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Long-term health outcomes of children born by cesarean section: A nationwide population-based retrospective cohort study in Taiwan

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ABSTRACT

Background: Taiwan had high cesarean rate which exceeded the recommended threshold (15%), set by WHO. However, there have not a comprehensive study to discuss the long-term offspring consequences of cesarean section (CS). This study aimed to show whether allergy disorders, obesity and respiratory infection of children are associated with modes of delivery, using the National Health Insurance Research Database (NHIRD) of Taiwan.

Methods: This study used the maternal and child health database of NHIRD. We included the children who birth between 2004 and 2013 and inter-linked the database of the mother and children. The participants were followed until 2018/12/31. We performed a Cox proportional hazards model to identify the association of CS with respiratory tract infection, allergy disorder, and obesity diagnosed in childhood.

Results: CS significantly increased the risk of developed childhood asthma (adjusted hazard ratio [aHR] = 1.03; 95% confidence interval [CI]: 1.02–1.03), allergy rhinitis (aHR = 1.04; 95% CI: 1.04–1.05), atopic dermatitis (aHR = 1.05; 95% CI: 1.04–1.06), respiratory tract infection (aHR = 1.07; 95% CI: 1.06–1.07) and overweight (aHR = 1.29; 95% CI: 1.18–1.40) even after adjusting with confounding factor. Development of food allergy (aHR = 1.13; 95% CI: 0.87–1.47) was not associated with cesarean section.

Conclusion: This study indicated that children delivered by CS more commonly developed respiratory tract infections, asthma, allergic rhinitis, atopic dermatitis, obesity than children delivered vaginally. Among these, obesity have a stronger association with cesarean section.

1. Introduction

Vaginal delivery (VD) is a physiological process that is more common and safest for childbirth. However, in certain circumstances, a cesarean section (CS) can be a life-saving intervention during pregnancy and childbirth that should be universally accessible. According to the World Health Organization (WHO) recommendations, the optimal rate for CS should range between 10 and 15% [1]. The rates of CS have increased beyond 15% in many countries all over the world. Recent research from the WHO showed CS rates have been rising since 1990, now accounting for over 1 in 5 (21%) of all childbirths, with averages ranging from 5% in sub-Saharan Africa to 42.8% in Latin America and the Caribbean [2]. This increased use of CS was majorly caused by increases in elective CS with non-medically indication in many middle-income and high-income countries. The fear of pain during birth, the convenience of scheduling the birth, and because CS can be perceived as being less traumatic for the baby, are more and more commonly leading to women choosing to deliver by CS.

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When medically necessary, a CS can effectively prevent maternal and newborn mortality, and also reduce newborn morbidities, such as intrapartum asphyxia, shoulder dystocia, and fractures. However, CS rates higher than 10% are not associated with reductions in maternal and newborn mortality rates [1]. Moreover, in recent years, concerns have been raised about the potential long-term effects of CS on the health of offspring [3]. Numerous evidence demonstrated that children delivered by CS would increase the risk of developing the respiratory disease [4–6], neurological disorders [3,7], immune-related diseases [8–10], and obesity [11,12] during childhood.

Taiwan has the high rate of CS. According to data from the Health Promotion Administration, Ministry of Health and Welfare of Taiwan, the CS rate in the past 2 decades has risen from 33% to 35–38%, which exceeded the recommended threshold (15%), set by WHO. Despite its high cesarean rate, there was limited study [13] that investigated the pediatric consequences of CS. Moreover, to our knowledge, there was no nationwide, population-based, matched cohort study to clarify the link between delivery mode and children's chronic health conditions. Therefore, we used the data of the National Health Insurance Research Database (NHIRD) of Taiwan to demonstrate whether allergy disease, respiratory tract infection, and obesity are associated with modes of delivery after controlling for potential confounding factors.

2. Methods

2.1. Data source and ethics

This was a retrospective cohort study. We obtained the data from the Taiwan Maternal and Child Health Database (TMCHD) of the National Health Insurance Research Database (NHIRD) established by the National Health Research Institute (NHRI). The National Health Insurance (NHI) program was launched in 1995, and currently covers over 99% of the population, approximately 23 million people in Taiwan [14]. The NHIRD, derived from claims data of NHI beneficiaries, contains comprehensive information, including demographic characteristics, prescription drugs, medication, and diagnostic procedures. It can thus illuminate the disease burden and health care process of the entire Taiwanese population. The diagnosis in NHIRD was recorded with using the International Classification of Diseases, Ninth Edition, Clinical Modification (ICD-9-CM) before 2016, and the Tenth Edition (ICD-10) has been used since 2016 [14].

TMCHD was derived from the NHIRD, Taiwan Birth Registration Database (BRD), and Birth Certificate Application (BCA) [15]. It interlinked the medical records of offspring and their parents. The TMCHD contained the information derived from inpatient/outpatient claims of all infants born since 2004, including birth weight, gestational age, single/multiple births, maternal smoking, maternal alcohol consumption, and newborn Apgar scores [15]. The medical records of parents retrieved from the NHIRD were also incorporated in separate files of the database.

This study was approved by the Research Ethics Committee of the Chang Gung Medical Foundation (IRB number: 202000880B0).

2.2. Study population and covariates

We identified all the infants born between January 1, 2004, and December 31, 2013, from TMCHD. The recruited infants were distinguished into two cohorts, children with CS and children with VD. The demographic characteristics of infants were recorded, including birth body weight, gestational age, and sex.

We interlinked the maternal medical records to obtain information on maternal underlying immune disorders and pregnancy complications that might affect the offspring's health condition. The maternal immune disorders were listed as below: asthma, allergy rhinitis, and atopic dermatitis. We considered the following pregnancy complications in this study: gestational diabetes mellitus, hypertension of pregnancy, pre-eclampsia, eclampsia, and preterm premature rupture of membrane.

Besides, if the participants had been diagnosed with neonatal sepsis after birth will also be recorded as a covariate factor for antibiotics' influence on bacteria in the intestine. The ICD code of covariate factor was recorded in supplement file 1.

2.3. Study outcome

All the participants in this study were followed from birth until December 31, 2018. The children were at least 5 years old at the endpoint of this study. We inspected whether the participant had been diagnosed with asthma, allergic rhinitis, atopic dermatitis, food allergy, respiratory tract infection, or childhood overweight during this period, if they have received at least three outpatient diagnoses or one inpatient diagnosis. The ICD code of study outcome was as supplement file 2.

2.4. Statistical analyses

In this study, we recorded continuous variables values as the mean with standard deviation. Independent *t*-test was used to compare continuous variables between children delivered by CS and by VD. For categorical variables, data was expressed as frequency with proportion. To estimate the difference between the two groups, Pearson's $\chi 2$ test was applied to compare categorical variables. We used The Cox proportional hazards regression model to determine the risk of allergy disease, respiratory infection, and obesity in children delivered by CS and by VD. All analysis was adjusted for maternal age at childbirth, maternal physical diseases, pregnancy complications, and child demographics. We used adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) to certify the risk and statistical significance of differences in incidence rates of allergy disease, respiratory infection, and obesity of offspring.

Table 1
Demographics and birth conditions, maternal covariates, and long-term outcome of children delivered by CS and by VD.

Variables	Children delivered by CS (n = 675,718)	Children delivered by VD (n = 1,208,983)	p-value
Child demographics and birth conditions			
AGE (years), mean (SD)	10.0 ± 2.9	10.1 ± 2.9	
Sex, *n* (%)			
Male	358549 (53.1)	624159 (51.6)	
Female	317169 (46.9)	584824 (48.4)	
Gestational age (weeks), mean (SD)	37.8 ± 1.9	38.6 ± 1.6	
Weight (g), mean (SD)	3039.0 ± 535.7	3093.8 ± 414.7	
Neonatal sepsis, *n* (%)	43303 (6.4)	82766 (6.8)	
Maternal covariates			
Age of childbirth (years), mean (SD)	31.1 ± 4.8	29.5 ± 4.7	
Gestational diabetes mellitus, *n* (%)	126084 (18.7)	158522 (13.1)	
Pre-eclampsia, *n* (%)	42722 (6.3)	25906 (2.1)	
Preterm premature rupture of membrane, *n* (%)	69609 (10.3)	115702 (9.6)	
Food allergy, *n* (%)	119 (0.02)	136 (0.01)	
Asthma, *n* (%)	47792 (7.1)	69298 (5.7)	
Allergy rhinitis, *n* (%)	179134 (26.5)	294676 (24.4)	
Atopic dermatitis, *n* (%)	30006 (4.4)	49974 (4.1)	
Child Outcomes			
Food allergy	105 (0.02)	153 (0.01)	<0.001
Asthma	168480 (24.9)	281059 (23.2)	<0.001
Allergy rhinitis	263052 (38.9)	442339 (36.6)	<0.001
Atopic dermatitis	136502 (20.2)	226741 (18.8)	<0.001
Respiratory tract infection	643098 (95.2)	1147220 (94.9)	<0.001
Overweight	991 (0.1)	1343 (0.1)	<0.001

Note. Abbreviations: CS = cesarean section; VD = vaginal delivery.

3. Result

Table 1 presents the child demographic, maternal covariate, and long-term health outcomes for the offspring birth with cesarean section and the matched controls. A total of 1,884,701 child births between 2004 and 2013 were recruited into this study. The cesarean section rate was 35.9% (675718 children). The mean gestational age of both cohorts was 37.8 weeks and 38.6 weeks, respectively. The children were all followed until 10 ± 2.9 years old. Male sex was slightly predominance in both cohorts (Cesarean section group: 53.1%, vaginal delivery group: 51.6%). The prevalence of allergy disease (food allergy, asthma, allergic rhinitis, and atopic dermatitis), respiratory tract infection, and overweight were higher in the cesarean section group (P value < 0.001).

Table 2 showed the adjusted hazard ratio which was conducted with controlling for maternal age of childbirth, mother's diseases (including food allergy, asthma, allergy rhinitis, atopic dermatitis), pregnancy complications (gestational diabetes mellitus, pre-eclampsia, premature rupture of membrane), neonatal infection and child demographics (i.e., birth weight, gestational age, and sex). Children delivered via CS were found to have a higher risk of asthma (adjusted hazard ratio [aHR] = 1.03; 95% confidence interval [CI]: 1.02–1.03), allergy rhinitis (aHR = 1.04; 95% CI: 1.04–1.05), atopic dermatitis (aHR = 1.05; 95% CI: 1.04–1.06), respiratory tract infection (aHR = 1.07; 95% CI: 1.06–1.07) and overweight (aHR = 1.29; 95% CI: 1.18–1.40) than children delivered vaginally. No association was found between the delivery mode with food allergy (aHR = 1.13; 95% CI: 0.87–1.47).

4. Discussion

This population-based cohort study in Taiwan demonstrated that children delivered by CS had significantly higher risks of asthma, allergic rhinitis, atopic dermatitis, respiratory tract infection, and obesity than those delivered by VD. Among these conditions, obesity later in life has stronger associations with cesarean section.

4.1. Hypothetical mechanisms of the influence of cesarean section on neonatal status

The precise reason for this observed association is currently unclear, however, several mechanisms to explain how mode of delivery could affect offspring outcomes have been proposed.

First, the hygiene hypothesis provides one possible mechanism, in which the delivery mode alters the initial gut microbiota composition [3]. Newborns delivered vaginally are exposed to maternal vaginal and fecal microbiota, which lead to optimal gut colonization with Lactobacillus, Bifidobacterium and Bacteroides, however, newborns born through CS, being exposed to maternal skin microbiota and external environment bacteria [3]. The initial gut colonization plays an important role in the regulation of the immune system [16]. The disturbance of normal colonization had been postulated to alter immune development and increased susceptibility to allergy disease [17]. The gut microbiota composition may also affect host metabolism and energy storage and usage which can affect the development of obesity [18]. In addition, Bifidobacteria and Bacteroides, both were reported to be protective factors against later obesity [19]. Therefore, similarly antibiotic administration in the early life of infant may alter the balance and composition of the microbiome and thus further affect the maturation of the immune system and adiposity [20].

Second, newborn born via CS had reduced exposure to mechanical forces and elevated stress hormone and cytokine which was thought to be crucial for the development of immune system and pulmonary maturity [3]. A Taiwan study found that the pro-inflammatory cytokine of children born via CS responds to TLR1-2 stimulation was significant reduced, thus increasing the risk of infantile wheezing [21]. Studies propose that lower levels of maternal and fetal corticosteroids in CS, may cause metabolic disturbance at birth and future obesity [22].

Third, numerous studies have reported that CS had lower rates of infants' breastfeeding, late initiation of breastfeeding [23], or even caused reduced breast milk production [24]. Breastfeeding has been identified as a protective factor for childhood obesity in many studies [25]. Exclusive breastfeeding was also thought to be associated with decreased childhood asthma [26].

Lastly, a hypothesis postulated that different methods of birth might alter epigenetic modification of gene expression which further affects future infant health [27]. A study found increased global DNA methylation in leukocytes obtained from umbilical cord blood of elective CS newborns compared with those born vaginally [28], however, another study showed lower global DNA methylation in the placenta of CS women [29]. 2012 study found no difference in the global DNA methylation between different methods of birth [30]. This difference in results might contribute to the variety of methodologies. Thus, this hypothesis has yet to be fully verified, and further studies on this topic are needed.

Table 2
Risks of diseases in children delivered by CS and by VD.

Model	aHR
Food allergy	1.13 (0.87–1.47)
Asthma	1.03 (1.02–1.03)
Allergy rhinitis	1.04 (1.04–1.05)
Atopic dermatitis	1.05 (1.04–1.06)
Respiratory tract infection	1.07 (1.06–1.07)
Overweight	1.29 (1.18–1.40)

Note. Abbreviations: aHR = adjusted hazard ratio; CS = cesarean section; VD = vaginal delivery.
The adjusted hazard ratio was calculated after controlling for maternal age at childbirth, maternal diseases (i.e., food allergy, asthma, allergic rhinitis, atopic dermatitis, gestational diabetes mellitus, preeclampsia, and preterm premature rupture of membrane), and child demographic factors (i.e., gestational age, gender, birth weight, and neonatal sepsis).

4.2. Cesarean section and childhood overweight/obesity

In 2020, an estimated 5.7% or 38.9 million children under 5 around the world were affected by overweight, and almost half of them were in Asia [31]. In this large cohort study of the Taiwan population, cesarean birth was associated with a higher risk of childhood overweight/obesity, even after adjusting for confounding factors, such as maternal immune disorder, pregnancy complications, and child demographic. Our finding is compatible with several previous studies conducted globally [11,12]. Of particular, a meta-analysis in 2015 that summarized data from twenty-four studies concluded that children born by CS have a 34% higher risk of developing obesity in childhood [32].

Maternal pre-pregnancy BMI is a possible predictor of childhood overweight/obesity which was not included as a confounding factor in this study. A German study found no significant increased risk of obesity among children at 6 (n = 1244, OR, 1.49, 95% CI, 0.55–4.05) or 10 years of age (n = 1170, OR, 1.16, 95% CI, 0.59–2.29) born through CS after adjusting for maternal pre-pregnancy BMI [33]. However, in a prospective cohort study with a larger sample size which included 22,068 individuals, found that Cesarean birth was associated with higher risk of obesity (RR = 1.30, 95% CI: 1.21–1.41). Although the association attenuated after adjustment for maternal pre-pregnancy BMI, it remained statistically significant (RR 1.15,95% CI: 1.06, 1.26; p = 0.002) [34]. Thus, we think that association of CS with childhood overweight/obesity is robust even though we did not adjust with maternal pre-pregnancy BMI.

Similar concerns arise regarding the endpoint of obesity. Childhood obesity tends to fluctuate during the growing process and is not necessarily an irreversible condition. However, we believe our results remain significant when comparing the two groups under the same background.

Additionally, based on the literature we have reviewed, most original studies investigating the association between cesarean section and childhood obesity also defined the outcome as children being diagnosed with obesity/overweight within a certain age range, similar to our study. While obesity can fluctuate during childhood, an increasing body of literature indicates that childhood obesity tends to persist into adulthood. For instance, Rundle et al. (2020) [35] found that experiencing obesity at age 5 was associated with significantly higher BMI, fat mass index, and lean mass index at around age 50 [35].

4.3. Cesarean section and immune-mediated disorder

Among the long-term outcome of children, the association of CS with asthma had always been a concern. Several epidemiological studies of different regions have investigated the risk of developing asthma among children delivered via CS, but the result was controversial in different regions. However, our result was consistent with few meta-analyses that we knew [3,36]. A systematic review and meta-analysis conducted in 2019 which included 37 studies with about 5 million samples worldwide found that children delivered via CS (elective and emergency) had a significantly higher risk of childhood asthma with a RR of 1.20 (95 CI 1.15–1.25) compared with those delivered vaginally [36]. In Taiwan, a population-based study investigated the impact of prenatal factor on childhood allergic diseases and found that CS were one of the prenatal risk factors for childhood asthma (aOR 1.10, 95% CI 1.08–1.13) [37].

In our study, food allergy is the only one allergy disorder that was not significantly increased with the cesarean section. This result is consistent with Currell et al., 2022 [38], which found no convincing evidence that CS increased the risk of developing food allergy in children. However, a systemic review and meta-analysis of cohort study in 2023 suggests that CS was associated with an increased risk of food and cow's milk allergies in children aged 0–3 years [9]. We believed that we may have underestimated the prevalence of food allergy in this study. According to a nationwide, random questionnaire-based survey in 2012 [39], the prevalence of food allergy in Taiwan was 3.44% in children under 3 years of age and 7.65% in children aged 4–18 years, but the percentage of food allergy in our study was only 0.02% in CS group and 0.01% in VD group. This underestimation might be due to the difficult definite diagnosis of food allergy (Food challenge is seldom done in Taiwan). In addition, food allergy patients might be diagnosed with other diagnosis codes, especially the clinical manifestations of food allergy, such as urticaria, gastrointestinal symptoms, or anaphylaxis reaction.

We found that allergic rhinitis and atopic dermatitis also slightly increased risk in offspring born via CS. This result is also consistent with some studies [8,10] and is different from others [8,40]. The heterogeneity of results could be owing to several factors, such as differences in methodology, type of study structure, ages of children examined, as well as a limited statistical significance because of small sample sizes of some study. In addition, it is possible that the relationship between CS and allergies differs in different communities and countries, because of the differences of socioeconomic and medical resource accessibility. However, this study collected data during the period of Taiwan's National Health Insurance (NHI). Under the NHI, nearly everyone in Taiwan has high healthcare accessibility regardless of wealth status. Therefore, we believe that all individuals in our study had access to similar medical care.

4.4. Cesarean section and respiratory tract infection of offspring

To our knowledge, this is the first study to investigate the relevance of CS and respiratory tract infection of offspring in Taiwan. In this study, we found that cesarean section significantly increased the risk of respiratory tract infection of offspring. Several large population cohort studies also demonstrated that CS especially elective CS was associated with an elevated risk of respiratory syncytial virus infection [6], bronchiolitis [5], and infection-related hospitalization [4]. A systemic review and meta-analysis were conducted based on 3 studies found that children of CS delivery had a higher rate of respiratory tract infections during childhood compared with those born vaginally [3]. As we know, children are highly susceptible to respiratory diseases and frequently seek outpatient care for these conditions, particularly in Taiwan, where medical resources are readily accessible. Our study found that a significant majority of children, regardless of delivery mode, had outpatient visits for respiratory illnesses, with the visit rate reaching up to 95%. Despite the high incidence rates in both groups, our findings remain meaningful. By controlling for various influencing factors and including a sufficient number of samples, we conducted comparisons under consistent conditions. The results indicate that children born via cesarean section are more prone to respiratory diseases compared to those born via natural delivery.

4.5. Association of CS and offspring outcome study in Taiwan

Before this study, to our knowledge, there was limited research on the association of mode of delivery with offspring outcome in Taiwan [13]. Chen et al. enrolled 19721 children (cohort CS rate: 33.2%) from the Taiwan Birth Cohort Study (TBCS) to investigate whether neurodevelopmental disorders, asthma, and obesity are associated with modes of delivery. The study found that CS birth was associated with childhood obesity which was consistent with our result, despite its different methodology and confounding factors controlling. However, asthma was only weakly associated with CS, and the effect attenuated after further controlling for GA and parental history of asthma. Another population-based study in Taiwan by Lin et al. [37] investigated the impact of prenatal factors on childhood allergic diseases. The authors highlighted the shared prenatal impact among these allergic diseases. In our study, childhood asthma was associated with CS, even after controlled with GA of children and maternal history of asthma. This discrepancy in result could be attributed to the difference of determination of asthma diagnosis. Our study relied on clinical diagnosis, while the study conducted by Chen et al. was based on parental questionnaire responses. Besides, we think that our result might be more appropriate as we had larger sample sizes, and this is a population-based study of Taiwan.

4.6. Strength and limitations

The major strength of our study is that we analyzed a large and comprehensive nationwide database, including both maternal and offspring's data, with a long follow-up period. Besides, the results had been controlled for multiple maternal and child factors which might influence the offspring outcome.

However, this study has some limitations that have to be noticed. First, we lack information on indications for cesarean delivery. In this study, we did not distinguish between elective and emergency cesarean delivery as the circumstances for each are different and may affect the risk of offspring outcome differently. Second, our dataset does not contain information on some potential confounding factors such as paternal history, socioeconomic history, environmental exposures, and breastfeeding which may also affect the relationship of CS and offspring outcome and these factors should be taken into account in future studies. Third, some may suggest that counting events of respiratory tract infection would be more suitable for statistical analysis. However, due to the nature of our database, we do not have access to the exact count of these infection occurrences. This limitation prevents us from employing event counting as suggested. Consequently, we have continued with our current methodology for the analysis. At last, the diagnostic accuracy of childhood outcomes was registered based on the national health insurance (NHI) database, and we did not attempt to validate the diagnostic coding, making potential misjudging of results inevitable. However, the Bureau of NHI randomly cross-checks medical records in all medical institutions to reduce error codes and misclassification bias.

5. Conclusion

Our results revealed that CS birth is associated with higher risk of asthma, allergic rhinitis, atopic dermatitis, respiratory tract infection, and obesity in offspring than those delivered by VD. Among these, obesity has stronger association with CS. Although this association was modest, considering the increasing rate of cesarean section in Taiwan, especially elective CS, this modest increase in risks in this study may also translate into a substantial excess burden of morbidity and need to be noticed.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jfma.2024.09.024.

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