

REVIEW

Caesarean delivery and risk of atopy and allergic diseases: meta-analyses

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Clinical and Experimental Allergy

Summary

Studies of delivery by caesarean section (c-section) and the offspring's risk of allergic diseases are of current interest due to concerns about the increased use of c-section in many countries. However, previous studies have reported inconsistent findings. We investigated whether delivery by c-section is associated with an increased risk of atopy and allergic disease by reviewing the literature, performing a meta-analysis, and assessing publication bias. We used a systematic literature search of MEDLINE (1966 to May 2007). Six common allergic outcomes were included: food allergy/food atopy, inhalant atopy, eczema/atopic dermatitis, allergic rhinitis, asthma, and hospitalization for asthma. For each outcome a meta-analysis was performed, where a summary odds ratio (OR) was calculated taking into account heterogeneity between the study-specific relative risks. Publication bias was assessed using the funnel plot method. We identified 26 studies on delivery by c-section and one or more of the six allergic outcomes. C-section was associated with an increased summary OR of food allergy/food atopy (OR 1.32, 95% CI 1.12–1.55; six studies), allergic rhinitis (OR 1.23, 95% CI 1.12–1.35; seven studies), asthma (OR 1.18, 95% CI 1.05–1.32; 13 studies), and hospitalization for asthma (OR 1.21, 95% CI 1.12–1.31; seven studies), whereas there was no association with inhalant atopy (OR 1.06, 95% CI 0.82–1.38; four studies) and eczema/atopic dermatitis (OR 1.03, 95% CI 0.98–1.09; six studies). Funnel plots indicated that the association with food allergy/food atopy could be difficult to interpret due to publication bias. For each significant association with an allergic outcome, only 1–4% of cases were attributable to c-section. In conclusion delivery by c-section is associated with a moderate risk increase for allergic rhinitis, asthma, hospitalization for asthma, and perhaps food allergy/food atopy, but not with inhalant atopy or atopic dermatitis. The increased use of c-section during the last decades is unlikely to have contributed much to the allergy epidemic observed during the same period.

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Introduction

Reports on the offspring's risk of developing allergic disease following delivery by caesarean section (c-section) [1–26] are of current interest due to the increased use of c-section in many countries. The proportion of c-sections has increased up to 30% of all deliveries, while in the 1970s, it was generally below 15%, as recommended by the World Health Organization [27, 28]. So far, the epidemiological association between c-section and risk of allergic outcomes has been inconsistent, and to the best of our knowledge, neither a review of studies nor a meta-analysis of the reported risk estimates has been published. The suspicion of an association has been raised because c-section babies have a different gut flora

[29–33], which has been suggested to prolong immunological immaturity and thereby increase the risk of later development of allergic disease [34, 35]. In addition, delivery by c-section is a well-recognized cause of neonatal respiratory morbidity, in specific transient tachypnea of the newborn (TTN) and respiratory distress syndrome (RDS) [36–39]. A number of studies suggest that TTN and RDS are associated with an increased risk of later asthma [21, 23, 40–42].

We aimed to provide a review and meta-analyses of epidemiological studies of delivery by c-section and risk of allergic outcomes, and evaluate publication bias. In addition, we investigated whether reported risk estimates might depend on characteristics of the study populations and the methods applied in the studies.

Materials and methods

Search strategy and inclusion criteria

We identified epidemiological studies of the association between c-section and allergic diseases, listed in PubMed between 1966 and 1 May 2007. Specifically, abstracts of studies in PubMed were searched for two strategic combinations of words. Strategy 1 was (*allergy OR allergic OR atopy OR IgE OR skin-prick test OR atopic dermatitis OR eczema OR allergic rhinitis OR hay fever OR asthma*) AND (*caesarean OR c-section OR mode of delivery*), and strategy 2 was (*allergy OR allergic OR atopy OR IgE OR skin-prick test OR atopic dermatitis OR eczema OR allergic rhinitis OR hay fever OR asthma*) AND [*delivery AND (birth OR perinatal OR obstetric complications OR pregnancy complications)*] AND NOT (*caesarean OR c-section OR mode of delivery*). On the basis of the abstracts, full texts of studies were retrieved if they were considered to present analysis of the potential association between obstetric complications and allergic outcome in offspring. Their reference lists were examined to retrieve similar studies using title and then abstract in PubMed; the process was repeated until no further references could be retrieved. For retrieved studies to be eligible for inclusion, they had to be published by a peer-reviewed journal, and to present information on the potential association between c-section and at least one of six outcomes: (1) food allergy/food atopy, (2) inhalant atopy, (3) eczema/atopic dermatitis, (4) allergic rhinitis, (5) asthma, and (6) hospitalization for asthma. In addition, eligible studies had to present information on measures of relative risks [e.g. unadjusted or adjusted odds ratios (OR)], or information sufficient to calculate such measures (e.g. numbers of cases and controls according to mode of delivery). The software Reference Manager version 11 was used for PubMed searches, and review of abstracts.

Data extraction and categorization

For included studies, data were extracted on the relative risk of allergic outcomes including 95% confidence intervals (CIs) (adjusted risks and risks for diagnoses/symptoms *ever* were chosen, if available). In addition, information on nine study characteristics was extracted and categorized as follows: adjustment of relative risks (see categorization in Table 1), whether the hypothesis of an association between c-section and allergic outcome was mentioned *a priori* in the abstract (yes, no), study design (cohort, case-control), year of birth (≤ 1990 , > 1990), the size of the study population (≤ 4000 , > 4000), country of the study population (Europe, other), exclusion of persons born < 37 weeks of gestation (preterm) and/or with a birth weight of < 2000 – 2500 g (yes, no), proportion of c-sections among all deliveries ($\leq 15\%$, $> 15\%$) (in case-control studies, the proportion among controls was

extracted), and ages at atopy test or allergic disease (≤ 10 , > 10 years); ages at allergic disease were defined as the age range from birth to maximum age at ascertainment if a study ascertained the life-time occurrence of allergic disease, and it was defined as the age(s) at ascertainment if a study used diagnosis or ascertained current allergic disease. The study characteristics were chosen partly because several authors have regarded them as important factors (e.g. preterm birth/low birth weight, and age at allergic disease), and partly because they are usually stratified for in meta-analyses.

Statistical methods

A meta-analysis was performed for each of the six studied outcomes. We calculated summary effects (OR) using the fixed- and random-effects model. The *fixed effect OR* is the inverse-variance weighted average of the study-specific estimates. For each fixed-effect OR, we calculated a *Q* statistic, which quantifies the degree of variability (heterogeneity) in the measures across the studies [43]. Under the null hypothesis of no difference in effect across studies, the *Q* statistic is χ^2 distributed with degrees of freedom equal to the number of studies minus one [43]. The *P*-value of the *Q* statistics indicates whether there is significant heterogeneity in the effect estimates. The *random effect OR* is a weighted average of study-specific relative risks that takes heterogeneity into account [43, 44]. The key distinction between the two models is the assumption that with increasing sample size, the study-specific effect estimates will tend to converge to unity (fixed-effect assumption), or still show heterogeneous/separate effects (random-effect assumption). Publication bias was evaluated using the funnel plot method; the natural log and standard error (SE) of study-specific estimates were calculated from the CIs or raw data presented in the articles. Stratified meta-analyses were used to evaluate whether the summary ORs varied according to the study characteristics (dichotomous variables). *P*-values were two-tailed, based on likelihood ratio tests, and considered to be significant at the 5% level. The proportion of cases attributable to c-section was calculated separately for the allergic outcomes as $P \times (\text{summary OR} - 1) / \text{summary OR}$, where *P* is the proportion of cases that were delivered by c-section. The software package SAS version 9.1 was used for statistical analyses (SAS Institute, Cary, NC, USA).

Results

Inclusion and exclusion of studies

The literature search yielded a total of 429 abstracts. Among these, 30 studies were selected and retrieved for a full review. The searches in reference lists yielded a further 28 studies that were retrieved for a full review. Overall, 58

studies were retrieved for a full review; 51 originated from search strategy 1, and seven from search strategy 2. We excluded 32 of the 58 studies for the following reasons: 20 studies presented information on perinatal factors but not c-section, seven studies had a non-eligible outcome definition (e.g. allergy, wheeze, total IgE, TTN, and RDS), two studies each had study populations that overlapped with another retrieved study (because the relative risks did not differ materially, we chose the two earliest publications [6, 25]), one study was reported as a congress abstract, and two studies presented results exclusively for acute or elective c-sections. Overall, 26 of the 58 studies were eligible for inclusion.

Description of included studies

Each of the 26 studies provided one or more estimates of relative risks for an allergic outcome included in the six

meta-analyses; the total number of estimates was 45. Table 1 specifies for each study the risk estimate(s) included in the meta-analysis, and Fig. 1 depicts for each outcome the risk estimates ordered by increasing size of the estimate. Table 1 and Fig. 1 also specify the data extracted on seven of the nine selected study characteristics, as well as the prevalence of outcomes. Characteristics not shown are study design and *a priori* aim of the study. Specifically, 23 studies had a cohort design, and three had a case-control design [16, 18, 23]. Furthermore, 14 studies *a priori* addressed the association between c-section and risk of allergic outcome(s), and 12 studies did not [1, 7, 8, 10, 11, 14–16, 18, 20, 22, 26].

Meta-analyses

Table 2 shows the summary ORs for the relation between delivery by c-section and the six types of allergic

Table 1. Selected study characteristics and relative risks extracted from the 26 studies included in the meta-analysis

Reference (number, first author)	Year of births	Country	Exclusion*	Risk adjustment [†]	Relative risks of allergic outcomes included in meta-analyses				
					Food allergy = 1	Eczema/atopic dermatitis	Allergic rhinitis	Asthma (hospitalization = [‡])	
					Food atopy = 2 Inhalant atopy = 3				
[1] Liem	1995	USA	No	No	1.16 (0.92–1.45) ¹	–	–	–	
[2] Salam	1975–1987	USA	Yes	Basic+ABC	1.18 (0.85–1.62) ¹	1.07 (0.67–1.70)	1.57 (1.24–1.99)	1.33 (1.01–1.75)	
[3] Rentz-Polster	1990–1992	USA	Yes	Basic+BC	1.34 (0.54–3.29) ^{1§}	0.9 (0.70–1.16)	1.37 (1.14–1.63)	1.24 (1.01–1.53)	
[4] Negele	1997–1999	Europe	Yes	AC	1.64 (1.03–2.63) ² 1.75 (0.98–3.12) ³	1.04 (0.79–1.39)	–	–	
[5] Laubereau	1995–1998	Germany	Yes	Basic+A	2.06 (1.12–3.80) ²	1.06 (0.56–2.00)	–	–	
[6] Eggesbo	1992–1993	Norway	Yes	BC	3.2 (1.4–7.3) ¹	–	–	–	
[7] Vonk	1975–1978	Nederland	No	No	0.75 (0.39–1.44) ^{3*}	–	–	–	
[8] Xu	1966	Finland	No	Basic+ABC	0.96 (0.59–1.56) ³	1.19 (0.62–2.28)	1.28 (0.73–2.24)	3.23 (1.53–6.80)	
[9] Maitra	1991–1992	UK	No	Basic+ABC	1.04 (0.8–1.3) ³	–	–	1.14 (0.9–1.4)	
[10] Sugiyama	2002–2003	Japan	Yes	No	–	0.77 (0.22–2.73) [¶]	–	–	
[11] Bernsen	1988–1990	Nederland	No	Basic+AC	–	0.94 (0.26–3.33)	–	1.03 (0.51–2.08)	
[12] McKeever	1988–1999	UK	No	No	–	1.04 (0.98–1.10)	1.01 (0.85–1.21)	1.09 (1.01–1.18)	
[13] Bager	1973–1977	Denmark	No	Basic	–	–	1.15 (0.90–1.48)	1.31 (1.01–1.71)	
[14] Nafstad	1992–1993	Norway	Yes	No	–	–	1.2 (0.7–2.1)	1.1 (0.7–1.8)	
[15] Montgomery	1970	UK	No	Basic+AC	–	–	1.21 (0.84–1.74)	–	
[16] Calvani	1991–98	Italy	No	No	–	–	–	0.78 (0.58–1.06) [¶]	
[17] Juhn	1976–1982	USA	No	C	–	–	–	0.93 (0.6–1.4)	
[18] Olivetti	1983–1989	USA	No	No	–	–	–	1.09 (0.62–1.91) [¶]	
[19] Werner	1984–1987	Denmark	Yes	BC	–	–	–	1.11 (0.88–1.39)	
[20] Gessner	1990–2001	USA	No	No	–	–	–	1.46 (1.28–1.67) [¶] 1.09 (1.00–1.18) [‡]	
[21] Smith	1992–95	UK	Yes	No	–	–	–	1.17 (1.02–1.57) [‡]	
[22] Benn	1992–1994	Denmark	No	B	–	–	–	1.2 (0.3–4.3) [‡]	
[23] Debley	1987–1994	USA	No	B	–	–	–	1.20 (1.04–1.39) [‡]	
[24] Kero	1987	Finland	No	Basic	–	–	–	1.21 (1.08–1.36) [‡]	
[25] Håkansson	1984–1996	Sweden	Yes	Basic+BC	–	–	–	1.35 (1.27–1.44) [‡]	
[26] Xu	1985–1986	Finland	No	Basic+A	–	–	–	1.38 (1.00–1.92) [‡]	

*Exclusion of persons born preterm (<37 weeks) and/or with a low birth weight (<2000–2500 g).

[†]Basic: Maternal age, prematurity (gestational age or birth weight), and sibship (parity, birth order, or sibship size). A, parental allergy; B, smoking in pregnancy; C, socioeconomic factor (parental education, level of income, or social class).

[§]Not adjusted.

[¶]Odds ratios or incidence rate ratios, and 95% confidence intervals were not presented in the article, but calculated for the meta-analyses based on numbers of exposed and unexposed cases and controls extracted from the article.

outcomes. Overall, delivery by c-section was associated with a significantly increased summary OR of food allergy/food atopy, allergic rhinitis, asthma, and hospitalized asthma, whereas there was no association with

inhalant atopy or eczema/atopic dermatitis. Taking into account the significant heterogeneity between the study-specific relative risks for asthma ($P < 0.01$), and hospitalization for asthma ($P < 0.01$) using the ran-

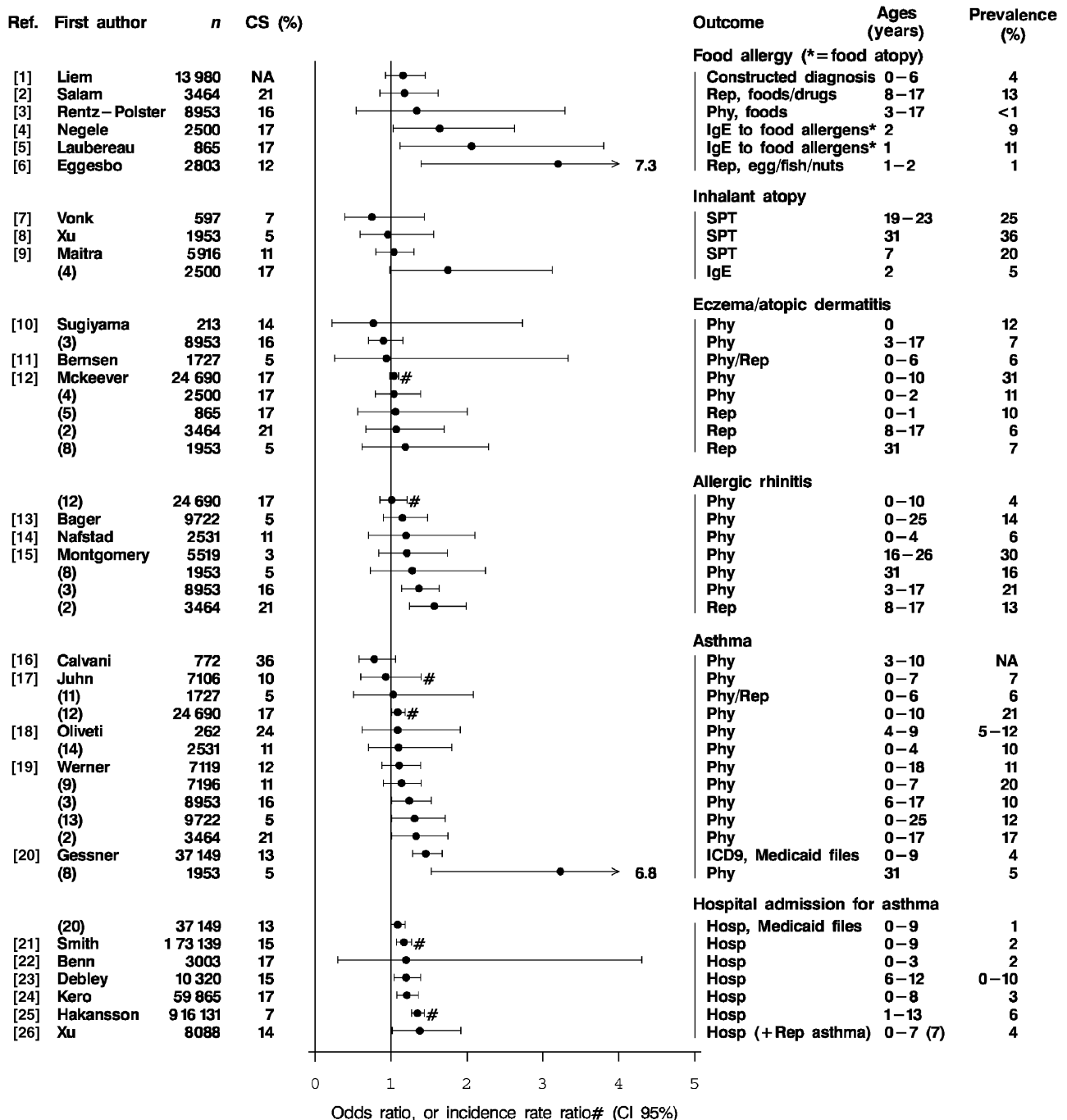


Fig. 1. Selected study characteristics, and relative risks according to category of allergic outcome(s) reported in the 26 studies included in the meta-analyses. For each study the reference number, first author (or reference number if the reference is repeated), population size, and proportion of persons delivered by c-section are shown (left side) along with (right side) the allergic outcome, age at outcome, and prevalence of outcome. Age at allergic disease was defined as the range from birth to maximum age at ascertainment of life-time occurrence of allergic disease, or the age(s) at ascertainment of diagnoses or current allergic disease. Ref., reference; *n*, population size; CS, caesarean section; Prop., proportion; Phy, physician-diagnosed; Rep, Parent- or self-reported; Hosp, Hospital admission; SPT, skin-prick test for allergens; IgE, specific IgE to allergens; NA, not available (e.g. due to a case-control design).

Table 2. Summary odds ratios for the potential association between delivery by c-section and the risk of common allergic outcomes reported in 26 studies

Outcome	N*	Summary ORs		Heterogeneity statistics	
		Fixed effects model OR, 95% CI	Random effects model OR, 95% CI	Q	P-value
Food allergy/food atopy	6	1.32 (1.12–1.55)	1.45 (1.12–1.86)	8.99	0.11
Inhalant atopy	4	1.06 (0.87–1.28)	1.07 (0.82–1.38)	4.14	0.25
Eczema/atopic dermatitis	8	1.03 (0.98–1.09)	1.03 (0.98–1.09)	1.64	0.98
Allergic rhinitis	7	1.23 (1.12–1.35)	1.24 (1.08–1.43)	10.60	0.10
Asthma	13	1.18 (1.11–1.23)	1.18 (1.05–1.32)	31.38	<0.01
Hospitalization for asthma	7	1.23 (1.18–1.27)	1.21 (1.12–1.31)	18.58	<0.01

*The number of studies included in each meta-analysis of an outcome. The sum of all studies is 45 and exceeds the number of 26 included studies because 11 studies reported on multiple types of allergic outcomes.

CI, confidence interval; c-section, caesarean section; OR, odds ratio.

dom-effects ORs, did not alter the significance of the summary ORs.

Publication bias

We assessed the potential for publication bias using one funnel plot for each outcome as shown in Fig. 2. The vertical line of the funnel plots indicates the fixed-effect OR listed in Table 2, and the corresponding pseudo 95% confidence limits converging as a function of the SE of the fixed-effects OR. For food allergy/food atopy, smaller studies with large SEs were imbalanced towards more positive estimates (i.e. larger than the fixed-effect OR), whereas larger studies with small SEs were imbalanced towards smaller estimates. The pattern resembles a typical publication bias in which the effect estimates from small studies would be biased towards large positive values. For the remaining outcomes, the larger studies with smaller SEs seemed to be scattered more or less symmetrically around the fixed-effect ORs, and the smaller studies with larger SEs had an imbalance towards estimates that were negative or below the summary OR, a pattern that differs from the typical publication bias. In support of this, the funnel plots for these outcomes showed that most of the small studies with large SE did not *a priori* address the association with c-section (dots of triangles in funnel plots). On the contrary, they addressed another or a broader *a priori* hypothesis that could have justified publication even if no association was found with c-section.

Stratified meta-analyses

We evaluated whether the significant summary ORs we found for four outcomes varied for each of nine selected study characteristics (data not shown), i.e. adjustment of relative risks, *a priori* aim, study design, year of birth, size of the study population, country, exclusion, proportion of

c-sections, and age. For food allergy/food atopy, the summary OR was significantly increased for studies conducted in European countries (OR 1.97, 95% CI 1.40–2.76, $N=3$), whereas there was no association for studies conducted in other countries (OR 1.17, 95% CI 0.98–1.41, $N=3$) ($P_{\text{country}}=0.04$). For asthma, the summary OR was higher for studies including ages above and below 10 years (OR 1.26, 95% CI 1.12–1.42, $N=8$), when compared with studies including ages below 10 years only (OR 1.07, 95% CI 1.00–1.15, $N=5$) ($P_{\text{age}}=0.04$). Furthermore, the summary OR was significantly increased for studies using a cohort design (OR 1.22, 95% CI 1.09–1.37, $N=11$), and no association was found for studies using a case-control design (OR 0.84, 95% CI 0.64–1.10, $N=2$) ($P_{\text{design}} < 0.01$). No other significant variations were found. However, for hospitalization for asthma, the influence of age could not be evaluated, because most subjects were 0–10 years of age, and for food allergy/food atopy and allergic rhinitis, the influence of study design could not be evaluated, because only cohort designs were used.

Attributable proportion

For most studies, sufficient data were presented to calculate the proportion of cases attributable to delivery by c-section. Thus, for food allergy/food atopy, the proportion was 4.0% ($N=6$), for allergic rhinitis it was 1.5% ($N=6$), for asthma 1.5% ($N=12$), and for hospitalization for asthma it was 1.1% ($N=7$).

Discussion

The review based on 26 epidemiological studies indicates that delivery by c-section is associated with a moderately increased risk of allergic rhinitis, asthma, and hospitalization for asthma, whereas there was no association with

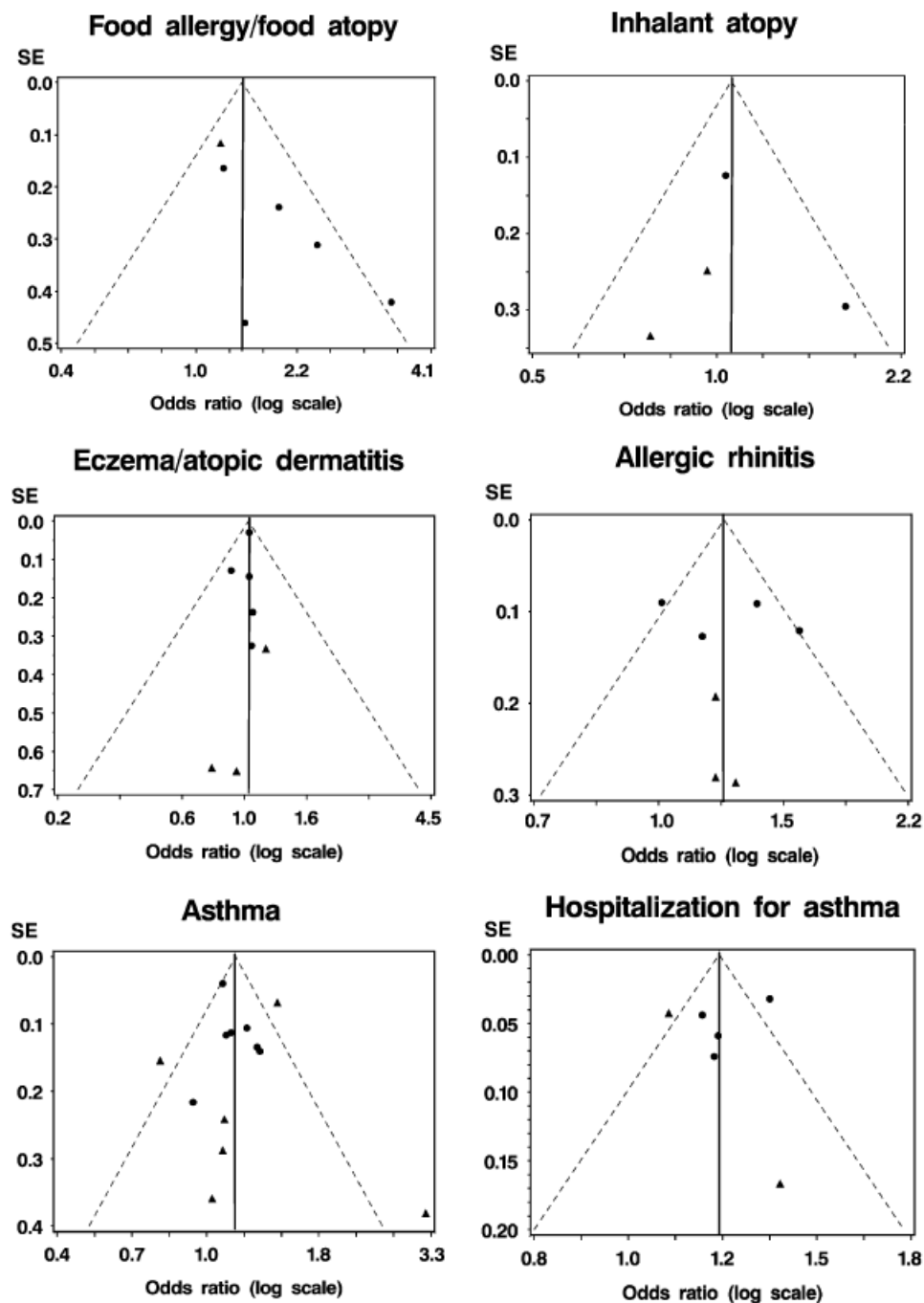


Fig. 2. Funnel plots for assessment of publication bias of the association between c-section and allergic outcomes. The funnel plots show the effect estimates (ln OR) by their standard error (SE of ln OR). The vertical line indicates the summary ORs (food allergy/food atopy, 1.32; inhalant atopy, 1.06; eczema/atopic dermatitis, 1.03; allergic rhinitis, 1.23; asthma, 1.18; hospitalization for asthma, 1.23) from the fixed-effects model according to the SE, and the dashed lines show pseudo 95% confidence limits for the summary ORs. Triangles indicate studies for which an association with c-section was not addressed as an *a priori* hypothesis, i.e. the studies addressed another or a broader hypothesis that could have justified publication even if no association was found with c-section. For the plot on hospitalization for asthma, one study is not shown because of too high SE (SE, 0.8; OR, 1.2); the study did not address an association with c-section *a priori*. OR, odds ratio; c-section, caesarean section.

inhalant atopy and eczema/atopic dermatitis. The funnel plot method indicated that the association with food allergy/food atopy could be publication biased. Whether these findings can be explained by the current two

hypotheses on causal pathways between c-section and allergic outcomes is controversial.

One hypothesis concerns the composition of the gut flora, which is established early in childhood, and remains

relatively constant in adulthood [45, 46]. Vaginal delivery leads to the first colonization of the gut with maternal vaginal bacteria, while c-section babies are deprived of this natural exposure, and exhibit a different gut flora [29, 31–33]. Several observations suggest that a particular, perhaps diverse, composition of the flora plays important roles in normal tolerance induction, as well as development and homeostasis of the immune system [34, 35, 46, 47]. It has therefore been hypothesized that the different gut flora of c-section babies increases susceptibility to atopic conditions [34, 35]. The results of our meta-analyses are, however, not entirely compatible with this hypothesis. Firstly, delivery by c-section was associated with increased risk of allergic rhinitis, but not inhalant atopy. Secondly, c-section was not associated with the risk of atopic dermatitis.

Another hypothesis strictly concerns the associations between c-section and increased risk of asthma and hospitalization for asthma. The associations have been hypothesized to be mediated by neonatal respiratory morbidity, in particular TTN and RDS [21], based on previous studies showing increased risks of asthma associated with TTN and RDS [21, 23, 40, 41].

For both the above hypotheses, it has been suspected that planned c-section might show a stronger association with allergic outcomes than acute c-sections [3, 25]. Specifically, for the hypothesis concerning the gut flora, rupture of foetal membranes, while rare before planned c-sections, is frequent before acute c-sections allowing ascending spread of vaginal bacteria to the foetus [48]. For the hypothesis concerning TTN and RDS, preterm delivery, while rare for planned c-section, is frequent for acute sections leading to TTN or RDS due to premature lungs and clearly not c-section alone. Analyses of planned or acute c-sections and allergic outcomes have been carried out in a number of studies [3, 17, 19, 21, 25, 40, 49], of which two studies included all planned and acute c-sections [21, 25]. In these two studies, the risk of hospitalization for asthma after c-section was found to be higher for planned compared with acute c-sections, although the difference was not significant.

We found that for each allergic outcome significantly associated with c-section, the proportion of cases attributable to c-section was between 1% and 4%. This suggests that the increase in use of c-section during the last decades is unlikely to have contributed much to the allergy epidemic also observed during the last decades.

We found no strong indication that the estimated summary ORs for food allergy/food atopy, inhalant atopy, eczema/atopic dermatitis, and allergic rhinitis were biased by heterogeneity between studies. In contrast, we observed a significant heterogeneity between studies of asthma and hospitalized asthma. However, performing estimation in random-effect models revealed that when taking the heterogeneity into account, the summary ORs

were still significant. As heterogeneity might be due to major differences between the populations and methodology [44], we furthermore explored the heterogeneity by performing stratified meta-analyses according to study characteristics. We found no significant differences for hospitalized asthma. However, for asthma, we observed higher summary ORs for cohort studies compared with case-control studies and in studies including older ages compared with younger ages. The difference according to study design is difficult to interpret as only two of the 13 studies on asthma were a case-control study. The difference according to age might be due to the potential misclassification of early asthma with transient wheezing of a different aetiology [2, 3]. This could indicate that the slightly higher summary OR of 1.26 for asthma based exclusively on studies including older ages is a more reasonable estimate of the association between c-section and asthma.

By inspecting funnel plots, we found no strong indication that the estimated summary ORs for inhalant atopy, eczema/atopic dermatitis, allergic rhinitis, asthma, and hospitalization for asthma were publication biased. In contrast, the funnel plot method indicated that this could be the case for the association between c-section and increased risk of food allergy/food atopy because the studies with higher summary ORs primarily were small studies [4–6]. However, an alternative explanation for the higher summary ORs observed for small [4–6] compared with larger studies [1–3] could be methodological differences between the studies. Thus, the small studies (all conducted in Europe) [4–6] used standardized methods to ascertain the outcomes, the methods were applied uniformly for all children, and the children were followed prospectively with the specific purpose of collecting information on allergies early in life. In contrast, the presence of these important qualities varied in the larger studies (all conducted in the USA) [1–3] and this could explain the weaker risk estimates rather than publication bias. Considering that food allergy is often transient early in life and difficult to diagnose compared with other allergic diseases, the issue needs to be addressed in larger and well-designed studies.

In conclusion, delivery by c-section was found to be associated with a moderately increased risk of allergic rhinitis, asthma, hospitalization for asthma, and perhaps food allergy/food atopy, but not with inhalant atopy and eczema/atopic dermatitis. As only 1–4% of cases of allergic outcomes were attributable to c-section, the increased use of c-section during the last decades is unlikely to have contributed much to the allergy epidemic observed during the same period.

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References

- 1 Liem JJ, Kozyrskyj AL, Huq SI, Becker AB. The risk of developing food allergy in premature or low-birth-weight children. *J Allergy Clin Immunol* 2007; 119:1203–9.
- 2 Salam MT, Margolis HG, McConnell R, McGregor JA, Avol EL, Gilliland FD. Mode of delivery is associated with asthma and allergy occurrences in children. *Ann Epidemiol* 2006; 16: 341–6.
- 3 Renz-Polster H, David MR, Buist AS *et al.* Caesarean section delivery and the risk of allergic disorders in childhood. *Clin Exp Allergy* 2005; 35:1466–72.
- 4 Negele K, Heinrich J, Borte M *et al.* Mode of delivery and development of atopic disease during the first 2 years of life. *Pediatr Allergy Immunol* 2004; 15:48–54.
- 5 Laubereau B, Filipiak-Pittroff B, von Berg A *et al.* Caesarean section and gastrointestinal symptoms, atopic dermatitis, and sensitisation during the first year of life. *Arch Dis Child* 2004; 89:993–7.
- 6 Eggesbo M, Botten G, Stigum H, Nafstad P, Magnus P. Is delivery by cesarean section a risk factor for food allergy? *J Allergy Clin Immunol* 2003; 112:420–6.
- 7 Vonk JM, Boezen HM, Postma DS, Schouten JP, van Aalderen WM, Boersma ER. Perinatal risk factors for bronchial hyperresponsiveness and atopy after a follow-up of 20 years. *J Allergy Clin Immunol* 2004; 114:270–6.
- 8 Xu B, Pekkanen J, Hartikainen AL, Jarvelin MR. Caesarean section and risk of asthma and allergy in adulthood. *J Allergy Clin Immunol* 2001; 107:732–3.
- 9 Maitra A, Sherriff A, Strachan D, Henderson J. Mode of delivery is not associated with asthma or atopy in childhood. *Clin Exp Allergy* 2004; 34:1349–55.
- 10 Sugiyama M, Arakawa H, Ozawa K *et al.* Early-life risk factors for occurrence of atopic dermatitis during the first year. *Pediatrics* 2007; 119:e716–23.
- 11 Bernsen RM, de Jongste JC, Koes BW, Aardoom HA, van der Wouden JC. Perinatal characteristics and obstetric complications as risk factors for asthma, allergy and eczema at the age of 6 years. *Clin Exp Allergy* 2005; 35:1135–40.
- 12 McKeever TM, Lewis SA, Smith C, Hubbard R. Mode of delivery and risk of developing allergic disease. *J Allergy Clin Immunol* 2002; 109:800–2.
- 13 Bager P, Melbye M, Rostgaard K, Benn CS, Westergaard T. Mode of delivery and risk of allergic rhinitis and asthma. *J Allergy Clin Immunol* 2003; 111:51–6.
- 14 Nafstad P, Magnus P, Jaakkola JJ. Risk of childhood asthma and allergic rhinitis in relation to pregnancy complications. *J Allergy Clin Immunol* 2000; 106:867–73.
- 15 Montgomery SM, Wakefield AJ, Morris DL, Pounder RE, Murch SH. The initial care of newborn infants and subsequent hay fever. *Allergy* 2000; 55:916–22.
- 16 Calvani M, Alessandri C, Sopo SM *et al.* Infectious and uterus related complications during pregnancy and development of atopic and nonatopic asthma in children. *Allergy* 2004; 59: 99–106.
- 17 Juhn YJ, Weaver A, Katusic S, Yunginger J. Mode of delivery at birth and development of asthma: a population-based cohort study. *J Allergy Clin Immunol* 2005; 116:510–6.
- 18 Oliveti JF, Kerckmar CM, Redline S. Pre- and perinatal risk factors for asthma in inner city African-American children. *Am J Epidemiol* 1996; 143:570–7.
- 19 Werner A, Ramlau-Hansen CH, Jeppesen SK, Thulstrup AM, Olsen J. Caesarean delivery and risk of developing asthma in the offspring. *Acta Paediatr* 2007; 96:595–6.
- 20 Gessner BD, Chimonas MA. Asthma is associated with preterm birth but not with small for gestational age status among a population-based cohort of Medicaid-enrolled children <10 years of age. *Thorax* 2007; 62:231–6.
- 21 Smith GC, Wood AM, White IR, Pell JP, Cameron AD, Dobbie R. Neonatal respiratory morbidity at term and the risk of childhood asthma. *Arch Dis Child* 2004; 89:956–60.
- 22 Benn CS, Thorsen P, Jensen JS *et al.* Maternal vaginal microflora during pregnancy and the risk of asthma hospitalization and use of antiasthma medication in early childhood. *J Allergy Clin Immunol* 2002; 110:72–7.
- 23 Debley JS, Smith JM, Redding GJ, Critchlow CW. Childhood asthma hospitalization risk after cesarean delivery in former term and premature infants. *Ann Allergy Asthma Immunol* 2005; 94:228–33.
- 24 Kero J, Gissler M, Gronlund MM *et al.* Mode of delivery and asthma – is there a connection? *Pediatr Res* 2002; 52:6–11.
- 25 Hakansson S, Kallen K. Caesarean section increases the risk of hospital care in childhood for asthma and gastroenteritis. *Clin Exp Allergy* 2003; 33:757–64.
- 26 Xu B, Pekkanen J, Jarvelin MR. Obstetric complications and asthma in childhood. *J Asthma* 2000; 37:589–94.
- 27 Porreco RP, Thorp JA. The cesarean birth epidemic: trends, causes, and solutions. *Am J Obstet Gynecol* 1996; 175:369–74.
- 28 Notzon FC. International differences in the use of obstetric interventions. *JAMA* 1990; 263:3286–91.
- 29 Hallstrom M, Eerola E, Vuento R, Janas M, Tammela O. Effects of mode of delivery and necrotising enterocolitis on the intestinal microflora in preterm infants. *Eur J Clin Microbiol Infect Dis* 2004; 23:463–70.
- 30 Adlerberth I, Carlsson B, de Man P *et al.* Intestinal colonization with *Enterobacteriaceae* in Pakistani and Swedish hospital-delivered infants. *Acta Paediatr Scand* 1991; 80:602–10.
- 31 Gronlund MM, Lehtonen OP, Eerola E, Kero P. Fecal microflora in healthy infants born by different methods of delivery: permanent changes in intestinal flora after cesarean delivery. *J Pediatr Gastroenterol Nutr* 1999; 28:19–25.
- 32 Adlerberth I, Lindberg E, Aberg N *et al.* Reduced enterobacterial and increased *Staphylococcal* colonization of the infantile bowel: an effect of hygienic lifestyle? *Pediatr Res* 2006; 59:96–101.
- 33 Salminen S, Gibson GR, McCartney AL, Isolauri E. Influence of mode of delivery on gut microbiota composition in seven year old children. *Gut* 2004; 53:1388–9.
- 34 Bjorksten B. Effects of intestinal microflora and the environment on the development of asthma and allergy. *Springer Semin Immunopathol* 2004; 25:257–70.
- 35 Kirjavainen PV, Gibson GR. Healthy gut microflora and allergy: factors influencing development of the microbiota. *Ann Med* 1999; 31:288–92.

- 36 Nielsen TF, Hokegard KH. The incidence of acute neonatal respiratory disorders in relation to mode of delivery. *Acta Obstet Gynecol Scand* 1984; **63**:109–14.
- 37 White E, Shy KK, Daling JR. An investigation of the relationship between cesarean section birth and respiratory distress syndrome of the newborn. *Am J Epidemiol* 1985; **121**:651–63.
- 38 Danforth DN. Cesarean section. *JAMA* 1985; **253**:811–8.
- 39 Levine EM, Ghai V, Barton JJ, Strom CM. Mode of delivery and risk of respiratory diseases in newborns. *Obstet Gynecol* 2001; **97**:439–42.
- 40 Birnkrant DJ, Picone C, Markowitz W, El KM, Shen WH, Tafari N. Association of transient tachypnea of the newborn and childhood asthma. *Pediatr Pulmonol* 2006; **41**:978–84.
- 41 Schaubel D, Johansen H, Dutta M, Desmeules M, Becker A, Mao Y. Neonatal characteristics as risk factors for preschool asthma. *J Asthma* 1996; **33**:255–64.
- 42 Liem JJ, Huq SI, Ekuma O, Becker AB, Kozyskyj AL. Transient tachypnea of the newborn may be an early clinical manifestation of wheezing symptoms. *J Pediatr* 2007; **151**:29–33.
- 43 Laird NM, Mosteller F. Some statistical methods for combining experimental results. *Int J Technol Assess Health Care* 1990; **6**:5–30.
- 44 Engels EA, Schmid CH, Terrin N, Olkin I, Lau J. Heterogeneity and statistical significance in meta-analysis: an empirical study of 125 meta-analyses. *Stat Med* 2000; **19**:1707–28.
- 45 Fanaro S, Chierici R, Guerrini P, Vigi V. Intestinal microflora in early infancy: composition and development. *Acta Paediatr Suppl* 2003; **91**:48–55.
- 46 Guarner F, Malagelada JR. Gut flora in health and disease. *Lancet* 2003; **361**:512–9.
- 47 Macdonald TT, Monteleone G. Immunity, inflammation, and allergy in the gut. *Science* 2005; **307**:1920–5.
- 48 Moller GH, Woods DL, Malan AF, Sinclair-Smith CC. Chorioamnionitis in relation to mode of delivery at term. *S Afr Med J* 1989; **76**:201–2.
- 49 Annesi-Maesano I, Moreau D, Strachan D. In utero and perinatal complications preceding asthma. *Allergy* 2001; **56**:491–7.