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A systematic review and meta-analysis on the relationship between cesarean delivery and childhood attention deficit hyperactivity disorder

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Wei, JL; Zheng, ZH; Pan, X; Qiu, Y; Han, M.

Corresponding author:

Mei Han

hanmeizoujin@163.com

Author Affiliation:

Beijing University of Chinese Medicine.

ADMINISTRATIVE INFORMATION

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Review Stage at time of this submission - Preliminary searches.

Conflicts of interest - None declared.

INPLASY registration number: INPLASY202470124

Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 30 July 2024 and was last updated on 30 July 2024.

INTRODUCTION

Review question / Objective To investigate the relationship between caesarean section and attention deficit hyperactivity disorder in children by conducting a systematic review and Meta-analysis of observational studies (case-control studies and cohort studies) on caesarean section and attention deficit hyperactivity disorder in children.

Rationale Meta-analysis serves as a robust methodology in consolidating data across studies to derive more reliable conclusions. In the context of ADHD (Attention-Deficit/Hyperactivity Disorder) research, particularly in observational studies, meta-analysis plays a crucial role in elucidating the potential correlation between caesarean section (C-section) and ADHD. Here's a structured overview of how meta-analysis can enhance our understanding: Pooling of Data for Reliable

Conclusions: Meta-analysis aggregates data from multiple studies, allowing for a quantitative synthesis. This approach enhances statistical power by increasing the sample size beyond what individual studies can achieve alone. By combining effect sizes (such as odds ratios, OR) and their associated confidence intervals (CI), meta-analysis provides a clearer estimate of the relationship between C-section and ADHD. This is particularly beneficial when individual studies might show conflicting results or lack statistical significance due to smaller sample sizes.

Types of Observational Studies: In ADHD research, observational studies typically fall into two main categories: **Case-Control Studies:** These compare individuals diagnosed with ADHD (cases) to healthy controls without ADHD. This design can assess whether a history of C-section is more prevalent among those with ADHD compared to the control group. **Cohort Studies:** These follow a group of individuals exposed to C-section

(exposed cohort) and a group of individuals born via vaginal delivery (non-exposed cohort) prospectively over time. Cohort studies can evaluate the incidence of ADHD in both groups and calculate relative risks or odds ratios.

Quantifying Associations: Meta-analytic techniques in observational studies involve calculating pooled odds ratios (OR) and their corresponding 95% confidence intervals (CI). These metrics quantify the strength and direction of the association between C-section and ADHD risk. A meta-analysis allows for the assessment of heterogeneity across studies, exploring potential sources of variation such as study design, population characteristics, and methodological differences.

Condition being studied Attention deficit hyperactivity disorder (ADHD), also known as childhood hyperactivity syndrome, is characterized by age-inappropriate tendencies such as easy distractibility, narrowed attention span, indiscriminate hyperactivity, emotional impulsivity, cognitive deficits, and learning difficulties, despite normal or near-normal intelligence. Symptoms typically manifest in childhood and often persist into adolescence and adulthood, significantly impacting personal development, family dynamics, and societal harmony. Globally, ADHD affects approximately 7.2% of children, with data from the 2016 US National Survey indicating a diagnosis rate of 9.4% among children aged one to two years in the United States. A recent meta-analysis reported a prevalence of 6.26% for ADHD among children and adolescents in China.

Childbirth is the process through which the fetus is delivered from the mother's body, marking the beginning of individual existence. Cesarean section (C-section) is a critical medical intervention used to safeguard the lives of both mother and baby in cases of difficult vaginal deliveries or certain pregnancy complications. However, elective C-sections, when not medically indicated, pose significant health risks to women and infants, including heightened chances of hemorrhage, anesthesia-related complications, and surgical site infections if wound care is inadequate, all of which can jeopardize maternal well-being. Furthermore, numerous studies have linked cesarean deliveries to increased incidences of immune and metabolic disorders, as well as neurodevelopmental outcomes in both humans and animals. Recent research involving mice born via C-section has demonstrated early-life deficits in social interaction and maternal bonding, as well as specific cognitive impairments related to novelty in adulthood. These animal studies underscore the potential

neurodevelopmental implications of cesarean delivery.

METHODS

Search strategy PubMed (mode of delivery[Title/Abstract] OR method of delivery[Title/Abstract] OR delivery[Title/Abstract] OR birth delivery[Title/Abstract] OR caesarean birth[Title/Abstract] OR cesarean[Title/Abstract] OR cesarean section[Title/Abstract] OR Caesarean section[Title/Abstract] OR cesarean delivery[Title/Abstract]) AND ((ADHD[Title/Abstract] OR adhd[Title/Abstract] OR attention deficit hyperactivity disorder[Title/Abstract] OR child hyperkinetic syndrome[Title/Abstract] OR childhood hyperkinetic syndrome[Title/Abstract] OR infantile hyperkinetic syndrome[Title/Abstract]))

the Cochrane Library mode of delivery OR method of delivery OR delivery OR birth delivery OR caesarean birth OR cesarean OR cesarean section OR Caesarean section OR cesarean delivery:ti,ab,kw ADHD OR adhd OR attention deficit hyperactivity disorder OR child hyperkinetic syndrome OR childhood hyperkinetic syndrome OR infantile hyperkinetic syndrome:ti,ab,kw

Web of Science TS=(mode of delivery OR method of delivery OR delivery OR birth delivery OR caesarean birth OR cesarean OR cesarean section OR Caesarean section OR cesarean delivery) AND TS= (ADHD OR adhd OR attention deficit hyperactivity disorder OR child hyperkinetic syndrome OR childhood hyperkinetic syndrome OR infantile hyperkinetic syndrome)

CNKI SU=('剖宫产'+cesarean delivery'+cesarean section'+剖腹产'+剖腹产术'+剖宫产术'+分娩方式') AND SU=('ADHD'+儿童多动症'+adhd'+attention deficit hyperactivity disorder'+child hyperkinetic syndrome'+childhood hyperkinetic syndrome'+infantile hyperkinetic syndrome'+注意力缺陷多动症'+多动综合症'+注意缺陷多动障碍'+多动症'+注意缺陷与多动障碍'+多动综合征'+注意力缺陷障碍'+注意力缺陷伴多动障碍'+注意缺陷-多动障碍'+多动性障碍'+儿童多动综合症'+儿童多动综合征'+多动儿童'+儿童注意力缺陷多动障碍'+儿童注意缺陷多动障碍)

Wanfang

主题:(剖宫产 or cesarean delivery or cesarean section or 剖腹产 or 剖腹产术 or 剖宫产术 or 分娩 or 分娩方式) and 主题:(ADHD or 儿童多动症 or adhd or attention deficit hyperactivity disorder or child hyperkinetic syndrome or childhood hyperkinetic syndrome or infantile hyperkinetic syndrome or 注意力缺陷多动症 or 多动综合症 or 注意缺陷多动障

碍或多动症或注意缺陷与多动障碍或多动综合征或注意力缺陷障碍或注意力缺陷伴多动障碍或注意缺陷-多动障碍或多动性障碍或儿童多动综合征或儿童多动综合征或多动儿童或儿童注意力缺陷多动障碍或儿童注意缺陷多动障碍)

VIP M=(剖宫产或cesarean delivery或cesarean section或剖腹产或剖腹产术或分娩或分娩方式) AND M=(ADHD或儿童多动症或adhd或attention deficit hyperactivity disorder或child hyperkinetic syndrome或childhood hyperkinetic syndrome或infantile hyperkinetic syndrome或注意力缺陷多动症或多动综合征或注意缺陷多动障碍或多动症或注意缺陷与多动障碍或多动综合征或注意力缺陷障碍或注意力缺陷伴多动障碍或注意缺陷-多动障碍或多动性障碍或儿童多动综合征或儿童多动综合征或多动儿童或儿童注意力缺陷多动障碍或儿童注意缺陷多动障碍).

Participant or population Patients with ADHD were diagnosed using a clear assessment tool.

Intervention This study performed a meta-analysis of observational studies and therefore included studies without interventions.

Comparator This study performed a meta-analysis of observational studies and therefore included studies without interventions.

Study designs to be included Observational studies (case-control studies or cohort studies) which studies the relationship between caesarean section and ADHD.

Eligibility criteria Inclusion criteria: (a) Patients with ADHD were diagnosed using a clear assessment tool; (b) The relationship between caesarean section and ADHD were studied; (c) Observational studies (case-control studies or cohort studies).

Exclusion criteria: (a) Studies used the same group of participants; (b) Studies had no corresponding OR and 95%CI; (c) The full text was not available; (d) Redundant publications.

Information sources The literature search will be conducted comprehensively across multiple databases including PubMed, the Cochrane Library, Web of Science, China National Knowledge Infrastructure Database (CNKI), China Science and Technology Journal Database (VIP), and China Wanfang Database.

Main outcome(s) Odd ratio(OR) and 95% confidence intervals (CI) in case-control studies or cohort studies.

Additional outcome(s) Odd ratio(OR) and 95% confidence intervals (CI) in emergency cesarean sections and elective cesarean sections.

Quality assessment / Risk of bias analysis The quality assessment of included case-control and cohort studies employed the Newcastle-Ottawa Scale (NOS) [10], which assesses three primary domains: participant selection, comparability of study groups, and outcome assessment (for cohort studies) or exposure assessment (for case-control studies). Each domain includes specific evaluation criteria. The assessment outcomes were depicted graphically.

Strategy of data synthesis Meta-analysis of the extracted data from the included cohort and case-control studies was performed using the meta-package in the R Studio software. The effect indicators for both case-control and cohort studies were expressed as odd ratio(OR) and their 95% confidence intervals (CI). If the test of heterogeneity (I^2 50%. The observational studies included in this study came from 11 countries on 4 continents, with large differences in ethnicity and sample size of the study population, and there was large heterogeneity among the trials in this study, which were combined using a random-effects model for the effect values.

Subgroup analysis Odd ratio(OR) and 95% confidence intervals (CI) in emergency cesarean sections and elective cesarean sections.

Sensitivity analysis Sensitivity analyses will be performed using the metainf package in R Studio to explore the source of the high heterogeneity.

Language restriction Yes, only Chinese and English languages were included in the search.

Country(ies) involved China.

Keywords Childhood attention deficit hyperactivity disorder (ADHD); caesarean section; Meta-analysis.

Contributions of each author

Author 1 - Jiali WEI - Writing – Original Draft Preparation: Drafting the initial version of the manuscript. Writing – Review & Editing: Revising and refining the manuscript for intellectual content, clarity, and coherence.

Email: weijiali@aliyun.com

Author 2 - Zehao Zheng -Writing – Original Draft Preparation: Drafting the initial version of the manuscript.Writing – Review & Editing: Revising and refining the manuscript for intellectual content, clarity, and coherence.

Email: zhengzehao0728@163.com

Author 3 - Xue Pan - Data Collection: Gathering and compiling the empirical or theoretical data essential for the study. Analysis: The application of analytical techniques to interpret the collected data or theoretical constructs.

Email: panx1346@126.com

Author 4 - Xinyu Li - Data Collection: Gathering and compiling the empirical or theoretical data essential for the study. Analysis: The application of analytical techniques to interpret the collected data or theoretical constructs.

Email: 1013782947@qq.com

Author 5 - Yue OIU - Visualization: Creating visual representations of data or concepts, such as figures, tables, or graphs. Supervision: Oversight and direction of the research activity, including project administration and coordination.

Email: springqiu@163.com

Author 6 - Mei Han - Funding Acquisition: Securing financial support or resources for the research project.

Email: hanmeizoujin@163.com