Early-life determinants of asthma from birth to age 20 years: A German birth cohort study

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Background: The lack of longitudinal data analyses from birth to adulthood is hampering long-term asthma prevention strategies.
Objective: We aimed to determine early-life predictors of asthma incidence up to age 20 years in a birth cohort study by applying time-to-event analysis.
Methods: In 1990, the Multicenter Allergy Study included 1314 newborns in 5 German cities. Children were evaluated from birth to age 20 years at 19 time points. Using a Cox regression model, we examined the associations between 36 early-life factors and onset of asthma based on a doctor's diagnosis or asthma medication (primary outcome), typical asthma symptoms, or allergic asthma (including positive IgE measurements).
Results: Response at 20 years was 71.6%. Two hundred eighteen subjects met the primary outcome criteria within 16,257 person years observed. Asthma incidence was lower in participants who were vaccinated (measles, mumps, and rubella vaccine/tick-borne encephalitis vaccine/BCG vaccine: adjusted hazard ratio [HR], 0.66 [95% CI, 0.47-0.93]). Up to age 20 years, asthma incidence was higher in subjects who had parents with allergic rhinitis (adjusted HR, 2.24 [95% CI, 1.67-3.02]), started day care early or late (before 18 months: adjusted HR, 1.79 [95% CI, 1.03-3.10]; after 3 years: adjusted HR, 1.64 [95% CI, 0.96-2.79]), had mothers who smoked during pregnancy (adjusted HR, 1.79 [95% CI, 1.20-2.67]), had poor parents (adjusted HR, 1.55 [95% CI, 1.09-2.22]), and had parents with asthma (adjusted HR, 1.65 [95% CI, 1.17-2.31]). Not associated with asthma were aspects of diet and breast-feeding, pet ownership, presence of older siblings, and passive smoking.
Conclusion: Parental asthma and nasal allergy increase asthma incidence in offspring up to adulthood. Avoiding tobacco smoke exposure during pregnancy, receiving vaccinations in early childhood, and starting day care between 1.5 and 3 years of age might prevent or delay the development of asthma. (J Allergy Clin Immunol 2014;■■■:■■■-■■■.)

Key words: *Infant, child, preschool, adolescent, heredity, risk factors, epidemiologic factors, survival analysis, hypersensitivity, immunization*

A vast number of potentially modifiable exposures and behavioral patterns during prenatal, perinatal, and postnatal periods have been suggested to either prevent or boost asthma development.[1-3] A family history of allergic disease as a surrogate for genetic predisposition,[4] indicative early symptoms, and sensitization patterns seem to be strong predictors of asthma in

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Abbreviations used
HR: Hazard ratio
ISAAC: International Study of Asthma and Allergies in Childhood
MAS-90: Multicenter Allergy Study

childhood and early school age.[5-10] Both their long-term effects and the role of the social family background on asthma in adolescence and early adulthood have rarely been examined in prospective studies.[11,12] Pregnancy and postnatal tobacco smoke exposure have been shown to trigger asthma-like symptom patterns (eg, wheezy bronchitis[13]), but its harmful influence on asthma development and aeroallergen sensitization remains equivocal.[14-16] Allergen exposure (eg, mites and pets) has a clear link to sensitization against specific allergens, although its causal role for asthma is not well established.[17,18] The hygiene hypothesis initiated exploration of immune maturation pathways as part of asthma pathogenesis, linking viral infections, day care attendance, and farming environment to disease progression.[19-21] Vaccinations have been examined as having an influence on asthma development.[22] Breast-feeding, which was initially thought to be protective, seems to have no or only limited effect,[23,24] and many other unmeasured factors associated with the socioeconomic background have been discussed to influence childhood asthma.[25]

In many cases results from observational and interventional studies did not confirm the proposed association with asthma or recommendations for primary prevention.[26-28] Differences in study design, setting, sampling schemes, and case definitions of asthma hamper comparability between projects, as well as clear conclusions. Additionally, most analyses focus on 1 exposure or a confined thematic setting of exposures and restrict their outcome to 1 or a few time points, not allowing for the best possible adjustment and robust estimation. The wealth of information collected in prospective birth cohorts over the years has been rarely analyzed and presented en bloc.

Some of these flaws can be targeted by using analytic techniques that are more appropriate for longitudinal studies. On the basis of the first German birth cohort focusing on asthma and allergies, the Multicenter Allergy Study (MAS-90), which has a follow-up of 20 years, we aimed to identify early-life determinants of asthma incidence by applying time-to-event analysis, including all 19 assessments and accounting for a wide array of exposures and indicators of heredity.

METHODS

Study design, sampling, and follow-up

The German MAS-90 set out to trace the development and risk factors of allergic diseases prospectively from birth. Of 7609 children born between January and December 1990 in 6 obstetrics departments across Germany, a risk-enriched population-based sample was recruited (n = 1314) and followed up for 20 years: 38% with 2 or more first-degree allergic family members or increased cord blood IgE levels (≥0.9 kU/L) were considered at increased risk for allergies, whereas 62% were at low risk for allergies (Fig 1).[29] A description of the study design and sampling details has been published earlier.[30]

During the 20-year follow-up period, participants' exposure to environmental and behavioral factors was assessed at 19 time points by using face-to-face, paper, telephone, and online questionnaires (at age 1, 3, 6, 12, and 18 months; from age 2-13 years every year; and at age 15 and 20 years). The national database for change of address orders, local residents' registration offices, delivery room documentation, and social media platforms were used to maximize long-term response at the age of 20 years.

The MAS-90 birth cohort study was approved by local institutional review boards. All parents and, at later stages, all adult participants provided written informed consent for data collection and analysis.

Definition of the primary outcome

Asthma was defined as satisfying 2 of the following 3 criteria: physician's diagnosis of asthma ever, asthma medication in the last 12 months, and any indicative symptom in the last 12 months (wheezing, shortness of breath, and dry cough at night). This definition is based on recommendations from consortia of the largest European birth cohorts on asthma and allergies and on validated standardized questionnaire items from the International Study of Asthma and Allergies in Childhood (ISAAC) project.[15,31-34] Items on asthma and indicative symptoms were considered too unspecific as outcomes before the age of 3 years.

Definition of secondary outcomes

Asthma symptoms were defined as at least 2 of 3 indicative symptoms in the last 12 months: wheezing, shortness of breath, and dry cough at night. *Allergic asthma* was defined as the primary outcome of asthma plus a positive serum specific IgE level of 0.35 kU/L or greater to any aeroallergen assessed (dust mite, dog, cat, birch, and timothy grass) determined at 9 time points (ImmunoCAP; Phadia GmbH, Freiburg, Germany) within the first 20 years.

Definition of exposure variables

Selection of independent variables was restricted to the first 3 years of life to reliably precede disease onset and to consider the presumed prenatal and postnatal critical period. All covariates are treated as time invariant, even those derived from multiple assessments. For categorization of continuous or multilevel variables, the influence of different cutoffs other than conventional and later used boundaries was checked; a sensitivity analysis was performed for all socioeconomic factors, income, mother's age at birth, obesity, parental allergies, cord blood IgE level, smoking during pregnancy, cord blood cotinine level, season of birth, breast-feeding, tobacco smoke exposure, child's overweight status, age starting day care attendance, and vaccinations. Overweight status of children at age 3 years was calculated as a standard deviation score based on age- and sex-specific growth curves.[35] The cord serum cotinine level, a surrogate of fetal tobacco exposure, was determined through gas chromatography and included in the analyses as a binary variable cut at the mean (21.5 ng/mL). Further details on definitions of all exposure variables are listed in Table E1 in this article's Online Repository at www.jacionline.org.

Initial selection of potential confounders was guided by using directed acyclic graphs.[36] A stepwise selection process was applied to exclude covariates not significantly linked to the outcome (entry and exclusion threshold at $P = .05$). All covariates were coded as dichotomous, and missing values were filled by using multiple imputation (5 repetitions) for each model separately, accounting for variability across imputations in estimation of SEs.[37]

Statistical methods

The association between early-life predictors and onset of asthma was evaluated by using time-to-event analysis with a Cox proportional (continuous time) hazards model, with raw and adjusted hazard ratios (HRs) and respective 95% CIs based on Wald tests as the main effect estimator.[38] We manually inspected individual data for participants with suspected asthma to define a comprehensive protocol for estimation of disease onset based on questionnaire items. Time was coded in days. Onset of symptoms, or first physician's diagnosis was assumed between the first point at which case definition criteria were met and the preceding negative assessment. Timing information was imputed by additional information on otherwise weak indicators of asthma

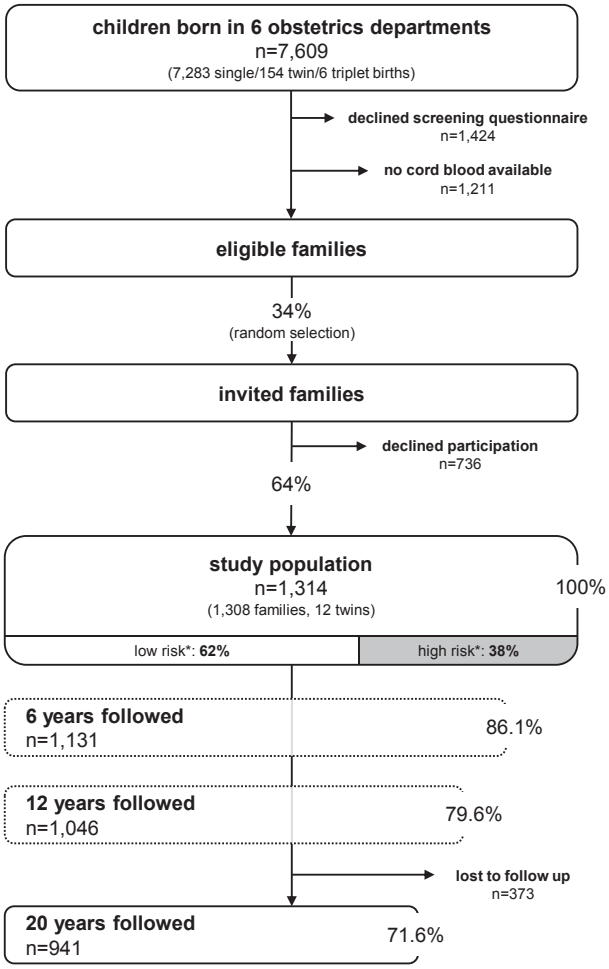

FIG 1. Study population sampling *(upper part)* and follow-up *(lower part)*. *High-risk study population defined through a positive family history, increased cord IgE levels, or both.

(eg, symptoms and self-reported age at onset). We did not account for recurrence of asthma after a disease-free interval and disease duration. Loss to follow-up or reaching the current end of study (20 years) was considered right censoring. Each successive observation period was coded separately (data were recoded into a counting process format) to account for temporary discontinuation of follow-up (interval censoring, which was present in 55.4% of children; see Fig E1 in this article's Online Repository at www.jacionline.org). Model assumption of proportional hazards was assessed through graphic inspection (eg, log-log curves, observed vs expected) and statistical tests (eg, time-dependence and Schoenfeld residuals; see Table E1). Effect estimates for exposure variables not meeting model assumptions were not calculated. Data management, data cleaning, and statistical evaluation were carried out with SAS software (version 9.3; SAS Institute, Cary, NC).

RESULTS

Study population

Of 1314 newborns recruited, 941 (71.6%) were followed up for 20 years. In total, 13.9% were lost during preschool age (until 6 years), and 6.5% were lost between 6 and 12 years of age (Fig 1). Median follow-up was 19.9 years (interquartile range, 15.0-20.2 years), with a total of 16,257 person years available for time-to-event analysis of the primary outcome, accounting for interval censoring.

Families with the lowest educational level were more likely to be lost during follow-up (followed vs lost: 19.4% vs 27.3% at education level 1 and 2 [International Standard Classification of Education]). A similar difference was seen for young mothers (<25 years at birth of participating child: 13.3% vs 20.2%) and smoking habits (eg, during pregnancy: 11.7% vs 20.2%). There was no differential loss to follow-up for overweight parents, parents with allergic disease, or parents who were sensitized to aeroallergens or food allergens and regarding the child's sex. At age 20 years, study centers achieved responses ranging from 64.0% to 95.0% of participants recruited at birth (Table I).

Incidence of outcomes

Up to age 20 years, 218 participants were classified with asthma (primary outcome). Regarding the incidence of the secondary outcomes, 264 subjects had at least 2 of 3 typical asthma symptoms, and 156 were defined as having allergic asthma (Table II). New onset of asthma was relatively constant until puberty, when it flattened out, and in preschool age it is almost always accompanied by specific sensitization (Fig 2).

Primary outcome asthma

HRs were calculated against the intermediate category as the reference group to detect a U-shaped association with higher (or lower) incidences of asthma in the outmost categories of measures of wealth and income. All assessed components characterizing family socioeconomics were linked to asthma, with higher frequencies in families with poor grandparents and families with wealthy grandparents compared with the intermediate category. A similar pattern was detected for the family's net income. Low educational level of one of the parents was associated with a lower incidence of asthma.

Parental asthma, allergic rhinitis, and eczema were strong risk factors for asthma up to age 20 years, whereas parental self-reported food hypersensitivity and urticaria showed no association. Total IgE level in cord blood, but not positive parental IgE level at birth, was an independent predictor of asthma development up to age 20 years (Fig 3).

Scrutinizing heredity's role in disease development, we estimated trajectories for families without parental allergies (asthma, allergic rhinitis, or eczema) compared with 1 or 2 parents with allergies (confidence bands shown in Fig 4). Real data compared with the model contrast an even stronger association in the first years, with a fairly good fit covering both decades (overlaid steps shown in Fig 4).

Proportionality assumptions were violated for early indicators of allergy in children themselves. Wheezing within the first 3 years (as measured at 1 of several time points) was associated with asthma up to 20 years of age. Estimation based on the proportional hazards model diverged from real data (confidence bands vs steps shown in Fig 5). Similar patterns of time-dependent hazards were established for eczema and sensitization against airborne and food allergens alike, both in the first 3 years (data not shown).

Heavy smoking during pregnancy (≥5 cigarettes per day until delivery) was one of the strongest modifiable risk factors of asthma. This was independently true for the cord blood cotinine level, an objective measure of recent tobacco smoke exposure. Other aspects of pregnancy (diet and drugs) and delivery (mode and complications) were not associated with asthma.

TABLE I. Characteristics of participants by follow-up status

	Followed 20 y			Lost to follow-up		
	No.	Percent	95% CI	No.	Percent	95% CI
All	941	100.0	—	373	100.0	—
Highest school education in family						
Low (ISCED 1/2)	173	19.4	16.8-22.1	92	27.3	22.3-31.8
Medium (ISCED 3/4)	374	41.9	39.2-46.0	150	44.5	39.5-50.1
High (ISCED 5/6)	345	38.7	35.7-41.6	95	28.2	23.7-32.9
Age of mother at birth						
<25 y	125	13.3	11.6-15.6	75	20.2	15.9-23.7
25-34 y	683	72.7	69.6-75.4	246	66.3	60.1-70.4
≥35 y	132	14.0	12.1-15.9	50	13.5	10.8-18.1
Overweight (BMI ≥25 kg/m^2)						
Mother	123	18.5	15.7-21.1	34	21.8	15.4-27.6
Father	278	45.3	41.5-48.7	60	42.3	33.1-52.1
Smoking						
At home	391	45.9	42.8-48.9	199	58.9	53.6-64.8
During pregnancy	101	11.7	9.9-14.3	70	20.2	15.9-24.6
Asthma, allergic rhinitis, or eczema						
Not in parents	468	50.8	47.1-54.3	196	54.4	50.0-59.7
Mother or father	352	38.2	34.9-41.7	126	35.0	28.3-39.4
Both parents	101	11.0	9.0-12.4	38	10.6	6.9-13.6
Positive allergy screening test result						
Mother	244	38.1	34.5-41.7	77	35.6	30.1-42.1
Father	144	40.8	36.0-46.2	54	45.0	32.5-55.0
Cord blood IgE ≥0.35 kU/L	331	36.7	33.6-40.4	120	33.4	27.9-39.6
Male sex	494	52.5	49.4-56.2	190	50.9	45.6-56.6
Place of birth (study center)						
Berlin	415	44.1	41.6-48.0	179	48.0	43.2-53.4
Düsseldorf	103	10.9	8.5-12.3	58	15.5	12.1-19.0
Mainz	136	14.5	12.1-16.2	76	20.4	16.1-24.1
Freiburg	155	16.5	14.6-18.8	53	14.2	10.5-17.4
Munich	132	14.0	12.2-15.8	7	1.9	0.8-3.2

Number of families and percentages, including bootstrapped 95% CIs, are shown.
BMI, Body mass index; *ISCED*, International Standard Classification of Education.

TABLE II. Primary and secondary outcomes, single questionnaire items (ISAAC), and aeroallergen sensitization

	Data collected		
	Age range (y)	Time points	Cases until 20 y
Asthma (primary outcome)	—	—	218
Asthma symptoms (secondary outcome)	—	—	264
Allergic asthma (secondary outcome)	—	—	156
Symptoms associated with asthma (current)			
Wheezing	3-20*	13	426
Shortness of breath	8-20	8	294
Dry cough at night	5-20	11	420
Asthma, physician's diagnosis (ever)	3-20*	12	245
Drugs for asthma (current)	8-20	8	220
Aeroallergen sensitization (IgE ≥0.35 kU/L)	1-20	9	531

Current was defined as since the last follow-up/during the last 12 months (for intervals >12 months). Aeroallergens used were mite, dog, cat, birch, and timothy grass.
*Assessments before 3 years were not considered valid.

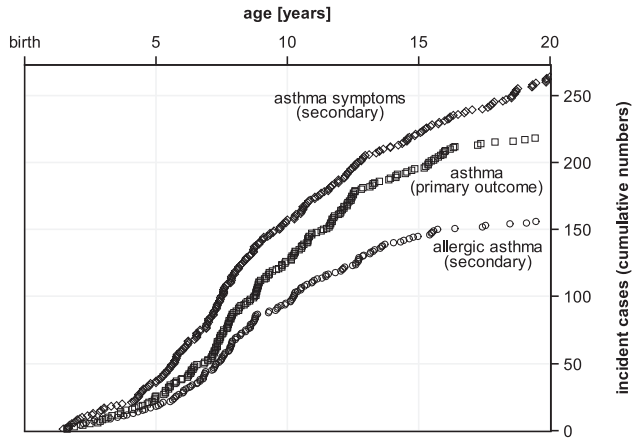

FIG 2. Age at incidence by case definitions: primary outcome asthma (at least 2 of: physician's diagnosis, indicative symptom, or asthma drugs; *open diamonds*); secondary outcome asthma symptoms (at least 2 of: wheezing, shortness of breath, or dry cough; *open squares*); and secondary outcome allergic asthma (primary outcome asthma plus aeroallergen sensitization, *open circles*).

Boys and those born in summer or autumn were more likely to have asthma. Breast-feeding, age at solid food introduction, and all assessed environmental exposures in infancy (eg, air pollution, living environment, and mold) were not linked to asthma.

Children being overweight at 3 years of age, tobacco smoke exposure during the first 3 years of life, and the presence of older siblings and pets in the household had no influence on the development of asthma. A strong protective effect for asthma

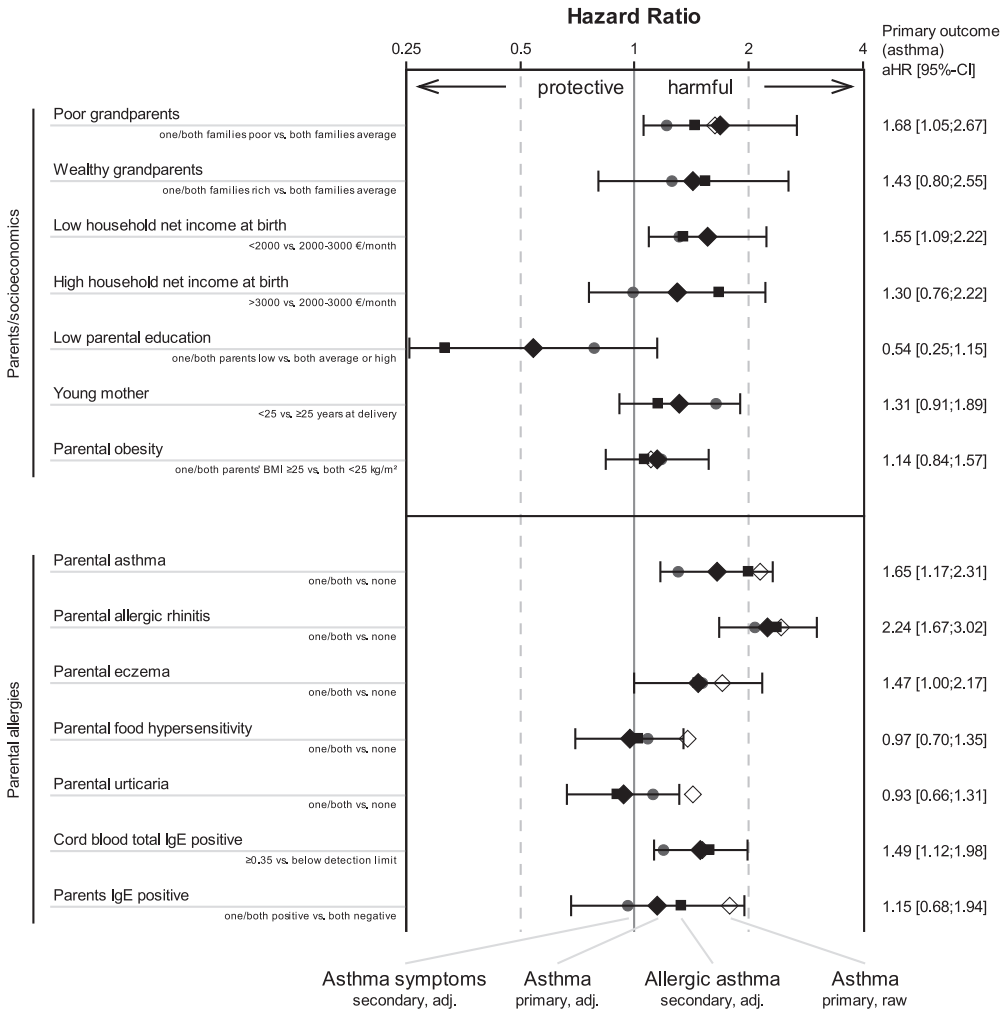

FIG 3. Influence of socioeconomic factors and heredity on asthma development in offspring. Raw *(open diamonds)* and adjusted (*solid diamonds* and *error bars*, exact numbers are shown at *right*) HRs for the primary outcome asthma (at least 2 of: physician's diagnosis, indicative symptom, or asthma drugs) and adjusted HRs for secondary outcomes asthma symptoms (*squares*: at least 2 of: symptoms of wheezing, shortness of breath, or dry cough) and allergic asthma (*circles*: primary outcome asthma plus aeroallergen sensitization). Details on model building, including adjustment and proportionality assessment, in Table E1. *aHR*, Adjusted HR; *BMI*, body mass index.

incidence up to age 20 years was seen for vaccinations based on whole organisms (measles, mumps, and rubella; tick-borne encephalitis; and BCG). Day care attendance revealed a U-shaped association, with the lowest incidence in the intermediate reference group, who started day care between 18 and 36 months of age (Fig 6).

Further information, including details on effect point and interval estimators (HRs), sample size accounted for in each model, selected confounders that were considered in the model, and proportional hazard assessment measures, can be found in Table E1.

Secondary outcome asthma symptoms

Results were mostly similar comparing the secondary outcome of asthma symptoms and the primary outcome, with few exceptions: having a mother who was young at birth (<25 years of age), tobacco smoke exposure during the first 3 years of life, child being overweight, and the presence of a dog in the household were particularly associated with a higher incidence of reported asthma symptoms. As described above, late or early start of day care attendance was linked to higher asthma incidence but not to incidence of asthma symptoms (Fig 3, Fig 6).

Secondary outcome allergic asthma

As for asthma symptoms, results were mostly similar comparing allergic asthma with the primary outcome, with some exceptions: allergic asthma was less frequent in children who had at least 1 parent with a low educational level (adjusted HR, 0.32) and less frequent in children who received vaccinations based on whole organisms (adjusted HR, 0.52). Furthermore, the effect of parental asthma on the incidence in offspring was stronger for allergic asthma than for the primary outcome. The strongest effect on allergic asthma was seen in children who started daycare at an early (adjusted HR, 3.55) or late age (adjusted HR, 2.79) (Fig 3, Fig 6).

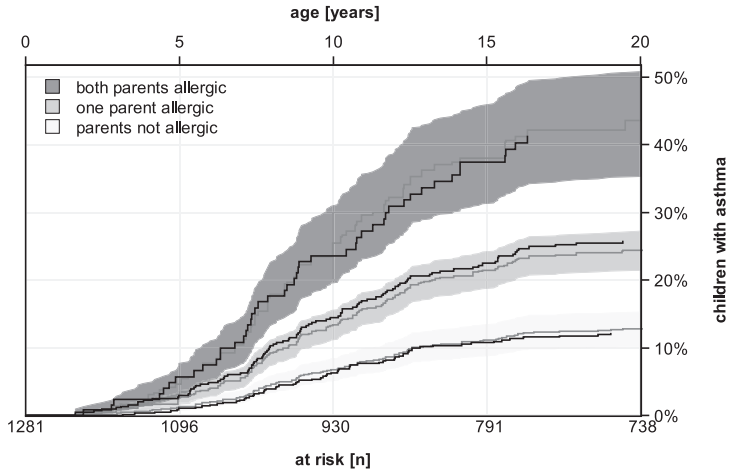

FIG 4. Onset of asthma (at least 2 of: physician's diagnosis, indicative symptom, or asthma drugs) stratified by parental history of allergic disease (asthma, allergic rhinitis, or eczema). *Black step function* depicts real data; *bands* and *gray steps* represent trajectory estimates and 95% CIs based on the Cox proportional model.

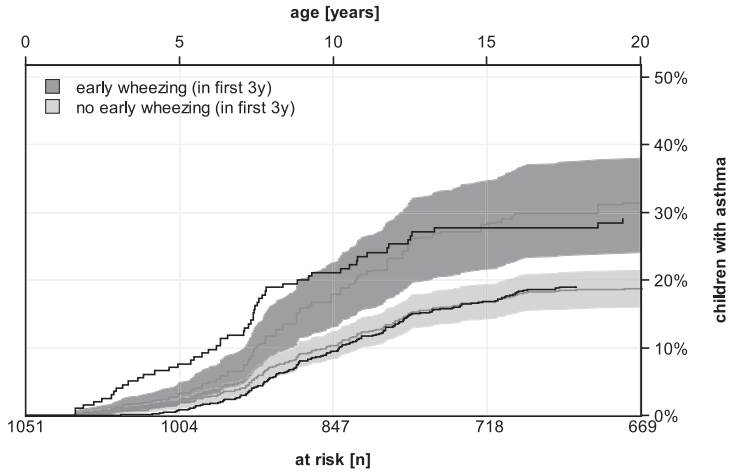

FIG 5. Onset of asthma (at least 2 of: physician's diagnosis, indicative symptom, or asthma drugs) stratified by wheezing within first 3 years. *Black step function* depicts real data; *bands* and *gray steps* represent trajectory estimates and 95% CIs based on the Cox proportional model.

DISCUSSION

Key findings

Of a large number of perinatal and early-life factors that we evaluated, only a few showed associations with asthma up to age 20 years using time-to-event analysis on the German MAS-90 birth cohort data set. Asthma incidence was lower in participants who were vaccinated and higher in children of parents with allergic rhinitis, asthma, eczema, or increased cord blood IgE levels; who started day care before 18 months or after 3 years; who had mothers who smoked during pregnancy; and who had poor parents or grandparents. Not associated with asthma were aspects of diet (breast-feeding, weaning, diet in pregnancy, and parental food hypersensitivity), mode of delivery, pet ownership (cat or dog), age of mother, presence of older siblings, and tobacco smoke exposure.

Nonmodifiable factors

Time-to-event analysis revealed higher asthma incidence up to age 20 years in both participants with a richer and participants with a poorer family background with reference to the intermediate category. Compared with this U-shaped association, previous studies predominantly from English-speaking countries have found either linear or no associations between asthma and poverty.[11,39-41] However, differences in the measurement of social status and poverty between countries, as well as the lack of a common standard of assessing asthma severity, hamper the comparability of results from epidemiologic studies.

As reported before, the strongest nonmodifiable determinants for asthma in offspring included parental allergic rhinitis and asthma, particularly in both parents.[12] Wheezing, eczema, or allergic sensitization all within the first 3 years were strong predictors for earlier onset of asthma up to adulthood in our current study (data not shown for the latter 2). These findings confirm the recently published results from a Danish birth cohort study up to age 26 years.[42] Although IgE in cord blood has been considered a risk factor from the beginning of our birth cohort study, its predictive value for allergies and asthma in childhood has been occasionally questioned. Our analysis showed an association of increased IgE levels in cord blood serum with

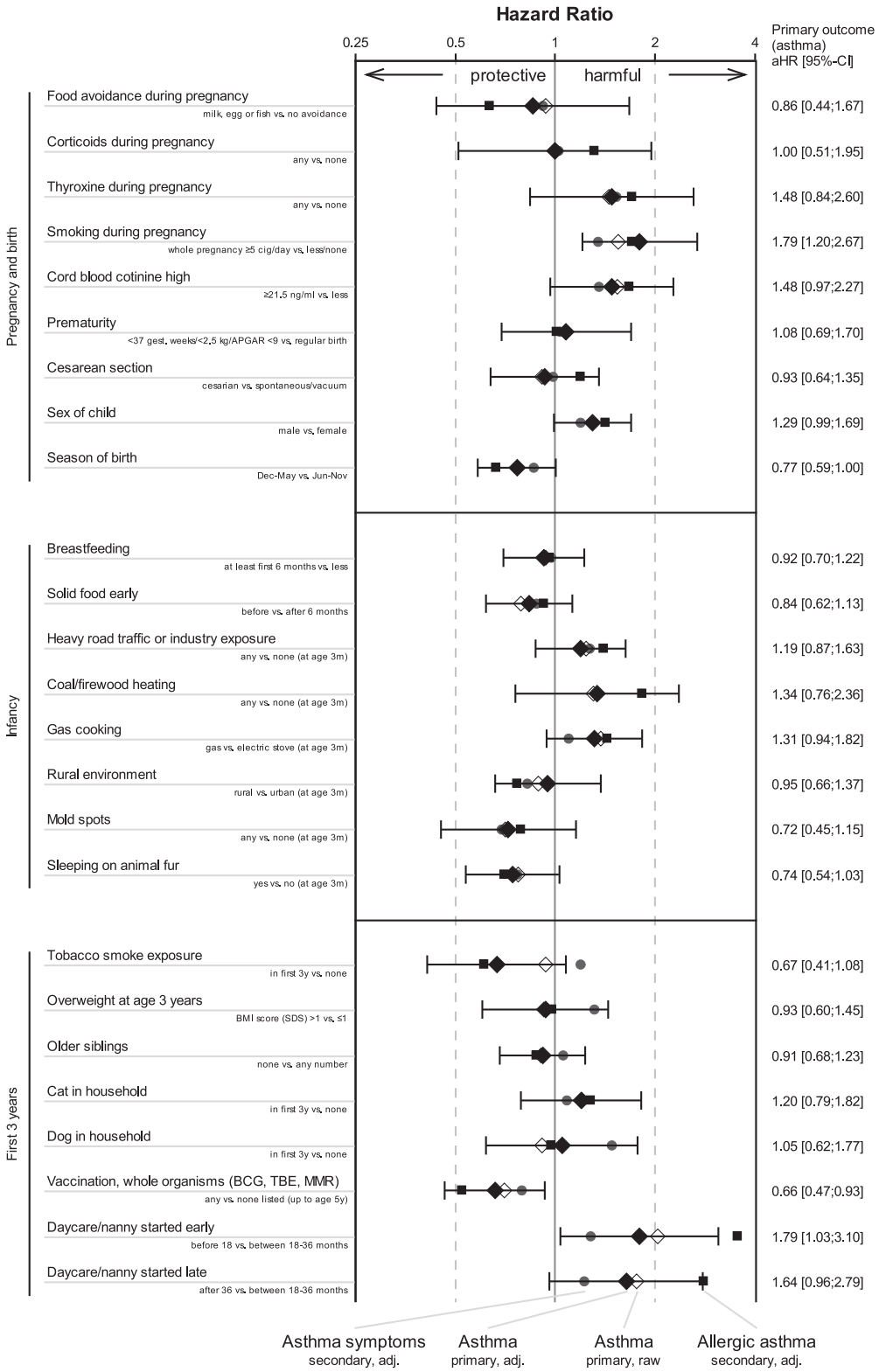

FIG 6. Influence of pregnancy and environmental and behavioral factors in the first 3 years of life on asthma development. Raw *(open diamonds)* and adjusted (*solid diamonds* and *error bars*, exact numbers are shown at *right*) HRs for the primary outcome of asthma (2 of physician's diagnosis, indicative symptom, or asthma drugs) and adjusted HRs for secondary outcomes of asthma symptoms (*squares*: 2 of wheezing, shortness of breath, or dry cough) and allergic asthma (*circles*: based on physician's diagnosis and aeroallergen sensitization) are shown. Details on model building, including adjustment and proportionality assessment, are shown in Table E1. *aHR*, Adjusted HR; *APGAR*, postnatal adaptation score; *MMR*, measles, mumps, and rubella vaccine; *SDS*, standard deviation score; *TBE*, tick-borne encephalitis vaccine.

asthma up to age 20 years, which is in line with a Finnish birth cohort analysis up to the same age.[43]

Pregnancy and birth exposures

Tobacco exposure during pregnancy was one of the strongest modifiable risk factors lasting until early adulthood, which is in line with other studies[44] and a recent meta-analysis.[15] As an objective surrogate for smoking in late pregnancy, the cord blood cotinine level was an independent predictor of asthma development. Other potentially modifiable aspects of pregnancy and birth that were assessed in MAS-90 were not related to asthma incidence. Being born in winter or spring was related to lower incidence of asthma up to age 20 years in our birth cohort, giving a hint toward early aeroallergen exposure or respiratory tract infections to influence disease development.

Infancy exposures

In line with the latest Cochrane review on this topic, breastfeeding duration did not seem to influence asthma development.[45] Environmental factors with parent-reported information from at least 1 time point were included in our analysis but showed no association with asthma, except a slightly increased incidence for participants who were exposed to gas cooking or coal/firewood heating at home. Some environmental exposures were not continuously assessed in MAS-90 during the first year of life. Therefore we cannot exclude the possibility that certain indoor or outdoor exposures during infancy might influence asthma development later in life.

Exposures in the first 3 years

A lower risk of allergy and asthma in 5-year-old children who were vaccinated against measles, mumps, and rubella has been shown before in our birth cohort, as well as for BCG vaccination in a large survey of children starting school in 1994.[46,47] The results of our current analyses showed that this protective effect for asthma seems to last until adulthood for participants who received at least some whole-organism vaccines in early childhood (measles, mumps, and rubella; tuberculosis; and tick-borne encephalitis) compared with those who did not receive any at all. We were not able to examine the effect of other vaccinations in our current analysis because the number of children who were not immunized at all against tetanus, for example, was too small for robust risk estimates.

Dichotomizing participants into exposed and unexposed categories is hampering identification of continuous or U-shaped dose-response associations. Using intermediate values as the reference category, we found that starting day care before age 18 months or after age 36 months increased the incidence of asthma throughout the first 2 decades of life. Whether respiratory tract infections during the second and third years of life or other exposures prevent allergic sensitization and possibly allergic asthma needs to be evaluated if other long-term birth cohort studies find similar U-shaped associations with the age at which children start day care.

Most exposure variables showed similar effects for our secondary outcome of allergic asthma (IgE-associated asthma) compared with our primary outcome of asthma, with few exceptions. The HR for an early (before 18 months) and a late (age 3 years and later) day care start was even higher for allergic asthma than for asthma and slightly stronger for children of parents with asthma and those who were vaccinated against tuberculosis or measles, mumps, and rubella. Different disease perception and symptom awareness might have led to higher effect sizes seen for younger mothers regarding our secondary outcome of asthma symptoms, which was based on parental reports during most of the follow-up. Although the effects on asthma symptoms were generally similar or less than for the primary outcome, the debate on whether increasing prevalences seen within recent decades are spurious or real[48] should always consider changes in disease perception, labeling, and awareness if based predominantly on symptoms in epidemiologic studies.

Strengths and limitations

The current study applied the method of time-to-event analysis, also known as survival analysis, on birth cohort data, assessing factors influencing the development of childhood asthma. It has been a routine tool in cancer and cardiovascular research but only rarely used in the field of asthma and allergy.[49] Only time-to-event analysis properly accounts for the timing of disease onset, as well as right censoring, mainly in terms of loss to follow-up in prospective birth cohorts[38] and interval censoring. Effect estimators are based on a large data fundament; our analysis included 16,257 person years. Sensitivity analysis supported the robustness of estimators based on almost unvaried results comparing various approaches for the calculation of exact disease onset, censoring age, and handling of missing covariate data.

Our approach, assessing a whole array of factors potentially influencing asthma incidence and at the same time allowing for comprehensive adjustment, included confounders that were preselected based on available knowledge[36] and assessed in a second step for each model separately by using a stepwise selection procedure. To reduce misclassification of exposures, we evaluated the influence of cutoffs for continuous items. Consistency between exposure data collected at different time points supported confidence in rejection of time-covarying exposures (eg, smoking at home).

Because of low case numbers in certain subgroups, patterns of asthma progression (eg, intermittent and remissive) were not further classified. Although the risk-enriched sampling of the cohort impedes generalizable estimates of disease frequencies (incidence), it can strengthen the evaluation of potential risk and protective factors, one of the main aims of this long-term birth cohort study. Future approaches will need to include evaluation of interaction of exposures; different asthma phenotypes, including age at onset, persistence, remission (as done in Savenije et al[50]), and sensitization patterns; other allergic diseases; details of or exposures not covered here; and aspects of behavior and environmental exposures beyond 3 years of age.

Up to age 20 years, a parental history of respiratory allergies and a mother who smoked during pregnancy were the strongest risk factors of asthma. Starting day care between 1.5 and 3 years of age and receiving vaccinations as recommended might delay onset or even prevent asthma later in life. Future evaluations of longitudinal asthma and allergy birth cohort data should include time-to-event analysis to identify risk and protective factors for improved preventive strategies.

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Key messages

- **Avoiding prenatal tobacco smoke exposure, starting day care between age 1.5 and 3 years, and receiving vaccinations in early life might decrease the risk of asthma up to adulthood.**
- **Parental respiratory allergies and low household income are risk factors for asthma beyond childhood and adolescence.**

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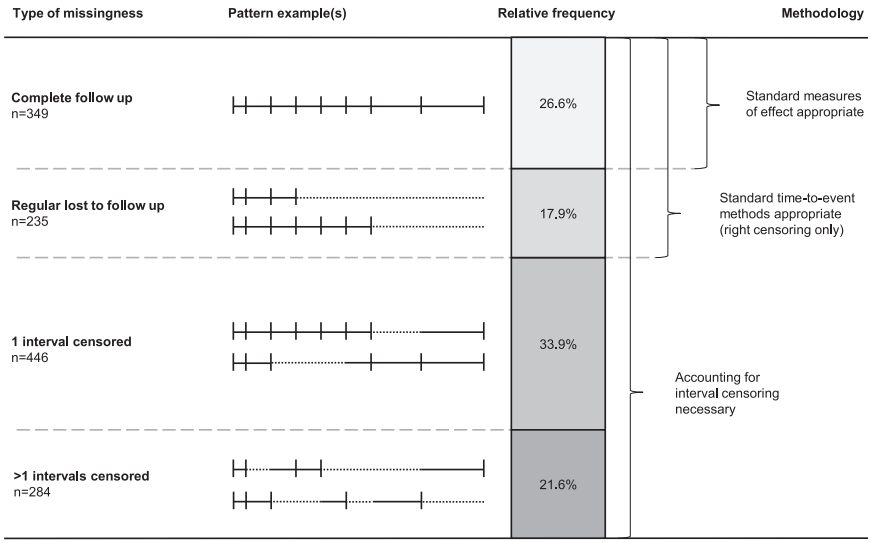

FIG E1. Missingness patterns, distribution, and appropriate methodology. With all 19 time points accounted for, the overall number of participants was 1314.

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TABLE E1. Cox regression model specifications

Exposure			Primary outcome			Secondary outcomes		Adjustment		Model assumptions (*P* values)		
	Categories	Numbers	Asthma	Asthma	Single factor in model	Asthma symptoms	Allergic asthma	Selected covariates				
Factor	Exposed vs unexposed	Exposed vs unexposed	Raw HR (95% CI)	Adjusted HR (95% CI)	*P* value	Adjusted HR	Adjusted HR	Placeholder*	Change in estimate	Schoenfeld residuals	Time dependency	Supremum test
Poor grandparents	One/both families poor vs both families average	427 vs 164	1.62 (1.02-2.58)	1.68 (1.05-2.67)	.03	1.22	1.44	1	3%	.70	.54	.78
Wealthy grandparents	One/both families rich vs both families average	113 vs 164	1.43 (0.80-2.55)	1.43 (0.80-2.55)	.23	1.26	1.54	1	0%	.40	.28	.80
Low household income at birth	<€2000 vs €2000-€3000/mo	523 vs 304	1.55 (1.09-2.22)	1.55 (1.09-2.22)	.02	1.31	1.35	2	0%	.90	.71	.80
High household income at birth	>€3000 vs €2000-€3000/mo	111 vs 304	1.31 (0.77-2.23)	1.30 (0.76-2.22)	.34	0.99	1.67	2,3	−1%	.92	.96	.69
Low parental education	One/both parents low vs both average or high	106 vs 1100	0.54 (0.25-1.15)	0.54 (0.25-1.15)	.11	0.78	0.32	2,3	0%	.92	.92	.90
Young mother	<25 vs ≥25 years of age at delivery	200 vs 1111	1.31 (0.91-1.89)	1.31 (0.91-1.89)	.14	1.64	1.15	3	0%	.64	.39	.97
Parental obesity	One/both parents' BMI ≥25 vs both <25 kg/m^2	403 vs 423	1.10 (0.81-1.50)	1.14 (0.84-1.57)	.40	1.18	1.07	2,3,4,5,6,7	4%	.11	.19	.13
Parental asthma	One/both vs none	183 vs 1075	2.14 (1.55-2.94)	1.65 (1.17-2.31)	<.01	1.30	2.00	3,4,6,7	−23%	.12	.15	.09
Parental allergic rhinitis	One/both vs none	536 vs 710	2.43 (1.83-3.23)	2.24 (1.67-3.02)	<.01	2.07	2.37	5,6,7	−8%	.93	.73	1.00
Parental eczema	One/both vs none	126 vs 1095	1.70 (1.16-2.49)	1.47 (1.00-2.17)	.05	1.51	1.47	3,4,5,6,7	−13%	.47	.63	.59
Parental food hypersensitivity	One/both vs none	271 vs 962	1.38 (1.02-1.87)	0.97 (0.70-1.35)	.86	1.08	1.02	3,4,5,6,7	−30%	.84	.65	.97
Parental urticaria	One/both vs none	239 vs 1015	1.42 (1.04-1.95)	0.93 (0.66-1.31)	.69	1.12	0.90	3,4,5,6,7,8	−35%	.83	.71	.91
Positive cord blood total IgE level	≥0.35 kU/L vs less than detection limit	451 vs 810	1.51 (1.15-1.99)	1.49 (1.12-1.98)	.01	1.19	1.57	3,4,5,6,7	−1%	.17	.29	.22
Positive parental IgE level	One/both positive vs both negative	449 vs 171	1.78 (1.11-2.85)	1.15 (0.68-1.94)	.60	0.96	1.33	3,4,5,7	−35%	.43	.26	.49
Food avoidance in pregnancy	Milk, egg, or fish vs no avoidance	63 vs 1223	0.94 (0.48-1.82)	0.86 (0.44-1.67)	.65	0.92	0.63	3,4,5,6,7,8,9,10	−9%	.72	.54	.22
Corticoids during pregnancy	Any vs none	51 vs 1209	1.00 (0.51-1.96)	1.00 (0.51-1.95)	.99	1.02	1.31	6,7	−1%	.55	.66	.49
Thyroxine during pregnancy	Any vs none	51 vs 1230	1.45 (0.83-2.54)	1.48 (0.84-2.60)	.18	1.53	1.70	3,6,7	2%	.48	.28	.62
Smoking during pregnancy	Whole pregnancy ≥5 cigarettes/d vs less/none	171 vs 1041	1.54 (1.05-2.27)	1.79 (1.20-2.67)	<.01	1.34	1.70	4,5,6,7,9,10	16%	.59	.48	.20
Cord blood cotinine level high	≥21.5 ng/mL vs less	159 vs 584	1.54 (1.04-2.27)	1.48 (0.97-2.27)	.07	1.35	1.67	4,5,9,11	−4%	.06	.05	.14
Prematurity	<37 gestational weeks/<2.5 kg/APGAR score <9 vs regular birth	122 vs 1072	1.08 (0.69-1.69)	1.08 (0.69-1.70)	.74	1.04	1.01	7	0%	.61	.89	.74
Cesarean section	Cesarean vs spontaneous/vacuum	205 vs 1108	0.91 (0.63-1.33)	0.93 (0.64-1.35)	.69	0.98	1.19	3,6,7	1%	.90	.86	.72
Sex of child	Male vs female	684 vs 630	1.29 (0.99-1.69)	1.29 (0.99-1.69)	.06	1.19	1.41	3,6,7	0%	.08	.04	.08

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Season of birth	December-May vs June-November	626 vs 688	0.77 (0.59-1.00)	0.77 (0.59-1.00)	.05	0.86	0.66	3,6,7	0%	.41	.65	.41
Breast-feeding	At least first 6 months vs less	642 vs 566	0.94 (0.71-1.23)	0.92 (0.70-1.22)	.57	0.97	0.96	4,5,7,8,9,10	−2%	.05	.04	.09
Solid food early	Before vs after 6 mo	780 vs 305	0.79 (0.59-1.06)	0.84 (0.62-1.13)	.24	0.88	0.92	3,4,5,7,9,10,12,13	6%	.30	.24	.76
Heavy road traffic/industry	Any vs none (at age 3 mo)	738 vs 382	1.24 (0.91-1.68)	1.19 (0.87-1.63)	.27	1.27	1.40	4,5,7,8,10	−4%	.23	.63	.12
Coal/firewood heating	Any vs none (at age 3 mo)	63 vs 1029	1.30 (0.76-2.25)	1.34 (0.76-2.36)	.32	1.33	1.82	4,5,7,8,9,10	2%	.61	.72	.86
Gas cooking	Gas vs electric stove (at age 3 mo)	225 vs 929	1.37 (0.99-1.90)	1.31 (0.94-1.82)	.11	1.09	1.44	4,5,7,8,9,10	−5%	.97	.49	.55
Rural environment	Rural vs urban (at age 3 mo)	236 vs 921	0.89 (0.63-1.26)	0.95 (0.66-1.37)	.78	0.82	0.77	3,4,5,7,9,10,11,14	7%	.95	.72	.57
Mold spots	Any vs none (at age 3 mo)	155 vs 985	0.71 (0.45-1.12)	0.72 (0.45-1.15)	.17	0.69	0.79	3,4,5,6,7,8,9,10,11	2%	.46	.96	.35
Sleeping on animal fur	Yes vs no (at age 3 mo)	341 vs 773	0.77 (0.56-1.06)	0.74 (0.54-1.03)	.08	0.77	0.70	3,4,5,7,9,10,11,15,16,17	−4%	.77	1.00	.38
Tobacco smoke exposure	In first 3 y vs none	212 vs 798	0.94 (0.65-1.35)	0.67 (0.41-1.08)	.10	1.19	0.61	4,5,7,9,10,11	−29%	.29	.67	.15
Overweight at age 3 y	BMI score (SDS) >1 vs ≤1	134 vs 882	0.92 (0.60-1.41)	0.93 (0.60-1.45)	.76	1.31	0.98	4,5,6,7,9,10,11	1%	.63	.33	.24
Older siblings	None vs any number	539 vs 612	0.90 (0.68-1.21)	0.91 (0.68-1.23)	.56	1.06	0.88	2,3,7	1%	.67	.35	.86
Cat in household	In first 3 y vs none	194 vs 550	1.19 (0.81-1.76)	1.20 (0.79-1.82)	.39	1.08	1.28	3,4,5,7,9,11,15,16,18	1%	.13	.27	.17
Dog in household	In first 3 y vs none	118 vs 550	0.91 (0.55-1.52)	1.05 (0.62-1.77)	.87	1.48	0.97	2,3,4,5,7,14	14%	.14	.20	.20
Vaccination (BCG, TBE, MMR)	Any vs none listed (up to age 5 y)	871 vs 185	0.70 (0.50-0.99)	0.66 (0.47-0.93)	.02	0.79	0.52	4,5,6,7,9,10,11,16,17	−6%	.44	.68	.55
Day care/nanny started early	Before 18 vs between 18-36 mo	180 vs 175	2.03 (1.18-3.49)	1.79 (1.03-3.10)	.04	1.28	3.55	4,5,8,9,14	−12%	.98	.70	.45
Day care/nanny started late	After 36 vs between 18-36 mo	224 vs 175	1.76 (1.04-2.98)	1.64 (0.96-2.79)	.07	1.22	2.79	4,8,10,11,19	−7%	.25	.16	.20

Exposure definition; numbers in exposure groups in analysis; effect estimation, including raw and adjusted HRs, for primary and secondary outcomes; covariates selected and change in estimate through adjustment; and test-based assessment of proportionality assumptions are shown.

APGAR, Postnatal adaptation score; *BMI*, body mass index; *MMR*, measles, mumps, and rubella vaccine; *SDS*, standard deviation score; *TBE*, tick-borne encephalitis vaccine.

*Multiply imputed factors used for adjustment in the final model. Numbers in parentheses indicate absolute frequency of being selected in all of 36 models: 1, study center Berlin (2); 2, wealthy grandparents (6); 3, poor grandparents (22); 4, parental allergic rhinitis (25); 5, parental asthma (24); 6, parents with low education (17); 7, low family net income (30); 8, parental eczema (9); 9, Increased cord blood IgE level (15); 10, male sex (14); 11, smoking during pregnancy (9); 12, young mother at birth (1); 13, parents' IgE level positive (1); 14, born December-May (3); 15, Increased cord blood cotinine level (2); 16, day care before 18 months of age (3); 17, day care after 36 months of age (2); 18, study center Freiburg (1); and 19, older siblings (1).