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A meta-analysis of the association between Caesarean section and childhood asthma

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Summary

Background Children born by Caesarean section have modified intestinal bacterial colonization and consequently may have an increased risk of developing asthma under the hygiene hypothesis. The results of previous studies that have investigated the association between Caesarean section and asthma have been conflicting.

Objective To review published literature and perform a meta-analysis summarizing the evidence in support of an association between children born by Caesarean section and asthma.

Methods MEDLINE, Web Science, Google Scholar and PubMed were searched to identify relevant studies. Odds ratio (OR) and 95% confidence interval (CI) were calculated for each study from the reported prevalence of asthma in children born by Caesarean section and in control children. Meta-analysis was then used to derive a combined OR and test for heterogeneity in the findings between studies.

Results Twenty-three studies were identified. The overall meta-analysis revealed an increase in the risk of asthma in children delivered by Caesarean section (OR = 1.22, 95% CI 1.14, 1.29). However, in this analysis, there was evidence of heterogeneity ($I^2 = 46\%$) that was statistically significant ($P < 0.001$). Restricting the analysis to childhood studies, this heterogeneity was markedly decreased ($I^2 = 32\%$) and no longer attained statistical significance ($P = 0.08$). In these studies, there was also evidence of an increase ($P < 0.001$) in the risk of asthma after Caesarean section (OR = 1.20, 95% CI 1.14, 12.6).

Conclusion In this meta-analysis, we found a 20% increase in the subsequent risk of asthma in children who had been delivered by Caesarean section.

Keywords asthma, Caesarean section, meta-analysis

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Introduction

The prevalence of asthma in childhood has increased over the past two decades from 6% in 1973 to 27% in 2003 using UK figures [1, 2]. Over a similar time period, there has been an increase in the rate of Caesarean section deliveries [3]. In England, Caesarean delivery accounted for only 9% in 1980 and this has increased to 22.7% in 2004 (half of which were elective) [3]. Children born by Caesarean section have been shown to have a delayed and altered development in establishment of gut flora and altered cytokine production [4–6]. These children may consequently have an increased risk of developing asthma under the hygiene hypothesis [7].

Numerous studies have investigated the association between Caesarean section and asthma, some of which have

reached conflicting conclusions. In such a situation, a meta-analysis may be valuable in synthesizing the available evidence. We therefore assessed the evidence for an association between asthma and Caesarean section by conducting a systematic review and meta-analysis of published epidemiological studies.

Materials and methods

Search

The literature search was conducted using MEDLINE, through OVID ONLINE, with the strategy [(Caesarean OR mode of delivery) and (asthma OR wheeze)] using text words and MEDLINE subject heading key words, where

available. A similar strategy was used in searches on Web of Science, Google Scholar and PubMed. On each database, the search was limited to studies on humans published before December 2006. Abstracts were screened independently by three investigators (S. T., C. R. C. and M. D. S.) to establish whether the studies were likely to provide relevant data based on the following inclusion criteria: (1) they identified groups of individuals delivered by Caesarean section (or instrumental delivery) and normal vaginal delivery and (2) they determined the prevalence of asthma or wheeze in both groups.

Most studies identified were of the cohort design, with case definition based on childhood asthma and Caesarean section considered as potential risk factors. The case-control studies compared Caesarean section experience in children with asthma (cases) with children without asthma (controls) apart from one study [6], which compared asthma experience in children born by Caesarean section (cases) with children not born by Caesarean section (controls). In two studies where data only for wheeze were available [8, 9], persistent wheeze was taken as the outcome measure as it was considered most similar to asthma.

Eligible studies were assessed independently by two reviewers (C. C. and S. T.) to abstract information about the study (country and year of publication), study subjects (source, area and age at diagnosis) and asthma exposure (methods of ascertainment and definitions used). The asthma prevalence in the naturally delivered and Caesarean section groups was then extracted. Authors were contacted to clarify ambiguities in their published results.

Statistical methods

Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for the association between asthma and Caesarean section for each study. Tests for heterogeneity between studies were conducted and random-effects models were used to calculate pooled ORs [10]. The I^2 statistic was calculated to attempt to quantify the degree of heterogeneity between studies [11]. This statistic measures the percentage of total variation across studies due to heterogeneity. Random-effect models were deemed more appropriate than fixed-effect models because they provide a more conservative OR estimate, representing the mean association in the populations, and it was anticipated that there would be heterogeneity because of the observational nature of these studies. Study-specific weights in the random-effects model were calculated and scaled to percentages. Publication/selection bias was investigated by checking for asymmetry in funnel plots of the study ORs against the standard error of the logarithm of the ORs [12, 13]. A subset analysis was conducted including only studies that ascertained asthma data before age 18. As the meta-analysis was conducted from summary figures rather than individual case records, the ORs

could not be adjusted for confounders. Sensitivity analyses were also conducted subdividing studies by study design (case-control or cohort), ascertainment of asthma (medical record or questionnaire) and geographic region (European, America or other). A further sensitivity analysis was conducted using the Trim and Fill method [14] to calculate pooled estimates after adjustment for any potential publication bias. Statistical analyses were performed using STATA 9.0 (Stata, College Station, TX, USA).

Results

The search identified 23 articles. Of these, 14 were obtained using MEDLINE [6, 8, 9, 15–25] and three through Web of Science [26–28]. The more general MEDLINE search identified four further articles [4, 29–31]. Review of reference lists revealed two more publications [32, 33]. On closer inspection, a published article [33] was excluded from further analysis as it was restricted only to pre-term infants. One of the articles [6] provided data for two studies.

Attempts were made to contact four authors [9, 17, 19, 27]. Three authors clarified numbers [17, 19, 27] and one author [9] whose paper presented data on asthma for children born by instrumental delivery provided data for children born by Caesarean section. The study characteristics are summarized in Table 1. The majority of the studies (17/23) were cohort studies. In most studies, the asthma diagnosis referred to the childhood period. Data on asthma symptoms and diagnosis were mainly collected by questionnaire (11/23) or from hospital and/or medical records (9/23).

The results from all identified studies that investigated the association between asthma and Caesarean section are summarized in Fig. 1. The analysis including all studies demonstrated an increase ($P < 0.001$) in the risk of asthma after Caesarean section (OR = 1.22, 95% CI 1.14, 1.29). However, in this analysis, there was evidence of heterogeneity ($I^2 = 46\%$) that was statistically significant ($P < 0.001$). Restricting the analysis to childhood studies (i.e. studies that ascertained asthma before age 18), this heterogeneity was markedly reduced ($I^2 = 32\%$) and no longer attained statistical significance ($P = 0.08$). In these studies, there was also evidence of a statistically significant increase ($P < 0.001$) in the risk of asthma after Caesarean section (OR = 1.20, 95% CI 1.14, 1.26).

The funnel plot, contained in Fig. 2, did not reveal any marked departures from symmetry that would be suggestive of publication/selection biases. The Trim and Fill method, which allows pooled estimates to be calculated after adjustment for publication bias, produced estimates that were little altered (overall OR = 1.19, 95% CI 1.12, 1.28, childhood asthma OR = 1.20, 95% CI 1.14, 1.26), suggesting that any publication bias would have had little effect on our results.

Table 1. Characteristics of studies that have investigated the association between asthma and Caesarean section, ordered by date of publication

Study First author (year)	Design	Country	Asthma	
			Diagnosis refers to (years)	Ascertainment method
Oliveti (1996)	Case-control	USA	3-9	Hospital clinic (diagnosis and medication)
Xu (2000)	Cohort	Finland	At 7	Parental questionnaire (diagnosis)
Nafstad (2000)	Cohort	Sweden	At 4	Questionnaire (diagnosis and symptoms)
Xu (2001)	Cohort	Finland	At 31	Questionnaire (diagnosis)
Annesi-Maesano (2001)	Cohort	UK	Under 18	Questionnaire (symptoms)
McKeever (2002)	Cohort	UK	Under 11	GP consultations (diagnosis)
Kero (2002)	Cohort	Finland	(i) Under 7 (ii) At 7	(i) Hospital admissions and medications databases (ICD code) (ii) Clinical visit (diagnosis)
Bager (2003)	Cohort	Denmark	Under 28	Interview (diagnosis)
Hakansson (2003)	Case-control	Sweden	1-12	Hospital discharge records (ICD code)
Negele (2004)	Cohort	Germany	1-2	Parental questionnaire (diagnosis)
Vonk (2004)	Cohort	The Netherlands	At 18-22	Methacholine test (bronchial hyperactivity)
Maitra (2004)	Cohort	UK	At 7	Parental questionnaire (diagnosis)
Smith (2004)	Cohort	UK	Under 10	Hospital admissions (ICD code)
Kurukulaaratchy (2005)	Cohort	UK	Under 4 and at 10	Questionnaire (symptoms)
Debley (2005)	Case-control	USA	6-12	Hospital admissions (ICD code)
Al-Kubaisy (2005)	Case-control	Iraq	Under 13	Questionnaire (diagnosis and medication)
Hagendorens (2005)	Cohort	Belgium	Under 2	Parental questionnaire (symptoms)
Bernsen (2005)	Cohort	The Netherlands	At 6	Medical records (diagnosis)
Juhn (2005)	Cohort	USA	Under 8	Medical records (diagnosis or symptoms)
Renz-Polster (2005)	Cohort	USA	3-10	Health maintenance organization* medical records (diagnosis)
Salam (2006)	Cohort	USA	Under 18	Parental questionnaire (diagnosis)
Rusconi (2006)	Cross-sectional	Italy	Under 2 and at 5	Parental questionnaire (symptoms)

*Equivalent to General Practitioners records.

Further analysis (not shown) conducted in subgroups of the studies defined by study design, ascertainment of asthma and geographic region revealed conclusions similar to the overall analysis.

Discussion

In this meta-analysis, which included 20 published articles, we found a 20% increase in the subsequent risk of asthma in children who had been delivered by Caesarean section. In studies of asthma at any age (including three adult studies [16, 28, 29]), a similar association was detected but as marked study heterogeneity was observed, we can be less certain about this result.

The hygiene hypothesis suggests that intestinal bacterial flora is important in immune development in children. The *Bacteriodes* and *Bifidobacterium* species live in the gut and have probiotic properties that are associated with a decreased risk of atopic disease. Caesarean section has been shown to delay and alter the development of intestinal bacterial flora. This may, in turn, alter immune development and subsequently increase the risk for atopic disease in children [4]. Alternatively, Caesarean section is associated with transient tachypnoea of the newborn [34] (due to altered pulmonary physiology resulting from

delayed removal of amniotic lung fluid), which has been shown to increase asthma risk ([27] and [35]).

To our knowledge, this is the first meta-analysis of the association between Caesarean section and childhood asthma. The main finding (of increased risk of asthma after Caesarean section) was observed in studies with different designs, conducted in different countries and using different measures of asthma conferring a level of robustness to this result.

There are limitations to meta-analyses-based upon summary statistics from observational studies. They cannot confirm causal relationships, which require randomized control trials, nor do they allow adjustments for confounding factors. One possible confounder is low birth weight (pre-term or *in utero* growth retardation), which has been reported to be associated with an increased asthma risk perhaps due to an altered immune system or abnormal pulmonary structural development [18, 36]. However, the majority of studies that have adjusted for low birth weight [4, 16, 18, 22, 29-31] found that this had little confounding influence on the association between asthma and Caesarean section.

Breastfeeding during the first 4-6 months of life is also believed to provide some protection against asthma because human milk provides an immunomodulatory and anti-inflammatory component to the baby [37]. It is

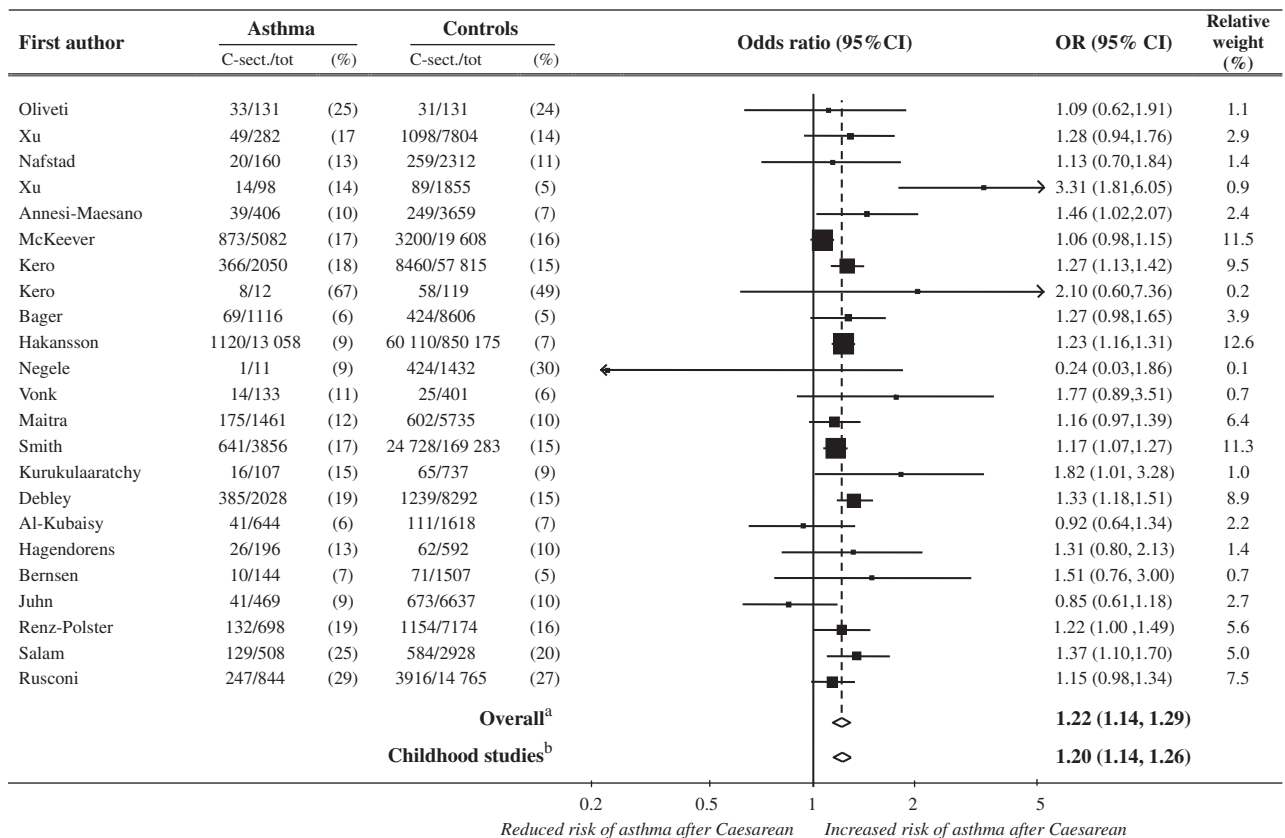


Fig. 1. Meta-analysis of studies of asthma and Caesarean section using the random-effects model, studies ordered by publication date.
^aTest for heterogeneity $\chi^2 = 40.36$, $df = 22$, $P = 0.01$; I^2 [95% confidence interval (CI)] = 46% (11%, 67%); test for overall effect $Z = 6.36$, $P < 0.001$.
^bExcludes studies [16, 28, 29]; test for heterogeneity $\chi^2 = 28.01$, $df = 19$, $P = 0.08$; I^2 (95% CI) = 32% (0%, 61%); test for overall effect $Z = 6.76$, $P < 0.001$.

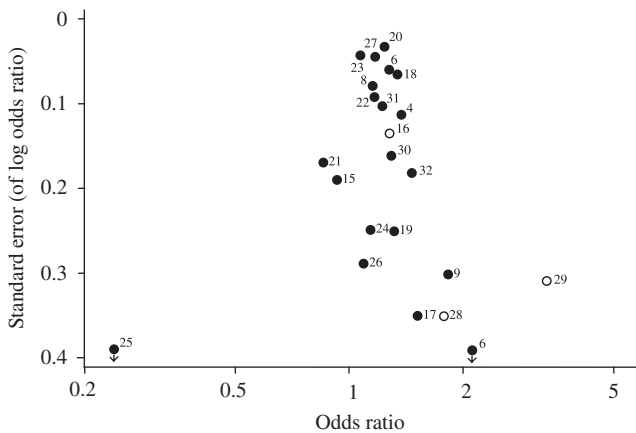


Fig. 2. Funnel plot of studies of asthma and Caesarean section. Studies of children (●) and adults (○) are labelled by reference number.

possible that breastfeeding could provide a confounding influence as children born by Caesarean section are less likely to be breastfed [20] but two studies that adjusted for breastfeeding [4, 22] noted little changes in the association between Caesarean section and asthma.

Passive smoking during prenatal or childhood acts as a risk factor for asthma development [15]. This *in utero* exposure can cause changes in fetal lung development and cause airflow obstruction and airway hyper-responsiveness [38]. Maternal smoking may also be positively related to Caesarean section and could therefore act as a confounder. However, as the positive association between asthma and Caesarean section remained after adjustment for maternal smoking in a number of studies [4, 18, 22, 29–31], any confounding influence is likely to be small.

As studies did not separately analyse the two classic childhood wheezing phenotypes (non-atopic viral-triggered wheeze and classic atopic allergic asthma) whose aetiology may differ we could make no adjustments for this in our analyses. Interestingly, all three studies [16, 28, 29] investigating asthma in adulthood, which are unlikely to contain many of the transient non-atopic viral-triggered wheezers, observed an increased risk of asthma after Caesarean section.

In conclusion, we found a 20% increase in the subsequent risk of asthma in children who had been delivered by Caesarean section. This increase could reflect the

hygiene hypothesis as such children are likely to have reduced exposure to environmental microbes in early life.

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