

## Systematic Review

# Maternal determinants of craniosynostosis: Insights from a systematic review and meta-analysis

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## Abstract

Craniosynostosis, a congenital condition caused by premature fusion of cranial sutures, poses serious challenges to neonatal health and development, and maternal factors have been increasingly recognized as contributors to its etiology. The aim of this study was to evaluate maternal determinants of craniosynostosis and quantify their associations through a systematic review and meta-analysis. A comprehensive search of PubMed, Scopus, and Google Scholar was conducted to identify observational studies reporting maternal risk factors. Eligible studies were assessed for quality, and meta-analyses were performed using random-effects models to calculate pooled odds ratios (ORs) and assess heterogeneity. Six studies met the inclusion criteria. Advanced maternal age ( $\geq 30$  years) was associated with a 53% higher risk of craniosynostosis (OR: 1.53; 95%CI: 1.25–1.87), while maternal obesity (BMI  $\geq 30$  kg/m<sup>2</sup>) was linked to a 42% higher risk (OR: 1.42; 95%CI: 1.18–1.71). Ethnic disparities were observed, with non-Hispanic Black (OR: 0.73; 95%CI: 0.58–0.92) and Hispanic mothers (OR: 0.81; 95%CI: 0.65–0.99) having lower risks compared with non-Hispanic White mothers. Heterogeneity was moderate for maternal age ( $I^2=48\%$ ) and low for BMI ( $I^2=22\%$ ). Overall, advanced maternal age and obesity emerged as consistent maternal risk factors for craniosynostosis, while ethnic differences suggest potential protective influences in certain populations. These findings highlight the importance of targeted preconception counseling, maternal health interventions, and further research to elucidate underlying mechanisms and guide preventive strategies.

**Keywords:** Craniosynostosis, maternal risk factors, congenital anomalies, maternal age, maternal obesity

## Introduction

Craniosynostosis is a congenital cranial malformation caused by the premature fusion of one or more cranial sutures [1]. Approximately 25% of cases are syndromic, often involving multiple sutures [2]. This condition may lead to increased intracranial pressure, delayed neurodevelopment, and impaired brain growth [1,3,4]. Although certain congenital anomalies are attributable to single-gene mutations, chromosomal abnormalities, or environmental factors, many cases remain of unknown origin [5].

The prevalence of craniosynostosis is estimated at 1 in 2,000 to 2,500 live births, with variation across populations [6]. Understanding its etiology is crucial for developing preventative strategies and enhancing treatment outcomes [7]. Maternal factors have gained increasing recognition as contributors to craniosynostosis risk [8]. Advanced maternal age has also been implicated as a risk factor for congenital anomalies, including craniosynostosis. A systematic



review indicated that women of older maternal age have increased odds of having children with congenital anomalies [5]. Additionally, a higher risk of non-syndromic craniosynostosis has been associated with maternal drug use during pregnancy, including oral progesterone intake [8].

Given the potential impact of maternal characteristics and exposures, a comprehensive synthesis of current evidence is warranted. Therefore, the aim of this study was to quantify associations between maternal risk factors and craniosynostosis, providing insights to guide preventive strategies and inform clinical interventions for at-risk populations.

## Methods

### Study design

This study was conducted in accordance with the preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines. The primary objective was to identify and synthesize evidence on maternal factors associated with craniosynostosis. Both qualitative and quantitative data from eligible studies were examined to generate pooled effect estimates and assess study heterogeneity.

### Search strategy

Four independent reviewers (AM, CSA, RCS, and ZS) conducted a comprehensive search for English-language publications from December 14 to 20, 2024, in two major global databases: PubMed and Scopus. Google Scholar was used as a supplementary source to identify grey literature. The search strategy combined craniosynostosis-related terms with maternal factor terms using Boolean operators: ("craniosynostosis" OR "cranial suture fusion" OR "cranial suture anomalies") AND ("maternal risk" OR "maternal risks" OR "risk factor" OR "risk factors" OR "pregnancy determinant" OR "pregnancy determinants" OR "maternal outcome" OR "maternal outcomes" OR "antenatal risk" OR "antenatal risks" OR "perinatal risk" OR "perinatal risks" OR "postnatal risk" OR "postnatal risks" OR "obstetric risk factor" OR "obstetric risk factors" OR "pregnancy outcome" OR "pregnancy outcomes"). Although the search was not restricted by language, English-language articles were prioritized as they were generally of higher quality and more accessible.

Duplicate records were removed prior to screening. Titles and abstracts were independently screened by all four reviewers against predefined inclusion criteria. Articles meeting these criteria underwent full-text assessment using the same eligibility framework. Screening was performed independently to minimize, and disagreements were resolved through discussion; if consensus could not be achieved, the corresponding author made the final decision.

### Eligibility criteria

Eligibility criteria were defined using the population, intervention, comparator, outcomes, and study design (PICOS) framework. Studies were considered eligible if they included either patients with syndromic or nonsyndromic craniosynostosis confirmed by radiographic imaging or clinical examination, or pregnant women at risk of having a child with craniosynostosis due to maternal characteristics or exposures. Maternal variables of interest included advanced maternal age, body mass index (BMI), smoking, drug use, environmental or occupational exposures such as polycyclic aromatic hydrocarbons (PAHs), and maternal medical conditions such as diabetes or thyroid disease.

Eligible comparators comprised mothers of children without craniosynostosis, groups with differing risk profiles (e.g., normal BMI vs obesity), unaffected siblings, or population-based averages. The primary outcome was the association between maternal variables and the risk of craniosynostosis, reported as prevalence ratios (PR), odds ratios (OR), or relative risks (RR). Secondary outcomes included variation in craniosynostosis prevalence, healthcare utilization, and demographic characteristics such as ethnicity and socioeconomic status. Only observational studies—including case-control, cohort, and population-based studies—published in peer-reviewed journals were included. In order to be eligible, studies were required to meet minimum methodological standards, such as having a clearly defined study population, explicit definitions

of exposures and outcomes, reporting of effect estimates with confidence intervals (CI), and adequate sample size to support statistical analysis.

Exclusion criteria included studies that did not assess maternal factors or quantitative associations; review articles, case reports, or conference abstracts without original data; non-English publications or inaccessible full texts; and studies without sufficient methodological information or statistical rigor. This stringent selection method ensured the inclusion of high-quality papers, thereby strengthening the reliability and validity of the review's conclusions.

### **Screening and selection**

The initial database search was conducted using predetermined keywords, and duplicate records were removed using Rayyan AI. Four independent reviewers (AM, CSA, RCS, and ZS) performed a two-stage screening process: first by titles and abstracts, followed by full-text review, in accordance with the predefined eligibility criteria. Each record was screened by two reviewers. Discrepancies were resolved through discussion until consensus was reached; if consensus could not be reached, a third reviewer was designated to adjudicate. However, no discrepancies arose during the screening process, and thus third-party adjudication was not required.

### **Quality appraisal**

Four independent reviewers assessed the risk of bias in the included randomized clinical trials (RCTs) using the Cochrane Collaboration's Risk of Bias 2 (RoB 2) technique. RoB 2 investigates five standard domains: (1) bias coming from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in outcome measurement; and (5) bias in selection of the reported result. Each domain was rated as having low risk, some concerns, or high risk of bias. Assessments were conducted independently and in duplicate, with disagreements resolved through discussion until consensus was reached. The RoBVis tool was used to visualize the risk-of-bias assessments.

### **Data extraction**

Data extraction was conducted systematically using a standardized form to ensure consistency across studies. Outcomes were categorized as primary or secondary. Primary outcomes investigated the links between specific maternal factors, including BMI, maternal age, and environmental exposures, and the prevalence or risk of craniosynostosis. Secondary outcomes included temporal trends in prevalence, healthcare utilization among affected children, and maternal or demographic characteristics such as ethnicity, socioeconomic status, and educational level. Extracted variables included study design, sample size, maternal factors assessed, statistical measures (such as odds ratios and prevalence ratios), CI, and main findings. The standardized form was tested on a limited subset of studies before being used for comprehensive data extraction to guarantee clarity and completeness. Data extraction was performed independently by two reviewers using Microsoft Excel, with discrepancies resolved through discussion until consensus was reached. This approach improved the derived dataset's reliability and validity.

### **Statistical analysis**

A random-effects model was applied to account for between-study heterogeneity when calculating effect estimates, including pooled odds ratios (ORs) and prevalence ratios (PRs). Heterogeneity was evaluated using Cochran's Q test ( $p < 0.10$ ) and quantified using the  $I^2$  statistic, with values of 25%, 50%, and 75% interpreted as low, moderate, and high heterogeneity, respectively. An  $I^2$  value  $> 50\%$  was considered indicative of substantial heterogeneity. Subgroup analyses were performed according to maternal age, BMI, type of craniosynostosis (e.g., sagittal, coronal, metopic, lambdoid), geographic region, and environmental exposure category. Sensitivity analyses were conducted to test the robustness of findings by excluding studies rated as high risk of bias according to the Cochrane RoB 2 tool. All statistical analyses were performed using Review Manager (RevMan) version 5.4 (The Nordic Cochrane Centre, Copenhagen, Denmark).

## Results

### Search and selection result

A total of 627 entries were found in three databases: PubMed (n=202), Scopus (n=353), and Google Scholar (n=72). After deleting 46 duplicates, 581 studies remained for title and abstract screening. Of these, 551 reports were excluded for not meeting the predefined PICOS criteria, resulting in 30 articles for full-text assessment. Twenty-four of these were subsequently excluded due to ineligible populations (n=3), irrelevance to research question (n=6), and non-relevant outcomes (n=15). Ultimately, six studies met the inclusion criteria and were retained for qualitative and quantitative analysis in this study [9-14]. A complete PRISMA flowchart of the study selection process is presented in **Figure 1**.

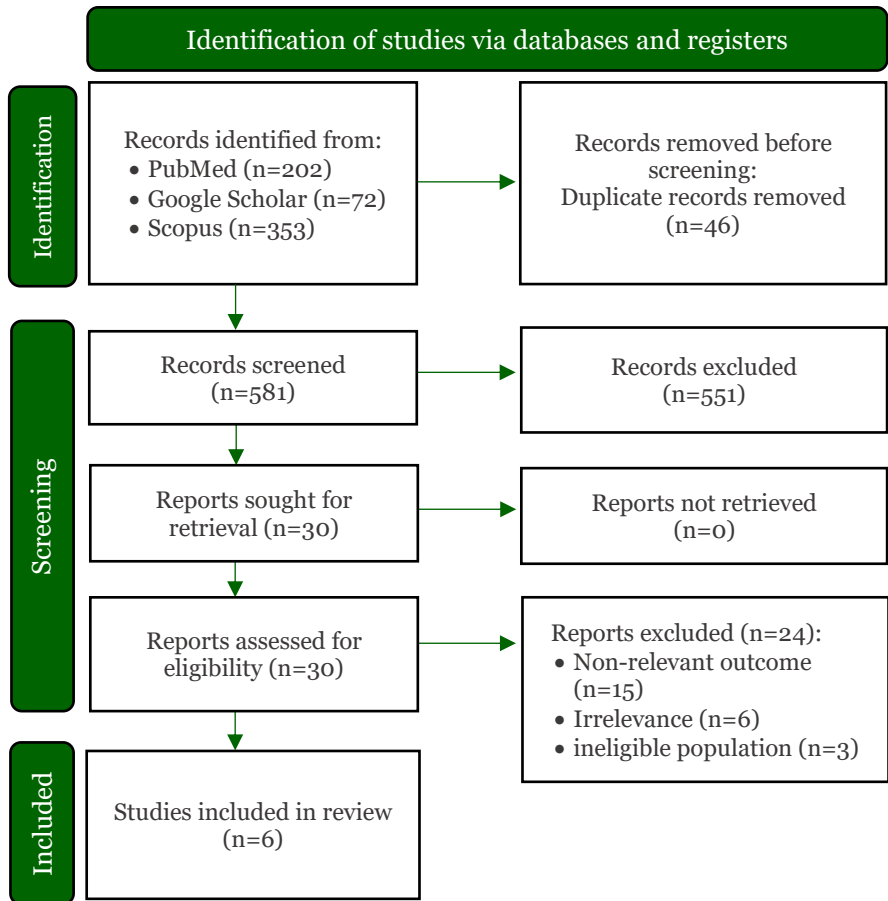


Figure 1. PRISMA flow-chart for the selection of studies reporting maternal determinants in craniosynostosis.

Six studies investigating maternal risk factors associated with craniosynostosis were included in the review. The study designs, populations, maternal risk factors examined, and key findings are summarized in **Table 1**. The studies covered various techniques, such as retrospective cohort studies, population-based cohorts, and hospital-based case-control studies. Sample sizes ranged from 70 to 2,111 people, representing populations in various areas and historical periods.

### Quality of the included studies

Risk of bias across the included studies was assessed across several key domains (**Figure 2**). The majority of studies had a low risk of bias for participant and personnel blinding (performance bias). However, one study lacked methodological detail in this domain, raising concerns regarding the effectiveness of blinding measures [11]. In terms of result assessment blinding (detection bias), two studies were found to be at high risk of bias, most likely due to poor blinding throughout the outcome assessment procedure.

Table 1. Summary of included studies reporting maternal risk factors associated with craniosynostosis

| Author, year                        | Study design                                                                                                                          | Population                                                                                            | Maternal risk factor                                                                                                                                                                                                                                                                             | Aim/parameter                                                                                                                                                                                                                                                                        | Follow-up time                                                                              | Main findings                                                                                                                                                                                                                                          | Analysis method                                                                                                                                                                                        |
|-------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Gabriela <i>et al.</i> , 2022 [14]  | Retrospective cohort study data from Optum Clinformatics Data Mart database, analyzing records from 2003 to 2020                      | 1,340 craniosynostosis patients (200 syndromic, 1,140 nonsyndromic).                                  | Not explicitly detailed in the study; focus on healthcare utilization rather than maternal contributors.                                                                                                                                                                                         | To compare long-term healthcare utilization in children with craniosynostosis to children with plagiocephaly and healthy controls. Parameters of this study are Rates of mental health care, rehabilitation therapies, and medical subspecialty service usage up to 6 years of age.  | From surgery until the age of 6 years.                                                      | Children with craniosynostosis had significantly higher utilization of healthcare services than healthy controls and children with plagiocephaly.                                                                                                      | Statistical tests (e.g., Wilcoxon rank-sum, ANOVA, Fisher's exact, and chi-square tests) to evaluate utilization differences.                                                                          |
| Schraw <i>et al.</i> , 2020 [9]     | Population-based, retrospective cohort study data from Texas Birth Defects Registry, covering births from 1999 to 2014.               | 2,111 children with isolated craniosynostosis                                                         | Maternal obesity (BMI $\geq 30$ ) was associated with a 27% increased prevalence. Increased maternal age (30–39 and $\geq 40$ years) showed higher prevalence ratios. Hispanic and non-Hispanic Black mothers had a lower prevalence of craniosynostosis compared to non-Hispanic White mothers. | To investigate maternal and infant characteristics associated with craniosynostosis and evaluate trends in its prevalence over time. The parameter is Prevalence ratios (PRs) for craniosynostosis by maternal and infant characteristics, and annual percent changes in prevalence. | Analysis focused on births within the study period, with no additional long-term follow-up. | Prevalence of isolated craniosynostosis increased from 2.86 to 3.74 per 10,000 live births (1999–2014). Male sex and preterm birth were strongly associated with craniosynostosis. Environmental and demographic changes may partly explain the trends | Poisson regression for prevalence ratios and Multivariable regression to adjust for potential confounders (maternal age, race/ethnicity, BMI, preterm birth, prior live births, and border residence). |
| Langlois, <i>et al.</i> , 2015 [12] | Case-control study data from National Birth Defects Prevention Study (NBDPS), Infants with estimated delivery dates from 1997 to 2002 | 316 infants diagnosed with craniosynostosis data from National Birth Defects Prevention Study (NBDPS) | Occupational exposure to polycyclic aromatic hydrocarbons (PAHs) during the month before conception through the third month of pregnancy. Also, maternal age, education, race/ethnicity, smoking history, exposure to secondhand smoke, and body mass index (BMI)                                | Investigate the association between maternal occupational exposure to PAHs and the risk of craniosynostosis in offspring using odds ratio (OR)                                                                                                                                       | 1 month before conception to the third month of pregnancy.                                  | Adjusted OR: 1.75 (95%CI: 1.01–3.05), indicating a moderate association between PAH exposure and craniosynostosis.                                                                                                                                     | Unconditional logistic regression used as the statistical tool and secondary analysis by expanded exposure window to assess the robustness of findings                                                 |

| Author, year                        | Study design                                                                                                                                                                                                         | Population                                                                                                      | Maternal risk factor                                                                                                                                                                                                                                     | Aim/parameter                                                                                                                                                                                             | Follow-up time                                                                                                              | Main findings                                                                                                                                                                                                                                     | Analysis method                                                                                                                                                 |
|-------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ardalan <i>et al.</i> , 2012 [11]   | Hospital-based case-control study in Children's Hospital Medical Center, Tehran, Iran, dates from September 2010 to 2011                                                                                             | 70 children diagnosed with craniosynostosis (syndromic or nonsyndromic), with a mean admission age of 13 months | Positive family history of craniosynostosis (OR:19.01; 95%CI: 2.24–160.7). Higher prevalence of maternal diabetes mellitus in the case group (11.6% vs 2.9%; $p<0.05$ ). Maternal thyroid disease and medication use were not statistically significant. | To investigate environmental and genetic risk factors contributing to craniosynostosis in children using odds ratios (OR) of craniosynostosis associated with various maternal and environmental factors. | Data collected at the time of admission and surgery. No extended follow-up reported.                                        | Positive family history and clomiphene citrate use were the strongest predictors of craniosynostosis. Postdate delivery was also a significant risk factor. Maternal smoking, age, and gravidity were not statistically significant risk factors. | Univariate analysis with Chi-square and t-tests, and multivariate analysis with Logistic regression.                                                            |
| Rasmussen <i>et al.</i> , 2007 [10] | Population-based case-control study, data from National Birth Defects Prevention Study (NBDPS), a multisite study in the United States with estimated delivery dates between October 1, 1997, and December 31, 2002. | 431 infants with craniosynostosis, confirmed by radiographic imaging                                            | Defined as maternal report of a thyroid disorder or use of thyroid medication during pregnancy.                                                                                                                                                          | To determine whether maternal thyroid disease or its treatment is associated with an increased risk of craniosynostosis, the parameter is odds ratios (ORs) adjusted for potential confounding factors.   | Maternal interviews were conducted between 6 weeks and 24 months postpartum. No extended follow-up of infants was reported. | Maternal interviews were conducted between 6 weeks and 24 months postpartum. No extended follow-up of infants was reported. Suggested involvement of maternal thyroid-stimulating immunoglobulins (TSIs) in fetal thyroid function.               | Unconditional logistic regression to calculate adjusted ORs. Controlled for maternal age and other potential confounders, including smoking, BMI, and diabetes. |
| Bradley, <i>et al.</i> 1995 [13]    | Population-based case-control study during 1986–1989                                                                                                                                                                 | 212 children born to Colorado residents and diagnosed with craniosynostosis                                     | The study examined maternal and paternal occupations, but no strong associations were found for maternal occupations.                                                                                                                                    | To examine the relationship between parental occupations and the risk of craniosynostosis in offspring.                                                                                                   | Not mentioned                                                                                                               | No strong associations for maternal occupations. Paternal occupations in agriculture and forestry, and mechanics and repairmen, were associated with moderately increased odds ratios for craniosynostosis.                                       | Odds ratios were adjusted for maternal smoking and altitude, and jobs were coded using 1980 Census occupation and industry codes                                |



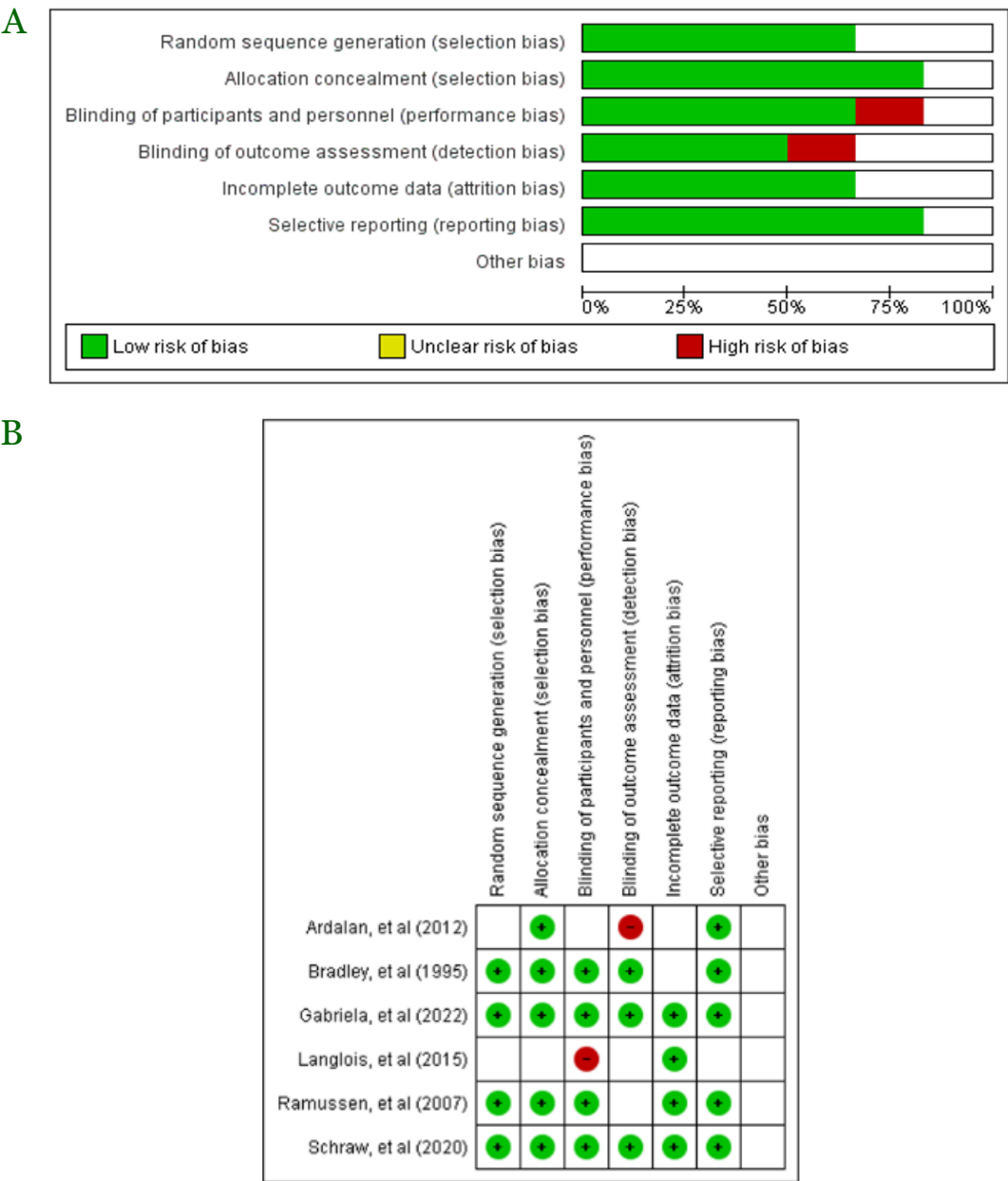


Figure 2. Summary of Risk of Bias assessment for included studies. (A) The distribution of risk across six bias domains (low, unclear, and high risk) and (B) risk of bias judgments for individual studies across each domain.

**Maternal age meta-analysis**

Maternal age was categorized into younger adult mothers (<29 years old) and older adult mothers (≥29 years). The pooled analysis demonstrated that older maternal age was significantly associated with an increased risk of craniosynostosis. The pooled OR was 1.53 (95%CI: 1.25–1.87,  $p<0.001$ ), indicating advanced maternal age as a strong risk factor. Moderate heterogeneity was observed among the included studies ( $I^2=48\%$ ), yet the overall findings remained consistent (Figure 3).

**Maternal BMI meta-analysis**

Maternal BMI was analyzed across four categories: underweight (<18.5 kg/m<sup>2</sup>), normal weight (18.5–24.9 kg/m<sup>2</sup>), overweight (25–29.9 kg/m<sup>2</sup>), and obese (≥30 kg/m<sup>2</sup>). The findings revealed a significant association between maternal obesity and the risk of craniosynostosis, with a pooled OR of 1.42 (95%CI: 1.18–1.71,  $p<0.01$ ). This underscores the critical impact of extreme BMI values, particularly obesity, on the likelihood of developing craniosynostosis.

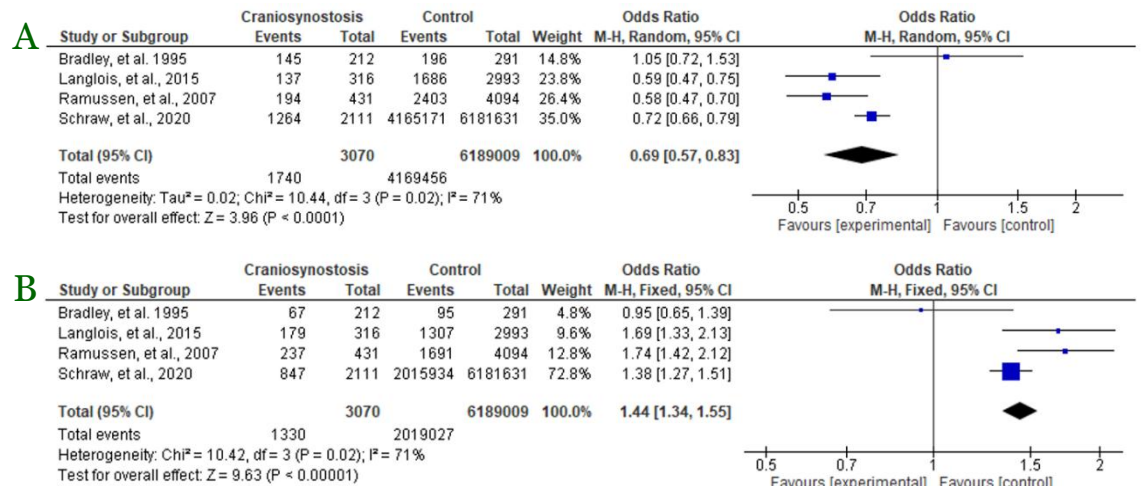


Figure 3. Forest plot of maternal age as a risk factor for craniosynostosis. (A) Younger adult mother (<29 years) and (B) older adult mothers ( $\geq 29$  years).

In contrast, associations were not statistically significant for the underweight and normal weight categories, suggesting these BMI ranges are less critical determinants of risk factors. The analysis exhibited low heterogeneity ( $I^2 = 22\%$ ), which supports the reliability and consistency of the pooled estimates across included studies. Results are presented in **Figure 4**.

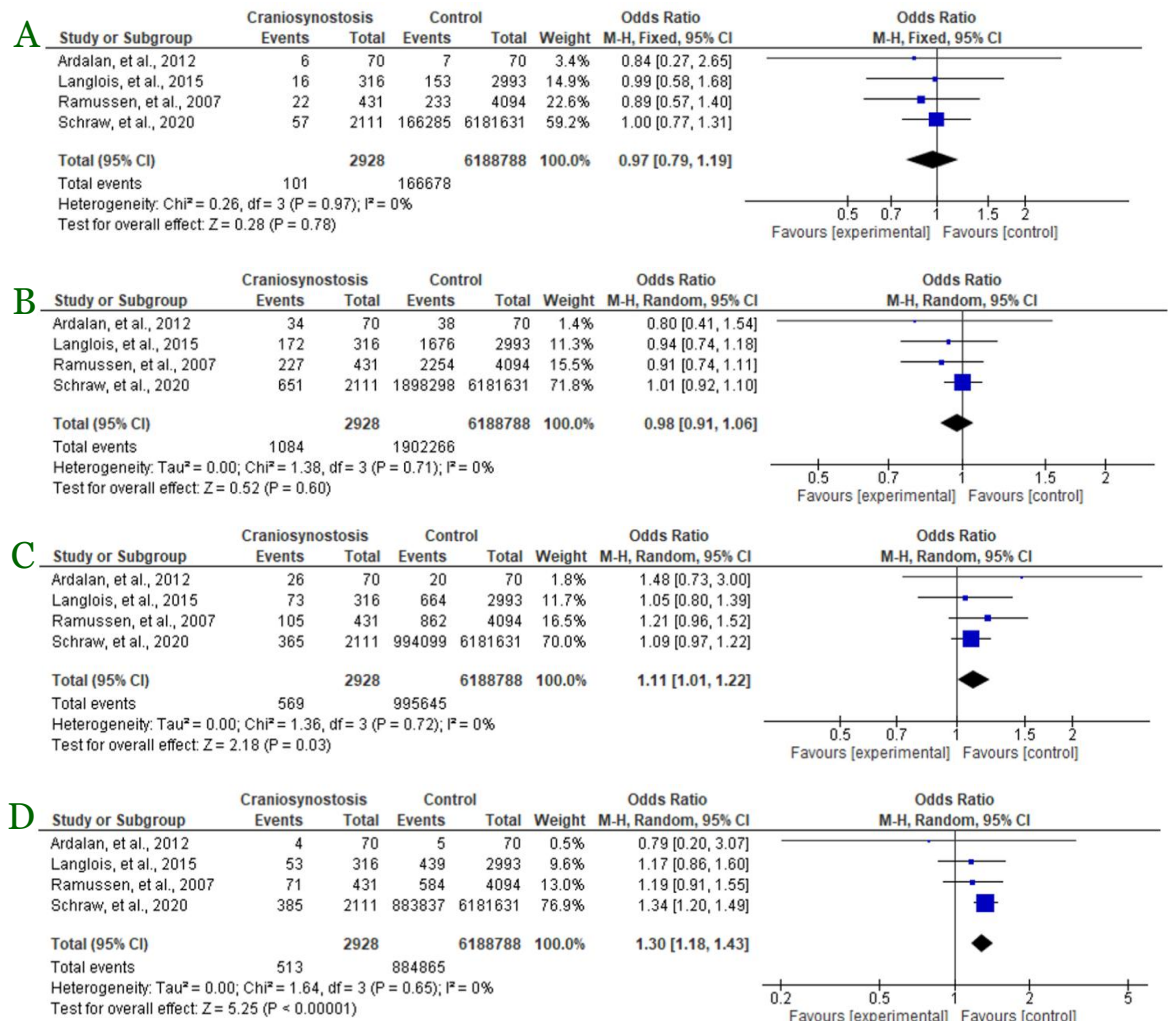


Figure 4. Forest plots of maternal body mass index (BMI) categories as risk factors for craniosynostosis. (A) Underweight (<18.5 kg/m<sup>2</sup>); (B) normal (18.5–24.9 kg/m<sup>2</sup>); (C) overweight (25–29.9 kg/m<sup>2</sup>); and (D) obese (>30 kg/m<sup>2</sup>).



Maternal race/ethnicity meta-analysis

The association between maternal race/ethnicity and craniosynostosis risk was examined across three groups: non-Hispanic white, non-Hispanic black, and Hispanic mothers. Non-hispanic White mothers served as the reference group. Compared with this group, both non-Hispanic Black and Hispanic mothers had significantly lower odds of craniosynostosis. The pooled OR was 0.73 (95%CI: 0.58–0.92,  $p=0.01$ ) for non-Hispanic Black mothers and 0.81 (95%CI: 0.65–0.99,  $p=0.04$ ) for Hispanic mothers. Moderate heterogeneity was observed ( $I^2=36\%$ ), indicating some variability among the included studies but overall consistent findings. Results are presented in Figure 5.

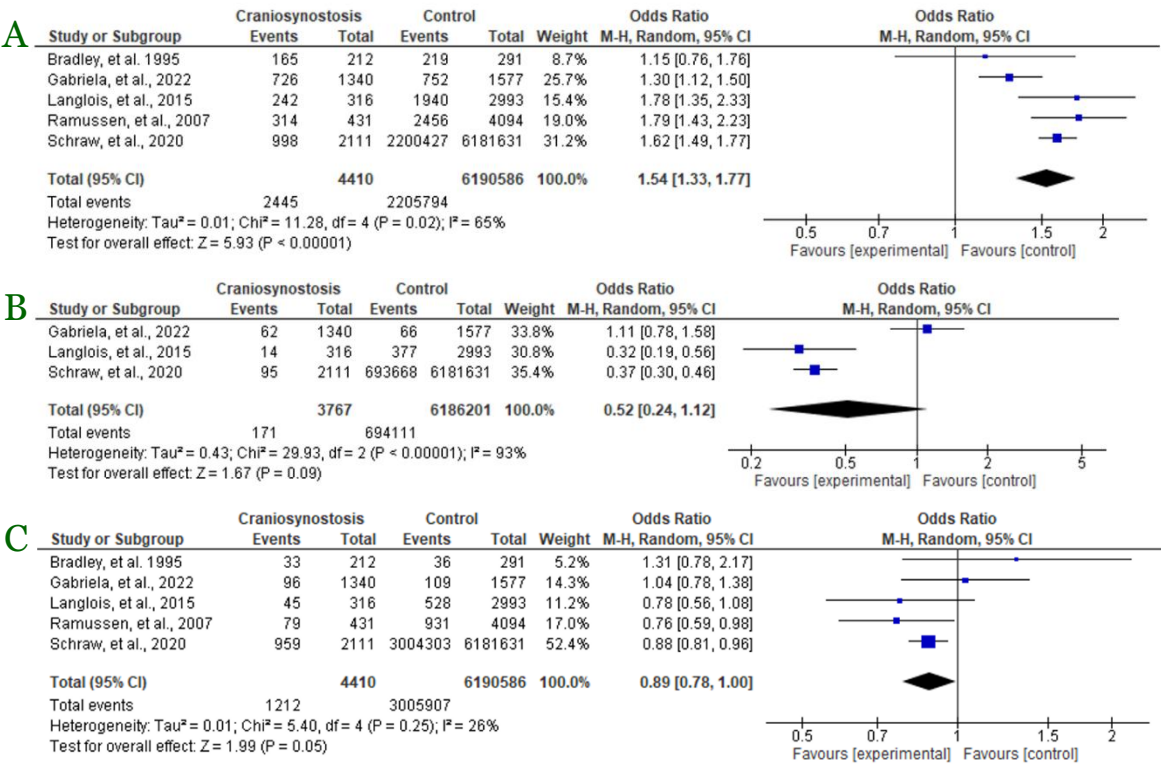


Figure 5. Forest plots of maternal race/ethnicity as a risk factor for craniosynostosis. Mother race/ethnicity: (A) Non-Hispanic white; (B) non-Hispanic black; and (C) Hispanic.

Discussion

This study analyzed maternal risk factors for craniosynostosis, focusing on advanced maternal age, body mass index (BMI), and ethnicity [8,15-18]. The meta-analysis found that advanced maternal age ( $\geq 30$  years) and maternal obesity ( $BMI \geq 30$  kg/m<sup>2</sup>) were significant risk factors. Ethnic disparities were also observed, with non-Hispanic White mothers displaying higher risks compared with other groups [19,20]. The present findings are consistent with previous research correlating maternal age to congenital abnormalities. Previous studies reported that women above 30 years had increased risks of craniosynostosis, consistent with the broader literature, which links increased maternal age to chromosomal abnormalities, decreased oocyte quality, and a higher prevalence of comorbidities such as diabetes and hypertension [8,17,19,20]. Similarly, other studies demonstrated that maternal obesity increases the risk of structural birth abnormalities during pregnancy due to metabolic, inflammatory, and hormonal mechanisms [8,21].

Several individual studies reinforce these findings. Schraw *et al.* (2020) reported a 27% higher risk of craniosynostosis among women with a  $BMI \geq 30$  [9]. Langlois *et al.* (2015) found that advanced maternal age was an independent risk factor using age-adjusted odds ratios. In addition, Langlois *et al.* (2015) observed a moderate association between periconceptional exposure to PAHs and craniosynostosis (adjusted OR: 1.75; 95%CI: 1.01–3.05) [12]. Ardan *et al.* (2012) identified genetic predisposition, showing family history as a major predictor (OR:

19.01; 95%CI: 2.24–160.7) [11]. Maternal comorbidities, such as diabetes mellitus, were also more prevalent among affected cases (11.6% vs 2.9%,  $p<0.05$ ). Collectively, these findings highlight the complex character of craniosynostosis, encompassing genetic predispositions, maternal health status, and environmental exposure.

In this study, advanced maternal age was associated with a 53% higher incidence of craniosynostosis compared with younger adult mothers. Despite moderate heterogeneity ( $I^2=48\%$ ), the effect was consistent across studies, demonstrating robustness of the association. Maternal obesity was also identified as a major risk factor, with low heterogeneity ( $I^2=22\%$ ), confirming the credibility of these results. The reduced risks observed in non-Hispanic Black and Hispanic mothers may reflect protective genetic, environmental, or lifestyle factors, though these require further investigation.

In terms of study quality, the majority of included studies demonstrated low risk of bias in random sequence generation, allocation concealment, attrition, and reporting. However, there were concerns regarding blinding of outcome assessment in several studies, which could restrict measurement reliability. Despite these limitations, the methodological quality offered an adequate basis for evidence synthesis in this meta-analysis.

This study emphasizes advanced maternal age ( $\geq 30$  years) and obesity (BMI 30 or above) as consistent and significant risk factors for craniosynostosis. These findings underline the crucial role of focused preconception counseling and maternal interventions in addressing both modifiable and non-modifiable risk factors. In terms of racial and ethnic inequalities, the reduced risk reported in non-Hispanic Black and Hispanic mothers shows the presence of potential protective factors, which might be genetic, environmental, or lifestyle-related. These findings need additional investigation to determine the underlying causes of these inequalities. Overall, the findings highlight the complex etiology of craniosynostosis, with maternal age and BMI playing significant roles. Understanding racial and ethnic differences adds to the complexity of risk assessment, emphasizing the need for more study and personalized solutions.

Similarly, previous studies demonstrated that maternal obesity raises the likelihood of structural birth defects during pregnancy due to metabolic, inflammatory, and hormonal changes [22]. Advanced maternal age has been linked to meiotic nondisjunction, cumulative genetic and epigenetic alterations, and declining gamete quality. Obesity-related chronic low-grade inflammation, hormonal imbalance, and dietary deficiencies (e.g., folate) may disrupt normal cranial suture formation [23-25]. Furthermore, obesity-related comorbidities such as diabetes and hypertension are independently associated with congenital anomalies [21,25,26]. Ethnic differences may reflect a complex interplay of genetic predisposition, environmental exposures, and social determinants [26,27]. For example, previous study noted that inequalities in healthcare access and utilisation among ethnic groups may contribute to craniosynostosis underdiagnosis or delayed detection [28].

Cultural perceptions of craniofacial traits may also influence whether certain cranial variations are reported or clinically assessed [29,30]. These issues highlight the necessity for future research to separate the relative contributions of genetics, socioeconomic, and healthcare factors to observed ethnic disparities. The implications for clinical practice and public health are considerable [31]. Identification of maternal risk factors such as age and BMI provides an opportunity for targeted preconception and prenatal interventions, including weight management programs, nutritional counseling, and genetic counseling for at-risk women [32,33]. Addressing modifiable risk factors may aid in the prevention of craniosynostosis and improving maternal-child health outcomes. Future research should also look into understudied factors such as maternal drug use (e.g., oral progesterone), smoking, and alcohol intake.

Finally, several limitations should be acknowledged. Variability in study design, particularly in ethnicity and BMI categorization, may affect comparability. Residual confounding was not consistently addressed across research, and publication bias cannot be completely avoided. Larger, prospective, and multicenter investigations are required to fine-tune these relationships and reveal underlying processes.

## Conclusion

This systematic review and meta-analysis identified advanced maternal age, maternal obesity, and ethnicity as significant risk factors for craniosynostosis. These findings underscore the need for further research to clarify the biological and environmental mechanisms underlying these associations and to address existing gaps in the evidence. Integrating these findings into prenatal care—through targeted risk assessment, counseling, and preventive strategies—may help reduce disease incidence and improve outcomes in high-risk populations.

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The authors have no acknowledgments to declare.

## Competing interests

The authors have no competing interests to declare.

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This study received no external funding.

## Underlying data

Derived data supporting the findings of this study are available from the corresponding author on request.

## Declaration of artificial intelligence use

AI-based language models (ChatGPT and Quillbot) were employed for language refinement (improving grammar, sentence structure, and readability of the manuscript). We confirm that all AI-assisted processes were critically reviewed by the authors to ensure the integrity and reliability of the results. The final decisions and interpretations presented in this article were solely made by the authors.

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