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Longitudinal investigation of the course of asthma and allergies in young German adults

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is congruent with the printed version both in content and format.

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List of abbreviations

BIC – Bayesian information criterion

CI – Confidence interval

DAG – Directed acyclic graph

IDA – Initial data analysis

ISAAC – International Study of Asthma and Allergies in Childhood

LCA – Latent class analysis

OR – Odds ratio

PPV – Positive predictive value

SES – Socio-economic status

SOLAR – Study on Occupational Allergy Risks

TAC – Thesis Advisory Committee

List of publications

Forster F, Ege MJ, Gerlich J, Weinmann T, Kreißl S, Weinmayr G, Genuneit J, Nowak D, Mutius E von, Vogelberg C, Radon K (2022) Trajectories of asthma and allergy symptoms from childhood to adulthood. Allergy 77(4):1192–1203

Forster F, Kreißl S, Wengenroth L, Vogelberg C, Mutius E von, Schaub B, Nowak D, Weinmann T, Radon K, Gerlich J (2021) Third Follow-Up of the Study on Occupational Allergy Risks (SOLAR III) in Germany: Design, Methods, and Initial Data Analysis. Frontiers in Public Health 9:591717

Kolberg L, Forster F, Gerlich J, Weinmayr G, Genuneit J, Windstetter D, Vogelberg C, Mutius E von, Nowak D, Drexler H, Schäfer T, Radon K (2020) Nickel allergy is associated with wheezing and asthma in a cohort of young German adults: results from the SOLAR study. ERJ Open Research 6:00178-2019

1. Your contribution to the publications

1.1 Contribution to paper I

Paper I is titled “Trajectories of asthma and allergy symptoms from childhood to adulthood”. [1]

In this article, the candidate analyzed data of Phase II of the International Study of Asthma and Allergies in Childhood (ISAAC) and three follow-up studies called Study on Occupational Allergy Risks (SOLAR). ISAAC and the first two SOLAR study phases finished before 2010. Therefore, the candidate was not involved in these study phases at all. The third SOLAR follow-up took place in 2017-18. The candidate was not involved in the conception and design of the third follow-up but coordinated the second half of data acquisition in the study center Munich. This included creation and management of the response database, sending out invitations, reminders, and other study-related documents to participants, digitalizing paper questionnaires, supervising student assistants, etc. In addition, the candidate processed the raw data from both study centers to arrive at an analyzable dataset. The objective of the analysis as well as the idea to use the method of repeated-measures latent class analysis (LCA) came from the Thesis Advisory Committee (TAC). The candidate conducted all analyses and filled in additional details of the analysis plan, e.g. regarding LCA model selection, handling of missing data, and considerations of classification uncertainty of the selected LCA model in additional regression analyses. Interpretation of results was done by the candidate and the TAC with help of the remaining co-authors. This input led e.g. to the decision on the final sensitivity analyses as well as table and figure structures. The candidate drafted the manuscript and included feedback by the TAC and remaining co-authors. The candidate acted as corresponding author during the publication process and answered reviewer comments with help of the TAC.

1.2 Contribution to paper II

Paper II is titled “Third Follow-up of the Study on Occupational Allergy Risks (SOLAR III) in Germany: Design, Methods, and Initial Data Analysis”. [2]

In this article, design and methods of the third SOLAR follow-up are described. As mentioned in “Contribution to paper I”, the candidate was not involved in the conception and design of the third follow-up but coordinated the second half of data acquisition in the study center Munich. This included creation and management of the response database, sending out invitations, reminders, and other study-related documents to participants, digitalizing paper questionnaires, supervising student assistants, etc. In addition, the candidate processed the raw data from both study centers to arrive at an analyzable dataset. The candidate suggested to apply the structure of the initial data analysis (IDA) framework. Planning the analysis, including variable selection for non-responder analysis, was mainly done by the supervisor and the paper’s last author based on suggestions by the candidate, which followed the analysis done in the methods paper of the previous study phase. The candidate conducted all statistical analyses. Interpretation of results was done by the candidate, the supervisor, and the paper’s last author. The candidate drafted the manuscript and included feedback by the co-authors. The candidate acted as corresponding author during the publication process and answered reviewer comments with help of the supervisor.

1.3 Contribution to paper III (Appendix)

Paper III is titled “Nickel allergy is associated with wheezing and asthma in a cohort of young German adults: results from the SOLAR study”. [3]

The candidate was not the paper’s first author. The paper resulted from the master thesis of the paper’s first author. The candidate acted as supporting supervisor of this master thesis. The first author ran the analysis, drafted the manuscript, and acted as corresponding author during the publication process, which included answering reviewer comments. The candidate supported all of this by giving feedback repeatedly and acting as a constant point of contact for the first author. Data from Phase II of ISAAC and two SOLAR follow-up studies was analyzed. As mentioned in “Contribution to paper I”, these study phases finished before 2010. Therefore, the candidate was not involved at all in conception and design of the study or in data acquisition. Regarding study objective, analysis plan, interpretation of results, and drafting the manuscript, candidate and first author were strongly supported by the last author, who also was the master thesis’ supervisor.

2. Introductory summary

2.1 Asthma and allergies as complex diseases

Asthma and allergies are complex diseases. Their development is based on complicated immunological pathways with genetic and environmental risk factors. [4, 5] Courses of disease also differ between individuals with age of onset, persistence of symptoms, and other traits being dimensions of variation. In asthma, for example, triggers and frequency of symptoms, their severity, as well as response to therapies are traits by which the clinical picture of asthma varies. [6] These patterns of clinically relevant variables are called phenotypes. Their existence leads to the idea that subtypes of disease might differ by pathomechanism. These subtypes of disease are called endotypes. [7] In asthma, traits of endotypes include e.g. presence vs. absence of markers for a type 2 immune response in the airways. [8] Knowledge about the pathomechanism is important because it opens up new ways of therapy.

Beyond single diseases, the interplay between different allergy-related outcomes, like asthma, allergic rhinitis, and atopic dermatitis, is important. Looking at all of them together expands the concept of phenotypes and gives a starting point for associating their pathways and risk factors and hence for learning about underlying endotypes.

As mentioned, age plays an important role in phenotyping asthma and allergies. Firstly, age of onset is an important trait of phenotypes with considerable differences between disease courses that start in infancy, in childhood, or in adulthood. Secondly, disease progression with age is of concern. [6] Therefore, age probably plays an important role in endotypes as well, e.g. in the form of age ranges, in which an individual is vulnerable to risk factors or protective factors that influence disease risk. Identification of these time windows can improve prevention and health promotion. As risk factors across all ages might influence onset or persistence of disease, expanding the knowledge on vulnerable time windows beyond early infancy requires the longitudinal investigation of the course of asthma and allergies from childhood to adulthood.

2.2 Methods

2.2.1 The German ISAAC and SOLAR cohort

To investigate the course of asthma and allergies longitudinally, data from a cohort that was followed for decades during both childhood and adulthood is necessary. The German cohort of the International Study of Asthma and Allergies in Childhood (ISAAC) and the Study on Occupational Allergy Risks (SOLAR) offers the possibility for such an investigation.

ISAAC started in the early 1990s with the goal of investigating prevalence and severity of childhood asthma, rhinitis, and eczema in multiple study centers around the world as well as risk factors, trends, and differences between study centers. [9] ISAAC Phase II focused on the investigation of determinants of previously found differences between study centers by recruiting children aged 9-11 years in more than 20 countries. [10] In Germany, two study centers in Munich and Dresden participated in Phase II of ISAAC and recruited 6399 children into the study (Figure 1). In both cities, children were recruited from a random sample of schools to arrive at a community-based cohort. [11]

SOLAR is the follow-up study of the German study centers of Phase II of ISAAC. As its name implies, one of the main goals of SOLAR was the investigation of occupational risk factors for asthma and allergies. However, other potential determinants like environmental factors and psychological stress were also included. [12] In 2002-03, 3785 ISAAC Phase II participants then aged 16-18 years could be recruited for the first SOLAR follow-up (SOLAR I). After a 12-year follow-up period, 2051 young adults participated in the second follow-up (SOLAR II) in 2007-09 (Figure 1). [12]

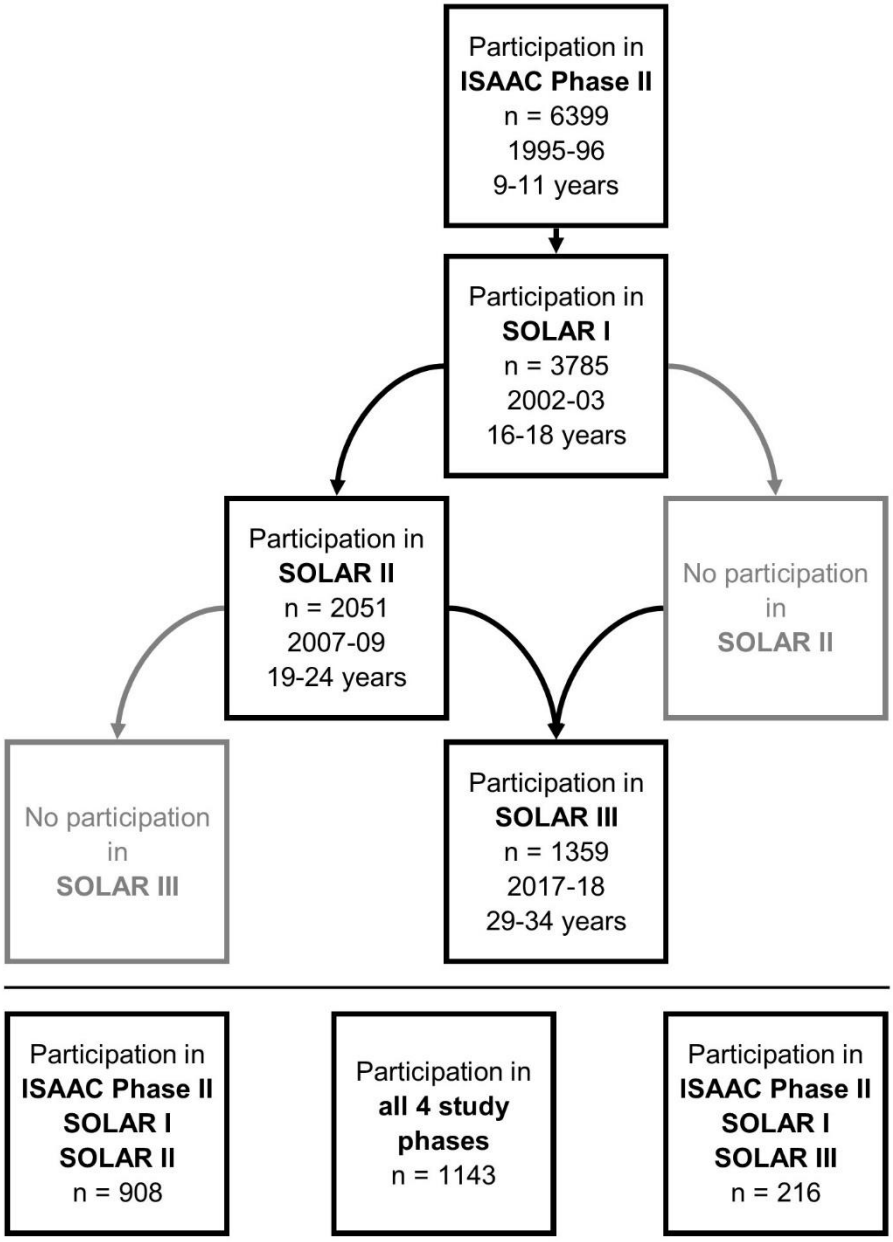

Figure 1: Flow chart of participation in the ISAAC/SOLAR study. Boxes of study phases give information on study phase name, number of participants, time period of data collection, and age of participants at data collection.

In 2017-18, a third follow-up of the ISAAC/SOLAR cohort was conducted (SOLAR III). [2] We contacted all participants of the first follow-up independently of their participation in the second follow-up. During the time of data collection, participants were between 29 and 34 years old.

Similar to the first follow-up, data was only collected via questionnaire without any examinations being conducted. This decision was made based on the assessment that accuracy is highest when maximizing response instead of reducing measurement error by conducting examinations. [2] In the end, 1359 young adults participated in the third follow-up, which includes those who skipped the second follow-up (Figure 1).

2.2.2 Conducting initial data analysis of the third follow-up

After recruitment for SOLAR III was finished, initial data analysis (IDA) was conducted. [2] IDA describes the part of a study between data collection and data analysis, i.e. the processing of raw data and a first analysis without thinking about the research question. This first analysis has the purpose of learning about the data, which can later inform analysis and interpretation. [13]

As only 21% of the initial ISAAC Phase II cohort were left after the third follow-up, potential of selection bias as well as limitations in generalizability were investigated during IDA. SOLAR III responders were compared with non-responders regarding ISAAC Phase II and SOLAR I variables. In addition, differences between missing data patterns of online and paper questionnaires were investigated.

2.2.3 Investigating symptom trajectories

Trajectories of symptoms of wheeze, rhinoconjunctivitis, and eczema across four time points from ISAAC Phase II up to SOLAR III were investigated using latent class analysis (LCA). [1] LCA postulates a categorical latent (i.e. not directly measureable) variable, which represented symptom trajectories. This latent variable is assumed to cause categorical observable indicator variables, i.e. asthma and allergy symptoms, by which the latent variable is indirectly measured. In addition, observable indicator variables are assumed to be measured with error. Based on this structure, LCA is able to summarize the table of response patterns, i.e. different combinations of all symptom variables and their occurrence, to a few latent classes while also considering missing values and measurement error. [14]

Conducting LCA includes the selection of a primary model from a set of potential candidates. Candidates were multiple-group LCA models for men and women as groups that allow for qualitative and quantitative differences between groups (i.e. without measurement invariance), multiple-group LCA models for men and women as groups that allow only for quantitative differences between groups (i.e. with measurement invariance), as well as single-group (“normal”) LCA models without considering men and women as separate groups. For all three types, models with 2 to 10 latent classes were considered. Candidate models need to be identified, which means that a maximum likelihood solution exists and has been found. [14] Sometimes, however, finding the maximum likelihood solution is difficult because different sets of starting values lead to different parameter estimates. Therefore, every model was calculated with 100 random starting values and identification was concluded if the majority of them led to the maximum likelihood solution. Multiple-group LCA models without measurement invariance as well as all models with 7 or more latent classes were not identified and therefore discarded. From among remaining candidates, the primary model was selected by considering interpretability, parsimony, as well as a statistical criterion, namely the Bayesian information criterion (BIC). Models with 4 or less latent classes were ruled out because more complex models were available and multiple-group LCA models with measurement invariance were discarded because only one latent class prevalence was considerably different. Of the remaining 5- and 6-class solutions of the single-group LCA, BIC preferred

the 5-class solution. However, because the 6-class solution offered an additional interpretable class, it was chosen as the primary model. Although multiple imputation was conducted to handle missing values, model selection was done in non-imputed data, because LCA uses all available information due to the maximum likelihood approach [15] and because pooling estimates from LCA models with varying numbers of latent classes is difficult. The primary model was, however, re-calculated using the multiply imputed data and pooled accordingly. Resulting latent classes were characterized regarding childhood traits, e.g. sensitization, and young adulthood traits, e.g. lung function. Because a considerable amount of participants dropped out before the second or third follow-up, we additionally investigated if missing values influenced how symptom trajectories looked like.

2.2.4 Investigating risk factors of symptom trajectories

To further characterize latent classes, associations with environmental determinants were investigated using logistic regression models. [1] For this, participants had to be assigned to latent classes. However, uncertainty of assignment had to be adequately considered. [14] Therefore, we randomly assigned a latent class 20 times based on the posterior probabilities of each participant, which is a list of probabilities that a certain participant is in a certain latent class. We investigated environmental determinants to which participants were only exposed during adolescence or young adulthood but not during childhood. For smoking, this meant active smoking in adolescence or young adulthood and no exposure to environmental tobacco smoke during childhood. For occupational exposures, childhood was always assumed to be unexposed time. Dog ownership, cat ownership, obesity, and exposure to mold were considered as well.

2.2.5 Investigating nickel allergy as additional dimension

Nickel allergy as a frequent type of contact allergy follows a different immunological mechanism than most allergies, e.g. against inhalant or food allergens, as it can cause a type IV hypersensitivity reaction. [16] Because of the different mechanism, it is interesting to see how the occurrence of nickel allergy relates to the longitudinal course of asthma and allergies, forming an additional dimension in its investigation. As a lot of research has been conducted on the complex relationship between contact allergies and atopic dermatitis [17], we focused on the question if nickel allergy is associated with incident wheeze, asthma, and rhinoconjunctivitis using data from the ISAAC/SOLAR cohort up to the second follow-up (SOLAR II). [3] We conducted logistic regression models with incident wheeze, asthma, and rhinoconjunctivitis as outcomes and nickel allergy as exposure variable with adjustment for potential confounders. Incidence was defined as symptoms at 19-24 years (second follow-up) while none were present at 16-18 years (first follow-up).

2.3 Results

2.3.1 Initial data analysis of the third follow-up

Selection processes during follow-up led to a study population with a higher proportion of women, never smokers, and participants with high parental as well as individual socio-economic status (SES), defined as at least 12 years of education, compared to SOLAR III non-participants from the corresponding study phase. Regarding asthma and allergies, SOLAR III participants had a

higher proportion of parental history of asthma or allergies as well as symptoms of atopic dermatitis shortly before or during the first follow-up. [2]

In general, paper questionnaires had higher proportions of missingness for questions in the first half of the questionnaire, while online questionnaires had higher proportions of missingness for questions in the second half of the questionnaire. [2] Missingness might be higher in paper questionnaires because answers or skip patterns cannot be forced. Missingness might be higher in online questionnaires, because long questionnaires might be less acceptable in an online setting or because we simply received unfinished online answers while unfinished paper questionnaires were not sent back. Because of this relation, questionnaire type is a potential variable for inclusion in the imputation model when multiply imputing missing values, as it is associated with missingness. [18] It was included in the imputation model when investigating symptom trajectories.

2.3.2 Symptom trajectories

The six derived latent classes included one asymptomatic class, three single-symptom classes, and two multiple-symptom classes (Figure 2).

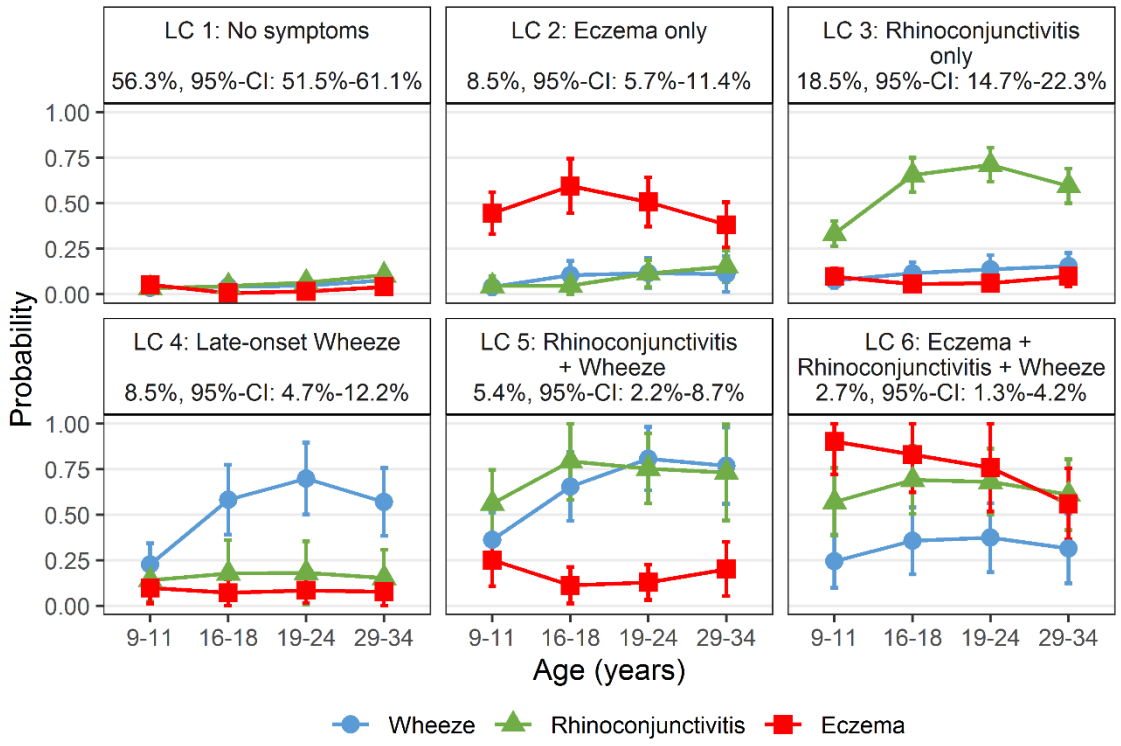

Figure 2: Symptom trajectories derived by latent class analysis as shown in Figure 2C from [1]. Graphs show symptom probability by symptom, age, and latent class (LC) with 95%-confidence intervals (CI). Point estimates of the same symptom are linked across age by lines. Below latent class name, the latent class prevalence is shown.

Several classes showed increasing symptom probabilities during adolescence and young adulthood, especially wheeze-related latent classes but also “Rhinoconjunctivitis only”. Descriptive analysis by latent class membership showed higher proportions of parental asthma and allergies

as well as sensitization in childhood for participants assigned to latent classes with multiple symptoms. When investigating if missing values influenced how symptom trajectories looked like, trajectories were found to be quite robust. [1]

2.3.3 Risk factors of symptom trajectories

Associations of environmental determinants to which participants were only exposed during adolescence or young adulthood but not during childhood with membership in symptomatic latent classes were strongest for smoking (Late-onset Wheeze: Odds Ratio (OR) 2.37, 95%- Confidence interval (CI) 1.52-3.71; Rhinoconjunctivitis + Wheeze: OR 1.95, 95%-CI 1.14-3.34). Dog ownership, mold, and occupational exposures were also associated but to a lesser extent. In general, associations were strongest for membership in wheeze-related latent classes, which also showed the strongest increase in symptom probability in adolescence and young adulthood. Although symptom probability increased in a similar fashion for latent class “Rhinoconjunctivitis only”, associations with environmental exposures only during adolescence or young adulthood were less pronounced. [1]

2.3.4 Nickel allergy as additional dimension

Our results suggested an association between self-reported nickel allergy and incident wheeze and asthma, while no association with incident rhinoconjunctivitis could be found. In men, both incident wheeze (OR 2.90, 95%-CI 1.29-6.52) and incident asthma (OR 4.34, 95%-CI 1.22-15.41) were associated with nickel allergy, while in women only incident wheeze was (incident wheeze: OR 1.57, 95%-CI 0.96-2.57; incident asthma: OR 0.93, 95%-CI 0.37-2.38). [3]

2.4 Discussion

After conducting the third follow-up of the ISAAC/SOLAR cohort in young adulthood, follow-up time reached more than two decades. This made it possible to investigate the course of asthma and allergies longitudinally, with a special focus on the development during the transition from childhood to adulthood.

The transition from childhood to adulthood was investigated by looking at symptom trajectories from 9-11 years of age up to 29-34 years. We found trajectories with a single symptom only as well as trajectories with multiple symptoms. Some trajectories showed increased symptom probabilities during adolescence and young adulthood, indicating that they still establish at this age. In addition, we found that nickel allergy might be associated with incident wheeze and asthma, especially in men. Associations of environmental determinants, to which participants were only exposed in adolescence or young adulthood, with latent classes that show increased symptom probabilities during that age further support that development of disease is still ongoing after childhood, especially for wheeze-related courses of disease.

The ISAAC/SOLAR cohort with its long follow-up time enabled us to conduct the described investigations, but the cohort’s limitations also translate to limitations in interpretation of results. Most notably, in the first study phase (ISAAC Phase II) participants were already 9-11 years old, which excluded infancy and early childhood and therefore important age ranges for the development of asthma and allergies. However, as the age of onset of wheeze was measured retrospectively in ISAAC Phase II, we could investigate which symptom trajectories early wheezers followed. Interestingly, their probabilities to be in a certain latent class were on average not too different from

the corresponding latent class prevalence in the whole cohort, which indicates that the found latent classes summarize symptom trajectories with and without symptoms in infancy or early childhood. [1]

In addition, participant selection is a potential concern in our cohort as results from the third follow-up [2] but also from earlier study phases [12] showed that, in general, there is a potential effect of asthma and allergy outcomes as well as socio-demographic variables on participation probabilities in our cohort. A potential effect of asthma and allergy outcomes on participation probabilities is the first step to selection bias. The second one would usually be that the exposure is another cause of participation ("usually" because it could be more complicated). Therefore, the potential of selection bias must be evaluated again for every new set of exposure and outcome. The reason for this is easiest to understand when using a causal graph framework, i.e. when working with directed acyclic graphs (DAG), which is a way of encoding causal assumptions in graph format and drawing conclusions based on it. [19] In general, our goal is to estimate the causal effect of the exposure on the outcome by estimating the association between exposure and outcome and accounting for other ways of how an association between these two variables can arise. One of these ways is called collider bias in the DAG framework, which means that we condition on a variable that is a common effect of exposure and outcome or variables that cause exposure or outcome. [19, 20] This often happens for participation as common effect because we can only estimate the exposure-outcome effect within the group of those who actually participate. To know that asthma and allergy outcomes are a potential cause of participation helps in specifying assumptions about the selection process, e.g. as a DAG, from which conclusions about the potential of selection bias can be drawn. Regarding nickel allergy, the difference between responders and non-responders was small [3] and therefore systematic error due to it should be limited as participation needs to be a common effect of both exposure and outcome to be of concern.

In addition, participation probabilities depending on asthma and allergy outcomes led to a study population with a higher prevalence of allergy-related outcomes compared to the general population. Therefore, although the ISAAC/SOLAR study is population-based, latent class prevalence estimates are probably not fully generalizable to the general population with, for example, a higher prevalence of the asymptomatic latent class than estimated. The population-based character of our cohort probably also had the effect that latent classes are combinations of less prevalent symptom trajectories, because a high percentage of the general population is asymptomatic. Therefore, despite the large study population, the numbers of participants with rare symptom trajectories were probably not high enough to result in their own latent classes.

The size of the study population with more than 2000 cohort members with at least three participations was only possible because participant burden was kept small by only using questionnaires in the first and third follow-up. In the second follow-up, response to questionnaires was also a lot higher than response to examinations. [12] The obvious disadvantage is that, when looking at the complete cohort, asthma and allergy outcomes need to be defined based on self-reports measured by self-administered questionnaires. For the investigation of the association between nickel allergy and incident asthma [3], this was true for both exposure and outcome. We used two definitions for the outcome of incident asthma. Firstly, asthma was defined based on presence of symptoms or intake of medication and named "incident wheeze". Secondly, the outcome "incident asthma" additionally considered a physician's diagnosis of asthma. However, both definitions were supposed to measure the same outcome. We used two versions to address measurement error which can usually be assumed to be larger for self-administered questionnaires than for

examinations. Including a physician's diagnosis of asthma was assumed to increase specificity and decrease sensitivity. [21] As asthma is relatively rare, at least compared to not having asthma, specificity is more important for reducing error [22], but a higher sensitivity should increase precision as less asthmatics are missed.

Comparing models that are based on different sets of assumptions, e.g. regarding measurement error, is a good way of learning about these assumptions. Comparing models that use different outcome definitions, which are based on different assumptions regarding sensitivity and specificity, helps in evaluating the impact of measurement error on the effect estimate of interest. If misclassification of a binary outcome can be assumed to be non-differential, i.e. not related to the exposure, and independent, i.e. not related to the measurement error of the exposure, the effect estimate can often be expected to be attenuated. [22] If incident wheeze is assumed to be measured with more non-differential and independent error than incident asthma, the attenuation of the estimated effect of nickel allergy in men for wheeze compared to asthma is expected. However, this pattern already breaks down when looking at effect estimates in women. Unfortunately, to assume that non-differential misclassification of a binary outcome leads to bias towards the null does usually not consider all relevant complexities of measurement error. First, additional assumptions need to be met, e.g. no interactions with other types of bias and exact not only approximate non-differentiality, and second, even if all assumptions are met, bias towards the null can only be expected on average, but a single study is only a single set of realizations of related probabilities. [23] Nonetheless, it is reassuring to see that both outcome definitions resulted in rather strong effect estimates in men.

The amount of misclassification regarding nickel allergy was estimated based on patch tests for nickel sulfate, which have been conducted in a small subset of the study population during the second follow-up. When compared with questionnaire responses, the positive predictive value (PPV), i.e. the probability of having a positive patch test when nickel allergy has been reported in the questionnaire, was 44%. In the literature, PPVs between 32% and 71% have been reported. [24–26] Hence, exposure mismeasurement might also influence effect estimates. Therefore, when interpreting the suggested relation between nickel allergy and asthma in the longitudinal course of asthma and allergies, one needs to be aware of potential bias due to measurement error.

2.5 Conclusion

Asthma and allergies are complex and related diseases with considerable differences between individuals and a dynamic development which even starts before birth. Therefore, applying a life course approach across allergy-related outcomes can help in identifying phenotypes beyond single outcomes and certain stages of life and, by doing so, in identifying related endotypes. We found that symptoms of different allergy-related outcomes can occur both together and on their own emphasizing the value of taking more than one disease into account. We also found that including nickel allergy can be of help as it might be associated to incident asthma in young adulthood. A dynamic disease course suggests the continued vulnerability to risk factors and protective factors beyond early infancy. By looking at the transition from childhood to adulthood we found an additional window of vulnerability in adolescence, which provides potential for prevention and health promotion in this age and shows the value of longitudinally investigating the course of asthma and allergies.

3. Paper I

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Allergy EAACI WILEY

ORIGINAL ARTICLE

Asthma and Lower Airway Disease

Trajectories of asthma and allergy symptoms from childhood to adulthood

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Abstract

Background: Phenotypes of asthma and allergic diseases are mainly studied separately for children and adults. To explore the role of adolescence and young adulthood, we investigated symptom trajectories at the transition from childhood into adulthood.

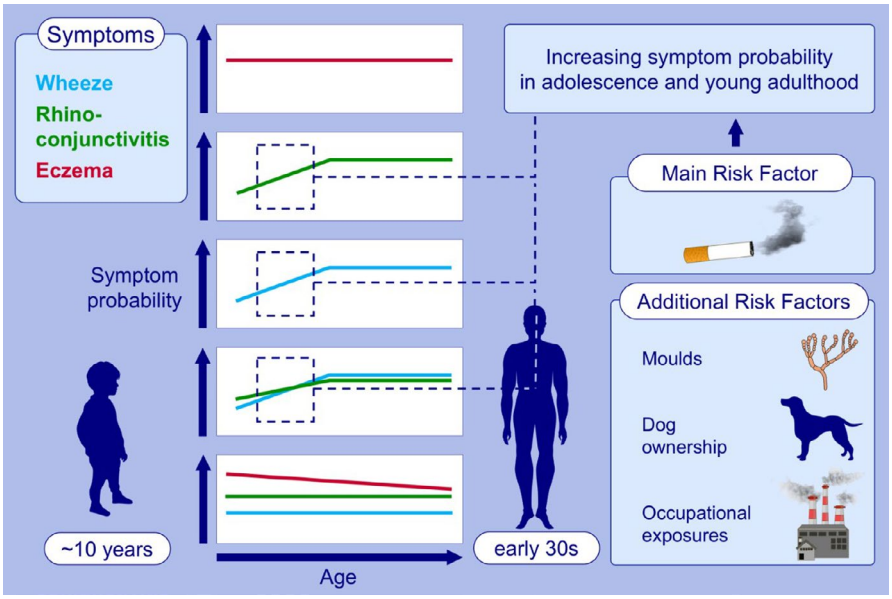
Methods: Latent class analysis (LCA) was conducted in a population initially recruited for the German arm of Phase II of the International Study of Asthma and Allergies in Childhood and followed-up three times until their early 30s (N=2267). Indicators included in LCA were 12-month prevalences of symptoms of wheeze, rhinoconjunctivitis, and eczema. Latent classes were further characterised regarding important traits such as skin prick tests. Logistic regression models were used to investigate associations with environmental determinants such as smoking and occupational exposures.

Results: Six latent classes were identified: an asymptomatic one as well as three with single and two with co-occurring symptoms. All trajectories essentially established between baseline assessment at around 10 years and the first follow-up at around 17 years. Probabilities for symptoms increased from childhood to adolescence, especially for wheeze-related latent classes, while they remained constant in adulthood. Wheeze-related latent classes were also positively associated with exposures during adolescence (e.g. active smoking).

Conclusion: Distinct trajectories of asthma and allergy symptoms establish from childhood through adolescence and stabilize during early adulthood. This pattern was most notable in wheeze-related latent classes which also showed the strongest positive associations with environmental exposures in adolescence/young adulthood. Therefore, not only childhood but also adolescence is relevant for disease development and offers considerable potential for prevention and health promotion.

KEYWORDS
asthma, eczema, latent class analysis, rhinoconjunctivitis

Abbreviations: BIC, Bayesian information criterion; bl, Baseline; fu, Follow-up; IgE, Immunoglobulin E; ISAAC, International Study of Asthma and Allergies in Childhood; LCA, Latent class analysis; SES, Socio-economic status; SOLAR, Study on Occupational Allergy Risks; SPT, Skin prick test; TAHS, Tasmanian Longitudinal Health Study.



GRAPHICAL ABSTRACT

We derived five symptomatic trajectories using latent class analysis in a cohort of German ISAAC participants followed-up until their early 30s. Some trajectories showed increasing symptom probabilities during adolescence. These trajectories showed the strongest associations with environmental exposures, especially smoking but also mould, dog ownership,and occupational exposures.
Abbreviation: ISAAC, International Study of Asthma and Allergies in Childhood

1 | INTRODUCTION

Asthma and allergic diseases like atopic dermatitis and allergic rhinitis are complex diseases influenced by environmental and genetic factors and interactions between them. [1,2] In addition, instead of being a single disease with a clearly defined development, the course and symptoms of asthma and allergic diseases can differ substantially between individuals, e.g. regarding time of onset, severity, and comorbidities. Some forms can also be induced or aggravated by environmental and occupational exposures, e.g. airborne dusts. [3]

An often discussed model of asthma and allergy occurrence, the "atopic march", postulates that atopic diseases follow a typical sequence, starting with atopic dermatitis in infancy which then determines the development of allergic asthma, allergic rhinitis, or both, in contrast to these diseases being simple comorbidities that are associated due to common causes. [4] The availability of plausible pathways, e.g. via skin barrier dysfunction, supports the atopic march model. [5,6] However, the prevalence of individual trajectories following the atopic march seems lower than anticipated with many patients not showing the expected sequence of symptoms. [7,8]

Individual atopic diseases are often classified by the underlying pathomechanism (endotype) [9] or by their visible course and clinical features (phenotype). Most studies investigating phenotypes of asthma and allergies focused on certain age ranges investigating for example childhood wheeze [10-15], childhood asthma [16-18], childhood atopic dermatitis [19-23], adulthood asthma [18,24-28], and adulthood rhinitis [29-31]. Although these studies are helpful to disentangle subgroups of patients within the investigated stage of life, they disregard an important phase of human development, namely the transition from childhood to adulthood. [32]

The objective of this analysis was to close this gap and to explore the role of adolescence and young adulthood by investigating trajectories of wheeze, rhinoconjunctivitis, and eczema symptoms from school age into adulthood by latent class analysis (LCA) and to characterize the traits and environmental determinants associated with the resulting latent classes. The Study on Occupational Allergy Risks (SOLAR) offered the unique opportunity to follow-up the German participants of Phase II of the International Study of Asthma and Allergies in Childhood (ISAAC) in three waves at ages 16–18, 19–24, and 29–34 years.

2 | METHODS

2.1 | Study design

The SOLAR cohort was initially recruited in 1995–1996 for ISAAC Phase II, when participants were 9–11 years old. [33] Individuals recruited by the German study centres in Munich and Dresden were followed-up three times in 2002–03 (SOLAR I, age: 16–18 years), 2007–09 (SOLAR II, age: 19–24 years), and 2017–18 (SOLAR III, age: 29–34 years). [34,35] We included 2267 young adults who participated in at least 3 of 4 study phases (Figure 1). In each study phase, individuals answered a questionnaire on asthma and allergies as well as on environmental and occupational risk factors. The baseline questionnaires were answered by the participants' parents while the follow-up questionnaires were answered by the participants themselves. In ISAAC Phase II and SOLAR II, clinical examinations were additionally conducted including e.g. spirometry, skin prick test (SPT), and

the collection of blood samples. All study phases were approved by the Ethical Committees of the Medical Faculty of the University of Dresden and the Bavarian Chamber of Physicians. Written informed consent, also for linking data across study phases, was obtained from all participants (SOLAR I to III) and their legal guardians (ISAAC Phase II, SOLAR I).

2.2 | Indicators

Three symptoms were included as LCA indicator variables (yes/no) measured at baseline (bl: ISAAC Phase II) and follow-up (fu: SOLAR) 1 to 3: wheeze (within the 12 months prior to the survey), rhino-conjunctivitis (having problems with sneezing or a runny or blocked nose without having a cold during the 12 months prior to the survey that were accompanied by itchy-watery eyes), and eczema (ever having had eczema for at least 6 months with symptoms during the 12 months prior to the survey which affected any of the following places at any time: the folds of the elbows, behind the knees, in front of the ankles, or around the neck, ears or eyes).

2.3 | Traits and environmental determinants

We characterised latent classes regarding:

childhood traits: sex (male vs. female), parental socio-economic status (SES; high vs. low; high: 12 or more years of school by at least one parent), parental asthma, hay fever, as well as atopic dermatitis (yes vs. no; yes: at least on parent), SPT to seasonal and perennial allergens (positive vs. negative) [36], and immunoglobulin E (IgE) against inhalant and food allergens (positive vs. negative; positive: >0.35 U/ml) [36];

young adulthood traits: bronchial hyperresponsiveness (yes vs. no) [34], lung function (forced expiratory volume in 1 second FEV1/ forced vital capacity FVC) [34], and exhaled nitric oxide [34];

as well as environmental determinants: active/passive smoking, mould, dog/cat ownership, obesity, and occupational exposures (see Table S1 for detailed variable descriptions).

A job-exposure-matrix [37] was used to estimate exposure to 30 different occupational agents in 2 groups (allergic and irritative exposures). Presence of occupational exposures up to 19–24 years of age (up to fu2) was used for both groups. Since information on environmental determinants was available in several study phases, they were investigated in a longitudinal way. For mould, dog and cat ownership, combinations of exposure in childhood (first year of life or first year of school or bl) and in adolescence/young adulthood (fu1 or fu2) were considered. The same approach was used for smoking and obesity. For smoking, childhood exposure was defined as environmental tobacco smoke in the first year of life or the first year of school or at baseline, while adolescence/young adulthood exposure was defined as active smoking in follow-up 1 or follow-up 2. Obesity was defined as body mass index >30kg/m^2 for participants of age 18 or older and according to cut-offs by the International Obesity Task Force for those below 18 years. [38] Childhood exposure was defined as obesity at baseline while adolescence/young adulthood exposure was defined as obesity at follow-up 1 or follow-up 2.

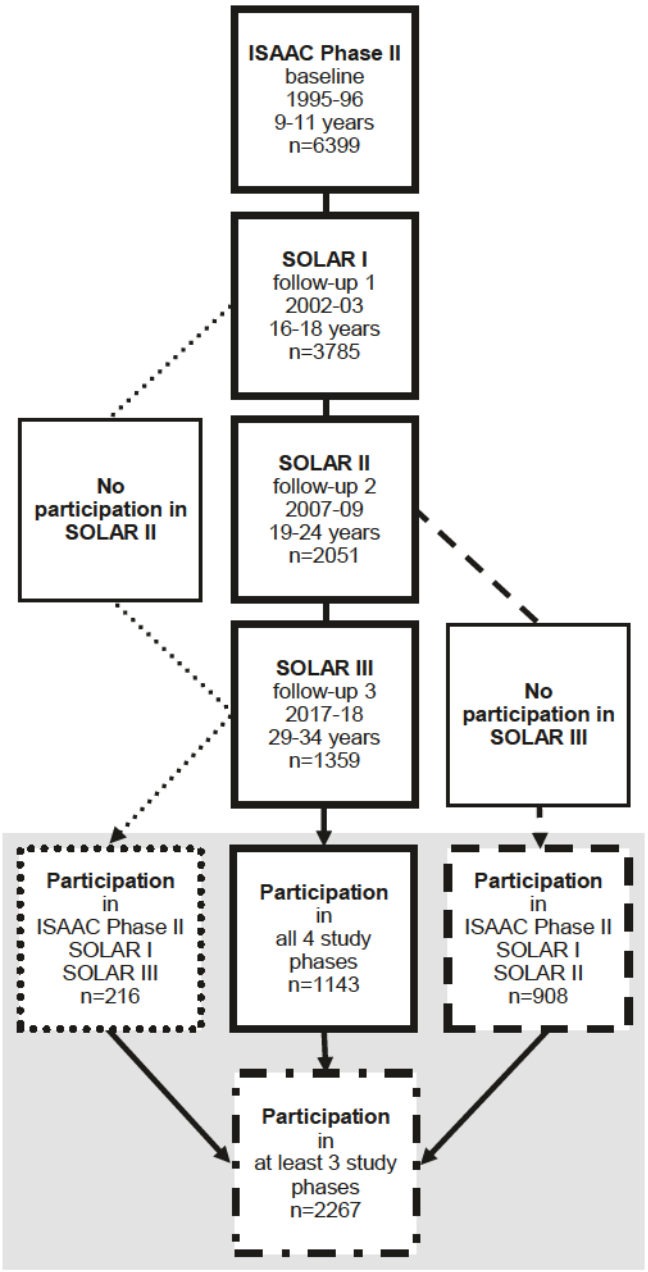


FIGURE 1 Flow chart of participation of included participants. Boxes of study phases give information on study phase name, label in presented analysis, time period of data collection, age of participants at data collection, number of participants; grey box: participants included in presented analysis

2.4 | Statistical analysis

Latent class analysis (LCA) is an unsupervised statistical method that identifies a set of latent classes based on response patterns of

categorical indicator variables while considering the influence of error on the observed data. The latent (i.e. not directly measureable) classes correspond to underlying categorical differences, e.g. different disease trajectories. Since LCA is basically a hypothesis-free method, it is useful in deriving disease phenotypes [39], and was used to analyse the course of asthma and allergy symptoms.

First, model selection was conducted based on interpretability, parsimony and the Bayesian information criterion (BIC). The number of latent classes had to be selected and we had to decide whether to use multiple-group LCA [39] with males and females as separate groups. Since only one latent class prevalence varied considerably between men and women, multiple-group models were ruled out because of parsimony. The BIC was lowest for the 5-class solution (Table S2). However, the 6-class solution offered an additional interpretable latent class that would have been lost when strictly following the statistical criterion. Therefore, the 6-class solution was selected. Second, the selected latent class model was recalculated in 20 imputed datasets and pooled afterwards, based on Rubin's rules. [40] Multiple imputation was used for handling missing values, with the exception of model selection which was done using Full Information Maximum Likelihood (FIML) methods [41] because pooling models with different numbers of latent classes is not straightforward.

In addition, latent classes were characterised regarding important traits in childhood and young adulthood and logistic regression models were calculated to investigate associations of environmental determinants with membership in symptomatic latent classes. For this, participants had to be assigned to individual latent classes. Twenty random values were drawn from the individual distribution of posterior probability of latent class membership in each of the 20 imputed datasets to avoid assigning individuals to one latent class only, which does not take uncertainty of classification into account. The random draws resulted in categorical variables (latent class indicator variables) that indicated membership in one of the latent classes for each participant. Relative frequencies or means and standard deviations were calculated for important traits grouped by these latent class indicator variables. The averaged value over all random draws as well as 5- and 95-percentiles were reported. The latent class indicator variables were also used as outcome variables in logistic regression models, comparing classes separately with a reference class. Regression coefficients and their standard errors were pooled within each imputed dataset (across the 20 assignments to an individual latent class) using Rubin's rules with the assumption of a between-imputation variance of 0, since there was no additional variance due to missing data. [42] Afterwards, pooled estimates of the 20 imputed datasets were pooled to a single value as usual. Environmental determinants were investigated in separate logistic regression models adjusted for sex, participant's SES, parental SES, and study centre.

In sensitivity analyses, we used data on age when symptoms of wheeze appeared for the first time and checked if participants with transient wheeze, which most phenotype studies of childhood wheeze found [7,10,11,13-15], were part of the asymptomatic latent class. In addition, LCA was repeated only with participants that filled in all 4 questionnaires, without considering baseline, and without the last two study phases.

LCA was conducted using PROC LCA [41] in SAS (Version 9.4, SAS Institute, Inc., Cary, NC). Remaining calculations were done in R (Version 4.0.2) [43] including multiple imputation (using the package MICE [44]). Additional details of the application of LCA are provided as supporting information.

3 | RESULTS

3.1 | Study population

In total, data from at least three study phases was available for 2267 participants (Figure 1). More participants were female (57.2%) and had high SES (56.3%). Within the four study phases, the proportion of participants reporting symptoms was between 8.1%-16.9% for wheeze, 14.3%-24.9% for rhinoconjunctivitis, and 9.2%-13.2% for eczema (Figure 2B). The amount of missing values depended on participation at individual study phases. For variables in follow-up 2, 216 values were missing due to non-participation while 908 were missing for variables from follow-up 3. Descriptive statistics showed sex differences for several indicator variables, especially a higher proportion of wheeze in males at baseline and more eczema throughout the study in females, as well as for traits and environmental determinants, e.g. higher proportion of positive SPT results in males (Tables 1-2).

3.2 | Latent classes

Figure 2C and Table S3 show the results of the LCA using 6 latent classes. The largest latent class 1 described participants without any symptoms from age 9–11 to age 29–34 years ("No symptoms"). Latent class 2 included participants with symptoms of eczema only, which culminated at age 16–18 years ("Eczema only"). Latent class 3 comprised participants with rhinoconjunctivitis ("Rhinoconjunctivitis only"), whose symptom probability increased substantially from childhood to adolescence and persisted at high levels throughout adulthood. Latent class 4 described participants with onset of wheeze mainly in adolescence ("Late-onset Wheeze"). Latent class 5 represented participants with symptoms of wheeze and rhinoconjunctivitis throughout the study, but with increasing probabilities in adolescence ("Rhinoconjunctivitis + Wheeze"). Latent class 6 included participants with symptoms of rhinoconjunctivitis throughout the study, partially with concomitant wheeze, and symptoms of eczema declining from a very high probability to the level of rhinoconjunctivitis ("Eczema + Rhinoconjunctivitis + Wheeze"). The comparison with the overall study population (Figure 2A & 2B) shows the value of LCA when investigating distinct trajectories. The 6-class solution offered a distinction between latent classes "Late-onset

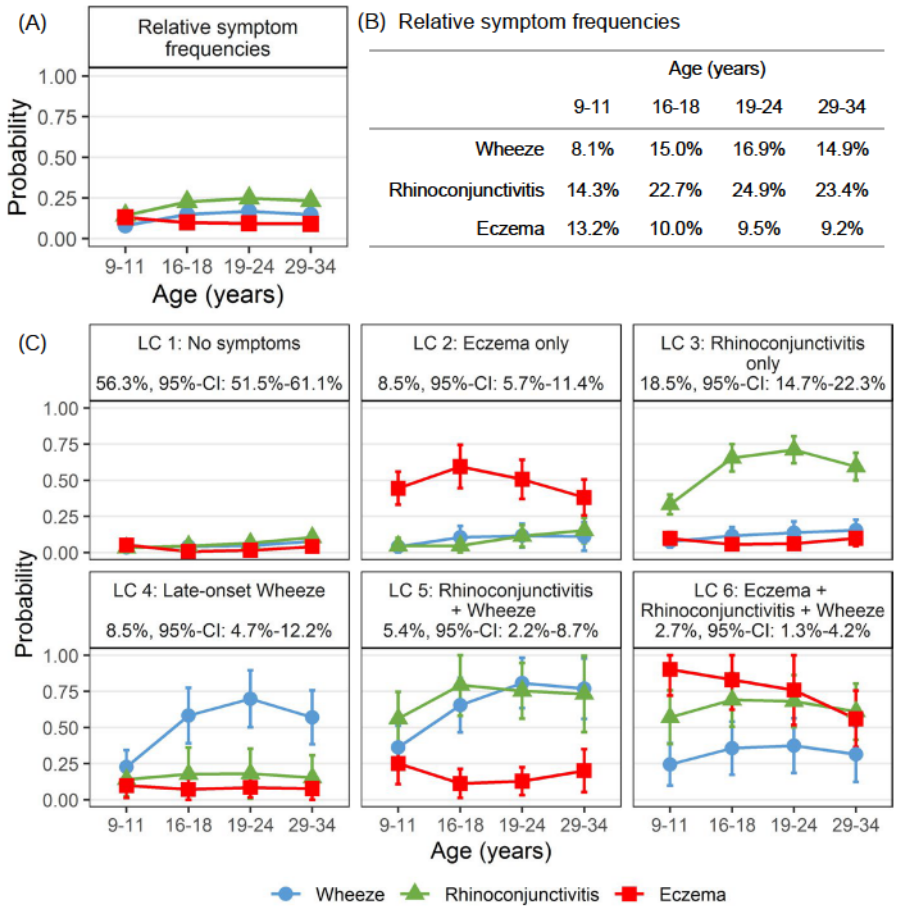


FIGURE 2 Observed relative symptom frequencies in study population (A, B) and probability of symptoms over time by latent class (C). Parts A and B describe the observed relative frequencies of symptoms of wheeze, rhinoconjunctivitis, and eczema in the study population as plot (A) and in a table (B). Part C shows latent classes (LC) which correspond to symptom trajectories. Each subplot of C shows symptom probabilities for one derived latent class with 95%-confidence intervals (CI) over time for symptoms of wheeze, rhinoconjunctivitis, and eczema, indicated by colour and symbol shape. Lines link point estimates of the same symptom. Latent class prevalences with 95%-confidence intervals are shown below latent class names. Part C plots the pooled values from 20 imputed datasets which are displayed in table S3

Wheeze" and "Rhinoconjunctivitis + Wheeze", while a sensitivity analysis using the 5-class solution combined these in one class with medium probabilities of wheeze at baseline and rhinoconjunctivitis in all study phases (Figure S1).

3.3 | Childhood and young adulthood traits

Looking at the trajectories' traits in childhood showed substantial differences (Table 3). In latent classes with co-occurring symptoms, parental history of asthma, hay fever, and atopic dermatitis were more prevalent compared to other latent classes (e.g. 18.0–25.1% vs. 7.8–13.3% for parental asthma). In addition, children following these trajectories were more often sensitized against any group of allergens (as measured by a positive SPT for seasonal or perennial allergens and specific IgE higher than 0.35 U/ml directed against inhalant or food allergens; e.g. 38.7–42.6% vs. 7.6–22.5% for positive SPT for perennial allergens). In contrast, children in latent class "Rhinoconjunctivitis only" were more likely to be sensitized against seasonal allergens only (e.g. 37.4% for positive SPT for seasonal allergens). With respect to sex differences, the proportion of women were highest in trajectories involving symptoms of eczema (67.2% & 60.6%). In contrast to all other latent classes, participants in "Late-onset Wheeze" often had low parental SES (54.1%). Traits in young adulthood differed as well, with bronchial hyperresponsiveness and lung function being worse for trajectories involving symptoms of wheeze. Exhaled nitric oxide values were highest in latent classes with co-occurring symptoms, further underlining their atopic character.

3.4 | Environmental determinants

Looking at environmental determinants, strongest associations with exposures, that were present only in adolescence/young adulthood but not in childhood were seen for latent classes with later starting points ("Late-onset Wheeze" and "Rhinoconjunctivitis + Wheeze"; Figure 3; see Table S4 for numerical values of effect estimates). For these latent classes, strongest associations were seen for active smoking ("Late-onset Wheeze" OR 2.37, 95% CI 1.52–3.71; "Rhinoconjunctivitis + Wheeze" OR 1.95, 95% CI 1.14–3.34), but also for exposure to mould, dog ownership, and occupational exposures. All associations were found after adjustment for potential confounders, including participant's SES and parental SES. Smoking and mould were also associated with membership in "Eczema only". Smoking was additionally related to "Rhinoconjunctivitis only", and irritative occupational exposures were associated with "Eczema + Rhinoconjunctivitis + Wheeze". Models regarding obesity were additionally adjusted for breastfeeding (yes vs. no) and "being born at least 3 weeks before the calculated date" (yes vs. no) in a separate analysis but effect estimates were almost identical (data not shown).

TABLE 1 Distribution of indicator variables and traits for male and female study population and amount of missing values per variable, non-imputed data

Variable	Missing values n (%†)	Males N=970 n (%‡)	Females N=1297 n (%‡)
Wheeze (bl)	35 (1.5)	105 (11.0)	76 (5.9)
Wheeze (fu1)	7 (0.3)	129 (13.3)	209 (16.2)
Wheeze (fu2)§	216 (9.5)	139 (16.1)	208 (17.5)
Wheeze (fu3)¶	909 (40.1)	85 (15.9)	118 (14.4)
Rhinoconjunctivitis (bl)	37 (1.6)	156 (16.4)	162 (12.7)
Rhinoconjunctivitis (fu1)	24 (1.1)	214 (22.3)	296 (23.0)
Rhinoconjunctivitis (fu2)§	241 (10.6)	214 (25.2)	290 (24.6)
Rhinoconjunctivitis (fu3)¶	918 (40.5)	141 (26.5)	174 (21.3)
Eczema (bl)	23 (1.0)	112 (11.6)	184 (14.4)
Eczema (fu1)	26 (1.1)	73 (7.7)	152 (11.8)
Eczema (fu2)§	231 (10.2)	64 (7.5)	129 (10.9)
Eczema (fu3)¶	913 (40.3)	48 (9.0)	76 (9.3)
Study centre (Munich)	0 (0.0)	473 (48.8)	624 (48.1)
Study centre (Dresden)		497 (51.2)	673 (51.9)
Parental SES (high)	39 (1.7)	563 (58.8)	732 (57.6)
SES (high)	14 (0.6)	515 (53.3)	753 (58.6)
Parental asthma	197 (8.7)	95 (10.6)	114 (9.7)
Parental hay fever	25 (1.1)	335 (34.9)	424 (33.1)
Parental dermatitis	28 (1.2)	171 (17.8)	208 (16.2)
SPT (seasonal allergens, bl)	325 (14.3)	193 (23.0)	148 (13.4)
SPT (perennial allergens, bl)	325 (14.3)	167 (19.9)	107 (9.7)
IgE (inhalant allergens, bl)	613 (27.0)	327 (45.7)	310 (33.0)
IgE (food allergens, bl)	1620 (71.5)	79 (24.6)	81 (24.8)
BHR (fu2)§	1842 (81.3)	28 (15.8)	48 (19.4)
	n (%)	mean (SD)	mean (SD)
FEV_1/FVC (fu2)§	1144 (50.5)	0.843 (0.075)	0.871 (0.068)
FeNO (in ppb, fu2)§	1200 (52.9)	27.0 (24.1)	19.3 (18.9)

Abbreviations: BHR, bronchial hyperresponsiveness; bl, baseline; FeNO, exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; fu, follow-up; FVC, forced vital capacity; IgE, immunoglobulin E; SES, social-economic status; SPT, skin prick test.

†of all 2267 included participants;

‡of all non-missing values;

§216 missing values due to non-participation, additional 884 missing values due to non-participation in clinical examination;

¶908 missing values due to non-participation.

3.5 | Sensitivity analyses

Among 351 participants with first wheeze symptoms before the age of 4, the mean posterior probability of being in latent class "No symptoms" was only slightly lower than the estimated latent class prevalence, which indicates that at least some participants with transient wheeze and probably other transient symptoms in early childhood were part of latent class "No symptoms" (Table S5).

When repeating LCA with a subset of participants or a subset of time points, the overall patterns remained the same, although some item-response probabilities and latent class prevalences differed (Figures S2-S4). Most notably, when only considering childhood and adolescence, probabilities for wheeze in "Rhinoconjunctivitis + Wheeze" were similar at both time points. The increasing probability that could be seen when considering all four time points was only present for "Late-onset Wheeze" which also showed an increasing probability for rhinoconjunctivitis and a higher latent class prevalence, indicating that participants with increasing probability of wheeze were summarized in one latent class independent of the presence of rhinoconjunctivitis.

TABLE 2 Distribution of environmental determinants for male and female study population and amount of missing values per variable, non-imputed data

Variable	Missing values n (%†)	Males N=970 n (%‡)	Females N=1297 n (%‡)
Smoking (never)	180 (7.9)	342 (38.6)	433 (36.1)
Smoking (only CH)		125 (14.1)	185 (15.4)
Smoking (only A/yAH)		234 (26.4)	297 (24.7)
Smoking (CH & A/yAH)		185 (20.9)	286 (23.8)
Mould (never)	495 (21.8)	245 (32.9)	333 (32.4)
Mould (only CH)		69 (9.3)	78 (7.6)
Mould (only A/yAH)		264 (35.5)	386 (37.5)
Mould (CH & A/yAH)		166 (22.3)	231 (22.5)
Dog ownership (never)	1183 (52.2)	270 (64.6)	419 (62.9)
Dog ownership (only CH)		26 (6.2)	26 (3.9)
Dog ownership (only A/yAH)		65 (15.6)	110 (16.5)
Dog ownership (CH & A/yAH)		57 (13.6)	111 (16.7)
Cat ownership (never)	1185 (52.3)	201 (48.2)	318 (47.8)
Cat ownership (only CH)		35 (8.4)	44 (6.6)
Cat ownership (only A/yAH)		73 (17.5)	130 (19.5)
Cat ownership (CH & A/yAH)		108 (25.9)	173 (26.0)
Obesity (never)	1278 (56.4)	383 (92.7)	546 (94.8)
Obesity (only CH)		8 (1.9)	6 (1.0)
Obesity (only A/yAH)		13 (3.1)	17 (3.0)
Obesity (CH & A/yAH)		9 (2.2)	7 (1.2)
Allergic occupational exposures	460 (20.3)	303 (40.2)	289 (27.4)
Irritative occupational exposures	460 (20.3)	504 (66.9)	598 (56.7)

Abbreviations: A/yAH, adolescence/young adulthood; CH, childhood.
†of all 2267 included participants;
‡of all non-missing values.

4 | DISCUSSION

The presented latent class model revealed different trajectories of symptoms of wheeze, rhinoconjunctivitis, and eczema from school age to adulthood. In total, six classes were identified by the model, including three with single and two with co-occurring symptoms (combining symptoms in upper and lower airways, and combining all three symptoms). Interestingly, the first two study phases in childhood and adolescence were most relevant for the determination of the trajectories into adulthood, with increasing symptom probabilities especially in latent classes "Late-onset Wheeze", "Rhinoconjunctivitis + Wheeze", and "Rhinoconjunctivitis only". This indicates that in addition to childhood, adolescence is a critical phase for development of atopic respiratory diseases by providing another time window of vulnerability before the trajectories stabilize in young adulthood. The associations with exposures to environmental determinants only in adolescence/young adulthood, especially active smoking but to a certain extent also mould, dog ownership, and occupational exposures, support that disease development is still ongoing. Associations with environmental determinants were strongest in latent classes "Late-onset Wheeze" and "Rhinoconjunctivitis + Wheeze" which are the two trajectories with the strongest increase of symptom probability in adolescence/young adulthood. While "Rhinoconjunctivitis only" also showed increased symptom probability in adolescence/young adulthood, associations with environmental determinants were limited which indicates that this trajectory is determined mainly via other factors like family history, similar to "Eczema only" and "Eczema +Rhinoconjunctivitis + Wheeze". Adolescence, therefore, might offer an opportunity for prevention and health promotion, especially for diseases that include symptoms of wheeze. In addition, a stronger cooperation between paediatricians and subsequent physicians seems to be warranted, especially since it was shown that the transition to adult health care for asthmatics is not a smooth one. [45]

4.1 | Consistency with similar studies

Regarding similar studies, Bui et al. recently analysed data from the Tasmanian Longitudinal Health Study (TAHS) collected at ages 7, 13, 45, and 53 years using LCA and found five asthma and allergy trajectories: late-onset hay fever, no asthma; early-onset remitted asthma

TABLE 3 Traits of derived latent classes in childhood (baseline) and young adulthood (follow-up 2)

	Latent class					
	1	2	3	4	5	6
	No symptoms	Eczema only	Rhinoconjunctivitis only	Late-onset Wheeze	Rhino-conjunctivitis + Wheeze	Eczema + Rhino-conjunctivitis + Wheeze
Childhood traits	%†	%†	%†	%†	%†	%†
Sex (female)	56.6 (55.8–57.4)	67.2 (63.4–71.2)	54.4 (52.4–56.7)	57.6 (53.5–61.6)	55.0 (50.0–60.0)	60.6 (53.1–67.4)
Parental SES (high)	58.7 (57.9–59.7)	63.2 (59.6–66.7)	59.4 (57.1–61.7)	45.9 (41.1–50.8)	55.7 (51.0–60.7)	60.7 (54.2–66.7)
Parental asthma	7.8 (7.2–8.4)	9.3 (6.9–11.8)	11.3 (10.0–12.6)	13.3 (10.6–16.5)	25.1 (21.0–32.1)	18.0 (13.1–22.9)
Parental hay fever	29.0 (28.2–29.8)	33.9 (30.5–37.4)	40.4 (37.9–42.8)	32.6 (27.7–36.6)	51.0 (45.5–57.5)	61.9 (54.8–68.6)
Parental atopic dermatitis	13.7 (13.0–14.3)	23.3 (20.3–26.2)	16.4 (14.6–18.3)	19.7 (15.9–23.8)	28.1 (23.1–33.7)	37.3 (31.9–43.1)
SPT (seasonal allergens)	7.2 (6.5–7.9)	12.2 (9.6–15.3)	37.4 (34.9–40.1)	20.4 (14.7–25.7)	52.6 (44.8–62.0)	55.6 (48.2–63.0)
SPT (perennial allergens)	7.6 (7.1–8.2)	12.0 (9.6–14.5)	21.0 (18.7–23.5)	22.5 (16.1–27.6)	42.6 (37.2–49.0)	38.7 (32.9–45.1)
IgE (inhalant allergens)	25.5 (24.3–26.8)	31.4 (28.0–35.1)	60.0 (56.4–63.3)	44.5 (36.5–51.1)	76.2 (70.2–83.9)	77.7 (70.9–84.9)
IgE (food allergens)	20.0 (16.8–23.5)	21.2 (15.7–27.1)	27.1 (23.8–30.8)	24.9 (18.0–32.1)	33.6 (27.5–40.4)	35.9 (28.6–48.1)
Young adulthood traits						
	%†	%†	%†	%†	%†	%†
BHR	22.0 (19.4–25.1)	26.4 (19.2–35.3)	30.8 (26.9–35.9)	41.3 (31.6–48.2)	49.8 (39.2–58.9)	41.1 (29.2–54.1)
	Mean† SD†	Mean† SD†	Mean† SD†	Mean† SD†	Mean† SD†	Mean† SD†
FEV_1/FVC (in %)	86.1 (85.8–86.3) 7.1 (7.0–7.4)	86.1 (85.3–86.8) 7.0 (6.3–7.6)	86.2 (85.7–86.7) 7.1 (6.8–7.5)	83.9 (83.2–84.7) 8.5 (7.9–9.1)	83.2 (82.2–84.3) 8.5 (7.7–9.4)	84.6 (83.1–85.8) 7.6 (6.8–8.7)
FeNO (in ppb)	18.9 (18.3–19.7) 16.3 (14.9–18.0)	20.3 (18.4–22.4) 18.7 (14.5–23.2)	26.3 (24.2–28.4) 23.7 (20.9–27.4)	25.9 (22.8–29.0) 26.1 (21.5–31.7)	35.5 (30.6–40.0) 33.5 (25.6–41.9)	34.3 (29.9–40.1) 37.5 (32.5–47.4)

Abbreviations: BHR, bronchial hyperresponsiveness; FeNO, exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IgE, immunoglobulin E; SES, social-economic status; SPT, skin prick test.

†averaged over 20 draws from each of the 20 imputed datasets with 5th and 95th percentiles in parentheses.

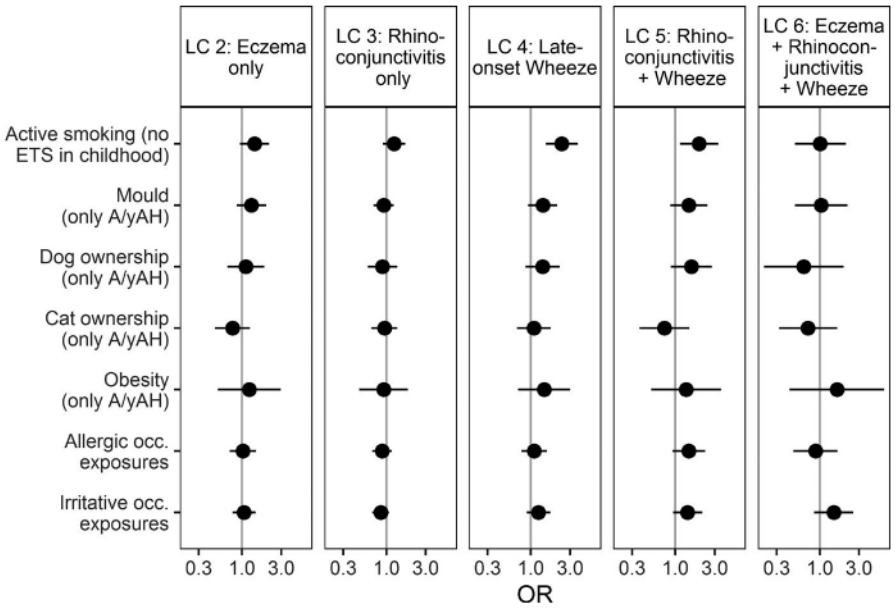


FIGURE 3 Associations of latent class membership with environmental determinants by latent class compared to reference class "No symptoms", only categories without exposure in childhood and with exposure in adolescence/young adulthood compared to no exposure in childhood and adolescence/young adulthood, multivariate logistic regression adjusted for sex, participant's socio-economic status, parental socio-economic status, and study centre. Abbreviations: LC, latent class; OR, Odds Ratio; ETS, environmental tobacco smoke; A/yAH, adolescence/young adulthood; occ, occupational

and allergies; late-onset asthma and allergies; early-onset persistent asthma and allergies; as well as an asymptomatic latent class. [46] The TAHS trajectories show similarities and differences compared to our study (SOLAR). In TAHS, asthma and allergies occurred in parallel in three latent classes with remitting, persisting, and late-onset symptoms. In SOLAR, no trajectory with remitting symptoms was found even though the age of participants at baseline was not too different. Persistent as well as late-onset asthma and allergies seemed to be combined in "Rhinoconjunctivitis + Wheeze" in SOLAR, while additional classes described participants with late-onset wheeze but without other symptoms and participants with a certain probability for all three considered symptoms. The SOLAR trajectory "Rhinoconjunctivitis only" seemed to be similar to the TAHS trajectory "late-onset hay fever, no asthma". Relative frequencies of parental asthma were very similar for comparable latent classes from both studies. TAHS trajectory "Late-onset asthma and allergies" was not associated with active smoking at 53 years of age. However, it was associated with obesity at age 53 years while in SOLAR estimates for obesity unfortunately had wide confidence intervals.

In the Swedish BAMSE cohort, Ödling et al. investigated the course of asthma between 1 and 24 years of age and found four trajectories using LCA: never/infrequent asthma; early-onset transient asthma; adolescent-onset asthma; and persistent asthma. [47] When focusing on the age range 8–24 years, the BAMSE trajectories are comparable to the wheeze trajectories found in SOLAR. Symptomatic BAMSE trajectories showed increased proportions of family history of allergic disease similarly to SOLAR. In addition, sensitization to inhalant and food allergens around the age of 8 years was not too different in comparable BAMSE and SOLAR classes. The most important exception was that SOLAR trajectory "Late-onset Wheeze" had a lower relative frequency of sensitizations and seemed to contain more non-allergic wheezers compared to its BAMSE and TAHS late-onset counterparts.

In accordance with Belgrave at al. who investigated developmental profiles of wheeze, rhinitis, and eczema in children from age 1 to 11 years [7], we found mainly trajectories that did not resemble a continuation of the atopic march into adulthood. The developmental profile "atopic march" found by Belgrave et al. was characterized by high probabilities for all three symptoms at age 8–11 years. In our model, the continuation of this profile was best reflected by latent class "Eczema + Rhinoconjunctivitis + Wheeze", although probabilities of wheeze were lower. This latent class might, however, additionally contain other phenotypes. The prevalence of trajectories being consistent with or continuing the atopic march was similarly low in both studies, which supports the hypothesis that most courses of asthma and allergies do not follow the expected sequence of symptoms.

4.2 | Strengths and limitations

Because of a large sample size, we were able to derive six trajectories of wheeze, rhinoconjunctivitis and eczema symptoms. Unfortunately, symptoms in early childhood could not be included in the study and phenotypes with symptoms before the age of 9 years might be mixed in among other phenotypes within the derived latent classes. The sensitivity analysis showed that participants with transient wheeze in early childhood were mixed in among all latent classes, including the class without symptoms after the age of 9–11 years. This needs to be kept in mind when using "No symptoms" as reference class. Other latent classes might also contain participants with and without early-life symptoms. In general, a single latent class might contain several phenotypes of asthma and allergic diseases. Since the data came from a population-based cohort, low-prevalent phenotypes might have been combined to one latent class by the maximum likelihood estimation procedure. For "Rhinoconjunctivitis only", the increased symptom probability in follow-ups might e.g. indicate a mixture of earlier-onset and later-onset phenotypes. In addition, because first measurements were made at baseline when participants were 9–11 years old,

environmental exposures during the first year of life and the first year of school were measured retrospectively. As for some children symptoms already appeared before baseline age, differential recall by the parents was possible.

Although the number of participants included in the analysis was quite high, several variables had high proportions of missing values mainly due to non-participation in later study phases and clinical examinations. Non-responder analyses showed that continued participation in SOLAR follow-ups was related to being female, high SES and parental SES, being a non-smoker, and a higher proportion of symptoms as well as parental history of asthma and allergies. [34,35] Handling missing values in the analysis, which was done by multiple imputation, was of high importance. Since pooling estimates from models with different numbers of latent classes is difficult, model selection was done before multiple imputation. However, with full information maximum likelihood methods all available information was used in this step. When looking at the BIC of the 5- and 6-class solutions within the 20 imputed datasets, BIC of the 6-class solution was lowest in six imputations; the 5-class solution was preferred in 14 imputations. In a sensitivity analysis, we investigated the possibility that the first two study phases were more important for the resulting latent classes because of high proportions of missing values in the last two study phases. However, the overall patterns were similar and agreement regarding latent class membership of individual participants with the main LCA was between 84.2–88.4%, 85.4–89.9%, and 67.8–72.4% within the 20 imputed datasets for restricting participants to a subset that filled in all 4 questionnaires, restricting study phases to follow-up only, and restricting study phases to childhood/adolescence only, respectively. Interestingly, when only considering childhood and adolescence, latent classes "Late-onset Wheeze" and "Rhinoconjunctivitis + Wheeze" changed towards one latent class with increasing and one with constant symptom probabilities, which resembles the late-onset/persistent distinction found in TAHS and BAMSE.

In conclusion, this study provides a classification of the course of asthma and allergy symptoms from age 9 to 34 years and, therefore, for the transition from childhood into adulthood. Distinct symptom trajectories establish from childhood through adolescence and stabilize during early adulthood. This pattern was most notable in wheeze-related latent classes which also showed the strongest associations with environmental exposures in adolescence/young adulthood. Therefore, not only childhood but also adolescence is relevant for disease development and offers considerable potential for prevention and health promotion.

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CONFLICTS OF INTEREST

MJE reports a patent EP 1 964 570 B1 issued, and a patent EP 2 361 632 B1 issued. EvM reports personal fees from Pharmaventures, from European Respiratory Society, from Deutsche Pharmazeutische Gesellschaft e.V., from Elsevier GmbH and Elsevier Ltd., from OM Pharma S.A., from Springer-Verlag GmbH, from The Chinese University of Hongkong, from Universität Salzburg, from Japanese Society of Pediatric Allergy and Clinical Immunology (JSPACI), from Universiteit Utrecht, Faculteit Diergeneeskunde, from Georg Thieme Verlag, from Böhringer Ingelheim International GmbH, from Tampereen Yliopisto, from European Commission, from Helsingin Yliopisto, from Peptinnovate Ltd., from Turun Yliopisto, from Massachusetts Medical Society, outside the submitted work; In addition, EvM has a patent LU101064 - Barn dust extract for the prevention and treatment of diseases pending, a patent EP2361632: Specific environmental bacteria for the protection from and/or the treatment of allergic, chronic inflammatory and/or autoimmune disorders with royalties paid to ProtectImmun GmbH, a patent EP 1411977: Composition containing bacterial antigens used for the prophylaxis and the treatment of allergic diseases licensed to ProtectImmnun GmbH, a patent number EP1637147: Stable dust extract for allergy protection licensed to ProtectImmun GmbH, and a patent EP 1964570: Pharmaceutical compound to protect against allergies and inflammatory diseases licensed to ProtectImmun GmbH. FF, JGer, TW, SK, GW, JGen, DN, CV and KR declare that they have no relevant conflicts of interest.

AUTHOR CONTRIBUTIONS

JGer, TW, SK, GW, JGen, DN, EvM, CV, and KR have made substantial contributions to conception and design of the study. FF, JGer, SK, GW, JGen, CV, and KR have made substantial contributions to acquisition of data. FF, MJE, JGen, DN, EvM, and KR have made substantial contributions to analysis and interpretation of data. FF, MJE, and KR have been involved in drafting the manuscript. All authors revised the manuscript and gave final approval of the version to be published.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Supporting Information

Trajectories of asthma and allergy symptoms from childhood to adulthood

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Detailed description of application of Latent Class Analysis (LCA)

Model selection

LCA was conducted for 2 to 10 classes using Full Information Maximum Likelihood (FIML) methods to handle missing values. (1) This means that we used the non-imputed data set in this step. Model identification was checked by comparing the likelihood of models with 100 random starting values. Models with 7 or more classes were ruled out because they were not identified (Table E2). Models with 2 to 4 latent classes were ruled out because they did not offer as much information as the 5- and 6-class solutions.

Multiple-group LCA (2) with males and females as separate groups were additionally considered. Models allowing for qualitative differences of latent classes between men and women were not identified and thus had to be discarded. Multiple-group models that restricted latent classes to be similar across males and females and only allowed for differences in latent class prevalences were identified but only the 5- and 6-class solutions were considered for the same reasons as before.

The 5- and 6-class solutions and their corresponding multiple-group versions, therefore, remained as candidates for the final model. Model selection was based on interpretability, parsimony and the Bayesian information criterion (BIC). Since only one latent class prevalence varied considerably between men and women, multiple-group models were ruled out because of parsimony. The BIC was lowest for the 5-class solution (Table E2). However, the 6-class solution offered an additional interpretable latent class that would have been lost when strictly following the statistical criterion. Therefore, the 6-class solution without considering men and women as separate groups was selected.

Calculating the final LCA model

The selected model was recalculated in 20 imputed datasets. This resulted in 20 estimates for all parameters of the LCA model, one from each imputed dataset. These estimates were

pooled based on Rubin's rules. (3) For item-response probabilities, estimates from the maximum likelihood solution of the previous step were used as starting values. Figure 2C and Table E3 report the pooled estimates.

Latent class assignments

For additional analyses, participant had to be assigned to latent classes. If, however, every participant is only assigned to a single latent class, uncertainty of classification is not taken into account. Considering uncertainty was important because entropy was between 0.753-0.788 in the 20 imputed datasets.

An individual vector of posterior probabilities of latent class membership for each participant is an output of the LCA model, e.g.: Participant 1 has a probability of 20% for being in latent class 1, 65% for being in latent class 2, 5% for being in latent class 3, 8% for being in latent class 4, 1% for being in latent class 5, and 1% for being in latent class 6. For an individual participant, these numbers always sum up to 1.

Twenty random values were drawn from this individual distribution of posterior probability of latent class membership. Random drawing was done in each of the 20 imputed datasets because the individual posterior probabilities differed, similarly to the parameter estimates. Based on these random draws, categorical variables that indicated membership in one of the latent classes for each participant were created. One categorical variable was created for every random draw.

Table E1: Definition of traits and environmental determinants

Variable	Measured at	Categories/unit	Description
Socio-demographics			
Study centre	bl	Munich, Dresden	
Sex	bl	male vs. female	
Parental SES	bl	high vs. low	high SES: 12 or more years of school by either father or mother
SES	fu1		high SES: 12 or more years of school
Parental medical history			
Parental asthma	bl	yes vs. no	yes: at least one parent
Parental hay fever	bl		
Parental atopic dermatitis	bl		
Medical history			
SPT (seasonal allergens)	bl	positive (for at least one allergen) vs. negative (for all allergens)	Allergens: mixed grass pollen, mixed tree pollen (4)
SPT (perennial allergens)	bl		Allergens: *Dermatophagoides pteronyssinus*, *D. farinae*, cat, *Alternaria tenuis* (4)
IgE (inhalant allergens)	bl	>0.35 U/ml vs. <0.35 U/ml	serum levels of IgE directed against local grass pollen, birch pollen, mugwort pollen, *Dermatophagoides pteronyssinus*, cat dander, dog dander, *Cladosporium herbarum* (4)
IgE (food allergens)	bl	>0.35 U/ml vs. <0.35 U/ml	serum levels of IgE directed against egg white, milk proteins, cod fish, wheat flour, peanut, soja bean (4)
BHR	fu2	yes vs. no	see (5)
Lung function	fu2	no unit	FEV_1/FVC (5)
FeNO	fu2	ppb	arithmetic mean of all ln-transformed measurements with valid flow (between 45 and 55 ml/s) (5)
Life style factors			
ETS	bl (1st year of life, 1st year of school were also measured at bl)	yes vs. no	
Current smoking	fu1, fu2	yes vs. no	
BMI	bl, fu1, fu2	kg/m^2	
Indoor exposures			
Mould	bl (1st year of life, 1st year of school were also measured at bl), fu1, fu2	yes vs. no	Mould at home measured by questionnaire (for fu1 to fu3: at the time of the survey or since last study phase)

Dog ownership	bl (1st year of life, 1st year of school were also measured at bl), fu1, fu2	yes vs. no	Dog in own home
Cat ownership	bl (1st year of life, 1st year of school were also measured at bl), fu1, fu2	yes vs. no	Cat in own home
Occupational exposures			
Allergic occupational exposures	complete job history up to fu2	presence of at least one agent from Job-Exposure-Matrix (6) at some point in time vs. no agent present at any time	Agents: animals, fish/shellfish, flour, foods, plant-related dusts, house dust mites, storage mites, plant mites, enzymes, latex, textiles, moulds, drugs, aliphatic amines, isocyanates, acrylates, epoxy resins, persulfates/henna, wood, metal, metal working fluids
Irritative occupational exposures			Agents: textiles, moulds, endotoxin, high-level chemical disinfectant, aliphatic amines, isocyanates, acrylates, epoxy resins, persulfates/henna, wood, metal, metal working fluids, herbicides, insecticides, fungicides, indoor cleaning, bleach, organic solvents, exhaust fumes

bl: baseline; fu: follow-up; SES: social-economic status; SPT: skin prick test; IgE: immunoglobulin E; BHR: bronchial hyperresponsiveness; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; FeNO: exhaled nitric oxide; ETS: environmental tobacco smoke; BMI: body mass index; baseline questionnaire was answered by participants' parents

Table E2: LCA model criteria for 2 to 10 classes; 100 random starting values; statistical criteria for maximum likelihood solution

# class	df	G^2	logL	AIC	BIC	ML starting values[†]
2	4070	1948.8	-9014.3	1998.8	2141.9	100/100
3	4057	1562.9	-8821.4	1638.9	1856.5	98/100
4	4044	1326.5	-8703.1	1428.5	1720.5	89/100
5	4031	1184.7	-8632.2	1312.7	**1679.1**	100/100
6	4018	1113.8	-8596.8	1267.8	1708.7	68/100
7	4005	1074.4	-8577.1	1254.4	1769.7	9/100
8	3992	1039.2	-8559.5	1245.2	1835.0	1/100
9	3979	1004.0	-8541.9	1236.0	1900.2	2/100
10	3966	974.6	-8527.2	**1232.6**	1971.3	1/100

[†] Number of random starting values that led to maximum likelihood (identification); df: degrees of freedom; G^2: likelihood-ratio statistic; logL: log likelihood; AIC: Akaike information criterion; BIC: Bayesian information criterion

Table E3: Latent class model regarding symptoms of asthma and allergies with 6 latent classes (pooled estimates of 20 imputed datasets), N=2267

Variable	Class1	Class2	Class3	Class4	Class5	Class6
Prevalence	**0.563** **0.515 - 0.611**	0.085 0.057 - 0.114	0.185 0.147 - 0.223	0.085 0.047 - 0.122	0.054 0.022 - 0.087	0.027 0.013 - 0.042
Wheeze (bl)	0.035 0.022 - 0.048	0.041 -0.006 - 0.087	0.076 0.035 - 0.117	0.228 0.112 - 0.344	0.364 0.214 - **0.513**	0.245 0.098 - 0.392
Rhinoconjunctivitis (bl)	0.034 0.021 - 0.048	0.046 -0.010 - 0.101	0.332 0.264 - 0.401	0.141 0.024 - 0.258	**0.562** 0.378 - **0.747**	**0.571** 0.385 - **0.757**
Eczema (bl)	0.052 0.035 - 0.070	0.445 0.330 - **0.560**	0.098 0.054 - 0.142	0.099 0.013 - 0.184	0.252 0.108 - 0.395	**0.903** **0.723 - 1.083**
Wheeze (fu1)	0.042 0.023 - 0.061	0.106 0.029 - 0.183	0.117 0.059 - 0.176	**0.583** 0.391 - **0.775**	**0.656** 0.467 - **0.844**	0.357 0.173 - **0.541**
Rhinoconjunctivitis (fu1)	0.046 0.025 - 0.067	0.047 -0.032 - 0.127	**0.656** **0.562 - 0.750**	0.179 -0.004 - 0.361	**0.794** **0.582 - 1.007**	**0.692** **0.506 - 0.877**
Eczema (fu1)	0.008 -0.007 - 0.023	**0.595** 0.445 - **0.746**	0.057 0.022 - 0.092	0.072 -0.003 - 0.146	0.113 0.013 - 0.213	**0.831** **0.624 - 1.037**
Wheeze (fu2)	0.048 0.024 - 0.072	0.117 0.035 - 0.199	0.137 0.060 - 0.214	**0.700** **0.503 - 0.896**	**0.809** **0.634 - 0.983**	0.375 0.186 - **0.564**
Rhinoconjunctivitis (fu2)	0.066 0.040 - 0.092	0.114 0.040 - 0.189	**0.711** **0.617 - 0.805**	0.181 0.008 - 0.355	**0.755** **0.562 - 0.947**	**0.682** **0.503 - 0.862**
Eczema (fu2)	0.016 0.000 - 0.032	**0.507** 0.371 - **0.643**	0.062 0.025 - 0.098	0.085 0.015 - 0.156	0.129 0.032 - 0.226	**0.760** **0.518 - 1.001**
Wheeze (fu3)	0.079 0.051 - 0.106	0.111 0.013 - 0.209	0.156 0.084 - 0.227	**0.571** 0.384 - **0.758**	**0.770** **0.560 - 0.979**	0.315 0.123 - **0.507**
Rhinoconjunctivitis (fu3)	0.105 0.076 - 0.134	0.153 0.066 - 0.240	**0.595** 0.500 - **0.690**	0.154 -0.002 - 0.309	**0.732** 0.468 - **0.997**	**0.611** 0.416 - **0.805**
Eczema (fu3)	0.041 0.022 - 0.061	0.382 0.258 - **0.506**	0.099 0.044 - 0.154	0.078 -0.007 - 0.162	0.202 0.053 - 0.351	**0.560** 0.365 - **0.756**

First line contains latent class prevalences with 95%-confidence intervals. Remaining numbers are item-response probabilities with 95%-confidence intervals, which describe the probability of reporting the corresponding symptom when being a member of the corresponding latent class. (bold: estimates > 0.5; bl: baseline; fu: follow-up)

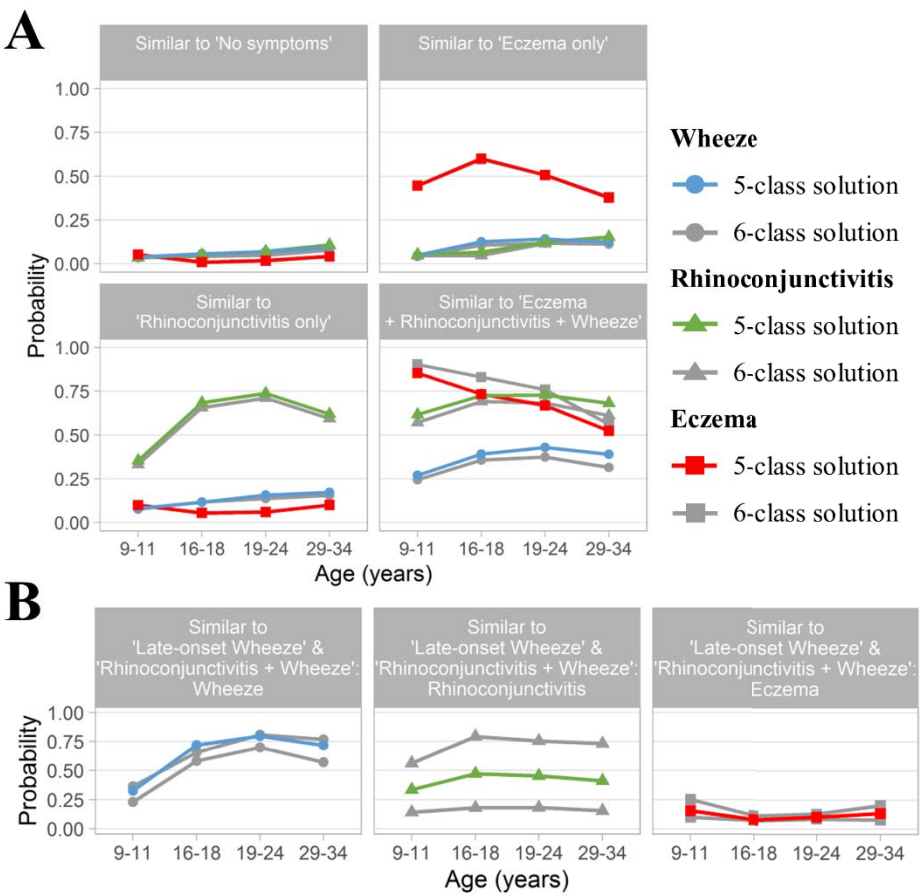

Figure E1: Comparison of the 5-class solution to the 6-class solution. Part A shows a comparison of 4 of the 5 trajectories from the 5-class solution (in colour) to the corresponding trajectories from the 6-class solution (in grey). All of them are very similar. In the top row both graphs even directly overlap. The titles give information on the corresponding latent class from the 6-class solution. Part B shows the same for the remaining trajectory from the 5-class solution, but symptom by symptom to avoid too much overlap. Wheeze and eczema are quite similar in both corresponding trajectories from the 6-class solution ("Late-onset Wheeze" & "Rhinoconjunctivitis + Wheeze") but probabilities of rhinoconjunctivitis strongly differ.

Table E4: Association of latent class membership with environmental determinants by latent class compared to reference class "No symptoms", every variable displayed here was analysed in a logistic regression model adjusted for sex, SES, parental SES, and study centre

Environmental determinants	LC 2: Eczema only	LC 3: Rhinoconjunctivitis only	LC 4: Late-onset Wheeze	LC 5: Rhinoconjunctivitis + Wheeze	LC 6: Eczema + Rhinoconjunctivitis + Wheeze
	OR (95%-CI)	OR (95%-CI)	OR (95%-CI)	OR (95%-CI)	OR (95%-CI)
Smoking (only CH)	1.24 (0.77-2.00)	1.18 (0.84-1.64)	0.76 (0.38-1.53)	0.93 (0.45-1.94)	0.66 (0.27-1.65)
Smoking (only A/yAH)	1.43 (0.95-2.14)	1.24 (0.91-1.69)	2.37 (1.52-3.71)	1.95 (1.14-3.34)	1.01 (0.50-2.07)
Smoking (CH & A/yAH)	1.23 (0.78-1.95)	0.96 (0.68-1.36)	2.85 (1.79-4.53)	1.99 (1.13-3.52)	1.14 (0.55-2.33)
Mould (only CH)	1.43 (0.81-2.52)	1.04 (0.67-1.62)	1.37 (0.73-2.56)	1.12 (0.50-2.52)	1.28 (0.44-3.72)
Mould (only A/yAH)	1.31 (0.87-1.97)	0.93 (0.70-1.23)	1.40 (0.93-2.09)	1.46 (0.87-2.45)	1.04 (0.50-2.17)
Mould (CH & A/yAH)	1.19 (0.74-1.90)	1.08 (0.78-1.50)	1.52 (0.95-2.45)	1.22 (0.65-2.30)	1.79 (0.89-3.61)
Dog ownership (only CH)	0.88 (0.44-1.77)	1.05 (0.68-1.63)	0.95 (0.53-1.70)	1.04 (0.49-2.19)	1.58 (0.69-3.64)
Dog ownership (only A/yAH)	1.12 (0.67-1.87)	0.90 (0.60-1.36)	1.39 (0.86-2.25)	1.57 (0.88-2.78)	0.64 (0.21-1.95)
Dog ownership (CH & A/yAH)	1.03 (0.55-1.92)	0.83 (0.52-1.33)	1.08 (0.60-1.94)	1.23 (0.59-2.58)	1.03 (0.36-2.94)
Cat ownership (only CH)	1.05 (0.62-1.79)	1.11 (0.73-1.67)	1.21 (0.73-2.00)	1.20 (0.64-2.25)	1.00 (0.40-2.52)
Cat ownership (only A/yAH)	0.77 (0.47-1.25)	0.95 (0.66-1.36)	1.09 (0.68-1.75)	0.74 (0.37-1.48)	0.72 (0.32-1.63)
Cat ownership (CH & A/yAH)	0.77 (0.46-1.28)	0.85 (0.60-1.22)	0.91 (0.56-1.49)	0.86 (0.45-1.64)	0.43 (0.15-1.22)
Obesity (only CH)	0.86 (0.21-3.49)	0.79 (0.25-2.43)	†	1.27 (0.33-4.87)	†
Obesity (only A/yAH)	1.23 (0.51-2.96)	0.93 (0.47-1.83)	1.45 (0.70-3.00)	1.35 (0.51-3.60)	1.62 (0.43-6.05)
Obesity (CH & A/yAH)	†	†	†	†	†
Allergic occupational exposures	1.03 (0.71-1.48)	0.89 (0.68-1.16)	1.10 (0.77-1.57)	1.46 (0.93-2.31)	0.89 (0.48-1.65)
Irritative occupational exposures	1.06 (0.77-1.47)	0.86 (0.68-1.08)	1.24 (0.89-1.73)	1.41 (0.94-2.13)	1.48 (0.85-2.55)

† no estimation due to small sample size; LC: latent class; OR: odds ratio; CI: confidence interval; CH: childhood; A/yAH: adolescence/young adulthood

Table E5: Range of mean of posterior probability of participants who report wheeze before or at the age of 4 (n=351) for the M=20 imputed datasets

Latent class	Range
No symptoms	41.1%-47.1%
Eczema only	6.9%-9.2%
Rhinoconjunctivitis only	15.4%-20.3%
Late-onset Wheeze	10.8%-18.8%
Rhinoconjunctivitis + Wheeze	8.2%-13.5%
Eczema + Rhinoconjunctivitis + Wheeze	4.0%-6.8%

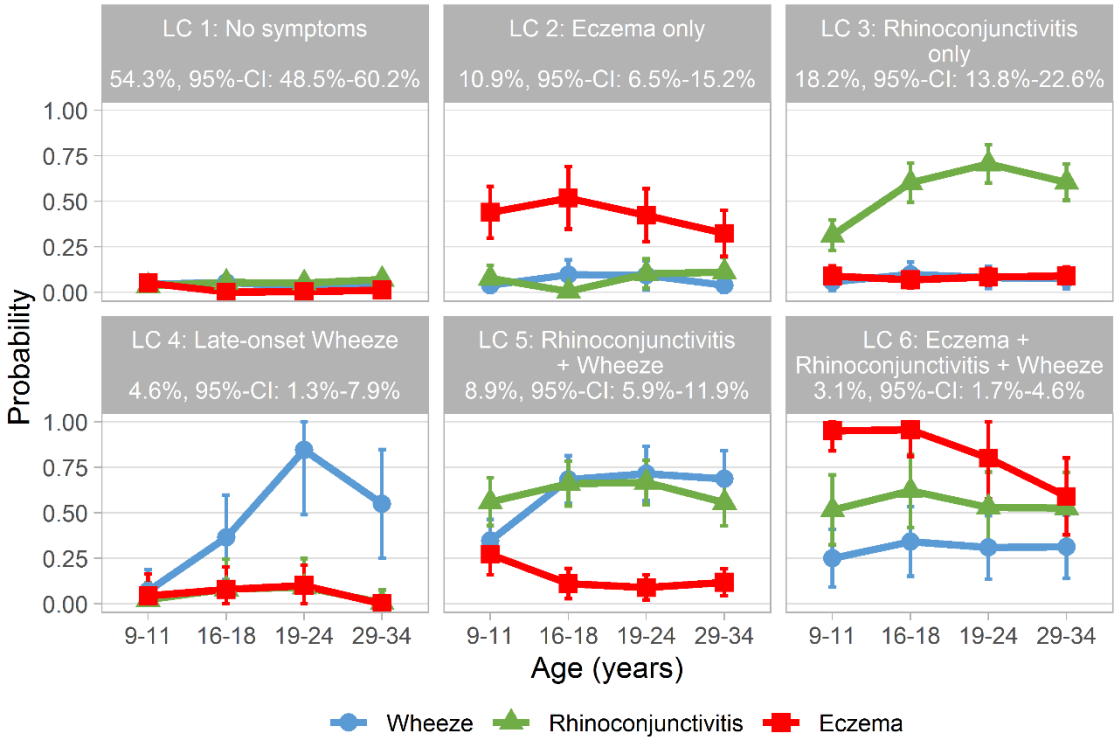

Figure E2: Probability of asthma and allergy symptoms over time by latent class; only participants that filled in all 4 questionnaires. The figure shows latent classes (LC) which correspond to symptom trajectories. Each subplot shows symptom probabilities for one derived latent class with 95%-confidence intervals (CI) over time for symptoms of wheeze, rhinoconjunctivitis, and eczema, indicated by colour and symbol shape. Lines link point estimates of the same symptom. Latent class prevalences with 95%-confidence intervals are shown below latent class names.

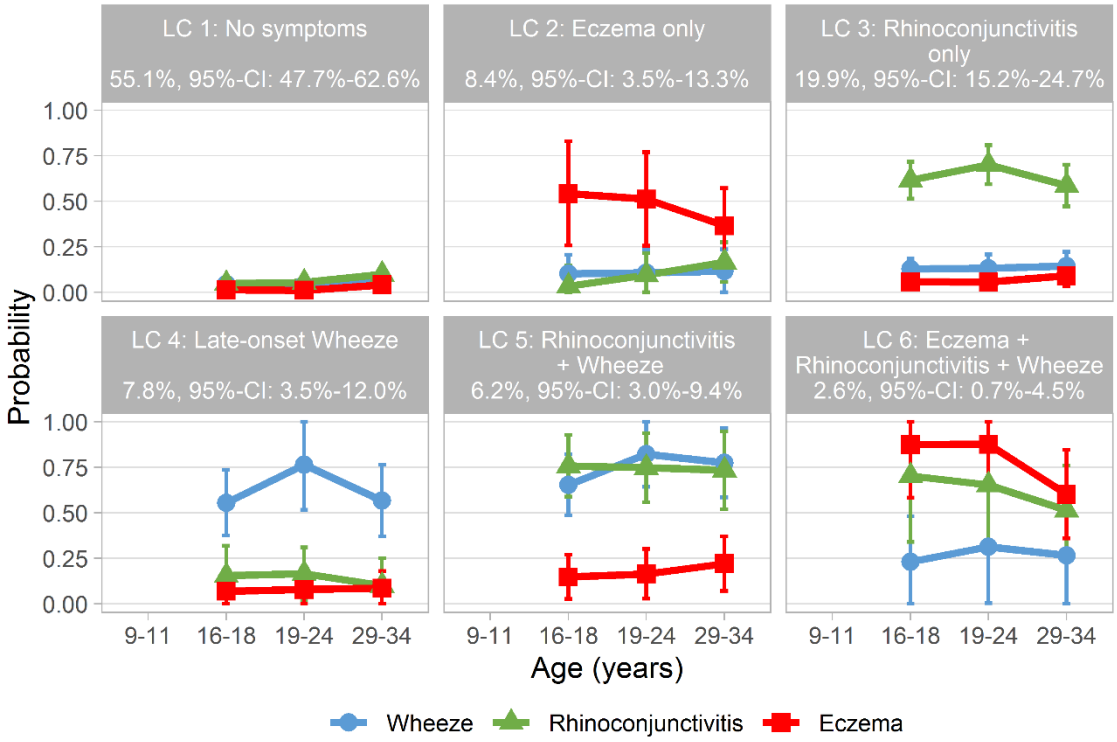

Figure E3: Probability of asthma and allergy symptoms over time by latent class without baseline. The figure shows latent classes (LC) which correspond to symptom trajectories. Each subplot shows symptom probabilities for one derived latent class with 95%-confidence intervals (CI) over time for symptoms of wheeze, rhinoconjunctivitis, and eczema, indicated by colour and symbol shape. Lines link point estimates of the same symptom. Latent class prevalences with 95%-confidence intervals are shown below latent class names.

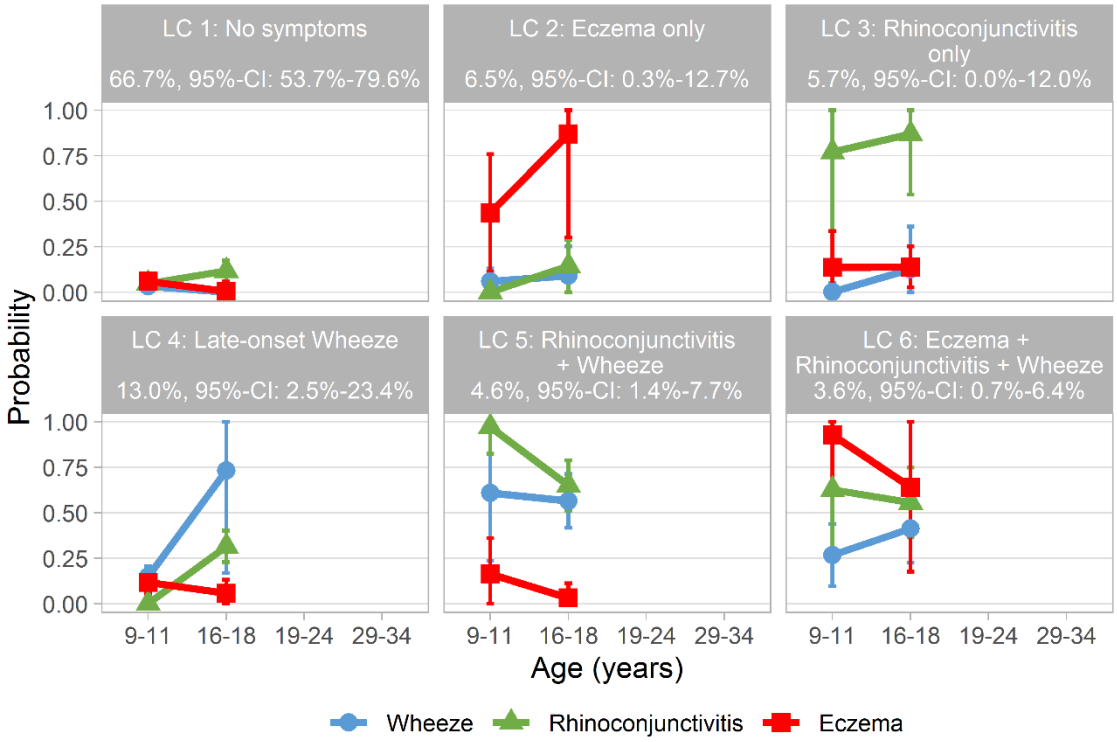

Figure E4: Probability of asthma and allergy symptoms over time by latent class without follow-ups 2 and 3. The figure shows latent classes (LC) which correspond to symptom trajectories. Each subplot shows symptom probabilities for one derived latent class with 95%-confidence intervals (CI) over time for symptoms of wheeze, rhinoconjunctivitis, and eczema, indicated by colour and symbol shape. Lines link point estimates of the same symptom. Latent class prevalences with 95%-confidence intervals are shown below latent class names.

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4. Paper II

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Third Follow-Up of the Study on Occupational Allergy Risks (SOLAR III) in Germany: Design, Methods, and Initial Data Analysis

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Introduction: Asthma and allergies are complex diseases affected by genetic and environmental factors, such as occupational and psychosocial factors, as well as interactions between them. Although childhood is a critical phase in the development of asthma and allergies, few cohort studies on occupational outcomes followed up participants from childhood onwards. We present design, methods, and initial data analysis for the third follow-up of SOLAR (Study on Occupational Allergy Risks), a prospective and population-based German asthma and allergy cohort.

Methods: The SOLAR cohort was initially recruited in 1995–1996 for Phase II of the German branch of the International Study of Asthma and Allergies in Childhood (ISAAC II) and followed up three times since, in 2002–2003, 2007–2009, and 2017–2018. During the third follow-up (SOLAR III), participants were between 29 and 34 years old. Since SOLAR focuses on occupational exposures, follow-ups were conducted at important points in time of the development of participants' career. To evaluate the potential of selection bias, responders and non-responders were compared based on variables from earlier study phases. In responders, frequency and pattern of missing values were examined and compared within the subsets of paper and online versions of the used questionnaires.

Results: In total, 1,359 participants completed the questionnaire of the third follow-up (47.3% of eligible participants). Initially, the cohort started with 6,399 participants from the ISAAC II questionnaire study. A selection process led to a study population that is more female, higher educated, smokes less and has a higher proportion of certain asthma and allergy symptoms (also in their parents) than the initial cohort. Pattern and frequency of missing values were different for paper and online questionnaires.

Discussion: The third follow-up of the SOLAR cohort offers the opportunity to analyze the course of asthma and allergies and their associations to environmental, occupational and psychosocial risk factors over more than 20 years from childhood to adulthood. Selection processes within the cohort might lead to bias that needs to be considered in future analyses.

Keywords: asthma, occupational asthma, atopic dermatitis, rhinitis, epidemiological methods, cohort study

INTRODUCTION

Asthma and allergies are complex diseases affected by environmental and genetic factors as well as interactions between them (1, 2). In addition, different phenotypes of asthma have been established, based for example on the time of onset. One important type of adult-onset asthma is work-related asthma, which is associated with workplace exposures (3). So far only few cohort studies on occupational outcomes follow up participants from childhood onwards. Nevertheless, the inclusion of childhood is important since it is a critical phase in the development of asthma and allergies and because childhood symptoms might affect later job choices (4). To investigate the course of asthma and allergies from childhood to adulthood elucidating especially the role of occupational risk factors, the SOLAR study (Study on Occupational Allergy Risks) was established based on the German part of the International Study of Asthma and Allergies in Childhood Phase II (ISAAC II). Three follow-up studies have been conducted since, with a total follow-up time of more than 20 years.

The third follow-up of the Study on Occupational Allergy Risks (SOLAR III) aims to:

- further investigate the course of asthma and allergies from childhood to adulthood;
- continue the collection of data on occupational, environmental and psychosocial risk factors and investigate associations with asthma and allergies;
- study risk factors in relation to participants' age.

This article presents design and methods of SOLAR III and reports processes and results from its initial data analysis (IDA). IDA is an essential part of the study process within the conduction of observational studies. It connects data collection and analysis including the set-up of metadata, data cleaning, and data screening. IDA is necessary to obtain an analyzable data set and to identify aspects that influence interpretation and future analyses (5).

METHODS

Study Design

The SOLAR cohort was initially recruited in 1995–1996 for Phase II of the German branch of the International Study of Asthma and Allergies in Childhood (ISAAC II). ISAAC II aimed to find potential determinants for asthma and allergy occurrence and severity around the world (6). For this, community-based random samples of children aged 9–11 years were drawn in the two study centers Munich and Dresden. An additional goal of the German branch was to investigate differences in asthma and allergies between east (Dresden) and west (Munich) of the recently reunified Germany (7). In total, 7,498 children were invited to participate and fill in a questionnaire. For both study centers, 6,399 children and their parents participated (85.3%). A random subset of children (n = 4,018) was also invited to clinical examinations including spirometry, tests for bronchial hyperresponsiveness using nebulized hypertonic saline, skin prick tests, specific IgE tests in blood serum, and standardized skin examinations.

In 2002–2003, the first phase of SOLAR (SOLAR I) followed-up the initial German ISAAC II cohort. Of 4,893 invited adolescents aged 16–18 years who could be re-contacted, 3,785 (77.4%) completed the questionnaire and agreed to link the data with the information from ISAAC II. Additionally, 3,053 participants (62.4%) agreed to be re-contacted for subsequent studies. In 2007–2009, 2,051 participants (70.6% of the eligible 2,904 participants) aged 19–24 years filled in the questionnaire for the second follow-up (SOLAR II). SOLAR II also included clinical examinations, comprising e.g., physical examinations, skin prick tests, and spirometry (8).

All participants who agreed to be re-contacted in SOLAR I and for whom either an e-mail or postal address was available were invited to complete a questionnaire for the third follow-up (SOLAR III), which means that cohort members were also asked to participate in SOLAR III if they did not participate in SOLAR II without actively refusing re-contact. No clinical examinations were conducted in the third follow-up. During the field phase in 2017–2018, the participants were between 29 and 34 years old. In total, 1,359 participants completed the questionnaire (**Figure 1**).

All study phases were approved by the Ethical Committees of the Medical Faculty of the University of Dresden and the Bavarian Chamber of Physicians. Written informed consent, also for linking data from all study phases, was obtained from all participants (SOLAR I to III) and their legal guardians (ISAAC II, SOLAR I).

Questionnaire Instruments

The SOLAR III questionnaire (121 items) included validated questions on:

- socio-demographics (six items)

Abbreviations: ETS, Environmental tobacco smoke; IDA, Initial data analysis; ISAAC, International Study of Asthma and Allergies in Childhood; ISCO, International Standard Classification of Occupations; JEM, Job-exposure-matrix; PA, Physical activity; SES, Socio-economic status; SOLAR, Study on Occupational Allergy Risks; TICS, Trier Inventory of the Assessment of Chronic Stress.

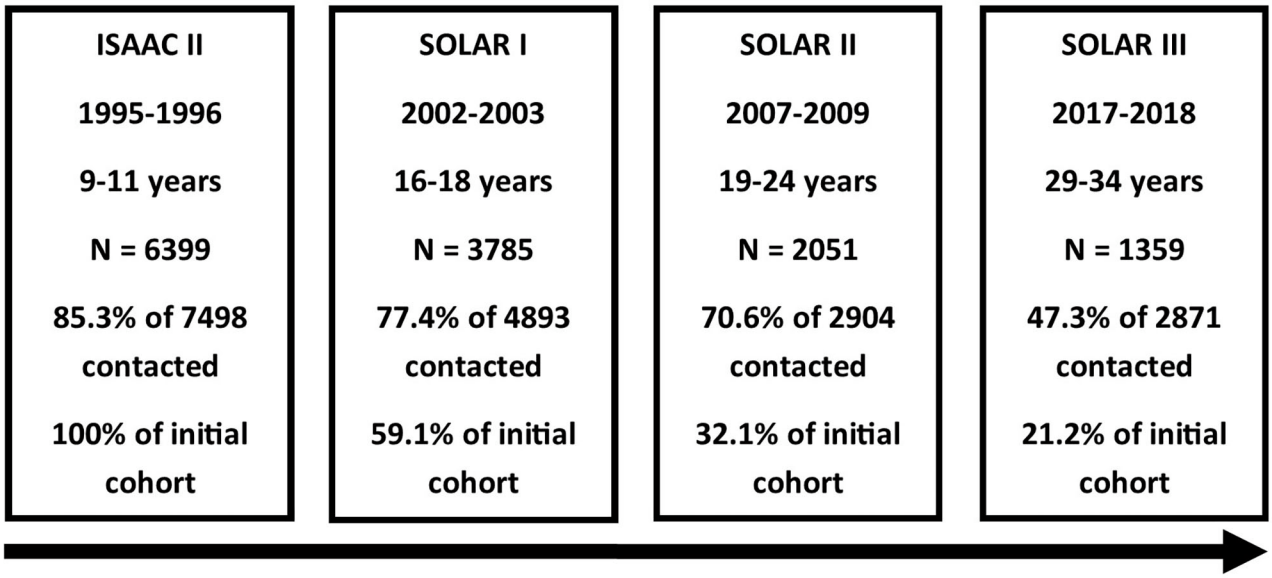

FIGURE 1 | Flowchart of the SOLAR study phases. From top to bottom: study phase, time period of data collection, age of participants, number of participants, response based on number of invited participants, and proportion of ISAAC II cohort remaining.

- respiratory symptoms and disease (including asthma and wheeze) (15 items)
- rhinoconjunctivitis and hay fever (7 items)
- atopic dermatitis and hand eczema (13 items)
- domestic exposures, use of skin care products, use of disinfectants (14 items)
- smoking, exposure to environmental tobacco smoke (13 items)
- occupation (19 items)
  - level of education and job type
  - job history for all jobs held for at least 1 month and for at least 8 h a week
  - occupational diseases and risk factors
- physical activity and use of entertainment electronics (5 items)
- body height and weight (2 items)
- use of oral contraceptives, number of pregnancies (3 items)
- depression (PHQ-2) (2 items) (9)
- work-related stress [TICS (Trier Inventory of the Assessment of Chronic Stress)] (22 items) (10, 11).

Throughout the study phases, the same questions on respiratory symptoms and disease as well as on atopic dermatitis and hand eczema were used. Those questions were originally in English and translated with back-translation into German for ISAAC (6). Questions on exposures and other variables were also kept as similar as possible throughout the study phases and came for example from the ECRHS (12) and the GA^{2}LEN survey (13). Compared to the second follow-up, questions on water pipe and electronic cigarette use (water pipe questions were modified for electronic cigarettes) (14), discrimination and harassment at work (15), working conditions (16), and depression screening (9) were added in SOLAR III. Questions on job choice, accidents involving steam, gas, or smoke, state of residence, glove material, and frequency of washing hands that were still in the second follow-up questionnaire were left out in phase III. Some questions on symptoms of asthma and rhinitis were no longer kept either in order to keep the length of the questionnaire acceptable for participants. Removed questions were either not relevant anymore because of participants' age or had many missing values in earlier study phases. The questionnaire used is available as **Supplementary Material**.

After assessment of face validity, the content validity of the newly added questions were evaluated in a pre-test. The seven pre-test participants were sampled based on convenience and were of both genders, between 27 and 35 years old, and had low to high level of education to represent the demographic characteristics of participants (17). They were no participants of ISAAC or SOLAR and were asked to explain the presented questions to the investigator. In case of difficulties understanding the meaning of the questions, the questionnaire was revised accordingly before the pilot study.

We additionally offered the possibility to complete the questionnaire online. The open source software LimeSurvey (LimeSurvey GmbH, Hamburg, Germany) was used for setting up the online version. The survey was hosted on servers of the University Hospital, LMU Munich (Munich, Germany) to ensure data protection.

Recruitment Methods

A pilot study including 25 participants from each study center indicated that the planned recruitment processes (e-mail and mail) worked out well. Participants for whom an e-mail address was available were contacted via e-mail with study information and were invited to fill in the online questionnaire. The

remaining participants received a letter including the paper questionnaire, an informed consent form, study information, and an envelope for sending the questionnaire back free of charge. In order to ensure written informed consent as requested by the data protection representative, all participants of the online questionnaire had to print-out and send-in the signed written consent form by fax, e-mail, or postal mail. Participants were reminded twice, firstly 1 week after the initial contact and secondly one (e-mail) or two (mail) weeks later. Letters were sent out on Thursdays and, e-mails on Fridays to ensure that participants received the questionnaire toward the weekend. Because a substantial proportion of participants already had children, school holidays were avoided for the contact phase. As an incentive, participants who completed the questionnaire had the chance of winning one of ten 200€ shopping vouchers.

When e-mail addresses were invalid or e-mail invitations remained unanswered, the participants were re-contacted via postal mail. When postal addresses were outdated, the local population registries were asked for the current address. Additionally, participants without informed consent form (mainly online participation, 85.8% in study center Munich and 98.4% in Dresden) were reminded via postal mail and, if no response was registered after 21 days, by telephone. The letter contained a ready-to-sign consent form and a post-paid envelope. Thereby, 92.0% (Munich) and 83.5% (Dresden) of the missing forms were received.

Data Processing and Cleaning

Paper questionnaires were entered manually by two independent staff members. Differences between both entries were compared to the paper questionnaire and changed accordingly. Every change was documented to assure the possibility of replication. Concordant entries were assumed correct. Missing values were coded either "missing" or "not applicable" depending on what applied.

Plausibility checks were conducted to obtain a dataset as error-free as possible. Questions filtering subsequent questions were checked for plausible values. If plain text answers contained options that were selectable in the corresponding single or multiple-choice questions, these options were assigned.

Job histories were coded manually by two independent staff members according to the International Standard Classification of Occupations 88 (ISCO-88) classification (18). Afterwards, differing codes were compared in an expert re-evaluation step. Exposure to potential occupational risk factors for asthma and allergies was assessed by linking exposure profiles from the asthma-specific job-exposure-matrix (JEM) by Le Moual and colleagues (19) with the ISCO-88 codes.

All steps of crude data processing and cleaning were documented either in R software (20) scripts, tables, or the data dictionary. This ensures that the cleaned, final dataset can be reproduced from the original variables.

Data Screening and Evaluation of Selection Bias

In order to identify relevant aspects that influence interpretation and future analysis (5), frequency and pattern of missing values were examined and compared within the subsets of answers given by paper and online questionnaires.

To evaluate the potential of selection bias, responders and non-responders were compared in two different ways: First, all SOLAR III responders were compared with ISAAC II participants not responding in SOLAR III with regard to sex, parental history of asthma, parental history of asthma or allergies, and parental socio-economic status (SES). These variables were measured in ISAAC II. Second, all SOLAR III responders were compared with SOLAR I participants not responding in SOLAR III in terms of the outcomes 12-months prevalence of wheezing, asthma, allergic rhinitis, and atopic dermatitis, life-time prevalence of doctor diagnosed asthma, participants own SES, smoking, physical activity (PA), work-related stress, and occupational exposure to potential occupational risk factors for asthma and allergies measured at SOLAR I. SOLAR I results were considered rather than SOLAR II results as they included a larger number of SOLAR III non-respondents.

Parental history of asthma was defined as present if at least one parent reported ever having had asthma. Parental history of asthma or allergies was defined as present if at least one parent reported ever having had asthma, hay fever, or dermatitis. Parental as well as participant's SES were considered high for 12 or more years of education (for at least one parent for parental SES). Twelve-months prevalence of asthma was defined as symptoms of wheezing within the last 12 months prior to the survey and a doctor diagnosis of asthma or multiple doctor diagnoses of asthmatic bronchitis (7). Twelve-months prevalence of allergic rhinitis was defined as having problems with sneezing or a runny blocked nose without having a cold during the last 12 months that were accompanied by itchy-watery eyes. Twelve-months prevalence of atopic dermatitis was defined as ever having had eczema for at least 6 months with symptoms during the 12 months prior to study and the itchy rash at any time affecting any of the following places: the folds of the elbows, behind the knees, in front of the ankles, in the face, or around the neck (21). Participants were defined as smokers if they smoked at least 20 packs in their life or at least one cigarette per day or one cigar per week for 1 year (22). PA was classified as no PA (never doing physical exercise), low PA (physical exercise between less than once a month and once a week), and high PA (physical exercise more than once a week). Work-related stress was measured by the TICS (10, 11). The items of two scales, work overload and work discontent, were summed up separately and translated to an age-specific T-value. For each scale, a binary variable was created which was defined as positive if the T-value and its 95% confidence interval exceeded the value of 50 (10). Occupational exposure to potential occupational risk factors for asthma and allergies was defined as present if the participant ever had a job that was linked to a relevant exposure by an asthma-specific job-exposure-matrix (23).

RESULTS

Response

In total, 3,053 participants, who agreed to be re-contacted in the first follow-up, were asked to participate in the SOLAR III study (**Table 1**). Of those, 153 could not be contacted because of missing e-mail and postal addresses, 15 had died, and 14 had actively refused to be re-contacted. Of the remaining 2,871 SOLAR I participants, 1,359 answered the questionnaire (47% of the eligible sample). Response was considerably higher in the study center Dresden (56%) compared to Munich (39%). Of the 1,359 participants in SOLAR III, 216 had not participated in SOLAR II (22% of SOLAR II non-responders).

Non-participation

A higher proportion of SOLAR III participants was female (61 vs. 47%) and had a high parental SES (59 vs. 46%) compared to ISAAC II participants not participating in SOLAR III (**Table 2**). While no difference was found for parental history of asthma, a higher proportion of SOLAR III participants had parents with a history of asthma or allergies (46 vs. 39%).

Compared to SOLAR I participants not participating in SOLAR III, participants' SES was also higher at SOLAR I (60 vs. 44%). In addition, during SOLAR I, SOLAR III participants were more likely to report symptoms of atopic dermatitis than SOLAR I participants not responding in SOLAR III (11 vs. 8%), and less likely to be ever smokers (29 vs. 38%). No differences were seen for the other variables under study (**Table 3**).

Missing Data Pattern

In the total SOLAR III dataset, 3% of values were missing. Questions with the highest proportion of missing values were on environmental tobacco smoke (ETS) (11%), quitting jobs because of symptoms of asthma or allergies (6%), doctor diagnosis of respiratory outcomes (6%), skin-straining activities at home, including cleaning without gloves, construction or renovation, gardening or farming, or other tasks that could be straining for the skin due to wet conditions, chemicals or other factors (6%), wheezing (6%) or symptoms of rhinoconjunctivitis (5%) due to an occupation, and duration of glove use (5%).

Generally speaking, online questionnaires had lower proportions of missing values in the first half of the questionnaire, while paper questionnaires had lower proportions of missing values in the second half (**Figure 2**). Questions with the highest difference in the proportions of missing values were on wheezing (9%-points) or symptoms of rhinoconjunctivitis (8%-points) due to an occupation, use of gloves (8%-points), including duration (8%-points), declaration of occupational disease, including its reason (8%-points), with a lower proportion of missing values for paper questionnaires, and on ETS (6%-points) and indoor mold (6%-points) with a lower proportion of missing values for online questionnaires.

TABLE 1 | Participation in the SOLAR study phases.

	Total *n* (%)	Munich *n* (%)	Dresden *n* (%)
ISAAC Phase II (Questionnaire study)	6,399 (85.3)[a]	3,354 (87.6)	3,045 (83.0)
SOLAR I	3,785 (77.4)[b]	2,043 (81.5)	1,742 (73.0)
Agreed to be re-contacted	3,053 (80.7)	1,534 (75.1)	1,519 (87.2)
SOLAR II	2,051 (70.6)[c]	1,008 (69.6)	1,043 (71.1)
SOLAR III			
Contacted	3,053 (100.0)	1,534 (100.0)	1,519 (100.0)
Lost participants	182 (6.0)	46 (3.0)	136 (9.0)
No valid address available	153 (5.0)	33 (2.2)	120 (7.9)
Deceased	15 (0.5)	6 (0.4)	9 (0.6)
Participant refused further contact	14 (0.5)	7 (0.5)	7 (0.5)
Eligible sample	2,871 (94.0)	1,488 (97.0)	1,383 (91.0)
Response	1,359 (47.3)[d]	585 (39.3)	774 (56.0)
of these			
Participation in SOLAR II	1,143 (84.1)	496 (84.8)	647 (83.6)
No participation in SOLAR II	216 (15.9)	89 (15.2)	127 (16.4)
Online questionnaire	787 (57.9)	323 (55.2)	464 (59.9)
Paper questionnaire	572 (42.1)	262 (44.8)	310 (40.1)

[a] *6,399 of 7,498 invited children.*
[b] *3,785 of 4,893 invited adolescents who could be re-contacted.*
[c] *2,051 of 2,904 invited adults who could be re-contacted.*
[d] *1,359 of 2,871 eligible participants.*

DISCUSSION

We present design, methods, and results from the initial data analysis for the third follow-up of a German prospective and population-based asthma and allergy cohort. SOLAR started with the German ISAAC II participants in two study centers. We followed this cohort for more than 20 years from elementary school until the early thirties. The follow-ups were placed at important points in time of the participant's career: around the transition from school to work or university, around the transition from university to work, and after being settled in working life. Because of the long follow-up time, the study offers the opportunity to link (occupational) information from adulthood to data from childhood.

In the presented follow-up, no clinical examinations were feasible. Although examinations might decrease errors for example in asthma measurement, it would have negatively affected the feasibility of the study and probably also the willingness of cohort members to further participate. In addition to the initial examination in the ISAAC II study phase, an examination was conducted in the second follow-up when participants had already reached adulthood. Back then, only 40% of the eligible study population participated in the clinical part (8). Because validated questions were used throughout the study, we came to the conclusion that accuracy is maximized best by focusing on reaching a high response in the questionnaire study.

Many cohort studies investigating work-related asthma recruited workers from a specific occupation to investigate effects of a certain exposure. Often these cohorts had a few hundred participants and were followed for a time period between a few months and several years (24). Usually, eligible workers were either already exposed for a certain time or enrolled at the beginning of their job. To focus on new and therefore unexposed

TABLE 2 | Non-responder-analysis comparing all SOLAR III participants to ISAAC II participants not responding in SOLAR III based on baseline data.

	Responders SOLAR III *N* = 1,359		**ISAAC II participants not responding in SOLAR III *N* = 5,040**	
	Available responses *n* (%)	**% (95%-CI)**	**Available responses *n* (%)**	**% (95%-CI)**
Female	1,359 (100.0)	60.5 (57.9–63.1)	5,036 (99.9)	46.5 (45.1–47.9)
Parental history of asthma[a]	1,243 (91.5)	9.5 (7.9–11.1)	4,466 (88.6)	9.9 (9.0–10.8)
Parental history of asthma or allergies[b]	1,346 (99.0)	46.0 (43.3–48.7)	4,932 (97.9)	39.3 (37.9–40.7)
Parental SES (high)[c]	1,338 (98.5)	59.3 (56.7–61.9)	4,789 (95.0)	45.8 (44.4–47.2)

[a] *At least one parent reported ever having had asthma.*
[b] *At least one parent reported ever having had asthma or hay fever or dermatitis.*
[c] *12 or more years of education for at least one parent.*

TABLE 3 | Non-responder-analysis comparing all SOLAR III participants to SOLAR I participants not responding in SOLAR III based on SOLAR I characteristics.

	Responders SOLAR III *N* = 1,359		**SOLAR I participants not responding in SOLAR III *N* = 2,570[a]**	
	Available responses *n* (%)	**% (95%-CI)**	**Available responses *n* (%)**	**% (95%-CI)**
Symptoms of wheezing within the last 12 months	1,354 (99.6)	14.7 (12.8–16.6)	2,547 (99.1)	15.0 (13.6–16.4)
Doctor diagnosis of asthma	1,334 (98.2)	7.2 (5.8–8.6)	2,515 (97.9)	8.1 (7.0–9.2)
12-months prevalence of asthma[b]	1,346 (99.0)	4.2 (3.1–5.3)	2,534 (98.6)	5.2 (4.3–6.1)
12-months prevalence of allergic rhinitis[c]	1,342 (98.7)	22.4 (20.2–24.6)	2,529 (98.4)	22.1 (20.5–23.7)
12-months prevalence of atopic dermatitis[d]	1,345 (99.0)	10.9 (9.2–12.6)	2,529 (98.4)	7.6 (6.6–8.6)
Participant's SES (high)[e]	1,351 (99.4)	59.5 (56.9–62.1)	2,548 (99.1)	44.1 (42.2–46.0)
Smoking[f]	1,346 (99.0)	29.1 (26.7–31.5)	2,546 (99.1)	37.9 (36.0–39.8)
Physical activity (high)[g]	1,353 (99.6)	50.3 (47.6–53.0)	2,554 (99.4)	48.9 (47.0–50.8)
Physical activity (low)[h]		44.3 (41.7–46.9)		42.2 (40.3–44.1)
Work overload[i]	1,348 (99.2)	27.7 (25.3–30.1)	2,516 (97.9)	25.7 (24.0–27.4)
Work discontent[i]	1,347 (99.1)	46.2 (43.5–48.9)	2,516 (97.9)	49.2 (47.2–51.2)
Exposure to any potential occupational risk factors for asthma and allergies[j]	1,335 (98.2)	14.2 (12.3–16.1)	2,450 (95.3)	13.8 (12.4–15.2)

[a] *The analysis for this table is based on all 3,929 SOLAR I participants including those, who did not give consent for linking the data to data from other study phases.*
[b] *Symptoms of wheezing within the last 12 months and a doctor diagnosis of asthma or multiple doctor diagnoses of asthmatic bronchitis.*
[c] *Having problems with sneezing or a runny blocked nose without having a cold during the last 12 months that were accompanied by itchy-watery eyes.*
[d] *Ever having had eczema for at least 6 months with symptoms during the 12 months prior to study and the itchy rash at any time affecting any of the following places: the folds of the elbows; behind the knees; in front of the ankles; under the buttocks; or around the neck, ears, or eyes.*
[e] *12 or more years of education.*
[f] *Smoked at least 20 packs in their life or for a year at least one cigarette per day or one cigar per week.*
[g] *Physical exercise more than once a week.*
[h] *Physical exercise between less than once a month and once a week.*
[i] *Age-specific T-value of item sum of corresponding scale and its 95% confidence interval exceeded the value of 50.*
[j] *Ever having had a job that was linked to a relevant exposure by an asthma-specific job-exposure-matrix.*

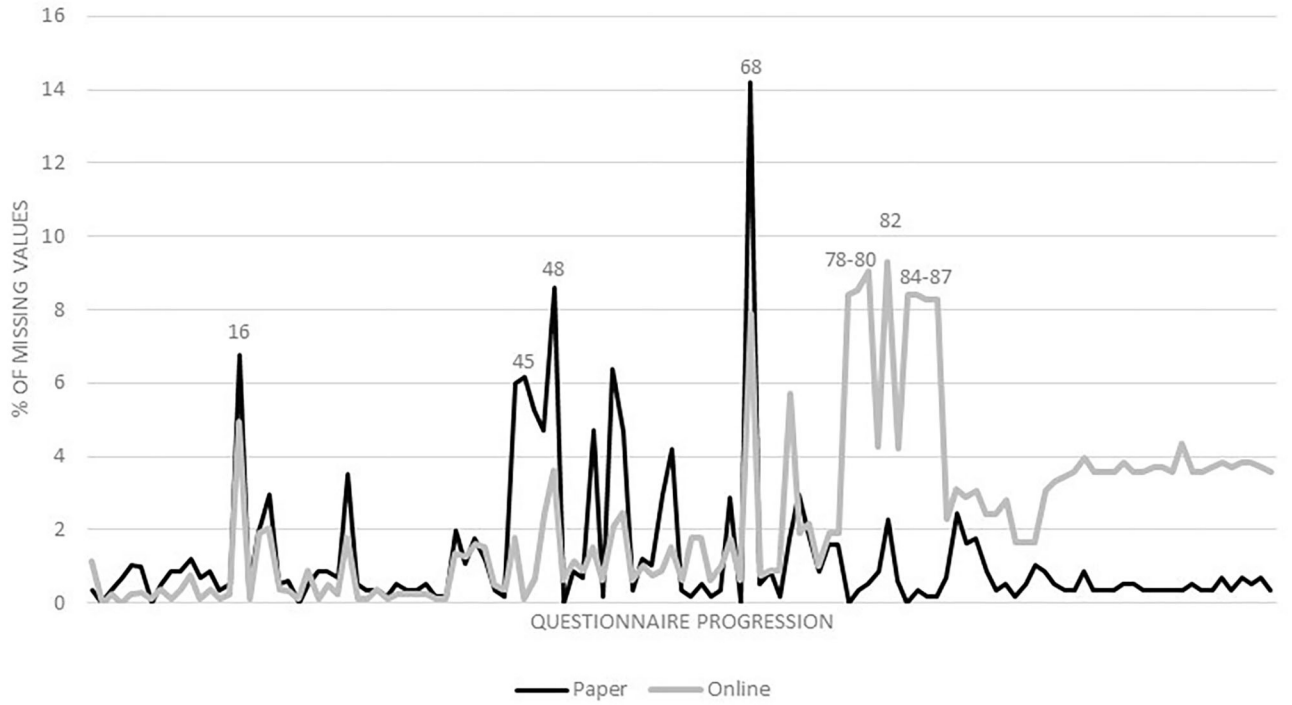

FIGURE 2 | Percentage of missing values for paper and online questionnaires from first to last questionnaire item. Question numbers: 16: doctor diagnosis of respiratory outcomes; 45: indoor mold; 48: skin-straining activities at home; 68: ETS; 78–79: symptoms of rhinoconjunctivitis due to an occupation; 80: wheezing due to an occupation; 82: quitting jobs because of symptoms of asthma or allergies; 84: use of gloves; 85: duration of glove use; 86: declaration of occupational disease; 87: reason of declaration of occupational disease.

workers, some cohorts recruited apprentices and followed them during their training (25). Other cohorts focused on estimating asthma incidences attributable to workplace exposures (26, 27). In contrast to the mentioned studies, SOLAR tries to investigate the course of asthma and allergies, including work-related phenotypes, from childhood to adulthood.

Although the initial cohort was population-based, a selection process led to a study population that is more female, higher educated, smokes less, and has a higher proportion of people with atopic dermatitis at the end of childhood. The proportion of participants with at least one parent that reported ever having had asthma, hay fever, or dermatitis was increased as well. The selection process was already present in earlier follow-ups (8). In the initial ISAAC cohort, however, participants and non-participants of clinical examinations were similar regarding atopic diseases in children and parents, parental education, family size, passive smoke exposure, and sex (28). Regarding the 1,099 invited children that didn't participate at all, no information on potential selection was available. It implies the potential of selection bias that needs to be considered carefully in analyses of follow-up data. Depending on the research question, the available information will be used to obtain less biased results, e.g., by adjusting estimates or multiply imputing missing values.

Since the cohort underwent a selection process over the years of follow-up, the generalizability of the study's results might be limited if selection bias affects the internal validity of the study. However, since the study's goal is the investigation of associations between occupational, environmental, and psychosocial exposures and asthma and allergy outcomes, this selection process does not affect the generalization of results on the basic association to other populations as long as the internal validity is not substantially affected. Nevertheless, asthma and allergies are complex diseases for which reason associations might vary for different genotypes, age groups and exposure histories. Therefore, genetic background and age of participants as well as environmental factors that might interact need to be considered when generalizing the results of the SOLAR study to other populations. After all, comparisons of future results to other cohorts is necessary for drawing conclusions about associations.

A strength of the SOLAR study is its still relatively high sample size after more than two decades of follow-up. This response could be reached using several methods to increase participation, including incentives, e-mail, postal, and telephone reminders as well as envelopes for returning study documents free of charge. Since e-mail addresses were collected in earlier study phases for a substantial part of the cohort, a valid postal address was not necessary for reaching these participants. An online version of the questionnaire was used to simplify participation for individuals with known e-mail addresses. One drawback of the online version was the difficulty to get informed consent, since it was necessary for the participants to conduct an extra step of

printing and sending the signed consent form. The number of missing forms and therefore of excluded questionnaires could be reduced substantially by sending out postal reminders, which made it necessary to get a valid postal address for some of the participants with known e-mail addresses after all.

The questions with higher proportions of missing values in the subset of online questionnaires mentioned earlier were all asked in the second half of the questionnaire. This might indicate that some participants quit before finishing and that 121 items are therefore too many for an online questionnaire. An alternative explanation for these differences might be that the questionnaire was too long in general and that we just received more incomplete online questionnaires than incomplete paper questionnaires as those were not sent-in.

In general, the online questionnaire was a good addition, because including logical links that made it possible to skip questions that were not applicable, and making it mandatory for continuing to answer certain questions, led to less missing values than in the paper version for most questions in the first half of the questionnaire. Apart from that, the use of online questionnaires saved time (of participants and the research team) and money for sending invitations and data entry. Although the proportion of missing values is not too high in total, multiple imputation methods should be used to limit potential biases. The information on the type of questionnaire (paper vs. online) should be included in the imputation process since it is a potential cause or correlate of missingness (29).

In conclusion, the third follow-up of the SOLAR cohort offers the opportunity to analyze the course and risk factors of asthma and allergies over more than 20 years from childhood to adulthood. The focus on the occupational environment, including the participants' full job histories, makes it possible to investigate occupational exposures in particular. The use of online questionnaires contributed to the feasibility of conducting a third follow-up and still yielding an adequate size of the study population. However, selection processes within the cohort might lead to sources of bias that need to be considered in future analyses.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of data protection reasons. Requests to access the datasets should be directed to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Ethical Committees of the Medical Faculty of the University of Dresden (EK 163042015) and the Bavarian Chamber of Physicians (mb BO 17015). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

FF drafted the manuscript. Data acquisition was coordinated by FF, SK, and LW. Data was interpreted by FF, JG, and KR. CV, JG, LW, TW, KR, DN, BS, EM, SK, and FF contributed substantially to the conception and design of the study. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2021.591717/full#supplementary-material

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The supplement of Paper II only contains the German and English versions of the SOLAR III questionnaire and is therefore not included here. It is available under the following link:

https://www.frontiersin.org/articles/10.3389/fpubh.2021.591717/full#supplementary-material

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Appendix: Paper III

ORIGINAL ARTICLE
ASTHMA

Nickel allergy is associated with wheezing and asthma in a cohort of young German adults: results from the SOLAR study

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ABSTRACT

Background: Nickel allergy is the most prevalent contact allergy. It belongs to a different hypersensitivity type to asthma and rhinoconjunctivitis. The aim of this analysis was to assess whether self-reported nickel allergy is associated with incident wheezing, asthma and rhinoconjunctivitis in young German adults, taking into account potential effect modification by sex.

Methods: In total, 2051 (70.6%) participants aged 19–24 years took part in the second phase of SOLAR (Study on Occupational Allergy Risks), a follow-up study of ISAAC II (the second phase of the International Study of Asthma and Allergies in Childhood) in Germany. Self-reported nickel allergy, as well as having pierced ears, and the three outcomes incident wheezing, asthma and rhinoconjunctivitis, were analysed stratified for sex. Logistic regression adjusted for potential confounders was performed.

Results: An association between self-reported nickel allergy and incident wheezing was observed for men and women, while only in males did pierced ears show a significant association with the outcome (adjusted OR 2.26, 95% CI 1.10–4.62). Also only in males, self-reported nickel allergy was associated with elevated odds for incident asthma (adjusted OR 4.34, 95% CI 1.22–15.41). Neither in men nor in women was a significant association observed for incident rhinoconjunctivitis.

Conclusion: Our results suggest that self-reported nickel allergy is associated with incident wheezing. Whether this association is due to environmental or genetic predisposition, or due to an overlap of the mechanisms of type I and type IV hypersensitivity, needs to be elucidated.

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Self-reported nickel allergy is associated with incident wheezing in young German males and females, and with incident asthma in males, whereas no significant association was observed for self-reported nickel allergy and incident rhinoconjunctivitis http://bit.ly/2YHmwBA

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Introduction

Nickel allergy, caused by skin contact to nickel, is the most common contact allergy in children, adolescents and adults. It is a cell-mediated hypersensitivity, where allergen-specific T-cells and memory T-cells proliferate. These memory T-cells are activated after renewed contact to nickel, resulting in inflammation [1]. With a point prevalence of 9.8–27.5%, it affects women more often than men (prevalence 2.1–5.1%) in all age groups [2–5]. In females, contact with earrings plays a major role in the sensitisation process [3, 6]. In 1994, the European Union adopted legislation to prevent further increase in nickel allergy. It has been in full force since 2001 and limits contact to nickel-releasing objects that are in direct or prolonged contact with the skin such as jewellery, watches and watch straps, buttons, and zips [7, 8]. So far, the restriction has been revised a few times and the nickel release of consumer objects further limited [9].

Like nickel allergy, asthma and rhinoconjunctivitis are high-prevalence diseases, especially in younger age groups [10, 11]. They are IgE mediated hypersensitivities, where naive T-cells develop into T-helper cells that produce cytokines. IgE produced by B-cells binds to mast cells and basophils. Allergen exposure leads to cellular degranulation, and the release of cytokines and chemokines [12]. While since 1973, many cases of asthma [13–16] and rhinitis/rhinoconjunctivitis [14, 17, 18] due to the inhalation of nickel have been reported, analyses of the association between nickel allergy, and atopy, atopic dermatitis [3, 6, 11, 19], hand dermatitis [4, 11, 20], and asthma or rhinoconjunctivitis [4, 21–24] have revealed conflicting results. Some population-based analyses and a record linkage of two registers concluded that there is no association between nickel allergy and asthma or rhinitis [11, 16–18]. In contrast to these results, Gül *et al.* [24] analysed data from 40 asthmatics and found an association with nickel allergy. Although the risk of developing asthma differs between males and females, with a reversal of prevalence in puberty, most studies did not analyse data from males and females separately [25]. Also lacking is an analysis focusing solely on the association of nickel allergy with incident wheezing, asthma and rhinoconjunctivitis in a general-population setting.

We therefore aimed to assess whether self-reported nickel allergy is associated with incident wheezing, asthma and rhinoconjunctivitis in young German adults and whether the effect is modified by sex. For this, we separately investigated longitudinal data from males and females from a population-based cohort study.

Methods

Study population

The present study population consisted of participants in the population-based cohort study SOLAR (Study on Occupational Allergy Risks). Details of the study design have been described elsewhere [26]. In short, SOLAR, with two German study centres in Munich and Dresden, is the follow-up study of ISAAC II (the second phase of the International Study of Asthma and Allergies in Childhood) [27]. ISAAC II was conducted in 1995–1996 and data from 6399 children (response rate 85.3%) aged 9–11 years were collected by means of parental questionnaires. These validated questionnaires included questions on atopic and respiratory symptoms, and on potential risk factors [27].

In 2002–2003, the then 16–18-year-old ISAAC II participants were re-contacted and 3785 of them (response rate 77.4%) took part in SOLAR I. Of those, 2051 young adults (response rate 70.6%) aged 19–24 years participated in the second follow-up (SOLAR II) during 2007–2009. The SOLAR questionnaires included, among others, questions on respiratory and atopic symptoms as well as questions on environmental and occupational risk factors. Mainly, they were adopted from the ECRHS (European Community Respiratory Health Survey) and ISAAC [28, 29].

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In the present analysis, data from the 2051 participants who took part in all three study phases were analysed. SOLAR I is considered the baseline and SOLAR II, the follow-up. As a source of information for some potential confounders, data from ISAAC II were used.

Written informed consent was obtained from the participants or their legal guardians. The ethical committees of the Medical Faculty of the University of Dresden, the Bavarian Chamber of Physicians and the University of Ulm approved the study phases.

Outcomes

The primary outcome of these analyses was incident wheezing, defined as no wheezing at baseline and current wheezing at follow-up. Wheezing, thereby, was defined as either wheezing or whistling in the chest without cold or the use of asthma medication during the last 12 months prior to the survey.

Incident asthma and incident rhinoconjunctivitis were considered secondary outcomes. They were defined analogously to incident wheezing as no symptoms of asthma or rhinoconjunctivitis at baseline and current symptoms at follow-up. The definition of asthma consisted of having physician-diagnosed asthma and either wheezing or whistling in the chest without cold or use of asthma medication during the last 12 months prior to the survey. Sneezing and having a runny or blocked nose without a cold accompanied by itchy or watery eyes within the previous 12 months before the survey characterised symptoms of rhinoconjunctivitis.

Only participants without asthma, wheezing or rhinoconjunctivitis at baseline (SOLAR I) were included in the analyses comparing participants without outcome at SOLAR I with those with outcome at SOLAR II.

Exposures

As exposure variables, we considered self-reported nickel allergy or having pierced ears as an indirect measurement for nickel allergy. In the questionnaires of SOLAR I and SOLAR II, the participants were asked whether they were allergic to nickel (question in SOLAR I and SOLAR II: "Are you allergic to nickel (*e.g.* earrings, jeans buttons, watchstraps)?"). Based on this information, two categories were created: those who reported nickel allergy at any time ("ever nickel allergy" group) and those who reported nickel allergy neither at SOLAR I nor at SOLAR II ("never nickel allergy" group). In SOLAR II, the participants were additionally asked if they had pierced ears (yes or no), which was considered as a second exposure variable.

Potential confounders

Based on the literature [19, 30], the following variables were taken into account as potential confounders: smoking status (never or ever), parental and participant's socioeconomic status (SES) (high or low), study centre (Dresden or Munich), and parental history of asthma (for the analyses of wheezing and asthma) and rhinitis (for the analyses of rhinoconjunctivitis) (yes or no). Age was not considered a confounder because all participants were about the same age.

Participants who had ever smoked were considered smokers and the others as never-smokers. School attendance for $\geqslant$12 years was assumed to correspond to a high SES and <12 years of school implied low SES. Parental history of asthma or rhinitis was given when at least one parent reported ever having had asthma or rhinitis.

Information on potential confounders was extracted from data from SOLAR I except for the information regarding the participants' parents (parental SES, and parental history of asthma and rhinitis), for which ISAAC II data were used.

Statistical analysis

The distribution of variables in the study population by sex was described in absolute numbers and percentages. Chi-squared tests were performed to check the independence of the results.

In multiple logistic regression analyses, the three outcomes, as well as the two exposures, were analysed separately. The number of participants included in the regression model varied due to the exclusion of participants who reported wheezing, asthma or rhinoconjunctivitis at baseline with respect to the outcome variables. Therefore, 1768 participants were included in the regression model for incident wheezing as the outcome variable. For the analysis of incident asthma, 1925 participants were included and 1578 for incident rhinoconjunctivitis (figure 1). Because of the differences in exposure and the different risk of developing asthma, we stratified for sex. The regression models were adjusted for the potential confounders. The variance inflation factors were assessed and implied that no multicollinearity was given.

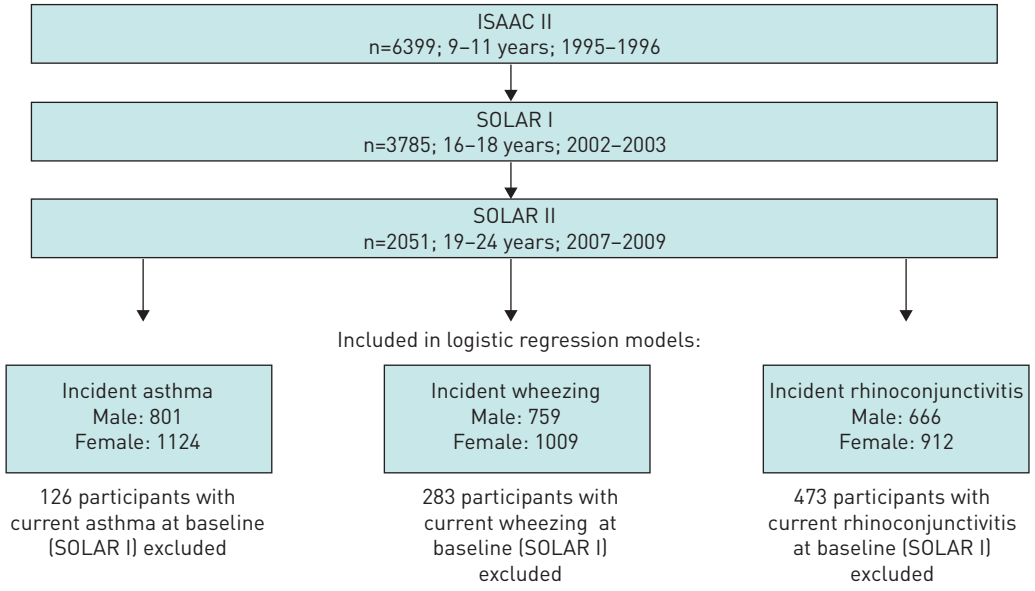

FIGURE 1 Study population included in ISAAC II (the second phase of the International Study of Asthma and Allergies in Childhood) with its two follow-ups SOLAR (Study on Occupational Allergy Risks) I and II, and participants included in the present analyses.

R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria) was used to perform the statistical analysis. Missing data were considered to be missing at random. The R package "mice" was used to impute the data applying m=5 imputations [31]. In addition, all models were repeated using nonimputed data without major changes in the effect estimates. The regression models analysing the nonimputed data, and the odds ratios and 95% confidence intervals of the potential confounders of the adjusted models are provided in the tables S1–S5.

Sensitivity analysis

For the sensitivity analysis, the dichotomised self-reported nickel allergy exposure variable (never or ever) was changed into four categories (never, persistent, remittent or incident). Participants that neither at the first nor at second survey reported being allergic to nickel were categorised as never having had nickel allergy. For the opposite scenario, participants reporting nickel allergy at both time points were grouped in the persistent nickel allergy category. The remittent nickel allergy group comprised those with nickel allergy at baseline and no nickel allergy at follow-up. Participants with no nickel allergy at baseline but nickel allergy at follow-up were categorised as having incident nickel allergy. Since there was no male participant with incident wheezing and incident nickel allergy, the incident nickel allergy category was excluded from the analysis for incident wheezing in males.

Results

Descriptive data

The study population comprised more females (58.1%) than males (41.9%). Females reported nickel allergy and pierced ears more often, and they were more likely to have ever smoked than male participants (table 1). Overall, the incidence of the three outcomes between SOLAR I and II was 126 for wheezing, 37 for asthma and 227 for rhinoconjunctivitis. Incidence did not differ by sex (figure 2).

Associations between nickel allergy and incident wheezing

An association between self-reported nickel allergy and incident wheezing was shown for males and females (table 2). After adjusting for potential confounders, this association was no longer statistically significant in females (adjusted OR 1.57, 95% CI 0.96–2.57). Having pierced ears was only statistically significantly associated with increased incidence of wheezing in males (adjusted OR 2.26, 95% CI 1.10–4.62) and not in females (adjusted OR 1.27, 95% CI 0.49–3.27) without indication of effect modification by sex. These results were basically confirmed when categorising the exposure (table S6).

TABLE 1 Description of exposures and potential confounders for males (n=860) and females (n=1191) in the study population (n=2051)

	Missing	Males	Females	Chi-squared test p-value
Nickel allergy	52 (2.5%)			<0.001
Never		772 (89.8%)	788 (66.2%)	
Ever		67 (7.8%)	372 (31.2%)	
Pierced ears	6 (0.3%)			<0.001
Yes		162 (18.8%)	1082 (90.8%)	
Smoking status	14 (0.7%)			<0.001
Ever		260 (30.2%)	458 (38.5%)	
Parental SES	29 (1.4%)			0.37
High[#]		513 (59.7%)	677 (56.8%)	
Participants' SES	10 (0.5%)			0.09
High[#]		487 (56.6%)	718 (60.3%)	
Study centre	0 (0.0%)			0.43
Dresden		428 (49.8%)	615 (51.6%)	
Parental history of asthma	55 (2.7%)			0.30
Yes[¶]		88 (10.2%)	103 (8.6%)	
Parental history of rhinitis	43 (2.1%)			0.17
Yes[¶]		312 (36.3%)	398 (33.2%)	

SES: socioeconomic status. [#]: ⩾12 years of school attendance for participant or at least one parent; [¶]: at least one parent ever had asthma or rhinitis.

Associations between nickel allergy and incident asthma

In males, the logistic regression model yielded a statistically significant association between self-reported nickel allergy and incident asthma (adjusted OR 4.34, 95% CI 1.22–15.41). For pierced ears, this association was no longer statistically significant after adjustment (adjusted OR 3.19, 95% CI 0.91–11.15). For females, no indication of an association between nickel allergy or pierced ears and incident asthma was observed (table 3). Categorisation of the exposure yielded similar results (table S6).

Associations between nickel allergy and incident rhinoconjunctivitis

No significant association with any of the two exposure variables and incident rhinoconjunctivitis was observed for males or females (table 4). Categorising the exposure revealed an association between incident nickel allergy and incident rhinoconjunctivitis in males (adjusted OR 4.45, 95% CI 1.19–16.67) (table S6).

Nonstratified analysis yielded similar results, with a significant association for nickel allergy and incident wheezing, and no association for incident asthma/rhinoconjunctivitis (table S7). The results of the regression models with interaction terms confirmed our results (table S8).

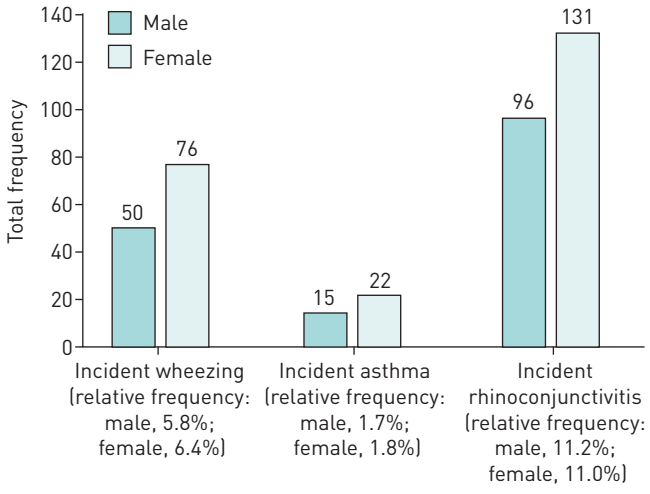

FIGURE 2 Total and relative frequency of participants with incident asthma, incident wheezing and incident rhinoconjunctivitis between SOLAR (Study on Occupational Allergy Risks) I and II by sex.

TABLE 2 Adjusted and unadjusted multiple logistic regression model for the association of self-reported nickel allergy and pierced ears with incident wheezing for males and females; imputed data, excluding those with wheezing at baseline

	Male (n=759)			Female (n=1009)		
	Incident wheezing[#]	cOR (95%CI)	aOR[¶] (95%CI)	Incident wheezing[#]	cOR (95%CI)	aOR[¶] (95%CI)
Nickel allergy						
Never	41 (6.0%) out of 688	1	1	43 (6.3%) out of 681	1	1
Ever	9 (16.4%) out of 55	3.05 (1.39–6.67)	2.90 (1.29–6.52)	32 (10.6%) out of 309	1.78 (1.10–2.87)	1.57 (0.96–2.57)
Pierced ears						
No	34 (5.5%) out of 617	1	1	5 (5.2%) out of 97	1	1
Yes	16 (11.6%) out of 138	2.22 (1.19–4.15)	2.26 (1.10–4.62)	71 (7.8%) out of 910	1.56 (0.61–3.96)	1.27 (0.49–3.27)

cOR: crude odds ratio; aOR: adjusted odds ratio. [#]: obtained from nonimputed data; [¶]: adjusted for potential confounders (smoking status, parental socioeconomic status (SES), participant's SES, study centre and parental history of asthma).

Discussion

In the present study, we aimed to investigate whether self-reported nickel allergy is associated with incident wheezing, asthma and rhinoconjunctivitis in young German adults. We separately analysed the data from male and female participants, and our analysis indicated an association between nickel allergy and incident wheezing and asthma. The observed associations differed between males and females, but confidence intervals were still overlapping thus not indicating effect modification by sex.

We observed strong effect estimates for nickel allergy and incident wheezing in males and females. The analyses of incident wheezing as the outcome had more statistical power than the analyses of incident asthma. Wheezing is a more sensitive means to assess asthma but the results may be less specific [32]. In our analysis, the statistical power of the analyses of incident asthma was limited. Due to the small number of participants, stratification for atopy was not possible. Regarding incident rhinoconjunctivitis, we observed no significant association with self-reported nickel allergy or pierced ears in either males or females. When stratifying for smoking status (never-smoker/ever-smoker) as a risk factor for contact allergy as well as wheezing, associations were stronger for never-smokers (table S9).

So far, three studies have investigated the association between contact allergy and atopy in a general population, with two of them analysing adolescents [4, 22] and the other analysing a broader age range (15–69 years) [21]. Nickel allergy as most prevalent contact allergy was investigated separately in these studies. Patch tests were used to determine nickel allergy [4, 21, 22]. In accordance with the results of our analysis of incident rhinoconjunctivitis, none of these studies found an association between nickel allergy and atopy. None of these studies used asthma symptoms or wheezing as a standalone outcome. Asthma and rhinoconjunctivitis share IgE-mediated inflammatory mechanisms but there are still differences that may explain our results showing no association for incident rhinoconjunctivitis but for incident wheezing/asthma. For severe asthma other mechanisms, not mediated by IgE are known. Additionally, asthma is more likely to occur due to low molecular weight agents than rhinitis, and the intensity of inflammation in asthma and rhinitis may differ [33–35]. Two other studies focussing on the coexistence of contact allergies in general in patients with allergic rhinitis and asthma found an inverse association between contact

TABLE 3 Adjusted and unadjusted multiple logistic regression model for the association of self-reported nickel allergy and pierced ears with incident asthma for males and females; imputed data, excluding those with asthma at baseline

	Male (n=801)			Female (n=1124)		
	Incident asthma[#]	cOR (95%CI)	aOR[¶] (95%CI)	Incident asthma[#]	cOR (95%CI)	aOR[¶] (95%CI)
Nickel allergy						
Never	11 (1.5%) out of 727	1	1	15 (2.0%) out of 747	1	1
Ever	4 (7.1%) out of 56	4.67 (1.44–15.18)	4.34 (1.22–15.41)	7 (2.0%) out of 346	1.04 (0.41–2.6)	0.93 (0.37–2.38)
Pierced ears						
No	9 (1.4%) out of 648	1	1	2 (1.9%) out of 103	1	1
Yes	6 (4.0%) out of 149	3.19 (1.11–9.11)	3.19 (0.91–11.15)	20 (2.0%) out of 1019	1.03 (0.24–4.47)	0.96 (0.21–4.33)

cOR: crude odds ratio; aOR: adjusted odds ratio. [#]: obtained from nonimputed data; [¶]: adjusted for potential confounders (smoking status, parental socioeconomic status (SES), participant's SES, study centre and parental history of asthma).

TABLE 4 Adjusted and unadjusted multiple logistic regression model for the association of self-reported nickel allergy and pierced ears with incident rhinoconjunctivitis for males and females; imputed data, excluding those with rhinoconjunctivitis at baseline

	Male (n=666)			Female (n=912)		
	Incident rhinoconjunctivitis[#]	cOR (95%CI)	aOR[¶] (95%CI)	Incident rhinoconjunctivitis[#]	cOR (95%CI)	aOR[¶] (95%CI)
Nickel allergy						
Never	84 (13.8%) out of 607	1	1	89 (14.3%) out of 622	1	1
Ever	8 (18.2%) out of 44	1.33 (0.60–2.99)	1.29 (0.56–2.94)	41 (15.4%) out of 267	1.12 (0.75–1.67)	1.14 (0.76–1.71)
Pierced ears						
No	79 (14.4%) out of 547	1	1	9 (11.2%) out of 80	1	1
Yes	16 (13.09%) out of 115	0.97 (0.54–1.73)	1.08 (0.58–2.02)	122 (14.7%) out of 830	1.35 (0.65–2.77)	1.43 (0.69–2.97)

cOR: crude odds ratio; aOR: adjusted odds ratio. [#]: obtained from nonimputed data; [¶]: adjusted for potential confounders (smoking status, parental socioeconomic status (SES), participant's SES, study centre and parental history of asthma).

allergies and atopic dermatitis, allergic rhinitis, allergic conjunctivitis and asthma [23, 36]. Nonetheless, a case–control study among 40 asthmatics and nonasthmatics indicated higher odds of sensitisation to nickel among cases compared to controls [24]. An increased frequency of contact allergy in atopics may be due to an altered cell-mediated immunity and a lower threshold for developing contact allergy in atopics [3, 36]. Case reports about asthma and rhinitis in association with occupational nickel exposure or work-related nickel allergy showed that the inhalation of nickel can cause respiratory symptoms [13–18].

The major strength of our study is the longitudinal design, which provides the opportunity to follow the participants over a long time. Due to our definition of the exposures and our outcome definitions we can ensure that the exposure preceded the outcomes. A negative aspect of the long follow-up time of our study is the loss of participants, which may cause selection bias. Previous analysis showed that participants with atopic diseases in ISAAC II and those whose parents had allergic diseases were more likely to participate in the follow-up studies [26]. In our study sample, selection bias should be limited though, since in a nonresponder analysis considering the outcomes and the exposures, we did not observe statistically significant differences between participants and nonparticipants (data not shown).

We analysed the association between self-reported nickel allergy and incident wheezing, asthma and rhinoconjunctivitis based on questionnaire answers and not based on objective measurements. Our variables are thereby susceptible to differential misclassification. The definitions of the outcome variables were based on standardised and validated questions from ISAAC, which were used throughout the different study phases [28]. The question on whether the participants have nickel allergy was integrated later in the SOLAR questionnaire. Studies analysing the validity of self-reported nickel allergy found a positive predictive value (PPV) ranging from 32% to 71%; thus, the validity of self-reported nickel allergy is rather low but still reasonable [5, 37, 38]. As part of the clinical examination in SOLAR II, 288 participants were patch tested for nickel sulfate. With a PPV of 44%, the validity of self-reported nickel allergy is thus in accordance to the findings of other studies. In general, comparing patch tests to self-reports revealed that self-reports overestimate the prevalence of nickel allergy [5, 37, 38]. In population-based studies, the response decreases when clinical examinations are involved. For patch tests, participants must visit the clinic twice (first to apply the patch and then to read the patch test). As a result, only 14% of the participants answering the SOLAR II questionnaire agreed to the test.

Because of the adoption of the nickel directive in 1994, the nickel release of consumer objects should be limited and pierced ears should not be associated with nickel allergy anymore. After the nickel legislation, there was indeed a decrease in the observed prevalence of nickel allergy in females aged 18–35 years and in dermatitis patients [39]. Unfortunately, there was no further decrease. Investigation has shown that ear piercings still exceed the nickel release threshold and therefore, nickel allergy remains highly prevalent [39, 40]. Pierced ears can still be considered an indirect measurement for nickel allergy. In our analysis, the statistical power of pierced ears in females was very low as piercing ears was common among them. This may explain why we observed an association of pierced ears with incident wheezing only in male participants. Contrary to our expectations, no effect modification could be proven due to overlapping

confidence intervals. Furthermore, the participants were asked whether they have pierced ears and not if they wear earrings. This may lead to systematic bias in our analysis.

Unmeasured confounding should be limited but cannot be excluded in our study. We adjusted for the most important confounders known from literature. Occupation could be considered an additional confounder. The literature concerning occupational risk factors for nickel allergy is based on just a number of jobs with very specific nickel exposures. Therefore, and since our study population consisted of a young age group that was just at the beginning of work life, we did not consider occupation as a potential confounder [19, 41]. Because we analysed data from young German adults, our results are not fully generalisable to other age groups and countries.

Overall, our results indicate that self-reported nickel allergy is associated with incident wheezing in young German males and females. Even though nickel allergy and asthma belong to two different hypersensitivity types with different mechanisms, our results indicate an association. It is important to further investigate whether this association is due to environmental or genetic predisposition, or due to an overlap of the mechanisms.

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SUPPLEMENTARY MATERIAL

S1: Adjusted and unadjusted multiple logistic regression model for the association of nickel allergy or pierced ears with incident wheezing for males and females, non-imputed data, excluding those with wheezing at baseline

	male (n=759)				female (n=1009)			
	n=736		n=715		n=972		n=913	
	cOR*	95 %CI	aOR**	95 %CI	cOR*	95 %CI	aOR**	95 %CI
nickel allergy								
never	1		1		1		1	
ever	3.08	1.41-6.72	2.71	1.17-6.30	1.78	1.10-2.88	1.64	0.99-2.72
pierced ears								
no	1		1		1		1	
yes	2.24	1.20-4.18	2.22	1.07-4.62	1.56	0.62-3.97	1.23	0.47-3.18

OR: odds ratio; CI: confidence interval; SES: socioeconomic status
*cOR: crude (unadjusted) Odds Ratio
**Odds Ratio adjusted for potential confounders: smoking status, parental SES, participant's SES, study centre and parental history of asthma

S2: Adjusted and unadjusted multiple logistic regression model for the association of nickel allergy or pierced ears with incident asthma for males and females, non-imputed data, excluding those with asthma at baseline

	male				female			
	n=767		n=743		n=1073		n=1006	
	cOR*	95 %CI	aOR**	95 %CI	cOR*	95 %CI	aOR**	95 %CI
nickel allergy								
never	1		1		1		1	
ever	5.25	1.61-17.08	5.01	1.42-17.70	1.01	0.41-2.49	0.97	0.38-2.47
pierced ears								
no	1		1		1		1	
yes	3.03	1.06-8.64	2.95	0.86-10.11	1.02	0.24-4.45	0.94	0.21-4.22

OR: odds ratio; CI: confidence interval; SES: socioeconomic status
*cOR: crude (unadjusted) Odds Ratio
**Odds Ratio adjusted for potential confounders: smoking status, parental SES, participant's SES, study centre and parental history of asthma

S3: Adjusted and unadjusted multiple logistic regression model for the association of nickel allergy or pierced ears with incident rhinoconjunctivitis for males and females, non-imputed data, excluding those with rhinoconjunctivitis at baseline

	male				female			
	n=643		n=619		n=872		n=832	
	cOR*	95 %CI	aOR**	95 %CI	cOR*	95 %CI	aOR**	95 %CI
nickel allergy								
never	1		1		1		1	
ever	1.41	0.63-3.14	1.46	0.64-3.33	1.11	0.75-1.67	1.01	0.66-1.55
pierced ears								
no	1		1		1		1	
yes	0.96	0.54-1.71	1.03	0.54-1.94	1.36	0.66-2.79	1.40	0.67-2.91

OR: odds ratio; CI: confidence interval; SES: socioeconomic status

*cOR: crude (unadjusted) Odds Ratio

**Odds Ratio adjusted for potential confounders: smoking status, parental SES, participant's SES, study centre and parental history of rhinitis

S4: Effect estimates for potential confounders, multiple logistic regression model for the association of self-reported nickel allergy and incident wheezing, asthma and rhinoconjunctivitis for males and females, imputed data, excluding those with † wheezing, ‡ asthma and § rhinoconjunctivitis at baseline

incident wheezing †				
	male (n=759)		female (n=1009)	
	OR	95 %CI	OR	95 %CI
ever smoking	2.27	1.22-4.24	2.34	1.43-3.86
low parental SES¶	0.97	0.51-1.86	1.12	0.67-1.89
low participant's SES¶	0.87	0.45-1.69	1.49	0.89-2.52
study centre (Dresden)	0.65	0.35-1.18	0.93	0.57-1.50
present parental history of asthma+	3.30	1.55-7.02	1.13	0.49-2.60
incident asthma ‡				
	male (n=801)		female (n=1124)	
	OR	95 %CI	OR	95 %CI
ever smoking	1.71	0.56-5.16	1.24	0.51-3.00
low parental SES¶	0.71	0.22-2.24	1.60	0.62-4.15
low participant's SES¶	2.00	0.59-6.74	1.38	0.54-3.54
study centre (Dresden)	0.61	0.21-1.78	1.18	0.49-2.81
present parental history of asthma+	7.50	2.47-22.79	2.86	0.90-9.02
incident rhinoconjunctivitis §				
	male (n=666)		female (n=912)	
	OR	95 %CI	OR	95 %CI
ever smoking	1.19	0.72-1.95	0.94	0.63-1.40
low parental SES¶	0.84	0.52-1.38	0.86	0.57-1.30
low participant's SES¶	0.84	0.51-1.38	1.20	0.79-1.82
study centre (Dresden)	0.71	0.45-1.10	1.03	0.71-1.50
present parental history of rhinitis+	1.49	0.95-2.34	1.43	0.97-2.12

OR: odds ratio; CI: confidence interval; SES: socioeconomic status

¶SES (socioeconomic status) high: at least 12 years of school attendance for participant or at least one parent

+ At least one parent ever had asthma or rhinitis

S5: Effect estimates for potential confounders, multiple logistic regression model for the association of earpiercing and incident wheezing, asthma and rhinoconjunctivitis for males and females, imputed data, excluding those with † wheezing, ‡ asthma and § rhinoconjunctivitis at baseline

incident wheezing †				
	male (n=759)		female (n=1009)	
	OR	95 %CI	OR	95 %CI
ever smoking	2.08	1.12-3.87	2.42	1.48-3.96
low parental SES¶	0.87	0.44-1.71	1.13	0.67-1.92
low participant's SES¶	0.81	0.41-1.60	1.51	0.90-2.54
study centre (Dresden)	0.64	0.35-1.16	0.90	0.56-1.46
present parental history of asthma+	3.36	1.59-7.12	1.19	0.52-2.74
incident asthma ‡				
	male (n=801)		female (n=1124)	
	OR	95 %CI	OR	95 %CI
ever smoking	1.40	0.45-4.37	1.24	0.51-3.01
low parental SES¶	0.54	0.16-1.80	1.63	0.64-4.15
low participant's SES¶	1.84	0.54-6.27	1.35	0.53-3.46
study centre (Dresden)	0.59	0.20-1.76	1.25	0.53-2.95
present parental history of asthma+	7.36	2.45-22.05	3.39	1.06-10.87
incident rhinoconjunctivitis §				
	male (n=666)		female (n=912)	
	OR	95 %CI	OR	95 %CI
ever smoking	1.16	0.70-1.94	0.96	0.65-1.44
low parental SES¶	0.82	0.49-1.37	0.87	0.57-1.32
low participant's SES¶	0.86	0.52-1.41	1.16	0.77-1.75
study centre (Dresden)	0.70	0.45-1.09	1.05	0.72-1.52
present parental history of rhinitis+	1.49	0.95-2.33	1.42	0.95-2.11

OR: odds ratio; CI: confidence interval; SES: socioeconomic status

¶ SES (socioeconomic status) high: at least 12 years of school attendance for participant or at least one parent

+ At least one parent ever had asthma or rhinitis

S6: Adjusted and unadjusted multiple logistic regression model for the association of nickel allergy (never/persistent/ remittent/ incident) and pierced ears with incident wheezing, asthma and rhinoconjunctivitis for males and females, imputed data, excluding those with † wheezing, ‡ asthma and § rhinoconjunctivitis at baseline

	incident wheezing †							
	male (n=759)				female (n=1009)			
	cOR*	95 %CI	aOR[1]	95 %CI	cOR*	95 %CI	aOR[1]	95 %CI
nickel allergy								
never		1		1		1		1
persistent	4.87	1.70-13.93	4.31	1.47-12.62	1.25	0.64-2.44	1.07	0.54-2.12
remittent	3.68	1.19-11.40	3.81	1.16-12.52	2.60	1.20-5.63	2.51	1.14-5.53
Incident ¶					2.51	1.23-5.10	2.26	1.09-4.69
pierced ears								
no		1		1		1		1
yes	2.22	1.19-4.15	2.26	1.10-4.62	1.56	0.61-3.96	1.27	0.49-3.27
	incident asthma ‡							
	male (n=801)				female (n=1124)			
	cOR*	95 %CI	aOR[2]	95 %CI	cOR*	95 %CI	aOR[2]	95 %CI
nickel allergy								
never		1		1		1		1
persistent	6.39	1.32-30.78	6.12	1.21-30.89	0.83	0.24-2.90	0.74	0.21-2.62
remittent	3.42	0.42-27.97	3.16	0.35-28.87	0.70	0.09-5.35	0.65	0.08-5.06
incident	6.33	0.74-53.86	5.20	0.45-60.11	1.90	0.53-6.79	1.68	0.47-6.08
pierced ears								
no		1		1		1		1
yes	3.19	1.11-9.11	3.19	0.91-11.15	1.03	0.24-4.47	0.96	0.21-4.33
	Incident rhinoconjunctivitis §							
	male (n=666)				female (n=912)			
	cOR*	95 %CI	aOR[3]	95 %CI	cOR*	95 %CI	aOR[3]	95 %CI
nickel allergy								
never		1		1		1		1
persistent	0.45	0.06-3.63	0.40	0.05-3.25	0.96	0.56-1.65	0.99	0.57-1.70
remittent	1.51	0.44-5.11	1.56	0.45-5.39	1.14	0.52-2.51	1.14	0.51-2.52
incident	4.05	1.12-14.69	4.45	1.19-16.67	1.50	0.79-2.84	1.55	0.82-2.94
pierced ears								
no		1		1		1		1
yes	0.97	0.54-1.73	1.08	0.58-2.02	1.35	0.65-2.77	1.43	0.69-2.97

OR: odds ratio; CI: confidence interval; SES: socioeconomic status

*cOR: crude (unadjusted) Odds Ratio

[1],[2] adjusted for potential confounders: smoking status, parental SES, participant's SES, study centre and parental history of asthma

[3] adjusted for potential confounders: smoking status, parental SES, participant's SES, study centre and parental history of rhinitis

¶ Due to a lack of male participants, incident nickel allergy was excluded from the regression models in males

S7: Adjusted and unadjusted multiple logistic regression model for association between

nickel allergy and pierced ears with incident wheezing, asthma and rhinoconjunctivitis, imputed data, excluding those with † wheezing, ‡ asthma and § rhinoconjunctivitis at baseline

incident wheezing † (n=1768)				
	cOR*	(95% CI)	aOR 1	(95% CI)
nickel allergy				
never	Reference		Reference	
ever	1.99	(1.35-2.96)	1.75	(1.15-2.68)
pierced ears				
no	Reference		Reference	
yes	1.55	(1.05-2.30)	1.60	(0.91-2.80)
incident asthma ‡ (n=1925)				
	cOR*	(95% CI)	aOR 2	(95% CI)
nickel allergy				
never	Reference		Reference	
ever	1.55	(0.75-3.19)	1.36	(0.62-2.95)
pierced ears				
no	Reference		Reference	
yes	1.58	(0.78-3.23)	1.95	(0.72-5.27)
incident rhinoconjunctivitis § (n=1578)				
	cOR*	(95% CI)	aOR 3	(95% CI)
nickel allergy				
never	Reference		Reference	
ever	1.14	(0.81-1.61)	1.16	(0.81-1.66)
pierced ears				
no	Reference		Reference	
yes	1.05	(0.79-1.40)	1.17	(0.75-1.82)

OR: odds ratio; CI: confidence interval; SES: socioeconomic status
*cOR: crude (unadjusted) Odds Ratio
[1],[2] adjusted for potential confounders: smoking status, parental SES, participant's SES, study centre and parental history of asthma
[3] adjusted for potential confounders: smoking status, parental SES, participant's SES, study centre and parental history of rhinitis

S8: P-values of the adjusted multiple logistic regression model with interaction term for association between nickel allergy and pierced ears with incident wheezing, asthma and rhinoconjunctivitis, imputed data, excluding those with † wheezing, ‡ asthma and § rhinoconjunctivitis at baseline

	p-value of the adjusted multiple logistic regression model with interaction term nickel allergy*sex	p-value of the adjusted multiple logistic regression model with interaction term pierced ears*sex
Incident wheezing †	0.38	0.70
Incident asthma ‡	0.06	0.35
Incident rhinoconjunctivitis §	0.73	0.45

S9: Adjusted multiple logistic regression model for the association of nickel allergy and pierced ears with incident wheezing, asthma and rhinoconjunctivitis for males and females, stratified for smoking status, imputed data, excluding those with † wheezing, ‡ asthma and § rhinoconjunctivitis at baseline

incident wheezing †								
	Never smoker				Ever smoker			
	male (n=537)		female (n=647)		male (n=217)		female (n=353)	
	aOR[1]	95 %CI	aOR[1]	95 %CI	aOR[1]	95 %CI	aOR[1]	95 %CI
nickel allergy								
never		1		1		1		1
ever	5.50	1.94-15.59	1.56	0.74-3.30	1.31	0.28-6.10	1.57	0.82-3.00
pierced ears								
no		1		1		1		1
yes	2.04	0.35-11.89	0.90	0.30-2.69	4.74	1.89-11.91	2.84	0.37-21.97
incident asthma ‡								
	male (n=557)		female (n=692)		male (n=239)		female (n=423)	
	aOR[2]	95 %CI	aOR[2]	95 %CI	aOR[2]	95 %CI	aOR[2]	95 %CI
nickel allergy ¶								
never		1		1		1		1
ever	7.40	1.32-41.50	3.58	1.11-11.58	4.22	0.61-29.0		-
pierced ears ¶								
no		1		1		1		1
yes	3.53	0.57-3.24		-	2.04	0.35-11.89	0.23	0.04-1.22
Incident rhinoconjunctivitis §								
	male (n=469)		female (n=571)		male (n=193)		female (n=336)	
	aOR[3]	95 %CI	aOR[3]	95 %CI	aOR[3]	95 %CI	aOR[3]	95 %CI
nickel allergy								
never		1		1		1		1
ever	2.39	0.94-6.08	1.07	0.63-1.83	0.32	0.04-2.41	1.24	0.64-2.39
pierced ears								
no		1		1		1		1
yes	1.07	0.35-3.24	1.50	0.65-3.46	0.87	0.35-2.16	1.37	0.30-6,28

OR: odds ratio; CI: confidence interval; SES: socioeconomic status

[1],[2] adjusted for potential confounders: smoking status, parental SES, participant's SES, study centre and parental history of asthma

[3] adjusted for potential confounders: smoking status, parental SES, participant's SES, study centre and parental history of rhinitis

¶ In our study population were no female smoker with incident asthma and nickel allergy, as well as no female nonsmokers with incident asthma and pierced ears

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