



Association between Caesarean Delivery and Childhood Asthma in India and Vietnam

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Abstract

Background: While there is evidence of an association between caesarean birth and increased asthma in children in high-income countries, it is unknown whether this association exists in low-to-middle-income countries (LMICs). We investigated whether children born through caesarean in India and Vietnam are at increased risk of caregiver-reported asthma by 8 years of age.

Methods: Data from an ongoing multi-national longitudinal cohort study (the Young Lives Study) in two LMICs (India $n = 2026$; Vietnam $n = 2000$) were used. Caregiver questionnaires captured information on caregiver-reported long-term respiratory problems such as asthma or wheeze at age 8 years, birth mode and a range of sociodemographic factors. Multivariable logistic regression models using propensity score adjustment were used to explore birth mode and asthma at age 8 years adjusted for a range of known confounders.

Results: Children delivered by caesarean in India (odds ratio (OR) 2.6, 95% confidence interval (CI) 1.3, 5.4) and Vietnam (OR 2.0, 95% CI 1.2, 3.3) had greater odds of asthma at age 8 years, after adjustment for other risk factors including wealth, liveborn parity, low birthweight, geographic location, cooking fuel used, livestock ownership, household size, housing quality and parental smoking.

Conclusions: The study suggests that caesarean birth may be associated with an increased risk of childhood asthma in India and Vietnam. The underlying mechanisms of this finding need to be further elucidated.

Keywords: asthma, caesarean birth, India, low-middle-income-countries, Vietnam, young Lives.

The prevalence of childhood asthma in low-and-middle-income countries (LMICs) has increased over the last 10 years.¹ The reasons for this increase are not known but may include smaller family size, reduced infant infections, changes to diet, and increased use of antibiotics, paracetamol and immunization.² A growing body of evidence also suggests that early-life factors, including caesarean delivery may modulate immune development and influence asthma risk during childhood.^{3,4} One hypothesis is that caesarean births may increase the risk of asthma by preventing initial newborn exposure to maternal microflora which occurs through vaginal birth, altering long-term intestinal microflora composition.⁵ Caesarean rates in LMICs have nearly tripled in the previous 10 years, particularly among wealthier women.⁶

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Several studies in affluent countries have reported an increased risk of asthma in children born through caesarean compared to vaginal birth,⁴ ranging from a 20% increased risk in American children at age 6–12 years⁷ to a 79% increased risk in Dutch children at age 8 years.⁸ Other studies, however, have found no such association.^{9,10} A recent meta-analysis of 23 studies in 10 high-income countries reported a pooled 20% increased odds of asthma (Odds Ratio (OR) 1.2, 95% Confidence Interval (CI) 1.1, 12.6) in children born through caesarean.⁴

Currently, knowledge on the association between caesarean birth and childhood asthma relies almost entirely on evidence from high-income countries in the Western world, with the exception of two studies in LMICs that have found no associations.^{11,12} These were both case-control studies and were limited by small sample size¹² and the grouping of children over a wide age range (3–15 years).^{11,12} The differential influence of environmental factors between affluent and non-affluent settings¹³ on wheeze and asthma

have been recognized, making the generalization of findings between high-income countries and LMICs difficult. For example some factors associated with poverty have been found to offer a protective effect against allergic disease, such as, over-crowding and unhygienic conditions,¹⁴ large number of siblings,¹⁴ and keeping cattle in the home.¹⁵ Other epidemiological studies suggest that the development of asthma may be influenced by the adoption of a Western life style² as suggested by higher lifetime prevalence of asthma symptoms in more affluent societies.¹⁶

Using a prospective birth cohort data, we investigated if caesarean birth is associated with increased risk of caregiver-reported asthma at age 8 years in two LMICs countries, India and Vietnam.

Methods

Participants

Young Lives is a multi-national longitudinal cohort study investigating the changing nature of childhood poverty from 2002–16.¹⁷ For the current study, data were used from the younger cohorts in India ($n = 2026$) and Vietnam ($n = 2000$) when the children were aged 6–18 months (median = 12 months in 2001–02) and 7.5–8.5 years old (median = 8 years in 2009), subsequently referred to as age 1 year and 8 years in this manuscript. Attrition across survey time-points from 1 year to 8 years was low at 2.2% in Vietnam and 4.0% in India. Preterm infants delivered at <37 weeks were excluded. The Young Lives study was approved by the London School of Hygiene Ethics Committee, the country project administering body, and participants provided informed consent prior to involvement. An ethics exemption was granted by the University of Western Australia.

Sampling method

In each country, 20 sentinel sites were selected using semi-purposive sampling.¹⁸ In-country experts selected sites to include key factors such as geographical location/type and particular population sub-groups. A primary target was that most sites should represent 'poor areas'.¹⁸ Within each geographic site, 100 households with children aged 6–18 months were randomly sampled after screening households for eligible children (twins and triplets were excluded). Where there was more than one eligible child, one

child was selected using a random sampling technique. Selection methods ensured that each sample was indistinguishable in composition from one drawn at random from qualifying households, field procedures for traversing each site were cost-effective and there was reasonable control of bias.¹⁹ Detailed information on country study sites can be found in Material S1, *Methods – Study Sites* and a detailed description of the sampling and recruitment procedures for the Young Lives study is published elsewhere.^{19,20}

Data collection

Individual questionnaire data were collected at baseline interviews (children were aged 6 to 18 months) and when the child was aged 8 years old through face-to-face interviews with mothers. Where the mother was not present the primary caregiver was interviewed (India $n = 13$; Vietnam, $n = 26$), referred to as 'caregiver' hereafter. Fieldworkers, who spoke the local language, were trained in questionnaire and interview delivery, with a focus on how to properly use the questionnaire in rural areas. Detailed information on data collection can be found in Material S1, *Data Collection*.

Primary outcome – Caregiver-reported asthma

At 8 years, the caregiver was asked through face-to-face interviews if the child had long-term respiratory problems such as asthma (may include clinical diagnosis or hospital admission) or wheeze (Y/N).

Risk factors and covariates

Data were also collected for a range of other factors that have been associated with childhood asthma in the published literature. These included family wealth, child's gender, parity, term low birthweight, breast feeding, household education, rural/urban living, cooking fuel, livestock ownership, smoking, maternal age, household size and housing quality.

Wealth Index is a proxy for household socio-economic status used in the Young Lives study and comprised a matrix of three indices: housing quality, consumer durables, and services²⁰ as observed by the data collector. The Index is scored between 0 and 1 where a higher score indicates higher socio-economic status.²⁰ This was used to categorise households into

wealth quartiles within the current sample. Term low birthweight was defined as <2500 g,¹¹ and breast feeding was defined as breast fed to at least 6 months of age. Liveborn parity was defined as number of children born alive prior to the index child. Household education was a dichotomous variable indicating whether the caregiver, partner of caregiver or household head had completed primary school. For urban or rural location, each study site was assessed individually by study co-ordinators and took into consideration a number of factors including agriculture and industry, environment and services to evaluate if the type of community/environment reflected a rural or urban setting.^{18, 19}

Cooking fuel referred to the main type of cooking fuel used in the previous 12 months (collected at 8-year-old survey), responses included bamboo, braches, charcoal, coal, dung, crop residue, leaves, straw, gas/electricity. Cooking fuel was transformed into a binomial category of gas/electricity or biomass (charcoal/wood/similar) burning. Livestock ownership indicated if the household owned any livestock in the previous 12 months (collected at 8-year-old survey) and household smoking referred to if anyone in the household currently smoked cigarettes (collected at 8 year old survey). Household size referred to the number of people living in the house. Housing quality was calculated using a continuous metric scored between 0–1 based on quality of housing (number rooms per person, materials walls, roof and floor). A higher score indicates better quality.²⁰

Statistical analyses

Multivariable logistic regression was used to explore the relationship between caesarean and asthma at 8 years of age. We used propensity score adjustment as a covariate in our multivariable logistic regression model.²¹ Briefly, propensity score adjustment was chosen as it can assist with data with rare outcomes as in the current study.²² Logistic regression was used to derive propensity scores with caesarean section as the dependent variable and the following independent variables as identified in the published literature: wealth quartile, gender, owned livestock in previous year, geographic location, cooking fuel used in previous year, smoker lives in household, household size, housing quality, mother's age, low birthweight and parity. Interactions were tested where a biological or clinically plausible interaction between

covariates was present. These included wealth*geographic location and low birthweight*parity, however, no interaction terms were included in the propensity score. From this model we derived the propensity scores being the adjusted probability of caesarean delivery. A sensitivity analysis was conducted comparing using propensity score as a continuous variable or as a categorical variable (quintiles), these were tested for linearity with a Box-Tidwell test. In a logistic regression model for the study outcome of asthma, we included the propensity score as a continuous variable, and further adjusted the model for breast fed to 6 months.

Breast fed to 6 months was included as a separate covariate in the model as breast feeding is reduced with caesarean birth,²³ and only baseline characteristics that cannot be modified with treatment can be incorporated into propensity scores.²⁴

The balance of baseline characteristics by propensity score was assessed by examining whether the distribution of measured baseline covariates is similar between treated and untreated subjects with similar propensity scores.²⁵

Negative control

To verify that the observed relationship between caesarean and asthma was not due to residual confounding or the methodical problem of over-reporting of disease in the children delivered by caesarean, we used a negative control as described in similar published work exploring caesarean birth and disease later in life.³ The purpose of a negative control is to have an outcome measure that does not involve the causal mechanism which is expected to produce a null result and verify that it does in fact produce a null result.²⁶ 'Serious burn' was selected as negative outcome measure as it was a health measure collected at the same 8 year survey as asthma and analysed with the same statistical methods as for the association between caesarean and asthma.

Sensitivity analysis for loss to follow-up data

The Indian sample had 4% lost to follow-up between baseline and 8 year old survey. Although loss to follow-up was equally distributed between exposure groups with 3.8% ($n = 11$) of children lost to follow-up from the caesarean group and 4.1% ($n = 71$) from the vaginal group, we conducted a sensitivity analysis

to assess the impact of loss to follow-up on our estimated effect measures. If a greater proportion of asthma among the vaginal birth children was present in those who were lost to follow-up the results would have been biased away from the null. A sensitivity analysis was done by comparing estimates of effect for asthma between participants with only complete data; and analysis with imputed missing data using multiple imputation methods for asthma.²⁷ Patterns of missing values were explored for variables with >0.01% of data missing to verify that data was 'missing at random' (i.e. no monotonicity was observed in the pattern of missing values). Final results were obtained by combining analyses from five imputed data sets using regression methods. Multiple imputation was employed using other sociodemographic variables from baseline survey as predictors for asthma and from the 8 year survey using imputed

sociodemographic variables. All data were analysed using SPSS version 22 statistical software.

Results

Characteristics of women who had caesarean

Table 1 presents the sociodemographic characteristics of the study women having vaginal and caesarean birth in India and Vietnam.

Women who had caesarean birth in India and Vietnam were mostly primipara, were from the highest wealth quartiles, had one household member who had completed primary school, used gas/electric cooking fuels and owned livestock.

Table 2 presents the sociodemographic characteristics of the study respondents and children with asthma at 8 years in India and Vietnam.

Table 1. Sociodemographic characteristics of women having caesarean birth

Characteristic	India		Vietnam	
	Vaginal birth (<i>n</i> = 1717) %	Caesarean birth (<i>n</i> = 289) %	Vaginal birth (<i>n</i> = 1760) %	Caesarean birth (<i>n</i> = 178) %
Wealth index				
Lowest quartile (Q1)	27.2	51.2	27	6.2
Lower middle quartile (Q2)	26.4	17.6	26.6	15.2
Upper middle quartile (Q3)	25.6	22.5	24.4	20.8
Highest quartile (Q4)	20.9	44.6	22	57.9
Child's gender (female)	46.9	42.6	49.1	42.7
Liveborn parity				
Primipara	35.2	52.2	42.4	55.6
Multipara	64.8	47.8	57.6	44.4
Term low birthweight (yes)	6.6	11.1	2.8	3.9
Not breast fed to 6 months of age	6.9	8.1	1.7	8.8
Primary education level of household				
No member completed	42.9	27	16.6	5.1
One member completed	57.1	73	83.4	94.9
Geographic Location				
Urban	22.1	43.9	16.9	51.1
Rural	77.9	56.1	83.1	48.9
Main cooking fuel used in previous year				
Gas or electric	28.2	48.8	39.4	71.3
Charcoal, wood or similar	71.8	51.2	60.6	28.7
Household owned livestock in last year (yes)	42.6	29.5	39.7	20.8
Smoker lives in household (yes)	41.7	27.7	55.2	52
Age mother (years) (mean $\pm$ SD)	23.7 (4.4)	23.7 (4.2)	26.9 (5.6)	30.2 (6.4)
Household size (mean $\pm$ SD)	5.5 (2.4)	5.1 (2.3)	4.9 (1.8)	5.0 (1.9)
Housing quality index (mean $\pm$ SD)	0.47 (0.29)	0.60 (0.28)	0.52 (0.31)	0.69 (0.20)

$P < 0.05$ wealth index, liveborn parity, geographic location, main cooking fuel used, livestock ownership and housing quality in India and Vietnam; $P < 0.05$ term low birthweight and smoker lives in household in India.

Table 2. Sociodemographic characteristics to respondents and children with caregiver-reported asthma in India ($n = 1901$) and Vietnam ($n = 1896$)

Characteristic	India		Vietnam	
	No asthma ($n = 1861$) %	Asthma age 8 years ($n = 40$) %	No asthma ($n = 1746$) %	Asthma age 8 years ($n = 155$) %
Delivery mode				
Vaginal	85.9	70.0	91.2	85.2
Caesarean	14.1	30.0	8.5	14.8
Wealth index				
Lowest quartile (Q1)	25.9	15.0	24.3	31
Lower middle quartile (Q2)	24.9	27.5	26.1	22.6
Upper middle quartile (Q3)	25.4	25.0	24.5	21.9
Highest quartile (Q4)	23.6	32.5	24.8	24.5
Child's sex (female)	48.8	55.0	52.7	43.2
Liveborn parity				
Primiparous	37.6	35.0	43.8	41.3
Multipara	62.4	65.0	55.8	58.7
Term low birthweight (yes)	6.6	10.0	3.0	1.3
Not breast fed to 6 months of age	6.5	10.0	2.2	1.9
Primary education level of household				
No member completed primary education	40.9	32.5	15.1	20.6
One member completed primary education	59.1	67.5	84.7	79.4
Geographic Location				
Urban	24.1	30.0	19.2	23.9
Rural	75.9	70.0	80.5	76.1
Main cooking fuel used in previous year				
Gas or electric	32.6	40.0	43.4	41.3
Charcoal, wood or similar	67.4	60.0	56.5	58.7
Household owned livestock in last year (yes)	40.5	47.5	41.0	38.3
Smoker lives in household (yes)	39.9	30.0	54.6	56.1
Age mother (years) (mean $\pm$ SD)	23.7 (4.3)	23.6 (4.8)	27.2 (5.7)	27.6 (6.0)
Household size (mean $\pm$ SD)	5.4 (2.4)	4.8 (2.4)	4.9 (1.8)	4.9 (1.9)
Housing quality index (mean $\pm$ SD)	0.49 (0.30)	0.56 (0.29)	0.54 (0.30)	0.50 (0.29)

Odds of asthma

Asthma prevalence in Indian and Vietnamese children at age 8 year were 2.1% and 8.2%, respectively. Children born through caesarean had greater odds of asthma at age 8 years, both in India (OR 2.6, 95% CI 1.3, 5.4) and Vietnam (OR 2.0, 95% CI 1.2, 3.3) (Table 3). In the negative control analysis, with 'serious burn' as a negative outcome measure we found no association between caesarean birth and serious burn (India OR 1.2, 95% CI 0.7, 2.1; Vietnam OR 0.3, 95% CI 0.2, 0.9).

Sensitivity analysis

Sensitivity analysis using multiple imputation found that the estimated effect was not different between

groups : participants born through caesarean with complete data had an odds ratio of 2.6 (95% CI 1.3, 5.4) for asthma, compared to 2.7 for participants with imputed data (OR 2.7, 95% CI 1.4, 5.6). As a secondary measure we calculated the prevalence of asthma in the lost to follow-up vaginal birth group required to affect the estimate of effect so that it was no longer statistically significant. This was found to be at least three times the prevalence observed in previous studies of asthma in India²⁸ and thus would be unlikely to occur.

Comment

This is the first published study to demonstrate significantly increased odds of childhood asthma after caesarean birth in LMICs. Furthermore, this association

Table 3. Association between caesarean birth and caregiver-reported asthma in children at age 8 years in India ($n = 1896$) and Vietnam ($n = 1870$)

	Adjusted odds ratio (95% confidence interval)	
	India age 8	Vietnam age 8
Caesarean delivery	2.6 (1.3, 5.2)	2.0 (1.2, 3.0)
Breast fed to 6 months	1.5 (0.5, 4.4)	0.7 (0.2, 2.5)

Propensity scores adjusted for wealth index, child's sex, liveborn parity, term low birthweight, geographic location, cooking fuel, livestock ownership, household smoking, maternal age, housing quality and household size.

was observed in both Indian and Vietnamese children at age 8 years, even after adjustment for sociodemographic risk factors. Children born through caesarean in India had odds of asthma two and half times that of children born through vaginal birth at 8 years of age, while children born through caesarean in Vietnam had odds twice that of children born through vaginal birth. These findings reflect a higher odds of asthma for caesarean birth compared to reports from high-income countries, where an increased asthma risk of around 20%⁴ for caesarean birth has been estimated, and studies in other LMICs, such as Malaysia and Iraq, which found no association between caesarean and asthma.^{11, 12} Asthma is very complex and there are many causative factors that influence childhood asthma and its diagnosis.²⁹ The heterogeneity of the disease has been demonstrated previously in studies showing considerable variability in the factors predicting asthma both between health centres and within countries due to the influence of the local environment and early-life exposures.¹³ Such jurisdictional variations may have also contributed to the differences seen in the findings of the current study compared to the other studies in LMICs.

The results of the current study fit with a growing body of evidence, from high income countries, that suggests asthma risk is increased due to altered early-life environment that influences the immune system.^{4, 5} Caesarean birth may increase the odds of asthma by preventing initial newborn exposure to maternal microflora which occurs through vaginal birth.⁵ Immediately after birth the human gut is colonized with different strains of bacteria important in shaping the immune system, with differences in the composition of intestinal flora between infants born through

vaginal birth and caesarean birth,⁵ potentially delaying the maturation of the immune system and increasing the risk of allergic disease and asthma.

Mode of delivery may also influence immune disease later in life through associated factors such as the use of anaesthetic agents and antibiotics during caesarean birth, differences in birth environment and physiological differences in newborns born vaginally and through caesarean.³ For example, the administration of maternal intrapartum prophylactic antibiotics for women having caesarean may enter the fetal bloodstream and stay in the blood stream for several hours.³⁰ Early-life exposure to antibiotics influence microflora colonisation, altering the immune response³¹ and antibiotic use during the first year of life has been associated with subsequent asthma development.³²

Limitations of the data

There are some limitations to our study. First, asthma was defined as caregiver-reported long-term respiratory problems such as wheeze or asthma. The self-reported nature of asthma diagnosis in the current study may overestimate asthma prevalence compared to the other studies in Malaysia and Iraq that used clinical asthma diagnosis¹² or the International Study of Allergy and Asthma questionnaire to determine asthma cases.¹¹ Although respiratory infection could be misdiagnosed by the caregiver as asthma, it is unlikely that respiratory infection would present as a long-term and ongoing problem. Studies in affluent countries have used various definitions for childhood asthma, such as hospitalisation for asthma,⁷ doctor-diagnosed asthma⁹ and parental reported asthma.⁸ In LMICs social, financial, cultural and health system barriers exist for asthma diagnosis and subsequent health service use,³³ therefore using measures such as doctor diagnosed asthma or hospitalization for asthma may not yield accurate estimates of asthma prevalence in the context of the current study population. The caregiver report of asthma may arguably be influenced by income level, where wealthier caregivers have better medical understanding and thus are more likely to report this condition. Wealth also influences likelihood of caesarean birth. While this may bias away from the null, the nature of the survey was based around symptoms rather than medical knowledge of asthma and survey development and validation carefully considered the differences in

caregiver knowledge across wealth and education level to reduce any bias.^{18, 19}

Further the negative control analysis did not suggest any evidence of bias of reported health conditions by maternal delivery mode and the asthma prevalence observed in both countries was within the range of other reported studies for children of similar age of 2.7% for India children and 4.8% for Vietnamese children.²⁸ Loss to follow-up was equally distributed between vaginal and caesarean groups and the sensitivity analysis suggested that loss to follow-up was not likely to impact on our estimated effect estimates. Although other studies have shown maternal asthma to be a strong predictor of childhood asthma⁴ and caesarean birth, we lacked data to explore this further.

Despite these limitations, the study suggests that caesarean birth is associated with increased odds of childhood asthma in India and Vietnam. The rate of caesarean birth, particularly among wealthier women in LMICs is increasing rapidly. Although caesarean rates are comparatively low compared to other countries in the region (Vietnam 8.8%, India 19.5%) in both countries inequitable access to caesarean delivery exist with women from wealthier households having greater access.^{34,35} It is important that the longer term health impact of caesarean birth are considered in the decision making process for birth mode, especially for elective and pre-labour caesareans without clear medical indication. As the diagnosis and treatment of asthma in LMICs is difficult, it is essential to consider how early-life exposures may moderate risk of childhood asthma.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Material S1. Methods