Prediction and prevention of allergic rhinitis: A birth cohort study of 20 years

Linus B. Grabenhenrich, MD, MPH,[a] Thomas Keil, MD, MSc,[a,b] Andreas Reich,[a] Hannah Gough,[a] John Beschorner, MD,[c] Ute Hoffmann, MD,[d] Carl-Peter Bauer, MD,[d] Johannes Forster, MD,[e] Antje Schuster, MD,[f] Dirk Schramm, MD,[f] Oliver Nitsche, MD,[g] Fred Zepp, MD,[g] Young-Ae Lee, MD,[h] Renate Bergmann, MD,[i] Karl Bergmann, MD,[i] Ulrich Wahn, MD,[j] and Susanne Lau, MD[j] *Berlin, Würzburg, Hagenow, Munich, Freiburg, Dusseldorf, and Mainz, Germany*

Background: Allergic rhinitis (AR) is one of the most common chronic diseases, usually starting in the first 2 decades of life. Information on predictors, risk, and protective factors is missing because of a lack of long-term prospective studies.
Objective: Our aim was to examine early-life environmental and lifestyle determinants for AR up to age 20 years.
Methods: In 1990, the Multicenter Allergy Study included 1314 newborns in 5 German cities. Children were evaluated at 19 time points. A Cox regression model examined the associations between 41 independent early-life factors and onset of AR (as the primary outcome), including sensitization against aeroallergens and the secondary outcomes of nonallergic rhinitis and AR plus asthma.
Results: Two hundred ninety subjects had AR within 13,179 person years observed. The risk of AR was higher with a parental history of AR (adjusted hazard ratio [aHR], 2.49; 95% CI, 1.93-3.21), urticaria (aHR, 1.32; 95% CI, 1.00-1.74), or asthma (aHR, 1.29; 95% CI, 0.95-1.75). Early allergic sensitization (aHR, 4.53; 95% CI, 3.25-6.32), eczema within the first 3 years of life (aHR, 1.83; 95% CI, 1.38-2.42), male sex (aHR, 1.28; 95% CI, 1.02-1.61), and birthday in summer or autumn (aHR, 1.26; 95% CI, 1.00-1.58) were independent predictors of AR up to age 20 years. None of the other socioeconomic, environmental, lifestyle, pregnancy, and birth-related factors were associated with AR.
Conclusion: Only nonmodifiable factors, particularly early allergic sensitization or eczema and parental AR, predicted AR up to age 20 years. No modifiable aspects of early-life environment or lifestyle were identified as targets for primary prevention. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: *Infant, preschool child, adolescent, heredity, risk factors, epidemiologic factors, survival analysis, primary prevention*

Because of its high prevalence in youth and young adults, allergic rhinitis (AR) limits quality of life and daily activities, with a notable effect at the population level.[1-4] Disease-modifying treatment is still limited to a small subset of specific immunophenotypes,[5] highlighting the importance of exploring risk and protective factors for better prevention of AR.[6]

A strong genetic background has been ascribed to AR, both in twin studies and through linking disease occurrence across generations.[7,8] Similarly, early sensitization to food or later airborne allergens as indicators of preclinical disease can only be used as predictors to identify subjects at increased risk.[9-11]

On the other hand, a number of potentially modifiable environmental exposures and behavior early in life that were present before the incipient steps of disease development have been linked to AR, often with inconclusive or conflicting findings.[12-15] Comparability of these findings is limited by the diversity of case definitions, sampling strategies, and study designs used. Thus there is no agreement on primary prevention recommendations for AR.[16]

Because potential early-life determinants do not closely precede the clinical appearance of rhinitis symptoms and diagnosis, specific methodologic demands are required to rule out or validly establish a link to disease onset or severity. Most promising approaches are prospective long-term observational studies on a population-based level.

Therefore our aim was to examine the association between environmental exposures, lifestyle, and biological determinants

From [a]the Institute for Social Medicine, Epidemiology and Health Economics, and the Departments of [i]Obstetrics and [j]Pediatric Pneumology and Immunology, Charité-Universitätsmedizin Berlin, Berlin; [b]the Institute of Clinical Epidemiology and Biometry, University of Würzburg; [c]the Department of Pediatrics, Westmecklenburg Hospital, Hagenow; [d]the Department of Pediatrics, Technical University of Munich; [e]the Department of Pediatrics, St Josefs Hospital, Freiburg; [f]the Department of Pediatrics, Heinrich-Heine-University, Dusseldorf; [g]the Center for Pediatric and Adolescent Medicine, University Medical Center Mainz; and [h]Max-Delbrück-Center, Berlin.

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Corresponding author: Linus B. Grabenhenrich, MD, MPH, Institute for Social Medicine, Epidemiology and Health Economics, Charité–Universitätsmedizin Berlin, Luisenstrasse 57, 10117 Berlin, Germany. E-mail: linus.grabenhenrich@charite.de.

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Abbreviations used
aHR: Adjusted hazard ratio
AR: Allergic rhinitis

in prenatal, postnatal, and early life on the development of AR up to age 20 years, when about 4 in 5 incident cases across life have emerged.[2]

METHODS

Study design

The German Multicenter Allergy Study is a birth cohort aiming to describe patterns and risk factors of allergic diseases, including AR. Methods have been described in detail.[17-19] In short, children born in 1990 in 6 German obstetrics departments, with oversampling for parental allergies (based on self-reported medical history and screening tests for parental sensitization), were followed up to age 20 years. Environmental and behavioral factors and medical history with a focus on allergies, including specific months when rhinitis symptoms without a cold occurred, were assessed at 9 time points by using face-to-face, paper, telephone, and online questionnaires (at 1, 3, 6, 12, and 18 months; annually from 2-13 years; and at 15 and 20 years). Questionnaires were answered by 1 or both parents up to age 15 years and by participants at age 20 years. Specific IgE levels were measured at 9 time points. The study was approved by local institutional review boards in all study centers. Parents and participants provided written informed consent.

Primary outcome

The primary outcome of AR was based on parent- and self-reported nasal symptoms (ie, "In the past 12 months, did your child/you have problems with sneezing, or a runny, or blocked nose when he/she/you DID NOT have a cold or the flu?") disturbing daily activities (ie, "In the past 12 months, has your child/have you been disturbed by a runny/itchy/blocked nose or itchy/watery/red eyes in daily activities?"), with both items answered yes. The seasonal pattern of symptoms must have been specified by reporting at least 1 symptomatic month. Questionnaire items (as proposed from the International Study of Asthma and Allergies in Childhood project) were considered unreliable to define AR before age 3 years.[16,20-23] The specific IgE level had to be 0.35 kU/L or greater to any of 5 aeroallergens (dust mite, dog, cat, birch, and timothy grass; ImmunoCAP; Phadia GmbH, Freiburg, Germany) measured at or before the report of symptoms. Associations between various specific IgE measures (reported only for age 20 years) were quantified through Pearson correlation of log-transformed raw levels (base 10, negative IgE coded as 10E-3).

Secondary outcomes

The case definition of nonallergic rhinitis included only those subjects with no prior aeroallergen sensitization. The definition of AR plus asthma (combined allergic rhinitis and asthma syndrome[24]) implied a current or prior diagnosis of asthma, which was defined by 2 of the following 3 criteria: physician's diagnosis, use of asthma medication in the last 12 months, and indicative symptoms in the last 12 months (wheezing, shortness of breath, or dry cough at night). Outcomes only assessed in sensitivity analyses include rhinitis symptoms irrespective of their effect and symptomatic months (rhinitis symptoms), symptoms limited to months between February and September (seasonal rhinitis), and physician-diagnosed AR based on a single item (ie, "Has your child/have you ever been diagnosed by a physician with having AR [rhinitis to pets, dust] or hay fever [rhinitis to pollens]?").

Exposures and behavior

Data available from pregnancy and the first 3 years of life were analyzed as risk or protective factors for AR. Variables were binary coded and treated as time invariant, including those merged from multiple time points. For example, tobacco smoke exposure in the first 3 years was assumed, even if only reported at some follow-ups within that interval. Results were presented in 5 categories based on prenatal, perinatal, and postnatal time periods: parental socioeconomic status, parental allergies, pregnancy and birth factors, exposures in infancy (up to age 1 year), and exposures in the first 3 years.

Specifically, children being overweight was defined through age- and sex-specific SD scores,[25] and intrauterine tobacco exposure was objectively quantified through cord serum cotinine levels by using the study population's mean as the cutoff (21.5 ng/mL). Details of all factors, including definition of exposure categories and considered ages, can be found in Table E1 in this article's Online Repository at www.jacionline.org.

Statistics

The influence of early-life exposures and behavior on AR was assessed by using time-to-event analysis (Cox proportional hazards model).[26] Disease onset was estimated at the midpoint between the first follow-up meeting case definition criteria and the prior negative (or missing) follow-up coded in days. Alternatively, random imputation with equal probabilities within the interval and using the exact age when meeting the case criteria produced very similar results. Right censoring was reached at the last assessment before loss to follow-up, the end of the study (age 20 years), or both. All subjects were left censored before age 2.5 years, assuming that a diagnosis of AR in very early childhood is not reliable for epidemiologic studies. Temporary discontinuation of follow-up (interval censoring observed in 55.4% of children)[17] was handled by using 2 different approaches. Initially, we ran basic Cox models (PROC PHREG), treating single or consecutive missed follow-ups as if participants would have been observed with disease status reported in the first assessment after temporary loss to follow-up. Properly accounting for the person time actually observed, we coded each successional observation period separately in a second approach using the counting process format, which was originally developed to handle competing risks and multiple events in PROC PHREG. Both approaches produced almost identical results; only the latter is reported in this article. Multiple events on the same day (ties) were presumed to result from imprecise measurement and handled through calculating exact likelihoods on a continuous time scale. Interaction was assessed through comparing stratified models for child's sex and parental AR, and formal interaction terms were not included. Ninety-five percent CIs were based on Wald tests. Hazard proportionality was assessed graphically (log-log curves, observed vs expected) and statistically through testing if an additional interaction term (predictor multiplied by time) contributed to the model (time dependency of predictor, see Table E1).

A separate model was estimated for each predictor, for which potential confounders were selected by using directed acyclic graphs.[27] Thereafter, stepwise selection excluded those not significantly linked to the outcome (entry/exclusion threshold, $P = .05$). Missing values (median missing frequency, 8.2%) in all confounder variables were filled through multiple imputation: 10 repetitions using the Markov chain Monte Carlo (MCMC, using PROC MI) method with rounding and truncation to yield binary levels.[28] Each imputed data set was analyzed separately, and effect estimates were joined by using PROC MIANALYZE, which accounts for SE variability across imputations.[29] The SAS system (version 9.3; SAS Institute, Cary, NC) was used for data management, cleaning, and statistics.

RESULTS

Of 1314 newborns recruited, 941 (71.6%) remained in the cohort until age 20 years. Participants lost to follow-up came from less educated families, with 27.3% of parents having low education status compared with 19.4% among the complete responders. Loss to follow-up did not differ considerably by mother's overweight status (21.8 vs 18.5%) and family's allergy history (35.0 vs 38.2%), as reported earlier in detail.[17]