Databases as Tools in Ophthalmic Research: Examples and a Machine-Learning Advancement

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1 Abstract

Databases are an increasingly important and frequent tool for research in Ophthalmology. Carefully considering potential sources of bias and appropriate methodology is paramount to drawing accurate conclusions. This thesis aims to demonstrate examples of study designs applied to databases in Ophthalmology and the potential for machine-learning extension. We present the analysis of a small academic epiphora database, the large academic UK Biobank database, and a large national administrative database of vitreoretinal procedures. In addition, we demonstrate the utility of a low-code named entity recognition workflow for constructing an ophthalmic disease registry from free-text electronic clinical records. Using the small academic epiphora database, we examined the correlation of dacryocystography (DCG) and dacryoscintigraphy (DSG) findings in fellow asymptomatic eyes. We found a high rate of DSG abnormalities compared to DCG in asymptomatic eyes. This high rate has important implications for using control eyes in lacrimal imaging studies of functional epiphora. In the UK Biobank, we found systolic blood pressure and pulse pressure were associated with incident primary open-angle glaucoma. In the administrative database study, we found population-wide decreases in the rates of scleral buckle use and increases in rates of vitrectomy for retinal detachment repair in Australia. Finally, we created a machine learning registry database of ophthalmic diseases from free-text electronic clinical records. In conclusion, study designs must be adapted to the structure of pre-existing databases when used for research. This approach contrasts with conventional prospective data collection and requires careful consideration of bias and limitations when designing analyses and interpreting results.

2 Declaration

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4 Publications and Presentations

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1 Chapter 1: Literature Review

1.1 Introduction to databases

A database is previously defined as 'a structured repository of data that allows for ongoing data collection, modification, and retrieval'.[1] Databases are employed across various clinical and administrative domains supporting activities such as risk factor identification, monitoring of outcomes between interventions, and recording routine administration and delivery of healthcare.[2] Databases vary by their 'design, geographic representation, definition of data variables, measurement of outcomes, and verification of data accuracy'.[3] The intended purpose of a database determines the structure of the data it contains.[4] Utilising the potential of databases for research relies on understanding their structure, potential applications, limitations, and sources of bias.[2] This is particularly important given clinicians often encounter databases after their creation. The most common databases clinicians encounter include administrative, registry and academic databases.[4]

1.1.1 Database definitions and characteristics

A registry database is a 'system functioning in patient management or research, in which a standardised and complete dataset including associated follow up is prospectively and systematically collected for a group of patients with a common disease or therapeutic intervention'.[1] There are currently at least 97 clinical registries in ophthalmology, covering a range of conditions, including blindness or low vision, corneal transplantation, glaucoma, cataract and refractive surgery, retinoblastoma, inherited retinal diseases, endophthalmitis or uveitis, ocular trauma, congenital ocular anomalies, and common retinal pathologies.[5] Registry databases are

primarily used to ‘monitor clinical experience and performance’.[4] The data included is limited to monitoring patient interaction with the healthcare system. In addition, registry databases monitor disease prevalence and epidemiology, ‘tracking outcomes and complications of drugs or procedures, recording adverse events’,[5] delivery of healthcare, practice patterns and compliance with standard treatment guidelines.[4] Some registries may collect more extensive data than is typically needed for monitoring healthcare outcomes and therefore become a hybrid registry and academic database.

Academic databases have been defined as ‘an organised and extensive dataset of an inception cohort of a carefully selected subset of patients’. [4] This ‘inception cohort’ could include patients with a specific disease or those who received a therapeutic intervention. The purpose of an academic database is investigational, to generate new knowledge.[4] More detailed and extensive data specific to the disease or research question is collected in an academic database compared to a registry. However, the registry database helps identify a subset of patients for participation in additional research studies. The structure of academic databases differs widely as research questions are limited to the included variables.[6] Academic database development requires clinician expertise and planning to ensure data collection is targeted and not prohibited by cost or time. Academic databases are used for ‘providing population characteristics, identifying risk factors and developing prediction models, observational studies comparing different interventions, exploring variation between healthcare providers, and as a supplementary data source for subsequent studies such as randomised controlled trials.[2,7,8] As global biobanks

become more common,[9] we will likely see an increasing number of studies produced using these large academic databases.

Administrative databases have been defined as 'pre-existing transactional data sets that store information routinely collected for billing purposes'.[10] The data associated with administrative databases is collected as part of routine healthcare delivery, for example, diagnostic and procedural billing codes and prescription data. Administrative databases provide accessible, real-world data on a large population of heterogeneous patients,[11] of which can cover people at the institutional, regional, or national levels.[6] They are not primarily designed for research purposes but instead intended as tools to monitor activity and outcomes to inform policy and service planning. However, due to their size, breadth, established infrastructure and prospective data collection, they are amenable to analysis and hypothesis testing.[12] However, as research is a secondary purpose, administrative databases are prone to bias, particularly coding bias.[13] Hospitals may prioritise coding for reimbursement rather than clinical accuracy,[14] and miss less impactful secondary conditions.[15] In addition, diagnostic accuracy may vary depending on the clinician or by the capability of different institutions to diagnose the disease, for example, if a diagnosis requires specialist imaging or equipment.[14] Furthermore, administrative database studies require careful interpretation of their results as their large sample sizes can produce statistically significant results that are not clinically significant.[16] Administrative databases are inexpensive and readily accessible due to their established infrastructure,[3] and may also be used for longitudinal analysis in cases where patients are followed with unique identifiers,[3] such as the personal identity number in Nordic countries.[17]

1.1.2 Observational data complements randomised controlled trials

Whilst high-quality randomised controlled trials are often considered the rigorist form of evidence; ethical, financial or practical constraints often limit their use.[18-20] In addition, a study design other than a randomised controlled trial may be needed for studies such as those investigating aetiological or prognostic factors for disease.[7] Large observational data obtained from registries and academic databases are increasingly being used to provide evidence in places where it cannot be provided through randomised controlled trials,[5] which is especially important in the case of rare diseases.[21] Randomised controlled trials may be limited in their external validity due to strict inclusion and exclusion criteria. A well-designed registry database may address these constraints through systematic data collection from a large and more representative patient group in which healthcare is provided. The results of such a registry database would be more generalised to routine practice compared to randomised controlled trials and may avoid non-representative samples and selection bias.[5 8] Due to their large sample size, large observational database studies may be better powered to study rare events and small effect sizes, and typically cover a longer period to capture these.[8] In addition, depending on the infrastructure associated with a database, observational studies may minimise to recall bias, non-participation bias, and loss to follow up. [8] Database research plays an important value-adding role in aiding hypothesis generation as the basis for randomised trials, confirming the findings of randomised trials on an unselected population of patients outside of the trial, and evaluating patient-oriented outcomes such as mortality as compared to disease-specific outcomes.[22]

Database studies have had important implications for health outcomes, where other study designs have been impractical. An example of this impact is a recent large longitudinal analysis providing further strong evidence of the association of Epstein-Barr Virus (EBV) with multiple sclerosis (MS). Bjornevick et al. used data from the electronic databases of the Physical Disability Agencies of the US Army and US Navy to identify cases of multiple sclerosis using diagnostic codes between 1993 and 2013.[23] Cases were subsequently confirmed by review of medical records. This database includes a racially diverse population of over 10 million military personnel. All active-duty members are screened for HIV at the start of military service and biennially thereafter. The residual serum from these blood tests is archived (>62 million serum samples). The authors tested samples, including the first available, the last collected before disease onset, and one in between for EBV status. The study included 801 cases of MS with available samples and 1566 matched controls. Only one of the 801 MS cases occurred in an EBV-negative individual in the last sample, which was collected at a median of 1 year before MS onset. The hazard ratio for MS between those who were EBV-positive compared to EBV-negative was 26.5 (CI 3.7 to 191.6). Further, at baseline 35 MS cases and 107 controls were EBV-negative. All but one of the 35 EBV-negative MS cases became infected with EBV during the follow-up, and all seroconverted before the onset of MS. The seroconversion rate among individuals who developed MS during follow-up was 97% compared to 57% among individuals who did not develop MS. The hazard ratio for MS comparing EBV seroconversion versus persistent EBV seronegativity was 32.4 (CI 4.3 to 245.3). Studying the association between EBV has been challenging. Both EBV seronegativity and MS are rare. Thus, it is challenging to find sufficient baseline

EBV-negative subjects to compare the incidence of MS in EBV-positive patients at baseline and those who subsequently develop seropositivity. Previous cohort studies investigating the association between EBV and MS have suffered from few cases,[24] reliant on case-control study designs. Utilising pre-existing databases and infrastructure allowed researchers to provide strong evidence for this association which would otherwise require a study with a lengthy and expensive recruitment and testing process to answer a single research question.

The Surveillance, Epidemiology and End Results (SEER) Registry database has played an important role in cancer research.[25] SEER contains cancer incidence and survival data from population-based cancer registries covering approximately 48% of the United States. The data collected includes patient demographics, primary tumour site, tumour morphology and stage at diagnosis, the first course of treatment, and follow-up for vital status. In the US, SEER is the only comprehensive source of population-based data that includes the cancer stage at the diagnosis and survival time. A variety of epidemiological studies across many cancers have been performed to identify important risk factors, and the use of this database is ongoing. The National Bladder Cancer Study (NBCS) is an early and important example of using SEER data to demonstrate occupational exposures are an important risk factor for bladder cancer. In 1978 the NBCS inaugurated the use of the entire SEER network to conduct a large study to determine whether saccharin increased the risk of developing bladder cancer.[26] Subsequently, NBCS was also used to investigate potential occupational exposures. Earlier descriptive studies of the geographical distribution of bladder cancer suggested a possible aetiological association with industrial areas.[27] Analyses of the NBCS showed associations with truck drivers, [28]

workers exposed to motor exhaust,[29] workers within the chemical,[30] rubber,[31] and plastics industries.[31] Among white men in the United States, it was estimated that 21%-25% of bladder cancer was attributable to occupational exposures.[28] The importance of occupational exposure in the aetiology of bladder cancer is well-appreciated by physicians today and demonstrates the power and utility of such large and comprehensive database studies.

The Medical Information Mart for Intensive Care (MIMIC) database has similarly demonstrated the utility of a large database and has been a landmark development for intensive care research.[32] MIMIC is a large, single-centre database of clinical data of critical care patients of a large tertiary hospital, initially published in 2006 and periodically updated. MIMIC is populated with data from hospital electronic health records, automated critical care information systems, and death registry records. The MIMIC dataset has led to thousands of research articles, with many examples of applications, including both statistical and machine learning analysis.[33] For example, van den Boom et al. investigated the optimal oxygen range for critically ill patients in the intensive care unit (ICU). The authors replicated the study in two databases, the eICU-CRD v2.0 and MIMIC v1.4.[34] The authors investigated the association of oxygen saturation (SPO_2) with in-hospital mortality adjusted for age, BMI, sex, Sequential Organ Failure Assessment (SOFA) score on the first day of the ICU stay, and duration of oxygen therapy. The study included 26,723 and 8,564 ICU stays from the eICU-CRD and MIMIC databases, respectively. Through non-linear analysis, they found the optimal range of SPO_2 was 94 – 98%, with a U-shaped relationship with mortality across both databases. The percentage of time within the optimal range was associated with a decreased odds of mortality (OR of 80% vs

40% of the measurements within the optimal range, 0.42 [CI 0.40-0.43] for eICU-CRD and 0.53 [CI 0.50-0.55] for MIMIC). Prior, studies were limited by arbitrary cut points for oxygen saturation, arbitrary categories of saturation, and infrequently measured arterial oxygen partial pressure. This study demonstrates that large real-world data has the potential to guide clinical practice where evidence is limited and provide data for planning future trials. In addition, the popularity of the MIMIC database has spurned the creation of similar intensive care datasets with varying characteristics,[35] which enable replication studies to strengthen the reliability of database findings.[36]

1.1.3 Database Studies in Ophthalmology

Database studies in Ophthalmology are now frequently encountered.[5] Like in other areas, they use many databases, including administrative claims data, registry data, electronic health records, and biobanks. They have provided important large-scale and real-world insights into a range of conditions. Examples of the use of each of these databases within the field of Ophthalmology will illustrate the wide variety of uses and advantages of a database approach.

Electronic medical records are datasets of large and diverse populations of an institution or network of institutions with the potential to provide valuable real-world insights into surgical outcomes and risk management. A retrospective analysis of risk factors for postoperative pseudophakic macular oedema (PME) by Chu et al. exemplifies the potential of electronic medical record data to provide real-world

insight into postoperative complications.[37] Chu et al. extracted structured clinical data from the electronic medical record system of 8 hospitals across the United Kingdom for an initial 81984 eyes undergoing cataract surgery. The data included gender, laterality, pupil size, surgeon experience, preoperative and postoperative visual acuity, presence or absence of operative complications, diabetic status, Early Treatment Diabetic Retinopathy Study (ETDRS) grade, diabetic maculopathy, and other macular and ocular pathology. Eyes were excluded from analysis if they had prior NSAID use, confounding pathologic features, or no record of diabetes or retinopathy status before and after surgery. They analysed patients in 3 groups, including no risk factors for PME and no diagnosis of diabetes at the time of surgery (35 563 eyes, reference cohort), eyes with ≥1 risk factor for PME and no diabetes at the time of surgery (11 429 eyes), and patients with diabetes and structured assessment of retinopathy (4485 eyes). The authors found that the risk for PME was significantly increased by an epiretinal membrane (RR 5.60, CI 3.45–9.07), previous retinal vein occlusion (RR 4.47, CI 2.56–7.82), uveitis (RR 2.88, CI 1.50–5.51), previous retinal detachment repair (RR 3.93, CI 2.60–5.92), and the occurrence of posterior capsule rupture (RR 2.61, CI, 1.57–4.34). In comparison, prostaglandin use (RR 1.11, CI 0.82–1.51), high myopia (RR 0.82, CI 0.56–1.19), and dry age-related macular degeneration (RR 0.80 CI 0.55–1.14) were not associated with a higher risk of PME. Furthermore, all grades of diabetic retinopathy were associated with an increased risk of PME, and the risk increased linearly with the severity of retinopathy. Strengths of this database included its multi-centre nature in a large population with structured and comprehensive data collection. The database was derived from the National Hospital Service (NHS) EMR system, which services >90% of the population of the United Kingdom, [38] and collects mandated structured

ophthalmological data before cataract surgery.[39] At the time, the study was the largest published cohort of patients with diabetes (4485 eyes) undergoing cataract surgery with precisely defined preoperative and postoperative ETDRS grading of DR. It allowed explicit estimation of risk for each ETDRS grading.[37] In addition, the effect of specific intraoperative complications on the risk of PME was isolated, which had not been performed at a large scale previously. Overall, using electronic medical records in an appropriate setting provided important and novel data regarding the risk of PME for grades of diabetic retinopathy, intraoperative complications and copathology.

The Intelligence Research in Site (IRIS) Registry is a well-known data registry showing important insights into ophthalmic surgical outcomes. The American Academy of Ophthalmology developed the IRIS Registry in 2014 to provide real-time and real-world data for 15 quality-control measures and 22 outcome measures for >60 million patients.[40] The IRIS Registry includes patient demographics, insurance and provider geographic information, medications, past medical history, and diagnostic and procedural codes. In addition, the registry contains clinical information such as visual acuity, intraocular pressure, and laterality. The addition of this clinical data is distinct from data in administrative databases. The IRIS Registry has provided real-world monitoring of postoperative endophthalmitis after cataract surgery. Pershing et al. investigated the incidence of endophthalmitis in 8 542 838 eyes in the IRIS registry, which underwent cataract surgery between 2013-2017.[41] In addition, they investigated several risk factors and post-endophthalmitis visual recovery. A total of 3629 eyes suffered acute postoperative endophthalmitis. They found an incidence rate of 0.04% overall, however, the incidence was higher in those

aged 0-17 years (0.37% over 5 years) and 18 to 44 years of age (0.18% over 5 years) compared to those aged 45 to 64 years of age (0.05% over 5 years). Furthermore, they identified that endophthalmitis occurred 4 times as often in cataract surgery combined with other ophthalmic procedures than in cataract surgery alone and a similarly higher rate when combined with anterior vitrectomy (0.35%). The authors also provided real-world data on visual outcomes, showing that, on average, vision remained poor at 6/30 at 3 months post-surgery, but 44% achieved 6/12 or better, and 4% achieved 6/6. The study's strengths included a large sample size which contained a broad age range, including younger patients and those greater than 85, compared to smaller sample sizes and limited age ranges in prior studies of administrative data or institution-specific data. Given the rarity of endophthalmitis, large databases afford important opportunities to investigate risk factors and monitor incidence and outcomes across a large heterogenous sample.

The US Medicare network is a widely used source of administrative data that similarly includes data for large and diverse populations interacting with healthcare systems, useful for confirming trends and associations in a real-world setting. Tseng et al. retrospectively investigated 1-year fracture incidence in 1 113 640 US Medicare beneficiaries aged 65 years and older diagnosed with cataracts from 2002 through 2009.[42] Out of this sample, 410 809 participants underwent cataract surgery during the study period, and 13 976 participants sustained a hip fracture. The adjusted odds ratio for hip fracture within 1 year in those who had cataract surgery compared to those that did not was 0.84 (CI 0.81-0.87). This analysis was adjusted for age, sex, ethnicity, geographical location, systemic comorbidities, Charlson Comorbidity Index (CCI), ocular comorbidities, cataract severity and presence of

physically limiting conditions. Furthermore, participant subgroups who experienced lower odds of hip fracture included patients with severe cataracts, patients most likely to receive cataract surgery based on the propensity score, patients 75 years and older, and patients with a CCI score of 3 or greater. This administrative database analysis demonstrated the real-world impact of cataract surgery in reducing the risk of hip fracture in those aged >65 years in a large and diverse population. Prior similar studies were limited to older women in smaller sample sizes.[43,44] Large administrative datasets are accessible resources for investigating longitudinal associations in the real-world environment across a diverse population, including large age ranges. In addition, the breadth of data allows the investigation of multi-disciplinary outcomes not limited to the data collected by a single speciality or targeted registry.

Biobanks are increasing, collecting a wide variety of clinical, laboratory and genetic data to create rich and varied datasets over large populations.[45] The genetic data collected as part of the UK Biobank has enabled the discovery of an increasing number of genetic associations with open-angle glaucoma. The UK Biobank is a cohort of over 500,000 participants that contains a vast amount of structured sociodemographic and health data collected through structured interviews, questionnaires, physical assessment, radiological imaging, blood work and genetic sequencing.[46] Additionally, a proportion of the cohort underwent ophthalmic investigations, including eye-related measurements such as intraocular pressure. Craig et al. conducted a genome-wide association study (GWAS) of intraocular pressure in 139,55 participants across three databases, including the UK Biobank, EPIC-Norfolk,[47] and the International Glaucoma Genetics Consortium.[48,49] In

addition, associations with 120 significant IOP loci with glaucoma were investigated among UK Biobank participants not included in the GWAS and participants with primary open-angle glaucoma in the NEIGHBORHOOD cohort study.[50] The study found 14 single-nucleotide polymorphisms (SNPs) that were associated with diagnosed primary open angle glaucoma. For these SNPs, there was a notable association between the effect size for IOP and primary open angle glaucoma suggesting the effects were mediated through IOP. A subanalysis showed the effect sizes were larger in high tension-glaucoma compared to normal-tension glaucoma. Given glaucoma is a complex heritable disease, a comprehensive knowledge of the genetic associations contributing to severity and progression will enable future risk stratification and may have important implications for screening. Polygenic risk scores have been developed using the genetic findings of these large database studies.[49] The combined genetic and clinical data in large databases will have an important role in interpreting the effect of environmental variables on the development and progression of open-angle glaucoma.[51,52]

1.1.4 Limitations of database research

Observational research conducted using databases exhibits inherent and important limitations.[53] These limitations may include treatment bias, missing and inaccurate data, inability to establish causality, unmeasured confounding variables or lack of data granularity, varying generalisability, misclassification bias, and changing eligibility over time.[3] Observational research, although an important tool for exploring hypotheses and associations, cannot establish causal relationships due to this inherent potential for bias.[54] A greater understanding of the disease and factors that influence outcomes following treatment is needed in a way that has less impact on randomised controlled trials that can avoid this bias through study design. Similarly, investigation of therapeutic interventions is limited as treatment selection is not randomised and dependent on 'patient, physician and institutional characteristics and preferences'.[18] Furthermore, accurate interpretation of associations depends on the informed adjustment of confounding variables for fair comparisons. However, this may be limited by the availability or granularity of relevant variables. Thus, although databases are alluring due to their often large sample size and ease of analyses, their analyses are complicated, and thoughtless analysis without careful examination of potential pitfalls yields inaccurate results.[55]

To summarise thus far, the aimless collection of data provides no benefit to interested parties.[56] Interrogating a database without a clear and informed conception of research questions within the limitations of available data and acknowledgements of biases is misguided and likely to produce poor results.[57] This thesis demonstrates the differential use of databases of different structures, sizes, and data sources in Ophthalmology, with commentary on the structure, limitations and bias present in each.

1.2 Lacrimal Imaging in Epiphora

1.2.1 Overview of Epiphora

Epiphora is the abnormal overflow of tears from the eye onto the face.[58] Although the prevalence of epiphora in the general population is unknown,[59] it is a common cause for referral to the oculoplastic clinic. Epiphora impacts quality of life and affects various activities such as reading, driving, household tasks and outdoor activities.[60]

There are numerous causes of epiphora necessitating a thorough clinical evaluation. The most common causes of epiphora are reflex tearing due to dry eyes,[61,62] and nasolacrimal duct obstruction.[63-65] Other less common causes of epiphora include eyelid laxity and malposition, functional obstruction, lacrimal hypersecretion, anterior segment disease (e.g. pterygium) and combinations of these described as multifactorial. The incidence of these causes varies by aetiology.[66] Similarly, age, gender and laterality show associations with specific aetiologies. Female gender is associated with unilateral epiphora, [61,65] [67] nasolacrimal obstruction, and upper lacrimal system obstructions such as punctal stenosis and canalicular obstruction. [61,68] In contrast, the male gender is associated with bilateral epiphora, [61,65] and eyelid malposition. [61,68] Nasolacrimal duct obstruction is more commonly unilateral.[67,68] The mean age of those presenting with epiphora varies between 55.9-69.4 years.[61,62,65,66,68,69] Upper lacrimal system obstructions are more common in younger age groups, whereas eyelid malposition is more common in older people.

[61,68] Risk factors for nasolacrimal duct obstruction include age, glaucoma, allergic conjunctivitis, dry eye, and allergic rhinitis.[70] Punctal stenosis is associated with chronic blepharitis and ectropion; however, many cases have an unknown cause.[71]

1.2.2 Current approaches to lacrimal imaging in the evaluation of epiphora

There are no consensus guidelines for the evaluation of epiphora. However, a comprehensive clinical assessment is required to identify the likely aetiology correctly. This is performed through a range of clinical tests and lacrimal imaging. Clinical tests assess the tear film's integrity, tear production and drainage. Assessment of the tear film includes measurement of the tear meniscus height, the tear film break-up time, and Schirmer's tests.[58] Assessment of lacrimal drainage includes the fluorescein dye disappearance test, Jones tests, probing and syringing, and nasal endoscopy. However, there is significant variation in the approach to the workup of cases of epiphora.[72] Conway surveyed American Oculoplastic and Reconstructive Surgery specialists regarding their approaches to a patient with epiphora and patency on syringing. [72] The survey found significant variation in the selection of clinical tests used in the workup of the theoretical patient. Cuthbertson and Webber similarly surveyed hospital-based ophthalmologists in the southwest of England and showed variation in clinical tests performed to evaluate patients presenting with epiphora.[73] In both these surveys, lacrimal imaging studies were infrequently utilised. This was specifically confirmed by Nagi and Meyer, who also surveyed Oculoplastic and Reconstructive Surgery specialists regarding their use of lacrimal imaging. The survey revealed that <5% of respondents routinely used any

lacrimal imaging often; that is, in more than 50% of their patients with epiphora thought to be due to lacrimal obstruction.[74] In addition, 55% and 76% of respondents never used DCG or DSG, respectively. The reasons for the lack of lacrimal imaging utilisation are unclear and may involve access to these studies or a lack of guidance regarding their utility in clinical practice.

1.2.3 Concordance between dacryocystography and dacryoscintigraphy

The main lacrimal imaging studies are digital subtraction dacryocystography (DCG) and dacryoscintigraphy (DSG). DCG was first performed by Galloway et al.,[75] and provided bone-free images of the morphology of the lacrimal drainage system. It is primarily used to identify the location of obstructions and stenosis.[76] DCG has shown utility in delineating unidentified factors of surgical significance in patients with suspected complicated or distorted anatomy or identifying suspected canalicular lesions. [77] The utility of DCG compared to syringing varies between studies, which show the variable correlation between DCG and syringing. [77-79] The interobserver agreement for DCG is moderate and higher than that for DSG,[80] however, the agreement between DCG with syringing and dacryoendoscopy is only fair.[79] DCG can highlight anatomical abnormalities not detectable on syringing or DSG.[77] DSG was first introduced by Rossomondo et al. in 1972.[81] It allows dynamic and physiological assessment of the lacrimal drainage system using a radiolabelled tracer. DSG provides less anatomical detail compared to DCG.[82] However, given DCG requires injection of contrast under pressure, DSG is considered a better representation of physiological function.

DSG and DCG display only moderate concordance. Rose and Clayton examined 66 lacrimal systems with DCG and DSG and found an abnormality in DSG in 77% compared to 51% on DCG.[83] A normal DSG was always seen with a normal DCG. However, 26% showed an abnormal DSG with a normal DCG. The overall concordance was 74%.[83] Similarly, Amanat et al. performed DCG and DSG in 81 symptomatic lacrimal systems.[84] DSG and DCG showed an obstruction in 41 (51%) systems. The agreement between DCG and DSG is similarly variable in the subset of patients with clinically patent but non-functioning lacrimal systems. Peter and Pearson performed both DCG and DGS in 181 eyes patent on syringing and demonstrated the concordance rate was 52%.[85] DSG was abnormal in 80% of symptomatic eyes compared to 57% having an abnormal DCG.

In contrast, a significantly higher concordance rate was seen in a 45 lacrimal systems patent study on syringing by Wearne et al. The authors reported a 91% agreement between DGC and DSG. Variable concordance is likely due to the high rates of abnormalities detected on DSG compared to DCG.[83,84,86] Similarly, there is often poor concordance in the anatomical location of abnormalities, where DSG tends to show more proximal abnormality than DCG.[85,87] This discrepancy is thought to be due to distal abnormalities causing a delay in tear clearance more proximally.

No gold standard exists with which to verify the abnormalities produced on DSG. This is reflected in the poor interobserver agreement for DSG compared to a moderate agreement for DCG. [80] Measuring transit times is unlikely to improve interpretation, given tear transit times vary significantly in normal eyes.[88] Attempts to improve the interpretation of DSG through quantitative methods have similarly shown significant variation in tear transit times in asymptomatic individuals.[88,89] Hilditch et

al. demonstrated that variable clearance is likely a feature of normal tear drainage, given the failure to demonstrate linear clearance in the compartmental analysis of the lacrimal drainage system.[90] It is unclear if the high rates of DSG abnormalities in symptomatic eyes truly represent abnormality or are a product of a highly sensitive study, variable physiological tear clearance, and unreliable interpretation. Furthermore, high rates of DSG abnormalities have been seen in asymptomatic eyes. [84-86,91,92] Amanet et al. performed lacrimal scintigraphy in 240 asymptomatic lacrimal systems of patients with unilateral epiphora and found that 42% showed an obstruction.[91] Similarly, Vonica et al. performed DSG in symptomatic eyes clinical patent on syringing and recorded data for fellow asymptomatic eyes. The authors found similar rates of abnormal DSG between asymptomatic (47%) and symptomatic (48%) eyes.[86] DSG abnormalities in asymptomatic eyes could represent subclinical functional epiphora, subclinical stenosis, or physiological variation in tear drainage.[91]

Asymptomatic DSG abnormalities are important for diagnosing functional epiphora,[93] without an external or anatomical cause attributed to a dysfunctional nasolacrimal system. The significance of a delay on DSG in the setting of functional epiphora, compared to those without delay, is currently unclear. In addition, the correlation between asymptomatic DSG abnormalities with anatomical abnormalities on DCG is unclear. Peter and Pearson performed DCG and DSG in symptomatic eyes with patent but non-functioning lacrimal systems and recorded data for 20 fellow asymptomatic systems.[85] They found that only 4 asymptomatic systems were abnormal on both DCG and DSG, and the DSG was abnormal in 64% of systems with a normal DCG. The clinical significance of these DSG abnormalities in

asymptomatic eyes is currently unclear, particularly in the absence of corresponding DCG data in a larger sample.

1.3 Systemic blood pressure and primary open-angle glaucoma

1.3.1 Current Need for modifiable risk factors in primary open-angle glaucoma

Despite intensive research to identify modifiable risk factors for incident primary open angle glaucoma (POAG), intraocular pressure remains the only modifiable risk factor.[94] Non-modifiable risk factors or glaucoma currently include age,[95] ethnic background,[96,97] family history of glaucoma,[98] and myopia.[99-101] Glaucoma is a highly heritable disease, and there are an increasing number of genetic variants associated with its development. Adult onset glaucoma occurs in the interaction of multiple genetic and gene-environment factors.[102] Polygenic risk scores are increasingly used to predict the risk of developing POAG.[49] Genetic subtypes of glaucoma, such as those related to myocilin gene variants,[103] are a future target of potential therapies to modify the progression or development of glaucoma,[104] but remain non-modifiable at present. Identifying further environmental factors is needed to broaden strategies to prevent the development of POAG.

Cardiovascular risk factors are hypothesised to contribute to glaucoma risk. This is particularly true of systemic blood pressure, given blood pressure has shown a consistent association with IOP.[105-108] Hennis et al. investigated the longitudinal relationship between systemic hypertension and intraocular pressure in 2996 persons without glaucoma at baseline. They found that hypertension was significantly associated with a 4 year increase in IOP.[105] Similarly, Klein et al. investigated the association between systemic blood pressure and intraocular pressure in 4926 participants without glaucoma at baseline.[106] At 5 years follow-up, multivariate analysis revealed an increase of 10 mm Hg in systolic blood pressure

was associated with an increase of 0.2 mm Hg in IOP. Additionally, an increase of 10 mm Hg in diastolic blood pressure was associated with a 0.4 mm Hg increase in IOP. The consistent relationship between blood pressure and intraocular pressure raises questions about whether systemic hypertension is a potentially modifiable risk factor for preventing POAG. Epidemiological studies investigating this association are heterogenous and report conflicting results.[109,110]

1.3.2 Hypertension and open-angle glaucoma

Few case-control studies have observed an association between systemic hypertension and open-angle glaucoma,[111] often limited by small sample sizes.[109] However, in a comparatively large case-control study using the Taiwan National Health Insurance Research Database, including 112,929 cases of POAG, Kuang et al. observed that prior hypertension (identified from diagnostic coding) conferred 1.31 (CI 1.29-1.33) increased odds of POAG after adjusting for age, sex, monthly income, geographic location and residential urbanization level, hyperlipidaemia, diabetes, coronary heart disease, migraine, hypotension, and obstructive sleep apnoea syndrome.[112] Most evidence for an association is derived from cross-sectional studies. However, few cross-sectional studies have observed an association.[110,111] In a cross-sectional study by Sun et al., hypertension (defined as antihypertensives or SBP ≥140mmHg or DBP ≥90 mmHg) showed 2.45 (CI 1.17–5.16) increased odds of open-angle glaucoma after adjusting for age, family history and IOP in a Chinese population.[113] Mitchell et al. similarly observed a 1.56 (CI 1.01-2.40) increased odds of open-angle glaucoma for those with hypertension (SBP ≥

160 mmHg or DBP ≥ 95 mmHg) in the Australian Blue Mountains Eye study.[114] Despite this evidence, longitudinal studies to confirm hypertension as a risk factor for incident open-angle glaucoma have largely failed to show a significant association. The Barbados Eye study is a well-designed prospective longitudinal study with 81-85% participation over 9 years of follow-up, investigating risk factors for incident primary open angle glaucoma. In this study, Leske et al. found no association with either systolic or diastolic blood pressure per 10 mmHg increase or across quartiles after adjusting for age, gender, intraocular pressure and intraocular-pressure-lowering and BP-lowering treatment.[94] Although the authors suggested an association with per 10 mmHg increase in systolic blood pressure, this should be interpreted cautiously given the confidence interval includes 1 (OR 0.91, CI 0.84 – 1.00, p = 0.05). The heterogeneity of these findings is influenced by varying study designs, sample populations, sample sizes and definitions of hypertension, as seen above.[109] Therefore, systemic hypertension likely exerts a weak effect on increasing the risk of open-angle glaucoma. However, given the heterogeneity in study designs and blood pressure targets used, the nature of the association is currently unclear, and further well-powered longitudinal studies are required.

1.3.3 Hypotension and open-angle glaucoma

Systemic hypotension has been associated with structural progression in open-angle glaucoma. Jammal et al. retrospectively analysed the effect of systemic blood pressure on rates of progressive structural damage over time (RNFL loss) in 7501 eyes of 3976 subjects with glaucoma or suspected of glaucoma followed over time from the Duke Glaucoma Registry.[115] The authors found that when adjusted for IOP, each 10 mmHg reduction in mean arterial pressure and mean diastolic blood pressure was associated with significantly faster RNFL thickness change over time. These associations remained significant after adjustment for baseline age, diagnosis, sex, race, follow-up time, disease severity, and corneal thickness. Systolic blood pressure was not significantly associated. Of note, blood pressure measures showed no significance in univariable models and were only significant after adjusting for IOP.

Further, in the Early Manifest Glaucoma Trial, Leske et al. investigated risk factors for progression in patients with higher and lower baseline IOP. The authors found lower systolic blood pressure was significantly associated with progression (≤125 mmHg; HR 0.46, CI 0.21-1.02) in patients with lower baseline IOP.[116] In addition, Lee et al. retrospectively analysed risk factors associated with structural progression in a cohort of 166 patients with medically treated normal-tension glaucoma.[117] Structural progression was defined as significant thickness differences in the peripapillary retinal nerve fibre layer (RNFL) or macular ganglion cell inner plexiform layer (GCIPL) that exceeded baseline test-retest variability. The authors found that lower minimum systolic blood pressure was significantly associated with functional progression (HR 0.968, CI 0.947–0.990). In addition, decision tree analysis showed

systolic and diastolic blood pressure as the most significant variables for progressive peripapillary RNFL thinning and progressive macular GCIPL thinning. Therefore, systolic and diastolic hypotension has been associated with structural progression in open-angle glaucoma when adjusting for IOP or in those with baseline lower IOP.

An association between nocturnal systemic hypotension and progression in glaucoma has also been observed. Graham et al. performed 24-hour ambulatory blood pressure monitoring in 84 patients with either primary open-angle glaucoma or normal-tension glaucoma.[118] Assessment of progression was performed using Humphrey 30-2 visual fields with glaucoma-change probability plots. The authors found nocturnal systolic and diastolic blood pressure measures were all significantly lower in those with visual field progression. In addition, nocturnal systolic and diastolic dips, defined as ≥10% dip from 24-hr mean systolic and diastolic blood pressures, were significantly associated with visual field progression. Similarly, Detry et al. monitored 24-hour ambulatory blood pressure in 36 patients with progressive and non-progressive open-angle glaucoma with satisfactory control of diurnal IOP (IOP ≤21 mmHg).[119] The authors found a significant difference between systolic and diastolic blood pressure dips when comparing the distribution of the nocturnal dip in the progressive and non-progressive groups. Further, Kashiwagi et al. performed 24 hours of ambulatory blood pressure monitoring in 43 subjects with normal-tension glaucoma and 266 controls. They found that blood pressure dips in patients with normal tension glaucoma showed no significant difference from controls, and progressive normal-tension glaucoma subjects showed a smaller dip than stable NTG subjects. Collignon et al. performed 24-hour ambulatory blood pressure monitoring in 51 patients with primary open-angle glaucoma and 19

patients with normal tension glaucoma. Visual field progression was assessed retrospectively using repeated perimetry.[120] The authors found that abnormal nocturnal blood pressure dips (either <5% or >10% dip) were significantly associated with visual field progression in POAG and NTG patients. Additionally, Bresson-Dumont et al. performed 24-hour ambulatory blood pressure monitoring in 83 patients with POAG, normal tension glaucoma and clinically stable IOP.[121] Visual field progression were assessed using perimetry, defined as with newly developed or extended scotoma as the definition of progressive field loss. They found systolic and diastolic dips were significantly associated with progression. A meta-analysis of the above studies conducted by Bowe et al. concluded that nocturnal dips >10% in systolic or diastolic blood pressure conferred 3.32 (CI 1.842-6) and 2.09 (CI 1.20–3.64) increased odds of visual field progression over 2 years respectively. However, there was no difference in mean systolic or diastolic diurnal and nocturnal blood pressure between patients with or without progressive visual field loss. [122]

1.3.4 Mean arterial pressure, pulse pressure, and glaucoma

The association between mean arterial pressure and open-angle glaucoma is less studied. In the longitudinal analysis of the Barbados Eye Study, Leske et al. found no significant association per 10mmHg increase or across quartiles in mean arterial pressure.[94] In contrast, Lee et al., in a study of the All of Us Research Program database, found that compared to medium MAP (83.0 ≤ MAP ≥ 103.3 mmHg), low MAP (MAP < 83.0 mmHg) was associated with an increased risk of developing OAG (HR 1.32, CI 1.04-1.67) after adjusting for age, gender, race, smoking status, and diabetes mellitus diagnosis.[123] No association was found for high MAP (MAP ≥103.3 mmHg). Calculating mean arterial pressure from systemic blood pressure measurements provides an estimate only. There is a range of formulas for MAP, and controversy exists over the correct form.[124] Alternative MAP formulas are better correlated with cardiovascular target organ deterioration, including left ventricular hypertrophy, aortic stiffness, and carotid wall hypertrophy.[124] Therefore, although there is limited evidence for an association with mean arterial pressure, this could reflect the limitations in accuracy with non-invasive estimates of this variable.

Pulse pressure is a similarly understudied blood pressure parameter. Leske et al. showed no significant association per 10 mmHg increase or across quartiles of pulse pressure in the longitudinal Barbados Eye study.[94] Further, in a Korean National Health Insurance Research Database study, Lee et al. investigated the association of fluctuations in pulse pressure with incident POAG. Fluctuations in pulse pressure were represented by standard deviations and coefficients of pulse pressure variation using multiple measurements during follow-up. The authors similarly found no significant association. Despite limited studies showing no association, pulse

pressure has significant associations with cardiovascular disease,[125] which warrants further investigation as part of a vascular hypothesis for open-angle glaucoma.

1.3.5 Proposed vascular mechanisms for the development of open-angle glaucoma

The two major theories proposed to explain the development of open-angle glaucoma include mechanical and vascular theories. The mechanical theory proposes that increased IOP causes deformation of the lamina cribosa and optic nerve head, disturbing neuronal axoplasmic transport.[126] This is supported by the beneficial effect of IOP lowering therapy in POAG and normal tension glaucoma.[127] However, the mechanical theory alone cannot account for several important observations. Firstly, not all patients with ocular hypertension will progress to develop glaucoma. The Ocular Hypertension Treatment study showed that over 5 years, the cumulative probability of developing POAG in the untreated group was 9.5%.[128] This study shows the majority of those left untreated did not develop POAG. Secondly, IOP reduction does not prevent all patients from progressing. The Ocular Hypertension Treatment study showed that despite treatment, there was still a cumulative probability of developing POAG of 4.4%.[128] Thirdly, a proportion of patients develop glaucoma without ocular hypertension, called normal tension glaucoma. Similarly to ocular hypertension, most patients with normal tension glaucoma still progress despite IOP lowering therapy. The vascular theory attempts to explain these observations.[129]

The vascular theory proposes that fluctuating blood pressure in the setting of reduced ocular blood flow and chronic vascular dysregulation results in a decreased ability to adapt to changes in ocular perfusion pressure. Unstable ocular blood flow results in repeated reperfusion injury to the optic nerve head leading to oxidative stress and causing glaucomatous damage.[129] Patients with both glaucoma and normal tension glaucoma have reduced ocular blood flow.[130,131] This reduction appears greater in normal tension glaucoma.[131] In contrast, ocular blood flow is not reduced in those with ocular hypertension.[132] Reduced ocular blood flow in normal tension glaucoma and normal ocular blood flow in ocular hypertension is consistent with a vascular cause of glaucomatous damage in these patients. Reduced blood flow is likely to be both a primary cause and secondary to atrophy. Primary reductions in blood flow are supported by observations that reduced peripheral capillary flow is seen in patients with glaucoma,[133] and >70% of disc haemorrhages are seen in patients without glaucoma despite a strong association with glaucoma.[134] Further reductions in ocular blood flow secondary to atrophy are supported by the reduced capillary volume in proportion to tissue volume loss in atrophic optic nerve heads.[135]

Patients with glaucoma are more vasospastic than controls,[133,136,137] and have reduced autoregulation.[138] This impaired autoregulation means they are vulnerable to fluctuations in ocular blood flow. As such, fluctuations in ocular blood flow are a risk factor for progression.[139] This risk occurs overnight with physiological nocturnal drops in blood pressure. Nocturnal dips in blood pressure of >10% are associated with visual field progression.[122] Similarly, a lack of adequate nocturnal blood pressure drop is associated with progression.[119,139] This unstable ocular blood flow

causes oxidative stress and apoptosis of the optic nerve cells.[140,141] The remodelling of the optic nerve head is thought to be due to the combination of reperfusion injury, IOP, and ischaemia rather than IOP or ischemia alone.[129,142] The primary cause of impaired autoregulation remains unknown. Sustained hypertension may cause impaired vascular dysregulation.[143] However, as mentioned previously, large longitudinal epidemiological studies show conflicting results.

1.4 Global Trends in Vitreoretinal Procedures

1.4.1 A brief history of vitrectomy, scleral buckling, and anti-vascular endothelial growth factor injections

The first pars plana vitrectomy is credited to Machemer in 1971 and was 17-gauge.[144] The initial 17-gauge vitreous infusion suction cutter (VISC) consisted of a battery-powered micromotor activating a drill bit inside a hypodermic needle adapted on a plastic syringe. The pars plana approach removed the need for a lensectomy with an anterior approach and enabled a closed system to reduce the risk of intraoperative hypotony.[145] Subsequently, in 1974, O'Malley and Heinz developed the three-port 20-gauge vitrectomy system, separating the components of vitreous cutting, infusion and illumination.[146] Further advances in technology that cemented the 20 gauge vitrectomy as the standard of care included improvements in vitrectomy cutters, endoscopic illumination, perfluorocarbon liquids, vital dyes and wide-angle viewing systems.[145,147] In 2002, Fujii et al. introduced and popularised the 25-gauge transconjunctival sutureless vitrectomy using microtrocars and cannulas.[148] Subsequently, further small gauge systems were developed, such as the 23-gauge system by Eckardt et al. in 2005,[149] and a 27-gauge system in 2010 by Oshima et al.[150] The advantages of small gauge vitrectomy, including shorter operating times, decreased postoperative inflammation and pain,[151] improved patient comfort, and faster visual recovery,[152] has increased its popularity and use.[153]

In contrast to vitrectomy, the techniques for scleral buckling have remained largely unchanged over the last half-century. The first reported use of an explant to buckle the sclera and reattach detached retina was by Custodis in 1949, who developed a polyvinol explant for buckling and sealed retinal breaks with diathermy.[154] Shortly after that, Schepens developed a polyethene encircling tube in the United States, draining subretinal fluid and sealing breaks with diathermy.[155] The now well-recognised technique for scleral buckling was developed by Brockhurst, including lamellar dissection, scleral bed diathermy, and silicone buckling materials varying in shapes, widths, and thicknesses with an encircling band to close retinal breaks.[156] Finally, Lincoff in the United States made important contributions to the further development of scleral buckling, such as using silicone sponges as explants, locating retinal breaks, the advantages of cryotherapy over diathermy, the reduced comorbidity with not draining subretinal fluid.[157] The developments made during this period remain used as established techniques for retinal detachment repair.

The existence of vascular endothelial growth factor (VEGF, also known as vascular permeability factor) was first reported in 1989.[158,159] Later in 1994, Miller et al. demonstrated that the hypoxic retina increased the production and upregulation of VEGF.[160] Further experimental studies confirmed the causative relationship between VEGF and ocular angiogenesis.[161] In 2004, Gragoudas et al. demonstrated a clinical trial comparing intravitreal pegaptanib, an RNA aptamer that neutralises the VEGF165 isoform, with sham injections, for the treatment of neovascular age-related macular degeneration.[162] They found pegaptanib significantly improved visual acuity. Around this time, bevacizumab, a humanized anti-VEGF antibody binding to all VEGF isoforms, was trialled for ocular angiogenesis after successful trials in

cancer.[163] Due to concerns regarding the retinal diffusion of bevacizumab, given its large molecular size compared to smaller antibody fragments,[164] the smaller ranibizumab molecule was developed and was subsequently shown to be successful for the treatment of neovascular age-related macular degeneration.[165,166] Studies of pegaptanib were limited by the majority of initial study eyes already being treated with verteporfin photodynamic therapy and the studies did not show the same degree of visual improvements as ranibizumab.[162] Subsequently, ranibizumab and bevacizumab were compared and showed equivalent efficacy.[167] Ranibizumab was registered with the Therapeutic Goods Administration (TGA) in 2007. The same parent company developed both bevacizumab and ranibizumab, and although studies have shown similar efficacy, bevacizumab is not listed on the Pharmaceutical Benefits Scheme for intravitreal injection. This is due to its preparation not being designed for intravitreal injection, significantly lower cost compared to ranibizumab and, therefore, a lack of incentive to list on the scheme. However, due to its cost-effectiveness bevacizumab has been used extensively off-label for treating age-related macular degeneration.

Aflibercept is a subsequent anti-VEGF strategy which works as a decoy receptor to sequester VEGF and was developed to improve the binding capacity for VEGF.[168] In 2009, Nguyen et al. trialled aflibercept in eyes with neovascular age-related macular degeneration and found significant improvement in visual acuity.[169] Aflibercept was registered with the TGA in 2012 in Australia. However, repetitive injections are a significant burden to both the patient and the healthcare system, and there is still a need for longer-lasting and higher-potency drugs. Another anti-VEGF molecule was developed to address this. Brolucizumab is a potent humanized single-chain antibody fragment that inhibits all isoforms of VEGF-A with longer administration

intervals. It has shown non-inferiority with aflibercept, [170] and was recently registered with the TGA in 2020 for age-related macular degeneration, not controlled with ranibizumab or aflibercept.

1.4.2 Australian Trends in Vitreoretinal Procedures

Australian data reporting trends in vitreoretinal procedures are limited. Manners et al. conducted a population-level retrospective observational study using routinely collected hospital separation data to evaluate cases of retinal detachment in WA. The authors used the WA Data Linkage System and WA Hospital Morbidity Data Collection, containing public and private hospital admission data at the population and patient levels. The authors investigated trends in retinal detachments and repair from 2000 to 2013. The authors found the use of scleral buckle (alone or in addition to vitrectomy) for retinal detachment repair decreased from 70% to 16% in 2013. In contrast, the use of vitrectomy alone increased from 25% in 2000 to 84% in 2013.[171]. In addition, the authors reported age and sex-adjusted incidence rates for retinal detachment standardised to the WA population. However, this was not reported for retinal detachment repair procedures, which remains unknown in Australia.

1.4.3 Global Trends in Retinal Detachment Repair Procedures

This increase in vitrectomy compared to scleral buckle has been seen across countries in Asia, the United States, and England. Wong et al. conducted a retrospective review of all retinal reattachment procedures performed at the Singapore National Eye Centre from 2005 to 2011 for primary RRD. The authors report the proportion of scleral buckle alone fell from 60.8% in 2005 to 39.4% in 2011 compared to PPV and simultaneous SB and PPV, which increased from 39.2% in 2005 to 60.6% in 2011. [172] In Japan, Hashimoto et al. performed a retrospective analysis of the Diagnostic Procedure Combination database across 2010–2017, including inpatient vitreoretinal surgical procedures. The database includes data from 82 academic hospitals in Japan. The 1985 Japanese population structure was used to standardise procedure rates. The authors found the age and population-standardised rate of scleral buckle alone decreased from 2.4 per 100,000 persons in 2010 to 1.7 per 100,00 persons in 2017.

In contrast, reattachment with vitrectomy alone increased from 3.3 per 100,000 persons in 2010 to 5.0 per 100,00 persons in 2017. [173] In addition, they showed that vitrectomy increased the most in the 50-59- and 60-69-years age groups. Scleral buckle alone similarly decreased the most in the 50-59- and 60-69-years age groups. In Taiwan, Ho et al. performed a retrospective analysis of the nationwide population-based Taiwan National Health Insurance Research Database from 1997 to 2005 to examine trends in the treatment of first-admission rhegmatogenous retinal detachment. [174] The authors found the portion of scleral buckle use significantly declined from 52.7% of surgical procedures in 1997 to 38.8% in 2005 (<0.001, chi-squared test). In contrast, reattachment with vitrectomy alone significantly increased

from 29.9% to 39.8% in 2005. There we no reported estimates adjusted for age, gender, or population.

In the United States, Reeves et al. retrospectively analysed an administrative claims database of beneficiaries in a large nationwide managed-care network to investigate trends in rhegmatogenous retinal detachment repair between 2003 to 2016. They found that reattachment with vitrectomy increased from 44% of procedures in 2003 to 64% in 2016. In contrast, the scleral buckle decreased from 23% in 2003 to 6% in 2016. [175] While the authors did not report age, gender, and population-standardised incidence rates, they found an age-specific predisposition to different repair procedures in multivariable logistic regression models.

In England, El-Amir et al. analysed retrospective data from Hospital In-patient Enquiry and Hospital Episode Statistics from 1968-2004 and the Oxford Record Linkage Study from 1963-2004 to investigate trends in retinal detachment repair. The authors found that national annual rates of scleral buckle declined from 12 episodes per 100,000 in 1995 to 6 per 100,000 in 2004.[176] In contrast, rates of reattachment with vitrectomy increased from approximately 13 episodes per 100 000 in 1995 to 26 episodes per 100 000 persons in 2004.

In summary, global analyses have shown increasing proportions and incidence of vitrectomy compared to a decrease in scleral buckle over time. However, previous studies are limited by the use of institution-specific populations, lack of standardisation to the age and gender structure of the populations of interest, and lack of age-stratified trends. Given previous studies have shown age influences

procedure selection,[175] there is a need for a truly population-based study of age, gender and population-standardised vitreoretinal surgical trends with age stratification in Australia.

1.4.4 Global Trends in anti-vascular endothelial growth factor injections

In England, Keenan et al. retrospectively analysed data from the Hospital Episode Statistics database from 1989/1990 to 2008/2009. The Hospital Episode Statistics database covers all-day and inpatient admissions in NHS hospitals in England and those performed by external providers funded by the NHS. They found the age and population-standardised national rates of intravitreal injections increased from 0.4 episodes per 100 000 to 10.7 (10.4–11.0) in 2006. Subsequently, the annual rate markedly increased to 24.4 in 2007 and 59.5 (58.8–60.2) in 2008. Most injections and growth of injections were seen in those with age-related macular degeneration compared to diabetic maculopathy.[177] Furthermore, Chopra et al. retrospectively analysed data on intravitreal injections from Moorfields Eye Hospital between 2009 to 2019.[178] They performed a time series analyses to forecast injection requirements to the year 2029. They found the absolute number of injections markedly increased over the study period mirroring national trends. However, they found the year-over-year growth factors declined throughout the study period indicating a reduction in the growth of injections over time.

Campbell et al. retrospectively analysed monthly fee claims for intravitreal injections submitted to the Ontario Health Insurance Plan between January 2000 and March

2008. [179] The authors found injections increased from <5 per 100,00 persons per month to 25.9 injections per 100,00 persons per month. The strength of this study is its population-based design, given the database covers all residents of Ontario and billing outside the program is not permitted. However, incidence rates were not age and gender-standardised.

In the United States, Ramulu et al. retrospectively analysed data from the Centres for Medicare and Medicaid Services from 1997 to 2007. The authors found that the absolute number of intravitreal injections increased from fewer than 5000 between 1997-2001 to 812 413 injections in 2007.[180] In a similar subsequent analysis, McLaughlin et al. retrospectively analysed US Medicare data from 2000 to 2014 to investigate trends in vitreoretinal procedures. They found a significant increase in intravitreal injections from 2922 injections in 2000 to 2 619 950 injections in 2014.[181] Furthermore, Parikh et al. retrospectively analysed a US administrative claims database that includes over 100 million commercially insured and Medicare Advantage individuals to investigate trends in specifically anti-VEGF injections.[182] Crude incidence rates showed an increasing incidence for bevacizumab and aflibercept. However, the incidence of ranibizumab increased until 2013, after which the incidence rate fell. Bevacizumab accounted for most injections in 2015, followed by aflibercept and ranibizumab. A similar US analysis by Berkowitz et al. analysed trends in specifically anti-VEGF injections in US Medicare beneficiaries between 2012 and 2015. The authors found that although ranibizumab and bevacizumab claims decreased by 7.1% and 17.1%, respectively, aflibercept claims increased by 69.4%. [183]

Global trends have identified increases in the absolute number and incidence of intravitreal injections from 1989 to 2015 in primarily population-based studies of administrative data for Medicare beneficiaries in the US and Canada and national inpatient hospital statistics in England. However, previous studies have not included age and gender standardisation or age stratification in trends. In addition, there is no available Australian data to guide future projections.

1.5 Natural language processing for patient cohort identification in electronic health records

1.5.1 Patient cohort identification

Various clinical activities, such as retrospective and prospective clinical research, registry creation and quality improvement activities, rely on patient cohort identification. Incomplete or inaccurate identification may introduce selection bias and influence the accuracy of findings. In a case study of non-small cell lung cancer cohort identification using electronic health records, Berger et al. found that methods to improve cohort identification showed median survival times in line with previous literature in the complete cohort, compared to a reduced survival time in the incomplete cohort.[184] Comprehensive cohort identification is important to prevent selection bias and ensure the validity of study results. Retrospective studies with electronic health records are particularly vulnerable to incomplete cohort identification, given the frequency of missing or incomplete data.[185,186] Given manual chart review is labour intensive, time-inefficient,[187] and costly,[188] there is a need for efficient computer-assisted and automated strategies. Strategies to improve patient cohort identification from electronic health records have focused on individual diseases.[189-194] There is a need to explore strategies to approach general patient cohort identification that applies across a range of diseases in addition to disease-specific considerations. NLP broadens the available repository of data available for cohort identification beyond relying on manually coded structured fields. Further, clinician involvement will be important in developing NLP systems and workflows. Clinician queries of electronic health records are more sophisticated than standard disease ontologies, [195] and clinician involvement has been shown to improve recall

for systems identifying patients matching trial selection criteria compared to those without clinician involvement.[196]

1.5.2 Diagnostic coding for cohort identification is specific but not sensitive

The increasing ubiquity of electronic health records presents an important opportunity to increase the efficiency of cohort identification by harnessing the breadth of data they contain. Electronic health records contain data in both structured and unstructured fields.[197] Structured fields usually consist of clinical measurements, laboratory values, medication lists, or other data with a standardised format. These have the advantage of being readily computer readable. Diagnostic coding is a commonly structured field used frequently for patient cohort identification. Although diagnostic coding in discharge summaries has shown to be generally accurate at a median accuracy rate of 80.3%,[198] coding of comorbidities in problem lists are often incomplete.[199-202] Therefore, the presence of a diagnostic code is likely to indicate its presence. However, the absence of a code is less reliable for determining the absence of the disease. Many authors have demonstrated this across various diseases, comorbidities, and centres. Goff et al. investigated the accuracy of using ICD-9 diagnostic coding to identify obstetric complications. They found diagnostic coding displayed a high specificity compared to sensitivity which varied from 0.15 – 1.0 for the selected codes.[203] Nimmo et al. investigated the accuracy of diagnostic coding for comorbidities in patients with advanced kidney disease. They found that the specificities ranged from 0.904 – 1.00 across the selected diagnoses, and sensitivities ranging from 0.155 – 0.977. Higgins et al. similarly demonstrated poor sensitivity for ICD-9 codes for identifying organism-

specific pneumonia compared to specificity in a large US hospital cohort.[204] Finally, Bozic et al. investigated the sensitivity and specificity of administrative codes for comorbidities and complications derived from hospital billing records for patients undergoing lower extremity arthroplasty. They found that although all comorbidities showed a specificity >0.92, sensitivity ranged from 0.29 – 1.00.[199] Similar findings have been observed in studies of coding for AKI, and comorbid chronic kidney disease in diabetes. [205,206] Thus, the sensitivity of diagnostic coding varies and is generally poor compared to consistently higher specificity. This is a major barrier to diagnostic coding for patient cohort identification, in which adequate sensitivity is required.

Coding accuracy is further affected by changes in coding systems,[201] or lack of suitably granular codes, which can affect data quality.[207] This is further compounded by data fragmentation across multiple sites leading to incomplete coding in a single centre,[208] and observations that the length of registration with an electronic health record affects the accuracy of diagnostic coding.[209] In light of these limitations, there is a need to use other elements of the electronic health record to increase the accuracy of patient identification. Other structured elements in electronic health records may be used in place or in addition to diagnostic coding, such as laboratory test results or dispensed medications. For example, Spratt et al. investigated the sensitivity and specificity of a range of criteria for diabetes in an electronic health record, including diagnostic coding, HbA1c, and diabetes medication use.[210] The authors found that although diagnostic coding displayed a higher sensitivity than HbA1c or medications, coding had a lower specificity. Therefore, searching single or multiple structured fields alone may not be adequate to increase the sensitivity of

patient cohort identification. Statistical methods such as multivariable models,[211] and bootstrapping algorithms,[212] are alternative methods to simple searching of structured fields that may offer improved predictive abilities for patient cohort identification. However, these are not widely used. Both the multivariable logistic regression and bootstrapping algorithms require useful structured elements which exist only for certain diseases. For example, diabetes is highly prevalent, and is associated with accurate and available laboratory tests such as glycated haemoglobin and fasting glucose, as well as disease-specific antidiabetic medications. Not all diseases have such readily available and salient structured elements, which is particularly pertinent for rare diseases. In addition, structured elements may not be available for many diseases that lack a single, standard, reliable diagnostic test or specific medications to identify their presence.[213] Kopcke et al. investigated the extent of structured data available among German university hospitals to match with eligibility criteria of 15 randomly selected clinical trials.[214] They found that the total completeness of electronic health record data for trial recruitment was 35%, finding that electronic health records still lack structured elements to match trial criteria.[214] The use of structured fields is further confounded by higher data completion rates in more unwell patients.[215] Therefore, alternatives to the use of structured fields are required to improve cohort identification accuracy.

1.5.3 Unstructured fields of electronic health records improve cohort identification

Unstructured fields of the electronic health records contain important clinical information that is more granular than available structured fields.[216] The use of unstructured elements offers opportunities to increase sensitivity and specificity for patient cohort identification in electronic health records.[217] However, information extraction from these fields is challenging due to their free-text nature. The clinical free text contains ambiguity,[218] redundancy, misspellings,[219] acronyms and abbreviations,[220-222] and variable representations of the same concept.[223] In addition, Hanauer et al. have previously shown clinical notes also contain wide variation in numerical representation, using lexical representation, Arabic and Roman numerals, which can have substantial impacts on the identification of diagnoses incorporating numerical elements such as type 2 diabetes.[224] These challenges require specialist information extraction techniques for patient cohort identification.

Unstructured free text is increasingly used to supplement diagnostic coding and has improved cohort identification.[225] For example, Blecker et al. found that a machine learning algorithm combining structured and unstructured elements of the electronic health record showed a large increase in sensitivity and specificity for the diagnosis of heart failure compared to using diagnostic coding alone.[226] Abhyankar et al. investigated the potential for querying unstructured data to increase patient cohort identification or patients receiving dialysis in the intensive care unit.[194] They found that using structured and unstructured data fields increased the accuracy of both fields for cohort identification. Virani et al. found that unstructured data increased the sensitivity of cohort identification for statin-related adverse drug reactions compared

to structured drug reaction data.[227] However, simple searching of text for keywords is unlikely to offer improved sensitivity over diagnostic coding,[228] and more sophisticated information retrieval methods for patient cohort identification are required.

Natural language processing is a developing field of techniques to extract information from unstructured text.[229] It encompasses a range of techniques, including the increasing use of machine learning.[225,230] Named entity recognition is assigning predefined labels or semantic categories to words or phrases in a text. It has been performed using dictionary-based, rule-based and machine-learning approaches.[231] Dictionary-based approaches use a lexical database for detecting named entity candidates, which may be subsequently filtered using rule-based methods. This approach requires an extensive biomedical dictionary with all desired terms to detect named entities. Rule-based approaches rely on sequential, manually derived heuristics to identify desired entities in text. This approach depends on the rules and patterns of named entities in a collection of documents. Although both dictionary rule-based systems can identify entities in large amounts of text quickly and reliably, they exhibit several disadvantages. Dictionaries require an extensive time investment to create, new words are generated frequently in the biomedical domain, and a single word could be recognised as diverse named entities dependent on their context.

Similarly, rule-based approaches are limited to a specific dataset and entity.[230] Statistical machine-learning approaches have now largely superseded these techniques. They can recognise named entities without a dictionary or set of rules. A variety of machine learning methods have been used in named entity recognition.[232]

Despite improvements in named entity recognition with machine learning and demonstrated accuracy, there is a lack of open source and accessible tools available to researchers for patient cohort identification,[230] where many approaches have been problem-specific.[233] Furthermore, these workflows require considerable machine learning expertise, which presents a major barrier to their deployment.[234] While the solutions to these tasks will require the ongoing support of community challenges, conferences and collaborative groups,[233] there is a need to increase the accessibility of this technology to clinicians without extensive NLP expertise and demonstrate the potential advantages in clinical and research workflows.

The chapters in this thesis illustrate the differential use of two academic databases, an administrative database, and a further chapter demonstrates the machine-learning-assisted construction of a disease registry. The chapters include a small specialised academic database of patients with epiphora, a large population-level academic database from the UK Biobank study, a national administrative database of vitreoretinal procedures in Australia, and a clinician-friendly workflow for creating a bespoke disease register from electronic health records to facilitate the further creation of academic or registry databases from the wealth of information contained in electronic health records.

2 Chapter 2: Lacrimal imaging findings in fellow asymptomatic eyes of unilateral epiphora

The results described in this chapter have been published as:

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2.1 Introduction

Dacryocystography (DCG) and dacryoscintigraphy (DSG) are common lacrimal imaging studies available in the evaluation of epiphora. DCG is used to assess the morphology of the lacrimal drainage system and has previously shown utility in detecting factors of surgical significance in patients with suspected complicated or distorted anatomy, or identifying suspected canalicular lesions.[77]. Although tear clearance has previously been assessed using DCG,[85] concerns that injecting contrast under pressure may overcome partial obstruction or obstructions due to functional epiphora mean this test is not considered physiological. The radiotracer used in DSG is not injected under pressure, and thus considered to better represent the function of lacrimal tear clearance. However, DSG provides significantly less anatomical detail compared to DSG.

The concordance of DCG and DSG for symptomatic eyes various significantly,[83-85,87] DSG shows higher rates of abnormalities,[83,84,86] often in the absence of findings on DCG. However, tear clearance has shown to be variable in normal individuals,[88] and it is unclear whether abnormalities on DSG truly reflect abnormalities in tear

clearance or physiological variation. Further evidence of this is seen in DSG studies of fellow asymptomatic eyes of unilateral epiphora. These asymptomatic eyes show similarly high rates of DSG abnormalities, where previous studies have shown an abnormality on DSG in 25-80% of cases. [83-86,91,92,235-237] However previous studies are mostly based on small sample sizes and lack correlation with anatomical imaging such as DCG. Therefore, we investigated the correlation between DSG and DCG in fellow asymptomatic eyes of unilateral epiphora.

We used a disease-specific departmental academic database to perform this analysis. Studies in asymptomatic eyes usually occur as part of collecting normative data or collected alongside studies in symptomatic eyes. This data is therefore affected by the characterises of the study context. Thus, an observational database approach can provide a broader range of data for these asymptomatic eyes without placing further burden on research studies of symptomatic eyes.

2.2 Methods

We constructed our database by retrospective case note review of adult patients presenting to the Royal Adelaide Hospital and The Queen Elizabeth Hospital (Adelaide, Australia) Oculoplastic clinic with unilateral epiphora between February 2011 and December 2021. Ethics approval was obtained from the Central Adelaide Local Health Network Huma Research Ethics Committee and the study adhered to the tenants of the Declaration of Helsinki.

We collected data including patient demographics (age and gender), laterality of symptomatic and asymptomatic side, reflux on lacrimal syringing, and findings on DCG and DSG. DCG findings were categorised as post sac obstruction (including in sac obstructions), pre sac obstruction, post sac stenosis, pre sac stenosis, and no obstruction.

DCG was performed in the supine position, using one drop of 1% tetracaine hydrochloride instilled into the inferior conjunctival fornix of both eyes, and punctum dilated using a 27-gauge lacrimal cannula. Baseline images were acquired before injection of iopromide contrast. Post contrast images were then acquired for subtraction using the pre-contrast images. We defined stenosis as ‘a duct diameter of less than that of the width of the lacrimal cannula tip on the X-ray image (27-gauge, 0.4 mm external diameter) but with patency’ as per the definition proposed by Sia et al.[80]

DSG was performed with the patient sitting upright. We instilled a10 μL drop of technetium-99m pertechnetate in both eyes. Sequential images at 1-minutely intervals taken with the gamma camera were acquired over 45 minutes. If the tracer had not reached the nasal cavity after 45 minutes, the patient was asked to clear their nasal passages and lacrimal massage was applied to both eyes. Further sequential images at 1-mintely intervals for 45 minutes were then acquired. The end-tracer location after 5 minutes was used to qualitatively determine the site of delay as pre or post sac delay if tracer had not reached the nasal passage.

Lacrimal imaging was assessed by an experienced Oculoplastic specialist. Syringing was performed by an experienced Oculoplastic specialist using a lacrimal cannula attached to a 2mL syringe inserted 1-2mm vertically through the inferior lacrimal punctum. Lateral traction was applied to the lower lid for continuous tension. The cannula was advanced until reaching a hard or soft stop. Syringing was performed using minimal pressure and the amount of reflux was noted.

2.3 Results

A total of 172 asymptomatic eyes, 88 (51%) right and 84 (49%) left, were included. The median age was 67 (range 18-96 years). The results of DCG were available for 98 (57%) of eyes, and results for DSG available for 130 (76%) eyes. An abnormality was present in 54 eyes (42%) that underwent DSG, and in 10 eyes (10%) that underwent DCG (Table 1). The most common finding on DSG was no delay (normal drainage) in 76 eyes (58%), and most common DSG abnormality reported was post sac delay in 51 eyes (39%; Table 1). The most common finding on DCG was no obstruction in 88 eyes (90%), and the most common DCG abnormality reported was post sac stenosis (7.1%; Table 1).

The correlation between the asymptomatic and symptomatic eye findings on DSG is detailed in Table 2. Out of the 51 asymptomatic eyes with post-sac delay on DSG, 40 (78%) had a concurrent post-sac delay in their fellow symptomatic eye. Out of the 3 asymptomatic eyes with pre-sac delay on DSG, 2 (67%) had a concurrent pre-sac delay in their fellow symptomatic eye.

The correlation between the asymptomatic and symptomatic eye findings on DCG is detailed in Table 3. Of the 2 asymptomatic eyes with post-sac obstruction, 2 (100%) had a concurrent post sac obstruction in the fellow symptomatic eye. Out of the 7 asymptomatic eyes with post-sac stenosis, 3 (43%) had a concurrent post sac stenosis, and 3 (43%) had a post sac obstruction in the fellow symptomatic eye.

The 1 asymptomatic eye with pre sac stenosis had a concurrent post sac obstruction in the fellow symptomatic eye.

Of the 92 asymptomatic eyes with both DCG and DSG results available, 53 (57%) showed no abnormality on DCG or delay on DSG, and 28 (30%) showed a post sac delay on DSG and no abnormality on DCG (Table 4).

Of the 63 asymptomatic eyes which had both lacrimal syringing and DCG results available, 17 (27%) had reflux ≥20%. Of eyes with ≥20% reflux, 3 (18%) showed obstruction or stenosis on DCG. Only 3 (6.5%) of the eyes patent to syringing showed stenosis on DCG.

The causes of epiphora in the symptomatic eyes included partial NLD obstruction in 68 (39.5%), nasolacrimal duct obstruction in 68 (39.5%), canalicular obstruction in 13 (7.6%), reflex tearing in 9 (5.2%), pump failure (eyelid laxity, malposition or palsy) in 7 (4%), punctal stenosis in 2 (1.2%), multifactorial in 3 (1.7%), with 2 unknown (1.2%).

2.4 Discussion

We observed that 39% of fellow asymptomatic eyes of adult patients with unilateral epiphora display a post sac delay on DSG. In contrast, 10% of asymptomatic eyes showed an abnormality on DCG. Furthermore, 30% of eyes with both DCG and DSG available showed a post sac delay on DSG and no anatomical abnormality on DCG. In fellow asymptomatic eyes of symptomatic eyes with post sac delay on DSG, 43% displayed corresponding post sac delay on DSG. The reported prevalence of DSG abnormalities in asymptomatic fellow eyes ranges 25-80%,[83-86,91,92,235,236] in small cohorts. A larger study by Amanat et al. performed DSG in 240 fellow asymptomatic eyes of patients with unilateral epiphora. DSG was normal in only 25% of eyes, where 42% showed a complete tracer block or delay.[91] Our analysis is consistent with previous observations of the higher than expected prevalence of delay on DSG in asymptomatic eyes.

Physiological variation in tear transit times render the results of DSG abnormalities in asymptomatic eyes difficult to interpret. Quantitative physiological studies of control eyes have also shown tear transit times to be highly variable,[88,89,238] mostly from below the lacrimal sac to the nasal cavity,[88] with non-linear flow through the lacrimal drainage system.[90] Barna et al showed a significant difference among symptomatic, asymptomatic and control eyes for whole eye tracer clearance but not nasolacrimal duct clearance parameters.[239] Similarly, other investigations of quantitative differences between asymptomatic and symptomatic eyes (without including control eyes) failed to find significant differences in parameters of nasolacrimal duct tracer

clearance.[236,240] Therefore, DSG abnormalities of the nasolacrimal duct may represent physiological variability. Post sac delay accounted for 39% of DSG delay in our analysis, and these results may be impacted by this variability.

We observed that DCG was normal for 90% of asymptomatic eyes of unilateral epiphora. Subclinical anatomical abnormalities in the fellow asymptomatic eyes of unilateral epiphora eye are therefore unlikely. These results are consistent with the observations that unilateral obstruction on DCG in patients with epiphora is six times more common compared to bilateral obstructions.[67] Peter and Pearson similarly compared the correlation between DCG and DSG in eyes with epiphora clinically patent to syringing and recorded data on 20 asymptomatic eyes.[85] They found that 57% of asymptomatic eyes displayed an anatomical abnormality, delay, or both on DCG. This higher prevalence compared to our sample is likely due to sample size and population sampled.

Of eyes with both DCG and DSG available, we found 28 eyes (30%) showed a post sac delay on DSG and no anatomical abnormality on DCG. In comparison, 53 eyes (58%) showed no delay on DSG or anatomical abnormality on DCG. DSG delay in the absence of an abnormality on DCG may represent anatomical stenoses not identified by DCG due to the injection of contrast under pressure into the lacrimal drainage system that may overcome partial obstructions. The sensitivity of DCG for detecting partial or functional lacrimal obstruction has previously reported to be 63.3% when compared to dacryoendoscopy.[79] It is possible DCG underreports anatomical stenosis. Undetected nasolacrimal duct stenosis may account for some proportion of the increased prevalence of DSG delay in asymptomatic eyes.

Abnormal reflux to syringing was higher compared to abnormalities on DCG. Of the asymptomatic eyes with syringing and DCG results in our study, 17 eyes (27%) showed ≥20% reflux to syringing, however 14 eyes (82%) of these showed no obstruction on DCG. DCG and syringing has previously shown to be poorly correlated.[79] There is little asymptomatic eye syringing data available for comparison, however Spikova et al reported that 10% of fellow asymptomatic eyes displayed an abnormal result using their modified manometric irrigation test.[235]

Our study is limited by its retrospective design, lack of anatomical correlation with dacryoendoscopy, and referral bias as the study was conducted at a tertiary Oculoplastic clinic. In addition, qualitative categorisation of the DCG and DSG results is a significant limitation. We have previously shown that in our hands DCG interpretation has moderate interobserver agreement, and only fair agreement for DSG.[80] The absence of a control group without functional abnormalities in both eyes for comparison is another limitation. Thus, the results of fellow asymptomatic eyes in unilateral epiphora may not represent a normal standard utilised for comparison. In addition, due to the cross-sectional nature of the study, follow up data for asymptomatic eyes was not available and it is possible that some eyes may become symptomatic in the future.

2.5 Conclusion

In summary, asymptomatic eyes of unilateral epiphora display a high prevalence of abnormalities on DSG compared to a low prevalence of anatomical abnormalities on DCG. The significance of subclinical DSG delay in the fellow eye of unilateral epiphora may represent physiological variation in tear drainage, bilateral lacrimal drainage system abnormalities (subclinical on one side), or anatomical stenosis not detected on DCG. Therefore, the DSG results of fellow asymptomatic eyes in unilateral epiphora should be interpreted with caution, and comparison should be made with control eyes. Further investigation with dacryoendoscopy, the inclusion of control eyes, and long term follow up is required.

2.6 Tables

Table 1: Summary of demographics of patients with unilateral epiphora, and DCG and DSG findings in the fellow asymptomatic eyes

Characteristic		N = 172[1]
age		67 (18, 96)
gender	female	121 (70%)
	male	51 (30%)
side	left	84 (49%)
	right	88 (51%)
DCG Finding	no obstruction	88 (90%)
	post sac obstruction	2 (2.0%)
	post sac stenosis	7 (7.1%)
	pre sac obstruction	1 (1.0%)
DSG Finding	no delay	76 (58%)
	post sac delay	51 (39%)
	pre sac delay	3 (2.3%)

[1] Median (Range); n (%)
DSG = dacryoscintigraphy, DCG = dacryocystography

Table 2: The correlation of DSG findings between the symptomatic and fellow asymptomatic eyes in patients with unilateral epiphora

	Asymptomatic eye DSG finding			
	no delay	post sac delay	pre sac delay	Total
Symptomatic eye DSG finding				
no delay	10	4	0	14
post sac delay	53	40	1	94
pre sac delay	13	7	2	22
Total	76	51	3	130

DSG = dacryoscintigraphy

Table 3: The correlation of DCG findings between the symptomatic and fellow asymptomatic eyes in patients with unilateral epiphora

	Asymptomatic eye DCG finding				
	no obstruction	post sac obstruction	post sac stenosis	pre sac obstruction	Total
Symptomatic eye DCG finding					
no obstruction	37	0	1	0	38
post sac obstruction	28	2	3	1	34
post sac stenosis	15	0	3	0	18
pre sac obstruction	7	0	0	0	7
pre sac stenosis	1	0	0	0	1
Total	88	2	7	1	98

DCG = dacryocystography

Table 4: The correlation of DCG and DSG findings in only the fellow asymptomatic eyes of unilateral epiphora

	Asymptomatic eye DSG finding			
	no delay	post sac delay	pre sac delay	Total
Asymptomatic eye DCG finding				
no obstruction	53	28	1	82
post sac obstruction	0	2	0	2
post sac stenosis	0	6	1	7
pre sac obstruction	0	1	0	1
Total	53	37	2	92

DSG = dacryoscintigraphy, DCG = dacryocystography

3 Chapter 3: Blood Pressure Measures and Incident Primary Open Angle Glaucoma

3.1 Introduction

Glaucoma is the leading cause of irreversible blindness worldwide.[241] Primary open-angle glaucoma (POAG) is the most common type of glaucoma,[242] with an estimated global burden of 65.5-79.6 million afflicted people in 2020.[242,243] Intraocular pressure (IOP) is currently the only modifiable risk factor to prevent disease progression.[116] The non-modifiable risk factors or glaucoma currently include age,[95] ethnic background,[96,97] family history of glaucoma,[98] and myopia[99-101] central corneal thickness and optic disc features. [244] The development and progression of POAG is influenced by complex gene/environment interactions.[245] There is a need for further modifiable environmental factors to prevent the develop or slow the progression of POAG.

Increased IOP has previously shown a consistent relationship with increasing blood pressure.[105-108] Given this close relationship, cardiovascular risk factors such as blood pressure have been postulated to be related to incident POAG.[246] Associations have been observed between low systolic blood pressure and incident POAG.[94] In addition, both systemic hypertension,[247] and nocturnal dips in systemic blood pressure,[248] have been associated with visual field progression. While the effect of these vascular parameters is thought to be mediated through influencing ocular blood flow, the microvascular beds of most importance are unknown.[249] Furthermore, studies investigating blood pressure and incident POAG have reported inconsistent

findings, limited by heterogeneity in design, sample size, and variations in representation of blood pressure in statistical models.[109]

The UK Biobank is a large prospective cohort study of over 500,000 participants aged 40-69 years across the United Kingdom.[46] The biobank collects baseline sociodemographic, health and lifestyle data at enrolment, and ongoing data collection is facilitated through repeat assessment visits, and linkage with hospital and Primary are data. It is a large academic database that collects specific health characteristics and measurements relating to population health, in an inception cohort, for the purpose of investigating risk and prognostic factors of diseases. The health characteristics included in the database are extensive, and health measurements include office measurements such as blood pressure and BMI, measurement of blood parameters, and various radiological imaging studies. The database overall is not disease specific but designed to investigate risk factors for diseases at the population level. Thus, we sought to investigate the association between systemic systolic (SBP), diastolic (DBP), mean arterial (MAP) and pulse (PP) pressure with incident POAG in participants of the UK Biobank.

3.2 Methods

We used data from the UK Biobank. The UK Biobank is a prospective cohort study of over 500,000 participants aged 40-69 years, recruited between 2006 and 2010 across the United Kingdom.[46] The subjects were recruited by postal invitation sent to individuals proximate to one of 22 assessment centres throughout England, Wales, and Scotland. The overall participation rate was 5.45%. The UK Biobank study was approved by the North-West Multicentre Research Ethics Committee. This research was conducted using the UK Biobank Resource under Application Number 62103.

Participants completed a touchscreen questionnaire and verbal interview at the initial assessment centre visit, participants completed a touchscreen questionnaire and verbal interview. Data collected included sociodemographic, lifestyle and health information. Standardised anthropomorphic and blood pressure measurements were recorded. Varying proportions of participants had repeat blood pressure measurements at subsequent visits including a repeat assessment visit between 2012-2013, an imaging visit (for non-ophthalmic radiological imaging) from 2014 onwards, and a repeat imaging visit from 2019 onwards, which were included in the analysis. Longitudinal data on incident diagnoses and operations is available via linkage to national hospital and primary care databases and updated periodically. The latest update of Showcase hospital data at the time of writing was 31 March 2021. The linked primary care data is available for approximately 45% of the cohort at the time of writing.

Participants

All participants of the biobank were considered for eligibility and were included if they had at least one systolic and diastolic automated or manual blood pressure reading at baseline. Participants were excluded if they had glaucoma of any type at baseline (identified from self-report touchscreen questionnaire, verbal interview, linked hospital inpatient data, and linked primary care data), or had prior glaucoma surgery (from linked hospital inpatient data, linked primary care data, or self-report). The specific codes identifying these cases are listed in the appendix.

Assessment of blood pressure

SBP and DBP were measured on the seated individual by a registered nurse from their right brachial artery using the Omron 705 IT electronic blood pressure monitor (OMRON Healthcare Europe B.V. Kruisweg 577 2132 NA Hoofddorp). Two blood pressure readings were taken during the baseline assessment visit. The first measurement was taken after the initial interview, and the second measurement was taken at the end of the assessment visit. If the largest cuff size was too small for the participant, or if the electronic blood pressure monitor failed to produce a reading, a sphygmomanometer with an inflatable cuff and stethoscope was used to manually assess the blood pressure. Varying proportions of participants had further blood pressure measurements at subsequent assessment or imaging visits. Automated blood pressure readings were preferred when available, otherwise manual measures were used for analyses. SBP and DBP readings were averaged between the two measurements. MAP was calculated from the averaged systolic and diastolic blood pressure readings using the formula MAP = DBP + 1/3(SBP-DBP).[124] Similarly, pulse pressure (PP) was calculated as PP = SBP – DBP.[250]

Assessment of other covariates

Body mass index (BMI) was calculated using the height and weight measurements taken during the first assessment centre visit (BMI = weight[kg]/height[m^2]). Standing height was measured using a Seca 202 device. Weight was measured using the Tanita BC418MA body composition analyser, or standard scales for participants that were medically unsuitable or refused the analyser. BMI was then categorised according to the World Health Organisation definition into underweight (BMI <18.5), healthy weight (18.5≤ BMI <25), overweight (25 ≤BMI <30) and obese (BMI ≥30).

Prevalent diabetes and cataract surgery was noted from self-report, hospital inpatient data and primary care data. The codes used to identify these cases are listed in the appendix. Education was categorised as secondary (A levels/AS levels or equivalent, O levels/GCSEs or equivalent, CSEs or equivalent), tertiary (NVQ or HND or HNC or equivalent, College or University degree), other (Other professional qualifications) or none of the above.

Assessment of outcomes

Incident cases of POAG were identified as the date of the first occurrence of the diagnostic code for POAG in hospital inpatient data, or primary care data if available. The codes used to identify POAG are listed in the appendix.

Statistical Analyses

Participant characteristics were presented by status of incident POAG. Continuous variables were summarised with mean, standard deviation, and range, compared using the t-test. Categorical variables were summarised by number and proportion and compared using the chi-squared test.

Cox regression was used to assess the effect of systemic blood pressure on the risk of incident POAG. Participants were considered at risk from the first assessment centre visit until either diagnosis of POAG, death, loss to follow up, or end of available follow up, defined as the date of latest available Showcase data update of hospital inpatient admission data (31/03/2021).

Analyses with blood pressure represented as categorical predictors were conducted for SBP(<120, [120-130), [130-140), [140-150), ≥ 150 mmHg), DBP (<70, [70-80), [80-90), [90-100), ≥ 100 mmHg), MAP (<90, [90-100), [100-110), [110-120), ≥120 mmHg) and PP (<40, [40-50), [50-60), [60-70), ≥70 mmHg). For patients who had repeat blood pressure measurements, blood pressure was analysed as a time-varying predictor. Multivariate models included adjustment for age, gender, ethnicity (White, Asian, Black, Other), BMI (underweight, healthy weight, overweight, obese), education (secondary, tertiary, other, none of the above), Townsend deprivation index quintiles (index of material deprivation based on census variables describing car and house ownership, overcrowding and unemployment), smoking status (never, previous, current), alcohol status (never, previous, current), diagnosis of diabetes at baseline and prevalent cataract surgery at baseline. Results are presented as hazard ratios with 95% confidence intervals (HR, 95% CI), including a p value for linear trend of ordered categories for blood pressure parameters.

The second analysis included blood pressure parameters as continuous variables. SBP, DBP, MAP and PP were included in the aforementioned multivariate model as time-varying continuous predictors modelled as restricted cubic splines with 4 knots placed at the 5th, 35th, 65th, and 95th percentiles, defined *a priori*.[251] The relative hazard ratio and 95% CI for POAG were plotted on the y axis as a function of either systolic, diastolic, mean arterial or pulse pressure on the x axis. The reference blood pressure values were set to SBP 120 mmHg, DBP 80 mmHg, MAP 93.3 mmHg and PP 40 mmHg. Dashed vertical lines represent the knot locations for the restricted cubic splines.

The proportional hazards assumption was tested graphically using Schoenfeld residuals. No major violations were present. A 2-tailed p value was set at 0.05 for statistical significance. Analyses were performed using R (v4.1.1) packages *rms* (v6.2-0),[252] and *survival* (v3.2-11).[253]

We conducted a further sensitivity analysis excluding participants who had taken antihypertensive medication anytime during the study. The antihypertensives medication classes included angiotensin converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, and diuretics (thiazides and thiazide-like diuretics, loop diuretics, and potassium-sparing diuretics). The codes used to identify these medications are listed in the appendix.

3.3 Results

Baseline Characteristics

The study population consisted of 484,268 participants after stepwise exclusion of 1,834 who did not have at least one SBP or DBP measurement at baseline, 5,071 who had any type of glaucoma diagnosis at baseline, 189 who had prevalent glaucoma surgery, and 11,128 missing other variables (stepwise exclusion of 2356 for Ethnicity, 1883 for Smoking, 532 for Alcohol, 607 for TDI, 3692 for Education, 2058 for BMI). The mean age was 56.5 years, and 54.5% were female. Mean baseline systemic blood pressure parameters were SBP 137.8 (SD 18.6) mmHg, DBP 82.3 (SD 10.1) mmHg, MAP 100.8 (SD 12.0) mmHg, and PP 55.6 (SD 13.6) mmHg. There were 2,390 incident POAG events over 5,715,480 person-years of follow up with a median follow up duration of 12.08 years. The baseline characteristics of the study participants are presented in Table 1.

All participants had a baseline SBP and DBP measurement. Over the study period 43 642 participants had two SBP measurements recorded, 9396 had three, and 494 had four. Similarly, 43 645 participants had two DBP measurements recorded, 9400 had three, and 494 had four.

Primary care data was available for 223 335 (46.1%) included participants.

Categorical Analyses

Kaplan-Meier plots shown in Figure 1 demonstrate statistically significant differences in incident POAG associated with SBP, PP and MAP ($p<0.001$ for all) but not DBP ($p=0.79$). Overall higher SBP, PP and MAP were associated with higher rates of incident POAG.

In univariate analyses, compared to a SBP of 120-130mmHg, SBP >130mmHg was significantly associated with an increased risk of incident POAG (Table 2). This remained significant in multivariate analyses for SBP 130-150 and significant for linear trend across all categories after adjustment for age, gender, ethnicity, BMI, education, Townsend deprivation index, smoking status, alcohol status, diabetes, and previous cataract surgery ($p = 0.038$). In comparison, there was no significant association between DBP and the risk of incident POAG in the unadjusted ($p = 0.46$) or adjusted models ($p = 0.80$).

In univariate analyses, compared to a pulse pressure of 40-50mmHg, PP <40mmHg was associated with a reduced risk of incident POAG, while PP categories >50mmHg were associated with incrementally higher hazards of incident POAG (Table 2). In multivariate analyses after adjustment for confounders, only PP ≥70mmHg remained significantly associated with an increased hazard of incident POAG, although the linear trend remained significant across all categories ($p=0.015$).

Compared to a MAP of 90-100mmHg, lower MAP <90mmHg was associated with a reduced risk of incident POAG, while MAP between 100-120mmHg was associated

with a higher hazard of incident POAG in univariate analyses, but these associations were no longer significant in multivariate analyses once adjusted for confounders.

Continuous Analyses

Figure 2 depicts the HR and 95% CI for each of the blood pressure parameters modelled as continuous variables, and after adjustment for confounders.

Compared to a SBP of 120mmHg, SBP <120mmHg was associated with a significantly decreased risk of incident POAG, whereas systolic blood pressure >120mmHg was associated with a significantly increased risk of incident POAG up to an SBP of approximately 185mmHg, after which there was no association (Figure 2). Compared to a DBP of 80mmHg, a lower DBP between 55-70 mmHg was associated with a small significant increased risk of incident POAG but was otherwise nonsignificant for all other ranges.

A PP between 50-100mmHg was found be associated with a significantly increased hazard of incident glaucoma compared to a PP of 40mmHg, while no significant associations were found for MAP.

The above findings were not significantly altered after excluding participants who had taken antihypertensive medication in the sensitivity analysis.

3.4 Discussion

In the predominantly Caucasian cohort of the UK Biobank, we found that higher SBP and PP were associated with an increased risk of incident POAG, while no significant association was found with DBP or MAP. Multivariable analyses showed SBP of 130-150mmHg (vs normal 120-130mmHg) was associated with a 1.16 higher hazard of incident POAG, while a PP of greater than 70mmHg (vs normal 40-50mmHg) was associated with a 1.13 higher hazard of incident glaucoma. In further secondary analyses of blood pressure parameters as continuous variables, higher SBP and PP were similarly significantly associated with a higher risk of incident POAG. Our findings suggest that SBP and PP may more strongly impact glaucoma risk compared to DBP and MAP. Thus, systolic hypertension may represent a modifiable risk factor for POAG. Further longitudinal interventional studies are required to better characterize this relationship.

The statistical representation of systemic blood pressure across previous studies investigating an association with open-angle glaucoma is heterogeneous.[109] Heterogenous representation and variation between studies impedes study comparison. Previous longitudinal cohort studies have represented blood pressure as dichotomised variables using a cut point value to determine hypertensive status,[94,254] discretisation of blood pressure ranges into categories,[94,254,255] and determining hypertensive status using diagnostic codes or use of antihypertensive medication found in medical records.[256,257] Within these approaches variation exists, for example discretisation has been defined using quantiles,[94] combinations of quantiles,[94,255] or prespecified ranges.[254] Both cross sectional and case control

studies also display this heterogeneity.[109] We modelled blood pressure parameters as both categorical, and continuous non-linear variables, and to the best of our knowledge, the latter has not been described before in incident POAG studies. Using restricted cubic splines to represent blood pressure in our analyses preserves the continuous nature of the measurement without assuming linearity. This approach was particularly useful in confirming parameters of significance, namely higher SBP and PP which were consistently associated with a higher hazard of incident POAG across both analyses.

Our study further supports existing data showing an association between systolic hypertension and increased risk of POAG. A meta-analysis by Zhao et al. found greater risk with each 10 mm Hg increase in SBP (RR 1.01, CI 1.00–1.03) in a dose response analysis.[111] This estimate was however pooled from predominantly cross sectional and case control studies. The same meta-analysis found an increased pooled relative risk for POAG comparing participants with hypertension (RR 1.16, CI 1.05–1.28) to those without. The analysis was limited by varying definitions of hypertension across study designs, using cut point values ranging from SBP > 130 to >160 mmHg, antihypertensive medication use, medical records, self-report, and studies including DBP in diagnostic criteria. The majority of positive associations between systemic hypertension and incident POAG are largely derived from cross sectional studies,[111] with most longitudinal studies unable to confirm such an association.[94,255,258,259] In contrast, in a longitudinal cohort study of the Korean National Health Insurance System, Jung et al. found hypertension (SBP ≥140 or DBP ≥90 mm Hg) conferred an increased risk of POAG (HR 1.68, CI 1.53-1.84).[254] Additionally, in a study of managed care network data, Newman-Casey et al. found a

significant association between hypertension defined by diagnostic coding and incident POAG (HR 1.17, CI 1.13–1.22).[257] A detailed characterisation of the influence of blood pressure on POAG risk, beyond the presence or absence of hypertension defined by a varying blood pressure level, has thus far been significantly limited. Similarly, exploration of a dose response relationship is limited by representation of blood pressure in categories or assuming linearity, and lack of longitudinal studies. We analysed blood pressure indices as both categorical and continuous variables. Both approaches showed that higher SBP, particularly >130mmHg, was associated with an increased risk of incident POAG. In addition, we found that there was no significant association between DBP and incident POAG, in keeping with both the Barbados (DBP as quartiles DBP ≤73, 73–80, 80–88, >88 mmHg and per 10 mmHg increase) and Rotterdam Eye Studies (DBP <65, 65 – 74, 75 – 85, >85 mmHg and per standard deviation).[94,260] If risk of disease is mediated by SBP alone, these findings may complicate the interpretation of incident POAG studies that use elevated DBP as part of the criteria for systemic hypertension. Taken together with the available literature, our findings suggest that systolic hypertension may represent a modifiable risk factor for glaucoma. It is further possible that hypertension, along with other cardiovascular risk factors may increase the risk of glaucoma progression.[247] More aggressive hypertension management may be warranted in patients who are at high risk of POAG. Additional prospective studies are required to further evaluate this relationship.

An elevated PP has been increasingly recognised as a risk factor for cardiovascular disease,[125] with a possible influence on glaucoma. The existing literature investigating PP and POAG is mixed. While the Barbados Eye Study found no

apparent relationship between PP (as categories PP ≤41, 41–51, 51–64, >64 mmHg and per 10 mmHg increase) and incident POAG,[948] the Rotterdam Eye Study, found a significant association between standard deviations of pulse pressure and hypertensive POAG.[261] In a further categorical analysis, compared to PP <55 mmHg, a PP 65-80 and > 80 mmHg was associated with a 2.81 (CI 1.35-5.82) and 2.87 (CI 1.34-6.17) higher odds respectively of POAG.[261] Similarly, we found that higher PP, particularly greater than 70 mmHg, was associated with an increased risk of incident POAG, with the relationship appearing to mirror that of SBP. As PP is derived from SBP and DBP, these findings may reflect the significant association between SBP and POAG.

Previous investigations of associations between MAP and incident POAG are also varied. We found no significant association for MAP in our analysis, consistent with Leske et al. who similarly found no significant association per 10 mmHg increase or by quartiles (MAP ≤89, 89–98, 98–107, >107 mmHg).[94] In contrast, in a longitudinal cohort study of the All of Us Research database, Lee et al observed that low MAP (<83.0 mmHg) was associated with an increased risk of incident POAG (HR 1.32, CI 1.04–1.67) compared to medium MAP (83.0 ≤ MAP ≥ 103.3 mmHg).[255] In addition, the authors found no association with high map (MAP >103.3 mmHg), while another longitudinal analysis of participants of the Nurses' Health Study and Health Professionals Follow Up Study found an increased risk of incident POAG with increasing mean arterial pressure (HR 1.05, CI 1.01 – 1.09, per 5mmHg).[262] The conflicting findings in the literature, combined with the lack of association found in our study suggest that further investigation is required to better understand this relationship. DBP plays the predominant role in the derivation of MAP compared with

SBP, which may account for the lack of association given previous longitudinal studies have similarly found no association between DBP and incident POAG.

Low systemic blood pressure has been shown to influence disease progression amongst patients diagnosed with POAG, predominantly with low IOP, in retrospective and longitudinal studies.[115-117] Similarly, nocturnal dips in systemic blood pressure are a risk factor for glaucoma progression.[248] It is not known whether those with untreated low blood pressure fair better, worse or the same with regard to disease progression relative to those who are treated, and sometimes overtreated, for systemic hypertension. This is a pertinent issue given that systemic hypertension is endemic in many populations.[263] The Low-Pressure Glaucoma Treatment Study showed antihypertensive medication was associated with disease progression.[264] It is possible that chronic hypertension results in vascular damage to the optic nerve. The subsequent lowering of blood pressure with treatment may result in further limitation of blood flow to the nerve in the setting of vascular dysregulation.[265] Our findings suggest that high SBP may be a more important determinant of incident glaucoma risk than high DBP. High SBP perhaps leads to initial optic nerve vascular compromise, that is subsequently further exacerbated by low BP, either systolic or diastolic, based upon prior work.

Our study exhibits several limitations. Diagnostic codes in hospital inpatient admission data or primary care data were used to identify cases of incident POAG. There is a possibility of undiagnosed, undocumented, or misdiagnosed incident cases. Only a subset of participants had primary care data available, therefore incident cases relied on inpatient hospital data. Similarly, we could not account for

undiagnosed cases at baseline or during follow up. It is possible the associations seen are with seeking early care, or receiving more care due to higher blood pressure, rather than POAG. We did not adjust for important confounders including family history of glaucoma, IOP, refractive error, central corneal thickness, or cerebrospinal fluid pressure as this data was not available for all UK Biobank participants. Repeat measurements were not available for all participants despite blood pressure included as a time-varying co-variable to account for longitudinal assessment of blood pressure. Lastly, the results may not be widely generalisable as the UK Biobank consists of predominantly Caucasian participants. Further, the biobank has shown a 'healthy volunteer' selection bias.[266] Thus, caution should be used when generalising findings to the population level. Our analysis also has several strengths, including standardised and comprehensive collection of sociodemographic, lifestyle, anthropomorphic and medical information in a large sample size, standardised measurement of blood pressure with large and repeated samples over a long follow up period of 12 years, and the examination of continuous, non-linear associations.

3.5 Conclusion

In summary, we found that higher SBP and PP were associated with a higher risk of incident POAG. In contrast, DBP and MAP were not found to be significantly correlated with POAG incidence. Multivariate categorical analysis showed SBP 130-150 mmHg compared to 120-130 mmHg was associated with 1.16 increased risk of incident POAG. A PP of >70 mmHg compared to 40-50 mmHg was associated with a 1.13 higher hazard. The relationship between both systolic blood pressure and pulse pressure was non-linear when modelled as a continuous variable. This study provides further evidence that specific systemic blood pressure parameters may contribute to incident POAG with important potential implications for disease prevention and screening.

3.6 Tables

Table 1: Comparison of the baseline characteristics between participants who did, and those who did not, develop incident POAG

	No POAG (N=481878)	POAG (N=2390)	p value
Mean Age (SD)	56.5 (8.1)	61.7 (6.2)	< 0.001
Females (N, %)	262873 (54.6%)	1219 (51.0%)	< 0.001
Ethnicity			< 0.001
- White	456634 (94.8%)	2216 (92.7%)	
- Asian	10659 (2.2%)	56 (2.3%)	
- Black	7482 (1.6%)	85 (3.6%)	
- Other	7103 (1.5%)	33 (1.4%)	
Smoking			< 0.001
- Never	264207 (54.8%)	1299 (54.4%)	
- Previous	166886 (34.6%)	915 (38.3%)	
- Current	50785 (10.5%)	176 (7.4%)	
Alcohol			0.037
- Never	21121 (4.4%)	111 (4.6%)	
- Previous	17079 (3.5%)	107 (4.5%)	
- Current	443678 (92.1%)	2172 (90.9%)	
Townsend Index			0.91
- 1st quintile	97487 (20.2%)	471 (19.7%)	
- 2nd quintile	96714 (20.1%)	496 (20.8%)	
- 3rd quintile	96585 (20.0%)	483 (20.2%)	
- 4th quintile	96409 (20.0%)	473 (19.8%)	
- 5th quintile	94683 (19.6%)	467 (19.5%)	
Diabetes (N, %)	24537 (5.1%)	187 (7.8%)	< 0.001
Education			< 0.001
- None	81480 (16.9%)	529 (22.1%)	
- Other	29745 (6.2%)	190 (7.9%)	
- Tertiary Education	188296 (39.1%)	843 (35.3%)	
- Secondary Education	182357 (37.8%)	828 (34.6%)	
Prior Cataract Surgery	9676 (2.0%)	93 (3.9%)	< 0.001
BMI			0.001
- healthy weight	157209 (32.6%)	830 (34.7%)	
- underweight	2505 (0.5%)	13 (0.5%)	
- overweight	204921 (42.5%)	1049 (43.9%)	
- obesity	117243 (24.3%)	498 (20.8%)	
Mean Baseline SBP (SD)	137.8 (18.6)	141.9 (18.3)	< 0.001
Mean Baseline DBP (SD)	82.3 (10.1)	82.1 (9.8)	0.55
Mean Baseline MAP (SD)	100.8 (12.0)	102.1 (11.4)	< 0.001
Mean Baseline PP (SD)	55.5 (13.6)	59.8 (14.2)	< 0.001

SD: standard deviation, N: number

Table 2: Relative risk of developing incident POAG among categories of systemic blood pressure measures in univariate and multivariate models

	HR (95% CI)					
Systolic Blood Pressure	SBP<120	SBP 120-130	SBP 130-140	SBP 140-150	SBP ≥150	p for linear trend
Univariate	0.89 (0.76-1.04)	Reference	**1.34** (1.17-1.53)	**1.51** (1.32-1.73)	**1.70** (1.5-1.93)	<0.001
Multivariate	1.02 (0.86-1.19)	Reference	**1.16** (1.01-1.32)	**1.16** (1.01-1.33)	1.12 (0.99-1.28)	0.038
Diastolic Blood Pressure	DBP <70	DBP 70-80	DBP 80-90	DBP 90-100	DBP ≥ 100	p for linear trend
Univariate	0.96 (0.83-1.1)	0.97 (0.88-1.07)	Reference	0.98 (0.87-1.10)	0.88 (0.72-1.08)	0.46
Multivariate	0.95 (0.82-1.1)	0.99 (0.90-1.09)	Reference	0.99 (0.88-1.11)	0.93 (0.75-1.14)	0.80
Mean Arterial Pressure	MAP <90	MAP 90-100	MAP 100-110	MAP 110-120	MAP ≥ 120	p for linear trend
Univariate	**0.82** (0.73-0.93)	Reference	**1.16** (1.05-1.28)	**1.23** (1.09-1.38)	1.04 (0.87-1.24)	<0.001
Multivariate	0.92 (0.81-1.05)	Reference	1.05 (0.95-1.17)	1.05 (0.93-1.19)	0.86 (0.71-1.03)	0.65
Pulse Pressure	PP <40	PP 40-50	PP 50-60	PP 60-70	PP ≥70	p for linear trend
Univariate	**0.74** (0.61-0.90)	Reference	**1.34** (1.19-1.5)	**1.72** (1.53-1.94)	**2.15** (1.90-2.42)	<0.001
Multivariate	0.90 (0.74-1.10)	Reference	1.05 (0.93-1.18)	1.09 (0.96-1.24)	**1.13** (1.00-1.29)	0.015

Statistically significant in bold

3.7 Figures

Figure 1: Kaplan-Meier curves of POAG-free survival probability for systemic blood pressure parameters

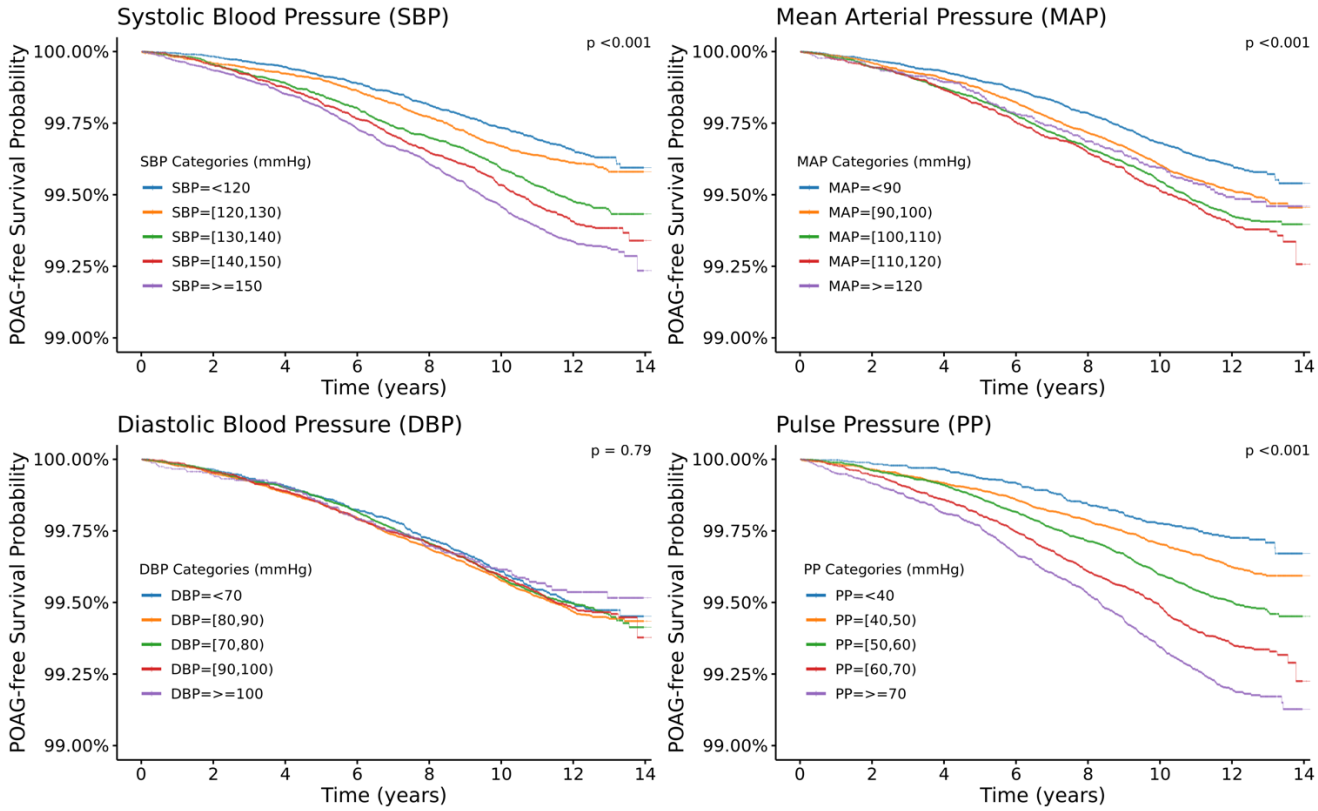
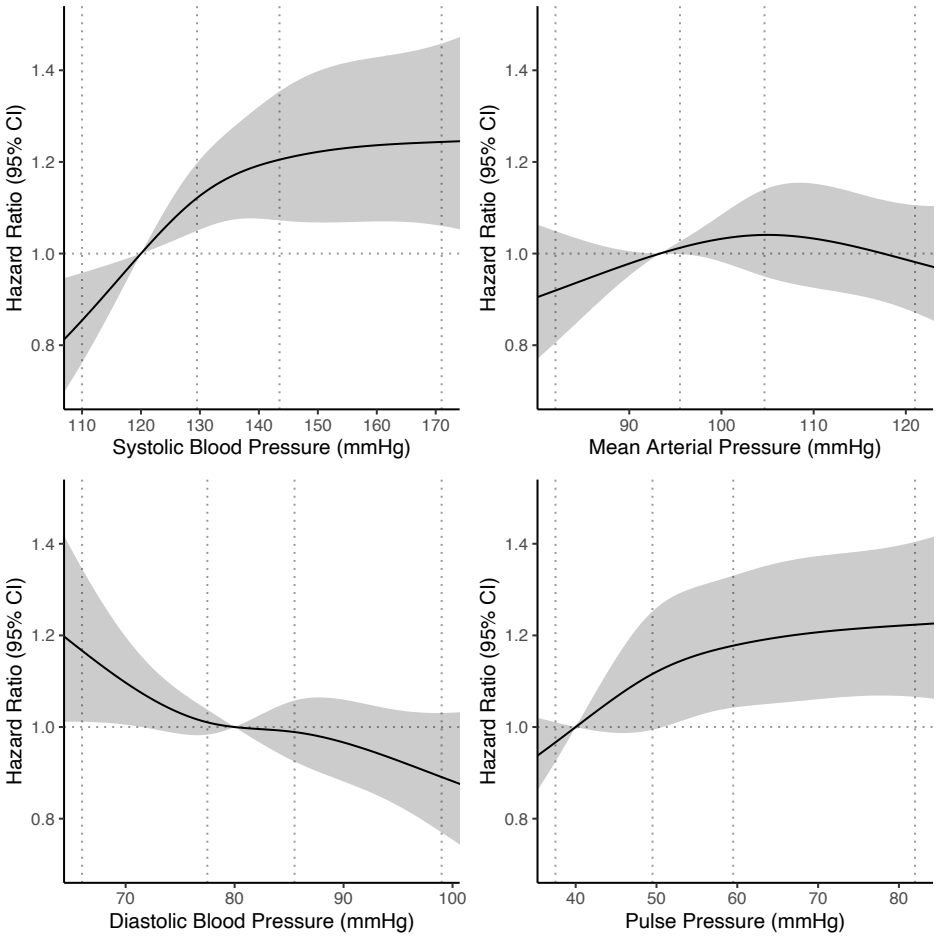


Figure 2: Hazard Ratio curves for incident POAG among systemic blood pressure parameters.

Blood pressure measures truncated at the 5th and 95th percentiles. Gray band represents the 95% confidence interval. Vertical dotted lines are the knot locations (5th, 35th, 65th, and 95th percentiles).



4 Chapter 4: Nationwide Trends in Vitreoretinal Procedures within Australia

4.1 Introduction

Increasing global rates of vitrectomy for the repair of retinal detachment and indications including macular holes and epiretinal membranes have occurred alongside considerable technological advances in pars plana vitrectomy (PPV). [171-176,267] Simultaneous technological advances in optical coherence tomography (OCT) have aided the detection, staging, surgical planning and prognostication of vitreoretinal interface disorders possibly enabling earlier detection and treatment to influence this trend.[268] Similar global growth in anti-vascular epithelial growth factor (anti-VEGF) injections has been seen due to the approval of multiple injectables with expanding indications, compounded by the recurring and long term nature of treatment with these agents.[177,180,269-271] However previous studies are limited by use of institution specific populations, lack of standardisation to the age and gender structure of the populations of interest, and lack of age stratified trends. Furthermore, data for the Australian population is limited to the treatment of retinal detachment.[171] Thus there is a need for an age and gender standardised population level analysis of trends in vitreoretinal procedures, stratified by age, in Australia. These trends inform future service provision and monitoring of practice patterns. We sought to investigate contemporary Australian trends in common vitreoretinal procedures stratified by age, using public and private hospital data from the Australian Institute of Health, Welfare and Ageing (AIHW) over the past two decades.

In this chapter, we use an administrative database to investigate nationwide age and gender stratified temporal trends in vitreoretinal procedures in Australia. The data is sourced from the Australian Institute of Health and Welfare (AIHW) National Hospital Morbidity Database (NHMD).[272] The NMHD is 'a compilation of episode-level records from admitted patient morbidity data collection systems in Australian public and private hospitals'.[272] The data is collected by individual administrative and clinical record systems and forwarded to state and territory health authorities for collation and submission to the AIHW annually. The NHMD qualifies as an administrative database as the data consists of procedural codes recorded during the delivery of routine healthcare covering the entire Australian population treated in public and private hospitals. The data is collated to monitor the activity of the Australian healthcare system. It does not collect other clinical or disease-specific data.

4.2 Methods

We retrospectively analysed temporal trends in vitreoretinal procedures using the Australian Institute of Health and Welfare's National Hospital Morbidity Database (NHMD). Annual data on vitreoretinal procedures was extracted from the NHMD over the period July 2000-June 2001 to July 2018-June 2019, the years hereafter referred to by the latter half of each 12-month period. THE NHMD captures vitreoretinal procedures performed in all Australian public and private hospitals. Data quality statements report that almost all public hospitals provide data except an early parenting centre in the Australian Capital Territory (ACT). Similarly, most private hospitals also provide data except the private free-standing day hospital facilities and some (year dependent) overnight private hospitals in the ACT.

The NMHD classifies procedure type according to the second edition of the International Statistical Classification of Diseases and Related Health Problems, 10th Revision, Australian Modification (ICD-10-AM) and the 3rd to 10th editions of Australian Classification of Health Interventions (ACHI). The procedure codes collected for retinal detachment repair included '42773-00—Repair of detachment by diathermy', '42809-01—Repair of detachment by photocoagulation' and '42776-00—Repair of detachment with scleral buckle'. The procedure codes collected for pars plana vitrectomy for indications other than retinal detachment repair included '42722-01—Pars plana vitrectomy with division of vitreal bands', '42725-00—Pars plana vitrectomy with division of vitreal bands and removal of preretinal membrane'. Intravitreal injections were extracted using '42740-03—Injection of therapeutic

substance into the posterior chamber'. There are no separate codes for the type of therapeutic substance injected therefore this code may encompasses agents such as anti-VEGF, dexamethasone or antibiotics.

We combined the codes for retinal detachment repair with diathermy and photocoagulation to represent an estimate of pars plana vitrectomy for retinal detachment repairs (PPV for RD), as they both require vitrectomy. We estimated the total numbers of PPV not involved in repairing retinal detachments (PPV unrelated to RD) by combining the codes for PPV and division of vitreal bands and PPV with removal of preretinal membrane. The procedures in the NHMD database are counted as single procedures, lacking linking data to identify procedures that were performed concurrently. As such, we were unable to estimate the proportion of single or combined procedures within total counts, such as scleral buckle alone or combined with vitrectomy.

We used Medicare Benefits Schedule (MBS) data from the period July 2000-June 2001 to July 2018-June 2019 for therapeutic injections to compare MBS injection data with the NMHD. The MBS injection data reflects injections performed in the outpatient setting compared to those performed in the inpatient setting captured by the NHMD. The MBS codes used were '42738' –injection of therapeutic substance as an independent procedure from 2012, and '42740'which was the MBS code for all ocular therapeutic injections before 2012, and from 2012 onwards representing therapeutic injections associated with intraocular surgery. These codes also include diagnostic and therapeutic aspiration of aqueous or vitreous, and aspiration of

vitreous respectively. It is important to note that ‘42740’ was the only available code for intravitreal injections before 2012.

We estimated the Australian resident population using publicly available population data from the Australian Bureau of Statistics. The ratio of the absolute number of procedures to the estimated Australian resident population in each corresponding year was used to calculate the procedure rate per 100,000 persons to account for yearly increases in population size.

The total number of procedures for each 20-year age group (<20, 20-39, 40-59, 60-79 and ≥80), gender, and year were calculated per procedure, and directly standardised to the Australian population in each year. Negative binomial regression models were used to assess trends in procedure numbers over time and were fitted to the data with year as a continuous predictor variable, age and gender as categorical predictor variables, and an interaction variable for age group and gender, offset by population as a continuous variable to control for population changes over time. Negative binomial regression models were also fitted to assess if temporal trends in procedure numbers varied trends by age group or gender. In this model the year was included as a continuous predictor, age group and gender as categorical predictors, and an interaction variable for age group and year was included, offset by population. In the negative binomial regression model for variation in temporal trends according to gender, the year as a continuous predictor, age group and gender as categorical predictors, and an interaction variable for gender and year was included, offset by population. Results are reported as incidence rate ratios (IRR) and 95% confidence interval, p value, and p for interaction with age over time. All analyses

were conducted using R v4.0.3, with statistical significance set at $p<0.05$. Negative binomial regression analysis was performed using the *MASS* package v7.3.54.

This study adhered to the principles outlined in the Declaration of Helsinki. Institutional review board approval was not required as the data used is available in a public repository, freely accessible, and non-identifiable. Participant consent was not obtained due to the public and deidentified nature of the data.

4.3 Results

The total number of vitreoretinal procedures included in this study increased from 8102 in 2001 to 136430 in 2019. The proportion of cases performed as a same day admission increased for all procedures over time, specifically from 16.8% in 2001 to 43.5% in 2019 for scleral buckle, from 26.34% in 2001 to 48.4% in 2019 for PPV for RD, from 22.9 in 2001 to 65.5% in 2019 for PPV unrelated to RD, and from 56.8% in 2001 to 98.8% in 2019 for intravitreal injections.

The incidence of PPV for RD increased from 7.5 per 100,000 persons in 2001 (n=1442) to 20.7 per 100,000 in 2019 (n=5253) whilst scleral buckling decreased from 10.5 per 100,000 persons in 2001 (n=2020) to 4.0 per 100,000 in 2019 (n=1016). (Table 1, Figure 1)

Incidence of PPV unrelated to RD increased from 18.4 per 100,000 persons in 2001 (n=3552) to 67.1 per 100,000 in 2019 (n=17023). Intravitreal injections demonstrated a dramatic increase from 5.6 per 100,000 persons in 2001 (n=1088) to 446.0 per 100,000 in 2019 (n=113138). (Table 1, Figure 1) Injections captured by the MBS injection code before 2012 showed an increase in incidence from 25.9 per 100,000 persons in 2001 (n=4984), to 739.7 per 100,000 in 2011 (n=165243). After 2012, injections as an independent procedure captured by a new MBS injection code increased in incidence from 280.7 per 100,00 persons in 2012 (n=63810) to 1955.0 per 100,000 in 2019 (n=495903).

Negative binomial regression analysis revealed a significant increase in the rate of PPV for RD by 5% annually (IRR 1.05, CI 1.03-1.07, p<0.001) compared to a significant decrease in the rate of scleral buckle procedures by 1% annually (IRR 0.99, CI 0.94-0.95, p<0.001). There was a significant interaction among age groups over time for scleral buckling (p<0.001), but not for PPV for RD (p=0.22), suggesting temporal trends differed among age groups for scleral buckling but not for PPV for RD (Table 2). When analysed within age groups, the rate of PPV for RD significantly increased across all age groups, the highest seen in the 40-59 group, followed by the 60-79, >80 age groups. The rates for the 20-39 and <20 age groups were not significant. The rates of scleral buckling significantly decreased among all age groups, the largest decreases seen in the >80 group followed by the 60-79, 40-59, <20, and 20-39 age groups (Table 2).

There was a significant increase in the rate of PPV unrelated to RD of 7% annually (IRR 1.07, CI 1.05-1.08, p<0.001). The rate of PPV unrelated to RD demonstrated a significant interaction among age groups over time (p<0.001) (Table 2). Rates of PPV unrelated to RD significantly increased for all age groups, increasing the most in the >80 group (Table 2).

We observed a significant increase in intravitreal injections of 21% annually (IRR 1.21, CI 1.20-1.223, P<0.001). There was also a significant interaction among age groups over time (p<0.001) (Table 2). Rates of intravitreal injection significantly increased across all age groups, where increasing age showed increasing rates of intravitreal injections (Table 2). The incidence of MBS injections increased from 25.9

per 100,000 persons in 2001 to 1955.0 per 100,000 persons in 2019 in parallel with increasing incidence of inpatient injections captured by the NHMD.

When stratified by gender, negative binomial regression showed no significant interaction over time for any procedure (all $p>0.05$).

4.4 Discussion

We found that between 2001 and 2019 the rate of scleral buckle procedures declined by 1% annually compared to a 5% annual increase in PPV for RD. The decline in scleral buckle use and increase in PPV for RD were more pronounced among those aged 40 years and above. Age-specific trends showed the annual decrease in buckle use was larger in older age groups while the annual increase in PPV for RD was highest in younger age groups. Furthermore, we found that PPV unrelated to RD and intravitreal injections increased across all age groups. The annual increase in intravitreal injections was markedly higher than any other procedure, increasing 21% annually. Our findings reflect changing trends in vitreoretinal procedures and suggest an increasing nationwide trend to PPV over scleral buckle for RD repair in Australia.

Previous reports have similarly found declining rates of scleral buckle use in favour of vitrectomy for retinal detachment repair. In Western Australia between 2000 and 2013, the proportion of scleral buckle with or without vitrectomy for retinal detachment repair decreased from 70% to 16%, compared to vitrectomy alone which increased from 25% to 84%.[171] The global proportion of scleral buckles performed for retinal detachment repair decreased 21.4% over 2005-2011 in Singapore,[172] 17.5% over 2010-2017 in Japan,[173] 13.9% over 1997-2005 in Taiwan,[174] and 17% over 2005-2016 in the United States,[175] in addition to a decrease in absolute numbers.[180,181] Similarly in England, national annual rates of scleral buckle declined from 12 episodes per 100,000 in 1995 to 6 per 100,000 in 2004.[176] In contrast, no

significant trends in surgical approach was observed from 2007 to 2011 in Korea, where the proportion of scleral buckle (47% in 2011) and vitrectomy (43% in 2011) remained similar over time.[273] Advances in transconjunctival sutureless vitrectomy have made this an attractive surgical approach.[171,173,175,273] Benefits include shorter convalescence and improved patient comfort,[172] ability to relieve retinal traction and drain subretinal fluid, and potentially superior outcomes in pseudophakia.[175] In addition, vitrectomy may avoid disadvantages of buckle procedures such as postoperative pain and axial myopia,[173,175] concern that buckles are prohibitive to future glaucoma surgery,[173,175] and longer buckle surgical time.[175] A decreasing proportion of scleral buckles performed compared to vitrectomy is reported by surgeons.[153] This decline is seen despite no significant difference in primary reattachment rates for rhegmatogenous retinal detachment between the approaches,[274] the increased risk of iatrogenic breaks and cataract progression or development with vitrectomy,[274,275] and being less cost-effective in both hospital and ambulatory settings.[276] Decreasing familiarity with the buckle procedure,[173,180] risks surgeons and trainees underutilising buckles, which have been shown to be an effective long term treatment option in well selected patients.[277]

There is a worldwide exponential rise in the use of intravitreal injections,[177,180-183,269-271,278] however lacking age stratified trends. We found an increase in rate of intravitreal injections across all age groups in line with previous reports. Age-stratified analyses showed rates increased with increasing age and the largest increases in incidence were 36% and 26.5% annually in the >80 and 60-79 age groups respectively. This may reflect the increasing incidence of retinal vascular occlusion and age-related macular degeneration with age.[279,280] The recurring nature

of intravitreal injections further contributes to increasing incidence compounded by an ageing population. Aflibercept and ranibizumab are the first and seventh most costly drugs to the Australian Pharmaceutical Benefits Scheme respectively.[281] Similarly, these injections represent a significant proportion of the health budget in the United States.[282] The dramatic rise in injections places significant financial strain on the Australian and global health systems with implications for future sustainability and financing.

Pars plana vitrectomy for retinal diseases other than retinal detachment showed increasing incidence for all age groups in our analysis. PPV unrelated to RD increased 8.9% annually in the >80 age group, 8.4% annually in the 40-59 age group, and 8.1% annually in the 60-79 group. There is a paucity of literature examining the trends in pars plana vitrectomy unrelated to RD over time, however the widespread use of optical coherence tomography and enhanced detection of vitreomacular interface disorders likely explain increasing surgical numbers. A similar increasing incidence in PPV unrelated to RD has been observed in United states from 2002-2014 for indications such as internal limiting membrane removal.[180,181] In addition, an increased volume of vitrectomies has been reported across Korea, England and the United States, however limited by the inclusion of retinal detachment repair in their data. [176,283,284] In contrast, an increase in vitrectomies has not been observed in patients with diabetes, who have seen declines in England and the United States,[284,285] likely due to the rapid increasing incidence of anti-VEGF injections, improved medical management of the disease, and decreasing incidence of proliferative diabetic retinopathy in resource rich countries.[286]

Our analysis has several limitations to consider. Firstly, the coding of procedures changed throughout the study period, being collected across the second to tenth editions of the ACHI. Changes from the ninth to tenth edition resulted in missing data for the code capturing repair by diathermy in the years 2018 and 2019. Secondly, we estimated the code for retinal detachment repair by vitrectomy alone by combining repair by photocoagulation and diathermy as there is no dedicated ACHI code. Thirdly, there is no dedicated code for repairs using a combination of scleral buckle and vitrectomy, therefore these cases are not reflected in the analysis. Fourthly, we did not include data for cryotherapy given the code for retinal detachment repair by cryotherapy did not distinguish between procedures that used either PPV, scleral buckling or both. The code for external cryotherapy as similarly excluded given this is more frequently performed as an outpatient procedure and not adequately captured by the NHMD. Similarly, pneumatic retinopexy which is also more commonly an outpatient procedure was newly introduced in the 10th edition of the ACHI, therefore data for pneumatic retinopexy is only available for the years 2018 and 2019 and not included in the analysis. Fifthly, MBS code for injections also captures aqueous and vitreous aspiration, therefore the incidence rates for these procedures are artificially inflated to an unknown but likely small degree. Sixthly, the study relies on accurate procedure coding possibly under or overestimating certain procedural codes. Lastly, the NMHD lacks additional detail such as hospital and state specific information, or objective clinical data to further inform the interpretation of the observed trends. The overall strengths of this analysis include the long timespan for data capture, all analysed codes besides repair by diathermy having complete data, and the consistency of these selected codes over time.

4.5 Conclusion

In summary, between 2001 and 2019 the overall rate of scleral buckles procedures declined in comparison to an overall increasing rate of PPV for RD. Both the decline in scleral buckles and increase in PPV for RD was more marked in those 40 years and above. Therefore, our analysis suggests an increasing preference for vitrectomy over scleral buckle for retinal detachment repair in Australia over the last two decades. In addition, PPV unrelated to RD and intravitreal injections increased across all age groups. Our findings mirror similar trends seen internationally and reflect the changing practice patterns in vitreoretinal procedures over time.

4.6 Tables

Table 1: Number and incidence of vitreoretinal procedures in Australia 2001-2019

Year	Number of procedures				Incidence (per 100,000 persons)				Population
	Scleral Buckle	PPV for RD	PPV unrelated to RD	Intravitreal Injection	Scleral Buckle	PPV for RD	PPV unrelated to RD	Intravitreal Injection	
2001	2,020	1,442	3,552	1,088	10.48	7.48	18.43	5.64	19,274,701
2002	1,894	1,753	4,207	1,440	9.72	8.99	21.58	7.39	19,495,210
2003	1,837	2,104	4,751	1,814	9.32	10.67	24.09	9.20	19,720,737
2004	1,764	2,364	5,259	2,515	8.85	11.86	26.38	12.62	19,932,722
2005	1,744	2,907	6,233	3,405	8.64	14.41	30.89	16.88	20,176,844
2006	1,839	3,269	6,752	4,872	8.99	15.98	33.02	23.82	20,450,966
2007	1,462	3,475	7,844	9,784	7.02	16.68	37.66	46.98	20,827,622
2008	1,660	3,552	8,778	17,733	7.81	16.72	41.31	83.45	21,249,199
2009	1,602	3,786	9,844	20,925	7.39	17.45	45.38	96.47	21,691,653
2010	1,268	4,037	10,577	30,058	5.76	18.32	48.01	136.43	22,031,750
2011	1,358	4,330	11,114	36,655	6.08	19.38	49.75	164.08	22,340,024
2012	1,152	4,635	12,165	47,110	5.07	20.39	53.51	207.23	22,733,465
2013	1,079	4,373	12,166	58,196	4.67	18.91	52.60	251.62	23,128,129
2014	1,019	4,226	12,842	63,679	4.34	18.00	54.70	271.26	23,475,686
2015	1,075	5,013	15,356	93,914	4.51	21.05	64.48	394.33	23,815,995
2016	1,046	4,916	14,713	88,017	4.32	20.32	60.82	363.84	24,190,907
2017	1,010	5,996	15,406	93,108	4.11	24.37	62.62	378.46	24,601,860
2018	1,005	5,084	16,107	105,456	4.02	20.35	64.47	422.12	24,982,688
2019	1,016	5,253	17,023	113,138	4.01	20.71	67.11	446.03	25,365,745

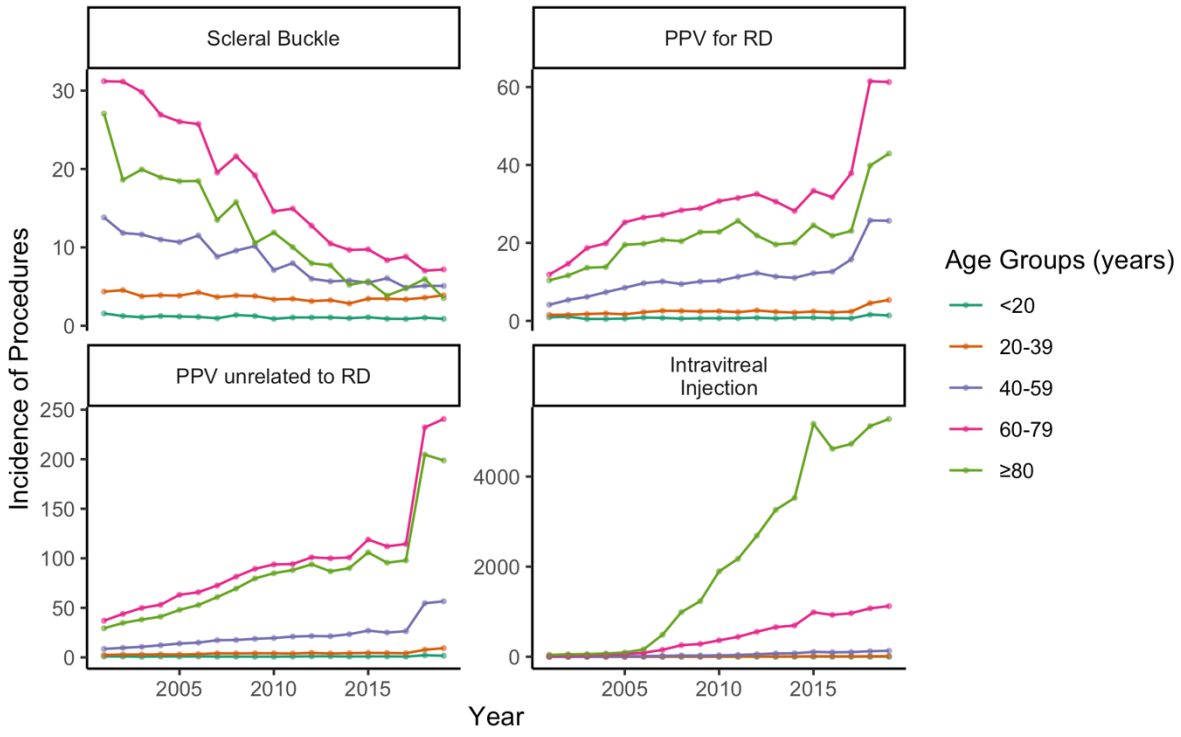
Table 2: All-age and age stratified incidence rate ratios (IRR) among vitreoretinal procedures in Australia over 2001-2019

Procedure	Age group	N	IRR	95% CI	p value	p for age interaction
Scleral Buckle	All ages	26850	0.94	0.94-0.95	<0.001	<0.001
	<20	1176	0.98	0.97-0.99	<0.01	
	20-39	4384	0.99	0.98-1.00	<0.01	
	40-59	9051	0.95	0.94-0.95	<0.001	
	60-79	10546	0.91	0.90-0.92	<0.001	
	≥80	1693	0.90	0.89-0.91	<0.001	
PPV for RD	All ages	72515	1.05	1.03-1.07	<0.001	0.22
	<20	1453	1.02	0.98-1.06	0.40	
	20-39	5338	1.04	1.00-1.08	0.06	
	40-59	23008	1.07	1.03-1.11	<0.001	
	60-79	36512	1.06	1.02-1.10	0.001	
	≥80	6204	1.05	1.01-1.09	<0.01	
PPV unrelated to RD	All ages	194689	1.07	1.05-1.08	<0.001	<0.001
	<20	1848	1.03	1.01-1.05	<0.01	
	20-39	9171	1.05	1.03-1.07	<0.001	
	40-59	43471	1.08	1.06-1.11	<0.001	
	60-79	116360	1.08	1.05-1.12	<0.001	
	≥80	23839	1.09	1.06-1.12	<0.001	
Intravitreal Injection	All ages	792907	1.21	1.20-1.23	<0.001	<0.001
	<20	1972	1.12	1.10-1.14	<0.001	
	20-39	8087	1.14	1.12-1.15	<0.001	
	40-59	59442	1.23	1.21-1.24	<0.001	
	60-79	340434	1.27	1.24-1.29	<0.001	
	≥80	382972	1.36	1.32-1.40	<0.001	

N: Number of procedures, IRR: incidence rate ratio, CI: 95% confidence interval

4.7 Figures

Figure 1: Age-stratified trends in the incidence of vitreoretinal procedures in Australia over 2001-2019



5 Chapter 5: Automated Disease Registry Using Low-Code Natural Language Processing

5.1 Introduction

The ability to extract information from unstructured free-text has significantly improved due to advances in machine learning approaches to natural language processing (NLP).[287] Given diagnostic doing in electronic health records is usually performed manually, improved machine learning techniques for entity extraction may assist diagnostic coding. The supplementation of diagnostic codes with information from free-text fields may improve patient cohort identification for studies involving the secondary use of electronic health records and patient cohort identification.[194] Applying new and advanced machine learning methods (e.g. named entity recognition) for diagnosis extraction requires expert knowledge of these techniques, and the skills to implement them. These skills are unfamiliar to most clinicians and are a significant barrier to the implementation of NLP clinical and research workflows.

Few studies involve easy to use, production ready, low-code machine learning capable tools in their workflows for cohort identification.[230] The available tools for biomedical NER rely on dictionary-based approaches to detect entities in text.[288-290] This dictionary-based approach is limited by a unique vocabulary of biomedical text and the challenges of natural language including abbreviations,[220-222] misspellings,[219] variable representations of similar concepts, [223] ambiguity, [218] and variable representations of numbers in text.[224] Machine learning offers more

generalisable approaches to disease identification without extensive clinician input or dictionaries.

We demonstrate the use of low code machine learning NLP tools applied to electronic clinical records to build an automated registry of ophthalmic diseases. This is accompanied by study files to replicate the registry in any setting or institution. While this registry does not meet the strictest criteria for a registry, it is classified as a registry due to the prospective record of patient diagnoses during their interaction with the Ophthalmology clinic for the purpose of monitoring global ophthalmic disease activity that could be used for further research or service planning.

5.2 Methods

This study was performed at the Royal Adelaide Hospital, Adelaide, Australia, and approved by the institutional Human Research Ethics Committee. The study adhered to the tenants of the Declaration of Helsinki. We extracted deidentified free-text ophthalmology clinic records from the electronic health record system for all adult outpatient ophthalmology clinics between November 2019 to May 2022. All notes were free-text and written in English.

We performed dataset annotation and NER model training using a low-code annotation software tool (*Prodigy*, https://prodi.gy/docs, ExplosionAI GmbH, Berlin, Germany). *Prodigy* is an active learning-based annotation tool and integrates with the spaCy NLP library (ExplosionAI GmbH, Berlin, Germany). The architecture of the NER model is based on a convolutional neural network.

Annotations are performed via text highlighting in a graphical user interface displayed in a web browser. (Figure 1) Simple, one-line text commands execute through the command terminal enable the various NLP tasks. These tasks used are pre-scripted Python functions that initialise dataset annotation, and train NER models. The workflow is summarised in Figure 2.

The clinical record text is tokenised into words when annotation is initialised. This prevents errors of partial selection when annotating. The diagnoses in the first 1000 clinical records were annotated through the graphical user interface to create an

initial annotation dataset. (Figure 2). All diagnoses were annotated in full. Multiple-word diagnoses were annotated as one annotation, and only words relevant to the diagnosis were annotated. An initial NER model was trained using this initial annotation dataset. The purpose of the initial model was to provide suggested annotations in subsequent dataset annotation to increase annotation efficiency.

Subsequently a larger annotation dataset was created by annotating a proportion of the remaining clinical records and correcting the suggestions made by the initial NER model. Further annotation only involved new records not previously annotated. At 500 note intervals we calculated accuracy statistics. The tool calculates these statistics by training a model using increasing proportions (25%, 50%, 75%, 100%) of the total annotations. Annotation of the clinical records was performed until model accuracy showed minimal-to-no further improvement within the last 25%, occurring at 1923 records.

We then trained a final NER model using both annotation datasets. The model was evaluated by calculating the precision, recall and F-score.[291] Precision refers to the ratio of true positives to the sum of true and false positives (TP/TP + FP), and recall refers to the ratio of true positives to the sum of true positives and false negatives (TP/TP + FN). The command for model training reserves a proportion of annotations to evaluate the model and produce the accuracy statistics. A separate evaluation set is therefore not required to evaluate the model. We used twenty percent of the annotations to produce the precision, recall, and F-score.

We used the *spaCy* (v3.1.4) NLP library to load and run the model over the entire set of clinical records to extract the diagnostic entities. Extracted entities were subsequently cleaned of capitalisation and non-alphanumeric characters using regular expressions. We calculated the term-frequency-inverse-document-frequency (TF-IDF) for each entity document pair using the *genism* (v4.1.2). A binary weight was used for the term frequency and pivoted unique normalisation for document length normalisation. A binary weight was chosen as only the appearance of the entity in the document was relevant. Pivoted unique normalisation was used to counter bias introduced by document length and align the probabilities of retrieval and relevance,[292] given clinical notes can vary in length.

Common terms were manually mapped to SNOMED-CT (International Edition, version 2021-07-31) by a medical officer. The datasets including the clinical records, extracted entities and their mapped SNOMED-CT terms were imported into a free and open-source database management tool (*Metabase*, https://www.metabase.com/, San Francisco, California, USA). Datasets were joined via common data elements to produce a final registry containing patient medical record numbers, clinical records, extracted entities, and linked SNOMED-CT terms. (Figure 3)

5.3 Results

The model achieved an F score of 0.821, precision (ratio of true positives to the sum of true positives and false positives) of 0.819, and recall (ratio of true positives to the sum of true positives and false negatives) of 0.823. The model was run over 33455 notes, and a total of 123194 named entities were extracted, 5070 of which were distinct (after decapitalisation and removing non-alphanumeric characters). The 20 most frequent extractions are presented in Table 1. Table 2 presents examples of lexical representations of cranial nerve palsies present in the clinical records. The entities exemplify misspellings, abbreviations, acronyms, variable forms for the same concept, variable representation of numbers using words, Arabic and roman numerals.

5.4 Discussion

We demonstrated a low code workflow that produced a NER model with a moderate precision (0.819) and recall (0.823), and overall performance (F score 0.821) in extracting diagnoses from free-text clinical records. In addition, we highlight the complexities of biomedical natural language through examples of entities representing cranial nerve palsies. These examples illustrate the presence of misspellings, abbreviations, acronyms, variable forms of similar concepts, and variable representations of numerical expressions in ophthalmic notes. Low-code NLP tools enable the rapid creation of a disease registry containing a broad range of diagnoses present in free-text electronic clinical records without the need for extensive clinician input.

New and advanced machine learning techniques for named entity recognition require significant expertise and skill to implement. Low-code approaches and tools are required to reduce barriers to implementation by clinicians and those without this expertise. We used a tool that features user-friendly, active learning-based annotation, easily initialised through the command line. Given annotated datasets are required for supervised learning techniques an increasing number of annotation tools are now available to create these datasets efficiently.[293] Features such as annotation suggestions are important to consider, given pre-annotation improves annotation speed.[294]

Registry creation from free-text fields have previously used complex multistage NLP techniques and tools. The pipeline developed by Oliwa et al. dynamically extracts pathology specimen attributes from semi-structured pathology records to populate a gastroesophageal tumour registry.[295] A support vector machine model was used to classify notes as internally or externally sourced. Subsequently, entities including 'label', 'received locations', 'dates and 'sublabels' were extracted using a Stanford NER model and processed using manual heuristics for each entity. The annotation dataset used to train the NER model was created using the *brat* annotation tool,[293] and custom software integrating the output of the tool with the NER model to train in an iterative loop. The pipeline achieved an F score of 0.90 overall, however a lower score of 0.78 for the 'sublabels' entity. The multi-tool pipeline is potentially complex to implement without the required expertise in NLP, coding and machine learning. In comparison, other low-code NLP tools such as *Prodigy* combine the ability to annotate datasets and train models into a single tool with a low-code interface.

NLP approaches to creating registries using free-text fields have included the use of regular expressions (text pattern matching), [296] modified tools based on regular expressions, [297] and NLP tools using pre-trained models augmented with rule-based techniques.[298,299] Intimate knowledge of how entities are represented in text is required when using regular expressions, as they require pre-specification of all patterns to detect. This must be performed manually and therefore is time consuming compared to document annotation using efficient tools. We provided examples of representations of cranial nerve palsies in Table 2, which exemplify the planning required to extract terms using regular expressions. Furthermore, cranial nerve entities additionally illustrate the challenges of diagnostic entities containing

numbers, that take on both lexical representations and Arabic or Roman numerals. Similarly, rule-based approaches to extracting entities are time consuming, task-specific and require significant clinician input.

Recognition of disease entities in electronic health records may improve the ability to identify and monitor rare diseases. It is estimated that 263-446 million persons are affected by rare diseases globally at any point in time.[300] Despite the clear burden of rare diseases and need for research, rare disease research is limited by issues with recruitment and sample size.[301] Rare diseases are underrepresented in common ontologies such as the International Classification of Diseases which impedes cohort identification.[302 303] Electronic health records have been used previously to identify rare diseases,[304,305] however approaches have relied on regular expressions.[306,307] Identification of rare diseases using machine learning derived diseases registry avoids the shortcomings of regular expressions and allows flexibility in the range of rare diseases to be monitored. De Lozier et al. previously developed a system to monitor rare diseases through electronic health records.[307] An email alert system was used to prompt investigators to review instances of rare drug reactions in clinical notes to improve recruitment in prospective clinical trials of drug induced torsades de pointes and Steven-Johnson's syndrome/toxic epidermal necrolysis.[307] The alert system increased the rate of recruitment and reduced the time to enrolment in the studies. Monitoring diseases in free text fields via integration with alerting systems has the potential to improve monitoring of rare diseases and reduce barriers to cohort identification for research.

Identifying diagnostic entities using free-text fields can improve the completeness of diagnostic problem lists in electronic health records. Despite diagnostic codes listed in discharge summaries showing an accuracy of 80.3%,[198] coding of comorbidities in problem lists are often incomplete.[199-202] Such lack of completeness results in poor sensitivity of diagnostic coding, despite achieving high specificity.[199,203-206] Therefore, the absence of a diagnostic code does not necessarily reflect the absence of the disease. Coding accuracy is further affected by changes in the coding systems used,[201] lack of suitably granular codes,[207] incomplete coding in single centres due to data fragmentation cross multiple sites,[208] and that length of time registered in an electronic health record is associated with coding completeness.[209] Supplementing diagnostic coding with unstructured fields can improve this sensitivity. [194,226,227] This increased sensitivity has important implications for case-finding ability of studies using electronic health records.

There are several limitations in our workflow. Firstly, the NER model extracts entities as they appear in the text and does not link these to a standard disease ontology. The linking process is considered a downstream task, which we performed manually for common terms. Most linking tools rely on a dictionary of entities and concepts to perform this linking. Secondly, we used clinical records from a single institution to train and evaluate our model. This reduces generalisability and performance of the model for externally sourced records. However, the use of low-code NLP tools increases the accessibility and efficiently of annotation dataset creation and NER model training to enable institution-specific solutions. Lastly, annotations were performed by a single annotator, thus the registry represents the annotating characteristics of a single annotator. Multiple annotators may reduce this bias,

however these annotators should be trained to follow annotation guidelines to ensure adequate inter-annotator agreement.[308]

5.5 Conclusion

In summary, we demonstrated a workflow using low-code NLP tools to produce an ophthalmic disease registry. We used low-code tools to produce a NER model with a moderate ability to extract diagnoses from free text electronic clinical records. Low-code tools increase the accessibility of improved machine learning named entity recognition techniques to clinicians without this expertise. Low-code solutions are needed to encourage widespread adoption, which could have a beneficial impact on patient cohort identification strategies through dynamic monitoring of electronic health records.

5.6 Tables

Table 1: The 20 most frequent diagnostic entities extracted from text after decapitalisation and removal of non-alphanumeric characters

Extracted entity	N	Proportion of total entities
cataract	6419	5.2
ppv	3744	3.0
erm	3476	2.8
rd	2887	2.3
pseudophakic	2727	2.2
cataracts	2533	2.1
iol	2296	1.9
phaco	2240	1.8
cmo	1956	1.6
poag	1940	1.6
pdr	1918	1.6
vh	1893	1.5
glaucoma	1746	1.4
pvd	1592	1.3
trab	1385	1.1
avastin	1382	1.1
pterygium	1367	1.1
dmo	1284	1.0
cnvm	1256	1.0
prp	1204	1.0

Table 2: Examples of the various lexical representations of cranial nerve palsies in ophthalmic clinical records after decapitalisation and removal of non-alphanumeric characters

Concept	Entities
Cranial nerve palsy	cn palsy, craneal nerve palsy, cranial nerve palsy
3rd Cranial nerve palsy	3rd cn palsy, 3rd nerve palsy, cn iii microvascular palsy, cn iii palsy, cn3 palsy, cn3fourth palsy, cniii palsy, iii cn palsy, iii n palsy, iii nerve palsy, microvascular third nerve palsy, third nerve palsy, third nerve palsy suspect, total cn3 palsy
4th Cranial Nerve Palsy	cn 4 palsy, cn 4th palsy, cn iv palsy, cn3fourth palsy, cn4 palsy, cniv palsy, congenital cn4 palsy, forth nerve palsy, fourht nerve palsy, fourth n palsy, fourth nerve palsy, fourth nerve paresis, iv cn palsy, iv n palsy, iv nerve palsy, iv palsy
5th Cranial Nerve Palsy	cn v palsy, cn5 palsy, trigeminal nerve palsy
6th Cranial Nerve palsy	6th nerve palsy, 6th palsy, abducens nerve palsy, abducens palsy, acute cn vi palsy, cn 6 palsy, cn 6th palsy, cn vi palsy, cn6 new palsy, cn6 palsy, cnvi palsy, cranial nerve vi palsy, traumatic cn vi palsy, vi and vii palsy, vi cn, vi cn palsy, vi cranial nerve palsy, vi n palsy, vi n paresis, vi nerve palsy, vi nerve paresis, vi palsy, vith cnp, vith cranial nerve palsy, vith nerve palsy
7th Cranial nerve palsy	bell's palsy, bells palsy, branch viin palsy, cn 7 palsy, cn vii, cn vii palsy, cnvii palsy, facial n palsy, facial nerve deficit, facial nerve palsies, facial nerve palsy, facial nerve paralysis, facial nerve static palsy, facial nerve weakness, facial palsy, facial vii palsy, parotid gland resection cn 7th palsy, total facial nerve palsy, vi and vii palsy, vii palsy, viith palsy

5.7 Figures

Figure 1: The graphical user interface for annotation dataset creation with example annotations of diagnostic entities

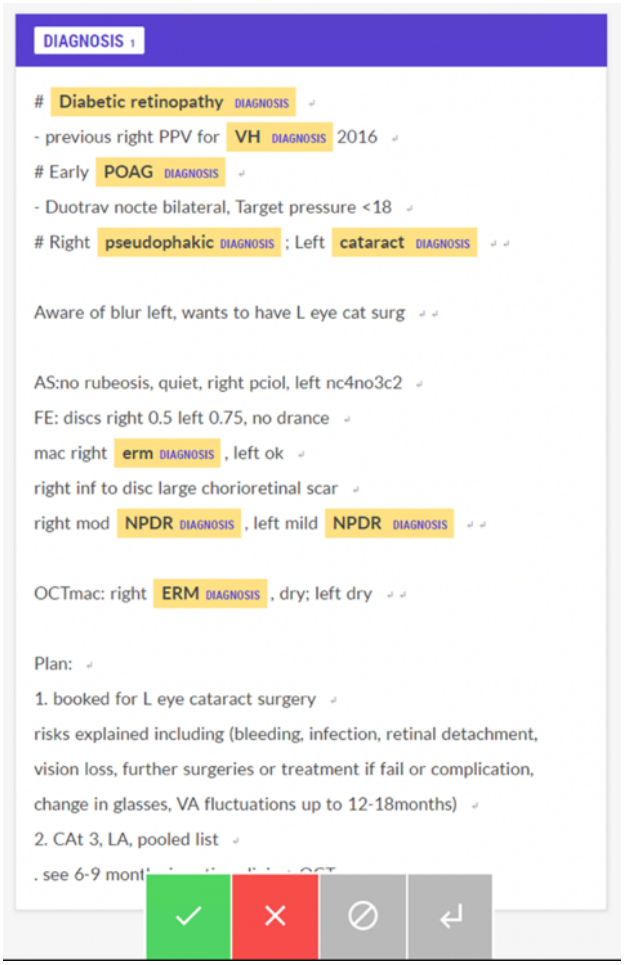


Figure 2: Summary of the sequence of steps and commands involved to create the disease registry using low-code NLP tools

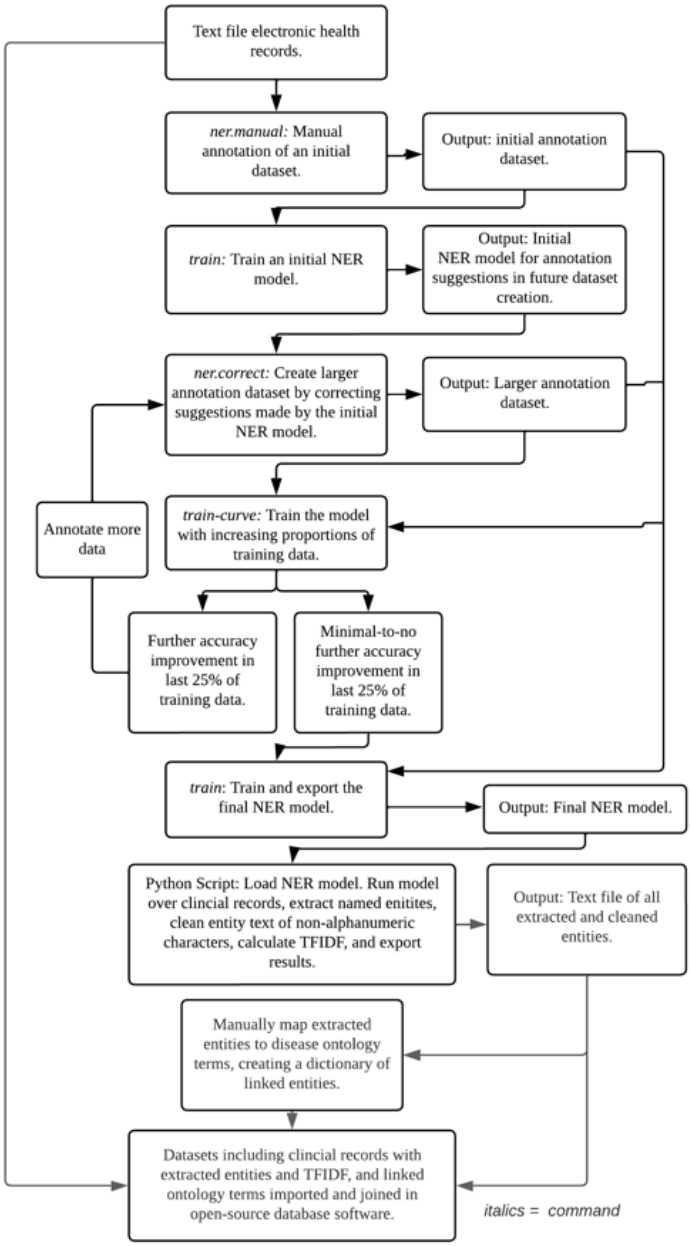
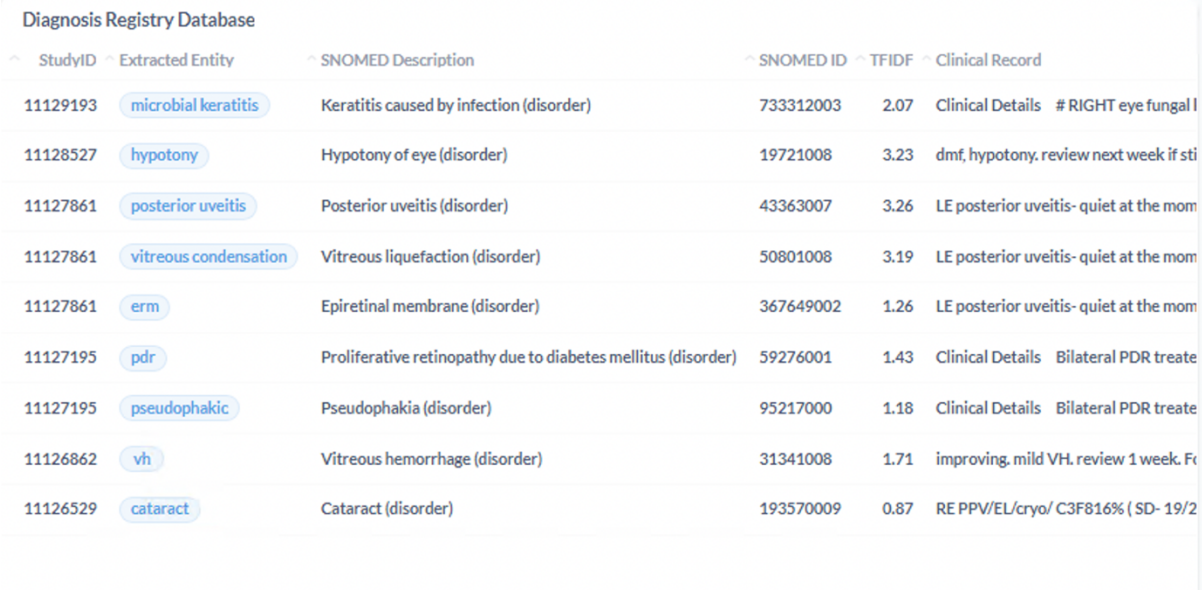


Figure 3: Interface of the Ophthalmic Disease Registry displaying entries for extracted diagnostic entities



Diagnosis Registry Database

StudyID	Extracted Entity	SNOMED Description	SNOMED ID	TFIDF	Clinical Record
11129193	microbial keratitis	Keratitis caused by infection (disorder)	733312003	2.07	Clinical Details # RIGHT eye fungal l
11128527	hypotony	Hypotony of eye (disorder)	19721008	3.23	dmf, hypotony. review next week if sti
11127861	posterior uveitis	Posterior uveitis (disorder)	43363007	3.26	LE posterior uveitis- quiet at the mom
11127861	vitreous condensation	Vitreous liquefaction (disorder)	50801008	3.19	LE posterior uveitis- quiet at the mom
11127861	erm	Epiretinal membrane (disorder)	367649002	1.26	LE posterior uveitis- quiet at the mom
11127195	pdr	Proliferative retinopathy due to diabetes mellitus (disorder)	59276001	1.43	Clinical Details Bilateral PDR treate
11127195	pseudophakic	Pseudophakia (disorder)	95217000	1.18	Clinical Details Bilateral PDR treate
11126862	vh	Vitreous hemorrhage (disorder)	31341008	1.71	improving. mild VH. review 1 week. F
11126529	cataract	Cataract (disorder)	193570009	0.87	RE PPV/EL/cryo/ C3F816% (SD- 19/2

6 Final Discussion

Observational research utilising databases has increased dramatically over time [309] and is now ubiquitous. However, utilising databases' full potential requires careful study design. In addition, careful examination of potential biases is required to interpret study results within the limitations of the database. Addressing areas of research need using databases provides cost and time-saving benefits compared to collecting specific study data for sequential research questions. However, this requires aligning research methods within the limitations of available databases.[7] Even when databases are specifically designed for research purposes, they may not be designed for any specific scientific question, rather collecting a range of data variables. Therefore, necessary data may not be available.[53] These considerations impact the design of database studies.

In the second chapter, we demonstrated the use of a small academic database to describe lacrimal imaging findings in fellow asymptomatic eyes of patients presenting to a tertiary Oculoplastic clinic with unilateral epiphora. This study was a cross-sectional design using descriptive analysis. The database was constructed retrospectively and, therefore, limited by missing data. A complete multivariate analysis adjusting for confounding variables was not possible in this case, and a purely descriptive approach was employed. We observed a high rate of subclinical abnormalities in DSG studies. Taken with the available literature, the significance of these abnormalities is unclear. This finding warrants further longitudinal assessment of these eyes. Asymptomatic eyes are not routinely the subject of specific

investigation except for determining normative data. Resources to conduct research are scarce and more likely to be directed to symptomatic eyes. We demonstrate that database analysis can supplement current understanding in areas less likely to have resources allocated. The biases present in this database include referral bias, as all patients were sourced from a tertiary Oculoplastic clinic, availability bias, given imaging is not performed routinely on all asymptomatic eyes of unilateral epiphora; and information bias, as symptomatic eyes with clinically obvious nasolacrimal duct obstruction may not require imaging, and thus this would not be performed for the fellow asymptomatic eye. The results of our study must therefore be interpreted in the context of the inherent limitations of our database.

In the third chapter, we demonstrated an analysis of a larger academic database from the UK Biobank Study. The UK biobank differs from the lacrimal database in that it is a population academic database rather than a focused academic database.[7] The UK Biobank lacks disease-specificity, instead collecting a vast array of in-depth and high-quality health data to conduct broad observational research related to population health. Researchers are responsible for the appropriate design, analysis, and interpretation of results using this data. We designed a longitudinal cohort study to examine the influence of various blood pressure measures on the risk of incident POAG. This longitudinal design is only possible through database linkage with inpatient hospital and primary care records, highlighting the advantage of linked databases. The UK Biobank study is an exciting opportunity for population health research; however, it exhibits several important biases. The biobank has been shown to have a ‘healthy volunteer’ selection bias and underrepresents ethnic minorities with predominantly White British participants.[310] A participation rate of

5.45%,[310] raises concerns about the generalisability of findings from this database, although the sample size is large.[311] Further information bias results from relying on diagnostic coding from inpatient admissions. However, the accuracy and validity of coding vary among databases; coding of secondary diagnoses is often inferior to primary diagnosis coding,[312] which may have affected codes for primary open-angle glaucoma. This was alleviated by linked primary care data for a subset of participants, which has shown good agreement with other databases for chronic conditions.[313] Despite these biases, risk factor associations in the UK Biobank appear similar to conventional generalisable prospective cohort studies.[314]

In the fourth chapter, we demonstrated the use of the NHMD, a nationwide administrative database collecting counts of procedures performed in public and private hospitals in Australia. This study further exemplifies the importance of considering database linkage. We linked population data from the Australian Bureau of Statistics to adjust for temporal changes in population and perform age and gender standardisation. Data augmentation through linkage is especially pertinent to administrative databases, which are not primarily intended for research. Advantages of database linkage have been seen elsewhere, such as in the Oxford Record Linkage Study,[315] which now has 32 years of linked statistical data since collecting linkable hospital admission statistics and death certificate datasets since 1960. This has enabled investigation into risk factor associations with various ophthalmic diseases.[316] The use of the NHMD database in our study has several limitations. The data quality of the NHMD relies on accurate procedural coding and consistent and accurate definitions of procedural codes over time. While procedural codes remained largely consistent over time, this study was affected by data granularity affecting

codes for retinal detachment repair, which could not distinguish between cryotherapy used in vitrectomy and scleral buckling. In addition, clinical or other health data is not collected, preventing adjustment for clinical confounders such as seniority or experience of the surgeon and geographical location. Despite these limitations, the nationwide scale of the data allows observation of real-world and population-level insights into changing practice patterns over time.

The fifth chapter presents a low-code entity recognition machine learning workflow to create an ophthalmic disease registry from electronic health records. Electronic health records represent the largest available database of clinical information. However, electronic records' unstructured and free-text nature is a significant barrier to information extraction. As seen in chapter one, retrospective database creation for uncommon diseases provides valuable insights for directing future research. However, case-finding tools that do not rely simply on diagnostic or administrative coding in health records are needed.[317] Low-code options for building bespoke named entity recognition models provide an efficient and accessible means for model creation without necessitating extensive coding experience. In this way, machine learning techniques can augment existing infrastructure to support case-finding and database construction. As natural language techniques evolve, more accessible tools will become available,[318] and encourage clinicians to incorporate machine learning into their research processes. Machine learning has already been applied to research processes such as participant identification and recruitment.[319-322] The production of annotation datasets for supervised machine learning techniques is not without bias, however. In our study, annotations were performed by a single annotator introducing an investigator bias to the final entities extracted. In

addition, annotations were performed using health records sourced from a single institution. Although this reduces the generalisability of the model created, the workflow produces bespoke models in any institution, which are specific to the local structure of health records and variations in entity representation between institutions, such as acronyms or abbreviations used. In this way, improving the efficiency and accessibility of natural language processing workflows may reduce barriers to implementation across different institutions and reduce concerns of external validity with institution-specific models.

Several authors have now developed practical and systematic frameworks and guides for the design of database studies.[323-327] Chang et al. provide a framework in three phases— study design, data preparation and analysis phases.[323] The study design phase includes determining the study inclusion and exclusion criteria, defining the outcomes variables and the confounders to adjust for. The data preparation phase consists of selecting an appropriate database, linking databases if necessary, selecting data elements and feature engineering if applicable. Finally, the analysis phase considers a univariate descriptive analysis, a bivariate analysis with unadjusted comparisons, and a multivariate analysis of adjusted comparisons if possible. Overall, these frameworks emphasise the importance of carefully considering the limitations of database research along every step of the research pathway, from hypothesis conception to final analysis and interpretation.

7 Future Directions

The increasing use of various clinical, administrative, electronic health record and biobank databases have highlighted the potential ways these databases are limited and where improvements are needed. These improvements can be enacted at multiple levels, leading to higher quality and more reliable conclusions.

Improvements to data quality at the local level are vital to all databases. Targeted efforts to improve data accuracy, granularity, and completeness in electronic health records or registries will improve their quality and potential uses. This may be achieved through mandated data collection standards for common or important conditions or procedures. This approach has already been adopted in the United Kingdom, where The Royal College of Ophthalmologists has published standards for data collection in electronic health records for various ophthalmic conditions.[39] Collecting targeted, high quality and relevant data are preferable to collecting large amounts of poor-quality and unusable data. Furthermore, data collection should be efficient and enhanced rather than inhibit clinical practice to be sustainable. Therefore, electronic health record systems should be developed with research as a primary use in addition to the administration of patient care, as high-quality research is vital to patient care.

At the national level, large-scale registries and administrative databases have the potential to collect high-quality data through already established reporting infrastructure. Linkage of these large-scale databases will be essential in increasing the potential of individual datasets. These benefits have been realised in Denmark, where citizens are assigned a unique personal identification number used in all medical databases, allowing unambiguous linkage between over 60 national registries managed by a national body.[328] Database linkage increases the variables available to control for confounding, increase the number of centres involved, increase sample size and may provide longitudinal data to study risk factor associations. However, large datasets often suffer from poor data granularity that linkage alone may not improve. Further efforts to improve the granularity of standardised coding systems and the ability to link large registry and administrative databases are needed.

Finally, an ongoing exploration of information extraction strategies applied to unstructured electronic health records fields is needed to supplement current data collection systems. For example, machine learning natural language processing approaches offer potential strategies to augment clinical data capture. Further, publicly available tools and datasets are required to address current translational gaps, and integration with existing electronic health record systems is required.

8 Conclusion

Research opportunities abound due to the wide variety of academic, registry and administrative databases available across healthcare settings. As shown in our studies, database research can support hypothesis generation and testing, description of the features of uncommon diseases, study risk factor associations, and monitor population trends. We have demonstrated the utility of various database designs, each with unique strengths and limitations. Firstly, we found a high prevalence of DSG abnormalities in fellow asymptomatic eyes using a small clinical database of patients with unilateral epiphora. This has implications for using asymptomatic eyes as control and DSG interpretation in functional epiphora. Secondly, in the large UK Biobank database, we found a significant association between higher systolic blood pressure and pulse pressure with incident primary open angle glaucoma. Thirdly, using the NHMD, we found that between 2001 and 2019, the overall rate of scleral buckle procedures declined compared to an overall increased rate of PPV for RD. These trends are more marked in those 40 years and above. Finally, we constructed an Ophthalmic Disease Registry for patient cohort identification using low-code machine learning-based natural language processing tools applied to unstructured free-text ophthalmic electronic clinical records. A careful examination of the biases and limitations of potential databases is vital from the conception and design of database studies to the interpretation of the results of any analysis. While these principles apply to all research, they are especially pertinent in the case of databases, given their wide heterogeneity in intended purposes, data collection strategies and the data elements they contain.

9 Appendix

Abbreviations
POAG: Primary open angle glaucoma
ICD: International Statistical Classification of Diseases and Related Health Problems
OPCS: Office of Population Censuses and Surveys Classification of Surgical Operations and Procedures
ACE: Angiotensin Converting Enzyme
AR: Angiotensin Receptor

9.1 Codes for glaucoma other than POAG for exclusion of prevalent glaucoma

9.1.1 Primary Care Read2 Glaucoma Codes

Read Code	Description
F4042	Blind hypertensive eye
F4042	Glaucoma - absolute
F45..	Glaucoma
F450.	Borderline glaucoma
F4502	Borderline glaucoma with anatomical narrow angle
F4503	Borderline glaucoma steroid responder
F450z	Borderline glaucoma NOS
F4513	Pigmentary glaucoma
F4513	Pigment dispersion syndrome
F4514	Glaucoma of childhood
F452.	Primary angle-closure glaucoma
F452.	Closed angle glaucoma
F4520	Unspecified primary angle-closure glaucoma
F4521	Intermittent primary angle-closure glaucoma
F4522	Acute primary angle-closure glaucoma
F4523	Chronic primary angle-closure glaucoma
F4524	Primary angle-closure glaucoma residual stage
F452z	Primary angle-closure glaucoma NOS
F453.	Steroid-induced glaucoma
F4530	Steroid-induced glaucoma glaucomatous stage
F4531	Steroid-induced glaucoma residual stage
F453z	Steroid-induced glaucoma NOS
F454.	Glaucoma due to disease EC
F4540	Glaucoma due to chamber angle anomaly
F4541	Glaucoma due to iris anomaly
F4542	Glaucoma due to other anterior segment anomaly
F4543	Glaucoma due to systemic syndrome
F4544	Glaucoma in endocrine, nutritional and metabolic diseases
F454z	Glaucoma due to disease NOS
F455.	Glaucoma associated with disorders of the lens
F4550	Phacolytic glaucoma
F4551	Pseudoexfoliation glaucoma
F455z	Glaucoma associated with disorders of the lens NOS
F456.	Glaucoma associated with other ocular disorders
F4560	Glaucoma due to unspecified ocular disorder
F4561	Glaucoma due to pupillary block
F4562	Glaucoma due to ocular inflammation
F4563	Glaucoma due to ocular vascular disorder
F4564	Glaucoma due to ocular tumour or cyst
F4564	Glaucoma due to ocular cyst
F4565	Glaucoma due to ocular trauma
F4566	Neovascular glaucoma

Read Code	Description
F4566	Rubeotic glaucoma
F456z	Glaucoma associated with other ocular disorders NOS
F45y.	Other specified forms of glaucoma
F45y0	Hypersecretion glaucoma
F45y1	Glaucoma due to episode of increased venous pressure
F45yz	Other specified glaucoma NOS
F45z.	Glaucoma NOS
FyuG.	[X]Glaucoma
FyuG0	[X]Other glaucoma
FyuG1	[X]Glaucoma in endocrine, nutritional and metabolic diseases classified elsewhere
FyuG2	[X]Glaucoma in other diseases classified elsewhere
P3200	Congenital glaucoma
P3200	Newborn glaucoma
Q20y7	Traumatic glaucoma due to birth trauma

9.1.2 Primary Care Read3 Glaucoma Codes

Read Code	Description
F4042	(Blind hypertensive eye) or (glaucoma absolute)
F4042	Blind hypertensive eye
F4042	Absolute glaucoma
F4042	Glaucoma - absolute
F45..	Glaucoma
F450.	Borderline glaucoma
F4502	Angle-closure glaucoma - borderline
F4503	Borderline glaucoma steroid responder
F4503	Steroid responder - borderline
F450z	Borderline glaucoma NOS
F4513	Pigmentary glaucoma
F4513	Pigment dispersion syndrome
F4513	Secondary open-angle glaucoma with pigment dispersion
F4513	Pigmentary dispersion syndrome
F4514	Glaucoma of childhood
F452.	Glaucoma: [primary angle-closure] or [closed angle]
F452.	Primary angle-closure glaucoma
F452.	Closed-angle glaucoma
F452.	Closed angle glaucoma
F4520	Unspecified primary angle-closure glaucoma
F4521	Intermittent angle-closure glaucoma
F4521	Subacute closed-angle glaucoma
F4521	Intermittent closed-angle glaucoma
F4522	Acute angle-closure glaucoma
F4522	Acute closed-angle glaucoma
F4523	Chronic angle-closure glaucoma
F4523	Chronic closed-angle glaucoma
F4523	Chronic narrow angle glaucoma

Read Code	Description
F453.	Steroid-induced glaucoma
F4530	Steroid-induced glaucoma glaucomatous stage
F4531	Steroid-induced glaucoma residual stage
F453z	Steroid-induced glaucoma NOS
F454.	Glaucoma due to disease EC
F4540	Glaucoma due to chamber angle anomaly
F4541	Glaucoma due to iris anomaly
F4542	Glaucoma due to other anterior segment anomaly
F4543	Glaucoma due to systemic syndrome
F4544	Glaucoma in endocrine, nutritional and metabolic diseases
F454z	Glaucoma due to disease NOS
F455.	Glaucoma with lens disorder
F4550	Phacolytic glaucoma
F4551	Pseudoexfoliation glaucoma
F4551	Glaucoma capsulare
F4551	Secondary open-angle glaucoma with pseudoexfoliation
F455z	Glaucoma associated with disorders of the lens NOS
F456.	Glaucoma associated with other ocular disorders
F4560	Glaucoma due to unspecified ocular disorder
F4561	Secondary angle-closure glaucoma with pupil block
F4561	Pupil block glaucoma
F4562	Glaucoma with ocular inflammation
F4563	Glaucoma due to ocular vascular disorder
F4564	Glaucoma due to ocular tumour &/or cyst
F4564	Glaucoma due to ocular tumour or cyst
F4564	Glaucoma due to ocular cyst
F4565	Glaucoma due to ocular trauma
F4565	Traumatic glaucoma
F456z	Glaucoma associated with other ocular disorders NOS
F45y.	Other specified forms of glaucoma
F45y0	Hypersecretion glaucoma
F45y1	Glaucoma due to raised episcleral venous pressure
F45yz	Other specified glaucoma NOS
F45z.	Glaucoma NOS

9.1.3 UK Biobank ICD10 Glaucoma Codes

Code	Description
H400	H40.0 Glaucoma suspect
H402	H40.2 Primary angle-closure glaucoma
H403	H40.3 Glaucoma secondary to eye trauma
H404	H40.4 Glaucoma secondary to eye inflammation
H405	H40.5 Glaucoma secondary to other eye disorders
H406	H40.6 Glaucoma secondary to drugs
H408	H40.8 Other glaucoma
H409	H40.9 Glaucoma, unspecified
H420	H42.0 Glaucoma in endocrine, nutritional and metabolic diseases
H428	H42.8 Glaucoma in other diseases classified elsewhere

9.1.4 UK Biobank ICD9 Glaucoma Codes

Code	Description
3650	3650 Borderline glaucoma
3653	3653 Corticosteroid-induced glaucoma
3654	3654 Glaucoma with congenital anomalies, dystrophies, systemic syndromes
3655	3655 Glaucoma associated with disorders of the lens
3656	3656 Glaucoma associated with other ocular disorders
3658	3658 Other specified glaucoma
3659	3659 Glaucoma, unspecified

9.1.5 UK Biobank Self-Reported Glaucoma Codes

Code	Description
1277	glaucoma

9.2 Codes for POAG used for exclusion of prevalent cases and identification of incident cases

9.2.1 Primary Care Read2 POAG Codes

Read Code	Description
F4501	Open angle glaucoma with borderline intraocular pressure
F451.	Open-angle glaucoma
F4510	Unspecified open-angle glaucoma
F4511	Primary open-angle glaucoma
F4511	Simple chronic glaucoma
F4512	Low tension glaucoma
F4512	Normal pressure glaucoma
F4515	Open-angle glaucoma residual stage
F451z	Open-angle glaucoma NOS
F45y2	Low tension glaucoma

9.2.2 Primary Care Read3 POAG Codes

Read Code	Description
F4501	Open-angle glaucoma - borderline
F451.	Open-angle glaucoma
F4510	Unspecified open-angle glaucoma
F4511	Primary open-angle glaucoma
F4511	POAG - Primary open-angle glaucoma
F4511	CSG - Chronic simple glaucoma
F4511	COAG - Chronic open-angle glaucoma
F4512	Low tension glaucoma
F4512	Normal pressure glaucoma
F4512	LTG - Low tension glaucoma
F4512	Normal tension glaucoma
F4515	Open-angle glaucoma residual stage
F451z	Open-angle glaucoma NOS
XaF9D	Primary open-angle glaucoma with narrow angles
.F542	Primary open-angle glaucoma
.F542	POAG - Primary open-angle glaucoma
.F542	CSG - Chronic simple glaucoma
.F542	COAG - Chronic open-angle glaucoma

9.2.3 UK Biobank ICD10 POAG Codes

CodeDescription
H401H40.1 Primary open-angle glaucoma

9.2.4 UK Biobank ICD9 POAG Codes

Code	Description
3651	3651 Open-angle glaucoma

9.3 Codes for identification of diabetes

9.3.1 Primary Care Read2 Diabetes Codes

Read Code	Description
C1000	Diabetes mellitus, juvenile type, with no mention of complication
C1000	Insulin dependent diabetes mellitus
C1001	Diabetes mellitus, adult onset, with no mention of complication
C1001	Maturity onset diabetes
C1001	Non-insulin dependent diabetes mellitus
C100z	Diabetes mellitus NOS with no mention of complication
C101.	Diabetes mellitus with ketoacidosis
C1010	Diabetes mellitus, juvenile type, with ketoacidosis
C1011	Diabetes mellitus, adult onset, with ketoacidosis
C101y	Other specified diabetes mellitus with ketoacidosis
C101z	Diabetes mellitus NOS with ketoacidosis
C102.	Diabetes mellitus with hyperosmolar coma
C1020	Diabetes mellitus, juvenile type, with hyperosmolar coma
C1021	Diabetes mellitus, adult onset, with hyperosmolar coma
C102z	Diabetes mellitus NOS with hyperosmolar coma
C103.	Diabetes mellitus with ketoacidotic coma
C1030	Diabetes mellitus, juvenile type, with ketoacidotic coma
C1031	Diabetes mellitus, adult onset, with ketoacidotic coma
C103y	Other specified diabetes mellitus with coma
C103z	Diabetes mellitus NOS with ketoacidotic coma
C105y	Other specified diabetes mellitus with ophthalmic complications
C107.	Diabetes mellitus with peripheral circulatory disorder
C107.	Diabetes mellitus with gangrene
C107.	Diabetes with gangrene
C1070	Diabetes mellitus, juvenile type, with peripheral circulatory disorder
C1071	Diabetes mellitus, adult onset, with peripheral circulatory disorder
C1072	Diabetes mellitus, adult with gangrene
C1073	IDDM with peripheral circulatory disorder
C1074	NIDDM with peripheral circulatory disorder
C107y	Other specified diabetes mellitus with peripheral circulatory complications
C107z	Diabetes mellitus NOS with peripheral circulatory disorder
C1083	Insulin dependent diabetes mellitus with multiple complications
C1083	Type I diabetes mellitus with multiple complications
C1083	Type 1 diabetes mellitus with multiple complications
C1084	Unstable insulin dependent diabetes mellitus
C1084	Unstable type I diabetes mellitus
C1084	Unstable type 1 diabetes mellitus
C1085	Insulin dependent diabetes mellitus with ulcer
C1085	Type I diabetes mellitus with ulcer
C1085	Type 1 diabetes mellitus with ulcer
C1086	Insulin dependent diabetes mellitus with gangrene
C1086	Type I diabetes mellitus with gangrene
C1086	Type 1 diabetes mellitus with gangrene
C1088	Insulin dependent diabetes mellitus - poor control

Read Code	Description
C1088	Type I diabetes mellitus - poor control
C1088	Type 1 diabetes mellitus - poor control
C1089	Insulin dependent diabetes maturity onset
C1089	Type I diabetes mellitus maturity onset
C1089	Type 1 diabetes mellitus maturity onset
C108A	Insulin-dependent diabetes without complication
C108A	Type I diabetes mellitus without complication
C108A	Type 1 diabetes mellitus without complication
C108E	Insulin dependent diabetes mellitus with hypoglycaemic coma
C108E	Type I diabetes mellitus with hypoglycaemic coma
C108E	Type 1 diabetes mellitus with hypoglycaemic coma
C108y	Other specified diabetes mellitus with multiple complications
C108z	Unspecified diabetes mellitus with multiple complications
C1091	Non-insulin-dependent diabetes mellitus with ophthalmic complications
C1091	Type II diabetes mellitus with ophthalmic complications
C1091	Type 2 diabetes mellitus with ophthalmic complications
C1093	Non-insulin-dependent diabetes mellitus with multiple complications
C1093	Type II diabetes mellitus with multiple complications
C1093	Type 2 diabetes mellitus with multiple complications
C1094	Non-insulin dependent diabetes mellitus with ulcer
C1094	Type II diabetes mellitus with ulcer
C1094	Type 2 diabetes mellitus with ulcer
C1095	Non-insulin dependent diabetes mellitus with gangrene
C1095	Type II diabetes mellitus with gangrene
C1095	Type 2 diabetes mellitus with gangrene
C1097	Non-insulin dependent diabetes mellitus - poor control
C1097	Type II diabetes mellitus - poor control
C1097	Type 2 diabetes mellitus - poor control
C1099	Non-insulin-dependent diabetes mellitus without complication
C1099	Type II diabetes mellitus without complication
C1099	Type 2 diabetes mellitus without complication
C109D	Non-insulin dependent diabetes mellitus with hypoglycaemic coma
C109D	Type II diabetes mellitus with hypoglycaemic coma
C109D	Type 2 diabetes mellitus with hypoglycaemic coma
C109J	Insulin treated Type 2 diabetes mellitus
C109J	Insulin treated non-insulin dependent diabetes mellitus
C109J	Insulin treated Type II diabetes mellitus
C109K	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10A2	Malnutrition-related diabetes mellitus with renal complications
C10A3	Malnutrition-related diabetes mellitus with ophthalmic complications
C10A4	Malnutrition-related diabetes mellitus with neurological complications
C10A5	Malnutrition-related diabetes mellitus with peripheral circulatory complications
C10A6	Malnutrition-related diabetes mellitus with multiple complications
C10B0	Steroid induced diabetes mellitus without complication
C10C.	Diabetes mellitus autosomal dominant
C10C.	Maturity onset diabetes in youth

Read Code	Description
C10C.	Maturity onset diabetes in youth type 1
C10D.	Diabetes mellitus autosomal dominant type 2
C10D.	Maturity onset diabetes in youth type 2
C10E3	Type 1 diabetes mellitus with multiple complications
C10E3	Type I diabetes mellitus with multiple complications
C10E3	Insulin dependent diabetes mellitus with multiple complications
C10E4	Unstable type 1 diabetes mellitus
C10E4	Unstable type I diabetes mellitus
C10E4	Unstable insulin dependent diabetes mellitus
C10E5	Type 1 diabetes mellitus with ulcer
C10E5	Type I diabetes mellitus with ulcer
C10E5	Insulin dependent diabetes mellitus with ulcer
C10E6	Type 1 diabetes mellitus with gangrene
C10E6	Type I diabetes mellitus with gangrene
C10E6	Insulin dependent diabetes mellitus with gangrene
C10E8	Type 1 diabetes mellitus - poor control
C10E8	Type I diabetes mellitus - poor control
C10E8	Insulin dependent diabetes mellitus - poor control
C10E9	Type 1 diabetes mellitus maturity onset
C10E9	Type I diabetes mellitus maturity onset
C10E9	Insulin dependent diabetes maturity onset
C10EA	Type 1 diabetes mellitus without complication
C10EA	Type I diabetes mellitus without complication
C10EA	Insulin-dependent diabetes without complication
C10EE	Type 1 diabetes mellitus with hypoglycaemic coma
C10EE	Type I diabetes mellitus with hypoglycaemic coma
C10EE	Insulin dependent diabetes mellitus with hypoglycaemic coma
C10EM	Type 1 diabetes mellitus with ketoacidosis
C10EM	Type I diabetes mellitus with ketoacidosis
C10EN	Type 1 diabetes mellitus with ketoacidotic coma
C10EN	Type I diabetes mellitus with ketoacidotic coma
C10ER	Latent autoimmune diabetes mellitus in adult
C10F3	Type 2 diabetes mellitus with multiple complications
C10F3	Type II diabetes mellitus with multiple complications
C10F4	Type 2 diabetes mellitus with ulcer
C10F4	Type II diabetes mellitus with ulcer
C10F5	Type 2 diabetes mellitus with gangrene
C10F5	Type II diabetes mellitus with gangrene
C10F7	Type 2 diabetes mellitus - poor control
C10F7	Type II diabetes mellitus - poor control
C10F8	Reaven's syndrome
C10F8	Metabolic syndrome X
C10F9	Type 2 diabetes mellitus without complication
C10F9	Type II diabetes mellitus without complication
C10FD	Type 2 diabetes mellitus with hypoglycaemic coma
C10FD	Type II diabetes mellitus with hypoglycaemic coma
C10FJ	Insulin treated Type 2 diabetes mellitus

Read Code	Description
C10FJ	Insulin treated Type II diabetes mellitus
C10FK	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
C10FK	Hyperosmolar non-ketotic state in type II diabetes mellitus
C10FN	Type 2 diabetes mellitus with ketoacidosis
C10FN	Type II diabetes mellitus with ketoacidosis
C10FP	Type 2 diabetes mellitus with ketoacidotic coma
C10FP	Type II diabetes mellitus with ketoacidotic coma
C10FS	Maternally inherited diabetes mellitus
C10G0	Secondary pancreatic diabetes mellitus without complication
C10H0	Diabetes mellitus induced by non-steroid drugs without complication
C10J0	Insulin autoimmune syndrome without complication
C10K0	Type A insulin resistance without complication
C10L0	Fibrocalculous pancreatopathy without complication
C10M0	Lipoatrophic diabetes mellitus without complication
C10N0	Secondary diabetes mellitus without complication
C10N1	Cystic fibrosis related diabetes mellitus
C10P0	Type I diabetes mellitus in remission
C10P0	Type 1 diabetes mellitus in remission
C10P1	Type II diabetes mellitus in remission
C10P1	Type 2 diabetes mellitus in remission
C10Q.	Maturity onset diabetes of the young type 5
C10y.	Diabetes mellitus with other specified manifestation
C10y0	Diabetes mellitus, juvenile type, with other specified manifestation
C10y1	Diabetes mellitus, adult onset, with other specified manifestation
C10yy	Other specified diabetes mellitus with other specified complications
C10yz	Diabetes mellitus NOS with other specified manifestation
C10z.	Diabetes mellitus with unspecified complication
C10z0	Diabetes mellitus, juvenile type, with unspecified complication
C10z1	Diabetes mellitus, adult onset, with unspecified complication
C10zy	Other specified diabetes mellitus with unspecified complications
C10zz	Diabetes mellitus NOS with unspecified complication
Cyu23	[X]Unspecified diabetes mellitus with renal complications
M0372	Cellulitis in diabetic foot
M2710	Ischaemic ulcer diabetic foot
M2711	Neuropathic diabetic ulcer - foot
M2712	Mixed diabetic ulcer - foot
R0542	[D]Gangrene of toe in diabetic
R0543	[D]Widespread diabetic foot gangrene

9.3.2 Primary Care Read3 Diabetes Codes

Read Code	Description
66AJ1	[Brittle] and/or [labile diabetes]
66AJ1	Brittle diabetes
66AJ1	Labile diabetes
66AJ2	Loss of hypoglycaemic warning

Read Code	Description
C10..	Diabetes mellitus
C10..	DM - Diabetes mellitus
C100.	Diabetes mellitus with no mention of complication
C1000	Diabetes mellitus: [juvenile type, with no mention of complication] or [insulin dependent]
C1000	Diabetes mellitus, juvenile type, with no mention of complication
C1000	Insulin dependent diabetes mellitus
C1001	Diabetes mellitus: [adult onset, with no mention of complication] or [maturity onset] or [non-insulin dependent]
C1001	Diabetes mellitus, adult onset, with no mention of complication
C1001	Non-insulin dependent diabetes mellitus
C1001	Maturity onset diabetes mellitus
C1001	Maturity onset diabetes
C100z	Diabetes mellitus NOS with no mention of complication
C101.	Diabetic ketoacidosis
C101.	Diabetes mellitus with ketoacidosis
C101.	DKA - Diabetic ketoacidosis
C1010	Type 1 diabetes mellitus with ketoacidosis
C1010	Diabetes mellitus, juvenile type, with ketoacidosis
C1011	Type 2 diabetes mellitus with ketoacidosis
C1011	Diabetes mellitus, adult onset, with ketoacidosis
C101y	Other specified diabetes mellitus with ketoacidosis
C101z	Diabetes mellitus NOS with ketoacidosis
C102.	Diabetes mellitus with hyperosmolar coma
C102.	Hyperosmolar coma
C1020	Diabetes mellitus, juvenile type, with hyperosmolar coma
C1021	Diabetes mellitus, adult onset, with hyperosmolar coma
C102z	Diabetes mellitus NOS with hyperosmolar coma
C103.	Diabetes mellitus with ketoacidotic coma
C1030	Type 1 diabetes mellitus with ketoacidotic coma
C1030	Diabetes mellitus, juvenile type, with ketoacidotic coma
C1031	Type II diabetes mellitus with ketoacidotic coma
C1031	Diabetes mellitus, adult onset, with ketoacidotic coma
C1031	Type 2 diabetes mellitus with ketoacidotic coma
C103y	Other specified diabetes mellitus with coma
C103z	Diabetes mellitus NOS with ketoacidotic coma
C107.	Diabetes mellitus with: [gangrene] or [peripheral circulatory disorder]
C107.	Diabetes mellitus with peripheral circulatory disorder
C107.	Diabetes mellitus with gangrene
C107.	Diabetes with gangrene
C1070	Diabetes mellitus, juvenile type, with peripheral circulatory disorder
C1071	Diabetes mellitus, adult onset, with peripheral circulatory disorder
C1072	Diabetes mellitus, adult with gangrene
C1073	IDDM with peripheral circulatory disorder
C1074	NIDDM with peripheral circulatory disorder
C107y	Other specified diabetes mellitus with peripheral circulatory complications
C107z	Diabetes mellitus NOS with peripheral circulatory disorder

Read Code	Description
C1083	Type I diabetes mellitus with multiple complications
C1083	Insulin-dependent diabetes mellitus with multiple complications
C1083	Type 1 diabetes mellitus with multiple complications
C1085	Type I diabetes mellitus with ulcer
C1085	Insulin-dependent diabetes mellitus with ulcer
C1085	Type 1 diabetes mellitus with ulcer
C1086	Type I diabetes mellitus with gangrene
C1086	Insulin-dependent diabetes mellitus with gangrene
C1086	Type 1 diabetes mellitus with gangrene
C1088	Type I diabetes mellitus - poor control
C1088	Insulin-dependent diabetes mellitus - poor control
C1088	Type 1 diabetes mellitus - poor control
C1089	Type I diabetes mellitus maturity onset
C1089	Insulin-dependent diabetes maturity onset
C1089	Type 1 diabetes mellitus maturity onset
C108y	Other specified diabetes mellitus with multiple complications
C108z	Unspecified diabetes mellitus with multiple complications
C1093	Type II diabetes mellitus with multiple complications
C1093	Non-insulin-dependent diabetes mellitus with multiple complications
C1093	Type 2 diabetes mellitus with multiple complications
C1094	Type II diabetes mellitus with ulcer
C1094	Non-insulin-dependent diabetes mellitus with ulcer
C1094	Type 2 diabetes mellitus with ulcer
C1095	Type II diabetes mellitus with gangrene
C1095	Non-insulin-dependent diabetes mellitus with gangrene
C1095	Type 2 diabetes mellitus with gangrene
C1097	Type II diabetes mellitus - poor control
C1097	Non-insulin-dependent diabetes mellitus - poor control
C1097	Type 2 diabetes mellitus - poor control
C10A6	Malnutrition-related diabetes mellitus with multiple complications
C10B0	Steroid-induced diabetes mellitus without complication
C10y.	Diabetes mellitus with other specified manifestation
C10y0	Diabetes mellitus, juvenile type, with other specified manifestation
C10y1	Diabetes mellitus, adult onset, with other specified manifestation
C10yy	Other specified diabetes mellitus with other specified complications
C10yz	Diabetes mellitus NOS with other specified manifestation
C10z.	Diabetes mellitus with unspecified complication
C10z0	Diabetes mellitus, juvenile type, with unspecified complication
C10z1	Diabetes mellitus, adult onset, with unspecified complication
C10zy	Other specified diabetes mellitus with unspecified complications
C10zz	Diabetes mellitus NOS with unspecified complication
C11y0	Steroid-induced diabetes
Cyu20	[X]Other specified diabetes mellitus
Cyu22	[X]Malnutrition-related diabetes mellitus with unspecified complications
L1805	Pre-existing diabetes mellitus, insulin-dependent
L1806	Pre-existing diabetes mellitus, non-insulin-dependent
L1807	Pre-existing malnutrition-related diabetes mellitus

Read Code	Description
L1808	Gestational diabetes mellitus
L1808	Gestational diabetes
L1808	GDM - Gestational diabetes mellitus
L1808	Diabetes mellitus arising in pregnancy
Lyu29	[X]Pre-existing diabetes mellitus, unspecified
M0372	Cellulitis in diabetic foot
M2710	Ischaemic ulcer diabetic foot
M2711	Neuropathic diabetic ulcer - foot
M2712	Mixed diabetic ulcer - foot
R0542	[D]Gangrene of toe in diabetic
R0543	[D]Widespread diabetic foot gangrene
X008t	Diabetes insipidus, diabetes mellitus, optic atrophy and deafness
X008t	DIDMOAD - Diabetes insipidus,diabetes mellitus, optic atrophy and deafness
X008t	Wolfram syndrome
X40J4	Type I diabetes mellitus
X40J4	Type 1 diabetes mellitus
X40J4	IDDM - Insulin-dependent diabetes mellitus
X40J4	Juvenile onset diabetes mellitus
X40J4	Insulin-dependent diabetes mellitus
X40J5	Type II diabetes mellitus
X40J5	Type 2 diabetes mellitus
X40J5	NIDDM - Non-insulin dependent diabetes mellitus
X40J5	Maturity onset diabetes mellitus
X40J5	Non-insulin-dependent diabetes mellitus
X40J5	Diabetes mellitus - adult onset
X40J6	Insulin treated Type 2 diabetes mellitus
X40J6	Insulin treated non-insulin dependent diabetes mellitus
X40J6	NIDDM - Insulin-treated non-insulin-dependent diabetes mellitus
X40J6	Insulin treated Type II diabetes mellitus
X40JA	Secondary diabetes mellitus
X40JB	Secondary pancreatic diabetes mellitus
X40JC	Secondary endocrine diabetes mellitus
X40JG	Genetic syndromes of diabetes mellitus
X40JI	Diabetes mellitus autosomal dominant
X40JI	Maturity onset diabetes in youth
X40JI	MODY - Maturity onset diabetes in youth type 1
X40JI	MODY - Maturity onset diabetes in youth type I
X40JI	Mason-type diabetes
X40JI	Maturity onset diabetes in youth type 1
X40JJ	Diabetes mellitus autosomal dominant type 2
X40JJ	Diabetes mellitus autosomal dominant type II
X40JJ	Maturity onset diabetes in youth type II
X40JJ	MODY - Maturity onset diabetes in youth type II
X40JJ	MODY - Maturity onset diabetes in youth type 2
X40JJ	Maturity onset diabetes in youth type 2
X40JJ	MODY - Maturity onset diabetes glucokinase-related

Read Code	Description
X40JQ	Muscular atrophy, ataxia, retinitis pigmentosa, and diabetes mellitus
X40JR	Photomyoclonus, diabetes mellitus, deafness, nephropathy and cerebral dysfunction
X40JR	Herrmann syndrome
X40JV	Hypogonadism, diabetes mellitus, alopecia ,mental retardation and electrocardiographic abnormalities
X40JW	Megaloblastic anaemia, thiamine-responsive, with diabetes mellitus and sensorineural deafness
X40JW	Rogers syndrome
X40JX	Pineal hyperplasia, insulin-resistant diabetes mellitus and somatic abnormalities
X40JX	Rabson-Mendenhall syndrome
X40JY	Insulin-dependent diabetes mellitus secretory diarrhoea syndrome
X40JY	IDDM - Insulin-dependent diabetes mellitus secretory diarrhoea syndrome
X40JY	Congenital insulin-dependent diabetes mellitus with fatal secretory diarrhoea
X40JZ	Diabetes-deafness syndrome maternally transmitted
X40JZ	Ballinger-Wallace syndrome
X40Ja	Abnormal metabolic state in diabetes mellitus
X40Jb	Diabetic severe hyperglycaemia
X40Jc	Poor glycaemic control
X40Jq	Hypoglycaemic event in diabetes
X40Jr	Hypoglycaemic state in diabetes
X40Js	Somogyi phenomenon
X40Js	Rebound phenomenon
X40Js	Dawn phenomenon
X40Js	Rebound hyperglycaemia
X40KG	Insulin resistance in diabetes
X40KH	Type A insulin resistance
X40KH	Insulin resistance - type A
X50GO	Soft tissue complication of diabetes mellitus
XE10E	Diabetes mellitus, juvenile type, with no mention of complication
XE10F	Diabetes mellitus, adult onset, with no mention of complication
XE10l	Diabetes mellitus with peripheral circulatory disorder
XE12M	Diabetes with other complications
XE1T3	Diabetic - poor control
XM0q4	Diabetic coma
XM1Qx	Diabetes mellitus with gangrene
XM1Xk	Unstable diabetes
XM1Xk	Brittle diabetes
XM1Xk	Labile diabetes
XSETH	Maturity onset diabetes mellitus in young
XSETI	Fibrocalculous pancreatic diabetes
XSETI	Fibrocalculous pancreatopathy
XSETK	Drug-induced diabetes mellitus
XSETe	Lipoatrophic diabetes
XSETe	Lipoatrophic diabetes mellitus

Read Code	Description
XSETp	Diabetes mellitus due to insulin receptor antibodies
XSETp	DM due to insulin receptor ab
Xa1J5	Diabetic foot
Xa3ee	Diabetes with ketoacidosis - no coma
Xa4g7	Unstable type I diabetes mellitus
Xa4g7	Unstable insulin dependent diabetes mellitus
Xa4g7	Unstable type 1 diabetes mellitus
XaBLf	O/E - Right diabetic foot at risk
XaBLg	O/E - Left diabetic foot at risk
XaCJ2	Diabetic hyperosmolar non-ketotic state
XaCJ2	HONKS - Diabetic hyperosmolar non-ketotic state
XaELP	Type I diabetes mellitus without complication
XaELP	Insulin-dependent diabetes without complication
XaELP	Type 1 diabetes mellitus without complication
XaELQ	Type II diabetes mellitus without complication
XaELQ	Non-insulin-dependent diabetes mellitus without complication
XaELQ	Type 2 diabetes mellitus without complication
XaFWG	Type I diabetes mellitus with hypoglycaemic coma
XaFWG	Insulin dependent diabetes mellitus with hypoglycaemic coma
XaFWG	Type 1 diabetes mellitus with hypoglycaemic coma
XaFWI	Type II diabetes mellitus with hypoglycaemic coma
XaFWI	Non-insulin dependent diabetes mellitus with hypoglycaemic coma
XaFWI	Type 2 diabetes mellitus with hypoglycaemic coma
XaIeJ	O/E - Right diabetic foot - ulcerated
XaIeK	O/E - Left diabetic foot - ulcerated
XaIrf	Hyperosmolar non-ketotic state in type II diabetes mellitus
XaIrf	Hyperosmolar non-ketotic state in type 2 diabetes mellitus
XaJUI	Diabetes mellitus induced by non-steroid drugs
XaJUI	DM induced by non-steroid drug
XaJlL	Secondary pancreatic diabetes mellitus without complication
XaJlM	Diabetes mellitus induced by non-steroid drugs without complication
XaJlN	Insulin autoimmune syndrome without complication
XaJlO	Type A insulin resistance without complication
XaJlQ	Lipoatrophic diabetes mellitus without complication
XaJlR	Secondary diabetes mellitus without complication
XaKHh	O/E - right chronic diabetic foot ulcer
XaKHi	O/E - left chronic diabetic foot ulcer
XaKyX	Type II diabetes mellitus with gastroparesis
XaKyX	Type 2 diabetes mellitus with gastroparesis
XaMzI	Cystic fibrosis related diabetes mellitus
XaOPt	Maternally inherited diabetes mellitus
XaOPu	Latent autoimmune diabetes mellitus in adult
Xaa8r	Erectile dysfunction due to diabetes mellitus
XaaEs	Wagner ulcer classification grade 1 foot ulcer
XaaEt	Wagner ulcer classification grade 2 foot ulcer
XaaEu	Wagner ulcer classification grade 3 foot ulcer
XaaEv	Wagner ulcer classification grade 4 foot ulcer

Read Code	Description
XaaEw	Wagner ulcer classification grade 5 foot ulcer
Xaagd	Diabetes mellitus in remission
Xaage	Type I diabetes mellitus in remission
Xaage	Type 1 diabetes mellitus in remission
Xaagf	Type II diabetes mellitus in remission
Xaagf	Type 2 diabetes mellitus in remission
XacoB	Maturity onset diabetes of the young type 5
XafjT	Eating disorder co-occurrent with diabetes mellitus type 1
XafjT	Diabulimia
XafjT	ED-DMT1 - Eating disorder-diabetes mellitus type 1

9.3.3 UK Biobank ICD10 Diabetes Codes

CodeDescription
E100E10.0 With coma
E101E10.1 With ketoacidosis
E102E10.2 With renal complications
E103E10.3 With ophthalmic complications
E104E10.4 With neurological complications
E105E10.5 With peripheral circulatory complications
E106E10.6 With other specified complications
E107E10.7 With multiple complications
E108E10.8 With unspecified complications
E109E10.9 Without complications
E110E11.0 With coma
E111E11.1 With ketoacidosis
E112E11.2 With renal complications
E113E11.3 With ophthalmic complications
E114E11.4 With neurological complications
E115E11.5 With peripheral circulatory complications
E116E11.6 With other specified complications
E117E11.7 With multiple complications
E118E11.8 With unspecified complications
E119E11.9 Without complications
E130E13.0 With coma
E131E13.1 With ketoacidosis
E132E13.2 With renal complications
E133E13.3 With ophthalmic complications
E134E13.4 With neurological complications
E135E13.5 With peripheral circulatory complications
E136E13.6 With other specified complications
E137E13.7 With multiple complications
E138E13.8 With unspecified complications
E139E13.9 Without complications
E140E14.0 With coma
E141E14.1 With ketoacidosis
E142E14.2 Withrenal complications

Code	Description
E143	E14.3 With ophthalmic complications
E144	E14.4 With neurological complications
E145	E14.5 With peripheral circulatory complications
E146	E14.6 With other specified complications
E147	E14.7 With multiple complications
E148	E14.8 With unspecified complications
E149	E14.9 Without complications

9.3.4 UK Biobank ICD 9 Diabetes Codes

Code	Description
2500025000	Diabetes mellitus without mention of complication (adult-onset type)
2500125001	Diabetes mellitus without mention of complication (juvenile type)
2500925009	Diabetes mellitus without mention of compl. (adult/juvenile unspec.)
2501025010	Diabetes with ketoacidosis (adult-onset type)
2501125011	Diabetes with ketoacidosis (juvenile type)
2501925019	Diabetes with ketoacidosis (adult/juvenile unspec.)
2502025020	Diabetes with coma (adult-onset type)
2502125021	Diabetes with coma (juvenile type)
2502925029	Diabetes with coma (unspecified whether adult-onset or juvenile type)
2503	2503 Diabetes with renal manifestations
2504	2504 Diabetes with ophthalmic manifestations
2505	2505 Diabetes with neurological manifestations
2506	2506 Diabetes with peripheral circulatory disorders
2507	2507 Diabetes with other specified manifestations
2509	2509 Diabetes with unspecified complications
2509025090	Diabetes with unspecified complications (adult-onset type)
2509125091	Diabetes with unspecified complications (juvenile type)
2509925099	Diabetes with unspecified complications (unspecified onset)

9.3.5 UK Biobank Self-Reported Diabetes Codes

Code	Description
1220	diabetes
1222	type 1 diabetes
1223	type 2 diabetes

9.4 Codes for identification of cataract surgery

9.4.1 Primary Care Read2 Cataract Surgery Codes

Read Code	Description
72630	Simple linear extraction of lens
72630	Needling of lens for cataract
72631	Phakoemulsification of lens
72631	Phacoemulsification of lens
72632	Aspiration of lens
7263y	Other specified extracapsular extraction of lens
7263z	Extracapsular extraction of lens NOS
72640	Forceps extraction of lens
72641	Suction extraction of lens
72642	Cryoextraction of lens
7264y	Other specified intracapsular extraction of lens
7264z	Intracapsular extraction of lens NOS

9.4.2 Primary Care Read3 Cataract Surgery Codes

Read Code	Description
7263.	Extracapsular extraction of lens
7263.	Extracapsular cataract extraction
7263.	ECCE - Extracapsular cataract extraction
72630	Lens: [simple linear extraction] or [cataract needling]
72630	Needling of lens for cataract
72630	Simple linear extraction of lens
72631	Phacoemulsification of lens
72631	Phakoemulsification of lens
72632	Aspiration of lens
7263y	Other specified extracapsular extraction of lens
7263z	Extracapsular extraction of lens NOS
7264.	Intracapsular extraction of lens
7264.	Intracapsular extraction of cataract
7264.	ICCE - Intracapsular cataract extraction
72640	Forceps extraction of lens
72641	Suction extraction of lens
72641	Erysophake extraction of lens
72642	Cryoextraction of lens
7264y	Other specified intracapsular extraction of lens
7264z	Intracapsular extraction of lens NOS
X00XJ	Vectis extraction of lens
XE0BR	Simple linear extraction of lens
XaBYN	Extracapsular cataract extraction and insertion of intraocular lens
XaBYN	ECCE - Extracapsular cataract extraction and insertion of intraocular lens
XaBYO	Intracapsular cataract extraction and insertion of intraocular lens
XaBYO	ICCE - Intracapsular cataract extraction and insertion of intraocular lens

Read Code	Description
XaEVB	Small incision phakoemulsification cataract and insertion of intraocular lens
XaIwQ	Phakoemulsification of lens and insertion of prosthetic replacement
XaIwQ	Phacoemulsification of lens and insertion of prosthetic replacement

9.4.3 UK Biobank OPCS4 Cataract Surgery Codes

Code	Description
C711	C71.1 Simple linear extraction of lens
C712	C71.2 Phacoemulsification of lens
C713	C71.3 Aspiration of lens
C718	C71.8 Other specified extracapsular extraction of lens
C719	C71.9 Unspecified extracapsular extraction of lens
C721	C72.1 Forceps extraction of lens
C722	C72.2 Suction extraction of lens
C723	C72.3 Cryoextraction of lens
C728	C72.8 Other specified intracapsular extraction of lens
C729	C72.9 Unspecified intracapsular extraction of lens

9.4.4 UK Biobank OPCS3 Cataract Surgery Codes

Code	Description
173	173 Extra-capsular extraction of cataract
174	174 Intra-capsular extraction of cataract
1745	174.5 Intra-capsular extraction of cataract : cryo-extraction
176	176 Other extraction of lens, not elsewhere classified

9.4.5 UK Biobank Self-reported Cataract Surgery Codes

Code	Description
1435	cataract extraction/lens implant

9.5 Codes for exclusion of prevalent glaucoma surgery

9.5.1 Primary Care Read2 Glaucoma Surgery Codes

Read Code	Description
72550	Trabeculectomy
72554	Insertion of tube into anterior chamber of eye to assist drainage of aqueous humour
72554	Insertion of Molteno implantation tube into anterior chamber of eye
72560	Laser trabeculoplasty
72561	Trabeculotomy
72562	Goniotomy
72562	Barkan goniotomy
72563	Goniopuncture
72563	Barkan goniopuncture
72564	Viscogonioplasty
72603	Laser photocoagulation of ciliary body
72605	Transcleral diode laser cycloablation

9.5.2 Primary Care Read3 Glaucoma Surgery Codes

Read Code	Description
72550	Trabeculectomy
72550	Creation of guarded fistula to sclera
72550	Creation of subscleral fistula to sclera
72554	Insertion anterior chamber drainage tube (& Molteno tube)
72554	Insertion of tube into anterior chamber of eye to assist drainage of aqueous humour
72554	Insertion of Molteno implantation tube into anterior chamber of eye
72560	Laser trabeculoplasty
72560	YAG trabeculopuncture
72560	LTP - Laser trabeculoplasty
72561	Trabeculotomy
72562	Goniotomy (& Barkan)
72562	Goniotomy
72562	Barkan goniotomy
72563	Goniopuncture (& Barkan)
72563	Goniopuncture
72563	Barkan goniopuncture
72603	Laser coagulation of ciliary body
X00Wr	Insertion of Molteno tube into anterior chamber
X00Ws	Insertion of Schocket tube into anterior chamber
X00XI	Cataract extraction, insertion of intraocular lens and trabeculectomy
XE0BN	Insertion of drainage tube into anterior chamber
XE0BO	Goniotomy
XE0BP	Goniopuncture
XaEXv	Revision of trabeculectomy

Read Code	Description
XaJdX	Insertion of Baerveldt tube into anterior chamber
XaJhf	Transcleral diode laser cycloablation
XaKPD	Injection of viscoelastic in anterior chamber of eye
XaKaz	Trabeculectomy with intraoperative application of 5-fluorouracil
XaKb1	Trabeculectomy with intraoperative application of mitomycin
XaKb3	Trabeculectomy with beta-irradiation
XaXCJ	Viscogonioplasty

9.5.3 UK Biobank OPCS3 Glaucoma Surgery Codes

Code	Description
1573	157.3 Destruction of ciliary body : goniotomy
1574	157.4 Destruction of ciliary body : trabeculectomy

9.5.4 UK Biobank OPCS4 Glaucoma Surgery Codes

Code	Description
C601	C60.1 Trabeculectomy
C605	C60.5 Insertion of tube into anterior chamber of eye to assist drainage of aqueous humour
C611	C61.1 Laser trabeculoplasty
C612	C61.2 Trabeculotomy
C613	C61.3 Goniotomy
C614	C61.4 Goniopuncture
C615	C61.5 Viscogonioplasty

9.5.5 UK Biobank Self-reported Glaucoma Surgery Codes

Code	Description
1436	glaucoma surgery/trabeculectomy

9.6 UK Biobank medication codes for antihypertensive sensitivity analysis

9.6.1 ACE inhibitor Medication Codes

Code	Description
1140860696	lisinopril
1140860706	carace 2.5mg tablet
1140860714	zestril 2.5mg tablet
1140860728	quinapril
1140860750	captopril
1140860752	acepril 12.5mg tablet
1140860758	capoten 12.5mg tablet
1140860776	innovace 2.5mg tablet
1140860802	coversyl 2mg tablet
1140860806	ramipril
1140860878	staril 10mg tablet
1140860882	cilazapril
1140860892	vascace 250micrograms tablet
1140860904	trandolapril
1140860912	gopten 500micrograms capsule
1140860918	odrik 500micrograms capsule
1140864910	carace 10 plus tablet
1140881706	accupro 5mg tablet
1140888552	enalapril
1140888556	fosinopril
1140888560	perindopril
1140923712	moexipril
1140923718	perdix 7.5mg tablet
1141150328	ecopace 12.5mg tablet
1141150560	kaplon 12.5mg tablet
1141164148	imidapril hydrochloride
1141164154	tanatril 5mg tablet
1141167758	hyteneze 12.5 tablet
1141167822	tensopril 12.5mg tablet
1141170870	pralenal 2.5mg tablet
1141188408	tritace 1.25mg tablet

9.6.2 ACE inhibitor/Thiazide Combination Medication Codes

Code	Description
1140851690	acezide 50mg tablets x56
1140851692	capozide 50mg tablets x28
1140860736	accuretic tablet
1140860738	quinalapril + hydrochlorothiazide 10mg/12.5mg tablet
1140860764	captopril + hydrochlorothiazide 25mg/12.5mg tablet
1140860784	innozide tablet
1140860790	enalapril maleate + hydrochlorothiazide 20mg/12.5mg tablet
1140864618	zestoretic 10 tablet
1140864952	lisinopril + hydrochlorothiazide 10mg/12.5mg tablet

Code	Description
1140881714	capozide tablet
1140881716	acezide tablet
1141170544	capto-co 25mg/12.5mg tablet
1141180592	perindopril + indapamide
1141180598	coversyl plus 4mg/1.25mg tablet
1141190934	caralpha 10/12.5mg tablet
1141200726	lisicostad hct 10/12.5mg tablet

9.6.3 ACE inhibitor/Calcium Channel Blocker Combination Medication Codes

Code	Description
1141153316	tarka 2mg/180mg m/r capsule
1141153328	trandolapril + verapamil hydrochloride
1141165470	felodipine + ramipril
1141165476	triapin mite 2.5mg/2.5mg tablet

9.6.4 AR Blocker Medication Codes

Code	Description
1140916356	losartan
1140916362	cozaar half strength 25mg tablet
1141145660	valsartan
1141145668	diovan 40mg capsule
1141152998	irbesartan
1141153006	aprovel 75mg tablet
1141156836	candesartan cilexetil
1141156846	amias 2mg tablet
1141166006	telmisartan
1141171336	eprosartan
1141171344	teveten 300mg tablet
1141172492	micardis 20mg tablet
1141179974	cozaar 25mg tablet
1141193282	olmesartan
1141193346	olmetec 10mg tablet

9.6.5 AR Blocker/Thiazide Combination Medication Codes

Code	Description
1141151016	losartan potassium + hydrochlorothiazide 50mg/12.5mg tablet
1141151018	cozaar-comp 50mg/12.5mg tablet
1141172682	irbesartan + hydrochlorothiazide 150mg/12.5mg tablet
1141172686	coaprovel 150mg/12.5mg tablet
1141187788	telmisartan + hydrochlorothiazide 40mg/12.5mg tablet
1141187790	micardisplus 40mg/12.5mg tablet
1141201038	valsartan + hydrochlorothiazide 80mg/12.5mg tablet
1141201040	co-diovan 80mg/12.5mg tablet

9.6.6 Calcium Channel Blocker Medication Codes

Code	Description
1140851730	calcicard 60mg tablet
1140851784	lidoflazine
1140851786	clinium 120mg tablet
1140851790	vasad 5mg capsule
1140861088	nifedipine
1140861090	adalat 5mg capsule
1140861106	calcilat 10mg capsule
1140861110	angiopine 5mg capsule
1140861114	nifensar xl 20mg m/r tablet
1140861120	coracten sr 10mg m/r capsule
1140861128	tildiem 60mg m/r tablet
1140861130	britiazim 60mg m/r tablet
1140861136	angiozem 60mg m/r tablet
1140861138	adizem-60 m/r tablet
1140861166	dilzem sr 60mg long acting m/r capsule
1140861176	cardene 20mg capsule
1140861190	isradipine
1140861194	prescal 2.5mg tablet
1140861202	istin 5mg tablet
1140861276	lacidipine
1140861282	motens 2mg tablet
1140866460	half securon sr 120mg m/r tablet
1140866466	securon 40mg tablet
1140866484	geangin 40mg tablet
1140866546	berkatens 40mg tablet
1140866554	cordilox 40mg tablet
1140868036	parmid 10mg tablet
1140872472	nimotop 30mg tablet
1140872568	nimodipine
1140879802	amlodipine
1140879806	diltiazem
1140879810	nicardipine
1140881692	univer 120mg m/r capsule
1140888510	verapamil
1140888646	felodipine
1140911088	nifelease 20mg m/r tablet
1140911698	slozem 120mg m/r capsule
1140916930	calanif 5mg capsule
1140917428	angitil sr 90 m/r capsule
1140917452	metazem 60mg m/r tablet
1140923572	adipine mr 10 m/r tablet
1140926188	unipine xl 30mg m/r tablet
1140926966	nimodrel mr 10 m/r tablet
1140927934	cardilate mr 10mg m/r tablet
1140927940	tensipine mr 10 m/r tablet
1140928212	plendil 2.5mg m/r tablet

Code	Description
1140928226	nisoldipine
1140928234	syscor mr 10mg m/r tablet
1141145870	fortipine la40 m/r tablet
1141150500	slofedipine 20mg m/r tablet
1141150538	nifedotard 20mr m/r tablet
1141150926	verapress mr 240 m/r tablet
1141151474	viazem xl 120mg m/r capsule
1141153026	lercanidipine
1141153032	zanidip 10mg tablet
1141153394	mibefradil
1141153400	posicor 50mg tablet
1141153454	calazem 60mg m/r tablet
1141156656	optil 60mg m/r tablet
1141157136	dilcardia sr 60mg m/r capsule
1141157140	nifedipress mr 10 m/r tablet
1141162546	nivaten retard 10mg m/r tablet
1141166752	coroday mr 20mg m/r tablet
1141167832	zemtard 120 xl m/r capsule
1141169096	ethimil mr 240 m/r tablet
1141169710	vertab sr 240 m/r tablet
1141169730	nifopress retard 20mg m/r tablet
1141173766	calchan mr 10mg m/r tablet
1141180238	horizem sr 90mg m/r capsule
1141184390	zolvera 40mg/5ml oral solution
1141185444	disogram sr 60mg m/r capsule
1141188152	felotens xl 5mg m/r tablet
1141188920	keloc sr 5mg m/r tablet
1141188936	hypolar retard 10mg m/r tablet
1141190160	vascalpha 5mg m/r tablet
1141190548	valni 20 retard 20mg m/r tablet
1141199858	cardioplen xl 5mg m/r tablet
1141200400	amlostin 5mg tablet
1141200782	neofel xl 5mg m/r tablet
1141201814	parmid xl 5mg m/r tablet

9.6.7 Calcium Channel Blocker/Thiazide Combination Medication Codes

Code	Description
1140926778	diltiazem hcl+hydrochlorothiazide 150mg/12.5mg m/r capsule
1140926780	adizem-xl plus m/r capsule

9.6.8 Calcium Channel/Beta-blocker Combination Medication Codes

Code	Description
1140860356	beta-adalat capsule
1140860358	tenif capsule
1140860426	atenolol+nifedipine 50mg/20mg m/r capsule

9.6.9 Beta-blocker Medication Codes

Code	Description
1140851480	slow-pren 160mg m/r tablet
1140851492	betadren 5mg tablet
1140851522	metoros 95mg tablet
1140851556	bedranol 10mg tablet
1140860172	totamol 25mg tablet
1140860180	arbralene 50mg tablet
1140860192	nadolol
1140860194	corgard 40mg tablet
1140860212	apsolox 20mg tablet
1140860220	slow-trasicor 160mg m/r tablet
1140860222	trasicor 20mg tablet
1140860230	oxyprenix sr 160mg m/r tablet
1140860232	kerlone 20mg tablet
1140860244	labrocol 100mg tablet
1140860250	trandate 50mg tablet
1140860266	betaloc 50mg tablet
1140860274	lopresor 50mg tablet
1140860278	mepranix 50mg tablet
1140860292	pindolol
1140860294	visken 5mg tablet
1140860304	beta-cardone 40mg tablet
1140860362	sotacor 80mg tablet
1140860434	monocor 5mg tablet
1140860492	emcor 10mg tablet
1140860498	celectol 200mg tablet
1140863724	cartrol 10mg tablet
1140864410	antipressan 25mg tablet
1140866704	angilol 10mg tablet
1140866712	cardinol 10mg tablet
1140866724	acebutolol
1140866726	sectral 100mg capsule
1140866738	atenolol
1140866756	tenormin 25 tablet
1140866758	vasaten 50mg tablet
1140866764	apsolol 10mg tablet
1140866766	propanix 10mg tablet
1140866778	betadur cr 160mg m/r capsule
1140866782	beta-prograne 160mg m/r capsule
1140866784	berkolol 10mg tablet
1140866798	half-betadur cr 80mg m/r capsule
1140866800	half-inderal la 80mg m/r capsule
1140866802	half beta-prograne 80mg m/r capsule
1140866804	inderal 10mg tablet
1140879758	betaxolol
1140879760	bisoprolol
1140879762	celiprolol

Code	Description
1140879818	metoprolol
1140879822	carteolol
1140879824	labetalol
1140879830	oxprenolol
1140879834	penbutolol
1140879842	propranolol
1140879854	sotalol
1140879866	timolol
1140909368	carvedilol
1140916730	sloprolol 80mg m/r capsule
1140916868	probeta la 160mg m/r capsule
1140917076	lopranol la 160mg m/r capsule
1140922930	atenix 25mg tablet
1141152076	half propanix la 80mg m/r capsule
1141164276	nebivolol
1141164280	nebilet 5mg tablet
1141168498	eucardic 3.125 tablet
1141171152	cardicor 1.25mg tablet
1141172742	syprol 5mg/5ml oral solution
1141182904	soloc 5mg tablet
1141184324	bipranix 5mg tablet
1141184722	latanoprost + timolol
1141187780	vivacor 5mg tablet

9.6.10 Beta-blocker/Thiazide Combination Medication Codes

Code	Description
1140851436	vasetic co-amilozide 5/50mg tablet
1140860308	metoprolol tartrate + chlorthalidone 100mg/12.5mg tablet
1140860312	nadolol + bendrofluazide 40mg/5mg tablet
1140860314	secadrex tablet
1140860316	nadolol + bendrofluazide 80mg/5mg tablet
1140860318	sotazide tablet
1140860322	pindolol + clopamide 10mg/5mg tablet
1140860324	tenoret 50 tablet
1140860328	tenoretic tablet
1140860330	tolerzide tablet
1140860332	sotalol hydrochloride + hydrochlorothiazide 80mg/12.5mg tablet
1140860334	trasidrex tablet
1140860336	timolol maleate + co-amilozide 10mg/2.5mg/25mg tablet
1140860338	viskaldix tablet
1140860340	timolol maleate + bendrofluazide 10mg/2.5mg tablet
1140860342	timolol maleate + bendrofluazide 20mg/5mg tablet
1140860348	atenixco 50mg/12.5mg tablet
1140860352	tenchlor 50mg/12.5mg tablet
1140860386	co-betaloc tablet
1140860390	corgaretic 40mg tablet

Code	Description
1140860394	inderetic capsule
1140860396	inderex capsule
1140860398	kalten capsule
1140860402	lopresoretic tablet
1140860404	metoprolol tartrate + hydrochlorothiazide 100mg/12.5mg tablet
1140860406	moducren tablet
1140860410	prestim tablet
1140860418	propranolol hydrochloride + bendrofluazide 80mg/2.5mg capsule
1140860422	acebutolol + hydrochlorothiazide 200mg/12.5mg tablet
1140864176	monozide 10 tablet
1140864950	bisoprolol fumarate + hydrochlorothiazide 10mg/6.25mg tablet
1140916628	totaretic 50mg/12.5mg tablet
1140923276	co-amilozide
1141146124	atenolol + chlorthalidone
1141146126	atenolol + bendrofluazide
1141146128	atenolol + co-amilozide
1141146184	tenben capsule
1141180778	atenolol + chlortalidone
1141194804	nadolol + bendroflumethiazide 40mg/5mg tablet
1141194808	timolol maleate + bendroflumethiazide 10mg/2.5mg tablet
1141194810	atenolol + bendroflumethiazide

9.6.11 Beta-blocker/Loop Diuretic Combination Medication Codes

Code	Description
1140860320	penbutolol sulphate+frusemide 40mg/20mg tablet
1140860400	lasipressin tablet

9.6.12 Thiazide Medication Codes

Code	Description
1140851332	centyl 2.5mg tablet
1140851338	enduron 5mg tablet
1140851362	esidrex k tablet
1140851364	hygroton k tablet combination pack
1140851368	navidrex-k tablet
1140851660	serpasil-esidrex tablet
1140864202	chlorthalidone tablet + potassium m/r tablet 25mg/6.7mmol pack
1140866072	hydroflumethiazide
1140866074	hydrenox 50mg tablet
1140866078	indapamide
1140866084	mefruside
1140866086	baycaron 25mg tablet
1140866090	methyclothiazide
1140866092	metolazone
1140866094	metenix-5 tablet
1140866096	xuret 500micrograms tablet
1140866102	polythiazide

Code	Description
1140866104	nephril 1mg tablet
1140866108	xipamide
1140866110	diurexan 20mg tablet
1140866122	bendrofluazide
1140866128	aprinox 2.5mg tablet
1140866132	berkozide 2.5mg tablet
1140866136	neo-naclex 5mg tablet
1140866138	chlorothiazide
1140866140	saluric 500mg tablet
1140866144	chlorthalidone
1140866146	hygroton 50mg tablet
1140866156	cyclopenthiazide
1140866158	navidrex 500mcg tablet
1140866162	hydrochlorothiazide
1140866164	esidrex 25mg tablet
1140866168	hydrosaluric 25mg tablet
1140866440	centyl k m/r tablet
1140866446	neo-naclex k m/r tablet
1140866450	bendrofluazide + potassium 2.5mg/7.7mmol m/r tablet
1140888922	nindaxa 2.5mg tablet
1140909706	chlortalidone
1140910442	bzt - bendrofluazide
1140916870	natramid 2.5mg tablet
1140917068	opumide 2.5mg tablet
1141146378	natrilix sr 1.5mg m/r tablet
1141194794	bendroflumethiazide
1141194800	bendroflumethiazide + potassium 2.5mg/7.7mmol m/r tablet

9.6.13 Potassium-Sparing Diuretic Medication Codes

Code	Description
1140851418	diatensec 50mg tablet
1140851420	laractone 25mg tablet
1140866220	midamor 5mg tablet
1140866222	amilospare 5mg tablet
1140866226	berkamil 5mg tablet
1140866230	potassium canrenoate
1140866232	spiroctan-m 200mg/10ml injection
1140866236	spironolactone
1140866244	aldactone 25mg tablet
1140866306	spirospare 25mg tablet
1140866308	spiretic 25mg tablet
1140866312	spiroctan 25mg tablet
1140866318	spirolone 25mg tablet
1140866388	triamterene
1140866390	dytac 50mg capsule
1140888512	amiloride
1140910630	canrenoate potassium

Code	Description
1140927174	amilamont 5mg/ml s/f oral solution
1141201244	eplerenone
1141201250	inspra 25mg tablet

9.6.14 Potassium-Sparing/Loop Diuretic Combination Medication Codes

Code	Description
1140864550	aridil 2.5mg/20mg tablet
1140866332	triamterene+frusemide 50mg/40mg tablet
1140866334	lasoride tablet
1140866356	burinex a tablet
1140866406	frumil tablet
1140866408	frusene tablet
1140866412	lasilactone capsule
1140866418	fru-co tablet
1140866426	amiloride hydrochloride+bumetanide 5mg/1mg tablet
1140928624	frusemek 5mg/40mg tablet
1141167108	froop co 5mg/40mg tablet
1141181520	komil 5/40 tablet
1141195254	triamterene+furosemide 50mg/40mg tablet

9.6.15 Potassium-Sparing/Thiazide Diuretic Combination Medication Codes

Code	Description
1140851428	normetic tablet
1140851430	synuretic tablet
1140851432	hypertane-50 tablet
1140851436	vasetic co-amilozide 5/50mg tablet
1140864574	spiro-co 25mg tablet
1140866324	triamterene+benzthiazide 50mg/25mg capsule
1140866330	triamterene+chlorthalidone 50mg/50mg tablet
1140866340	delvas tablet
1140866352	navispare tablet
1140866354	amilmaxco 5/50 tablet
1140866360	triamaxco tablet
1140866396	aldactide 25 tablet
1140866400	amil-co tablet
1140866402	dyazide tablet
1140866404	dytide capsule
1140866410	kalspare tablet
1140866416	moduret 25 tablet
1140866420	moduretic tablet
1140866422	amiloride hcl+cyclopenthiazide 2.5mg/250micrograms tablet
1140922324	zida-co 5mg/50mg tablet
1141180772	triamterene+chlortalidone 50mg/50mg tablet

9.6.16 Loop Diuretic Medication Codes

Code	Description
1140851342	aluzine 20mg tablet
1140851412	frusetic 40mg tablet
1140851414	frumax 40mg tablet
1140864874	torem 2.5mg tablet
1140866116	frusemide
1140866182	dryptal 40mg tablet
1140866192	froop 40mg tablet
1140866194	frusid 40mg tablet
1140866202	edecrin 50mg tablet
1140866210	piretanide
1140866212	arelix 6mg capsule
1140866248	lasix 20mg tablet
1140866262	rusyde 20mg tablet
1140866280	bumetanide
1140866282	burinex 1mg tablet
1140866438	burinex k m/r tablet
1140866442	diumide-k continus m/r tablet
1140866444	lasikal m/r tablet
1140866448	bumetanide+potassium 500micrograms/7.7mmol m/r tablet
1140866506	frusemide+potassium 20mg/10mmol m/r tablet
1140881728	lasix+k tablet combination pack
1140888496	torasemide
1140909708	furosemide
1140927790	toremifene
1141168964	betinex 1mg tablet
1141169088	frusol 20mg/5ml s/f oral solution
1141181098	etacrynic acid product
1141195258	furosemide+potassium 20mg/10mmol m/r tablet

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