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Investigating the association between maternal age and cerebral palsy incidence

A meta-analysis

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Abstract

Background: Cerebral palsy (CP) is a group of nonprogressive motor and postural disorders resulting from early developmental brain injury. While maternal age is a known factor associated with CP risk, previous studies have shown inconsistent findings, particularly regarding advanced maternal age. In addition, earlier meta-analyses often lack stratification by gestational age or do not include recent population-based studies. This meta-analysis aims to provide an updated and more detailed assessment of the association between maternal age at delivery and the risk of CP, using refined age group classifications and subgroup analyses based on gestational age.

Methods: We systematically searched the Embase, PubMed & Medline databases (from inception to March 2024) for English publications; we searched for all published studies comparing the number of cases (CP) and the number of controls according to maternal age. A meta-analysis was performed using R Statistical Software version 4.2.2 (The R Foundation for Statistical Computing). The odds of CP were examined among the maternal ages at delivery of 18 years old or younger, 25 years old or younger, 35 years old or older, or 40 years old or older, with a positive log odds ratio (OR) indicating higher odds of CP.

Results: From 9237 initially identified articles, 12 studies were ultimately included. Young maternal age (≤18 years old) was found to significantly increase the risk of CP (OR = 0.1374, $P < .0001$). The maternal groups defined by the ages of 25 and 35 years showed mixed risks, with term infants from mothers aged 35 years and older having higher odds of CP (OR = 0.9198, $P = .0023$).

Conclusions: CP risk is higher in children born to mothers aged 18 years or younger and may also increase in full-term births to mothers aged 35 years or older. These findings may help guide risk assessment and public health planning.

Abbreviations: CI = confidence interval, CP = cerebral palsy, OR = odds ratio.

Keywords: cerebral palsy, influence, maternal age, odds ratio

1. Introduction

Cerebral palsy (CP) encompasses a spectrum of nonprogressive motor and postural dysfunctions, which are often accompanied by additional neurological symptoms that are indicative of permanent brain damage arising in the early developmental phases.[1] These disabilities are attributed to nonprogressive disturbances that occur in the developing fetal or infant brain. CP is not a specific syndrome but rather a collection of pathologic symptoms that vary both etiologically and clinically. The data in the existing literature show that the rate of CP ranges from 1 to up to 2.4 per 1000 live born children.[2–6] This diversity complicates accurate determinations of its prevalence.

There are a wide variety of factors that influence CP; among them, maternal age has emerged as a significant variable. Advanced maternal age increases the likelihood of obstetric complications, which potentially raises CP risk, while very young maternal age may also amplify risks due to biological immaturity and socio-economic challenges. Many prior studies have investigated the correlations between maternal age and CP.[7–11] However, these studies have shown inconsistent results, thus indicating the need for further research to clarify these relationships.

While previous studies have explored the relationship between maternal age and the incidence of CP, these studies have reported inconsistent findings, particularly regarding the risk posed by advanced maternal age. Moreover, earlier

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This article does not include studies with human participants.

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meta-analyses either lack subgroup analyses stratified by gestational age or are outdated due to the exclusion of recently published population-based studies. Our meta-analysis offers a timely update and includes more detailed age group stratifications – specifically, mothers aged 18 years or younger, 25 years or younger, 35 years or older, and 40 years or older – providing greater granularity than prior works.

Given the importance of understanding how maternal age might affect the incidence of CP, a meta-analysis is warranted. Hence, we categorized previous publications by maternal age and conducted a meta-analysis to investigate their impact on the incidence of CP.

2. Materials and methods

2.1. Data search and study selection

We performed systematic searches of Embase, PubMed & Medline (from inception to March 2024) for publications written in English using keywords such as "CP" and "maternal age"; all searches were limited to human studies. We collected all published studies comparing the number of cases (CP) and the number of controls according to maternal age at delivery. (The PICO criteria used for the literature search are provided in Appendix 1, Supplemental Digital Content, https://links.lww.com/MD/P42). Review articles, abstracts, editorials, and duplicate data were excluded. If more than 1 study was published by the same institution, only the report with the information that was most relevant to this study was included. The quality of the included observational studies was assessed using the Newcastle-Ottawa Scale (NOS), which evaluates studies based on 3 domains: selection of study groups, comparability of groups, and ascertainment of either the exposure or outcome. The searches were performed by 2 authors who screened the studies independently, and any discrepancies were resolved by reaching a consensus.

2.2. Data extraction and statistical analysis

Data were independently extracted from the publications by 2 reviewers, and the following information was recorded: the number of cases, the number of controls according to maternal age at delivery (18 years or younger, 25 years or younger, 35 years or older, and 40 years or older), year of publication, and country. The effect size was defined as a log-transformed odds ratio (OR) with 95% confidence intervals (CIs). Therefore, a positive log OR indicates that the odds of CP were higher among the groups defined by maternal ages at delivery of 18 years or younger, 25 years or younger, 35 years or older, or 40 years or older. Heterogeneity among the studies was assessed using the I^2 statistics.[12] An I^2 value >50% was considered to be indicative of substantial heterogeneity. When heterogeneity was observed, pooled analysis was performed based on the random-effects model; when heterogeneity was not observed, pooled analysis was conducted based on the fixed-effect model. Publication bias was assessed visually using funnel plots and statistically using Egger regression test. Statistical analyses were performed using R Statistical Software version 4.2.2 (The R Foundation for Statistical Computing).

3. Results

3.1. Study characteristics

The electronic search initially identified 9237 articles. Non-English studies (n = 471), conference abstracts (n = 2946), and nonhuman studies (n = 422) were excluded. Another 5300 studies that did not meet the inclusion criteria based on their titles and abstracts were excluded. After reviewing the full text of the remaining 98 articles, 12 studies were found to be eligible for inclusion.[9,11,13–22] Based on the NOS assessment, the majority of studies were of moderate to high quality, with most scoring between 6 and 8 stars (Table S1, Supplemental Digital Content, https://links.lww.com/MD/P43). The detailed procedure for inclusion is illustrated in Figure 1, while the study characteristics are summarized in Table 1.

3.2. Influence of maternal age on the incidence of cerebral palsy in offspring

3.2.1. Maternal age at delivery of 18 years or younger. Five studies reported the number of cases and the number of controls with the maternal age at delivery of 18 years or you nger.[9,11,15,18,19] The pooled OR was 0.1374 (95% CI = 0.0685–0.2062; $P < .0001$, $I^2 = 0\%$), indicating that the odds of CP were higher at the maternal age at delivery of 18 years and younger (Fig. 2). Visual inspection of the funnel plot and Egger regression test was not statistically significant ($P = .1694$) (Fig. S1, Supplemental Digital Content, https://links.lww.com/MD/P44).

3.2.2. Maternal age at delivery of 25 years or younger. Five studies reported the number of cases and the number of controls with the maternal age at delivery of 25 years or younger.[14,17,19–21] The pooled OR was 0.2947 (95% CI = −0.1322 to 0.7216; $P = .1760$, $I^2 = 98.2\%$) (Fig. 3). Publication bias was assessed visually using funnel plots and statistically using Egger regression test ($P = .4722$) (Fig. S1, Supplemental Digital Content, https://links.lww.com/MD/P44).

3.2.3. Maternal age at delivery of 35 years or older. Eleven studies reported the number of cases and the number of controls with the maternal age at delivery of 35 years or older.[9,11,13,14,16–22] The pooled OR was 0.3060 (95% CI = −0.0386 to 0.6505; $P = .0818$, $I^2 = 98.2\%$) (Fig. 4). In a subgroup analysis of studies with term infants, the pooled OR was 0.9198 (95% CI = 0.3296 to 1.5101; $P = .0023$, $I^2 = 58.7\%$), indicating that the odds of CP were higher in the maternal age at delivery of 35 years or older. Publication bias was assessed visually using funnel plots and statistically using Egger regression test ($P = .5166$) (Fig. S1, Supplemental Digital Content, https://links.lww.com/MD/P44).

3.2.4. Maternal age at delivery of 40 years or older. Four studies reported the number of cases and the number of controls with the maternal age at delivery of 40 years or older.[15,19,20,22] The pooled OR was 0.7134 (95% CI = −0.1064 to 1.5333; $P = .0881$, $I^2 = 99.1\%$). Publication bias was assessed visually using funnel plots and statistically using Egger regression test ($P = .1877$) (Fig. S1, Supplemental Digital Content, https://links.lww.com/MD/P44).

4. Discussion

CP comprises a set of nonprogressive motor dysfunction syndromes that are attributed to early developmental brain lesions.[1,23] Epidemiologically, the incidence of CP ranges from 1.0 to 2.4 per 1000 live births.[2–6] These conditions are caused by anomalies or injuries to the developing brain, which typically manifest before, during, or shortly after birth.[1] While the manifestations of CP vary significantly among individuals, common symptoms include spasticity, difficulties with coordination, and motor skills deficits. There are many cases in which the causative factors behind CP remain unidentified. Although symptoms may change over time, the underlying disorder does not worsen.[1] The pathophysiology of CP is complex and multifactorial, and it involves genetic, developmental, metabolic, and environmental factors. Considerable progress has been made in identifying the potential causes and underlying mechanisms of CP, although it is still characterized by a wide range of etiological factors. Both prenatal and perinatal influences are crucial in the pathogenesis

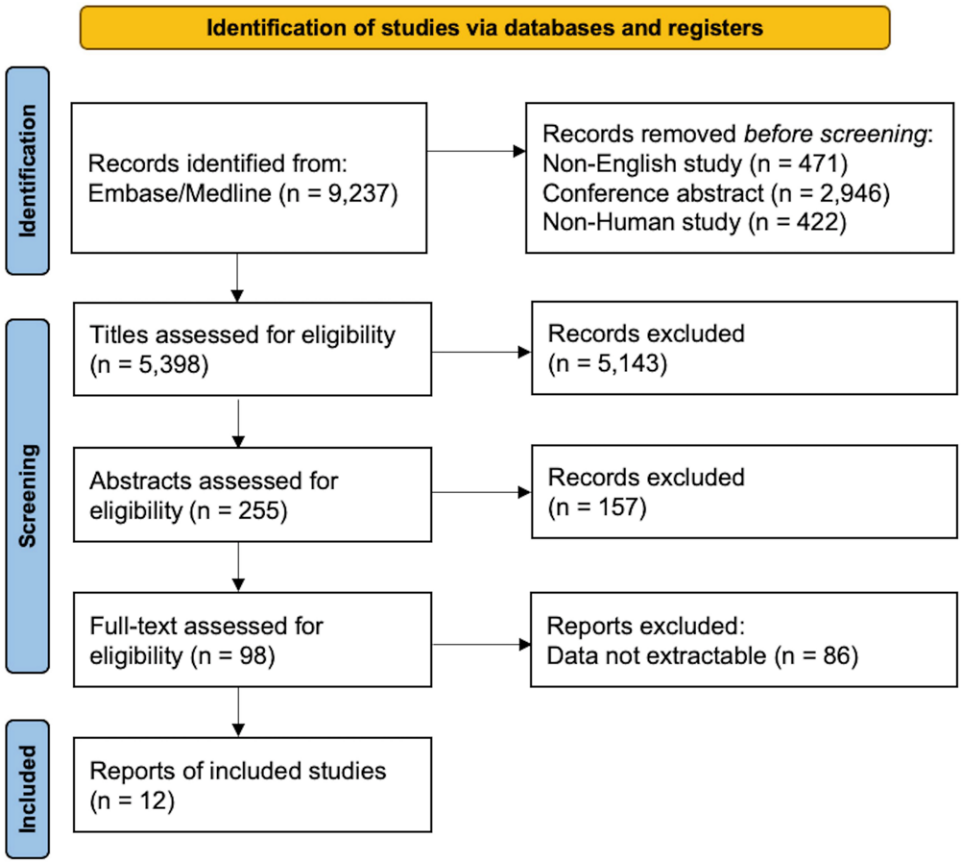

Figure 1. Flowchart for the inclusion of studies in this meta-analysis.

Table 1

Studies included in the meta-analysis.

Author	Year of publication	Country	Gestational age	Cutoffs of maternal age at birth (years old)	No. of CP	No. of controls
Nabors	1963	USA		35	382	89,203
Petridou	1996	Greece	Preterm and Term	25, 35	103	254
Wu	2006	USA	Term	18, 35	377	326,005
Moster	2010	Norway	Term	18, 40	1938	1,680,503
Soleimani	2013	Iran	Term	18, 35	53	106
Monokwane	2017	Botswana	Preterm and Term	35	56	56
Xiang	2021	China	Term	25, 35	109	327
Gincota	2021	Moldova	Preterm and Term	18, 35	351	417
Zhou	2023	USA	Preterm and Term	18, 25, 35, 40	8736	90,250
Ahmed	2023	Canada	Preterm and Term	25, 35, 40	5317	2,104,860
Aubert	2023	Europe	Preterm	25, 35	108	339
Chen	2024	Taiwan	Preterm and Term	35, 40	3254	1,237,509

Abbreviation: CP = cerebral palsy.

of CP. Moreover, specific prenatal risk factors may predispose infants to acute brain injuries during labor and delivery, thus underscoring the complex interplay of conditions that contribute to the development of CP.

Among the risk factors that have been identified for CP, maternal age has emerged as a significant determinant. The influence of maternal age on the incidence of CP in offspring is an area seeing increased research, drawing considerable interest and concern. Previous studies have indicated that both very young and advanced maternal ages may increase the risk of CP, which could potentially be due to a combination of biological and socio-economic factors impacting pregnancy outcomes.[7–11] Specifically, advanced maternal age is associated with a higher incidence of obstetric complications, which are believed to augment the likelihood of CP.[5] These complications may stem from physiological changes in older pregnant individuals that adversely affect fetal development. These associations may imply that physiological alterations in older pregnant women might create conditions that are favorable for the development of neurological impairments in the fetus. Conversely, very young maternal ages also introduce additional risks, which are often associated with biological immaturity and socio-economic challenges, which can in turn negatively affect pregnancy outcomes, and subsequently, child development.

The biological mechanisms through which maternal age impact CP risk may involve both direct and indirect pathways. Direct effects could include the physiological changes in older mothers that influence placental function and fetal growth,

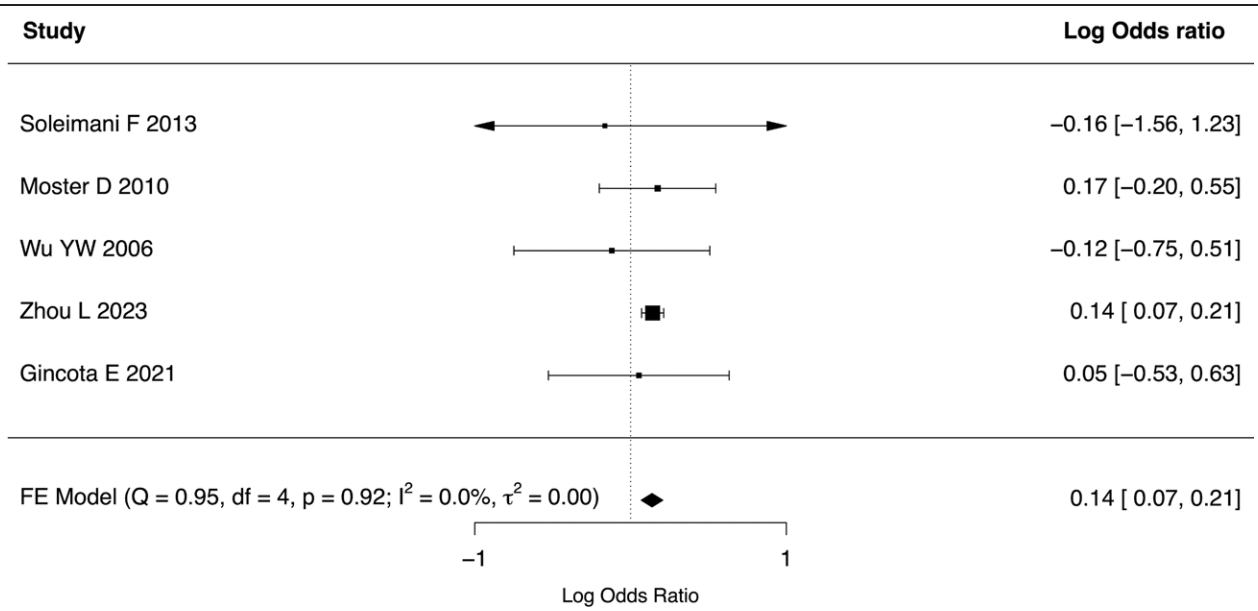

Figure 2. Forest plot of the occurrence of CP according to maternal age of 18 years or younger. CP = cerebral palsy.

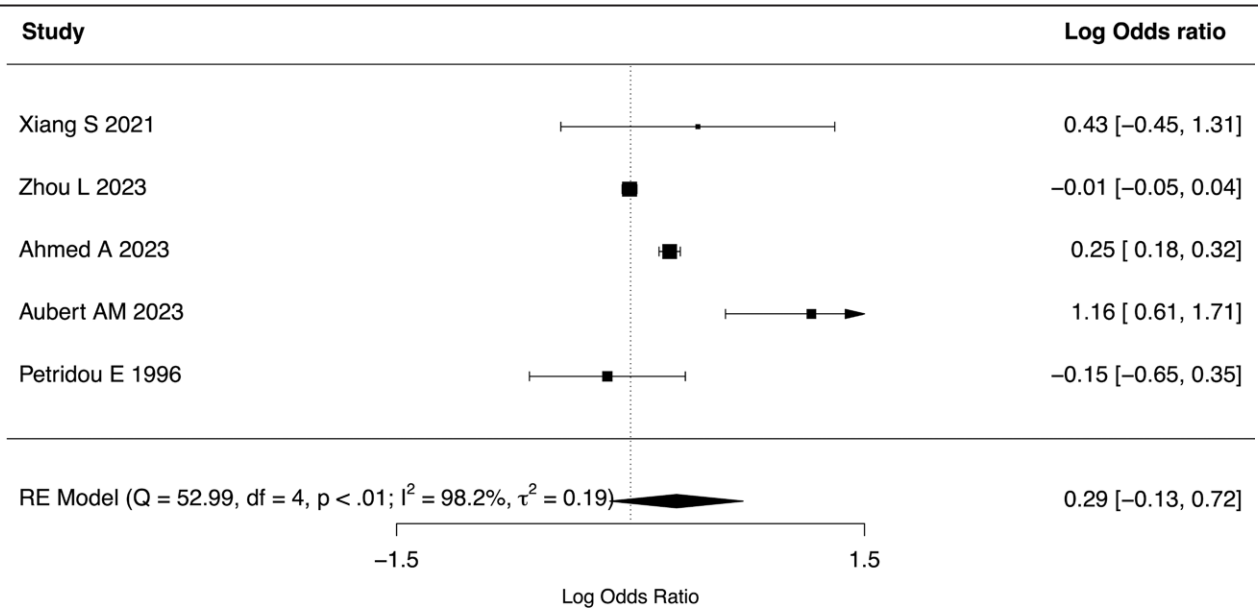

Figure 3. Forest plot of the occurrence of CP according to maternal age of 25 years or younger. CP = cerebral palsy.

while indirect effects partially encompass socio-economic factors, such as access to healthcare, nutritional status, and lifestyle choices. However, the existing literature investigating the impact of maternal age on CP development is characterized by variability, with studies often producing divergent outcomes. This inconsistency likely arises from variations in study designs, population demographics, and research methodologies, thereby underscoring the challenge of isolating age as a singular predictive factor for CP.

Our meta-analysis was designed to investigate the relationship between maternal age and the incidence of CP, with the aim of addressing a notable gap in existing research. This finding aligns with previous studies, but our analysis expands on earlier work by including more granular age subgroups and examining full-term versus preterm deliveries separately, which had not been consistently evaluated before. Furthermore, the use of a comprehensive and updated dataset enables us to provide stronger statistical support for the association between maternal age and the risk of CP. Our findings revealed an increased incidence of CP in offspring born to mothers under the age of 18. This elevated risk likely reflects both biological and socio-economic factors associated with teenage pregnancies, such as nutritional deficiencies and inadequate prenatal care, which can lead to neurological deficits in the developing fetus.[24] Early brain injury associated with CP often results in lifelong disabilities, which cause severe adverse effects and implications for the child as well as their family and broader society.[25] Moreover, our analysis indicated that, although the increase in CP incidence in children of mothers aged 35 to 45 years old was not statistically significant, there was a trend suggestive of a higher risk. This finding is consistent with existing literature that has identified maternal age as a risk factor for various developmental challenges in offspring, potentially due to age-related genetic variations and an increased likelihood of obstetric complications.[26–28] Notably, we observed a significant rise in CP risk among full-term births in mothers

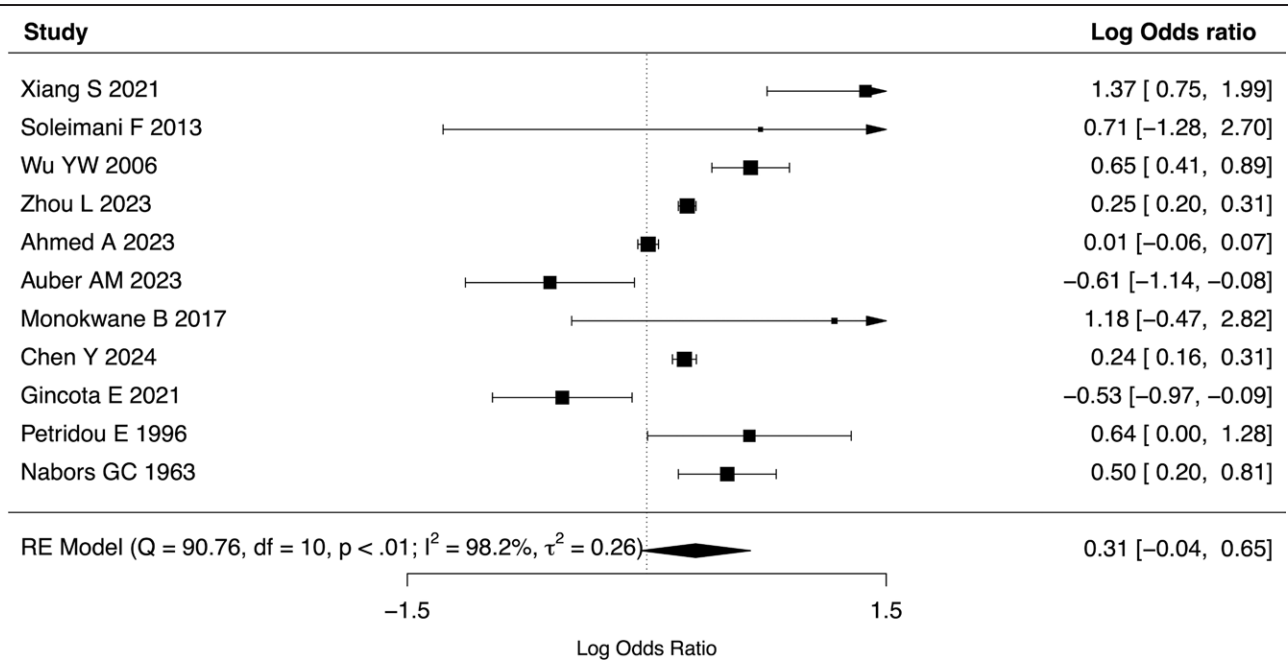

Figure 4. Forest plot of the occurrence of CP according to maternal age of 35 years or older. CP = cerebral palsy.

aged 35 years old or older. This increase may be attributable to more prevalent intrinsic maternal factors such as hypertension and diabetes in this age group, which are known to complicate pregnancy and adversely affect fetal development.[8,9,27,28] Given global trends of increasing maternal age and changing fertility patterns, these results carry relevant public health implications. These insights carry significant implications for clinical practice and public health, ultimately highlighting the necessity for tailored prenatal screening and care protocols for women at both extremes of maternal age. It underscores the importance of comprehensive obstetric monitoring and intervention. Our findings also suggest that public health initiatives should prioritize education and resource provision for both younger and older expectant mothers to mitigate risks associated with adverse neonatal outcomes.

This study has several limitations that should be acknowledged and provide directions for future research. First, the inclusion of only a small number of studies may affect the generalizability of the findings. After systematically searching the literature, various studies were assessed for inclusion. However, many of these studies originated from the same institution and involved overlapping participant groups, thus leading to the selection of only the most pertinent publications from this overlapping cohort for our analysis. Secondly, our research focused exclusively on the influence of maternal age on the incidence of CP in offspring. Our analysis did not consider critical variables such as maternal underlying diseases, which may limit the comprehensiveness of our findings. Further research is needed to explore factors other than maternal age that may contribute to CP. Although our study provides substantial insights into maternal age as a significant risk factor, the results suggest that a broader investigation would be beneficial for fully understanding the range of contributory elements. Consequently, caution must be exercised in interpreting these results, and further studies are warranted to comprehensively assess the impact of maternal age on CP across different maternal age groups.

5. Conclusion

Based on our analysis, the incidence of CP appears to be higher among offspring of mothers at the age of 18 years or younger. In addition, for maternal ages of 35 years and older, there may be an increased risk of CP, particularly in full-term births. These findings may guide public health strategies aimed at reducing the burden of CP and improving outcomes for affected individuals and their families.

Author contributions

Conceptualization: Kyoungjune Pak.
Data curation: Jae Meen Lee, Kyoungjune Pak.
Formal analysis: Kyoungjune Pak.
Writing – original draft: Jae Meen Lee, Kyoungjune Pak.

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