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Caesarean delivery, preterm birth and risk of food allergy – Nationwide Swedish cohort study of over 1 million children

Short title: Association between perinatal factors and food allergy in children

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ABSTRACT

Background & Objectives: Little is known about early life risk factors for food allergy in children. We examined the association between perinatal characteristics and future risk of food allergy in offspring.

Methods: This nationwide Swedish cohort study of 1,086,378 children born in Sweden in 2001-2012 used prospectively recorded data from health care registers. Using Cox regression, we estimated hazard ratios (HRs) with 95% confidence intervals (CIs) for the association between perinatal characteristics (e.g. caesarean delivery, preterm birth) and food allergy as defined by diagnoses in the National Patient Register, adjusting for infant sex and maternal factors (age at delivery, country of birth, parity, smoking, body mass index and asthma/pulmonary disease).

Results: During the 13-year follow-up, 26,732 children (2.5%) were diagnosed with food allergy. Food allergy was positively associated with caesarean delivery (HR=1.21; 95%CI=1.18-1.25), large for gestational age (HR=1.15; 95%CI=1.10-1.19) and low 5-minute Apgar score (HR=1.22, 95CI=1.10-1.36) but negatively associated with very preterm birth (<32 weeks of gestation: HR=0.74; 95%CI=0.56-0.98). No association was found between food allergy and moderately preterm birth, low birth weight or small for gestational age. Risk estimates were similar when the outcome was restricted to two records of diagnosed food allergy.

In 1,000 children undergoing caesarean delivery, an extra 5 developed food allergy compared with the reference group, suggesting that 17% of food allergy in children born with caesarean delivery can be explained by this exposure (attributable fraction).

Conclusions: Caesarean delivery was associated with increased risk of food allergy, whereas very preterm birth with decreased risk.

Key messages:

- caesarean delivery, large for gestational age and low 5-minute Apgar score increased the risk of food allergy
- inversely, very preterm birth was associated with lower risk of later food allergy

Capsule Summary: This study found an increased risk of food allergy in offspring exposed to caesarean delivery and a decreased risk in children born very preterm illustrating the impact of early life influences on the development of food allergy.

Keywords: Food allergy; preterm birth; caesarean delivery; children.

Abbreviations used:
HR: Hazard ratio
CI: Confidence interval
SGA: Small for gestational age
LGA: Large for gestational age
MBR: Medical Birth Register
NPR: National Patient Register
BMI: Body Mass Index
ICD: International classification of disease

INTRODUCTION

Food allergy, defined as a reproducible adverse immune response to food proteins, represents a global public health concern.[1-3] The prevalence of food allergy is still increasing[4-6] and although there is an interest in potentially aetiological environmental components, very little is known about early life risk factors, such as perinatal influences.[7, 8] Two meta-analyses have shown that caesarean delivery is associated with moderately increased risk of asthma and atopic disease.[9, 10] A delayed and altered gastrointestinal microbe colonisation has been suggested as a possible aetiological factor[11, 12], however, one large register-based sibling study from Sweden proposed that the underlying indications for caesarean delivery may explain this association.[13] One retrospective study reported an increased risk of allergic rhinoconjunctivitis and asthma after caesarean delivery. Yet, this association was gender-specific and was only seen in girls.[14]

Preterm birth and low birth weight have also been linked to an increased risk of asthma.[15-18] A meta-analysis of 17 studies reported a 1.46-fold increased risk of asthma or childhood wheeze after preterm birth.[19] Although caesarean delivery and preterm birth may predispose offspring to asthma, there is insufficient and conflicting data on the impact of perinatal factors on the development of food allergy.[14, 20-23] A systematic review suggested that caesarean delivery increases the risk of sensitisation to food allergens.[24]

The aim of this study was to examine the association between caesarean delivery, preterm birth, low birth weight, small for gestational age, large for gestational age

(LGA) and low Apgar score (<7) at 5 minutes and future food allergy in over 1 million children born in Sweden between 2001 and 2012.

METHODS

Study design and population

This nationwide longitudinal cohort study used prospectively recorded data from the Swedish Medical Birth Register (MBR) and the National Patient Register (NPR) to investigate the association between perinatal characteristics and food allergy. Information from the MBR was linked to the NPR using the unique personal identity number assigned to all Swedish residents.[25]

We identified 1,232,739 consecutively born children in Sweden between 2001 and 2012 in the MBR, retrieving data on offspring sex, mode of delivery, gestational age, birth weight and 5-minute Apgar score and we examined the risk of developing food allergy up to the year 2013. Among these children, 1,088,990 (88.3%) had complete data on all covariates (listed in Table 1). We restricted our cohort to offspring with a follow-up of at least 60 days after birth by excluding individuals who died before that age or had a diagnosis of food allergy in the first 2 months of life (we deemed that a diagnosis <2 months had low validity). In our final analyses 1,086,378 children (88.1%) were included (age range at end of follow-up: 0.2 to 12.8 years). Follow-up time ended with first diagnosis of food allergy, death or December 31, 2013, whichever came first.

Covariates

Maternal characteristics analysed in this study were extracted from the MBR and consisted of age at delivery, country of birth, parity, self-reported smoking habits at first antenatal visit, body mass index (BMI) in early pregnancy, and maternal asthma/pulmonary disease. We divided our data into three calendar periods based on year of birth. Covariates are described in Supplementary eTable 1.

Exposures

Mode of delivery was categorised as vaginal or caesarean. Caesarean delivery was further divided into elective (before the onset of labour) or emergency. Other exposures are described in the appendix.

Outcome - Food allergy

Through the Swedish NPR, we identified children in our cohort diagnosed with food allergy during follow-up. We restricted our study to individuals born in 2001 or later since outpatient care was first included in the NPR in 2001.[26] In this study, food allergy was defined as having a relevant ICD (international classification of disease)-10 code: Z91.0A-E.

Statistical analyses

Cox regression was used to estimate hazard ratios (HRs) for the association between exposures and food allergy diagnosis adjusting for sex and maternal factors: age at delivery, country of birth, parity, early pregnancy smoking, BMI and asthma/pulmonary disease (Tables 1 and 2). We further examined the risk of having at

least two records of a diagnosis of food allergy (Table 1). In a separate analysis, we stratified for years of follow-up (Table 2). For instance, the HR for the follow-up time <1 year reflects food allergy diagnosed in children aged between 2 and 14 months. Finally, we calculated excess risks and population attributable fractions (%) for developing food allergy in children by pregnancy outcomes based on observed and expected incidence rates per 100,000 person-years standardised as regards covariates (Table 1).

HRs with 95% confidence intervals (CIs) that did not include 1.0 were considered statistically significant.

Ethics

The study was approved by the Regional Ethical Review Board in Stockholm, Sweden (Dnr. 2008/1182-31/4).

RESULTS

Among the 1,086,378 children included in this study during the 13-year follow-up, 26,732 (2.5%) developed food allergy; of these, 14,534 (1.3%) had at least two hospital-based diagnoses of food allergy. The median age at first diagnosis of food allergy was 1.6 years (range 0.2-12.8 years). The median follow-up was 6.4 years (range 0.2-13 years). Food allergy was more likely to occur in female children, children to Swedish mothers and to mothers with asthma/pulmonary disease (eTable 1).

Adjusted HRs were calculated to estimate the association between perinatal

characteristics and risk of future food allergy (Tables 1 and 2). Food allergy was positively associated with caesarean delivery (HR=1.21; 95%CI=1.18-1.25), both elective (HR=1.18; 95%CI=1.13-1.23) and emergency (HR=1.24; 95%CI=1.19-1.29). Inversely, food allergy was negatively associated with very preterm birth (HR=0.74; 95%CI=0.56-0.98) but not with moderately preterm (HR=0.96, 95%CI=0.90-1.03) or post-term birth (HR=1.01; 95%CI=0.97-1.06). The risk of future food allergy increased in infants born LGA (HR=1.15; 95%CI=1.10-1.19) and infants with a low Apgar score (HR=1.22; 95%CI=1.10-1.36). No association was found between low birth weight or SGA and future food allergy (Table 1). Adjusting for calendar period did not change the association between caesarean delivery and food allergy (HR=1.20; 95%CI=1.17-1.24).

When the outcome was restricted to offspring with at least two recorded diagnoses of food allergy, we found similar risk estimates for all but one exposure: a borderline positive association between post-term birth and food allergy (HR=1.07; 95%CI=1.00-1.13) (Table 1). The results did not change more than marginally when we stratified for follow-up (<1 year, 1-4.99 years, ≥5 years). The risk of food allergy in offspring with caesarean delivery and a ≥5-year follow-up was still 21% higher than vaginal delivery (HR=1.21; 95%CI=1.12-1.30). Moreover, the HR point estimate for food allergy related to very preterm birth was unchanged, albeit no longer statistically significant and with a wide confidence interval (HR=0.74; 95%CI=0.38-1.43). No difference was found in the HRs for food allergy in LGA infants, low 5-minute Apgar score and the other exposures among the three subgroups (<1 year, 1-4.99 years, ≥5 years) during the follow-up or in risk estimates between boys and girls

(Table 2). We found no difference in HRs when we divided our data into three calendar periods of birth (2001-2004, 2005-2008, 2009-2012).

Excess risks of future food allergy per 100,000 person-years (adjusted for covariates) and population attributable fractions were calculated. As per our findings, in 1,000 children exposed to caesarean delivery, an extra 5 developed food allergies during the follow-up compared with the reference group. The population attributable fraction was 17% for caesarean delivery, suggesting that 17% of all food allergy in children born with caesarean delivery may be due to this exposure. The excess risks and population attributable fractions for the other exposures are shown in Table 1.

DISCUSSION

In this population-based study of over 1 million children we found that caesarean delivery (elective and emergency) increased the risk of food allergy in the offspring. In addition, children born LGA or with low 5-minute Apgar score were more likely to have a diagnosis of food allergy. Inversely, very preterm birth was associated with lower risk.

The increased risk of food allergy observed in children born via caesarean section is consistent with most previous research[24, 27, 28], but contrasts to data from Renz-Polster et al. Yet, the proportion of children developing food allergy was low in their study (0.37% compared with 2.5% in ours).[14] Furthermore, a second study of 512 Norwegian children failed to demonstrate an association between caesarean delivery and food allergy.[23] However, that study included a very high proportion children born

preterm (31.5%). Considering that half of these children were born by caesarean delivery, this may have influenced the findings of the study.

It is noteworthy that our study suggests that both elective and emergency caesarean deliveries predispose to food allergy. This positive association strengthens the theory that exposure to the vaginal microflora may reduce the risk of offspring atopic manifestations. It has previously been implied that mode of delivery is a significant determinant of the post-partum adaptation of the immune system.[29] Moreover, the hygiene hypothesis stipulates that intestinal microbiota composition influences oral tolerance and the immune response to allergens in children. Van Nimwegen et al found that caesarean delivery is strongly associated with C. *difficile* colonisation which consequently increases the risk of wheeze, eczema and sensitisation to food allergens in childhood.[11] Caesarean delivery seems to delay and alter the development of the offspring immune system, subsequently increasing the risk of atopic disease.[11,12]

Our results also suggest that very preterm birth is negatively associated with food allergy. In contrast, Liem et al found no association between low birth weight or preterm birth and risk of food allergy.[20] Our cohort was substantially larger, hence, a further examination of the hypothesis that an immature gastrointestinal tract leads to increased permeability and food antigen uptake and predisposes to early food sensitisation[30] is needed. The observed negative association between very preterm birth and food allergy indicates that either very preterm birth *per se*, or associated neonatal care initiated in very preterm-born children (including early introduction of foods orally), may be involved in the induction of tolerance to foods. These findings

are in accordance with observations that the risk of atopy is influenced by factors operating during early stages of development.[31] Our findings are intriguing in view of the results from recent trials on early introduction of allergenic foods and current discussions worldwide on strategies to prevent food allergy in children.[7, 32]

Strengths of the present study include its longitudinal population-based design and large size of more than one million births. Through nationwide registers, we could include virtually all births in Sweden between 2001 and 2012, minimising selection bias typically seen in studies from tertiary centres.[33]

The main methodological concern in this study relates to potential confounding factors. We controlled for a broad range of covariates but were unable to investigate the role of breastfeeding or antibiotic use. Another limitation is the lack of nutritional information. Early nutrition may differ between preterm and full-term-born infant children.

In this study, the diagnosis of food allergy was based on relevant ICD-10 codes. Such codes may have low sensitivity and thus there is a risk that mild food allergy has not been captured. We chose to use a narrow definition of food allergy. A drawback with a specific definition is that we may have missed some cases with food allergy and that absolute risks for food allergy may therefore be underestimated. We are unaware of any validation study of the specificity of ICD-10 codes for food allergy in the NPR but the positive predictive value for most diagnoses ranges from 85-95%.[26, 34] However, to increase specificity we examined the risk of having at least two diagnoses of food allergy during the follow-up. This sensitivity analysis demonstrated

similar risk estimates, except for a slightly higher risk of food allergy in children born post-term.

In conclusion, using a large population database, we found an increased risk of food allergy in children born through elective or emergency caesarean delivery compared with those delivered vaginally. In contrast, children born very preterm were at a lower risk of food allergy.

REFERENCES

1. Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, et al. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. Allergy. 2014;69(8):1008-25.
2. Burks AW, Tang M, Sicherer S, Muraro A, Eigenmann PA, Ebisawa M, et al. ICON: food allergy. J Allergy Clin Immunol. 2012;129(4):906-20.
3. Sackeyfio A, Senthinathan A, Kandaswamy P, Barry PW, Shaw B, Baker M. Diagnosis and assessment of food allergy in children and young people: summary of NICE guidance. BMJ. 2011;342:d747.
4. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: summary of the NIAID-sponsored expert panel report. Nutr Res. 2011;31(1):61-75.
5. Sicherer SH, Sampson HA. Food allergy: Epidemiology, pathogenesis, diagnosis, and treatment. J Allergy Clin Immunol. 2014;133(2):291-307; quiz 8.
6. Savage J, Sicherer S, Wood R. The Natural History of Food Allergy. J Allergy Clin Immunol Pract. 2016;4(2):196-203; quiz 4.
7. Turcanu V, Brough HA, Du Toit G, Foong RX, Marrs T, Santos AF, et al. Immune mechanisms of food allergy and its prevention by early intervention. Curr Opin Immunol. 2017;48:92-8.
8. Gupta M, Sicherer SH. Timing of food introduction and atopy prevention. Clin Dermatol. 2017;35(4):398-405.
9. Thavagnanam S, Fleming J, Bromley A, Shields MD, Cardwell CR. A meta-analysis of the association between Caesarean section and childhood asthma. Clin Exp Allergy. 2008;38(4):629-33.
10. Bager P, Wohlfahrt J, Westergaard T. Caesarean delivery and risk of atopy and allergic disease: meta-analyses. Clin Exp Allergy. 2008;38(4):634-42.
11. van Nimwegen FA, Penders J, Stobberingh EE, Postma DS, Koppelman GH, Kerkhof M, et al. Mode and place of delivery, gastrointestinal microbiota, and their influence on asthma and atopy. J Allergy Clin Immunol. 2011;128(5):948-55.e1-3.

12. 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(5):341-6.
13. Almqvist C, Cnattingius S, Lichtenstein P, Lundholm C. The impact of birth mode of delivery on childhood asthma and allergic diseases--a sibling study. Clin Exp Allergy. 2012;42(9):1369-76.
14. Renz-Polster H, David MR, Buist AS, Vollmer WM, O'Connor EA, Frazier EA, et al. Caesarean section delivery and the risk of allergic disorders in childhood. Clin Exp Allergy. 2005;35(11):1466-72.
15. Castro-Rodriguez JA, Forno E, Rodriguez-Martinez CE, Celedon JC. Risk and Protective Factors for Childhood Asthma: What Is the Evidence? J Allergy Clin Immunol Pract. 2016;4(6):1111-22.
16. Jaakkola JJ, Ahmed P, Ieromnimon A, Goepfert P, Laiou E, Quansah R, et al. Preterm delivery and asthma: a systematic review and meta-analysis. J Allergy Clin Immunol. 2006;118(4):823-30.
17. Ortqvist AK, Lundholm C, Carlstrom E, Lichtenstein P, Cnattingius S, Almqvist C. Familial factors do not confound the association between birth weight and childhood asthma. Pediatrics. 2009;124(4):e737-43.
18. Sonnenschein-van der Voort AM, Arends LR, de Jongste JC, Annesi-Maesano I, Arshad SH, Barros H, et al. Preterm birth, infant weight gain, and childhood asthma risk: a meta-analysis of 147,000 European children. J Allergy Clin Immunol. 2014;133(5):1317-29.
19. Been JV, Lugtenberg MJ, Smets E, van Schayck CP, Kramer BW, Mommers M, et al. Preterm birth and childhood wheezing disorders: a systematic review and meta-analysis. PLoS Med. 2014;11(1):e1001596.
20. 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(5):1203-9.
21. Siltanen M, Kajosaari M, Pohjavuori M, Savilahti E. Prematurity at birth reduces the long-term risk of atopy. J Allergy Clin Immunol. 2001;107(2):229-34.
22. Siltanen M, Wehkalampi K, Hovi P, Eriksson JG, Strang-Karlsson S, Jarvenpaa AL, et al. Preterm birth reduces the incidence of atopy in adulthood. J Allergy Clin Immunol. 2011;127(4):935-42.

23. Kvenshagen B, Halvorsen R, Jacobsen M. Is there an increased frequency of food allergy in children delivered by caesarean section compared to those delivered vaginally? Acta Paediatr. 2009;98(2):324-7.
24. Koplin J, Allen K, Gurrin L, Osborne N, Tang ML, Dharmage S. Is caesarean delivery associated with sensitization to food allergens and IgE-mediated food allergy: a systematic review. Pediatr Allergy Immunol. 2008;19(8):682-7.
25. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol. 2009;24(11):659-67.
26. Ludvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450.
27. 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(2):420-6.
28. Laubereau B, Filipiak-Pittroff B, von Berg A, Grubl A, Reinhardt D, Wichmann HE, et al. Caesarean section and gastrointestinal symptoms, atopic dermatitis, and sensitisation during the first year of life. Arch Dis Child. 2004;89(11):993-7.
29. Schlinzig T, Johansson S, Stephansson O, Hammarstrom L, Zetterstrom RH, von Dobeln U, et al. Surge of immune cell formation at birth differs by mode of delivery and infant characteristics-A population-based cohort study. PLoS One. 2017;12(9):e0184748.
30. Alpan O. Oral tolerance and gut-oriented immune response to dietary proteins. Curr Allergy Asthma Rep. 2001;1(6):572-7.
31. Hanson M, Gluckman P. Developmental origins of noncommunicable disease: population and public health implications. Am J Clin Nutr. 2011;94(6 Suppl):1754s-8s.
32. Allen KJ, Koplin JJ. Prospects for Prevention of Food Allergy. J Allergy Clin Immunol Pract. 2016;4(2):215-20.
33. Rothman KJ, Greenland S, Lash TL. Modern epidemiology. Philadelphia: Lippincott Williams & Wilkins; 2008.

34. Ortqvist AK, Lundholm C, Wettermark B, Ludvigsson JF, Ye W, Almqvist C. Validation of asthma and eczema in population-based Swedish drug and patient registers. Pharmacoepidemiol Drug Saf. 2013;22(8):850-60.