

DR. JESSICA GERLICH (Orcid ID : 0000-0002-0737-9506)

DR. JON GENUNEIT (Orcid ID : 0000-0001-5764-1528)

PROF. ERIKA VON MUTIUS (Orcid ID : 0000-0002-8893-4515)

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Pregnancy and perinatal conditions and atopic disease prevalence in childhood and adulthood

Short Title: Perinatal conditions and atopic disease prevalence

Jessica Gerlich*, Dr. rer. biol. hum.,^{a,g} Nora Benecke*, Dr. med.,^b Astrid S. Peters-Weist, Dr. med.,^a Sabine Heinrich, Dr. rer. biol. hum.,^a Diana Roller, Dr. med.,^b Jon Genuneit, Dr. med.,^c Gudrun Weinmayr, PhD,^c Doris Windstetter, Dr. med.,^a Holger Dressel, Dr. med.,^{a,f} U Range, Dipl.-Math.,^d Dennis Nowak, Dr. med.,^{a,g} Erika von Mutius, Dr. med.,^{e,g} Katja Radon, Dr. rer. biol. hum.,^{a,g} Christian Vogelberg, Dr. med.^b

^a Institute and Clinic for Occupational, Social, and Environmental Medicine, University Hospital, LMU Munich, Germany

^b Paediatric Department, University Hospital Carl Gustav Carus, Dresden, TU Dresden, Germany

^c Institute of Epidemiology and Medical Biometry, Ulm University, Germany

^d Institute for Medical Informatics and Biometry, Medical Faculty „Carl Gustav Carus“, TU Dresden, Germany

^e Dr v Haunersches Kinderspital, University Hospital, LMU Munich, Munich, Germany

^f Institute for Epidemiology, Biostatistics and Prevention, Zürich University, Switzerland

^g Comprehensive Pneumology Center Munich, German Center for Lung Research

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* These authors contributed equally to this paper.

Corresponding author

Christian Vogelberg, MD, PhD

Division of Pediatric Pulmonology and Allergology

University Children's Hospital

Fetscherstraße 74, 01307 Dresden, Germany

Phone: +49 (0)351 458-4763

Fax: +49 (0)351 458-4334.

E-mail: Christian.Vogelberg@uniklinikum-dresden.de

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Author Contributions

JGer was one of the principal investigators responsible for coordination, data acquisition, analysis and interpretation and writing the manuscript. NB was responsible for analysis and interpretation of the data and writing the manuscript. AP-W was also one of the principle investigators, responsible for coordination, data acquisition and revising the manuscript. SH was one of the principle investigators as well, responsible for coordination, data acquisition and revising the manuscript. DR was the principle investigator for the Dresden study centre and thus responsible for data acquisition and revising the manuscript as well. JGen contributed to conception and design of the study and was responsible for data management

and revision of the manuscript. GW was responsible for data management and made contributions to conception and design and drafting the manuscript. DW made contributions to data acquisition as well as revision of the manuscript. HD was also responsible for data acquisition and contributed to revising the manuscript. UR was involved in the data analyses and revised the manuscript. DN made contributions to conception, design, analysis and interpretation of the data as well as drafting the manuscript. EvM contributed to conception, design, analyses and interpretation of the data as well as drafting the manuscript. KR contributed to conception and design as well as to data analyses and interpretation and drafting the manuscript. CV was responsible for coordination and data acquisition and contributed to conception and design and drafting the manuscript.

Conflict of Interest Statement

The authors do not have any conflict of interest to declare.

Abstract

Background:

Previous studies showed controversial results for the influence of pregnancy-related and perinatal factors on subsequent respiratory and atopic diseases in children. The aim of this study was to assess the association between perinatal variables and the prevalence of asthma, bronchial hyperreactivity, flexural eczema, allergic rhinitis, and sensitization in childhood and early adulthood.

Methods:

The studied population was first examined in Munich and Dresden in 1995/1996 at age 9-11 yrs. Participants were followed until age 19-24 yrs. using questionnaires and clinical

examinations. Associations between perinatal data and subsequent atopic diseases were examined using logistic regression analyses adjusting for potential confounders.

Results:

Cesarean section was statistically significantly associated with BHR in early adulthood (Odds Ratio 4.8, 95% confidence interval 1.5-15.2), while assisted birth was associated with presence of asthma symptoms in childhood (2.2, 1.2-3.9), flexural eczema symptoms (2.2, 1.2-4.3) and doctor's diagnosis of atopic dermatitis (1.9, 1.0-3.4) in childhood, and sensitization in early adulthood (2.2, 1.1-4.3). Lower birth length (1.9, 1.1-3.2), lower birth weight (0.5, 0.3-0.9) and higher birth weight (0.6 (0.4-1.0)) were predictive of sensitization in early adulthood compared to average birth length and birth weight, respectively. None of the other perinatal factors showed statistically significant associations with the outcomes.

Conclusions:

Our results indicate that children, who are born by Cesarean section and especially by assisted birth, might be at greater risk for developing asthma, flexural eczema and sensitization and should hence be monitored. Prenatal maternal stress might partly explain these associations, which should be further investigated.

Key words

Allergy, atopic disease, birth length, oxygen supplementation, perinatal, pregnancy, sensitization, delivery mode

Abbreviations used

AD	atopic dermatitis
AR	allergic rhinitis
BHR	bronchial hyperreactivity
CI	confidence interval
FE	flexural eczema
FEV ₁	forced expiratory volume in 1 second
ISAAC	International Study of Asthma and Allergies in Childhood
OR	odds ratio
SOLAR	Study on Occupational Allergy Risks
SPT	skin prick test

INTRODUCTION

Within the past decades, the increasing frequency of atopic diseases has become a matter of growing concern. Recent studies showed that the prevalence of asthma is still rising in many parts of the world (1). During the perinatal period, a child is exposed to a range of environmental factors which might have an impact on the newborn's respiratory and immunological development.

Existing information focusing on the influence of pregnancy-related and perinatal factors on subsequent atopic diseases or lung function parameters in children are contradictory. Aspects like maternal age, birth weight and birth length, APGAR-score, and prematurity have been analyzed for a possible relation with subsequent asthma or further atopic diseases (2-5). Moreover, the biological and physiological impact of mode of delivery on the child has come into focus lately (6).

Factors such as epigenetic markers (7), socioeconomic variables (8), respiratory diseases, inflammation of the child's airways (9, 10), infections or a changed cellular composition of the lungs (11) have been discussed as potential underlying causes.

Only few studies presented so far were able to follow a large population-based cohort of children, even fewer studies had the chance to track the children until adulthood. The aim of this analysis was to identify whether pregnancy-related and perinatal parameters are associated with the development of atopic diseases and asthma in childhood and early adulthood.

METHODS

Study population

The study population comprised of participants of the International Study of Asthma and Allergies in Childhood (ISAAC) Phase II enrolled in Munich and Dresden (Germany) in 1995/1996, aged 9–11 years. Baseline data of 6,399 children were collected using parental questionnaires and clinical examinations (response 85%) (12, 13). In 2002/2003, ISAAC Phase II participants were re-contacted in the first Study on Occupational Allergy Risks (SOLAR I). 3,929 of them completed a self-administered questionnaire (response 80%). In the second follow-up SOLAR II (2007-2009), 2,051 subjects participated in the questionnaire survey (response 71%), 57% of these also in clinical examinations. Complete pregnancy-related and perinatal data were obtained from the mothers of 1,006 SOLAR II participants (49%) (14).

The same validated instruments from ISAAC Phase II and the European Community Respiratory Health Survey (ECRHS) were included in the questionnaires of the three study time-points if procurable (12, 15). Spirometry and bronchial provocation were performed according to the ISAAC Phase II protocol in ISAAC Phase II in a randomly selected

subpopulation and the ECRHS II protocol in SOLAR II. In SOLAR II, bronchial provocation was only conducted for those who had undergone spirometry in ISAAC Phase II.

Informed consent was acquired from all study participants or their legal guardians. All study phases were approved by the relevant Ethical Committees.

Baseline and follow-up study procedures were described in detail elsewhere (12-14). The study population and analysis subsets are described in Figure 1.

Outcomes

The outcomes for these analyses reported at ISAAC Phase II and SOLAR II were defined as follows:

- Sensitization: Positive Skin Prick Test (SPT) reaction (average wheal size ≥ 3 mm larger than the negative control) to ≥ 1 of the following allergens: *Alternaria tenuis*, cat, *Dermatophagoides pteronyssinus*, *Dermatophagoides farinae*, mixed grass pollen, mixed tree pollen.
- Allergic rhinitis (AR) symptoms: 12-month prevalence of rhinoconjunctivitis symptoms.
- AR doctor's diagnosis: doctor's diagnosis of allergic rhinitis ("hay fever") ever.
- Flexural eczema (FE): 12-month prevalence of itchy rash in the typical predilection areas (flexural folds of the extremities, face, neck) coming and going for ≥ 6 months.
- Atopic dermatitis (AD) doctor's diagnosis: doctor's diagnosis of neurodermatitis (atopic eczema, endogenous eczema, atopic dermatitis) ever.
- Wheezing/asthma medication: 12-month prevalence of wheezing or taking asthma medication.
- Bronchial hyperreactivity (BHR):

- In ISAAC Phase II: a fall in forced expiratory volume in 1 second (FEV₁) of $\geq 15\%$ after bronchial provocation with hypertonic saline (0.9%).
- In SOLAR II: a $\geq 20\%$ fall in FEV₁ after bronchial provocation with methacholine.

Sensitization and BHR were assessed from clinical examinations, while the other outcomes were evaluated according to self-report from validated questionnaires. SOLAR I outcomes were not taken into account due to missing clinical data.

Potential predictors

In Germany, pregnant women receive standardized maternity cards from their gynecologists or midwives when pregnancy is medically ascertained. These are used to document medical information in the course of the pregnancy assessed at prenatal check-ups and right after birth. In SOLAR II, participants were asked to provide their mothers' maternity card data. If these were not available, clinical documentation of routine well-child visits was used if possible (N=13, 1.3%).

The following variables were evaluated as potential predictors (Table 1):

- Maternal age at delivery:
 - >35
 - ≤ 35 years
- Mode of delivery:
 - Spontaneous birth
 - Cesarean section
 - Assisted birth (labor induction, precipitate delivery, manual expression, application of speculum, forceps or vacuum extractor)
- Birth weight:
 - lower tertile ($\leq 3150\text{g}$)
 - middle tertile ($>3150\text{g}, \leq 3550\text{g}$)
 - upper tertile ($>3550\text{g}$)
- Birth length:

- lower tertile (<50cm)
- middle tertile ($\geq$ 50cm, <52 cm)
- upper tertile ($\geq$ 52cm)
- Oxygen (O₂) supplementation after birth: yes vs. no

It was not possible to assess the impact of very young maternal age at birth as only two participants' mothers were younger than 18 years of age.

Birth length and weight were assessed in tertiles to represent low, average and high birth length/birth weight.

Sensitivity analyses were conducted using additional or alternative potential predictors, e.g., ponderal index ((birth weight)/(birth length)³) instead of birth weight and length, or preterm birth replacing birth weight and length and O₂ supplementation. Since the results of these sensitivity analyses hardly differed from the main analyses, they are presented in the Online Repository (Tables E1 – E12).

Participants with non-German place of birth or nationality were excluded from the analyses due to heterogeneity in genetic and environmental characteristics (N=137).

Potential confounders

Several environmental and personal factors were considered as potential confounders for these analyses; they are described in Table 1.

Statistical analyses

Complete case analyses were performed using SAS software (version 9.4; SAS Institute, Inc., Cary, NC) and Stata (StataCorp. 2011. Stata Statistical Software: Release 12. College Station, TX: StataCorp LP). First, bivariate analyses on the association between the potential predictors, potential confounders and the occurrence of atopic diseases were carried out.

In a second step, multiple logistic regression models were fitted for each of the outcomes described above, including all potential predictors and all potential confounders to facilitate comparisons between the different models.

RESULTS

Of the 1,006 study participants with available perinatal information, 801 could be included in the analyses as the other 205 had missing information on potential predictors or confounders. Depending on the different outcomes under investigation, the number of observations on which the analyses were based was further reduced by missing values (Figure 1).

Maternal age at delivery ranged from 17 to 43 years (mean and median: 27 yrs.). Only 6% of participants were born to mothers older than 35 years of age. While 82% of births were spontaneous vaginal, 10% of the participants were delivered by Cesarean section. Oxygen supplementation after birth was received by 7% of the study population (Table 1). Birth weight in this study ranged from 1,120 to 5,200 grams with a mean of 3,336. Participants were on average 51 cm long when they were born (range 36-59 cm), while their head circumference was between 27 and 46 cm (mean 35 cm).

Wheezing/asthma medication and bronchial hyperreactivity

None of the perinatal data were predictive for the prevalence of BHR or wheezing/asthma medication in ISAAC Phase II. At SOLAR II, assisted birth was the only potential predictor that was statistically significantly associated with wheezing/asthma medication after adjustment for potential confounders (odds ratio (OR) 2.2; 95% confidence interval (CI) 1.2-3.9). Likewise, the prevalence of BHR at SOLAR II was statistically significantly associated with Cesarean section delivery (OR 4.8; 95% CI 1.5-15.2) (Table 2).

Allergic rhinitis

Neither symptoms nor doctor's diagnosis of AR were statistically significantly associated with any of the examined potential perinatal predictors. At ISAAC Phase II, having been born in fall (Sep.-Nov.) appeared to be inversely related to both symptoms and diagnosis of AR compared to being born in spring (Mar.-May), while maternal AD increased the risk for these outcomes in childhood. Maternal AR was also predictive of statistically significantly higher odds of symptoms and doctor's diagnosis of AR at both ISAAC Phase II and SOLAR II (Table 3).

Flexural eczema/atopic dermatitis

At ISAAC Phase II, assisted birth was a risk factor for reporting FE (OR 2.3; 95% CI 1.2-4.3) or doctor's diagnosis of AD (OR 1.9; 95% CI 1.0-3.4) compared to spontaneous births. This association did not persist until SOLAR II, while maternal AD was statistically significantly associated with presence of FE in ISAAC Phase II and doctor's diagnosis of AD at both time points. Being female increased the risk of presenting with FE in childhood or doctor's diagnosis of AD in adulthood (Table 4).

Skin prick test reactivity

At ISAAC Phase II, participants with maternal AR were at increased risk of presenting with sensitization. At SOLAR II, this association was confirmed. Moreover, assisted births were associated with a statistically significantly increased risk for a positive SPT compared to spontaneous births (OR 2.2 (1.1-4.3)). A birth weight in the lower and upper tertile was statistically significantly inversely related with a positive SPT (0.5 (0.3-0.9) and 0.6 (0.4-1.0)), respectively. Furthermore, being in the lower tertile of birth length increased the odds of SPT reactivity compared to being in the middle tertile (OR 1.9 (1.1-3.2)) (Table 5).

DISCUSSION

This study showed some statistically significant associations between perinatal factors, especially mode of delivery, and the development of subsequent asthma, eczema and atopic sensitization in childhood and early adulthood in Germany. Previous studies in this field presented controversial results. These inconsistencies might be attributed to different environmental and behavior-related factors, and genetic variations.

Maternal age at delivery

It has been argued that maternal age at delivery might influence allergic and respiratory health in the offspring due to factors such as the time between age at menarche and conception, or the number of pregnancies and thus also the number of siblings representing possible cross infections (2). Moreover, maternal age is associated with pregnancy outcomes such as prematurity, birth weight, and mode of delivery (16, 17), and might thus confound the influence of these perinatal factors on the presence of atopic diseases in the offspring.

We did not find any influence of maternal age on the presence of atopic diseases in their offspring. Since we directly accounted for many of the above-mentioned factors associated with maternal age in our analyses, it might be speculated that not maternal age itself but these other factors are more relevant for the research question under study.

Our results are in line with previous studies in which no such association was seen (5, 18, 19). Another study showed an increased risk of hospitalization for asthma at ages ≥ 2 for both younger (<25 yrs) and older (>34 yrs) mothers in univariate analyses, but this association was not confirmed in multivariate models adjusting for other maternal and perinatal factors (20).

Mode of delivery

In recent years, the role of microbial colonization during birth received much attention. One of the main hypotheses is that passing through the birth canal and being exposed to the maternal gut flora might be important for the proper formation of the child's microbiota and hence development of the immune system (6, 21, 22). To that effect, some studies suggested that children born by Cesarean section are at higher risk of allergies and other disease due to irregular bacterial colonization (6, 21, 23). However, other studies could not confirm such associations for atopic diseases (22). Irrespective of the microbiota theory, several other studies also showed increased risks of asthma/atopic disease after Cesarean section (5, 24, 25) or assisted births (26), or both (27), while others did not (28, 29).

In the present analyses, among all perinatal factors examined, most of the statistically significant associations with the outcomes were seen for mode of delivery. Compared to spontaneous vaginal births, assisted births (speculum/forceps/vacuum extraction, manual expression, labor induction, precipitate delivery) were associated with higher odds of both FE and doctor's diagnosis of AD in childhood, and wheezing or sensitization in adolescence. Moreover, BHR in early adulthood was almost 5 times more likely in participants born by Cesarean section than in those born by spontaneous vaginal births.

It is not exactly clear why assisted births seem to be associated with an increased risk of atopic dermatitis, wheezing and sensitization. It has yet to be established whether subsequent health risks can be causally attributed to these modes of delivery per se, or if this type of birth is rather indicative of other underlying causes that necessitate assisted modes of delivery. On the one hand, children born by assisted births pass through the regular birth canal and are thus exposed to the maternal microbes and gut flora. On the other hand, higher stress hormone levels were seen for these assisted birth types for both mother and child than for regular spontaneous vaginal birth or Cesarean section (30).

Prenatal maternal stress such as anxiety, depression or job-strain was shown to increase the risk of eczema and asthma in the offspring (31-33). Moreover, prenatal stress seems to be associated with higher rates of epidural anesthesia (34) and both elective and unplanned Cesarean sections (35, 36). Type and timing of pain relief methods during birth may also influence the risk of assisted birth and neonate outcomes (37). It seems therefore plausible that prenatal maternal stress, which is associated both with mode of delivery and subsequent health in the offspring, may confound the association between these two factors. Unfortunately, no information on prenatal stress was available in this study to further investigate this hypothesis.

Birth weight

Compared to average birth weight, low and high birth weight in our study were statistically significantly associated with lower prevalence of sensitization in early adulthood only. None of the other outcomes were related with any birth weight category.

Recent meta-analyses found statistically significantly increased risks of wheezing and asthma in childhood in children with low birth weight (4, 40), while the chances of developing AD later in life were increased in children with high birth weight and reduced in children with low birth weight compared to normal weight (41). Neither of these associations was confirmed in our study. Regarding the risk of AR or sensitization, previous studies did not find any association with birth weight (3, 42), which is in line with our findings.

There is no standardized definition of low, normal or high birth weight being used in the literature; instead, most authors define these categories based on their research question of interest. Different criteria are used to define the outcomes such as AR. This might explain the discrepancies between the results in different publications.

Birth length

While the effect of birth weight was studied in detail, the effects of birth length on subsequent atopic disease were not studied extensively so far, with controversial results. Some studies showed an inverse association between birth length and risk of developing AD later in life (43), while others found an influence on the risk of wheeze or asthma but not for AD, AR or sensitization (3).

In the presented analyses, the only statistically significant influence of birth length was found for presence of a positive SPT in SOLAR II – participants with a lower birth length had an increased risk compared to those with an average birth length. As discussed above, these inconsistent results might be attributed to varying definitions of exposure and outcomes. Moreover, mutual adjustment for different other maternal or perinatal factors may have played a role in the disagreement. We took length and weight at birth into account simultaneously, as we considered this combination (and their relation) more meaningful than each of the factors on their own.

Oxygen supplementation

The use of neonatal respiratory support has increased during the last decades and is now a well-established method in neonatal intensive care. The respiratory support and respiratory diseases themselves can affect the airway function (9, 42). It is known that former ventilation methods led to impairment of the lung structure (44). Nowadays, this could still be a possible explanation, unfortunately further studies are missing.

Even though neonatal oxygen supplementation was a statistically significant predictor of asthma (42), we could not find any significant association with any of the other outcomes. The proportion of participants who received oxygen after birth in our study was rather low (6%, Table 1), which might explain the lack of power to detect such associations. Moreover,

duration and intensity of supplementation might have been even more informative, but could not be taken into account due to insufficient availability of these data. However, administration of oxygen by itself is an indicator of an adverse neonatal condition. Taking delivery mode and birth weight/length simultaneously into account with oxygen supplementation should yield sufficient information regarding the overall condition of the neonate.

Strengths and limitations

The long-time follow-up of participants from the perinatal period up until infancy and adolescence is one of the major strengths of this study. However, this long observation period inevitably involved a loss of follow-up between baseline and second follow-up, which might be considered a limitation of this study and raises the question of a possible selection bias. In a previous analysis, some self-selection was shown for this cohort, e.g., persons with higher SES, less environmental tobacco smoke exposure and more parental allergic disease were more likely to continue participation (14). Therefore, some selection bias cannot be excluded for the analyses presented and should be considered when interpreting the results.

Thorough measures were taken to prevent information bias in this study. Outcomes were defined based on standardized, validated questionnaire items that were consistently applied throughout the study, or were based on clinical measures such as bronchial challenge and allergy tests that did not change over time. To avoid poor recall or recall bias, only medical documents were used to assess perinatal conditions (45).

We focused on the most objective perinatal factors that were available to us. Unfortunately, it was not possible to distinguish between elective and medically indicated Cesarean sections from the data at our disposal, even though this distinction is meaningful (22, 27). On the

other hand, it would have been difficult to analyze more subgroups of delivery mode due to statistical power issues.

Some factors included in our questionnaire were not included in the analyses, partly because they are based on subjective evaluation (e.g., Apgar Scores) and partly due to insufficient information (e.g., maternal weight gain, gestational age). Moreover, many of these elements were highly correlated with other factors included in the main analyses (e.g., maternal age at delivery and high-risk pregnancy status). Therefore, we restricted the main analyses to the five most objective and readily available perinatal factors and assessed the other factors' influence in additional sensitivity analyses presented in the Online Repository. Overall, results did not change considerably.

We tried to include the most relevant potential confounders based on the literature and previous analyses. Unfortunately, it was not possible to include all of them, since only a certain number of variables was available in our study (e.g., information on prenatal maternal stress was not collected) and because of missing data for some of the available variables (e.g., for intestinal microflora, maternal diet or antibiotic use during pregnancy) or too small subgroups (e.g., the proportion of multiples was only 2.6%). Hence, as in any epidemiological study, residual confounding cannot be excluded for the presented analyses. However, the most important factors were considered and adjusted for.

Conclusion

Among the five perinatal factors taken into account, assisted birth and Cesarean section showed some statistically significant associations with asthma, eczema and atopic sensitization in childhood/early adulthood. Being associated both with mode of delivery and the outcomes, prenatal maternal stress might explain these findings to some extent, which should be further investigated. In either case, children who are not delivered by spontaneous

vaginal birth seem to be at greater risk for developing atopic diseases and should therefore be subjected to closer medical supervision.

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Table 1 – Description of perinatal data and potential confounders in the study population (N=801)

Variable	Categories	Frequency n (%)
Maternal age at delivery	>35 vs. ≤ 35 years	49 (6.1)
Mode of delivery		
	Spontaneous birth	653 (81.5)
	Cesarean section	77 (9.6)
	Assisted birth*	71 (8.9)
Birth weight		
	lower tertile (≤3150g)	269 (33.6)
	middle tertile (>3150g, ≤3550g)	275 (34.3)
	upper tertile (>3550g)	257 (32.1)
Birth length		
	lower tertile (<50cm)	233 (29.1)
	middle tertile (≥50cm, <52 cm)	294 (36.7)
	upper tertile (≥52cm)	274 (34.2)
O ₂ supplementation after birth	yes vs. no	52 (6.5)
Firstborn	yes vs. no	403 (50.3)
Season of birth		
	spring (March-May)	191 (23.9)
	summer (June-August)	208 (26.0)
	fall (September-November)	192 (24.0)
	winter (December-February)	210 (26.2)
Place of birth	East vs. West Germany (Dresden vs. Munich)	484 (60.4)
Sex	female vs. male	455 (56.8)
Maternal asthma	yes vs. no	40 (5.0)
Maternal atopic dermatitis	yes vs. no	107 (13.4)
Maternal allergic rhinitis	yes vs. no	180 (22.5)
Maternal smoking during pregnancy	yes vs. no	40 (5.0)
Parental SES	low vs. high**	290 (36.2)

CI, confidence interval; ISAAC, International Study of Asthma and Allergies in Childhood; OR, odds ratio; SES, socioeconomic status; SOLAR, Study on Occupational Allergy Risks.

* labor induction, precipitate delivery, manual expression, application of speculum, forceps or vacuum extractor

** high: at least one parent qualified for university entrance or university diploma (≥ 12 years of schooling)

Table 2 – Multiple logistic regression models for wheezing/asthma medication and bronchial hyperreactivity at ISAAC Phase II and SOLAR II

	Wheezing or asthma medication		Bronchial hyperreactivity	
	ISAAC Phase II OR (95% CI) N=798	SOLAR II OR (95% CI) N=800	ISAAC Phase II OR (95% CI) N=348	SOLAR II OR (95% CI) N=201
Intercept	0.1 (0.0, 0.5)	0.3 (0.1, 0.9)	1.0 (0.2, 5.0)	0.0 (0.0, 0.3)
Maternal age at delivery (>35 vs. ≤ 35 years)	1.4 (0.6, 3.4)	0.7 (0.3, 1.6)	0.5 (0.1, 2.0)	1.0 (0.2, 5.6)
Mode of delivery				
Spontaneous birth	1	1	1	1
Cesarean section	1.5 (0.8, 3.1)	0.8 (0.4, 1.5)	1.7 (0.7, 3.9)	4.8 (1.5, 15.2)
Assisted birth*	1.7 (0.8, 3.6)	2.2 (1.2, 3.9)	1.4 (0.5, 3.7)	0.8 (0.2, 4.2)
Birth weight				
Lower tertile	1.4 (0.7, 2.9)	1.2 (0.7, 2.0)	1.3 (0.6, 3.0)	1.0 (0.3, 3.6)
Middle tertile	1	1	1	1
Upper tertile	1.4 (0.7, 2.6)	0.8 (0.5, 1.3)	1.0 (0.5, 2.1)	1.1 (0.3, 3.5)
Birth length				
Lower tertile	1.1 (0.5, 2.2)	0.9 (0.5, 1.6)	0.5 (0.2, 1.3)	0.8 (0.2, 3.1)
Middle tertile	1	1	1	1
Upper tertile	1.0 (0.5, 1.9)	1.1 (0.7, 1.8)	0.8 (0.4, 1.8)	2.0 (0.6, 6.9)
O ₂ supplementation after birth	1.5 (0.6, 3.4)	1.9 (0.9, 3.7)	0.6 (0.2, 2.2)	0.9 (0.1, 5.2)
Firstborn	0.9 (0.6, 1.5)	0.8 (0.5, 1.1)	1.5 (0.8, 2.8)	1.1 (0.4, 2.6)
Season of birth				
Spring (Mar.-May)	1	1	1	1
Summer (June-Aug.)	0.8 (0.4, 1.6)	1.3 (0.8, 2.3)	1.0 (0.5, 2.4)	0.4 (0.1, 1.5)
Fall (Sept.-Nov.)	1.0 (0.5, 2.0)	1.4 (0.8, 2.4)	0.8 (0.3, 2.1)	0.8 (0.2, 2.6)
Winter (Dec.-Feb.)	1.1 (0.6, 2.1)	1.2 (0.7, 2.1)	1.2 (0.5, 2.7)	0.5 (0.1, 1.7)
Place of birth (East vs. West Germany)	0.6 (0.4, 1.0)	0.6 (0.4, 0.9)	0.5 (0.3, 1.0)	2.4 (0.8, 6.6)
Sex (female vs. male)	0.4 (0.3, 0.7)	0.9 (0.6, 1.3)	0.4 (0.2, 0.6)	1.1 (0.5, 2.8)
Maternal asthma	2.4 (1.0, 5.7)	2.0 (0.9, 4.2)	0.4 (0.1, 2.2)	1.4 (0.2, 8.8)
Maternal atopic dermatitis	2.0 (1.1, 3.7)	1.5 (0.9, 2.4)	1.2 (0.5, 3.0)	0.4 (0.1, 2.3)
Maternal allergic rhinitis	1.0 (0.5, 1.7)	1.5 (1.0, 2.3)	1.0 (0.5, 2.1)	1.3 (0.5, 3.4)
Maternal smoking during pregnancy	1.1 (0.4, 2.9)	1.5 (0.7, 3.3)	0.8 (0.2, 3.1)	–
Parental SES (low vs. high)**	1.5 (0.9, 2.5)	1.1 (0.8, 1.7)	1.0 (0.5, 1.8)	1.6 (0.7, 3.8)

CI, confidence interval; ISAAC, International Study of Asthma and Allergies in Childhood; OR, odds ratio; SES, socioeconomic status; SOLAR, Study on Occupational Allergy Risks.

* labor induction, precipitate delivery, manual expression, application of speculum, forceps or vacuum extractor

** high: at least one parent qualified for university entrance or university diploma (≥ 12 years of schooling)

Table 3 – Multiple logistic regression models for symptoms and doctors' diagnosis of allergic rhinitis at ISAAC Phase II and SOLAR II

	Rhinoconjunctivitis symptoms		Doctor's diagnosis of allergic rhinitis	
	ISAAC Phase II OR (95% CI) N=790	SOLAR II OR (95% CI) N=788	ISAAC Phase II OR (95% CI) N=784	SOLAR II OR (95% CI) N=790
Intercept	0.2 (0.1, 0.6)	0.5 (0.2, 1.3)	0.0 (0.0, 0.2)	0.5 (0.2, 1.1)
Maternal age at delivery (>35 vs. ≤ 35 years)	1.1 (0.5, 2.5)	1.4 (0.7, 2.8)	0.9 (0.3, 2.9)	1.2 (0.6, 2.4)
Mode of delivery				
Spontaneous birth	1	1	1	1
Cesarean section	1.6 (0.8, 3.1)	0.5 (0.3, 1.0)	1.0 (0.4, 2.5)	0.7 (0.4, 1.3)
Assisted birth*	1.0 (0.5, 2.1)	1.1 (0.6, 1.9)	0.9 (0.3, 2.2)	1.4 (0.8, 2.5)
Birth weight				
Lower tertile	0.7 (0.4, 1.4)	0.7 (0.4, 1.1)	0.6 (0.3, 1.3)	0.7 (0.4, 1.1)
Middle tertile	1	1	1	1
Upper tertile	0.9 (0.5, 1.5)	1.1 (0.7, 1.7)	1.4 (0.7, 2.8)	0.7 (0.5, 1.1)
Birth length				
Lower tertile	1.5 (0.8, 2.8)	1.3 (0.8, 2.2)	1.9 (0.9, 4.2)	1.1 (0.6, 1.7)
Middle tertile	1	1	1	1
Upper tertile	1.0 (0.6, 1.7)	0.9 (0.6, 1.4)	0.7 (0.4, 1.4)	0.9 (0.6, 1.4)
O ₂ supplementation after birth	0.8 (0.3, 2.0)	0.8 (0.4, 1.7)	1.5 (0.6, 3.9)	0.8 (0.4, 1.7)
Firstborn	1.1 (0.7, 1.7)	1.0 (0.7, 1.4)	1.3 (0.8, 2.3)	1.0 (0.7, 1.5)
Season of birth				
Spring (Mar.-May)	1	1	1	1
Summer (June-Aug.)	1.1 (0.6, 1.9)	0.9 (0.6, 1.5)	0.5 (0.3, 1.1)	1.1 (0.7, 1.8)
Fall (Sept.-Nov.)	0.5 (0.2, 0.9)	0.7 (0.4, 1.1)	0.4 (0.2, 0.9)	0.8 (0.5, 1.4)
Winter (Dec.-Feb.)	0.8 (0.5, 1.4)	0.7 (0.4, 1.1)	0.6 (0.3, 1.1)	1.0 (0.6, 1.6)
Place of birth (East vs. West Germany)	0.7 (0.4, 1.1)	0.9 (0.6, 1.3)	1.1 (0.6, 1.9)	0.9 (0.6, 1.3)
Sex (female vs. male)	0.8 (0.5, 1.1)	0.8 (0.6, 1.1)	0.6 (0.4, 1.0)	0.6 (0.4, 0.9)
Maternal asthma	1.8 (0.8, 3.8)	1.2 (0.6, 2.4)	2.1 (0.9, 4.7)	1.6 (0.8, 3.2)
Maternal atopic dermatitis	1.8 (1.0, 3.0)	1.5 (1.0, 2.4)	2.0 (1.1, 3.8)	1.4 (0.9, 2.2)
Maternal allergic rhinitis	2.7 (1.7, 4.3)	1.6 (1.1, 2.3)	4.0 (2.3, 7.0)	2.2 (1.5, 3.3)
Maternal smoking during pregnancy	0.2 (0.1, 1.1)	0.7 (0.3, 1.6)	0.7 (0.2, 2.6)	0.9 (0.4, 1.9)
Parental SES (low vs. high)**	1.3 (0.8, 2.0)	1.0 (0.7, 1.4)	1.5 (0.9, 2.6)	1.1 (0.8, 1.6)

CI, confidence interval; ISAAC, International Study of Asthma and Allergies in Childhood; OR, odds ratio; SES, socioeconomic status; SOLAR, Study on Occupational Allergy Risks.

* labor induction, precipitate delivery, manual expression, application of speculum, forceps or vacuum extractor

** high: at least one parent qualified for university entrance or university diploma (≥ 12 years of schooling)

Table 4 – Multiple logistic regression models for flexural eczema and doctors' diagnosis of atopic dermatitis at ISAAC Phase II and SOLAR II

	Flexural eczema		Doctor's diagnosis of atopic dermatitis	
	ISAAC Phase II OR (95% CI) N=794	SOLAR II OR (95% CI) N=797	ISAAC Phase II OR (95% CI) N=787	SOLAR II OR (95% CI) N=797
Intercept	0.1 (0.0, 0.3)	0.1 (0.0, 0.3)	0.4 (0.1, 1.1)	0.1 (0.1, 0.4)
Maternal age at delivery (>35 vs. ≤ 35 years)	0.7 (0.2, 1.8)	1.6 (0.7, 3.9)	1.5 (0.7, 3.2)	1.0 (0.4, 2.1)
Mode of delivery				
Spontaneous birth	1	1	1	1
Cesarean section	1.1 (0.5, 2.4)	1.2 (0.6, 2.6)	0.7 (0.3, 1.4)	1.2 (0., 2.3)
Assisted birth*	2.2 (1.2, 4.3)	1.1 (0.5, 2.5)	1.9 (1.0, 3.4)	1.3 (0.7, 2.4)
Birth weight				
Lower tertile	0.7 (0.4, 1.2)	1.5 (0.7, 2.9)	0.7 (0.4, 1.2)	1.2 (0.7, 2.1)
Middle tertile	1	1	1	1
Upper tertile	0.8 (0.4, 1.4)	1.6 (0.8, 2.9)	0.8 (0.5, 1.4)	0.9 (0.6, 1.5)
Birth length				
Lower tertile	1.1 (0.6, 2.1)	0.7 (0.3, 1.3)	1.1 (0.6, 1.9)	0.8 (0.5, 1.4)
Middle tertile	1	1	1	1
Upper tertile	0.9 (0.5, 1.6)	0.8 (0.4, 1.5)	1.0 (0.6, 1.6)	1.2 (0.7, 1.9)
O ₂ supplementation after birth	1.5 (0.7, 3.4)	1.4 (0.6, 3.2)	0.7 (0.3, 1.6)	0.6 (0.3, 1.4)
Firstborn	0.8 (0.5, 1.3)	1.0 (0.6, 1.6)	1.0 (0.7, 1.5)	0.8 (0.5, 1.1)
Season of birth				
Spring (Mar.-May)	1	1	1	1
Summer (June-Aug.)	0.9 (0.5, 1.7)	0.7 (0., 1.3)	1.1 (0.6, 1.9)	0.8 (0.5, 1.4)
Fall (Sept.-Nov.)	1.5 (0.8, 2.8)	0.7 (0.4, 1.3)	1.2 (0.7, 2.2)	1.0 (0.6, 1.6)
Winter (Dec.-Feb.)	1.3 (0.7, 2.3)	0.6 (0.3, 1.1)	0.9 (0.5, 1.6)	0.8 (0.5, 1.4)
Place of birth (East vs. West Germany)	1.1 (0.7, 1.7)	1.2 (0.7, 2.0)	0.8 (0.5, 1.3)	1.3 (0.9, 2.0)
Sex (female vs. male)	1.9 (1.2, 3.0)	1.4 (0.9, 2.3)	1.3 (0.9, 2.0)	1.5 (1.0, 2.2)
Maternal asthma	1.4 (0.6, 3.4)	0.8 (0.3, 2.6)	1.1 (0.5, 2.5)	1.2 (0.5, 2.8)
Maternal atopic dermatitis	3.2 (1.9, 5.4)	1.6 (0.9, 3.0)	6.3 (4.0, 10.0)	2.4 (1.5, 3.9)
Maternal allergic rhinitis	1.2 (0.8, 2.1)	1.1 (0.7, 2.0)	1.4 (0.9, 2.1)	1.1 (0.7, 1.7)
Maternal smoking during pregnancy	1.4 (0.5, 3.6)	1.5 (0.6, 4.0)	2.1 (0.9, 4.7)	1.7 (0.8, 3.8)
Parental SES (low vs. high)**	0.9 (0.6, 1.4)	1.0 (0.6, 1.7)	0.6 (0.4, 0.9)	0.9 (0.6, 1.3)

CI, confidence interval; ISAAC, International Study of Asthma and Allergies in Childhood; OR, odds ratio; SES, socioeconomic status; SOLAR, Study on Occupational Allergy Risks.

* labor induction, precipitate delivery, manual expression, application of speculum, forceps or vacuum extractor

** high: at least one parent qualified for university entrance or university diploma (≥ 12 years of schooling)

Table 5 – Multiple logistic regression models for sensitization as assessed by Skin Prick Test reactivity at ISAAC Phase II and SOLAR II

	Sensitization	
	ISAAC Phase II OR (95% CI) N=695	SOLAR II OR (95% CI) N=497
Intercept	0.3 (0.1, 0.7)	1.7 (0.6, 5.1)
Maternal age at delivery (>35 vs. ≤ 35 years)	1.6 (0.7, 3.5)	2.1 (0.9, 4.8)
Mode of delivery		
Spontaneous birth	1	1
Cesarean section	0.9 (0.5, 1.6)	1.0 (0.5, 1.9)
Assisted birth*	1.0 (0.5, 1.9)	2.2 (1.1, 4.3)
Birth weight		
Lower tertile	1.0 (0.6, 1.7)	0.5 (0.3, 0.9)
Middle tertile	1	1
Upper tertile	0.9 (0.6, 1.5)	0.6 (0.4, 1.0)
Birth length		
Lower tertile	1.0 (0.6, 1.7)	1.9 (1.1, 3.2)
Middle tertile	1	1
Upper tertile	0.7 (0.5, 1.2)	0.9 (0.5, 1.5)
O ₂ supplementation after birth	1.5 (0.7, 2.9)	1.0 (0.4, 2.3)
Firstborn	1.1 (0.8, 1.7)	1.0 (0.7, 1.5)
Season of birth		
Spring (Mar.-May)	1	1
Summer (June-Aug.)	1.1 (0.7, 1.)	1.2 (0.7, 2.1)
Fall (Sept.-Nov.)	0.9 (0.6, 1.6)	1.1 (0.6, 2.0)
Winter (Dec.-Feb.)	1.0 (0.6, 1.8)	1.0 (0.6, 1.8)
Place of birth (East vs. West Germany)	1.3 (0.8, 2.0)	0.8 (0.5, 1.2)
Sex (female vs. male)	0.3 (0.2, 0.5)	0.4 (0.3, 0.6)
Maternal asthma	1.9 (0.9, 4.1)	1.6 (0.6, 4.1)
Maternal atopic dermatitis	1.5 (0.9, 2.4)	0.7 (0.4, 1.2)
Maternal allergic rhinitis	1.8 (1.1, 2.7)	2.1 (1.3, 3.3)
Maternal smoking during pregnancy	1.0 (0.4, 2.4)	1.0 (0.4, 2.5)
Parental SES (low vs. high)**	1.1 (0.8, 1.6)	1.2 (0.8, 1.8)

CI, confidence interval; ISAAC, International Study of Asthma and Allergies in Childhood; OR, odds ratio; SES, socioeconomic status; SOLAR, Study on Occupational Allergy Risks.

* labor induction, precipitate delivery, manual expression, application of speculum, forceps or vacuum extractor

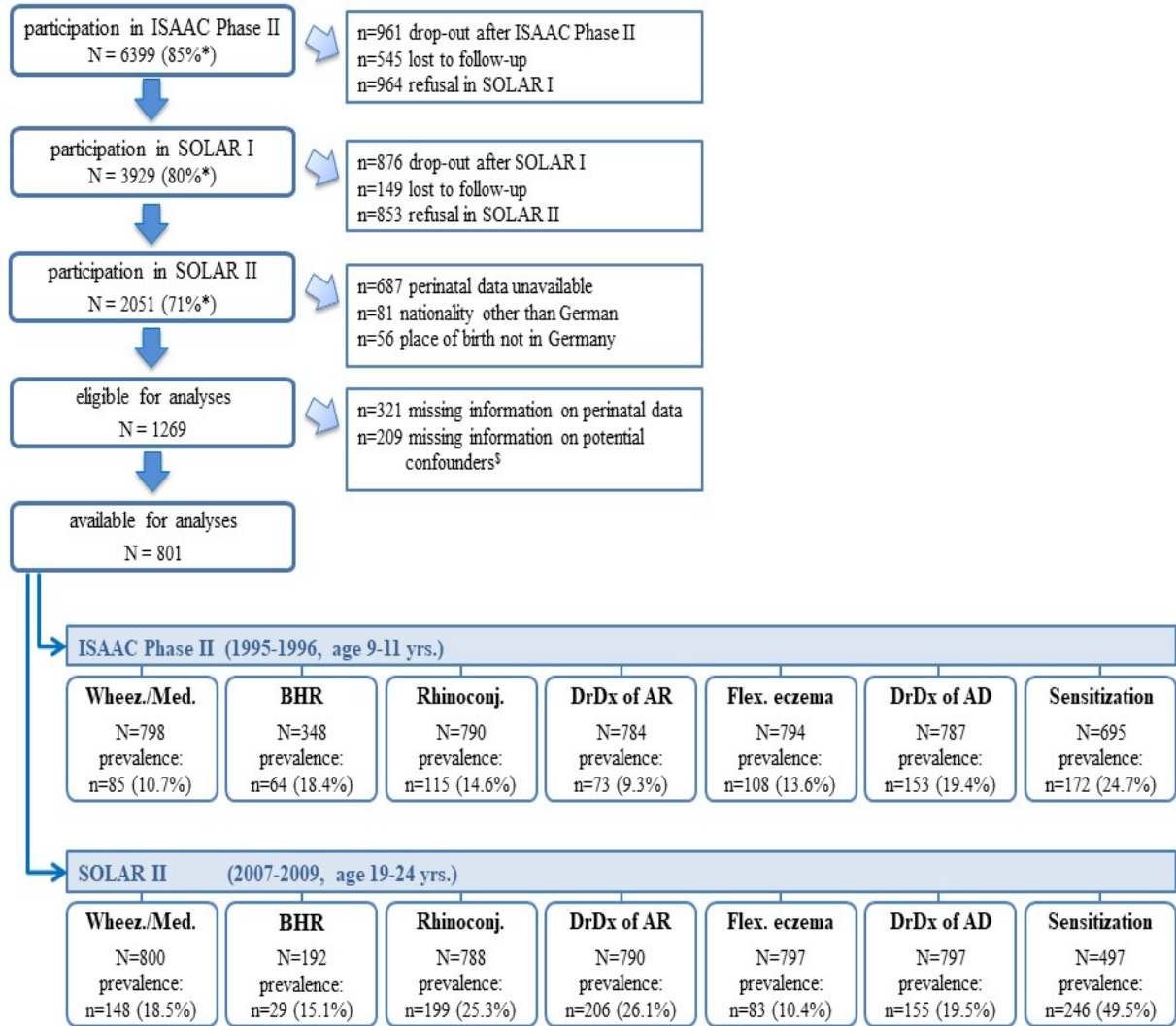
** high: at least one parent qualified for university entrance or university diploma (≥ 12 years of schooling)

Figure 1 – Study flow chart. Overview of study participation and formation of the final data analysis subsets.

Excluded participants may belong to several exclusion groups, thus numbers may not add up due to overlap. *Drop-out*: persons that refused to be contacted again after participation in ISAAC Phase II, respectively SOLAR I. *Loss to follow-up*: persons that could not be traced or contacted, e.g., due to unknown address, health reasons or death. *Refusal*: persons that could be traced and contacted but refused to participate in the first or second follow-up. *AD*, atopic dermatitis; *AR*, allergic rhinitis; *BHR*, bronchial hyperreactivity; *DrDx*, doctor's diagnosis; *Flex.*: Flexural; *ISAAC*, International Study of Asthma and Allergies in Childhood; *Rhinoconj.*, rhinoconjunctivitis symptoms; *SOLAR*, Study on Occupational Allergy Risks; *Wheez./Med.*, wheezing or asthma medication.

* response referring to the net sample, after exclusion of drop-outs and loss to follow-up.

^s potential confounders: sex, parental socioeconomic status as defined by level of education, study location, place of birth, maternal asthma, maternal allergic rhinitis, maternal atopic dermatitis, presence of siblings, maternal smoking during pregnancy, season of birth.



Pregnancy and perinatal conditions and atopic disease prevalence in childhood and adulthood

Jessica Gerlich*, Dr. rer. biol. hum.,^{a,g} Nora Benecke*, Dr. med.,^b Astrid S. Peters-Weist, Dr. med.,^a Sabine Heinrich, Dr. rer. biol. hum.,^a Diana Roller, Dr. med.,^b Jon Genuneit, Dr. med.,^c Gudrun Weinmayr, PhD,^c Doris Windstetter, Dr. med.,^a Holger Dressel, Dr. med.,^a U Range, Dipl.-Math.,^d Dennis Nowak, Dr. med.,^{a,g} Erika von Mutius, Dr. med.,^{e,g} Katja Radon, Dr. rer. biol. hum.,^{a,g} Christian Vogelberg, Dr. med.^b

^a Institute and Clinic for Occupational, Social, and Environmental Medicine, University Hospital, LMU Munich, Germany

^b Paediatric Department, University Hospital Carl Gustav Carus, Dresden, TU Dresden, Germany

^c Institute of Epidemiology and Medical Biometry, Ulm University, Germany

^d Institute for Medical Informatics and Biometry, Medical Faculty „Carl Gustav Carus“, TU Dresden, Germany

^e Dr v Haunersches Kinderspital, University Hospital Munich (LMU), Munich, Germany

^f Institute for Epidemiology, Biostatistics and Prevention, Zürich University, Switzerland

^g Comprehensive Pneumology Center Munich, German Center for Lung Research

* These authors contributed equally to this paper.

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19 RESULTS – SENSITIVITY ANALYSIS

20 A. Additional covariate: head circumference

21 **Table E 1– Multiple logistic regression models for wheezing/asthma medication and bronchial hyperreactivity at**
 22 **ISAAC Phase II and SOLAR II**

	Wheezing or asthma medication		Bronchial hyperreactivity	
	ISAAC Phase II	SOLAR II	ISAAC Phase II	SOLAR II
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
	N=498	N=500	N=217	N=135
Intercept	0.1 (0.0; 0.4)	0.3 (0.1; 1.0)	0.7 (0.1; 4.5)	0.0 (0.0; 0.2)
Maternal age at delivery (>35 vs. ≤ 35 years)	1.1 (0.4; 3.2)	0.6 (0.2; 1.6)	0.4 (0.1; 2.1)	1.0 (0.1; 12.4)
Mode of delivery				
Spontaneous birth	1	1	1	1
Cesarean section	1.9 (0.8; 4.3)	0.9 (0.4; 1.9)	1.8 (0.7; 5.1)	6.7 (1.5; 29.0)
Assisted birth*	1.9 (0.7; 5.2)	1.8 (0.8; 4.0)	1.1 (0.3; 3.7)	0.9 (0.1; 9.9)
Birth weight				
Lower tertile	2.0 (0.8; 5.4)	1.4 (0.7; 2.9)	0.9 (0.3; 2.6)	1.2 (0.2; 8.7)
Middle tertile	1	1	1	1
Upper tertile	2.5 (1.0; 6.1)	1.1 (0.6; 2.2)	1.1 (0.4; 2.7)	0.7 (0.1; 3.9)
Birth length				
Lower tertile	1.0 (0.4; 2.7)	1.1 (0.5; 2.2)	0.6 (0.2; 1.8)	1.3 (0.2; 7.9)
Middle tertile	1	1	1	1
Upper tertile	0.7 (0.3; 1.7)	1.3 (0.7; 2.5)	0.7 (0.3; 1.9)	2.9 (0.5; 16.8)
O ₂ supplementation after birth	2.4 (0.8; 7.2)	0.9 (0.3; 2.9)	0.6 (0.1; 3.6)	–
Head circumference				
Lower tertile	1.7 (0.7; 4.0)	0.8 (0.4; 1.4)	1.9 (0.7; 5.3)	2.6 (0.5; 14.8)
Middle tertile	1	1	1	1
Upper tertile	1.6 (0.8; 3.6)	0.7 (0.4; 1.2)	1.6 (0.7; 3.9)	1.8 (0.4; 8.6)
Firstborn	0.8 (0.4; 1.5)	0.7 (0.4; 1.2)	1.2 (0.6; 2.6)	0.3 (0.1; 1.3)
Season of birth				
Spring (Mar.-May)	1	1	1	1
Summer (June-Aug.)	0.8 (0.3; 1.8)	1.4 (0.7; 2.8)	1.2 (0.4; 3.1)	1.6 (0.2; 13.3)
Fall (Sept.-Nov.)	0.8 (0.3; 1.8)	1.4 (0.7; 2.8)	0.5 (0.2; 1.6)	4.0 (0.5; 31.5)
Winter (Dec.-Feb.)	0.8 (0.4; 1.9)	1.3 (0.7; 2.7)	0.7 (0.3; 2.0)	1.5 (0.2; 11.9)
Place of birth (East vs. West Germany)	0.6 (0.3; 1.1)	0.5 (0.3; 0.9)	0.8 (0.3; 1.7)	1.6 (0.4; 5.9)
Sex (female vs. male)	0.4 (0.2; 0.7)	0.9 (0.5; 1.4)	0.3 (0.1; 0.7)	0.8 (0.2; 3.1)
Maternal asthma	1.8 (0.6; 5.1)	1.9 (0.8; 4.4)	0.2 (0.0; 2.4)	5.0 (0.6; 42.7)

Maternal atopic dermatitis	2.6 (1.2; 5.4)	1.0 (0.5; 2.1)	0.4 (0.1; 1.7)	0.7 (0.1; 8.8)
Maternal allergic rhinitis	1.4 (0.7; 2.9)	1.6 (0.9; 2.8)	1.4 (0.6; 3.2)	1.7 (0.5; 6.6)
Maternal smoking during pregnancy	0.9 (0.3; 3.1)	1.2 (0.5; 3.1)	0.8 (0.2; 3.3)	–
Parental SES (low vs. high)**	1.7 (0.9; 3.1)	1.4 (0.9; 2.2)	1.1 (0.5; 2.2)	2.1 (0.6; 7.1)

23 CI, confidence interval; ISAAC, International Study of Asthma and Allergies in Childhood; OR, odds ratio;

24 SES, socioeconomic status; SOLAR, Study on Occupational Allergy Risks.

25 * labor induction, precipitate delivery, manual expression, application of speculum, forceps or vacuum extractor

26 ** high: at least one parent qualified for university entrance or university diploma (≥ 12 years of schooling)

27 **Table E 2 – Multiple logistic regression models for symptoms and doctors' diagnosis of allergic rhinitis at ISAAC**
 28 **Phase II and SOLAR II**

	Rhinoconjunctivitis symptoms		Doctor's diagnosis of allergic rhinitis	
	ISAAC Phase II	SOLAR II	ISAAC Phase II	SOLAR II
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
	N=495	N=494	N=489	N=493
Intercept	0.3 (0.1; 1.3)	0.6 (0.2; 1.8)	0.1 (0.0; 0.6)	0.6 (0.2; 2.0)
Maternal age at delivery (>35 vs. ≤ 35 years)	0.9 (0.3; 2.5)	1.3 (0.6; 2.9)	1.1 (0.3; 3.8)	1.3 (0.6; 2.8)
Mode of delivery				
Spontaneous birth	1	1	1	1
Cesarean section	2.32(1.0; 4.8)	0.8 (0.4; 1.6)	2.1 (0.8; 5.8)	1.2 (0.6; 2.4)
Assisted birth*	1.2 (0.5; 3.2)	1.0 (0.5; 2.2)	1.0 (0.3; 4.0)	1.4 (0.7; 3.1)
Birth weight				
Lower tertile	0.5 (0.2; 1.1)	0.5 (0.3; 1.0)	0.4 (0.1; 1.3)	0.5 (0.3; 1.0)
Middle tertile	1	1	1	1
Upper tertile	0.8 (0.4; 1.7)	1.3 (0.8; 2.3)	2.2 (0.9; 5.8)	0.7 (0.4; 1.3)
Birth length				
Lower tertile	2.0 (0.9; 4.6)	1.7 (0.9; 3.4)	3.1 (1.1; 9.3)	1.0 (0.5; 2.0)
Middle tertile	1	1	1	1
Upper tertile	1.1 (0.6; 2.2)	0.9 (0.5; 1.5)	0.4 (0.2; 1.1)	0.8 (0.5; 1.4)
O ₂ supplementation after birth	0.6 (0.1; 2.4)	0.6 (0.2; 1.9)	1.3 (0.3; 6.2)	0.5 (0.2; 1.7)
Head circumference				
Lower tertile	1.1 (0.6; 2.2)	1.1 (0.6; 1.9)	0.6 (0.2; 1.6)	1.0 (0.5; 1.7)
Middle tertile	1	1	1	1
Upper tertile	0.6 (0.3; 1.2)	0.6 (0.4; 1.1)	0.8 (0.4; 1.9)	0.6 (0.4; 1.1)
Firstborn	0.7 (0.4; 1.2)	0.9 (0.6; 1.4)	1.0 (0.5; 2.1)	1.0 (0.6; 1.5)
Season of birth				
Spring (Mar.-May)	1	1	1	1
Summer (June-Aug.)	1.0 (0.5; 1.9)	0.9 (0.5; 1.6)	0.4 (0.1; 0.9)	1.2 (0.7; 2.1)
Fall (Sept.-Nov.)	0.4 (0.2; 1.0)	0.6 (0.3; 1.1)	0.3 (0.1; 0.8)	0.7 (0.4; 1.3)
Winter (Dec.-Feb.)	0.7 (0.3; 1.5)	0.6 (0.3; 1.1)	0.3 (0.1; 0.8)	0.9 (0.5; 1.6)
Place of birth (East vs. West Germany)	0.8 (0.5; 1.4)	1.1 (0.7; 1.7)	1.0 (0.5; 2.2)	1.1 (0.7; 1.7)
Sex (female vs. male)	0.7 (0.4; 1.2)	0.7 (0.4; 1.0)	0.6 (0.3; 1.2)	0.5 (0.3; 0.7)
Maternal asthma	1.9 (0.8; 4.7)	1.0 (0.4; 2.3)	2.3 (0.9; 5.9)	1.6 (0.7; 3.5)
Maternal atopic dermatitis	1.9 (1.0; 3.7)	1.6 (0.9; 2.9)	3.5 (1.5; 8.0)	1.4 (0.8; 2.6)
Maternal allergic rhinitis	2.5 (1.4; 4.5)	1.6 (0.9; 2.6)	5.0 (2.3; 10.6)	2.4 (1.5; 3.9)
Maternal smoking during	0.4 (0.1; 1.7)	0.7 (0.2; 1.9)	0.8 (0.1; 4.3)	0.9 (0.3; 2.3)

pregnancy				
Parental SES (low vs. high)**	1.0 (0.6; 1.8)	0.9 (0.6; 1.4)	1.1 (0.5; 2.3)	1.0 (0.6; 1.5)

29 CI, confidence interval; ISAAC, International Study of Asthma and Allergies in Childhood; OR, odds ratio;

30 SES, socioeconomic status; SOLAR, Study on Occupational Allergy Risks.

31 * labor induction, precipitate delivery, manual expression, application of speculum, forceps or vacuum extractor

32 ** high: at least one parent qualified for university entrance or university diploma (≥ 12 years of schooling)

33 **Table E 3 – Multiple logistic regression models for flexural eczema and doctors' diagnosis of atopic dermatitis at**
 34 **ISAAC Phase II and SOLAR II**

	Flexural eczema		Doctor's diagnosis of atopic dermatitis	
	ISAAC Phase II OR (95% CI) N=496	SOLAR II OR (95% CI) N=498	ISAAC Phase II OR (95% CI) N=493	SOLAR II OR (95% CI) N=498
Intercept	0.2 (0.0; 0.7)	0.1 (0.0; 0.3)	0.7 (0.2; 2.6)	0.2 (0.0; 0.5)
Maternal age at delivery (>35 vs. ≤ 35 years)	0.6 (0.2; 2.2)	2.2 (0.8; 6.1)	1.7 (0.7; 4.1)	0.9 (0.3; 2.3)
Mode of delivery				
Spontaneous birth	1	1	1	1
Cesarean section	1.3 (0.5; 3.1)	0.9 (0.3; 2.4)	0.7 (0.3; 1.6)	1.3 (0.6; 2.6)
Assisted birth*	2.4 (1.0; 5.8)	1.5 (0.6; 4.0)	1.9 (0.8; 4.6)	1.2 (0.5; 2.8)
Birth weight				
Lower tertile	0.7 (0.3; 1.5)	1.1 (0.5; 2.7)	0.6 (0.3; 1.3)	0.9 (0.4; 1.7)
Middle tertile	1	1	1	1
Upper tertile	0.9 (0.4; 2.0)	1.6 (0.7; 3.5)	0.8 (0.4; 1.6)	1.2 (0.7; 2.3)
Birth length	1	1	1	1
Lower tertile	1.5 (0.7; 3.2)	0.6 (0.3; 1.5)	1.4 (0.6; 2.9)	0.8 (0.4; 1.7)
Middle tertile				
Upper tertile	0.7 (0.3; 1.6)	0.6 (0.3; 1.2)	1.0 (0.5; 1.9)	0.9 (0.5; 1.6)
O ₂ supplementation after birth	0.9 (0.2; 3.6)	1.2 (0.3; 4.4)	0.4 (0.1; 1.8)	0.8 (0.3; 2.6)
Head circumference				
Lower tertile	0.5 (0.2; 0.9)	0.9 (0.4; 2.0)	0.5 (0.3; 1.1)	0.8 (0.5; 1.5)
Middle tertile	1	1	1	1
Upper tertile	0.4 (0.2; 0.9)	0.9 (0.5; 1.9)	0.7 (0.4; 1.3)	0.7 (0.4; 1.3)
Firstborn	0.8 (0.5; 1.5)	1.0 (0.5; 1.8)	0.8 (0.5; 1.3)	0.7 (0.5; 1.2)
Season of birth				
Spring (Mar.-May)	1	1	1	1
Summer (June-Aug.)	0.6 (0.3; 1.4)	0.8 (0.3; 1.7)	1.2 (0.6; 2.4)	0.8 (0.4; 1.5)
Fall (Sept.-Nov.)	1.2 (0.6; 2.6)	1.0 (0.4; 2.1)	1.1 (0.5; 2.1)	0.9 (0.5; 1.7)
Winter (Dec.-Feb.)	0.9 (0.4; 2.0)	0.6 (0.2; 1.3)	0.7 (0.3; 1.5)	0.8 (0.4; 1.5)
Place of birth (East vs. West Germany)	1.4 (0.8; 2.5)	1.5 (0.8; 2.9)	0.9 (0.5; 1.5)	1.6 (1.0; 2.6)
Sex (female vs. male)	1.4 (0.8; 2.5)	1.2 (0.7; 2.3)	1.1 (0.7; 1.9)	1.5 (0.9; 2.4)
Maternal asthma	1.4 (0.5; 3.9)	0.8 (0.2; 2.7)	1.3 (0.5; 3.3)	1.1 (0.4; 2.7)
Maternal atopic dermatitis	4.0 (2.1; 7.8)	1.3 (0.6; 3.0)	5.8 (3.1; 10.8)	2.1 (1.1; 3.8)
Maternal allergic rhinitis	1.5 (0.8; 2.9)	1.2 (0.6; 2.4)	1.4 (0.8; 2.5)	1.5 (0.9; 2.6)
Maternal smoking during	2.4 (0.8; 7.2)	1.5 (0.4; 4.8)	3.0 (1.1; 7.9)	1.8 (0.7; 4.6)

pregnancy				
Parental SES (low vs. high)**	0.7 (0.4; 1.3)	1.2 (0.7; 2.2)	0.5 (0.3; 0.8)	0.8 (0.5; 1.4)

35 CI, confidence interval; ISAAC, International Study of Asthma and Allergies in Childhood; OR, odds ratio;

36 SES, socioeconomic status; SOLAR, Study on Occupational Allergy Risks.

37 * labor induction, precipitate delivery, manual expression, application of speculum, forceps or vacuum extractor

38 ** high: at least one parent qualified for university entrance or university diploma (≥ 12 years of schooling)

39 **Table E 4 – Multiple logistic regression models for sensitization as assessed by Skin Prick Test reactivity at ISAAC**
 40 **Phase II and SOLAR II**

	Sensitization	
	ISAAC Phase II OR (95% CI) N=434	SOLAR II OR (95% CI) N=316
Intercept	0.1 (0.0; 0.6)	1.6 (0.4; 6.0)
Maternal age at delivery (>35 vs. ≤ 35 years)	1.1 (0.4; 3.0)	1.9 (0.7; 5.3)
Mode of delivery		
Spontaneous birth	1	1
Cesarean section	1.8 (0.8; 3.7)	1.5 (0.6; 3.3)
Assisted birth*	0.9 (0.4; 2.3)	2.2 (0.8; 5.7)
Birth weight		
Lower tertile	1.0 (0.5; 2.1)	0.4 (0.2; 0.8)
Middle tertile	1	1
Upper tertile	1.6 (0.8; 3.2)	0.9 (0.4; 1.7)
Birth length		
Lower tertile	0.8 (0.4; 1.8)	1.9 (0.9; 3.9)
Middle tertile	1	1
Upper tertile	0.5 (0.3; 1.0)	0.7 (0.4; 1.3)
O ₂ supplementation after birth	0.8 (0.2; 2.6)	0.7 (0.2; 2.7)
Head circumference		
Lower tertile	2.2 (1.1; 4.1)	2.2 (1.2; 4.2)
Middle tertile	1	1
Upper tertile	0.9 (0.5; 1.7)	0.7 (0.4; 1.3)
Firstborn	1.0 (0.6; 1.6)	1.0 (0.6; 1.6)
Season of birth		
Spring (Mar.-May)	1	1
Summer (June-Aug.)	1.5 (0.7; 2.9)	1.5 (0.7; 3.1)
Fall (Sept.-Nov.)	0.8 (0.4; 1.6)	1.2 (0.6; 2.6)
Winter (Dec.-Feb.)	0.9 (0.5; 1.9)	0.8 (0.4; 1.7)
Place of birth (East vs. West Germany)	1.5 (0.9; 2.6)	0.9 (0.5; 1.5)
Sex (female vs. male)	0.2 (0.1; 0.4)	0.3 (0.2; 0.5)
Maternal asthma	2.6 (1.1; 6.4)	1.3 (0.5; 3.6)
Maternal atopic dermatitis	1.7 (0.9; 3.3)	0.7 (0.3; 1.4)
Maternal allergic rhinitis	2.2 (1.3; 3.9)	2.7 (1.4; 5.1)
Maternal smoking during pregnancy	1.2 (0.4; 3.5)	0.8 (0.2; 2.9)
Parental SES (low vs. high)**	1.2 (0.7; 2.0)	1.1 (0.7; 1.9)

- 41 CI, confidence interval; ISAAC, International Study of Asthma and Allergies in Childhood; OR, odds ratio;
42 SES, socioeconomic status; SOLAR, Study on Occupational Allergy Risks.
43 * labor induction, precipitate delivery, manual expression, application of speculum, forceps or vacuum extractor
44 ** high: at least one parent qualified for university entrance or university diploma (≥ 12 years of schooling)

B. Replacement of birth length and birth weight by ponderal index

Table E 5– Multiple logistic regression models for wheezing/asthma medication and bronchial hyperreactivity at ISAAC Phase II and SOLAR II

	Wheezing or asthma medication		Bronchial Hyperreactivity	
	ISAAC Phase II OR (95% CI) N=498	SOLAR II OR (95% CI) N=500	ISAAC Phase II OR (95% CI) N=217	SOLAR II OR (95% CI) N=135
Intercept	0.1 (0.0; 0.4)	0.4 (0.1; 1.3)	0.8 (0.1; 4.7)	0.0 (0.0; 0.3)
Maternal age at delivery (>35 vs. ≤ 35 years)	1.2 (0.4; 3.4)	0.6 (0.2; 1.6)	0.4 (0.1; 2.0)	1.2 (0.1; 13.3)
Mode of delivery				
Spontaneous birth	1	1	1	1
Cesarean section	1.9 (0.8; 4.3)	0.9 (0.4; 2.0)	1.7 (0.6; 4.7)	6.0 (1.4; 25.2)
Assisted birth*	1.9 (0.7; 5.2)	1.8 (0.8; 4.0)	1.2 (0.4; 3.9)	1.0 (0.1; 10.4)
Ponderal index				
Lower tertile	1.2 (0.6; 2.5)	1.1 (0.6; 1.8)	0.6 (0.3; 1.5)	0.5 (0.1; 2.2)
Middle tertile	1	1	1	1
Upper tertile	1.5 (0.7; 3.2)	0.7 (0.4; 1.3)	0.8 (0.3; 1.8)	1.0 (0.2; 3.8)
O ₂ supplementation after birth	2.7 (0.9; 8.1)	0.9 (0.3; 3.1)	0.7 (0.1; 4.0)	–
Head circumference				
Lower tertile	1.9 (0.8; 4.1)	0.8 (0.4; 1.4)	1.6 (0.6; 3.9)	3.3 (0.7; 15.0)
Middle tertile	1	1	1	1
Upper tertile	1.7 (0.8; 3.7)	0.7 (0.4; 1.2)	1.6 (0.7; 3.8)	2.0 (0.4; 9.4)
Firstborn	0.8 (0.4; 1.5)	0.7 (0.4; 1.1)	1.2 (0.6; 2.5)	0.3 (0.1; 1.2)
Season of birth				
Spring (Mar.-May)	1	1	1	1
Summer (June-Aug.)	0.8 (0.3; 1.8)	1.4 (0.7; 2.8)	1.1 (0.4; 2.9)	1.9 (0.2; 16.3)
Fall (Sept.-Nov.)	0.8 (0.3; 1.9)	1.4 (0.7; 2.8)	0.5 (0.2; 1.5)	4.9 (0.6; 41.6)
Winter (Dec.-Feb.)	0.9 (0.4; 2.0)	1.3 (0.7; 2.6)	0.8 (0.3; 2.0)	1.7 (0.2; 14.5)
Place of birth (East vs. West Germany)	0.6 (0.3; 1.1)	0.5 (0.3; 0.9)	0.7 (0.3; 1.6)	1.1 (0.3; 3.6)
Sex (female vs. male)	0.4 (0.2; 0.7)	0.9 (0.5; 1.4)	0.3 (0.2; 0.7)	0.7 (0.2; 2.7)
Maternal asthma	1.9 (0.7; 5.3)	1.9 (0.8; 4.4)	0.2 (0.0; 1.8)	4.2 (0.5; 39.4)
Maternal atopic dermatitis	2.5 (1.2; 5.2)	1.0 (0.5; 2.0)	0.4 (0.1; 1.7)	0.7 (0.1; 7.8)
Maternal allergic rhinitis	1.3 (0.6; 2.6)	1.6 (0.9; 2.8)	1.5 (0.6; 3.5)	1.8 (0.5; 6.8)
Maternal smoking during pregnancy	1.0 (0.3; 3.3)	1.2 (0.5; 3.1)	0.7 (0.2; 3.2)	–

Parental SES (low vs. high)**	1.6 (0.9; 2.9)	1.4 (0.9; 2.2)	1.1 (0.5; 2.3)	2.6 (0.8; 8.8)
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48 CI, confidence interval; ISAAC, International Study of Asthma and Allergies in Childhood; OR, odds ratio;
49 SES, socioeconomic status; SOLAR, Study on Occupational Allergy Risks.
50 * labor induction, precipitate delivery, manual expression, application of speculum, forceps or vacuum extractor
51 ** high: at least one parent qualified for university entrance or university diploma (≥ 12 years of schooling)

Table E 6 – Multiple logistic regression models for symptoms and doctors' diagnosis of allergic rhinitis at ISAAC Phase II and SOLAR II

	Rhinoconjunctivitis symptoms		Doctor's diagnosis of allergic rhinitis	
	ISAAC Phase II OR (95% CI) N=495	SOLAR II OR (95% CI) N=494	ISAAC Phase II OR (95% CI) N=489	SOLAR II OR (95% CI) N=493
Intercept	0.3 (0.1; 1.0)	0.6 (0.2; 1.8)	0.1 (0.0; 0.4)	0.5 (0.2; 1.4)
Maternal age at delivery (>35 vs. ≤ 35 years)	1.0 (0.4; 2.5)	1.2 (0.6; 2.7)	1.2 (0.4; 4.0)	1.1 (0.5; 2.6)
Mode of delivery				
Spontaneous birth	1	1	1	1
Cesarean section	2.2 (1.0; 4.8)	0.8 (0.4; 1.6)	2.0 (0.7; 5.4)	1.2 (0.6; 2.4)
Assisted birth*	1.2 (0.5; 3.2)	1.0 (0.5; 2.2)	1.0 (0.2; 3.6)	1.5 (0.7; 3.1)
Ponderal index				
Lower tertile	1.1 (0.6; 2.0)	0.9 (0.5; 1.5)	1.2 (0.5; 2.7)	0.9 (0.6; 1.5)
Middle tertile	1	1	1	1
Upper tertile	0.9 (0.5; 1.8)	0.8 (0.5; 1.4)	1.6 (0.7; 3.8)	0.8 (0.5; 1.4)
O ₂ supplementation after birth	0.6 (0.1; 2.2)	0.6 (0.2; 1.8)	1.5 (0.4; 6.2)	0.4 (0.1; 1.4)
Head circumference				
Lower tertile	1.1 (0.6; 2.0)	0.9 (0.6; 1.5)	0.7 (0.3; 1.6)	0.8 (0.5; 1.4)
Middle tertile	1	1	1	1
Upper tertile	0.6 (0.3; 1.2)	0.7 (0.4; 1.2)	0.9 (0.4; 1.9)	0.6 (0.4; 1.0)
Firstborn	0.7 (0.4; 1.1)	0.9 (0.6; 1.3)	0.9 (0.4; 1.7)	0.9 (0.6; 1.5)
Season of birth				
Spring (Mar.-May)	1	1	1	1
Summer (June-Aug.)	1.1 (0.5; 2.1)	1.0 (0.5; 1.7)	0.5 (0.2; 1.1)	1.2 (0.7; 2.1)
Fall (Sept.-Nov.)	0.4 (0.2; 1.0)	0.6 (0.3; 1.1)	0.3 (0.1; 0.8)	0.6 (0.3; 1.2)
Winter (Dec.-Feb.)	0.7 (0.4; 1.5)	0.6 (0.3; 1.0)	0.4 (0.1; 1.0)	0.8 (0.5; 1.5)
Place of birth (East vs. West Germany)	0.9 (0.5; 1.6)	1.2 (0.8; 1.8)	1.3 (0.6; 2.7)	1.1 (0.7; 1.8)
Sex (female vs. male)	0.7 (0.4; 1.2)	0.7 (0.4; 1.0)	0.6 (0.3; 1.2)	0.5 (0.3; 0.8)
Maternal asthma	2.0 (0.9; 4.8)	1.0 (0.5; 2.3)	2.4 (0.9; 6.3)	1.5 (0.7; 3.4)
Maternal atopic dermatitis	1.8 (0.9; 3.4)	1.5 (0.9; 2.7)	2.8 (1.2; 6.2)	1.4 (0.8; 2.6)
Maternal allergic rhinitis	2.5 (1.4; 4.5)	1.5 (0.9; 2.5)	4.0 (2.0; 8.2)	2.5 (1.5; 4.0)
Maternal smoking during pregnancy	0.4 (0.1; 1.7)	0.7 (0.2; 1.9)	0.8 (0.2; 4.4)	0.8 (0.3; 2.2)
Parental SES (low vs. high)**	1.1 (0.6; 1.9)	0.9 (0.6; 1.4)	1.1 (0.5; 2.2)	1.0 (0.6; 1.5)

CI, confidence interval; ISAAC, International Study of Asthma and Allergies in Childhood; OR, odds ratio; SES, socioeconomic status; SOLAR, Study on Occupational Allergy Risks.

- 56 * labor induction, precipitate delivery, manual expression, application of speculum, forceps or vacuum extractor
57 ** high: at least one parent qualified for university entrance or university diploma (≥ 12 years of schooling)

Table E 7 – Multiple logistic regression models for flexural eczema and doctors' diagnosis of atopic dermatitis at ISAAC Phase II and SOLAR II

	Flexural eczema		Doctor's diagnosis of atopic dermatitis	
	ISAAC Phase II OR (95% CI) N=496	SOLAR II OR (95% CI) N=498	ISAAC Phase II OR (95% CI) N=493	SOLAR II OR (95% CI) N=498
Intercept	0.1 (0.0; 0.5)	0.1 (0.0; 0.3)	0.6 (0.2; 2.2)	0.2 (0.1; 0.6)
Maternal age at delivery (>35 vs. ≤ 35 years)	0.6 (0.2; 2.2)	2.2 (0.8; 6.1)	1.6 (0.7; 4.0)	0.8 (0.3; 2.2)
Mode of delivery				
Spontaneous birth	1	1	1	1
Cesarean section	1.3 (0.6; 3.2)	0.9 (0.3; 2.4)	0.7 (0.3; 1.6)	1.2 (0.6; 2.6)
Assisted birth*	2.4 (1.0; 5.8)	1.6 (0.6; 4.1)	1.9 (0.8; 4.5)	1.2 (0.5; 2.8)
Ponderal index				
Lower tertile	0.9 (0.5; 1.8)	0.7 (0.3; 1.4)	0.8 (0.4; 1.5)	0.9 (0.5; 1.5)
Middle tertile	1	1	1	1
Upper tertile	1.0 (0.5; 2.0)	0.9 (0.4; 1.8)	0.9 (0.5; 1.6)	0.9 (0.5; 1.6)
O ₂ supplementation after birth	0.9 (0.2; 3.3)	1.1 (0.3; 4.2)	0.3 (0.1; 1.6)	0.8 (0.2; 2.4)
Head circumference				
Lower tertile	0.5 (0.3; 0.9)	0.8 (0.4; 1.7)	0.5 (0.3; 1.0)	0.7 (0.4; 1.3)
Middle tertile	1	1	1	1
Upper tertile	0.4 (0.2; 0.8)	1.0 (0.5; 2.0)	0.7 (0.4; 1.2)	0.8 (0.5; 1.4)
Firstborn	0.8 (0.5; 1.4)	0.9 (0.5; 1.7)	0.8 (0.5; 1.3)	0.7 (0.4; 1.1)
Season of birth				
Spring (Mar.-May)	1	1	1	1
Summer (June-Aug.)	0.6 (0.3; 1.5)	0.7 (0.3; 1.6)	1.3 (0.7; 2.5)	0.7 (0.4; 1.4)
Fall (Sept.-Nov.)	1.3 (0.6; 2.7)	1.0 (0.5; 2.1)	1.1 (0.5; 2.1)	0.9 (0.5; 1.6)
Winter (Dec.-Feb.)	1.0 (0.5; 2.2)	0.5 (0.2; 1.3)	0.7 (0.3; 1.5)	0.8 (0.4; 1.5)
Place of birth (East vs. West Germany)	1.5 (0.9; 2.7)	1.5 (0.8; 2.8)	0.9 (0.5; 1.5)	1.6 (1.0; 2.5)
Sex (female vs. male)	1.5 (0.8; 2.6)	1.3 (0.7; 2.3)	1.2 (0.7; 1.9)	1.5 (0.9; 2.4)
Maternal asthma	1.5 (0.6; 4.0)	0.7 (0.2; 2.6)	1.3 (0.5; 3.3)	1.1 (0.5; 2.7)
Maternal atopic dermatitis	3.9 (2.1; 7.6)	1.3 (0.6; 3.0)	5.6 (3.1; 10.4)	2.0 (1.1; 3.7)
Maternal allergic rhinitis	1.5 (0.8; 2.8)	1.2 (0.6; 2.3)	1.5 (0.8; 2.6)	1.6 (0.9; 2.6)
Maternal smoking during pregnancy	2.2 (0.7; 6.8)	1.6 (0.5; 5.3)	2.9 (1.1; 7.6)	1.9 (0.7; 4.8)
Parental SES (low vs. high)**	0.7 (0.4; 1.3)	1.1 (0.6; 2.1)	0.5 (0.3; 0.9)	0.8 (0.5; 1.4)

CI, confidence interval; ISAAC, International Study of Asthma and Allergies in Childhood; OR, odds ratio; SES, socioeconomic status; SOLAR, Study on Occupational Allergy Risks.

- 62 * labor induction, precipitate delivery, manual expression, application of speculum, forceps or vacuum extractor
63 ** high: at least one parent qualified for university entrance or university diploma (≥ 12 years of schooling)

64 **Table E 8 – Multiple logistic regression models for sensitization as assessed by Skin Prick Test reactivity at ISAAC**
 65 **Phase II and SOLAR II**

	Sensitization	
	ISAAC Phase II OR (95% CI) N=434	SOLAR II OR (95% CI) N=316
Intercept	0.2 (0.0; 0.6)	1.1 (0.3; 4.1)
Maternal age at delivery (>35 vs. ≤ 35 years)	1.1 (0.4; 3.0)	2.3 (0.8; 6.5)
Mode of delivery		
Spontaneous birth	1	1
Cesarean section	1.8 (0.9; 3.7)	1.4 (0.6; 3.2)
Assisted birth*	0.9 (0.4; 2.3)	2.1 (0.8; 5.4)
Ponderal index		
Lower tertile	0.7 (0.4; 1.3)	0.6 (0.3; 1.0)
Middle tertile	1	1
Upper tertile	1.2 (0.7; 2.2)	1.3 (0.7; 2.3)
O ₂ supplementation after birth	0.9 (0.3; 2.8)	0.6 (0.1; 2.5)
Head circumference		
Lower tertile	2.1 (1.1; 3.8)	2.1 (1.1; 3.8)
Middle tertile	1	1
Upper tertile	0.9 (0.5; 1.7)	0.7 (0.4; 1.3)
Firstborn	1.0 (0.6; 1.6)	1.0 (0.6; 1.7)
Season of birth		
Spring (Mar.-May)	1	1
Summer (June-Aug.)	1.4 (0.7; 2.7)	1.7 (0.8; 3.5)
Fall (Sept.-Nov.)	0.8 (0.4; 1.7)	1.2 (0.6; 2.5)
Winter (Dec.-Feb.)	1.0 (0.5; 2.0)	0.9 (0.4; 1.8)
Place of birth (East vs. West Germany)	1.5 (0.9; 2.6)	0.9 (0.5; 1.5)
Sex (female vs. male)	0.2 (0.1; 0.4)	0.3 (0.2; 0.5)
Maternal asthma	2.6 (1.1; 6.4)	1.3 (0.5; 3.7)
Maternal atopic dermatitis	1.7 (0.9; 3.2)	0.7 (0.4; 1.4)
Maternal allergic rhinitis	2.1 (1.2; 3.7)	2.9 (1.5; 5.3)
Maternal smoking during pregnancy	1.3 (0.4; 3.8)	0.8 (0.2; 2.7)
Parental SES (low vs. high)**	1.1 (0.7; 1.8)	1.2 (0.7; 2.0)

66 CI, confidence interval; ISAAC, International Study of Asthma and Allergies in Childhood; OR, odds ratio;
 67 SES, socioeconomic status; SOLAR, Study on Occupational Allergy Risks.

68 * labor induction, precipitate delivery, manual expression, application of speculum, forceps or vacuum extractor

69 ** high: at least one parent qualified for university entrance or university diploma (≥ 12 years of schooling)

C. Replacement of birth weight, birth length and O₂ supplementation by prematurity

Table E 9 – Multiple logistic regression models for wheezing/asthma medication and bronchial hyperreactivity at ISAAC Phase II and SOLAR II

	Wheezing or asthma medication		Bronchial hyperreactivity	
	ISAAC Phase II OR (95% CI) N=623	SOLAR II OR (95% CI) N=626	ISAAC Phase II OR (95% CI) N=264	SOLAR II OR (95% CI) N=151
Intercept	0.2 (0.1; 0.8)	0.4 (0.1; 1.1)	1.6 (0.3; 7.9)	0.1 (0.0; 1.1)
Maternal age at delivery (>35 vs. ≤ 35 years)	1.1 (0.4; 2.6)	0.9 (0.4; 1.8)	0.2 (0.1; 1.1)	0.8 (0.1; 4.4)
Mode of delivery				
Spontaneous birth	1	1	1	1
Cesarean section	1.7 (0.8; 3.6)	0.8 (0.4; 1.7)	1.4 (0.5; 3.7)	4.0 (1.0; 15.3)
Assisted birth*	1.9 (0.8; 4.2)	2.3 (1.2; 4.4)	1.9 (0.7; 5.2)	1.6 (0.3; 9.3)
Prematurity	3.4 (1.4; 8.3)	1.5 (0.7; 3.4)	0.8 (0.2; 4.2)	0.5 (0.1; 5.2)
Firstborn	0.9 (0.5; 1.6)	0.7 (0.4; 1.0)	1.1 (0.6; 2.3)	0.6 (0.2; 2.0)
Season of birth				
Spring (Mar.-May)	1	1	1	1
Summer (June-Aug.)	0.7 (0.3; 1.6)	1.3 (0.7; 2.4)	0.8 (0.3; 2.1)	0.8 (0.2; 3.4)
Fall (Sept.-Nov.)	1.0 (0.5; 2.2)	1.6 (0.9; 2.9)	0.9 (0.3; 2.5)	1.1 (0.3; 4.9)
Winter (Dec.-Feb.)	1.2 (0.6; 2.4)	1.3 (0.7; 2.5)	1.2 (0.5; 3.0)	0.4 (0.1; 2.3)
Place of birth (East vs. West Germany)	0.5 (0.3; 1.0)	0.5 (0.3; 0.9)	0.5 (0.2; 1.0)	1.2 (0.4; 3.6)
Sex (female vs. male)	0.3 (0.2; 0.5)	0.7 (0.5; 1.1)	0.3 (0.; 0.6)	0.6 (0.2; 1.6)
Maternal asthma	2.3 (0.9; 5.7)	3.1 (1.5; 6.6)	0.8 (0.2; 3.4)	2.0 (0.3; 13.5)
Maternal atopic dermatitis	2.4 (1.2; 4.8)	1.3 (0.7; 2.3)	0.8 (0.2; 2.9)	0.9 (0.1; 8.8)
Maternal allergic rhinitis	1.2 (0.6; 2.2)	1.3 (0.8; 2.2)	0.8 (0.3; 1.8)	1.5 (0.4; 5.1)
Maternal smoking during pregnancy	1.0 (0.4; 3.0)	1.5 (0.7; 3.4)	1.0 (0.3; 4.0)	–
Parental SES (low vs. high)**	1.4 (0.8; 2.4)	1.1 (0.7; 1.7)	0.8 (0.4; 1.6)	1.5 (0.5; 4.4)

CI, confidence interval; ISAAC, International Study of Asthma and Allergies in Childhood; OR, odds ratio; SES, socioeconomic status; SOLAR, Study on Occupational Allergy Risks.

* labor induction, precipitate delivery, manual expression, application of speculum, forceps or vacuum extractor

** high: at least one parent qualified for university entrance or university diploma (≥ 12 years of schooling)

Table E 10 – Multiple logistic regression models for symptoms and doctors' diagnosis of allergic rhinitis at ISAAC Phase II and SOLAR II

	Rhinoconjunctivitis symptoms		Doctor's diagnosis of allergic rhinitis	
	ISAAC Phase II	SOLAR II	ISAAC Phase II	SOLAR II
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
	N=620	N=618	N=616	N=616
Intercept	0.3 (0.1; 0.8)	0.6 (0.2; 1.5)	0.1 (0.0; 0.3)	0.4 (0.2; 1.1)
Maternal age at delivery (>35 vs. ≤ 35 years)	0.9 (0.4; 2.1)	1.1 (0.5; 2.2)	0.8 (0.3; 2.5)	1.0 (0.5; 2.0)
Mode of delivery				
Spontaneous birth	1	1	1	1
Cesarean section	1.6 (0.8; 3.3)	0.7 (0.3; 1.4)	1.9 (0.8; 4.6)	0.9 (0.5; 1.8)
Assisted birth*	1.1 (0.5; 2.3)	1.2 (0.6; 2.2)	0.8 (0.3; 2.3)	1.9 (1.0; 3.4)
Prematurity	1.6 (0.6; 3.8)	1.0 (0.5; 2.2)	3.0 (1.2; 7.8)	0.8 (0.4; 1.8)
Firstborn	0.8 (0.5; 1.4)	0.8 (0.6; 1.2)	1.2 (0.6; 2.1)	0.9 (0.6; 1.4)
Season of birth				
Spring (Mar.-May)	1	1	1	1
Summer (June-Aug.)	1.2 (0.6; 2.1)	0.8 (0.5; 1.4)	0.8 (0.4; 1.7)	1.2 (0.7; 2.0)
Fall (Sept.-Nov.)	0.5 (0.2; 1.0)	0.7 (0.4; 1.2)	0.5 (0.2; 1.2)	0.9 (0.5; 1.6)
Winter (Dec.-Feb.)	0.7 (0.4; 1.3)	0.7 (0.4; 1.2)	0.4 (0.2; 1.0)	1.1 (0.7; 1.9)
Place of birth (East vs. West Germany)	0.8 (0.5; 1.2)	0.9 (0.6; 1.4)	1.2 (0.6; 2.2)	0.9 (0.6; 1.4)
Sex (female vs. male)	0.7 (0.4; 1.1)	0.8 (0.5; 1.2)	0.5 (0.3; 0.9)	0.6 (0.4; 0.9)
Maternal asthma	2.3 (1.1; 5.0)	1.6 (0.8; 3.3)	2.5 (1.0; 5.8)	1.4 (0.7; 2.9)
Maternal atopic dermatitis	1.6 (0.8; 3.1)	1.5 (0.8; 2.5)	1.8 (0.8; 3.8)	1.6 (0.9; 2.7)
Maternal allergic rhinitis	2.6 (1.6; 4.4)	1.5 (0.9; 2.3)	3.9 (2.1; 7.3)	2.2 (1.4; 3.4)
Maternal smoking during pregnancy	0.3 (0.1; 1.2)	0.6 (0.3; 1.6)	1.0 (0.3; 3.6)	0.8 (0.3; 1.9)
Parental SES (low vs. high)**	1.1 (0.7; 1.8)	0.9 (0.6; 1.3)	1.1 (0.6; 2.1)	0.9 (0.6; 1.4)

CI, confidence interval; ISAAC, International Study of Asthma and Allergies in Childhood; OR, odds ratio; SES, socioeconomic status; SOLAR, Study on Occupational Allergy Risks.

* labor induction, precipitate delivery, manual expression, application of speculum, forceps or vacuum extractor

** high: at least one parent qualified for university entrance or university diploma (≥ 12 years of schooling)

Table E 11 – Multiple logistic regression models for flexural eczema and doctors' diagnosis of atopic dermatitis at ISAAC Phase II and SOLAR II

	Flexural eczema		Doctor's diagnosis of atopic dermatitis	
	ISAAC Phase II	SOLAR II	ISAAC Phase II	SOLAR II
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
	N=622	N=625	N=616	N=622
Intercept	0.1 (0.0; 0.3)	0.0 (0.0; 0.2)	0.4 (0.1; 1.2)	0.2 (0.1; 0.5)
Maternal age at delivery (>35 vs. ≤ 35 years)	0.7 (0.2; 1.9)	1.9 (0.8; 4.9)	1.4 (0.6; 3.0)	1.0 (0.5; 2.3)
Mode of delivery				
Spontaneous birth	1	1	1	1
Cesarean section	1.3 (0.5; 3.1)	1.5 (0.6; 3.6)	0.6 (0.3; 1.5)	1.0 (0.5; 2.2)
Assisted birth*	3.1 (1.5; 6.4)	1.4 (0.6; 3.3)	2.6 (1.3; 5.0)	1.4 (0.7; 2.9)
Prematurity	0.8 (0.3; 2.5)	0.2 (0.0; 1.3)	0.9 (0.3; 2.2)	0.6 (0.2; 1.6)
Firstborn	0.8 (0.5; 1.4)	1.1 (0.6; 2.0)	0.9 (0.6; 1.4)	0.7 (0.5; 1.2)
Season of birth				
Spring (Mar.-May)	1	1	1	1
Summer (June-Aug.)	0.5 (0.2; 1.2)	0.4 (0.2; 1.0)	0.9 (0.5; 1.8)	0.7 (0.4; 1.3)
Fall (Sept.-Nov.)	1.1 (0.5; 2.1)	0.7 (0.3; 1.5)	1.2 (0.7; 2.2)	0.9 (0.5; 1.6)
Winter (Dec.-Feb.)	0.8 (0.4; 1.6)	0.5 (0.3; 1.1)	0.7 (0.4; 1.4)	0.6 (0.3; 1.1)
Place of birth (East vs. West Germany)	0.9 (0.5; 1.5)	1.4 (0.8; 2.6)	0.8 (0.5; 1.2)	1.1 (0.7; 1.8)
Sex (female vs. male)	1.8 (1.1; 3.1)	1.3 (0.8; 2.3)	1.0 (0.7; 1.6)	1.5 (0.9; 2.3)
Maternal asthma	1.4 (0.6; 3.5)	0.8 (0.3; 2.5)	1.2 (0.5; 2.9)	1.3 (0.6; 3.0)
Maternal atopic dermatitis	3.4 (1.8; 6.3)	1.8 (0.9; 3.8)	7.0 (4.0; 12.2)	2.6 (1.5; 4.7)
Maternal allergic rhinitis	1.5 (0.8; 2.7)	1.3 (0.7; 2.6)	1.4 (0.8; 2.4)	1.2 (0.7; 2.1)
Maternal smoking during pregnancy	1.7 (0.6; 4.5)	2.1 (0.8; 5.4)	2.6 (1.1; 6.1)	2.4 (1.1; 5.3)
Parental SES (low vs. high)**	1.0 (0.6; 1.7)	1.2 (0.7; 2.1)	0.6 (0.4; 1.0)	0.9 (0.5; 1.4)

CI, confidence interval; ISAAC, International Study of Asthma and Allergies in Childhood; OR, odds ratio;

SES, socioeconomic status; SOLAR, Study on Occupational Allergy Risks.

* labor induction, precipitate delivery, manual expression, application of speculum, forceps or vacuum extractor

** high: at least one parent qualified for university entrance or university diploma (≥ 12 years of schooling)

Table E 12 – Multiple logistic regression models for sensitization as assessed by Skin Prick Test reactivity at ISAAC Phase II and SOLAR II

	Sensitization	
	ISAAC Phase II OR (95% CI) N=535	SOLAR II OR (95% CI) N=360
Intercept	0.2 (0.1; 0.5)	1.3 (0.5; 3.8)
Maternal age at delivery (>35 vs. ≤ 35 years)	1.4 (0.6; 3.1)	2.8 (1.1; 6.8)
Mode of delivery		
Spontaneous birth	1	1
Cesarean section	1.2 (0.6; 2.4)	1.3 (0.6; 2.8)
Assisted birth*	1.1 (0.5; 2.1)	2.0 (0.9; 4.3)
Prematurity	1.1 (0.5; 2.6)	0.7 (0.3; 1.9)
Firstborn	1.1 (0.7; 1.7)	0.8 (0.5; 1.3)
Season of birth		
Spring (Mar.-May)	1	1
Summer (June-Aug.)	1.1 (0.6; 2.0)	0.9 (0.5; 1.7)
Fall (Sept.-Nov.)	1.0 (0.5; 1.8)	1.4 (0.8; 2.7)
Winter (Dec.-Feb.)	1.0 (0.6; 1.8)	1.1 (0.6; 2.0)
Place of birth (East vs. West Germany)	1.6 (1.0; 2.5)	1.0 (0.6; 1.6)
Sex (female vs. male)	0.3 (0.2; 0.5)	0.4 (0.3; 0.7)
Maternal asthma	2.1 (1.0; 4.5)	1.7 (0.6; 4.5)
Maternal atopic dermatitis	1.7 (0.9; 3.1)	0.9 (0.5; 1.8)
Maternal allergic rhinitis	1.5 (0.9; 2.5)	2.2 (1.2; 3.9)
Maternal smoking during pregnancy	1.4 (0.6; 3.3)	0.6 (0.2; 1.8)
Parental SES (low vs. high)**	0.9 (0.7; 1.6)	1.0 (0.6; 1.6)

CI, confidence interval; ISAAC, International Study of Asthma and Allergies in Childhood; OR, odds ratio; SES, socioeconomic status; SOLAR, Study on Occupational Allergy Risks.

* labor induction, precipitate delivery, manual expression, application of speculum, forceps or vacuum extractor

** high: at least one parent qualified for university entrance or university diploma (≥ 12 years of schooling)