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Mode of delivery and childhood hospitalizations for asthma and other wheezing disorders

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Mode of delivery and hospitalizations for childhood wheezing disorders

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ABSTRACT

Background

Observationally, delivery by Caesarean section is associated with higher risk of childhood asthma and wheeze in developed Western settings, but associations are less consistent in other settings.

Objective

To examine the association of mode of delivery with hospitalizations for asthma and other wheezing disorders in a developed non-Western setting with high rates of Caesarean section.

Methods

Using Cox regression, we examined the adjusted association of mode of delivery with public hospital admissions for asthma, bronchitis and bronchiolitis (International Classification of Diseases, Ninth Version Clinical Modification 466, 490 and 493) from 9 days to 12 years of age in a population-representative prospective birth cohort of 8327 Chinese children in Hong Kong. Confounders included sex, birth and parental characteristics, and socioeconomic position (SEP).

Results

Delivery by Caesarean section accounted for 27% of all births, and was not clearly associated with hospitalizations for asthma and other wheezing disorders to 12 years [hazard ratio (HR) 1.11, 95% confidence interval (CI) 0.91 to 1.36] compared to vaginal delivery. Similarly, there were no clear associations to 2 years (HR 1.07, 95% CI 0.83 to

1.38) or 6 years (HR 1.12, 95% CI 0.91 to 1.37), although we cannot rule out residual confounding by SEP.

Conclusions and Clinical Relevance

We cannot rule out an association, but our findings suggest that the observed associations of delivery by Caesarean section with childhood wheezing disorders may vary with setting and may not be biologically mediated. Further studies with different designs are needed to clarify the role of the microbiome and mode of delivery in the aetiology of asthma and other childhood wheezing disorders.

Keywords

Asthma, Caesarean section, children, cohort study, delivery, wheeze

INTRODUCTION

Asthma is one of the most common chronic diseases in children (1). The aetiology of childhood wheezing disorders is poorly understood, but early life exposures are thought to influence the infant's immune profile, thereby affecting future risk of asthma and wheeze (2). Increasing evidence suggests that indigenous microbiota in the human gut and airways may influence the risk of childhood asthma (3, 4). Bacterial communities vary widely across different body sites and time (5). The microbiome of infants born by Caesarean section differs from that of infants born vaginally, both in composition and timing of colonization (6). Infants delivered by Caesarean section have less bifidobacteria and Bacteroides but more *Clostridium difficile* in their gut, compared to infants delivered vaginally (7). *Clostridium* in the gut have also recently been linked to allergies (8). Additionally, Caesarean section may be associated with higher DNA

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methylation in the infant, which may mediate the association of mode of delivery with childhood wheezing disorders (9, 10).

Systematic reviews and meta-analyses of observational studies in developed Western settings show higher risk of asthma and wheeze in children born by Caesarean section than children born vaginally (11, 12). Contrary to such observations, more recent studies from other settings have found no association despite relatively high rates of Caesarean section (13-15). These inconsistent findings may be due to varying ages at which wheeze is assessed (12), different socioeconomic patterning of mode of delivery and wheezing disorders (16), the underlying indications for Caesarean section (9), and/or different microbiota across settings. The immune system undergoes rapid development and the diagnosis of asthma is less reliable in the first few years of life (17, 18), which may give rise to different results by age. Further, observed associations in Western settings may be confounded by socioeconomic position (SEP), because delivery by Caesarean section is associated with higher SEP (16), and childhood wheeze with lower SEP (19). Given that randomized controlled trials may not be feasible due to ethical and practical concerns (20), there is a need to test associations in other settings.

Hong Kong is a developed non-Western setting with a high rate of Caesarean section (21), relative to other developed settings such as North America or Western Europe (22). Caesarean section is associated with higher socioeconomic position (SEP) and is more common in private hospitals in Hong Kong, where it is frequently elective (23). Here we took advantage of a large population-representative birth cohort to examine prospectively the adjusted association of mode of delivery with public hospital admissions for asthma, bronchitis and bronchiolitis to 12 years of age.

METHODS

Sources of data

The “Children of 1997” is a population-representative Chinese birth cohort (n=8327), covering 88% of all births in Hong Kong from 1 April 1997 to 31 May 1997, described in detail elsewhere (24). This study was initially designed to examine the effects of second-hand smoke exposure and breastfeeding on infant health services utilization (25, 26). Mother-infant pairs were recruited at the first post-natal visit to any of the 49 government-run Maternal and Child Health Centres in Hong Kong, where parents of all newborns are encouraged to attend for free preventive care and vaccinations. Baseline characteristics obtained at recruitment included infant characteristics (mode of delivery, type of hospital at birth, sex, gestational age, birth weight, and birth order), parental characteristics (mother’s age at birth, mother’s place of birth, and parental history of allergies) and SEP (highest parental education), using a standardized, self-administered questionnaire in Chinese completed by the primary caregiver (most commonly mothers). Follow-up questionnaires were administered at 3, 9 and 18 months. In 2005, hospital discharge data were obtained by record linkage from the Hospital Authority. In 2007, a program was instituted to re-establish direct contact with the birth cohort families, and three postal surveys were conducted between 2008 and 2012. Any missing baseline data were updated with each wave of data collection and any discrepancies between waves reconciled.

Hospital discharge data to age 12 years were obtained from the Hospital Authority, which oversees all public hospitals and provides in-patient services accounting for about 90% of total bed days and 77% of all admissions in Hong Kong (27, 28). All Hong Kong citizens are entitled to public healthcare with minimal out-of-pocket payments as the government subsidizes 97% of hospitalization costs in public hospitals (29).

Discharge records include the date of each hospital admission and discharge, name of hospital, principal and secondary diagnoses or reasons for admission, and principal medical procedures.

Exposure: mode of delivery

We considered mode of delivery as either vaginal delivery or Caesarean section. Mode of delivery was reported by the mother or primary caregiver at baseline, originally as normal vaginal birth without instrumentation, vaginal birth with instrumentation (such as forceps or vacuum extraction), or Caesarean section. We classified vaginal births as a single reference category, which included assisted and unassisted vaginal deliveries. We did not have information on whether Caesarean sections were performed as emergency or elective procedures, whether they were primary or repeat procedures, or their possible medical indications.

Outcome: hospitalizations for asthma and other wheezing disorders

Our primary outcome was public hospital admissions for asthma and other wheezing disorders from 9 days to 12 years of age. Admissions were coded at discharge according to the International Classification of Diseases, Ninth Version Clinical Modification (ICD-9CM). Asthma and other wheezing disorders were defined as a diagnosis of acute bronchitis and bronchiolitis (ICD9-CM 466), bronchitis, not specified as acute or chronic (ICD9-CM 490), and asthma (ICD9-CM 493), because these conditions typically present with wheezing (30). As a secondary outcome, we also considered asthma as ICD-9CM 493 only. We further considered hospitalizations to 2 years and 6 years so as to assess if associations varied by age and for consistency with our previous studies.

We included both day-patient and in-patient admissions. Children with no record of hospitalization were assumed to have none, although private hospital admission is possible but not obtainable by record linkage, as in our previous studies (31, 32). We excluded hospitalizations occurring within the first 8 days of life for consistency with our previous studies. As the average hospital stay of infants following Caesarean section was 7.9 days (23), the inclusion of hospitalizations in the immediate neonatal period could also have introduced bias.

Statistical analysis

We used Cox regression to examine the adjusted association of mode of delivery with time to first hospitalization, from which we report the hazard ratios (HRs) for hospitalization with associated 95% confidence intervals (CIs). Children who died were censored at the date of death. The proportional hazards assumption was checked by Schoenfeld's global test and visual inspection of plots of $\log(-\log S)$ against time, where S is the estimated survival function (33). With a Caesarean section rate of 27%, a hospitalization rate of 8% and a sample size of 8327, we had 80% power ($\alpha=0.05$) to detect an HR of 1.3.

Potential confounders included type of hospital at birth, sex, gestational age, birth weight, birth order, mother's age at birth, mother's place of birth, parental history of allergies, highest parental education, and type of housing at birth. We did not consider breastfeeding or early life second-hand smoke exposure as potential confounders, because they could be mediators on the causal pathway between the exposure and the outcome, and adjustment for such factors could introduce bias (34). To illustrate potential confounding effects, we present 3 models. Model 1 adjusted for type of

hospital at birth and sex only. Model 2 additionally adjusted for gestational age, birth weight, birth order, mother's age at birth, mother's place of birth, and parental history of allergies. Model 3 additionally adjusted for SEP (highest parental education and type of housing at birth). To further examine potential confounding by SEP, we also restricted the analysis to children who resided in public rental housing at birth, the eligibility to which is conditional upon comprehensive means testing of household income and assets by the Hong Kong government (35). Finally, we assessed whether associations varied by measures of SEP from the heterogeneity across strata and the significance of the relevant interaction terms. Statistical analyses were conducted using Stata, version 13.0 (Stata Corp, College Station, Texas).

Ethics approval

Ethics approval was obtained from the Institutional Review Board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster.

RESULTS

Of the original 8327 cohort members, 27 had permanently withdrawn, 95 were known to have migrated without further contact, and 20 were known to have died as of January 2014. Of the 8300 children who remained in the study, 4% had missing data for mode of delivery. Overall, 0.4% to 6% of data on confounders were missing, with 14% of children missing at least one confounder. Of the 8300 children who remained in the study, 671 (8.1%) had a first hospitalization from 9 days to 12 years, including 429 admissions for acute bronchitis and bronchiolitis (ICD-9CM 466), 16 for bronchitis, not specified as acute or chronic (ICD-9CM 490), 219 for asthma (ICD9-CM 493), and 7 for both ICD9-CM 466 and 493. The mean age at first hospitalization was 2.1 years.

Table 1 shows baseline characteristics by mode of delivery. A substantial proportion of children were delivered by Caesarean section (27%), while the others (73%) were delivered vaginally. About half of the children delivered by Caesarean section (52%) were born in private hospitals, and the majority of children delivered vaginally (80%) were born in public hospitals. Children with higher SEP (higher parental education or residing in private housing at birth) were more likely to be born by Caesarean section. Caesarean section was more common for boys, firstborns, older mothers, mothers born in Hong Kong, and children with parental history of allergies.

Table 2 shows the association of mode of delivery with time to first hospitalization for asthma and other wheezing disorders (ICD-9CM 466, 490 and 493). Mode of delivery was not clearly associated with hospitalizations for asthma and other wheezing disorders, adjusted for type of hospital at birth and sex (Model 1), or additionally adjusted for gestational age, birth weight, birth order, mother's age at birth, mother's place of birth, and parental history of allergies (Model 2). Further adjustment for SEP little changed the estimates (Model 3). From 9 days to 12 years, the point estimate for Caesarean section compared to vaginal delivery had HR 1.11 (95% CI 0.91 to 1.36). Estimates from 9 days to 2 years, >2 years to 6 years, and 9 days to 6 years were similar. Restricting the analysis to children residing in public rental housing at birth, i.e. those who most likely only use public hospitals, yielded higher estimates with HR 1.28 (95% CI 0.98 to 1.68) from 9 days to 12 years (Supplementary Table S2).

Table 3 shows the association of mode of delivery with time to first hospitalization for asthma only (ICD 9-CM 493). There was no association of mode of delivery with hospitalizations, with the overall point estimate from 9 days to 12 years very close to

unity (HR 0.96, 95% CI 0.71 to 1.30). Estimates were consistent by age and adjustment for SEP little changed the estimates.

DISCUSSION

In this population-representative Chinese birth cohort from a developed setting with high rates of Caesarean section, mode of delivery was not clearly associated with hospitalizations for asthma and other wheezing disorders to 12 years of age, although our estimates were in the direction of higher risk. These estimates were accentuated among children who resided in public rental housing at birth.

Our cohort has the advantages of being large, prospective and population-representative, with a very low attrition rate. In addition, cases of asthma and other wheezing disorders were ascertained from physician-coded diagnoses, avoiding bias from self-report. We also accounted for a range of potential confounders, including parental history of allergies and SEP. Nevertheless, our study has several limitations. First, hospitalizations generally represent relatively severe or poorly controlled cases, and we may have missed milder cases of wheeze that did not require hospitalization. However, it is unlikely that misclassification of cases depended on mode of delivery, so misclassification is most likely non-differential, which usually biases towards the null. Missing milder cases that did not require hospitalization means we can only provide a comparison of rates, and not an estimate of the absolute effect of mode of delivery on all wheezing disorders. We are also unable to distinguish between initial manifestation and exacerbation of wheeze, although we did obtain similar results with number of hospitalizations (data not shown). Second, we do not have information on admissions to private hospitals, which may be more likely for families with higher SEP. As in previous

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studies (31, 32), we adjusted for indicators of private hospital use (i.e., type of hospital at birth and SEP), which means we have compared children within type of hospital use and SEP. We also repeated the analysis restricted to the sub-group most likely to use only public hospitals, i.e., children living in public rental housing, and found similar results with slightly higher estimates, which might be less susceptible to any bias from confounding or selection. Public hospitals account for the majority of all admissions in Hong Kong, and the association of mode of delivery with hospitalizations did not vary by type of hospital at birth or type of housing at birth (data not shown), consistent with findings elsewhere showing that parental preference for health services use did not alter the association of Caesarean section with childhood asthma (36). Third, the diagnosis of asthma and wheezing disorders is difficult, particularly in younger children, owing to non-specific symptoms, variable phenotypes and the lack of definitive diagnostic tests (37). We have thus included and excluded hospitalizations for bronchitis and bronchiolitis in our analysis, arriving at similar results using both outcomes. Misclassification of wheezing disorders is possible, but bias would not be a concern unless the physician based the diagnoses on the child's mode of delivery at birth, which is unlikely. Fourth, we do not have information on the medical indications for Caesarean sections, or whether the Caesarean sections were performed as elective or emergency procedures, which may confound the association of Caesarean section with childhood wheezing disorders. The choice of mode of delivery depends on local clinical practice, maternal characteristics, anticipated foetal outcomes and urgency of the situation (9, 38). The foetal membranes could have ruptured prior to emergency or unplanned Caesarean sections, possibly leading to contamination of the uterine cavity by vaginal bacteria (11). However, most Caesarean sections in private hospitals are performed electively before the onset of labour, while public hospitals do not perform

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Caesarean sections without medical indications (21), and we have adjusted for type of hospital at birth. Finally, despite high Caesarean section and hospitalization rates, our sample size is not large enough to rule out an association, especially by various ages (39). Nonetheless, our estimates are consistent with other studies and will contribute towards future meta-analyses on this research question.

Our overall point estimate for the association of mode of delivery with asthma and other wheezing disorders is consistent with the point estimates from two meta-analyses based on studies from Western settings, which showed higher risk of asthma and wheeze [odds ratio (OR) 1.22, 95% CI 1.14 to 1.29] (12) and hospitalizations for asthma (OR 1.21, 95% CI 1.12 to 1.31) (11) in children born by Caesarean section than those delivered vaginally. This further suggests that our study may have been underpowered to detect an association, and highlights the need for additional studies in other settings. More recent studies since the publication of the two meta-analyses have shown inconsistent findings. Two population-representative birth cohorts in Brazil found no association of delivery by Caesarean section with current wheezing to 4, 11, and 15 years of age (14). A longitudinal study in the United States found higher risk of allergic rhinitis and atopy but not asthma (OR 1.1, 95% CI 0.6 to 2.3) in children born by Caesarean section than those delivered vaginally (40). A case-control study in Malaysia also showed no association of Caesarean section with childhood asthma, with a similar point estimate (OR 1.21, 95% CI 0.60 to 2.41) (15). A cross-sectional study in Finland showed no association of Caesarean section with childhood asthma compared to vaginal delivery (OR 0.96, 95% CI 0.53 to 1.65) (41), while another cross-sectional study in Korea found no association of mode of delivery with childhood asthma, but its point estimate for Caesarean section was in the direction of lower risk compared to vaginal

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delivery (OR 0.76, 95% CI 0.37 to 1.57) (13). However, these studies have used different definitions of asthma and wheeze, are susceptible to residual confounding as most did not account for potential confounding by SEP or indications for Caesarean section (9), and may be underpowered to detect small differences in risk. Their divergent observations again underscore the need to further replicate these findings in other settings.

Our findings are consistent with the mixed findings elsewhere regarding mode of delivery and childhood wheezing disorders, which appear to vary with age (11, 12). Meta-analyses have shown higher risk of asthma in studies including adolescents and adults compared to younger ages (11), and consistently higher risk in studies investigating adult-onset asthma in sub-group analyses (12). According to the hygiene hypothesis, exposure to diverse microbes in early life may confer immunological protection against asthma (42), although recent evidence on the microbiome suggests this hypothesis may be over-simplistic in explaining the aetiology of asthma (43). Contact with the mother's vaginal and intestinal flora through vaginal delivery may play an important role in the establishment of the infant's intestinal microbiota, which in turn influences immune function (17). The immune system undergoes age-dependent maturation after birth (17). Therefore, the effect of mode of delivery on risk of wheezing disorders may be most apparent in the first few years of life, which is consistent with our results.

Several cohort studies from Europe have assessed whether emergency and elective Caesarean sections have different associations with the risk of childhood asthma and found inconsistent results (44-47). In addition, some observational studies suggest that

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assisted vaginal delivery by forceps or vacuum extraction may be associated with higher risk of asthma compared to spontaneous vaginal delivery (48, 49). Although we are unable to distinguish between emergency and elective Caesarean sections, we found no difference for assisted deliveries (data not shown). While unmeasured confounding may be a concern of these studies, the role of the microbiome in the aetiology of asthma remains unclear. It has also been suggested that infants delivered by Caesarean section have higher DNA methylation, which may modulate the risk of asthma (10). Currently the determinants of the human microbiome and gene expression are not well characterized, so variation in key drivers by setting could generate contextually specific results. Nevertheless, the human microbiome is established almost immediately after birth (6) and DNA methylation has been observed several days after birth (10). As such, mode of delivery may prove to be an important modifiable determinant of health.

Caesarean section rates remain high in Asia, particularly in China (20), despite the World Health Organization's recommendation in 1985 that Caesarean section rates not exceed 15% in any region (50). In Hong Kong, elective Caesarean sections are frequently carried out for reasons other than obstetric indications, such as maternal and/or physician preference (21). The American College of Obstetricians and Gynaecologists recommends planned vaginal delivery in the absence of maternal or foetal indications for Caesarean section (51). However, elective Caesarean section on maternal request is now endorsed by clinical guidelines in settings such as the United Kingdom, which emphasize the importance of enabling women to make informed decisions about delivery (52). From a public health perspective, further studies with different designs are needed to confirm or refute our findings, and to clarify the role of

the microbiome and mode of delivery in the aetiology of asthma and other childhood wheezing disorders.

Conclusions

In a large, population-representative Chinese birth cohort, mode of delivery was not clearly associated with hospitalizations for asthma and other wheezing disorders in children. Although we cannot rule out residual confounding by SEP, our findings suggest that the observed associations of delivery by Caesarean section with childhood wheezing disorders may vary with setting and may not be biologically mediated.

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Table 1. Baseline Characteristics by Mode of Delivery in 8300 Children from Hong Kong's "Children of 1997" Birth Cohort

Characteristics			Mode of delivery				P value ^a
			Vaginal		Caesarean		
			(n = 5814)		(n = 2143)		
	n	%	Mean (SD)	%	Mean (SD)	%	
Infant characteristics							
Type of hospital at birth							
Public	5429	71.3		79.6		48.4	< 0.001
Private or overseas	2190	28.7		20.4		51.6	
Child's sex							
Girl	3768	47.4		48.3		44.9	0.009
Boy	4189	52.7		51.8		55.1	
Gestational age, weeks	7941	100.0	39.08 (1.53)		38.49 (1.78)		< 0.001
Birth weight, kg	7956	100.0	3.20 (0.42)		3.17 (0.50)		0.02
Birth order							
1st	3778	47.6		44.8		55.0	< 0.001
2nd	3286	41.4		43.1		36.8	
≥ 3rd	878	11.1		12.1		8.3	
Parental characteristics							
Mother's age at birth, years							
≤ 24	990	12.5		14.7		6.5	< 0.001
25-29	2470	31.2		34.0		23.7	
30-34	3022	38.1		36.1		43.6	
≥ 35	1441	18.2		15.2		26.3	
Mother's place of birth							
Mainland China or elsewhere	2879	38.0		42.0		27.2	< 0.001
Hong Kong	4707	62.1		58.0		72.8	
Parental history of allergies							
Neither parent	4701	59.6		61.1		55.7	< 0.001
Mother or father	2498	31.7		30.7		34.3	
Both parents	686	8.7		8.2		10.0	
Socioeconomic position							
Highest parental education							
Grade 9 or below	2392	30.1		32.7		23.2	< 0.001
Grade 10-11	3388	42.7		42.7		42.5	
Grade 12 or above	2160	27.2		24.6		34.4	
Type of housing at birth							
Public rental housing	3559	45.0		47.7		37.6	< 0.001
Subsidized home ownership scheme	1119	14.1		13.0		17.2	
Private	3238	40.9		39.3		45.3	

Abbreviations: SD, standard deviation

^a *P* values obtained from chi-squared tests for categorical variables and from ANOVA for continuous variables.

Table 2. Association of Mode of Delivery with Public Hospital Admissions for Asthma and Other Wheezing Disorders (ICD9-CM 466, 490 and 493) in Hong Kong's "Children of 1997" Birth Cohort

Mode of delivery	Age	Events	Unadjusted		Model 1 ^a		Model 2 ^b		Model 3 ^c	
			HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Vaginal	9 days to 12 years	671	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Caesarean			0.92	0.77, 1.10	1.13	0.93, 1.36	1.13	0.93, 1.38	1.11	0.91, 1.36
Vaginal	9 days to 2 years	415	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Caesarean			0.81	0.64, 1.02	1.07	0.84, 1.36	1.09	0.85, 1.41	1.07	0.83, 1.38
Vaginal	> 2 years to 6 years	273	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Caesarean			1.00	0.76, 1.31	1.00	0.74, 1.35	1.04	0.75, 1.43	1.02	0.74, 1.40
Vaginal	9 days to 6 years	625	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Caesarean			0.91	0.76, 1.10	1.12	0.92, 1.36	1.13	0.92, 1.39	1.12	0.91, 1.37
Vaginal	> 6 years to 12 years	74	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Caesarean			0.78	0.46, 1.35	0.67	0.34, 1.34	0.79	0.34, 1.80	0.82	0.34, 1.94

Abbreviations: CI, confidence interval; HR, hazard ratio.

^a Model 1 adjusted for type of hospital at birth and sex.

^b Model 2 adjusted for type of hospital at birth, sex, gestational age, birth weight, birth order, mother's age at birth, mother's place of birth and parental history of allergies.

^c Model 3 adjusted for type of hospital at birth, sex, gestational age, birth weight, birth order, mother's age at birth, mother's place of birth, parental history of allergies, highest parental education and type of housing at birth.

Table 3. Association of Mode of Delivery with Public Hospital Admissions for Asthma (ICD9-CM 493) in Hong Kong's "Children of 1997" Birth Cohort

Mode of delivery	Age	Events	Unadjusted		Model 1 ^a		Model 2 ^b		Model 3 ^c	
			HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Vaginal	9 days to 12 years	307	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Caesarean			0.92	0.71, 1.20	1.00	0.75, 1.33	0.97	0.72, 1.31	0.96	0.71, 1.30
Vaginal	9 days to 2 years	52	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Caesarean			0.69	0.35, 1.39	0.75	0.35, 1.60	0.87	0.40, 1.88	0.83	0.38, 1.79
Vaginal	> 2 years to 6 years	225	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Caesarean			1.04	0.77, 1.41	1.01	0.73, 1.41	1.05	0.73, 1.50	1.03	0.71, 1.48
Vaginal	9 days to 6 years	260	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Caesarean			0.91	0.68, 1.22	0.98	0.72, 1.35	0.96	0.69, 1.34	0.95	0.69, 1.33
Vaginal	> 6 years to 12 years	69	1.00	Referent	1.00	Referent	1.00	Referent	1.00	Referent
Caesarean			0.80	0.46, 1.39	0.71	0.35, 1.43	1.02	0.43, 2.40	1.04	0.41, 2.60

Abbreviations: CI, confidence interval; HR, hazard ratio.

^a Model 1 adjusted for type of hospital at birth and sex.

^b Model 2 adjusted for type of hospital at birth, sex, gestational age, birth weight, birth order, mother's age at birth, mother's place of birth and parental history of allergies.

^c Model 3 adjusted for type of hospital at birth, sex, gestational age, birth weight, birth order, mother's age at birth, mother's place of birth, parental history of allergies, highest parental education and type of housing at birth.