Cesarean delivery, allergy and lung function in children: findings from two Australian cohorts

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Abbreviations: CI, confidence interval; OR, odds ratio; aOR, adjusted odds ratio; SD, standard deviation; LSAC, Longitudinal Study of Australian Children; SEIFA, Socio-Economic Indexes for Areas Disadvantage Index; FVC, the maximal volume of air exhaled with maximally forced effort from a maximal inspiration; FEV1, the maximal volume of air exhaled in the first second of a forced expiration from full inspiration to total lung capacity; MMEF, mean flow rate between 25 and 75% of FVC.

Table of Contents Summary: Across two Australian population-based longitudinal cohorts, this study examines whether cesarean delivery is associated with allergy and lung function during the elementary school years.

What's Known on This Subject:

Older studies suggested a modest association between delivery mode and asthma, but not eczema, in childhood. The rapid rise in both cesarean delivery and childhood allergy and the plausibility of causal associations warrant re-examination in contemporary cohorts.

What This Study Adds:

In two contemporary population-based, longitudinal studies of Australian children, a modest effect of cesarean delivery was observed for the outcome of current asthma. However, no association was observed between delivery mode and eczema or lung function.

SUBMITTED

Contributors' Statements:

Prof Wake, Dr Peters and Dr Lamb conceptualized and designed the study, supervised data analyses, and reviewed and revised the manuscript.

Ms Zijun Liao conceptualized and designed the study, carried out the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript.

All authors critically reviewed the manuscript for interpretation, intellectual content and approved the final manuscript as submitted. All authors agree to be accountable for all aspects of the work.

SUBMITTED

ABSTRACT

Background and objective: As both cesarean delivery and childhood allergy continue to rise, their inter-relationships may change. We aimed to determine whether cesarean delivery predicts later childhood allergic disease and impaired lung function in children from two contemporary harmonized population-based cohorts.

Methods: Parent-reported asthma and eczema data were drawn from two prospective Australian birth cohorts, HealthNuts (n=5276, born 2006-2010) and the Longitudinal Study of Australian Children (LSAC, n=5107, born 2003-2004) at age 6-7 years, and spirometric lung function from LSAC's Child Health CheckPoint phase (n=1756) at age 11-12 years. We used logistic regression to estimate associations between delivery mode and current asthma and eczema at age 6-7y, and linear regression to examine lung function at age 11-12y. Models included adjustment for potential confounding factors.

Results: Complete case analysis included 3135 HealthNuts and 3654 LSAC children (32.2% and 30.9% born by cesarean respectively). Children born by cesarean delivery had slightly higher odds of asthma at age 6-7y (HealthNuts: adjusted OR 1.25, 95% CI 1.00 to 1.57; LSAC: adjusted OR 1.05, 95% CI 0.86 to 1.28), but not eczema (HealthNuts: adjusted OR 1.09, 95% CI 0.88 to 1.35; LSAC: adjusted OR 0.89, 95% CI 0.69 to 1.15). Spirometric lung function parameters at age 11-12y were similar for children born by cesarean and vaginal delivery.

Conclusions: In two unselected populations using harmonized protocols, the likely effects of cesarean delivery on childhood allergy were small and limited to parent-reported asthma at age 6-7y. Whether this small excess represents allergic lung disease is uncertain.

INTRODUCTION

Rates of both cesarean delivery¹ and childhood allergic diseases² have risen over the last 30 years and they may be causally associated. America,³ Australia¹ and China⁴ all now have cesarean rates in excess of 30%, while the rates of current asthma and eczema in 6 to 7-year-old children globally are 12% and 8% respectively, with higher prevalence reported in Australia (20% for asthma and 17% for eczema).^{5,6} A cesarean delivery can effectively prevent maternal and perinatal mortality and morbidity, when medically justified; however, it is also associated with short- and long-term risk.⁷ Childhood allergic diseases may be an adverse consequence of cesarean delivery on offspring's health.⁸⁻¹¹ One plausible mechanism is that sub-optimal early microbial exposure in infants delivered by cesarean may modulate the developing immune system and contribute to an increased risk of allergic diseases.¹² Other possible mechanisms specific to asthma include the higher rates of respiratory distress syndrome and transient tachypnea that result from cesarean delivery.¹³⁻¹⁵

In meta-analyses examining these associations, the risk of asthma (the most-studied outcome) was around 20% higher in children delivered by cesarean,⁸⁻¹¹ but findings of individual studies were notably inconsistent and included null studies.¹⁶⁻²⁴ Cesarean delivery does not appear to predict lung function in older children and adolescents in two birth cohort studies which are, to our knowledge, the only population-based studies to have explored these associations.^{25,26} However, as these cohorts were born in the early-mid 1990s, they may not reflect today's epidemiology. Far fewer studies have examined eczema as an outcome, also with overall null associations reported,⁹ despite positive association of eczema with asthma.²⁷ Very few studies have simultaneously examined multiple allergic phenotypes within and

across population-based samples using a harmonized protocol, which could give a clearer relative picture of possible causal effects. In addition, several studies have reported that the effect of cesarean delivery on allergic disease is modified by breastfeeding duration or maternal history of allergy.^{28,29} This warrants further examination in large population-based cohorts, as well as markers of microbial exposure.

In the present study, we assessed associations between cesarean delivery and (1) childhood asthma and eczema in 6 to 7-year-old children in two contemporaneous Australian population-based cohorts (HealthNuts and the Longitudinal Study of Australian Children (LSAC)), and (2) spirometric lung function at age 11 to 12 years in LSAC's Child Health CheckPoint module. We also explored potential effect modification by breastfeeding duration, maternal history of allergy, and factors related to microbial exposure such as childcare attendance, pet and sibling exposure.

METHODS

Study design and Procedures

The HealthNuts study is a population-based, longitudinal study of childhood allergic diseases undertaken in Melbourne, Australia. Recruitment has been described in detail elsewhere.^{30,31} In brief, 5276 infants aged 11-15 months were recruited from council-run immunization sessions in Melbourne, 2007-2011 (74% participation). This cohort has been followed up at ages 4 years (wave 2) and 6 years (wave 3). At wave 3 (2012-2016), all 5276 children were invited to undergo a skin prick test to a panel of food and aeroallergens (house

dust mite, rye grass, Bermuda grass, cat hair, alternaria, birch mix, cladosporium, and dog hair). Parents completed a questionnaire which captured detailed information on the child's health including history of allergy incorporating questions from the ISAAC study.³² At wave 3 (age 6 years), 84% of children participated, with 3663 completing the full written questionnaire.³²

LSAC is Australia's only national population-based longitudinal study of children's health, development and wellbeing, and its methods have been described previously.³³⁻³⁵ Our present study used data from the Baby (B) cohort, which recruited 5107 children aged 0-1 years at baseline in 2004. LSAC interviewers have collected data in participants' homes with children's primary caregivers (usually the biological mother) biennially since 2004. In wave 4 (age 6-7 years), 83.1% (n=4242) were retained,³⁶ with almost all (n=4238) having data on delivery mode and at least one allergic outcome.

The Child Health CheckPoint, an objective physical health and biomarkers module for LSAC, was conducted between LSAC's 6th and 7th waves. Children aged 11-12 years attended an assessment with a primary caregiver, usually their mother,³⁷ which included spirometry. The CheckPoint sample size was fixed by LSAC retention to wave 6.³⁸ Ultimately, the CheckPoint analytic sample included 1874 parent-child pairs (54% uptake), with 1756 (93.7%) children having available data on delivery mode and child's lung function.

HealthNuts was approved by the Victorian State Government Office for Children (CDF/07/492), the Victorian State Government Department of Human Services (10/07) and the Royal Children's Hospital Human Research Ethics Committee (27047 and 32294); LSAC

by the Australian Institute of Family Studies Ethics Committee; and CheckPoint by the Royal Children's Hospital Human Research Ethics Committee (HREC33225) and the Australian Institute of Family Studies Ethics Committee (AIFS14-26). Parents provided written informed consent for all elements.

Measures

Delivery mode

At the baseline (12 months), parents reported delivery mode by written questionnaire in HealthNuts and by interviewer question in LSAC. Delivery was dichotomized as cesarean or vaginal.

Asthma and eczema (age 6 to 7 years)

In HealthNuts and LSAC, current asthma was defined as parent report of ever having a doctor diagnosis of asthma, plus either wheeze or use of asthma medication in the last 12 months. In HealthNuts, asthma was further classified as atopic or non-atopic based on the presence of sensitization to one or more aeroallergens (i.e. positive SPT wheal 3mm greater than negative control).³² In HealthNuts, current eczema was derived from the ISAAC questionnaire.³⁹ Current eczema was defined as a response of "yes" to all the following questions: 1) Has your child ever had an itchy rash which was coming and going for at least six months? 2) Has your child had this itchy rash at any time in the last 12 months? 3) Has this itchy rash at any time affected any of the following places: the folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears or eyes? In LSAC current eczema was defined as a response of "yes" to both 1) Does study child have

ongoing eczema? and 2) Has that ongoing eczema affected at least one of these parts (the folds of the elbows, behind the knees, under the buttocks, or around the neck).

Lung function (age 11 to 12 years)

Spirometry at the CheckPoint was performed in accordance with American Thoracic Society /European Respiratory Society guidelines.⁴⁰ Spirometer (Vyntus, California (Ca), USA) and Sentry Suite software (Ca, USA) were used for collection. Children performed 3-8 maximal exhalation maneuvers, inhaled 4 puffs of bronchodilator (salbutamol), waited 10 minutes, and then repeated the test. The spirometric indices were FVC (the maximal volume of air exhaled with maximally forced effort from a maximal inspiration), FEV₁ (the maximal volume of air exhaled in the first second of a forced expiration from full inspiration to total lung capacity), the ratio of FEV₁/ FVC, and MMEF (mean flow rate between 25 and 75% of FVC). We generated standardized z-scores of these lung function parameters using the Global Lung Function Initiative (GLI)-2012 multi-ethnic all-age reference equations for spirometry.⁴¹ Reversible airflow limitation was recorded when FEV₁ increased by $\geq 12\%$ after bronchodilator.⁴²

Statistical Analyses

All statistical analyses were performed in Stata 15.0. The prevalence of allergy was estimated as the observed proportion with 95% confidence intervals (CIs) generated using the normal approximation to the binomial distribution. Crude and adjusted odds ratios (ORs) of allergic disease outcomes for children born by cesarean compared against the reference category of those born vaginally were estimated using logistic regression models. Given the cross-cohort focus, we adjusted for the same covariates in both studies, including maternal

age at birth, neighborhood disadvantage (Socio-Economic Indexes for Areas Disadvantage Index (SEIFA), quintiles), gestational age (weeks), birth weight (grams), maternal smoking during pregnancy (none/any) and mother's country of birth (Australia, Asia, Europe and other). The selection of covariates was based on literature showing associations of each with both the exposure and outcome. Linear regression models were used to estimate mean differences in lung function parameters between the delivery modes (children born vaginally as the reference group), adjusting for the same covariates as in the logistic regressions, in addition to corresponding parental lung function parameters.

Effect modification was assessed by adding an interaction term between the potential modifying variable and delivery mode into the regression models and comparing the models with and without the interaction terms using likelihood ratio tests. Effect modifiers assessed were breastfeeding (<6 or ≥ 6 months), maternal history of asthma/eczema, presence of older siblings (0, ≥ 1) attendance at day care center within the 1st year (none/any), and pet exposure within the 1st year (none/any).

In sensitivity analyses, we adjusted our models for additional covariates related to outcomes, including child sex, presence of older siblings, and maternal history of asthma/eczema; the latter were not included in the main analyses because of the relatively high proportion of missing data for each (~10%) in LSAC. We also applied inverse probability weighting in both cohorts to allow for the potential impact of differential loss to follow-up in those who did and did not participate at age 6-7 years.^{32,43}

RESULTS

Figure 1 presents the study flow and participation of the HealthNuts, LSAC and CheckPoint studies. A total of 3135 and 3654 children had data for both delivery mode, at least one allergic outcome at 6-7 years and all covariates in the main analyses in HealthNuts and LSAC respectively. For CheckPoint, the corresponding number for lung function was 1502 children.

Table 1 shows the characteristics of the samples in the studies. The proportion of infants born by cesarean section was similar across the cohorts (32.2% for HealthNuts, 30.9% for LSAC and 30.0% for CheckPoint). For all three, maternal characteristics of all cases compared to cases included in the complete case analysis were similar (supplementary Table 1).

The prevalence of current asthma was 12.9% (95% CI 11.8% to 14.0%) in HealthNuts and 16.0% (95% CI 14.9% to 17.2%) in LSAC. As shown in Table 2 and Figure 2, compared with the reference group of vaginal delivery, cesarean delivery was associated with modest increased odds of asthma in HealthNuts (aOR 1.25, 95% CI 1.00 to 1.57) but unconvincingly in LSAC (aOR 1.05, 95% CI 0.86 to 1.28). In HealthNuts, these weak associations with cesarean delivery were similar for atopic (aOR 1.33, 95% CI 1.00 to 1.77) and non-atopic asthma (aOR 1.48, 95% CI 0.97 to 2.26, supplementary Table 2).

Cesarean delivery did not predict current eczema at age 6-7 years in HealthNuts or LSAC (Table 2, Figure 2), reductions in lung function parameters at age 11-12 years in CheckPoint (Table 3, Figure 3), with point estimates close to those of the reference vaginal

delivery category. Nor did it predict reversible airflow limitation (supplementary Table 2).

The associations between delivery mode and allergic disease outcomes did not differ after considering any of the potential effect modifiers, ie duration of breastfeeding, maternal history of asthma/eczema (supplementary Table 3), childcare attendance, the number of older siblings or pet exposure (data not shown). In sensitivity analyses, the associations appeared similar after adjustment for additional covariates (supplementary Table 4), and when inverse probability weights were applied (supplementary Table 5).

DISCUSSION

Principal findings

In two contemporary population-based cohorts of Australian children that used very similar protocols, the odds of parent-report asthma were around 5-25% higher at age 6-7 years in children born by cesarean than vaginal delivery, with the higher risk seen in the HealthNuts study. However, we found evidence of neither increased odds of eczema at age 6-7 years nor poorer measured lung function at age 11-12 years. Breastfeeding, maternal history of asthma/eczema and other markers suggestive of higher microbial exposure did not modify the associations.

Strengths and limitations

The study has a number of strengths. First, we used a uniform protocol with harmonized definitions of exposure, outcomes and covariates at the same ages to replicate our analyses in two separate but simultaneously-conducted Australian population-based cohorts.

This avoids the inconsistencies in study settings, methodologies, lengths of follow-up (e.g. age 3 year⁴⁴ and 8-17 year⁴⁵), definitions (e.g. current/ever asthma) and confounders that have marred previous cross-cohort meta-analyses. We waited until age 6-7 years to define current asthma, because a diagnosis of asthma in younger children is difficult to distinguish from viral-induced wheezing.⁴⁶ Second, our multiple allergic outcomes may have improved the robustness of the cesarean-allergy association, comprising both measured parameters of lung function and reversible airflow limitation (which have seldom been reported) as well as parent-reported asthma and eczema. Furthermore, we were able to categorize current asthma into atopic and non-atopic asthma to further tease out that the association with parent-reported asthma is not allergy-related. Finally, our results are relevant to current population health, since its participants are still children today and reflect today's high rates of cesarean delivery and childhood allergy.

The study also has several limitations. First, asthma and eczema were reported by questionnaire. Estimating the prevalence of asthma and eczema in childhood is difficult due to both the absence of gold standard tools accessible to large-scale, population-based studies and the episodic nature of these conditions. Validated questionnaires are therefore commonly used, such as those from the ISAAC in this study, to capture information on allergic diseases, as well as the parental report of a doctor diagnosis. Previous reports suggest that self-reported doctor diagnosis of asthma has high specificity and medium-high sensitivity when compared with clinical methods.⁴⁷ Second, we could not distinguish differences between emergency and elective cesarean. It remains possible that more convincing or sizeable associations might emerge for some subgroups, which might enable potential mechanisms (such as epigenetic

changes, stress mediators and cesarean indication effects⁴⁸) to be explored. However, a recent meta-analysis reported similar risk of asthma with elective and emergency cesarean.¹⁰ Finally, lung function and current asthma were measured at different ages; it remains possible that there may have been a transient effect on lung function at age 6-7 that had resolved by 11 years. Reversible airflow limitation at age 11 years, detectable on spirometry and a feature of asthma, was not associated with mode of delivery.

Interpretation in light of other studies

Our results suggested that cesarean delivery may lead to a small excess of childhood asthma, especially in the HealthNuts population study. The size of our association was consistent with previous meta-analyses (OR ranging between 1.16 and 1.21).⁸⁻¹¹ Our finding that cesarean birth was not associated with eczema was also consistent with previous studies (OR in a meta-analysis⁹ 1.03, 95% CI 0.98 to 1.09). This apparent inconsistency (delivery mode associated with asthma but not eczema) was also seen in the few other studies that considered more than one subsequent allergic disease. For example, an American study showed an increased odds of diagnosed asthma (OR 1.24, 95% CI 1.01 to 1.53) but not atopic dermatitis (OR 0.94, 95% CI 0.75 to 1.19).⁴⁹

Two prior studies have similarly shown no difference in measured lung function in children delivered by cesarean section.^{25,26} Our study detected the similar results as these studies, and also showed no difference in risk of reversible airflow limitation, a predictor of asthma.⁵⁰ The null associations with childhood eczema and lung function, despite positive association with asthma, suggest that even if there is an effect of cesarean delivery on childhood allergic diseases, it is modest. This pattern of results might suggest that cesarean

delivery has a more direct impact on respiratory health (for example clearance of fluids from the lung during delivery) than on an allergy pathway. This possibility is perhaps supported by our analyses that did not suggest differences in cesarean-asthma associations by allergic sensitization. Alternatively, we may simply have examined eczema at an older age when it is less prevalent.

Cesarean delivery is associated with differences in the infant's microbiome,⁵¹ which may be restored by breastfeeding.⁵² However, unlike a previous study,²⁸ we did not find any evidence that the association between mode of delivery and asthma was modified by duration of breastfeeding or factors indicative of increased microbial load (pet or sibling exposure, childcare attendance). In addition, although maternal asthma increases the likelihood of child asthma,⁵³ unlike the study reporting that maternal history of asthma modified the association in young children (3 years),⁴⁴ the corresponding modification effect was not found in our study.

Implications

Although many studies have explored the association between cesarean delivery and childhood allergic disease, causality remains unclear. In many studies, the cesarean-allergy association was proposed to be linked to the hygiene hypothesis.¹² Cesarean-delivered newborns are predominantly colonized by bacteria originating from the hospital environment rather than bacteria from the mother's birth canal and perianal region, potentially increasing the risk of allergic diseases in later life.¹² If delivered by elective cesarean (ie before the onset of labor), these infants also lack the surge of stress hormones. This may result in altered DNA

methylation, which is proposed to be a determinant of health and disease in later life.¹² Part of the observed associations could also reflect the underlying medical indications for cesarean.⁴⁸ Impaired lung function such as respiratory distress syndrome and transient tachypnea is also the cause of asthma.¹³⁻¹⁵ Future studies that include cesarean indications may improve our understanding of the mechanisms that contribute to the observed effects.

CONCLUSION

Our cross-cohort analysis with harmonized protocols showed a small excess of parent-reported asthma at age 6 years in children born by cesarean delivery, but not for current eczema or impaired lung function. Given that this small excess did not appear to reflect allergic mechanisms, further population studies should include objective measures to determine whether and how lung function is altered in this group of children. Even if there is an effect of cesarean on childhood allergy, it is small.

REFERENCES

1. Betran AP, Ye J, Moller AB, Zhang J, Gulmezoglu AM, Torloni MR. The Increasing Trend in Caesarean Section Rates: Global, Regional and National Estimates: 1990-2014. *PloS one*. 2016;11(2):e0148343.
2. Valovirta E. *Allergy: a burden for the patient and for the society*. Allergy Frontiers: Epigenetics, Allergens and Risk Factors: Springer; 2009:33-46.
3. Martin JA, Hamilton BE, Osterman MJK, Driscoll AK, Drake P. Births: Final Data for 2016. *Natl Vital Stat Rep*. 2018;67(1):1-55.
4. Li HT, Luo S, Trasande L, et al. Geographic Variations and Temporal Trends in Cesarean Delivery Rates in China, 2008-2014. *JAMA*. 2017;317(1):69-76.
5. Mallol J, Crane J, von Mutius E, Odhiambo J, Keil U, Stewart A. The International

- Study of Asthma and Allergies in Childhood (ISAAC) Phase Three: a global synthesis. *Allergol Immunopathol (Madr)*. 2013;41(2):73-85.
6. Williams H, Stewart A, von Mutius E, Cookson W, Anderson HR. Is eczema really on the increase worldwide? *J Allergy Clin Immunol*. 2008;121(4):947-954.e915.
 7. WHO Statement on caesarean section rates. *Reprod Health Matters*. 2015;23(45):149-150.
 8. 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):629-633.
 9. Bager P, Wohlfahrt J, Westergaard T. Caesarean delivery and risk of atopy and allergic disease: meta-analyses. *Clin Exp Allergy*. 2008;38(4):634-642.
 10. Huang L, Chen Q, Zhao Y, Wang W, Fang F, Bao Y. Is elective cesarean section associated with a higher risk of asthma? A meta-analysis. *J Asthma*. 2015;52(1):16-25.
 11. Keag OE, Norman JE, Stock SJ. Long-term risks and benefits associated with cesarean delivery for mother, baby, and subsequent pregnancies: Systematic review and meta-analysis. *PLoS Med*. 2018;15(1):e1002494.
 12. Cho CE, Norman M. Cesarean section and development of the immune system in the offspring. *Am J Obstet Gynecol*. 2013;208(4):249-254.
 13. Noutsios GT, Floros J. Childhood asthma: causes, risks, and protective factors; a role of innate immunity. *Swiss Med Wkly*. 2014;144:w14036.
 14. Birnkrant DJ, Picone C, Markowitz W, El Khwad M, Shen WH, Tafari N. Association of transient tachypnea of the newborn and childhood asthma. *Pediatr Pulmonol*. 2006;41(10):978-984.
 15. Liem JJ, Huq SI, Ekuma O, Becker AB, Kozyrskyj AL. Transient tachypnea of the newborn may be an early clinical manifestation of wheezing symptoms. *J Pediatr*. Jul 2007;151(1):29-33.
 16. Pyrhonen K, Nayha S, Hiltunen L, Laara E. Caesarean section and allergic manifestations: insufficient evidence of association found in population-based study of children aged 1 to 4 years. *Acta Paediatr*. 2013;102(10):982-989.
 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(3):510-516.
 18. Metsala J, Kilkkinen A, Kaila M, et al. Perinatal factors and the risk of asthma in childhood--a population-based register study in Finland. *Am J Epidemiol*. 2008;168(2):170-178.
 19. Black M, Bhattacharya S, Philip S, Norman JE, McLernon DJ. Planned Cesarean Delivery at Term and Adverse Outcomes in Childhood Health. *JAMA*. 2015;314(21):2271-2279.
 20. Magnus MC, Haberg SE, Stigum H, et al. Delivery by Cesarean section and early childhood respiratory symptoms and disorders: the Norwegian mother and child cohort study. *Am J Epidemiol*. 2011;174(11):1275-1285.
 21. Maitra A, Sherrieff A, Strachan D, Henderson J. Mode of delivery is not associated with asthma or atopy in childhood. *Clin Exp Allergy*. 2004;34(9):1349-1355.
 22. McKeever TM, Lewis SA, Smith C, Hubbard R. Mode of delivery and risk of

- developing allergic disease. *J Allergy Clin Immunol*. 2002;109(5):800-802.
23. Roduit C, Scholtens S, de Jongste JC, et al. Asthma at 8 years of age in children born by caesarean section. *Thorax*. 2009;64(2):107-113.
 24. Leung JY, Li AM, Leung GM, Schooling CM. Mode of delivery and childhood hospitalizations for asthma and other wheezing disorders. *Clin Exp Allergy*. 2015;45(6):1109-1117.
 25. Bruske I, Pei Z, Thiering E, et al. Caesarean Section has no impact on lung function at the age of 15 years. *Pediatr Pulmonol*. 2015;50(12):1262-1269.
 26. Kotecha SJ, Watkins WJ, Lowe J, Henderson AJ, Kotecha S. Effect of early-term birth on respiratory symptoms and lung function in childhood and adolescence. *Pediatr Pulmonol*. 2016;51(11):1212-1221.
 27. Lowe A, Hosking C, Bennett C, et al. Skin prick test can identify eczematous infants at risk of asthma and allergic rhinitis. *Clin Exp Allerg*. 2007;37(11):1624-1631.
 28. Chu S, Chen Q, Chen Y, Bao Y, Wu M, Zhang J. Cesarean section without medical indication and risk of childhood asthma, and attenuation by breastfeeding. *PloS one*. 2017;12(9):e0184920.
 29. Xu R, DeMauro SB, Feng R. The impact of parental history on children's risk of asthma: a study based on the National Health and Nutrition Examination Survey-III. *J Asthma Allergy*. 2015;8:51-61.
 30. Koplin JJ, Wake M, Dharmage SC, et al. Cohort Profile: The HealthNuts Study: Population prevalence and environmental/genetic predictors of food allergy. *Int J Epidemiol*. 2015;44(4):1161-1171.
 31. Osborne N, Koplin J, Martin P, et al. The HealthNuts population-based study of paediatric food allergy: validity, safety and acceptability. *Clin Exp Allerg*. 2010;40(10):1516-1522.
 32. Suaini NHA, Koplin JJ, Peters RL, et al. Children with East Asian-Born Parents Have an Increased Risk of Allergy but May Not Have More Asthma in Early Childhood. *J Allergy Clin Immunol Pract*. 2018.
 33. Sanson A, Johnstone R. 'Growing Up in Australia' Takes Its First Steps. *Fam Matters*. 2004(67):46.
 34. Edwards B. Growing up in Australia: the longitudinal study of Australian children: entering adolescence and becoming a young adult. *Fam Matters*. 2014(95):5.
 35. Gray M, Sanson A. Growing up in Australia: the longitudinal study of Australian children. *Fam Matters*. 2005(72):4.
 36. Daraganova G, Siphthorp M. *Wave 4 weights*. Australian Institute of Family Studies Melbourne; 2011.
 37. Wake M, Clifford S, York E, et al. Introducing growing up in Australia's child health checkpoint: a physical and biomarkers module for the longitudinal study of Australian children. *Fam Matters*. 2014;95:15-23.
 38. Susan. C, Sarah. D, Melissa. W. Growing Up in Australia's Child Health CheckPoint cohort summary and methodology. *BMJ open*. 2017. In press.
 39. Asher MI, Keil U, Anderson HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J*. 1995;8(3):483-491.
 40. Miller MR, Hankinson J, Brusasco V, et al. Standardisation of spirometry. *Eur Respir*

- J. 2005;26(2):319-338.
41. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012;40(6):1324-1343.
 42. National Asthma Council Australia. Assessing lung function in children 6 years and over. 2018; <http://www.asthmahandbook.org.au/diagnosis/children/initial-investigations/lung-function>.
 43. Little RJ, Rubin DB. *Statistical analysis with missing data*. Vol 333: John Wiley & Sons; 2014.
 44. Magnus MC, Haberg SE, Stigum H, et al. Delivery by Cesarean Section and Early Childhood Respiratory Symptoms and Disorders. *Am J Epidemiol*. 2011;174(11):1275-1285.
 45. 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):341-346.
 46. Edwards CA, Osman LM, Godden DJ, Douglas JG. Wheezy bronchitis in childhood: a distinct clinical entity with lifelong significance? *Chest*. 2003;124(1):18-24.
 47. Jenkins MA, Clarke JR, Carlin JB, et al. Validation of questionnaire and bronchial hyperresponsiveness against respiratory physician assessment in the diagnosis of asthma. *Int J Epidemiol*. 1996;25(3):609-616.
 48. Almqvist C, Oberg AS. The association between caesarean section and asthma or allergic disease continues to challenge. *Acta Paediatr*. 2014;103(4):349-351.
 49. 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(11):1466-1472.
 50. Pellegrino R, Viegi G, Brusasco V, et al. Interpretative strategies for lung function tests. *Eur Respir J*. Nov 2005;26(5):948-968.
 51. Jakobsson HE, Abrahamsson TR, Jenmalm MC, et al. Decreased gut microbiota diversity, delayed Bacteroidetes colonisation and reduced Th1 responses in infants delivered by caesarean section. *Gut*. 2014;63(4):559-566.
 52. Azad MB, Konya T, Persaud RR, et al. Impact of maternal intrapartum antibiotics, method of birth and breastfeeding on gut microbiota during the first year of life: a prospective cohort study. *BJOG*. 2016;123(6):983-993.
 53. Stokholm J, Blaser MJ, Thorsen J. Maturation of the gut microbiome and risk of asthma in childhood. *Nat Commun*. 2018;9(1):141.

TABLE HEADINGS AND FIGURE LEGENDS

TABLES

TABLE 1 Maternal and child characteristics for the HealthNuts, LSAC and CheckPoint samples

TABLE 2 Estimated prevalence and odds ratios (ORs) of asthma and eczema at 6-7 years for cesarean compared to vaginal delivery (reference) by study

TABLE 3 Mean differences in lung function parameters at 11-12 years for cesarean compared to vaginal delivery (reference) in CheckPoint

FIGURES

FIGURE 1 Flowchart of HealthNuts, Growing up in Australia (LSAC) and Child Health CheckPoint [^a Sample has information on delivery mode and at least one outcome. ^b Sample has complete data for all covariates included in the main analyses (maternal age at birth, mother's country of birth, maternal smoking during pregnancy, SEIFA, gestational age and birth weight).]

FIGURE 2 Odds ratios for the association between cesarean compared to vaginal delivery (reference) for the outcomes of current asthma and eczema at age 6-7 years [Models adjusted for maternal age at birth, mother's country of birth, maternal smoking during pregnancy, SEIFA, gestational age and birth weight. SEIFA, Socio-Economic Indexes for Areas Disadvantage Index.]

FIGURE 3 Mean differences of lung function parameters (pre-bronchodilator) for cesarean compare to vaginal delivery (reference) at age 11-12 years [Models adjusted for maternal age at birth, mother's country of birth, maternal smoking during pregnancy, corresponding parental lung function parameter, SEIFA, gestational age and birth weight. SEIFA, Socio-Economic Indexes for Areas Disadvantage Index.]

SUPPLEMENTARY TABLES

SUPPLEMENTARY TABLE 1 Maternal and child characteristics of all, complete and omitted cases in main analyses by study

SUPPLEMENTARY TABLE 2 Estimated prevalence and ORs of atopic and non-atopic asthma at 6-7 years in HealthNuts and reversible airflow limitation at 11-12 years in CheckPoint for cesarean compared to vaginal delivery (reference)

SUPPLEMENTARY TABLE 3 Adjusted ORs and mean differences (95% CIs) of allergic diseases and lung function for cesarean compared with vaginal delivery (reference), stratified by duration of breastfeeding or maternal history of asthma/eczema

SUPPLEMENTARY TABLE 4 Sensitivity analyses with additional confounder adjustment for ORs/mean differences (95% CIs) of allergic diseases/lung function for cesarean compared

with vaginal delivery (reference)

SUPPLEMENTARY TABLE 5 Crude and adjusted ORs of childhood asthma and eczema by inverse probability weighting at 6-7 years for cesarean compared with vaginal delivery (reference)

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