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Caesarean section delivery and the risk of allergic disorders in childhood

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Summary

Background The composition of the intestinal flora in young children, if unfavourable, may increase the susceptibility to allergic disorders. Beneficial intestinal microbes originate from the maternal vaginal tract and thus are more likely to be transferred during vaginal births than during Caesarean sections (C-sections).

Objective To determine whether children born by C-section have a different risk of allergic disorders compared with those delivered vaginally. We also tested the hypothesis that the risk of allergic disorders is highest for children born after 'repeat C-sections'.

Methods A retrospective cohort study of 8953 children aged 3–10 years. Children diagnosed with allergic rhinoconjunctivitis (AR), asthma, atopic dermatitis (AD), or food allergies were identified from the Kaiser Permanente Northwest Region electronic records. The children's sex, birth weight, birth order, postnatal exposure to antibiotics as well as the mothers' age, ethnicity, education, marital status, smoking status during pregnancy, and use of asthma or hayfever medications were identified through the mothers' medical records or through the Oregon Birth Registry.

Results The risk of being diagnosed with AR was significantly higher in the children born by C-section than in those delivered vaginally: adjusted odds ratio (OR) = 1.37%, 95% confidence interval (CI) = 1.14–1.63. Delivery by C-section was also associated with the subsequent diagnosis of asthma (OR = 1.24%, 95% CI = 1.01–1.53); this association was gender specific, with a positive association restricted to girls (OR for asthma in girls: OR = 1.53%, 95% CI = 1.11–2.10; in boys: OR = 1.08%, 95% CI = 0.81–1.43). There was no significant association between mode of delivery and AD.

If children born in a 'repeat C-section' were considered separately the risk of being diagnosed with AR increased further (OR = 1.78%, 95% CI = 1.34–2.37). The same increase was noted for asthma in girls (OR = 1.83%, 95% CI = 1.13–2.97) but not in boys.

Conclusion Caesarean sections may be associated with an increased risk of developing AR in childhood.

Keywords allergic rhinoconjunctivitis, asthma, atopic dermatitis, atopy, allergy, Caesarean section, intestinal flora, intestinal microbes, risk of allergic disorders
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Introduction

According to the hygiene hypothesis [1], the increasing prevalence of allergic diseases is caused by a decreased exposure to microorganisms early in life. The lack of microbial priming signals may alter the way in which the immune system subsequently reacts to potential allergens [2]. This hypothesis is supported by epidemiological findings that relate 'unhygienic' exposures to a decreased risk of allergic disorders, e.g. larger family size [1], higher birth order [3], traditional life styles [4], pet ownership [5], use of daycare [6], and exposure to a farm environment as a child [7].

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However, there is debate about the putative *route* through which the microbial exposure could act. Researchers variously implicate infections [8], parasites [9], endotoxin [10], and microbes that naturally inhabit the human intestinal tract [11].

Components of the intestinal flora have been shown to affect systemic immune responses, including T-helper cell function [12]. The experimental disruption of the postnatal colonization of the intestinal tract in mice leads to high immune globulin E levels against food components [13]. The make-up of the intestinal flora has been shown to differ between individuals with allergic disorders and those without [14]. Also, the supplementation of pregnant mothers with a component of the intestinal flora, Lactobacillus GG, was followed by a roughly 50% decreased risk of eczema in the offspring at 2 and 4 years of life [15, 16].

Although the intestinal flora remains adaptable throughout life, it is most variable in the immediate postnatal period, when the previously sterile gut is first colonized [17, 18].

Vaginally born children acquire their intestinal flora mainly through the mother's vaginal tract, which closely reflects the mother's intestinal flora. Children born by Caesarean section (C-section), on the other hand, acquire their intestinal bacteria from skin contact and environmental surfaces. The result is a quantitatively and qualitatively different intestinal flora [19], with decreased prevalence of bifidobacteria, bacteroides, and lactobacilli [20], at least during the first several months of life [21]. Recent evidence suggests that some differences in the composition of the gut microflora after C-section may persist beyond 7 years of age [22].

In most C-sections, the baby is evacuated from the sterile amniotic environment. However, some C-sections are performed after the protective amniotic membranes have ruptured, allowing for ascending colonization of the amniotic fluid with vaginal microflora. If membranes have ruptured before onset of labour (a condition occurring in about 10% of term deliveries, called 'premature rupture of membranes' or PROM), transfer of vaginal bacteria to the intestinal tract of the baby occurs *in utero*. Thus, intestinal colonization in 'PROM C-sections' is biologically similar to that in vaginal deliveries.

Subsequent C-sections in the same mother are generally elective procedures performed because of a previous C-section and constitute about one-third of C-sections in American hospitals [23]. In these 'repeat' C-sections, the amniotic membranes are usually unbreached. Thus, because of their high likelihood of being associated with unbreached membranes, we use these 'uncontaminated' C-sections as a proxy for deliveries least likely to involve transfer of maternal vaginal flora.

Materials and methods

Study population

We used the electronic medical records of a large health maintenance organization, Kaiser Permanente Northwest Region (KPNW), to follow a cohort of children born from 1/1/1990 through 31/12/1992. Children born prematurely and those with no KPNW health care coverage during the follow-up period were excluded. We identified 8953 births and linked their health care data both with that of their mothers and with the birth registry of the state of Oregon. Linkage was successful for 7936 (88.6%) of the 8953 births. Data on mode of delivery were available from both KPNW and the Oregon Birth Registry, with 99.2% concordance, leaving 7872 children in the final analysis sample. Members of the cohort were aged 3 to 10 years during the follow-up period (1996–2000).

The study was approved by the institutional review boards at the Oregon Health & Science University and the Kaiser Permanente Center for Health Research.

Assessment of allergic manifestations

We searched the children's electronic medical records for diagnoses of asthma, allergic rhinoconjunctivitis (AR), atopic dermatitis (AD), and food allergies (FA) made at outpatient visits from 1996 to 2000. Children were classified as having AR, AD, or FA if the respective diagnosis appeared at least once in this period. Children were classified as having asthma if they had at least one diagnosis of asthma at age 6 or thereafter. The latter age limit was set in order to reduce the proportion of early onset and of transient wheezers in our 'asthma' sample – both of these phenotypes are common before age 6 but unlikely to be associated with allergic sensitization [24].

Potential confounders

From the child's medical record, we extracted information on sex, multiple gestation, and exposure to antibiotics in the immediate postnatal period. We classified a child as presumptively exposed to antibiotics if a procedure code for 'injection of antibiotic', 'spinal tap', 'blood culture', 'perinatal infection', 'prophylactic chemotherapy', 'septicaemia' or 'perinatal infection' was entered in the medical record.

From the mother's medical records, we gathered information on prescribing patterns for medications typically used to treat asthma and AR. We also gathered information from the Oregon Birth Registry on maternal education, marital status, and smoking during pregnancy, as well as the child's ethnicity, birth weight, and birth order.

Information on maternal education, ethnicity, maternal smoking, and birth order was available from over 96% of participants. We had complete data on maternal marital status, maternal age, maternal history of receipt of asthma and hayfever medications, the child's birth weight, the child's gender, the child's postnatal receipt of antibiotics, and whether the child was the product of a multiple birth.

Statistical analyses

Using logistic regression, we first estimated the effect of delivery by C-section ($n = 1286$) on the probability that the child was subsequently diagnosed with any allergic disease (asthma, AR, AD, and/or FA). We then modelled the effect of C-section on the probability of asthma only, AR only, AD only, and FA only (four separate models). All of the models adjusted for the effects of the child's sex, age at diagnosis, birth weight, birth order, exposure to antibiotics in the postpartum period, and multiple gestation, as well as maternal age, ethnicity, education, marital status, smoking status during pregnancy, and use of asthma and/or hayfever medications.

We then attempted a more stringent test of our hypothesis by re-running all of our models using as our predictor not the presence vs. absence of a C-section *per se*, but the presence of an 'uncontaminated' C-section ($n = 425$) vs. either a vaginal delivery ($n = 6586$) or a PROM C-section ($n = 73$) ('contaminated' C-sections). We defined an 'uncontaminated' C-section as a birth carrying the diagnostic code for 'repeat C-section' but *not* carrying a code for PROM.

We suspect that some PROM was not coded, as the frequency of codes for PROM in these data was much lower than expectation (0.97% of non-C-sections were coded as PROM; 5.68% of c-sections were coded as PROM). As we are not confident that the absence of a code for PROM indicates that no PROM occurred, we treated the 788 observations associated with a primary (non-repeat) C-section and no evidence of PROM as uninformative with regard to the presence of intrauterine contamination. These

788 observations were dropped, leaving 7084 observations in our secondary analysis dataset.

All *P*-values are unadjusted for multiple comparisons. Because the four outcomes (any allergic disease, asthma, AR, and AD) are clinically related, these analyses are not independent of one another and hence traditional adjustment procedures would be overly conservative. All statistical analyses was performed using SAS Version 8.2.

Results

Compared with children delivered vaginally, those born by C-section were heavier at birth and more likely to be male, to have an older mother, to receive antibiotics after delivery, to be a multiplet, to have parents of higher socio-economic background, to be of lower birth order, and to be born to a mother who used medications for AR (Table 1). Although statistically significant, these differences were generally small.

We found that 1791 (22.8%) of the children in the primary analysis sample were treated for at least one of the four allergic diseases, including 697 (10.2%) for asthma, 1001 (12.7%) for AR, 582 (7.4%) for AD, and 29 (0.4%) for FA. In simple (unadjusted) bivariate analyses, subjects born by C-section were significantly more likely than vaginally born children to be diagnosed with any allergic disease (26.4% vs. 22.1%, odds ratio (OR) = 1.27%, 95% confidence interval (CI) 1.10–1.45), asthma (10.3% vs. 8.6%, OR = 1.24%, 95% CI 1.01–1.51), and AR (16.6% vs. 12.0%, OR = 1.47%, 95% CI 1.25–1.73). The mode of delivery was not significantly associated with either AD (7.1% vs. 7.5%, OR = 0.94%, 95% CI 0.75–1.19), or FA (0.5% vs. 0.4%, OR = 1.34%, 95% CI 0.54–3.29).

Based on the results of multiple logistic regression analysis, which included adjustment for the child's sex, age at diagnosis, birth weight, birth order, exposure to antibiotics in the postpartum period, ethnicity, multiple gestation, as well as maternal age, education, marital status, smoking status during pregnancy, and use of asthma and/or hayfever medications, birth by C-section was associated with significantly increased risk for developing any allergic disease (OR = 1.23%, 95% CI 1.06–1.43) (Table 2).

When we re-ran our multivariate model of any allergic disease using 'uncontaminated' delivery (i.e. births by 'repeat C-section', with those carrying a diagnostic code for PROM excluded) vs. 'contaminated' delivery (i.e. vaginal birth or any birth carrying a diagnostic code for PROM) as the exposure of interest, the OR for mode of delivery increased to 1.41 (95% CI 1.10–1.80) (Table 2).

Delivery by C-section was also associated with significantly increased risk for AR (OR = 1.37%, 95% CI 1.14–1.63). The estimated odds ratio for C-section increased to 1.78 (95% CI 1.34–2.37) when we limited the exposed group to children born by 'uncontaminated' C-sections.

Delivery via C-section was also associated with significantly increased risk for asthma (OR = 1.24%, 95% CI 1.01–1.53). Contrary to the previous outcomes, the association between C-section and asthma decreased and was no longer significant when we defined exposure as birth by an 'uncontaminated' C-section (OR = 1.17, CI 0.81–1.69).

To see if the effect of C-section on risk for asthma is modulated by one of the other predictors, we examined two-way interactions with mode of delivery and discovered a significant interaction of 'uncontaminated' C-section with gender ($P = 0.009$). When we used our multivariate model to predict risk of asthma among girls only, we found an OR of 1.53 ($P = 0.009$) for the effect of any C-section on asthma, and an even higher OR of 1.83 ($P = 0.01$) for the effect of 'uncontaminated' C-section on asthma (Table 2). Among boys, neither any C-section nor 'uncontaminated' C-section predicted risk for asthma (OR for any C-section = 1.08, $P = 0.62$; OR for 'uncontaminated' C-section = 0.71, $P = 0.23$). We did not see a comparable sex by mode of delivery interaction in models predicting outcomes other than asthma.

For AD, no significant associations were seen either in the original analysis (OR = 0.9%, 95% CI 0.7–1.16) or in the analysis restricted to an 'uncontaminated' C-section (OR = 0.84%, 95% CI 0.54–1.3).

Table 1. Baseline characteristics of the primary analysis sample

	Children born by C-section	Children born vaginally	*P*-value*
N†	1286	6586	
White	1071	5476	0.9
	(83%)	(83%)	*0.97 (0.81–1.16)*
Female	586	3285	0.02
	(46%)	(50%)	*0.84 (0.75–0.95)*
Exposed to antibiotics	29	68	< 0.01
in the postpartum	(2%)	(1%)	*2.21 (1.43–3.43)*
period			
Exposed to maternal	244	1398	0.07
smoking during	(19%)	(21%)	*1.15 (0.99–1.34)*
pregnancy			
Multiple gestation	24	28	< 0.01
	(1.9%)	(0.4%)	*4.45 (2.57–7.71)*
Birth order			< 0.01
1	610	2450	
	(47%)	(37%)	
2	388	2266	*0.69 (0.60–0.79)*
	(30%)	(34%)	
3	185	1127	*0.66 (0.55–0.79)*
	(14%)	(17%)	
>3	103	743	*0.56 (0.44–0.70)*
	(8%)	(11%)	
Married or separated	1,031	5062	< 0.01
	(80%)	(77%)	*0.82 (0.71–0.95)*
Maternal use of	312	1492	0.2
asthma medication	(24%)	(23%)	*1.09 (0.95–1.26)*
Maternal use of	453	1988	< 0.01
hayfever medication	(35%)	(30%)	*1.26 (1.11–1.43)*
Birth weight (kg)‡	3.6 (± 0.6)	3.5 (± 0.5)	< 0.01
			0.11 (0.08–0.14)
Maternal age at	28.8 (± 5.8)	27.4 (± 5.9)	< 0.01
delivery (years)‡			*1.4 (1.1–1.8)*
Maternal education	13.2 (± 2.1)	12.9 (± 2.1)	< 0.01
(years)‡			*0.25 (0.12–0.38)*

C-section, Caesarean section.

*two-sided P-value based on the Pearson's χ^2 test for proportions and *t*-test for continuous data. Below the P-values in italic: point estimate for the mean differences (continuous variables) or odds ratio (categorical variables) and the 95% confidence limit.

†Denominators vary slightly for each outcome due to missing data.

‡Data presented as mean (SD).

Table 2. Results of multivariate logistic regression analysis* estimating the effects of different modes of delivery on the rates of any allergic disorder, AR, asthma, and AD

	Any C-section vs. vaginal delivery	Uncontaminated† C-section vs. contaminated† delivery‡
Any allergic disorder	OR = 1.23 (1.06–1.43) [P = 0.007]	OR = 1.41 (1.10–1.80) [P = 0.006]
AR	OR = 1.37 (1.14–1.63) [P = 0.0006]	OR = 1.78 (1.34–2.37) [P < 0.0001]
Asthma		
Both genders§	OR = 1.24 (1.01–1.53) [P = 0.04]	OR = 1.17 (0.81–1.69) [P = 0.4]
Boys only§	OR = 1.08 (0.81–1.43) [P = 0.62]	OR = 0.71 (0.41–1.24) [P = 0.23]
Girls only§	OR = 1.23 (1.06–1.43) [P = 0.009]	OR = 1.83 (1.13–2.97) [P = 0.01]
AD	OR = 0.90 (0.70–1.16) [P = 0.41]	OR = 0.84 (0.54–1.30) [P = 0.43]

AR, allergic rhinoconjunctivitis; C-section, Caesarean section; OR, odds ratio; AD, atopic dermatitis; PROM, premature rupture of membranes.
*ORs are based on multivariate logistic regression analysis adjusting for the child's sex, age at diagnosis, birthweight, birth order, exposure to antibiotics in the postpartum period, ethnicity, multiple gestation, as well as maternal age, education, marital status, smoking status during pregnancy, and use of asthma and/or hay fever medications.
†'Uncontaminated' C-sections are defined as births by repeat C-section that are not coded as PROM. 'Contaminated' C-sections are defined as vaginal deliveries or PROM C-sections.
‡95% confidence intervals are shown in parentheses.
§Gender effects are only reported for asthma. There was no significant sex by mode of delivery interaction for the other outcomes.

Only 29 children (0.37%) in our cohort had a diagnosis of FA, which did not allow for a statistically meaningful separate analysis (data not presented).

Confounding variables that had highly significant ($P<0.001$) effects on the outcomes assessed (i.e. any allergic disorder, AR, asthma, and AD) were as follows: male gender (highly significant associations for any allergic disorder: OR = 1.24%, 95% CI 1.11–1.40; for AR: OR = 1.39%, 95% CI 1.20–1.60; for asthma: OR = 1.49%, 95% CI 1.26–1.76), birth order (highly significant associations for any allergic disorder: OR for one step increase = 0.86%, 95% CI 0.81–0.91; for AR: OR = 0.77%, 95% CI 0.72–0.83), ethnicity (highly significant negative association of white ethnicity and any allergic disorder: OR = 0.7%, 95% CI 0.59–0.83; for AD: OR = 0.42%, 95% CI 0.33–0.53), administration of antibiotics in the postpartum period (highly significant positive effect on asthma in boys: OR = 3.36%, 95% CI 1.73–6.54, but not in girls: OR = 0.28%, 95% CI 0.04–2.06), maternal use of asthma medication (highly significant associations for any allergic disease and for asthma, significant associations for AR and AD), maternal use of hayfever medication (highly significant associations for any allergic disease and for AR) and maternal age at delivery (highly significant positive association for any allergic disease and AR). Notable yet less significant effects ($0.001<P<0.05$) were seen for multiple gestation if all outcomes were considered (OR for any allergic disorder = 0.40%, 95% CI 0.17–0.97, $P=0.04$), for marital status (negative effect on asthma in girls: OR = 0.6%, 95% CI 0.42–0.84, $P=0.003$; but not in boys: OR = 0.82%, 95% CI 0.61–1.11, $P=0.20$) and for birth weight (significant effect only in AD: OR = 1.29%, 95% CI 1.07–1.57, $P=0.009$).

Discussion

In our study, children born by C-section had a significantly higher risk than vaginally delivered children of being diagnosed with AR. A similar association was seen for asthma, but unlike the results in AR, this correlation was gender specific: when boys and girls were considered separately, the association of C-section and asthma was only significant in girls.

We believe that these findings can be plausibly explained by the hygiene hypothesis, and more specifically, the influence of the intestinal flora on the risk of acquiring allergic disease.

First, biologically, one of the striking differences between C-sections and vaginal deliveries is the extent of bacterial 'loading' of the formerly sterile fetus [19]. Initial population of the intestines with microbes has been shown to confer the immune system with important regulatory signals needed for developing adequate tolerance of the environment [11].

Second, the results in this study fall into a dose–response pattern. For all the positive associations in our main analysis, the risk moved in conjunction with the presumptive degree of bacterial loading associated with the exposure; that is, the risk increased when only 'uncontaminated' C-sections were considered.

Other explanations are possible. C-sections could be a marker for biologically compromised fetuses predestined for developing allergic disease. However, in our study, it was the babies born by elective C-section, i.e., procedures typically *not* preceded by fetal distress, who had the highest risk of developing allergic conditions. Therefore, an *a priori* disadvantage of children born by C-section seems unlikely.

We are unable to explain the gender-specific association between mode of delivery and asthma: while mode of delivery is not associated with a later diagnosis of asthma in boys in our cohort, there is a sizable and highly significant effect of mode of delivery in girls. To our knowledge, this is the first study that has specifically looked at or reported on this issue.

The gender-specific results are hard to reconcile with our hypothesis – the effect of the transfer of intestinal microbes should be similar in boys and girls. There is no support from our own data that girls and boys vary in their 'immunological make-up'. The atopic family background does not vary much between boys and girls in our study, if use of anti-allergic medication in the mother is used as a proxy. Also, asthmatic girls do not have a higher rate of AD comorbidity in our study, which could be construed as a somewhat similar degree of atopy. From the literature, we know that asthma in children is a heterogeneous disease of allergic and non-allergic origins [25], and that some of this heterogeneity may be gender specific: asthma in girls is more likely to be of later onset [26], to persist [26], and to be associated with other allergic conditions [27] and with a family history of atopy [27]. It is therefore possible – although not borne out by the limited data available to us – that the sample of boys in our cohort does not share the same burden of allergic predilection as the girls do and may therefore not be showing the same

effects of an intervention that putatively influences allergic responses. However, this is a speculation that we cannot back up with our data.

The results as they pertain to asthma need to be interpreted with caution for other reasons: C-sections have been reported to be associated with an increased risk of neonatal respiratory distress [28], which in turn may set some of the affected individuals up for lasting respiratory pathology unrelated to the status of the immune system [29]. Also, asthma is a heterogeneous disease lacking specific clinical markers and is therefore prone to misclassification.

Other potential biases could have skewed our results. Mothers of higher socioeconomic background, who have been shown to be more allergic [30], may be more likely to deliver by C-section and thus confer their children with a higher likelihood of allergic diseases. We are confident, however, that the inclusion of maternal education level and maternal marital status in our analyses allowed us to minimize confounding because of socio-economic status.

Our results could also be explained by a genetic bias: allergic mothers are more likely to give birth to allergic children, and at the same time, may be more likely to give birth by C-section; the latter association has been documented for asthmatic mothers [31]. By using prescription patterns for allergy medications as a proxy for maternal atopy, we were able to control for genetic predisposition to some extent.

A shortcoming of our study could be the lack of 'objective' ascertainment of the outcomes, like skin prick tests (SPTs) as a measure of atopy. Outcomes analysed in our study are all based on provider diagnoses within the KPNW system, which may not be uniform. Health-care provision in the KPNW system resembles general practice and relies on paediatricians and family practice physicians as well as nurse practitioners and physician assistants. Diagnoses were documented in a standardized manner by the provider at the time of the visit. The frequencies of the diagnoses match nationally reported figures. However, we cannot exclude the possibility that the quality of ascertainment may have skewed our results.

SPTs have been widely used as a measure of atopy. While this may be a worthy measure for clinical assessment and management of allergic disorders, it may not be the most appropriate tool in epidemiological studies designed to study hygiene-related exposures. There is good evidence that the lack of microbial stimulation postulated by the hygiene hypothesis primarily affects inflammatory control mechanisms (theory of inadequate inflammatory dampening) rather than just the degree of allergic sensitization [32]. The event of interest may therefore lie 'downstream' from the process of sensitization and may relate rather to the question as to how sensitization translates into inflammation, i.e. clinical disease. Studies that have looked at the effect of C-section on allergic sensitization show conflicting results: while no association of mode of delivery and allergic sensitization was seen in the Avon Longitudinal Study of Parents and Children (ALSPAC) birth cohort study [33], two smaller studies with younger children show a positive association, but only for food allergens [34, 35].

The results of other investigations on the clinical effects of mode of delivery are conflicting. While none of the studies reports a significant association between C-section and either AR or AD [34, 35, 36–39], most studies report an increased risk for asthma [36–42]. However, populations examined in previous studies differ greatly from our cohort. Some of the previously published studies predominantly included children 4 years of age or younger [34, 37, 39], in which AR is rare and ascertainment of asthma is unreliable because of the then-dominating non-allergic phenotypes [43]. Other studies report on adults only and had to rely on self-report [38], looked at hospitalized cases only [42], or included up to 50% of either preterm or medically compromised subjects [36]. A recent large-scale, prospective study did not observe any association of delivery by C-section and the development of asthma [33]. However, the latter study only examined children in the first 7 years of life.

Some results of our study may need further exploration. Most importantly, we did not observe a positive association between C-section and AD. Although in line with all previous studies on this subject this is nevertheless surprising, as intervention trials with intestine-derived lactobacilli suggest a close link between AD and the intestinal flora [15, 16]. However, it may be overly simplistic to equate this intervention with a mere 'enhancement' of the intestinal flora – the effects of the supplementation with lactobacilli may constitute an effect on top of or independent of the physiologic influences of the intestinal flora.

A second putative explanation emerges from our own data. It is possible that children must suffer an additional insult to the immune system for birth by C-section to confer an increased risk for AD. In a model that estimates the combined effect of C-section and postnatal receipt of antibiotics (which may further suppress the intestinal flora), we found some support for such a 'double-hit' hypothesis: the point estimates for the effect of antibiotics plus C-section, although not statistically significant, were positive and relatively large, with a very strong trend observed for receipt of antibiotics and 'uncontaminated' C-section (OR 7.9, $P = 0.08$).

Our study is limited in that there are potential confounders that we have not been able to control for, especially breastfeeding. Several studies suggest that C-sections are an impediment to the initiation of breastfeeding [44, 45], and breastfeeding may protect against allergies. Yet, we believe that this does not explain our findings, even if a protective effect of breastfeeding is assumed, which is controversial [46]. Several studies have shown that the untoward effect of C-sections on breastfeeding rates is restricted to unscheduled C-sections [47]. If breastfeeding were a major determinant of the associations seen in our study, it would be hard to explain why subjects born in an elective C-section should carry the highest risk of allergic disorders in our study.

Another limitation of our study is the fact that outcomes were assessed between the ages of 3 and 10 years, which may especially limit the interpretation of findings relating to AD, as up to half of the cases of AD may have already resolved at the ages at which diagnoses were recorded in the study [48]. While this is not a concern for AR (which only starts to manifest itself after the first 2 years of age and becomes increasingly prevalent as children grow older [49]), it is conceivable that the effect size for AR reported in this study may be different for older age groups.

The effect size in this study is modest: 26.4% of children born by C-section were later diagnosed with an allergic disease vs. 22.1% of the children who were delivered

vaginally. However, from a clinical or a public health perspective, a risk increase in the range of 20–25% is substantial: given the fact that nearly a quarter of all children born in the US and many other industrial countries are now exposed to C-sections and that the baseline prevalence in childhood allergic diseases is over 10%, even a modest increase in risk as reported in this study translates into a substantial excess burden of morbidity.

In conclusion, the results of this study indicate that children born by C-section have an increased risk of developing AR, and in girls, asthma. Our findings imply a potential role of the intestinal flora in the observed increase in the prevalence of AR and asthma, which needs further investigation.

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References

1 Strachan DP. Hayfever, hygiene, and household size. BMJ 1989; 299:1259–60.
2 Martinez FD, Holt PG. Role of microbial burden in aetiology of allergy and asthma. Lancet 1999; 354 (Suppl. 2):SII12–5.
3 Strachan DP, Taylor EM, Carpenter RG. Family structure, neonatal infection, and hay fever in adolescence. Arch Dis Child 1996; 74:422–6.
4 Alm JS, Swartz J, Lilja G, Scheynius A, Pershagen G. Atopy in children of families with an anthroposophic lifestyle. Lancet 1999; 353:1485–8.
5 Hesselmar B, Aberg N, Aberg B, Eriksson B, Bjorksten B. Does early exposure to cat or dog protect against later allergy development? Clin Exp Allergy 1999; 29:611–7.
6 Ball TM, Castro-Rodriguez JA, Griffith KA, Holberg CJ, Martinez FD, Wright AL. Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. N Engl J Med 2000; 343:538–43.
7 Braun-Fahrlander C, Gassner M, Grize L et al. Prevalence of hay fever and allergic sensitization in farmer's children and their peers living in the same rural community. Clin Exp Allergy 1999:28–34.
8 Martinez FD. Role of viral infections in the inception of asthma and allergies during childhood: could they be protective? Thorax 1994; 49:1189–91.
9 van den Biggelaar AH, van Ree R, Rodrigues LC et al. Decreased atopy in children infected with *Schistosoma haematobium*: a role for parasite-induced interleukin-10. Lancet 2000; 356:1723–7.
10 Braun-Fahrlander C, Riedler J, Herz U et al. Environmental exposure to endotoxin and its relation to asthma in school-age children. N Engl J Med 2002; 347:869–77.
11 Bjorksten B. The intrauterine and postnatal environments. J Allergy Clin Immunol 1999; 104:1119–27.
12 Pessi T, Sutas Y, Hurme M, Isolauri E. Interleukin-10 generation in atopic children following oral *Lactobacillus rhamnosus* GG. Clin Exp Allergy 2000; 30:1804–8.
13 Sudo N, Sawamura S, Tanaka K, Aiba Y, Kubo C, Koga Y. The requirement of intestinal bacterial flora for the development of an IgE production system fully susceptible to oral tolerance induction. J Immunol 1997; 159:1739–45.
14 Bjorksten B, Naaber P, Sepp E, Mikelsaar M. The intestinal microflora in allergic Estonian and Swedish 2-year-old children. Clin Exp Allergy 1999; 29:342–6.
15 Kalliomaki M, Salminen S, Arvilommi H, Kero P, Koskinen P, Isolauri E. Probiotics in primary prevention of atopic disease: a randomised placebo-controlled trial. Lancet 2001; 357:1076–9.
16 Kalliomaki M, Salminen S, Poussa T, Arvilommi H, Isolauri E. Probiotics and prevention of atopic disease: 4-year follow-up of a randomised placebo-controlled trial. Lancet 2003; 361: 1869–71.
17 Rotimi VO, Duerden BI. The development of the bacterial flora in normal neonates. J Med Microbiol 1981; 14:51–62.
18 Guarner F, Malagelada JR. Gut flora in health and disease. Lancet 2003; 361:512–9.
19 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.
20 Hall MA, Cole CB, Smith SL, Fuller R, Rolles CJ. Factors influencing the presence of faecal lactobacilli in early infancy. Arch Dis Child 1990; 65:185–8.
21 Gronlund MM, Nuutila J, Pelto L et al. Mode of delivery directs the phagocyte functions of infants for the first 6 months of life. Clin Exp Immunol 1999; 116:521–6.
22 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.
23 Anonymous. Rates of cesarean delivery – United States, 1991. MMWR Morb Mortal Wkly Rep 1993; 42:285–9.
24 Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. N Engl J Med 1995; 332:133–8.
25 Pearce N, Pekkanen J, Beasley R. How much asthma is really attributable to atopy? Thorax 1999; 54:268–72.
26 Jenkins MA, Hopper JL, Bowes G, Carlin JB, Flander LB, Giles GG. Factors in childhood as predictors of asthma in adult life. BMJ 1994; 309:90–3.
27 Withers NJ, Low L, Holgate ST, Clough JB. The natural history of respiratory symptoms in a cohort of adolescents. Am J Respir Crit Care Med 1998; 158:352–7.
28 Annibale DJ, Hulsey TC, Wagner CL, Southgate WM. Comparative neonatal morbidity of abdominal and vaginal deliveries after uncomplicated pregnancies. Arch Pediatr Adolesc Med 1995; 149:862–7.
29 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.
30 Butland BK., Strachan DP, Lewis S, Bynner J, Butler N, Britton J. Investigation into the increase in hay fever and eczema at age 16 observed between the 1958 and 1970 British birth cohorts. BMJ 1997; 315:717–21.
31 Demissie K, Breckenridge MB, Rhoads GG. Infant and maternal outcomes in the pregnancies of asthmatic women. Am J Respir Crit Care Med 1998; 158:1091–5.
32 Wills-Karp M, Santeliz J, Karp CL. The germless theory of allergic disease: revisiting the hygiene hypothesis. Nat Rev Immunol 2001; 1:69–75.
33 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.

34 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.
35 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.
36 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.
37 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.
38 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.
39 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.
40 Xu B, Pekkanen J, Jarvelin MR. Obstetric complications and asthma in childhood. J Asthma 2000; 37:589–94.
41 Kero J, Gissler M, Gronlund MM. Mode of delivery and asthma – is there a connection? Pediatr Res 2002; 52:6–11.
42 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.
43 Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. N Engl J Med 1995; 332:133–8.
44 Leung GM, Lam TH, Ho LM. Breast-feeding and its relation to smoking and mode of delivery. Obstet Gynecol 2002; 99:785–94.
45 DiMatteo MR, Morton SC, Lepper HS. Cesarean childbirth and psychosocial outcomes: a meta-analysis. Health Psychol 1996; 15:303–14.
46 Sears MR, Greene JM, Willan AR. Long-term relation between breastfeeding and development of atopy and asthma in children and young adults: a longitudinal study. Lancet 2002; 360:901–7.
47 Chapman DJ, Perez-Escamilla R. Identification of risk factors for delayed onset of lactation. J Am Diet Assoc 1999; 99:450–4.
48 Illi S, von Mutius E, Lau S, Nickel R, Gruber C, Niggemann B, Wahn U The natural course of atopic dermatitis from birth to age 7 years and the association with asthma. J Allergy Clin Immunol 2004; 113:925–31.
49 Wahn U, von Mutius E. Childhood risk factors for atopy and the importance of early intervention. J Allergy Clin Immunol 2001; 107:567–74.