

Prenatal adverse life events increase the risk for atopic diseases in children, which is enhanced in the absence of a maternal atopic predisposition

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Background: There is evidence to suggest an association between prenatal maternal stress and the development of asthma or other atopic diseases in offspring. Yet, insights on the lasting effect of multiple, common prenatal stressors are rare, and the effects of prenatal timing are poorly understood. Further, it remains elusive if prenatal life events modify the risk for atopic diseases in the context of a parental predisposition to atopy.

Objective: We tested whether women's experiences of common, adverse life events during the first or second half of pregnancy predicted the risk of developing atopic diseases in their children and whether a reported parental atopic disease moderated this association.

Methods: We calculated the odds of a child developing asthma, eczema, and/or allergic rhinitis at ages 6 or 14 years, depending on maternal prenatal exposure to negative life events in a sample of 1587 children from the Western Australian Pregnancy Cohort (Raine) Study by using multivariable logistic regression. **Results:** We observed that the likelihood of asthma and eczema at age 14 years was significantly increased in children of mothers who had experienced adverse life events during the second half of gestation (1 life event: adjusted odds ratio for asthma, 2.08 [95% CI, 1.22-3.54]). A stronger increase in the odds to develop asthma upon prenatal life events was present in children of mothers without asthma compared with mothers with asthma.

Conclusions: Maternal adverse life events during the second half of gestation are linked to an increased risk for the development of atopic disorders, asthma, and eczema, in the case of asthma, particularly in the absence of a maternal asthma. (*J Allergy Clin Immunol* 2014;■■■:■■■-■■■.)

Key words: Atopic disease, eczema, asthma, allergic rhinitis, negative life events, prenatal programming, child, pregnancy

An unprecedented increase in prevalence of asthma and atopic diseases has been observed worldwide over the past decades.^{1,2} This trend is notably apparent in Westernized societies, where often one-third of the children are reported to have an atopic disease.¹ Despite considerable research efforts, there is no unifying hypothesis to explain this "atopic epidemic." Clearly, a strong hereditary component is associated with atopic diseases.^{3,4} However, genetic factors alone do not suffice to explain these recent increases because such substantial changes to the human genome are not presumed to emerge over a few decades. Accordingly, the causes of asthma and atopic diseases have been hypothesized to be related to changing environmental challenges observed over the past decades, such as pollution, microbial exposure, diet, and psychosocial factors (eg, high stress perception).⁵⁻¹⁵ Moreover, a stronger maternal parent-of-origin effect has been reported in the context of determining the risk for asthma.³ This observation strongly supports that *in utero* challenges significantly determine the later risk for atopic diseases.^{5,12,16-18} Indeed, the prenatal period has recently been identified as particularly susceptible to environmental challenges and exposures, that is, smoking during pregnancy has been shown to increase the risk for atopic diseases in children later in life.^{5,12,17,18}

Strikingly, in coinciding with the increased prevalence of atopic diseases, an increase in psychosocial stresses in populations of varying socioeconomic conditions also has been reported.^{19,20} These findings have been amalgamated and fostered epidemiologic studies that aimed to test an association between prenatal psychosocial stress and an increased risk for atopic diseases in children later in life.^{21,22} Published evidence available to date on this presumed association reports rather ambiguous findings, which range from a significantly increased risk, for example, for childhood asthma, to only weak evidence for an association.^{22,23} This ambiguity of findings likely results from the differences in study designs used in respective epidemiologic studies, that is, the gestational periods examined or the definition or measurement of stress. For example, maternal prenatal anxiety symptoms have been used to index prenatal stress and revealed a strong association with childhood asthma.^{22,23} However, anxiety, defined as manifest feelings of fear and insecurity, may be a limited proxy for stress perception. Alternatively, prenatal

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Abbreviation used

OR: Odds ratio

bereavement, which was weakly associated with childhood asthma in boys only, is a very severe yet rare stressor. Other studies investigated the effect of prenatal life events in a selected, potentially biased population, for example, in low-income minority groups.^{24,25} Hence, extrapolation of these findings for other social groups may be limited. Another recent study showed that children of mothers who experienced prenatal negative life events are at greater risk to develop repeated wheezing within the first 2 years of life.²⁶ However, wheezing early in life may be a transient phenomenon, and evidence for an association between prenatal negative life events and a long-term manifestation of asthma would be helpful to strengthen these findings. Moreover, little is known on whether or not prenatal psychological challenges affect the risk for children's atopic diseases irrespective of a pre-existing maternal atopic disease. Thus, here we aimed to test for a differential effect of prenatal maternal stress, depending on the presence or absence of maternal or paternal atopic disease.

Thus, evidence from large, prospectively designed birth cohorts to support an association between prenatal stressors and the risk for manifest atopic diseases in children later in life is still limited. Given the reported rise in stress levels among Western societies today, additional studies in which such limitations have been addressed as much as possible are urgently required to validate the alleged association. In this context, the evaluation of common adverse life events may serve as a suitable proxy for stress perception and physiological stress response because adverse life events have previously been associated with increased levels of cortisol in pregnant women.²⁷

In the present study, we evaluated the associations among common adverse life events (eg, a residential move, economic or marital problems, job loss) in a prospectively designed large pregnancy cohort. Life events were assessed at 2 critical time points during gestation: (1) at mid gestation (gestation week 18), when the development of the fetal immune system is completed, and (2) at week 34, when the fetal airway epithelial development has occurred, lung air spaces have expanded, and production of a surfactant factor has begun. The onset of atopic diseases in children was evaluated twice, at 6 years of age to identify a possible effect of prenatal life events on early life atopic diseases, and at age 14 years to unveil an association between prenatal life events and a manifestation of atopic diseases (asthma, eczema, and allergic rhinitis) during puberty. Further, we determined whether parental atopic disease modifies any effect of prenatal maternal life events. We investigated these associations in a population-based birth cohort from Australia, in which women's life events were self-reported both during pregnancy and after birth.

METHODS

We conducted a longitudinal evaluation of 1587 children and their mothers from the Western Australian Pregnancy Cohort (Raine) Study. Both mother and child completed a questionnaire at follow-up and the children took part in a clinical examination at the Telethon Institute for Health Research at the age of 14. In the Raine Study, between 1989 and 1991, mothers between 16 to 20 weeks of gestation were enrolled by research midwives at antenatal clinics at the main tertiary maternal hospital or nearby medical practices in Perth,

Western Australia. The original purpose of the study was to determine the effects of intensive fetal monitoring on pregnancy outcomes. Full details regarding recruitment are outlined by Newnham et al.²⁸ The study protocol was approved by the human ethics committee at King Edward Memorial Hospital and/or Princess Margaret Hospital in Perth. Details of pregnancies, deliveries, and neonatal outcomes were taken from hospital notes. The cohort initially consisted of 2860 live born children. These children were followed-up at 1, 2, 3, 6, 8, 10, and 14 years of age. At 14 years of age, 1587 children still participated in the assessments, whereas 1273 were lost to follow-up. Complete data were available for 994 mothers and their children. Measures for this investigation were obtained from parent surveys administered during the Raine Cohort study and from clinical examinations at age 6 years and 14 years, which included allergy and lung function testing.

Prenatal negative life events

Prenatal stress was evaluated via questionnaire as part of the study protocol and comprised 10 typically stressful life events taken from a broader life-stress inventory.²⁹ Pregnant women were assessed twice during pregnancy, first, at gestational week 18 when the women were asked whether or not they had experienced any of the life events since the beginning of pregnancy and, second, at gestational week 34 when the women were asked whether any of these events had been experienced since the last survey at gestational week 18. This ensured that the same event was not recorded twice. Negative life events surveyed were separation or divorce, marital problems, problems with the children, pregnancy problems, experience of involuntary job loss, partner experienced involuntary job loss, money problems, a residential move, death of a close relative, and death of a close friend. These items were selected because they were deemed the most salient for a population-based sample and to save space in the larger health and lifestyle questionnaire that mothers completed during pregnancy.³⁰ Moderately stressful life events, such as a residential move, money problems, and pregnancy problems were among the life events most often experienced, whereas more-severe life events, such as death of a relative or friend, were rare. An overview of the frequency of the individual life events is shown in Table E1 (in this article's Online Repository at www.jacionline.org). Further some life events were significantly associated with each other, that is, separation or divorce and residential move or money problems and partner's involuntary job loss. The frequency of co-occurrences of life events is shown in Table E2 (in this article's Online Repository at www.jacionline.org) for life events from conception to gestational week 18 and between gestational week 18 and 34, respectively.

In the Raine study, no additional information is available that would allow us to appraise the stress level perceived in response to the respective life events or the duration of the stressful experience. Thus, we could not assign predetermined weights to life events. Therefore, we postulated an additive effect of multiple life events and evaluated the total number of life events experienced during the first (until gestational week 18) as well as the second half of pregnancy (gestational week 18 to 34) for each woman.

Atopic disease outcomes

Current asthma at ages 6 and 14 years was defined as ever having been diagnosed with asthma by a physician and the presence of a wheeze or nocturnal cough in the absence of respiratory infection, in addition to receipt of asthma medications (controller and reliever drugs) in the previous 12 months. One might argue that this definition for asthma is rather stringent because so-called wheezers were excluded. However, because we observed that, in only 18.5% of the 54 children who experienced only wheezing at age 6 years, a manifestation of asthma could be detected at age 14 years, we gave the stringent definition our preference. Moreover, children who met the stringent definition of current asthma used in this study exhibited significant deficits in lung function and greater sensitivity to methacholine challenge tests for bronchial hyperreactivity.^{31,32}

Atopy was assessed at ages 6 years and 14 years, and was defined as a specific IgE level of more than or equal to 0.35 kU/L for any of the following allergens: house dust mite (*Dermatophagoides pteronyssinus*), rye grass pollen (*Lolium perenne*), cat, couch grass (*Cynodon dactylon*), mold mix-2

(*Penicillium notatum*, *Cladosporium herbarum*, *Aspergillus fumigatus*, *Candida albicans*, *Alternaria alternata*, *Helminthosporium halodes*), peanut, or food mix-5 (egg white, milk, fish, wheat, peanut, and soybean).

Eczema at age 6 years and 14 years was defined as either ever having had eczema (self-diagnosed or diagnosed by someone other than a physician) or ever having been diagnosed with eczema by a physician and have itchy rashes in skinfolds. Allergic rhinitis at age 6 years and 14 years was defined as a hay fever diagnosis by a physician and with concurrent nose problems with itchy watering eyes. Comorbidities among atopic disorders at age 6 years and 14 years are displayed in Fig E1 (in this article's Online Repository at www.jacionline.org).

Mediators and confounders

Possible confounders or mediators of the relation between prenatal stress and the atopic diseases (asthma, eczema, and allergic rhinitis) were derived from parent survey responses or hospital notes. Confounders included sex, maternal age, number of siblings, multiple birth, maternal low education (<11 years), diabetes during pregnancy (gestational diabetes and pre-existing diabetes), use of steroid medication (unspecified) during pregnancy, breastfeeding, tobacco smoke exposure at ages 6 years and 14 years, history of paternal and maternal atopic disease (asthma, eczema, and hay fever), and cat or dog ownership during the child's first year of life.

Further, because exposure to pollution in childhood has been suggested as a determinant of wheeze and asthma,³³ we investigated associations between prenatal life events and maternal environmental exposures to solvents, glues, chemicals or poisons, dyes, paint, dust, insulation materials, air or water pollution, sewerage problems, and pest spray as well as herbicides and fungicides, all assessed via questionnaire at both time points during pregnancy. We explored associations for residential move (see Table E3 in this article's Online Repository at www.jacionline.org) as a life event likely to be associated with environmental pollution. A residential move was significantly associated with exposure to paint and dust both between conception and gestational week 18 and between gestational weeks 18 and 34. To account for these associations, these environmental exposures were included as potential mediators in our analyses. Moreover, we could exclude that the number of prenatal life events experienced were associated with environmental pollution, except for an association with air pollution, which was subsequently included as a confounder (data not shown). In addition, these environmental exposures were included as potential mediators of the effect of prenatal life events in our analyses.

Further, low birth weight (<2500 g), preterm birth (<37 weeks), and tobacco smoke exposure, as a behavioral mediator, were included as mediators of the effect of prenatal life events on atopic disease. Moreover, because the use of acetaminophen-based medication and antibiotics has previously been associated with asthma,^{34,35} both types of medication were examined for potential associations with prenatal life events (see Table E4 in this article's Online Repository at www.jacionline.org) and included as potential mediators in our analyses. In addition, the same life events that had been recorded prenatally were available postnatally during the first year of life. Because early postnatal stressors have been associated with asthma and are correlated with prenatal stressors, they also were included as a separate score of cumulative life events for this time period.¹⁴

Statistical analyses

Life event scores, unsurprisingly, were not normally distributed because the majority of women had experienced no or only one life event. Thus, life events were each analyzed as a categorical variable with 4 categories: 0 life events, 1 life event, 2 life events, 3 or more life events. This categorization was chosen to investigate a possible dose-response relationship between life events and atopic diseases, which allowed a sufficient number of women within each category to ensure statistical power. Few women experienced 3 or more life events at any time point, which constituted the smallest category. Yet, some women in this category had up to 7 life events at each time period, so we chose to retain it as a group of "severely stressed" women.

Comparisons between groups (complete vs incomplete cases; women with or those without asthma) were carried out with *t* tests for independent samples

for continuous, normally distributed data, and the Pearson χ^2 test for categorical data. For data presentation, continuous variables were calculated as mean (SD). Analyses were performed for asthma, eczema, and allergic rhinitis at age 6 years and 14 years as binary outcomes. Odds ratios (OR) and 95% CIs for life events between conception and gestational week 18 and between weeks 18 and 34 were calculated by using logistic regression models with and without adjustment for confounders listed above. Further generalized estimating equations were used to look at atopic outcomes across both ages 6 years and 14 years. For these analyses, a *P* value of <.05 was considered as statistically significant in all analyses, although they cannot be interpreted as error probabilities in a confirmatory sense. Mediation analyses were carried out in R to identify mediators of the effect of prenatal life events on asthma, allergic rhinitis, or eczema.^{36,37} In subsequent analyses, interactions between maternal and paternal atopic disease and both prenatal life event scores were assessed separately because stronger associations of maternal disease with atopic outcome in children have been reported.³ Noteworthy, in the present study, parental atopy was not clinically assessed, and information in this matter was based on self-reports. We assessed the reported maternal and paternal atopic diseases separately for each disease, so that interactions between prenatal life events and maternal or paternal asthma, eczema, and allergic rhinitis, were investigated separately for the logistic regression model of each disease. Interaction terms were created and tested by adding them to their respective full adjusted model and by assessing their significance at a 5% level and a trend at a 10% level by using log likelihood tests in accordance with Hosmer and Lemeshow.³⁸ Analyses with a significant interaction term or a trend for an interaction were subsequently stratified by parental atopic disease status. Statistical analyses were conducted by using SPSS 20 (SPSS Inc, Chicago, Ill) and R.³⁷

RESULTS

For the present analyses, data were available for 1587 mothers and their children. Complete data on asthma status at children's age of 6 and 14 years and information on all confounders required for the analyses were available for 994 children. Thus, we first evaluated a true participation bias by comparing all available data at each time point of the study with those with complete data at age 14 years (Table I). Mothers of children with incomplete data were younger, less educated, more likely to be exposed to tobacco smoke and steroids during pregnancy, and more likely to have asthma and a dog in the household compared with those with complete data. They also were more likely to have prenatal and postnatal stressful life events. The children were more often twins and born preterm or at low birth weight. Furthermore, fewer of these children were breastfed for at least 4 months and more of them were exposed to tobacco smoke at ages 6 years and 14 years compared with children with complete data. When considering that these factors largely increase the atopy risk in children, the analyses that we could presently perform arise from a population with a lower risk of developing atopic diseases.

Next, we estimated the associations between maternal prenatal life events and the risk for asthma in children at ages 6 years and age 14 years (Table II). The percentage of children with asthma at ages 6 years and 14 years increased with an increasing number of prenatal life events. Asthma at ages 6 years and 14 years was significantly associated with prenatal maternal life events between gestational weeks 18 and 34. Upon adjustment for confounders, the risk of asthma in response to prenatal life events remained to be statistically significant at age 14 years (1 life event OR 2.24, 2 life events OR 1.96, 3 or more life events OR 1.81; *P* = .02) but not at age 6 years (1 life event OR 1.10, 2 life events OR 1.34, 3 or more life events OR 0.99; *P* = .70). We were intrigued by this lack of effect at age 6 years and

TABLE I. Comparison of population with complete data with population with incomplete data

	Data available	Study population (N = 994)*	Incomplete (N = 1866)	P value†
Prenatal measures				
Main exposures				
Maternal life events until 18 wk, no.	2860			
Maternal life events until 18 wk, %				
No life events		44.0%	35.9%	
1 life event		33.1%	31.5%	<.001
2 life events		15.9%	15.4%	
3 or more life events		7.0%	17.2%	
Maternal life events between wk 18 and 34, no.	2860			
Maternal life events between wk 18 and 34, %				
No life events		49.85%	34.5%	
1 life event		29.3%	24.7%	<.001
2 life events		14.3%	13.9%	
3 or more life events		6.6%	26.9%	
Confounders				
Maternal age (mean [SD])	2860	29.43 (5.46)	26.54 (5.94)	<.001
Sex (female)	2860	48.1%	49.9%	.37
Low birth weight <2.5 kg	2859	4.7%	11.0%	<.001
Preterm <37 wk	2803	5.2%	9.1%	<.001
Multiple birth	2860	1.4%	6.0%	<.001
≥1 Sibling	2804	53.5%	50.4%	.12
Maternal low education‡	2804	31.5%	49.0%	<.001
Tobacco smoke exposure during pregnancy	2675	44.1%	64.7%	<.001
Diabetes during pregnancy	2759	3.9%	4.0%	1.00
Steroids during pregnancy	2803	0.9%	3.6%	<.001
Acetaminophen until 18 wk	1587	19.9%	20.9%	.65
Acetaminophen between wk 18 and 34	1587	13.3%	10.5%	.11
Antibiotics until 18 wk	1587	10.9%	12.1%	.46
Antibiotics between wk 18 and 34	1587	9.3%	9.1%	.93
Postnatal measures				
Main outcomes				
Current asthma at 6 y	1474	18.1%	17.3%	.70
Current asthma at 14 y	1535	10.5%	11.8%	.41
Other exposures				
Maternal life events in first year	1427			
No life events		26.2%	17.6%	
1 life event		32.2%	26.3%	<.001
2 life events		20.9%	22.2%	
3 or more life events		20.7%	33.9%	
Confounders				
Breastfed (≥4 months)	1503	71.1%	55.2%	<.001
Tobacco smoke exposure at 6 y	1439	11.5%	26.1%	<.001
Tobacco smoke exposure at 14 y	1532	6.0%	14.1%	<.001
History of paternal asthma	1237	19.6%	33.3%	<.001
History of maternal asthma	1442	25.8%	37.1%	<.001
Cats in household	1504	24.1%	23.5%	.80
Dogs in household	1578	29.1%	19.7%	<.001

All comparisons were carried out between the study population and those cases with incomplete data.

*Children with data on maternal life events during pregnancy at 18 and 34 weeks, current asthma at age 6 years and age 14 years, and all confounders.

†P value for the *t* test for comparison of means or the Pearson χ^2 test for comparisons of proportions.

‡Less than 11 years of maternal education.

presumed that it could be explained by the presence of so-called transient wheezer, which leads to an unclear asthma diagnosis at an early age that does not manifest. Indeed, in almost 60% of the children who fulfilled the criteria for asthma at age 6 years, this diagnosis could not be confirmed at age 14 years (Fig 1, A). Further, we tested if the strength of the association between prenatal life events during gestational weeks 18 and 34 was the same for atopic or nonatopic asthma in children at age 14 years. In a subset of 564 children, blood IgE levels to indicate atopy were available in addition to the information on asthma. By using

IgE levels more than or equal to 0.35 kU/L as a cutoff, this subset was divided into children who were atopic and those who were not atopic with asthma and, as expected from published evidence,³⁹ the majority of the children at age 14 years had atopic asthma. Interestingly, one life event between gestational weeks 18 and 34 significantly increased the odds to develop atopic asthma but not the odds for nonatopic, potentially indicating a stronger effect on atopic asthma (Fig 1, B). Surprisingly, 2 or more prenatal life events did not further increase the risk for atopic asthma, likely because these analyses were underpowered due to the low number

TABLE II. Relation between maternal life events before 18 weeks and between 18 and 34 weeks of gestation and asthma in children at age 6 and 14 years (n = 994)

	For asthma at 6 y			For asthma at 14 y		
	No. asthma/no. asthma (% with asthma)	Crude, OR (95% CI)	Adjusted, OR (95% CI)*†	No. asthma/no. asthma (% with asthma)	Crude, OR (95% CI)	Adjusted, OR (95% CI)*†
Maternal life events until 18 wk						
No life events	63/374 (14.4)	1 (reference)	1 (reference)	37/400 (8.5)	1 (reference)	1 (reference)
1 life event	65/264 (19.8)	1.46 (0.99-2.14)	1.30 (0.86-1.95)	36/293 (10.9)	1.33 (0.82-2.15)	1.12 (0.67-1.87)
2 life events	32/126 (20.3)	1.51 (0.94-2.42)	1.21 (0.72-2.04)	19/139 (12.0)	1.48 (0.82-2.66)	1.08 (0.56-2.07)
3 or more life events	20/50 (28.6)	2.38 (1.33-4.26)	1.73 (0.87-3.44)	12/58 (17.1)	2.24 (1.10-4.54)	1.26 (0.54-2.91)
P (trend)		.02	.40		.13	.95
Maternal life events between wk 18 and 34						
No life events	75/420 (15.2)	1 (reference)	1 (reference)	33/462 (6.7)	1 (reference)	1 (reference)
1 life event	55/236 (18.9)	1.31 (0.89-1.91)	1.10 (0.72-1.66)	41/250 (14.1)	2.30 (1.42-3.72)	2.24 (1.33-3.75)
2 life events	35/107 (24.6)	1.83 (1.16-2.88)	1.34 (0.80-2.24)	20/122 (14.1)	2.30 (1.27-4.14)	1.96 (1.01-3.79)
3 or more life events	15/51 (22.7)	1.65 (0.88-3.08)	0.99 (0.47-2.08)	10/56 (15.2)	2.50 (1.17-5.35)	1.81 (0.74-4.46)
P (trend)		.04	.70		<.01	.02

*Adjusted for sex, preterm delivery, low birth weight, multiple birth, parity, maternal age, prenatal tobacco smoke exposure, prenatal exposure to paint, dust, and air pollution; problems during pregnancy (diabetes, steroid intake); use of antibiotics or acetaminophen-based medication in pregnancy; breastfeeding; maternal education; maternal or paternal history of asthma; postnatal tobacco smoke exposure; cat or dog ownership; postnatal maternal life events.

†Generalized estimating equation results: maternal life events until week 18: Wald $\chi^2 = 1.601$, df = 3, $P = .66$; maternal life events between weeks 18 and 34: Wald $\chi^2 = 8.052$, df = 3, $P = .04$.

of cases of children with asthma when data on IgE levels were available.

Next, we tested if the risk for allergic rhinitis during childhood is altered by prenatal life events and observed that, similar to asthma, the odds of children to develop allergic rhinitis at age 14 years but not at age 6 years significantly increased with an increase in the number of prenatal life events experienced between gestational weeks 18 and 34 (Table III). Similar to asthma, almost 50% of the children who fulfilled the criteria for rhinitis at age 6 years showed a transiency of the disease because the diagnosis could not be confirmed at age 14 years (Fig 1, C). Upon adjustment for confounders, the association between prenatal life events and rhinitis at age 14 years no longer reached levels of significance ($P = .07$).

Subsequently, we tested the association between prenatal maternal life events and eczema in children (Table IV). Again, prenatal life events between gestational weeks 18 and 34 were significantly associated with an increased risk of eczema in children at age 14 years but not at age 6 years. Again, a transient eczema diagnosis was observed in young children because no disease manifestation at age 14 years was observed in approximately 30% of children diagnosed with eczema at age 6 years (Fig 1, D). This effect between prenatal life events and eczema at age 14 years remained significant after adjustment for confounders and showed a dose-response effect. Similar to the risk for allergic rhinitis, prenatal maternal stress between conception and gestational week 18 did not significantly increase the risk for eczema later in the life of the children. Generalized estimating equation models confirmed the presence of an effect of life events between gestational weeks 18 and 34 on asthma, rhinitis, or eczema. As expected, children's age also significantly affected the risk for these atopic diseases. Yet, an interaction between children's age and life events between gestational weeks 18 and 34 could be ruled out (data not shown).

Next, we tested the association between prenatal stressful life event exposure and atopic disease in offspring in the absence or presence of a parental hereditary component for atopy by testing interactions between maternal asthma, allergic rhinitis, or

eczema, and maternal prenatal life events for each respective atopic disease by adding interaction terms to the models with both prenatal life event variables and confounders. We found a trend for an interaction between maternal asthma and prenatal maternal life events between gestational age 18 weeks and 34 weeks in the model that predicted children's asthma at age 14 years at the .10 level by using a likelihood ratio test that compared the model that contained the interaction to the one without the interaction term ($X^2(3) = 6.656$; $P = .08$). Strikingly, when stratifying for maternal asthma, an association between maternal life events between weeks 18 and 34 of pregnancy was significantly associated with children's asthma at age 14 years exclusively if the mother did not have asthma (Table V). This finding was even more remarkable when we identified that the overall percentage of women who reported one or more life events between gestational week 18 and 34 was higher in women who also had asthma (Chi-Square Test of Independence: $X^2(3, N = 994) = 16.633$; $P < .01$) (Table VI).

We then aimed to identify whether prenatal life events were associated with atopy in general as a common denominator for all atopic diseases. We defined atopy if specific-IgE level was higher than 0.35 kU/L serum and could not confirm such an association (see Table E5 in this article's Online Repository at www.jacionline.org). Similarly, when using skin prick tests in response to at least one of the commonly tested allergens (ie, house dust mite, cat dander, mold, peanut, couch grass, or grass mix) as a general atopy marker, no link between prenatal life events and a positive skin prick test could be identified (data not shown). Further, we excluded that atopy at age 14 years mediated the effect of prenatal maternal life events. Also, no significant mediation effect of prenatal factors, including environmental exposures, medication or pregnancy complications, or postnatal factors (eg, postnatal stress), could be detected with regard to the association of life events between gestational weeks 18 and 34 and atopic outcomes (see Table E6 in this article's Online Repository at www.jacionline.org).

We report that the risk for children's asthma, eczema, or allergic rhinitis at the age of 14 years increases in response to life events experienced by the pregnant woman between gestational

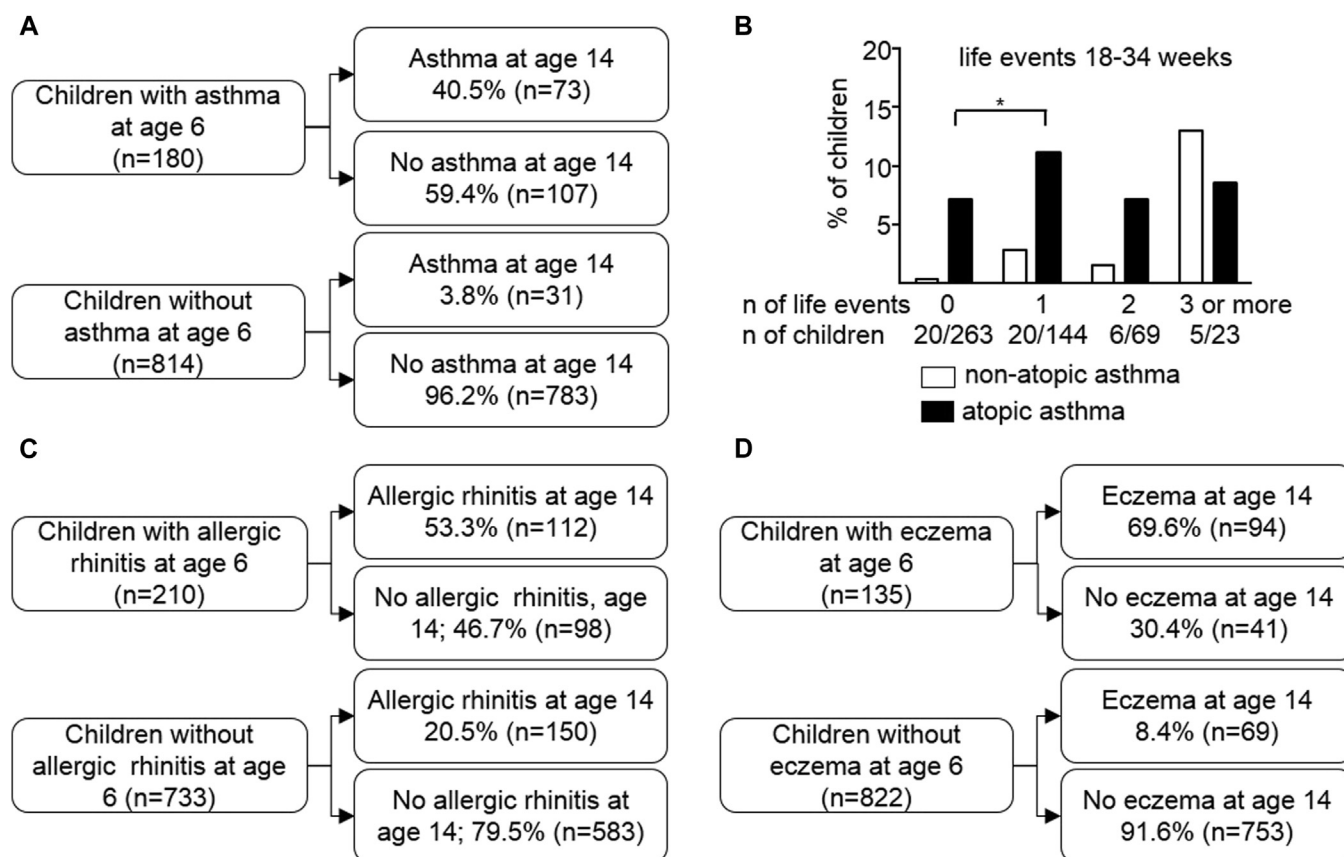


FIG 1. A differential diagnosis of the atopic diseases asthma, rhinitis, and eczema in the study population and frequency of nonatopic and atopic asthma among children in response to prenatal life events. **A**, Prevalence of asthma in children at age 6 years and age 14 years; the percentages relate to the population with or without a diagnosis at age 6 years. **B**, The frequency of children with atopic or nonatopic asthma at age 14 years, depicted in response to number (n) of prenatal life events that occurred between gestational weeks 18 and 34. *Indicates significant adjusted OR of 1.52 (95% CI: 1.14-3.25) for atopic asthma in children of mothers who had 1 life event compared with those with no life events. These results were derived from a post hoc multinomial regression analysis adjusted for confounders. The numbers below the life event categories show the total number of children with asthma (atopic and nonatopic) per total number of children within category. **C**, Prevalence of allergic rhinitis in children at age 6 years and age 14 years; the percentages relate to the population with or without diagnosis at age 6 years. **D**, The prevalence of eczema in children at age 6 years and age 14 years. The percentages relate to the population with or without a diagnosis at age 6 years.

weeks 18 and 34. Hence, our recent observations amend and strengthen the concept of fetal programming of allergic diseases in response to prenatal challenges, for example, stress.^{40,41} Further, we report a stronger association between prenatal stress and increased risk for asthma in children in the absence of a pre-existing maternal hereditary component. Thus, it is likely that these “first-generation” individuals with asthma may then confer an increased risk for atopic diseases to their children, hereby perpetuating the prevalence of asthma. Moreover, we could exclude that challenges such as environmental pollution or maternal health-related behaviors such as smoking or use of antibiotics or acetaminophen-based medication mediated the association between prenatal life events and atopic diseases in the children.

However, the association between prenatal life events and a significantly increased risk for asthma or eczema (upon adjustment for confounder) could only be established for children at age 14 years but not yet at age 6 years. This appears to be counterintuitive because one might expect an attenuation of the

association during the life course when postnatal factors may have contributed to disease development. One explanation for this effect may be that it is due to different entities of atopic diseases at age 6 years because the respective diagnosis was only transient in a large percentage of children and absent at age 14 years. Thus, we propose that prenatal life events increase the risk for manifest atopic diseases in children, whereas the risk for a transient atopic disease is not significantly altered. Another explanation may be that a clear diagnosis of atopic diseases is easier in older children. In our study population, the reported prevalence of asthma was 18.1% at age 6 years but 10.5% at age 14 years. A false-positive diagnosis for asthma at age 6 years could provide an explanation for this ambiguity; however, the study design does not permit verifying or objecting to such a misclassification. In light of continuously improving diagnostic criteria, future studies may allow assessment of the effect of prenatal life events on the pathogenesis of transient or manifest atopic diseases at an earlier age, possibly if clinical assessments are accompanied by immunologic and epigenetic predictors of atopy risks.

TABLE III. Relation between maternal life events before 18 weeks and between 18 and 34 weeks of gestation and allergic rhinitis in children at age 6 and 14 years (n = 943)

	For allergic rhinitis at 6 y			For allergic rhinitis at 14 y		
	No. allergic rhinitis/no. allergic rhinitis (% with allergic rhinitis)	Crude, OR (95% CI)	Adjusted, OR (95% CI)*†	No. allergic rhinitis/no. allergic rhinitis (% with allergic rhinitis)	Crude, OR (95% CI)	Adjusted, OR (95% CI)*†
Maternal life events until 18 wk						
No life events	81/330 (19.7)	1 (reference)	1 (reference)	100/311 (24.3)	1 (reference)	1 (reference)
1 life event	74/244 (23.3)	1.24 (0.87-1.76)	1.10 (0.75-1.63)	94/224 (29.6)	1.31 (0.94-1.82)	1.09 (0.76-1.56)
2 life events	32/116 (21.6)	1.12 (0.71-1.78)	0.92 (0.54-1.55)	43/105 (29.1)	1.27 (0.84-1.94)	0.96 (0.59-1.54)
3 or more life events	23/43 (34.8)	2.18 (1.24-3.82)	1.62 (0.81-3.26)	25/41 (37.9)	1.90 (1.10-3.27)	0.96 (0.49-1.88)
P (trend)		.06	.45		.10	.94
Maternal life events between wk 18 and 34						
No life events	91/380 (19.3)	1 (reference)	1 (reference)	108/363 (22.9%)	1 (reference)	1 (reference)
1 life event	69/210 (24.7)	1.37 (0.96-1.96)	1.05 (0.71-1.56)	82/197 (29.4%)	1.40 (1.00-1.96)	1.16 (0.80-1.67)
2 life events	33/101 (15.7)	1.36 (0.87-2.15)	1.10 (0.65-1.87)	46/88 (34.3%)	1.76 (1.16-2.66)	1.49 (0.93-2.40)
3 or more life events	17/42 (28.8)	1.69 (0.92-3.11)	1.24 (0.58-2.62)	26/33 (44.1%)	2.65 (1.52-4.62)	2.38 (1.21-4.70)
P (trend)		.16	.95		<.01	.07

*Adjusted for sex, preterm delivery, low birth weight, multiple birth, parity, maternal age, prenatal tobacco smoke exposure, prenatal exposure to paint, dust and air pollution, problems during pregnancy (diabetes, steroid intake), use of antibiotics or acetaminophen-based medication in pregnancy, breastfeeding, maternal education, maternal or paternal history of allergic rhinitis, postnatal tobacco smoke exposure, cat or dog ownership, postnatal maternal life events.

†Generalized estimating equations results: maternal life events until week 18: Wald $\chi^2 = 2.471$, df = 3, $P = .48$; maternal life events between weeks 18 and 34: Wald $\chi^2 = 7.904$, df = 3, $P = .05$.

TABLE IV. Relation between maternal life events before 18 weeks and between 18 and 34 weeks of gestation and eczema in children at age 6 y and 14 y (n = 957)

	For eczema at 6 y			For eczema at 14 y		
	No. eczema/no. eczema (% with eczema)	Crude, OR (95% CI)	Adjusted, OR (95% CI)*†	No. eczema/no. eczema (% with eczema)	Crude, OR (95% CI)	Adjusted, OR (95% CI)*†
Maternal life events until 18 wk						
No life events	56/361 (13.4)	1 (reference)	1 (reference)	71/346 (17.0)	1 (reference)	1 (reference)
1 life event	47/275 (14.6)	1.10 (0.73-1.67)	1.09 (0.69-1.71)	50/272 (15.5)	0.90 (0.60-1.33)	0.79 (0.51-1.22)
2 life events	20/132 (13.2)	0.98 (0.57-1.69)	0.89 (0.48-1.65)	27/125 (17.8)	1.05 (0.65-1.72)	0.85 (0.49-1.50)
3 or more life events	12/54 (18.2)	1.43 (0.72-2.84)	1.41 (0.61-3.29)	15/51 (22.7)	1.43 (0.76-2.69)	1.18 (0.54-2.60)
P (trend)		.75	.75		.56	.61
Maternal life events between wk 18 and 34						
No life events	60/412 (12.7)	1 (reference)	1 (reference)	69/403 (14.6)	1 (reference)	1 (reference)
1 life event	41/243 (14.4)	1.16 (0.76-1.78)	1.11 (0.70-1.76)	50/234 (17.6)	1.24 (0.84-1.86)	1.25 (0.80-1.93)
2 life events	19/123 (13.4)	1.06 (0.61-1.85)	1.17 (0.63-2.19)	23/119 (16.2)	1.13 (0.68-1.89)	1.26 (0.70-2.29)
3 or more life events	15/44 (25.4)	2.34 (1.23-4.47)	2.38 (0.63-2.19)	21/38 (35.6)	3.23 (1.79-5.83)	4.19 (1.97-8.89)
P (trend)		.08	.21		<.01	<.01

*Adjusted for sex, preterm delivery, low birth weight, multiple birth, parity, maternal age, prenatal tobacco smoke exposure, prenatal exposure to paint, dust and air pollution, problems during pregnancy (diabetes, steroid intake), use of antibiotics or acetaminophen-based medication in pregnancy, breastfeeding, maternal education, maternal or paternal history of eczema, postnatal tobacco smoke exposure, cat or dog ownership, postnatal maternal life events.

†Generalized estimating equation results: maternal life events until weeks 18: Wald $\chi^2 = 2.242$, df = 3, $P = .52$; maternal life events between weeks 18 and 34: Wald $\chi^2 = 17.685$, df = 3, $P < .01$.

Moreover, a clear-cut “dose-response” relationship between the number of prenatal life events and asthma, allergic rhinitis, or eczema, as it has been shown by Mathilda Chui et al²⁶ in the context of wheezing, could not be confirmed in the present study in response to 3 or more prenatal life events. This may be because the present study was underpowered with regard to the subgroup of women who reported 3 or more prenatal life events. However, one could speculate that the increased risk for atopic diseases in response to prenatal stress does not follow a dose-response curve but reaches a plateau once a certain stress threshold is reached. Another possibility is that the population in the higher exposure category was biased. To exclude this, we compared the women

in the different life event categories with regard to a number of potential confounding factors and could not detect such bias (see Table E4 in this article’s Online Repository at www.jacionline.org). Yet, we cannot exclude that the women differ with regard to an exposure that was not recorded in this study, that is, noise pollution. Further studies that collect more detailed information on quality and quantity of stressors, and that include women at risk to experience a large number of life events may help to exclude or confirm which type of dose-response relationship is indeed present.

A limitation of this study is that no information on maternal prenatal perceived stress, depression, anxiety, resilience, coping

TABLE V. Relation between maternal life events between 18 and 34 weeks of gestation and asthma at age 14 years stratified by maternal history of asthma

	No. asthma/no. asthma (% with asthma)	For asthma in children of mothers without asthma (n = 738)		No. asthma/no. asthma (% with asthma)	For asthma in children of mothers with asthma (n = 256)	
		Crude, OR (95% CI)	Adjusted, OR (95% CI)*		Crude, OR (95% CI)	Adjusted, OR (95% CI)*
Maternal life events between wk 18 and 34						
No life events	14/380 (3.6)	1 (reference)	1 (reference)	19/82 (18.8)	1 (reference)	1 (reference)
1 life event	22/181 (13.8)	3.30 (1.65-6.60)	3.52 (1.64-7.55)	19/69 (21.6)	1.19 (0.58-2.42)	1.14 (0.51-2.56)
2 life events	11/89 (11.0)	3.36 (1.47-7.64)	3.07 (1.15-8.15)	9/33 (21.4)	1.18 (0.48-2.87)	0.77 (0.26-2.26)
3 or more life events	3/38 (7.3)	2.14 (0.59-7.79)	1.92 (0.42-8.69)	7/18 (28.0)	1.68 (0.61-4.59)	0.98 (0.28-3.40)
P (trend)		.00	.01		.79	.91

*Adjusted for sex, preterm delivery, low birth weight, multiple birth, parity, maternal age, prenatal tobacco smoke exposure, prenatal exposure to paint, dust and air pollution, problems during pregnancy (diabetes, steroid intake), use of antibiotics or acetaminophen-based medication in pregnancy, breastfeeding, maternal education, paternal history of asthma, postnatal tobacco smoke exposure, cat or dog ownership, postnatal maternal life events.

TABLE VI. Comparison of women with and those without asthma across life event categories

	Mothers with asthma, % within category (no.) (n = 256)	Mothers without asthma, % within category (no.) (n = 738)	χ^2
Maternal life events until 18 wk			7.204
No life events	37.5 (96) ^a	46.2 (341) ^a	
1 life event	36.3 (93) ^b	32.0 (236) ^b	
2 life events	16.8 (43)	15.6 (115)	
3 or more life events	9.4 (24) ^c	6.2 (46) ^c	
Maternal life events between wk 18 and 34*			16.633
No life events	39.5 (101) ^d	53.4 (394) ^d	
1 life event	34.4 (88)	27.5 (203)	
2 life events	16.4 (42)	13.6 (100)	
3 or more life events	9.8 (25)	5.6 (41)	

Associations between mothers with asthma and mothers without asthma and life event category were assessed with the χ^2 test.

*Indicates significance at $P < .01$.

^{a,b,c,d}Proportions with the same superscript letter are significantly different at P value $< .05$ by using z tests.

with stress, or social support is available. Such information may have provided insights into whether or not these life events were indeed perceived as distressing, although these events are intuitively regarded as negative. We could confirm an association of a residential move, a life event that could be perceived as a positive event, with an involuntary job loss by a partner, separation or divorce, or problems with children, and identified significant associations, and, thus, we strongly assume that all prenatal life events tested here can be considered as negative stressors. However, it would be helpful to confirm this assumption by combining life event assessment with questionnaires validated for the evaluation of stress perceptions. The evaluation of common adverse life events may serve as a suitable proxy for stress perception and physiological stress response. Clearly, the assessment of a biologic stress marker would also be desirable, that is, levels of serum cortisol. However, the feasibility of analyzing biomarkers in large studies is often limited because circadian rhythms are difficult to obey. Because adverse life events have previously been associated with increased levels of cortisol in a smaller cohort of pregnant women²⁷ and testing common adverse life events could easily be envisioned to be

included in future prenatal routine checkups, the evaluation of common adverse life events may thus seem to be the most practicable approach.

The prevalence of pregnancy-related risk factors, such as preterm birth and low birth weight, and postnatal risk factors, for example, tobacco smoke exposure, was significantly lower in the population analyzed when compared with participants who discontinued or provided incomplete data. Hence, we can assume that the subpopulation that we evaluated in the present study was generally at a lower risk to develop atopic diseases, which may have biased our findings. Therefore, the effect of prenatal stressors in an unbiased population or even in a high-risk population may be even stronger than in the present cohort, which should urgently be assessed in future studies.

In such future studies, it will now be necessary to identify pathways involved in modulating the developmental origin of atopy, that is, via immunologic, endocrine, and epigenetic pathways. In this context, it also will be important to understand why children born by mothers with asthma appear to be refractory to additionally increased risk for asthma upon prenatal stress. Because immune and lung development occur largely *in utero*, prenatal environmental stressors may have adverse effects on immune ontogeny and organ development, although are not mutually exclusive. This concept is supported by a growing number of studies that showed altered immune function in nonhuman adult mammals in response to prenatal stress, and a predisposition to airway inflammation and hyperresponsiveness.^{39,40} In human studies, newborns to mothers who had experienced high levels of stress during pregnancy demonstrated an altered phenotype of innate and adaptive immune cells in cord blood.^{24,25,41} Such altered immune status may increase the risk for atopic diseases later in life.^{42,43} Atopy, therefore, is a likely mediator of the relationship between prenatal stress, altered immune status, and development of atopic disease. In the current study, we were unable to establish a mediation through atopy. Postnatal factors may exert a greater influence on the development of atopy by the age of 6 years or 14 years compared with prenatal factors. Further, the number of children of whom data on atopy were available was small, which limits the detection of such an effect. Atopy testing earlier in life and, therefore, closer to the prenatal period, may shed some light on whether prenatal life events have indeed no effect on atopy. However, the possibility that the effects that we here present are due to reporting bias is very unlikely due to the prospective nature of

the study design and the duration of time between assessment of life events and atopic disease. Moreover, insights on why prenatal challenges occurring during certain gestational time windows confer a greater risk for atopic diseases in the children are still pending. We here identify the second half of human pregnancy to be the more vulnerable period. These findings are in accordance with Cookson et al,²² who observed a stronger association between maternal anxiety at gestational week 32 and asthma in children. Pivotal hallmarks of immune organ development and acquisition of cellular effector functions must be reached during this time period, including the maturation of cellular and humoral immune response and the development of mucosal barrier functions.⁴³ Potential mechanisms that interfere with the development of the immune system could involve maternal microchimerism, which denotes the transplacental migration of maternal cells and has been proposed to support the developing immune system of the fetus *in utero* because maternal cells can be found in fetal immune organs, where they can persist postnatally.⁴⁴ Another mechanism could be a modulation of maternal and fetal glucocorticoid levels in response to prenatal stress challenge because adequate levels of glucocorticoids are critical for immune maturation as well as lung development, whereas increased levels may negatively affect immune ontogeny.^{44,45}

Clearly, the findings we present do not exclude that other prenatal factors besides stress increase the risk for atopic diseases later in life, that is, the effects of the microbiome. Also, the stress of survival in developing countries, where asthma prevalence is rather low, does seem to contradict the concept of a developmental origin of atopic diseases upon prenatal stress observed in Western societies. Insights on prenatal challenges in birth cohorts recruited in developing countries are still limited. However, because a wealth of these countries are currently in transition, future research endeavors should aim at addressing a great number of factors that may potentially be involved in the developmental origin of atopic diseases, such as prenatal stress, a modulated microbiome, pollution, infection, or smoking. Hence, the developmental origin of immune diseases in the context of prenatal stress challenges requires a continuous evaluation to identify the biomarkers involved in the purported associations.

Key messages

- Adverse life events that occurred during the second half of pregnancy increase the risk for asthma and eczema in teenage children.
- The association between adverse prenatal challenges and asthma in teenage children is enhanced if a pre-existing maternal hereditary component is absent.

REFERENCES

- Asher MI, Montefort S, Bjorksten B, Lai CKW, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. *Lancet* 2006;368:733-43.
- Bach JF. Mechanisms of disease: the effect of infections on susceptibility to autoimmune and allergic diseases. *N Engl J Med* 2002;347:911-20.
- Lim RH, Kobzik L, Dahl M. Risk for asthma in offspring of asthmatic mothers versus fathers: a meta-analysis. *PLoS One* 2010;5:1-9.
- Young S, Lesouef PN, Geelhoed GC, Stick SM, Chir B, Turner KJ, et al. The influence of a family history of asthma and parental smoking on airway responsiveness in early infancy. *N Engl J Med* 1991;324:1168-73.
- Thornton CA, Macfarlane TV, Holt PG. The hygiene hypothesis revisited: role of materno-fetal interactions. *Curr Allergy Asthma Rep* 2010;10:444-52.
- von Mutius E. Genes and the environment: two readings of their interaction. *J Allergy Clin Immunol* 2008;122:99-100.
- Kozyrskyj AL, Kendall GE, Jacoby P, Sly PD, Zubrick SR. Association between socioeconomic status and the development of asthma: analyses of income trajectories. *Am J Public Health* 2010;100:540-6.
- Shankardass K, McConnell R, Jerrett M, Milam J, Richardson J, Berhane K. Parental stress increases the effect of traffic-related air pollution on childhood asthma incidence. *Proc Natl Acad Sci U S A* 2009;106:12406-11.
- Wright RJ. Epidemiology of stress and asthma: from constricting communities and fragile families to epigenetics. *Immunol Allergy Clin North Am* 2011;31:19-39.
- Yonas MA, Lange NE, Celedon JC. Psychosocial stress and asthma morbidity. *Curr Opin Allergy Clin Immunol* 2012;12:202-10.
- Chida Y, Hamer M, Steptoe A. A bidirectional relationship between psychosocial factors and atopic disorders: a systematic review and meta-analysis. *Psychosom Med* 2008;70:102-16.
- Willers SM, Wijga AH, Brunekreef B, Kerkhof M, Gerritsen J, Hoekstra MO, et al. Maternal food consumption during pregnancy and the longitudinal development of childhood asthma. *Am J Resp Crit Care* 2008;178:124-31.
- von Hertzen LC. Maternal stress and T-cell differentiation of the developing immune system: possible implications for the development of asthma and atopy. *J Allergy Clin Immunol* 2002;109:923-8.
- Wright RJ, Cohen S, Carey V, Weiss ST, Gold DR. Parental stress as a predictor of wheezing in infancy: a prospective birth-cohort study. *Am J Respir Crit Care Med* 2002;165:358-65.
- Lange NE, Bunyavanich S, Silberg JL, Canino G, Rosner BA, Celedon JC. Parental psychosocial stress and asthma morbidity in Puerto Rican twins. *J Allergy Clin Immunol* 2011;127:734-40.
- Lim RH, Kobzik L. Maternal transmission of asthma risk. *Am J Reprod Immunol* 2009;61:1-10.
- Pincus M, Keil T, Rucke M, Bruenahl C, Magdorf K, Klapp BF, et al. Fetal origin of atopic dermatitis. *J Allergy Clin Immunol* 2010;125:273-5.
- Pincus M, Arck P. Developmental programming of allergic diseases. *Chem Immunol Allergy* 2012;98:70-84.
- Turner RJ, Wheaton B, Lloyd DA. The epidemiology of social stress. *Am Sociol Rev* 1995;60:104-25.
- World Health Organisation. Fact sheet EURO0/03/03 Copenhagen. Vienna; 2003.
- Wright RJ, Finn P, Contreras JP, Cohen S, Wright RO, Staudenmayer J, et al. Chronic caregiver stress and IgE expression, allergen-induced proliferation, and cytokine profiles in a birth cohort predisposed to atopy. *J Allergy Clin Immunol* 2004;113:1051-7.
- Cookson H, Granell R, Joinson C, Ben-Shlomo Y, Henderson AJ. Mothers' anxiety during pregnancy is associated with asthma in their children. *J Allergy Clin Immunol* 2009;123:847-53.
- Fang F, Hoglund CO, Arck P, Lundholm C, Langstrom N, Lichtenstein P, et al. Maternal bereavement and childhood asthma: analyses in two large samples of Swedish children. *PLoS One* 2011;6:1-7.
- Peters JL, Cohen S, Staudenmayer J, Hosen J, Platts-Mills TAE, Wright RJ. Prenatal negative life events increases cord blood IgE: interactions with dust mite allergen and maternal atopy. *Allergy* 2012;67:545-51.
- Wright RJ, Visness CM, Calatroni A, Grayson MH, Gold DR, Sandel MT, et al. Prenatal maternal stress and cord blood innate and adaptive cytokine responses in an inner-city cohort. *Am J Respir Crit Care Med* 2010;182:25-33.
- Mathilda Chiu Y-H, Coull BA, Cohen S, Wooley A, Wright RJ. Prenatal and postnatal maternal stress and wheeze in urban children: effect of maternal sensitization. *Am J Respir Crit Care Med* 2012;186:147-54.
- Obel C, Hedegaard M, Henriksen TB, Secher NJ, Olsen J, Levine S. Stress and salivary cortisol during pregnancy. *Psychoneuroendocrinology* 2005;30:647-56.
- Newnham JP, Evans SF, Michael CA, Stanley FJ, Landau LI. Effects of frequent ultrasound during pregnancy: a randomized controlled trial. *Lancet* 1993;342:887-91.
- Tennant C, Andrews G. Scale to measure stress of life events. *Aust N Z J Psychiatry* 1976;10:27-32.
- Robinson M, Oddy WH, Li J, Kendall GE, De Klerk NH, Silburn SR, et al. Pre- and postnatal influences on preschool mental health: a large-scale cohort study. *J Child Psychol Psychiatry* 2008;49:1118-28.
- Joseph-Bowen J, de Klerk N, Holt PG, Sly PD. Relationship of asthma, atopy, and bronchial responsiveness to serum eosinophil cationic proteins in early childhood. *J Allergy Clin Immunol* 2004;114:1040-5.

32. Joseph-Bowen J, de Klerk NH, Firth MJ, Kendall GE, Holt PG, Sly PD, et al. Lung function, bronchial responsiveness, and asthma in a community cohort of 6-year-old children. *Am J Respir Crit Care Med* 2004;169:850-4.
33. Kozyskyj AL, Bahreinian S, Azad MB. Early life exposures: impact on asthma and allergic disease. *Curr Opin Allergy Clin Immunol* 2011;11:400-6.
34. Garcia-Marcos L, Sanchez-Solis M, Perez-Fernandez V. Early exposure to acetaminophen and allergic disorders. *Curr Opin Allergy Clin Immunol* 2011;11:162-73.
35. Dom S, Droste JHJ, Sariachvili MA, Hagendorens MM, Oostveen E, Bridts CH, et al. Pre- and post-natal exposure to antibiotics and the development of eczema, recurrent wheezing and atopic sensitization in children up to the age of 4 years. *Clin Exp Allergy* 2010;40:1378-87.
36. Imai K, Keele L, Tingley D. A general approach to causal mediation analysis. *Psychol Methods* 2010;15:309-34.
37. R Development Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2010.
38. Hosmer DW, Lemeshow S. Applied logistic regression. 2nd ed. Hoboken (NJ): John Wiley Sons; 2000.
39. Pearce N, Pekkanen J, Beasley R. How much asthma is really attributable to atopy? *Thorax* 1999;54:268-272.
40. Martino D, Prescott S. Epigenetics and prenatal influences on asthma and allergic airways disease. *Chest* 2011;139:640-7.
41. Drever N, Saade GR, Bytautiene E. Fetal programming: early-life modulations that affect adult outcomes. *Curr Allergy Asthma Rep* 2010;10:453-9.
42. Sly PD, Boner AL, Bjorksten B, Bush A, Custovic A, Eigenmann PA, et al. Early identification of atopy in the prediction of persistent asthma in children. *Lancet* 2008;372:1100-6.
43. Roduit C, Wohlgensinger J, Frei R, Bitter S, Bieli C, Loeliger S, et al. Prenatal animal contact and gene expression of innate immunity receptors at birth are associated with atopic dermatitis. *J Allergy Clin Immunol* 2011;127:179-85.
44. Kavelaars A, van der Pompe G, Bakker JM, van Hasselt PM, Cats B, Visser GH, et al. Altered immune function in human newborns after prenatal administration of betamethasone: enhanced natural killer cell activity and decreased T cell proliferation in cord blood. *Pediatr Res* 1999;45:306-12.
45. Diepenbruck I, Much CC, Krumbholz A, Kolster M, Thieme R, Thieme D, et al. Effect of prenatal steroid treatment on the developing immune system. *J Mol Med* 2013;91:1293-302.

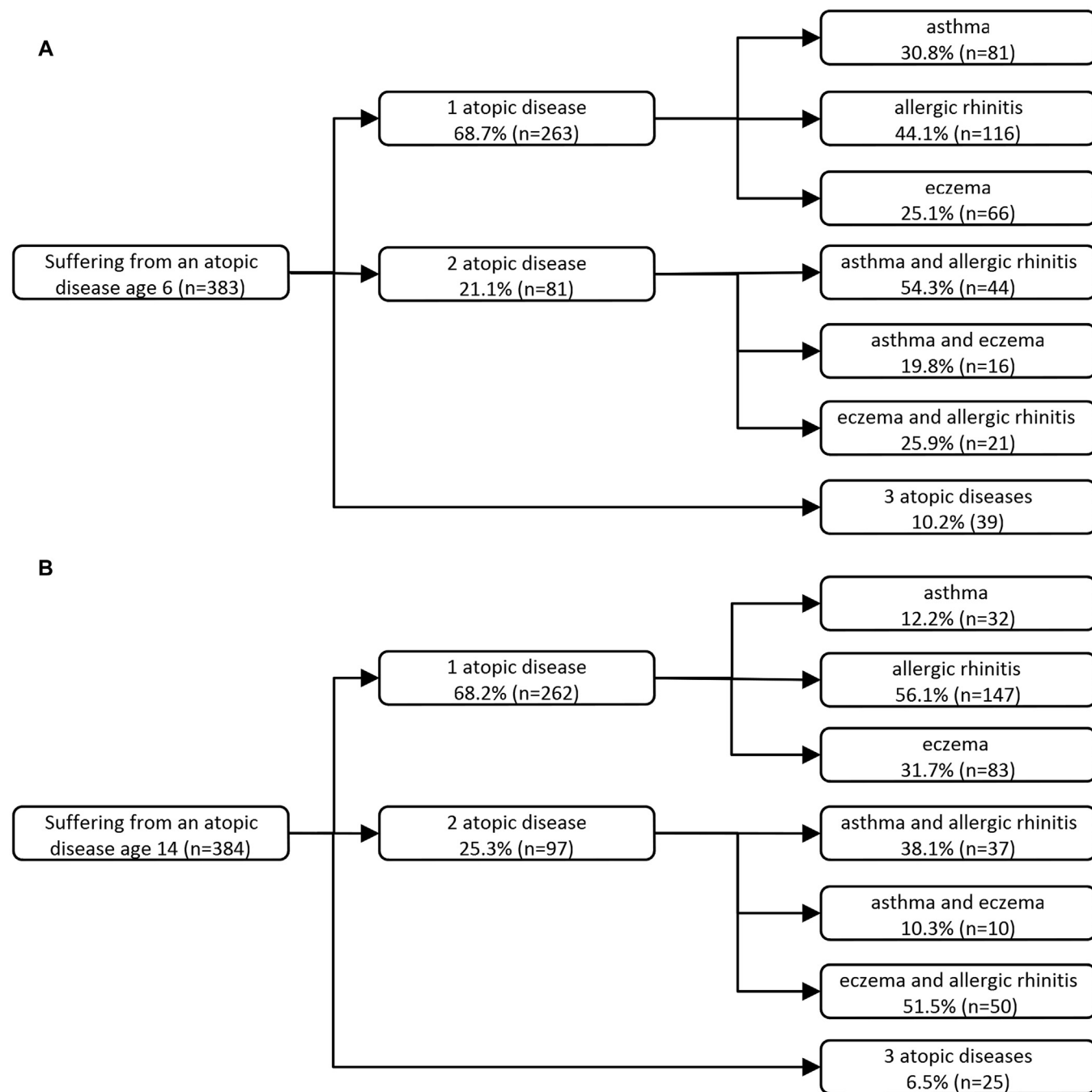


FIG E1. Number of children with 1 or multiple atopic diseases at age 6 years (**A**) and 14 years (**B**). Percentages relate to the parent population. Children with 3 atopic diseases, with asthma, allergic rhinitis, and eczema.

TABLE E1. Frequency for type of life event until gestational week 18 and between gestational weeks 18 and 34

Type of life event	From conception to gestational wk 18, % with life event (no. with life event/no. with no life event)	Between gestational wk 18 and wk 34, % with life event (no. with life event/no. with no life event)	Life events during the first year after birth, % with life event (no. with life event/no. with no life event)*	χ^2 †
Separation or divorce	1.7 (17/977)	1.3 (13/981)	5.0 (50/944)	0.542
Marital problems	5.4 (54/940)	5.0 (50/944)	15.3 (132/862)	0.162
Problems with children	6.5 (65/929)	6 (60/934)	14.0 (139/855)	0.213
Involuntary job loss (self)	2.3 (23/971)	1.1 (11/983)	1.6 (16/978)	4.309
Involuntary job loss (partner)	4.9 (49/945)	4.3 (43/951)	12.0 (119/875)	0.410
Money problems	21 (209/785)	20.9 (208/786)	35.8 (356/638)	0.003
Residential move	14 (139/855)	16.1 (160/834)	31.0 (308/686)	1.736
Pregnancy problems‡	25.4 (252/742)	18.9 (188/806)	7.1 (71/923)	11.955
Death of a close relative	5.2 (52/942)	4.9 (49/945)	16.4 (163/831)	0.094
Death of a close friend	1.9 (19/975)	2.0 (20/974)	5.1% (51/943)	0.026

*Due to a much longer 12-month period and thus a higher frequency, life events during the first year were not included in this comparison.

†Frequencies of each life event for both prenatal assessments were compared using the χ^2 test.

‡Indicated significance at $P < .01$.

TABLE E2. Co-occurrence of life events experienced during pregnancy*

	Separation or divorce	Marital problems	Problems with children	Involuntary job loss (self)	Involuntary job loss (partner)	Money problems	Residential move	Pregnancy problems	Death of a close relative	Death of a close friend
Life events between conception and gestational wk 18										
Separation or divorce	5.9% (1/17) [†]									
Marital problems	0.8% (5) [‡]	20.4% (11/54) [†]								
Problems with children	0.2% (1)	0.8% (5)	33.9% (22/65) [†]							
Involuntary job loss (self)	0.4% (2)	0.4% (2)	0.4% (2)	16.7% (4/23) [†]						
Involuntary job loss (partner)	0.0% (0)	0.7% (4)	0.7% (4)	0.5% (3)	26.5% (13/49) [†]					
Money problems	1.3% (7)	4.3% (24)	3.8% (21)	1.6% (9)	5.4% (30) [§]	32.5% (68/209) [†]				
Residential move	1.4% (8) [‡]	2.2% (12)	1.8% (10)	1.6% (9)	2.5% (14)	8.4% (47)	33.1% (46/139) [†]			
Pregnancy problems	0.8% (5)	3.4% (19)	3.6% (20) [‡]	1.3% (7)	2.3% (13) [§]	10.8% (60) [§]	7.4% (41) [§]	53.2% (134/252) [†]		
Death of a close relative	0.2% (1)	0.4% (2)	0.5% (3)	0.2% (1)	0.4% (2)	2.5% (14)	1.1% (6) [‡]	2.7% (15) [‡]	44.2% (23/52) [†]	
Death of a close friend	0.4% (2)	0.0% (0)	0.4% (2)	0.2% (1)	0.2% (1)	1.1% (6)	0.7% (4)	0.5% (3) [§]	0.0% (0)	36.8% (7/19) [†]
Life events between gestational wk 18 and 34										
Separation or divorce	2.9% (1/35) [†]									
Marital problems	0.8% (6) [§]	9.4% (9/96) [†]								
Problems with children	0.4% (3)	0.8% (6)	18.7% (17/91) [†]							
Involuntary job loss (self)	0.1% (1)	0.1% (1)	0.1% (1)	5.0% (1/20) [†]						
Involuntary job loss (partner)	0.1% (1)	0.5% (4)	1.2% (9)	0.3% (2)	9.0% (6/67) [†]					
Money problems	1.0% (8)	4.0% (31) [§]	3.1% (24)	0.9% (7)	4.0% (31)	19.3% (66/342) [†]				
Residential move	0.5% (4)	1.7% (13)	1.2% (9) [§]	0.5% (4)	1.3% (10) [§]	7.3% (57)	28.3% (71/251) [†]			
Pregnancy problems	0.3% (2)	1.7% (13)	2.7% (21)	0.4% (3)	1.0% (8) [§]	6.2% (48) [§]	4.1% (32) [§]	32.8% (95/290) [†]		
Death of a close relative	0.1% (1)	0.6% (5)	0.8% (6)	0.4% (3)	0.5% (4)	1.9% (15)	1.2% (9) [‡]	1.4% (11) [‡]	27.8% (20/72) [†]	
Death of a close friend	0.1% (1)	0.1% (1)	0.6% (5)	0.0% (0)	0.1% (1)	0.8% (6)	0.6% (5)	0.9% (7)	0.4% (3)	18.5% (5/27) [†]

*Association is depicted at percentage of co-occurrences out of all experienced life events (n = 557 from conception until gestational week 18 and n = 777 between gestational weeks 18 and 34) and the number of co-occurrences out of total occurrences.

[†]Depicts percentage of women who experienced solely this life event compared with those who experienced it in conjunction with another life event.

[‡]Significant association determined by the χ^2 test at $P < .05$.

[§]Significant association as determined by the χ^2 test at $P < .01$.

TABLE E3. Association of residential move with exposure to pollution

Type of environmental exposure	No. with exposure	% (no.) women with exposure in women who moved	% (no.) women with exposure in women who did not move	χ^2 *
From conception until wk 18, exposure to:		n = 139	n = 855	
Solvents	69	9.4 (13)	6.6 (56)	1.454
Glues	43	3.6 (5)	4.4 (38)	0.207
Chemicals or poisons	82	5.8 (8)	8.7 (74)	1.328
Dyes	43	4.3 (6)	4.3 (37)	0.000
Paint†	135	20.1 (28)	12.5 (107)	5.929
Dust†	87	9.4 (19)	8.0 (68)	4.891
Insulation materials	12	0.7 (1)	1.3 (11)	0.322
Air pollution	65	7.2 (10)	6.4 (55)	0.113
Water pollution	5	0.7 (1)	0.5 (4)	0.151
Sewerage problems	25	2.9 (4)	2.5 (21)	0.087
Pest spray	91	9.4 (13)	9.1 (78)	0.008
Herbicides and fungicides	54	2.9 (4)	5.9 (50)	2.053
Between wk 18 and 34, exposure to:		n = 160	n = 834	
Solvents	46	4.4 (7)	4.6 (39)	0.028
Glues	21	19.0 (4)	2.0 (17)	0.138
Chemicals or poisons	66	18.2 (12)	6.5 (54)	0.228
Dyes	76	13.2 (10)	7.9 (66)	0.526
Paint†	214	21.5 (46)	20.1 (168)	5.885
Dust†	74	27 (20)	6.5 (54)	7.073
Insulation materials	10	0.0 (0)	1.2 (10)	1.938
Air pollution	39	15.4 (6)	4.0 (33)	0.015
Water pollution	4	0.0 (0)	0.5 (4)	0.770
Sewage problems	24	12.5 (3)	2.5 (21)	0.236
Pest spray	85	18.8 (16)	8.3 (69)	0.512
Herbicides and fungicides	41	12.2 (5)	4.3 (36)	0.482

*Frequencies of life events for prenatal assessments were compared by using the χ^2 test.†Indicates significance at $P < .05$.

TABLE E4. Association between prenatal life events and women's medication intake during pregnancy*

	Use of acetaminophen before wk 18	Use of acetaminophen between wk 18 and 34	Use of antibiotics before wk 18	Use of antibiotics between wk 18 and 34	Prematurity	Low birth weight
Maternal life events before wk 18						
No life events	81/356 (18.5)	52/385 (11.9)	32/405 (7.3)	36/401 (8.2)	22/415 (5.0)	20/417 (4.6)
1 life event	65/264 (19.8)	40/289 (12.2)	42/287 (12.8)	29/300 (8.8)	14/315 (4.3)	13/316 (4.0)
2 life events	33/125 (20.9)	23/135 (14.6)	26/132 (16.5)	18/140 (11.4)	11/147 (7.0)	10/148 (6.3)
3 or more life events	19/51 (27.1)	17/53 (24.3)	8/62 (11.4)	9/61 (12.9)	5/65 (7.1)	4/66 (5.7)
χ^2	2.912	8.669 [†]	12.012 [‡]	2.555	2.137	1.513
Maternal life events between wk 18 and 34						
No life events	93/402 (18.8)	63/435 (12.7)	43/452 (8.7)	41/454 (8.3)	22/473 (4.4)	24/471 (4.8)
1 life event	56/235 (19.2)	41/250 (14.1)	38/253 (13.1)	26/265 (8.9)	19/272 (6.5)	16/275 (5.5)
2 life events	31/111 (21.8)	17/135 (12.0)	15/127 (10.6)	15/127 (10.6)	5/137 (3.5)	3/139 (2.1)
3 or more life events	18/48 (27.3)	11/55 (16.7)	12/54 (18.2)	10/56 (15.2)	6/60 (9.1)	4/62 (6.1)
χ^2	3.043	1.165	7.532	3.614	4.428	2.815

*No. women who took medication/no. women who did not take medication (% with exposure).

[†]Significant χ^2 test at $P < .05$.[‡]Significant χ^2 test at $P < .01$.

TABLE E5. Relation between maternal life events before 18 weeks and between 18 and 34 weeks of gestation and atopy in children at age 6 and 14 years (n = 564)

	For atopy at 6 y			For atopy at 14 y		
	No. atopy/no. with no atopy (% with atopy)	Crude, OR (95% CI)	Adjusted, OR (95% CI)*	No. atopy/no. with no atopy (% with atopy)	Crude, OR (95% CI)	Adjusted, OR (95% CI)*
Maternal life events until 18 wk						
No life events	112/135 (45.3)	1 (reference)	1 (reference)	139/108 (56.3)	1 (reference)	1 (reference)
1 life event	97/96 (50.3)	1.22 (0.84-1.78)	1.25 (0.84-1.87)	128/65 (66.3)	1.53 (1.04-2.26)	1.47 (0.97-2.24)
2 life events	34/46 (42.5)	0.89 (0.54-1.48)	0.94 (0.54-1.65)	44/36 (55.0)	0.95 (0.57-1.58)	0.86 (0.49-1.51)
3 or more life events	18/26 (40.9)	0.83 (0.44-1.60)	0.70 (0.41-1.21)	23/21 (52.3)	0.85 (0.45-1.62)	0.72 (0.33-1.57)
P (trend)		.52	.63		.10	.10
Maternal life events between wk 18 and 34						
No life events	140/145 (49.1)	1 (reference)	1 (reference)	169/116 (59.3)	1 (reference)	1 (reference)
1 life event	75/94 (44.4)	0.75 (0.50-1.11)	0.80 (0.53-1.21)	98/71 (58.0)	0.95 (0.64-1.40)	0.88 (0.58-1.34)
2 life events	35/47 (42.7)	0.79 (0.47-1.33)	0.75 (0.43-1.29)	48/34 (58.5)	0.97 (0.59-1.60)	0.94 (0.54-1.66)
3 or more life events	11/17 (39.3)	0.80 (0.33-1.91)	0.73 (0.29-1.84)	19/9 (67.9)	1.45 (0.63-3.32)	1.71 (0.64-4.61)
P (trend)		.50	.63		.81	.58

*Adjusted for sex, preterm delivery, low birth weight, multiple birth, parity, maternal age, prenatal tobacco smoke exposure, prenatal exposure to paint, dust and air pollution, problems during pregnancy (diabetes, steroid intake), use of antibiotics or paracetamol-based medication in pregnancy, breastfeeding, maternal education, maternal or paternal history of atopy, postnatal tobacco smoke exposure, cat or dog ownership, postnatal maternal life events.

TABLE E6. Mediation effects in the association of life events between gestational week 18 and 34* and allergic disease outcomes

Mediator	Asthma at age 14 y		Eczema at age 14 y		Allergic rhinitis at age 14 y	
	Average proportion of effect via mediation		Average proportion of effect via mediation		Average proportion of effect via mediation	
	(95% CI)†‡	P value	(95% CI)†‡	P value	(95% CI)†‡	P value
Prenatal factors						
Low birth weight§	0.010 (−0.038 to 0.045)	.86	−0.003 (−0.171 to 0.251)	.69	−0.002 (−0.136 to 0.110)	.98
Prematurity	0.007 (−0.043 to 0.158)	.62	−0.002 (−0.175 to 0.292)	.63	−0.070 (−0.294 to 0.226)	.48
Prenatal maternal smoking	0.008 (−0.133 to 0.146)	.90	−0.122 (−0.894 to 0.492)	.38	−0.051 (−0.674 to 0.515)	.57
Use of antibiotics in pregnancy	0.008 (−0.065 to 0.111)	.84	0.060 (−0.110 to 0.466)	.28	−0.050 (−0.524 to 0.120)	.32
Use of paracetamol-based medication in pregnancy	0.002 (−0.037 to 0.062)	.81	−0.006 (−0.077 to 0.104)	.86	0.017 (−0.099 to 0.195)	.72
Exposure to dust in pregnancy	−0.036 (−0.229 to 0.037)	.19	−0.054 (−0.405 to 0.273)	.47	−0.139 (−1.364 to 0.573)	.12
Exposure to paint in pregnancy	0.005 (−0.060 to 0.039)	.91	0.000 (−0.096 to 0.081)	.96	−0.030 (−0.197 to 0.161)	.89
Exposure to air pollution in pregnancy	0.031 (−0.036 to 0.170)	.30	0.031 (−0.116 to 0.308)	.43	−0.056 (−0.466 to 0.144)	.35
Postnatal factors						
Postnatal stress	−0.028 (−0.372 to 0.203)	.85	−0.136 (−1.439 to 1.001)	.57	0.249 (−0.023 to 1.179)	.06
Atopic predisposition	−0.44 (−2.09 to 2.49)	.91	−0.014 (−0.834 to 1.182)	.89	−1.363 (−3.563 to 4.199)	.96

*For the purpose of mediation analysis life events between gestation wk 18 and 34 were dichotomized into 0 life events or 1 or more life events.

†Average proportion of effect via mediation = (total effect − average causal mediation effect)/(total effect).

‡95% CI is based on nonparametric bootstrap.

§Low birth weight defined as weight <2.5 kg.

||Atopic predisposition based on a positive specific IgE (≥0.35 kU/L) available in a subpopulation of 499 children with IgE data.