Single-Suture Non-Syndromic Craniosynostosis and its Association with Attention Deficit/Hyperactivity Disorder: Systematic Review and Meta-Analysis

This thesis is submitted in partial fulfilment of the Honours degree of

Bachelor of Psychological Science.

School of Psychology

University of Adelaide

September 2023

Word Count: 6272

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CRANIOSYNOSTOSIS AND ITS ASSOCIATION WITH ADHD

CONTRIBUTOR ROLES

ROLE	Role Description	Student	Supervisor 1	Supervisor 2
Conceptualization	Ideas: formulation or evolution of overarching research goals and aims.	X	X	X
Methodology	Development or design of methodology; creation of models.	X	X	X
Project Administration	Management and coordination responsibility for the research activity planning and execution.		X	X
Supervision	Oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team.		X	X
Resources	Provision of study materials, laboratory samples, instrumentation, computing resources, or other analysis tools.	X		X
Software	Programming, software development; designing computer programs; implementation of the computer code and supporting algorithms; testing of existing code.			
Investigation	Conducting research - specifically performing experiments, or data/evidence collection.	X		X
Validation	Verification of the overall replication/reproducibility of results/experiments.	X		X
Data Curation	Management activities to annotate (produce metadata), scrub data and maintain research data (including software code, where it is necessary for interpreting the data itself) for initial use and later re-use.	X	X	
Formal Analysis	Application of statistical, mathematical, computational, or other formal techniques to analyze or synthesize study data.	X		X
Visualization	Visualization/data presentation of the results.	X		
Writing – Original Draft	Specifically writing the initial draft.	X		
Writing – Review & Editing	Critical review, commentary or revision of original draft	X	X	X

ABSTRACT

It is not yet understood if and to what extent craniosynostosis impacts development of attention deficit/hyperactivity disorder (ADHD) or ADHD symptomology (inattention, hyperactivity). This systematic review and meta-analysis examines the association between ADHD (screened, diagnosed) and ADHD symptomology in individuals with single suture, non-syndromic craniosynostosis. Data were consolidated from 21 studies published prior to April 2023 that examined ADHD and ADHD symptomology in individuals ($N_{participants}$ = 2637; M_{age} = 7.36 years) with single-suture, non-syndromic craniosynostosis. Odds Ratios were calculated to determine the likelihood of observing diagnosed ADHD, screened ADHD, or ADHD symptomology (inattention, hyperactivity) in cases compared with control groups. In studies without a control group, prevalence rates were used to calculate mean effect size. Hedges' *g* was used to measure the standardised mean difference in scores on measures of ADHD symptomology between cases and control groups. Individuals with single-suture, non-syndromic craniosynostosis had higher rates of ADHD (10%), inattention (24%), and hyperactivity (25%) than that of general populations (8%, 16%, and 9% respectively). Sub-analysis yielded no significant differences between cases and control groups. Overall, ADHD, inattention, and hyperactivity were high in individuals with single-suture, non-syndromic craniosynostosis when compared to general populations, but no differences were found between cases and controls. However, sample sizes were small, data for sub-analyses (age, craniosynostosis type) were limited, and the current scope of the literature restricted the context in which results can be interpreted. Nevertheless, findings suggested that there may be a relationship between ADHD and single-suture, non-syndromic craniosynostosis.

Key Words: single-suture craniosynostosis, non-syndromic craniosynostosis, metopic synostosis, sagittal synostosis, coronal synostosis, lambdoid synostosis, attention deficit/hyperactivity disorder, hyperactivity, inattention

DECLARATION

This thesis contains no material which has been accepted for the award of any other degree of diploma in any University, and, to the best of my knowledge, this thesis contains no material previously published except where due reference is made. I give permission for the digital version of this thesis to be made available on the web, via the University of Adelaide's digital thesis repository, the Library Search and through web search engines, unless permission has been granted by the School to restrict access for a period of time.

[redacted]

29th September 2023

CHAPTER 1

Introduction

1.1 Overview of Craniosynostosis

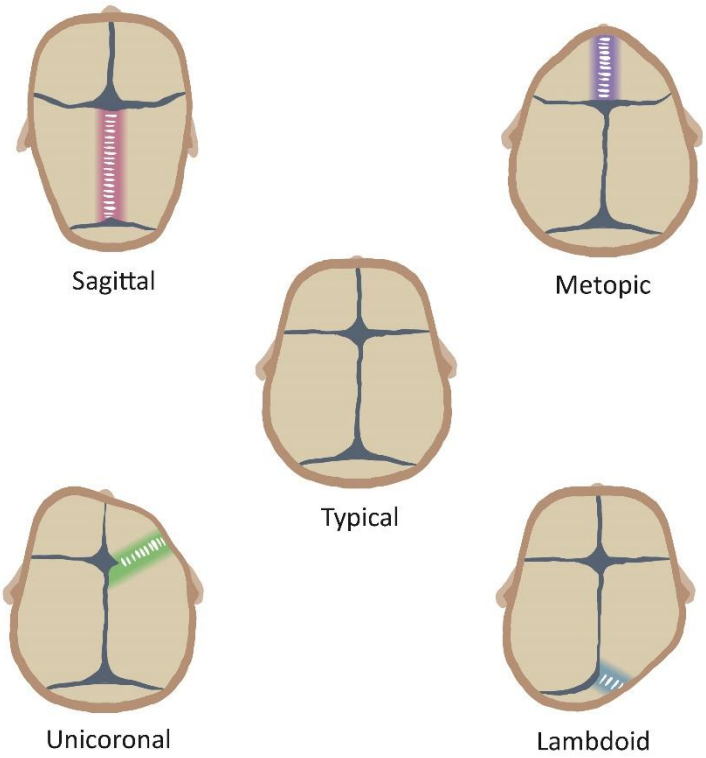
Single-suture craniosynostosis is characterised by the early fusion of a single cranial suture (sagittal, metopic, coronal, or lambdoid) (Speltz et al., 2004). Cranial sutures are dense fibrous joints found between two cranial bones that allow the skull to expand, accommodating for periods of rapid brain growth (Kajdic et al., 2018). Sutures typically fuse during early adulthood, with the exception of the metopic suture which generally fuses in early infancy (Betances et al., 2023). Single-suture craniosynostosis occurs in one of every 2000 live births, with a male to female ratio of ~2:1 (Cornelissen et al., 2016; Edwards-Bailey et al., 2023). Syndromic craniosynostosis is characterised by premature fusion of one or more cranial sutures with co-occurrence of specific, clinically recognised syndromes such as Pfeiffer or Apert syndrome (Derderian & Seaward, 2012). Nonetheless up to 85% of craniosynostosis cases are single-suture and non-syndromic (Speltz et al., 2004).

1.1.1 Outcomes, Pathogenesis, and Etiology.

Craniosynostosis may result in abnormal growth of the skull with individual skull shapes corresponding to location of the fused suture (Figure 1). Craniosynostosis can affect social, emotional, and physical outcomes. Common craniosynostosis outcomes include elevated intercranial pressure, increased behavioural issues, social isolation, and decreased psychological wellbeing, cognitive, verbal, and visuospatial skills (Speltz et al., 2004; Osborn et al., 2021; Wójcicki & Prudel, 2019). It is still unclear as to what the pathogenesis and etiology of craniosynostosis are, however there is believed to be a gene environment correlation (Osborn et al., 2021). Genetic risk factors include single-gene mutations and chromosomal structural aberrations (Kajdic et al., 2018). Environmental risk factors include foetal head restraint, metabolic and hematologic disorders, maternal thyroid dysfunction, and maternal substance use (Speltz et al., 2004; Tillman et al., 2020).

Figure 1

Craniosynostosis Suture Locations



Note: Figure 1 displays the different *c*raniosynostosis types with colour indicating affected suture locations. Original figure adapted from Buchanan et al., (2017) and Kajdic et al., (2019).

1.2 Overview of ADHD

Attention deficit/hyperactivity disorder (ADHD), previously diagnosed as attention deficit disorder (ADD), is a lifelong neurodevelopmental disorder which can be characterised by ongoing changes in attention, hyperactivity, and impulsivity (Krieger et al., 2020). For a diagnosis of ADHD to be made using the Diagnostic and Statistical Manual of Mental Disorders 5th ed (DSM-5, American Psychiatric Association, 2013) a child needs to present with, for at least six months, persistent patterns of six or more well defined symptoms in two categories: inattention, and hyperactivity/impulsivity. In adults the number of symptoms that need to be observed reduces from six to five, due to adults' increased ability to mask symptomology though emotional, mental, and physical regulation (DSM-5, American Psychiatric Association, 2013). When diagnosing ADHD using the International Statistical Classification of Diseases and Related Health Problems 11th ed

(ICD-11, World Health Organization, 2019), the same time frames are present as seen in the DSM-5, however, only persistent patterns of either inattention or hyperactivity/impulsivity must be present. While there is some variation between the diagnostic criteria for ADHD in the DSM-5 and ICD-11, the same assessment categories of inattention and hyperactivity/impulsivity are maintained, with similar descriptions of symptomology (Table 1). As hyperactivity and impulsivity are assessed within a single symptom category in both the DSM-5 and ICD-11, this review has chosen to focus on attention and hyperactivity as the two outcome indicators of ADHD symptomology.

Table 1

Example of the Similarity in DSM-5 and ICD-11 Descriptions of ADHD Symptomology

Diagnostic Criteria	DSM-5 Symptom Examples	ICD-11 Symptom Examples
Inattention	"Is often easily distracted."	"Easily distracted by extraneous stimuli or thoughts not related to the task at hand."
Inattention	"Often does not seem to listen when spoken to directly."	"Often does not seem to listen when spoken to directly."
Hyperactivity/Impulsivity	"Often leaves seat in situations when remaining seated is expected."	"Leaves seat when expected to sit still; often runs about."
Hyperactivity/Impulsivity	" Often fidgets with or taps hands or feet, or squirms in seat."	"Has difficulty sitting still without fidgeting."

Note: Table 1 provides an example of the similarity in DSM-5 and ICD-11 descriptions of ADHD Symptomology. Original table adapted from DSM-5 (American Psychiatric Association, 2013, Neurodevelopmental Disorders section) and ICD-11 (World Health Organization, 2019, 6A05 Attention Deficit Hyperactivity Disorder section) information.

A recent systematic review reported global prevalence rates of ADHD in children and adolescents at 8.0%, with a male to female ratio of 2:1 (Ayano et al., 2023). However, prevalence

statistics vary, ranging from 3-8%, with higher prevalence seen in children (Thomas et al., 2015). Further, prevalence of ADHD is increasing and while the reason for increase is not entirely clear there are some factors understood to be instrumental to this increase (Ayano et al., 2023). As revisions are made to ADHD diagnostic criteria, the validity and reliability of ADHD diagnostic tools increases (Leffa et al., 2022). This change in criterion improves the accuracy of a diagnostic tool to better represent a wider range of individuals, increasing the number of individuals meeting the diagnostic criteria needed to receive an ADHD diagnosis (Kessi et al., 2022). As the prevalence of ADHD diagnoses increase so do the number of clinics offering assessment, enhancing accessibility to assessment and therefore number of diagnoses (Thomas et al., 2015). Further, genetic factors are recognised to be instrumental to the increasing prevalence of ADHD; heritability of ADHD is estimated to be as high as 80% with some twin studies suggesting that ADHD may become more prominent as generations progress (Kessi et al., 2022).

Global prevalence rates of hyperactivity and inattention are not as widely available, however prevalence data in smaller samples are available. In normative data clinically significant symptoms of hyperactivity were observed in up to 9% of individuals aged 12 - 17 years (Vugteveen et al., 2022). In primary care settings 16% of individuals aged 6 - 10 years exhibited clinically significant inattention (Spencer et al., 2018). These data show that inattention and hyperactivity are just prevalent as diagnosed ADHD in general and primary care populations. As both outcomes are considered potential indicators of ADHD they should be considered when assessing the relationship between ADHD and craniosynostosis (Spencer et al., 2018).

1.2.1 Outcomes, Pathogenesis, and Etiology

ADHD can negatively affect academic outcomes, overall wellbeing, and social interactions (Kessi et al., 2022). Inattentive outcomes can include difficulty with sustained attention, frequent daydreaming, and consistent forgetfulness (DSM-5, American Psychiatric Association, 2013; ICD-11, World Health Organization, 2019). Hyperactive outcomes can include difficulty controlling vocal volume, excessive speech, and frequent fidgeting and movement (DSM-5, American Psychiatric Association, 2013; ICD-11, World Health Organization, 2019). Further, ADHD is associated with

dysregulated emotional and behavioural responses, executive dysfunction, and early mortality (Krieger et al., 2020)

It is still unclear as to what the pathogenesis and etiology of ADHD are, however, evidence suggests that gene environment interactions contribute to its development (Li et al., 2019). Genetic factors include alterations in dopaminergic pathways, and polymorphisms in genes responsible for encoding dopamine receptors (Kian et al., 2022). Environmental factors include prenatal stress and anxiety, and exposure to certain environmental toxins such as manganese, and food additives (Palladino et al., 2019).

1.3 Single-Suture, Non-syndromic Craniosynostosis and ADHD

Persistent patterns of inattention are one of the two symptoms required for a diagnosis of ADHD to be made. One example of the relatedness between ADHD symptomology and craniosynostosis can be seen in a case control study ($N_{participants}$ = 30, N_{range} 2.5 - 25 years) where those with single-suture, non-syndromic craniosynostosis exhibited increased inattention compared to unaffected controls (Boltshauser et al., 2003). In a different sample of 179 children, cases once again exhibited increased inattention (Collette et al., 2017). Attention deficits have been observed in studies assessing samples ($N_{participants}$ = 35) with sagittal synostosis (Chieffo et al., 2010) and studies ($N_{participants}$ = 61) partitioned by craniosynostosis type (sagittal, metopic; Kljajić et al., 2020).

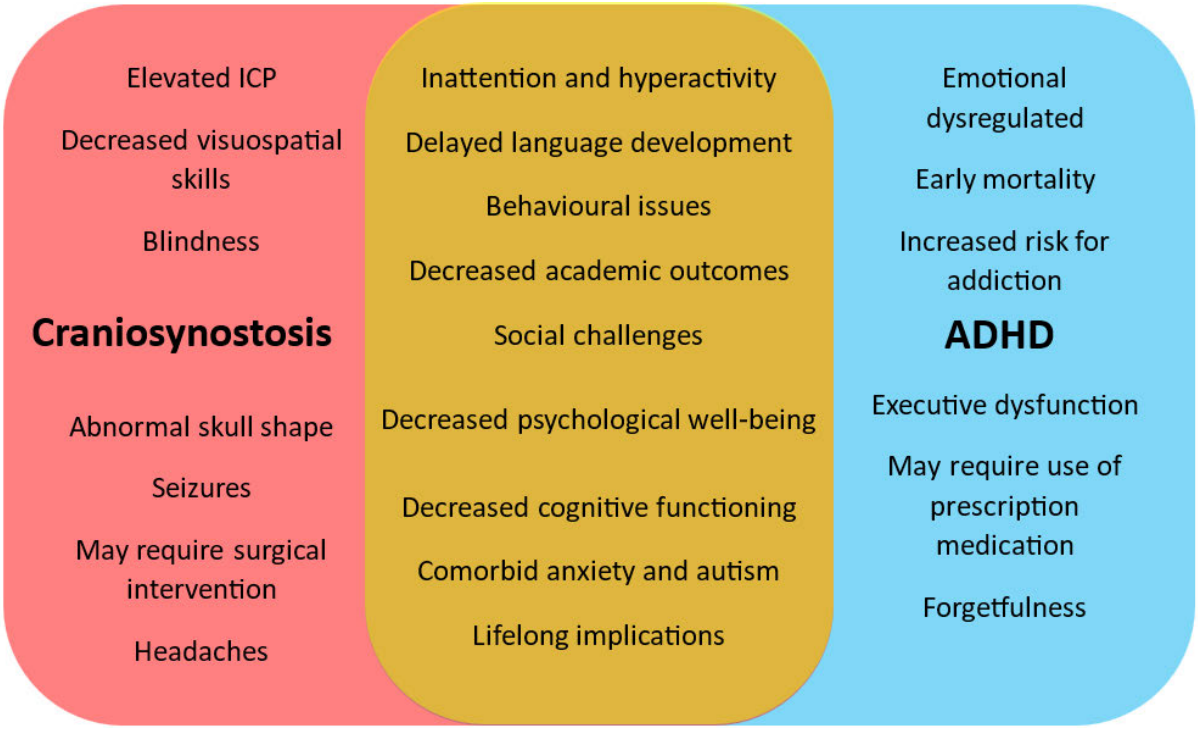
Hyperactivity is the second symptom required to make a diagnosis of ADHD. An example of the potential relationship between hyperactivity and craniosynostosis can be seen in two studies assessing developmental outcomes in five-year-old children ($N_{participants}$ = 80) with sagittal or metopic synostosis (Care et al., 2021 Edwards-Bailey et al., 2023). These children were found to exhibit high levels of hyperactivity when compared to standardised test norms. High levels of hyperactivity were again observed in 54 seven-year-old children with metopic synostosis (Qi et al., 2022). Increased hyperactivity has also been reported in individuals (2 - 30 years) with metopic synostosis when compared to unaffected age matched controls (Osborn et al., 2021).

1.4 Summary and Aims

While increased hyperactivity and inattention are a recurring theme in papers examining individuals with craniosynostosis, and the two conditions share overlapping symptomology (Figure 2), it is not yet clear if and to what extent craniosynostosis impacts the development of ADHD or ADHD symptomology (inattention, hyperactivity). This thesis aims to systematically review and meta-analyse ADHD (screened, diagnosed) and ADHD symptomology (inattention, hyperactivity) in individuals with single-suture, non-syndromic craniosynostosis. Further this review explores how craniosynostosis type (sagittal, metopic, lambdoid, coronal), and age (infant 0-1, preschool 2-4, lower primary 5-8, upper primary 9-12, high school 13-17, adult 18+ years) may influence this relationship. Narrowing in on a specific craniosynostosis type provides information about which suture locations may be more impacted, and broadening ADHD diagnosis to screened ADHD and symptomology provides information on populations who may be affected by ADHD symptomology but have not undergone ADHD assessment.

Figure 2

Overlapping Outcomes of Single-Suture, Non-Syndromic Craniosynostosis and ADHD



Note: This is not an exhaustive list of potential overlapping outcomes. Further, all outcomes listed may co-occur in either disorder given the correct circumstances. Original figure, information adapted from multiple sources (Speltz et al., 2004; Dosher et al., 2015; Palladino et al., 2019; Kljajić et al., 2020; Tillman et al., 2020; Kian et al., 2022). ICP = intercranial pressure.

CHAPTER 2

Methodology

2.1 Literature Search

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA guidelines; Moher, Liberati, Tetzlaff, & Altman, 2009) were used in the design and reporting of this systematic review and meta-analysis. The review protocol was preregistered online at the International Register of Systematic Reviews (hyperlink to protocol removed for de-identification purposes).

A comprehensive online search of four electronic databases (PubMed, Scopus, EMBASE, and PsycINFO) was conducted under the guidance of an expert research librarian with the purpose of identifying eligible articles which examine the prevalence of ADHD (diagnosed and/or screened), and/or ADHD symptomology (hyperactivity, inattention) in individuals diagnosed with single-suture, non-syndromic craniosynostosis; no additional filters or limitations were applied and databases were last accessed on April 3rd 2023 (see Appendix A for detailed logic grids tailored to each database). Reference lists of included studies were manually searched, and a Scopus citation search was conducted by one author (Author A) in order to identify additional relevant articles; Scopus was last accessed on August 1st, 2023.

2.2 Study Selection

The initial database search was undertaken by one author (Author A) identifying 1993 articles. Duplicates were removed, reducing the article count to 1274. Using Covidence systematic review software (Veritas Health Innovation, Melbourne, Australia, www.covidence.org), retrieved studies were then independently co-screened by title and abstract against the eligibility criteria by one author and one reviewer (Author A, Reviewer A), reducing the number of articles to 110. Full text versions of the articles were obtained, and the eligibility criteria were once again applied by one author and one reviewer (Author A, Reviewer A) resulting in a reduction to 18 articles. An additional

three studies were identified in the manual reference list and Scopus citation search resulting in 21 eligible studies (refer to Figure 3 for a summary of the search process).

Five studies appeared to meet all inclusion criteria, however two (Care et al., 2019; Chandler et al., 2020) were excluded for not providing data suitable for meta-analysis, two (Shimoji & Tairen., 2019; Tolchin et a., 2020) due to more than 10% of the sample including additional conditions known to affect functioning, and one (Shimoji et al., 2002) appeared to identify its sample due to having cognitive or behavioural problems.

2.3 Eligibility Criteria

2.3.1 Inclusion Criteria

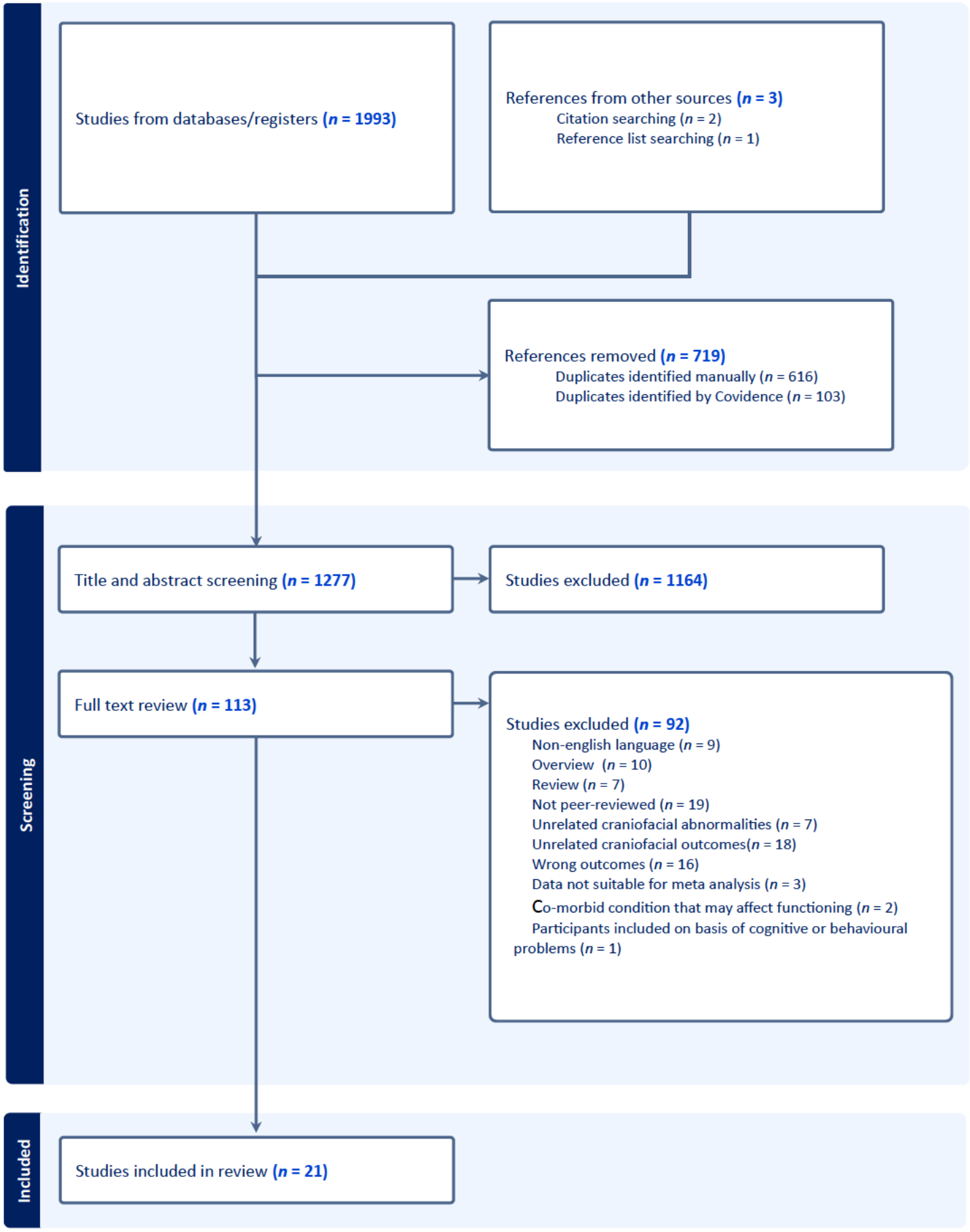
All prospective and retrospective studies examining diagnosed or screened ADHD, and/or ADHD symptomology (hyperactivity, inattention) in individuals with single-suture, non-syndromic craniosynostosis (metopic, sagittal, coronal, lambdoid) which include data suitable for meta-analysis.

2.3.2 Exclusion Criteria

Case studies ($N_{participants} = 1$), reviews, books, and papers with limited access (i.e., only title and abstract), non-English language papers, secondary sources (i.e., systematic reviews and meta-analyses), non-peer reviewed studies, inclusion of other conditions known to affect functioning (>10% of the sample), and studies which identified participants for inclusion due to having cognitive or behavioural problems.

Figure 3

PRISMA Flowchart of the Study Selection Process



2.4 Data Collection Process

Key demographic information, study characteristics, craniosynostosis and ADHD outcome data, and measurement statistics were manually co-extracted by two independent reviewers (Author A, Reviewer B; see Appendix B for coding sheet). Demographic data extracted were age, sex, socioeconomic status, type of craniosynostosis, family history of craniosynostosis, family history of ADHD, and surgical status. Study characteristics included sample size, country of origin, recruitment source, and study design. Outcome data included results from teacher-report, parent-report, self-report and clinician-administered measures of attention or hyperactivity and ADHD screening tools, in addition to diagnosis of ADHD. Measurement statistics included statistics necessary for calculating effect size: mean, standard deviation (*SD*), and event rates. If outcome data from multiple timepoints were available all data were collected: where appropriate, data were analysed by age, and in all other analyses data were combined. Outcomes were grouped by hyperactivity, attention, ADHD screening, and ADHD diagnosis. Additionally, where data were sufficient, outcomes were grouped and analysed according to craniosynostosis type (sagittal, metopic, coronal, lambdoid) and age (infant 0-1, preschool 2-4, lower primary 5-8, upper primary 9-12, high school 13-17, adults 18+ years).

2.5 Data Preparation

In studies where limited age could be analysed due to reported age categories encompassing multiple age ranges (Osborn et al., 2021) remaining age data were reported as combined. If all age data could not be determined (Tillman et al., 2020), data were reported as combined. If suture location could not be determined (Kapp Simon, 1998, Kapp Simon et al., 2012; Speltz et al., 2016; Collett et al., 2017, Tillman et al., 2020), data were reported as combined. Two studies reported diagnosis of ADD (Kapp Simon, 1998; Scheuerle et al., 2004) and were combined with studies reporting diagnosis of ADHD. Subgroups which were not relevant to this review were combined (e.g., groups categorised by surgical status).

Prior to data analysis, clinical categories for data from the Strengths and Difficulties Questionnaire (SDQ: Muris et al., 2003) reported in four Craniofacial Collaboration United Kingdom

(CC-UK) papers (Care et al., 2019; Culshaw et al., 2021; Edwards-Bailey., 2022; Qi et al., 2023) were combined in order to consistently report clinically significant outcomes across studies. This review pooled the SDQ data from individual CC-UK studies respectively to reflect two distinct categories: a) above average hyperactivity, and b) average hyperactivity. Three overlapping samples were combined and treated as non-independent studies for combined outcome and suture analyses: 1) Kapp Simon et al., 2012, Speltz et al., 2016 and Collett et al., 2017, 2) Culshaw et al., 2020 and Edwards-Bailey., 2022, and 3) Kljajic et al., 2019, Kljajic et al, 2020 and Kljajic et al., 2021.

In order to maintain consistency all age statistics were converted from months to years. In cases where <5% of a study's original sample was excluded from this review for not meeting the inclusion criteria, mean age of the original paper's sample was maintained (Osborn et al., 2021; Snyder & Pope 2009). Where multiple age data points were reported, the youngest age at assessment was used to calculate total mean age and sample size for the statistics for this analysis.

2.6 Statistical Analysis and Interpretation

Outcome data from included studies were analysed using Comprehensive Meta-Analysis Software version 4 (CMA; Englewood, NJ, USA: Biostat, Inc). Random effects models were applied with the assumption that the true effect was similar but not identical across individual studies (Borenstein et al., 2010).

In studies where prevalence data (diagnosis ADHD, screened ADHD, or ADHD symptomology) were provided and control groups were present Odds Ratios (*OR*) were calculated to determine the likelihood (increased occurrence, $OR > 1$; decreased occurrence, $OR < 1$) of diagnosed ADHD, screened ADHD, or ADHD symptomology (inattention, hyperactivity) in individuals with craniosynostosis compared with control groups; with $OR = 1.68$, 3.47.5 and 6.71 equating to small, medium, and large effects respectively (Chen et al., 2010). In studies without a control group, prevalence rates were used to calculate mean effect size.

In papers where mean, standard deviation (*SD*) and sample size data were provided, and controls were present, Hedges' g (*g*) was used to measure the standardised mean difference between

craniosynostosis groups and control groups, with g = 0.2, 0.5 and 0.8 equating to small, medium, and large effects respectively (Cohen et al., 2013).

In all analyses containing two or more studies *Q*-values were calculated to explain between-study heterogeneity (Borenstein et al., 2017). Orwin's Fail Safe N (N_{fs}) (1983) statistics were calculated for analyses including three or more samples with the purposes of addressing publication bias caused by the tendency for journals to favour statistically significant results, and the current reviews exclusion of papers that were not published or peer-reviewed: with smaller N_{fs} indicating potential susceptibility to publication bias. Mean effect sizes were calculated with 95% confidence intervals (95% *CI*s) to determine the precision of each effect. Probability values (p) were used to assess statistical significance. I-squared statistics (I^2) were calculated to explain what percentage of the variance in observed effects reflected the variance in true effects rather than sampling error (Borenstein et al., 2020). Tau-squared (τ^2) was used to explain the variance of true effect size (logit units) and Tau (τ) to explain the standard deviation of true effect. Z-values were calculated to test the null hypothesis, which stated that mean effect size was zero (Borenstein et al., 2020).

CHAPTER 3

Results

3.1 Study Characteristics

Of the 21 studies included in this analysis the majority originated from Europe ($N_{studies}$ = 12), followed by North America ($N_{studies}$ = 8), then Australia ($N_{studies}$ = 1). All studies were published between 1996 and 2023, and study sample sizes varied considerably (N_{range} = 12 -1238). The most frequently used study design was observational cohort (76%), followed by case control (24%). Most studies utilised craniofacial hospital units as their primary recruitment source ($N_{studies}$ = 14), although retrospective medical records ($N_{studies}$ = 7), and community data ($N_{studies}$ = 2) were also utilised (refer to Appendix E for full study characteristics).

Eight studies provided data on ADHD diagnosis alone, three on attention problems alone, three on hyperactivity alone and seven studies provided data on more than one ADHD outcome (see Appendix F for outcome data provided by each study).

A total of six standardised measures and two diagnostic tools of ADHD, hyperactivity or attention were used across the 21 studies (see Appendix G for a full details), of which multiple scales and subscales were used. Both the DSM and ICD were used as diagnostic tools for ADHD. Two versions of the ICD were used (ICD-9a, ICD10b), two versions of the Child Behaviour Checklist (CBCL) were used (CBCL 1 1/2 - 5a, CBCL 4 - 11b), and three versions of the Wechsler Intelligence Scale for Children (WISC) were used (WISC IIIa, WISC-IVb, WISC-Vc). However, some studies did not report one or all diagnostic tools and measures used, where measures and diagnostic tools could not be determined study data were still included.

3.2 Participant Characteristics

The 21 studies included in this meta-analysis provided data for 2637 cases with single-suture non-syndromic craniosynostosis and 12838 unaffected controls (Table 2). Participants varied in age from infant (0-1 years) to adult (18+ years), with a mean age of 7.36 years. Data on sex were available

for 1896 cases and 404 controls and in both groups the majority were male (case = 66%: control = 62%). Number of cases presenting with craniosynostosis type were reported in 67% of studies, where reported metopic synostosis was most common (65%), followed by sagittal (35%) and no studies reported case number for coronal or lambdoid synostosis. Surgical status of craniosynostosis was reported in 86% of studies, 68% of studies contained participants which had undergone surgery, 21% managed craniosynostosis conservatively and 11% contained a combined sample of operated and unoperated cases. Family history of craniosynostosis was reported in one study, and family history of ADHD was reported in no studies. ADHD diagnosis was reported in 11 studies.

Table 2

Demographic Details for the 21 Independent Studies Included in the Meta-Analysis

Variable	Case				Control			
	$N_{studies}$	$N_{participants}$	*M(SD)*	*Median*	$N_{studies}$	$N_{participants}$	*M(SD)*	*Median*
Sample Size	21	2637	125.75 (261.57)	55.00	5	12838	2567.60 (5486.02)	183.00
Age (years)	19	1354	7.36 (3.39)	7.85	3	421	5.88 (3.79)	7.40
Sex	9	1896	-	-	2	404	-	-
Male	9	1253	139.33 (273.79)	43.00	2	252	126.00 (16.97)	126.00
Female	9	643	71.44 (116.20)	24.00	2	152	76.00 (9.90)	76.00
Socioeconomic Status Reported								
Yes	5	-	-	-	5	-	-	-
No	16	-	-	-	0	-	-	-
Craniosynostosis Type	14	624						
Sagittal	7	209	20.71 (26.46)	8.00	-	-	-	-
Metopic	11	406	29.00 (29.00)	23.5	-	-	-	-
Coronal	1	9	0.60 (2.32)	0.00	-	-	-	-
Lambdoid	0	0	-	-	-	-	-	-
Not Reported	20	-	-	-	-	-	-	-

Table 2 Continued

Variable	Case				Control			
	$N_{studies}$	$N_{participants}$	*M(SD)*	*Median*	$N_{studies}$	$N_{participants}$	*M(SD)*	*Median*
Family History of ADHD								
Yes	0	-	-	-	0	-	-	-
No	0	-	-	-	0	-	-	-
Not reported	21	-	-	-	5	-	-	-
Family History of Craniosynostosis								
Yes	1	-	-	-	-	-	-	-
No	0	-	-	-	-	-	-	-
Surgical Status	19							
Operated	13	-	-	-	-	-	-	-
Combined (unoperated + operated)	2	-	-	-	-	-	-	-
Conservatively managed	4	-	-	-	-	-	-	-

Note: Table 2 shows descriptive statistics reflecting single-suture, non-syndromic participant details extracted from each paper; where appropriate data from non-independent papers were combined and treated as a single study in analyses. Where multiple age data points were reported, the youngest age at assessment was used to calculate mean age and sample size statistics

3.3 Study Risk of Bias Assessment

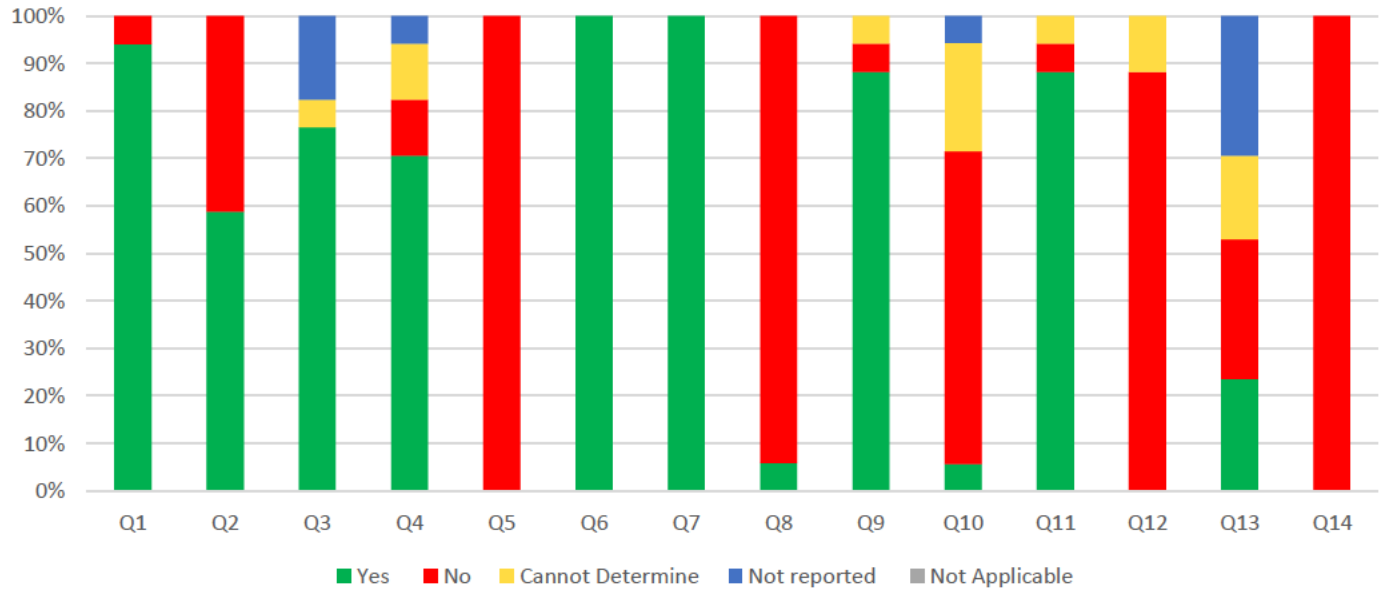
A risk of bias assessment was independently conducted by one author (Author A) using two National Heart, Lung, and Blood Institute Quality Assessment Tools (NHLBI; Maryland, United States, www.nhlbi.nih.gov) *Observational Cohort and Cross-Sectional Studies* (OC-CS), and *Case-Control Studies* (CCS), to assess all included studies for potential methodological bias. The OC-CS tool consists of 14 criteria, and the CCS consists of 12 (refer to Appendix C & D for full quality assessment sheets), each criterion was assessed (yes, no, not reported, not applicable, or cannot determine), and the percentage of papers which met the criterion was calculated (Figures 4 & 5).

Overall quality of reporting for included OC-CS studies was poor. All studies failed to report sample size justifications (e.g., statistical power, effect estimate), whether assessors were blind to the participants' craniosynostosis diagnoses, and whether key confounding variables were considered and adjusted for statistically: criterion 5, 12, and 14 respectively. In more than half of OC-CS studies criteria assessing severity of craniosynostosis (e.g., mild, severe), frequency of craniosynostosis assessments, and participant follow-up after baseline were not met: criterion 8, 10 and 13 respectively. However, all studies reported timeline of ADHD, hyperactivity and/or attention assessment in relation to craniosynostosis diagnosis, and the measures or diagnostic tools used to assess ADHD and ADHD outcomes were selected appropriately: criterion 6 and 7 respectively. The remaining criterion (1, 2, 3, 4, 9, 11) were inconsistently met (see Appendix C for individual OC-CS quality assessments).

The quality of included CCS studies was higher than that of the OC-CS. All studies provided research objectives, inclusion, and exclusion criteria, clearly differentiated between cases and controls, concurrent controls were used, and measures and diagnostic tools were clearly defined: criterion 1, 5, 6, 8, and 10 respectively. Over 80% of studies clearly defined their study populations, selected cases and controls from similar populations, and considered and statistically adjusted for key confounding variables: criterion 2, 4 and 12 respectively. However, no studies provided sample size justification: criterion 3. Further, in all studies methodology for selection of eligible participants, and whether the assessors were blind to the participants craniosynostosis diagnoses were not clear: criterion 7 and 11.

Figure 4

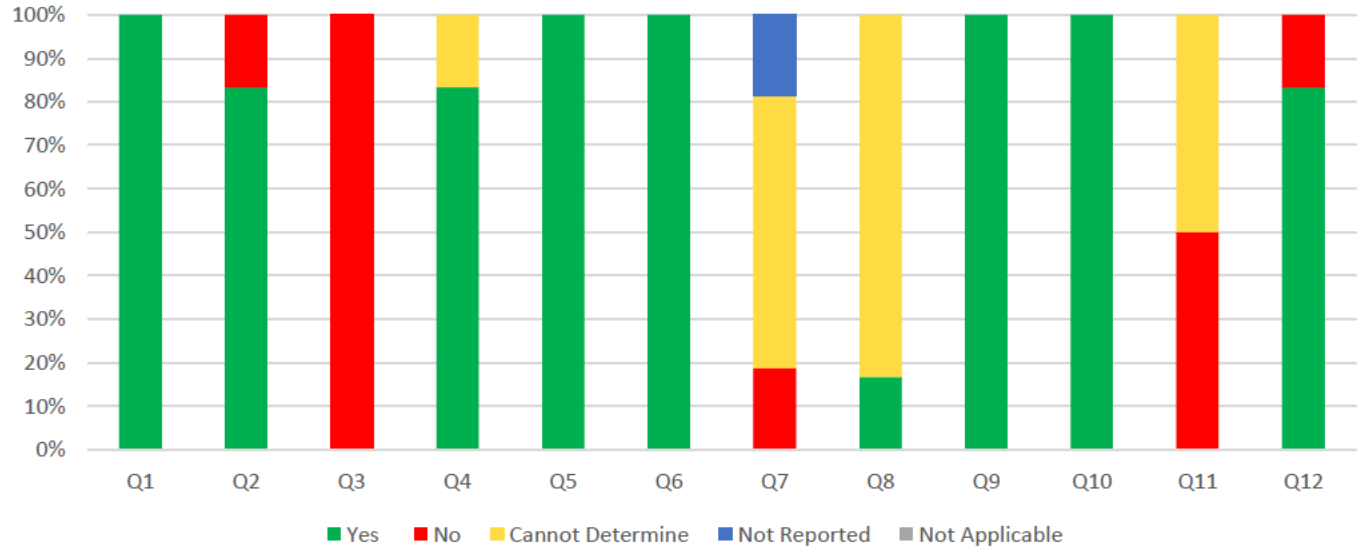
NHLBI Quality Assessment of Observational Cohort and Cross-Sectional Studies



Note: Figure 4 shows results from the NHLBI OC-CS quality assessment tool. Colour indicates results of assessment for each criterion, with percentage displaying the proportion of papers in each result category. See Appendix C for complete NHLBI OC-CS quality assessment sheet.

Figure 5

NHLBI Quality Assessment of Case-Control Studies



Note: Figure 5 shows results from the NHLBI CCS quality assessment tool. Colour indicates results of assessment for each criterion, with percentage displaying the proportion of papers in each result category. See Appendix D for complete NHLBI CCS quality assessment sheet.

3.4 Craniosynostosis and ADHD, Diagnosis and Screened

When studies examining formal diagnosis of ADHD were combined, ADHD diagnoses were higher (10%) in individuals with single-suture, non-syndromic craniosynostosis compared to the general population (3-8%; Ayano et al., 2023). Between study heterogeneity was observed (I^2 = 67.00, p = 0.01) and results may be susceptible to publication bias (N_{fs} = 2; Table 3). When studies were partitioned according to suture type, individuals with sagittal synostosis reported the highest rates of diagnosed ADHD (17%), followed by those with metopic synostosis (14%; Table 4). Sagittal synostosis results should be interpreted with caution as they were based on a single independent study. Further, between study heterogeneity was not observed in the metopic synostosis sample (I^2 = 47.18, p = 0.11), and results may be susceptible to publication bias (N_{fs} = 4; Table 4). When studies were partitioned by age range, diagnosed ADHD was highest (19%) in lower primary (5 – 8 years) aged populations and in upper primary (9 – 12 years) aged populations diagnosis of ADHD was lower (4%) than even that of the general population (3-8%; Ayano et al., 2023) (Table 5). Between study heterogeneity was not observed in both lower primary (I^2 = 48.12, p = 0.15) and upper primary (I^2 = 0.00, p = 0.52) analyses (Table 5), with results from both age cohorts having susceptibility to publication bias (N_{fs} = 4, N_{fs} =2 respectively); Table 5.

When studies observing prevalence of formally diagnosed ADHD in cases with single-suture, non-syndromic craniosynostosis versus unaffected control were combined there was no significant difference in the probability of observing diagnosed ADHD between groups (*OR* = 1.37, 95% *CI* [0.941, 2.004], p = 0.10; Table 6). When data were further partitioned by age group there was again no significant difference between lower primary (5 – 8 years) aged cases when compared to unaffected age matched controls (*OR* = 0.68. 95% *CI* [0.11, 4.11], p = 0.67; Table 6).

One study observed differences in scores on ADHD screening tests in preschool (2 – 4 years) aged individuals compared to age matched controls and found no difference in scores between groups (g = 0.18, p = 0.21; Table 7). However, results should be interpreted with caution due to their basis on a single independent study.

3.5 Craniosynostosis and Inattention

Overall, inattentive behaviours were higher in individuals with non-syndromic craniosynostosis (24%; Table 3) when compared to general populations (16%; Spencer et al., 2018). When studies were partitioned by age, inattentive behaviours remained high in both lower primary (2 – 4 years; 29%) and high school aged (13 – 17 years; 17%) groups (Table 5). However, age results should be interpreted with caution due to being based on single independent studies.

Where studies which compared prevalence of inattentive behaviours in cases versus controls were combined there was no significant difference in the probability of observing inattentive behaviours between cases and controls (*OR* = 0.78, 95% *CI* [0.12, 5.25], $p = 0.80$; Table 6). Where studies were further partitioned by age, there was again no significant difference in scoring in upper primary (9 – 12 years) aged individuals (*OR* = 0.78, 95% *CI* [0.112, 5.25], $p = 0.80$; Table 6).

Where studies that compared scores on measures of attention in cases versus controls were combined there was no significant difference in scores ($g = -0.16$, $p = 0.68$; Table 7). However, when studies were partitioned by suture type (sagittal, metopic, coronal, lambdoid) cases scored significantly lower on measures of attention than controls (Table 8) suggesting inattention was more common in the craniosynostosis group. When studies were partitioned by age, adult (18+ years; $g = -0.93$, $p = 0.10$) and preschool aged (2 – 4 years; $g = -0.16$, $p = 0.63$) cases showed no significant difference in scores of attention compared to age matched controls (Table 9). However, lower primary (5 – 8 years) aged individuals exhibited a large significant increase in inattentive behaviours when compared to age matched controls ($g = -1.01$, $p = 0.02$; Table 9). Adult and lower primary results should be interpreted with caution due to being based on single independent studies.

3.6 Craniosynostosis and Hyperactivity

Overall, hyperactivity was higher in individuals with single-suture, non-syndromic craniosynostosis (25%; Table 3) when compared to population norms (9%; Vugteveen et al., 2022). Heterogeneity was not observed in studies that combined hyperactivity data ($I^2 = 00$, $p = 0.76$) and results may be

susceptible to publication bias (N_{fs} = 9; Table 3). When studies were partitioned by craniosynostosis type, individuals with metopic synostosis had high levels of hyperactivity (24%; Table 4). Where studies were partitioned by age, preschool aged (2 – 4 years) individuals with single-suture, non-syndromic craniosynostosis exhibited high levels of hyperactivity (27%; Table 5).

One study compared scores on measures of hyperactivity in cases with metopic synostosis (g = 0.04, p = 0.91; Table 7) and found no significant difference in scores. When studies were partitioned by age there was again no significant difference in scores (g = 0.04, p = 0.91; Table 9) in preschool (2 – 4 years) aged individuals.

Table 3

Prevalence of Diagnosed ADHD, Inattention and Hyperactivity in Individuals with Single-Suture, Non-Syndromic Craniosynostosis Partitioned by Outcome

Author (year)	Suture	$N_{participants}$	$N_{studies}$	Prevalence	Prevalence and 95% *CI*	N_{fs}	Heterogeneity Statistics					
Outcome Measured					0% 50% 100%		τ	$\tau 2$	Q	df	p	I^2
ADHD					→ Increase prevalence							
Doshier et al., 2015	Combined	37		5%								
Kljajic et al., [2019; 2020; 21]	Combined	73		1%								
Scheuerle et al., 2004	Metopic	14		36%								
Sidoti et al., 1996	Metopic	32		13%								
Van der Vlugt et al., 2012	Metopic	55		15%								
Wojcicki & Prudel., 2019	Metopic	30		3%								
ADHD combined		**241**	**6**	10%		2	0.88	0.77	15.04	5	0.01	67.00
Inattention												
Chieffo et al., 2010	Sagittal	35		17%								
Snyder & Pope	Combined	34		29%								
Inattention combined		**69**	**2**	24%			0.27	0.07	1.43	1	0.23	30.05

Table 3 Continued

Author (year)	Suture	$N_{participants}$	$N_{studies}$	Prevalence	Prevalence and 95% *CI*	N_{fs}	Heterogeneity Statistics					
Outcome Measured					0% 50% 100%		τ	$\tau 2$	*Q*	*df*	*p*	I^2
Hyperactivity												
Care et al., 2017	Sagittal	89		27%								
Culshaw et al., [2021]/ Edwards-bailey et al., [2022]	Metopic	98		24%								
Qi et al., 2023	Metopic	40		23%								
Qi et al., 2023	Sagittal	18		14%								
Hyperactivity combined		**165**	**4**	25%		9	0.00	0.00	1.17	3	0.76	0.00

Note: Table 3 shows prevalence rates of diagnosed ADHD, inattention, and hyperactivity in individuals with single-suture, non-syndromic craniosynostosis. N_{fs} = Orwins Failsafe *N*, τ = tau, τ^2 = tau squared, *Q* = *Q*-value, I^2 = I-squared.

Table 4

Prevalence of Diagnosed ADHD and Hyperactivity in Individuals with Single-Suture, Non-Syndromic Craniosynostosis Partitioned by Craniosynostosis Type

Study Name (year)	Outcome	$N_{participants}$	$N_{studies}$	Prevalence	Prevalence and 95% *CI*	N_{fs}	Heterogeneity Statistics					
					0% 50% 100%		τ	τ^2	Q	df	p	I^2
Type of Craniosynostosis												
Sagittal												
Chieffo et al., 2010	ADHD	35		17%								
Metopic												
Culshaw et al., [2021]/ Edwards-bailey et al., [2022]	Hyperactivity	98		24%								
Qi et al., 2023	Hyperactivity	40		23%								
Metopic hyperactivity combined		**138**	**2**	**24%**			0.00	0.00	0.01	1	0.91	0.00
Kljajic et al., 2020	ADHD	23		9%								
Scheuerle et al., 2004	ADHD	14		36%								
Sidoti et al., 1996	ADHD	32		13%								
Van der Vlugt et al., 2012	ADHD	55		15%								
Wojcicki & Prudel., 2019	ADHD	30		3%								
Metopic ADHD combined		**131**	**5**	**14%**		4	0.56	0.31	7.67	4	0.11	47.81

Note: Table 3 shows prevalence of diagnosed ADHD and hyperactivity in individuals with single-suture, non-syndromic craniosynostosis partitioned by craniosynostosis type N_{fs} = Orwins Failsafe *N*, τ = tau, τ^2 = tau squared, *Q* = *Q*-value, I^2 = I-squared

Table 5

Prevalence of Diagnosed ADHD, Inattention and Hyperactivity in Individuals with Single-Suture, Non-Syndromic Craniosynostosis Partitioned by Age

Author (year)	Outcome	$N_{participants}$	$N_{studies}$	Prevalence	Prevalence and 95% *CI*	N_{fs}	Heterogeneity Statistics					
Age Range (years)					0% 50% 100%		τ	τ^2	Q	df	P	I^2
Preschool (2 - 4)					→ Increase prevalence							
Care et al., 2019	Hyperactivity	89		27%								
Lower Primary (5 - 8)												
Scheuerle et al., 2004	ADHD	14		36%								
Sidoti et al., 1996	ADHD	32		13%								
Van der Vlugt et al., 2012	ADHD	55		15%								
ADHD lower primary combined		**98**	**3**	**19%**		4	0.47	0.22	3.86	2	0.15	48.12
Snyder & Pope., 2010	Inattention	34		29%								
Upper Primary (9 - 12)												
Dosher et al., 2015	ADHD	37		5%								
Kljajic et al., [2019; 2020; 21]	ADHD	73		1%								
Wojcicki & Prudel., 2019	ADHD	30		3%								

ADHD upper primary combined	**140**	**3**	**4%**		2	0.00	0.00	1.30	2	0.52	0.00

Table 5 Continued

Age Range (years)	Outcome	$N_{participants}$	$N_{studies}$	Prevalence and 95% *CI* 0% 50% 100%	N_{fs}	Heterogeneity Statistics				
Highschool (13 – 17)										
Chieffo et al., 2010	Inattention	35	17%							

Note: Table 5 shows prevalence of diagnosed ADHD, inattention, and hyperactivity in individuals with single-suture, non-syndromic craniosynostosis partitioned by age. N_{fs} = Orwins Failsafe *N*, τ = tau, τ^2 = tau squared, Q = Q-value, I^2 = I-squared

Table 6

Prevalence of Diagnosed ADHD and Inattention in Cases with Single-Suture, Non-Syndromic Craniosynostosis Versus Controls

Author (year)	Suture	Age	$N_{participants}$	$N_{studies}$	*OR*	*p*	Prevalence and 95% *CI*	Heterogeneity Statistics					
							0.01 0.1 1 10 100	τ	τ^2	*Q*	*df*	*p*	I^2
Outcome Measured													
ADHD													
Collett et al., 2017	Combined	Lower primary	179		0.68	0.67							
Tillman et al., 2020	Combined	Combined	1238		1.42	0.08							
ADHD combined			**1417**	**2**	**1.37**	**0.10**		0.00	0.00	0.62	1	0.43	0.00
Inattention													
Boltshauser et al., 2003	Sagittal	Upper primary	26		0.78	0.80							

Note: Table 6 shows Odds ratio results for individuals with single-suture, non-syndromic craniosynostosis compared to unaffected control groups. Due to a low number of studies, data for suture and age analyses were reported in a single table. τ = tau, τ^2 = tau squared, *Q* = *Q*-value, I^2 = I-squared.

Table 7

Difference in Scores on Measures of Attention, Hyperactivity and Screened ADHD in Cases with Single-Suture, Non-Syndromic Craniosynostosis Versus Controls Partitioned by Outcome

Author (year)	Suture	$N_{participants}$	$N_{studies}$	*g* and 95% *CI*			Heterogeneity Statistics					
Outcome Measured ADHD Screened				*g*	*p*	-2.00 -1.00 0.00 1.00 2.00 Outcomes Worse | Outcomes Better	τ	τ^2	*Q*	*df*	*p*	I^2
Kapp Simon et al., [2012]/ Speltz et al., [2016]/ Collett et al., [2017]	Combined	219		0.18	0.21							
Attention												
Kapp Simon et al., [2012]/ Speltz et al., [2016]/ Collett et al., [2017]	Combined	219		0.12	0.41							
Osborn et al., 2021	Metopic	37		-0.69	0.14							
Attention combined		**256**	**2**	**-0.16**	**0.68**		0.45	0.20	2.70	1	0.10	62.97
Hyperactivity												
Osborn et al., 2021	Metopic	19		0.04	0.91							

Note: Table 7 shows Hedges' *g* results for attention, hyperactivity, and screened ADHD in cases with single-suture, non-syndromic craniosynostosis and controls groups partitioned by outcome. *g* = Hedges' *g*, τ = tau, τ^2 = tau squared, *Q* = *Q*-value, I^2 = I-squared.

Table 8

Difference in Scores on Measures of Attention and Hyperactivity in Cases with Single-Suture, Non-Syndromic Craniosynostosis Versus Controls Partitioned by Craniosynostosis Type

Author (year)	Outcome	$N_{participants}$	*g*	*p*	*g* and 95% *CI*
Craniosynostosis Type					-2.50 -1.50 0.00 1.50 2.50
Sagittal					Outcomes Worse | Outcomes Better
Kapp Simon et al., [2012]/	Attention	76	-1.54	<.001	
Speltz et al., [2016]/					
Collett et al., [2017]					
Metopic					
Osborn et al., 2021	Hyperactivity	19	0.04	0.91	
Kapp Simon et al., [2012]/	Attention	45	-1.13	<.001	
Speltz et al., [2016]/					
Collett et al., [2017]					
Coronal					
Kapp Simon et al., [2012]/	Attention	45	-1.28	<.001	
Speltz et al., [2016]/					
Collett et al., [2017]					
Lambdoid					
Kapp Simon et al., [2012]/	Attention	12	-1.39	<.001	
Speltz et al., [2016]/					
Collett et al., [2017]					

Note: Table 8 shows Hedges' *g* results for measure of attention and hyperactivity in cases with single-suture, non-syndromic craniosynostosis and control groups partitioned by craniosynostosis type.

Table 9

Difference in Scores on Measures of Attention and Hyperactivity in Cases with Single-Suture, Non-Syndromic Craniosynostosis Versus Controls Partitioned by Age

Author (year)	Outcome	$N_{participants}$	$N_{studies}$	*g*	*p*	*g* and 95% *CI*	Heterogeneity Statistics					
							τ	τ^2	*Q*	*df*	*p*	I^2
Age Range (years)						-2.50 -1.50 0.00 1.50 2.50						
Preschool (2 - 4)						Outcomes Worse / Outcomes Better						
Osborn et al., 2021	Attention	19		-0.58	0.08							
ILP 2012;16;18	Attention	219		0.12	0.41							
Preschool attention combined		**238**	**2**	**-0.16**	**0.63**		0.42	0.18	3.70	1	0.06	72.94
Osborn et al., 2021	Hyperactivity	19		0.04	0.91							
ILP 2012;16;18	ADHD screened	219		0.18	0.21							
Lower Primary (5 – 8)		238										
ILP 2012;16;18	Attention	172		-1.01	0.02							
Adult (18+)												
Osborn et al., 2021	Attention	19		-0.93	0.10							

Note: Table 9 shows Hedges *g* results for attention and hyperactivity in cases with single-suture, non-syndromic craniosynostosis and controls partitioned by age. *g* = Hedges' *g*, N_{fs} = Orwins Failsafe *N*, τ = tau, τ^2 = tau squared, *Q* = *Q*-value, I^2 = I-squared

CHAPTER 4

Discussion

4.1 Key Findings

Data from 21 independent studies ($N_{participants}$ = 2637) were analysed in order to determine whether, and to what extent, single-suture, non-syndromic craniosynostosis impacts the development of ADHD. Overall, individuals with single-suture, non-syndromic craniosynostosis had higher rates of diagnosed ADHD, inattention, and hyperactivity than general population and primary care estimates (Table 3; Spencer et a., 2018; Vugteveen et al., 2020; Ayano et al., 2023). However, hyperactivity findings may not reflect the extent of hyperactivity in those with single-suture, non-syndromic craniosynostosis. For instance, two studies included in this analysis (Edwards-Bailey et al., 2022; Qi et al., 2023) excluded participants on a basis of having known disabilities. Such disabilities were not reported, so it is not clear if individuals with ADHD were excluded. However, if individuals with ADHD were excluded it is possible that this analyses hyperactivity results were lower than what may be typically observed in those with single-suture, non-syndromic craniosynostosis.

Where cases with single-suture, non-syndromic craniosynostosis were compared to unaffected control groups, there was no significant difference in scores on measures of attention, hyperactivity, or ADHD screening tests (Table 7). However, the lack of difference in scores between cases and controls may partially be explained by the limited numbers of studies available for analysis ($N_{studies}$ = <3). Further, the inclusion of one study (Colette et al., 2017) may have skewed attention results. In this study diagnosed ADHD was 1.5 times lower in cases compared to unaffected controls. The increased ADHD in controls may have skew data to reflect higher ADHD outcomes in cases diminishing the potential difference in scores between groups. However, Colette et al., (2017) sampled through both clinical and community centres (Appendix E) making it possible that these results reflect the increasing prevalence of ADHD in general populations (Thomas et al., 2015).

Between study heterogeneity was only observed in some analyses, and sub-analyses. Lack of between study heterogeneity may be explained by small sample sizes, uniformity in assessment

measures, and similar qualifying factors (age, craniosynostosis type) for sub-analyses inclusion. Where data were available and N_{fs} were calculated results were susceptible to publication bias.

4.2 Craniosynostosis Type Analysis

Atypical brain morphology, especially that of the prefrontal cortex has been observed in individuals with ADHD (Kapp-Simon et al., 2007). As the metopic and coronal sutures are situated closet to the prefrontal cortex it is possible that these sutures may have the greatest impact on ADHD development (Kajdic et al., 2018).

When studies were partitioned by craniosynostosis type, individuals with sagittal synostosis had the highest rates of diagnosed ADHD, followed by those with metopic synostosis (Table 4): in both groups diagnosed ADHD was more than twice that of general population rates. Further, those with metopic synostosis had levels of hyperactivity twice that of population rates. Data were not available for other craniosynostosis types.

One study compared scores on measures of attention by craniosynostosis type and found a significant increase in inattention for all craniosynostosis types (sagittal, metopic, coronal, lambdoid) compared to unaffected controls (Table 8). However, this was among studies which excluded participants on a basis of having known disabilities potentially excluding individuals with ADHD and influencing outcomes. Although, these results were based on a single independent study and should be interpreted with caution.

Limited data for coronal and lambdoid synostosis may be attributed to infrequent occurrence of both craniosynostosis types (Betances et al., 2023). The reduced frequency of coronal and lambdoid synostosis comparative to sagittal and metopic synostosis has created a disparity in data available for analysis and therefor limited this analysis ability to evaluate and conclude the impact of craniosynostosis type on ADHD (Cornelissen et al., 2016).

The aim of this sub-analysis was to provide information about if suture locations impacted ADHD outcomes in individuals with single-suture, non-syndromic craniosynostosis. While data were

limited, this analysis has been able to contribute to the currently limited pool of data regarding craniosynostosis type and ADHD, hyperactivity, and inattention.

4.3 Age Analysis

Data for age analyses were limited. In most cases age analyses included a small number of studies (N_{range} = 1- 3) yielding data for one or two age ranges. Diagnosed ADHD was higher in lower primary (5 - 8 years) aged individuals (Table 5) when compared to the general population. However, diagnosed ADHD was lower in upper primary (9 - 12 years) aged individuals (Table 5) compared to the general population. These results are not consistent with what is typically observed in diagnosed ADHD, ADHD is normally most prevalent in younger individuals, and does not decline until adulthood (18+; Leffa et al., 2022).

Inattention and hyperactivity were highest in younger populations (5 - 17 years) and decreased in adult populations (18+ years; (Table 5), but remained higher than that of the general population in both cohorts. The reduction in symptomology with age is consistent with what is observed in general populations (Spencer et al., 2018). As individuals age they become more adept at regulating attention, and hyperactivity decreasing observed symptomology in both neurotypical and ADHD populations (Leffa et al., 2022).

When studies which compared scores on measures of attention in cases versus controls were partitioned by age (Table 9) there was no difference in scores in preschool (2 - 4 years) or adult (18+ years) aged individuals. However, lower primary (5 - 8 years) aged individuals scored lower on measures of attention when compared to age matched controls. Analyses, once again, contained a control group in which diagnosed ADHD was lower in cases compared to unaffected controls. Therefore, differences in scores may reflect differences in sampling rather than true effect.

The aim of this sub-analysis was to provide information about how age may impact the relationship between ADHD and single-suture, non-syndromic craniosynostosis. While data were limited, this analysis has been able to contribute to the currently limited pool of data regarding ADHD, hyperactivity, and inattention outcomes in those with single-suture, non-syndromic craniosynostosis. Further, while ADHD, and ADHD outcomes were higher in individuals with single-

suture non-syndromic craniosynostosis the developmental trajectory of ADHD by age was largely consistent with what is typically observed in general populations.

4.4 Socioeconomic Status, Craniosynostosis and ADHD

Socioeconomic disparities have been shown to have a large impact on both ADHD and craniosynostosis outcomes. For individuals with craniosynostosis, lower socioeconomic. status has been linked to poorer health care outcomes, longer diagnostic timeframes, and decreased access to relevant clinical treatments (Blum et al., 2023). For individuals with ADHD, lower socioeconomic status has been linked to underdiagnosis, decreased access to treatment and medication, and worse ADHD outcomes (Spencer et al., 2016). Further, Spencer et al., suggested that ADHD is more prevalent in lower socioeconomic areas. While socioeconomic status was not instrumental to this analysis, a number of studies that provided data on socioeconomic status were recorded. With only 23% of included studies providing data on socioeconomic status, it is suggests that socioeconomic status should be more centrally considered in analyses of craniosynostosis, especially where ADHD is concerned.

4.5 Limitations

There are a number of limitations to be considered. First, many studies did not provide important data for sub analysis i.e., craniosynostosis type and age, thus limiting the ability of this analysis to perform in depth moderator analyses. Studies commonly reported craniosynostosis type in demographic tables but did not provide outcome data partitioned by craniosynostosis type. Further, mean age of sample was often reported, however it was not always clear what the age range of the sample was. It is possible that mean age data did not accurately reflect the age range of individuals included in this analysis limiting the validity of age analyses. Future research should endeavour to report outcome data for individual ages and suture locations separately. Likewise, research should strive to report each ADHD outcome to increase reliability of ADHD outcome results. Additionally, as data were limited analyses combined data from parent, teacher, and self-report, data from a number of different measures, scales, and diagnostic tools. Combination of data may have impacted the

validity of results. Further, Orwins Failsafe *N* statistics were calculated where possible to consider publication bias, however, the majority of studies did not meet the minimum number of included studies ($N_{studies} = 3$) required to calculate N_{fs} statistics. Where N_{fs} statistics were calculated, analyses were susceptible to publication bias.

4.6 Conclusion

This meta-analysis provides evidence to support the idea that there may be a relationship between ADHD and single-suture, non-syndromic craniosynostosis. While evidence was not conclusive it demonstrated emerging trends which require more research in order to confirm the relationship. Overall, those with craniosynostosis generally had higher rates of diagnosed ADHD, hyperactivity and inattention when compared to general populations. While there was no difference in scores on measures of hyperactivity and attention between cases and unaffected controls, small sample sizes, and sample characteristics (i.e., papers excluding those with known disabilities) may have influenced findings. Age range and craniosynostosis type had no apparent influence on the relationship between single-suture, non-syndromic craniosynostosis as data were limited, and findings were disparate. Further, the majority of data only pertained to a single timepoint and for a diagnosis of ADHD to be made inattentive and hyperactive symptoms must be persistent for at least six months. Therefore, there is a need for additional and longitudinal data to be collected in order to assess if and to what extent craniosynostosis affects ADHD.

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APPENDICES

Appendix A – Search Terms Applied to Individual Database Searches

Pubmed Logic Grid

AND ⟹

Craniosynostosis	ADHD
"Craniosynostoses"[mh] OR Craniosynostosis[tiab] OR Craniostenosis[tiab] OR Craniosynostose[tiab] OR Sagittal Synostos*[tiab] OR Scaphocephal*[tiab] OR Metopic Synostos*[tiab] OR Trigonocephal*[tiab] OR Coronal Synostos*[tiab] OR Unilateral Coronal Synostos*[tiab] OR Unilateral Lambdoid Synostos*[tiab] OR Lambdoid Synostos*[tiab]	"Attention-Deficit Disorder with Hyperactivity"[mh] OR "ADHD"[all] OR "ADDH"[all] OR "Attention-Deficit*"[all] OR "Attention Disorder*"[all] OR "Attention-Deficit Disorder*"[all] OR "Attention-Deficit Disorder Hyperactiv*"[all] OR "Attention-Deficit Hyperactivity Disorder*"[all] OR "Attention-Deficit Disorders with Hyperactivity"[all] OR "Child Attention-Deficit Disorder*"[all] OR "Hyperactivity"[all] OR Hyperactiv*[tiab] OR "Hyperkinetic Syndrome*"[tiab] OR "Syndrome Hyperkinetic"[tiab] OR "Hyperkinetic Disorder*"[tiab] OR "Attention-Deficit Hyperkinetic Disorder*"[tiab] OR "Attention Span"[all] OR "Attention"[all] OR Overactive[tiab] OR Inattent*[tiab] OR "Impuls*"[all] OR "Distract*"[all] OR "Working Memory"[all]

Note: Truncating terms ending with an asterisk indicate all suffix variations of the term were included in searching.

SCOPUS Logic Grid

AND ⇨

Craniosynostosis	ADHD
(TITLE-ABS-KEY (craniosynostosis OR craniostenosis OR craniosynostoses OR "Sagittal Synostos*" OR scaphocephal* OR "Metopic Synostos*" OR trigonocephal* OR "Coronal Synostos*" OR "Unilateral Coronal Synostos*" OR "Unilateral Lambdoid Synostos*" OR "Lambdoid Synostos*"))	(ALL (adhd OR addh OR "Attention-Deficit*" OR "Attention Disorder*" OR "Attention-Deficit Disorder*" OR "Attention-Deficit Disorder Hyperactiv*" OR "Attention-Deficit Hyperactivity Disorder*" OR "Attention-Deficit Disorder with Hyperactiv*" OR "Attention-Deficit Disorders with Hyperactiv*" OR Hyperactivity OR "Child Attention-Deficit Disorder*" OR "Attention Span" OR Attention OR "Overactive Child Syndrome*" OR impuls* OR distract* OR Working Memory)) OR (TITLE-ABS-KEY (hyperactiv* OR "Hyperkinetic Syndrome*" OR "Syndrome Hyperkinetic" OR "Hyperkinetic Disorder*" OR "Attention-Deficit Hyperkinetic Disorder*" OR overactiv* OR inattent*))

Note: Truncating terms ending with an asterisk indicate all suffix variations of the term were included in searching.

Embase Logic Grid

AND ⇨

Craniosynostosis	ADHD
Craniofacial Synostosis.sh OR craniosynostosis.mp. OR Craniosynostosis.kf,ti,ab. OR Craniostenosis.ti,kf,ab. OR Craniosynostose.ti,kf,ab. OR Sagittal Synostos*.ti,ab. OR Scaphocephal*.ti,ab. OR Metopic Synostos*.ti,ab. OR Trigonocephal*.ti,ab. OR Coronal Synostos*.ti,ab. OR Unilateral Coronal Synostos*.ti,ab. OR Unilateral Lambdoid Synostos*.ti,ab. OR Lambdoid Synostos*.ti,ab.	AHDH.mp OR attention deficit hyperactivity disorder.sh OR "Attention-Deficit Disorder with Hyperactivity".ti,ab,kf,af. OR ADHD.ti,ab,kf,af. OR ADDH.ti,ab,kf,af. OR Attention-Deficit*.ti,ab,kf,af. OR Attention Disorder*.ti,ab,kf,af. OR Attention-Deficit Disorder*.ti,ab,kf,af. OR Attention-Deficit Disorder Hyperactiv*.ti,ab,kf,af. OR Attention-Deficit Hyperactivity Disorder*.ti,ab,kf,af. OR "Attention-Deficit Disorder with Hyperactiv*".ti,ab,kf,af. OR "Attention-Deficit Disorders with Hyperactiv*".ti,ab,kf,af. OR Child Attention-Deficit Disorder*.ti,ab,kf,af. OR Hyperactivity.ti,ab,kf,af. OR Hyperactiv*.ti,ab. OR "Hyperkinetic Syndrome*".ti,ab. OR "Syndrome Hyperkinetic".ti,ab. OR Hyperkinetic Disorder*.ti,ab. OR Attention-Deficit Hyperkinetic Disorder*.ti,ab. OR Attention Span.ti,ab,kf,af. OR Attention.ti,ab,kf,af. OR Overactiv*.ti,ab. OR "Overactive Child Syndrome*".ti,ab,kf,af. OR Inattent*.ti,ab. OR Impuls*.ti,ab,kf,af. OR Distract*.ti,ab,kf,af. OR Working Memory.ti,ab,kf,af.

Note: Truncating terms ending with an asterisk indicate all suffix variations of the term were included in searching.

PsychINFO Logic Grid

AND ⇨

Craniosynostosis	ADHD
Craniosynostosis.id,md,ti,ab,sv OR Craniostenosis.id,ti,ab OR Craniosynostose.id,ti,ab OR Sagittal Synostos*.ti,ab OR Scaphocephal*.ti,ab OR Metopic Synostos* OR Trigonocephal*.ti,ab OR Coronal Synostos*.ti,ab OR Unilateral Coronal Synostos*.ti,ab OR Unilateral Lambdoid Synostos*.ti,ab OR Lambdoid Synostos*.ti,ab	Attention-Deficit Disorder with Hyperactivity.sh OR ADHD.md,ti,ab,sv OR ADDH.md,ti,ab,sv OR Attention-Deficit*.md,ti,ab,sv OR Attention Disorder*.md,ti,ab,sv OR Attention-Deficit Disorder*.md,ti,ab,sv OR Attention-Deficit Disorder Hyperactiv*.md,ti,ab,sv OR Attention-Deficit Hyperactivity Disorder*.md,ti,ab,sv OR Attention-Deficit Disorder with Hyperactiv*.md,ti,ab,sv OR Attention-Deficit Disorders with Hyperactiv*.md,ti,ab,sv OR Child Attention-Deficit Disorder*.md,ti,ab,sv OR Hyperactivity.md,ti,ab,sv OR Hyperactiv*.ti,ab OR Hyperkinetic Syndrome*.ti,ab OR Syndrome Hyperkinetic.ti,ab OR Hyperkinetic Disorder*.ti,ab OR Attention-Deficit Hyperkinetic Disorder*.ti,ab OR Attention Span.md,ti,ab,sv OR Attention.md,ti,ab,sv OR Overactiv*.ti,ab OR Overactive Child Syndrome*.md,ti,ab,sv OR Inattent*.ti,ab OR Impuls*.md,ti,ab,sv OR Distract*.md,ti,ab,sv OR Working Memory.md,ti,ab,sv

Note: Truncating terms ending with an asterisk indicate all suffix variations of the term were included in searching.

Appendix B – Coding Sheet

Lead Author: **Year:** **Article Title:**				
Sample size:				
Country of origin:			**SES reported:** Yes No	
Recruitment source:			**Type of study:**	
Biological sex: Total male	Total female	Not reported		
Sagittal female	Sagittal male	Metopic female	Metopic male	
Coronal female	Coronal male	Lambdoid female	Lambdoid male	
Family history of CS:			**Age at study:**	
Yes No	Not reported		M/SD Other	Not reported
Type of CS:	Sagittal Metopic	Coronal	Lambdoid	
	Combined	Not Reported		
Surgical status:	Pre-surgery	Post-surgery	Conservatively managed	
	Combined	Not reported		
ADHD Diagnosis: Yes No			**Diagnostic tool:**	
			DSM ICD	Not diagnosed
ADHD presentation: Hyperactive	Inattentive	Combine	Not reported	
Family history of ADHD: Yes	No	Not reported		
Outcome: Attention	Hyperactivity	ADHD Screening Tool		
Measure(s): * Note who they are administered by				

Control group: No	Yes (next page)		
Control coding article title:			
Sample size:			
Biological sex: Total male		Total female	Not reported
Age at study: M/SD	Other	Not reported	
SES reported: Yes	No		
Type of control group:			
Recruitment source:			
Outcome: Attention	Hyperactivity	ADHD Screening Tool	
Measure(s): * Note who they are administered by			

Note: Combined = operated + unoperated, MP = medical professional, and CS = craniosynostosis.

Appendix C – Quality Assessment Criterion for Observational Cohort and Cross-Sectional Studies

Author/Date:	**Yes**	**No**	**Other (CD, NR, NA)***
Criteria			
1. Was the research question or objective in this paper clearly stated?			
2. Was the study population clearly specified and defined?			
3. Was the participation rate of eligible persons at least 50%?			
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			
5. Was a sample size justification, power description, or variance and effect estimates provided?			
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?			
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
10. Was the exposure(s) assessed more than once over time?			
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			
12. Were the outcome assessors blinded to the exposure status of participants?			
13. Was loss to follow-up after baseline 20% or less?			
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?			

Note: NHLBI questionnaire use to assess OC-CS. Q = question, Y = yes, N = no, CD = cannot determine, N = not reported.

Appendix C Continued – Quality Assessment Criterion for Observational Cohort and Cross-Sectional Studies

Author (date)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12	Q13	Q14
Care et al., 2019	Y	Y	NR	Y	N	Y	Y	N	Y	N	Y	N	NR	N
Chieffo et al., 2010	Y	N	Y	CD	N	Y	Y	N	Y	N	N	CD	Y	N
Culshaw et al., 2022	Y	Y	Y	Y	N	Y	Y	N	Y	N	Y	N	N	N
Doshier et al., 2015	Y	N	Y	Y	N	Y	Y	N	Y	CD	Y	N	Y	N
Edwards-Bailey., 2023	Y	Y	Y	Y	N	Y	Y	N	Y	N	Y	N	Y	N
Kapp Simon, 1998	Y	N	Y	N	N	Y	Y	N	Y	N	Y	N	N	Y
Kljajic et al., 2019	Y	Y	Y	Y	N	Y	Y	N	Y	N	Y	N	NR	Y
Kljajic et al., 2020	Y	N	Y	N	N	Y	Y	N	Y	N	Y	N	N	Y
Kljajic et al., 2021	Y	Y	Y	Y	N	Y	Y	N	Y	N	Y	N	CD	Y
Osborn et al., 2021	Y	Y	NR	Y	N	Y	Y	N	Y	N	Y	N	NR	Y
Qi et al., 2023	Y	Y	CD	Y	N	Y	Y	N	Y	N	Y	N	N	N
Scheuerle et al., 2004	N	N	Y	CD	N	Y	Y	N	Y	CD	CD	N	N	N
Sidoti et al., 1996	Y	N	NR	Y	N	Y	Y	N	CD	Y	Y	N	Y	N
Snyder & Pope 2009	Y	N	Y	Y	N	Y	Y	N	N	NR	Y	N	NR	N
Speltz et al., 2016	Y	Y	Y	Y	N	Y	Y	N	Y	N	Y	N	CD	Y
Van der Vlugt et al., 2012	Y	Y	Y	Y	N	Y	Y	N	Y	CD	Y	CD	NR	N
Wojcicki & Prudel, 2019	Y	Y	Y	Y	N	Y	Y	Y	Y	CD	Y	N	CD	N

Note: Assessment of included studies against the NHLBI OC-CS quality assessment criterion Q = question, Y = yes, N = no, CD = cannot determine, N = not reported.

Appendix D – Quality Assessment Criterion for Case Control Studies

Author/Date:	**Yes**	**No**	**Other (CD, NR, NA)***
Criteria			
1. Was the research question or objective in this paper clearly stated and appropriate?			
2. Was the study population clearly specified and defined?			
3. Did the authors include a sample size justification?			
4. Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?			
5. Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?			
6. Were the cases clearly defined and differentiated from controls?			
7. If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?			
8. Was there use of concurrent controls?			
9. Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?			
10. Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?			
11. Were the assessors of exposure/risk blinded to the case or control status of participants?			
12. Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?			

Note: NHLBI questionnaire use to assess OC-CS. Q = question, Y = yes, N = no, CD = cannot determine, N = not reported.

Appendix D Continued – Quality Assessment Criterion for Case Control Studies

Author (date)	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12
Boltshauser et al., 2003	Y	N	N	Y	Y	Y	CD	Y	Y	Y	CD	N
Colett et al., 2017	Y	Y	N	Y	Y	Y	CD	CD	Y	Y	N	Y
Kapp Simon et al., 2012	Y	Y	N	CD	Y	Y	N	CD	Y	Y	N	Y
Tillman et al., 2020	Y	Y	N	Y	Y	Y	NR	CD	Y	Y	CD	Y

Note: Assessment of included studies against the NHLBI OC-CS quality assessment criterion Q = question, Y = yes, N = no, CD = cannot determine, N = not reported.

Appendix E – Study Characteristics for 21 Independent Studies Included in the Meta-Analysis

Author (year)	Country of Origin	Sample Size ($N_{participants}$)	Study Design	Recruitment Source
Boltshauser et al., 2003	Switzerland	Case = 30 Control = 17	Case control	Case = retrospective medical records Control = Siblings
Care et al., 2019	United Kingdom	89	Cross-sectional	Craniofacial hospital unit
Chieffo et al., 2010	Italy	35	Cross-sectional	Cannot determine
Collett et al., 2017 [A]	America	Case = 179 Control = 183	Case control	Case = craniofacial hospital unit and retrospective medical records Control = paediatric practices and community announcements
Culshaw et al., 2021 [B]	United Kingdom	98	Cross-sectional	Craniofacial hospital unit
Doshier et al., 2015	America	37	Cross-sectional	Retrospective medical records
Edwards-Bailey., 2022 [B]	United Kingdom	75	Cross-sectional	Craniofacial hospital unit
Kapp Simon, 1998	America	34	Cross-sectional	Craniofacial hospital unit
Kapp Simon et al., 2012 [A]	America	Case = 219 Control = 221	Case control	Case = craniofacial hospital unit and retrospective medical records Control = paediatric practices and community announcements
Kljajic et al., 2019[C]	Sweden	63	Cross-sectional	Community data

Kljajic et al., 2020[C]	Sweden	61	Cross-sectional	Craniofacial hospital unit
Kljajic et al., 2021 [C]	Sweden	63	Cross-sectional	Combine data from Kljajic 2019 & 2020
Osborn et al., 2021	Australia	Case = 37 Control = 37	Case control	Craniofacial hospital unit Control = community announcements
Qi et al., 2023	United Kingdom	54	Cross-sectional	Craniofacial hospital unit
Scheuerle et al., 2004	America	14	Cross-sectional	Craniofacial hospital unit
Sidoti et al., 1996	America	31	Cross-sectional	Craniofacial hospital unit
Snyder & Pope 2009	America	34	Cross-sectional	Retrospective medical records
Speltz et al., 2016 [A]	America	179	Cross-sectional	Craniofacial hospital unit and retrospective medical records
Tillman et al., 2020	Sweden	Case = 1238 Control = 12380	Case control	Case = community data Control = community data
Van der Vlugt et al., 2012	Netherlands	55	Cross-sectional	Craniofacial hospital unit
Wojcicki & Prudel, 2019	Poland	12	Cross-sectional	Retrospective medical records

Note: A, B, and C= represent repeating samples.

Appendix F– Summary of Outcome Data Provided by Each Independent Study

No.	Author (year)	Attention	Hyperactivity	ADHD Screened	ADHD Diagnosed
1	Boltshauser et al., 2003	✓	-	-	-
2	Care et al., 2019	-	✓	-	-
3	Chieffo et al., 2010	✓	-	-	-
4	Collett et al., 2017	✓	✓	-	✓
5	Culshaw et al., 2021	-	✓	-	-
6	Doshier et al., 2015	-	-	-	✓
7	Edwards-Bailey., 2022	-	✓	-	-
8	Kapp Simon, 1998	-	-	-	✓
9	Kapp Simon et al., 2012	✓	-	✓	-
10	Kljajic et al., 2019	✓	-	-	✓
11	Kljajic et al., 2020	✓	-	-	✓
12	Kljajic et al., 2021	✓	-	-	-
13	Osborn et al., 2021	✓	✓	-	-
14	Qi et al., 2023	-	✓	-	-
15	Scheuerle et al., 2004	-	-	-	✓
16	Sidoti et al., 1996	-	-	-	✓
17	Snyder & Pope 2009	✓	-	-	-
18	Speltz et al., 2016	✓	-	-	-
19	Tillman et al., 2020	-	-	-	✓
20	Van der Vlugt et al., 2012	-	-	-	✓
21	Wojcicki & Prudel, 2019	-	-	-	✓

Appendix G – Diagnostic tools, Measures, Scales, and Subscales Used in the 21 Independent Studies Included in the Meta-Analysis

Author (date)	Measures and Diagnostic Tools Used	Outcome Assessed	Scale and Subscale Used
Boltshauser et al., 2003	TAP	Attention	Alertness tonic, alertness phasic, go/nogo, divided attention, sustained attention
	WISC-III	Attention	Freedom from distractibility, digit span
Care et al., 2019	SDQ	Hyperactivity	Hyperactivity subscale
Chieffo et al., 2010	Cannot determine	Attention	Selective & Sustained Attention
Collett et al., 2017 [A]	Cannot determine	ADHD	Cannot determine
	TEA-Ch	Attention	Sky search, score!, sky search DT, score DT
	ASEBA	Attention	Attention problem subscale
Culshaw et al., 2021 [B]	SDQ	Hyperactivity	Hyperactivity subscale
Doshier et al., 2015	Cannot determine	ADHD	Cannot determine
Edwards-Bailey., 2022 [B]	SDQ	Hyperactivity	Hyperactivity scale
Kapp Simon, 1998	Cannot determine	ADHD	Cannot determine

Kapp Simon et al., 2012 [A]	CBCL 1 1/2-5	Attention	Attention Problems
	CBCL	ADHD	ADHD screening subscale
Kljajic et al., 2019[C]	Cannot determine	ADHD	Cannot determine
	WISC-IV	Attention	Digit span test
Kljajic et al., 2020[C]	WISC-IV	Attention	Digit span test
	Connors CPT-3	Attention	Response style, detectability, omissions, commissions, preservation, HRT, HRT-DS, variability, HRT-BC, HRT-iC
Kljajic et al., 2021 [C]	WISC-IV	Attention	Digit span test
Osborn et al., 2021	SDQ	Hyperactivity	Hyperactivity scale
	WISC-V	Attention	Working memory index
Qi et al., 2023	SDQ	Hyperactivity	Hyperactivity scale
Scheuerle et al., 2004	Cannot determine	ADHD	Cannot determine
Sidoti et al., 1996	Cannot determine	ADHD	Cannot determine
Snyder & Pope 2009	CBCL 4-11	Attention	Attention Problems
Speltz et al., 2016 [A]	ASEBA	Attention	Attention Problems

Tillman et al., 2020	ICD 9, ICD 10	ADHD	6A05 Attention Deficit Hyperactivity Disorder
Van der Vlugt et al., 2012	DSM	ADHD	Neurodevelopmental Disorders section
Wojcicki & Prudel, 2019	Cannot determine	ADHD	Cannot determine

Note: A, B, and C= represent repeating samples. Measures and scales used reflect only those that were reported by the original paper and may not reflect all measures used in that paper. ASEBA = Achenbach System of Empirically Based Assessment, CBCL = Child Behaviour Checklist, Connors CPT = Conners Continuous Performance Test, DSM = Diagnostic and Statistical Manual of Mental Disorders, ICD = International Classification of Diseases, SDQ = Strengths and Difficulties Questionnaire, TAP = Test for Attention Performance, TEA-Ch = Test of Everyday Attention in Children, WISC = Wechsler Intelligence Scale for Children.