



## ORIGINAL ARTICLE

## Asthma and Lower Airway Disease

# Trajectories of asthma and allergy symptoms from childhood to adulthood

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## Funding information

German Ministry for Economy and Labour; German Ministry of Education and Research; German Ministry of Labour and Social Affairs; German Federal Institute for Occupational Safety and Health; Deutsche Forschungsgemeinschaft

## 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.

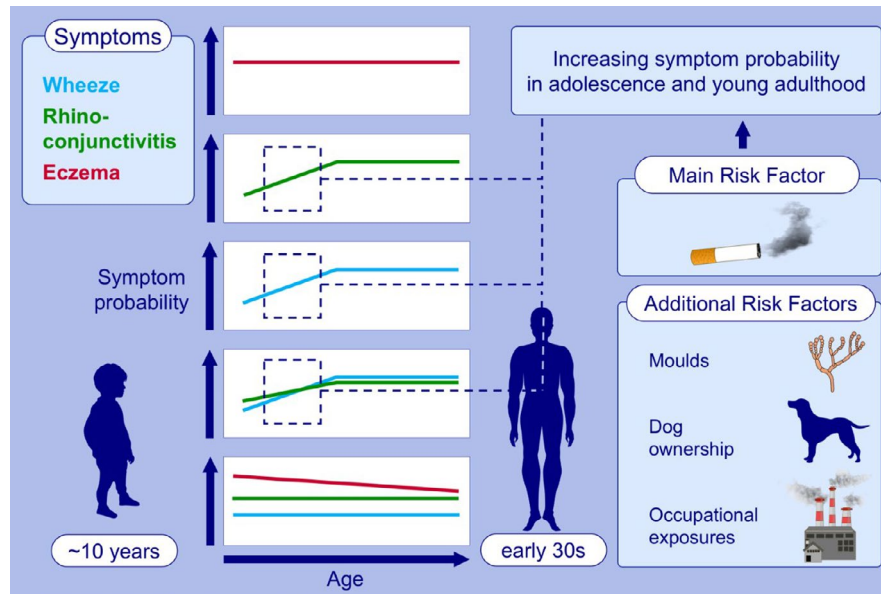
## KEYWORDS

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.

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## 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.<sup>1,2</sup> 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.<sup>3</sup>

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.<sup>4</sup> The availability of plausible pathways, e.g. via skin barrier dysfunction, supports the atopic march model.<sup>5,6</sup> However, the prevalence of individual trajectories following the atopic march seems lower than anticipated with many patients not showing the expected sequence of symptoms.<sup>7,8</sup>

Individual atopic diseases are often classified by the underlying pathomechanism (endotype)<sup>9</sup> 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<sup>10-15</sup>, childhood asthma<sup>16-18</sup>, childhood atopic dermatitis<sup>19-23</sup>, adulthood asthma<sup>18,24-28</sup>, and adulthood rhinitis<sup>29-31</sup>. 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.<sup>32</sup>

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.<sup>33</sup> 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).<sup>34,35</sup> 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

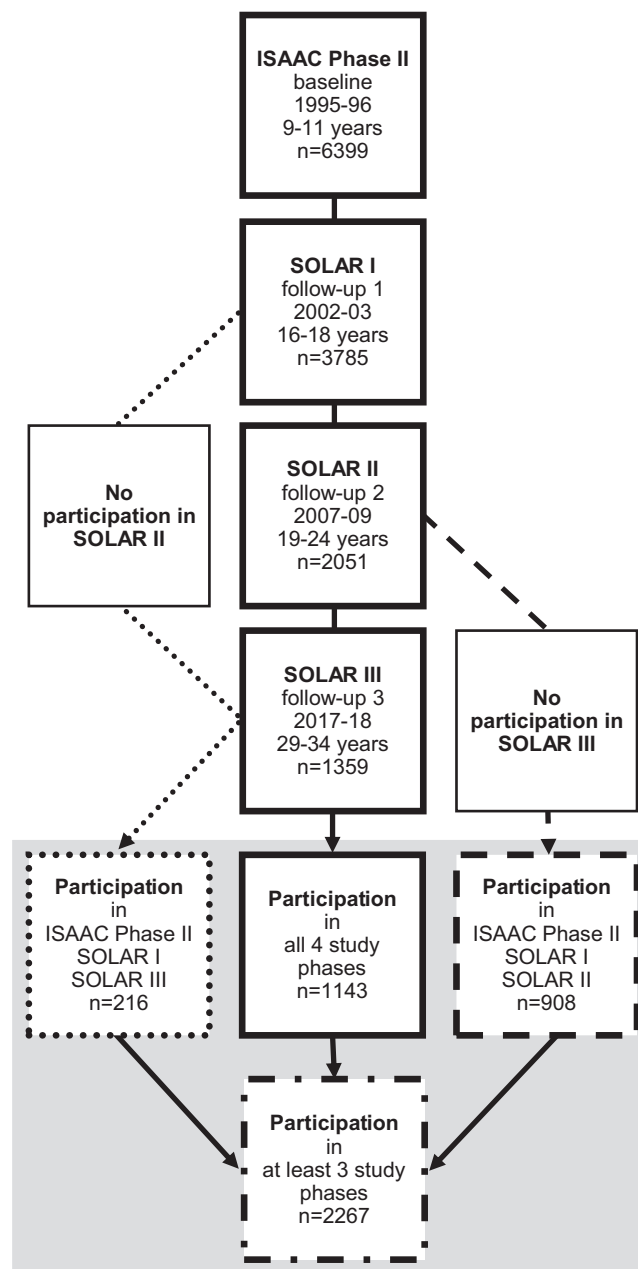
Three symptoms were included as LCA indicator variables (yes/no) measured at baseline (bl: ISAAC Phase II) and follow-up (fu: SOLAR) 1 to 3: wheeze (within the 12 months prior to the survey), rhinoconjunctivitis (having problems with sneezing or a runny or blocked nose without having a cold during the 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)<sup>36</sup>, and immunoglobulin E (IgE) against inhalant and food allergens (positive vs. negative; positive: >0.35 U/ml)<sup>36</sup>;  
 young adulthood traits: bronchial hyperresponsiveness (yes vs. no)<sup>34</sup>, lung function (forced expiratory volume in 1 second FEV1/ forced vital capacity FVC)<sup>34</sup>, and exhaled nitric oxide<sup>34</sup>;  
 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<sup>37</sup> 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<sup>2</sup> for participants of age 18



**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

or older and according to cut-offs by the International Obesity Task Force for those below 18 years.<sup>38</sup> 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.

## 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 measurable) 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<sup>39</sup>, 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<sup>39</sup> 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.<sup>40</sup> Multiple imputation was used for handling missing values, with the exception of model selection which was done using Full Information Maximum Likelihood (FIML) methods<sup>41</sup> 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.<sup>42</sup> 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<sup>7,10,11,13-15</sup>, 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<sup>41</sup> in SAS (Version 9.4, SAS Institute, Inc., Cary, NC). Remaining calculations were done in R (Version 4.0.2)<sup>43</sup> including multiple imputation (using the package MICE<sup>44</sup>). Additional details of the application of LCA are provided as supporting information.

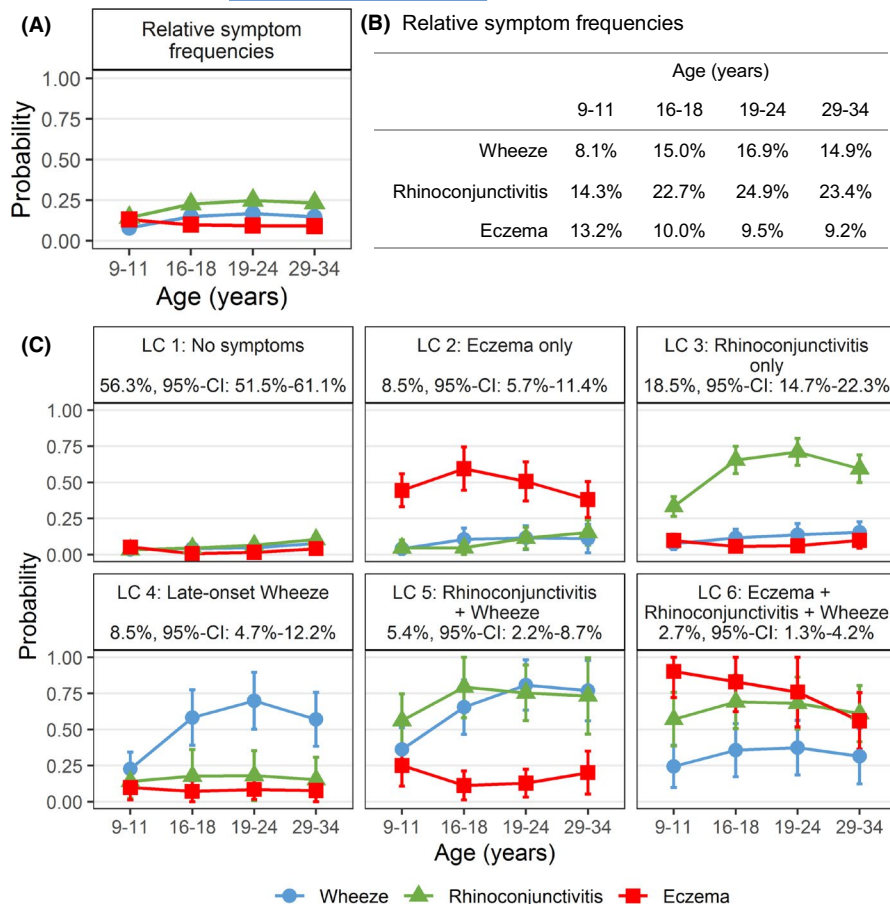
## 3 | RESULTS

### 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	Males N=970	Females N=1297
	n (% <sup>†</sup> )	n (% <sup>‡</sup> )	n (% <sup>‡</sup> )
Wheeze (bl)	35 (1.5)	105 (11.0)	76 (5.9)
Wheeze (fu1)	7 (0.3)	129 (13.3)	209 (16.2)
Wheeze (fu2) <sup>§</sup>	216 (9.5)	139 (16.1)	208 (17.5)
Wheeze (fu3) <sup>¶</sup>	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) <sup>§</sup>	241 (10.6)	214 (25.2)	290 (24.6)
Rhinoconjunctivitis (fu3) <sup>¶</sup>	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) <sup>§</sup>	231 (10.2)	64 (7.5)	129 (10.9)
Eczema (fu3) <sup>¶</sup>	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) <sup>§</sup>	1842 (81.3)	28 (15.8)	48 (19.4)
	n (%)	mean (SD)	mean (SD)
FEV <sub>1</sub> /FVC (fu2) <sup>§</sup>	1144 (50.5)	0.843 (0.075)	0.871 (0.068)
FeNO (in ppb, fu2) <sup>§</sup>	1200 (52.9)	27.0 (24.1)	19.3 (18.9)

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

<sup>†</sup>of all 2267 included participants;

<sup>‡</sup>of all non-missing values;

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

<sup>¶</sup>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.

Variable	Missing values	Males N=970	Females N=1297
	n (% <sup>†</sup> )	n (% <sup>‡</sup> )	n (% <sup>‡</sup> )
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.

<sup>†</sup>of all 2267 included participants;

<sup>‡</sup>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

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

“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.<sup>45</sup>

### 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

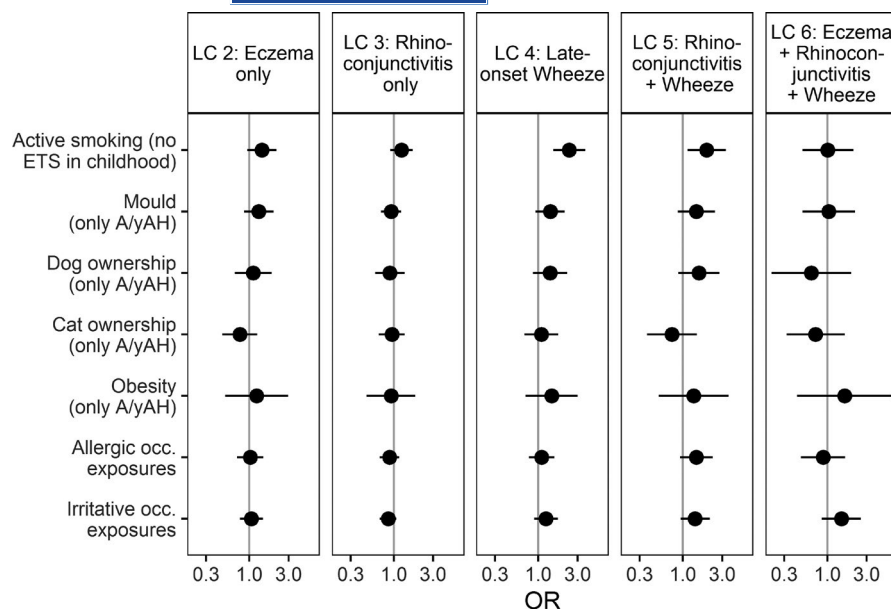
TABLE 3 Traits of derived latent classes in childhood (baseline) and young adulthood (follow-up 2)

Latent class	1		2		3		4		5		6	
	No symptoms	Eczema only	Rhinoconjunctivitis only	Late-onset Wheeze	Rhinoconjunctivitis + Wheeze	Eczema + Rhinoconjunctivitis + Wheeze	% <sup>†</sup>	% <sup>†</sup>	% <sup>†</sup>	% <sup>†</sup>	% <sup>†</sup>	% <sup>†</sup>
<b>Childhood traits</b>	% <sup>†</sup>	% <sup>†</sup>	% <sup>†</sup>	% <sup>†</sup>	% <sup>†</sup>	% <sup>†</sup>	% <sup>†</sup>	% <sup>†</sup>	% <sup>†</sup>	% <sup>†</sup>	% <sup>†</sup>	% <sup>†</sup>
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)						
<b>Young adulthood traits</b>	% <sup>†</sup>	% <sup>†</sup>	% <sup>†</sup>	% <sup>†</sup>	% <sup>†</sup>	% <sup>†</sup>						
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 <sup>†</sup> SD <sup>†</sup>	Mean <sup>†</sup> SD <sup>†</sup>	Mean <sup>†</sup> SD <sup>†</sup>	Mean <sup>†</sup> SD <sup>†</sup>	Mean <sup>†</sup> SD <sup>†</sup>	Mean <sup>†</sup> SD <sup>†</sup>						
FEV <sub>1</sub> /FVC (in %)	86.1 (85.8–86.3)	86.1 (85.3–86.8)	86.2 (85.7–86.7)	83.9 (83.2–84.7)	83.2 (82.2–84.3)	84.6 (83.1–85.8)						
	7.1 (7.0–7.4)	7.0 (6.3–7.6)	7.1 (6.8–7.5)	8.5 (7.9–9.1)	8.5 (7.7–9.4)	7.6 (6.8–8.7)						
FeNO (in ppb)	18.9 (18.3–19.7)	20.3 (18.4–22.4)	26.3 (24.2–28.4)	25.9 (22.8–29.0)	35.5 (30.6–40.0)	34.3 (29.9–40.1)						
	16.3 (14.9–18.0)	18.7 (14.5–23.2)	23.7 (20.9–27.4)	26.1 (21.5–31.7)	33.5 (25.6–41.9)	37.5 (32.5–47.4)						

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

<sup>†</sup>averaged over 20 draws from each of the 20 imputed datasets with 5<sup>th</sup> and 95<sup>th</sup> 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.<sup>46</sup> 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.<sup>47</sup> 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 et al. who investigated developmental profiles of wheeze, rhinitis, and eczema in children from age 1

to 11 years<sup>7</sup>, 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.<sup>34,35</sup> 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.

## ACKNOWLEDGEMENTS

The authors cordially thank all study participants and the students that helped entering paper questionnaires. The ISAAC Phase Two study in Dresden and Munich was supported by the German Ministry of Education and Research (01 EE 9411-3). The SOLAR I study was supported by the German Ministry for Economy and Labour. The SOLAR II study was supported by the German Federal Institute

for Occupational Safety and Health and the German Ministry of Labour and Social Affairs. The SOLAR III study was supported by the German Research Foundation (DFG) under project number GZ: RA 857/12-1 AOBJ: 629972; GZ: VO 839/2-1 AOBJ: 629973.

## 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 Böhlinger 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 ProtectImmun 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.

**How to cite this article:** Forster F, Ege MJ, Gerlich J, et al. Trajectories of asthma and allergy symptoms from childhood to adulthood. *Allergy*. 2022;77:1192–1203. <https://doi.org/10.1111/all.15075>