

EDITORIAL

Clinical & Experimental Allergy

Birth by caesarean section and wheezing, asthma, allergy, and intestinal disease

This editorial discusses the findings of the paper in this issue by Menezes et al. [1] pp. 218–223.

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In this edition of *Clinical & Experimental Allergy*, the authors Menezes et al. [1] address the possible relationship between birth by caesarean section (c-section) and the increased risk of wheezing by using data from birth cohorts of 9537 children in Pelotas, Brazil. Despite an increase in births by c-section (31–45%) and wheezing among 4-year-olds (20–28%), there was no association, not even with wheezing at ages 11 and 15 years [1].

Their null finding is relevant because two meta-analyses, presented in previous issues of *Clinical & Experimental Allergy* suggest that the increase in births by c-section in Europe and USA might have had a small impact on the concurrent increase in the prevalence of asthma [2, 3]. The summary risk estimate for asthma based on 23 studies was 1.22 (95% CI 1.14–1.29) [2], and theoretically then 2% of asthma cases could be due to c-section [3]. Causality was discussed in an accompanying editorial by Adams and Doull [4], but the possibility of confounding was put forward. The fact is, however, that adjustment for potential confounding variables had none or little effect in any study, and causality then remains an issue, in particular if the use of c-section continues to rise. At least, with reports of very high prevalence of births by c-section in Latin American countries (24–43%, eight countries) [5], then the lack of association with wheezing among children in a Brazilian city is reassuring.

Neonatal respiratory problems caused by the caesarean delivery, e.g. neonatal respiratory distress syndrome (RDS) and transient tachypnoea of the newborn (TTN), have been suggested to explain the association with the increased risk of asthma and wheezing (Smith et al.) [6]. It is unclear how RDS or TTN could affect lung function beyond the neonatal period. Because few caesarean deliveries cause RDS and TTN

(3–4% vs. 1% for vaginal deliveries), Smith et al. suggested that this is why the overall association between birth by c-section and asthma is weak. If one assumes the worst case that RDS and TTN have a harmful long-term effect on lung function, then a stronger association between birth by c-section and an increased risk of persistent wheezing or asthma could be suspected. The suspicion is compatible with the cited meta-analyses because the summary risk estimate for asthma was higher for studies where asthma was ascertained in adolescence (1.26, ages 0–31 years, eight studies) vs. in childhood only (1.07, ages ≤ 10 years, five studies; $P = 0.04$) [3]. It is reassuring that the study by Menezes and colleagues does not support a *significant* association between birth by c-section and persistent wheezing, when considering the high c-section frequency. A few studies in the cited meta-analyses had information on comparable outcomes in USA and Europe [3]. A cohort study with a c-section frequency of 20% reported a risk increase (1.48) for late-onset persistent asthma diagnosed at age 4–18 years [7], and a recent cohort study with a c-section frequency of 9% reported a risk increase (1.77) for chronic asthma defined as wheezing, dyspnoea, and/or use of inhaled steroids at age 3–7 and still at 8 years of age [8]. Thus, the issue of causality remains controversial.

One other suggested causal link between birth by c-section and an increased risk of asthma concerns establishment of the intestinal flora [9]. Newborns delivered by c-section have a different (less indigenous) intestinal flora, because the first bacteria colonizing their body habitats are from skin bacteria only [10], e.g. of the mother, midwife, doctor. In contrast, newborns delivered vaginally are initially colonized with bacteria from the mother's vaginal and anal regions subsequent to the passage of the birth canal [10]. In addition, c-section babies are more often separated from the mother, have longer hospital stays, and delayed or shorter breastfeeding periods [11, 12] – factors that alter, delay or deprive bacterial exposure as well as bacterial growth conditioned by breastmilk.

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The different intestinal flora of c-section babies has been hypothesized to prolong the immunological immaturity after birth and thereby increase the risk of later development of allergic diseases [13] – not exclusively asthma [14]. However, in our meta-analyses [3] and recent studies [15, 16], except for one [17], we found limited evidence for an association between birth by c-section and an increased risk of other allergic diseases than asthma. Accordingly, the meta-analyses identified a risk increase for allergic rhinitis (1.23), which, however, might as well represent a risk increase due to many subjects with asthma and rhinitis. Furthermore, there was no significant association with atopy (IgE or skin reactivity) to, e.g. house dust mites or pollen (1.06) and with atopic eczema (1.03) that could support a strong association with atopic asthma and rhinitis. In contrast, the meta-analyses identified a potential association between birth by c-section and an increased risk of food allergy and atopy to foods early in life (1.32) – a finding that could support an atopic component and at the same time make good biological sense because the intestinal flora and manifestation of an intestinal disease could be connected. A recent small study by Kvenshagen et al. [15] addressed the association with food allergy but now using a reliable objective procedure to diagnose food allergy. The results did not, however, confirm an association between birth by c-section and increased risk of food allergy. One reason could be a bias in previous studies, e.g. over-reporting of reactions to food by anxious mothers after c-section, in particular if the mothers had allergy. On the other hand, two of the meta-analysed studies reported that birth by c-section was associated with an increased risk of atopy to food items (2.06) and parent-reported diarrhoea (1.46) among infants with allergic parents, and with an increased risk of hospitalization for unspecified gastroenteritis in childhood (1.31) [18, 19]. In a recent study, we had more precise information, and demonstrated that birth by c-section was not a clinically relevant determinant of risk of laboratory-confirmed intestinal bacterial infections, e.g. with *Salmonella* and *Campylobacter*, among 1.7 million infants, children, and young adults in Denmark [16].

In summary, the possible impact of increasing c-section frequencies on the overall burden of wheezing, asthma, allergy, and intestinal disease appears negligible at the population level. Furthermore, the causal relationship remains controversial.

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