	13	-1.739327672	0.605762653	0.014055778	56.73574237	30.8877901	NA	NA	NA	NA	NA	NA
Overall Healthy Diet	T2DM	Inverse variance weighted	11	-0.490994532	0.317897005	0.122465266	47.74363875	33.10983192	104.5709966	6.60E-18	90.31144635	NA	NA	NA
Overall Healthy Diet	T2DM	MR Egger	11	0.062685831	1.64400854	0.970416524	47.74363875	33.10983192	NA	NA	NA	-0.014267017	0.041484509	0.7388109
Overall Healthy Diet	T2DM	Weighted median	11	-0.393285985	0.152333501	0.009830269	47.74363875	33.10983192	NA	NA	NA	NA	NA	NA
Overall Healthy Diet	T2DM	Weighted mode	11	-0.416952931	0.171252452	0.03516475	47.74363875	33.10983192	NA	NA	NA	NA	NA	NA
Overall Healthy Diet	Triglycerides	Inverse variance weighted	10	0.563547502	0.52832723	0.286123704	60.16360273	30.8877901	1035.86078	3.18E-217	98.98301202	NA	NA	NA
Overall Healthy Diet	Triglycerides	MR Egger	10	-1.091509899	1.508772739	0.490017552	60.16360273	30.8877901	NA	NA	NA	0.051934346	0.044466834	0.276459715
Overall Healthy Diet	Triglycerides	Weighted median	10	0.02503049	0.075661452	0.740778776	60.16360273	30.8877901	NA	NA	NA	NA	NA	NA
Overall Healthy Diet	Triglycerides	Weighted mode	10	0.067451364	0.081858854	0.431235884	60.16360273	30.8877901	NA	NA	NA	NA	NA	NA
Peak Expiratory Flow	BMI	Inverse variance weighted	112	0.023515485	0.036035435	0.514036376	52.0409633	29.7248747	725.9835212	5.09E-91	84.6241145	NA	NA	NA
Peak Expiratory Flow	BMI	MR Egger	112	-0.064114077	0.11693328	0.584599555	52.0409633	29.7248747	NA	NA	NA	0.00142548	0.001809265	0.432462563
Peak Expiratory Flow	BMI	Weighted median	112	-0.008357925	0.02632214	0.750845643	52.0409633	29.7248747	NA	NA	NA	NA	NA	NA
Peak Expiratory Flow	BMI	Weighted mode	112	-0.048128131	0.045691233	0.294475449	52.0409633	29.7248747	NA	NA	NA	NA	NA	NA
Peak Expiratory Flow	DBP	Inverse variance weighted	101	0.154343869	0.421337091	0.714126899	52.89889064	29.7248747	1050.372804	2.94E-158	90.4495047	NA	NA	NA
Peak Expiratory Flow	DBP	MR Egger	101	0.900826381	1.400381937	0.52153492	52.89889064	29.7248747	NA	NA	NA	-0.012061288	0.021570807	0.577322983
Peak Expiratory Flow	DBP	Weighted median	101	0.167634557	0.293102243	0.567368031	52.89889064	29.7248747	NA	NA	NA	NA	NA	NA
Peak Expiratory Flow	DBP	Weighted mode	101	0.527057382	0.328463624	0.111732425	52.89889064	29.7248747	NA	NA	NA	NA	NA	NA
Peak Expiratory Flow	HbA1c	Inverse variance weighted	60	0.01446461	0.039114354	0.711529187	56.85406091	29.9537886	80.52816947	0.032765873	26.56956597	NA	NA	NA
Peak Expiratory Flow	HbA1c	MR Egger	60	-0.029157687	0.127266949	0.819592097	56.85406091	29.9537886	NA	NA	NA	0.00071482	0.001982981	0.719799692
Peak Expiratory Flow	HbA1c	Weighted median	60	-0.005265913	0.054182481	0.92257671	56.85406091	29.9537886	NA	NA	NA	NA	NA	NA
Peak Expiratory Flow	HbA1c	Weighted mode	60	-0.039216686	0.097161087	0.687947355	56.85406091	29.9537886	NA	NA	NA	NA	NA	NA
Peak Expiratory Flow	HDL	Inverse variance weighted	61	-0.040893126	0.054678257	0.454528668	55.66131695	29.9537886	92.65044638	0.004346524	34.15732891	NA	NA	NA
Peak Expiratory Flow	HDL	MR Egger	61	0.131117422	0.181586568	0.473106347	55.66131695	29.9537886	NA	NA	NA	-0.002822769	0.002841581	0.324581681
Peak Expiratory Flow	HDL	Weighted median	61	0.062095866	0.079519714	0.434869289	55.66131695	29.9537886	NA	NA	NA	NA	NA	NA
Peak Expiratory Flow	HDL	Weighted mode	61	0.065735443	0.114724614	0.568796315	55.66131695	29.9537886	NA	NA	NA	NA	NA	NA
Peak Expiratory Flow	LDL	Inverse variance weighted	61	0.115515668	0.066135575	0.08069816	55.66131695	29.9537886	114.9187976	2.58E-05	47.60561341	NA	NA	NA
Peak Expiratory Flow	LDL	MR Egger	61	0.019882866	0.220253338	0.928376273	55.66131695	29.9537886	NA	NA	NA	0.001572657	0.003452577	0.650419836
Peak Expiratory Flow	LDL	Weighted median	61	0.00952607	0.079951064	0.905157497	55.66131695	29.9537886	NA	NA	NA	NA	NA	NA
Peak Expiratory Flow	LDL	Weighted mode	61	-0.08367088	0.110310509	0.451119066	55.66131695	29.9537886	NA	NA	NA	NA	NA	NA
Peak Expiratory Flow	MetS	Inverse variance weighted	123	-0.100516426	0.077104111	0.192354489	50.91207135	29.7248747	359.3280565	3.13E-25	65.95993528	NA	NA	NA
Peak Expiratory Flow	MetS	MR Egger	123	0.035428104	0.255027161	0.889745146	50.91207135	29.7248747	NA	NA	NA	-0.002172577	0.003883834	0.576929718
Peak Expiratory Flow	MetS	Weighted median	123	-0.052703566	0.083747808	0.529144307	50.91207135	29.7248747	NA	NA	NA	NA	NA	NA
Peak Expiratory Flow	MetS	Weighted mode	123	-0.018924564	0.141415826	0.893763749	50.91207135	29.7248747	NA	NA	NA	NA	NA	NA
Peak Expiratory Flow	SBP	Inverse variance weighted	101	1.57846526	0.719378723	0.028220589	52.89889064	29.7248747	1010.595033	1.93E-150	90.07205708	NA	NA	NA
Peak Expiratory Flow	SBP	MR Egger	101	0.270582762	2.395069205	0.910279207	52.89889064	29.7248747	NA	NA	NA	0.021114671	0.036868656	0.56814639
Peak Expiratory Flow	SBP	Weighted median	101	0.887942095	0.516002092	0.085285119	52.89889064	29.7248747	NA	NA	NA	NA	NA	NA
Peak Expiratory Flow	SBP	Weighted mode	101	0.353769094	0.606336143	0.560901512	52.89889064	29.7248747	NA	NA	NA	NA	NA	NA
Peak Expiratory Flow	T2DM	Inverse variance weighted	79	0.467022819	0.124051174	0.00016671	51.1072145	29.9537886	268.1533239	1.08E-22	70.86330954	NA	NA	NA
Peak Expiratory Flow	T2DM	MR Egger	79	0.627546522	0.463478369	0.179699238	51.1072145	29.9537886	NA	NA	NA	-0.002453371	0.006822178	0.720117959
Peak Expiratory Flow	T2DM	Weighted median	79	0.201175011	0.124056302	0.104879849	51.1072145	29.9537886	NA	NA	NA	NA	NA	NA
Peak Expiratory Flow	T2DM	Weighted mode	79	-0.002495197	0.186882431	0.989381298	51.1072145	29.9537886	NA	NA	NA	NA	NA	NA
Peak Expiratory Flow	Triglycerides	Inverse variance weighted	61	0.08869681	0.046020687	0.053939168	55.66131695	29.9537886	68.92368054	0.201128667	12.71529009	NA	NA	NA
Peak Expiratory Flow	Triglycerides	MR Egger	61	0.030582106	0.153741009	0.843009519	55.66131695	29.9537886	NA	NA	NA	0.000954141	0.002406728	0.693205115
Peak Expiratory Flow	Triglycerides	Weighted median	61	0.072672753	0.069065975	0.292697612	55.66131695	29.9537886	NA	NA	NA	NA	NA	NA
Peak Expiratory Flow	Triglycerides	Weighted mode	61	0.089308228	0.094201762	0.346905572	55.66131695	29.9537886	NA	NA	NA	NA	NA	NA
Phosphate	BMI	Inverse variance weighted	148	-0.006654827	0.016873354	0.693286778	97.25889748	29.74666366	770.8762464	2.89E-85	80.8979284	NA	NA	NA
Phosphate	BMI	MR Egger	148	0.00567155	0.029833509	0.849489592	97.25889748	29.74666366	NA	NA	NA	-0.000402017	0.000801459	0.61669981
Phosphate	BMI	Weighted median	148	0.006828036	0.013563522	0.614674835	97.25889748	29.74666366	NA	NA	NA	NA	NA	NA
Phosphate	BMI	Weighted mode	148	-3.56E-05	0.012058559	0.997650868	97.25889748	29.74666366	NA	NA	NA	NA	NA	NA
Phosphate	DBP	Inverse variance weighted	133	-0.010016787	0.209516288	0.961868379	100.8386639	29.74666366	1266.106611	1.96E-184	89.43147053	NA	NA	NA
Phosphate	DBP	MR Egger	133	0.396657543	0.368459807	0.283669441	100.8386639	29.74666366	NA	NA	NA	-0.01349019	0.010068576	0.182619856

Phosphate	DBP	Weighted median	133	0.015275086	0.13302099	0.908578169	100.8386639	29.74666366	NA	NA	NA	NA	NA	NA
Phosphate	DBP	Weighted mode	133	-0.045349336	0.124513564	0.716282454	100.8386639	29.74666366	NA	NA	NA	NA	NA	NA
Phosphate	HbA1c	Inverse variance weighted	62	-0.056192285	0.02409379	0.019688538	97.10182034	29.74666366	48.79756319	0.870119294	0	NA	NA	NA
Phosphate	HbA1c	MR Egger	62	-0.037051333	0.051307934	0.473015711	97.10182034	29.74666366	NA	NA	NA	-0.00047809	0.001131447	0.674135896
Phosphate	HbA1c	Weighted median	62	-0.035850294	0.036352171	0.324037913	97.10182034	29.74666366	NA	NA	NA	NA	NA	NA
Phosphate	HbA1c	Weighted mode	62	-0.029147665	0.049795082	0.560470164	97.10182034	29.74666366	NA	NA	NA	NA	NA	NA
Phosphate	HDL	Inverse variance weighted	59	0.024239169	0.046235821	0.600104076	74.59929989	29.74666366	112.3225379	2.49E-05	46.95447729	NA	NA	NA
Phosphate	HDL	MR Egger	59	-0.100383126	0.110028992	0.365435887	74.59929989	29.74666366	NA	NA	NA	0.002920018	0.002341791	0.217527728
Phosphate	HDL	Weighted median	59	-0.030686663	0.057668323	0.59464055	74.59929989	29.74666366	NA	NA	NA	NA	NA	NA
Phosphate	HDL	Weighted mode	59	-0.007237508	0.067981622	0.915582621	74.59929989	29.74666366	NA	NA	NA	NA	NA	NA
Phosphate	LDL	Inverse variance weighted	59	-0.086226036	0.0539564	0.110027678	74.59929989	29.74666366	130.0764786	1.88E-07	55.32995483	NA	NA	NA
Phosphate	LDL	MR Egger	59	-0.048223427	0.130088744	0.712237786	74.59929989	29.74666366	NA	NA	NA	-0.00089092	0.002770527	0.748954383
Phosphate	LDL	Weighted median	59	-0.085037187	0.05702087	0.135873708	74.59929989	29.74666366	NA	NA	NA	NA	NA	NA
Phosphate	LDL	Weighted mode	59	-0.077847366	0.066046835	0.243342918	74.59929989	29.74666366	NA	NA	NA	NA	NA	NA
Phosphate	MetS	Inverse variance weighted	168	0.004426673	0.039590637	0.910973184	94.03431755	29.74666366	483.9138471	1.32E-32	65.47928235	NA	NA	NA
Phosphate	MetS	MR Egger	168	-0.008956249	0.071707854	0.900754523	94.03431755	29.74666366	NA	NA	NA	0.000421806	0.001882044	0.822938714
Phosphate	MetS	Weighted median	168	0.037632594	0.039014263	0.334752449	94.03431755	29.74666366	NA	NA	NA	NA	NA	NA
Phosphate	MetS	Weighted mode	168	0.009630297	0.038339251	0.801978835	94.03431755	29.74666366	NA	NA	NA	NA	NA	NA
Phosphate	SBP	Inverse variance weighted	133	-0.00102766	0.337102563	0.997567647	100.8386639	29.74666366	1079.813913	1.83E-148	87.63628884	NA	NA	NA
Phosphate	SBP	MR Egger	133	0.597773293	0.594364604	0.31639716	100.8386639	29.74666366	NA	NA	NA	-0.019820718	0.016217797	0.223842228
Phosphate	SBP	Weighted median	133	0.173172972	0.23928011	0.469234646	100.8386639	29.74666366	NA	NA	NA	NA	NA	NA
Phosphate	SBP	Weighted mode	133	0.11826386	0.220472696	0.592577762	100.8386639	29.74666366	NA	NA	NA	NA	NA	NA
Phosphate	T2DM	Inverse variance weighted	107	0.040769288	0.060592159	0.501044259	94.1693929	29.87461474	320.7134109	1.92E-23	66.71089082	NA	NA	NA
Phosphate	T2DM	MR Egger	107	0.118437881	0.108005388	0.275328291	94.1693929	29.87461474	NA	NA	NA	-0.002382965	0.002741681	0.386740905
Phosphate	T2DM	Weighted median	107	0.097342094	0.056353776	0.084106737	94.1693929	29.87461474	NA	NA	NA	NA	NA	NA
Phosphate	T2DM	Weighted mode	107	0.105155089	0.056158353	0.063896864	94.1693929	29.87461474	NA	NA	NA	NA	NA	NA
Phosphate	Triglycerides	Inverse variance weighted	59	0.017019853	0.047229303	0.71857316	74.59929989	29.74666366	123.2229752	1.33E-06	52.82270702	NA	NA	NA
Phosphate	Triglycerides	MR Egger	59	0.054198417	0.113219879	0.633982901	74.59929989	29.74666366	NA	NA	NA	-0.000874094	0.00241534	0.718770373
Phosphate	Triglycerides	Weighted median	59	0.035901081	0.048755631	0.461519321	74.59929989	29.74666366	NA	NA	NA	NA	NA	NA
Phosphate	Triglycerides	Weighted mode	59	0.055654034	0.073716921	0.453322062	74.59929989	29.74666366	NA	NA	NA	NA	NA	NA
Potassium in Urine	BMI	Inverse variance weighted	13	0.051739717	0.162263478	0.749830882	42.32458099	30.11243805	217.750869	6.95E-40	94.48305096	NA	NA	NA
Potassium in Urine	BMI	MR Egger	13	-0.061880754	1.046537337	0.953909853	42.32458099	30.11243805	NA	NA	NA	0.001872116	0.01701636	0.914376146
Potassium in Urine	BMI	Weighted median	13	0.162882663	0.082764862	0.049066071	42.32458099	30.11243805	NA	NA	NA	NA	NA	NA
Potassium in Urine	BMI	Weighted mode	13	0.256761474	0.128114058	0.068155262	42.32458099	30.11243805	NA	NA	NA	NA	NA	NA
Potassium in Urine	DBP	Inverse variance weighted	12	0.154751988	1.32759047	0.907203936	43.34225957	30.34274375	159.3924372	1.78E-28	91.99723994	NA	NA	NA
Potassium in Urine	DBP	MR Egger	12	-9.647708963	7.865804841	0.248092139	43.34225957	30.34274375	NA	NA	NA	0.16017887	0.126784088	0.235105618
Potassium in Urine	DBP	Weighted median	12	1.131468653	0.674343416	0.093370145	43.34225957	30.34274375	NA	NA	NA	NA	NA	NA
Potassium in Urine	DBP	Weighted mode	12	1.80259291	0.95080698	0.084541162	43.34225957	30.34274375	NA	NA	NA	NA	NA	NA
Potassium in Urine	HbA1c	Inverse variance weighted	9	0.186554752	0.090426556	0.039107619	41.01330347	30.11243805	8.673618097	0.370572617	0	NA	NA	NA
Potassium in Urine	HbA1c	MR Egger	9	0.974021632	0.482690089	0.083387946	41.01330347	30.11243805	NA	NA	NA	-0.012825138	0.007733084	0.14118544
Potassium in Urine	HbA1c	Weighted median	9	0.15187379	0.111492194	0.173137258	41.01330347	30.11243805	NA	NA	NA	NA	NA	NA
Potassium in Urine	HbA1c	Weighted mode	9	0.130501692	0.160445759	0.439540834	41.01330347	30.11243805	NA	NA	NA	NA	NA	NA
Potassium in Urine	HDL	Inverse variance weighted	9	-0.241217705	0.188652432	0.201025427	41.01330347	30.11243805	24.94805451	0.001586378	67.80042907	NA	NA	NA
Potassium in Urine	HDL	MR Egger	9	-0.047441122	1.155157307	0.96838775	41.01330347	30.11243805	NA	NA	NA	-0.00315296	0.018508217	0.869550453
Potassium in Urine	HDL	Weighted median	9	-0.161493619	0.165658533	0.329630483	41.01330347	30.11243805	NA	NA	NA	NA	NA	NA
Potassium in Urine	HDL	Weighted mode	9	-0.066802231	0.206996046	0.755178674	41.01330347	30.11243805	NA	NA	NA	NA	NA	NA
Potassium in Urine	LDL	Inverse variance weighted	9	-0.139264378	0.237141409	0.557027079	41.01330347	30.11243805	33.2473725	5.56E-05	75.93793114	NA	NA	NA
Potassium in Urine	LDL	MR Egger	9	-0.136056011	1.463170762	0.928519223	41.01330347	30.11243805	NA	NA	NA	-5.21E-05	0.023418827	0.998285694
Potassium in Urine	LDL	Weighted median	9	0.179139461	0.183821942	0.329794898	41.01330347	30.11243805	NA	NA	NA	NA	NA	NA
Potassium in Urine	LDL	Weighted mode	9	0.188108847	0.223647624	0.424720027	41.01330347	30.11243805	NA	NA	NA	NA	NA	NA
Potassium in Urine	MetS	Inverse variance weighted	16	-0.000425173	0.256806555	0.99867901	40.54940061	30.11243805	73.77622458	9.41E-10	79.55159141	NA	NA	NA
Potassium in Urine	MetS	MR Egger	16	0.441431766	1.581396315	0.7842182	40.54940061	30.11243805	NA	NA	NA	-0.007048401	0.024869202	0.7810037
Potassium in Urine	MetS	Weighted median	16	-0.0286417	0.190588337	0.88054336	40.54940061	30.11243805	NA	NA	NA	NA	NA	NA
Potassium in Urine	MetS	Weighted mode	16	-0.154089879	0.268823656	0.575002169	40.54940061	30.11243805	NA	NA	NA	NA	NA	NA
Potassium in Urine	SBP	Inverse variance weighted	12	3.420046991	1.924899556	0.075610946	43.34225957	30.34274375	110.3524284	1.56E-18	88.89453039	NA	NA	NA
Potassium in Urine	SBP	MR Egger	12	-8.846142593	11.64125302	0.464854418	43.34225957	30.34274375	NA	NA	NA	0.200261662	0.187475883	0.310538191
Potassium in Urine	SBP	Weighted median	12	2.982103725	1.160950451	0.010208832	43.34225957	30.34274375	NA	NA	NA	NA	NA	NA
Potassium in Urine	SBP	Weighted mode	12	2.59718635	1.925121499	0.204419169	43.34225957	30.34274375	NA	NA	NA	NA	NA	NA
Potassium in Urine	T2DM	Inverse variance weighted	8	0.079317453	0.30323217	0.793650395	41.44070781	30.34274375	16.46739483	0.021172884	57.06066839	NA	NA	NA
Potassium in Urine	T2DM	MR Egger	8	-0.366821822	1.837744915	0.848382923	41.44070781	30.34274375	NA	NA	NA	0.00716951	0.029064745	0.813383579
Potassium in Urine	T2DM	Weighted median	8	0.363508556	0.290182496	0.210318741	41.44070781	30.34274375	NA	NA	NA	NA	NA	NA
Potassium in Urine	T2DM	Weighted mode	8	0.653774597	0.481272851	0.216478989	41.44070781	30.34274375	NA	NA	NA	NA	NA	NA

Potassium in Urine	Triglycerides	Inverse variance weighted	9	-0.367477289	0.286042376	0.198898789	41.01330347	30.11243805	60.3149098	4.04E-10	84.22272542	NA	NA	NA
Potassium in Urine	Triglycerides	MR Egger	9	-2.205232109	1.620057076	0.215641363	41.01330347	30.11243805	NA	NA	NA	0.029865149	0.025930092	0.287235585
Potassium in Urine	Triglycerides	Weighted median	9	-0.281805085	0.153562479	0.066488385	41.01330347	30.11243805	NA	NA	NA	NA	NA	NA
Potassium in Urine	Triglycerides	Weighted mode	9	-0.240992427	0.164393003	0.18083125	41.01330347	30.11243805	NA	NA	NA	NA	NA	NA
Red Cell Distribution Width	BMI	Inverse variance weighted	208	0.120792373	0.176154932	0.492891793	217.5315482	38.84145942	0.048154552	1	0	NA	NA	NA
Red Cell Distribution Width	BMI	MR Egger	208	0.049545284	0.443629993	0.911184655	217.5315482	38.84145942	NA	NA	NA	0.001497718	0.008559039	0.861261973
Red Cell Distribution Width	BMI	Weighted median	208	0.144274932	0.250105031	0.564035806	217.5315482	38.84145942	NA	NA	NA	NA	NA	NA
Red Cell Distribution Width	BMI	Weighted mode	208	0.145132821	7.679840988	0.984940762	217.5315482	38.84145942	NA	NA	NA	NA	NA	NA
Red Cell Distribution Width	DBP	Inverse variance weighted	186	0.653482528	0.009998698	0	220.2908615	38.84145942	5.068001145	1	0	NA	NA	NA
Red Cell Distribution Width	DBP	MR Egger	186	0.244307265	0.278692581	0.381836558	220.2908615	38.84145942	NA	NA	NA	0.019504301	0.013275984	0.143502035
Red Cell Distribution Width	DBP	Weighted median	186	0.653984721	0.049462493	6.56E-40	220.2908615	38.84145942	NA	NA	NA	NA	NA	NA
Red Cell Distribution Width	DBP	Weighted mode	186	0.648043808	4.707736734	0.89066274	220.2908615	38.84145942	NA	NA	NA	NA	NA	NA
Red Cell Distribution Width	HbA1C	Inverse variance weighted	81	0.060896498	0.13943178	0.662294392	196.3774112	38.84145942	0.13917916	1	0	NA	NA	NA
Red Cell Distribution Width	HbA1C	MR Egger	81	0.008039466	0.206513154	0.969044761	196.3774112	38.84145942	NA	NA	NA	0.003801509	0.010956142	0.729532623
Red Cell Distribution Width	HbA1C	Weighted median	81	0.043022861	0.150147099	0.774466035	196.3774112	38.84145942	NA	NA	NA	NA	NA	NA
Red Cell Distribution Width	HbA1C	Weighted mode	81	0.039967945	0.275177643	0.884883424	196.3774112	38.84145942	NA	NA	NA	NA	NA	NA
Red Cell Distribution Width	HDL	Inverse variance weighted	88	0.067496218	0.05981487	0.259143129	214.8460104	38.84145942	0.137753096	1	0	NA	NA	NA
Red Cell Distribution Width	HDL	MR Egger	88	0.024145387	0.145501657	0.868589121	214.8460104	38.84145942	NA	NA	NA	0.004840062	0.014808886	0.74458683
Red Cell Distribution Width	HDL	Weighted median	88	0.064799654	0.061879345	0.295010303	214.8460104	38.84145942	NA	NA	NA	NA	NA	NA
Red Cell Distribution Width	HDL	Weighted mode	88	0.065057009	2.420062687	0.978615127	214.8460104	38.84145942	NA	NA	NA	NA	NA	NA
Red Cell Distribution Width	LDL	Inverse variance weighted	88	0.374943492	0.108723676	0.000563519	214.8460104	38.84145942	0.061557199	1	0	NA	NA	NA
Red Cell Distribution Width	LDL	MR Egger	88	0.141187309	1.207553676	0.907195978	214.8460104	38.84145942	NA	NA	NA	0.003627135	0.018661202	0.846346366
Red Cell Distribution Width	LDL	Weighted median	88	0.378184731	0.125319237	0.002546414	214.8460104	38.84145942	NA	NA	NA	NA	NA	NA
Red Cell Distribution Width	LDL	Weighted mode	88	0.378417202	1.655066412	0.819683992	214.8460104	38.84145942	NA	NA	NA	NA	NA	NA
Red Cell Distribution Width	MetS	Inverse variance weighted	81	-0.005594205	0.020381024	0.783714958	192.184732	38.84145942	1272.986981	4.37E-214	93.70614044	NA	NA	NA
Red Cell Distribution Width	MetS	MR Egger	81	-0.016338171	0.037336669	0.662877189	192.184732	38.84145942	NA	NA	NA	0.000380261	0.001104586	0.73156799
Red Cell Distribution Width	MetS	Weighted median	81	-0.024782586	0.008927923	0.005505738	192.184732	38.84145942	NA	NA	NA	NA	NA	NA
Red Cell Distribution Width	MetS	Weighted mode	81	-0.021508082	0.007869737	0.007722217	192.184732	38.84145942	NA	NA	NA	NA	NA	NA
Red Cell Distribution Width	SBP	Inverse variance weighted	186	1.180756195	0.030852148	0	220.2908615	38.84145942	260.8109888	0.000202258	0	NA	NA	NA
Red Cell Distribution Width	SBP	MR Egger	186	0.498681057	0.069656731	1.88E-11	220.2908615	38.84145942	NA	NA	NA	0.020496659	0.001942125	1.16E-20
Red Cell Distribution Width	SBP	Weighted median	186	0.898222308	0.062024518	1.58E-47	220.2908615	38.84145942	NA	NA	NA	NA	NA	NA
Red Cell Distribution Width	SBP	Weighted mode	186	0.895616048	3.044517208	0.768955187	220.2908615	38.84145942	NA	NA	NA	NA	NA	NA
Red Cell Distribution Width	T2DM	Inverse variance weighted	213	0.519506797	0.061843517	4.45E-17	202.7474603	38.84145942	334.6314851	1.55E-07	31.24915098	NA	NA	NA

Red Cell Distribution Width	T2DM	MR Egger	213	0.190401976	0.097806166	0.052894773	202.7474603	38.84145942	NA	NA	NA	0.021540211	0.005080353	3.34E-05
Red Cell Distribution Width	T2DM	Weighted median	213	0.481199445	0.052679363	6.57E-20	202.7474603	38.84145942	NA	NA	NA	NA	NA	NA
Red Cell Distribution Width	T2DM	Weighted mode	213	0.473132668	0.214816256	0.028707683	202.7474603	38.84145942	NA	NA	NA	NA	NA	NA
Red Cell Distribution Width	Triglycerides	Inverse variance weighted	88	0.201486106	0.127606479	0.114344189	214.8460104	38.84145942	0.348544294	1	0	NA	NA	NA
Red Cell Distribution Width	Triglycerides	MR Egger	88	0.019810401	0.340222072	0.953702217	214.8460104	38.84145942	NA	NA	NA	0.004451913	0.007728421	0.566089656
Red Cell Distribution Width	Triglycerides	Weighted median	88	0.240906706	0.151870934	0.112680464	214.8460104	38.84145942	NA	NA	NA	NA	NA	NA
Red Cell Distribution Width	Triglycerides	Weighted mode	88	0.241767732	5.36983128	0.964191888	214.8460104	38.84145942	NA	NA	NA	NA	NA	NA
Serum Phosphate	BMI	Inverse variance weighted	284	-0.046495812	0.018489241	0.011911694	88.19477982	29.04012346	1744.49901	1.66E-208	83.68235109	NA	NA	NA
Serum Phosphate	BMI	MR Egger	284	-0.093571478	0.040985612	0.023172623	88.19477982	29.04012346	NA	NA	NA	0.000993385	0.000772097	0.199287021
Serum Phosphate	BMI	Weighted median	284	-0.059553197	0.015397872	0.0001099	88.19477982	29.04012346	NA	NA	NA	NA	NA	NA
Serum Phosphate	BMI	Weighted mode	284	-0.073984638	0.034746477	0.034095093	88.19477982	29.04012346	NA	NA	NA	NA	NA	NA
Serum Phosphate	DBP	Inverse variance weighted	249	-0.392185388	0.240785081	0.103360071	91.15288649	29.28719723	3008.584749	0	91.73925985	NA	NA	NA
Serum Phosphate	DBP	MR Egger	249	-0.040720272	0.539907278	0.939940911	91.15288649	29.28719723	NA	NA	NA	-0.00741785	0.010196651	0.467621523
Serum Phosphate	DBP	Weighted median	249	-0.200259958	0.186737951	0.283535169	91.15288649	29.28719723	NA	NA	NA	NA	NA	NA
Serum Phosphate	DBP	Weighted mode	249	0.391602214	0.662748034	0.555141307	91.15288649	29.28719723	NA	NA	NA	NA	NA	NA
Serum Phosphate	HbA1c	Inverse variance weighted	98	-0.012474546	0.027651251	0.651889687	92.11663725	29.28719723	144.7075915	0.001220068	32.91712608	NA	NA	NA
Serum Phosphate	HbA1c	MR Egger	98	-0.030059238	0.070664895	0.67151374	92.11663725	29.28719723	NA	NA	NA	0.000337307	0.001246312	0.787245939
Serum Phosphate	HbA1c	Weighted median	98	-0.01179972	0.037180909	0.750970719	92.11663725	29.28719723	NA	NA	NA	NA	NA	NA
Serum Phosphate	HbA1c	Weighted mode	98	-0.004588572	0.05138683	0.929031809	92.11663725	29.28719723	NA	NA	NA	NA	NA	NA
Serum Phosphate	HDL	Inverse variance weighted	108	-0.093811311	0.058131681	0.106576773	92.63193206	29.04012346	505.3315866	5.43E-53	78.79544437	NA	NA	NA
Serum Phosphate	HDL	MR Egger	108	-0.04256124	0.143873181	0.767942707	92.63193206	29.04012346	NA	NA	NA	-0.001035575	0.002657203	0.697522832
Serum Phosphate	HDL	Weighted median	108	0.014432061	0.049241287	0.769454409	92.63193206	29.04012346	NA	NA	NA	NA	NA	NA
Serum Phosphate	HDL	Weighted mode	108	0.184066739	0.152923143	0.231379031	92.63193206	29.04012346	NA	NA	NA	NA	NA	NA
Serum Phosphate	LDL	Inverse variance weighted	108	0.220246778	0.100424887	0.028296618	92.63193206	29.04012346	1291.267437	2.50E-202	91.69670937	NA	NA	NA
Serum Phosphate	LDL	MR Egger	108	0.325695036	0.248436541	0.192697945	92.63193206	29.04012346	NA	NA	NA	-0.002135579	0.004598723	0.643324162
Serum Phosphate	LDL	Weighted median	108	-0.024231998	0.052123794	0.642007924	92.63193206	29.04012346	NA	NA	NA	NA	NA	NA
Serum Phosphate	LDL	Weighted mode	108	-0.0773103	0.058074321	0.185942642	92.63193206	29.04012346	NA	NA	NA	NA	NA	NA
Serum Phosphate	MetS	Inverse variance weighted	317	-0.014619247	0.045276768	0.746781373	87.38664623	29.04012346	1198.452777	8.01E-103	73.54707527	NA	NA	NA
Serum Phosphate	MetS	MR Egger	317	0.079041366	0.103094969	0.443843026	87.38664623	29.04012346	NA	NA	NA	-0.001956114	0.001934411	0.31268752
Serum Phosphate	MetS	Weighted median	317	0.091369066	0.043261501	0.034684914	87.38664623	29.04012346	NA	NA	NA	NA	NA	NA
Serum Phosphate	MetS	Weighted mode	317	0.145043914	0.061535646	0.019029353	87.38664623	29.04012346	NA	NA	NA	NA	NA	NA
Serum Phosphate	SBP	Inverse variance weighted	248	-0.040370492	0.403143732	0.920233812	91.30582693	29.28719723	2769.625541	0	91.0661119	NA	NA	NA
Serum Phosphate	SBP	MR Egger	248	0.492582216	0.904512993	0.586533799	91.30582693	29.28719723	NA	NA	NA	-0.011241428	0.017073979	0.510899855
Serum Phosphate	SBP	Weighted median	248	0.409258855	0.345456675	0.236140282	91.30582693	29.28719723	NA	NA	NA	NA	NA	NA
Serum Phosphate	SBP	Weighted mode	248	1.39908165	1.170057285	0.232945593	91.30582693	29.28719723	NA	NA	NA	NA	NA	NA
Serum Phosphate	T2DM	Inverse variance weighted	189	0.066457513	0.057415217	0.247072407	94.92197305	29.04012346	520.8484478	4.84E-33	63.81767894	NA	NA	NA
Serum Phosphate	T2DM	MR Egger	189	-0.013979943	0.132667074	0.916190304	94.92197305	29.04012346	NA	NA	NA	0.001682513	0.002500826	0.501915829
Serum Phosphate	T2DM	Weighted median	189	0.103247616	0.064373506	0.108739694	94.92197305	29.04012346	NA	NA	NA	NA	NA	NA
Serum Phosphate	T2DM	Weighted mode	189	0.116211879	0.09356486	0.215766701	94.92197305	29.04012346	NA	NA	NA	NA	NA	NA
Serum Phosphate	Triglycerides	Inverse variance weighted	108	0.303657518	0.097396833	0.001822466	92.63193206	29.04012346	1493.578532	6.03E-243	92.65705717	NA	NA	NA
Serum Phosphate	Triglycerides	MR Egger	108	0.658077199	0.238297682	0.00678133	92.63193206	29.04012346	NA	NA	NA	-0.00716292	0.004402107	0.106672833
Serum Phosphate	Triglycerides	Weighted median	108	-0.017720623	0.046978153	0.70601764	92.63193206	29.04012346	NA	NA	NA	NA	NA	NA
Serum Phosphate	Triglycerides	Weighted mode	108	-0.076144058	0.062441502	0.225356122	92.63193206	29.04012346	NA	NA	NA	NA	NA	NA
Serum Urea	BMI	Inverse variance weighted	172	0.052329472	0.021390528	0.014429675	85.30137521	27.30877933	1272.417247	1.51E-167	86.54954798	NA	NA	NA
Serum Urea	BMI	MR Egger	172	0.06852694	0.047633921	0.152097743	85.30137521	27.30877933	NA	NA	NA	-0.000407713	0.001070639	0.703817647
Serum Urea	BMI	Weighted median	172	0.027936508	0.015968617	0.080210974	85.30137521	27.30877933	NA	NA	NA	NA	NA	NA
Serum Urea	BMI	Weighted mode	172	0.01286814	0.022036181	0.560020061	85.30137521	27.30877933	NA	NA	NA	NA	NA	NA
Serum Urea	DBP	Inverse variance weighted	160	-0.806208771	0.270843088	0.002914035	86.15217238	28.02790172	2281.527269	0	93.03091502	NA	NA	NA
Serum Urea	DBP	MR Egger	160	-0.827354145	0.599691208	0.169648864	86.15217238	28.02790172	NA	NA	NA	0.000535193	0.013531114	0.968499635
Serum Urea	DBP	Weighted median	160	-0.479285729	0.16905941	0.004582373	86.15217238	28.02790172	NA	NA	NA	NA	NA	NA
Serum Urea	DBP	Weighted mode	160	-0.202925229	0.394885814	0.608047	86.15217238	28.02790172	NA	NA	NA	NA	NA	NA
Serum Urea	HbA1c	Inverse variance weighted	103	-0.050332838	0.020545462	0.014292468	88.74606209	28.02790172	137.0540493	0.011778807	25.18111139	NA	NA	NA
Serum Urea	HbA1c	MR Egger	103	-0.019883494	0.04637458	0.669012084	88.74606209	28.02790172	NA	NA	NA	-0.000739127	0.001008631	0.465376154
Serum Urea	HbA1c	Weighted median	103	-0.009676699	0.029416081	0.742186311	88.74606209	28.02790172	NA	NA	NA	NA	NA	NA
Serum Urea	HbA1c	Weighted mode	103	-0.012959861	0.046186384	0.779586193	88.74606209	28.02790172	NA	NA	NA	NA	NA	NA

Serum Urea	HDL	Inverse variance weighted	107	-0.004508946	0.037535297	0.904383733	90.45815944	28.02790172	307.6319597	1.56E-21	65.52254374	NA	NA	NA
Serum Urea	HDL	MR Egger	107	-0.024341045	0.087505572	0.781432219	90.45815944	28.02790172	NA	NA	NA	0.000485331	0.001932477	0.802193125
Serum Urea	HDL	Weighted median	107	0.009643348	0.039891813	0.808983544	90.45815944	28.02790172	NA	NA	NA	NA	NA	NA
Serum Urea	HDL	Weighted mode	107	0.04300199	0.047678778	0.36914922	90.45815944	28.02790172	NA	NA	NA	NA	NA	NA
Serum Urea	LDL	Inverse variance weighted	107	-0.026912057	0.053682632	0.616147513	90.45815944	28.02790172	536.4039158	9.72E-59	80.05080125	NA	NA	NA
Serum Urea	LDL	MR Egger	107	0.085764685	0.124874045	0.493716813	90.45815944	28.02790172	NA	NA	NA	-0.002755698	0.002757392	0.319905611
Serum Urea	LDL	Weighted median	107	-0.019324703	0.040653361	0.634535295	90.45815944	28.02790172	NA	NA	NA	NA	NA	NA
Serum Urea	LDL	Weighted mode	107	0.002017496	0.059428954	0.972982439	90.45815944	28.02790172	NA	NA	NA	NA	NA	NA
Serum Urea	MetS	Inverse variance weighted	175	0.081817829	0.043937695	0.062584351	86.13060902	28.02790172	513.6935389	2.99E-35	66.1186062	NA	NA	NA
Serum Urea	MetS	MR Egger	175	0.062865567	0.098514659	0.524230156	86.13060902	28.02790172	NA	NA	NA	0.000478903	0.002226528	0.829950998
Serum Urea	MetS	Weighted median	175	0.053536371	0.044611141	0.230113208	86.13060902	28.02790172	NA	NA	NA	NA	NA	NA
Serum Urea	MetS	Weighted mode	175	0.024234257	0.066506528	0.716009884	86.13060902	28.02790172	NA	NA	NA	NA	NA	NA
Serum Urea	SBP	Inverse variance weighted	160	-1.482505389	0.460211043	0.001275838	86.15217238	28.02790172	2176.342479	0	92.68580946	NA	NA	NA
Serum Urea	SBP	MR Egger	160	-1.096607573	1.01835127	0.283190484	86.15217238	28.02790172	NA	NA	NA	-0.009768971	0.02298154	0.671357409
Serum Urea	SBP	Weighted median	160	-0.893629487	0.308676821	0.00379119	86.15217238	28.02790172	NA	NA	NA	NA	NA	NA
Serum Urea	SBP	Weighted mode	160	0.672249933	0.518626268	0.196780496	86.15217238	28.02790172	NA	NA	NA	NA	NA	NA
Serum Urea	T2DM	Inverse variance weighted	135	0.0269629	0.077179852	0.726825413	85.1982626	28.02790172	660.6963373	1.39E-70	79.6747489	NA	NA	NA
Serum Urea	T2DM	MR Egger	135	0.114816782	0.181582068	0.528267593	85.1982626	28.02790172	NA	NA	NA	-0.002110586	0.003946303	0.593663168
Serum Urea	T2DM	Weighted median	135	0.05286466	0.066692762	0.427976158	85.1982626	28.02790172	NA	NA	NA	NA	NA	NA
Serum Urea	T2DM	Weighted mode	135	0.053327266	0.097539814	0.585478264	85.1982626	28.02790172	NA	NA	NA	NA	NA	NA
Serum Urea	Triglycerides	Inverse variance weighted	107	-0.158517166	0.075557278	0.035907488	90.45815944	28.02790172	1308.077623	3.13E-206	91.89357223	NA	NA	NA
Serum Urea	Triglycerides	MR Egger	107	-0.189530865	0.176264547	0.284721299	90.45815944	28.02790172	NA	NA	NA	0.0007588	0.00389227	0.845808327
Serum Urea	Triglycerides	Weighted median	107	-0.034163871	0.038390271	0.373514432	90.45815944	28.02790172	NA	NA	NA	NA	NA	NA
Serum Urea	Triglycerides	Weighted mode	107	-0.019310468	0.046942151	0.681633733	90.45815944	28.02790172	NA	NA	NA	NA	NA	NA
Serum Uric Acid	BMI	Inverse variance weighted	200	-0.080258124	0.030310063	0.008099262	87.87801984	30.04663923	2696.465594	0	92.29633112	NA	NA	NA
Serum Uric Acid	BMI	MR Egger	200	0.094443436	0.066329225	0.156061389	87.87801984	30.04663923	NA	NA	NA	-0.004027739	0.001366873	0.003597489
Serum Uric Acid	BMI	Weighted median	200	-0.011078499	0.016929448	0.512859161	87.87801984	30.04663923	NA	NA	NA	NA	NA	NA
Serum Uric Acid	BMI	Weighted mode	200	-0.001167921	0.021847354	0.957420421	87.87801984	30.04663923	NA	NA	NA	NA	NA	NA
Serum Uric Acid	DBP	Inverse variance weighted	171	-1.391103784	0.274185231	3.90E-07	90.21808124	30.04663923	2119.862816	0	91.97644879	NA	NA	NA
Serum Uric Acid	DBP	MR Egger	171	-1.559939726	0.632770231	0.014690868	90.21808124	30.04663923	NA	NA	NA	0.003799001	0.012823972	0.767408889
Serum Uric Acid	DBP	Weighted median	171	-0.841820389	0.164836505	3.27E-07	90.21808124	30.04663923	NA	NA	NA	NA	NA	NA
Serum Uric Acid	DBP	Weighted mode	171	-0.964861245	0.177967556	2.00E-07	90.21808124	30.04663923	NA	NA	NA	NA	NA	NA
Serum Uric Acid	HbA1c	Inverse variance weighted	84	0.002631815	0.024780519	0.915419703	101.1573046	30.25	113.96865	0.013660733	24.30799202	NA	NA	NA
Serum Uric Acid	HbA1c	MR Egger	84	0.086903877	0.052911047	0.104325959	101.1573046	30.25	NA	NA	NA	-0.002015889	0.001122397	0.07616865
Serum Uric Acid	HbA1c	Weighted median	84	0.076223062	0.033834831	0.024271848	101.1573046	30.25	NA	NA	NA	NA	NA	NA
Serum Uric Acid	HbA1c	Weighted mode	84	0.085745338	0.039846841	0.034312583	101.1573046	30.25	NA	NA	NA	NA	NA	NA
Serum Uric Acid	HDL	Inverse variance weighted	95	0.100396858	0.052637321	0.056477583	108.998349	30.25	468.2935043	4.59E-51	79.82952854	NA	NA	NA
Serum Uric Acid	HDL	MR Egger	95	0.038928337	0.105562683	0.713137447	108.998349	30.25	NA	NA	NA	0.001638771	0.002437131	0.502984931
Serum Uric Acid	HDL	Weighted median	95	0.054245418	0.044694343	0.224863214	108.998349	30.25	NA	NA	NA	NA	NA	NA
Serum Uric Acid	HDL	Weighted mode	95	0.079853989	0.039033422	0.043571293	108.998349	30.25	NA	NA	NA	NA	NA	NA
Serum Uric Acid	LDL	Inverse variance weighted	95	0.027652103	0.054271452	0.6103915	108.998349	30.25	426.6313148	7.20E-44	77.90441476	NA	NA	NA
Serum Uric Acid	LDL	MR Egger	95	-0.020815621	0.108958358	0.84890915	108.998349	30.25	NA	NA	NA	0.001293718	0.002518616	0.608706533
Serum Uric Acid	LDL	Weighted median	95	0.065022941	0.044865826	0.147260668	108.998349	30.25	NA	NA	NA	NA	NA	NA
Serum Uric Acid	LDL	Weighted mode	95	0.041554033	0.060808515	0.496061113	108.998349	30.25	NA	NA	NA	NA	NA	NA
Serum Uric Acid	MetS	Inverse variance weighted	222	0.202556673	0.038259567	1.19E-07	172.2784941	30.04663923	1034.6379	2.58E-105	76.37741749	NA	NA	NA
Serum Uric Acid	MetS	MR Egger	222	0.045733993	0.048836685	0.350059123	172.2784941	30.04663923	NA	NA	NA	0.007036589	0.001457683	2.59E-06
Serum Uric Acid	MetS	Weighted median	222	0.056510483	0.023920805	0.018157095	172.2784941	30.04663923	NA	NA	NA	NA	NA	NA
Serum Uric Acid	MetS	Weighted mode	222	0.049439733	0.02259868	0.029737971	172.2784941	30.04663923	NA	NA	NA	NA	NA	NA
Serum Uric Acid	SBP	Inverse variance weighted	171	-2.335480135	0.436839093	8.98E-08	90.21808124	30.04663923	1776.328488	2.96E-265	90.41202714	NA	NA	NA
Serum Uric Acid	SBP	MR Egger	171	-2.842402516	1.007523042	0.005358095	90.21808124	30.04663923	NA	NA	NA	0.011403861	0.020414652	0.577166203
Serum Uric Acid	SBP	Weighted median	171	-2.0666159	0.315472983	5.72E-11	90.21808124	30.04663923	NA	NA	NA	NA	NA	NA
Serum Uric Acid	SBP	Weighted mode	171	-2.390599358	0.307909097	7.36E-13	90.21808124	30.04663923	NA	NA	NA	NA	NA	NA
Serum Uric Acid	T2DM	Inverse variance weighted	142	-0.093593729	0.08685878	0.281239509	97.23432537	30.25	815.1091055	2.16E-95	81.5512545	NA	NA	NA
Serum Uric Acid	T2DM	MR Egger	142	0.425887207	0.190020524	0.026582478	97.23432537	30.25	NA	NA	NA	-0.012052843	0.003949969	0.002725932
Serum Uric Acid	T2DM	Weighted median	142	-0.107016053	0.065580469	0.102715701	97.23432537	30.25	NA	NA	NA	NA	NA	NA
Serum Uric Acid	T2DM	Weighted mode	142	-0.111350739	0.075852206	0.144332533	97.23432537	30.25	NA	NA	NA	NA	NA	NA
Serum Uric Acid	Triglycerides	Inverse variance weighted	94	-0.361985782	0.091597213	7.75E-05	109.6406468	30.25	1482.783581	5.30E-249	93.64811812	NA	NA	NA
Serum Uric Acid	Triglycerides	MR Egger	94	-0.533042683	0.1825992	0.004411947	109.6406468	30.25	NA	NA	NA	0.00457643	0.004227438	0.281835636
Serum Uric Acid	Triglycerides	Weighted median	94	-0.004766226	0.038858024	0.902378355	109.6406468	30.25	NA	NA	NA	NA	NA	NA
Serum Uric Acid	Triglycerides	Weighted mode	94	0.010158264	0.039637448	0.798301101	109.6406468	30.25	NA	NA	NA	NA	NA	NA
Sodium in Urine	BMI	Inverse variance weighted	38	-0.598398715	0.1592695	0.000171862	44.25941958	30.12830164	1866.652001	0	97.95280795	NA	NA	NA
Sodium in Urine	BMI	MR Egger	38	0.037455775	0.606257661	0.951078228	44.25941958	30.12830164	NA	NA	NA	-0.010940984	0.010067123	0.284347137

Sodium in Urine	BMI	Weighted median	38	-0.271012847	0.062490752	1.45E-05	44.25941958	30.12830164	NA	NA	NA	NA	NA	NA
Sodium in Urine	BMI	Weighted mode	38	-0.375022277	0.088689224	0.000148008	44.25941958	30.12830164	NA	NA	NA	NA	NA	NA
Sodium in Urine	DBP	Inverse variance weighted	32	-0.730300176	0.829840496	0.378832846	45.66093924	30.12830164	475.9743262	4.04E-81	93.09119106	NA	NA	NA
Sodium in Urine	DBP	MR Egger	32	3.825785568	3.472051251	0.279275587	45.66093924	30.12830164	NA	NA	NA	-0.077803129	0.057618077	0.187011362
Sodium in Urine	DBP	Weighted median	32	0.126622559	0.463778996	0.78483516	45.66093924	30.12830164	NA	NA	NA	NA	NA	NA
Sodium in Urine	DBP	Weighted mode	32	0.617768805	0.904405771	0.499638676	45.66093924	30.12830164	NA	NA	NA	NA	NA	NA
Sodium in Urine	HbA1c	Inverse variance weighted	19	-0.01692818	0.064878317	0.79415266	46.66504127	30.12830164	24.17080365	0.149511241	19.54619743	NA	NA	NA
Sodium in Urine	HbA1c	MR Egger	19	-0.422589561	0.352982356	0.24765777	46.66504127	30.12830164	NA	NA	NA	0.006586421	0.005635435	0.258632479
Sodium in Urine	HbA1c	Weighted median	19	0.01449134	0.082614751	0.860758561	46.66504127	30.12830164	NA	NA	NA	NA	NA	NA
Sodium in Urine	HbA1c	Weighted mode	19	0.085914691	0.142265925	0.553444306	46.66504127	30.12830164	NA	NA	NA	NA	NA	NA
Sodium in Urine	HDL	Inverse variance weighted	21	0.165875772	0.098180756	0.091124851	47.44756171	30.12830164	44.10280662	0.001457946	52.20931593	NA	NA	NA
Sodium in Urine	HDL	MR Egger	21	0.675250894	0.513042774	0.203776018	47.44756171	30.12830164	NA	NA	NA	-0.00853223	0.008435023	0.324474626
Sodium in Urine	HDL	Weighted median	21	0.170841023	0.105046201	0.103876975	47.44756171	30.12830164	NA	NA	NA	NA	NA	NA
Sodium in Urine	HDL	Weighted mode	21	0.176333661	0.180504432	0.340290918	47.44756171	30.12830164	NA	NA	NA	NA	NA	NA
Sodium in Urine	LDL	Inverse variance weighted	21	-0.078157482	0.133706666	0.558854107	47.44756171	30.12830164	70.52892051	1.49E-07	70.67845155	NA	NA	NA
Sodium in Urine	LDL	MR Egger	21	0.477937709	0.704827111	0.505888352	47.44756171	30.12830164	NA	NA	NA	-0.009342976	0.011622892	0.43143067
Sodium in Urine	LDL	Weighted median	21	0.048229047	0.110796377	0.663348721	47.44756171	30.12830164	NA	NA	NA	NA	NA	NA
Sodium in Urine	LDL	Weighted mode	21	0.097269198	0.151422504	0.527928863	47.44756171	30.12830164	NA	NA	NA	NA	NA	NA
Sodium in Urine	MetS	Inverse variance weighted	42	0.86236784	0.200659642	1.73E-05	44.31980824	30.12830164	330.69827	5.89E-47	87.08964868	NA	NA	NA
Sodium in Urine	MetS	MR Egger	42	-0.128912678	0.796301243	0.872208001	44.31980824	30.12830164	NA	NA	NA	0.01690977	0.013152351	0.205946901
Sodium in Urine	MetS	Weighted median	42	0.584024084	0.136616904	1.91E-05	44.31980824	30.12830164	NA	NA	NA	NA	NA	NA
Sodium in Urine	MetS	Weighted mode	42	0.526539594	0.280230081	0.067372446	44.31980824	30.12830164	NA	NA	NA	NA	NA	NA
Sodium in Urine	SBP	Inverse variance weighted	33	-0.688439843	1.517443867	0.650056361	45.35829783	30.12830164	555.9935235	6.85E-97	93.45649673	NA	NA	NA
Sodium in Urine	SBP	MR Egger	33	11.52757664	6.103201534	0.06830954	45.35829783	30.12830164	NA	NA	NA	-0.20716296	0.100553479	0.047855017
Sodium in Urine	SBP	Weighted median	33	-0.757355897	0.868545603	0.383218345	45.35829783	30.12830164	NA	NA	NA	NA	NA	NA
Sodium in Urine	SBP	Weighted mode	33	-2.478117968	1.945702128	0.211965967	45.35829783	30.12830164	NA	NA	NA	NA	NA	NA
Sodium in Urine	T2DM	Inverse variance weighted	25	-0.669846803	0.433171261	0.12201314	42.5408272	30.12830164	364.3484255	1.49E-62	93.3920168	NA	NA	NA
Sodium in Urine	T2DM	MR Egger	25	0.112431724	2.930568345	0.969727603	42.5408272	30.12830164	NA	NA	NA	-0.012202345	0.045189956	0.789550296
Sodium in Urine	T2DM	Weighted median	25	-0.768567858	0.197533434	9.99E-05	42.5408272	30.12830164	NA	NA	NA	NA	NA	NA
Sodium in Urine	T2DM	Weighted mode	25	-0.923070215	0.366676019	0.018906442	42.5408272	30.12830164	NA	NA	NA	NA	NA	NA
Sodium in Urine	Triglycerides	Inverse variance weighted	21	-0.835990582	0.460175348	0.069266382	47.44756171	30.12830164	1035.43905	1.08E-206	97.8546778	NA	NA	NA
Sodium in Urine	Triglycerides	MR Egger	21	-4.160218992	2.335756104	0.090889921	47.44756171	30.12830164	NA	NA	NA	0.055827407	0.038498651	0.163334885
Sodium in Urine	Triglycerides	Weighted median	21	-0.147446516	0.117000787	0.207590676	47.44756171	30.12830164	NA	NA	NA	NA	NA	NA
Sodium in Urine	Triglycerides	Weighted mode	21	-0.306295653	0.195484407	0.132834838	47.44756171	30.12830164	NA	NA	NA	NA	NA	NA
Tea Consumption	BMI	Inverse variance weighted	33	-0.000450226	0.138763494	0.997411224	66.91564026	30.02117124	1559.994937	3.35E-308	97.71964791	NA	NA	NA
Tea Consumption	BMI	MR Egger	33	-0.481037352	0.290859895	0.108251478	66.91564026	30.02117124	NA	NA	NA	0.01067253	0.005736171	0.07231483
Tea Consumption	BMI	Weighted median	33	-0.241663206	0.035094061	5.73E-12	66.91564026	30.02117124	NA	NA	NA	NA	NA	NA
Tea Consumption	BMI	Weighted mode	33	-0.223155617	0.032288647	7.99E-08	66.91564026	30.02117124	NA	NA	NA	NA	NA	NA
Tea Consumption	DBP	Inverse variance weighted	29	0.731942629	0.485106145	0.131342272	70.82898655	30.11659629	198.566799	1.28E-27	85.85393478	NA	NA	NA
Tea Consumption	DBP	MR Egger	29	1.013226423	1.077579354	0.355410742	70.82898655	30.11659629	NA	NA	NA	-0.006281796	0.021396326	0.771314449
Tea Consumption	DBP	Weighted median	29	0.370440587	0.437606458	0.397265311	70.82898655	30.11659629	NA	NA	NA	NA	NA	NA
Tea Consumption	DBP	Weighted mode	29	2.006620017	1.682357808	0.242980015	70.82898655	30.11659629	NA	NA	NA	NA	NA	NA
Tea Consumption	HbA1c	Inverse variance weighted	12	-0.001295122	0.053614531	0.980728035	105.5775051	30.11659629	6.898654523	0.807230254	0	NA	NA	NA
Tea Consumption	HbA1c	MR Egger	12	-0.033236877	0.101352836	0.749725467	105.5775051	30.11659629	NA	NA	NA	0.000881436	0.00237348	0.718110266
Tea Consumption	HbA1c	Weighted median	12	-0.030878143	0.068099005	0.650239021	105.5775051	30.11659629	NA	NA	NA	NA	NA	NA
Tea Consumption	HbA1c	Weighted mode	12	-0.034292531	0.066164838	0.614521651	105.5775051	30.11659629	NA	NA	NA	NA	NA	NA
Tea Consumption	HDL	Inverse variance weighted	11	-0.041118177	0.106624039	0.699765508	107.6434515	30.02117124	33.40345092	0.000232956	66.00210555	NA	NA	NA
Tea Consumption	HDL	MR Egger	11	0.131511579	0.188503772	0.503013272	107.6434515	30.02117124	NA	NA	NA	-0.005250474	0.004751953	0.297860711
Tea Consumption	HDL	Weighted median	11	-0.0607884	0.079748999	0.445912863	107.6434515	30.02117124	NA	NA	NA	NA	NA	NA
Tea Consumption	HDL	Weighted mode	11	-0.042903774	0.093159493	0.654980188	107.6434515	30.02117124	NA	NA	NA	NA	NA	NA
Tea Consumption	LDL	Inverse variance weighted	11	-0.012909006	0.069481983	0.852610034	107.6434515	30.02117124	12.30782071	0.264983316	0	NA	NA	NA
Tea Consumption	LDL	MR Egger	11	-0.239791726	0.111913605	0.060758779	107.6434515	30.02117124	NA	NA	NA	0.006939905	0.002836976	0.036984545
Tea Consumption	LDL	Weighted median	11	-0.090438154	0.075523774	0.231119796	107.6434515	30.02117124	NA	NA	NA	NA	NA	NA
Tea Consumption	LDL	Weighted mode	11	-0.112201591	0.077338824	0.177475247	107.6434515	30.02117124	NA	NA	NA	NA	NA	NA
Tea Consumption	MetS	Inverse variance weighted	32	0.018325741	0.181175995	0.919432312	67.98535662	30.02117124	233.1198712	7.51E-33	86.2273411	NA	NA	NA
Tea Consumption	MetS	MR Egger	32	0.385721127	0.398458106	0.340767155	67.98535662	30.02117124	NA	NA	NA	-0.008081552	0.007808713	0.308967792
Tea Consumption	MetS	Weighted median	32	-0.091999137	0.113024722	0.41566009	67.98535662	30.02117124	NA	NA	NA	NA	NA	NA
Tea Consumption	MetS	Weighted mode	32	-0.059258108	0.147456673	0.690538538	67.98535662	30.02117124	NA	NA	NA	NA	NA	NA
Tea Consumption	SBP	Inverse variance weighted	29	1.133644409	0.852581857	0.183630158	70.82898655	30.11659629	201.7488189	3.20E-28	85.97930193	NA	NA	NA
Tea Consumption	SBP	MR Egger	29	0.251301654	1.887667817	0.895079332	70.82898655	30.11659629	NA	NA	NA	0.019684186	0.03744398	0.603390035
Tea Consumption	SBP	Weighted median	29	1.210117867	0.749805714	0.10654726	70.82898655	30.11659629	NA	NA	NA	NA	NA	NA
Tea Consumption	SBP	Weighted mode	29	2.317336064	1.470760079	0.126349741	70.82898655	30.11659629	NA	NA	NA	NA	NA	NA

Tea Consumption	T2DM	Inverse variance weighted	23	0.162862203	0.352073928	0.643665762	54.18541941	30.02117124	243.4444253	2.93E-39	90.23197477	NA	NA	NA
Tea Consumption	T2DM	MR Egger	23	-0.996263355	0.954477253	0.308454953	54.18541941	30.02117124	NA	NA	NA	0.020828025	0.015979928	0.20655234
Tea Consumption	T2DM	Weighted median	23	-0.360648427	0.178621402	0.043480345	54.18541941	30.02117124	NA	NA	NA	NA	NA	NA
Tea Consumption	T2DM	Weighted mode	23	-0.333937666	0.180955202	0.078480157	54.18541941	30.02117124	NA	NA	NA	NA	NA	NA
Tea Consumption	Triglycerides	Inverse variance weighted	11	0.086028164	0.099117045	0.385424331	107.6434515	30.02117124	31.19455323	0.000544849	62.85402599	NA	NA	NA
Tea Consumption	Triglycerides	MR Egger	11	-0.085763523	0.173424608	0.632778961	107.6434515	30.02117124	NA	NA	NA	0.005306509	0.004439438	0.262510413
Tea Consumption	Triglycerides	Weighted median	11	0.115084045	0.074672599	0.123272565	107.6434515	30.02117124	NA	NA	NA	NA	NA	NA
Tea Consumption	Triglycerides	Weighted mode	11	0.128157858	0.090475942	0.187022197	107.6434515	30.02117124	NA	NA	NA	NA	NA	NA
Total Testosterone	BMI	Inverse variance weighted	172	-0.046851522	0.014220972	0.000985839	87.44368116	23.65371828	1044.05057	3.34E-125	83.57897255	NA	NA	NA
Total Testosterone	BMI	MR Egger	172	-0.062907323	0.028056059	0.026241362	87.44368116	23.65371828	NA	NA	NA	0.000601564	0.000905621	0.507426837
Total Testosterone	BMI	Weighted median	172	-0.033503015	0.010313281	0.001160025	87.44368116	23.65371828	NA	NA	NA	NA	NA	NA
Total Testosterone	BMI	Weighted mode	172	-0.041631912	0.011125781	0.000249057	87.44368116	23.65371828	NA	NA	NA	NA	NA	NA
Total Testosterone	DBP	Inverse variance weighted	157	-0.10393377	0.208795739	0.61864105	88.68764106	23.65371828	2405.934172	0	93.46722649	NA	NA	NA
Total Testosterone	DBP	MR Egger	157	-0.488977605	0.413066669	0.238314773	88.68764106	23.65371828	NA	NA	NA	0.014373106	0.013306702	0.281757502
Total Testosterone	DBP	Weighted median	157	-0.13787519	0.121810957	0.257685565	88.68764106	23.65371828	NA	NA	NA	NA	NA	NA
Total Testosterone	DBP	Weighted mode	157	-0.084844499	0.127953332	0.508251901	88.68764106	23.65371828	NA	NA	NA	NA	NA	NA
Total Testosterone	HbA1c	Inverse variance weighted	61	-0.028250188	0.022450259	0.208266739	73.35700023	27.99132969	76.19067305	0.077460368	19.91372556	NA	NA	NA
Total Testosterone	HbA1c	MR Egger	61	-0.083730947	0.059817393	0.16681675	73.35700023	27.99132969	NA	NA	NA	0.001667766	0.001666683	0.321082489
Total Testosterone	HbA1c	Weighted median	61	-0.055546902	0.029641488	0.060936224	73.35700023	27.99132969	NA	NA	NA	NA	NA	NA
Total Testosterone	HbA1c	Weighted mode	61	-0.058233278	0.045405584	0.204595323	73.35700023	27.99132969	NA	NA	NA	NA	NA	NA
Total Testosterone	HDL	Inverse variance weighted	58	-0.016586969	0.039900661	0.677624691	72.59454649	27.99132969	140.5096898	5.29E-09	59.42988745	NA	NA	NA
Total Testosterone	HDL	MR Egger	58	-0.009357311	0.111316492	0.933308182	72.59454649	27.99132969	NA	NA	NA	-0.000219185	0.003146452	0.944711659
Total Testosterone	HDL	Weighted median	58	0.011699163	0.04052755	0.772832506	72.59454649	27.99132969	NA	NA	NA	NA	NA	NA
Total Testosterone	HDL	Weighted mode	58	0.024529804	0.064011708	0.702990975	72.59454649	27.99132969	NA	NA	NA	NA	NA	NA
Total Testosterone	LDL	Inverse variance weighted	58	0.10637865	0.045390631	0.019097325	72.59454649	27.99132969	155.0407304	5.24E-11	62.66224322	NA	NA	NA
Total Testosterone	LDL	MR Egger	58	0.216478436	0.126285802	0.092023403	72.59454649	27.99132969	NA	NA	NA	-0.003336634	0.003570811	0.354099613
Total Testosterone	LDL	Weighted median	58	0.12469365	0.045273783	0.005883343	72.59454649	27.99132969	NA	NA	NA	NA	NA	NA
Total Testosterone	LDL	Weighted mode	58	0.149252903	0.089139377	0.099535664	72.59454649	27.99132969	NA	NA	NA	NA	NA	NA
Total Testosterone	MetS	Inverse variance weighted	185	-0.006981892	0.038502364	0.856103291	84.86877883	23.65371828	788.3386402	1.01E-75	76.23042831	NA	NA	NA
Total Testosterone	MetS	MR Egger	185	0.113944052	0.076207237	0.136588152	84.86877883	23.65371828	NA	NA	NA	-0.004428071	0.002413441	0.068165674
Total Testosterone	MetS	Weighted median	185	0.072053447	0.037636467	0.055561623	84.86877883	23.65371828	NA	NA	NA	NA	NA	NA
Total Testosterone	MetS	Weighted mode	185	0.072965284	0.038710663	0.061021335	84.86877883	23.65371828	NA	NA	NA	NA	NA	NA
Total Testosterone	SBP	Inverse variance weighted	157	-0.531551923	0.337096012	0.114828626	88.68764106	23.65371828	2062.02304	0	92.30019154	NA	NA	NA
Total Testosterone	SBP	MR Egger	157	-1.485104809	0.665225046	0.02701614	88.68764106	23.65371828	NA	NA	NA	0.035500033	0.021391554	0.099029969
Total Testosterone	SBP	Weighted median	157	-0.431612378	0.202881831	0.033386219	88.68764106	23.65371828	NA	NA	NA	NA	NA	NA
Total Testosterone	SBP	Weighted mode	157	-0.672212765	0.214696721	0.002080498	88.68764106	23.65371828	NA	NA	NA	NA	NA	NA
Total Testosterone	T2DM	Inverse variance weighted	117	0.078639319	0.062541892	0.208613784	82.95857477	23.65371828	569.9929843	4.39E-61	79.49839073	NA	NA	NA
Total Testosterone	T2DM	MR Egger	117	-0.038597707	0.141704254	0.78581667	82.95857477	23.65371828	NA	NA	NA	0.003898024	0.004227155	0.358386693
Total Testosterone	T2DM	Weighted median	117	0.024620456	0.053644433	0.64626548	82.95857477	23.65371828	NA	NA	NA	NA	NA	NA
Total Testosterone	T2DM	Weighted mode	117	-3.44E-05	0.080781043	0.999660595	82.95857477	23.65371828	NA	NA	NA	NA	NA	NA
Total Testosterone	Triglycerides	Inverse variance weighted	58	0.292869547	0.113411657	0.009812762	72.59454649	27.99132969	1194.184142	1.95E-212	95.18174409	NA	NA	NA
Total Testosterone	Triglycerides	MR Egger	58	0.505795098	0.314020971	0.112866979	72.59454649	27.99132969	NA	NA	NA	-0.006477615	0.008902775	0.469892722
Total Testosterone	Triglycerides	Weighted median	58	0.049828165	0.041392634	0.22866958	72.59454649	27.99132969	NA	NA	NA	NA	NA	NA
Total Testosterone	Triglycerides	Weighted mode	58	0.048381207	0.062104799	0.439187204	72.59454649	27.99132969	NA	NA	NA	NA	NA	NA
Urate	BMI	Inverse variance weighted	229	-0.089122325	0.029620885	0.002623107	126.707554	29.72735385	4832.620658	0	94.80207741	NA	NA	NA
Urate	BMI	MR Egger	229	0.083490549	0.045717036	0.069126769	126.707554	29.72735385	NA	NA	NA	-0.00530835	0.001104609	2.81E-06
Urate	BMI	Weighted median	229	0.012905648	0.013201689	0.328284277	126.707554	29.72735385	NA	NA	NA	NA	NA	NA
Urate	BMI	Weighted mode	229	0.014285043	0.011480514	0.214671937	126.707554	29.72735385	NA	NA	NA	NA	NA	NA
Urate	DBP	Inverse variance weighted	205	-1.168432625	0.246821612	2.20E-06	122.7790626	29.72735385	3330.397829	0	93.72328215	NA	NA	NA
Urate	DBP	MR Egger	205	-0.431739219	0.409834674	0.293388313	122.7790626	29.72735385	NA	NA	NA	-0.021559435	0.00962727	0.026213742
Urate	DBP	Weighted median	205	-0.48333936	0.133065543	0.000280862	122.7790626	29.72735385	NA	NA	NA	NA	NA	NA
Urate	DBP	Weighted mode	205	-0.416256298	0.106988154	0.000135296	122.7790626	29.72735385	NA	NA	NA	NA	NA	NA
Urate	HbA1c	Inverse variance weighted	99	0.004450389	0.023163387	0.847640132	106.1369885	29.75086661	144.3091654	0.001632982	29.13348804	NA	NA	NA
Urate	HbA1c	MR Egger	99	0.087832033	0.046536743	0.062100351	106.1369885	29.75086661	NA	NA	NA	-0.002019614	0.000982745	0.042559901
Urate	HbA1c	Weighted median	99	0.070958621	0.032442526	0.02872719	106.1369885	29.75086661	NA	NA	NA	NA	NA	NA
Urate	HbA1c	Weighted mode	99	0.057371649	0.032291502	0.078723984	106.1369885	29.75086661	NA	NA	NA	NA	NA	NA
Urate	HDL	Inverse variance weighted	112	0.076140113	0.058481776	0.192934855	111.109648	29.75086661	799.7112912	9.54E-105	85.98186197	NA	NA	NA
Urate	HDL	MR Egger	112	-0.028997849	0.116254522	0.803490148	111.109648	29.75086661	NA	NA	NA	0.002637939	0.002521279	0.297730006
Urate	HDL	Weighted median	112	0.036957133	0.039506343	0.349544384	111.109648	29.75086661	NA	NA	NA	NA	NA	NA
Urate	HDL	Weighted mode	112	0.074887944	0.04230942	0.079471755	111.109648	29.75086661	NA	NA	NA	NA	NA	NA
Urate	LDL	Inverse variance weighted	112	-0.017426214	0.065181853	0.78920152	111.109648	29.75086661	850.662581	2.36E-114	86.92601285	NA	NA	NA
Urate	LDL	MR Egger	112	-0.06928228	0.12988326	0.594819306	111.109648	29.75086661	NA	NA	NA	0.001302732	0.002818902	0.644892487

Urate	LDL	Weighted median	112	-0.016568156	0.049274504	0.736688411	111.109648	29.75086661	NA	NA	NA	NA	NA	NA
Urate	LDL	Weighted mode	112	-0.026899869	0.05988961	0.654193768	111.109648	29.75086661	NA	NA	NA	NA	NA	NA
Urate	MetS	Inverse variance weighted	262	0.309804977	0.049063857	2.71E-10	114.1605273	29.72482214	1421.306799	9.79E-159	79.81192698	NA	NA	NA
Urate	MetS	MR Egger	262	-0.014219573	0.079132998	0.857534278	114.1605273	29.72482214	NA	NA	NA	0.009176667	0.001805427	7.11E-07
Urate	MetS	Weighted median	262	0.085058525	0.044013613	0.053291609	114.1605273	29.72482214	NA	NA	NA	NA	NA	NA
Urate	MetS	Weighted mode	262	0.052895118	0.039124145	0.177551646	114.1605273	29.72482214	NA	NA	NA	NA	NA	NA
Urate	SBP	Inverse variance weighted	205	-1.818709774	0.384833233	2.29E-06	122.7790626	29.72735385	2667.258747	0	92.21963939	NA	NA	NA
Urate	SBP	MR Egger	205	-0.853710952	0.641855049	0.184988236	122.7790626	29.72735385	NA	NA	NA	-0.028194636	0.015059736	0.062618776
Urate	SBP	Weighted median	205	-0.630869946	0.279626635	0.024063407	122.7790626	29.72735385	NA	NA	NA	NA	NA	NA
Urate	SBP	Weighted mode	205	-0.734227571	0.205985179	0.000454063	122.7790626	29.72735385	NA	NA	NA	NA	NA	NA
Urate	T2DM	Inverse variance weighted	159	-0.177134623	0.080408972	0.027600308	117.3179742	29.7425998	1025.25764	5.63E-127	83.60354311	NA	NA	NA
Urate	T2DM	MR Egger	159	0.215474478	0.146510733	0.143371512	117.3179742	29.7425998	NA	NA	NA	-0.010235396	0.003229946	0.001839579
Urate	T2DM	Weighted median	159	-0.087673665	0.05713401	0.124900126	117.3179742	29.7425998	NA	NA	NA	NA	NA	NA
Urate	T2DM	Weighted mode	159	-0.117411307	0.050197619	0.020588346	117.3179742	29.7425998	NA	NA	NA	NA	NA	NA
Urate	Triglycerides	Inverse variance weighted	112	-0.299437198	0.073672444	4.81E-05	111.109648	29.75086661	1338.80993	1.22E-209	91.51176746	NA	NA	NA
Urate	Triglycerides	MR Egger	112	-0.502581177	0.145312196	0.000773292	111.109648	29.75086661	NA	NA	NA	0.005107327	0.003156821	0.108554561
Urate	Triglycerides	Weighted median	112	-0.072794636	0.044724364	0.103603748	111.109648	29.75086661	NA	NA	NA	NA	NA	NA
Urate	Triglycerides	Weighted mode	112	0.000569954	0.047758304	0.990499583	111.109648	29.75086661	NA	NA	NA	NA	NA	NA
Urea	BMI	Inverse variance weighted	157	0.003811718	0.034175957	0.911194375	77.61263976	29.82428679	2529.294515	0	93.7072186	NA	NA	NA
Urea	BMI	MR Egger	157	0.144324362	0.086224157	0.096181316	77.61263976	29.82428679	NA	NA	NA	-0.003308154	0.001866097	0.078231704
Urea	BMI	Weighted median	157	0.004138227	0.016919938	0.806783996	77.61263976	29.82428679	NA	NA	NA	NA	NA	NA
Urea	BMI	Weighted mode	157	-0.012173554	0.02335999	0.60301632	77.61263976	29.82428679	NA	NA	NA	NA	NA	NA
Urea	DBP	Inverse variance weighted	133	-0.727714663	0.315046243	0.020895564	75.40850114	29.82428679	1914.229285	1.61148891521861e -313	93.09678544	NA	NA	NA
Urea	DBP	MR Egger	133	-1.001819761	0.792473353	0.208414303	75.40850114	29.82428679	NA	NA	NA	0.006344164	0.016819759	0.706646328
Urea	DBP	Weighted median	133	-0.42773291	0.181630223	0.018524425	75.40850114	29.82428679	NA	NA	NA	NA	NA	NA
Urea	DBP	Weighted mode	133	-0.331922238	0.42498789	0.436191687	75.40850114	29.82428679	NA	NA	NA	NA	NA	NA
Urea	HbA1c	Inverse variance weighted	66	-0.041205979	0.030436662	0.175791528	68.08322328	29.82428679	87.27686269	0.034093064	22.62771836	NA	NA	NA
Urea	HbA1c	MR Egger	66	0.098400972	0.093463829	0.296380424	68.08322328	29.82428679	NA	NA	NA	-0.002760249	0.001749516	0.119559963
Urea	HbA1c	Weighted median	66	-0.015743642	0.039090405	0.687132495	68.08322328	29.82428679	NA	NA	NA	NA	NA	NA
Urea	HbA1c	Weighted mode	66	-0.024233658	0.067093631	0.719127556	68.08322328	29.82428679	NA	NA	NA	NA	NA	NA
Urea	HDL	Inverse variance weighted	71	0.015151444	0.069487023	0.827392413	76.08361263	29.82428679	382.1878727	1.53E-44	81.68321499	NA	NA	NA
Urea	HDL	MR Egger	71	0.002460771	0.20238095	0.990333765	76.08361263	29.82428679	NA	NA	NA	0.000266734	0.003991219	0.946910229
Urea	HDL	Weighted median	71	0.015042521	0.054834869	0.783835637	76.08361263	29.82428679	NA	NA	NA	NA	NA	NA
Urea	HDL	Weighted mode	71	0.027171636	0.085588349	0.751832899	76.08361263	29.82428679	NA	NA	NA	NA	NA	NA
Urea	LDL	Inverse variance weighted	71	0.112027982	0.057350006	0.050771224	76.08361263	29.82428679	222.9557784	7.51E-18	68.49922342	NA	NA	NA
Urea	LDL	MR Egger	71	0.037221135	0.166468963	0.823735433	76.08361263	29.82428679	NA	NA	NA	0.001573009	0.003283694	0.633427408
Urea	LDL	Weighted median	71	0.033471279	0.057078942	0.557604541	76.08361263	29.82428679	NA	NA	NA	NA	NA	NA
Urea	LDL	Weighted mode	71	-0.020972402	0.094307919	0.824663946	76.08361263	29.82428679	NA	NA	NA	NA	NA	NA
Urea	MetS	Inverse variance weighted	176	0.133802637	0.055175292	0.015306435	76.44505595	29.82428679	747.5182794	9.29E-72	76.39126325	NA	NA	NA
Urea	MetS	MR Egger	176	-0.026458884	0.143157995	0.853583145	76.44505595	29.82428679	NA	NA	NA	0.003743088	0.003086022	0.226805646
Urea	MetS	Weighted median	176	0.130494034	0.046240331	0.004771288	76.44505595	29.82428679	NA	NA	NA	NA	NA	NA
Urea	MetS	Weighted mode	176	0.120265587	0.074247284	0.107076364	76.44505595	29.82428679	NA	NA	NA	NA	NA	NA
Urea	SBP	Inverse variance weighted	134	-1.025857395	0.583405788	0.078680447	75.1448482	29.82428679	2194.297581	0	93.93504493	NA	NA	NA
Urea	SBP	MR Egger	134	-1.412875127	1.468828519	0.337855535	75.1448482	29.82428679	NA	NA	NA	0.008947193	0.031143115	0.774338636
Urea	SBP	Weighted median	134	-0.755761418	0.33381802	0.02357459	75.1448482	29.82428679	NA	NA	NA	NA	NA	NA
Urea	SBP	Weighted mode	134	-0.267612057	0.62166787	0.667547407	75.1448482	29.82428679	NA	NA	NA	NA	NA	NA
Urea	T2DM	Inverse variance weighted	113	0.019017643	0.091210365	0.834836168	77.75373445	29.82428679	600.1221918	8.23E-68	80.53638905	NA	NA	NA
Urea	T2DM	MR Egger	113	0.527421706	0.249642437	0.036867416	77.75373445	29.82428679	NA	NA	NA	-0.011349829	0.005200797	0.031192812
Urea	T2DM	Weighted median	113	0.086154566	0.068280464	0.20702985	77.75373445	29.82428679	NA	NA	NA	NA	NA	NA
Urea	T2DM	Weighted mode	113	0.122233735	0.108553228	0.262561614	77.75373445	29.82428679	NA	NA	NA	NA	NA	NA
Urea	Triglycerides	Inverse variance weighted	71	-0.23429494	0.123228878	0.057262862	76.08361263	29.82428679	1264.482909	1.60E-218	94.42930663	NA	NA	NA
Urea	Triglycerides	MR Egger	71	-0.454805384	0.356795801	0.206693591	76.08361263	29.82428679	NA	NA	NA	0.004638843	0.007040089	0.512141254
Urea	Triglycerides	Weighted median	71	-0.00497977	0.055394908	0.928370009	76.08361263	29.82428679	NA	NA	NA	NA	NA	NA
Urea	Triglycerides	Weighted mode	71	-0.07869097	0.103575155	0.449956677	76.08361263	29.82428679	NA	NA	NA	NA	NA	NA
Urinary Albumin Excretion	BMI	Inverse variance weighted	31	0.139997857	0.089869269	0.11928196	53.71729284	30.29627376	286.5182052	1.18E-43	88.25927704	NA	NA	NA
Urinary Albumin Excretion	BMI	MR Egger	31	-0.226891429	0.213807591	0.297359758	53.71729284	30.29627376	NA	NA	NA	0.005828078	0.003107259	0.070805919
Urinary Albumin Excretion	BMI	Weighted median	31	-0.014034252	0.052863915	0.790640588	53.71729284	30.29627376	NA	NA	NA	NA	NA	NA

Urinary Albumin Excretion	BMI	Weighted mode	31	0.010719954	0.057302619	0.852860374	53.71729284	30.29627376	NA	NA	NA	NA	NA	NA
Urinary Albumin Excretion	DBP	Inverse variance weighted	27	-2.201289497	1.008762715	0.029097152	53.31490108	30.29627376	347.112321	7.07E-58	89.83691213	NA	NA	NA
Urinary Albumin Excretion	DBP	MR Egger	27	4.364543649	2.369112048	0.077327912	53.31490108	30.29627376	NA	NA	NA	-0.100220632	0.033555391	0.006233768
Urinary Albumin Excretion	DBP	Weighted median	27	-1.245815584	0.597571055	0.037087543	53.31490108	30.29627376	NA	NA	NA	NA	NA	NA
Urinary Albumin Excretion	DBP	Weighted mode	27	-1.110731119	0.646796267	0.097818676	53.31490108	30.29627376	NA	NA	NA	NA	NA	NA
Urinary Albumin Excretion	HbA1c	Inverse variance weighted	15	-0.065581522	0.081558045	0.421334281	64.82442738	30.29627376	18.78855153	0.173187155	19.9680562	NA	NA	NA
Urinary Albumin Excretion	HbA1c	MR Egger	15	0.1207326	0.206698467	0.569150415	64.82442738	30.29627376	NA	NA	NA	-0.003073166	0.003132001	0.344395725
Urinary Albumin Excretion	HbA1c	Weighted median	15	-0.048211762	0.100449678	0.631256298	64.82442738	30.29627376	NA	NA	NA	NA	NA	NA
Urinary Albumin Excretion	HbA1c	Weighted mode	15	-0.023449818	0.113980987	0.839959932	64.82442738	30.29627376	NA	NA	NA	NA	NA	NA
Urinary Albumin Excretion	HDL	Inverse variance weighted	18	-0.039487023	0.201174023	0.844388736	60.02660642	30.29627376	93.25573728	1.55E-12	81.77037319	NA	NA	NA
Urinary Albumin Excretion	HDL	MR Egger	18	-0.032881496	0.557816126	0.95372441	60.02660642	30.29627376	NA	NA	NA	-0.000101778	0.007978863	0.989980236
Urinary Albumin Excretion	HDL	Weighted median	18	0.032555925	0.145562858	0.82302542	60.02660642	30.29627376	NA	NA	NA	NA	NA	NA
Urinary Albumin Excretion	HDL	Weighted mode	18	-0.028676193	0.16995714	0.868003392	60.02660642	30.29627376	NA	NA	NA	NA	NA	NA
Urinary Albumin Excretion	LDL	Inverse variance weighted	18	-0.078875857	0.1027591	0.442736596	60.02660642	30.29627376	20.78804996	0.235914668	17.7078112	NA	NA	NA
Urinary Albumin Excretion	LDL	MR Egger	18	0.004667921	0.283714106	0.987076494	60.02660642	30.29627376	NA	NA	NA	-0.001288954	0.004062836	0.755152591
Urinary Albumin Excretion	LDL	Weighted median	18	-0.008231709	0.131571824	0.950113397	60.02660642	30.29627376	NA	NA	NA	NA	NA	NA
Urinary Albumin Excretion	LDL	Weighted mode	18	-0.162175113	0.18268426	0.387071392	60.02660642	30.29627376	NA	NA	NA	NA	NA	NA
Urinary Albumin Excretion	MetS	Inverse variance weighted	31	0.122267431	0.236517216	0.605191487	53.71729284	30.29627376	182.0629219	1.06E-23	83.48420449	NA	NA	NA
Urinary Albumin Excretion	MetS	MR Egger	31	-0.018284781	0.59440122	0.975670336	53.71729284	30.29627376	NA	NA	NA	0.002235037	0.008645339	0.797827755
Urinary Albumin Excretion	MetS	Weighted median	31	-0.140736869	0.173534441	0.417364225	53.71729284	30.29627376	NA	NA	NA	NA	NA	NA
Urinary Albumin Excretion	MetS	Weighted mode	31	-0.403428735	0.293663741	0.179689635	53.71729284	30.29627376	NA	NA	NA	NA	NA	NA
Urinary Albumin Excretion	SBP	Inverse variance weighted	26	-4.756105387	1.711342798	0.00544987	53.85139303	30.29627376	308.9883875	9.41E-51	88.03875258	NA	NA	NA
Urinary Albumin Excretion	SBP	MR Egger	26	7.793033909	3.972509443	0.061491504	53.85139303	30.29627376	NA	NA	NA	-0.188442179	0.055615713	0.002426407
Urinary Albumin Excretion	SBP	Weighted median	26	-3.088299681	1.085140838	0.004427362	53.85139303	30.29627376	NA	NA	NA	NA	NA	NA
Urinary Albumin Excretion	SBP	Weighted mode	26	-1.617726458	1.178108773	0.181895587	53.85139303	30.29627376	NA	NA	NA	NA	NA	NA
Urinary Albumin Excretion	T2DM	Inverse variance weighted	23	-0.374590951	0.265644536	0.158503944	52.8698448	30.29627376	84.75423569	2.63E-09	70.60524165	NA	NA	NA
Urinary Albumin Excretion	T2DM	MR Egger	23	0.666635423	0.674642076	0.334337326	52.8698448	30.29627376	NA	NA	NA	-0.015763888	0.009453056	0.11024055
Urinary Albumin Excretion	T2DM	Weighted median	23	-0.036426551	0.216383126	0.866313568	52.8698448	30.29627376	NA	NA	NA	NA	NA	NA
Urinary Albumin Excretion	T2DM	Weighted mode	23	0.079543558	0.250667604	0.753987607	52.8698448	30.29627376	NA	NA	NA	NA	NA	NA
Urinary Albumin Excretion	Triglycerides	Inverse variance weighted	18	-0.052549166	0.101745891	0.605522994	60.02660642	30.29627376	25.54444371	0.0831699	33.42415174	NA	NA	NA
Urinary Albumin Excretion	Triglycerides	MR Egger	18	-0.072715875	0.279637485	0.79815245	60.02660642	30.29627376	NA	NA	NA	0.000312476	0.004016731	0.938956806

Urinary Albumin Excretion	Triglycerides	Weighted median	18	0	0.120200657	1	60.02660642	30.29627376	NA	NA	NA	NA	NA	NA
Urinary Albumin Excretion	Triglycerides	Weighted mode	18	-0.044720149	0.171426572	0.797326167	60.02660642	30.29627376	NA	NA	NA	NA	NA	NA
Water Consumption	BMI	Inverse variance weighted	41	-0.07797175	0.081753009	0.340211331	41.78297824	29.75020792	1977.803212	0	97.88715811	NA	NA	NA
Water Consumption	BMI	MR Egger	41	0.458299669	0.414176391	0.275274923	41.78297824	29.75020792	NA	NA	NA	-0.016081053	0.012179966	0.194435704
Water Consumption	BMI	Weighted median	41	-0.026458512	0.027499335	0.335973774	41.78297824	29.75020792	NA	NA	NA	NA	NA	NA
Water Consumption	BMI	Weighted mode	41	-0.047355678	0.065854264	0.476260736	41.78297824	29.75020792	NA	NA	NA	NA	NA	NA
Water Consumption	DBP	Inverse variance weighted	38	0.157038226	0.299279529	0.599777222	42.4009009	29.75020792	296.4296784	3.16E-42	87.49596917	NA	NA	NA
Water Consumption	DBP	MR Egger	38	-0.228581287	1.555504213	0.883991397	42.4009009	29.75020792	NA	NA	NA	0.011725196	0.046390028	0.801897142
Water Consumption	DBP	Weighted median	38	0.519855567	0.184707544	0.004885632	42.4009009	29.75020792	NA	NA	NA	NA	NA	NA
Water Consumption	DBP	Weighted mode	38	0.510888998	0.269393424	0.065730237	42.4009009	29.75020792	NA	NA	NA	NA	NA	NA
Water Consumption	HbA1c	Inverse variance weighted	21	0.022759813	0.036348433	0.531212192	46.90395713	31.07647237	33.51244338	0.029618313	38.49164424	NA	NA	NA
Water Consumption	HbA1c	MR Egger	21	0.157852259	0.180804555	0.393533739	46.90395713	31.07647237	NA	NA	NA	-0.004204982	0.005510472	0.4547812
Water Consumption	HbA1c	Weighted median	21	0.038680753	0.042866388	0.366867655	46.90395713	31.07647237	NA	NA	NA	NA	NA	NA
Water Consumption	HbA1c	Weighted mode	21	0.061737515	0.07202782	0.40152504	46.90395713	31.07647237	NA	NA	NA	NA	NA	NA
Water Consumption	HDL	Inverse variance weighted	22	0.142786215	0.10588874	0.177512042	46.73725884	31.46439873	202.3014413	1.28E-31	89.61398718	NA	NA	NA
Water Consumption	HDL	MR Egger	22	0.092092698	0.505844811	0.857370436	46.73725884	31.46439873	NA	NA	NA	0.001628702	0.015873911	0.919300282
Water Consumption	HDL	Weighted median	22	0.073360852	0.060889534	0.228273278	46.73725884	31.46439873	NA	NA	NA	NA	NA	NA
Water Consumption	HDL	Weighted mode	22	0.100423878	0.08717049	0.262251635	46.73725884	31.46439873	NA	NA	NA	NA	NA	NA
Water Consumption	LDL	Inverse variance weighted	22	-0.126148449	0.237884686	0.595909192	46.73725884	31.46439873	871.0613979	7.54E-171	97.58421695	NA	NA	NA
Water Consumption	LDL	MR Egger	22	-0.349617596	1.131389891	0.760505414	46.73725884	31.46439873	NA	NA	NA	0.007200468	0.035600475	0.841758538
Water Consumption	LDL	Weighted median	22	0.062144621	0.054711246	0.256012833	46.73725884	31.46439873	NA	NA	NA	NA	NA	NA
Water Consumption	LDL	Weighted mode	22	0.074446763	0.075447345	0.335004469	46.73725884	31.46439873	NA	NA	NA	NA	NA	NA
Water Consumption	MetS	Inverse variance weighted	43	0.16805338	0.114660644	0.142741265	41.77455394	29.75020792	392.4281281	2.00E-58	89.29696248	NA	NA	NA
Water Consumption	MetS	MR Egger	43	0.19248534	0.605777392	0.752287832	41.77455394	29.75020792	NA	NA	NA	-0.000733555	0.01785124	0.967421495
Water Consumption	MetS	Weighted median	43	0.119221591	0.066608006	0.073470178	41.77455394	29.75020792	NA	NA	NA	NA	NA	NA
Water Consumption	MetS	Weighted mode	43	0.22606753	0.133836741	0.098606478	41.77455394	29.75020792	NA	NA	NA	NA	NA	NA
Water Consumption	SBP	Inverse variance weighted	38	0.188067009	0.467568098	0.687519341	42.4009009	29.75020792	238.8610004	2.37E-31	84.38856809	NA	NA	NA
Water Consumption	SBP	MR Egger	38	-1.075552094	2.426776672	0.660271769	42.4009009	29.75020792	NA	NA	NA	0.038405503	0.072348071	0.59878715
Water Consumption	SBP	Weighted median	38	0.761968114	0.354984835	0.031834643	42.4009009	29.75020792	NA	NA	NA	NA	NA	NA
Water Consumption	SBP	Weighted mode	38	1.238428195	0.51692147	0.021757501	42.4009009	29.75020792	NA	NA	NA	NA	NA	NA
Water Consumption	T2DM	Inverse variance weighted	33	-0.151228893	0.163834367	0.355976124	40.22478662	29.75020792	313.0667715	7.32E-48	89.76947482	NA	NA	NA
Water Consumption	T2DM	MR Egger	33	-0.310135444	0.972783105	0.752006925	40.22478662	29.75020792	NA	NA	NA	0.004612887	0.027822739	0.869394401
Water Consumption	T2DM	Weighted median	33	-0.0603863	0.089304072	0.498921592	40.22478662	29.75020792	NA	NA	NA	NA	NA	NA
Water Consumption	T2DM	Weighted mode	33	-0.034991137	0.165626551	0.834019996	40.22478662	29.75020792	NA	NA	NA	NA	NA	NA
Water Consumption	Triglycerides	Inverse variance weighted	22	-0.230415322	0.17201253	0.18039937	46.73725884	31.46439873	564.8237995	3.93E-106	96.27534475	NA	NA	NA
Water Consumption	Triglycerides	MR Egger	22	-0.079754826	0.813967312	0.922921266	46.73725884	31.46439873	NA	NA	NA	-0.004853572	0.025601141	0.85154582
Water Consumption	Triglycerides	Weighted median	22	-0.076661832	0.064601585	0.235351283	46.73725884	31.46439873	NA	NA	NA	NA	NA	NA
Water Consumption	Triglycerides	Weighted mode	22	-0.095681611	0.113122447	0.407186147	46.73725884	31.46439873	NA	NA	NA	NA	NA	NA
x_11440	BMI	Inverse variance weighted	3	-0.023578849	0.015514935	0.128573384	240.4535011	32.18825489	1.381663896	0.501158957	0	NA	NA	NA
x_11440	BMI	MR Egger	3	-0.045484134	0.024260309	0.31193945	240.4535011	32.18825489	NA	NA	NA	0.002669201	0.002272626	0.449021379
x_11440	BMI	Weighted median	3	-0.025385705	0.015802101	0.108169244	240.4535011	32.18825489	NA	NA	NA	NA	NA	NA
x_11440	BMI	Weighted mode	3	-0.028229311	0.015266935	0.205690864	240.4535011	32.18825489	NA	NA	NA	NA	NA	NA
x_11440	DBP	Inverse variance weighted	3	-0.25997168	0.137673129	0.058982266	240.4535011	32.18825489	0.470303017	0.790451081	0	NA	NA	NA
x_11440	DBP	MR Egger	3	-0.372629579	0.21466427	0.332726263	240.4535011	32.18825489	NA	NA	NA	0.013610331	0.019897879	0.618083507
x_11440	DBP	Weighted median	3	-0.272451267	0.144550026	0.059453689	240.4535011	32.18825489	NA	NA	NA	NA	NA	NA
x_11440	DBP	Weighted mode	3	-0.282395064	0.148227966	0.197047691	240.4535011	32.18825489	NA	NA	NA	NA	NA	NA
x_11440	HbA1c	Inverse variance weighted	3	0.038072843	0.027823431	0.171195215	240.4535011	32.18825489	0.72102132	0.697320142	0	NA	NA	NA
x_11440	HbA1c	MR Egger	3	0.044570816	0.043356332	0.491207319	240.4535011	32.18825489	NA	NA	NA	-0.000789685	0.004040922	0.877138923
x_11440	HbA1c	Weighted median	3	0.042459745	0.028261497	0.132996839	240.4535011	32.18825489	NA	NA	NA	NA	NA	NA
x_11440	HbA1c	Weighted mode	3	0.04330353	0.028950825	0.273362813	240.4535011	32.18825489	NA	NA	NA	NA	NA	NA
x_11440	HDL	Inverse variance weighted	3	-0.065877786	0.090649263	0.4673897	240.4535011	32.18825489	11.18574983	0.003724305	0	NA	NA	NA
x_11440	HDL	MR Egger	3	0.068917414	0.055981018	0.434296181	240.4535011	32.18825489	NA	NA	NA	-0.013901351	0.00420767	0.18711166
x_11440	HDL	Weighted median	3	-0.030938757	0.040897196	0.449349063	240.4535011	32.18825489	NA	NA	NA	NA	NA	NA
x_11440	HDL	Weighted mode	3	-0.021907947	0.040160099	0.640109039	240.4535011	32.18825489	NA	NA	NA	NA	NA	NA
x_11440	LDL	Inverse variance weighted	3	-0.041236178	0.078856819	0.601026655	240.4535011	32.18825489	7.154906812	0.027946777	0	NA	NA	NA
x_11440	LDL	MR Egger	3	-0.159654446	0.060920462	0.23206337	240.4535011	32.18825489	NA	NA	NA	0.012200956	0.004576652	0.228459677
x_11440	LDL	Weighted median	3	-0.065959108	0.042410256	0.119883408	240.4535011	32.18825489	NA	NA	NA	NA	NA	NA
x_11440	LDL	Weighted mode	3	-0.078010157	0.046897314	0.238129047	240.4535011	32.18825489	NA	NA	NA	NA	NA	NA
x_11440	MetS	Inverse variance weighted	3	-0.038074935	0.08108347	0.638657242	240.4535011	32.18825489	5.011936154	0.081596568	4.178970104	NA	NA	NA
x_11440	MetS	MR Egger	3	0.067280132	0.115746464	0.664797551	240.4535011	32.18825489	NA	NA	NA	-0.012849555	0.010855033	0.446560198

x_11440	MetS	Weighted median	3	-0.026534276	0.052087327	0.610458532	240.4535011	32.18825489	NA	NA	NA	NA	NA	NA
x_11440	MetS	Weighted mode	3	-0.004519162	0.055161044	0.942166044	240.4535011	32.18825489	NA	NA	NA	NA	NA	NA
x_11440	SBP	Inverse variance weighted	3	-0.321032676	0.23801476	0.177403418	240.4535011	32.18825489	1.491238286	0.474440462	0	NA	NA	NA
x_11440	SBP	MR Egger	3	-0.50643093	0.384807861	0.413656909	240.4535011	32.18825489	NA	NA	NA	0.022511806	0.035904568	0.643474423
x_11440	SBP	Weighted median	3	-0.339698936	0.242773189	0.161739817	240.4535011	32.18825489	NA	NA	NA	NA	NA	NA
x_11440	SBP	Weighted mode	3	-0.345066633	0.246168088	0.296029264	240.4535011	32.18825489	NA	NA	NA	NA	NA	NA
x_11440	T2DM	Inverse variance weighted	3	0.023388345	0.101062551	0.816985073	240.4535011	32.18825489	5.370732076	0.068196227	0	NA	NA	NA
x_11440	T2DM	MR Egger	3	0.188045902	0.094450917	0.296325266	240.4535011	32.18825489	NA	NA	NA	-0.019388944	0.008423698	0.260921789
x_11440	T2DM	Weighted median	3	0.04757565	0.065820833	0.46979948	240.4535011	32.18825489	NA	NA	NA	NA	NA	NA
x_11440	T2DM	Weighted mode	3	0.058118504	0.068969125	0.488121294	240.4535011	32.18825489	NA	NA	NA	NA	NA	NA
x_11440	Triglycerides	Inverse variance weighted	3	-0.035694788	0.133607449	0.789344694	240.4535011	32.18825489	25.83653612	2.45E-06	0	NA	NA	NA
x_11440	Triglycerides	MR Egger	3	-0.237020553	0.054334434	0.143459606	240.4535011	32.18825489	NA	NA	NA	0.020730986	0.004080607	0.123728031
x_11440	Triglycerides	Weighted median	3	-0.079105105	0.041255169	0.055179616	240.4535011	32.18825489	NA	NA	NA	NA	NA	NA
x_11440	Triglycerides	Weighted mode	3	-0.099122958	0.039446303	0.128532802	240.4535011	32.18825489	NA	NA	NA	NA	NA	NA

Supplementary Table 4.6 - Metabolic Traits Effects on Candidate Biomarkers (MR)

Exposure	Outcome	Method	nSNP	Beta	SE	P-Value	F Stat (Mean)	F Stat (Min)	Q Stat	Q Stat P-Value	I^2	Egger Intercept	Egger Intercept SE	Egger Intercept P-Value
BMI	Bilirubin	Inverse variance weighted	75	0.037821343	0.023424402	0.106394543	156.7	85.3	82.38	0.2362	10.2	NA	NA	NA
BMI	Bilirubin	MR Egger	75	0.030933314	0.067835388	0.649739685	156.7	85.3	NA	NA	NA	0.000207	0.001908	0.9141
BMI	Bilirubin	Weighted median	75	0.0339413	0.036097588	0.347081621	156.7	85.3	NA	NA	NA	NA	NA	NA
BMI	Bilirubin	Weighted mode	75	0.052759059	0.055618703	0.34591942	156.7	85.3	NA	NA	NA	NA	NA	NA
BMI	Blood Urea Nitrogen	Inverse variance weighted	75	-0.132230565	0.035576083	0.000201731	156.7	85.3	275.46	0	73.1	NA	NA	NA
BMI	Blood Urea Nitrogen	MR Egger	75	-0.428095703	0.096213024	3.03E-05	156.7	85.3	NA	NA	NA	0.008872	0.002705	0.0016
BMI	Blood Urea Nitrogen	Weighted median	75	-0.080596913	0.035416522	0.022864759	156.7	85.3	NA	NA	NA	NA	NA	NA
BMI	Blood Urea Nitrogen	Weighted mode	75	-0.052566576	0.076842994	0.496062853	156.7	85.3	NA	NA	NA	NA	NA	NA
BMI	CRP	Inverse variance weighted	41	-0.479013168	0.134896849	0.00038383	146.4	85.3	1249.42	0	96.8	NA	NA	NA
BMI	CRP	MR Egger	41	-0.303789219	0.430534446	0.48462459	146.4	85.3	NA	NA	NA	-0.00491	0.011443	0.6702
BMI	CRP	Weighted median	41	-0.396925473	0.039772961	1.87E-23	146.4	85.3	NA	NA	NA	NA	NA	NA
BMI	CRP	Weighted mode	41	-0.385223052	0.05508384	1.92E-08	146.4	85.3	NA	NA	NA	NA	NA	NA
BMI	Coffee Consumption	Inverse variance weighted	100	-0.138708555	0.014816641	7.85E-21	150.7	85.3	490.96	0	79.8	NA	NA	NA
BMI	Coffee Consumption	MR Egger	100	-0.291352211	0.037667821	9.29E-12	150.7	85.3	NA	NA	NA	0.004564	0.00105	0
BMI	Coffee Consumption	Weighted median	100	-0.152087886	0.013679532	1.03E-28	150.7	85.3	NA	NA	NA	NA	NA	NA
BMI	Coffee Consumption	Weighted mode	100	-0.23383983	0.023743074	2.34E-16	150.7	85.3	NA	NA	NA	NA	NA	NA
BMI	Cotinine	Inverse variance weighted	100	-0.052355469	0.008974231	5.41E-09	150.7	85.3	362.24	0	72.7	NA	NA	NA
BMI	Cotinine	MR Egger	100	-0.042621199	0.024890472	0.089994755	150.7	85.3	NA	NA	NA	-0.000291	0.000694	0.6757
BMI	Cotinine	Weighted median	100	-0.057652769	0.008996813	1.47E-10	150.7	85.3	NA	NA	NA	NA	NA	NA
BMI	Cotinine	Weighted mode	100	-0.092179009	0.03967038	0.0221907	150.7	85.3	NA	NA	NA	NA	NA	NA
BMI	Creatinine	Inverse variance weighted	99	0.091137106	0.020791868	1.17E-05	150.8	85.3	467.14	0	79	NA	NA	NA
BMI	Creatinine	MR Egger	99	0.005884015	0.056677562	0.917530033	150.8	85.3	NA	NA	NA	0.002554	0.001581	0.1096
BMI	Creatinine	Weighted median	99	0.063633931	0.018732216	0.000681211	150.8	85.3	NA	NA	NA	NA	NA	NA
BMI	Creatinine	Weighted mode	99	-0.025718503	0.076243079	0.736595233	150.8	85.3	NA	NA	NA	NA	NA	NA
BMI	Cystatin C	Inverse variance weighted	42	0.068469304	0.014633519	2.88E-06	142.8	85.3	56.98	0.0497	28	NA	NA	NA
BMI	Cystatin C	MR Egger	42	0.059011034	0.049685665	0.241961525	142.8	85.3	NA	NA	NA	0.000256	0.001281	0.8429
BMI	Cystatin C	Weighted median	42	0.04696998	0.019368749	0.015306722	142.8	85.3	NA	NA	NA	NA	NA	NA
BMI	Cystatin C	Weighted mode	42	0.045938127	0.030979322	0.145757094	142.8	85.3	NA	NA	NA	NA	NA	NA
BMI	Fresh Fruit Consumption	Inverse variance weighted	91	-0.209187535	0.040346062	2.16E-07	154	85.3	379.34	0	76.3	NA	NA	NA
BMI	Fresh Fruit Consumption	MR Egger	91	-0.435638315	0.105960364	8.74E-05	154	85.3	NA	NA	NA	0.006927	0.003008	0.0236
BMI	Fresh Fruit Consumption	Weighted median	91	-0.202908914	0.038062009	9.77E-08	154	85.3	NA	NA	NA	NA	NA	NA
BMI	Fresh Fruit Consumption	Weighted mode	91	-0.198443059	0.070721064	0.006147543	154	85.3	NA	NA	NA	NA	NA	NA
BMI	Gamma Glutamyl Transferase	Inverse variance weighted	75	-0.066955756	0.025580918	0.008859978	156.7	85.3	107.33	0.0069	31.1	NA	NA	NA
BMI	Gamma Glutamyl Transferase	MR Egger	75	0.137214556	0.069547718	0.052287441	156.7	85.3	NA	NA	NA	-0.006124	0.001956	0.0025
BMI	Gamma Glutamyl Transferase	Weighted median	75	-0.049508475	0.035977482	0.168791865	156.7	85.3	NA	NA	NA	NA	NA	NA
BMI	Gamma Glutamyl Transferase	Weighted mode	75	0.036311954	0.053247868	0.497404609	156.7	85.3	NA	NA	NA	NA	NA	NA
BMI	Impedance of Arm (Left)	Inverse variance weighted	99	-0.433750069	0.018691934	4.03E-119	150.8	85.3	679.27	0	85.6	NA	NA	NA
BMI	Impedance of Arm (Left)	MR Egger	99	-0.504779717	0.051046393	2.33E-16	150.8	85.3	NA	NA	NA	0.002128	0.001424	0.1384
BMI	Impedance of Arm (Left)	Weighted median	99	-0.432370774	0.015370393	4.20E-174	150.8	85.3	NA	NA	NA	NA	NA	NA
BMI	Impedance of Arm (Left)	Weighted mode	99	-0.458160366	0.023980825	8.16E-35	150.8	85.3	NA	NA	NA	NA	NA	NA
BMI	Impedance of Arm (Right)	Inverse variance weighted	99	-0.425164351	0.018173197	4.79E-121	150.8	85.3	647.55	0	84.9	NA	NA	NA
BMI	Impedance of Arm (Right)	MR Egger	99	-0.482587195	0.049805763	6.28E-16	150.8	85.3	NA	NA	NA	0.00172	0.00139	0.2188
BMI	Impedance of Arm (Right)	Weighted median	99	-0.415905446	0.015400845	1.28E-160	150.8	85.3	NA	NA	NA	NA	NA	NA
BMI	Impedance of Arm (Right)	Weighted mode	99	-0.438299481	0.02724721	3.00E-29	150.8	85.3	NA	NA	NA	NA	NA	NA
BMI	Overall Healthy Diet	Inverse variance weighted	100	-0.002488779	0.009430559	0.791852515	150.7	85.3	112.89	0.1607	12.3	NA	NA	NA
BMI	Overall Healthy Diet	MR Egger	100	0.013759416	0.026077204	0.598940773	150.7	85.3	NA	NA	NA	-0.000486	0.000727	0.5053
BMI	Overall Healthy Diet	Weighted median	100	-0.008193611	0.013960104	0.557250359	150.7	85.3	NA	NA	NA	NA	NA	NA
BMI	Overall Healthy Diet	Weighted mode	100	-0.014671954	0.021951951	0.505454883	150.7	85.3	NA	NA	NA	NA	NA	NA
BMI	Peak Expiratory Flow	Inverse variance weighted	99	-0.013100893	0.017060649	0.442545873	150.8	85.3	356.2	0	72.5	NA	NA	NA
BMI	Peak Expiratory Flow	MR Egger	99	0.092682707	0.045701331	0.045301509	150.8	85.3	NA	NA	NA	-0.003168	0.001275	0.0147
BMI	Peak Expiratory Flow	Weighted median	99	0.026761166	0.016641733	0.107818597	150.8	85.3	NA	NA	NA	NA	NA	NA
BMI	Peak Expiratory Flow	Weighted mode	99	0.051251935	0.023582756	0.03216883	150.8	85.3	NA	NA	NA	NA	NA	NA

BMI	Potassium in Urine	Inverse variance weighted	99	0.049384674	0.01668073	0.00307058	150.8	85.3	267.42	0	63.4	NA	NA	NA
BMI	Potassium in Urine	MR Egger	99	0.051398854	0.046076797	0.267390438	150.8	85.3	NA	NA	NA	-6.00E-05	0.001286	0.9627
BMI	Potassium in Urine	Weighted median	99	0.048736687	0.017748925	0.006034603	150.8	85.3	NA	NA	NA	NA	NA	NA
BMI	Potassium in Urine	Weighted mode	99	0.077154698	0.029758078	0.010978304	150.8	85.3	NA	NA	NA	NA	NA	NA
BMI	Red Blood Cell Distribution	Inverse variance weighted	99	-0.116681806	0.036134018	0.001241631	151.3	85.3	599.5	0	83.7	NA	NA	NA
BMI	Red Blood Cell Distribution	MR Egger	99	0.014921945	0.099351528	0.880923896	151.3	85.3	NA	NA	NA	-0.003948	0.002778	0.1586
BMI	Red Blood Cell Distribution	Weighted median	99	-0.070190795	0.024781047	0.004619444	151.3	85.3	NA	NA	NA	NA	NA	NA
BMI	Red Blood Cell Distribution	Weighted mode	99	-0.099517552	0.039092617	0.012465083	151.3	85.3	NA	NA	NA	NA	NA	NA
BMI	Serum Phosphate	Inverse variance weighted	45	0.00467338	0.010692911	0.662072164	141.3	85.3	54.95	0.1247	19.9	NA	NA	NA
BMI	Serum Phosphate	MR Egger	45	0.066985234	0.031709856	0.040494152	141.3	85.3	NA	NA	NA	-0.001768	0.000851	0.0437
BMI	Serum Phosphate	Weighted median	45	0.02284851	0.014365711	0.111724554	141.3	85.3	NA	NA	NA	NA	NA	NA
BMI	Serum Phosphate	Weighted mode	45	0.031274474	0.019396993	0.114039545	141.3	85.3	NA	NA	NA	NA	NA	NA
BMI	Uric Acid	Inverse variance weighted	75	-0.115728072	0.035295487	0.001042366	156.7	85.3	191.72	0	61.4	NA	NA	NA
BMI	Uric Acid	MR Egger	75	-0.065665437	0.102005366	0.521758225	156.7	85.3	NA	NA	NA	-0.001501	0.002868	0.6022
BMI	Uric Acid	Weighted median	75	-0.127904175	0.03725807	0.000597106	156.7	85.3	NA	NA	NA	NA	NA	NA
BMI	Uric Acid	Weighted mode	75	-0.073684222	0.054767651	0.182605402	156.7	85.3	NA	NA	NA	NA	NA	NA
BMI	Sodium in Urine	Inverse variance weighted	99	0.107685136	0.021142547	3.52E-07	150.8	85.3	457.01	0	78.6	NA	NA	NA
BMI	Sodium in Urine	MR Egger	99	0.028356723	0.057758115	0.624566133	150.8	85.3	NA	NA	NA	0.002376	0.001611	0.1436
BMI	Sodium in Urine	Weighted median	99	0.129709055	0.019311201	1.86E-11	150.8	85.3	NA	NA	NA	NA	NA	NA
BMI	Sodium in Urine	Weighted mode	99	0.219473393	0.039373214	2.19E-07	150.8	85.3	NA	NA	NA	NA	NA	NA
BMI	Tea Consumption	Inverse variance weighted	100	1.02027163	4.275073791	0.811372407	150.7	85.3	126.79	0.0313	21.9	NA	NA	NA
BMI	Tea Consumption	MR Egger	100	13.06121869	11.77637839	0.270100001	150.7	85.3	NA	NA	NA	-0.360313	0.328407	0.2753
BMI	Tea Consumption	Weighted median	100	4.132111803	6.084599978	0.497068259	150.7	85.3	NA	NA	NA	NA	NA	NA
BMI	Tea Consumption	Weighted mode	100	-1.003777864	19.50062345	0.959051423	150.7	85.3	NA	NA	NA	NA	NA	NA
BMI	Testosterone	Inverse variance weighted	91	-0.065465261	0.022351405	0.003401525	154	85.3	248.79	0	63.8	NA	NA	NA
BMI	Testosterone	MR Egger	91	0.036644137	0.059305009	0.538223938	154	85.3	NA	NA	NA	-0.003122	0.001683	0.0669
BMI	Testosterone	Weighted median	91	-0.026359395	0.024152068	0.275100053	154	85.3	NA	NA	NA	NA	NA	NA
BMI	Testosterone	Weighted mode	91	0.010927689	0.032755437	0.739446507	154	85.3	NA	NA	NA	NA	NA	NA
BMI	Urea	Inverse variance weighted	96	-0.157824518	0.069250534	0.022664877	149	85.3	73.96	0.946	0	NA	NA	NA
BMI	Urea	MR Egger	96	-0.626296143	0.198125959	0.002115689	149	85.3	NA	NA	NA	0.013743	0.005446	0.0133
BMI	Urea	Weighted median	96	-0.293538005	0.107840808	0.006489665	149	85.3	NA	NA	NA	NA	NA	NA
BMI	Urea	Weighted mode	96	-0.358106124	0.158729168	0.026358835	149	85.3	NA	NA	NA	NA	NA	NA
BMI	Urinary Albumin Excretion	Inverse variance weighted	98	-0.015899866	0.012229816	0.193569983	151.4	85.3	302.98	0	68	NA	NA	NA
BMI	Urinary Albumin Excretion	MR Egger	98	-0.073040869	0.03319079	0.030159658	151.4	85.3	NA	NA	NA	0.001717	0.000929	0.0676
BMI	Urinary Albumin Excretion	Weighted median	98	-0.004949505	0.012490525	0.691912653	151.4	85.3	NA	NA	NA	NA	NA	NA
BMI	Urinary Albumin Excretion	Weighted mode	98	-0.000247319	0.028964175	0.993204642	151.4	85.3	NA	NA	NA	NA	NA	NA
BMI	25 Hydroxyvitamin D	Inverse variance weighted	99	-0.058810611	0.016518855	0.000370557	150.8	85.3	403.53	0	75.7	NA	NA	NA
BMI	25 Hydroxyvitamin D	MR Egger	99	-0.043291973	0.045594131	0.344722251	150.8	85.3	NA	NA	NA	-0.000465	0.001272	0.7156
BMI	25 Hydroxyvitamin D	Weighted median	99	-0.02703231	0.01438759	0.060263203	150.8	85.3	NA	NA	NA	NA	NA	NA
BMI	25 Hydroxyvitamin D	Weighted mode	99	-0.005681454	0.04207629	0.892867127	150.8	85.3	NA	NA	NA	NA	NA	NA
BMI	Water Consumption	Inverse variance weighted	100	-0.026843178	0.015525394	0.08381173	150.7	85.3	427.87	0	76.9	NA	NA	NA
BMI	Water Consumption	MR Egger	100	-0.116356557	0.041985919	0.006681158	150.7	85.3	NA	NA	NA	0.002677	0.00117	0.0243
BMI	Water Consumption	Weighted median	100	-0.039527658	0.013922079	0.004522587	150.7	85.3	NA	NA	NA	NA	NA	NA
BMI	Water Consumption	Weighted mode	100	-0.046382826	0.040924207	0.259790432	150.7	85.3	NA	NA	NA	NA	NA	NA
BMI	X_11440	Inverse variance weighted	45	-0.001131289	0.032419988	0.972163617	141.3	85.3	43.48	0.4936	0	NA	NA	NA
BMI	X_11440	MR Egger	45	0.054915741	0.103148289	0.597192243	141.3	85.3	NA	NA	NA	-0.001546	0.0027	0.57
BMI	X_11440	Weighted median	45	-0.0046143	0.048598044	0.924355923	141.3	85.3	NA	NA	NA	NA	NA	NA
BMI	X_11440	Weighted mode	45	0.039707422	0.084898564	0.642304403	141.3	85.3	NA	NA	NA	NA	NA	NA
BMI	X_14473	Inverse variance weighted	45	-0.029937518	0.030001024	0.318335993	141.3	85.3	42.52	0.5352	0	NA	NA	NA
BMI	X_14473	MR Egger	45	0.043666718	0.095773093	0.650727998	141.3	85.3	NA	NA	NA	-0.002025	0.002502	0.4228
BMI	X_14473	Weighted median	45	-0.021053667	0.044034754	0.632568504	141.3	85.3	NA	NA	NA	NA	NA	NA
BMI	X_14473	Weighted mode	45	-0.025273404	0.070589701	0.722030993	141.3	85.3	NA	NA	NA	NA	NA	NA
DBP	Bilirubin	Inverse variance weighted	79	-0.00106105	0.002568558	0.679539359	197	114	131.47	1.00E-04	40.7	NA	NA	NA
DBP	Bilirubin	MR Egger	79	0.007001936	0.0090908	0.443524805	197	114	NA	NA	NA	-0.002478	0.00268	0.358
DBP	Bilirubin	Weighted median	79	-0.003016048	0.00321685	0.348461289	197	114	NA	NA	NA	NA	NA	NA
DBP	Bilirubin	Weighted mode	79	-0.00565341	0.006197229	0.364449078	197	114	NA	NA	NA	NA	NA	NA
DBP	Blood Urea Nitrogen	Inverse variance weighted	79	-0.001020143	0.003488256	0.769942137	197	114	351.63	0	77.8	NA	NA	NA
DBP	Blood Urea Nitrogen	MR Egger	79	0.003518411	0.012403766	0.777434776	197	114	NA	NA	NA	-0.001395	0.003657	0.7039

DBP	Blood Urea Nitrogen	Weighted median	79	-0.005663796	0.002851403	0.046997966	197	114	NA	NA	NA	NA	NA	NA
DBP	Blood Urea Nitrogen	Weighted mode	79	-0.009070322	0.004345423	0.04012396	197	114	NA	NA	NA	NA	NA	NA
DBP	CRP	Inverse variance weighted	43	-0.009272398	0.004244345	0.028914675	196.1	114	141.75	0	70.4	NA	NA	NA
DBP	CRP	MR Egger	43	-0.006147805	0.016384056	0.70942295	196.1	114	NA	NA	NA	-9.00E-04	0.004552	0.8443
DBP	CRP	Weighted median	43	-0.004430006	0.003730513	0.235028071	196.1	114	NA	NA	NA	NA	NA	NA
DBP	CRP	Weighted mode	43	-7.92E-06	0.006922735	0.999093035	196.1	114	NA	NA	NA	NA	NA	NA
DBP	Coffee Consumption	Inverse variance weighted	100	0.006219905	0.001109493	2.07E-08	209.5	114	299.92	0	67	NA	NA	NA
DBP	Coffee Consumption	MR Egger	100	0.004610683	0.003829531	0.231496835	209.5	114	NA	NA	NA	0.000498	0.001133	0.6615
DBP	Coffee Consumption	Weighted median	100	0.004276186	0.001089058	8.62E-05	209.5	114	NA	NA	NA	NA	NA	NA
DBP	Coffee Consumption	Weighted mode	100	0.004218239	0.001967555	0.034489983	209.5	114	NA	NA	NA	NA	NA	NA
DBP	Cotinine	Inverse variance weighted	100	0.001157554	0.000705964	0.101072065	209.5	114	244.15	0	59.5	NA	NA	NA
DBP	Cotinine	MR Egger	100	-0.001923117	0.002417275	0.428203486	209.5	114	NA	NA	NA	0.000953	0.000715	0.1859
DBP	Cotinine	Weighted median	100	0.001056986	0.000760915	0.164802772	209.5	114	NA	NA	NA	NA	NA	NA
DBP	Cotinine	Weighted mode	100	0.001182491	0.00145525	0.41841508	209.5	114	NA	NA	NA	NA	NA	NA
DBP	Creatinine	Inverse variance weighted	100	6.56E-05	0.001613754	0.967588633	209.5	114	312.3	0	68.3	NA	NA	NA
DBP	Creatinine	MR Egger	100	-0.013083491	0.005398993	0.017214438	209.5	114	NA	NA	NA	0.004069	0.001598	0.0125
DBP	Creatinine	Weighted median	100	0.000324853	0.001588839	0.837994724	209.5	114	NA	NA	NA	NA	NA	NA
DBP	Creatinine	Weighted mode	100	0.00067668	0.00401861	0.866622653	209.5	114	NA	NA	NA	NA	NA	NA
DBP	Cystatin C	Inverse variance weighted	42	0.000355974	0.001820352	0.844960552	196.7	114	96.41	0	57.5	NA	NA	NA
DBP	Cystatin C	MR Egger	42	-0.001696922	0.006909953	0.807265786	196.7	114	NA	NA	NA	0.000594	0.001926	0.7595
DBP	Cystatin C	Weighted median	42	0.000815087	0.001868235	0.662628363	196.7	114	NA	NA	NA	NA	NA	NA
DBP	Cystatin C	Weighted mode	42	0.001984192	0.003616077	0.586177641	196.7	114	NA	NA	NA	NA	NA	NA
DBP	Fresh Fruit Consumption	Inverse variance weighted	100	0.000368628	0.002484916	0.882069447	209.5	114	185.47	0	46.6	NA	NA	NA
DBP	Fresh Fruit Consumption	MR Egger	100	-0.006190531	0.008556202	0.471087654	209.5	114	NA	NA	NA	0.002029	0.002533	0.4249
DBP	Fresh Fruit Consumption	Weighted median	100	0.000238816	0.002861226	0.933480762	209.5	114	NA	NA	NA	NA	NA	NA
DBP	Fresh Fruit Consumption	Weighted mode	100	0.000293943	0.005673014	0.958781113	209.5	114	NA	NA	NA	NA	NA	NA
DBP	Gamma Glutamyl Transferase	Inverse variance weighted	79	-0.001560613	0.003378411	0.644126524	197	114	248.31	0	68.6	NA	NA	NA
DBP	Gamma Glutamyl Transferase	MR Egger	79	0.002083989	0.012016669	0.8627726	197	114	NA	NA	NA	-0.00112	0.003543	0.7527
DBP	Gamma Glutamyl Transferase	Weighted median	79	0.001839054	0.00292707	0.529812803	197	114	NA	NA	NA	NA	NA	NA
DBP	Gamma Glutamyl Transferase	Weighted mode	79	0.002199062	0.004361808	0.61556805	197	114	NA	NA	NA	NA	NA	NA
DBP	Impedance of Arm (Left)	Inverse variance weighted	100	0.006404265	0.002260063	0.004601729	209.5	114	1101.78	0	91	NA	NA	NA
DBP	Impedance of Arm (Left)	MR Egger	100	0.015084773	0.00775337	0.054570801	209.5	114	NA	NA	NA	-0.002686	0.002295	0.2448
DBP	Impedance of Arm (Left)	Weighted median	100	0.005810998	0.001409966	3.77E-05	209.5	114	NA	NA	NA	NA	NA	NA
DBP	Impedance of Arm (Left)	Weighted mode	100	0.005297217	0.002639993	0.047527314	209.5	114	NA	NA	NA	NA	NA	NA
DBP	Impedance of Arm (Right)	Inverse variance weighted	100	0.006745615	0.002233753	0.002528943	209.5	114	1085.43	0	90.9	NA	NA	NA
DBP	Impedance of Arm (Right)	MR Egger	100	0.014772311	0.007669787	0.056997406	209.5	114	NA	NA	NA	-0.002484	0.00227	0.2767
DBP	Impedance of Arm (Right)	Weighted median	100	0.005987438	0.001290469	3.49E-06	209.5	114	NA	NA	NA	NA	NA	NA
DBP	Impedance of Arm (Right)	Weighted mode	100	0.006471727	0.002518782	0.011679171	209.5	114	NA	NA	NA	NA	NA	NA
DBP	Overall Healthy Diet	Inverse variance weighted	100	-0.000209311	0.000846181	0.804630045	209.5	114	95.19	0.5896	0	NA	NA	NA
DBP	Overall Healthy Diet	MR Egger	100	-0.00080527	0.002908522	0.782466219	209.5	114	NA	NA	NA	0.000184	0.000861	0.8309
DBP	Overall Healthy Diet	Weighted median	100	-0.000607238	0.001252418	0.62778083	209.5	114	NA	NA	NA	NA	NA	NA
DBP	Overall Healthy Diet	Weighted mode	100	-0.002491767	0.002320833	0.285588632	209.5	114	NA	NA	NA	NA	NA	NA
DBP	Peak Expiratory Flow	Inverse variance weighted	100	0.00232266	0.001728696	0.179080638	209.5	114	405.89	0	75.6	NA	NA	NA
DBP	Peak Expiratory Flow	MR Egger	100	-0.007704666	0.005877716	0.192979833	209.5	114	NA	NA	NA	0.003103	0.00174	0.0777
DBP	Peak Expiratory Flow	Weighted median	100	0.001942322	0.001503098	0.196283538	209.5	114	NA	NA	NA	NA	NA	NA
DBP	Peak Expiratory Flow	Weighted mode	100	0.002737663	0.003060848	0.373270105	209.5	114	NA	NA	NA	NA	NA	NA
DBP	Potassium in Urine	Inverse variance weighted	100	0.002893242	0.001681734	0.085361222	209.5	114	301.66	0	67.2	NA	NA	NA
DBP	Potassium in Urine	MR Egger	100	-0.00482154	0.005752096	0.40394511	209.5	114	NA	NA	NA	0.002387	0.001703	0.1641
DBP	Potassium in Urine	Weighted median	100	0.000946051	0.001649717	0.566331422	209.5	114	NA	NA	NA	NA	NA	NA
DBP	Potassium in Urine	Weighted mode	100	0.00083494	0.003950175	0.833034713	209.5	114	NA	NA	NA	NA	NA	NA
DBP	Red Blood Cell Distribution	Inverse variance weighted	99	0.017021575	0.0064331	0.008146509	210	114	2076.29	0	95.3	NA	NA	NA
DBP	Red Blood Cell Distribution	MR Egger	99	0.015188417	0.022014703	0.491890903	210	114	NA	NA	NA	0.000569	0.006536	0.9308
DBP	Red Blood Cell Distribution	Weighted median	99	0.005602622	0.002515263	0.025917224	210	114	NA	NA	NA	NA	NA	NA
DBP	Red Blood Cell Distribution	Weighted mode	99	0.008644687	0.006437309	0.18240514	210	114	NA	NA	NA	NA	NA	NA
DBP	Serum Phosphate	Inverse variance weighted	49	-9.25E-05	0.000931508	0.920940406	191.3	114	35.67	0.906	0	NA	NA	NA
DBP	Serum Phosphate	MR Egger	49	0.001209841	0.003444746	0.726997758	191.3	114	NA	NA	NA	-0.000379	0.000966	0.6963
DBP	Serum Phosphate	Weighted median	49	0.00033881	0.001347748	0.801512687	191.3	114	NA	NA	NA	NA	NA	NA
DBP	Serum Phosphate	Weighted mode	49	0.000575927	0.002767623	0.836035631	191.3	114	NA	NA	NA	NA	NA	NA

DBP	Uric Acid	Inverse variance weighted	79	-0.006707225	0.004389591	0.126516522	197	114	393.53	0	80.2	NA	NA	NA
DBP	Uric Acid	MR Egger	79	0.018837038	0.015320132	0.22260537	197	114	NA	NA	NA	-0.007853	0.004518	0.0861
DBP	Uric Acid	Weighted median	79	-0.007077426	0.003380726	0.036307829	197	114	NA	NA	NA	NA	NA	NA
DBP	Uric Acid	Weighted mode	79	-0.010113927	0.007592928	0.186732902	197	114	NA	NA	NA	NA	NA	NA
DBP	Sodium in Urine	Inverse variance weighted	100	-0.00299023	0.001618281	0.064633953	209.5	114	297.12	0	66.7	NA	NA	NA
DBP	Sodium in Urine	MR Egger	100	-0.015659491	0.005427847	0.004813082	209.5	114	NA	NA	NA	0.00392	0.001607	0.0165
DBP	Sodium in Urine	Weighted median	100	-0.003866485	0.001637991	0.018250132	209.5	114	NA	NA	NA	NA	NA	NA
DBP	Sodium in Urine	Weighted mode	100	-0.007288571	0.004069315	0.076332282	209.5	114	NA	NA	NA	NA	NA	NA
DBP	Tea Consumption	Inverse variance weighted	100	0.383494973	0.412782491	0.352863929	209.5	114	128.76	0.0238	23.1	NA	NA	NA
DBP	Tea Consumption	MR Egger	100	1.012199179	1.424505721	0.479043502	209.5	114	NA	NA	NA	-0.194548	0.421736	0.6456
DBP	Tea Consumption	Weighted median	100	0.405456325	0.556346605	0.466133998	209.5	114	NA	NA	NA	NA	NA	NA
DBP	Tea Consumption	Weighted mode	100	-0.384487103	1.274721445	0.763571067	209.5	114	NA	NA	NA	NA	NA	NA
DBP	Testosterone	Inverse variance weighted	100	0.002309642	0.002876231	0.421969096	209.5	114	531.29	0	81.4	NA	NA	NA
DBP	Testosterone	MR Egger	100	0.012237491	0.009879817	0.21843922	209.5	114	NA	NA	NA	-0.003072	0.002925	0.2962
DBP	Testosterone	Weighted median	100	0.001198798	0.002260154	0.59583095	209.5	114	NA	NA	NA	NA	NA	NA
DBP	Testosterone	Weighted mode	100	-0.000430365	0.005807284	0.941074115	209.5	114	NA	NA	NA	NA	NA	NA
DBP	Urea	Inverse variance weighted	96	-0.004774247	0.007823363	0.541692873	209.9	114	131.36	0.008	27.7	NA	NA	NA
DBP	Urea	MR Egger	96	-0.018407704	0.028396563	0.518412003	209.9	114	NA	NA	NA	0.004148	0.008302	0.6185
DBP	Urea	Weighted median	96	-0.001008821	0.01002288	0.919826827	209.9	114	NA	NA	NA	NA	NA	NA
DBP	Urea	Weighted mode	96	-0.010700885	0.01904883	0.575601969	209.9	114	NA	NA	NA	NA	NA	NA
DBP	Urinary Albumin Excretion	Inverse variance weighted	99	-0.005736305	0.001300804	1.03E-05	210	114	380.02	0	74.2	NA	NA	NA
DBP	Urinary Albumin Excretion	MR Egger	99	-0.007261606	0.004474264	0.107841	210	114	NA	NA	NA	0.000472	0.001325	0.7223
DBP	Urinary Albumin Excretion	Weighted median	99	-0.006419247	0.001122515	1.07E-08	210	114	NA	NA	NA	NA	NA	NA
DBP	Urinary Albumin Excretion	Weighted mode	99	-0.007818229	0.002038308	0.000221615	210	114	NA	NA	NA	NA	NA	NA
DBP	25 Hydroxyvitamin D	Inverse variance weighted	99	7.62E-05	0.001502489	0.959577191	210.2	114	364.34	0	73.1	NA	NA	NA
DBP	25 Hydroxyvitamin D	MR Egger	99	0.000619026	0.005187572	0.905261711	210.2	114	NA	NA	NA	-0.000168	0.00154	0.9131
DBP	25 Hydroxyvitamin D	Weighted median	99	4.41E-05	0.001331468	0.97356655	210.2	114	NA	NA	NA	NA	NA	NA
DBP	25 Hydroxyvitamin D	Weighted mode	99	0.001341533	0.002891526	0.643710148	210.2	114	NA	NA	NA	NA	NA	NA
DBP	Water Consumption	Inverse variance weighted	100	-0.004874995	0.001200644	4.90E-05	209.5	114	278.67	0	64.5	NA	NA	NA
DBP	Water Consumption	MR Egger	100	-0.009093111	0.004124168	0.02980465	209.5	114	NA	NA	NA	0.001305	0.001221	0.2877
DBP	Water Consumption	Weighted median	100	-0.005169742	0.001225698	2.47E-05	209.5	114	NA	NA	NA	NA	NA	NA
DBP	Water Consumption	Weighted mode	100	-0.006459787	0.003822886	0.094219369	209.5	114	NA	NA	NA	NA	NA	NA
DBP	X_11440	Inverse variance weighted	49	-0.006393175	0.003097731	0.039034308	191.3	114	39.61	0.8003	0	NA	NA	NA
DBP	X_11440	MR Egger	49	-0.014601488	0.011755854	0.220376259	191.3	114	NA	NA	NA	0.002353	0.003252	0.4728
DBP	X_11440	Weighted median	49	-0.005285615	0.004423616	0.232140572	191.3	114	NA	NA	NA	NA	NA	NA
DBP	X_11440	Weighted mode	49	-0.002569332	0.007875826	0.745668346	191.3	114	NA	NA	NA	NA	NA	NA
DBP	X_14473	Inverse variance weighted	49	-0.00065405	0.002853587	0.818711226	191.3	114	42.77	0.6865	0	NA	NA	NA
DBP	X_14473	MR Egger	49	0.00265517	0.010915028	0.808863994	191.3	114	NA	NA	NA	-0.000946	0.003013	0.7548
DBP	X_14473	Weighted median	49	0	0.0043702	1	191.3	114	NA	NA	NA	NA	NA	NA
DBP	X_14473	Weighted mode	49	-0.001451953	0.009122676	0.874211656	191.3	114	NA	NA	NA	NA	NA	NA
HbA1c	Bilirubin	Inverse variance weighted	10	0.176628505	0.14517958	0.223748502	54.8	30.1	59.12	0	84.8	NA	NA	NA
HbA1c	Bilirubin	MR Egger	10	-0.517358161	0.49808143	0.329315648	54.8	30.1	NA	NA	NA	0.020418	0.014088	0.1853
HbA1c	Bilirubin	Weighted median	10	-0.120188618	0.088299965	0.173469439	54.8	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Bilirubin	Weighted mode	10	-0.116301266	0.090385015	0.230297132	54.8	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Blood Urea Nitrogen	Inverse variance weighted	10	0.012615861	0.049761811	0.799862574	54.8	30.1	10.09	0.3433	10.8	NA	NA	NA
HbA1c	Blood Urea Nitrogen	MR Egger	10	0.030617531	0.191444405	0.876901215	54.8	30.1	NA	NA	NA	-0.00053	0.005417	0.9245
HbA1c	Blood Urea Nitrogen	Weighted median	10	-0.009709426	0.061971331	0.875500127	54.8	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Blood Urea Nitrogen	Weighted mode	10	-0.010674585	0.082031804	0.899327665	54.8	30.1	NA	NA	NA	NA	NA	NA
HbA1c	CRP	Inverse variance weighted	15	0.053573958	0.058131649	0.356738785	66.7	30.1	36.85	8.00E-04	62	NA	NA	NA
HbA1c	CRP	MR Egger	15	0.111007178	0.149976805	0.472358061	66.7	30.1	NA	NA	NA	-0.00209	0.005004	0.683
HbA1c	CRP	Weighted median	15	-0.025244497	0.053458693	0.636766652	66.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	CRP	Weighted mode	15	-0.028969106	0.06467057	0.661043869	66.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Coffee Consumption	Inverse variance weighted	16	0.010492886	0.014658756	0.474108591	64.7	30.1	16.48	0.3512	9	NA	NA	NA
HbA1c	Coffee Consumption	MR Egger	16	-0.038285732	0.0331533	0.267499704	64.7	30.1	NA	NA	NA	0.001869	0.001152	0.1269
HbA1c	Coffee Consumption	Weighted median	16	-0.011760244	0.020113528	0.558754005	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Coffee Consumption	Weighted mode	16	-0.012591067	0.023262046	0.596269004	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Cotinine	Inverse variance weighted	16	-0.003012007	0.009863493	0.760084936	64.7	30.1	11.64	0.7057	0	NA	NA	NA
HbA1c	Cotinine	MR Egger	16	0.029780158	0.02337747	0.223447445	64.7	30.1	NA	NA	NA	-0.001256	0.000812	0.1441

HbA1c	Cotinine	Weighted median	16	-0.000166392	0.013901888	0.990450353	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Cotinine	Weighted mode	16	0.006526655	0.017815636	0.719224032	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Creatinine	Inverse variance weighted	16	0.062396755	0.02036305	0.002182423	64.7	30.1	15.68	0.4038	4.3	NA	NA	NA
HbA1c	Creatinine	MR Egger	16	0.140168066	0.047148138	0.010077823	64.7	30.1	NA	NA	NA	-0.002983	0.001639	0.0902
HbA1c	Creatinine	Weighted median	16	0.091026007	0.027300699	0.000855449	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Creatinine	Weighted mode	16	0.088020356	0.032918465	0.017342648	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Cystatin C	Inverse variance weighted	14	0.011471088	0.019272374	0.551703865	69.1	30.1	11.48	0.5707	0	NA	NA	NA
HbA1c	Cystatin C	MR Egger	14	-0.003627189	0.051528099	0.9450408	69.1	30.1	NA	NA	NA	0.000525	0.001662	0.7575
HbA1c	Cystatin C	Weighted median	14	0.006511815	0.025995179	0.80220003	69.1	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Cystatin C	Weighted mode	14	-0.005233039	0.036181311	0.887218276	69.1	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Fresh Fruit Consumption	Inverse variance weighted	16	0.018551886	0.052635593	0.724494092	64.7	30.1	26.19	0.0361	42.7	NA	NA	NA
HbA1c	Fresh Fruit Consumption	MR Egger	16	0.042101027	0.129016277	0.749006683	64.7	30.1	NA	NA	NA	-0.000902	0.004482	0.8434
HbA1c	Fresh Fruit Consumption	Weighted median	16	0.016908397	0.061860174	0.784597625	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Fresh Fruit Consumption	Weighted mode	16	0.011869905	0.067701647	0.863167751	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Gamma Glutamyl Transferase	Inverse variance weighted	10	-0.02861621	0.054160984	0.597253184	54.8	30.1	7.88	0.5468	0	NA	NA	NA
HbA1c	Gamma Glutamyl Transferase	MR Egger	10	-0.206272084	0.196485429	0.324482268	54.8	30.1	NA	NA	NA	0.00523	0.00556	0.3744
HbA1c	Gamma Glutamyl Transferase	Weighted median	10	-0.022374556	0.069285073	0.746744678	54.8	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Gamma Glutamyl Transferase	Weighted mode	10	-0.017609988	0.092181741	0.85273778	54.8	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Impedance of Arm (Left)	Inverse variance weighted	16	-0.075681354	0.029840978	0.011207704	64.7	30.1	60.55	0	75.2	NA	NA	NA
HbA1c	Impedance of Arm (Left)	MR Egger	16	-0.173200108	0.067231039	0.021971354	64.7	30.1	NA	NA	NA	0.00374	0.002337	0.1319
HbA1c	Impedance of Arm (Left)	Weighted median	16	-0.090875117	0.023936325	0.000146732	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Impedance of Arm (Left)	Weighted mode	16	-0.092759101	0.025677285	0.002559234	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Impedance of Arm (Right)	Inverse variance weighted	16	-0.072485813	0.027187329	0.00767228	64.7	30.1	50.69	0	70.4	NA	NA	NA
HbA1c	Impedance of Arm (Right)	MR Egger	16	-0.148467032	0.062739478	0.032917035	64.7	30.1	NA	NA	NA	0.002914	0.002181	0.2028
HbA1c	Impedance of Arm (Right)	Weighted median	16	-0.09375161	0.02309848	4.93E-05	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Impedance of Arm (Right)	Weighted mode	16	-0.093034112	0.026435911	0.003098798	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Overall Healthy Diet	Inverse variance weighted	16	-0.038783904	0.018601554	0.037070936	64.7	30.1	11.36	0.727	0	NA	NA	NA
HbA1c	Overall Healthy Diet	MR Egger	16	-0.07790102	0.044098329	0.099091833	64.7	30.1	NA	NA	NA	0.001498	0.001531	0.3445
HbA1c	Overall Healthy Diet	Weighted median	16	-0.050510033	0.025569805	0.048225256	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Overall Healthy Diet	Weighted mode	16	-0.057172213	0.029668055	0.073130597	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Peak Expiratory Flow	Inverse variance weighted	16	-0.003835245	0.027540355	0.889245398	64.7	30.1	32.47	0.0055	53.8	NA	NA	NA
HbA1c	Peak Expiratory Flow	MR Egger	16	-0.009357326	0.067465186	0.891663657	64.7	30.1	NA	NA	NA	0.000212	0.002345	0.9293
HbA1c	Peak Expiratory Flow	Weighted median	16	0.019106395	0.027914249	0.493680018	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Peak Expiratory Flow	Weighted mode	16	0.017700718	0.035838308	0.628527188	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Potassium in Urine	Inverse variance weighted	16	0.046523909	0.024248434	0.055030465	64.7	30.1	19.77	0.1808	24.1	NA	NA	NA
HbA1c	Potassium in Urine	MR Egger	16	0.171095231	0.049991482	0.00412423	64.7	30.1	NA	NA	NA	-0.004778	0.001738	0.0157
HbA1c	Potassium in Urine	Weighted median	16	0.069196719	0.032190319	0.031585864	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Potassium in Urine	Weighted mode	16	0.087618696	0.036156266	0.028493713	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Red Blood Cell Distribution	Inverse variance weighted	16	-0.617366748	0.385304318	0.109092934	64.7	30.1	2389.36	0	99.4	NA	NA	NA
HbA1c	Red Blood Cell Distribution	MR Egger	16	0.062896768	0.920290943	0.946477986	64.7	30.1	NA	NA	NA	-0.026181	0.032087	0.4282
HbA1c	Red Blood Cell Distribution	Weighted median	16	0.31184682	0.053785862	6.71E-09	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Red Blood Cell Distribution	Weighted mode	16	0.263890106	0.041498465	1.28E-05	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Serum Phosphate	Inverse variance weighted	16	0.003529733	0.013900378	0.799549103	64.7	30.1	11.28	0.7322	0	NA	NA	NA
HbA1c	Serum Phosphate	MR Egger	16	-0.008163136	0.033343443	0.810147897	64.7	30.1	NA	NA	NA	0.000449	0.001163	0.7054
HbA1c	Serum Phosphate	Weighted median	16	0.0171016	0.018825907	0.363662817	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Serum Phosphate	Weighted mode	16	0.022162378	0.024607657	0.382017988	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Uric Acid	Inverse variance weighted	10	0.014344603	0.05740063	0.802662186	54.8	30.1	9.49	0.3938	5.1	NA	NA	NA
HbA1c	Uric Acid	MR Egger	10	0.195758832	0.210685583	0.379992343	54.8	30.1	NA	NA	NA	-0.005339	0.00596	0.3965
HbA1c	Uric Acid	Weighted median	10	-0.018548389	0.072224924	0.797322176	54.8	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Uric Acid	Weighted mode	10	-0.044225562	0.095872782	0.655533109	54.8	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Sodium in Urine	Inverse variance weighted	16	0.053946455	0.022848485	0.018223188	64.7	30.1	18.67	0.2289	19.7	NA	NA	NA
HbA1c	Sodium in Urine	MR Egger	16	0.135028231	0.050625036	0.018399538	64.7	30.1	NA	NA	NA	-0.003109	0.00176	0.099
HbA1c	Sodium in Urine	Weighted median	16	0.091173718	0.029040531	0.001692171	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Sodium in Urine	Weighted mode	16	0.088928943	0.031641893	0.013178005	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Tea Consumption	Inverse variance weighted	16	7.925729748	7.956944056	0.319212686	64.7	30.1	5.19	0.9904	0	NA	NA	NA
HbA1c	Tea Consumption	MR Egger	16	26.65172242	18.86307537	0.17952894	64.7	30.1	NA	NA	NA	-0.717001	0.654847	0.292
HbA1c	Tea Consumption	Weighted median	16	16.10991962	10.71536614	0.132725388	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Tea Consumption	Weighted mode	16	16.74148351	14.01707627	0.250881187	64.7	30.1	NA	NA	NA	NA	NA	NA

HbA1c	Testosterone	Inverse variance weighted	16	-0.043424419	0.037847061	0.251230519	64.7	30.1	28.94	0.0164	48.2	NA	NA	NA
HbA1c	Testosterone	MR Egger	16	-0.168557638	0.085232374	0.068001173	64.7	30.1	NA	NA	NA	0.004793	0.00296	0.1277
HbA1c	Testosterone	Weighted median	16	-0.09691875	0.042039237	0.021142192	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Testosterone	Weighted mode	16	-0.10698054	0.049321007	0.046559223	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Urea	Inverse variance weighted	15	0.494135089	0.158948107	0.0018786	63.4	30.1	12.42	0.5725	0	NA	NA	NA
HbA1c	Urea	MR Egger	15	0.024033646	0.422737696	0.955527326	63.4	30.1	NA	NA	NA	0.0164	0.013665	0.2515
HbA1c	Urea	Weighted median	15	0.500185699	0.218770681	0.022233964	63.4	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Urea	Weighted mode	15	0.428378504	0.320747833	0.203000961	63.4	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Urinary Albumin Excretion	Inverse variance weighted	16	0.020353546	0.01442131	0.158140802	64.7	30.1	12.75	0.6219	0	NA	NA	NA
HbA1c	Urinary Albumin Excretion	MR Egger	16	0.023522798	0.034131523	0.501972567	64.7	30.1	NA	NA	NA	-0.000122	0.001187	0.9199
HbA1c	Urinary Albumin Excretion	Weighted median	16	0.020445468	0.021102	0.332601215	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Urinary Albumin Excretion	Weighted mode	16	0.02111981	0.024121121	0.395066828	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	25 Hydroxyvitamin D	Inverse variance weighted	16	-0.031941696	0.035003273	0.3614874	64.7	30.1	63.66	0	76.4	NA	NA	NA
HbA1c	25 Hydroxyvitamin D	MR Egger	16	-0.126730926	0.081045772	0.140206022	64.7	30.1	NA	NA	NA	0.003638	0.002819	0.2178
HbA1c	25 Hydroxyvitamin D	Weighted median	16	-0.033331164	0.027154214	0.219643485	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	25 Hydroxyvitamin D	Weighted mode	16	-0.045428061	0.035517935	0.220324154	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Water Consumption	Inverse variance weighted	16	-0.004919202	0.022359736	0.825869048	64.7	30.1	30.42	0.0105	50.7	NA	NA	NA
HbA1c	Water Consumption	MR Egger	16	0.022641177	0.054255197	0.682781263	64.7	30.1	NA	NA	NA	-0.001056	0.001884	0.5841
HbA1c	Water Consumption	Weighted median	16	-0.020600901	0.021883369	0.346502329	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	Water Consumption	Weighted mode	16	-0.01309075	0.025339852	0.612962626	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	X_11440	Inverse variance weighted	16	-0.043090034	0.047690299	0.366240018	64.7	30.1	12.52	0.639	0	NA	NA	NA
HbA1c	X_11440	MR Egger	16	0.04439886	0.117218413	0.710540628	64.7	30.1	NA	NA	NA	-0.003237	0.003962	0.4276
HbA1c	X_11440	Weighted median	16	-0.019294663	0.06781541	0.776013915	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	X_11440	Weighted mode	16	0.020965397	0.093439768	0.825494412	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	X_14473	Inverse variance weighted	16	-0.044966167	0.043918516	0.305904041	64.7	30.1	11.61	0.7084	0	NA	NA	NA
HbA1c	X_14473	MR Egger	16	0.051184556	0.1093462	0.646919762	64.7	30.1	NA	NA	NA	-0.003512	0.003658	0.3533
HbA1c	X_14473	Weighted median	16	-0.007198195	0.062967071	0.908986654	64.7	30.1	NA	NA	NA	NA	NA	NA
HbA1c	X_14473	Weighted mode	16	0.007382263	0.087087886	0.933566908	64.7	30.1	NA	NA	NA	NA	NA	NA
HDL	Bilirubin	Inverse variance weighted	87	-0.020936179	0.012882999	0.104140957	173.5	59.2	164.55	0	47.7	NA	NA	NA
HDL	Bilirubin	MR Egger	87	-0.054668042	0.027646251	0.051235677	173.5	59.2	NA	NA	NA	0.002332	0.001693	0.1721
HDL	Bilirubin	Weighted median	87	-0.021823344	0.014751407	0.13903141	173.5	59.2	NA	NA	NA	NA	NA	NA
HDL	Bilirubin	Weighted mode	87	-0.029946085	0.020376841	0.145315311	173.5	59.2	NA	NA	NA	NA	NA	NA
HDL	Blood Urea Nitrogen	Inverse variance weighted	87	-0.002482399	0.009546535	0.794839511	173.5	59.2	131.01	0.0013	34.4	NA	NA	NA
HDL	Blood Urea Nitrogen	MR Egger	87	-0.041423301	0.020158288	0.042959047	173.5	59.2	NA	NA	NA	0.002692	0.001235	0.032
HDL	Blood Urea Nitrogen	Weighted median	87	-0.009884072	0.012604101	0.432925767	173.5	59.2	NA	NA	NA	NA	NA	NA
HDL	Blood Urea Nitrogen	Weighted mode	87	-0.015983739	0.013051035	0.224028423	173.5	59.2	NA	NA	NA	NA	NA	NA
HDL	CRP	Inverse variance weighted	86	-0.028107852	0.037522576	0.453801913	202.7	59.2	1744.41	0	95.1	NA	NA	NA
HDL	CRP	MR Egger	86	-0.073689937	0.076459753	0.337925534	202.7	59.2	NA	NA	NA	0.003178	0.00464	0.4953
HDL	CRP	Weighted median	86	-0.004965581	0.015559302	0.749621058	202.7	59.2	NA	NA	NA	NA	NA	NA
HDL	CRP	Weighted mode	86	-0.015375997	0.017944266	0.39392323	202.7	59.2	NA	NA	NA	NA	NA	NA
HDL	Coffee Consumption	Inverse variance weighted	100	-0.006403244	0.004628976	0.16657411	193.1	59.2	208.4	0	52.5	NA	NA	NA
HDL	Coffee Consumption	MR Egger	100	0.003229417	0.009110651	0.723751182	193.1	59.2	NA	NA	NA	-0.000704	0.000574	0.223
HDL	Coffee Consumption	Weighted median	100	8.02E-05	0.005107904	0.987479893	193.1	59.2	NA	NA	NA	NA	NA	NA
HDL	Coffee Consumption	Weighted mode	100	0.00087576	0.00576795	0.879628323	193.1	59.2	NA	NA	NA	NA	NA	NA
HDL	Cotinine	Inverse variance weighted	100	0.002682679	0.003116862	0.389403942	193.1	59.2	189.91	0	47.9	NA	NA	NA
HDL	Cotinine	MR Egger	100	0.016106348	0.005977838	0.008299113	193.1	59.2	NA	NA	NA	-0.000982	0.000377	0.0106
HDL	Cotinine	Weighted median	100	0.002134699	0.003769945	0.571229716	193.1	59.2	NA	NA	NA	NA	NA	NA
HDL	Cotinine	Weighted mode	100	0.004363224	0.004007249	0.278871093	193.1	59.2	NA	NA	NA	NA	NA	NA
HDL	Creatinine	Inverse variance weighted	100	-0.012036432	0.005779799	0.037296816	193.1	59.2	160.13	1.00E-04	38.2	NA	NA	NA
HDL	Creatinine	MR Egger	100	-0.015721483	0.011442131	0.172576312	193.1	59.2	NA	NA	NA	0.00027	0.000722	0.7094
HDL	Creatinine	Weighted median	100	-0.017703901	0.007590478	0.019680566	193.1	59.2	NA	NA	NA	NA	NA	NA
HDL	Creatinine	Weighted mode	100	-0.015777776	0.008475193	0.065620125	193.1	59.2	NA	NA	NA	NA	NA	NA
HDL	Cystatin C	Inverse variance weighted	86	-0.001952365	0.005003836	0.696408098	188.5	59.2	108.46	0.044	21.6	NA	NA	NA
HDL	Cystatin C	MR Egger	86	-0.001985192	0.011205716	0.85981009	188.5	59.2	NA	NA	NA	2.00E-06	0.000627	0.9974
HDL	Cystatin C	Weighted median	86	0.001166328	0.00683113	0.864430357	188.5	59.2	NA	NA	NA	NA	NA	NA
HDL	Cystatin C	Weighted mode	86	0.002785666	0.009322428	0.765811816	188.5	59.2	NA	NA	NA	NA	NA	NA
HDL	Fresh Fruit Consumption	Inverse variance weighted	92	0.007678107	0.010606163	0.469109481	201.7	59.2	118.99	0.0261	23.5	NA	NA	NA
HDL	Fresh Fruit Consumption	MR Egger	92	-0.012309238	0.020725756	0.554062051	201.7	59.2	NA	NA	NA	0.00151	0.001346	0.2649

HDL	Fresh Fruit Consumption	Weighted median	92	0.00404241	0.014567908	0.781405912	201.7	59.2	NA	NA	NA	NA	NA	NA
HDL	Fresh Fruit Consumption	Weighted mode	92	0.004532095	0.016776591	0.787661191	201.7	59.2	NA	NA	NA	NA	NA	NA
HDL	Gamma Glutamyl Transferase	Inverse variance weighted	87	-0.018501858	0.016354864	0.257939125	173.5	59.2	289.44	0	70.3	NA	NA	NA
HDL	Gamma Glutamyl Transferase	MR Egger	87	-0.026445173	0.035478503	0.458094743	173.5	59.2	NA	NA	NA	0.000549	0.002173	0.8011
HDL	Gamma Glutamyl Transferase	Weighted median	87	-0.006231789	0.016097807	0.698667107	173.5	59.2	NA	NA	NA	NA	NA	NA
HDL	Gamma Glutamyl Transferase	Weighted mode	87	-0.005805403	0.022161706	0.793981399	173.5	59.2	NA	NA	NA	NA	NA	NA
HDL	Impedance of Arm (Left)	Inverse variance weighted	100	0.015093721	0.008753516	0.084652996	193.1	59.2	660.66	0	85	NA	NA	NA
HDL	Impedance of Arm (Left)	MR Egger	100	-0.000442326	0.017247173	0.979591631	193.1	59.2	NA	NA	NA	0.001137	0.001088	0.2985
HDL	Impedance of Arm (Left)	Weighted median	100	0.010970845	0.005878292	0.061994915	193.1	59.2	NA	NA	NA	NA	NA	NA
HDL	Impedance of Arm (Left)	Weighted mode	100	0.0138742	0.006587196	0.037712701	193.1	59.2	NA	NA	NA	NA	NA	NA
HDL	Impedance of Arm (Right)	Inverse variance weighted	100	0.017167851	0.008876191	0.053095154	193.1	59.2	685.09	0	85.5	NA	NA	NA
HDL	Impedance of Arm (Right)	MR Egger	100	-0.003053554	0.017425748	0.861258649	193.1	59.2	NA	NA	NA	0.00148	0.001099	0.1812
HDL	Impedance of Arm (Right)	Weighted median	100	0.013373957	0.005933899	0.024207304	193.1	59.2	NA	NA	NA	NA	NA	NA
HDL	Impedance of Arm (Right)	Weighted mode	100	0.014119587	0.006762518	0.039372207	193.1	59.2	NA	NA	NA	NA	NA	NA
HDL	Overall Healthy Diet	Inverse variance weighted	100	0.015621378	0.004240882	0.000230034	193.1	59.2	97.96	0.5106	0	NA	NA	NA
HDL	Overall Healthy Diet	MR Egger	100	0.00776627	0.00837677	0.356141978	193.1	59.2	NA	NA	NA	0.000574	0.000528	0.2795
HDL	Overall Healthy Diet	Weighted median	100	0.019364642	0.006861905	0.004771769	193.1	59.2	NA	NA	NA	NA	NA	NA
HDL	Overall Healthy Diet	Weighted mode	100	0.015853421	0.007698227	0.042084708	193.1	59.2	NA	NA	NA	NA	NA	NA
HDL	Peak Expiratory Flow	Inverse variance weighted	100	0.009548232	0.005369096	0.075343321	193.1	59.2	156.47	2.00E-04	36.7	NA	NA	NA
HDL	Peak Expiratory Flow	MR Egger	100	0.013485124	0.010629101	0.207553885	193.1	59.2	NA	NA	NA	-0.000288	0.00067	0.6683
HDL	Peak Expiratory Flow	Weighted median	100	0.014535432	0.006574353	0.027040717	193.1	59.2	NA	NA	NA	NA	NA	NA
HDL	Peak Expiratory Flow	Weighted mode	100	0.014085886	0.006905696	0.044039071	193.1	59.2	NA	NA	NA	NA	NA	NA
HDL	Potassium in Urine	Inverse variance weighted	100	-0.000997533	0.005613525	0.858957292	193.1	59.2	134.35	0.0105	26.3	NA	NA	NA
HDL	Potassium in Urine	MR Egger	100	0.004732423	0.01110058	0.67080811	193.1	59.2	NA	NA	NA	-0.000419	7.00E-04	0.5506
HDL	Potassium in Urine	Weighted median	100	-0.002807412	0.007609454	0.712174426	193.1	59.2	NA	NA	NA	NA	NA	NA
HDL	Potassium in Urine	Weighted mode	100	0.001099124	0.008190157	0.8935164	193.1	59.2	NA	NA	NA	NA	NA	NA
HDL	Red Blood Cell Distribution	Inverse variance weighted	99	-0.081852655	0.024168861	0.00070739	193.7	59.2	1160.86	0	91.6	NA	NA	NA
HDL	Red Blood Cell Distribution	MR Egger	99	-0.008576803	0.047032018	0.855680065	193.7	59.2	NA	NA	NA	-0.005373	0.002971	0.0736
HDL	Red Blood Cell Distribution	Weighted median	99	-0.02324279	0.013359579	0.081896847	193.7	59.2	NA	NA	NA	NA	NA	NA
HDL	Red Blood Cell Distribution	Weighted mode	99	0.000210358	0.011695516	0.985686445	193.7	59.2	NA	NA	NA	NA	NA	NA
HDL	Serum Phosphate	Inverse variance weighted	94	-0.020986448	0.003666891	1.05E-08	193.5	59.2	110.73	0.1014	16	NA	NA	NA
HDL	Serum Phosphate	MR Egger	94	-0.020551506	0.007754555	0.009469024	193.5	59.2	NA	NA	NA	-2.90E-05	0.000456	0.9493
HDL	Serum Phosphate	Weighted median	94	-0.020110588	0.005289388	0.000143496	193.5	59.2	NA	NA	NA	NA	NA	NA
HDL	Serum Phosphate	Weighted mode	94	-0.021512964	0.006707481	0.001837863	193.5	59.2	NA	NA	NA	NA	NA	NA
HDL	Uric Acid	Inverse variance weighted	87	0.029280658	0.012012201	0.01478609	173.5	59.2	146.65	1.00E-04	41.4	NA	NA	NA
HDL	Uric Acid	MR Egger	87	0.005522648	0.025898721	0.83165024	173.5	59.2	NA	NA	NA	0.001642	0.001586	0.3034
HDL	Uric Acid	Weighted median	87	0.024306563	0.015016514	0.105521399	173.5	59.2	NA	NA	NA	NA	NA	NA
HDL	Uric Acid	Weighted mode	87	0.017380455	0.01937813	0.372270413	173.5	59.2	NA	NA	NA	NA	NA	NA
HDL	Sodium in Urine	Inverse variance weighted	100	-0.004055798	0.006058485	0.50321429	193.1	59.2	166.45	0	40.5	NA	NA	NA
HDL	Sodium in Urine	MR Egger	100	0.018507158	0.011707531	0.117148144	193.1	59.2	NA	NA	NA	-0.001652	0.000739	0.0276
HDL	Sodium in Urine	Weighted median	100	0.007763754	0.007709364	0.313908372	193.1	59.2	NA	NA	NA	NA	NA	NA
HDL	Sodium in Urine	Weighted mode	100	0.005364154	0.009089629	0.556441419	193.1	59.2	NA	NA	NA	NA	NA	NA
HDL	Tea Consumption	Inverse variance weighted	100	-2.689029899	1.814106078	0.138263353	193.1	59.2	98.77	0.4876	0	NA	NA	NA
HDL	Tea Consumption	MR Egger	100	2.285297723	3.583317454	0.525117049	193.1	59.2	NA	NA	NA	-0.363306	0.225695	0.1107
HDL	Tea Consumption	Weighted median	100	0.379498411	2.784046135	0.891574776	193.1	59.2	NA	NA	NA	NA	NA	NA
HDL	Tea Consumption	Weighted mode	100	-0.865406186	3.351197078	0.796759379	193.1	59.2	NA	NA	NA	NA	NA	NA
HDL	Testosterone	Inverse variance weighted	92	-0.024242907	0.010950161	0.026833491	201.7	59.2	270.84	0	66.4	NA	NA	NA
HDL	Testosterone	MR Egger	92	0.003881414	0.021284451	0.855711015	201.7	59.2	NA	NA	NA	-0.002123	0.001381	0.1278
HDL	Testosterone	Weighted median	92	-0.016637566	0.010477173	0.112290313	201.7	59.2	NA	NA	NA	NA	NA	NA
HDL	Testosterone	Weighted mode	92	-0.015918259	0.011314485	0.162865592	201.7	59.2	NA	NA	NA	NA	NA	NA
HDL	Urea	Inverse variance weighted	97	-0.053228651	0.030643116	0.082378198	196.9	59.2	82.6	0.8333	0	NA	NA	NA
HDL	Urea	MR Egger	97	-0.080479949	0.059528266	0.179597492	196.9	59.2	NA	NA	NA	0.00206	0.003858	0.5946
HDL	Urea	Weighted median	97	-0.034325202	0.045027475	0.44587093	196.9	59.2	NA	NA	NA	NA	NA	NA
HDL	Urea	Weighted mode	97	-0.035054848	0.047500391	0.462320298	196.9	59.2	NA	NA	NA	NA	NA	NA
HDL	Urinary Albumin Excretion	Inverse variance weighted	99	0.007754416	0.004908005	0.114117664	193.7	59.2	216.3	0	54.7	NA	NA	NA
HDL	Urinary Albumin Excretion	MR Egger	99	0.003403495	0.009673301	0.725718318	193.7	59.2	NA	NA	NA	0.00032	0.000611	0.6024
HDL	Urinary Albumin Excretion	Weighted median	99	0.006313628	0.005998111	0.292523063	193.7	59.2	NA	NA	NA	NA	NA	NA
HDL	Urinary Albumin Excretion	Weighted mode	99	0.002289377	0.00605782	0.706306684	193.7	59.2	NA	NA	NA	NA	NA	NA

HDL	25 Hydroxyvitamin D	Inverse variance weighted	95	0.056973559	0.016601219	0.000599391	193.1	59.2	1627.21	0	94.2	NA	NA	NA
HDL	25 Hydroxyvitamin D	MR Egger	95	0.072559186	0.032394632	0.027482985	193.1	59.2	NA	NA	NA	-0.001149	0.002048	0.5761
HDL	25 Hydroxyvitamin D	Weighted median	95	0.076266248	0.007769148	9.56E-23	193.1	59.2	NA	NA	NA	NA	NA	NA
HDL	25 Hydroxyvitamin D	Weighted mode	95	0.077166402	0.00804071	1.32E-15	193.1	59.2	NA	NA	NA	NA	NA	NA
HDL	Water Consumption	Inverse variance weighted	100	0.013278106	0.005936102	0.025296854	193.1	59.2	271.85	0	63.6	NA	NA	NA
HDL	Water Consumption	MR Egger	100	0.007312571	0.011750945	0.535192226	193.1	59.2	NA	NA	NA	0.000436	0.000741	0.5573
HDL	Water Consumption	Weighted median	100	0.007498897	0.005601406	0.180651261	193.1	59.2	NA	NA	NA	NA	NA	NA
HDL	Water Consumption	Weighted mode	100	0.00858713	0.005497264	0.121461807	193.1	59.2	NA	NA	NA	NA	NA	NA
HDL	X_11440	Inverse variance weighted	94	-0.010641631	0.012545963	0.396320145	193.5	59.2	113.95	0.0692	18.4	NA	NA	NA
HDL	X_11440	MR Egger	94	-0.005782994	0.026091583	0.825083723	193.5	59.2	NA	NA	NA	-0.000326	0.001531	0.832
HDL	X_11440	Weighted median	94	-0.024210902	0.018368625	0.187484445	193.5	59.2	NA	NA	NA	NA	NA	NA
HDL	X_11440	Weighted mode	94	-0.027333608	0.020756399	0.191115904	193.5	59.2	NA	NA	NA	NA	NA	NA
HDL	X_14473	Inverse variance weighted	94	0.025715813	0.010449251	0.013854269	193.5	59.2	81.98	0.786	0	NA	NA	NA
HDL	X_14473	MR Egger	94	0.017403371	0.021705234	0.424731801	193.5	59.2	NA	NA	NA	0.000555	0.00127	0.6632
HDL	X_14473	Weighted median	94	-0.002048058	0.016254435	0.899731984	193.5	59.2	NA	NA	NA	NA	NA	NA
HDL	X_14473	Weighted mode	94	-0.006799903	0.018511829	0.714209355	193.5	59.2	NA	NA	NA	NA	NA	NA
LDL	Bilirubin	Inverse variance weighted	77	-0.005908362	0.010320083	0.566975746	209.8	56.8	111.77	0.0048	32	NA	NA	NA
LDL	Bilirubin	MR Egger	77	-0.009013228	0.017687721	0.611845104	209.8	56.8	NA	NA	NA	0.000277	0.001276	0.8289
LDL	Bilirubin	Weighted median	77	0.002147642	0.012996188	0.868745865	209.8	56.8	NA	NA	NA	NA	NA	NA
LDL	Bilirubin	Weighted mode	77	-0.003527557	0.011872335	0.767182363	209.8	56.8	NA	NA	NA	NA	NA	NA
LDL	Blood Urea Nitrogen	Inverse variance weighted	77	0.001686189	0.010505381	0.872481607	209.8	56.8	168.01	0	54.8	NA	NA	NA
LDL	Blood Urea Nitrogen	MR Egger	77	0.040618865	0.01713679	0.020346271	209.8	56.8	NA	NA	NA	-0.00347	0.001236	0.0064
LDL	Blood Urea Nitrogen	Weighted median	77	0.018969522	0.011195212	0.090183292	209.8	56.8	NA	NA	NA	NA	NA	NA
LDL	Blood Urea Nitrogen	Weighted mode	77	0.014463582	0.010871726	0.187369754	209.8	56.8	NA	NA	NA	NA	NA	NA
LDL	CRP	Inverse variance weighted	90	0.109196645	0.043164075	0.011412629	199.1	56.8	2946.52	0	97	NA	NA	NA
LDL	CRP	MR Egger	90	0.167176756	0.080428673	0.040568492	199.1	56.8	NA	NA	NA	-0.004576	0.005353	0.3949
LDL	CRP	Weighted median	90	-0.013386645	0.017065012	0.432776229	199.1	56.8	NA	NA	NA	NA	NA	NA
LDL	CRP	Weighted mode	90	-0.026530704	0.021098725	0.211878423	199.1	56.8	NA	NA	NA	NA	NA	NA
LDL	Coffee Consumption	Inverse variance weighted	100	0.003947272	0.003393274	0.24472253	207.8	56.4	144.03	0.0021	31.3	NA	NA	NA
LDL	Coffee Consumption	MR Egger	100	0.010496076	0.005904431	0.078561469	207.8	56.4	NA	NA	NA	-0.000571	0.000422	0.1793
LDL	Coffee Consumption	Weighted median	100	0.002119906	0.00461747	0.64615837	207.8	56.4	NA	NA	NA	NA	NA	NA
LDL	Coffee Consumption	Weighted mode	100	0.003110328	0.005901292	0.599331845	207.8	56.4	NA	NA	NA	NA	NA	NA
LDL	Cotinine	Inverse variance weighted	100	0.010756816	0.002233197	1.46E-06	207.8	56.4	125.46	0.0374	21.1	NA	NA	NA
LDL	Cotinine	MR Egger	100	0.008374274	0.003910819	0.034728872	207.8	56.4	NA	NA	NA	0.000208	0.00028	0.4593
LDL	Cotinine	Weighted median	100	0.011241931	0.003236134	0.000512995	207.8	56.4	NA	NA	NA	NA	NA	NA
LDL	Cotinine	Weighted mode	100	0.001028293	0.005495721	0.851958851	207.8	56.4	NA	NA	NA	NA	NA	NA
LDL	Creatinine	Inverse variance weighted	99	-0.018041737	0.005752469	0.001710668	208.9	56.4	200.74	0	51.2	NA	NA	NA
LDL	Creatinine	MR Egger	99	-0.019759055	0.010086775	0.052995113	208.9	56.4	NA	NA	NA	0.00015	0.000723	0.8359
LDL	Creatinine	Weighted median	99	-0.019750266	0.006525558	0.002473196	208.9	56.4	NA	NA	NA	NA	NA	NA
LDL	Creatinine	Weighted mode	99	-0.016208562	0.006794202	0.018971307	208.9	56.4	NA	NA	NA	NA	NA	NA
LDL	Cystatin C	Inverse variance weighted	90	0.004671555	0.004666741	0.316811492	194	56.4	120.71	0.0142	26.3	NA	NA	NA
LDL	Cystatin C	MR Egger	90	0.003193478	0.009637467	0.741159873	194	56.4	NA	NA	NA	0.000106	0.000603	0.861
LDL	Cystatin C	Weighted median	90	0.010939527	0.006501816	0.092465335	194	56.4	NA	NA	NA	NA	NA	NA
LDL	Cystatin C	Weighted mode	90	0.013730151	0.009608948	0.156535624	194	56.4	NA	NA	NA	NA	NA	NA
LDL	Fresh Fruit Consumption	Inverse variance weighted	93	-0.044750225	0.010688925	2.83E-05	203	56.8	149.11	2.00E-04	38.3	NA	NA	NA
LDL	Fresh Fruit Consumption	MR Egger	93	-0.048474295	0.018624053	0.010796158	203	56.8	NA	NA	NA	0.000325	0.001328	0.8072
LDL	Fresh Fruit Consumption	Weighted median	93	-0.027464634	0.013207115	0.037568372	203	56.8	NA	NA	NA	NA	NA	NA
LDL	Fresh Fruit Consumption	Weighted mode	93	-0.033778149	0.016549784	0.044115518	203	56.8	NA	NA	NA	NA	NA	NA
LDL	Gamma Glutamyl Transferase	Inverse variance weighted	77	0.0054958	0.025211522	0.827438746	209.8	56.8	728.77	0	89.6	NA	NA	NA
LDL	Gamma Glutamyl Transferase	MR Egger	77	0.004959568	0.043234609	0.908979234	209.8	56.8	NA	NA	NA	4.80E-05	0.003119	0.9878
LDL	Gamma Glutamyl Transferase	Weighted median	77	0.012478256	0.014149098	0.377824527	209.8	56.8	NA	NA	NA	NA	NA	NA
LDL	Gamma Glutamyl Transferase	Weighted mode	77	0.0137815	0.013173443	0.298804119	209.8	56.8	NA	NA	NA	NA	NA	NA
LDL	Impedance of Arm (Left)	Inverse variance weighted	99	0.017004145	0.005804139	0.003393345	208.9	56.4	367.69	0	73.3	NA	NA	NA
LDL	Impedance of Arm (Left)	MR Egger	99	0.018807482	0.010175701	0.067609386	208.9	56.4	NA	NA	NA	-0.000158	0.00073	0.8292
LDL	Impedance of Arm (Left)	Weighted median	99	0.014738717	0.005034299	0.003415232	208.9	56.4	NA	NA	NA	NA	NA	NA
LDL	Impedance of Arm (Left)	Weighted mode	99	0.015071403	0.005262159	0.005115878	208.9	56.4	NA	NA	NA	NA	NA	NA
LDL	Impedance of Arm (Right)	Inverse variance weighted	99	0.016383274	0.005736011	0.004287264	208.9	56.4	362.16	0	72.9	NA	NA	NA
LDL	Impedance of Arm (Right)	MR Egger	99	0.018785865	0.010054364	0.064720327	208.9	56.4	NA	NA	NA	-0.00021	0.000721	0.7712

LDL	Impedance of Arm (Right)	Weighted median	99	0.011961988	0.005207653	0.021618679	208.9	56.4	NA	NA	NA	NA	NA	NA
LDL	Impedance of Arm (Right)	Weighted mode	99	0.012582122	0.005050465	0.014408444	208.9	56.4	NA	NA	NA	NA	NA	NA
LDL	Overall Healthy Diet	Inverse variance weighted	100	0.006755321	0.0039586	0.087916413	207.8	56.4	111.3	0.1874	11.1	NA	NA	NA
LDL	Overall Healthy Diet	MR Egger	100	0.002335354	0.006920065	0.73648006	207.8	56.4	NA	NA	NA	0.000386	0.000496	0.4376
LDL	Overall Healthy Diet	Weighted median	100	0.006865918	0.006234817	0.270800017	207.8	56.4	NA	NA	NA	NA	NA	NA
LDL	Overall Healthy Diet	Weighted mode	100	0.002307753	0.007401152	0.755840702	207.8	56.4	NA	NA	NA	NA	NA	NA
LDL	Peak Expiratory Flow	Inverse variance weighted	99	-0.0051614	0.005051944	0.306938972	208.9	56.4	175.35	0	44.1	NA	NA	NA
LDL	Peak Expiratory Flow	MR Egger	99	0.006232565	0.008747996	0.477892516	208.9	56.4	NA	NA	NA	-0.000997	0.000627	0.1152
LDL	Peak Expiratory Flow	Weighted median	99	-0.002799652	0.006472886	0.665363625	208.9	56.4	NA	NA	NA	NA	NA	NA
LDL	Peak Expiratory Flow	Weighted mode	99	0.002185768	0.00794881	0.783910098	208.9	56.4	NA	NA	NA	NA	NA	NA
LDL	Potassium in Urine	Inverse variance weighted	99	-0.003885039	0.004949468	0.432488415	208.9	56.4	132.18	0.0122	25.9	NA	NA	NA
LDL	Potassium in Urine	MR Egger	99	-0.00156462	0.008675836	0.857260125	208.9	56.4	NA	NA	NA	-0.000203	0.000622	0.7448
LDL	Potassium in Urine	Weighted median	99	0.003476309	0.006783858	0.608344289	208.9	56.4	NA	NA	NA	NA	NA	NA
LDL	Potassium in Urine	Weighted mode	99	0.003116937	0.007905837	0.694247428	208.9	56.4	NA	NA	NA	NA	NA	NA
LDL	Red Blood Cell Distribution	Inverse variance weighted	99	0.067169949	0.02726507	0.013755342	207.7	56.4	1917.29	0	94.9	NA	NA	NA
LDL	Red Blood Cell Distribution	MR Egger	99	0.113894908	0.047344494	0.018038664	207.7	56.4	NA	NA	NA	-0.004092	0.003394	0.2308
LDL	Red Blood Cell Distribution	Weighted median	99	0.096499195	0.015129697	1.79E-10	207.7	56.4	NA	NA	NA	NA	NA	NA
LDL	Red Blood Cell Distribution	Weighted mode	99	0.121509823	0.045725338	0.009195965	207.7	56.4	NA	NA	NA	NA	NA	NA
LDL	Serum Phosphate	Inverse variance weighted	96	-0.019818146	0.00368256	7.38E-08	205.5	56.4	145.55	7.00E-04	34.7	NA	NA	NA
LDL	Serum Phosphate	MR Egger	96	-0.026356451	0.006848628	0.000216604	205.5	56.4	NA	NA	NA	0.000523	0.000462	0.2607
LDL	Serum Phosphate	Weighted median	96	-0.020289446	0.005273622	0.000119404	205.5	56.4	NA	NA	NA	NA	NA	NA
LDL	Serum Phosphate	Weighted mode	96	-0.012248266	0.007562583	0.108635981	205.5	56.4	NA	NA	NA	NA	NA	NA
LDL	Uric Acid	Inverse variance weighted	77	0.005488579	0.011549441	0.63462684	209.8	56.8	143.25	0	46.9	NA	NA	NA
LDL	Uric Acid	MR Egger	77	0.006708751	0.019830145	0.73607427	209.8	56.8	NA	NA	NA	-0.000109	0.001429	0.9397
LDL	Uric Acid	Weighted median	77	0.017997775	0.015053631	0.231861666	209.8	56.8	NA	NA	NA	NA	NA	NA
LDL	Uric Acid	Weighted mode	77	0.010291118	0.016005392	0.522173459	209.8	56.8	NA	NA	NA	NA	NA	NA
LDL	Sodium in Urine	Inverse variance weighted	99	-0.012592484	0.00586787	0.031872493	208.9	56.4	197.62	0	50.4	NA	NA	NA
LDL	Sodium in Urine	MR Egger	99	-0.017489459	0.010273487	0.091885423	208.9	56.4	NA	NA	NA	0.000429	0.000737	0.5621
LDL	Sodium in Urine	Weighted median	99	-0.012299667	0.006916329	0.075346091	208.9	56.4	NA	NA	NA	NA	NA	NA
LDL	Sodium in Urine	Weighted mode	99	-0.011980862	0.008119719	0.143276766	208.9	56.4	NA	NA	NA	NA	NA	NA
LDL	Tea Consumption	Inverse variance weighted	100	-0.025146195	1.805583286	0.988888293	207.8	56.4	126.56	0.0323	21.8	NA	NA	NA
LDL	Tea Consumption	MR Egger	100	-0.217158096	3.166040814	0.945455896	207.8	56.4	NA	NA	NA	0.016783	0.226756	0.9412
LDL	Tea Consumption	Weighted median	100	-0.185317631	2.65667437	0.944388272	207.8	56.4	NA	NA	NA	NA	NA	NA
LDL	Tea Consumption	Weighted mode	100	-0.902142571	3.417997409	0.792375614	207.8	56.4	NA	NA	NA	NA	NA	NA
LDL	Testosterone	Inverse variance weighted	93	0.004363087	0.009250639	0.637174865	203	56.8	238.91	0	61.5	NA	NA	NA
LDL	Testosterone	MR Egger	93	-0.001158523	0.01610644	0.942816115	203	56.8	NA	NA	NA	0.000482	0.001148	0.6757
LDL	Testosterone	Weighted median	93	0.010960819	0.009799781	0.2633638	203	56.8	NA	NA	NA	NA	NA	NA
LDL	Testosterone	Weighted mode	93	0.005132418	0.011496381	0.656330153	203	56.8	NA	NA	NA	NA	NA	NA
LDL	Urea	Inverse variance weighted	96	0.036786239	0.032713708	0.260805187	206	56.4	128.23	0.0131	25.9	NA	NA	NA
LDL	Urea	MR Egger	96	0.067761739	0.058080606	0.246289147	206	56.4	NA	NA	NA	-0.002686	0.004155	0.5196
LDL	Urea	Weighted median	96	0.037671055	0.0445891	0.398195175	206	56.4	NA	NA	NA	NA	NA	NA
LDL	Urea	Weighted mode	96	0.02279391	0.055107803	0.680081756	206	56.4	NA	NA	NA	NA	NA	NA
LDL	Urinary Albumin Excretion	Inverse variance weighted	99	-0.017358429	0.003999845	1.43E-05	207.7	56.4	184.21	0	46.8	NA	NA	NA
LDL	Urinary Albumin Excretion	MR Egger	99	-0.018986505	0.006996243	0.007872196	207.7	56.4	NA	NA	NA	0.000142	0.000501	0.7768
LDL	Urinary Albumin Excretion	Weighted median	99	-0.020203964	0.004876624	3.43E-05	207.7	56.4	NA	NA	NA	NA	NA	NA
LDL	Urinary Albumin Excretion	Weighted mode	99	-0.021065333	0.005194633	0.000100577	207.7	56.4	NA	NA	NA	NA	NA	NA
LDL	25 Hydroxyvitamin D	Inverse variance weighted	96	0.087265302	0.011221703	7.46E-15	213.2	56.4	1004.64	0	90.5	NA	NA	NA
LDL	25 Hydroxyvitamin D	MR Egger	96	0.093981353	0.019548506	5.79E-06	213.2	56.4	NA	NA	NA	-0.000598	0.001423	0.6751
LDL	25 Hydroxyvitamin D	Weighted median	96	0.087169918	0.006765113	5.45E-38	213.2	56.4	NA	NA	NA	NA	NA	NA
LDL	25 Hydroxyvitamin D	Weighted mode	96	0.087875901	0.006142064	1.96E-25	213.2	56.4	NA	NA	NA	NA	NA	NA
LDL	Water Consumption	Inverse variance weighted	100	-0.012761047	0.004911993	0.009378582	207.8	56.4	239.48	0	58.7	NA	NA	NA
LDL	Water Consumption	MR Egger	100	-0.017679784	0.008606465	0.042614223	207.8	56.4	NA	NA	NA	0.000429	0.000616	0.4875
LDL	Water Consumption	Weighted median	100	-0.010598372	0.005714791	0.063660368	207.8	56.4	NA	NA	NA	NA	NA	NA
LDL	Water Consumption	Weighted mode	100	-0.003607076	0.006179064	0.560711095	207.8	56.4	NA	NA	NA	NA	NA	NA
LDL	X_11440	Inverse variance weighted	96	0.032550258	0.011503086	0.004659198	205.5	56.4	129.09	0.0115	26.4	NA	NA	NA
LDL	X_11440	MR Egger	96	0.020910939	0.021519624	0.333686243	205.5	56.4	NA	NA	NA	0.000929	0.00145	0.5232
LDL	X_11440	Weighted median	96	0.022057596	0.015831222	0.163529969	205.5	56.4	NA	NA	NA	NA	NA	NA
LDL	X_11440	Weighted mode	96	0.01758973	0.020011475	0.381628821	205.5	56.4	NA	NA	NA	NA	NA	NA

LDL	X_14473	Inverse variance weighted	96	0.004259686	0.009785149	0.663329028	205.5	56.4	107.49	0.1796	11.6	NA	NA	NA
LDL	X_14473	MR Egger	96	0.017966745	0.018416498	0.331777199	205.5	56.4	NA	NA	NA	-0.001081	0.00123	0.3817
LDL	X_14473	Weighted median	96	0.010379078	0.01508317	0.491375253	205.5	56.4	NA	NA	NA	NA	NA	NA
LDL	X_14473	Weighted mode	96	0.014260162	0.018768569	0.44926178	205.5	56.4	NA	NA	NA	NA	NA	NA
MetS	Bilirubin	Inverse variance weighted	66	-0.002996318	0.013596331	0.825577571	98.6	41	191.58	0	66.1	NA	NA	NA
MetS	Bilirubin	MR Egger	66	0.047383475	0.032197995	0.146021697	98.6	41	NA	NA	NA	-0.004616	0.002683	0.0901
MetS	Bilirubin	Weighted median	66	0.017068869	0.012767799	0.181265552	98.6	41	NA	NA	NA	NA	NA	NA
MetS	Bilirubin	Weighted mode	66	0.022185627	0.014202617	0.123125074	98.6	41	NA	NA	NA	NA	NA	NA
MetS	Blood Urea Nitrogen	Inverse variance weighted	66	0.001776548	0.010234865	0.862197047	98.6	41	157.46	0	58.7	NA	NA	NA
MetS	Blood Urea Nitrogen	MR Egger	66	-0.015108462	0.024677451	0.54254977	98.6	41	NA	NA	NA	0.001547	0.002057	0.4545
MetS	Blood Urea Nitrogen	Weighted median	66	-0.000597272	0.010791344	0.955861742	98.6	41	NA	NA	NA	NA	NA	NA
MetS	Blood Urea Nitrogen	Weighted mode	66	-0.010404699	0.012534046	0.409512345	98.6	41	NA	NA	NA	NA	NA	NA
MetS	CRP	Inverse variance weighted	40	0.024207255	0.043257758	0.575748941	110.9	42.1	966.36	0	96	NA	NA	NA
MetS	CRP	MR Egger	40	-0.022374415	0.111630595	0.842211115	110.9	42.1	NA	NA	NA	0.004085	0.009007	0.6528
MetS	CRP	Weighted median	40	0.005834856	0.014240112	0.681990922	110.9	42.1	NA	NA	NA	NA	NA	NA
MetS	CRP	Weighted mode	40	0.007712308	0.016835584	0.649426045	110.9	42.1	NA	NA	NA	NA	NA	NA
MetS	Coffee Consumption	Inverse variance weighted	96	-0.003369162	0.006513871	0.604996371	97.8	41	616.29	0	84.6	NA	NA	NA
MetS	Coffee Consumption	MR Egger	96	-0.018770925	0.0151516	0.218476753	97.8	41	NA	NA	NA	0.001429	0.00127	0.2632
MetS	Coffee Consumption	Weighted median	96	-0.007925792	0.004192387	0.058688449	97.8	41	NA	NA	NA	NA	NA	NA
MetS	Coffee Consumption	Weighted mode	96	-0.006978466	0.006477442	0.284052452	97.8	41	NA	NA	NA	NA	NA	NA
MetS	Cotinine	Inverse variance weighted	96	0.006374746	0.00272129	0.019152686	97.8	41	216.25	0	56.1	NA	NA	NA
MetS	Cotinine	MR Egger	96	-0.003576372	0.006269142	0.569718573	97.8	41	NA	NA	NA	0.000924	0.000526	0.0821
MetS	Cotinine	Weighted median	96	0.00315731	0.003013271	0.29473007	97.8	41	NA	NA	NA	NA	NA	NA
MetS	Cotinine	Weighted mode	96	0.001358708	0.006498634	0.83483665	97.8	41	NA	NA	NA	NA	NA	NA
MetS	Creatinine	Inverse variance weighted	96	-0.013280867	0.00624666	0.033497037	97.8	41	279.17	0	66	NA	NA	NA
MetS	Creatinine	MR Egger	96	-0.000102977	0.014531143	0.994360764	97.8	41	NA	NA	NA	-0.001224	0.001219	0.3178
MetS	Creatinine	Weighted median	96	-0.010323052	0.006159927	0.093769577	97.8	41	NA	NA	NA	NA	NA	NA
MetS	Creatinine	Weighted mode	96	-0.004380246	0.011056113	0.692858331	97.8	41	NA	NA	NA	NA	NA	NA
MetS	Cystatin C	Inverse variance weighted	38	-0.004078749	0.004925074	0.407579924	112.1	42.1	43.03	0.229	14	NA	NA	NA
MetS	Cystatin C	MR Egger	38	-0.008000272	0.012549309	0.527828715	112.1	42.1	NA	NA	NA	0.000341	0.001003	0.7355
MetS	Cystatin C	Weighted median	38	8.72E-05	0.007129812	0.990237787	112.1	42.1	NA	NA	NA	NA	NA	NA
MetS	Cystatin C	Weighted mode	38	0.00452218	0.011000093	0.683367862	112.1	42.1	NA	NA	NA	NA	NA	NA
MetS	Fresh Fruit Consumption	Inverse variance weighted	91	0.014453212	0.011650872	0.214780815	100.4	41	223.88	0	59.8	NA	NA	NA
MetS	Fresh Fruit Consumption	MR Egger	91	-0.01527571	0.026712616	0.568862598	100.4	41	NA	NA	NA	0.002798	0.002264	0.2197
MetS	Fresh Fruit Consumption	Weighted median	91	-0.007096173	0.011430873	0.534737739	100.4	41	NA	NA	NA	NA	NA	NA
MetS	Fresh Fruit Consumption	Weighted mode	91	-0.019271745	0.020769126	0.355939466	100.4	41	NA	NA	NA	NA	NA	NA
MetS	Gamma Glutamyl Transferase	Inverse variance weighted	66	0.021308511	0.019756933	0.280795823	98.6	41	442.04	0	85.3	NA	NA	NA
MetS	Gamma Glutamyl Transferase	MR Egger	66	0.011164708	0.047835563	0.816197546	98.6	41	NA	NA	NA	0.00093	0.003986	0.8164
MetS	Gamma Glutamyl Transferase	Weighted median	66	0.019173194	0.012567256	0.127097853	98.6	41	NA	NA	NA	NA	NA	NA
MetS	Gamma Glutamyl Transferase	Weighted mode	66	0.01763144	0.013880021	0.208515025	98.6	41	NA	NA	NA	NA	NA	NA
MetS	Impedance of Arm (Left)	Inverse variance weighted	96	0.049504176	0.012033807	3.89E-05	97.8	41	1863.74	0	94.9	NA	NA	NA
MetS	Impedance of Arm (Left)	MR Egger	96	-0.027996314	0.026718837	0.297412021	97.8	41	NA	NA	NA	0.007199	0.002241	0.0018
MetS	Impedance of Arm (Left)	Weighted median	96	0.018719334	0.004842613	0.000110842	97.8	41	NA	NA	NA	NA	NA	NA
MetS	Impedance of Arm (Left)	Weighted mode	96	0.017649497	0.006122081	0.004872772	97.8	41	NA	NA	NA	NA	NA	NA
MetS	Impedance of Arm (Right)	Inverse variance weighted	96	0.050585052	0.01208421	2.84E-05	97.8	41	1895.39	0	95	NA	NA	NA
MetS	Impedance of Arm (Right)	MR Egger	96	-0.028275094	0.026791313	0.293955242	97.8	41	NA	NA	NA	0.007326	0.002247	0.0016
MetS	Impedance of Arm (Right)	Weighted median	96	0.018976737	0.004590696	3.57E-05	97.8	41	NA	NA	NA	NA	NA	NA
MetS	Impedance of Arm (Right)	Weighted mode	96	0.017281022	0.005588999	0.002610019	97.8	41	NA	NA	NA	NA	NA	NA
MetS	Overall Healthy Diet	Inverse variance weighted	95	0.01113522	0.003405379	0.001075889	98.4	41	75.39	0.9207	0	NA	NA	NA
MetS	Overall Healthy Diet	MR Egger	95	0.021673874	0.007928403	0.007497482	98.4	41	NA	NA	NA	-0.00098	0.000666	0.1444
MetS	Overall Healthy Diet	Weighted median	95	0.016018496	0.004901221	0.001082084	98.4	41	NA	NA	NA	NA	NA	NA
MetS	Overall Healthy Diet	Weighted mode	95	0.020550093	0.009611981	0.035113235	98.4	41	NA	NA	NA	NA	NA	NA
MetS	Peak Expiratory Flow	Inverse variance weighted	96	0.000621368	0.005430256	0.908899304	97.8	41	238.92	0	60.2	NA	NA	NA
MetS	Peak Expiratory Flow	MR Egger	96	0.000570762	0.012701702	0.964253753	97.8	41	NA	NA	NA	5.00E-06	0.001065	0.9965
MetS	Peak Expiratory Flow	Weighted median	96	0.011171649	0.005485305	0.041685085	97.8	41	NA	NA	NA	NA	NA	NA
MetS	Peak Expiratory Flow	Weighted mode	96	0.018506032	0.008108849	0.02470876	97.8	41	NA	NA	NA	NA	NA	NA
MetS	Potassium in Urine	Inverse variance weighted	96	0.001209995	0.005516093	0.826371693	97.8	41	193.62	0	50.9	NA	NA	NA
MetS	Potassium in Urine	MR Egger	96	0.028327059	0.012522932	0.026000366	97.8	41	NA	NA	NA	-0.002519	0.00105	0.0184

MetS	Potassium in Urine	Weighted median	96	0.007197408	0.006689963	0.281993613	97.8	41	NA	NA	NA	NA	NA	NA
MetS	Potassium in Urine	Weighted mode	96	0.009801667	0.010584736	0.356782564	97.8	41	NA	NA	NA	NA	NA	NA
MetS	Red Blood Cell Distribution	Inverse variance weighted	100	-0.089072919	0.016046135	2.84E-08	97.4	41	841.47	0	88.2	NA	NA	NA
MetS	Red Blood Cell Distribution	MR Egger	100	-0.100985806	0.036812704	0.007234867	97.4	41	NA	NA	NA	0.001108	0.003079	0.7197
MetS	Red Blood Cell Distribution	Weighted median	100	-0.100421653	0.01152905	3.03E-18	97.4	41	NA	NA	NA	NA	NA	NA
MetS	Red Blood Cell Distribution	Weighted mode	100	-0.133173068	0.025341684	8.51E-07	97.4	41	NA	NA	NA	NA	NA	NA
MetS	Serum Phosphate	Inverse variance weighted	41	-0.01638736	0.003957979	3.47E-05	110.4	42.1	47.39	0.1966	15.6	NA	NA	NA
MetS	Serum Phosphate	MR Egger	41	-0.000781301	0.00998831	0.93805178	110.4	42.1	NA	NA	NA	-0.001359	0.000802	0.0981
MetS	Serum Phosphate	Weighted median	41	-0.012933585	0.005643564	0.021920607	110.4	42.1	NA	NA	NA	NA	NA	NA
MetS	Serum Phosphate	Weighted mode	41	-0.009841349	0.009396725	0.301240879	110.4	42.1	NA	NA	NA	NA	NA	NA
MetS	Uric Acid	Inverse variance weighted	66	0.037238327	0.014089406	0.008217459	98.6	41	210.93	0	69.2	NA	NA	NA
MetS	Uric Acid	MR Egger	66	-0.033801191	0.032698521	0.305156435	98.6	41	NA	NA	NA	0.006511	0.002725	0.0198
MetS	Uric Acid	Weighted median	66	0.014520813	0.013333293	0.276125536	98.6	41	NA	NA	NA	NA	NA	NA
MetS	Uric Acid	Weighted mode	66	0.002719416	0.015218505	0.858735795	98.6	41	NA	NA	NA	NA	NA	NA
MetS	Sodium in Urine	Inverse variance weighted	96	-0.009762049	0.007061889	0.166862257	97.8	41	337.56	0	71.9	NA	NA	NA
MetS	Sodium in Urine	MR Egger	96	0.027724583	0.015950517	0.085456846	97.8	41	NA	NA	NA	-0.003483	0.001338	0.0107
MetS	Sodium in Urine	Weighted median	96	0.001641185	0.005976547	0.783620349	97.8	41	NA	NA	NA	NA	NA	NA
MetS	Sodium in Urine	Weighted mode	96	0.003618474	0.01033695	0.7270743	97.8	41	NA	NA	NA	NA	NA	NA
MetS	Tea Consumption	Inverse variance weighted	96	-2.077424983	1.661151775	0.211082962	97.8	41	124.1	0.0242	23.4	NA	NA	NA
MetS	Tea Consumption	MR Egger	96	4.613007755	3.816416443	0.229799276	97.8	41	NA	NA	NA	-0.620694	0.319815	0.0553
MetS	Tea Consumption	Weighted median	96	-1.886992892	2.218871368	0.395086535	97.8	41	NA	NA	NA	NA	NA	NA
MetS	Tea Consumption	Weighted mode	96	-0.776129066	3.764001188	0.837077604	97.8	41	NA	NA	NA	NA	NA	NA
MetS	Testosterone	Inverse variance weighted	91	-0.043974541	0.010479746	2.71E-05	100.4	41	386.82	0	76.7	NA	NA	NA
MetS	Testosterone	MR Egger	91	0.003004705	0.023619877	0.899060472	100.4	41	NA	NA	NA	-0.00442	0.002001	0.0298
MetS	Testosterone	Weighted median	91	-0.034325468	0.007686925	7.99E-06	100.4	41	NA	NA	NA	NA	NA	NA
MetS	Testosterone	Weighted mode	91	-0.032833813	0.010758585	0.002989041	100.4	41	NA	NA	NA	NA	NA	NA
MetS	Urea	Inverse variance weighted	92	-0.025007055	0.025719924	0.330909581	97.5	41	92.06	0.4493	1.1	NA	NA	NA
MetS	Urea	MR Egger	92	-0.005292876	0.060159176	0.930087097	97.5	41	NA	NA	NA	-0.001812	0.004993	0.7175
MetS	Urea	Weighted median	92	-0.006583247	0.038779192	0.865197038	97.5	41	NA	NA	NA	NA	NA	NA
MetS	Urea	Weighted mode	92	-0.000792482	0.057034043	0.988944253	97.5	41	NA	NA	NA	NA	NA	NA
MetS	Urinary Albumin Excretion	Inverse variance weighted	96	0.014223408	0.004223372	0.000757747	97.8	41	243.24	0	60.9	NA	NA	NA
MetS	Urinary Albumin Excretion	MR Egger	96	0.009559829	0.009864632	0.334981501	97.8	41	NA	NA	NA	0.000433	0.000827	0.6018
MetS	Urinary Albumin Excretion	Weighted median	96	0.012207157	0.004606338	0.008047311	97.8	41	NA	NA	NA	NA	NA	NA
MetS	Urinary Albumin Excretion	Weighted mode	96	0.012681698	0.009223891	0.17240424	97.8	41	NA	NA	NA	NA	NA	NA
MetS	25 Hydroxyvitamin D	Inverse variance weighted	89	-0.020710068	0.013319191	0.119968849	101.5	41	1539.28	0	94.3	NA	NA	NA
MetS	25 Hydroxyvitamin D	MR Egger	89	-0.015063033	0.030448034	0.62204987	101.5	41	NA	NA	NA	-0.000534	0.002586	0.8369
MetS	25 Hydroxyvitamin D	Weighted median	89	-0.020766065	0.006780626	0.002194535	101.5	41	NA	NA	NA	NA	NA	NA
MetS	48 Hydroxyvitamin D	Weighted mode	89	-0.018947501	0.010079668	0.063447722	101.5	41	NA	NA	NA	NA	NA	NA
MetS	Water Consumption	Inverse variance weighted	96	0.017757287	0.005045301	0.000432248	97.8	41	293.33	0	67.6	NA	NA	NA
MetS	Water Consumption	MR Egger	96	0.007738008	0.011757777	0.512070732	97.8	41	NA	NA	NA	0.00093	0.000986	0.3478
MetS	Water Consumption	Weighted median	96	0.010144638	0.004765546	0.033275249	97.8	41	NA	NA	NA	NA	NA	NA
MetS	Water Consumption	Weighted mode	96	0.00632067	0.007171161	0.380325291	97.8	41	NA	NA	NA	NA	NA	NA
MetS	X_11440	Inverse variance weighted	41	-0.001238209	0.014584734	0.932342791	110.4	42.1	60.2	0.021	33.6	NA	NA	NA
MetS	X_11440	MR Egger	41	0.029540821	0.037326911	0.433492898	110.4	42.1	NA	NA	NA	-0.002685	0.002996	0.3756
MetS	X_11440	Weighted median	41	-0.008690566	0.018589563	0.64014432	110.4	42.1	NA	NA	NA	NA	NA	NA
MetS	X_11440	Weighted mode	41	-0.008007754	0.026094493	0.760530238	110.4	42.1	NA	NA	NA	NA	NA	NA
MetS	X_14473	Inverse variance weighted	41	0.005895679	0.012361205	0.633397615	110.4	42.1	50.81	0.1177	21.3	NA	NA	NA
MetS	X_14473	MR Egger	41	-0.021979896	0.031751958	0.492889408	110.4	42.1	NA	NA	NA	0.002431	0.00255	0.3463
MetS	X_14473	Weighted median	41	-0.010611901	0.015822623	0.502425041	110.4	42.1	NA	NA	NA	NA	NA	NA
MetS	X_14473	Weighted mode	41	-0.006057341	0.019306603	0.755345446	110.4	42.1	NA	NA	NA	NA	NA	NA
SBP	Bilirubin	Inverse variance weighted	85	-0.000588444	0.001525836	0.699753359	182.5	103.5	162.85	0	48.4	NA	NA	NA
SBP	Bilirubin	MR Egger	85	0.007060611	0.004448051	0.116236033	182.5	103.5	NA	NA	NA	-0.004055	0.002219	0.0712
SBP	Bilirubin	Weighted median	85	-0.000383283	0.001817311	0.832960094	182.5	103.5	NA	NA	NA	NA	NA	NA
SBP	Bilirubin	Weighted mode	85	0.002381337	0.002864198	0.408096426	182.5	103.5	NA	NA	NA	NA	NA	NA
SBP	Blood Urea Nitrogen	Inverse variance weighted	85	-0.001774552	0.001808126	0.326379932	182.5	103.5	331.57	0	74.7	NA	NA	NA
SBP	Blood Urea Nitrogen	MR Egger	85	0.000502361	0.005369598	0.925686846	182.5	103.5	NA	NA	NA	-0.001207	0.002679	0.6534
SBP	Blood Urea Nitrogen	Weighted median	85	-0.003599253	0.001596009	0.024123415	182.5	103.5	NA	NA	NA	NA	NA	NA
SBP	Blood Urea Nitrogen	Weighted mode	85	-0.005344546	0.002303784	0.022772859	182.5	103.5	NA	NA	NA	NA	NA	NA

SBP	CRP	Inverse variance weighted	43	-0.003710222	0.002496407	0.137219651	188.3	103.5	145.59	0	71.2	NA	NA	NA
SBP	CRP	MR Egger	43	0.012607049	0.007606554	0.10507362	188.3	103.5	NA	NA	NA	-0.008134	0.003601	0.0293
SBP	CRP	Weighted median	43	-0.001491963	0.002123756	0.482360112	188.3	103.5	NA	NA	NA	NA	NA	NA
SBP	CRP	Weighted mode	43	-0.001481352	0.003580064	0.681142104	188.3	103.5	NA	NA	NA	NA	NA	NA
SBP	Coffee Consumption	Inverse variance weighted	100	0.001829723	0.000719249	0.010961099	189.9	103.5	344.08	0	71.2	NA	NA	NA
SBP	Coffee Consumption	MR Egger	100	0.005264659	0.002361213	0.028054048	189.9	103.5	NA	NA	NA	-0.001735	0.001136	0.1302
SBP	Coffee Consumption	Weighted median	100	0.001882592	0.000626919	0.002673961	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	Coffee Consumption	Weighted mode	100	0.002320442	0.001070394	0.03256794	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	Cotinine	Inverse variance weighted	100	0.000616234	0.000420338	0.14263633	189.9	103.5	236.31	0	58.1	NA	NA	NA
SBP	Cotinine	MR Egger	100	0.001118744	0.00139514	0.424558943	189.9	103.5	NA	NA	NA	-0.000254	0.000672	0.7063
SBP	Cotinine	Weighted median	100	0.000696691	0.000427726	0.103349695	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	Cotinine	Weighted mode	100	0.000847675	0.000842451	0.316772166	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	Creatinine	Inverse variance weighted	100	-0.001661861	0.000963601	0.084592952	189.9	103.5	303.92	0	67.4	NA	NA	NA
SBP	Creatinine	MR Egger	100	-0.003208526	0.003196812	0.318012148	189.9	103.5	NA	NA	NA	0.000781	0.001539	0.6129
SBP	Creatinine	Weighted median	100	-0.000471991	0.00096363	0.624271927	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	Creatinine	Weighted mode	100	-6.03E-05	0.002040744	0.976490674	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	Cystatin C	Inverse variance weighted	43	0.000856907	0.000863318	0.320917525	188.3	103.5	65.29	0.0122	35.7	NA	NA	NA
SBP	Cystatin C	MR Egger	43	-0.005605731	0.002581356	0.035723198	188.3	103.5	NA	NA	NA	0.003203	0.001215	0.0118
SBP	Cystatin C	Weighted median	43	0.000567965	0.001019142	0.577324384	188.3	103.5	NA	NA	NA	NA	NA	NA
SBP	Cystatin C	Weighted mode	43	-0.000222975	0.001923479	0.908266177	188.3	103.5	NA	NA	NA	NA	NA	NA
SBP	Fresh Fruit Consumption	Inverse variance weighted	100	-0.00216331	0.001661949	0.19302889	189.9	103.5	226.51	0	56.3	NA	NA	NA
SBP	Fresh Fruit Consumption	MR Egger	100	0.003922457	0.005480544	0.475874932	189.9	103.5	NA	NA	NA	-0.003074	0.002638	0.2468
SBP	Fresh Fruit Consumption	Weighted median	100	-0.004077349	0.001693276	0.016041768	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	Fresh Fruit Consumption	Weighted mode	100	-0.00520334	0.003341352	0.122600849	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	Gamma Glutamyl Transferase	Inverse variance weighted	85	-0.000638363	0.001530457	0.67660092	182.5	103.5	178.85	0	53	NA	NA	NA
SBP	Gamma Glutamyl Transferase	MR Egger	85	0.000167435	0.004549946	0.970733361	182.5	103.5	NA	NA	NA	-0.000427	0.00227	0.8512
SBP	Gamma Glutamyl Transferase	Weighted median	85	0.002040505	0.001686153	0.226219729	182.5	103.5	NA	NA	NA	NA	NA	NA
SBP	Gamma Glutamyl Transferase	Weighted mode	85	0.001805122	0.002530159	0.477549627	182.5	103.5	NA	NA	NA	NA	NA	NA
SBP	Impedance of Arm (Left)	Inverse variance weighted	100	0.002023139	0.001499375	0.177233723	189.9	103.5	1323.51	0	92.5	NA	NA	NA
SBP	Impedance of Arm (Left)	MR Egger	100	0.007319906	0.004949433	0.142363986	189.9	103.5	NA	NA	NA	-0.002675	0.002382	0.2643
SBP	Impedance of Arm (Left)	Weighted median	100	0.00197435	0.000877187	0.024399808	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	Impedance of Arm (Left)	Weighted mode	100	0.002075668	0.001395729	0.140151479	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	Impedance of Arm (Right)	Inverse variance weighted	100	0.002179683	0.001501936	0.146710603	189.9	103.5	1339.33	0	92.6	NA	NA	NA
SBP	Impedance of Arm (Right)	MR Egger	100	0.006861482	0.004964955	0.170119058	189.9	103.5	NA	NA	NA	-0.002364	0.00239	0.3249
SBP	Impedance of Arm (Right)	Weighted median	100	0.00160014	0.000828594	0.053464381	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	Impedance of Arm (Right)	Weighted mode	100	0.002100561	0.001509079	0.167057173	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	Overall Healthy Diet	Inverse variance weighted	100	-0.000607223	0.000512035	0.235660811	189.9	103.5	74.04	0.9714	0	NA	NA	NA
SBP	Overall Healthy Diet	MR Egger	100	-0.00034693	0.0016912	0.837889684	189.9	103.5	NA	NA	NA	-0.000132	0.000814	0.872
SBP	Overall Healthy Diet	Weighted median	100	-0.000827603	0.000720004	0.250373782	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	Overall Healthy Diet	Weighted mode	100	-0.001558706	0.00170657	0.363274288	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	Peak Expiratory Flow	Inverse variance weighted	100	-0.002569742	0.000907254	0.004619447	189.9	103.5	305.12	0	67.6	NA	NA	NA
SBP	Peak Expiratory Flow	MR Egger	100	-0.003213267	0.003012955	0.28882555	189.9	103.5	NA	NA	NA	0.000325	0.00145	0.8232
SBP	Peak Expiratory Flow	Weighted median	100	-0.002429845	0.00087949	0.005730992	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	Peak Expiratory Flow	Weighted mode	100	-0.004150873	0.001900464	0.031313338	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	Potassium in Urine	Inverse variance weighted	100	-0.000681927	0.00094384	0.469985456	189.9	103.5	259.34	0	61.8	NA	NA	NA
SBP	Potassium in Urine	MR Egger	100	0.002450145	0.003117769	0.433842691	189.9	103.5	NA	NA	NA	-0.001582	0.001501	0.2945
SBP	Potassium in Urine	Weighted median	100	0.00011509	0.00099687	0.90808716	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	Potassium in Urine	Weighted mode	100	0.001365506	0.001868313	0.466580849	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	Red Blood Cell Distribution	Inverse variance weighted	100	0.002467242	0.002974515	0.40684402	189.9	103.5	1240.58	0	92	NA	NA	NA
SBP	Red Blood Cell Distribution	MR Egger	100	0.003782931	0.009688576	0.697049226	189.9	103.5	NA	NA	NA	-0.00067	0.00469	0.8868
SBP	Red Blood Cell Distribution	Weighted median	100	0.000620555	0.00153198	0.685428285	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	Red Blood Cell Distribution	Weighted mode	100	-2.34E-05	0.003670995	0.994918675	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	Serum Phosphate	Inverse variance weighted	45	-0.000433759	0.000558342	0.437236204	186.3	103.5	32.37	0.9026	0	NA	NA	NA
SBP	Serum Phosphate	MR Egger	45	0.000879142	0.001769214	0.621783214	186.3	103.5	NA	NA	NA	-0.00066	0.000844	0.4385
SBP	Serum Phosphate	Weighted median	45	0.000253315	0.00083635	0.761979628	186.3	103.5	NA	NA	NA	NA	NA	NA
SBP	Serum Phosphate	Weighted mode	45	0.000670253	0.001456022	0.64754496	186.3	103.5	NA	NA	NA	NA	NA	NA
SBP	Uric Acid	Inverse variance weighted	85	-0.004594299	0.002554599	0.072106933	182.5	103.5	467.85	0	82	NA	NA	NA
SBP	Uric Acid	MR Egger	85	0.000739518	0.007566952	0.922382368	182.5	103.5	NA	NA	NA	-0.002829	0.003776	0.4559

SBP	Uric Acid	Weighted median	85	-0.005274108	0.001983519	0.007838111	182.5	103.5	NA	NA	NA	NA	NA	NA
SBP	Uric Acid	Weighted mode	85	-0.008393874	0.002930212	0.005273066	182.5	103.5	NA	NA	NA	NA	NA	NA
SBP	Sodium in Urine	Inverse variance weighted	100	-0.003478329	0.000946968	0.000239606	189.9	103.5	277.69	0	64.3	NA	NA	NA
SBP	Sodium in Urine	MR Egger	100	-0.004766046	0.003142807	0.132613844	189.9	103.5	NA	NA	NA	0.00065	0.001513	0.6682
SBP	Sodium in Urine	Weighted median	100	-0.004092914	0.001001853	4.40E-05	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	Sodium in Urine	Weighted mode	100	-0.005642877	0.002612036	0.033159966	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	Tea Consumption	Inverse variance weighted	100	-0.109320407	0.256746464	0.670259936	189.9	103.5	136.04	0.008	27.2	NA	NA	NA
SBP	Tea Consumption	MR Egger	100	-1.034848012	0.846657431	0.224535368	189.9	103.5	NA	NA	NA	0.467579	0.407658	0.2542
SBP	Tea Consumption	Weighted median	100	-0.534585855	0.329797571	0.105028049	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	Tea Consumption	Weighted mode	100	-0.841448639	0.78007444	0.283352735	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	Testosterone	Inverse variance weighted	100	0.000593966	0.001829089	0.745383076	189.9	103.5	586.83	0	83.1	NA	NA	NA
SBP	Testosterone	MR Egger	100	0.001427933	0.006071628	0.814558798	189.9	103.5	NA	NA	NA	-0.000421	0.002923	0.8857
SBP	Testosterone	Weighted median	100	6.01E-05	0.001324058	0.96377356	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	Testosterone	Weighted mode	100	-0.000155379	0.002573822	0.951983616	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	Urea	Inverse variance weighted	99	-0.00734979	0.004657598	0.114560676	189.4	103.5	150.82	5.00E-04	35	NA	NA	NA
SBP	Urea	MR Egger	99	0.010710499	0.014364794	0.457707501	189.4	103.5	NA	NA	NA	-0.009364	0.007049	0.1871
SBP	Urea	Weighted median	99	0.002373344	0.005855137	0.685224808	189.4	103.5	NA	NA	NA	NA	NA	NA
SBP	Urea	Weighted mode	99	0.003393179	0.009937184	0.733486258	189.4	103.5	NA	NA	NA	NA	NA	NA
SBP	Urinary Albumin Excretion	Inverse variance weighted	100	-0.004707544	0.000726229	9.04E-11	189.9	103.5	329.06	0	69.9	NA	NA	NA
SBP	Urinary Albumin Excretion	MR Egger	100	-0.003122138	0.002406633	0.197571781	189.9	103.5	NA	NA	NA	-0.000801	0.001158	0.4911
SBP	Urinary Albumin Excretion	Weighted median	100	-0.005158872	0.000685208	5.12E-14	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	Urinary Albumin Excretion	Weighted mode	100	-0.005905265	0.001338312	2.61E-05	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	25 Hydroxyvitamin D	Inverse variance weighted	100	-0.00100149	0.000955913	0.294786474	189.9	103.5	409.76	0	75.8	NA	NA	NA
SBP	25 Hydroxyvitamin D	MR Egger	100	-0.002502885	0.00316856	0.431486102	189.9	103.5	NA	NA	NA	0.000758	0.001525	0.6202
SBP	25 Hydroxyvitamin D	Weighted median	100	-0.000696695	0.000803147	0.385692251	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	25 Hydroxyvitamin D	Weighted mode	100	-0.000404689	0.001847251	0.827041589	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	Water Consumption	Inverse variance weighted	100	-0.001025561	0.000695003	0.140045579	189.9	103.5	254.95	0	61.2	NA	NA	NA
SBP	Water Consumption	MR Egger	100	-0.00195486	0.002306441	0.398745134	189.9	103.5	NA	NA	NA	0.000469	0.00111	0.6734
SBP	Water Consumption	Weighted median	100	-0.000794666	0.000715608	0.266793856	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	Water Consumption	Weighted mode	100	-0.00311679	0.002207933	0.161193323	189.9	103.5	NA	NA	NA	NA	NA	NA
SBP	X_11440	Inverse variance weighted	45	-0.000749373	0.001961589	0.702444182	186.3	103.5	50.36	0.2363	12.6	NA	NA	NA
SBP	X_11440	MR Egger	45	-0.006435314	0.006257883	0.309533819	186.3	103.5	NA	NA	NA	0.002841	0.002969	0.344
SBP	X_11440	Weighted median	45	-0.003811593	0.002631496	0.147491015	186.3	103.5	NA	NA	NA	NA	NA	NA
SBP	X_11440	Weighted mode	45	-0.00456572	0.004400524	0.305152701	186.3	103.5	NA	NA	NA	NA	NA	NA
SBP	X_14473	Inverse variance weighted	45	0.002390173	0.001840004	0.193942447	186.3	103.5	51.98	0.1911	15.3	NA	NA	NA
SBP	X_14473	MR Egger	45	0.008654195	0.005873794	0.147938051	186.3	103.5	NA	NA	NA	-0.003117	0.002776	0.2678
SBP	X_14473	Weighted median	45	0.003456891	0.002617135	0.18654521	186.3	103.5	NA	NA	NA	NA	NA	NA
SBP	X_14473	Weighted mode	45	0.00915192	0.005538287	0.105555656	186.3	103.5	NA	NA	NA	NA	NA	NA
T2DM	Bilirubin	Inverse variance weighted	86	-0.011487805	0.008176017	0.160003041	92.5	38.6	98.44	0.1511	13.7	NA	NA	NA
T2DM	Bilirubin	MR Egger	86	-0.004339391	0.023623383	0.854698965	92.5	38.6	NA	NA	NA	-0.000569	0.001763	0.7477
T2DM	Bilirubin	Weighted median	86	-0.019065289	0.011754818	0.104822024	92.5	38.6	NA	NA	NA	NA	NA	NA
T2DM	Bilirubin	Weighted mode	86	-0.018662903	0.018067794	0.304563135	92.5	38.6	NA	NA	NA	NA	NA	NA
T2DM	Blood Urea Nitrogen	Inverse variance weighted	86	-0.026922641	0.011182211	0.016056384	92.5	38.6	267.11	0	68.2	NA	NA	NA
T2DM	Blood Urea Nitrogen	MR Egger	86	-0.031876048	0.032315056	0.326762443	92.5	38.6	NA	NA	NA	0.000394	0.002412	0.8705
T2DM	Blood Urea Nitrogen	Weighted median	86	-0.021899982	0.01008208	0.029842908	92.5	38.6	NA	NA	NA	NA	NA	NA
T2DM	Blood Urea Nitrogen	Weighted mode	86	-0.013965146	0.013804642	0.314587587	92.5	38.6	NA	NA	NA	NA	NA	NA
T2DM	CRP	Inverse variance weighted	80	-0.036401294	0.012349417	0.003202382	93.8	38.6	349.12	0	77.4	NA	NA	NA
T2DM	CRP	MR Egger	80	0.010719194	0.027317152	0.695834442	93.8	38.6	NA	NA	NA	-0.004301	0.002234	0.0578
T2DM	CRP	Weighted median	80	-0.005555439	0.010400514	0.593237475	93.8	38.6	NA	NA	NA	NA	NA	NA
T2DM	CRP	Weighted mode	80	-0.008456534	0.012107412	0.48694104	93.8	38.6	NA	NA	NA	NA	NA	NA
T2DM	Coffee Consumption	Inverse variance weighted	100	0.002213344	0.005410583	0.682483365	89.6	38.5	525.17	0	81.1	NA	NA	NA
T2DM	Coffee Consumption	MR Egger	100	0.010717182	0.01293496	0.409375888	89.6	38.5	NA	NA	NA	-0.000753	0.00104	0.4707
T2DM	Coffee Consumption	Weighted median	100	0.007880539	0.004830126	0.102776636	89.6	38.5	NA	NA	NA	NA	NA	NA
T2DM	Coffee Consumption	Weighted mode	100	0.007641655	0.00444145	0.088459985	89.6	38.5	NA	NA	NA	NA	NA	NA
T2DM	Cotinine	Inverse variance weighted	100	-0.000291635	0.002335998	0.900647158	89.6	38.5	196.85	0	49.7	NA	NA	NA
T2DM	Cotinine	MR Egger	100	0.008280094	0.005517416	0.136643163	89.6	38.5	NA	NA	NA	-0.000759	0.000444	0.0902
T2DM	Cotinine	Weighted median	100	0.000610389	0.003303384	0.853404065	89.6	38.5	NA	NA	NA	NA	NA	NA
T2DM	Cotinine	Weighted mode	100	0.002421798	0.003343821	0.470613871	89.6	38.5	NA	NA	NA	NA	NA	NA

T2DM	Creatinine	Inverse variance weighted	100	-0.001862121	0.004810263	0.698671748	89.6	38.5	204.37	0	51.6	NA	NA	NA
T2DM	Creatinine	MR Egger	100	0.001253857	0.011523349	0.913575581	89.6	38.5	NA	NA	NA	-0.000276	0.000927	0.7664
T2DM	Creatinine	Weighted median	100	-0.010148409	0.006490225	0.117900898	89.6	38.5	NA	NA	NA	NA	NA	NA
T2DM	Creatinine	Weighted mode	100	-0.013932182	0.007022667	0.050037298	89.6	38.5	NA	NA	NA	NA	NA	NA
T2DM	Cystatin C	Inverse variance weighted	83	0.00016823	0.003691904	0.963655051	95.9	38.6	133.24	3.00E-04	38.5	NA	NA	NA
T2DM	Cystatin C	MR Egger	83	0.008101112	0.008541343	0.345717144	95.9	38.6	NA	NA	NA	-0.000711	0.00069	0.3061
T2DM	Cystatin C	Weighted median	83	0.000650131	0.005400929	0.904186893	95.9	38.6	NA	NA	NA	NA	NA	NA
T2DM	Cystatin C	Weighted mode	83	-0.001040338	0.005284355	0.844415314	95.9	38.6	NA	NA	NA	NA	NA	NA
T2DM	Fresh Fruit Consumption	Inverse variance weighted	91	-0.015494276	0.011345142	0.172027166	88.4	38.5	232.04	0	61.2	NA	NA	NA
T2DM	Fresh Fruit Consumption	MR Egger	91	0.003200949	0.026222521	0.903119807	88.4	38.5	NA	NA	NA	-0.001674	0.002116	0.4309
T2DM	Fresh Fruit Consumption	Weighted median	91	-0.002019493	0.013556335	0.881576952	88.4	38.5	NA	NA	NA	NA	NA	NA
T2DM	Fresh Fruit Consumption	Weighted mode	91	-0.002884128	0.013824755	0.835215886	88.4	38.5	NA	NA	NA	NA	NA	NA
T2DM	Gamma Glutamyl Transferase	Inverse variance weighted	86	0.038290055	0.01584684	0.015680944	92.5	38.6	404.24	0	79	NA	NA	NA
T2DM	Gamma Glutamyl Transferase	MR Egger	86	0.043603444	0.045767465	0.343466935	92.5	38.6	NA	NA	NA	-0.000423	0.003417	0.9017
T2DM	Gamma Glutamyl Transferase	Weighted median	86	0.032686257	0.012647028	0.009752004	92.5	38.6	NA	NA	NA	NA	NA	NA
T2DM	Gamma Glutamyl Transferase	Weighted mode	86	0.039157719	0.023796135	0.103549647	92.5	38.6	NA	NA	NA	NA	NA	NA
T2DM	Impedance of Arm (Left)	Inverse variance weighted	100	-0.029164463	0.011969546	0.014827897	89.6	38.5	2276.93	0	95.7	NA	NA	NA
T2DM	Impedance of Arm (Left)	MR Egger	100	0.033077574	0.027835686	0.237580971	89.6	38.5	NA	NA	NA	-0.005514	0.002239	0.0155
T2DM	Impedance of Arm (Left)	Weighted median	100	0.018982141	0.004889681	0.000103566	89.6	38.5	NA	NA	NA	NA	NA	NA
T2DM	Impedance of Arm (Left)	Weighted mode	100	0.019134865	0.004886766	0.000165774	89.6	38.5	NA	NA	NA	NA	NA	NA
T2DM	Impedance of Arm (Right)	Inverse variance weighted	100	-0.030279734	0.011865516	0.010713403	89.6	38.5	2256.56	0	95.6	NA	NA	NA
T2DM	Impedance of Arm (Right)	MR Egger	100	0.03308732	0.027546983	0.232598356	89.6	38.5	NA	NA	NA	-0.005614	0.002215	0.0129
T2DM	Impedance of Arm (Right)	Weighted median	100	0.019695452	0.004674174	2.51E-05	89.6	38.5	NA	NA	NA	NA	NA	NA
T2DM	Impedance of Arm (Right)	Weighted mode	100	0.020279289	0.004689981	3.66E-05	89.6	38.5	NA	NA	NA	NA	NA	NA
T2DM	Overall Healthy Diet	Inverse variance weighted	100	-0.000733684	0.003453023	0.831735924	89.6	38.5	121.32	0.0633	18.4	NA	NA	NA
T2DM	Overall Healthy Diet	MR Egger	100	-0.000758858	0.008281335	0.927175316	89.6	38.5	NA	NA	NA	2.00E-06	0.000666	0.9973
T2DM	Overall Healthy Diet	Weighted median	100	-0.004240889	0.005141383	0.409454621	89.6	38.5	NA	NA	NA	NA	NA	NA
T2DM	Overall Healthy Diet	Weighted mode	100	-0.005599251	0.006807627	0.412770885	89.6	38.5	NA	NA	NA	NA	NA	NA
T2DM	Peak Expiratory Flow	Inverse variance weighted	100	-0.012394524	0.006130216	0.043189396	89.6	38.5	375.9	0	73.7	NA	NA	NA
T2DM	Peak Expiratory Flow	MR Egger	100	-0.018226267	0.014681265	0.217397526	89.6	38.5	NA	NA	NA	0.000517	0.001181	0.6627
T2DM	Peak Expiratory Flow	Weighted median	100	-0.003081687	0.006360311	0.628018048	89.6	38.5	NA	NA	NA	NA	NA	NA
T2DM	Peak Expiratory Flow	Weighted mode	100	-0.005110866	0.006640361	0.443330048	89.6	38.5	NA	NA	NA	NA	NA	NA
T2DM	Potassium in Urine	Inverse variance weighted	100	-0.005059539	0.00481312	0.293168025	89.6	38.5	181.98	0	45.6	NA	NA	NA
T2DM	Potassium in Urine	MR Egger	100	0.009793431	0.011416357	0.393072843	89.6	38.5	NA	NA	NA	-0.001316	0.000918	0.155
T2DM	Potassium in Urine	Weighted median	100	-0.005249795	0.006864488	0.444405022	89.6	38.5	NA	NA	NA	NA	NA	NA
T2DM	Potassium in Urine	Weighted mode	100	-0.008084851	0.007082118	0.256379665	89.6	38.5	NA	NA	NA	NA	NA	NA
T2DM	Red Blood Cell Distribution	Inverse variance weighted	100	0.012137764	0.014012632	0.386379636	89.6	38.5	733.04	0	86.5	NA	NA	NA
T2DM	Red Blood Cell Distribution	MR Egger	100	0.057114335	0.033221673	0.088737101	89.6	38.5	NA	NA	NA	-0.003983	0.002671	0.1391
T2DM	Red Blood Cell Distribution	Weighted median	100	0.036386337	0.010227851	0.000374296	89.6	38.5	NA	NA	NA	NA	NA	NA
T2DM	Red Blood Cell Distribution	Weighted mode	100	0.034299634	0.010551422	0.001573766	89.6	38.5	NA	NA	NA	NA	NA	NA
T2DM	Serum Phosphate	Inverse variance weighted	90	-0.001023993	0.002380264	0.667049206	94.1	38.6	96.37	0.2785	7.6	NA	NA	NA
T2DM	Serum Phosphate	MR Egger	90	-0.00244406	0.005538075	0.660064212	94.1	38.6	NA	NA	NA	0.000129	0.000454	0.7768
T2DM	Serum Phosphate	Weighted median	90	-0.004809505	0.003862698	0.213089294	94.1	38.6	NA	NA	NA	NA	NA	NA
T2DM	Serum Phosphate	Weighted mode	90	-0.005515642	0.004471245	0.220607009	94.1	38.6	NA	NA	NA	NA	NA	NA
T2DM	Uric Acid	Inverse variance weighted	86	0.042257723	0.012715751	0.000889725	92.5	38.6	244.29	0	65.2	NA	NA	NA
T2DM	Uric Acid	MR Egger	86	0.060321554	0.036655505	0.103576068	92.5	38.6	NA	NA	NA	-0.001439	0.002736	0.6005
T2DM	Uric Acid	Weighted median	86	0.030690321	0.013177589	0.019860203	92.5	38.6	NA	NA	NA	NA	NA	NA
T2DM	Uric Acid	Weighted mode	86	0.032551661	0.019205562	0.093753619	92.5	38.6	NA	NA	NA	NA	NA	NA
T2DM	Sodium in Urine	Inverse variance weighted	100	0.007541065	0.005704701	0.186200251	89.6	38.5	271.95	0	63.6	NA	NA	NA
T2DM	Sodium in Urine	MR Egger	100	0.002508628	0.013660739	0.854677017	89.6	38.5	NA	NA	NA	0.000446	0.001099	0.6858
T2DM	Sodium in Urine	Weighted median	100	0.001311077	0.005791358	0.820901939	89.6	38.5	NA	NA	NA	NA	NA	NA
T2DM	Sodium in Urine	Weighted mode	100	-0.006581283	0.006932161	0.344737177	89.6	38.5	NA	NA	NA	NA	NA	NA
T2DM	Tea Consumption	Inverse variance weighted	100	0.844891355	1.380948017	0.54065698	89.6	38.5	106.05	0.2957	6.7	NA	NA	NA
T2DM	Tea Consumption	MR Egger	100	4.6585545	3.284617941	0.159277101	89.6	38.5	NA	NA	NA	-0.337656	0.264044	0.204
T2DM	Tea Consumption	Weighted median	100	2.297069194	2.335239055	0.325285253	89.6	38.5	NA	NA	NA	NA	NA	NA
T2DM	Tea Consumption	Weighted mode	100	2.382727821	2.696525493	0.379037386	89.6	38.5	NA	NA	NA	NA	NA	NA
T2DM	Testosterone	Inverse variance weighted	91	0.009574112	0.008971488	0.285894579	88.4	38.5	310.19	0	71	NA	NA	NA
T2DM	Testosterone	MR Egger	91	0.007408659	0.020805811	0.72261883	88.4	38.5	NA	NA	NA	0.000194	0.001679	0.9083

T2DM	Testosterone	Weighted median	91	0.001023838	0.009995002	0.918411406	88.4	38.5	NA	NA	NA	NA	NA	NA
T2DM	Testosterone	Weighted mode	91	-0.007316986	0.010055152	0.468695141	88.4	38.5	NA	NA	NA	NA	NA	NA
T2DM	Urea	Inverse variance weighted	99	-0.055226263	0.024936577	0.026782796	90.1	38.5	111.3	0.1692	12	NA	NA	NA
T2DM	Urea	MR Egger	99	-0.079724148	0.059368752	0.182449954	90.1	38.5	NA	NA	NA	0.002162	0.004751	0.6501
T2DM	Urea	Weighted median	99	-0.113653679	0.03923289	0.003768723	90.1	38.5	NA	NA	NA	NA	NA	NA
T2DM	Urea	Weighted mode	99	-0.112867711	0.049033976	0.023461689	90.1	38.5	NA	NA	NA	NA	NA	NA
T2DM	Urinary Albumin Excretion	Inverse variance weighted	100	-0.01749938	0.004043304	1.50E-05	89.6	38.5	275.22	0	64	NA	NA	NA
T2DM	Urinary Albumin Excretion	MR Egger	100	-0.020757134	0.009685777	0.034584847	89.6	38.5	NA	NA	NA	0.000289	0.000779	0.7118
T2DM	Urinary Albumin Excretion	Weighted median	100	-0.022909327	0.004064921	1.74E-08	89.6	38.5	NA	NA	NA	NA	NA	NA
T2DM	Urinary Albumin Excretion	Weighted mode	100	-0.023527274	0.005194062	1.65E-05	89.6	38.5	NA	NA	NA	NA	NA	NA
T2DM	25 Hydroxyvitamin D	Inverse variance weighted	100	0.015634362	0.007090706	0.027460464	89.6	38.5	609.9	0	83.8	NA	NA	NA
T2DM	25 Hydroxyvitamin D	MR Egger	100	0.008656798	0.01697168	0.61114711	89.6	38.5	NA	NA	NA	0.000618	0.001365	0.6516
T2DM	25 Hydroxyvitamin D	Weighted median	100	0.012667587	0.005616247	0.024100389	89.6	38.5	NA	NA	NA	NA	NA	NA
T2DM	25 Hydroxyvitamin D	Weighted mode	100	0.008362589	0.007004477	0.235373105	89.6	38.5	NA	NA	NA	NA	NA	NA
T2DM	Water Consumption	Inverse variance weighted	100	-0.009761887	0.004454911	0.028432664	89.6	38.5	282.52	0	65	NA	NA	NA
T2DM	Water Consumption	MR Egger	100	-0.011987952	0.010675451	0.26420407	89.6	38.5	NA	NA	NA	0.000197	0.000858	0.8188
T2DM	Water Consumption	Weighted median	100	-0.006814747	0.005246002	0.193931479	89.6	38.5	NA	NA	NA	NA	NA	NA
T2DM	Water Consumption	Weighted mode	100	-0.005199639	0.005486535	0.345585152	89.6	38.5	NA	NA	NA	NA	NA	NA
T2DM	X_11440	Inverse variance weighted	90	0.000766009	0.008873099	0.931204574	94.1	38.6	120.77	0.0141	26.3	NA	NA	NA
T2DM	X_11440	MR Egger	90	0.018155455	0.021115181	0.392219418	94.1	38.6	NA	NA	NA	-0.001547	0.001704	0.3665
T2DM	X_11440	Weighted median	90	0.003799405	0.014939818	0.799252978	94.1	38.6	NA	NA	NA	NA	NA	NA
T2DM	X_11440	Weighted mode	90	0.009837515	0.015528703	0.528028396	94.1	38.6	NA	NA	NA	NA	NA	NA
T2DM	X_14473	Inverse variance weighted	90	0.000804496	0.007322307	0.912513066	94.1	38.6	96.12	0.2845	7.4	NA	NA	NA
T2DM	X_14473	MR Egger	90	0.026950596	0.017271407	0.122250652	94.1	38.6	NA	NA	NA	-0.002325	0.001394	0.0989
T2DM	X_14473	Weighted median	90	0.018592313	0.011461419	0.104768014	94.1	38.6	NA	NA	NA	NA	NA	NA
T2DM	X_14473	Weighted mode	90	0.018797471	0.014207995	0.189217639	94.1	38.6	NA	NA	NA	NA	NA	NA
TG	Bilirubin	Inverse variance weighted	76	-0.00667934	0.021293969	0.753769505	159.8	43	299.34	0	74.9	NA	NA	NA
TG	Bilirubin	MR Egger	76	-0.058955697	0.036098476	0.106676934	159.8	43	NA	NA	NA	0.003689	0.002072	0.0792
TG	Bilirubin	Weighted median	76	-0.036101789	0.016529743	0.028958555	159.8	43	NA	NA	NA	NA	NA	NA
TG	Bilirubin	Weighted mode	76	-0.029874132	0.016076682	0.067060912	159.8	43	NA	NA	NA	NA	NA	NA
TG	Blood Urea Nitrogen	Inverse variance weighted	76	-0.015046846	0.012873817	0.24248647	159.8	43	158.78	0	52.8	NA	NA	NA
TG	Blood Urea Nitrogen	MR Egger	76	0.003880537	0.022117762	0.861206133	159.8	43	NA	NA	NA	-0.001336	0.00127	0.2962
TG	Blood Urea Nitrogen	Weighted median	76	0.004316783	0.014346216	0.763490426	159.8	43	NA	NA	NA	NA	NA	NA
TG	Blood Urea Nitrogen	Weighted mode	76	0.001158409	0.013654768	0.932618201	159.8	43	NA	NA	NA	NA	NA	NA
TG	CRP	Inverse variance weighted	88	-0.115898601	0.051030185	0.023136243	148	43	2503.81	0	96.5	NA	NA	NA
TG	CRP	MR Egger	88	-0.203394019	0.099225369	0.043428293	148	43	NA	NA	NA	0.005282	0.005138	0.3068
TG	CRP	Weighted median	88	-0.076008995	0.019786748	0.00012233	148	43	NA	NA	NA	NA	NA	NA
TG	CRP	Weighted mode	88	-0.066130533	0.01956986	0.001089753	148	43	NA	NA	NA	NA	NA	NA
TG	Coffee Consumption	Inverse variance weighted	100	0.038498486	0.007238134	1.04E-07	149.4	43	360.43	0	72.5	NA	NA	NA
TG	Coffee Consumption	MR Egger	100	0.03362736	0.013262266	0.012807659	149.4	43	NA	NA	NA	0.000313	0.000712	0.6616
TG	Coffee Consumption	Weighted median	100	0.024764451	0.00696442	0.000376755	149.4	43	NA	NA	NA	NA	NA	NA
TG	Coffee Consumption	Weighted mode	100	0.015249118	0.007220921	0.037221205	149.4	43	NA	NA	NA	NA	NA	NA
TG	Cotinine	Inverse variance weighted	100	-0.004484762	0.003054057	0.141979227	149.4	43	129.03	0.0229	23.3	NA	NA	NA
TG	Cotinine	MR Egger	100	0.004306875	0.005499297	0.435416941	149.4	43	NA	NA	NA	-0.000564	0.000295	0.0589
TG	Cotinine	Weighted median	100	-0.001884519	0.004240419	0.656740417	149.4	43	NA	NA	NA	NA	NA	NA
TG	Cotinine	Weighted mode	100	0.001744281	0.006246925	0.780656743	149.4	43	NA	NA	NA	NA	NA	NA
TG	Creatinine	Inverse variance weighted	99	0.001084408	0.010457061	0.917406622	150.5	43	364.98	0	73.1	NA	NA	NA
TG	Creatinine	MR Egger	99	-0.020049084	0.019054442	0.295321949	150.5	43	NA	NA	NA	0.001364	0.001029	0.1884
TG	Creatinine	Weighted median	99	-0.000973299	0.010898337	0.928837832	150.5	43	NA	NA	NA	NA	NA	NA
TG	Creatinine	Weighted mode	99	-0.011249569	0.012519366	0.371082392	150.5	43	NA	NA	NA	NA	NA	NA
TG	Cystatin C	Inverse variance weighted	85	-0.003201865	0.006346848	0.613923282	160.5	43	145.17	0	42.1	NA	NA	NA
TG	Cystatin C	MR Egger	85	-0.006971453	0.011552261	0.547841182	160.5	43	NA	NA	NA	0.000235	6.00E-04	0.6965
TG	Cystatin C	Weighted median	85	0.002303027	0.008781122	0.793113083	160.5	43	NA	NA	NA	NA	NA	NA
TG	Cystatin C	Weighted mode	85	0.011508361	0.012747417	0.369213937	160.5	43	NA	NA	NA	NA	NA	NA
TG	Fresh Fruit Consumption	Inverse variance weighted	93	0.027090931	0.01620141	0.094497871	143.3	43	180.67	0	49.1	NA	NA	NA
TG	Fresh Fruit Consumption	MR Egger	93	0.025076441	0.031814881	0.432629061	143.3	43	NA	NA	NA	0.000122	0.001654	0.9414
TG	Fresh Fruit Consumption	Weighted median	93	0.015255802	0.019716617	0.439076552	143.3	43	NA	NA	NA	NA	NA	NA
TG	Fresh Fruit Consumption	Weighted mode	93	0.013556918	0.02708318	0.617872031	143.3	43	NA	NA	NA	NA	NA	NA

TG	Gamma Glutamyl Transferase	Inverse variance weighted	76	-0.099560322	0.026653739	0.000187475	159.8	43	512.86	0	85.4	NA	NA	NA
TG	Gamma Glutamyl Transferase	MR Egger	76	-0.109168336	0.046113306	0.020529479	159.8	43	NA	NA	NA	0.000678	0.002648	0.7986
TG	Gamma Glutamyl Transferase	Weighted median	76	-0.02147355	0.018224034	0.238673312	159.8	43	NA	NA	NA	NA	NA	NA
TG	Gamma Glutamyl Transferase	Weighted mode	76	-0.01886829	0.015843394	0.237438638	159.8	43	NA	NA	NA	NA	NA	NA
TG	Impedance of Arm (Left)	Inverse variance weighted	99	0.010902521	0.015175075	0.472480341	150.5	43	1382.82	0	92.9	NA	NA	NA
TG	Impedance of Arm (Left)	MR Egger	99	0.078178593	0.026680535	0.004223908	150.5	43	NA	NA	NA	-0.004341	0.001441	0.0033
TG	Impedance of Arm (Left)	Weighted median	99	-0.003070263	0.008062212	0.703335754	150.5	43	NA	NA	NA	NA	NA	NA
TG	Impedance of Arm (Left)	Weighted mode	99	-0.010590584	0.006891272	0.127562027	150.5	43	NA	NA	NA	NA	NA	NA
TG	Impedance of Arm (Right)	Inverse variance weighted	99	0.008570391	0.01548206	0.579873716	150.5	43	1451.6	0	93.2	NA	NA	NA
TG	Impedance of Arm (Right)	MR Egger	99	0.077509362	0.027209044	0.005360991	150.5	43	NA	NA	NA	-0.004448	0.00147	0.0032
TG	Impedance of Arm (Right)	Weighted median	99	0.00153194	0.008181093	0.851461757	150.5	43	NA	NA	NA	NA	NA	NA
TG	Impedance of Arm (Right)	Weighted mode	99	-0.011439024	0.007537884	0.132350324	150.5	43	NA	NA	NA	NA	NA	NA
TG	Overall Healthy Diet	Inverse variance weighted	100	-0.003023613	0.005522279	0.584014711	149.4	43	119.04	0.0831	16.8	NA	NA	NA
TG	Overall Healthy Diet	MR Egger	100	-0.006981694	0.010114433	0.49165566	149.4	43	NA	NA	NA	0.000254	0.000543	0.6409
TG	Overall Healthy Diet	Weighted median	100	-0.006675316	0.008476904	0.431006175	149.4	43	NA	NA	NA	NA	NA	NA
TG	Overall Healthy Diet	Weighted mode	100	-0.013110458	0.011246254	0.246511521	149.4	43	NA	NA	NA	NA	NA	NA
TG	Peak Expiratory Flow	Inverse variance weighted	99	0.009668599	0.007690895	0.208699799	150.5	43	223.56	0	56.2	NA	NA	NA
TG	Peak Expiratory Flow	MR Egger	99	0.004233162	0.014126844	0.765082418	150.5	43	NA	NA	NA	0.000351	0.000763	0.6469
TG	Peak Expiratory Flow	Weighted median	99	0.009112471	0.008992432	0.310893534	150.5	43	NA	NA	NA	NA	NA	NA
TG	Peak Expiratory Flow	Weighted mode	99	-0.015818659	0.011079387	0.156541117	150.5	43	NA	NA	NA	NA	NA	NA
TG	Potassium in Urine	Inverse variance weighted	99	-0.006507043	0.009258356	0.482162142	150.5	43	254.46	0	61.5	NA	NA	NA
TG	Potassium in Urine	MR Egger	99	-0.020113107	0.016941903	0.238055406	150.5	43	NA	NA	NA	0.000878	0.000915	0.3399
TG	Potassium in Urine	Weighted median	99	-0.017402354	0.009538437	0.068084811	150.5	43	NA	NA	NA	NA	NA	NA
TG	Potassium in Urine	Weighted mode	99	-0.024017158	0.011889919	0.046117179	150.5	43	NA	NA	NA	NA	NA	NA
TG	Red Blood Cell Distribution	Inverse variance weighted	100	0.175378242	0.026619451	4.45E-11	149.4	43	1012.21	0	90.2	NA	NA	NA
TG	Red Blood Cell Distribution	MR Egger	100	0.133322647	0.048628159	0.007266742	149.4	43	NA	NA	NA	0.002695	0.002608	0.304
TG	Red Blood Cell Distribution	Weighted median	100	0.20572459	0.016479277	9.15E-36	149.4	43	NA	NA	NA	NA	NA	NA
TG	Red Blood Cell Distribution	Weighted mode	100	0.200355897	0.015982479	3.71E-22	149.4	43	NA	NA	NA	NA	NA	NA
TG	Serum Phosphate	Inverse variance weighted	94	0.008140981	0.004769558	0.087847566	155.1	43	148.91	2.00E-04	37.5	NA	NA	NA
TG	Serum Phosphate	MR Egger	94	-0.008840976	0.008546431	0.303630835	155.1	43	NA	NA	NA	0.001063	0.000449	0.0199
TG	Serum Phosphate	Weighted median	94	0.002585468	0.006307957	0.681898347	155.1	43	NA	NA	NA	NA	NA	NA
TG	Serum Phosphate	Weighted mode	94	7.00E-05	0.007000157	0.992046648	155.1	43	NA	NA	NA	NA	NA	NA
TG	Uric Acid	Inverse variance weighted	76	-0.040656142	0.018934332	0.031775913	159.8	43	242.98	0	69.1	NA	NA	NA
TG	Uric Acid	MR Egger	76	-0.000341237	0.032252149	0.99158679	159.8	43	NA	NA	NA	-0.002847	0.001853	0.1286
TG	Uric Acid	Weighted median	76	-0.000399035	0.017945295	0.98225956	159.8	43	NA	NA	NA	NA	NA	NA
TG	Uric Acid	Weighted mode	76	0.006345159	0.018364955	0.730682964	159.8	43	NA	NA	NA	NA	NA	NA
TG	Sodium in Urine	Inverse variance weighted	99	0.044438245	0.010499664	2.31E-05	150.5	43	348.14	0	71.9	NA	NA	NA
TG	Sodium in Urine	MR Egger	99	0.029892598	0.019223144	0.123195314	150.5	43	NA	NA	NA	0.000939	0.001039	0.3684
TG	Sodium in Urine	Weighted median	99	0.033864173	0.011169712	0.002431118	150.5	43	NA	NA	NA	NA	NA	NA
TG	Sodium in Urine	Weighted mode	99	-0.003951831	0.013361723	0.768040991	150.5	43	NA	NA	NA	NA	NA	NA
TG	Tea Consumption	Inverse variance weighted	100	0.063423734	2.230986318	0.977320344	149.4	43	106.18	0.2926	6.8	NA	NA	NA
TG	Tea Consumption	MR Egger	100	-1.033028611	4.088622107	0.801060655	149.4	43	NA	NA	NA	0.070394	0.219546	0.7492
TG	Tea Consumption	Weighted median	100	0.453190213	3.493583106	0.896787367	149.4	43	NA	NA	NA	NA	NA	NA
TG	Tea Consumption	Weighted mode	100	2.491301557	5.329040569	0.641172943	149.4	43	NA	NA	NA	NA	NA	NA
TG	Testosterone	Inverse variance weighted	93	0.10684884	0.016791764	1.98E-10	143.3	43	414.94	0	77.8	NA	NA	NA
TG	Testosterone	MR Egger	93	0.119475815	0.03293331	0.000471398	143.3	43	NA	NA	NA	-0.000764	0.001712	0.6564
TG	Testosterone	Weighted median	93	0.063317516	0.014493695	1.25E-05	143.3	43	NA	NA	NA	NA	NA	NA
TG	Testosterone	Weighted mode	93	0.05856908	0.016991235	0.000856345	143.3	43	NA	NA	NA	NA	NA	NA
TG	Urea	Inverse variance weighted	93	-0.000386078	0.038948213	0.99209103	155.9	43	101.69	0.2298	9.5	NA	NA	NA
TG	Urea	MR Egger	93	-0.005550345	0.06834891	0.935456422	155.9	43	NA	NA	NA	0.000352	0.003818	0.9268
TG	Urea	Weighted median	93	0.041240886	0.062890987	0.511983753	155.9	43	NA	NA	NA	NA	NA	NA
TG	Urea	Weighted mode	93	0.040877586	0.068407648	0.551602425	155.9	43	NA	NA	NA	NA	NA	NA
TG	Urinary Albumin Excretion	Inverse variance weighted	100	-0.032048104	0.00713657	7.10E-06	149.4	43	328.22	0	69.8	NA	NA	NA
TG	Urinary Albumin Excretion	MR Egger	100	-0.030000094	0.013093002	0.02408673	149.4	43	NA	NA	NA	-0.000131	0.000703	0.8521
TG	Urinary Albumin Excretion	Weighted median	100	-0.033375699	0.007601584	1.13E-05	149.4	43	NA	NA	NA	NA	NA	NA
TG	Urinary Albumin Excretion	Weighted mode	100	-0.033990123	0.009710408	0.000698178	149.4	43	NA	NA	NA	NA	NA	NA
TG	25 Hydroxyvitamin D	Inverse variance weighted	91	0.141499832	0.017113781	1.36E-16	149.6	43	1125.55	0	92	NA	NA	NA
TG	25 Hydroxyvitamin D	MR Egger	91	0.128597378	0.03069004	6.55E-05	149.6	43	NA	NA	NA	0.000849	0.001674	0.6131

TG	25 Hydroxyvitamin D	Weighted median	91	0.146409374	0.013218692	1.64E-28	149.6	43	NA	NA	NA	NA	NA	NA
TG	25 Hydroxyvitamin D	Weighted mode	91	0.177950323	0.017103915	4.15E-17	149.6	43	NA	NA	NA	NA	NA	NA
TG	Water Consumption	Inverse variance weighted	100	-0.029164515	0.007988902	0.000261599	149.4	43	348.41	0	71.6	NA	NA	NA
TG	Water Consumption	MR Egger	100	-0.019188607	0.014601779	0.19187078	149.4	43	NA	NA	NA	-0.00064	0.000784	0.416
TG	Water Consumption	Weighted median	100	-0.016437374	0.007905776	0.037602636	149.4	43	NA	NA	NA	NA	NA	NA
TG	Water Consumption	Weighted mode	100	-0.013469366	0.010881014	0.218689017	149.4	43	NA	NA	NA	NA	NA	NA
TG	X_11440	Inverse variance weighted	94	0.005043125	0.013731587	0.713421716	155.1	43	113.64	0.0718	18.2	NA	NA	NA
TG	X_11440	MR Egger	94	-0.006782223	0.025014905	0.786900543	155.1	43	NA	NA	NA	0.000744	0.001313	0.5725
TG	X_11440	Weighted median	94	-0.009333703	0.020318333	0.645965978	155.1	43	NA	NA	NA	NA	NA	NA
TG	X_11440	Weighted mode	94	-0.018711606	0.022462305	0.40696626	155.1	43	NA	NA	NA	NA	NA	NA
TG	X_14473	Inverse variance weighted	94	-0.014915484	0.011492888	0.194355657	155.1	43	90.22	0.5623	0	NA	NA	NA
TG	X_14473	MR Egger	94	-0.025472179	0.020910053	0.226270965	155.1	43	NA	NA	NA	0.000666	0.001101	0.5471
TG	X_14473	Weighted median	94	-0.017128274	0.017794082	0.335757028	155.1	43	NA	NA	NA	NA	NA	NA
TG	X_14473	Weighted mode	94	-0.015945254	0.018140732	0.381680157	155.1	43	NA	NA	NA	NA	NA	NA

Supplementary Table 4.7 – LDSC Genetic Correlation Results

Trait 1	*Trait 2*	r_g	*SE*	*P*	*nSNPs*
Impedance of Left Arm	Impedance of Right Arm	0.963752391	9.73E-05	6.19E-83	7521790
Creatinine	Albumin	0.594758013	0.000293725	8.23E-117	7490805
Creatinine	Sodium in Urine	0.555134801	0.000303199	0.023465436	7525592
Sodium in Urine	Albumin	0.367295082	0.000339835	0.034561347	7490805
Impedance of Right Arm	Urate	0.192619443	0.000359554	4.25E-05	7448195
Impedance of Left Arm	Urate	0.190486497	0.000359703	7.25E-161	7448377
Creatinine	Impedance of Right Arm	-0.171358971	0.00035922	9.21E-78	7522019
Creatinine	Impedance of Left Arm	-0.169005465	0.000359364	9.30E-119	7522218
Creatinine	Urate	-0.155793442	0.00036186	7.68E-118	7451550
Uric Acid	Urate	0.153037055	0.000437205	0.086768066	5109022
Impedance of Left Arm	Sodium in Urine	-0.145802052	0.000360712	0.161346521	7522220
Impedance of Right Arm	Sodium in Urine	-0.145212484	0.000360749	7.22E-145	7522021
Gamma-Glutamyl Transferase	Uric Acid	0.135569255	0.000436429	5.95E-126	5153659
25-Hydroxyvitamin D	Impedance of Right Arm	0.123428146	0.000375788	6.23E-193	6973456
25-Hydroxyvitamin D	Impedance of Left Arm	0.11994815	0.000375944	1.19E-79	6973633
Cystatin C	Urate	-0.102948043	0.000682634	4.35E-137	2123227
Sodium in Urine	Urate	-0.099370967	0.00036452	2.68E-16	7451551
Coffee	Impedance of Right Arm	0.079010977	0.000363638	7.25E-184	7515225
Coffee	Impedance of Left Arm	0.078885023	0.000363637	6.21E-75	7515425
Testosterone	Urate	0.068477761	0.000344656	9.33E-128	8378923
Impedance of Right Arm	Albumin	-0.062587302	0.000364743	7.68E-16	7487232
Urate	Albumin	-0.055772064	0.000364133	0.054675069	7518438
Impedance of Left Arm	Albumin	-0.055426374	0.000364893	0.005089174	7487430
Gamma-Glutamyl Transferase	Urate	0.048871731	0.000441883	1.24E-06	5109118
Impedance of Right Arm	Testosterone	0.038600427	0.000364534	1.24E-06	7514097
Impedance of Left Arm	Testosterone	0.038007017	0.000364538	1.39E-10	7514278
Impedance of Right Arm	Peak Expiratory Flow	-0.037195757	0.000364368	0.001756414	7521746
25-Hydroxyvitamin D	Albumin	-0.036311691	0.000378087	0.000989817	6986246
Cystatin C	Albumin	0.03527595	0.000688735	0.086768066	2105499
Coffee	Red Cell Distribution Width	0.034562873	0.000363416	9.99E-96	7562633
Peak Expiratory Flow	Albumin	0.03353113	0.000365174	2.10E-21	7490529
Cystatin C	Impedance of Left Arm	-0.033217995	0.000689667	0.016134652	2100106
Cystatin C	Impedance of Right Arm	-0.033166274	0.000689681	0.054675069	2100031
Cystatin C	Uric Acid	-0.032479434	0.000735575	0.081235452	1846240
Impedance of Left Arm	Peak Expiratory Flow	-0.032465394	0.000364423	7.35E-124	7521945
Creatinine	Testosterone	-0.032218978	0.00036453	3.68E-18	7517640
Coffee	Creatinine	0.031877638	0.000364509	7.24E-194	7518695
Coffee	Albumin	0.031868098	0.000363736	2.58E-132	7550671
Creatinine	Cystatin C	0.029909401	0.000689504	0.002967123	2101538
Peak Expiratory Flow	Sodium in Urine	-0.026769476	0.000364403	3.55E-08	7525319
Impedance of Right Arm	Red Cell Distribution Width	0.02640069	0.000365658	4.57E-11	7473890
Coffee	Sodium in Urine	0.024501513	0.000364585	6.30E-144	7518695
Impedance of Left Arm	Red Cell Distribution Width	0.024127715	0.000365674	6.56E-132	7474084
Sodium in Urine	Testosterone	-0.023205989	0.000364621	1.83E-106	7517642
25-Hydroxyvitamin D	Peak Expiratory Flow	-0.021926327	0.000378518	1.10E-48	6976177
Coffee	Urate	-0.021888582	0.000363907	3.22E-148	7547655
Peak Expiratory Flow	Red Cell Distribution Width	0.02124133	0.000365623	5.12E-126	7477180
Urea	Urate	0.019487301	0.000646937	6.23E-193	2388421
Gamma-Glutamyl Transferase	Urea	-0.01909846	0.001055171	3.19E-79	897834
Cystatin C	Red Cell Distribution Width	-0.01842678	0.000686856	3.53E-137	2118955
Peak Expiratory Flow	Urate	0.017568948	0.000366284	8.68E-16	7451274
Gamma-Glutamyl Transferase	Sodium in Urine	-0.017386746	0.000452648	2.06E-31	4879187
25-Hydroxyvitamin D	Red Cell Distribution Width	0.016730421	0.000365073	2.60E-73	7500979
25-Hydroxyvitamin D	Urate	0.015572662	0.000364819	3.60E-76	7511747
Red Cell Distribution Width	Phosphate	0.015253695	0.000635868	3.64E-127	2472665
25-Hydroxyvitamin D	Sodium in Urine	-0.015144451	0.000378559	8.35E-06	6976445
Cystatin C	Testosterone	-0.014974748	0.000685294	7.51E-106	2128866
Creatinine	Peak Expiratory Flow	0.014591541	0.000364495	4.36E-08	7525317

Gamma-Glutamyl Transferase	Albumin	0.013826144	0.0004526	5.96E-205	4880762
Impedance of Left Arm	Urea	-0.013373857	0.000667853	3.32E-89	2241615
Impedance of Right Arm	Uric Acid	0.013323737	0.000452899	3.16E-190	4874385
Cystatin C	Sodium in Urine	0.012955041	0.000689755	1.06E-78	2101540
25-Hydroxyvitamin D	Cystatin C	-0.012641131	0.000697973	2.60E-73	2052360
Impedance of Left Arm	Uric Acid	0.012198582	0.000452896	8.64E-160	4874597
Coffee	Peak Expiratory Flow	-0.011789549	0.000364675	2.75E-229	7518418
Impedance of Right Arm	Urea	-0.011573684	0.000667869	2.83E-67	2241607
Gamma-Glutamyl Transferase	Red Cell Distribution Width	-0.011278448	0.000441619	7.30E-144	5126829
Uric Acid	Testosterone	0.010698283	0.000440704	3.56E-130	5148210
Peak Expiratory Flow	Uric Acid	0.009923038	0.000452777	1.83E-106	4877393
25-Hydroxyvitamin D	Phosphate	0.009479879	0.000646473	1.10E-48	2392547
Red Cell Distribution Width	Testosterone	0.009134743	0.000345298	3.22E-154	8386419
Coffee	Testosterone	0.009075307	0.000362211	1.53E-138	7621496
Peak Expiratory Flow	Testosterone	-0.009012444	0.000364712	8.12E-135	7517365
Urea	Sodium in Urine	-0.008398002	0.000667866	2.92E-36	2241769
Coffee	Phosphate	0.008260794	0.000635666	1.30E-38	2474645
Gamma-Glutamyl Transferase	Testosterone	0.008047546	0.000440647	1.63E-74	5149809
Creatinine	Urea	-0.007856851	0.000667869	5.98E-32	2241769
Cystatin C	Gamma-Glutamyl Transferase	-0.007383254	0.000735846	1.08E-23	1846725
Cystatin C	Urea	0.007003053	0.002043372	0.0609831	239488
Cystatin C	Phosphate	-0.006722946	0.00068676	1.25E-22	2120169
Phosphate	Urea	0.006593483	0.001570467	2.69E-05	405437
Coffee	Uric Acid	0.006593177	0.000451273	2.42E-48	4910234
Gamma-Glutamyl Transferase	Impedance of Right Arm	0.006559325	0.000452857	1.52E-47	4875943
Gamma-Glutamyl Transferase	Peak Expiratory Flow	0.006461413	0.00045272	3.25E-46	4878915
Creatinine	Phosphate	-0.006312024	0.00063769	4.24E-23	2459027
Gamma-Glutamyl Transferase	Impedance of Left Arm	0.006089379	0.000452849	3.21E-41	4876142
Impedance of Right Arm	Phosphate	0.006032922	0.000637896	3.15E-21	2457451
Red Cell Distribution Width	Albumin	-0.005752272	0.000363653	2.34E-56	7561550
Red Cell Distribution Width	Sodium in Urine	0.005676472	0.000365693	2.44E-54	7477454
Impedance of Left Arm	Phosphate	0.005080032	0.000637888	1.67E-15	2457533
Red Cell Distribution Width	Urea	0.005010812	0.000640179	4.99E-15	2439982
Red Cell Distribution Width	Uric Acid	-0.00485626	0.00044171	4.07E-28	5125247
Urea	Testosterone	0.004663309	0.00064461	4.68E-13	2406556
Testosterone	Albumin	-0.004546697	0.000363914	8.06E-36	7550802
Creatinine	Gamma-Glutamyl Transferase	0.004398553	0.000452712	2.58E-22	4879187
Urea	Albumin	-0.00439331	0.000662283	3.28E-11	2279839
Cystatin C	Peak Expiratory Flow	-0.003934865	0.00068983	1.17E-08	2101399
Creatinine	Uric Acid	0.003855043	0.000452784	1.68E-17	4877665
Uric Acid	Albumin	0.003694565	0.000452712	3.32E-16	4879217
Urea	Uric Acid	0.003671381	0.001055541	0.0504798	897519
Peak Expiratory Flow	Phosphate	0.00362509	0.000637717	1.31E-08	2458886
Uric Acid	Sodium in Urine	0.003601034	0.000452784	1.82E-15	4877665
Phosphate	Urate	-0.003483476	0.000635391	4.20E-08	2476926
Coffee	Gamma-Glutamyl Transferase	-0.003340332	0.00045121	1.33E-13	4911763
Peak Expiratory Flow	Urea	-0.003322435	0.000667886	6.54E-07	2241769
25-Hydroxyvitamin D	Gamma-Glutamyl Transferase	-0.002942951	0.00045087	6.70E-11	4919186
25-Hydroxyvitamin D	Testosterone	0.002351178	0.000364539	1.12E-10	7525064
25-Hydroxyvitamin D	Coffee	0.002299751	0.00037802	1.17E-09	6997889
Phosphate	Testosterone	-0.002279267	0.00063372	0.000322344	2490022
Creatinine	Red Cell Distribution Width	-0.001610809	0.000365698	1.06E-05	7477452
Phosphate	Sodium in Urine	-0.001600081	0.000637702	0.01210267	2459029
Phosphate	Uric Acid	0.001596409	0.000691707	0.021003187	2090040
25-Hydroxyvitamin D	Uric Acid	0.001339761	0.000450941	0.002967984	4917674
25-Hydroxyvitamin D	Creatinine	-0.001285099	0.000378602	0.00068797	6976443
Phosphate	Albumin	0.001225726	0.000637917	0.054675069	2457371
25-Hydroxyvitamin D	Urea	0.001195373	0.00697947	0.008676807	2052837
Coffee	Cystatin C	-0.000962985	0.00687573	0.016134652	2115251
Gamma-Glutamyl Transferase	Phosphate	-0.000874829	0.00691603	0.20589623	2090674
Coffee	Urea	0.000672694	0.066364	0.310753388	2270570
Red Cell Distribution Width	Urate	0.000668291	0.0345845	0.053317303	8360584

Supplementary Table 4.8 – Biomarker Heritability Estimates

Exposure	*Outcome*	*Beta*	*SE*	*P-Value*	*nSNPs*	*F Stat*	*Q Stat*	*Q P-Value*
Creatinine	BMI	-0.0804671	0.026684048	0.003061737	139	9.7188928	123.4125	0.01374515
Sodium Urine	BMI	-0.026296435	0.028199483	0.352723098	139	12.5984769	123.4125	0.01374515
Albumin	BMI	-0.093932231	0.003029786	1.60E-63	139	11.9667808	123.4125	0.01374515
Creatinine	DBP	2.340025361	0.27548723	5.22E-14	127	9.2342592	47.1274	0.01498976
Sodium Urine	DBP	-2.112041412	0.264444575	8.08E-13	127	12.9564407	47.1274	0.01498976
Albumin	DBP	-0.888572065	0.031013782	1.60E-56	127	11.6998972	47.1274	0.01498976
Creatinine	SBP	2.92027086	0.505349831	5.73E-08	127	9.2342592	170.37463	0.2087211
Sodium Urine	SBP	-0.454522452	0.37611707	0.229169845	127	12.9564407	170.37463	0.2087211
Albumin	SBP	-1.052501447	0.039215985	1.73E-53	127	11.6998972	170.37463	0.2087211
Creatinine	MetS	0.112246921	0.143574404	0.4381698	51	9.15578698	234.84189	8.77E-02
Sodium Urine	MetS	-0.297686156	0.136470182	0.034089175	51	11.6565284	234.84189	8.77E-02
Albumin	MetS	0.12831458	0.1028238	0.218118463	51	10.2547788	234.84189	8.77E-02

Supplementary Table 4.9 – Multivariable MR Renal Cluster Results

Exposure	*Outcome*	*Beta*	*SE*	*P-Value*	*nSNPs*	*F Stat*	*Q Stat*	*Q P-Value*
Creatinine	BMI	-0.0804671	0.026684048	0.003061737	139	9.7188928	123.4125	0.01374515
Sodium Urine	BMI	-0.026296435	0.028199483	0.352723098	139	12.5984769	123.4125	0.01374515
Albumin	BMI	-0.093932231	0.003029786	1.60E-63	139	11.9667808	123.4125	0.01374515
Creatinine	DBP	2.340025361	0.27548723	5.22E-14	127	9.2342592	47.1274	0.01498976
Sodium Urine	DBP	-2.112041412	0.264444575	8.08E-13	127	12.9564407	47.1274	0.01498976
Albumin	DBP	-0.888572065	0.031013782	1.60E-56	127	11.6998972	47.1274	0.01498976
Creatinine	SBP	2.92027086	0.505349831	5.73E-08	127	9.2342592	170.37463	0.2087211
Sodium Urine	SBP	-0.454522452	0.37611707	0.229169845	127	12.9564407	170.37463	0.2087211
Albumin	SBP	-1.052501447	0.039215985	1.73E-53	127	11.6998972	170.37463	0.2087211
Creatinine	MetS	0.112246921	0.143574404	0.4381698	51	9.15578698	234.84189	8.77E-02
Sodium Urine	MetS	-0.297686156	0.136470182	0.034089175	51	11.6565284	234.84189	8.77E-02
Albumin	MetS	0.12831458	0.1028238	0.218118463	51	10.2547788	234.84189	8.77E-02

Supplementary Table 4.10 – Full Multivariable MR Results

Exposure	*Beta*	*SE*	*P Value*	*nSNPs*	*Outcome*	*F Stat*
25-Hydroxyvitamin D	0.036741	0.005198	2.19E-12	1946	BMI	1.121879
Coffee	0.115134	0.026896	1.95E-05	1946	BMI	1.121879
Creatinine	-0.26114	0.025996	3.53E-23	1946	BMI	1.121879
Cystatin C	0.032222	0.021746	0.138567	1946	BMI	1.121879
Gamma-Glutamyl Transferase	0.030156	0.007179	2.79E-05	1946	BMI	1.121879
Impedance of Left Arm	0.365675	0.070945	2.81E-07	1946	BMI	1.121879
Impedance of Right Arm	-0.68338	0.07375	4.99E-20	1946	BMI	1.121879
Peak Expiratory Flow	-0.11636	0.012566	5.27E-20	1946	BMI	1.121879
Red Cell Distribution Width	0.001471	0.004172	0.724474	1946	BMI	1.121879
Phosphate	0.090512	0.018696	1.39E-06	1946	BMI	1.121879
Urea	0.070092	0.007497	2.35E-20	1946	BMI	1.121879
Uric Acid	-0.00507	0.002274	0.02599	1946	BMI	1.121879
Sodium Urine	0.411296	0.01425	1.37E-152	1946	BMI	1.121879
Testosterone	0.101369	0.003386	4.74E-162	1946	BMI	1.121879
Urate	-0.05157	0.003318	2.06E-51	1946	BMI	1.121879
Albumin	0.40408	0.030097	2.34E-39	1946	BMI	1.121879
25-Hydroxyvitamin D	-0.40493	0.040443	5.28E-23	1823	DBP	1.149121
Coffee	-4.12401	0.151367	3.18E-137	1823	DBP	1.149121
Creatinine	-5.55084	0.214854	1.61E-125	1823	DBP	1.149121
Cystatin C	-0.46198	0.084326	4.89E-08	1823	DBP	1.149121
Gamma-Glutamyl Transferase	0.433549	0.059613	5.22E-13	1823	DBP	1.149121
Impedance of Left Arm	-6.71355	0.651275	2.99E-24	1823	DBP	1.149121
Impedance of Right Arm	7.191368	0.650898	1.66E-27	1823	DBP	1.149121
Peak Expiratory Flow	2.995662	0.116708	3.80E-124	1823	DBP	1.149121
Red Cell Distribution Width	0.50566	0.057222	2.28E-18	1823	DBP	1.149121
Phosphate	1.224969	0.324918	0.000168	1823	DBP	1.149121
Urea	-0.44945	0.106808	2.70E-05	1823	DBP	1.149121
Uric Acid	-0.65874	0.037504	6.92E-64	1823	DBP	1.149121
Sodium Urine	6.822594	0.177281	3.57E-237	1823	DBP	1.149121
Testosterone	0.04669	0.030034	0.120218	1823	DBP	1.149121
Urate	0.083701	0.062881	0.183323	1823	DBP	1.149121
Albumin	0.270222	0.173136	0.118759	1823	DBP	1.149121
25-Hydroxyvitamin D	0.08088	0.088836	0.362714	1803	SBP	1.130693
Coffee	-4.95809	0.244188	1.22E-82	1803	SBP	1.130693
Creatinine	-4.09543	0.328658	3.08E-34	1803	SBP	1.130693
Cystatin C	-2.82541	0.33063	2.70E-17	1803	SBP	1.130693
Gamma-Glutamyl Transferase	1.611787	0.096307	1.61E-58	1803	SBP	1.130693
Impedance of Left Arm	-1.55385	0.959869	0.105664	1803	SBP	1.130693
Impedance of Right Arm	7.142803	0.984807	6.05E-13	1803	SBP	1.130693
Peak Expiratory Flow	-1.45584	0.209036	4.61E-12	1803	SBP	1.130693
Red Cell Distribution Width	-0.235	0.076795	0.002245	1803	SBP	1.130693
Phosphate	-2.50893	0.264304	6.93E-21	1803	SBP	1.130693
Urea	1.182672	0.133055	1.48E-18	1803	SBP	1.130693
Uric Acid	0.117342	0.027579	2.20E-05	1803	SBP	1.130693
Sodium Urine	6.558183	0.368931	3.19E-65	1803	SBP	1.130693
Testosterone	-1.59084	0.155442	6.27E-24	1803	SBP	1.130693
Urate	0.135663	0.042237	0.001342	1803	SBP	1.130693
Albumin	2.94989	0.425951	6.04E-12	1803	SBP	1.130693
25-Hydroxyvitamin D	-0.17881	0.009781	1.21E-68	1825	HbA1c	1.151031
Coffee	-0.0701	0.036671	0.056095	1825	HbA1c	1.151031
Creatinine	0.252717	0.047836	1.42E-07	1825	HbA1c	1.151031
Cystatin C	0.288326	0.023263	6.41E-34	1825	HbA1c	1.151031
Gamma-Glutamyl Transferase	-0.00666	0.003951	0.092084	1825	HbA1c	1.151031
Impedance of Left Arm	2.203457	0.092963	2.21E-108	1825	HbA1c	1.151031
Impedance of Right Arm	-1.81762	0.087933	2.19E-85	1825	HbA1c	1.151031
Peak Expiratory Flow	0.16186	0.022467	8.52E-13	1825	HbA1c	1.151031
Red Cell Distribution Width	-0.09255	0.010802	2.22E-17	1825	HbA1c	1.151031
Phosphate	0.383521	0.064896	4.08E-09	1825	HbA1c	1.151031

Urea	0.07609	0.011102	9.83E-12	1825	HbA1c	1.151031
Uric Acid	0.052234	0.005285	1.79E-22	1825	HbA1c	1.151031
Sodium Urine	-0.42012	0.024269	3.04E-62	1825	HbA1c	1.151031
Testosterone	0.215304	0.012891	2.35E-58	1825	HbA1c	1.151031
Urate	-0.05449	0.00666	5.24E-16	1825	HbA1c	1.151031
Albumin	-0.27388	0.051314	1.06E-07	1825	HbA1c	1.151031
25-Hydroxyvitamin D	0.08669	0.011083	8.58E-15	1906	HDL	1.107075
Coffee	0.334356	0.039983	1.18E-16	1906	HDL	1.107075
Creatinine	-0.33075	0.041854	4.60E-15	1906	HDL	1.107075
Cystatin C	-0.15589	0.040885	0.000142	1906	HDL	1.107075
Gamma-Glutamyl Transferase	0.080502	0.009207	4.88E-18	1906	HDL	1.107075
Impedance of Left Arm	0.142476	0.142202	0.316504	1906	HDL	1.107075
Impedance of Right Arm	-0.13072	0.152009	0.389943	1906	HDL	1.107075
Peak Expiratory Flow	-0.49303	0.019745	3.66E-119	1906	HDL	1.107075
Red Cell Distribution Width	-0.11721	0.006067	4.81E-76	1906	HDL	1.107075
Phosphate	1.270655	0.066825	6.60E-74	1906	HDL	1.107075
Urea	0.097513	0.020775	2.88E-06	1906	HDL	1.107075
Uric Acid	-0.21492	0.009151	3.07E-107	1906	HDL	1.107075
Sodium Urine	1.301575	0.034452	3.64E-233	1906	HDL	1.107075
Testosterone	0.110097	0.014753	1.28E-13	1906	HDL	1.107075
Urate	0.263986	0.010114	1.69E-128	1906	HDL	1.107075
Albumin	-0.50434	0.052588	2.66E-21	1906	HDL	1.107075
25-Hydroxyvitamin D	0.025377	0.018165	0.162568	1906	LDL	1.107075
Coffee	0.267917	0.064948	3.87E-05	1906	LDL	1.107075
Creatinine	0.261233	0.059098	1.04E-05	1906	LDL	1.107075
Cystatin C	0.356594	0.039362	3.19E-19	1906	LDL	1.107075
Gamma-Glutamyl Transferase	0.103369	0.012187	4.40E-17	1906	LDL	1.107075
Impedance of Left Arm	0.92207	0.170168	6.78E-08	1906	LDL	1.107075
Impedance of Right Arm	-0.85575	0.184077	3.57E-06	1906	LDL	1.107075
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Red Cell Distribution Width	-0.04045	0.01256	0.001301	1906	LDL	1.107075
Phosphate	1.378855	0.098384	1.57E-42	1906	LDL	1.107075
Urea	0.369447	0.019896	7.80E-71	1906	LDL	1.107075
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Sodium Urine	0.423382	0.063064	2.50E-11	1906	LDL	1.107075
Testosterone	0.010613	0.01975	0.591055	1906	LDL	1.107075
Urate	0.153765	0.008034	9.06E-75	1906	LDL	1.107075
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Impedance of Right Arm	0.829624	0.131996	4.05E-10	1906	Triglycerides	1.107075
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Red Cell Distribution Width	-0.18702	0.006079	7.73E-169	1906	Triglycerides	1.107075
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Albumin	-0.56437	0.078155	7.44E-13	1906	Triglycerides	1.107075
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Coffee	-1.99199	0.305544	8.99E-11	1937	T2D	1.123534
Creatinine	1.663269	0.455558	0.000268	1937	T2D	1.123534
Cystatin C	-0.04113	0.569972	0.942485	1937	T2D	1.123534
Gamma-Glutamyl Transferase	1.275898	0.153134	1.49E-16	1937	T2D	1.123534
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Impedance of Right Arm	0.069045	1.562228	0.964752	1937	T2D	1.123534
Peak Expiratory Flow	2.244235	0.476172	2.62E-06	1937	T2D	1.123534

Red Cell Distribution Width	-0.1449	0.08972	0.106478	1937	T2D	1.123534
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Urea	0.180346	0.211187	0.393232	1937	T2D	1.123534
Uric Acid	0.395829	0.116465	0.000691	1937	T2D	1.123534
Sodium Urine	2.301616	0.483582	2.09E-06	1937	T2D	1.123534
Testosterone	0.824131	0.171599	1.69E-06	1937	T2D	1.123534
Urate	0.515043	0.1185	1.46E-05	1937	T2D	1.123534
Albumin	0.882247	0.580831	0.128942	1937	T2D	1.123534
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Coffee	0.075297	0.027721	0.006666	1838	MetS	1.173883
Creatinine	-0.08162	0.029443	0.005628	1838	MetS	1.173883
Cystatin C	-0.32062	0.02823	6.24E-29	1838	MetS	1.173883
Gamma-Glutamyl Transferase	0.001214	0.006784	0.857979	1838	MetS	1.173883
Impedance of Left Arm	0.310972	0.092419	0.000782	1838	MetS	1.173883
Impedance of Right Arm	-0.09167	0.091886	0.318605	1838	MetS	1.173883
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Red Cell Distribution Width	-0.01318	0.004906	0.007296	1838	MetS	1.173883
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Urea	-0.06738	0.011453	4.78E-09	1838	MetS	1.173883
Uric Acid	0.017383	0.00545	0.001451	1838	MetS	1.173883
Sodium Urine	-0.17884	0.026152	1.09E-11	1838	MetS	1.173883
Testosterone	0.024392	0.01101	0.026847	1838	MetS	1.173883
Urate	0.056425	0.007101	3.35E-15	1838	MetS	1.173883
Albumin	0.180384	0.031411	1.09E-08	1838	MetS	1.173883

Supplementary Figures

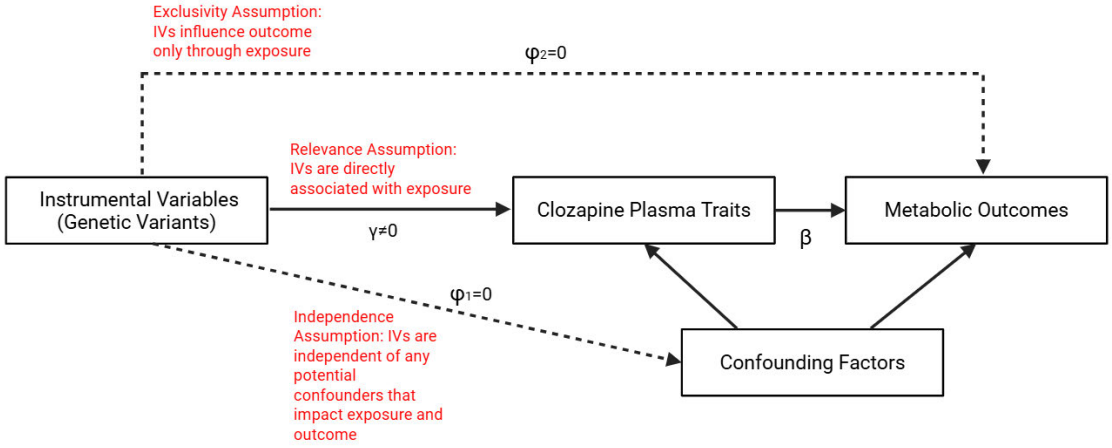
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Supplementary Figures 4.1 - Directive Acyclic Graphs

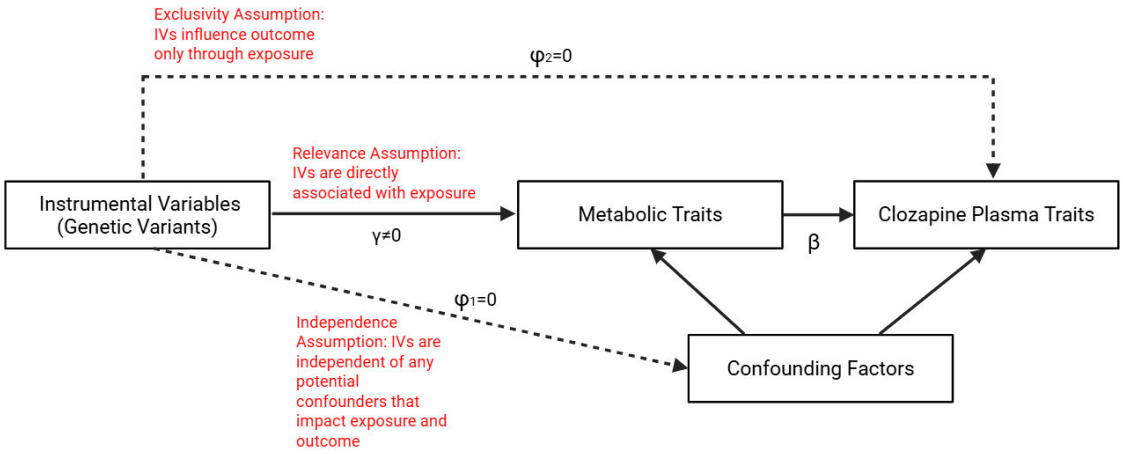
Directive acyclic graphs (DAGs) representing the assumptions of valid causal inference in Mendelian randomization: the genetic variant must be strongly associated with the exposure (relevance assumption), it must be independent of the outcome except through the exposure (independence assumption), and it must affect the outcome only through the exposure (exclusion restriction).

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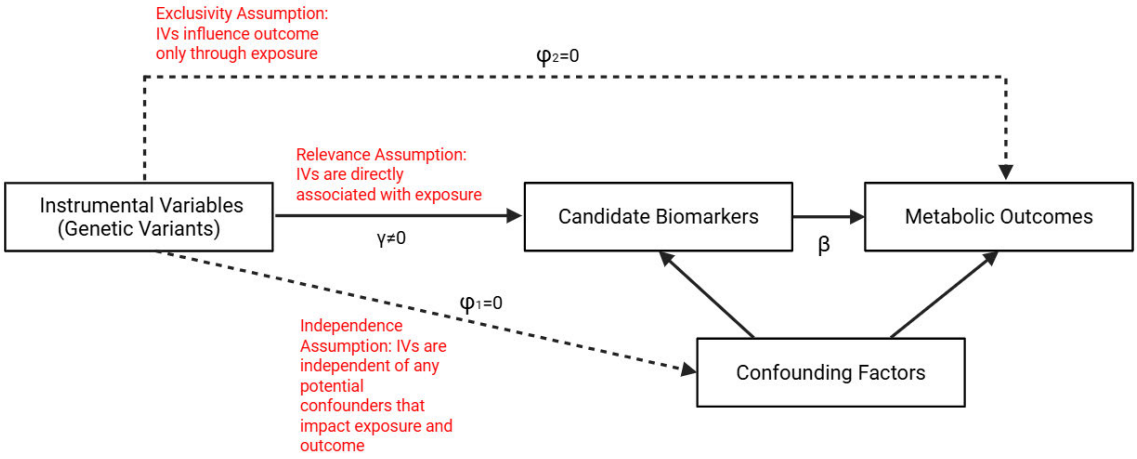
Supplementary Figures 4.1.1 - Clozapine Plasma Traits Effects on Cardiometabolic Traits



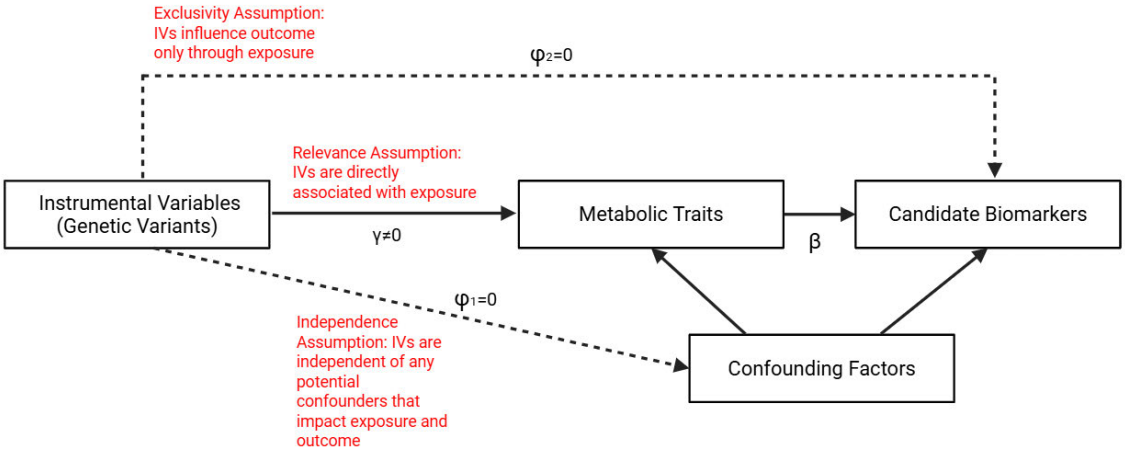
Supplementary Figures 4.1.2 - Cardiometabolic Effects on Clozapine Plasma Traits



Supplementary Figures 4.1.3 - Candidate Biomarkers Effects on Cardiometabolic Traits



Supplementary Figures 4.1.4 - Cardiometabolic Effects on Candidate Biomarkers

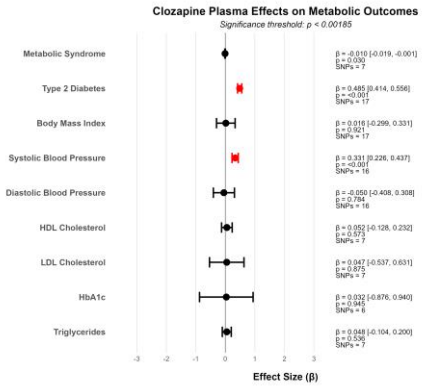


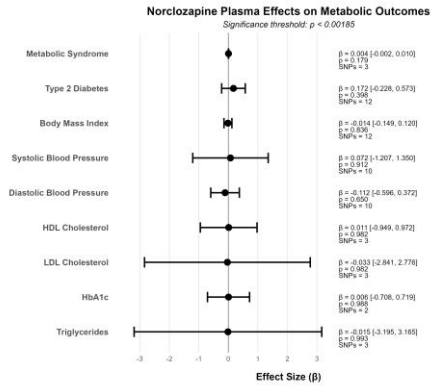
Supplementary Figures 4.2 - Bidirectional Effects of Clozapine Plasma Traits on Cardiometabolic Outcomes

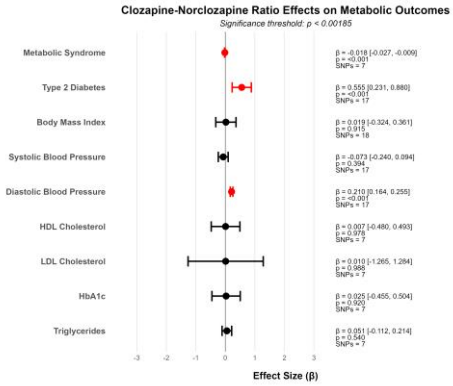
Analysis results from linkage-disequilibrium-aware bidirectional Mendelian randomization of clozapine on cardiometabolic outcomes. Forest plots demonstrate the causal estimate of the exposure ($\boldsymbol{\beta}$) on $\boldsymbol{n}$ outcomes with $\mathbf{95\%}\ \boldsymbol{CIs}$ and $\boldsymbol{Pvals}$. Significance threshold is adjusted for multiple testing (Bonferroni Correction) ($\boldsymbol{Pval\ (adj) = 0.05/n}$). Scatterplots depict sensitivity analyses results including MR-Egger and weighted median to test for directional pleiotropy and causal estimate assessment under invalid instruments respectively. Leave-one-out plots demonstrate the robustness of causal inference by testing if one genetic variant is driving the observed association. Raw results for direct and inverse linkage-disequilibrium-aware bidirectional Mendelian randomization are available in Supplementary Table 4.1 and 4.2. Information about the Mendelian randomization analysis can be found in the Supplementary Methods (Appendix C).

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Supplementary Figures 4.2.1 - Forest Plots - Clozapine Plasma Traits Effects on Cardiometabolic Outcomes

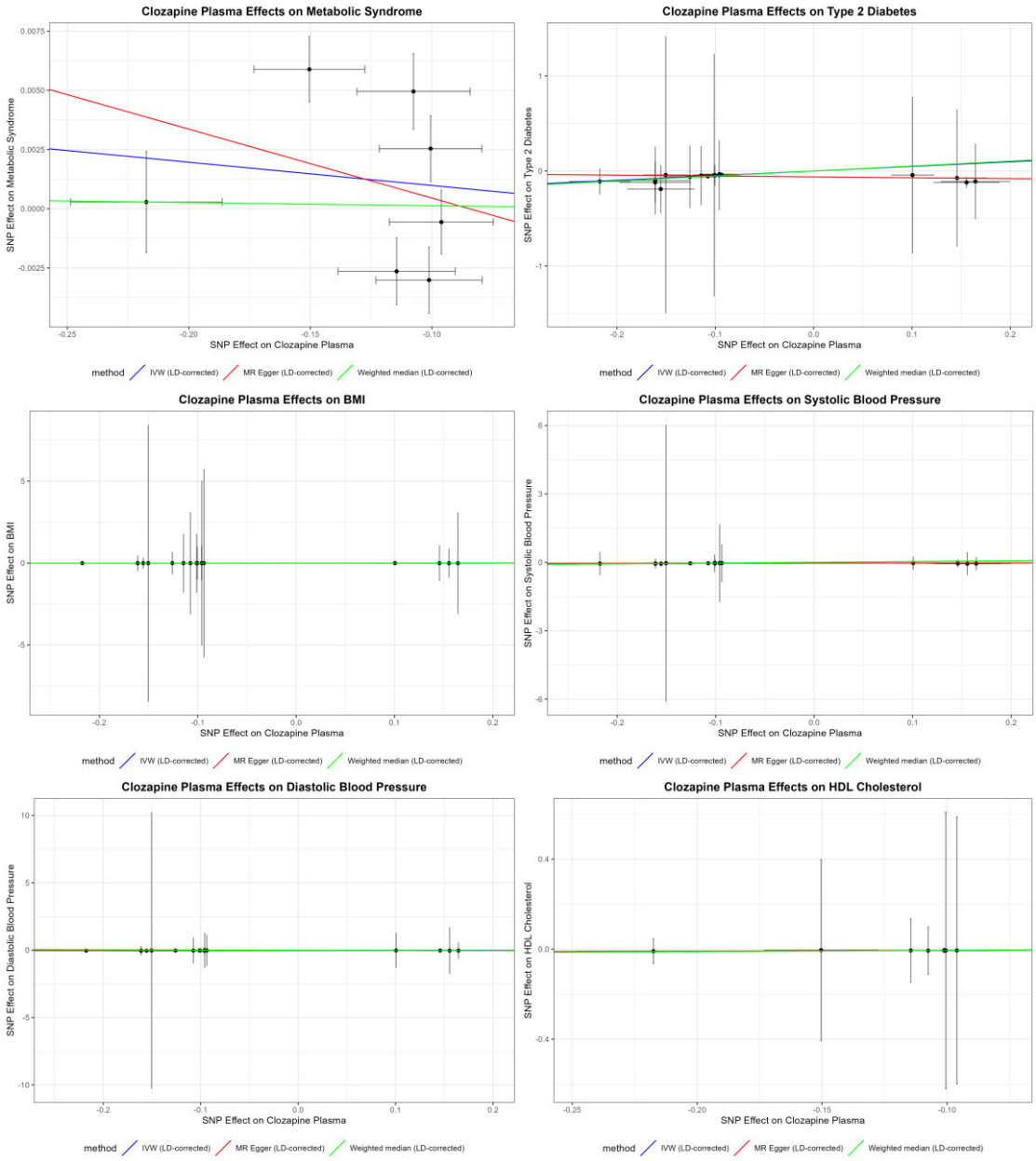


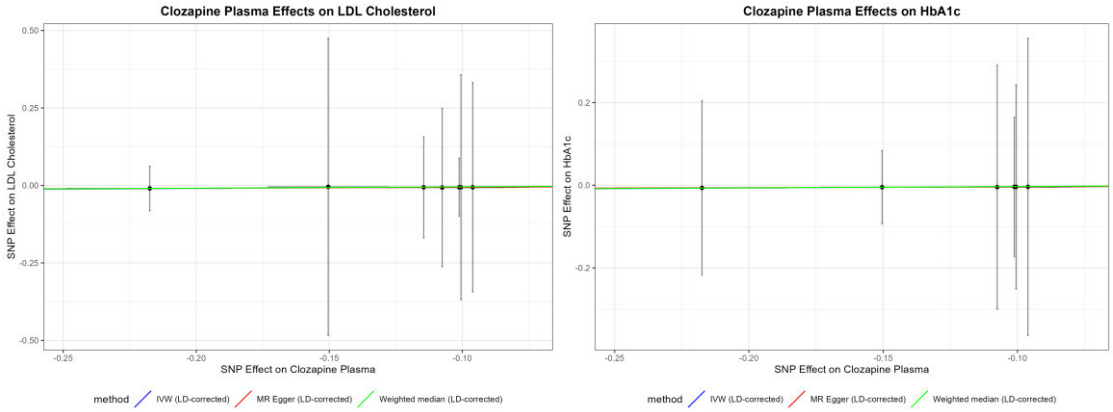


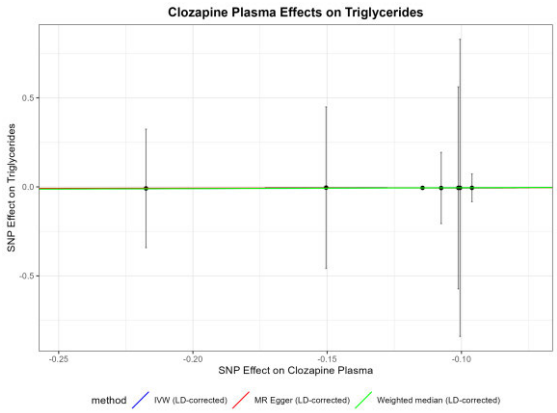


Supplementary Figures 4.2.2 - Scatterplots - Clozapine Plasma Traits Effects on Cardiometabolic Outcomes

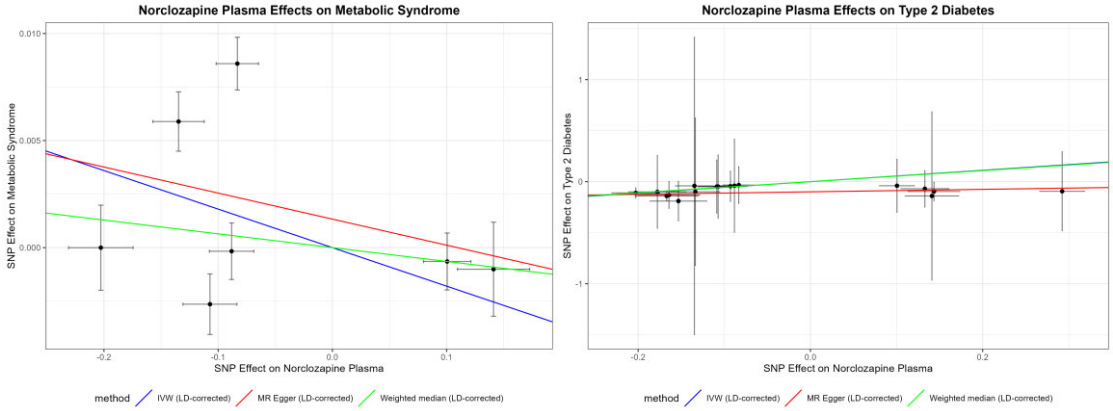
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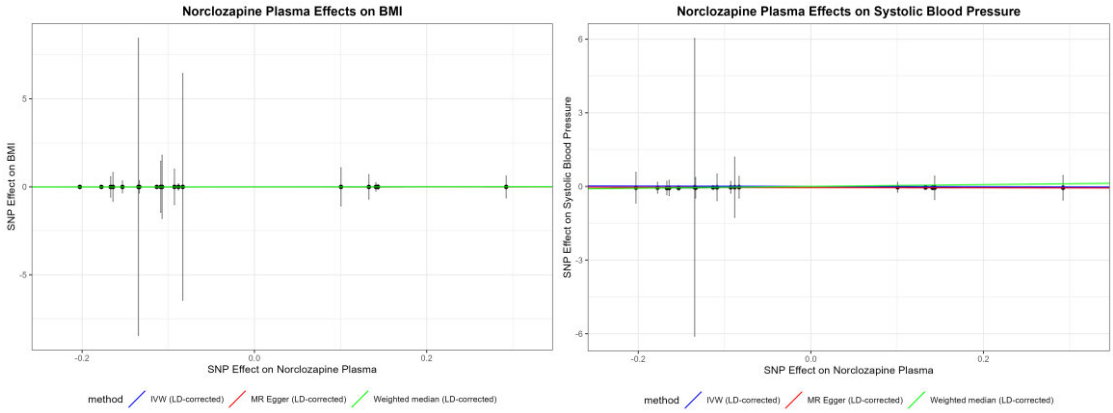


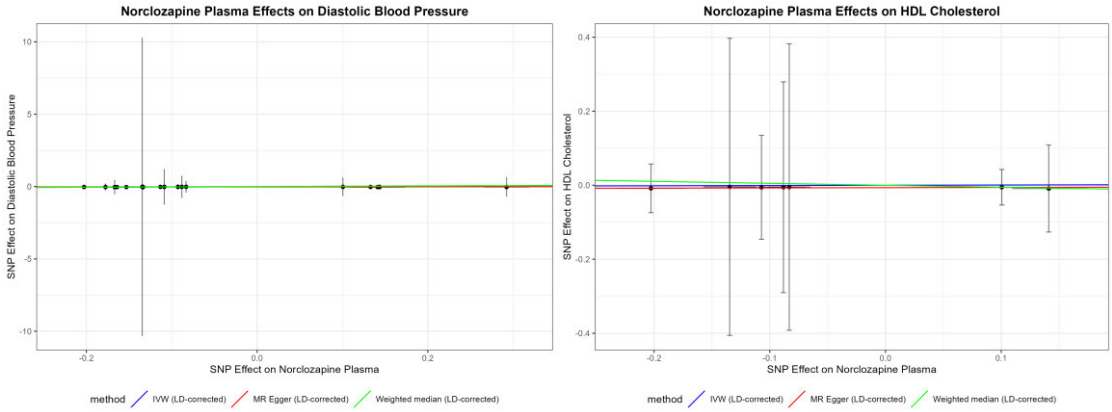




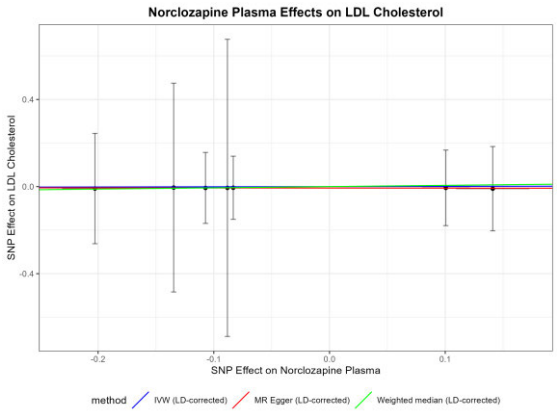
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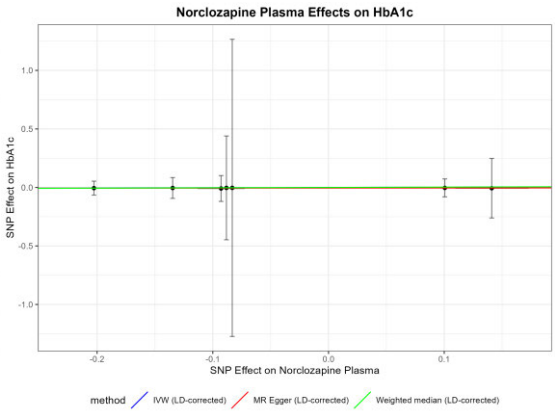


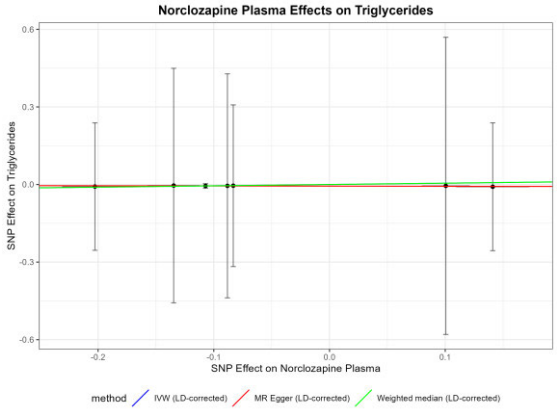



Norclozapine Plasma Effects on Diastolic Blood Pressure
SNP Effect on Diastolic Blood Pressure
SNP Effect on Norclozapine Plasma
method
IVW (LD-corrected)
MR Egger (LD-corrected)
Weighted median (LD-corrected)

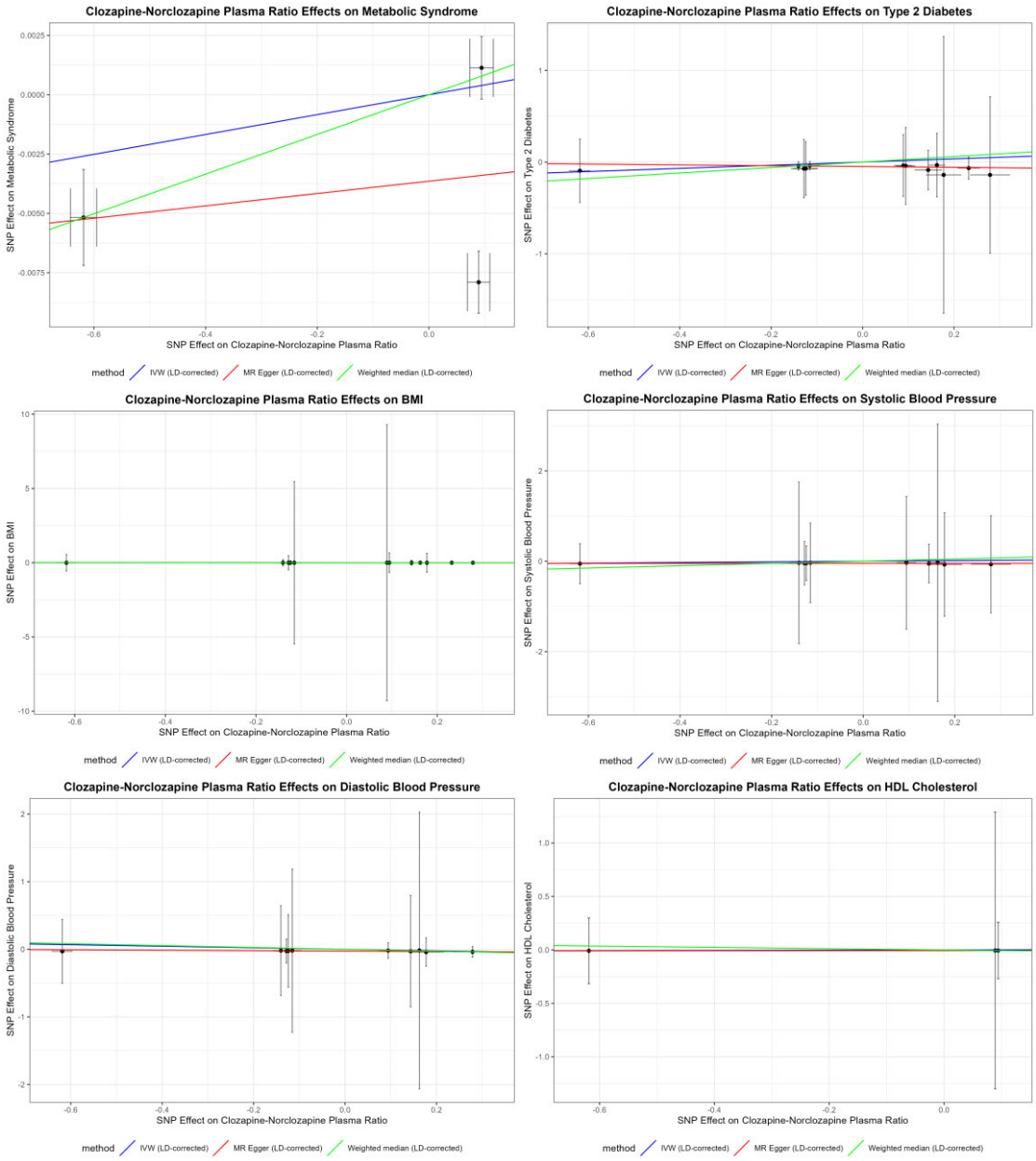
Norclozapine Plasma Effects on HDL Cholesterol
SNP Effect on HDL Cholesterol
SNP Effect on Norclozapine Plasma
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MR Egger (LD-corrected)
Weighted median (LD-corrected)

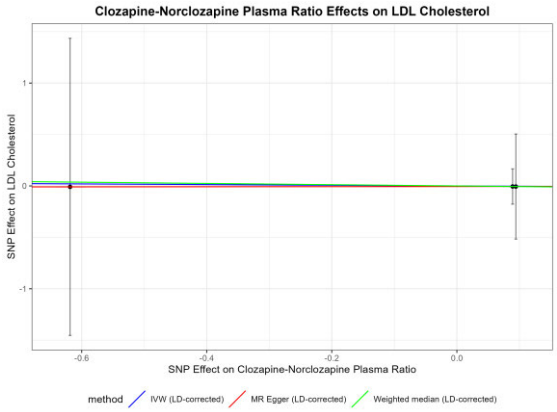

Norclozapine Plasma Effects on LDL Cholesterol
SNP Effect on LDL Cholesterol
SNP Effect on Norclozapine Plasma
method
IVW (LD-corrected)
MR Egger (LD-corrected)
Weighted median (LD-corrected)

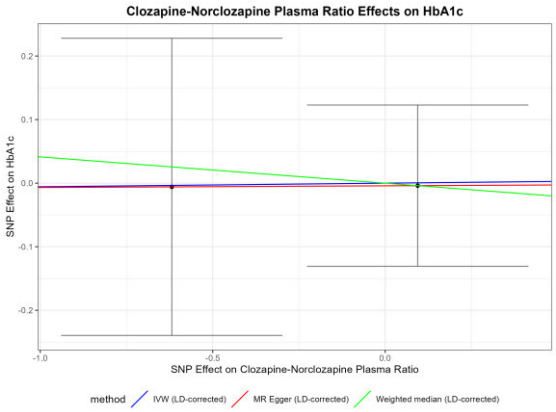

Norclozapine Plasma Effects on HbA1c
SNP Effect on HbA1c
SNP Effect on Norclozapine Plasma
method
IVW (LD-corrected)
MR Egger (LD-corrected)
Weighted median (LD-corrected)

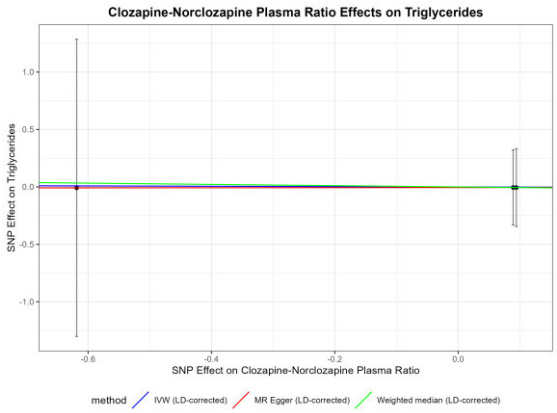

Norclozapine Plasma Effects on Triglycerides
SNP Effect on Triglycerides
SNP Effect on Norclozapine Plasma
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MR Egger (LD-corrected)
Weighted median (LD-corrected)

Clozapine-Norclozapine Plasma Ratio:



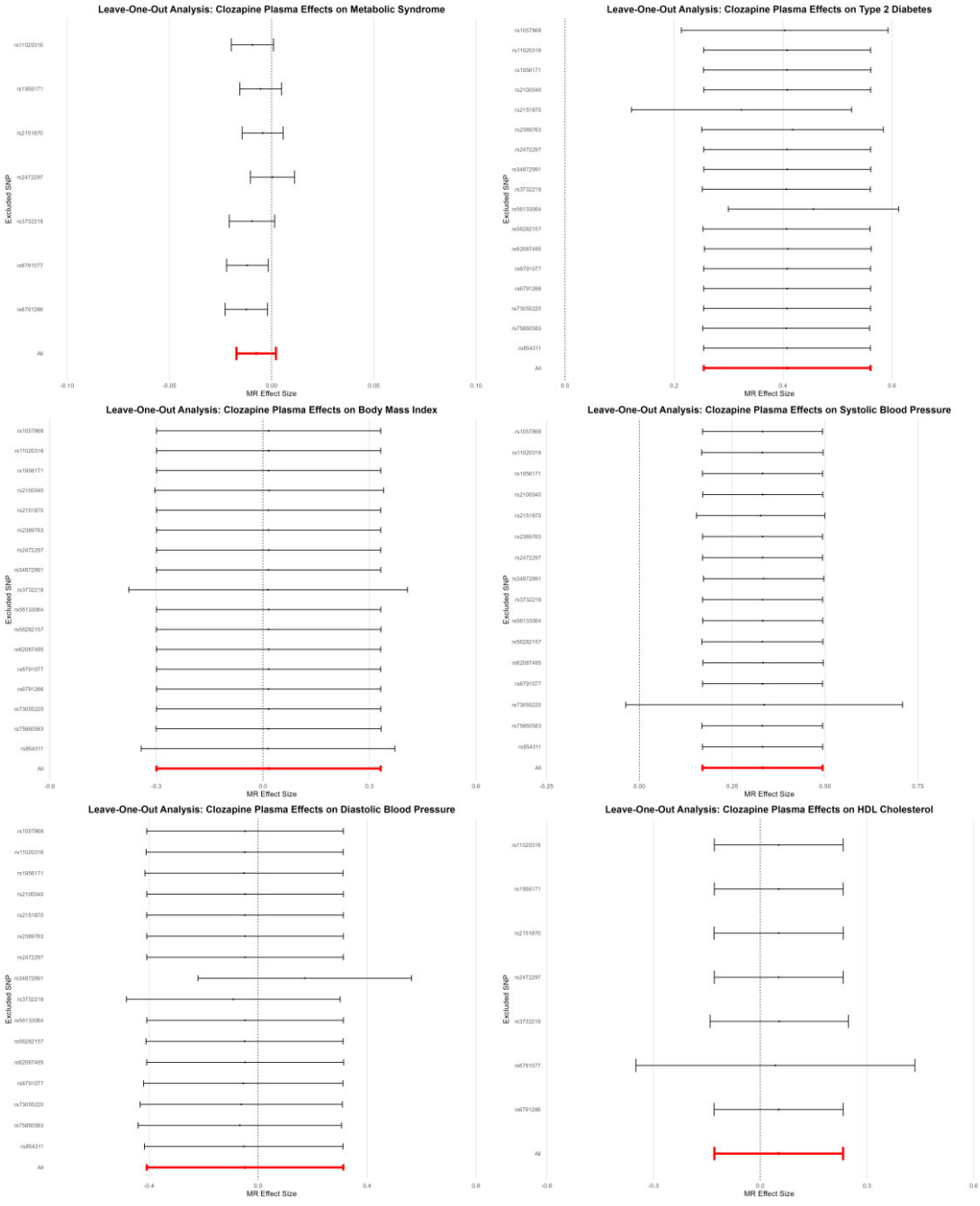

Clozapine-Norclozapine Plasma Ratio Effects on LDL Cholesterol
SNP Effect on LDL Cholesterol
SNP Effect on Clozapine-Norclozapine Plasma Ratio
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MR Egger (LD-corrected)
Weighted median (LD-corrected)

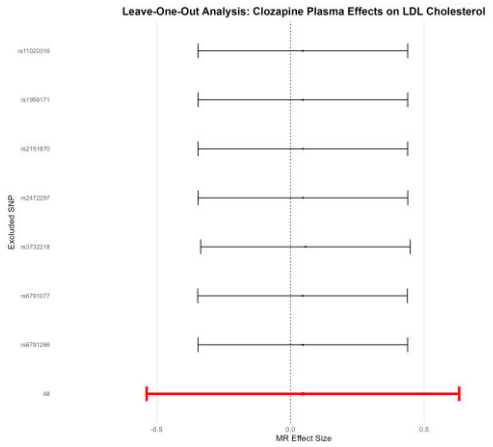

Clozapine-Norclozapine Plasma Ratio Effects on HbA1c
SNP Effect on HbA1c
SNP Effect on Clozapine-Norclozapine Plasma Ratio
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MR Egger (LD-corrected)
Weighted median (LD-corrected)

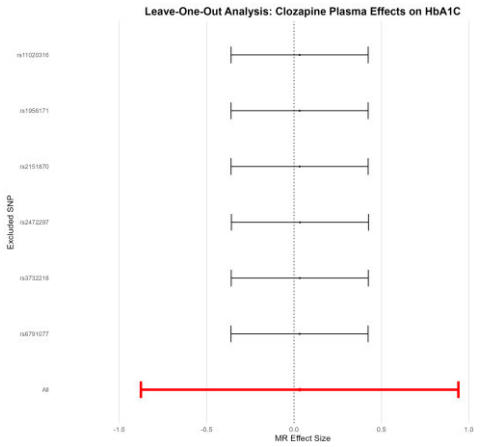

Clozapine-Norclozapine Plasma Ratio Effects on Triglycerides
SNP Effect on Triglycerides
SNP Effect on Clozapine-Norclozapine Plasma Ratio
method
IVW (LD-corrected)
MR Egger (LD-corrected)
Weighted median (LD-corrected)

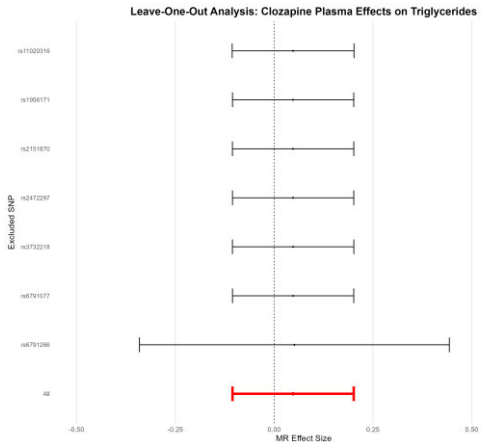
Supplementary Figures 4.2.3 – Leave-One-Out Plots - Clozapine Plasma Traits Effects on Cardiometabolic Traits

Clozapine Plasma:

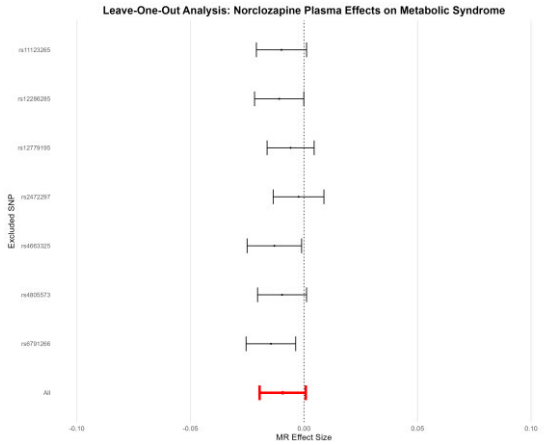


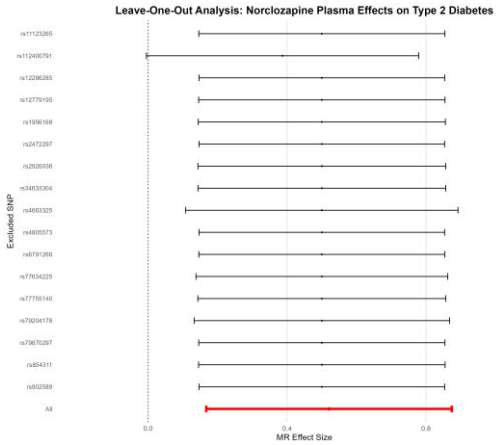


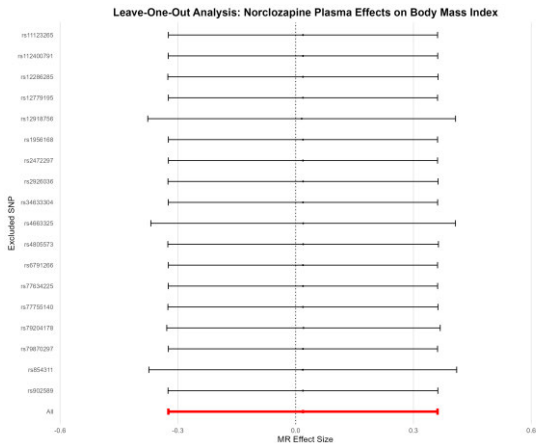


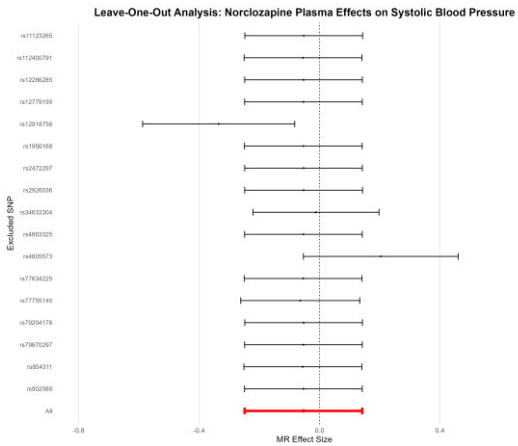


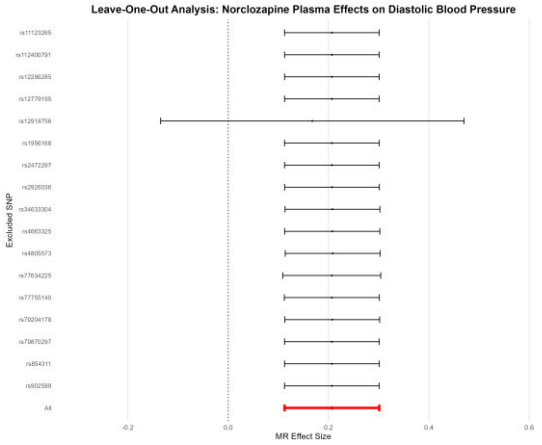
Norclozapine Plasma:

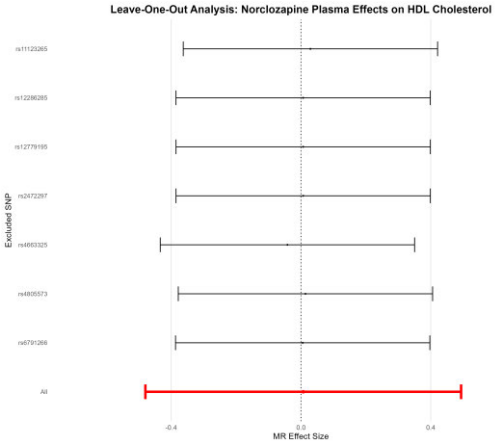


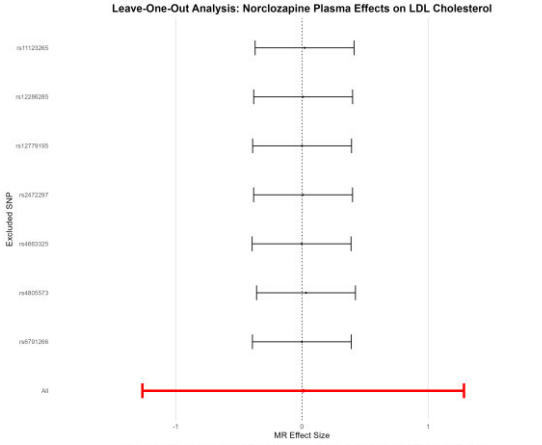


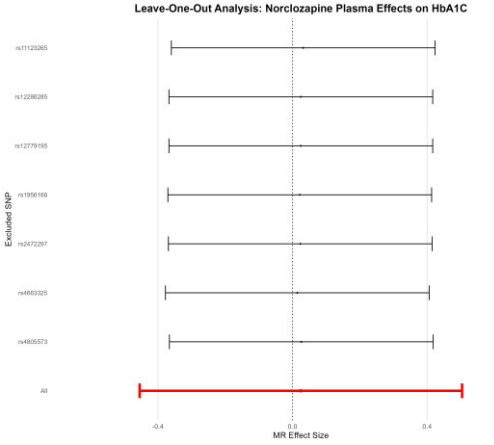


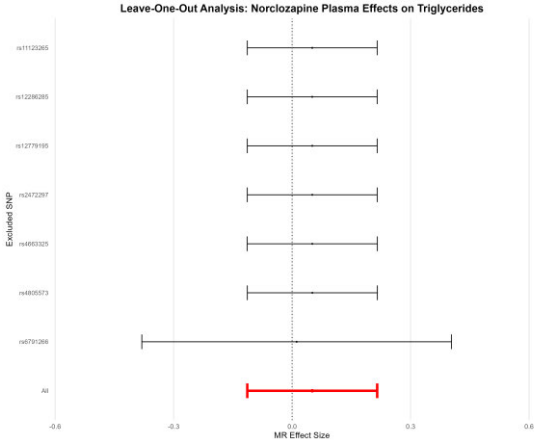



Leave-One-Out Analysis: Norclozapine Plasma Effects on Diastolic Blood Pressure
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rs12286285
rs12779195
rs12918756
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rs2472297
rs2926036
rs34633004
rs4663325
rs4805573
rs77634225
rs77755140
rs79204178
rs79870297
rs854311
rs902589
All
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0.0
0.2
0.4
0.6
MR Effect Size

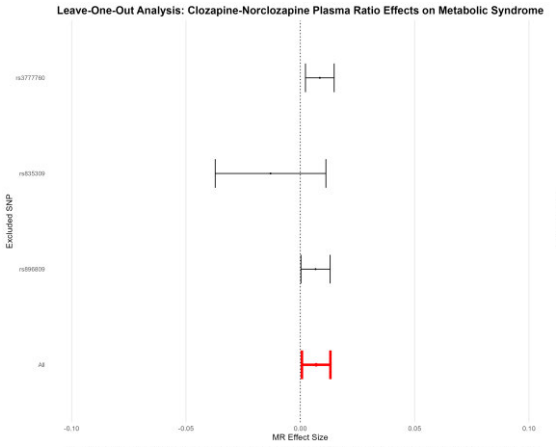

Leave-One-Out Analysis: Norclozapine Plasma Effects on HDL Cholesterol
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rs11123265
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rs2472297
rs4663325
rs4805573
rs6791266
All
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MR Effect Size

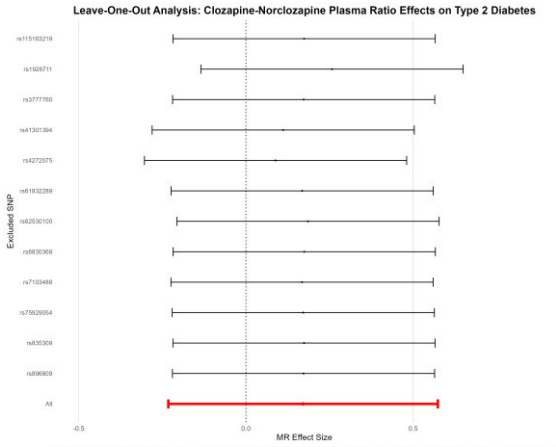

Leave-One-Out Analysis: Norclozapine Plasma Effects on LDL Cholesterol
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rs12779195
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All
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1
MR Effect Size

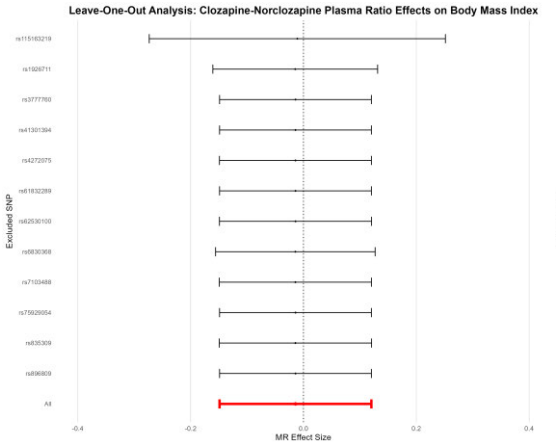

Leave-One-Out Analysis: Norclozapine Plasma Effects on HbA1C
Excluded SNP
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All
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MR Effect Size

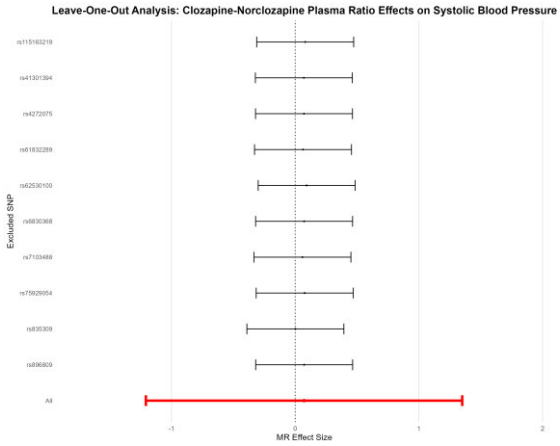

Leave-One-Out Analysis: Norclozapine Plasma Effects on Triglycerides
Excluded SNP
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rs12286285
rs12779195
rs2472297
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rs4805573
rs6791266
All
-0.6
-0.3
0.0
0.3
0.6
MR Effect Size

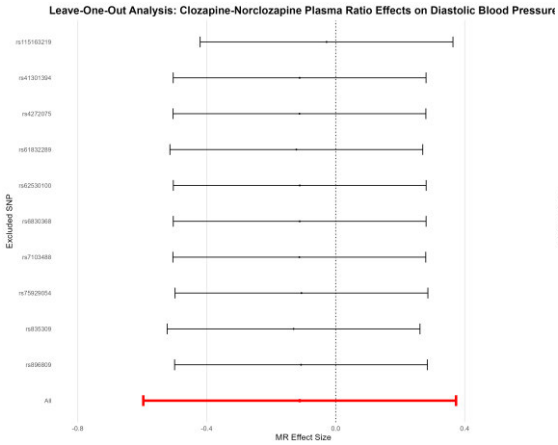
Clozapine-Norclozapine Plasma Ratio:

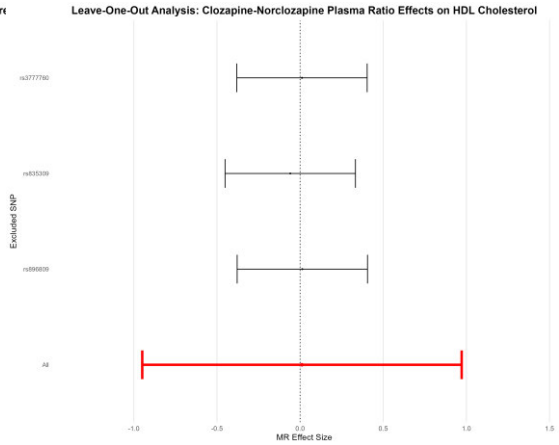


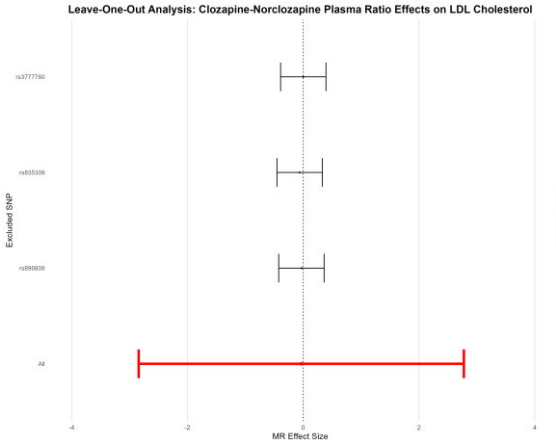


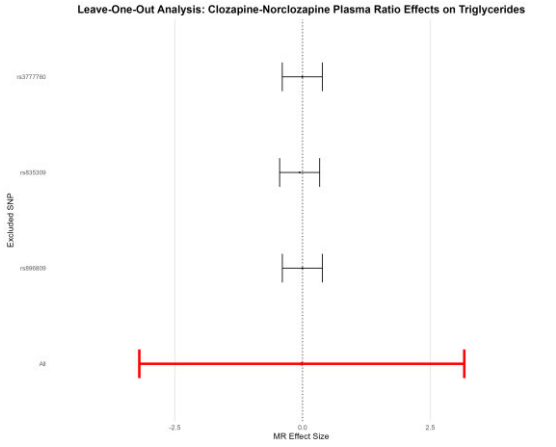




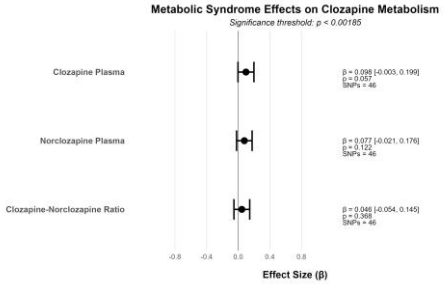


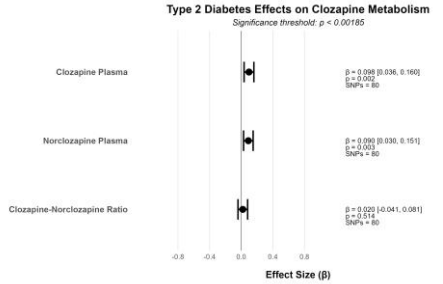


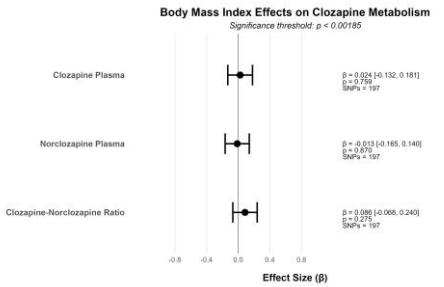


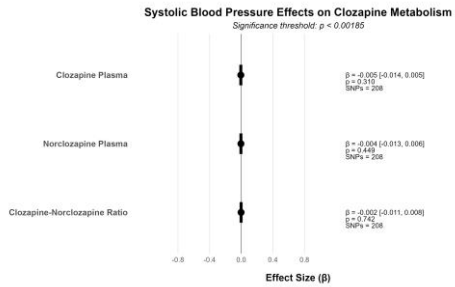


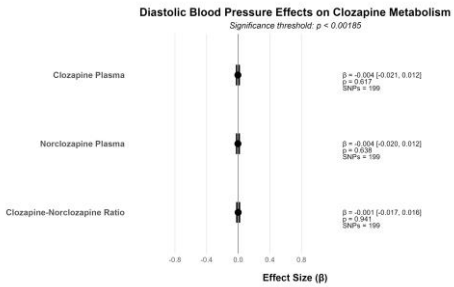
Supplementary Figures 4.2.4 - Forest Plots - Cardiometabolic Effects on Clozapine Plasma Traits

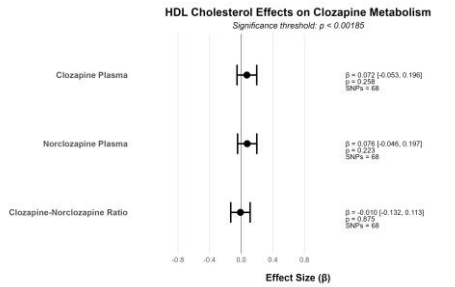


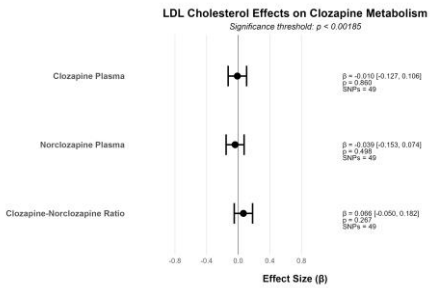


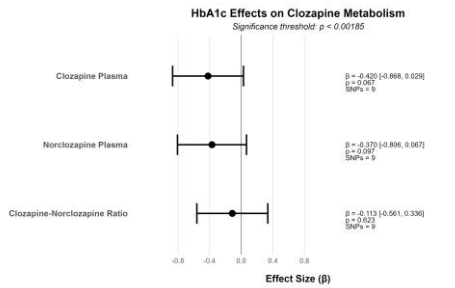


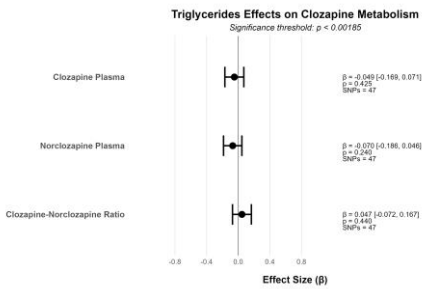






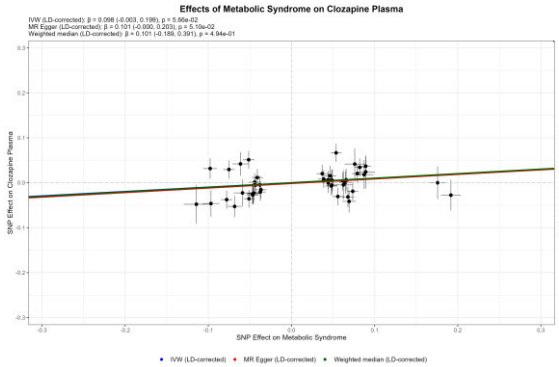


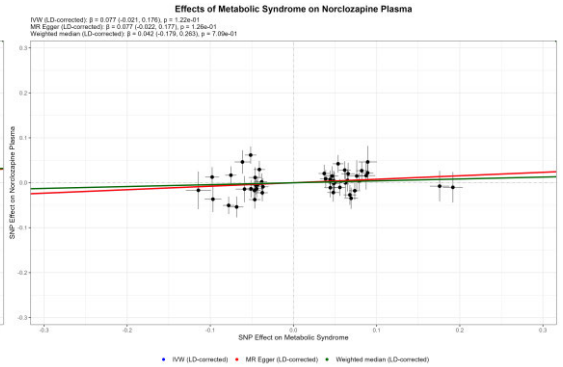


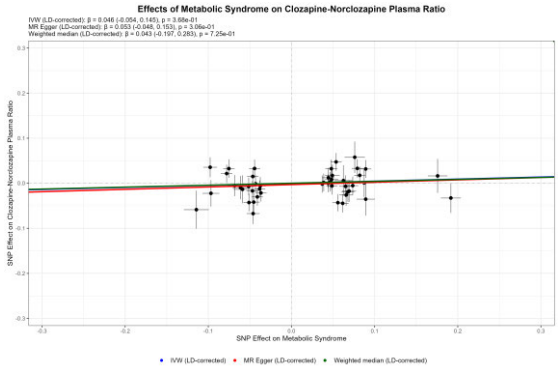


Supplementary Figures 4.2.5 - Scatterplots - Cardiometabolic Effects on Clozapine Plasma Traits

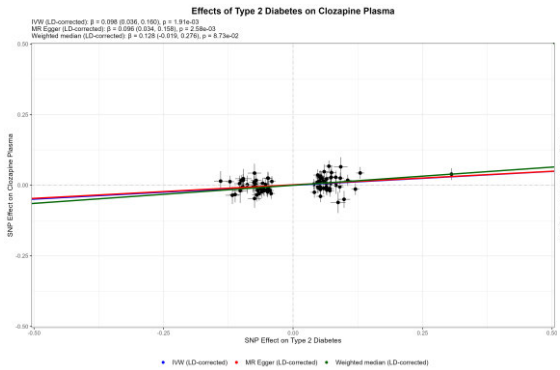
Metabolic Syndrome:

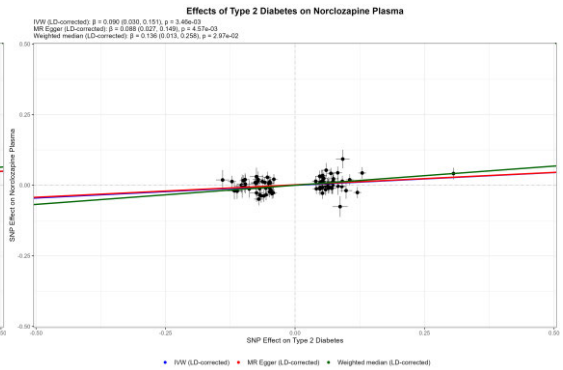


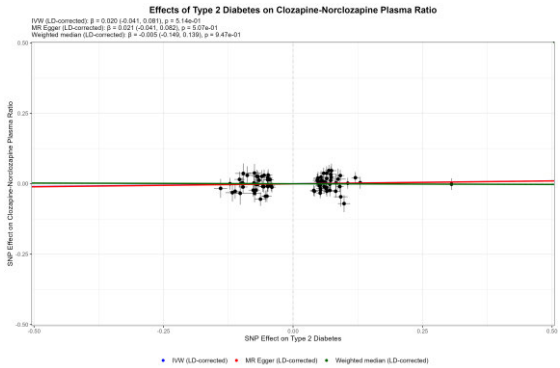




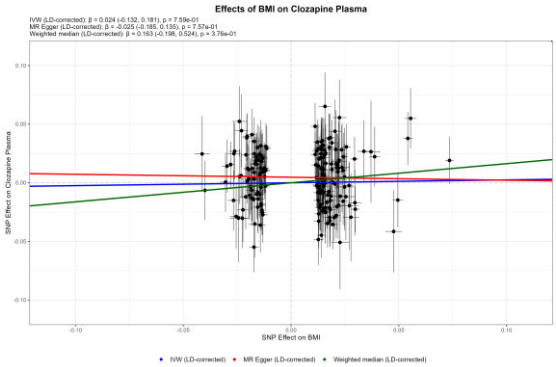
Type 2 Diabetes:

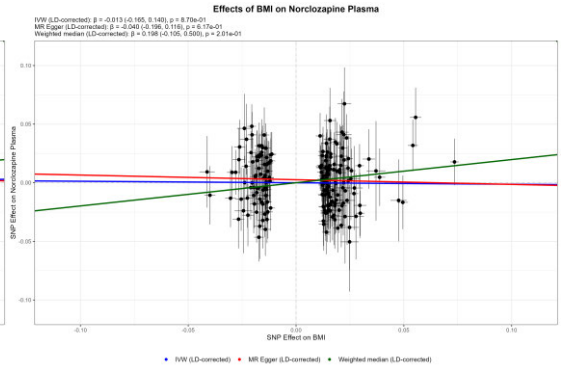


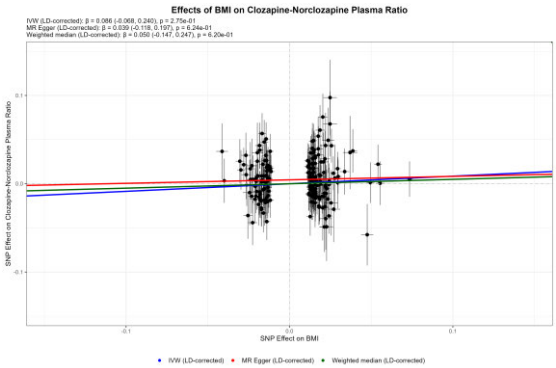




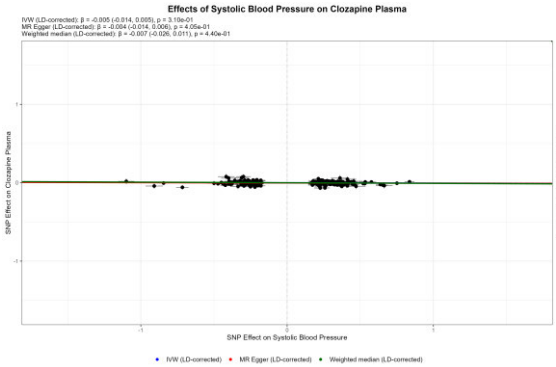
Body Mass Index:

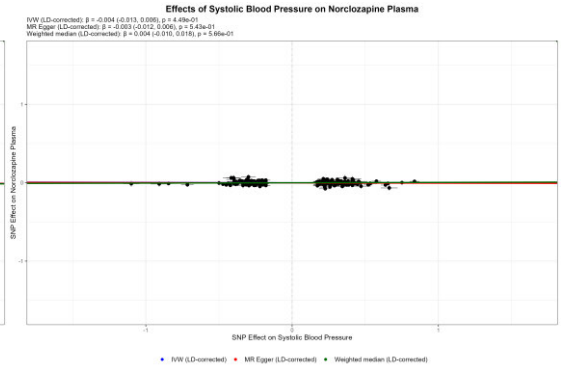


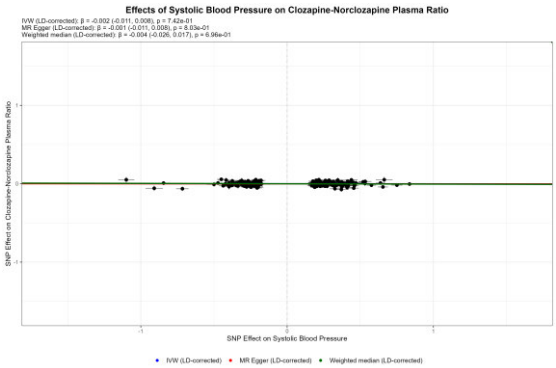




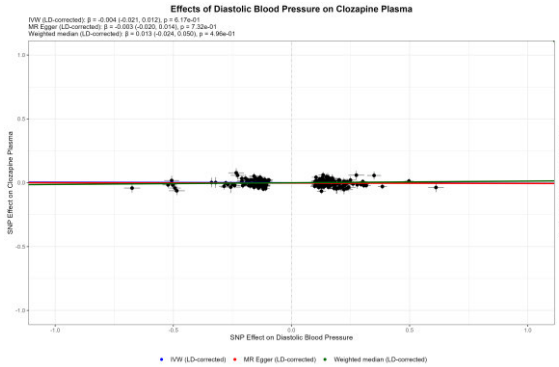
Systolic Blood Pressure:

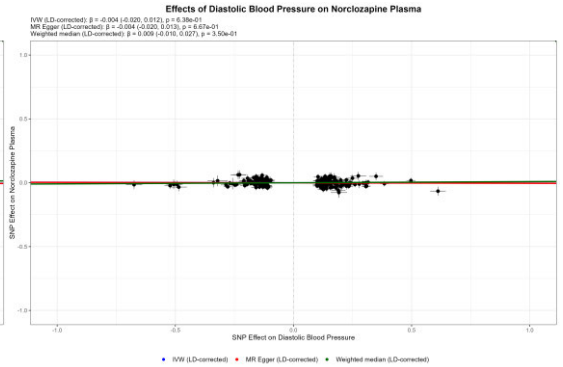


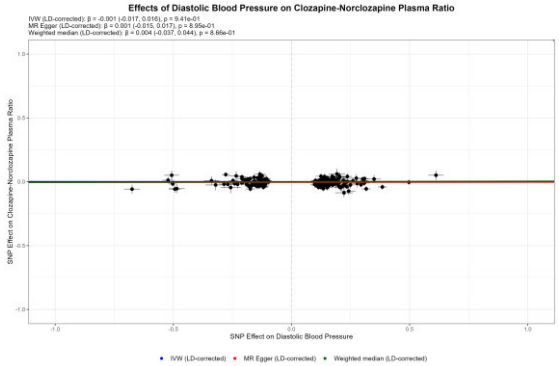




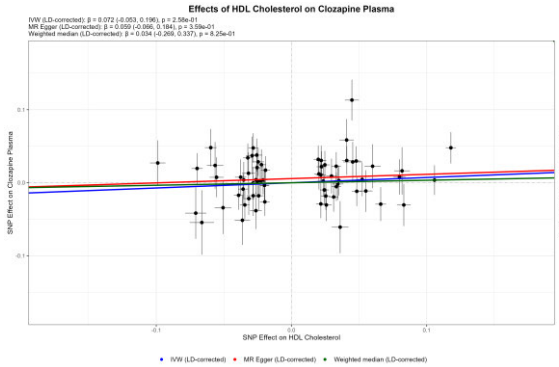
Diastolic Blood Pressure:

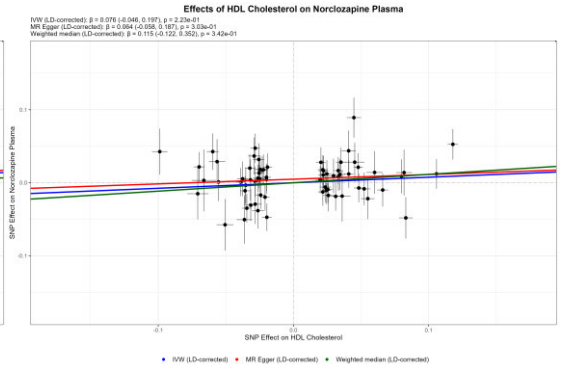


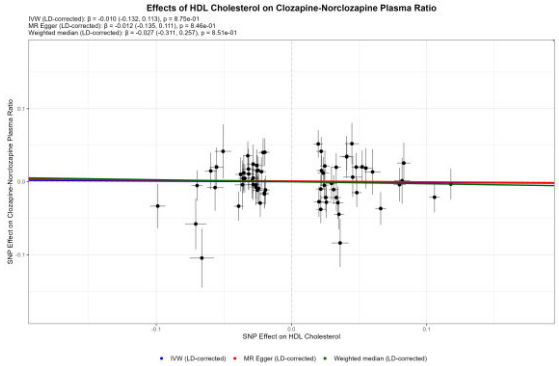




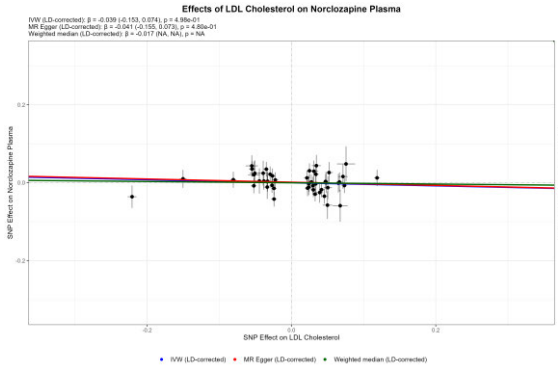
HDL:

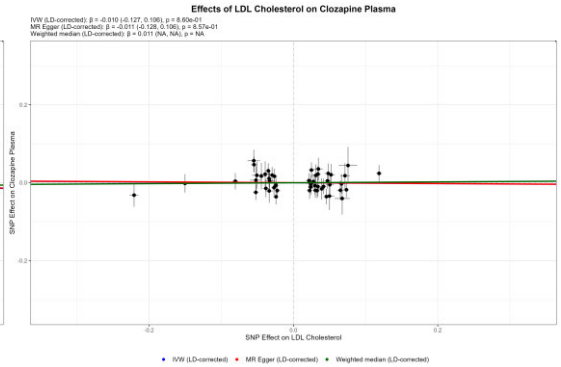


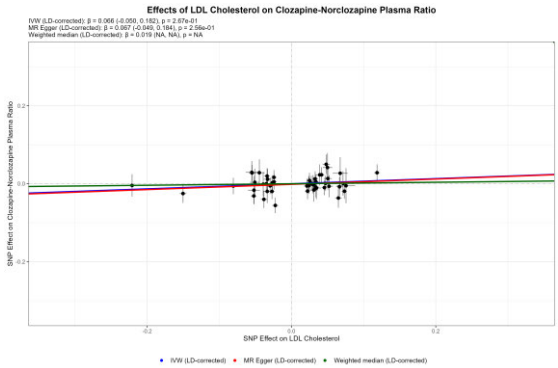




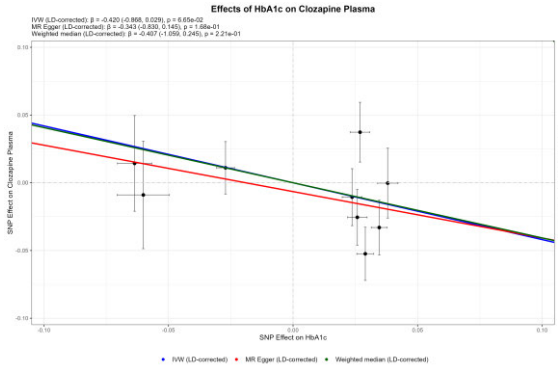
LDL:

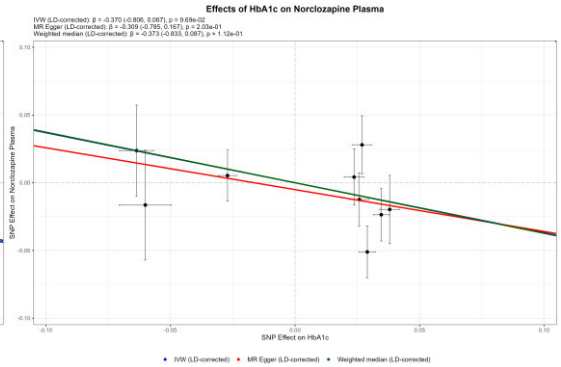

Effects of LDL Cholesterol on Norclozapine Plasma
SNP Effect on Norclozapine Plasma
SNP Effect on LDL Cholesterol
IVW (LD-corrected)
MR Egger (LD-corrected)
Weighted median (LD-corrected)

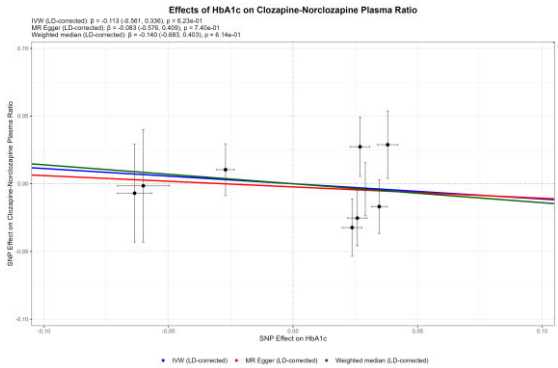

Effects of LDL Cholesterol on Clozapine Plasma
SNP Effect on Clozapine Plasma
SNP Effect on LDL Cholesterol
IVW (LD-corrected)
MR Egger (LD-corrected)
Weighted median (LD-corrected)


Effects of LDL Cholesterol on Clozapine-Norclozapine Plasma Ratio
SNP Effect on Clozapine-Norclozapine Plasma Ratio
SNP Effect on LDL Cholesterol
IVW (LD-corrected)
MR Egger (LD-corrected)
Weighted median (LD-corrected)

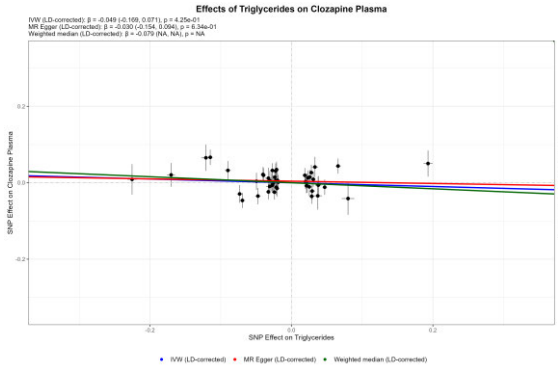
HbA1c:

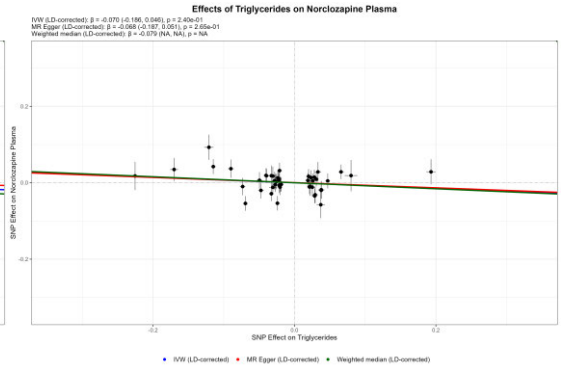

Effects of HbA1c on Clozapine Plasma
SNP Effect on Clozapine Plasma
SNP Effect on HbA1c
IVW (LD-corrected)
MR Egger (LD-corrected)
Weighted median (LD-corrected)

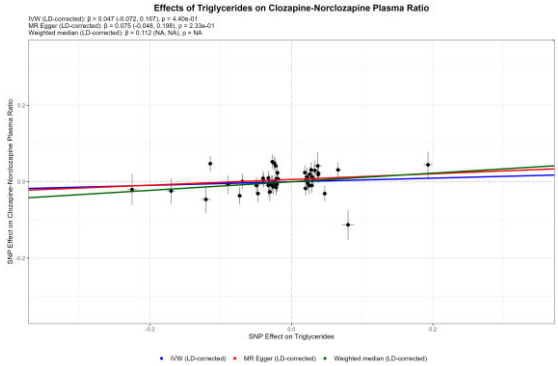

Effects of HbA1c on Norclozapine Plasma
SNP Effect on Norclozapine Plasma
SNP Effect on HbA1c
IVW (LD-corrected)
MR Egger (LD-corrected)
Weighted median (LD-corrected)


Effects of HbA1c on Clozapine-Norclozapine Plasma Ratio
SNP Effect on Clozapine-Norclozapine Plasma Ratio
SNP Effect on HbA1c
IVW (LD-corrected)
MR Egger (LD-corrected)
Weighted median (LD-corrected)

Triglycerides:

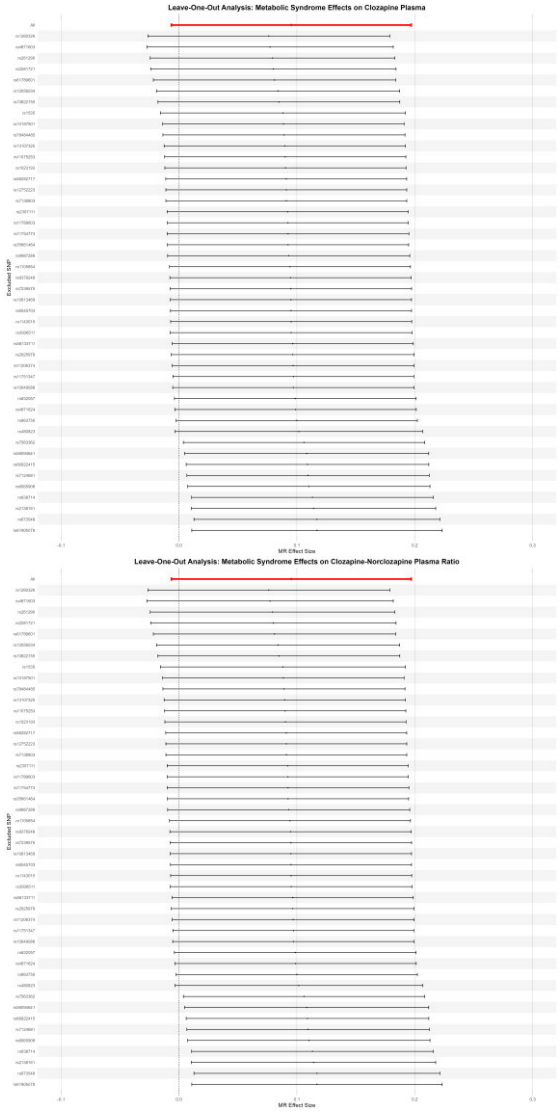






Supplementary Figures 4.2.6 - Leave-One-Out Plots - Cardiometabolic Effects on Clozapine Plasma Traits

Metabolic Syndrome:





Type 2 Diabetes:







Body Mass Index:







Systolic Blood Pressure:







Diastolic Blood Pressure:







HDL:


Leave-One-Out Analysis: HDL Cholesterol Effects on Clozapine Plasma
Excluded SNP
MR Effect Size


Leave-One-Out Analysis: HDL Cholesterol Effects on Norclozapine Plasma
Excluded SNP
MR Effect Size


Leave-One-Out Analysis: HDL Cholesterol Effects on Clozapine-Norclozapine Plasma Ratio
Excluded SNP
MR Effect Size

LDL:


Leave-One-Out Analysis: LDL Cholesterol Effects on Clozapine Plasma
All
Excluded SNP
-0.1
0.0
0.1
0.2
0.3
MR Effect Size


Leave-One-Out Analysis: LDL Cholesterol Effects on Norclozapine Plasma
All
Excluded SNP
-0.1
0.0
0.1
0.2
0.3
MR Effect Size


Leave-One-Out Analysis: LDL Cholesterol Effects on Clozapine-Norclozapine Plasma Ratio
All
Excluded SNP
-0.1
0.0
0.1
0.2
0.3
MR Effect Size

HbA1c:


Leave-One-Out Analysis: HbA1C Effects on Clozapine Plasma
Excluded SNP
MR Effect Size


Leave-One-Out Analysis: HbA1C Effects on Norclozapine Plasma
Excluded SNP
MR Effect Size


Leave-One-Out Analysis: HbA1C Effects on Clozapine-Norclozapine Plasma Ratio
Excluded SNP
MR Effect Size

Triglycerides:





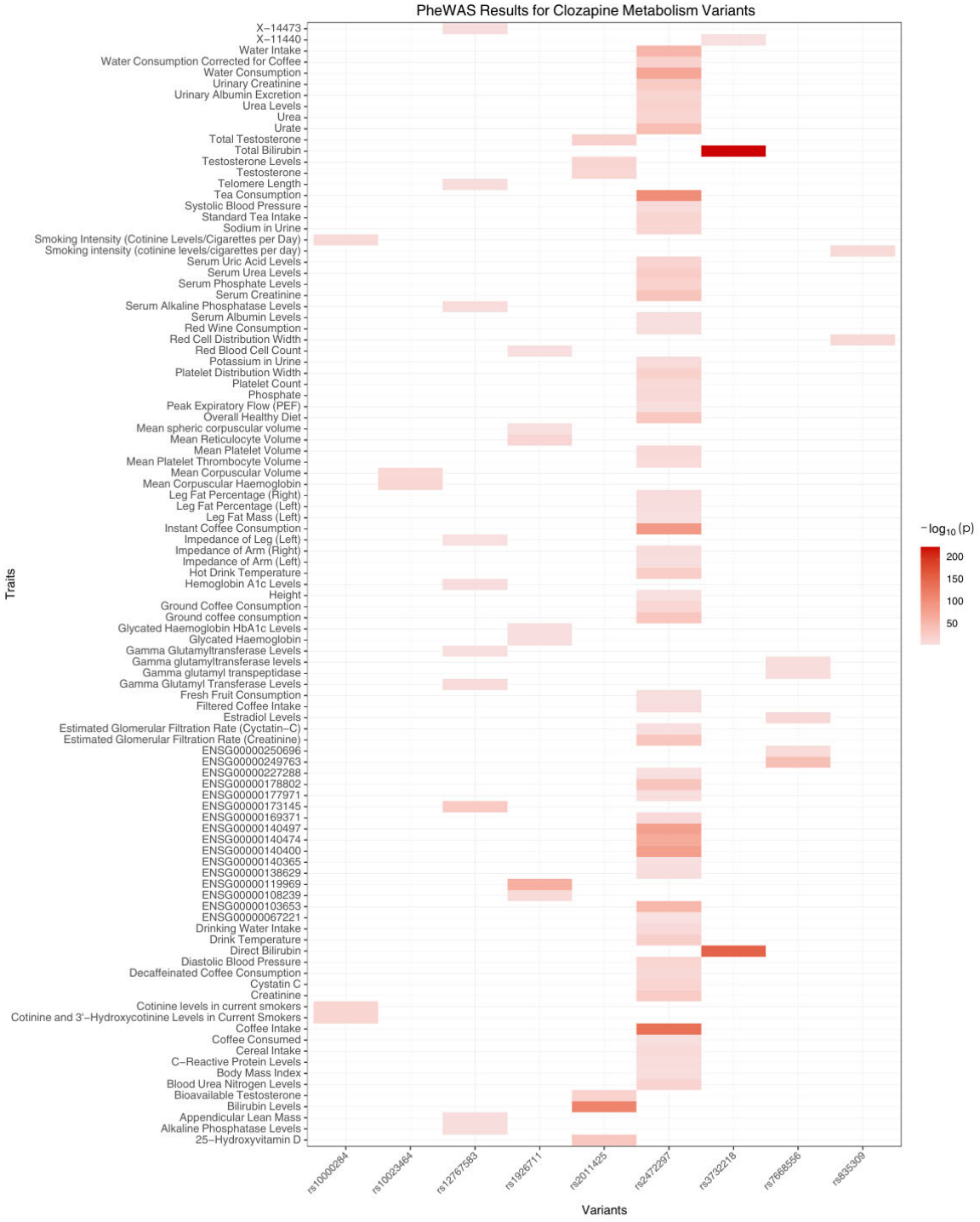


Supplementary Figures 4.3 - Phenome-wide Association Study Results

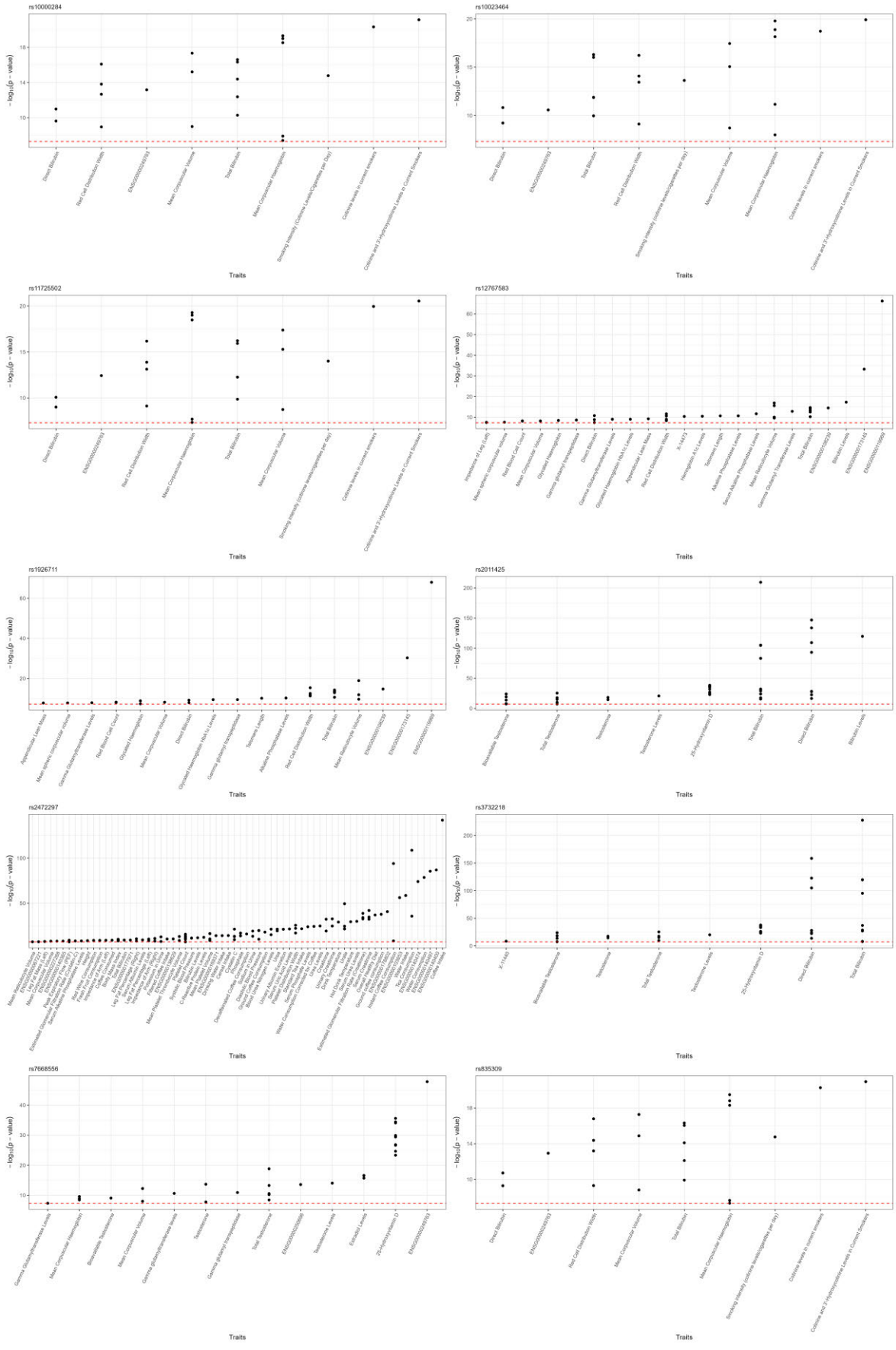
Extra plots depicting the output from the phenome-wide scan using clozapine variants (SNPs) (Table 4.2). The heatmap demonstrates the $(-\boldsymbol{log}(\boldsymbol{P}))$ of phenotypes identified through the PheWAS analysis with the highest p-value. The heatmap also demonstrates which traits are linked to which genetic variant used as a lead in phenome-scan. The individual variant phenotype hits (4.3.2) further demonstrate this information whilst also demonstrating if a trait was identified through multiple GWAS studies and their relative $(-\boldsymbol{log}(\boldsymbol{P}))$. Phenome-wide raw results can be found in Supplementary Table 4.3 and information surrounding the PheWAS analysis itself can be found in the Supplementary Methods (Appendix C).

Supplementary Figures 4.3.1 - PheWAS Results for Clozapine Variants, Heatmap 261
Supplementary Figures 4.3.2 - PheWAS Individual Variant Phenotype Hits 262

Supplementary Figures 4.3.1 - PheWAS Results for Clozapine Variants, Heatmap



Supplementary Figures 4.3.2 - PheWAS Individual Variant Phenotype Hits

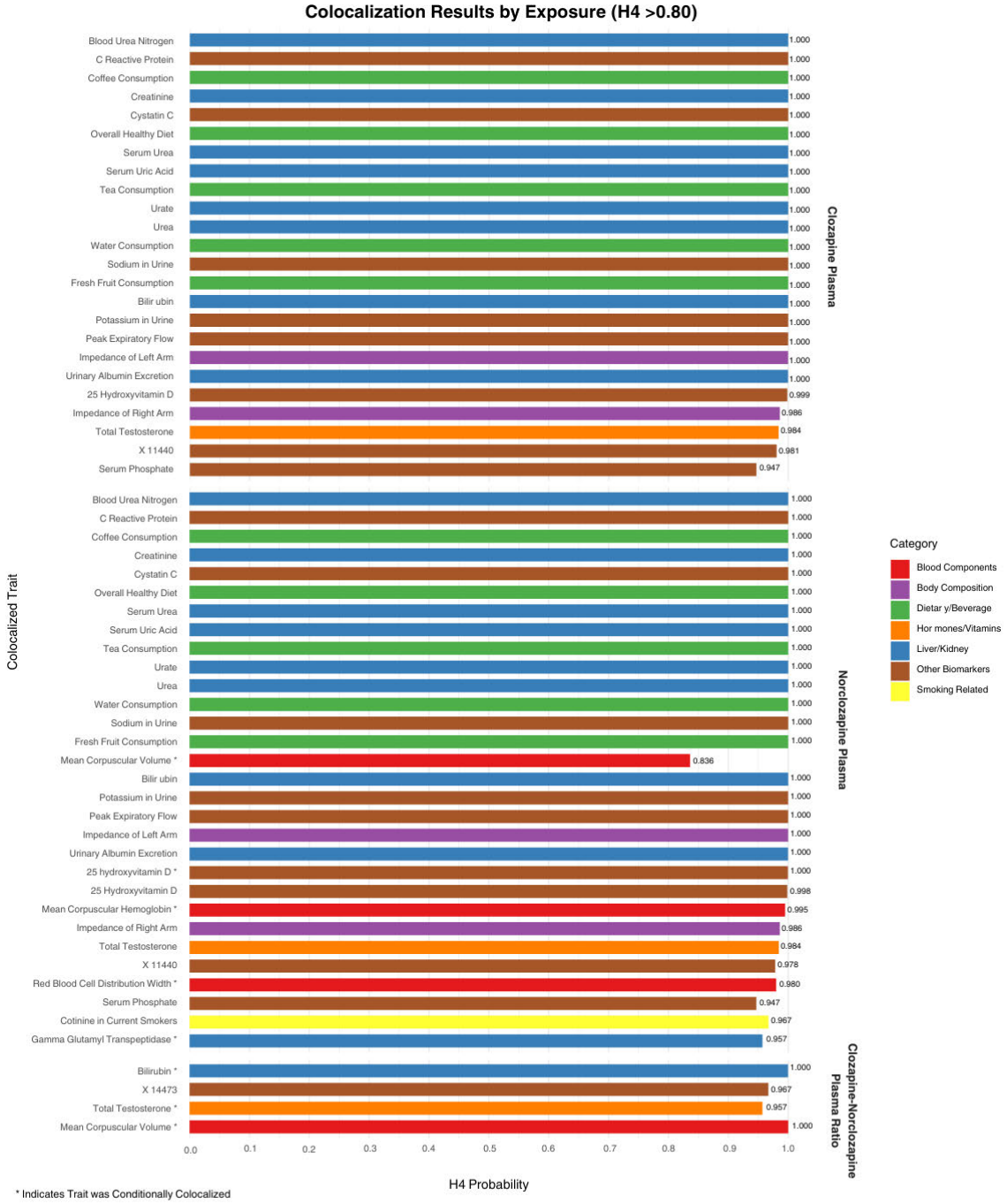


Supplementary Figures 4.4 - Colocalization Results

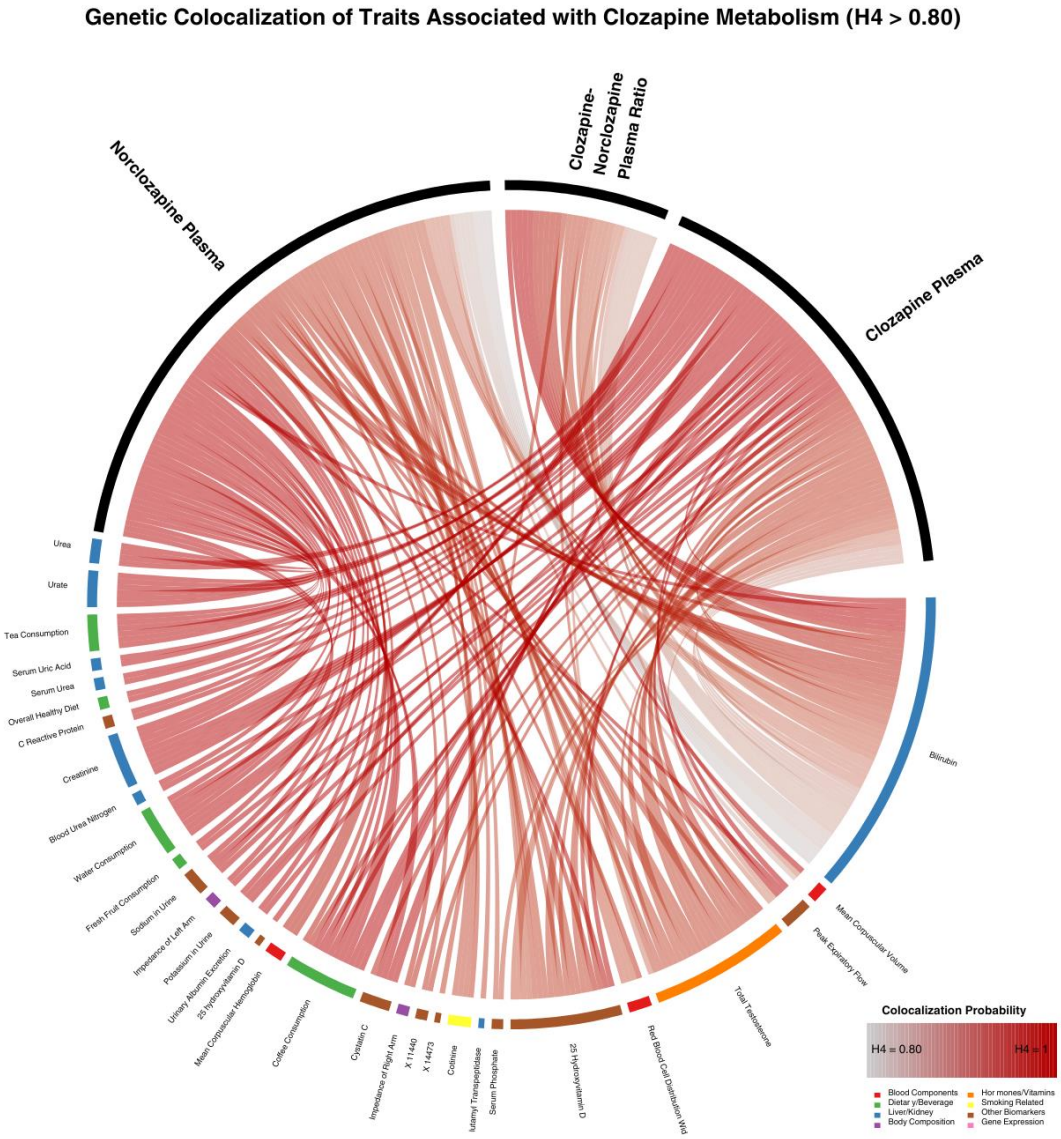
Extra plots depicting the PWCoCo colocalization results. All graphical representations show only results with a $\boldsymbol{PP.H_4 > 0.80}$, indicating robust colocalization. The bar graph demonstrates robust colocalization results split by clozapine metabolism exposure trait (4.4.1). Colocalized phenotypes are also split into trait categories. The circular plots demonstrate visually which intermediate phenotypes is being colocalized by which clozapine metabolism trait, even when the intermediate phenotype is colocalizing at multiple clozapine traits. Intermediate phenotypes are also categorised by colour depending upon their classification (4.4.2). The Stacked regional plots demonstrate the statistical strength of associations between genetic variants and a trait or disease within a specific genomic region. These plots demonstrate these relationships for trait that colocalized with a $\boldsymbol{PP.H_4 > 0.80}$. These plots demonstrate the genomic regions in chromosomes; 2, 4, 10, and 15 around the lead variants used for the PheWAS analysis (Table 4.2). Raw results can be found in Supplementary Table 4.4.

Supplementary Figures 4.4.1 - Bar Graph of Colocalization Results (PP.H4 > 0.80) for Clozapine Plasma, Norclozapine Plasma and Clozapine-Norclozapine Plasma Ratio. 264
Supplementary Figures 4.4.2 - Circular Plots Demonstrating Clozapine Plasma Traits Colocalizing with PheWAS Phenotypes (PP.H_4 > 0.80). 265
Supplementary Figures 4.4.3 - Stacked Regional Association Plots for Clozapine Colocalizing with PheWAS Identified Candidate Biomarkers Across 4 Lead Chromosomes. 266
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Supplementary Figures 4.4.5 - Stacked Regional Association Plots for Clozapine-Norclozapine Ratio Colocalizing with PheWAS Identified Candidate Biomarkers Across 4 Lead Chromosomes. 290

Supplementary Figures 4.4.1 - Bar Graph of Colocalization Results (PP.H4 > 0.80) for Clozapine Plasma, Norclozapine Plasma and Clozapine-Norclozapine Plasma Ratio.

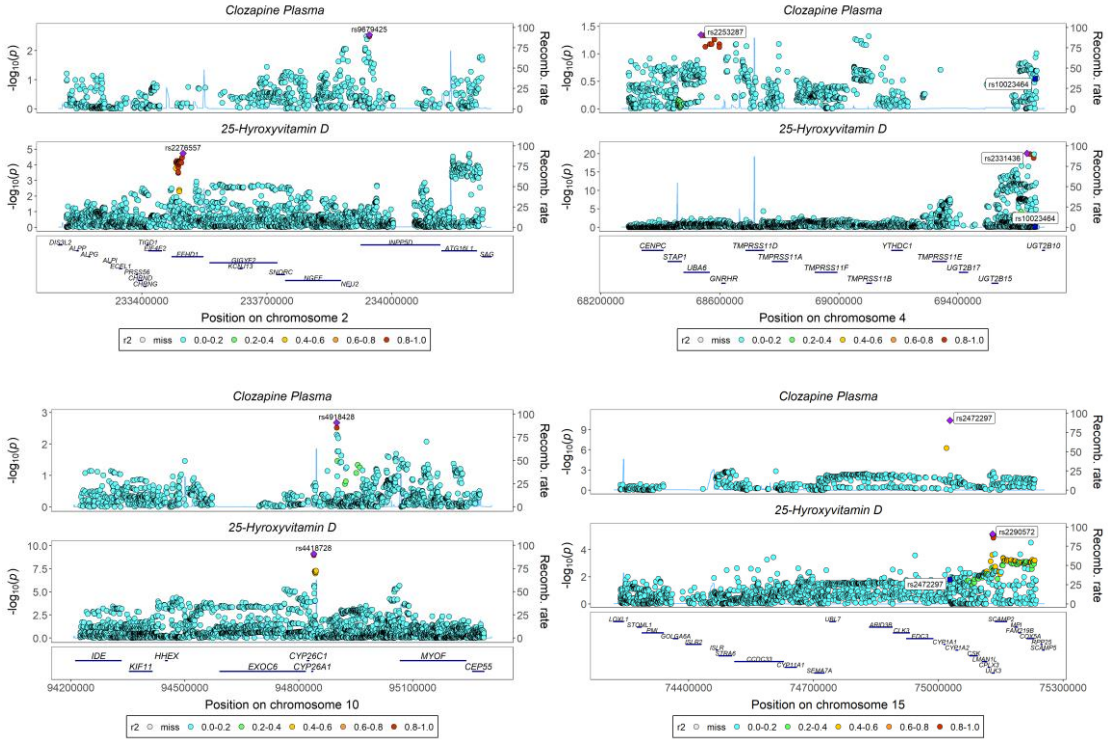


Supplementary Figures 4.4.2 - Circular Plots Demonstrating Clozapine Plasma Traits Colocalizing with PheWAS Phenotypes ($PP.H_4 > 0.80$).

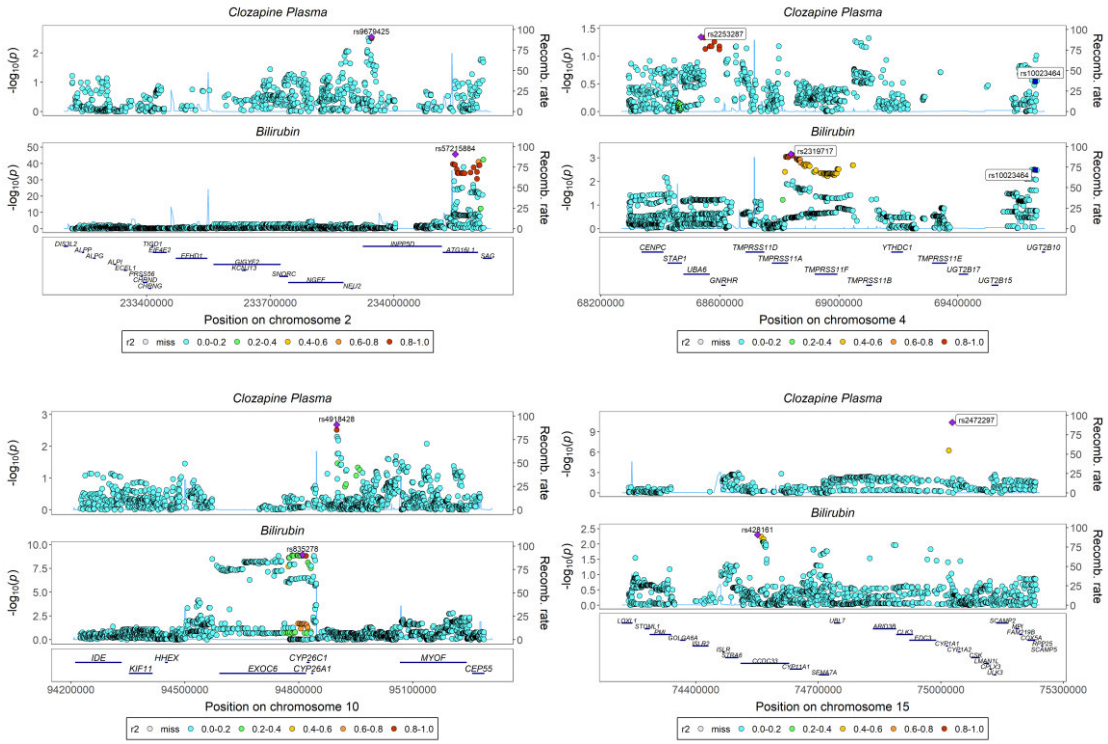


Supplementary Figures 4.4.3 - Stacked Regional Association Plots for Clozapine Colocalizing with PheWAS Identified Candidate Biomarkers Across 4 Lead Chromosomes.

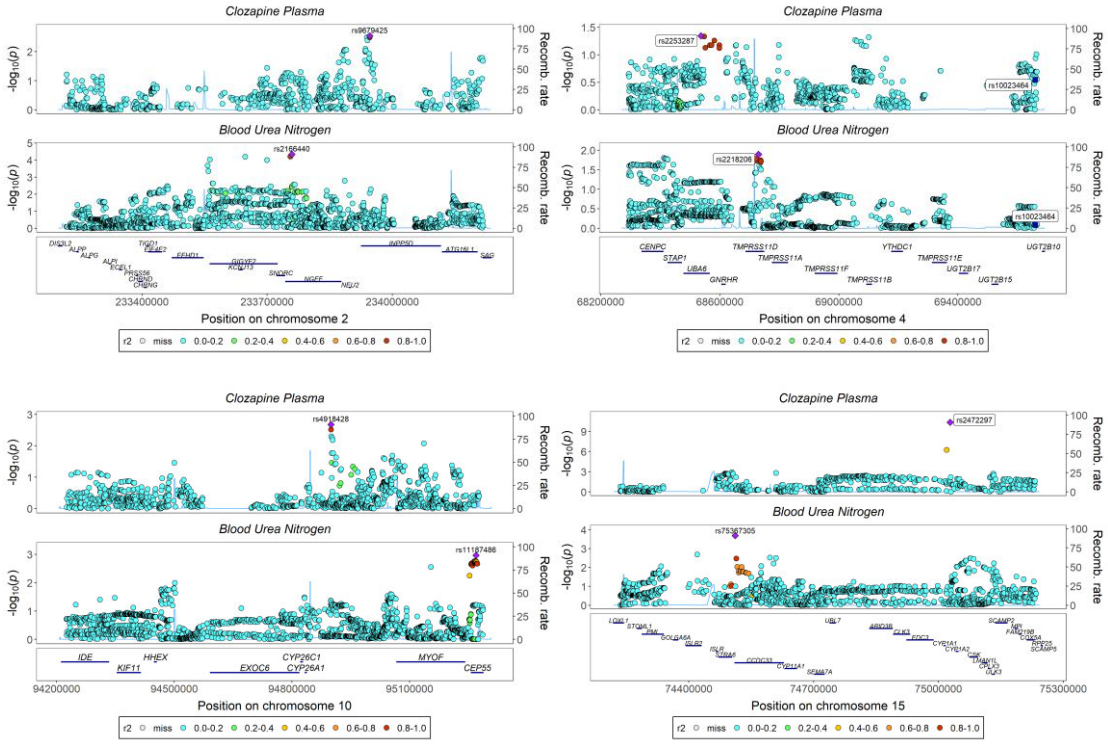
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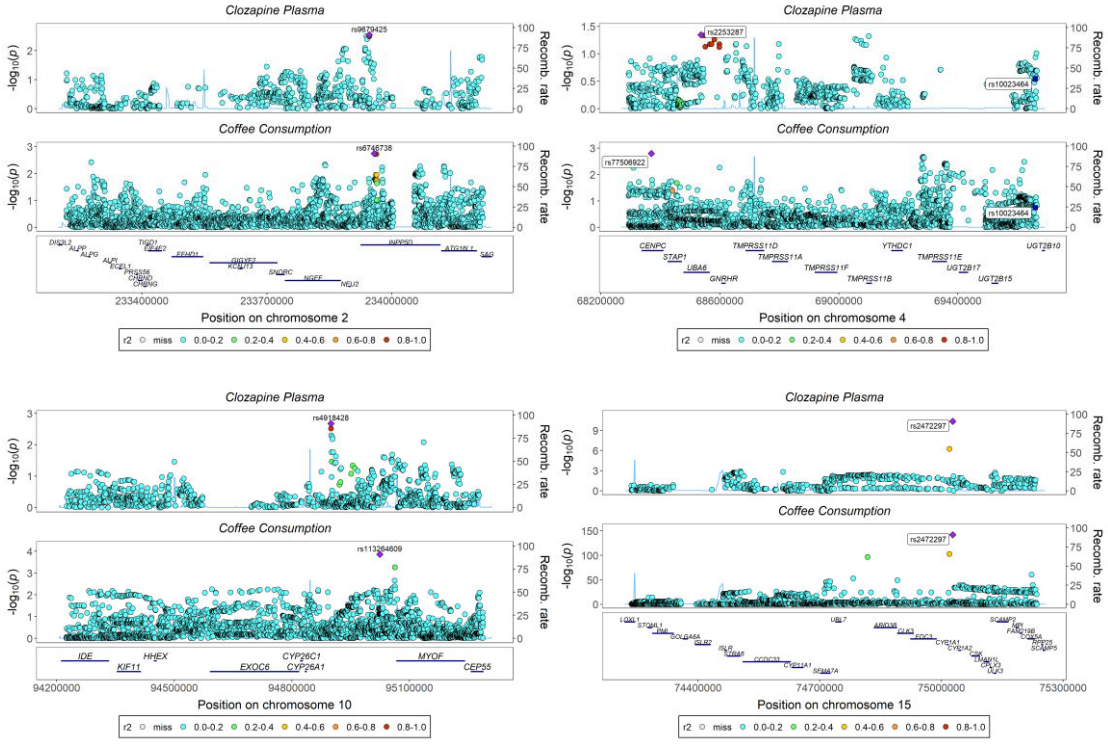
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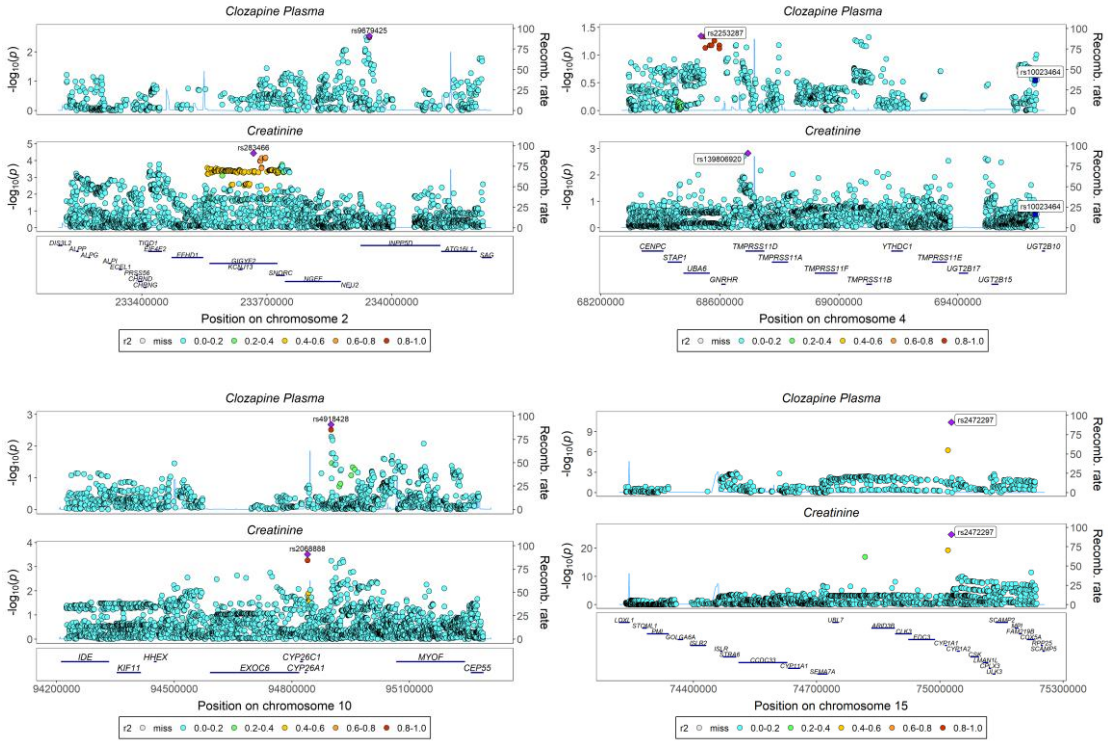
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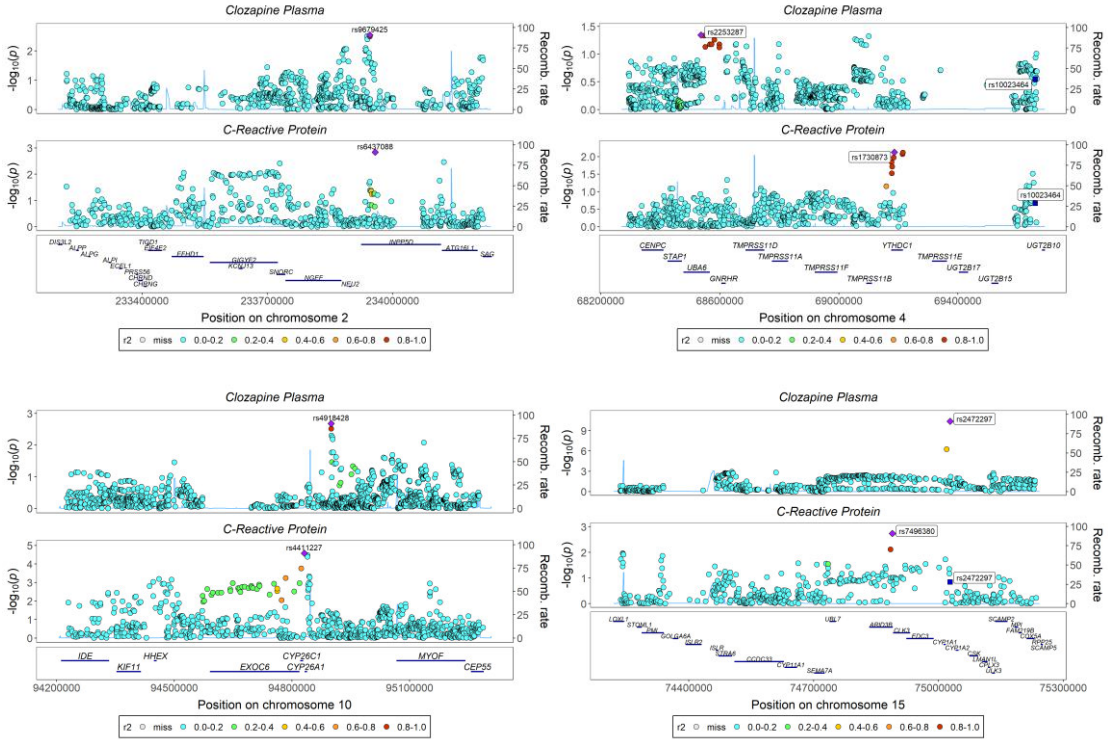
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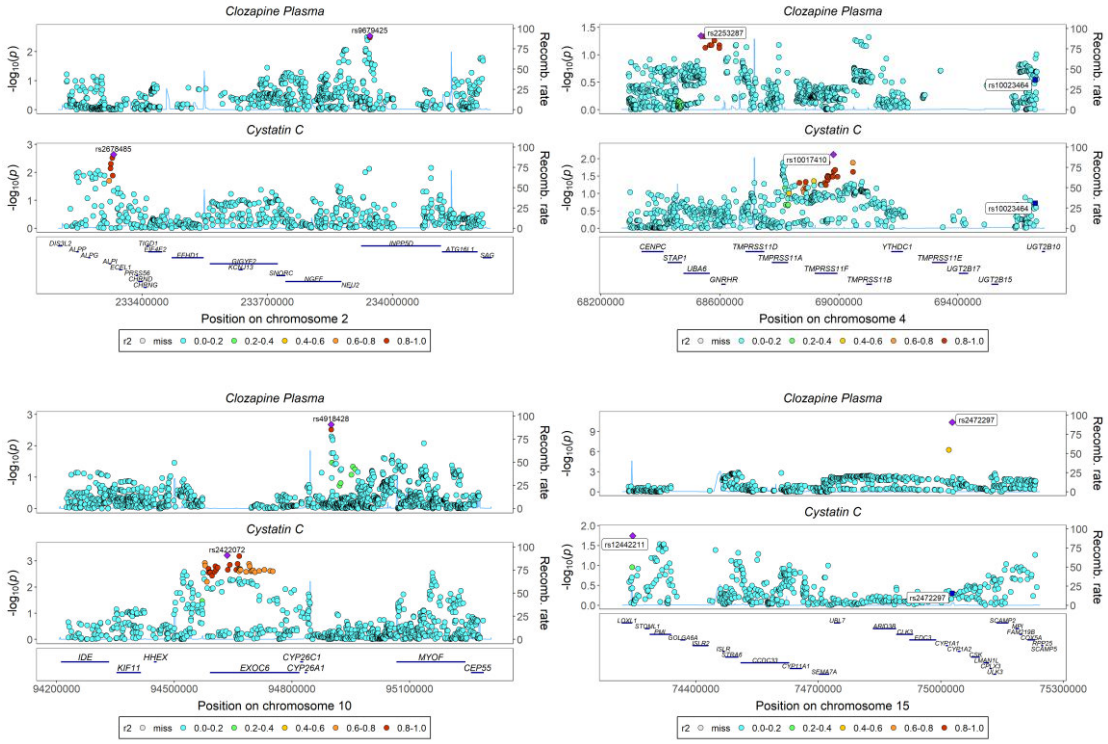
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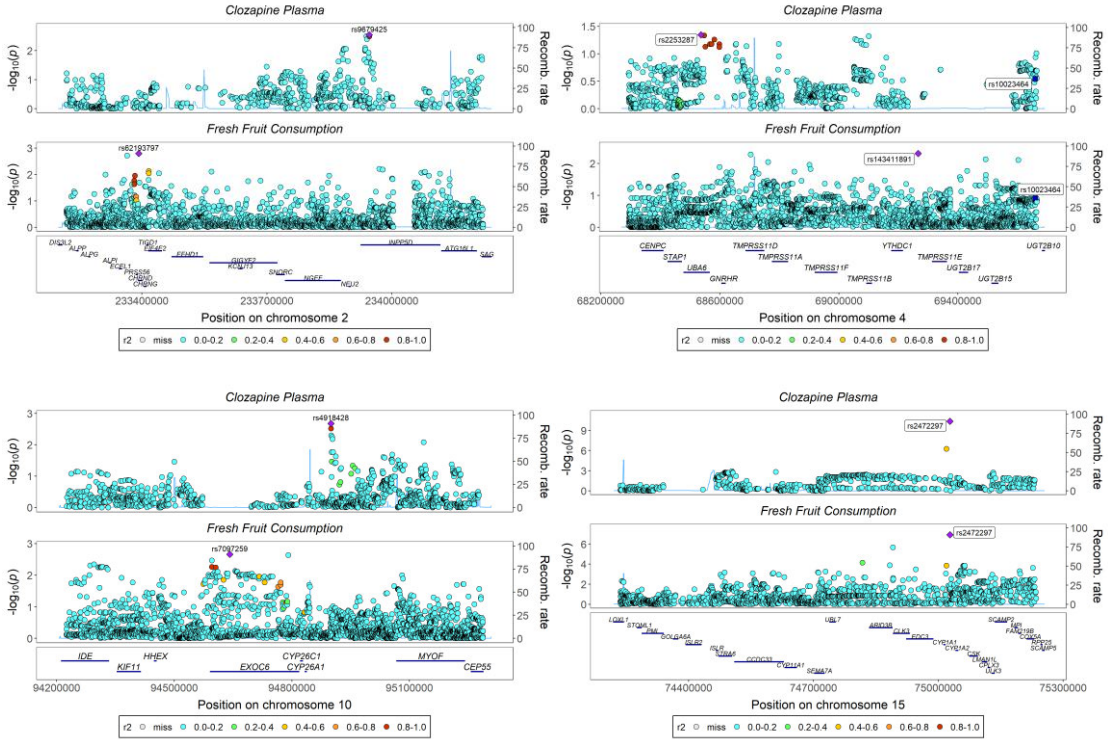
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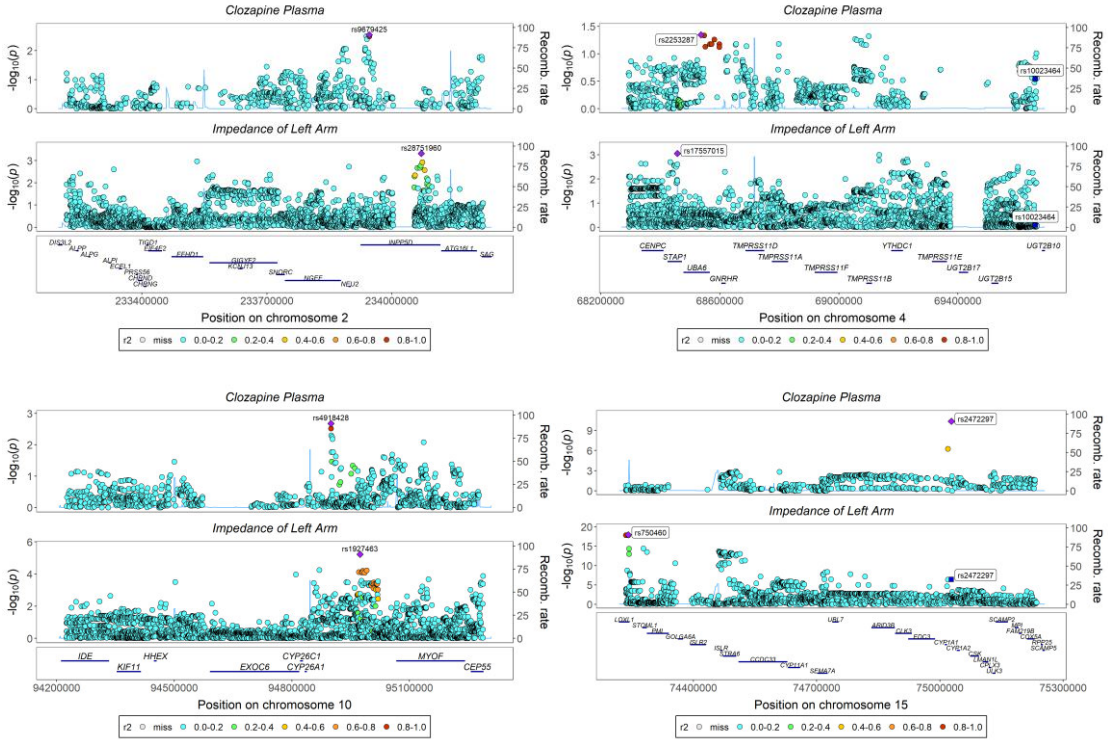
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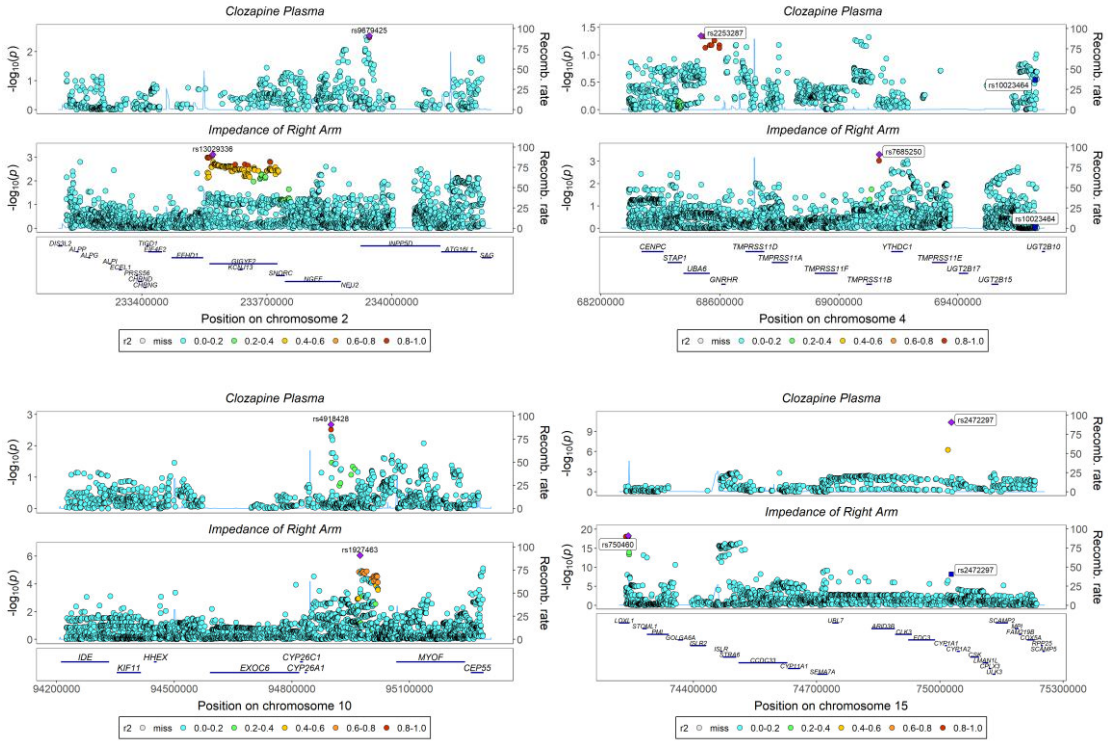
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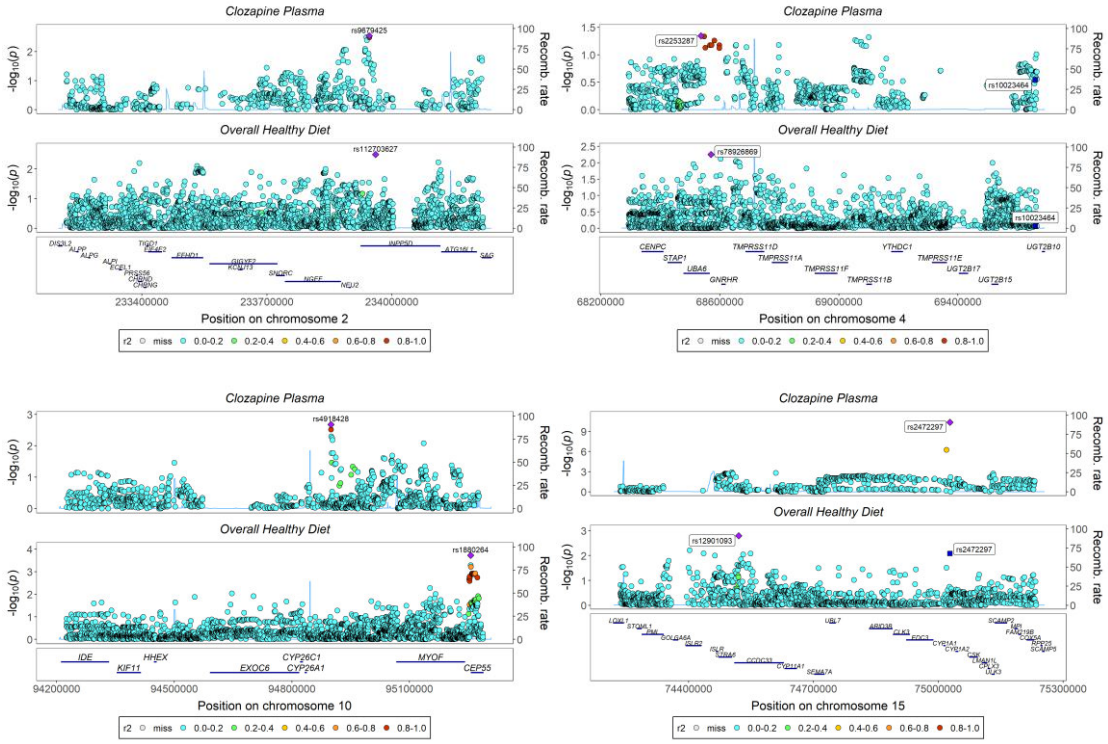
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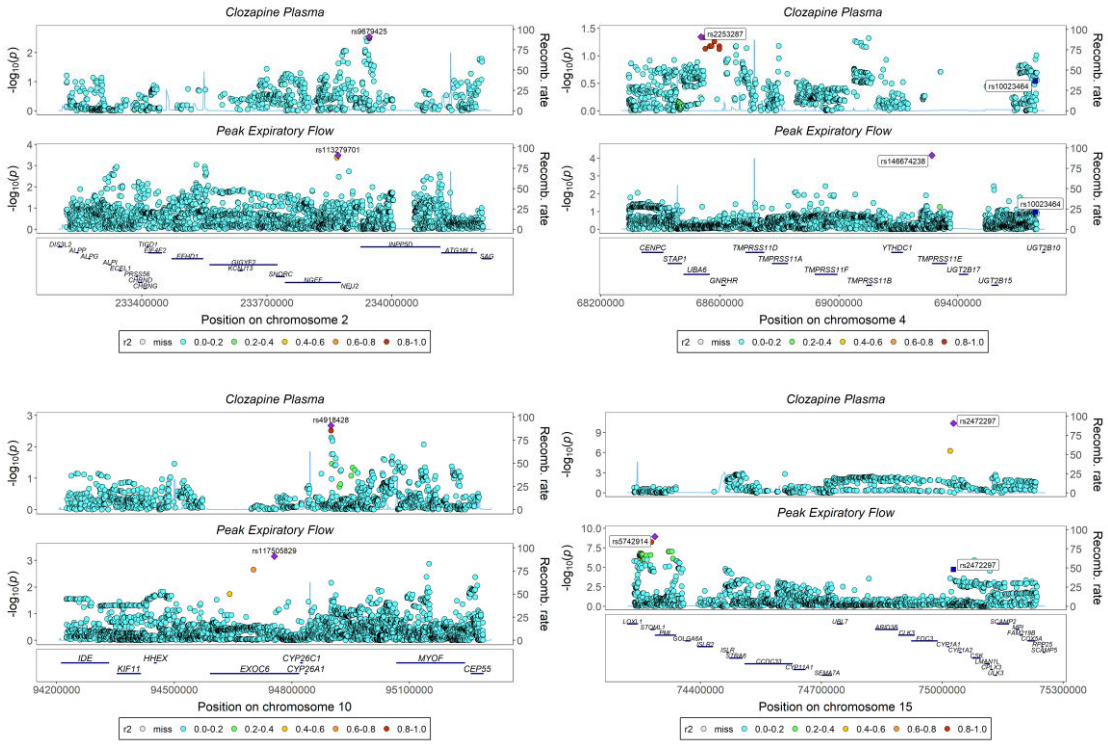
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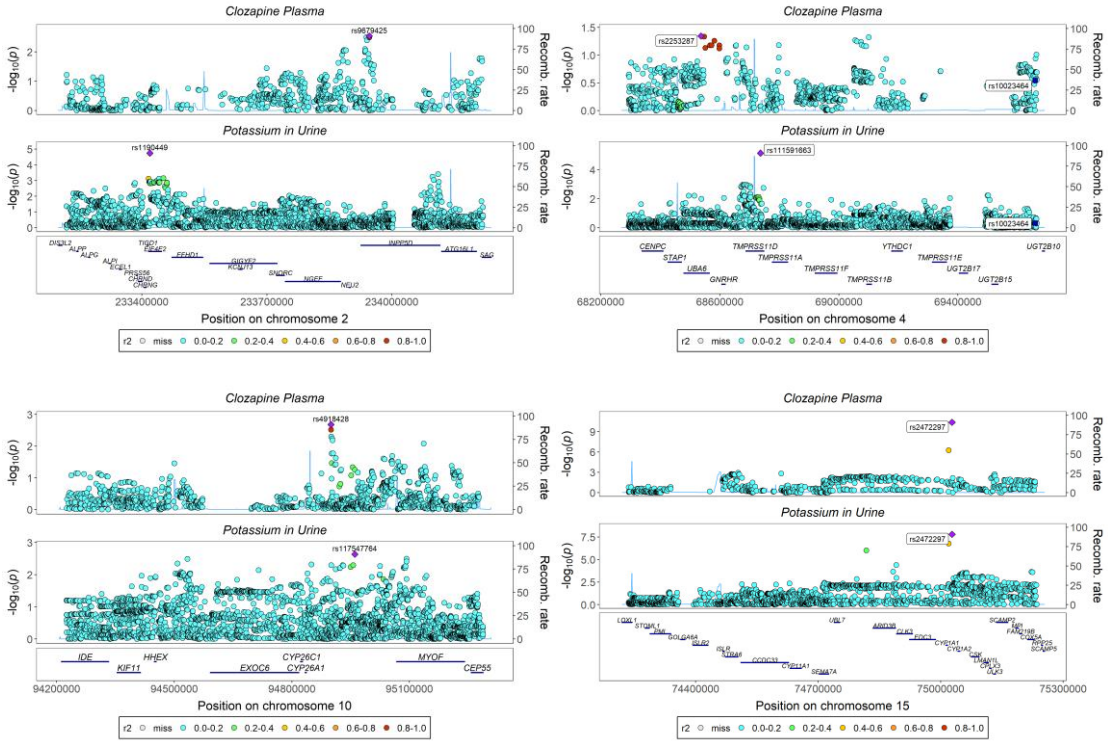
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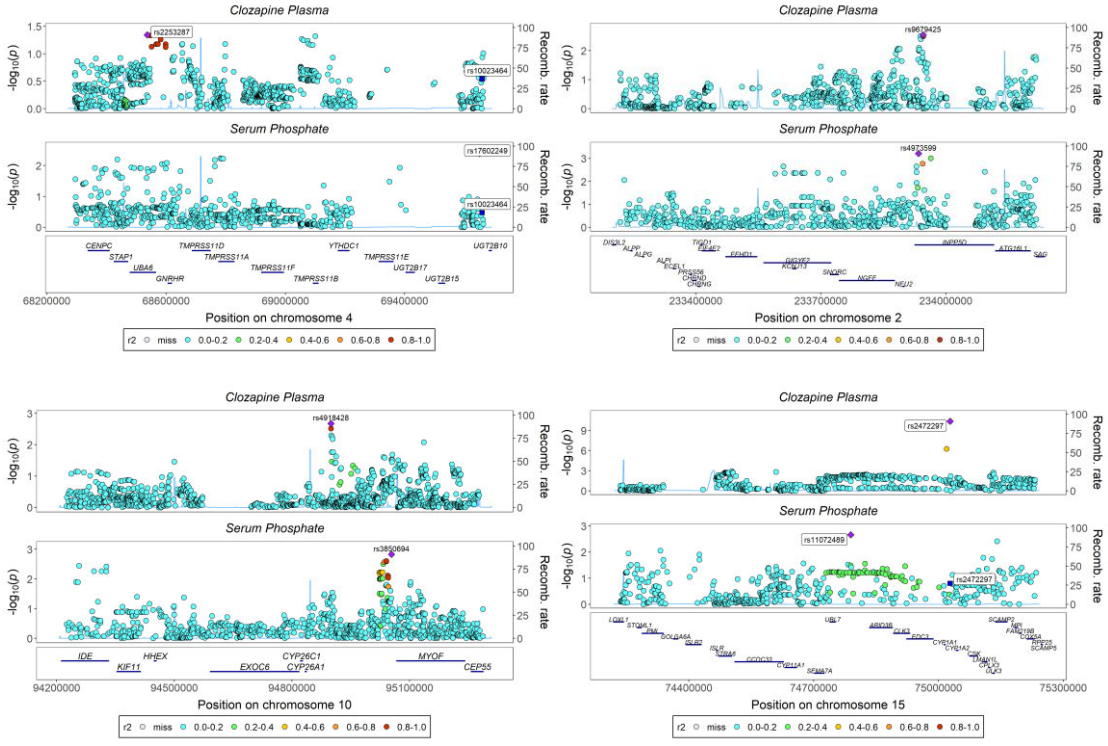
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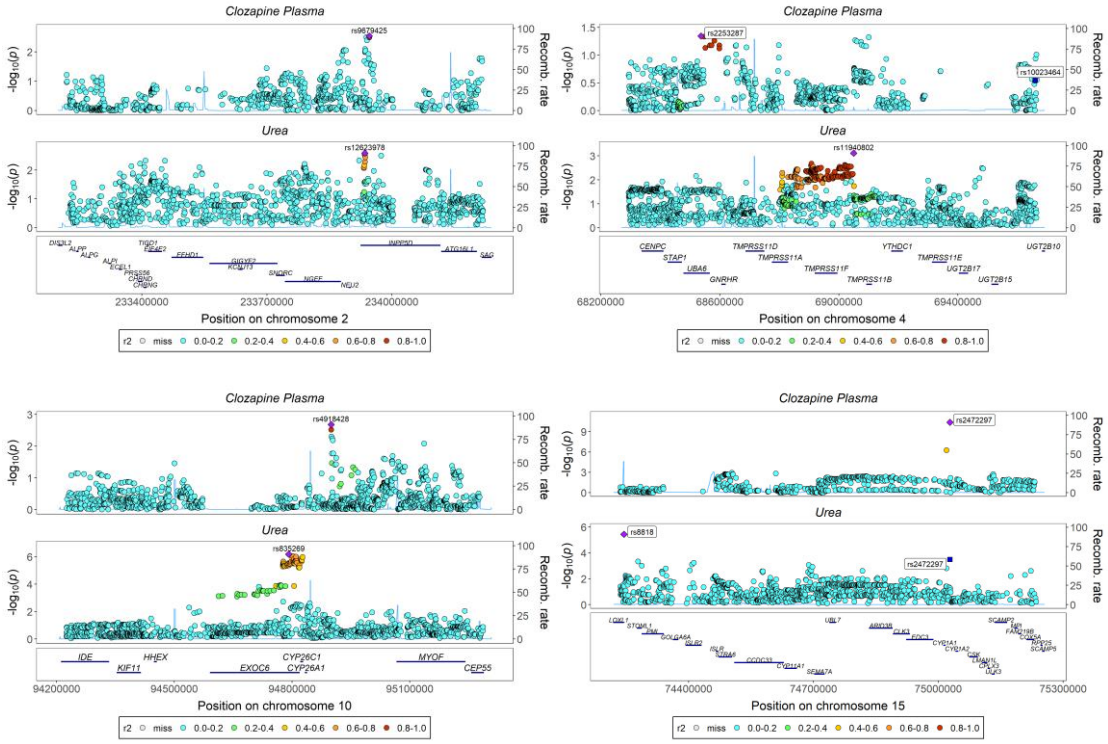
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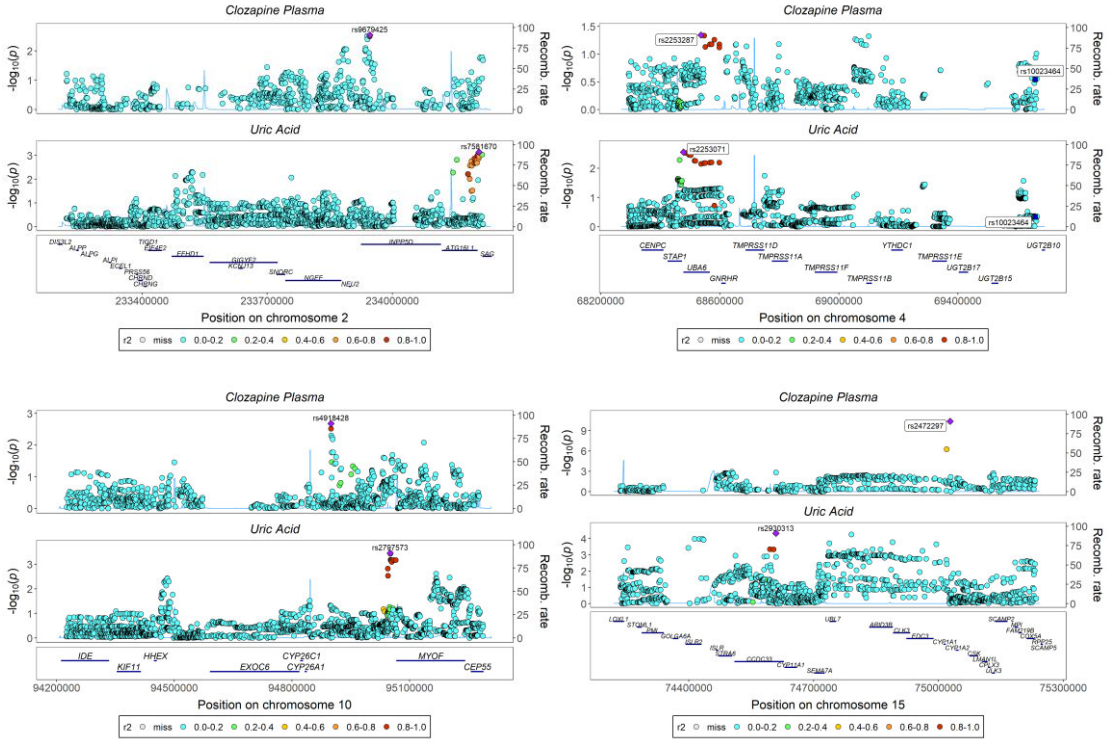
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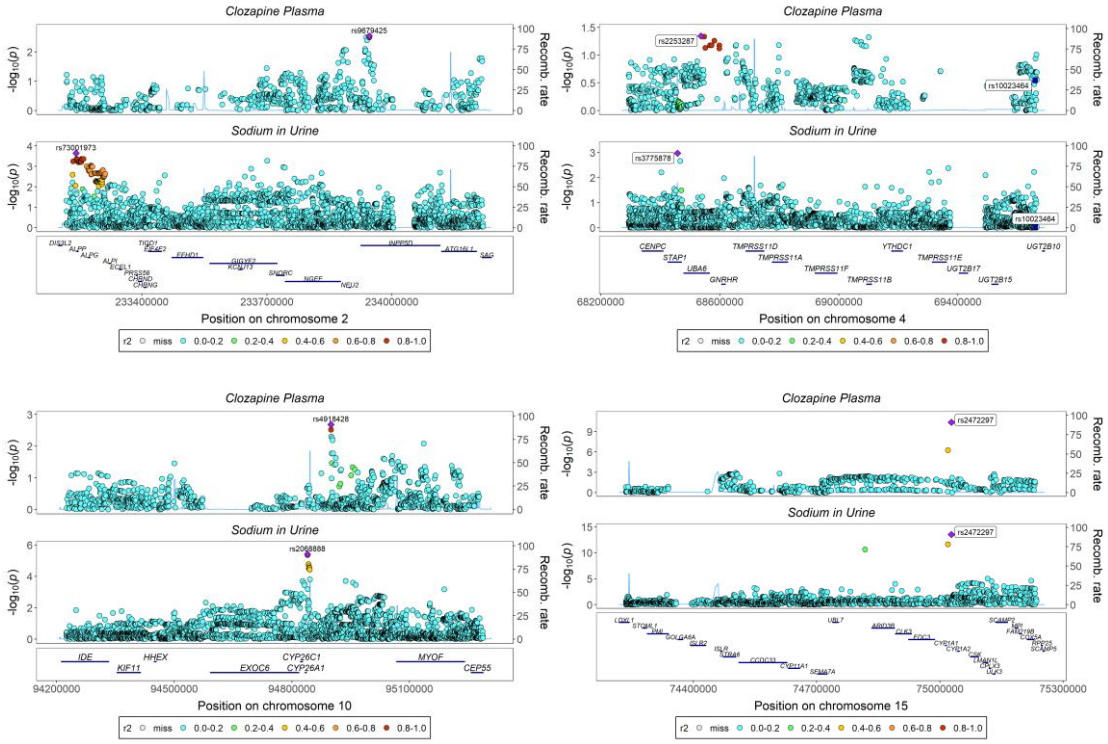
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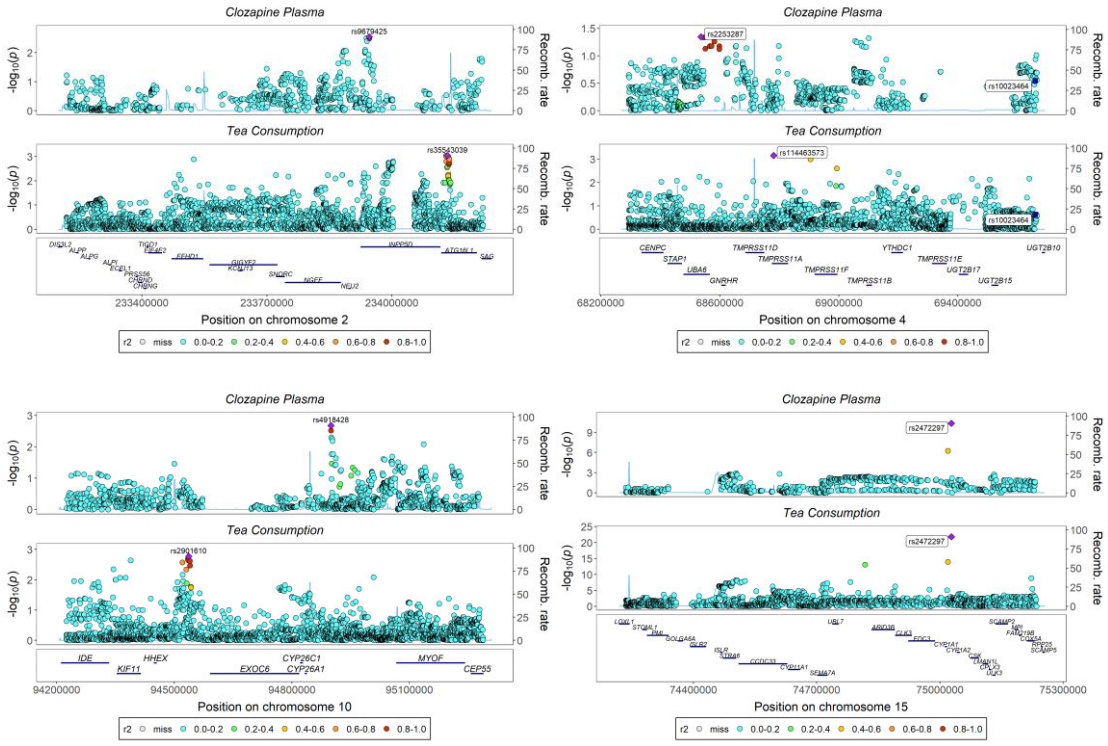
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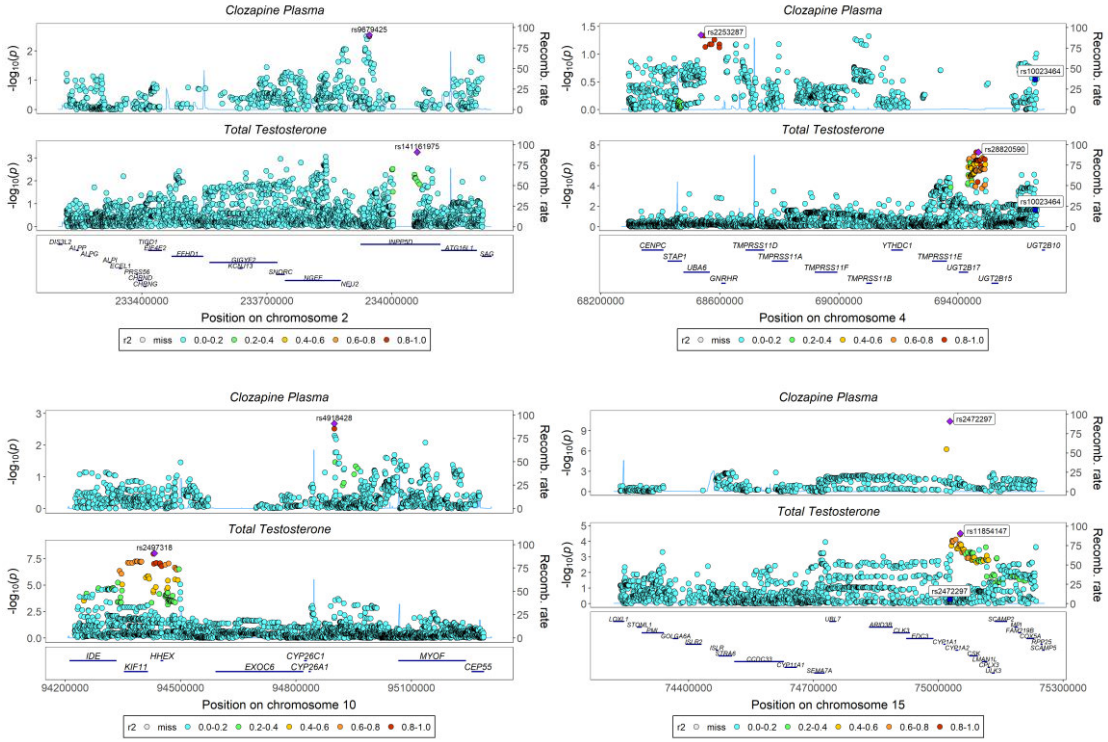
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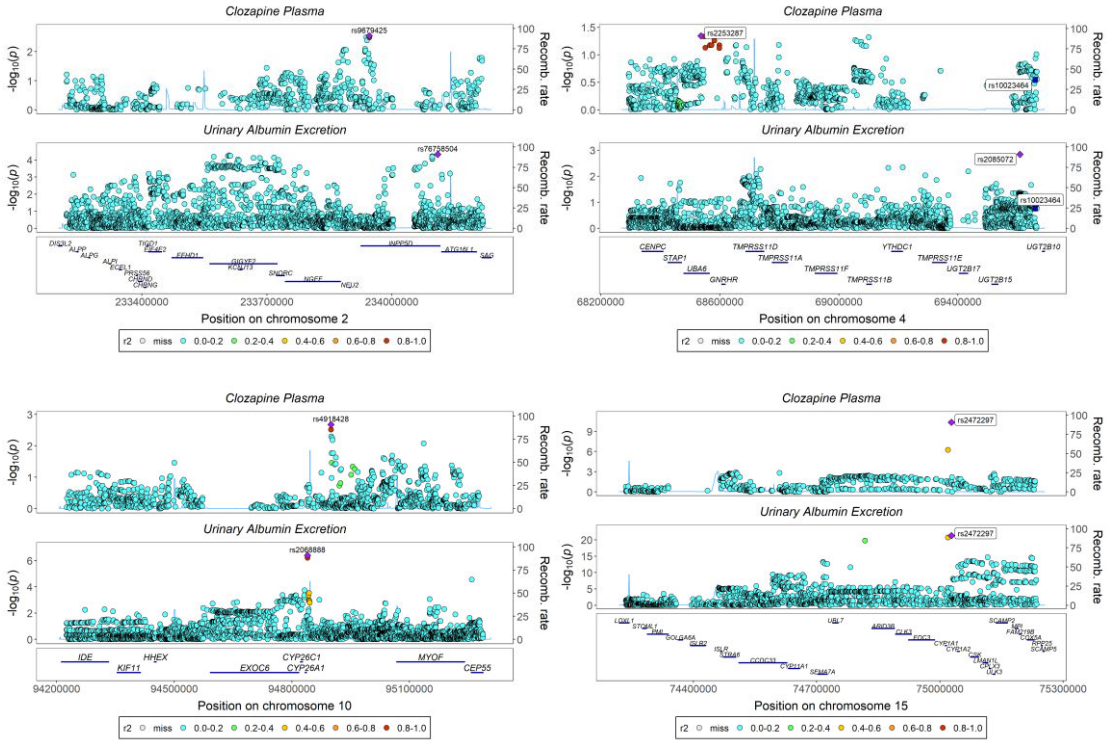
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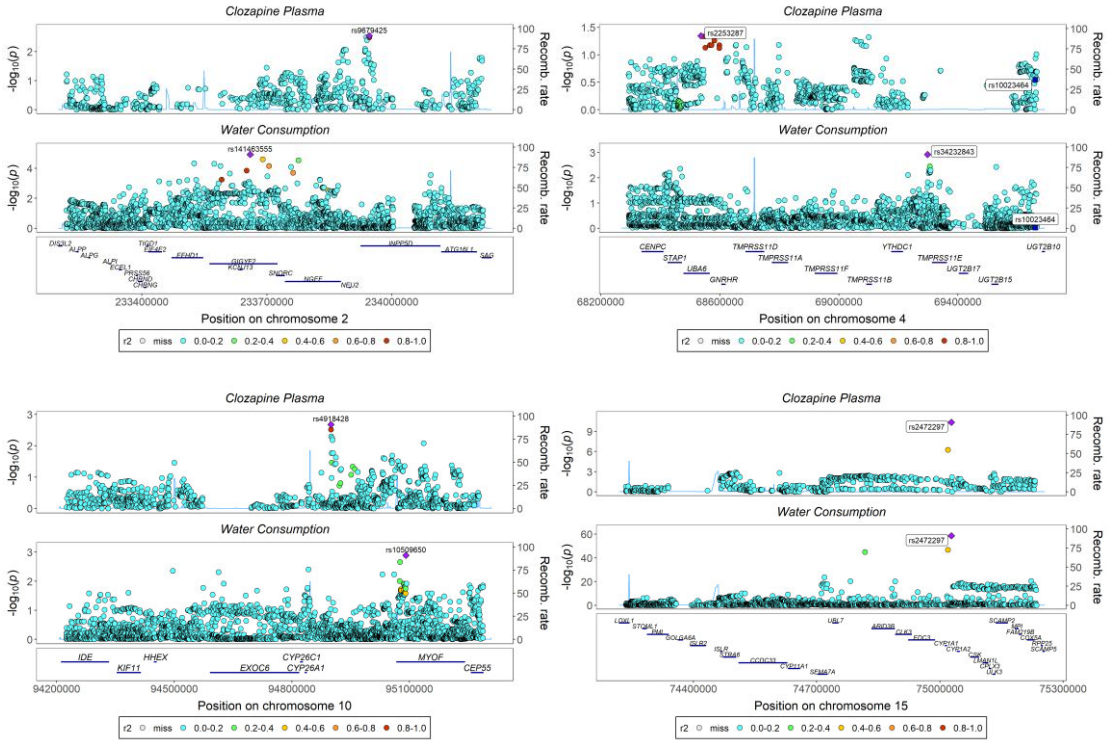
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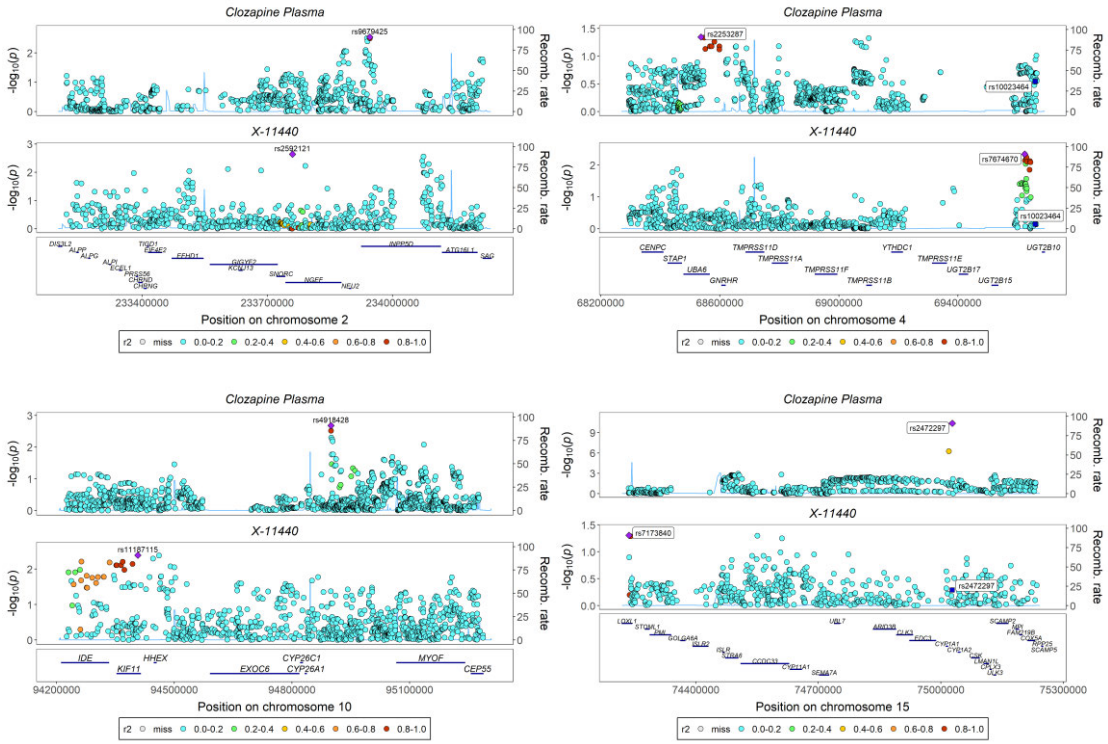
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Water Consumption:

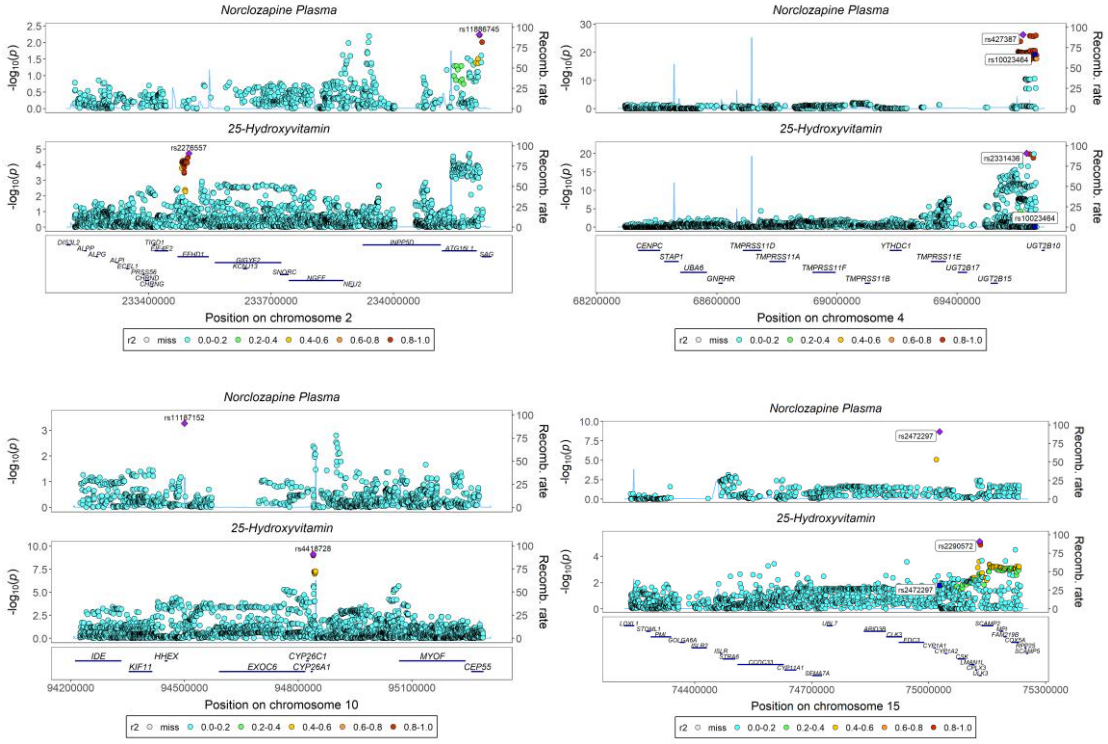


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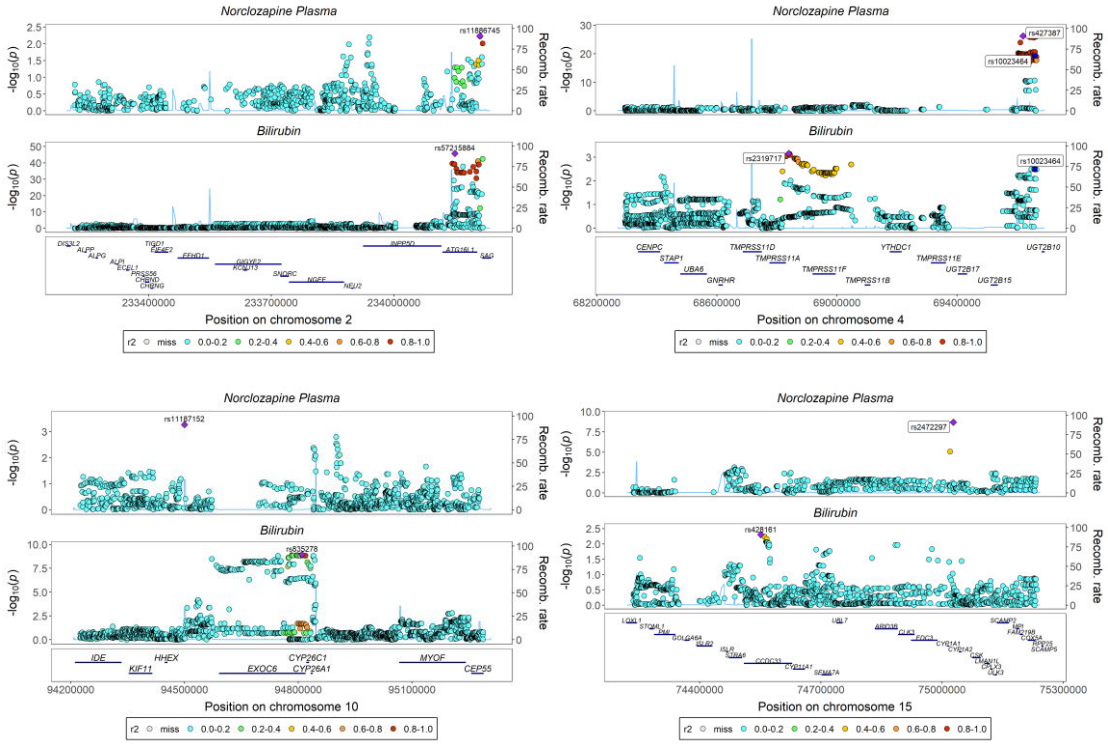


Supplementary Figures 4.4.4 - Stacked Regional Association Plots for Norclozapine Colocalizing with PheWAS Identified Candidate Biomarkers Across 4 Lead Chromosomes.

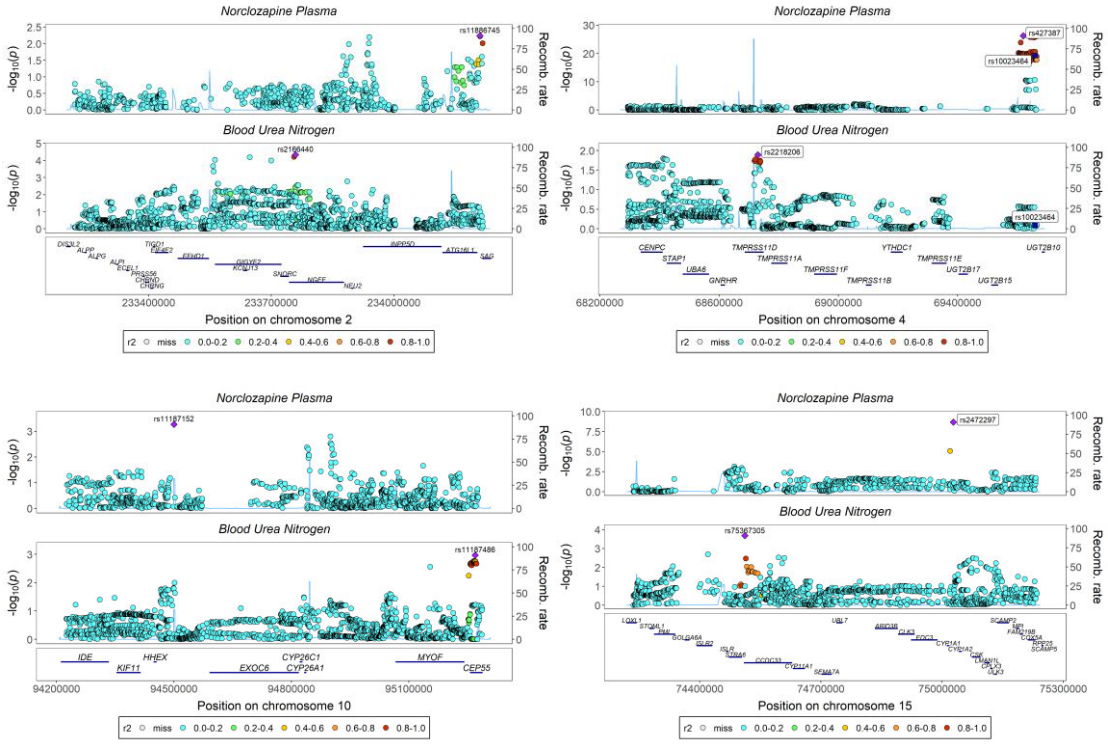
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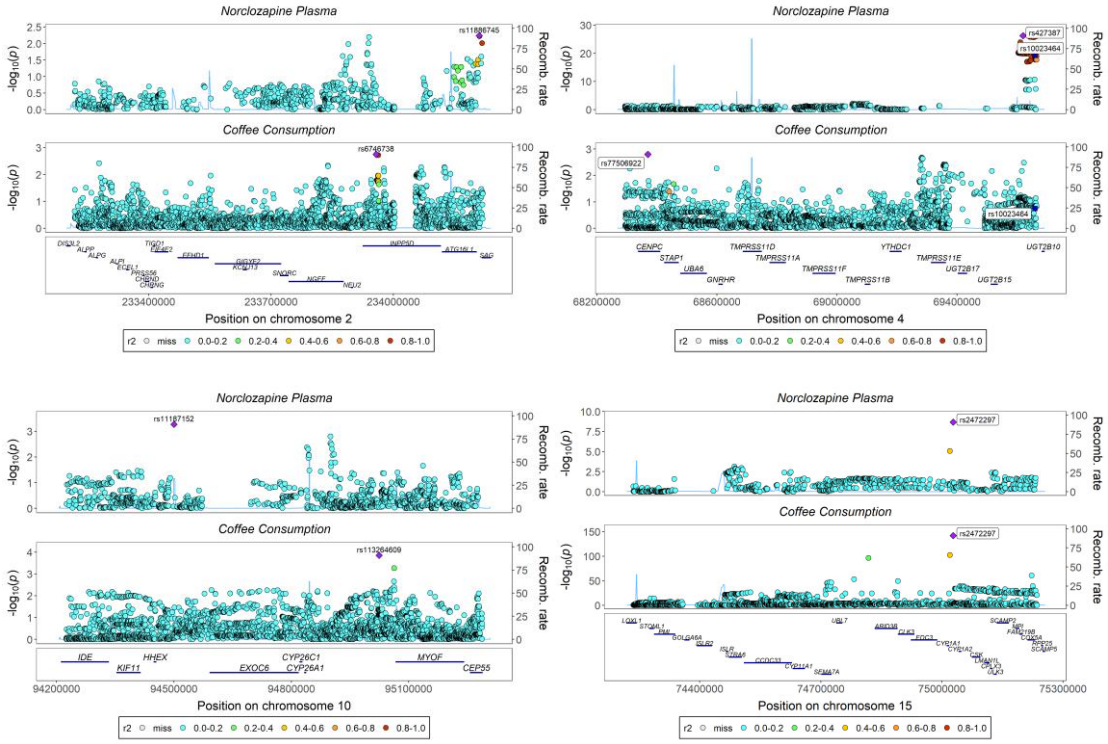
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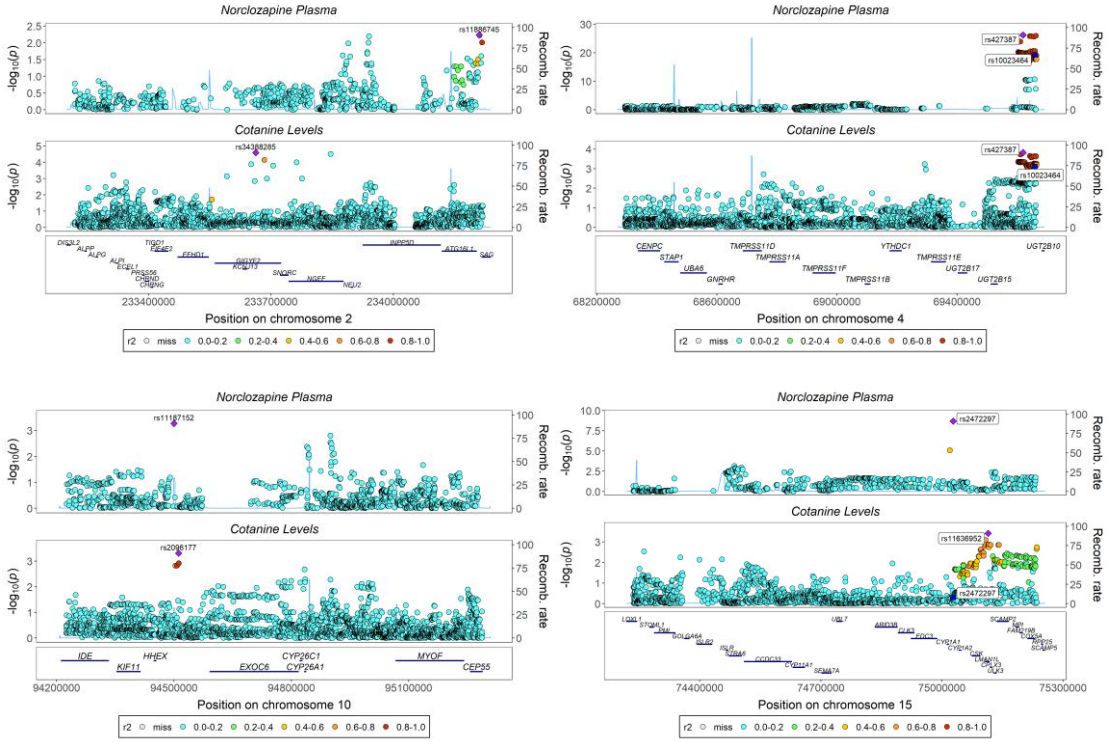
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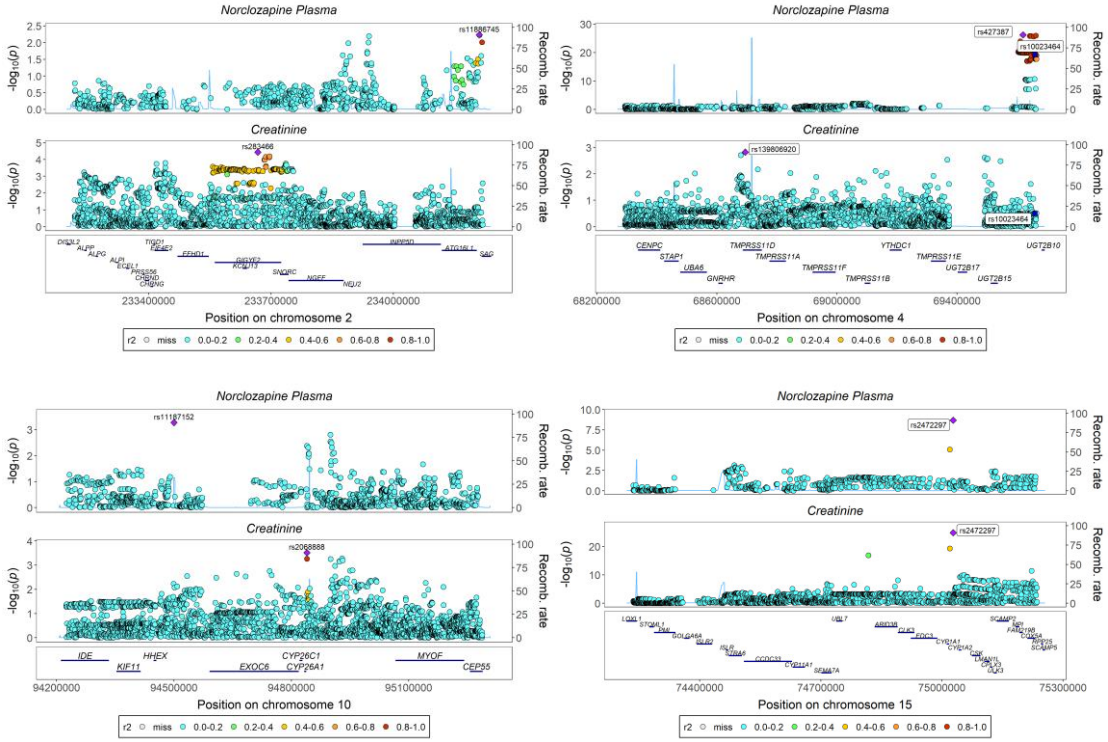
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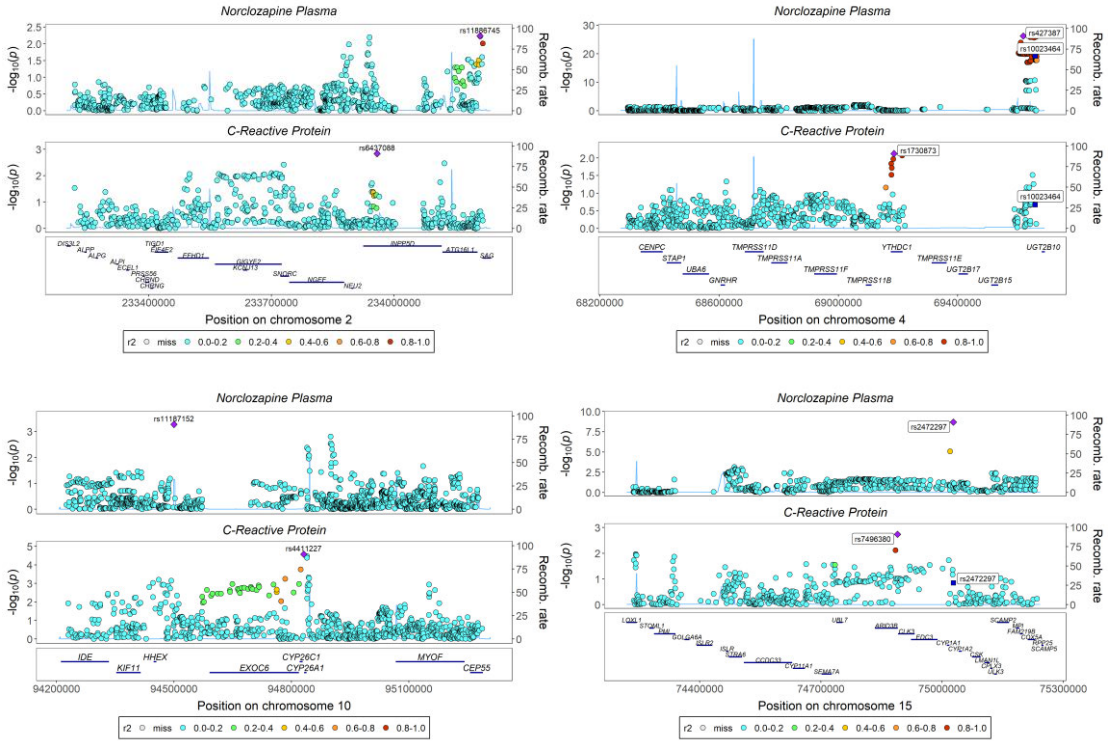
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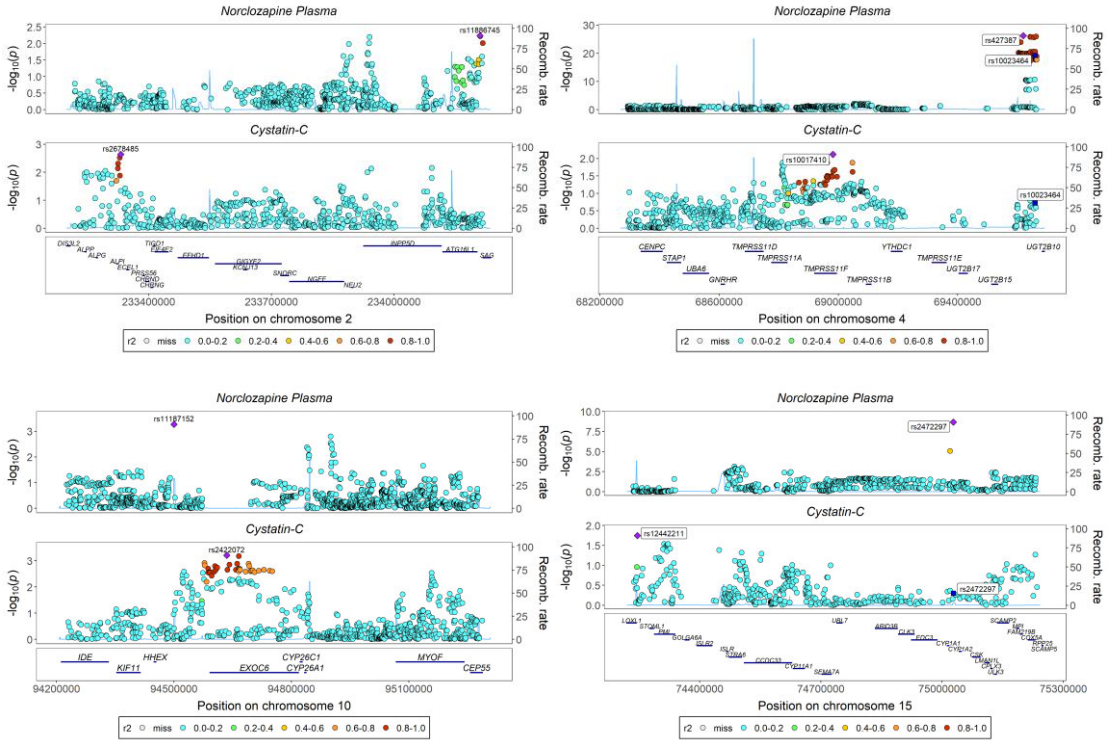
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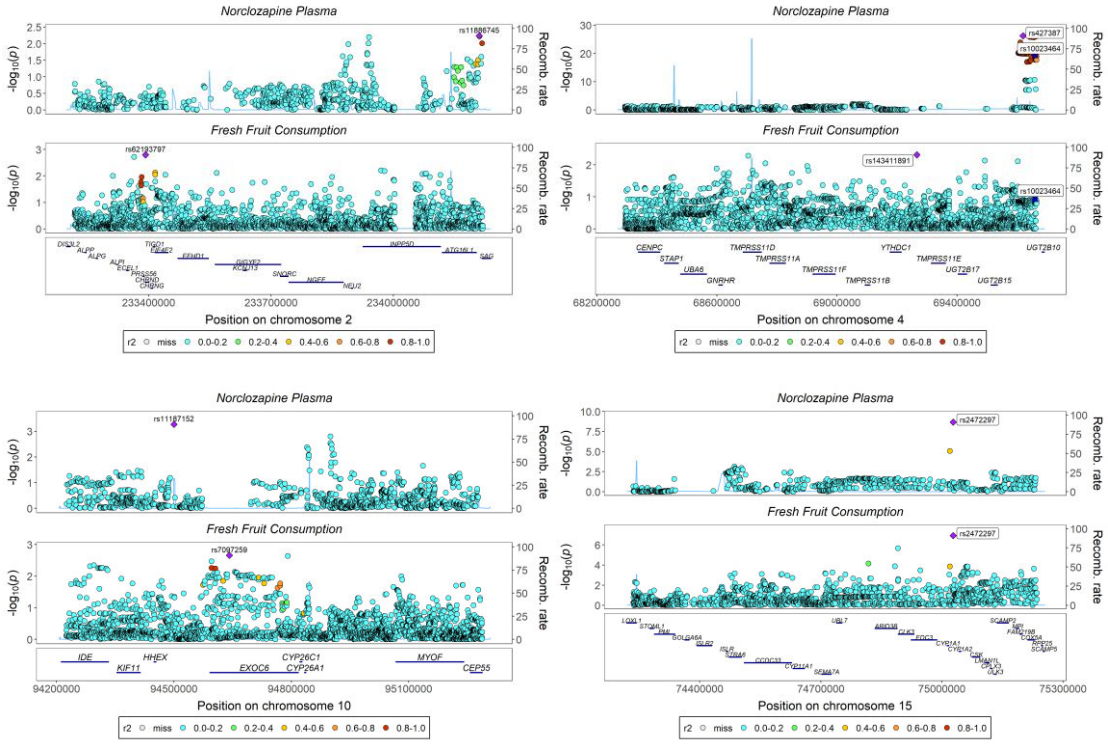
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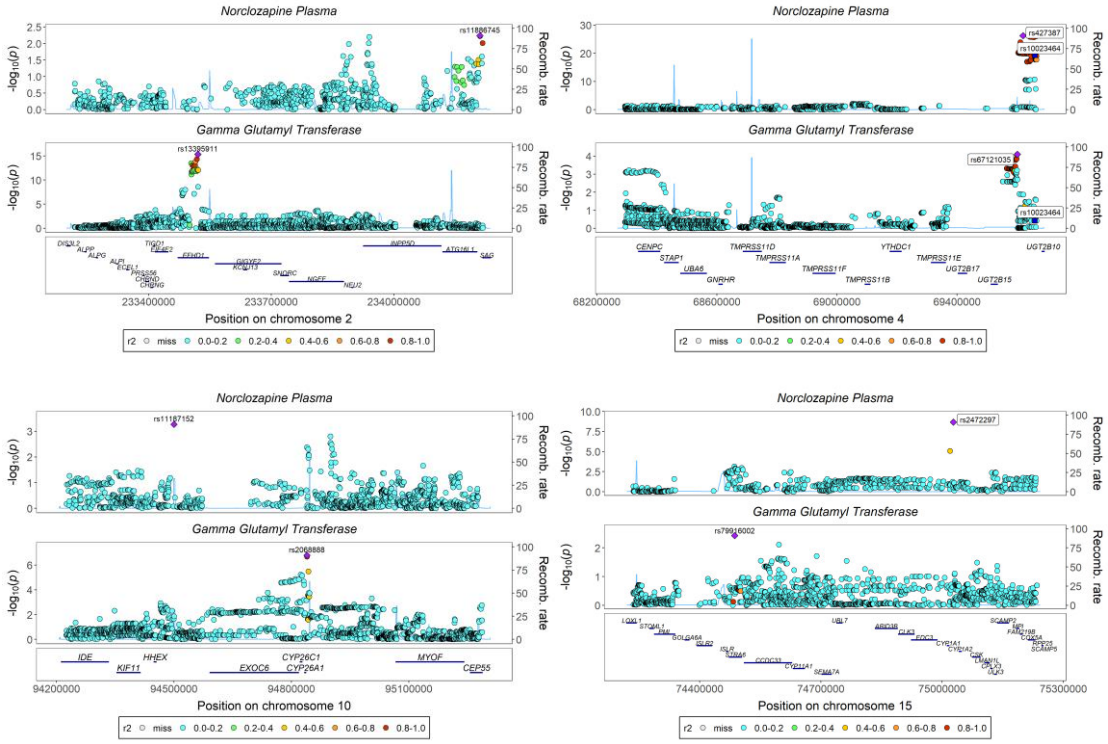
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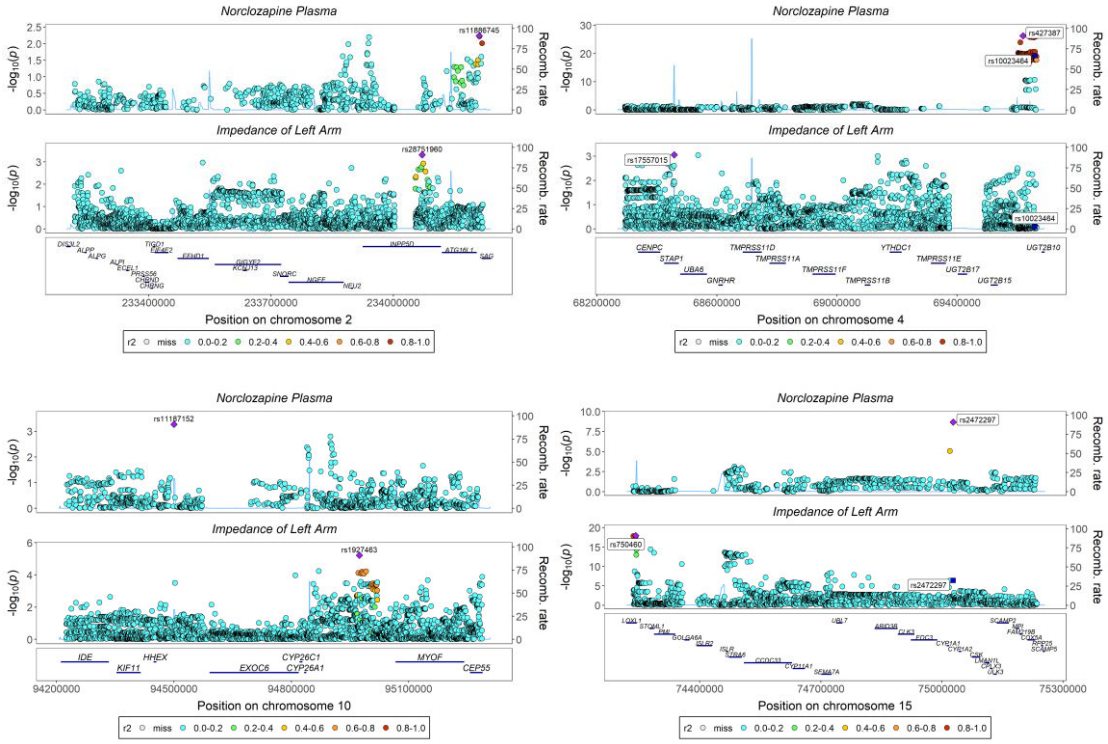
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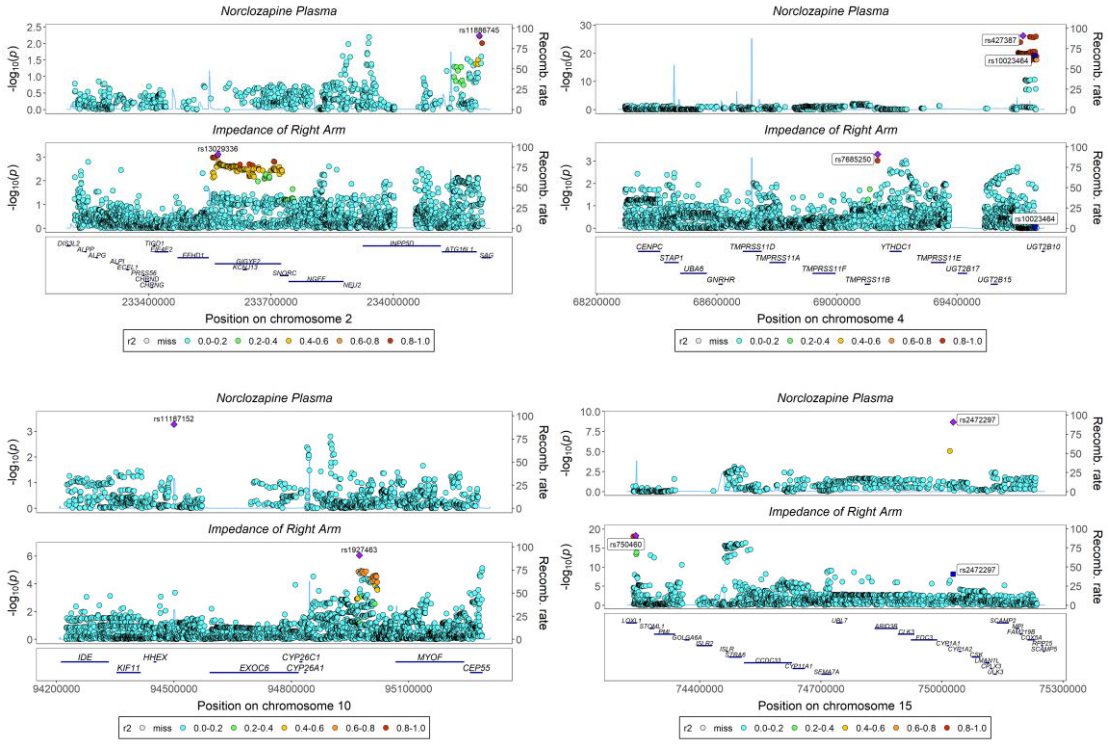
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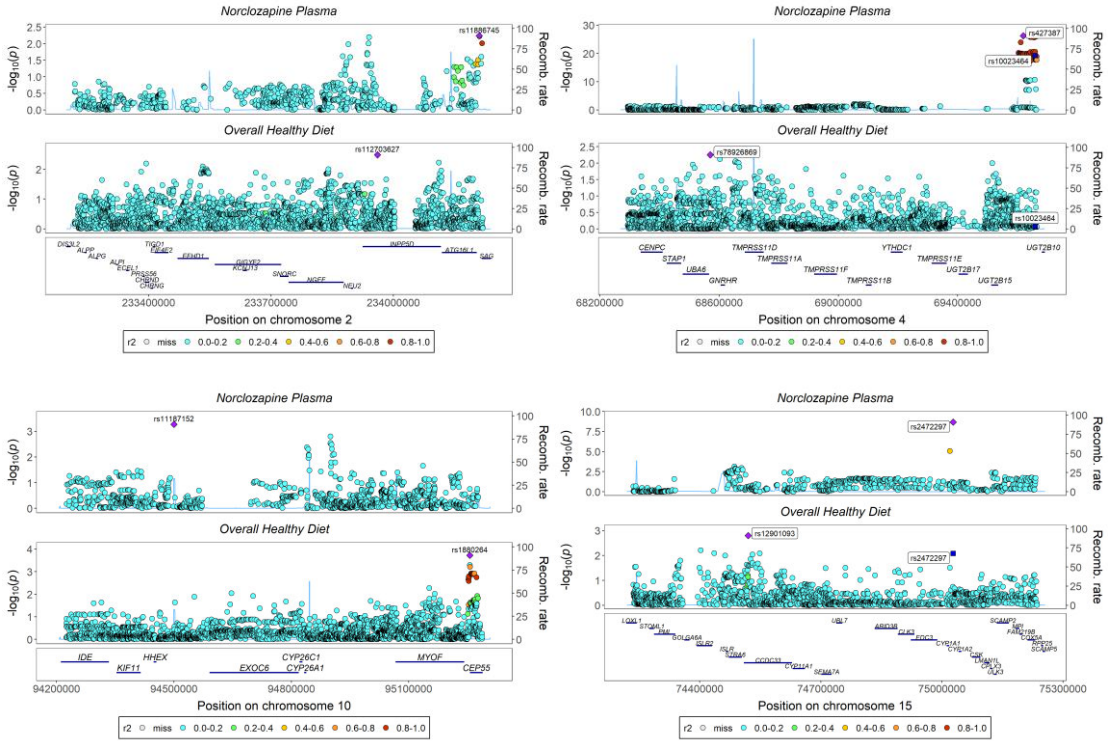
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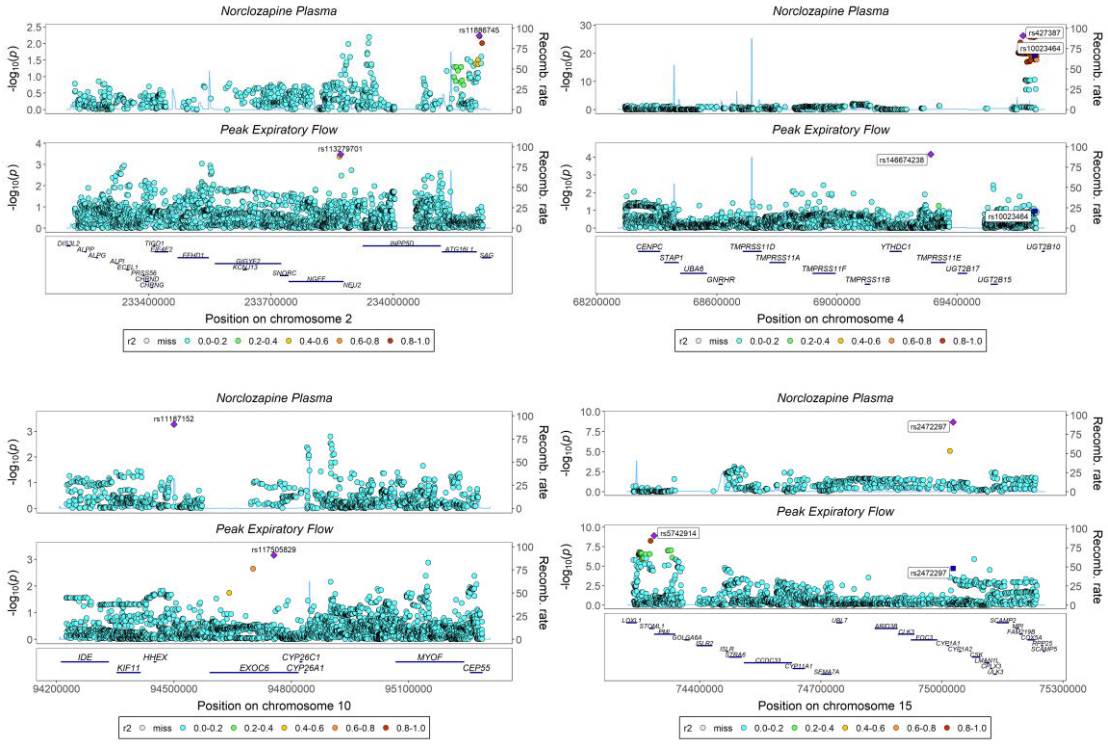
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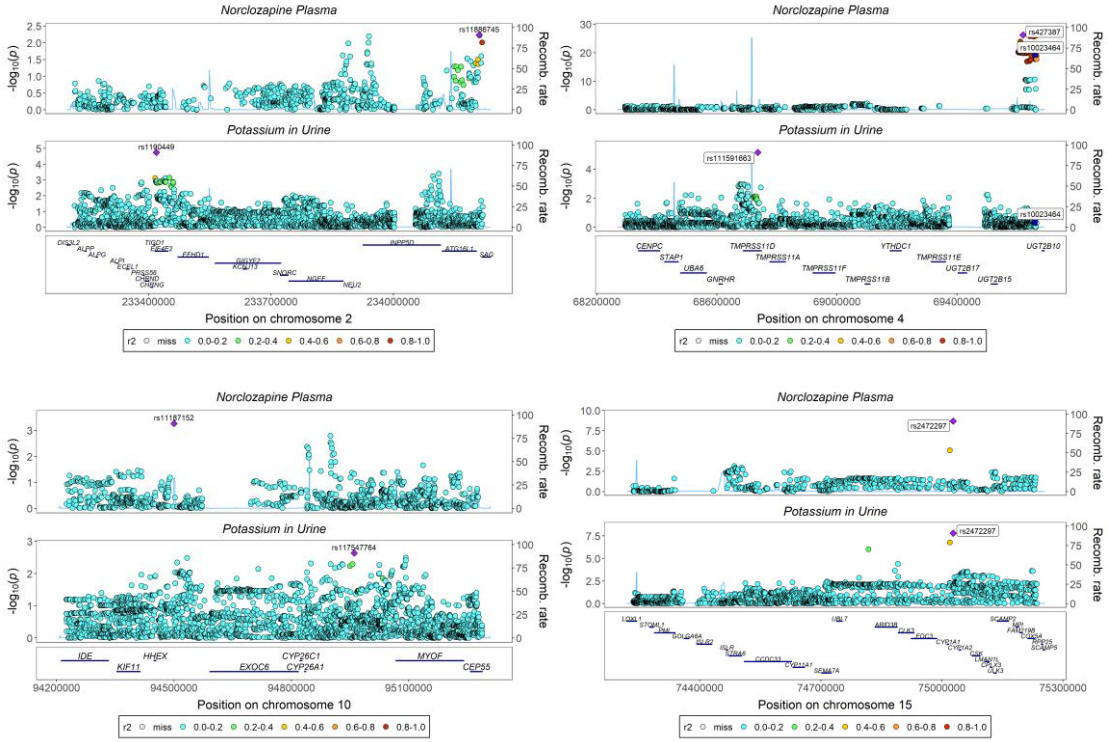
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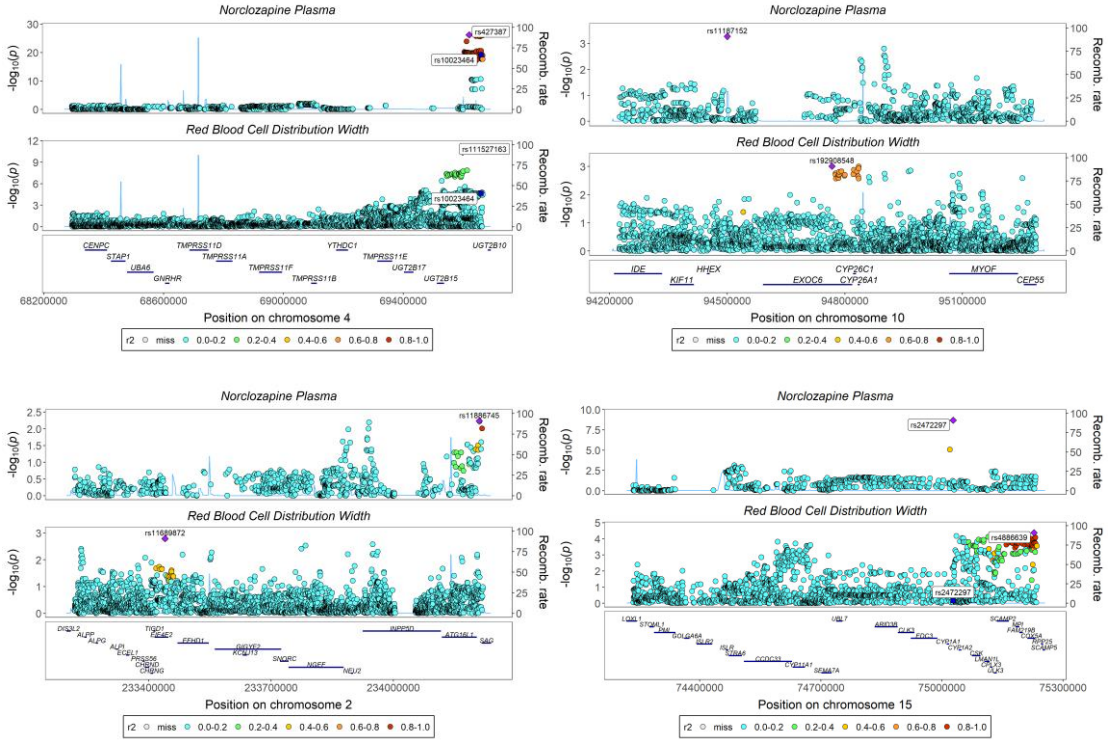
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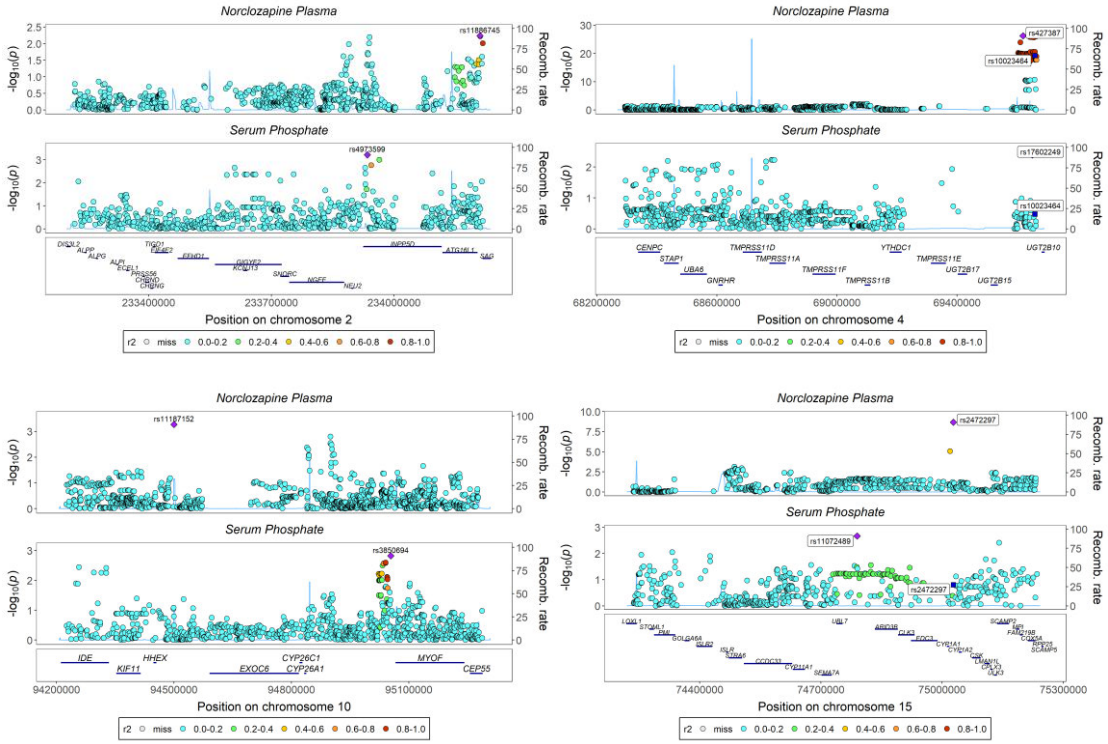
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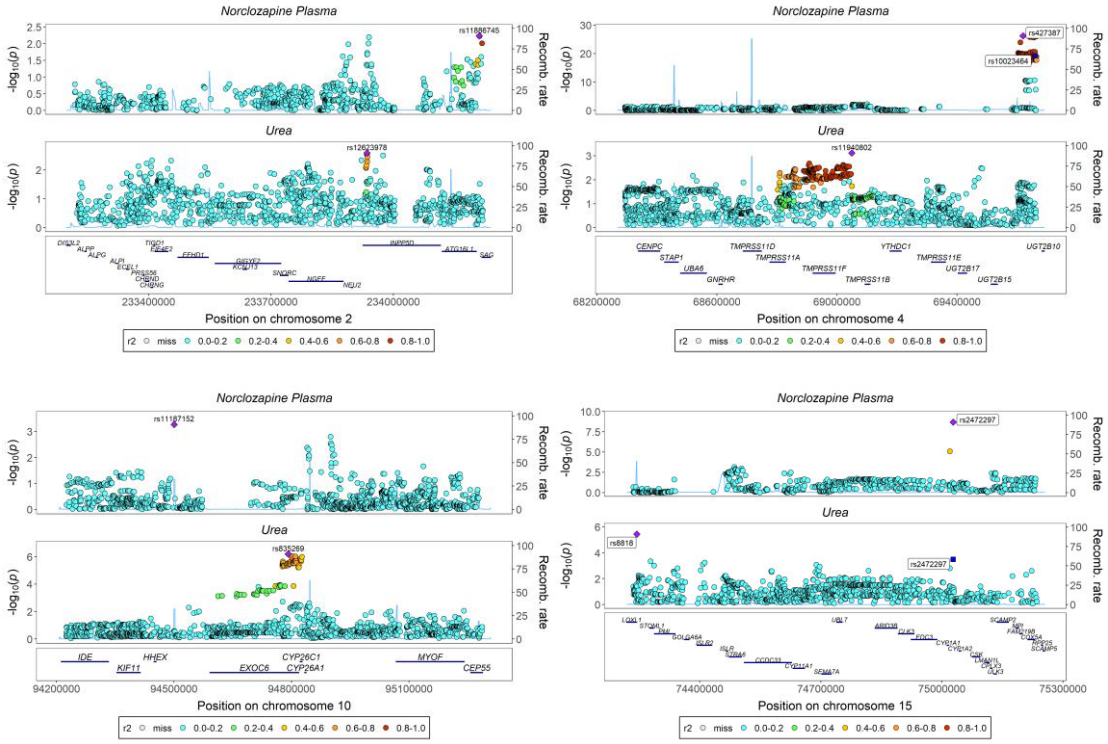
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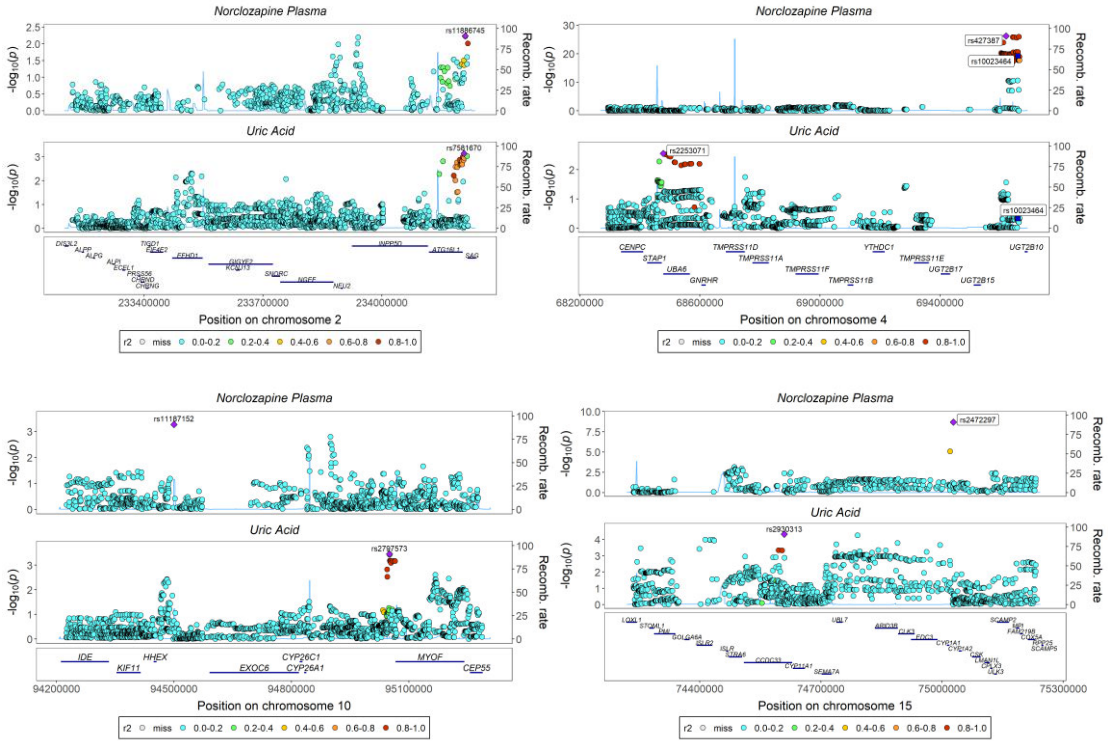
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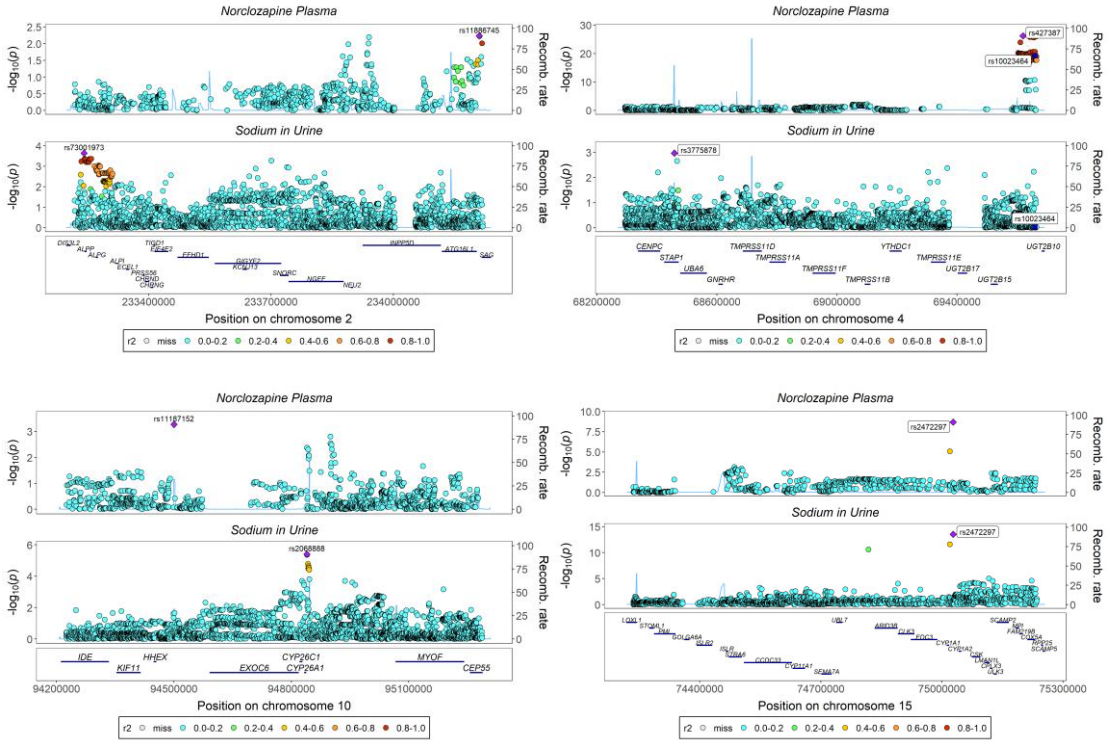
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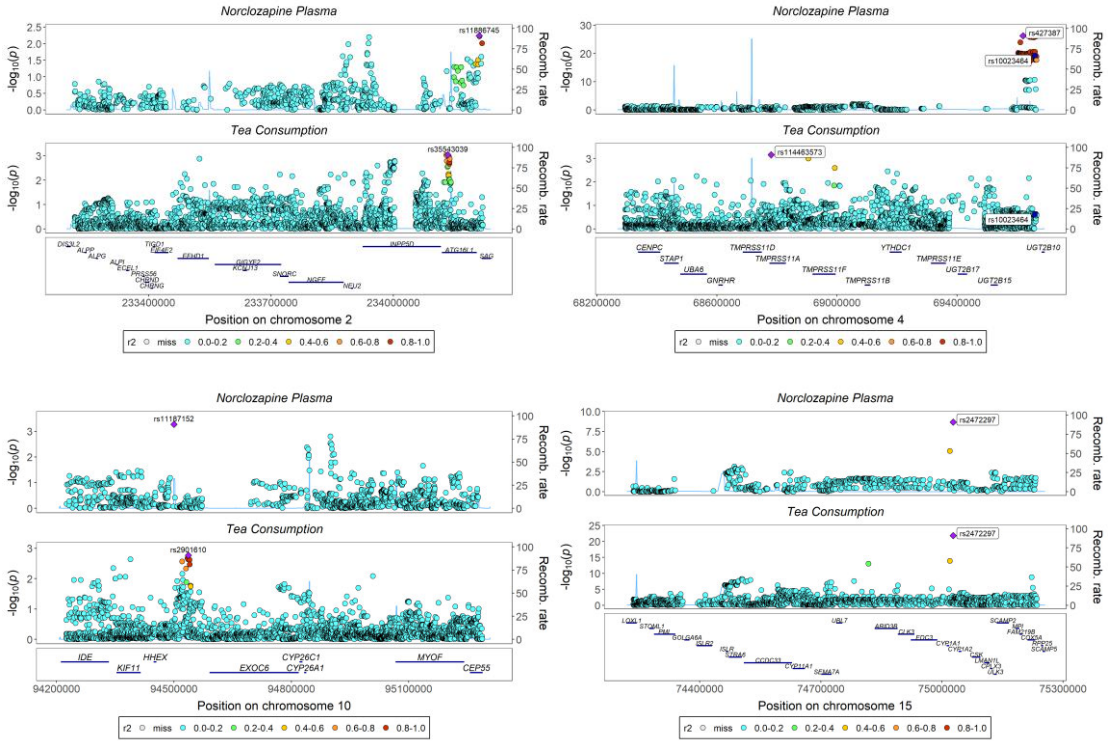
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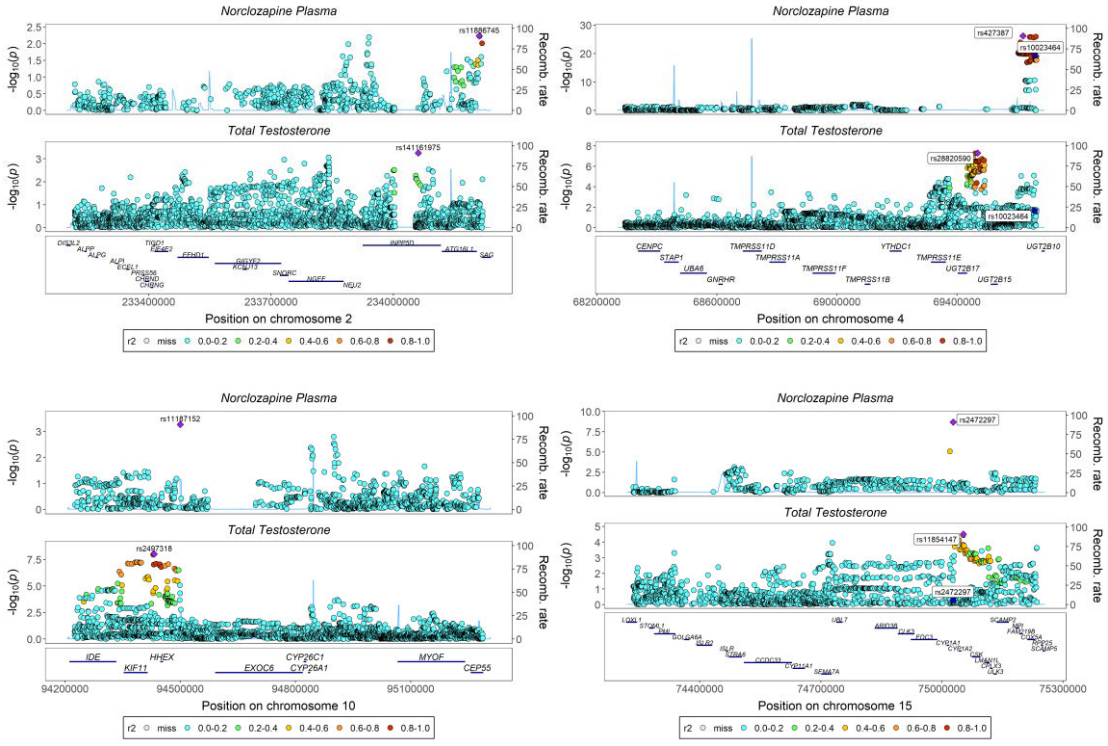
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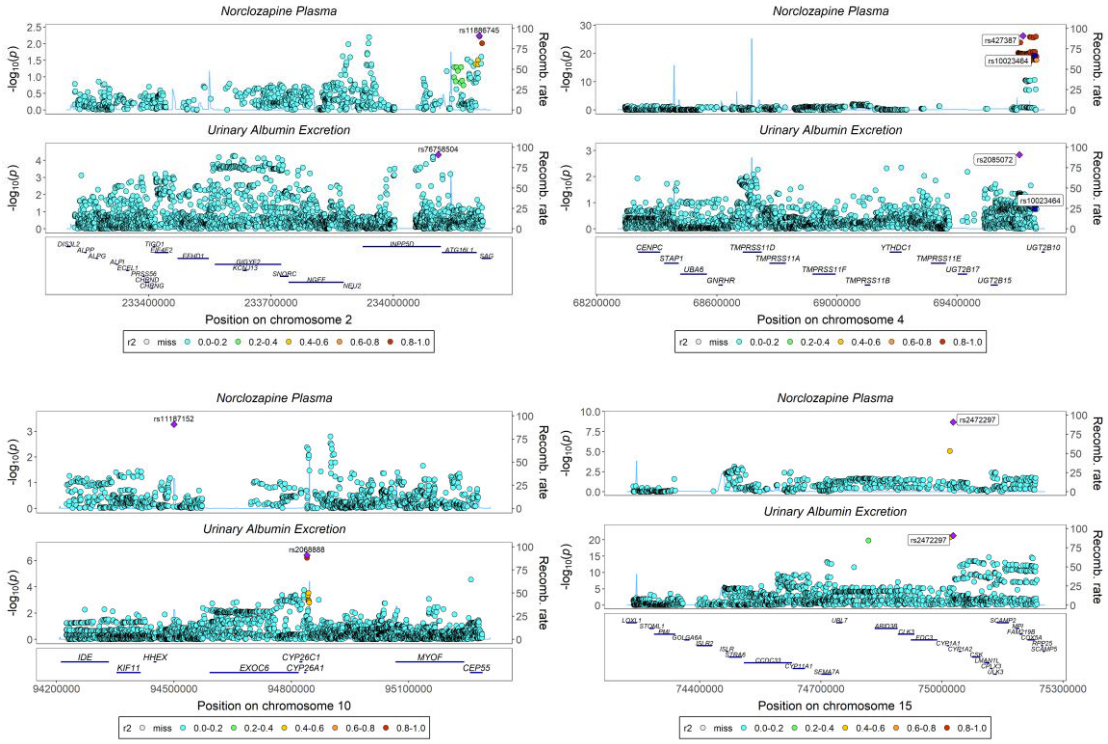
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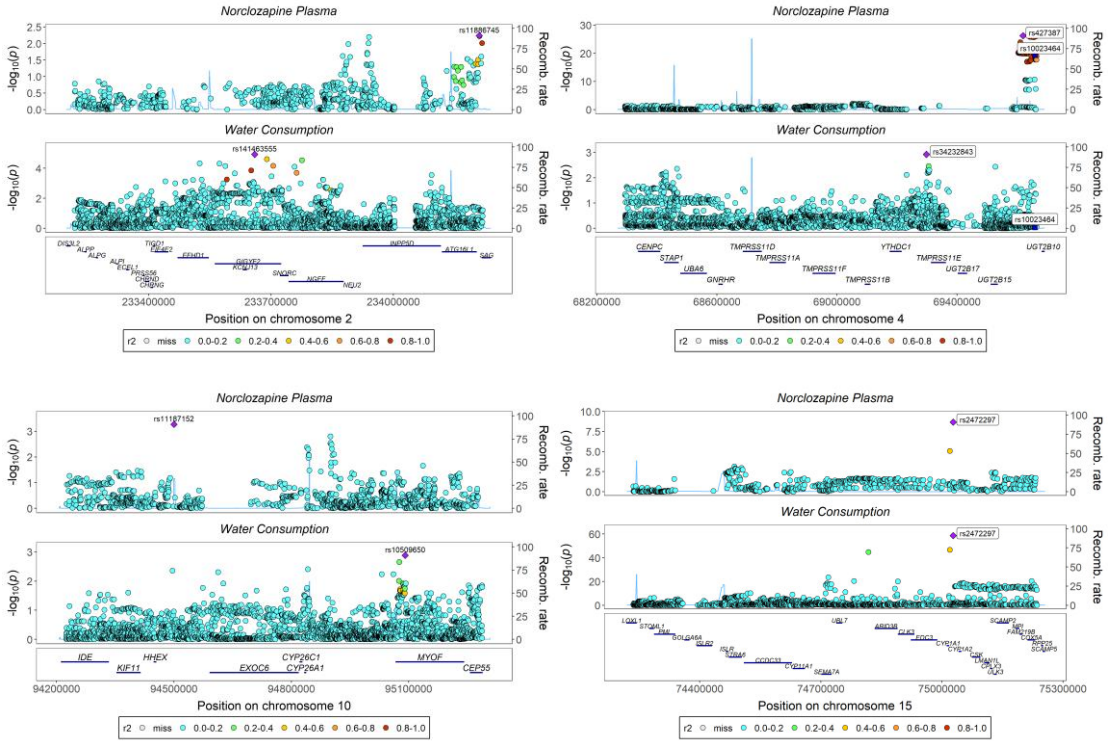
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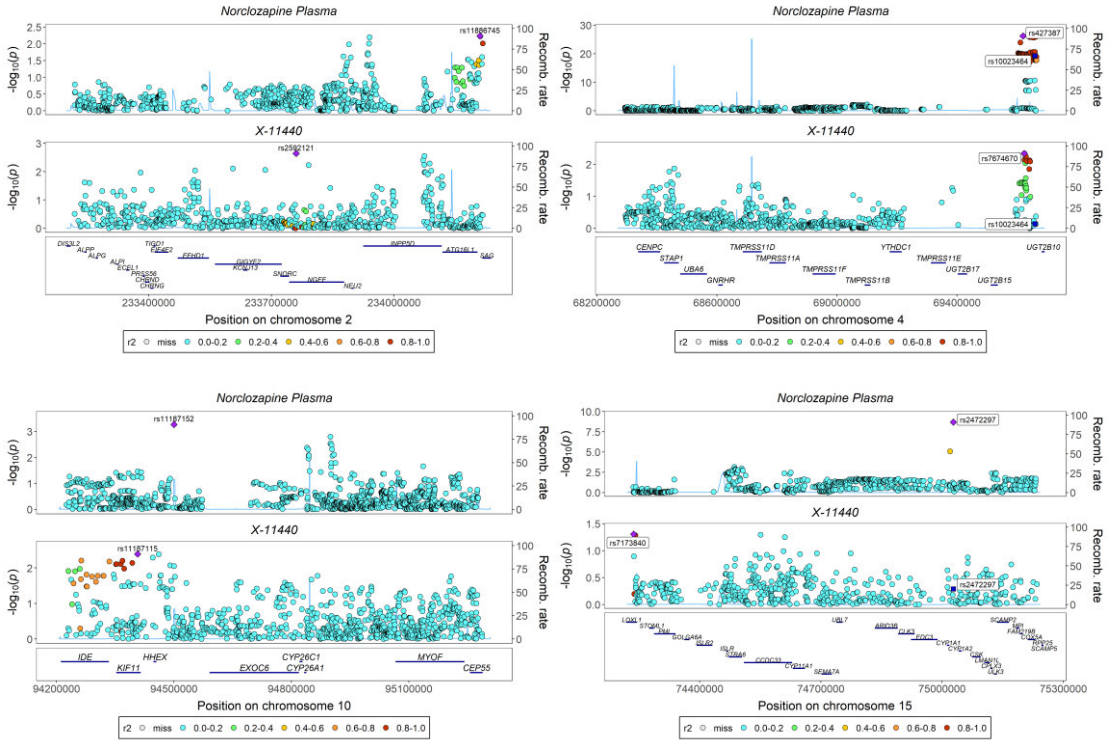
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Water Consumption:

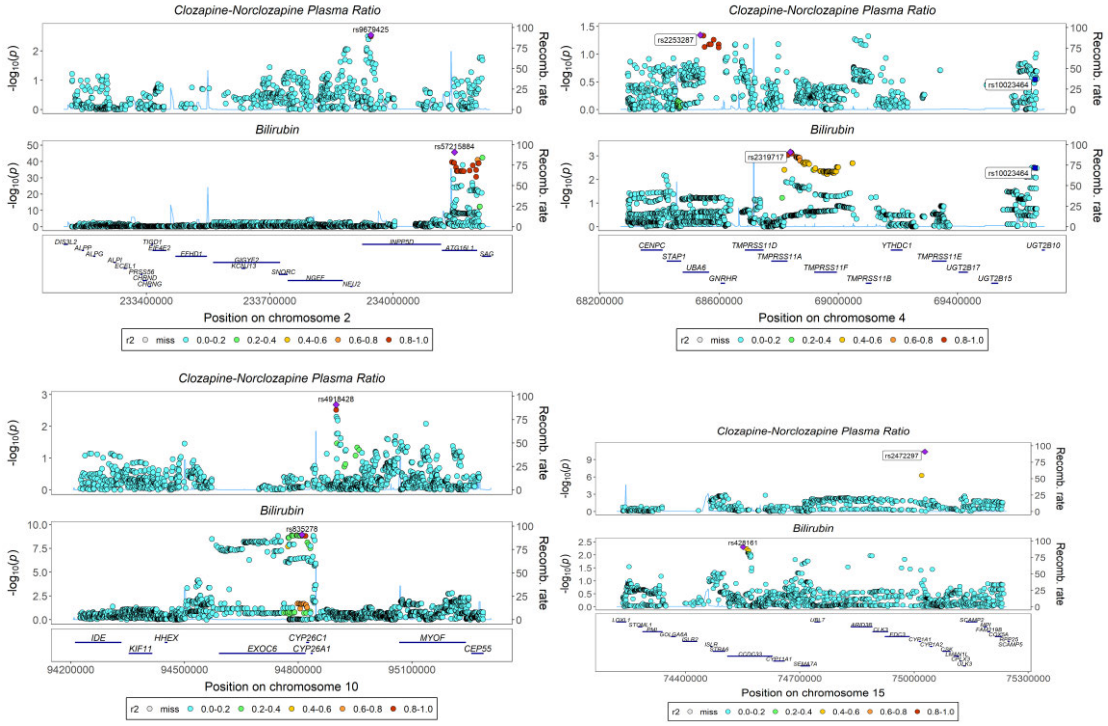


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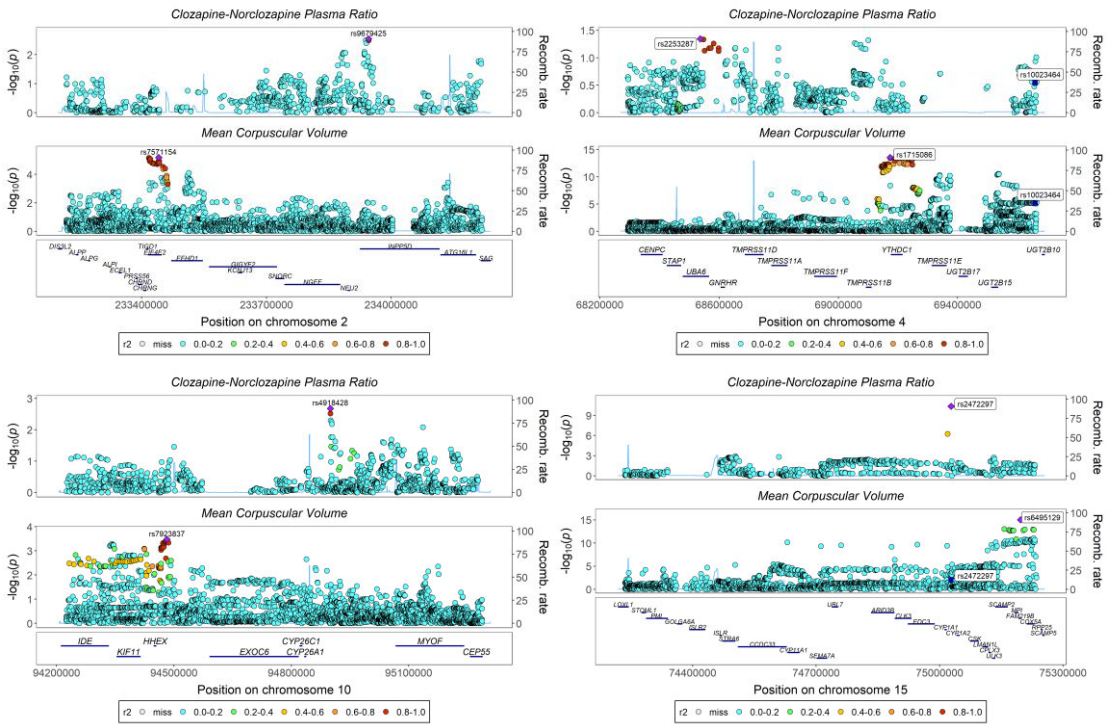

Norclozapine Plasma
X-11440
Position on chromosome 2
Position on chromosome 4
Position on chromosome 10
Position on chromosome 15
Recomb. rate
r2 miss 0.0-0.2 0.2-0.4 0.4-0.6 0.6-0.8 0.8-1.0

Supplementary Figures 4.4.5 - Stacked Regional Association Plots for Clozapine-Norclozapine Ratio Colocalizing with PheWAS Identified Candidate Biomarkers Across 4 Lead Chromosomes.

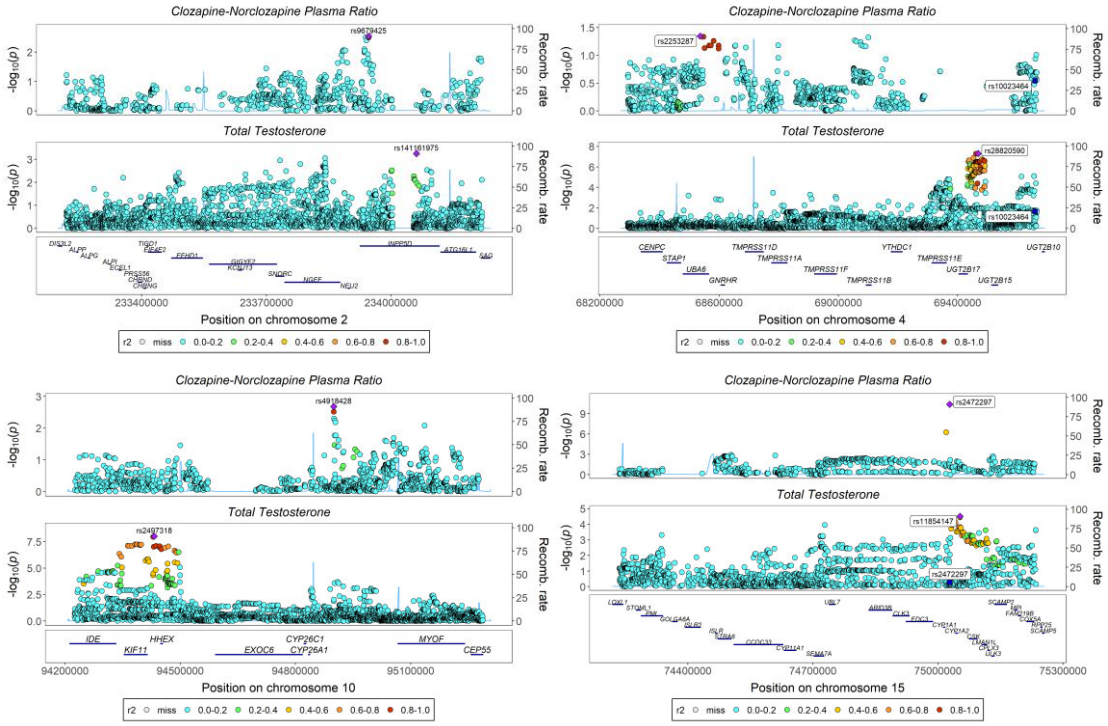
Bilirubin:



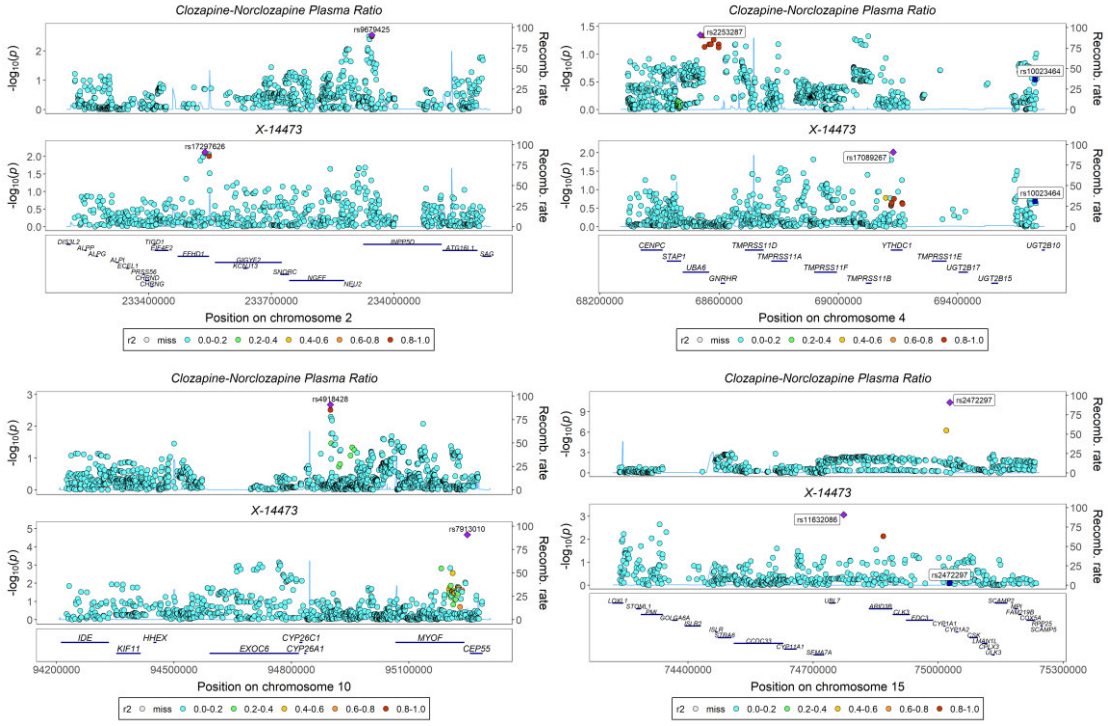
Mean Corpuscular Volume:



Total Testosterone:



X-14473:

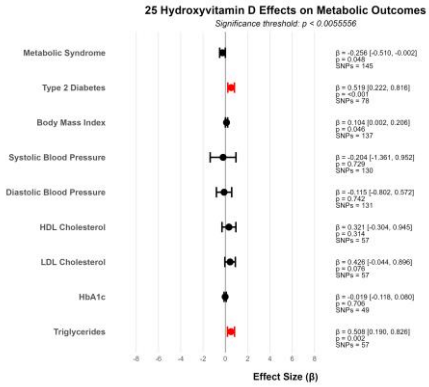


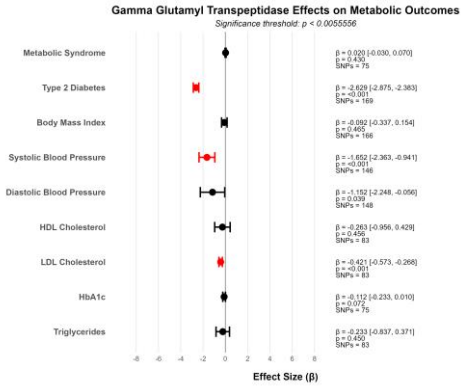
Supplementary Figures 4.5 - Candidate Biomarkers Effects on Cardiometabolic Traits

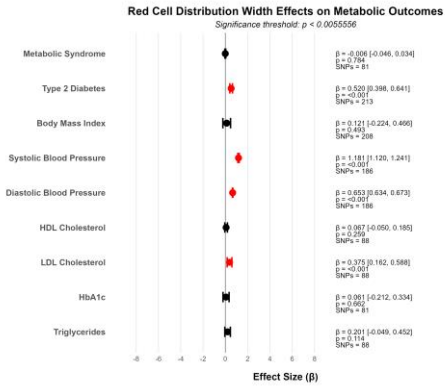
Analysis results from linkage-disequilibrium-aware bidirectional MR of clozapine on cardiometabolic outcomes where a colocalized phenotype ($\boldsymbol{PP.H_4 > 0.80}$) demonstrated significant causal effects on at least 1 of the 9 metabolic phenotypes after multiple testing correction (16/28 colocalized phenotypes). Forest plots demonstrate the causal estimate of the exposure ($\boldsymbol{\beta}$) on $\boldsymbol{n}$ outcomes with $\boldsymbol{95\%CIs}$ and $\boldsymbol{P}$. Significance threshold is adjusted for multiple testing (Bonferroni Correction) ($\boldsymbol{P(adj) = 0.05/n}$). Scatterplots depict sensitivity analyses results including MR-Egger and weighted median to test for directional pleiotropy and causal estimate assessment under invalid instruments respectively. Weighted mode demonstrates the causal estimate even if there are pleiotropic effects. Leave-one-out plots demonstrate the robustness of causal inference by testing if one genetic variant is driving the observed association. Raw results for bidirectional MR are available in Supplementary Table 4.5 and 4.6. Information about the Mendelian randomization analyses is available in the Supplementary Methods (Appendix C).

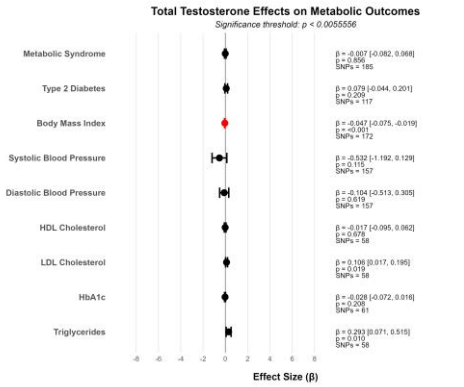
Supplementary Figures 4.5.1 - Forest Plots - Candidate Biomarkers on Cardiometabolic Traits 293
Supplementary Figures 4.5.2 - Scatterplots - Candidate Biomarkers on Cardiometabolic Traits 295
Supplementary Figures 4.5.3 - Leave-one-out Plots - Candidate Biomarkers Effect on Cardiometabolic Traits 304
Supplementary Figures 4.5.4 - Forest Plots - Cardiometabolic Traits Effects on Candidate Biomarkers.....313

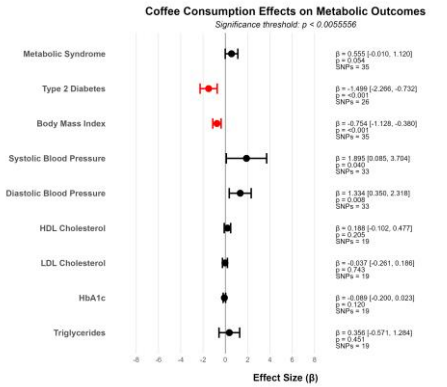
Supplementary Figures 4.5.1 - Forest Plots - Candidate Biomarkers on Cardiometabolic Traits

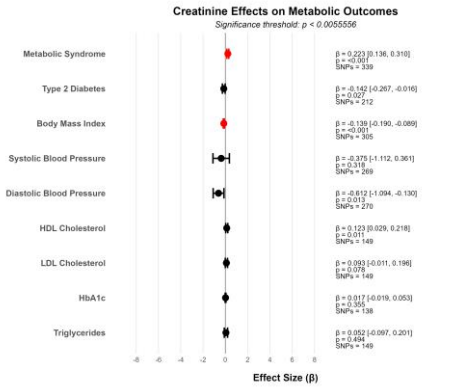


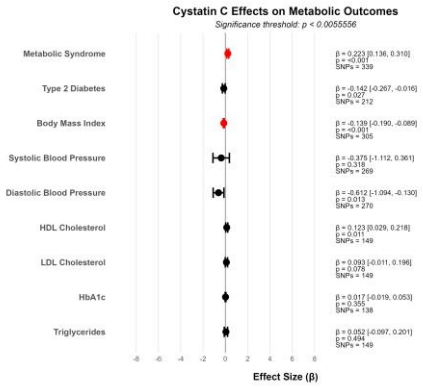


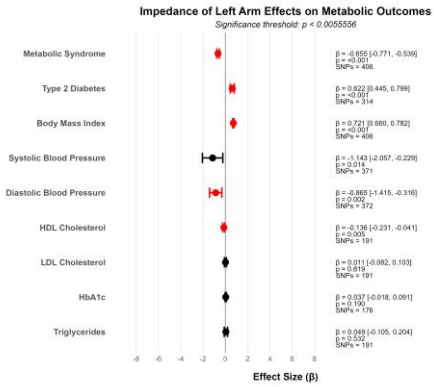


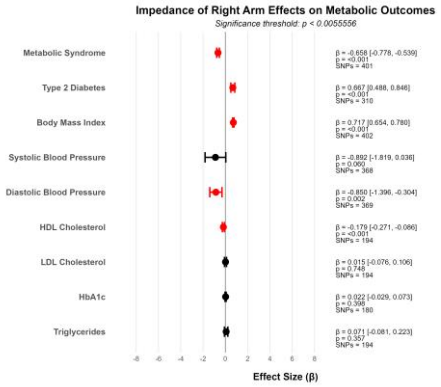


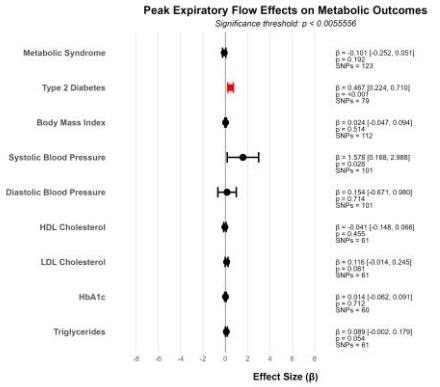


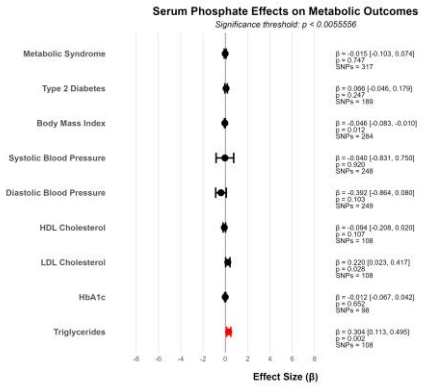




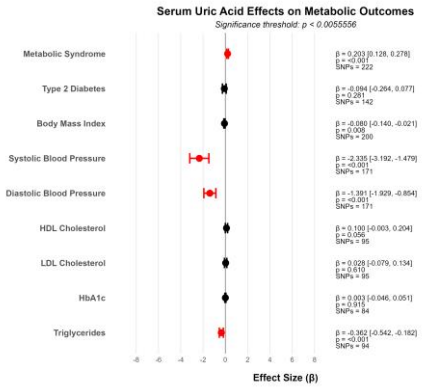


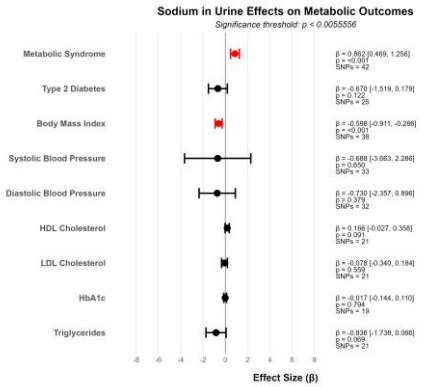

Impedance of Right Arm Effects on Metabolic Outcomes
Significance threshold: p < 0.0055556
Metabolic Syndrome
Type 2 Diabetes
Body Mass Index
Systolic Blood Pressure
Diastolic Blood Pressure
HDL Cholesterol
LDL Cholesterol
HbA1c
Triglycerides
Effect Size (β)

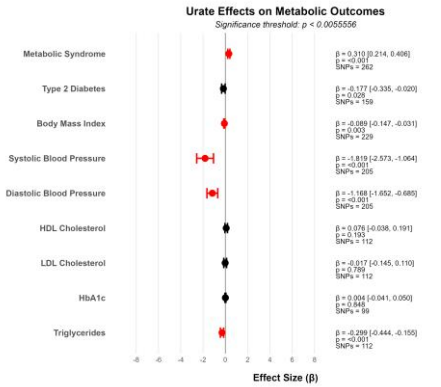

Peak Expiratory Flow Effects on Metabolic Outcomes
Significance threshold: p < 0.0055556
Metabolic Syndrome
Type 2 Diabetes
Body Mass Index
Systolic Blood Pressure
Diastolic Blood Pressure
HDL Cholesterol
LDL Cholesterol
HbA1c
Triglycerides
Effect Size (β)

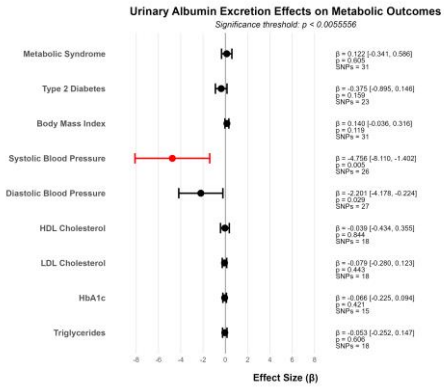

Serum Phosphate Effects on Metabolic Outcomes
Significance threshold: p < 0.0055556
Metabolic Syndrome
Type 2 Diabetes
Body Mass Index
Systolic Blood Pressure
Diastolic Blood Pressure
HDL Cholesterol
LDL Cholesterol
HbA1c
Triglycerides
Effect Size (β)


Serum Urea Effects on Metabolic Outcomes
Significance threshold: p < 0.0055556
Metabolic Syndrome
Type 2 Diabetes
Body Mass Index
Systolic Blood Pressure
Diastolic Blood Pressure
HDL Cholesterol
LDL Cholesterol
HbA1c
Triglycerides
Effect Size (β)


Serum Uric Acid Effects on Metabolic Outcomes
Significance threshold: p < 0.0055556
Metabolic Syndrome
Type 2 Diabetes
Body Mass Index
Systolic Blood Pressure
Diastolic Blood Pressure
HDL Cholesterol
LDL Cholesterol
HbA1c
Triglycerides
Effect Size (β)

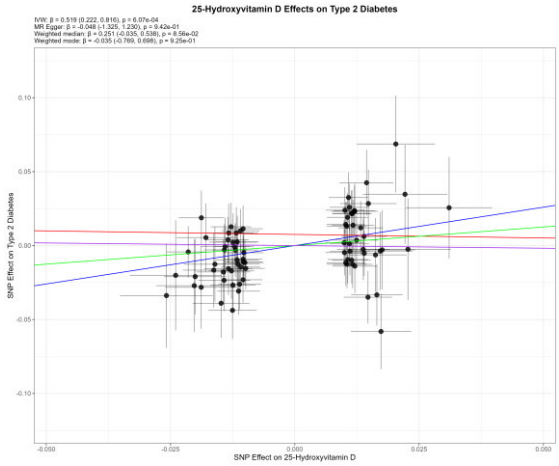

Sodium in Urine Effects on Metabolic Outcomes
Significance threshold: p < 0.0055556
Metabolic Syndrome
Type 2 Diabetes
Body Mass Index
Systolic Blood Pressure
Diastolic Blood Pressure
HDL Cholesterol
LDL Cholesterol
HbA1c
Triglycerides
Effect Size (β)

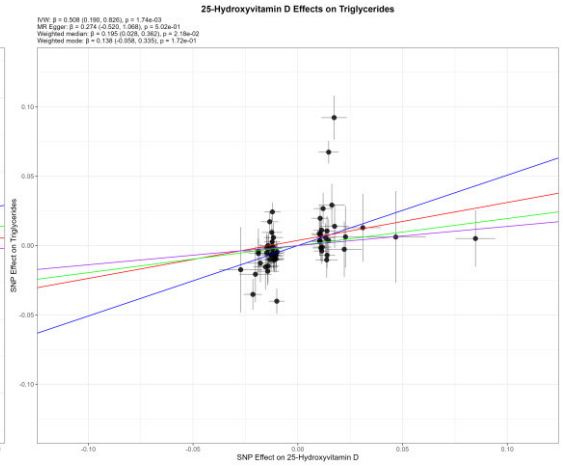

Urate Effects on Metabolic Outcomes
Significance threshold: p < 0.0055556
Metabolic Syndrome
Type 2 Diabetes
Body Mass Index
Systolic Blood Pressure
Diastolic Blood Pressure
HDL Cholesterol
LDL Cholesterol
HbA1c
Triglycerides
Effect Size (β)


Urinary Albumin Excretion Effects on Metabolic Outcomes
Significance threshold: p < 0.0055556
Metabolic Syndrome
Type 2 Diabetes
Body Mass Index
Systolic Blood Pressure
Diastolic Blood Pressure
HDL Cholesterol
LDL Cholesterol
HbA1c
Triglycerides
Effect Size (β)

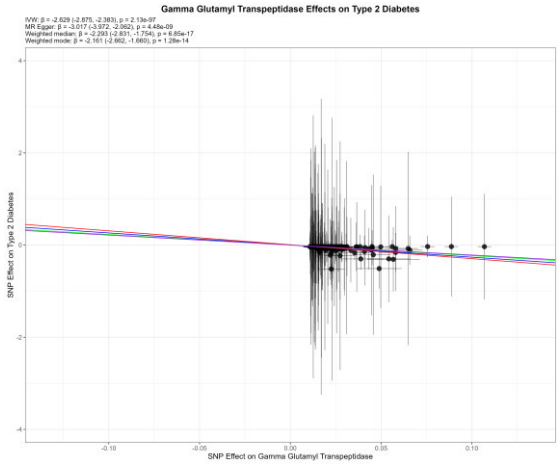
Supplementary Figures 4.5.2 - Scatterplots - Candidate Biomarkers on Cardiometabolic Traits

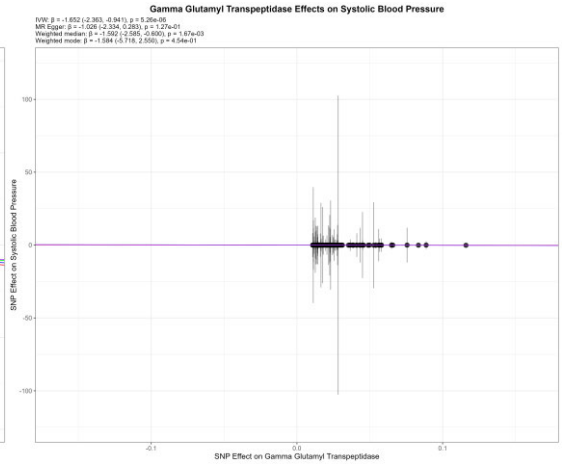
25-Hydroxyvitamin D:

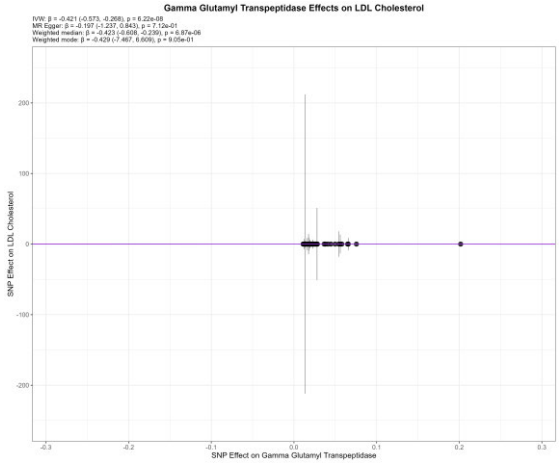




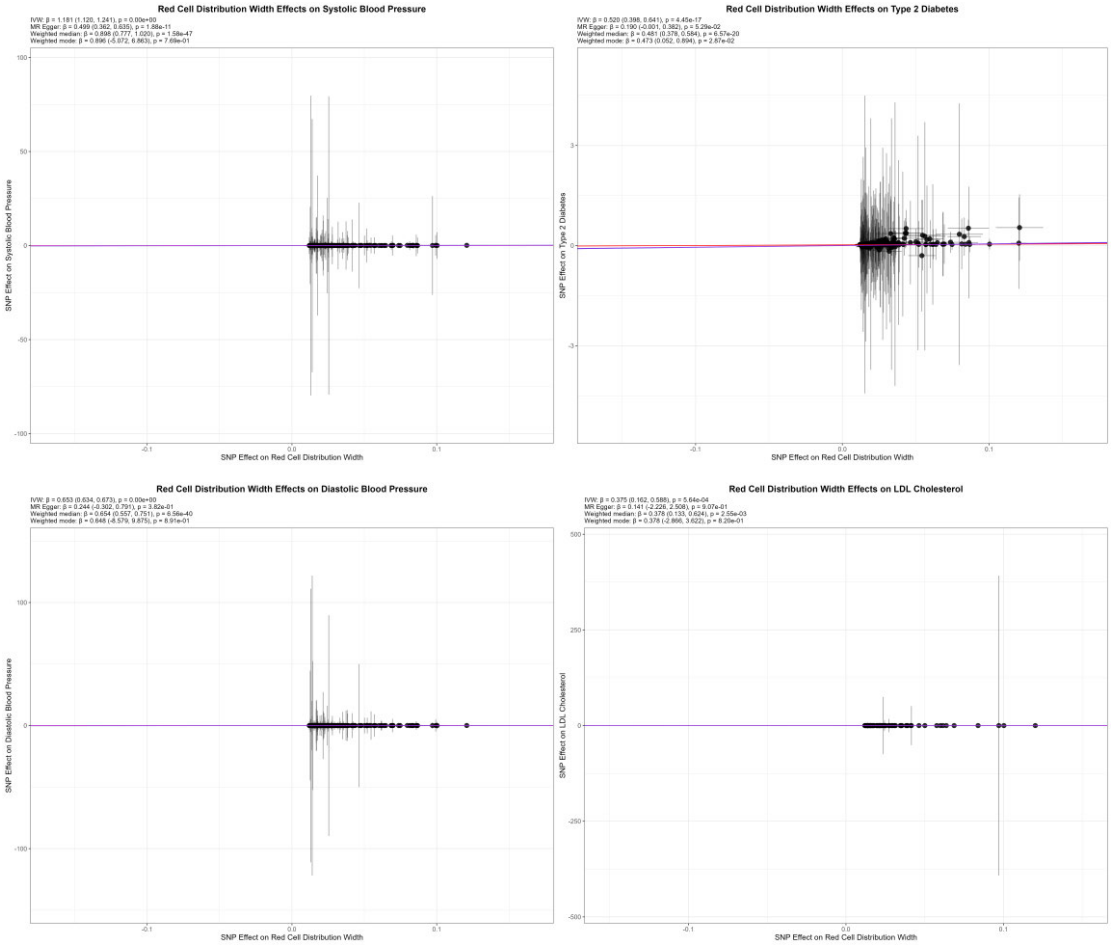
Gamma Glutamyl Transferase:



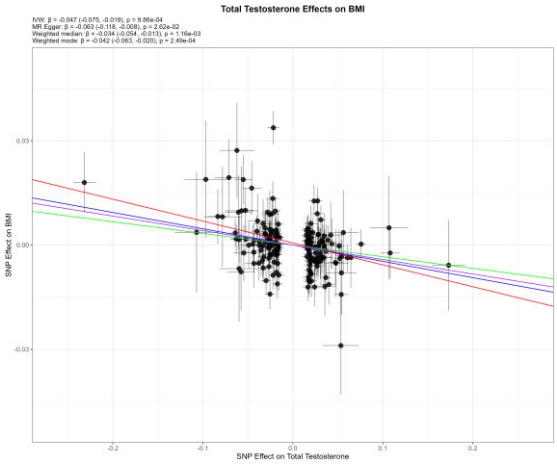




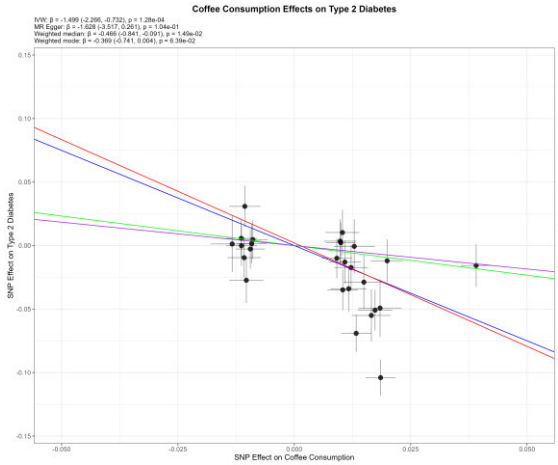
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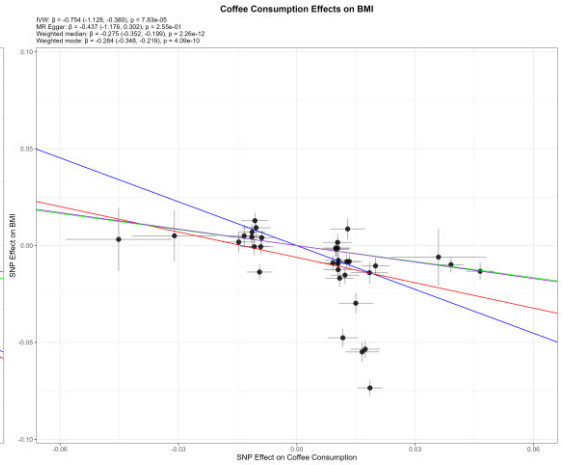


Total Testosterone:

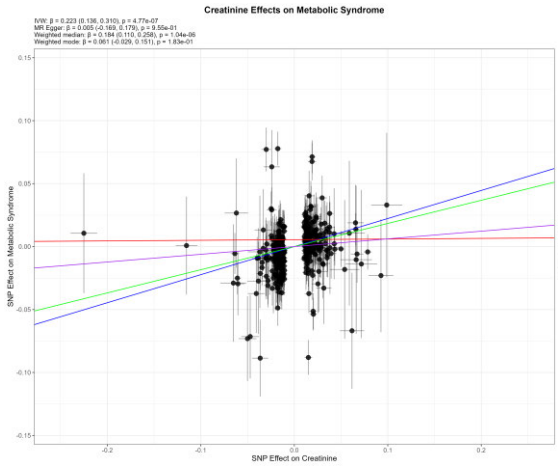


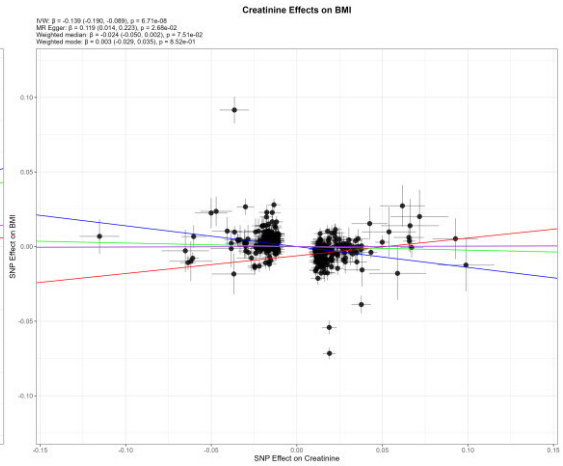
Coffee Consumption:



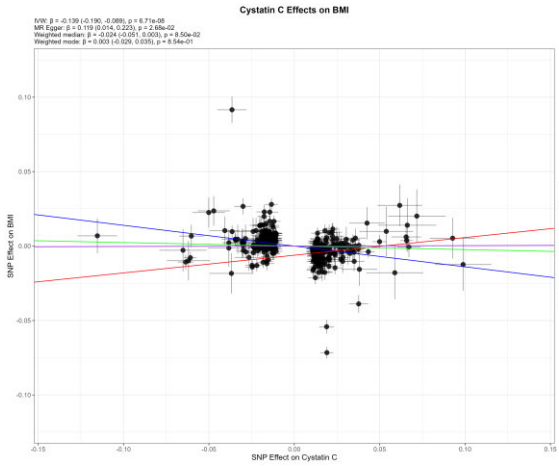


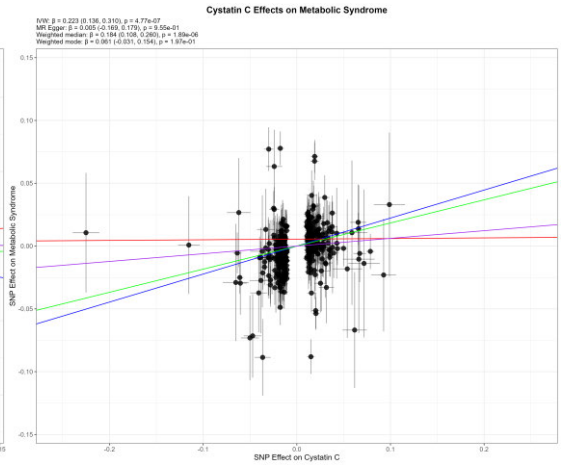
Creatinine:



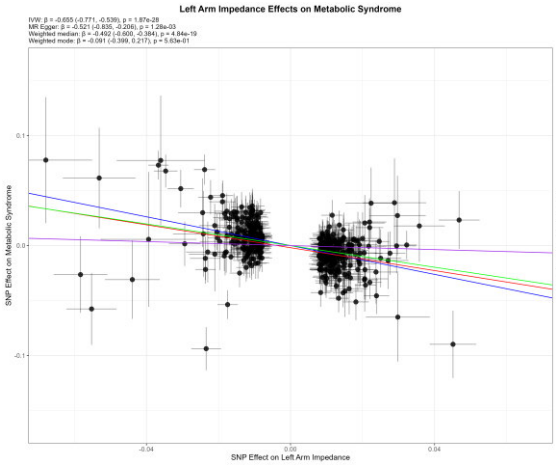


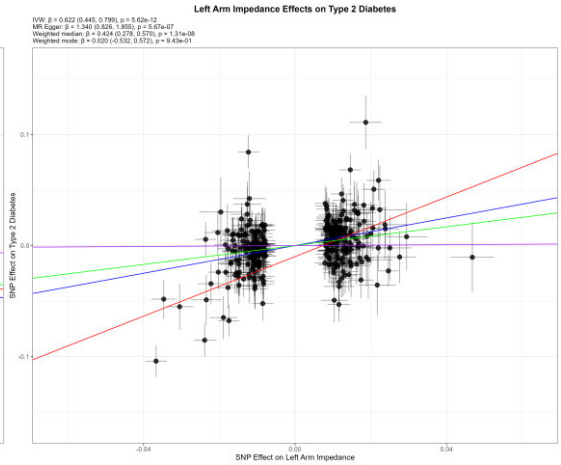
Cystatin C:

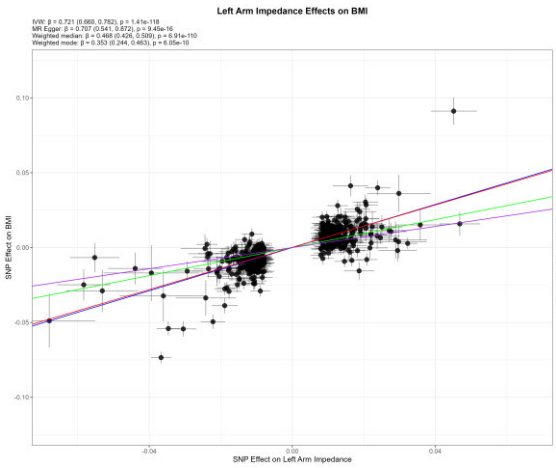


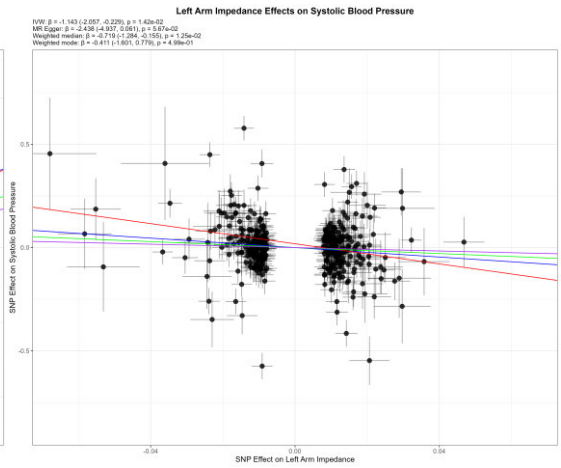


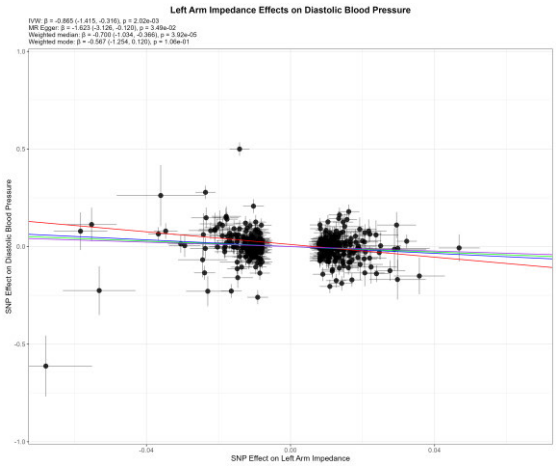
Impedance of Left Arm:



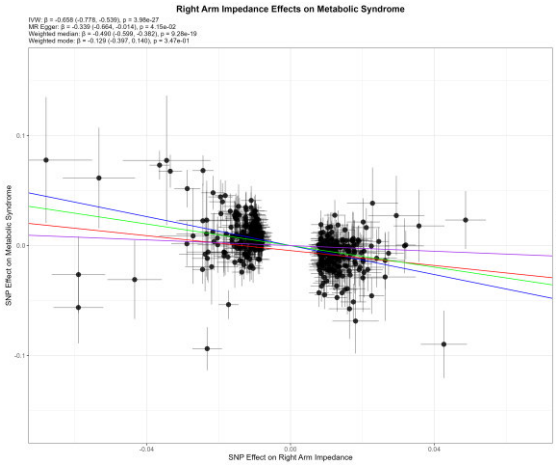


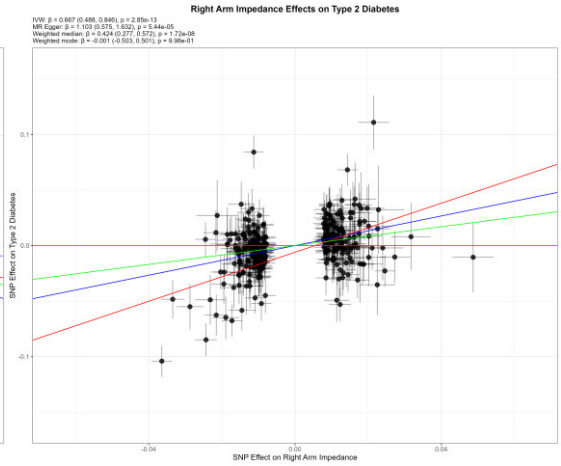


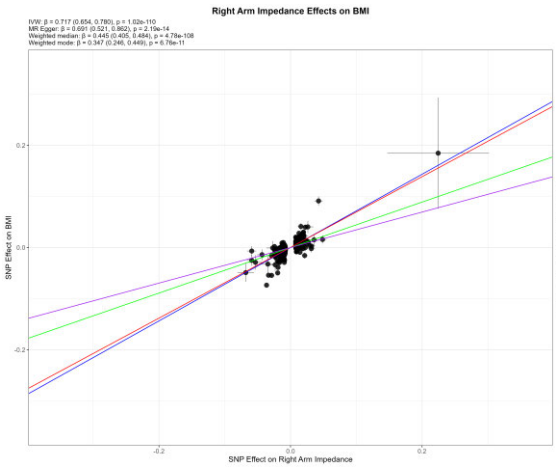


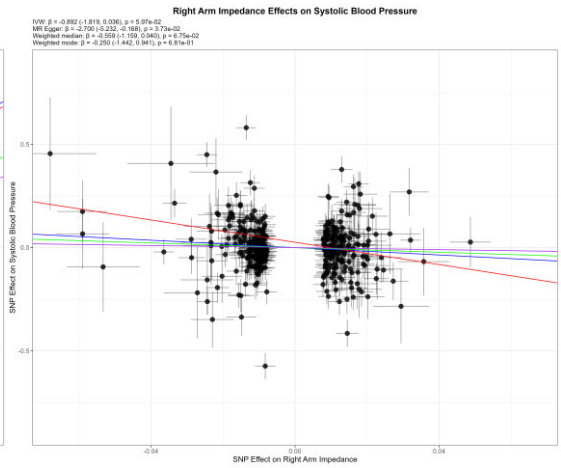


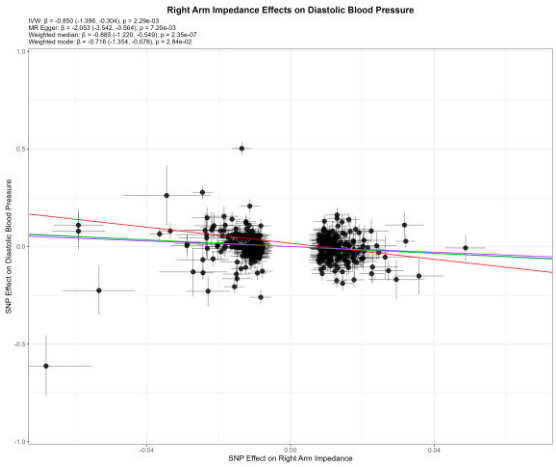
Impedance of Right Arm:



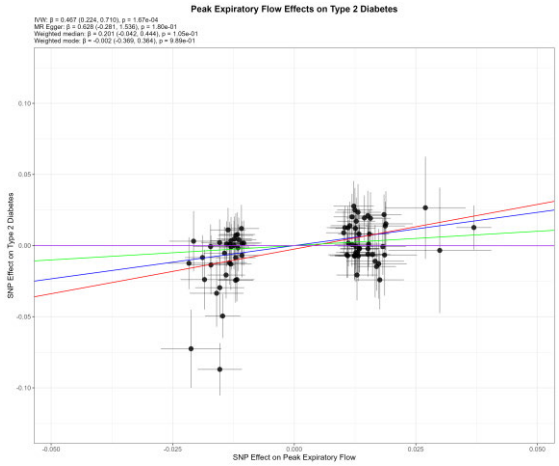




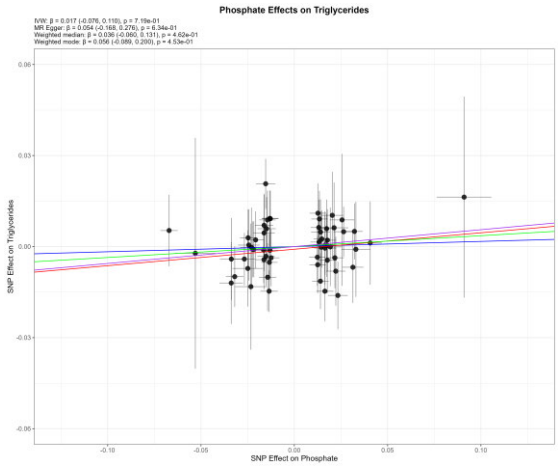




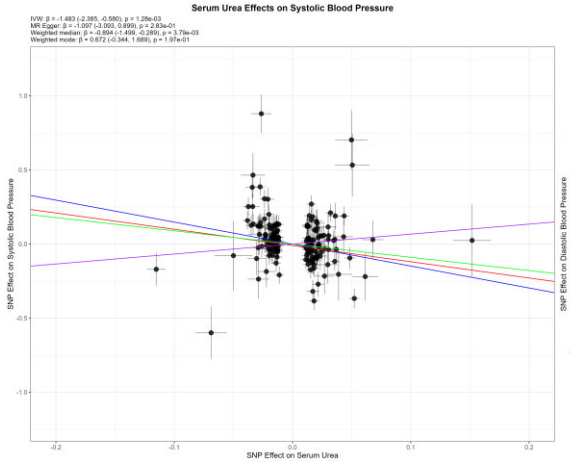
Peak Expiratory Flow:

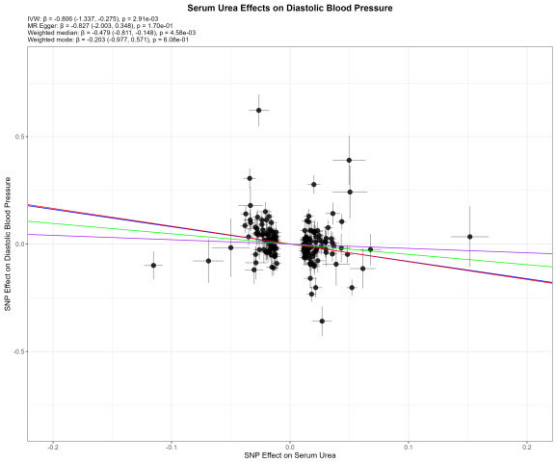


Phosphate:

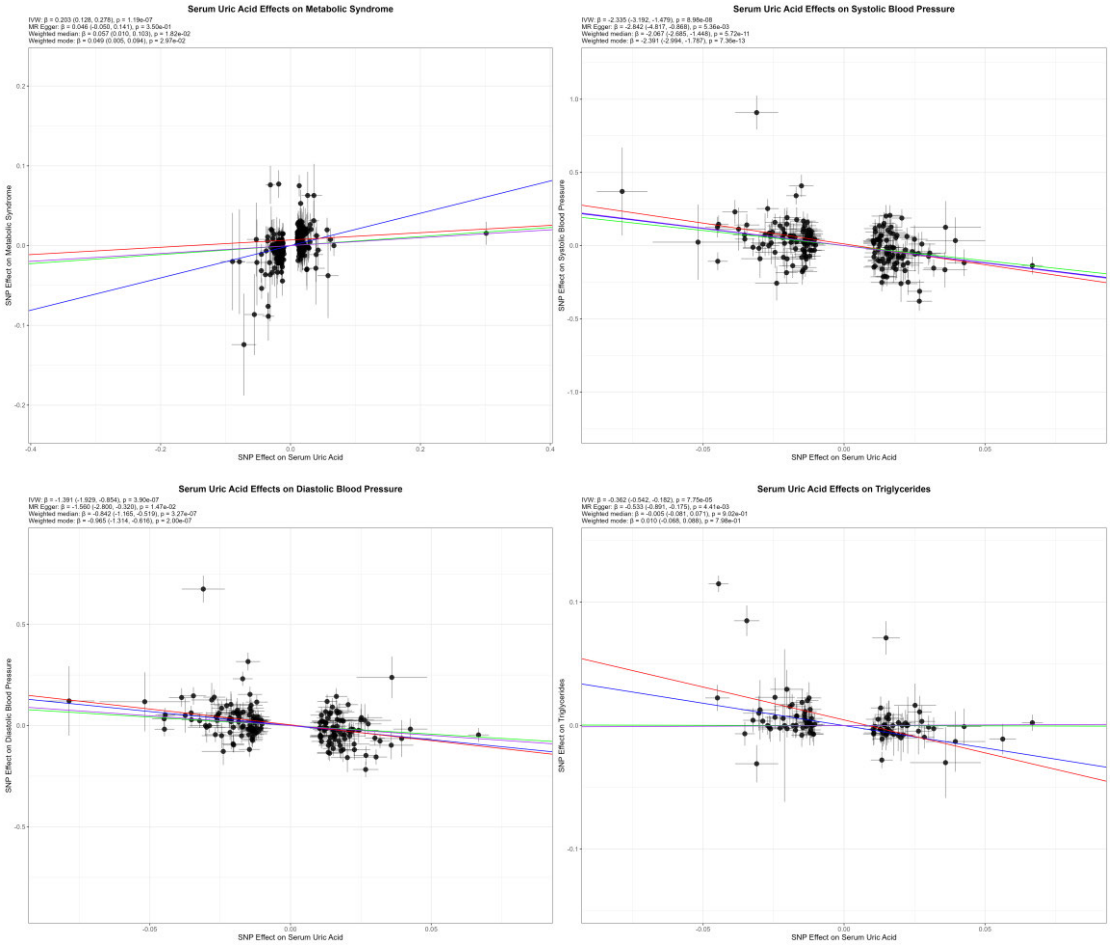


Urea:

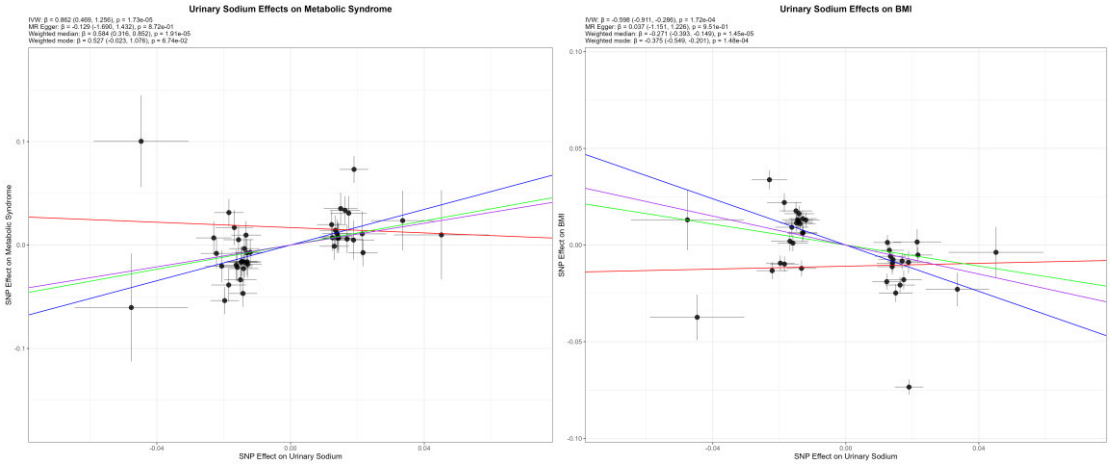




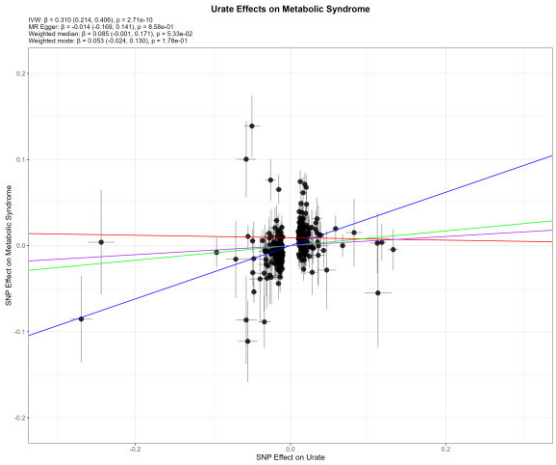
Uric Acid:

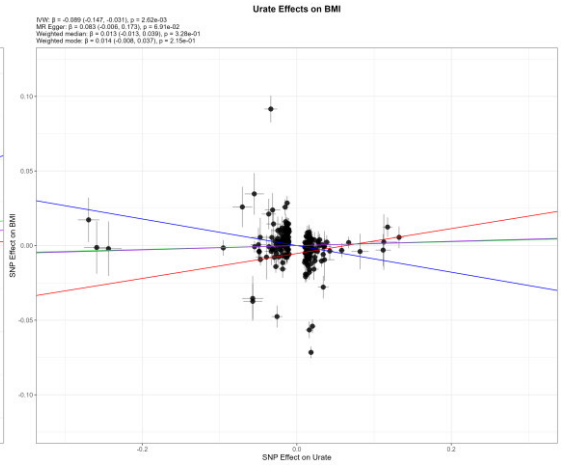


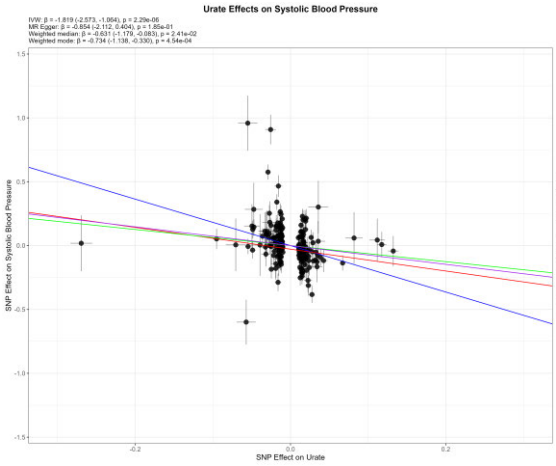
Sodium in Urine:

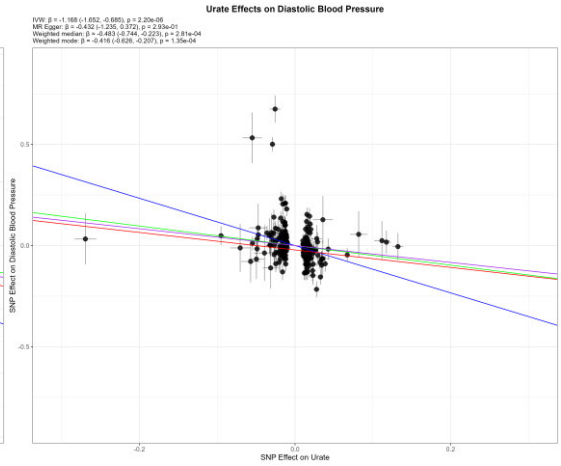


Urate:


Urate Effects on Metabolic Syndrome
IVW: β = 0.310 (0.214, 0.406), p = 2.71e-10
MR Egger: β = -0.014 (-0.169, 0.141), p = 8.58e-01
Weighted median: β = 0.085 (-0.001, 0.171), p = 5.33e-02
Weighted mode: β = 0.053 (-0.024, 0.130), p = 1.78e-01
SNP Effect on Metabolic Syndrome
SNP Effect on Urate

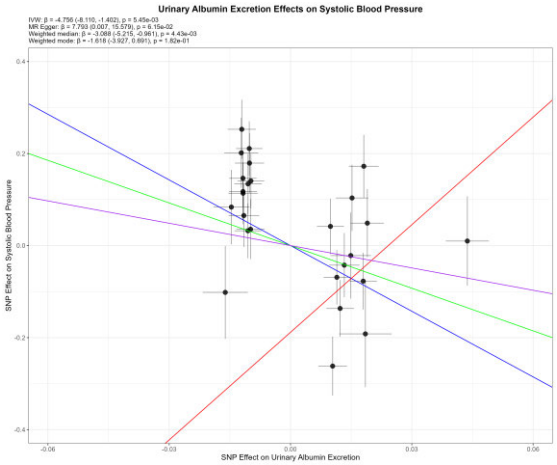

Urate Effects on BMI
IVW: β = -0.089 (-0.147, -0.031), p = 2.62e-03
MR Egger: β = 0.083 (-0.006, 0.173), p = 6.91e-02
Weighted median: β = 0.013 (-0.013, 0.039), p = 3.28e-01
Weighted mode: β = 0.014 (-0.008, 0.037), p = 2.15e-01
SNP Effect on BMI
SNP Effect on Urate


Urate Effects on Systolic Blood Pressure
IVW: β = -1.819 (-2.573, -1.064), p = 2.29e-06
MR Egger: β = -0.854 (-2.112, 0.404), p = 1.85e-01
Weighted median: β = -0.631 (-1.179, -0.083), p = 2.41e-02
Weighted mode: β = -0.734 (-1.136, -0.330), p = 4.54e-04
SNP Effect on Systolic Blood Pressure
SNP Effect on Urate


Urate Effects on Diastolic Blood Pressure
IVW: β = -1.168 (-1.652, -0.685), p = 2.20e-06
MR Egger: β = -0.432 (-1.235, 0.372), p = 2.93e-01
Weighted median: β = -0.483 (-0.744, -0.223), p = 2.81e-04
Weighted mode: β = -0.416 (-0.626, -0.207), p = 1.35e-04
SNP Effect on Diastolic Blood Pressure
SNP Effect on Urate

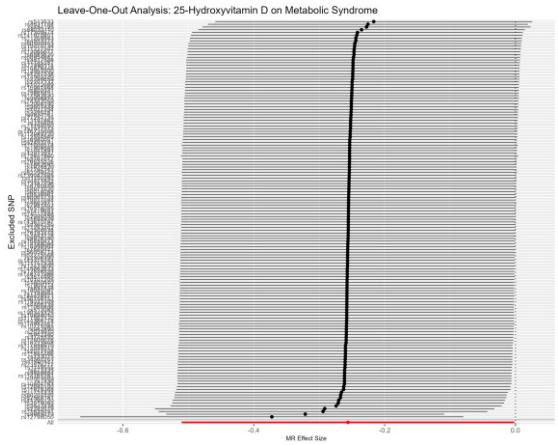

Urate Effects on Triglycerides
IVW: β = -0.299 (-0.444, -0.155), p = 4.81e-05
MR Egger: β = -0.503 (-0.787, -0.218), p = 7.73e-04
Weighted median: β = -0.073 (-0.160, 0.015), p = 1.04e-01
Weighted mode: β = 0.001 (-0.093, 0.094), p = 9.90e-01
SNP Effect on Triglycerides
SNP Effect on Urate

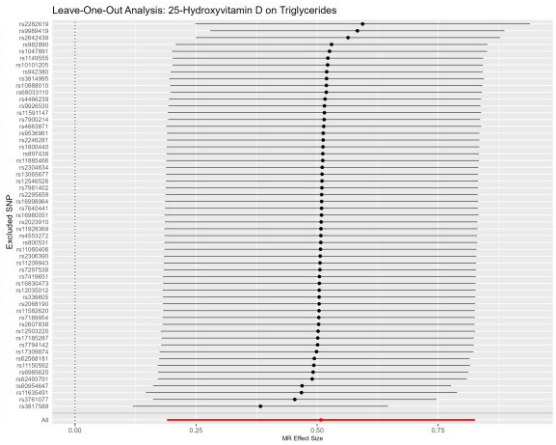
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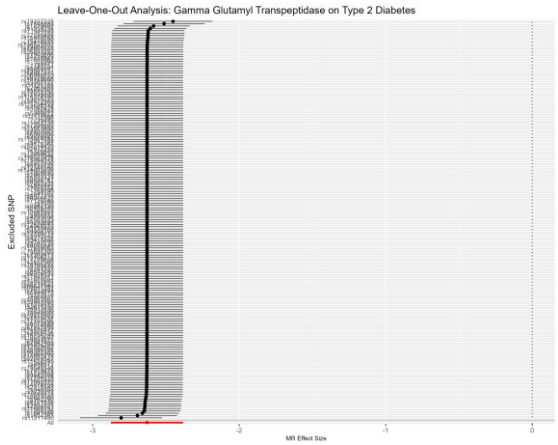
Supplementary Figures 4.5.3 - Leave-one-out Plots - Candidate Biomarkers Effect on Cardiometabolic Traits

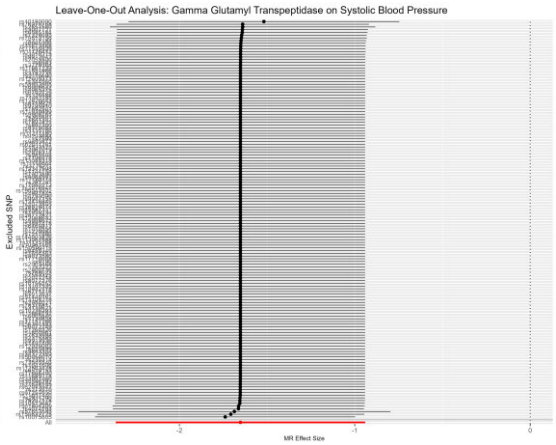
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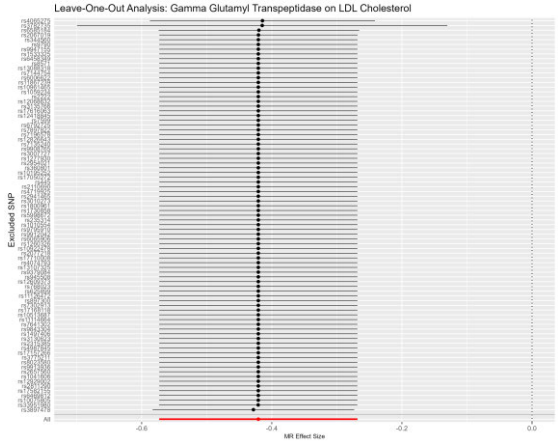




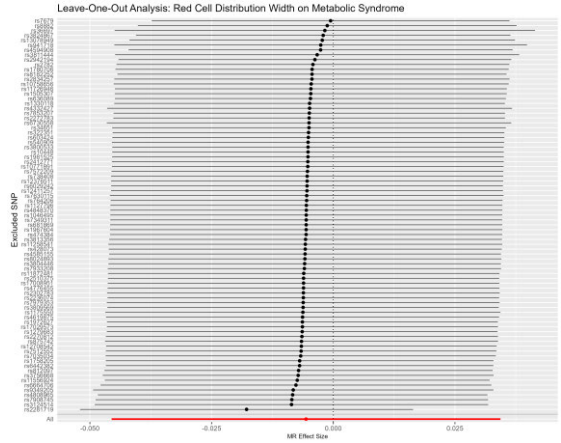
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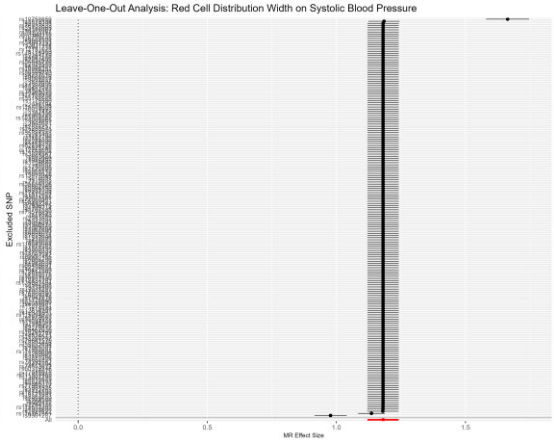


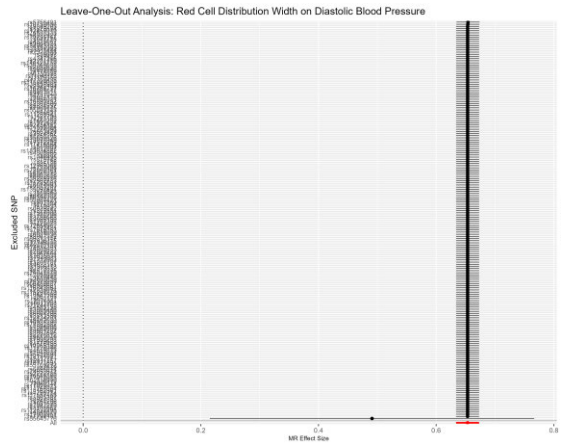


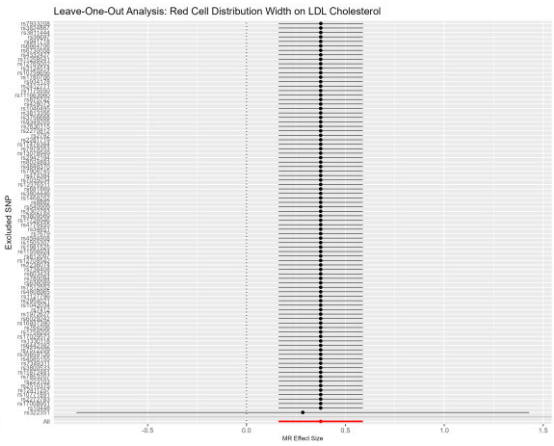


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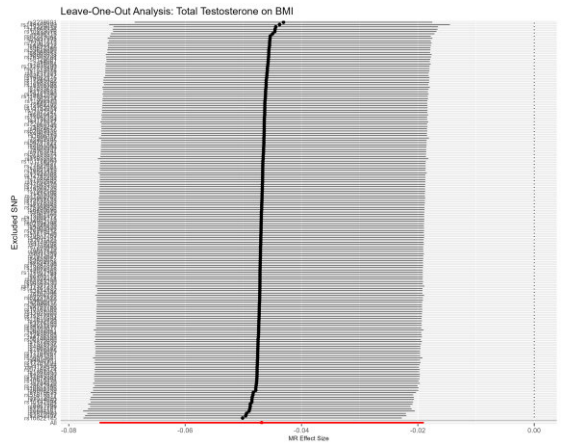




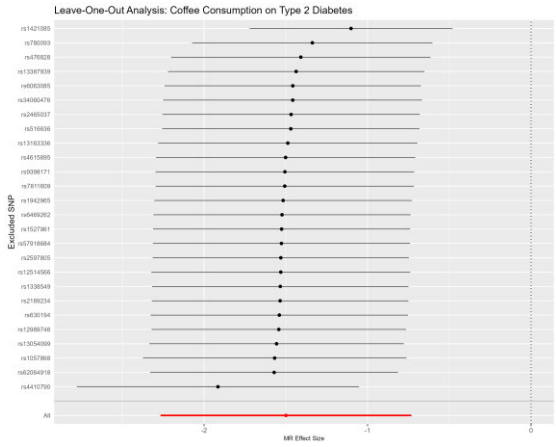


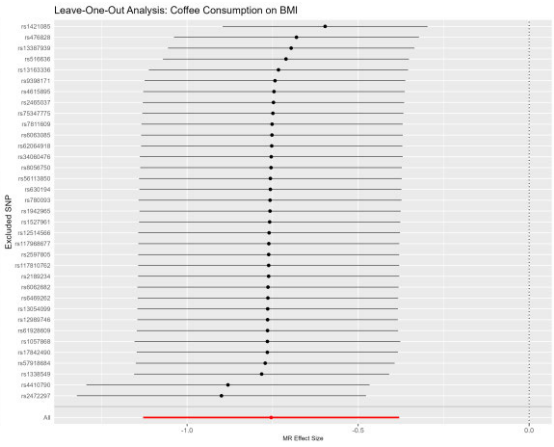


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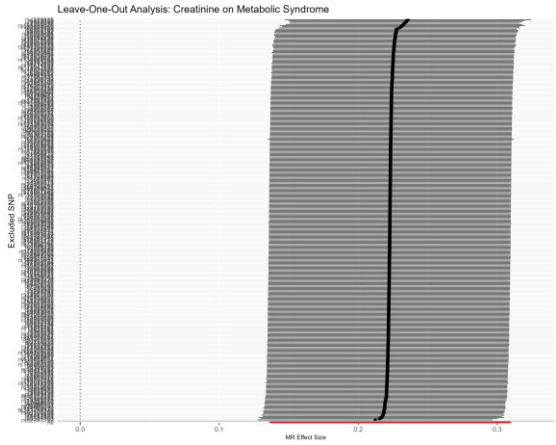


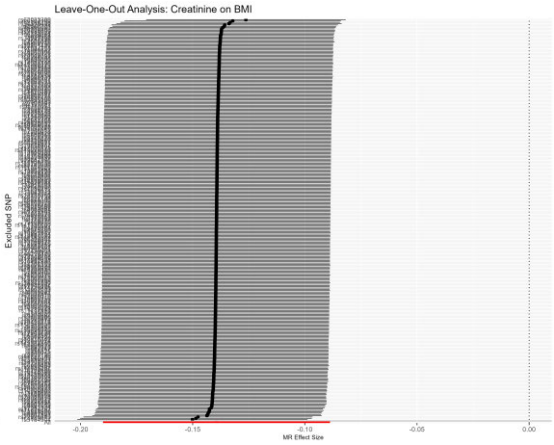
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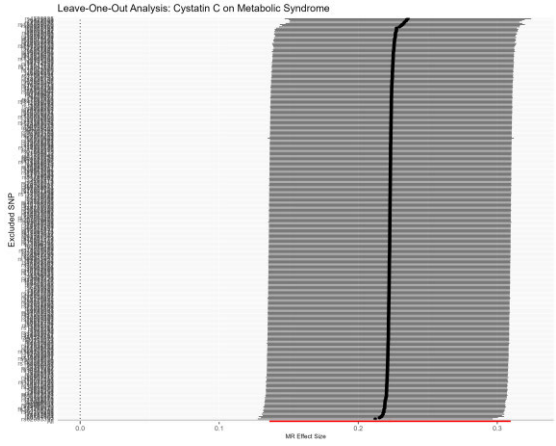


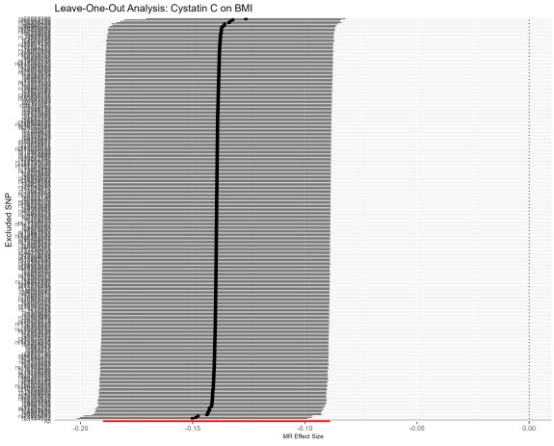
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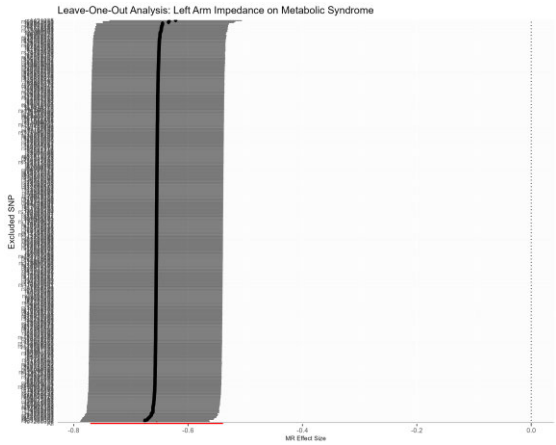


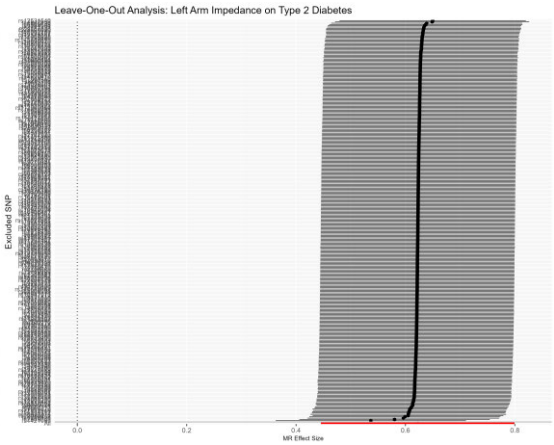
Cystatin C:

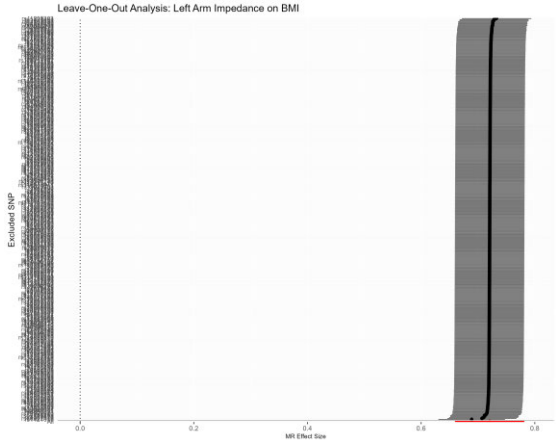


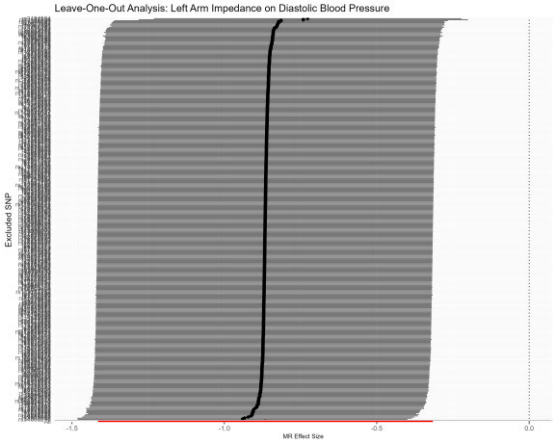


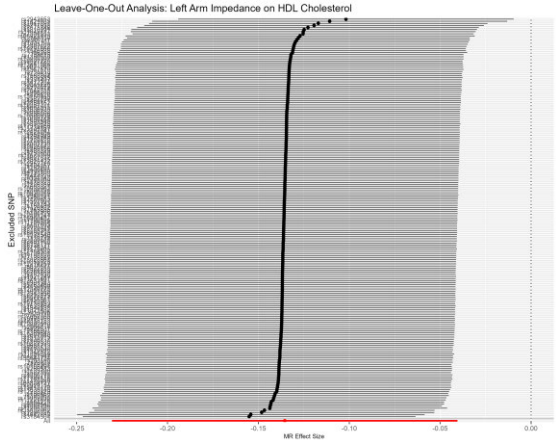
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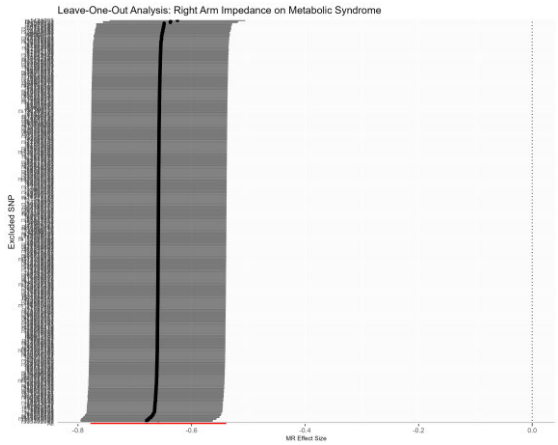


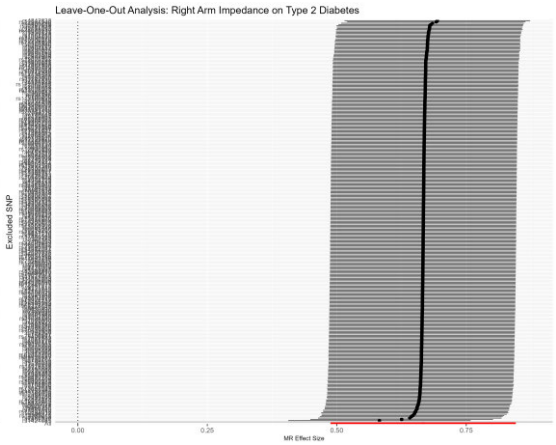


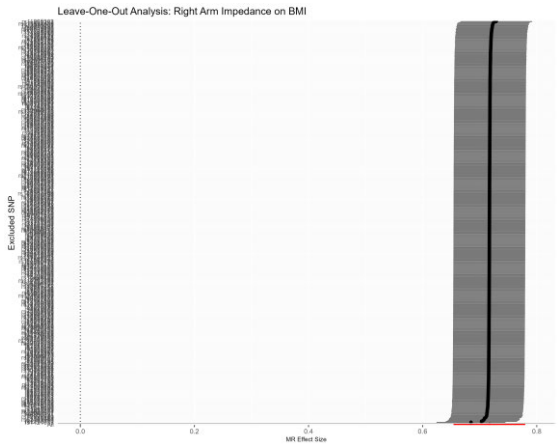


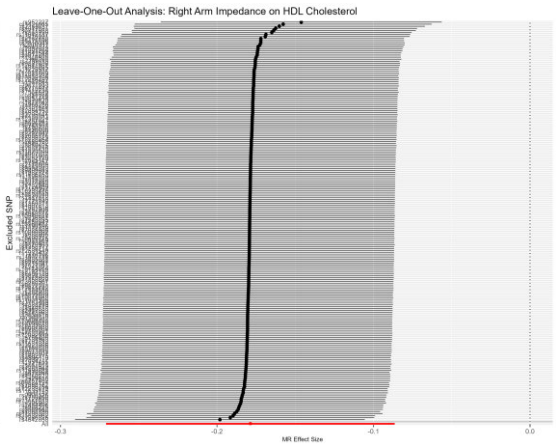


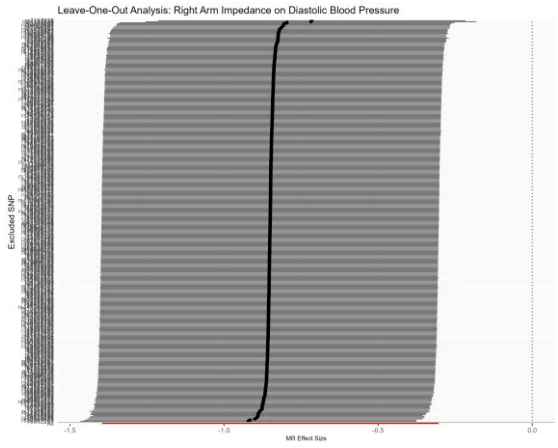
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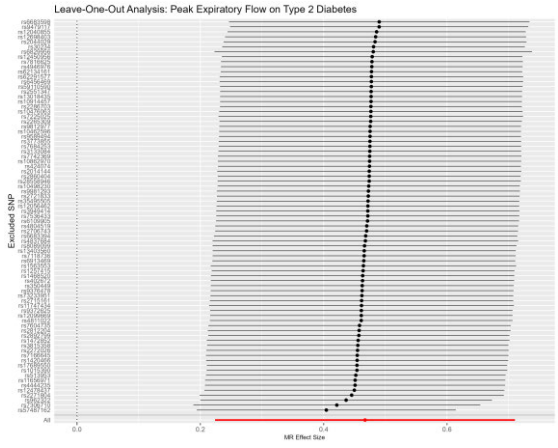




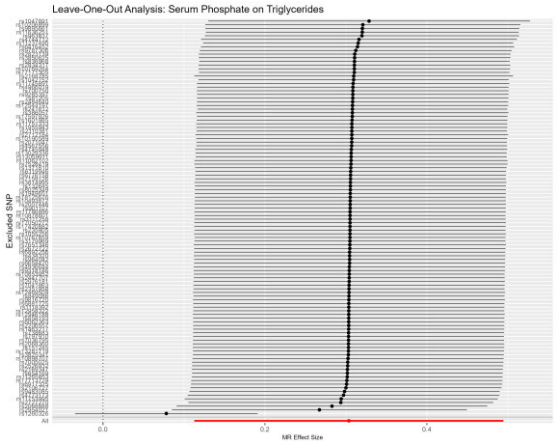




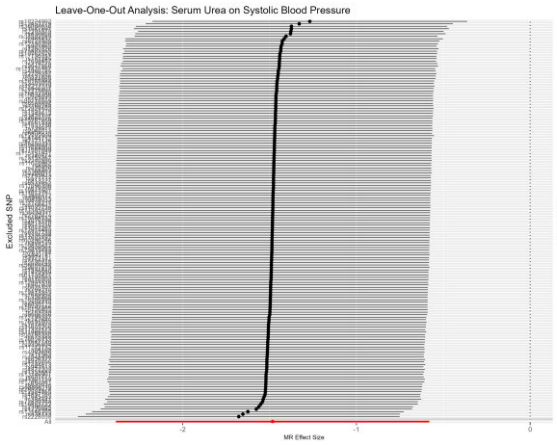
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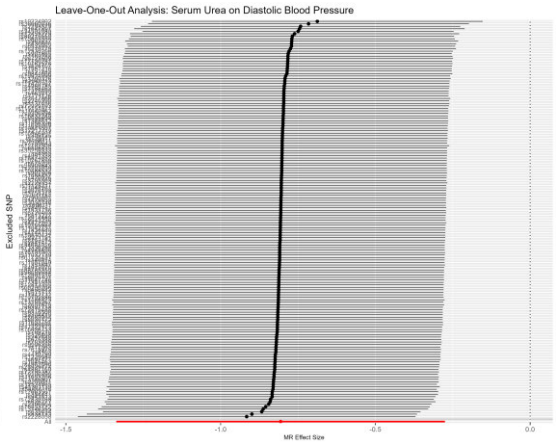


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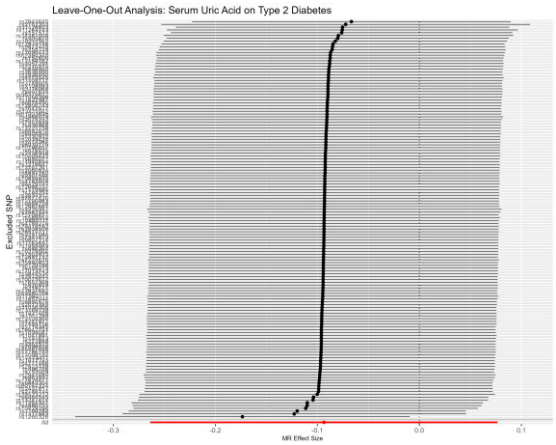


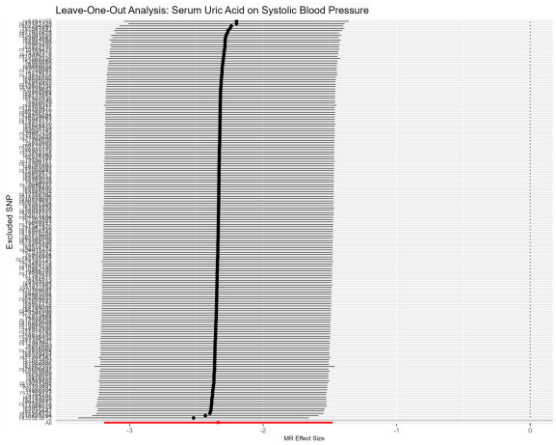
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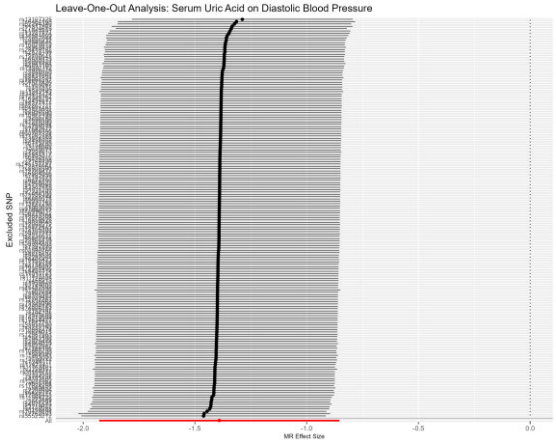


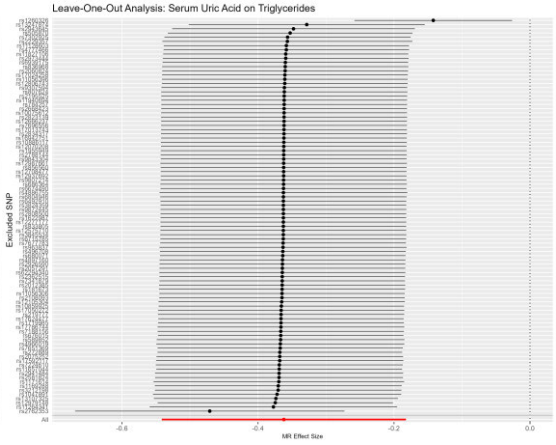


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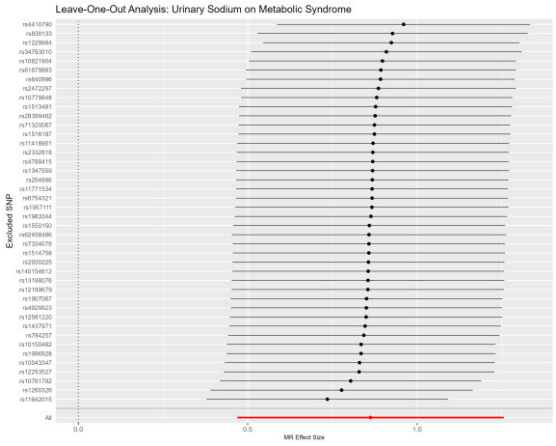


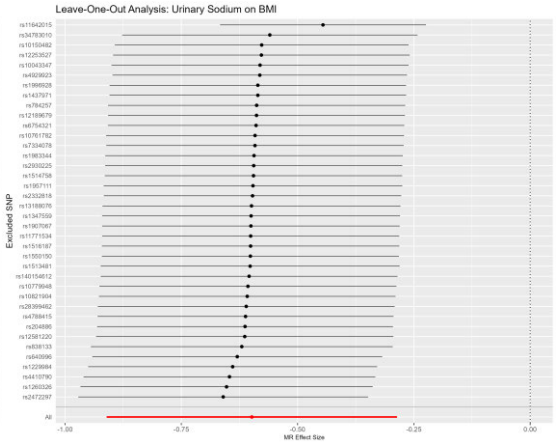




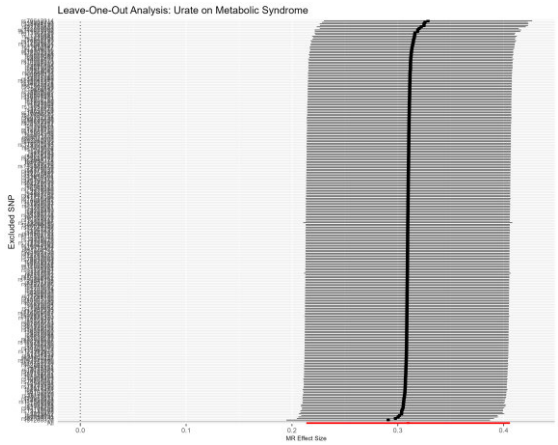


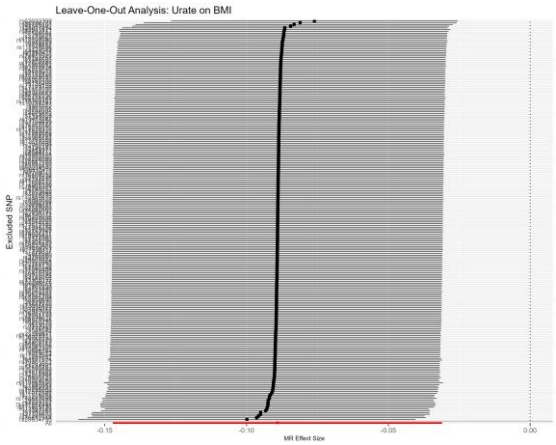
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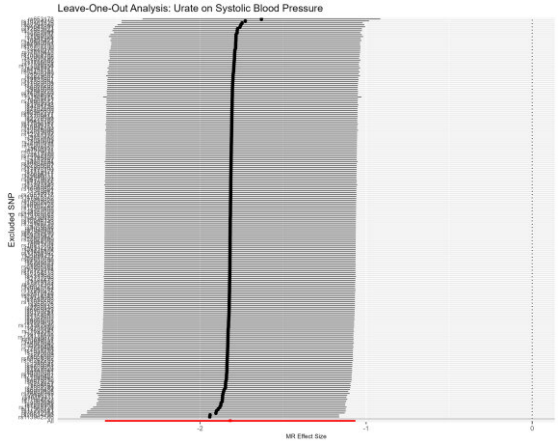


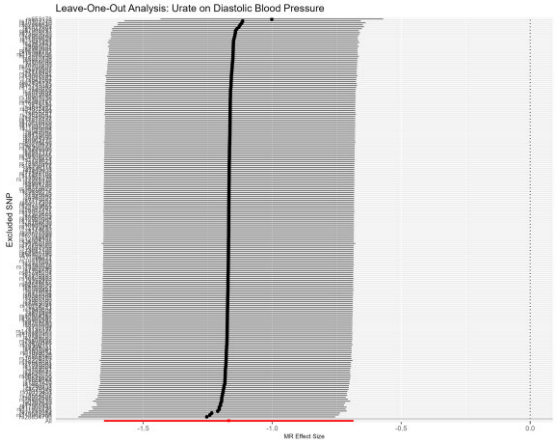


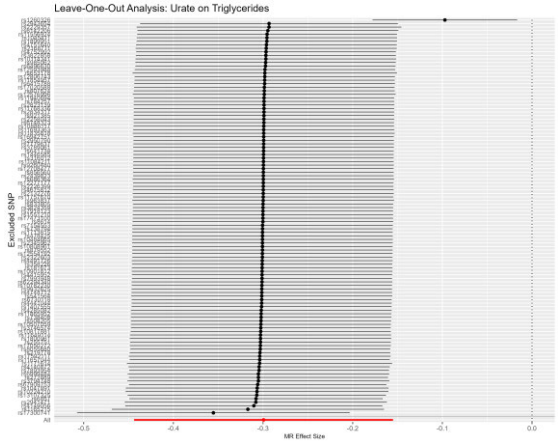
Urate:


Leave-One-Out Analysis: Urate on Metabolic Syndrome
Excluded SNP
MR Effect Size

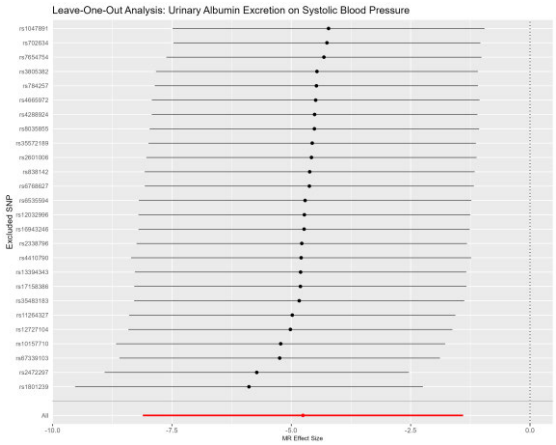

Leave-One-Out Analysis: Urate on BMI
Excluded SNP
MR Effect Size


Leave-One-Out Analysis: Urate on Systolic Blood Pressure
Excluded SNP
MR Effect Size


Leave-One-Out Analysis: Urate on Diastolic Blood Pressure
Excluded SNP
MR Effect Size

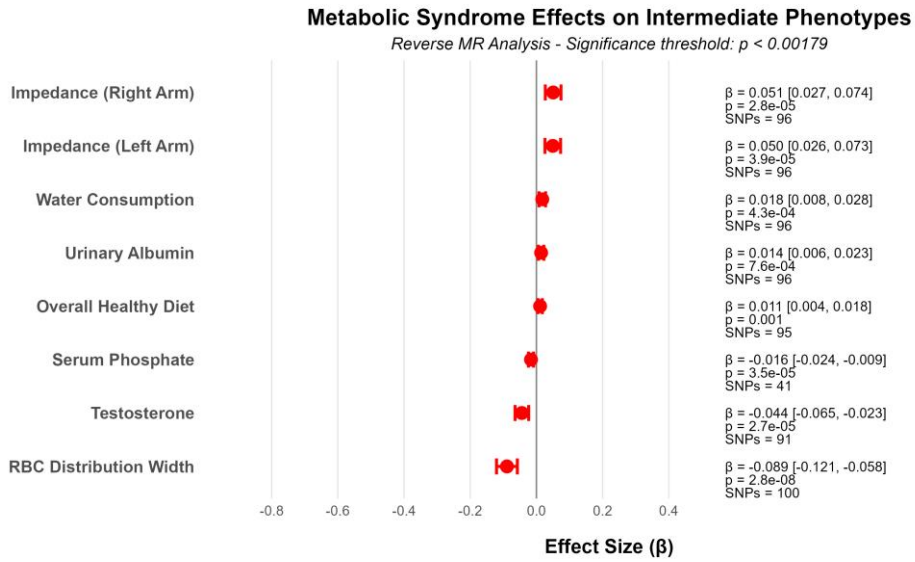

Leave-One-Out Analysis: Urate on Triglycerides
Excluded SNP
MR Effect Size

Urinary Albumin Excretion:

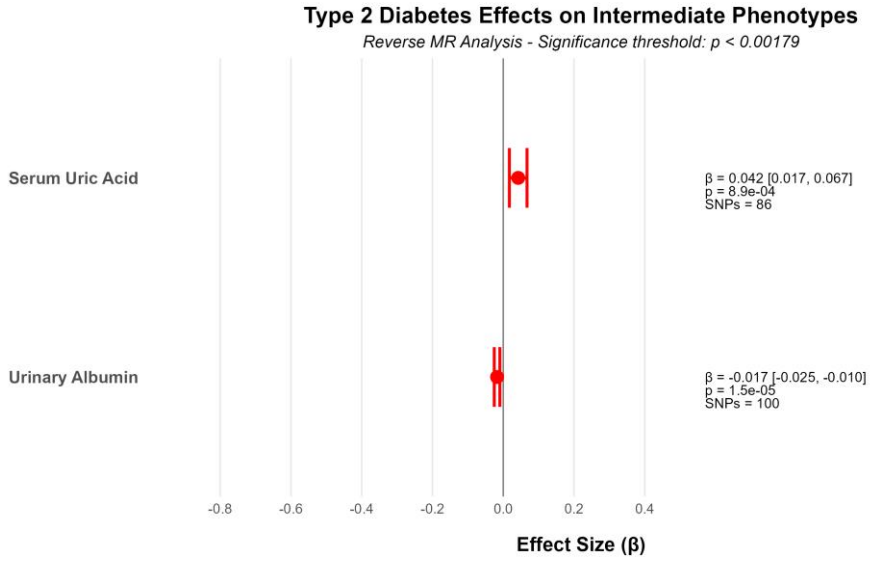


Supplementary Figures 4.5.4 - Forest Plots - Cardiometabolic Traits Effects on Candidate Biomarkers

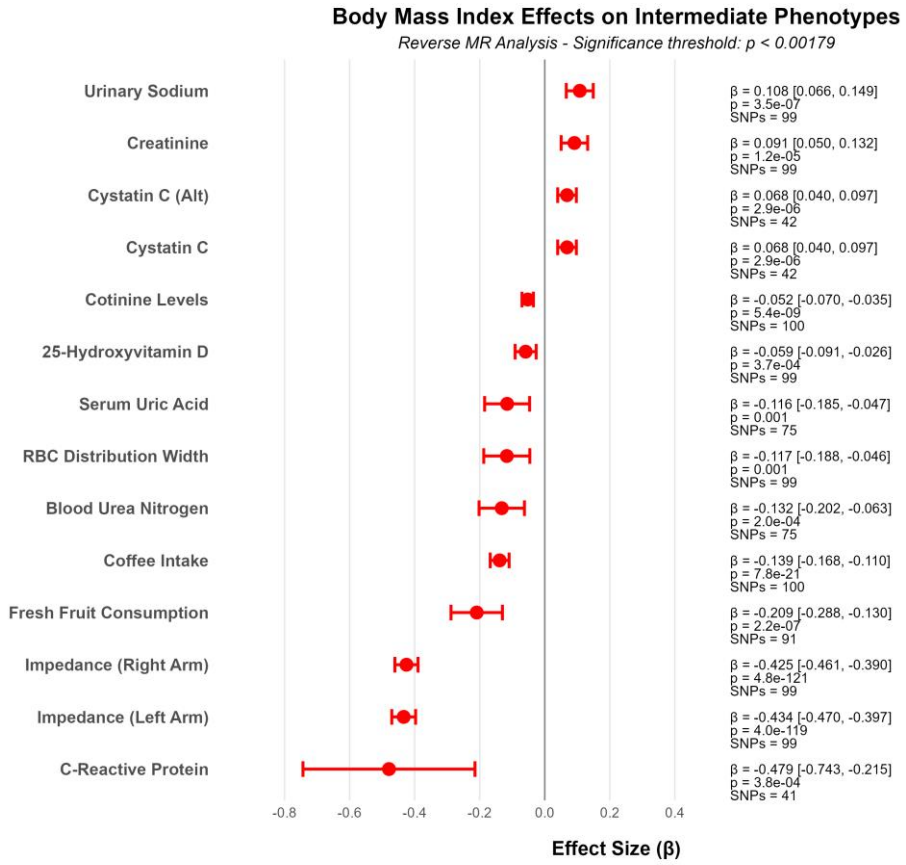
Metabolic Syndrome:



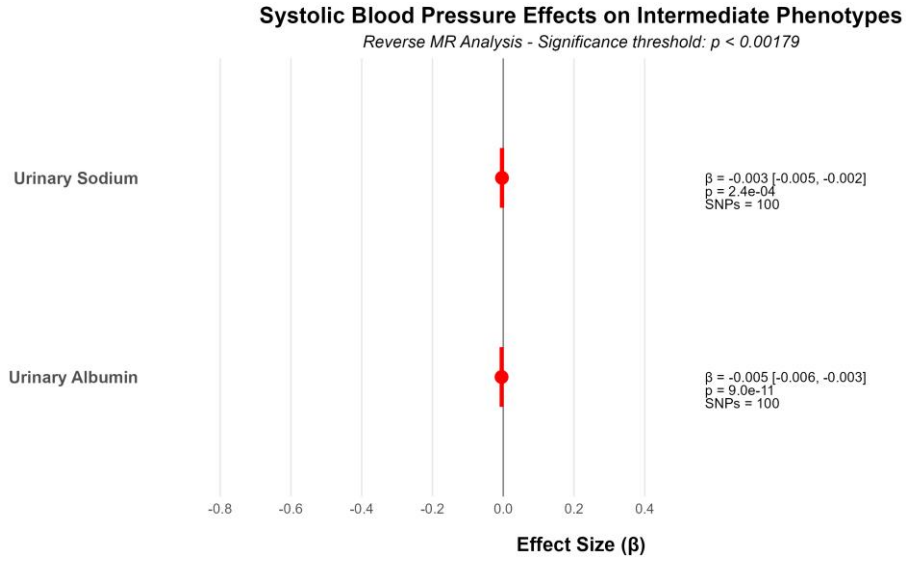
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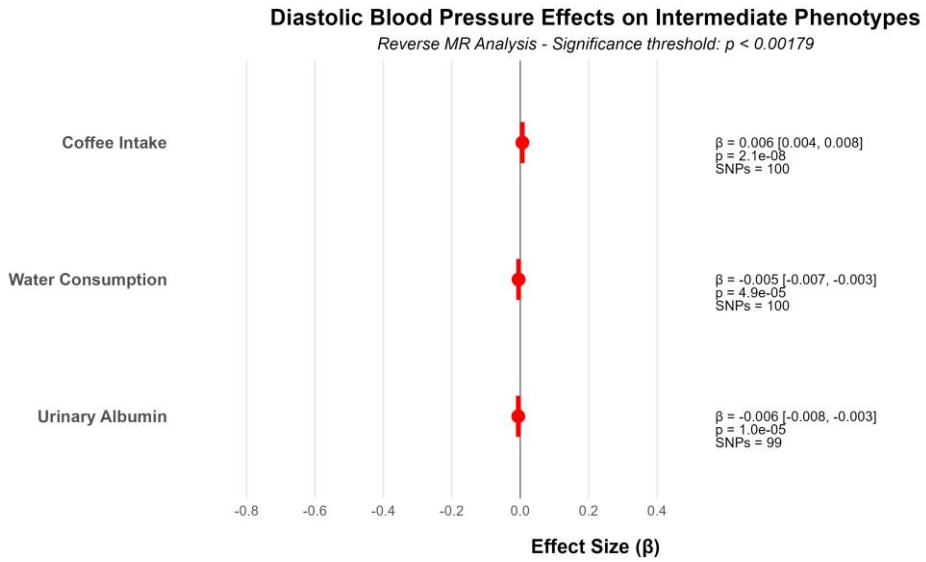
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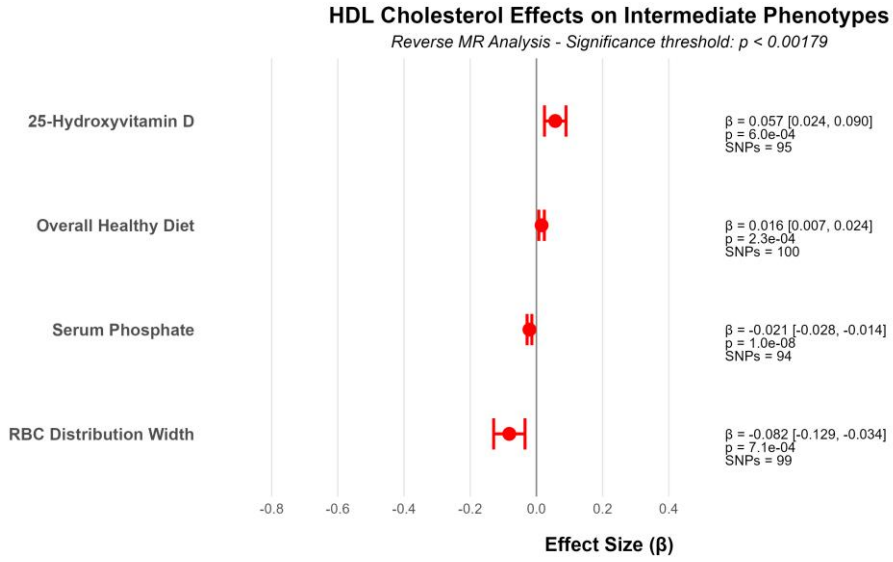
Systolic Blood Pressure:



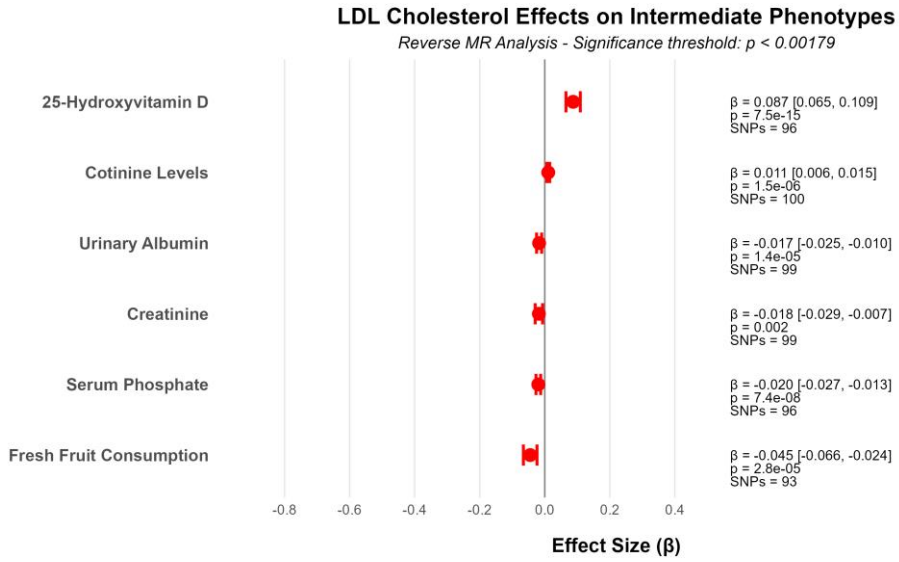
Diastolic Blood Pressure:



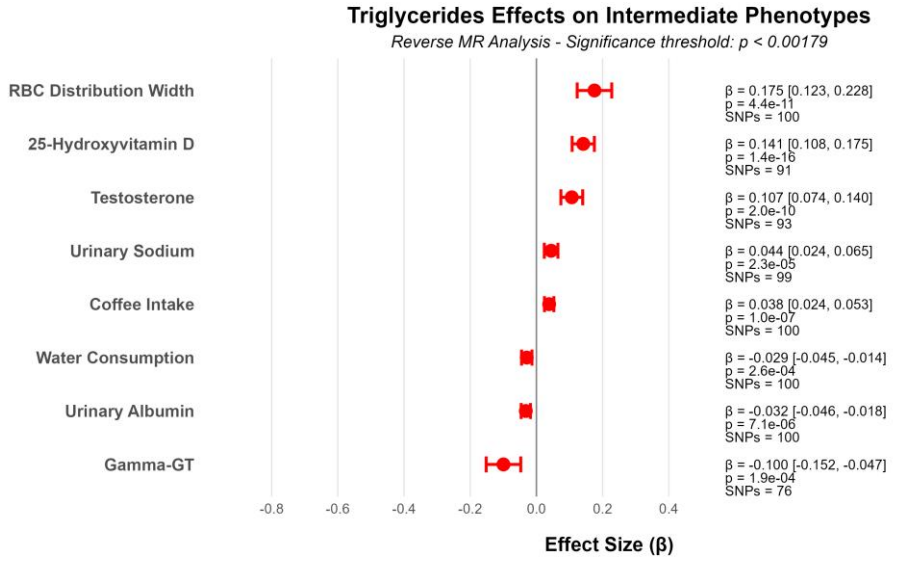
HDL:



LDL:



Triglycerides:

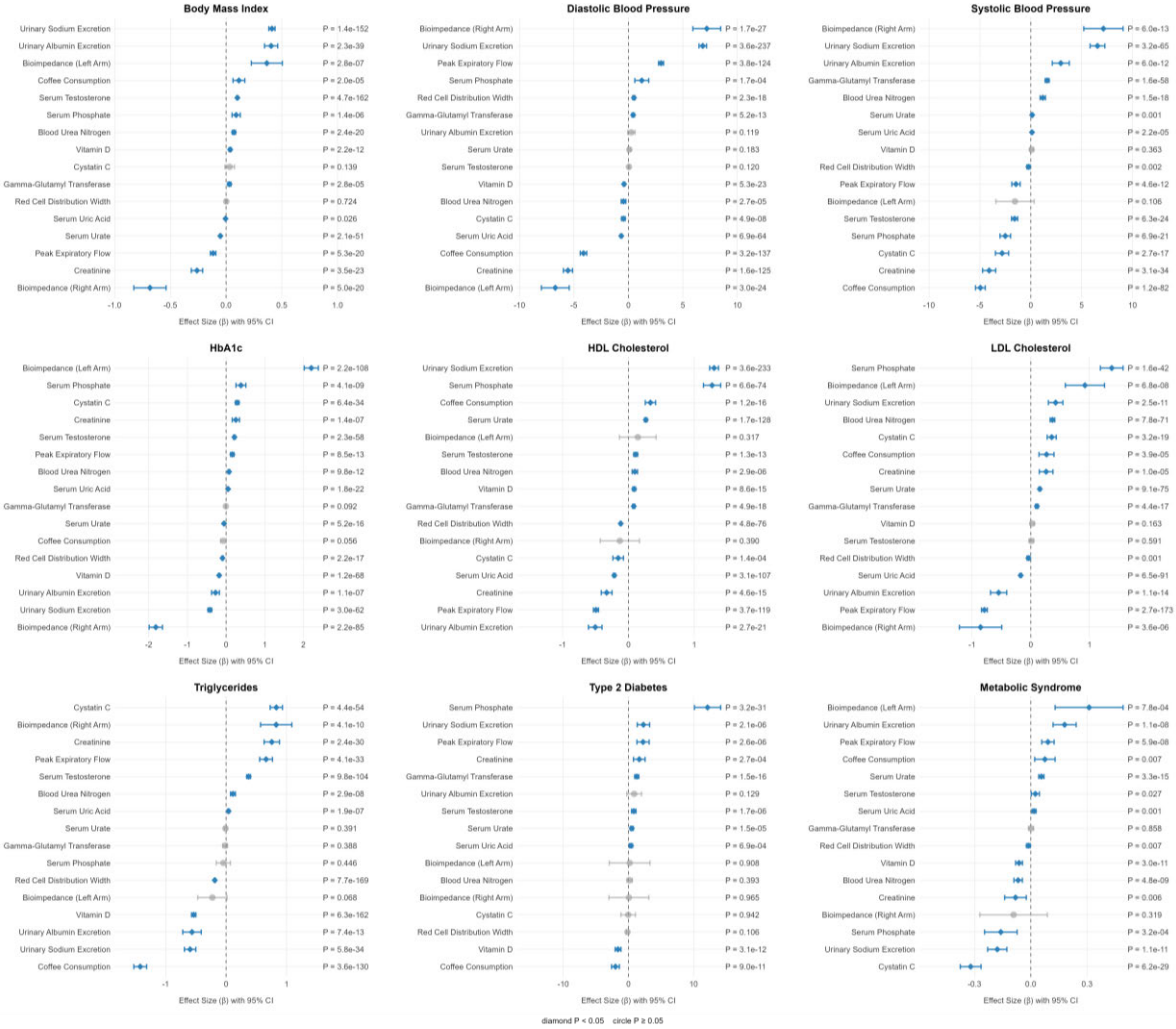


Supplementary Figures 4.6 - Candidate Biomarkers Effects on Cardiometabolic Traits

Forest plots showing multivariable Mendelian randomization results (MVMR) for the 16 candidate biomarkers against cardiometabolic outcomes. Effect estimates (β) with 95% confidence intervals shown. Blue markers indicate P < 0.05 and grey markers indicate P > 0.05. Each biomarker shows independent causal effects despite genetic correlation.

Supplementary Figures 4.6.1 – Forest Plots – MVMR of Candidate Biomarkers on Cardiometabolic Outcomes.....318

Supplementary Figures 4.6.1 – Forest Plots – MVMR of Candidate Biomarkers on Cardiometabolic Outcomes



Appendix D - Computational Methods and Code Descriptions

Overview

This appendix provides comprehensive documentation of the computational methods, software packages, and analytical workflows employed in Chapter 4 to ensure reproducibility. The multi-layered analytical framework integrated MR, PheWAS, and colocalization techniques to investigate causal relationships between clozapine metabolism and cardiometabolic outcomes.

Computational Environment

Software and System Information

Primary Analysis Environment: R version 4.3.3 (2024-02-29)
High-Performance Computing: Unix-based HPC system for PWCoCo analysis National Computational Infrastructure (NCI)
External Tools: PLINK v1.9 for genetic data handling (called from R)
Reference Data: 1000 Genomes European reference panel (EUR)

Genetic Data Quality Control Parameters

Significance threshold: $P < 5.00 \times 10^{-8}$ for genome-wide significance
LD clumping: $r^2 < 0.001$, window = 10,000 kb
Minor allele frequency: MAF > 0.01
Genotype missingness: < 5%
Imputation quality: INFO > 0.8
Hardy-Weinberg equilibrium: $P > 1.00 \times 10^{-6}$

Core Analyses Code Implementation

All analyses run in R (v4.3.3) excluding statistical colocalization, which was run on NCI HPC system (Unix, command line system).

Primary Mendelian Randomization Analysis (LD-Aware)

IVW (LD-corrected):

- Formula:

$$\hat{\beta}_{IVW} = (X'\Omega^{-1}X)^{-1}X'\Omega^{-1}Y$$

- Incorporates LD matrices (Ω) from 1000 Genomes European panel
- Accounts for correlated genetic instruments

MR Egger (LD-corrected):

- Tests for directional pleiotropy with LD correction
- Provides intercept test:

$$\beta_Y = \beta_0 + \beta_{Egger} \times \beta_X + \varepsilon$$

- LD-adjusted variance-covariance structure

Weighted Median (LD-corrected):

- LD-aware robust estimation
- Consistent when up to 50% of instruments are invalid

```
# Primary analysis: LD-aware methods for clozapine plasma traits → metabolic
outcomes
# Custom LD-aware implementation of core MR methods
# LD-aware methods implemented:

mr_ivw_ld_corrected()                    # IVW (LD-corrected)
mr_egger_ld_corrected()                  # MR Egger (LD-corrected)
mr_weighted_median_ld_corrected()        # Weighted median (LD-corrected)

# Core supporting functions:
harmonise_data()                    # Exposure-outcome data harmonization
```

Inverse Variance Weighted

- Formula:

$$\hat{\beta}_{IVW} = \frac{\sum_{j=1}^{n} \beta_{Y_j} \times \beta_{X_j} \times w_j}{\sum_{j=1}^{n} \beta_{X_j}^2 \times w_j}$$

- Standard IVW without LD correction
- Assumes independent instruments

MR Egger

- Standard pleiotropy assessment
- Intercept term for directional pleiotropy

Weighted Median:

- Formula:

$$\hat{\beta}_{WMed} = Median_{w_j}(\beta_j)$$

Weighted Mode:

- Formula:

$$\hat{\beta}_{WMode} = argmax_{\beta}[\sum_{j=1}^{n} K_h(\beta - \beta_j) \times w_j]$$

- Identifies modal causal effect estimate
- Additional sensitivity analysis for candidate biomarkers

```
# Intermediate analysis: Standard MR methods for colocalized phenotypes → metabolic outcomes
# Uses standard TwoSampleMR functions without LD correction
# Standard MR methods:

mr()                            # Main MR function with method selection
mr_egger_regression()               # Standard MR-Egger
mr_weighted_median()                # Standard weighted median
mr_weighted_mode()                  # Weighted mode estimation
mr_heterogeneity()                  # Cochran's Q heterogeneity test
mr_pleiotropy_test()                # Egger intercept pleiotropy test
```

Phenome-Wide Association Study

PheWAS Analysis Parameters:

- Lead variants: 10 genome-wide significant SNPs (Table 3.2) for clozapine plasma levels
- Significance threshold: $P < 5.00 \times 10^{-8}$
- Database: OpenGWAS platform comprehensive GWAS collection
- Filtering: Biological relevance to metabolic outcomes

```
# OpenGWAS API integration

associations()                # Query associations for specific variants
tophits()                     # Extract top genetic instruments
gwasinfo()                    # GWAS metadata retrieval

# PheWAS pipeline implementation:

phewas_results <- list()

      for(variant in lead_variants) {
      associations <- associations(
      variants = variant,
      p1 = 5e-8,
      clump = 0
)
      phewas_results[[variant]] <- associations
}
```

Statistical Colocalization Analysis (HPC-Based)

PWCoCo (Pairwise Colocalization with Conditioning) - Unix HPC Implementation:

- Analysis window: ± 500kb around lead variants
- Reference data: 1000 Genomes European panel (processed for HPC)
- Computing environment: Unix HPC system with dedicated PWCoCo installation
- Threshold: PP.H_4 > 0.80 for robust colocalization evidence
- Conditional analysis: Systematic conditioning on independent signals
- Data preparation: Summary statistics formatted for PWCoCo input requirements
- Formula:

$$PP(H_4) = \frac{P(D|H_4) \times prior_4}{\sum_{j=0}^{4} P(D|H_i) \times prior_i}$$

```
# PWCoCo analysis performed on HPC system
# Custom scripts implementing Bayesian colocalization framework

# Bayesian hypothesis testing framework:
# H₀: No association with either trait
# H₁: Association with trait 1 only
# H₂: Association with trait 2 only
# H₃: Association with both traits, different causal variants
# H₄: Association with both traits, shared causal variant

#Run PWCoCo
./pwcoco
      --bfile ../../"directory"     #Attach reference file (1000 Genomes)
--sum-stats1 ../../"directory"      #Attach summary statistics (trait 1)
--sum_stats2 ../../"directory"                  #Attach  summary  statistics
(trait 2)
--chr X                             #Define chromosome of interest
--maf 0.01                          #Define minor allele frequency

# Input format requirements:
# GWAS summary statistics: CHR POS SNP A1 A2 BETA SE P N
# Reference data: 1000 Genomes European ancestry panel
# Regional windows: ±500kb around each lead variant

# Output format:
# Posterior probabilities: PP.H0, PP.H1, PP.H2, PP.H3, PP.H4
# Bayes factors: BF comparisons between hypotheses
# Conditional analysis results: Independent signals identified
```

Linkage Disequilibrium Score Regression

- Package: GenomicSEM (v0.0.5)
- Reference: 1000 Genomes Phase 3 EUR (503 individuals, ~1.2M HapMap3 SNPs)
- QC filters: MAF > 0.01, INFO > 0.90
- Method: Pairwise genetic correlations for 16 candidate biomarkers
- Clustering: Hierarchical (complete linkage), height threshold = 0.85
- Threshold: $|r_g| > 0.15$ for moderate/strong correlations

```
# LDSC implementation using GenomicSEM
library(GenomicSEM)

# Munge summary statistics
munged_data <- lapply(biomarker_files, function(file) {
munge(file, hm3 = "w_hm3.snplist", info.filter = 0.90, maf.filter = 0.01)
})

# Compute genetic correlations
ldsc_results <- ldsc( traits = munged_data, ld = "eur_w_ld_chr/", wld =
"eur_w_ld_chr/" )

# Hierarchical clustering on genetic correlation distance matrix
rg_matrix <- ldsc_results$S_Stand
hclust_result <- hclust(as.dist(1 - abs(rg_matrix)), method = "complete")
clusters <- cutree(hclust_result, h = 0.85)
```

Multivariable Mendelian Randomization

- Package: MVMR (v0.4)
- Method: Inverse-variance weighted MVMR
- Instruments: Genome-wide significant SNPs ($P < 5 \times 10^{-8}$)
- Strength: Conditional F-statistics (threshold F > 10)
- Analyses: (1) Exploratory; all 16 candidate biomarkers (weak, F < 10)
  (2) Focused renal cluster (strong instruments)
- Formula:

$$\Gamma Y_j = \beta_1 \Gamma X_{1j} + \beta_2 \Gamma X_{2j} + \ldots + \beta_K \Gamma X_{Kj} + \varepsilon_j,$$

```
# MVMR implementation
library(MVMR)

# Format data for MVMR (multiple exposures, single outcome)
mvmr_input <- format_mvmr(
BXGs = exposure_matrix,       # SNP-exposure effects (SNPs × exposures)
BYG = outcome_effects,        # SNP-outcome effects se
BXGs = se_matrix,             # Standard errors seBYG = outcome_se )

# Assess instrument strength (conditional F-statistics)
strength <- strength_mvmr(r_input = mvmr_input, gencov = 0)

# Perform IVW MVMR
mvmr_results <- ivw_mvmr(r_input = mvmr_input)

# Extract independent causal effects
estimates <- mvmr_results$coef
pvalues <- mvmr_results$pvalue
```

Data Management, Processing, and Visualisation

Core Data Handling

Data handling primary run through R, with the exception of statistical colocalization.

```
# Data transformation:

dplyr (v1.1.4)
- filter(), mutate(), summarise() - group_by(), arrange()

# GWAS data harmonization pipeline:

harmonize_gwas_data <- function(exposure_data, outcome_data) {
# 1. Ensure consistent effect allele alignment
# 2. Remove palindromic SNPs
# 3. Quality control filtering
# 4. LD clumping if required
}
```

Statistical Implementation Details

MULTIPLE TESTING CORRECTION

- Formula:

$$P_{adj} = \frac{0.05}{n_{tests}}$$

```
# Bonferroni correction implementation



apply_bonferroni <- function(p_values, n_tests) {
  p_adjusted <- p_values * n_tests
  p_adjusted[p_adjusted > 1] <- 1
  return(p_adjusted)
}
```

Instrument Strength Assessment

- Formulas:

$$F_j = \left(\frac{\beta_{X_j}}{SE_{X_j}}\right)^2, \qquad \bar{F} = \left(\frac{1}{n}\right)\sum_{j=1}^{n} F_j$$

```
# F-statistic calculation for each instrument:

calculate_f_statistics <- function(beta, se) {
  f_stats <- (beta / se) ^ 2
  mean_f <- mean(f_stats)

  # Weak instrument threshold: F > 10
  weak_instruments <- f_stats < 10

  return(list(
    individual_f = f_stats,
    mean_f = mean_f,
    weak_count = sum(weak_instruments)
  ))
}
```

Heterogeneity Assessment

- Formulas:

$$Q = \sum_{j=1}^{n} w_j\left(\frac{(\beta_{Y_j})}{(\beta_{X_j})} - \hat{\beta}_{IVW}\right)^2, \qquad I^2 = \max\left[0,100\% \times \frac{Q - df}{Q}\right]$$

```
# Cochran's Q statistic and I² calculation:
assess_heterogeneity <- function(beta_iv, weights) {

  q_stat <- sum(weights * (beta_iv - weighted.mean(beta_iv, weights))^2)
  df <- length(beta_iv) - 1
  i_squared <- max(0, 100 * (q_stat - df) / q_stat)

  return(list(Q = q_stat, I2 = i_squared, df = df))
}
```

Plink Integration

Plink1.9 used for handling of standardized genetic summary statistics files in conjunction with a 1000 genomes (EUR) reference panel for purposes such as formatting and instrument clumping and selection for subsequent analyses. Plink was called through R.

```
# PLINK operations called from R:

system_plink <- function(command) {
  plink_cmd <- paste("plink", command)
  system(plink_cmd)
}

# LD clumping implementation:

perform_ld_clumping <- function(bfile, clump_snps, clump_r2 = 0.001,
                                clump_kb = 10000) {

  clump_cmd <- paste(
    "--bfile", bfile,
    "--clump", clump_snps,
    "--clump-r2", clump_r2,
    "--clump-kb", clump_kb,
    "--out clumped_results"
  )

  system_plink(clump_cmd)

  # Read clumped results:

  clumped <- fread("clumped_results.clumped")
  return(clumped)
}
```

Visualisation and Output

PRIMARY VISUALIZATION

- ggplot2 (v3.5.1)
  - Forest plots for MR results
  - Scatter plots for instrument-outcome relationships
  - Leave-one-out sensitivity plots

```
#Forest plots for MR results:

create_forest_plot <- function(mr_results) {
  ggplot(mr_results, aes(x = b, y = reorder(outcome, b))) +
    geom_point(size = 3) +
    geom_errorbarh(aes(xmin = b - 1.96*se, xmax = b + 1.96*se), height = 0.2)
+
    geom_vline(xintercept = 0, linetype = "dashed") +
    theme_minimal() +
    labs(x = "Effect Estimate (95% CI)", y = "Outcome")
}

# Scatter plots for instrument-outcome relationships:

create_scatter_plot <- function(harmonized_data) {
  ggplot(harmonized_data, aes(x = beta.exposure, y = beta.outcome)) +
    geom_point() +
    geom_smooth(method = "lm", se = TRUE) +
    theme_minimal() +
    labs(x = "SNP effect on exposure", y = "SNP effect on outcome")
}

# Leave-one-out sensitivity plots:

create_loo_plot <- function(loo_results) {
  ggplot(loo_results, aes(x = b, y = reorder(SNP, b))) +
    geom_point() +
    geom_errorbarh(aes(xmin = b - 1.96*se, xmax = b + 1.96*se)) +
    geom_vline(xintercept = 0, linetype = "dashed") +
    theme_minimal() +
    labs(x = "MR Effect", y = "SNP removed")
}
```

- circlize (v0.3.16)
  - Circular representation of PheWAS results
  - Network visualization of colocalization patterns

```
# Circular representation of PheWAS results:

create_circular_phewas <- function(phewas_results) {
  circos.clear()
  circos.par("track.height" = 0.1)
  circos.initialize(factors = phewas_results$phenotype,
                    x = -log10(phewas_results$p))
  circos.track(factors = phewas_results$phenotype,
               y = -log10(phewas_results$p),
               panel.fun = function(x, y) {
                 circos.points(x, y, pch = 16, cex = 0.5)
               })
}
```


- geni.plots (v0.1.2)
  - Stacked regional association plots
  - LD structure visualization
  - Gene annotation overlays

```
# Stacked regional association plots (using geni.plots):

create_regional_plot <- function(region_data) {
  geni.plots::stack_assoc_plot(
    marker_col = region_data$variant,
    pval_col = region_data$pval,
    pos_col = region_data$position,
    chr_col = region_data$chromosome,
    build = "hg19"
  )
}
```

Data Sources and Access

Clozapine Plasma Dataset

- Genetic instruments for clozapine plasma levels were derived from summary statistics from the CLOZUK2 GWAS (Walters Group Data Repository, Centre for Neuropsychiatric Genetics and Genomics)
- n = 4,495
- Provided variant-level data for clozapine plasma concentration, N-desmethylclozapine (norclozapine) plasma concentration, and clozapine-norclozapine plasma ratio.

Cardiometabolic Datasets

Cardiometabolic outcome data (variant level summary statistics) were obtained from large-scale European GWAS through the OpenGWAS platform and GWAS Catalog, including:

- Metabolic syndrome (GCST009602; n = 291,107)
- Type 2 diabetes (ieu-a-1090; n = 120,286)
- Body mass index (ukb-b-19953; n = 461,460)
- Systolic blood pressure (ieu-b-38; n = 757,601)
- Diastolic blood pressure (ieu-b-39; n = 757,601)
- HDL cholesterol (ieu-a-299; n = 187,167)
- LDL cholesterol (ieu-a-300; n = 173,082)
- HbA1c (ieu-b-103; n = 46,368)
- Triglycerides (ieu-b-111; n = 441,016)

Other Datasets

- Candidate biomarker datasets obtained from the study resulting in a trait hit (PheWAS) via OpenGWAS.
- Schizophrenia summary data obtained from the Psychiatric Genomics Consortium (PGC) used to demonstrate no overlap with clozapine variants (2022, n = 320,404, ieu-b-5099)

Appendix E - Award Certificates

Sheer Science Research Grant



ASCEPT
ASCEPT Pharmacogenomics
Special Interest Group Prize
2024
Proudly presented to
Rory Shepherd
On 4th December 2024
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Associate Professor Nicola Smith
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