ORIGINAL ARTICLE

Longitudinal Asthma Phenotypes from Childhood to Middle-Age
A Population-based Cohort Study

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Abstract

Rationale: Asthma is a heterogeneous condition, and longitudinal phenotyping may provide new insights into the origins and outcomes of the disease.

Objectives: We aimed to characterize the longitudinal phenotypes of asthma between the first and sixth decades of life in a population-based cohort study.

Methods: Respiratory questionnaires were collected at seven time points in the TAHS (Tasmanian Longitudinal Health Study) when participants were aged 7, 13, 18, 32, 43, 50, and 53 years. Current-asthma and ever-asthma status was determined at each time point, and group-based trajectory modeling was used to characterize distinct longitudinal phenotypes. Linear and logistic regression models were fitted to investigate associations of the longitudinal phenotypes with childhood factors and adult outcomes.

Measurements and Main Results: Of 8,583 original participants, 1,506 had reported ever asthma. Five longitudinal asthma phenotypes were identified: early-onset adolescent-remitting (40%), early-onset adult-remitting (11%), early-onset persistent (9%), late-onset remitting (13%), and late-onset persistent (27%). All phenotypes were associated with chronic obstructive pulmonary disease at age 53 years, except for late-onset remitting asthma (odds ratios: early-onset adolescent-remitting, 2.00 [95% confidence interval (CI), 1.13–3.56]; early-onset adult-remitting, 3.61 [95% CI, 1.30–10.02]; early-onset persistent, 8.73 [95% CI, 4.10–18.55]; and late-onset persistent, 6.69 [95% CI, 3.81–11.73]). Late-onset persistent asthma was associated with the greatest comorbidity at age 53 years, with increased risk of mental health disorders and cardiovascular risk factors.

Conclusions: Five longitudinal asthma phenotypes were identified between the first and sixth decades of life, including two novel remitting phenotypes. We found differential effects of these phenotypes on risk of chronic obstructive pulmonary disease and nonrespiratory comorbidities in middle age.

Keywords: asthma phenotypes; longitudinal phenotypes; trajectories; chronic obstructive pulmonary disease; comorbidities

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At a Glance Commentary

Scientific Knowledge on the Subject: Longitudinal modeling of current asthma has been limited to children and young adults.

What This Study Adds to the Field: Modeling of asthma data collected over five decades identified five common pathways (longitudinal phenotypes) that asthma follows from childhood to middle age. These phenotypes were differentially associated with childhood exposures and adult outcomes. Most asthma patients, including some with remitted disease, were at substantially increased risk of chronic obstructive pulmonary disease and nonrespiratory comorbidities in middle age.

Asthma is a common chronic respiratory disease in both children and adults and affects an estimated 300 million people worldwide (1). It is associated with substantial personal and community health burdens across all age groups, and although mortality has decreased in recent decades as management has improved, morbidity remains high (1). Asthma is known to be a heterogeneous condition, with multiple subgroups and varied natural histories over the life course (2, 3). Better characterization of these subgroups and their distinct etiologies and outcomes may help facilitate novel prevention and improved management strategies.

In recent years, substantial effort has been invested in phenotyping asthma, and the findings have advanced our understanding of the disease (4, 5), especially in severe asthma (6, 7). These studies have led to new therapeutic options and targeted management, including the "treatable traits" approach to airway disease (8). To date, most research has focused on cross-sectional asthma phenotypes (9, 10), though some prospective studies have also characterized distinct patterns of asthma activity over time (10–13). These "longitudinal phenotypes," also called asthma or wheeze "trajectories," have the potential to provide novel insights into the natural history of asthma across different age groups.

To date, longitudinal asthma phenotypes have generally been characterized using two approaches. Earlier studies used manual classifications to define phenotypes on the basis of *a priori* clinical criteria, such as in the Dunedin Study, which described seven early wheeze phenotypes from ages 7–26 years (14). More recently, studies have used data-driven techniques such as latent class analysis (LCA) and group-based trajectory modeling (GBTM) to identify distinct subgroups (10–13). These studies have consistently identified four phenotypes from childhood to adulthood ("never or infrequent," "early transient," "early persistent," and "late-onset wheeze") but have had limited follow-up of participants into only their mid-20 s. In contrast, although the TAHS (Tasmanian Longitudinal Health Study) characterized trajectories of "asthma and allergic diseases" over a longer follow-up period, the study did not delineate asthma-specific phenotypes (15), and a major gap remains in our understanding of asthma transition over the life course.

We applied a data-driven approach to respiratory data collected on participants at seven time points in the TAHS from ages 7–53 years. We aimed to characterize the longitudinal phenotypes of asthma from childhood to middle age and investigated associations with early-life exposures and adult clinical outcomes. Some of the results of these studies have been previously reported in the form of an abstract (16).

Methods

Study Design and Data Collection

The TAHS is a population-based cohort of children born in 1961 and attending school in Tasmania, Australia, in 1968 (17). Respiratory questionnaires were first collected when participants were aged 7 years (baseline) and subsequently in follow-up studies conducted at ages 13, 18, 30, 43, 50, and 53 years. All studies were approved by the human ethics review committees of the relevant institutions, and written informed consent was obtained from all participants.

Procedures

Pre–bronchodilator (BD) spirometry was measured at all but one follow-up time point (age 30 yr), in accordance with American Thoracic Society and European Respiratory Society guidelines (18–20). In the studies at ages 45 and 53 years, post-BD spirometry was measured 15 minutes after administration of an inhaled BD (salbutamol 300 μg). Predicted values for spirometry were derived from Global Lung Initiative reference values (21). Lung function trajectories of FEV_1 growth and subsequent decline over the course of the study were developed as previously described (22). An overview of this process is also provided in the online supplement (*see* Methods E1).

Definitions

At each time point, we defined "ever asthma" as an affirmative response to the question "Have you, at any time in your life, suffered from attacks of asthma or wheezy breathing?" In participants who met the definition of ever asthma, we defined "current asthma" as an affirmative response to the question "Have you had an attack of asthma or wheezy breathing in the last 12 months?" These questions were answered by parents when participants were aged 7 and 13 years and by the participants themselves at the follow-up visits at ages 18, 30, 43, 50, and 53 years. These questions have been previously validated against physician assessments of asthma (23).

Childhood exposures (eczema, allergic rhinitis, food allergy, bronchitis, pneumonia, breastfeeding, parental asthma, and smoking) were assessed using parents' responses to the baseline study questionnaire. Adult outcomes (respiratory symptoms, healthcare use, comorbidities) were assessed using participants' responses to the age 53 questionnaire. The specific questions corresponding to these variables are presented in Methods E2. Chronic obstructive pulmonary disease (COPD) was defined spirometrically as a post-BD FEV_1:FVC ratio below the lower limit of normal (21).

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This article has a related editorial.

This article has an online supplement, which is accessible from this issue's table of contents at www.atsjournals.org.

Statistical Analysis

To ensure that only participants with sufficient data were included, we limited the study sample to participants with asthma data (current asthma, ever-asthma) in at least three of the three whole-cohort studies conducted at ages 7, 43, and 53 years. Among these participants, those who reported ever asthma at any of the seven follow-up time points were assigned to the "ever-asthma sample." The remaining participants who did not report ever asthma at any follow-up time point were assigned to the reference "never-asthma sample."

In the ever-asthma sample, we used GBTM to identify participants whose current asthma status followed similar patterns over time. GBTM is a form of finite fixture modeling whose aim is to explain population heterogeneity by identifying distinct subgroups within the population that follow similar patterns over time (24). Models with an increasing number of subgroups (longitudinal phenotypes) were developed, and a final model was selected using maximum likelihood estimation and a minimum class membership of 5% (25). GBTM was used to estimate the population prevalence of each subgroup and the posterior probability of each participant belonging to each subgroup. GBTM also allowed the retention of participants with incomplete data by imputing missing observations (24). Assignment of participants to a single phenotype was based on the modal method (the subgroup with the highest posterior probability for that individual). Further details on the process used to select the final model are provided in the online supplement (*see* Methods E3). Using the output of the GBTM models, we then calculated the prevalence of current asthma within the cohort (whole sample) stratified by asthma phenotype at each time point (*see* Methods E4).

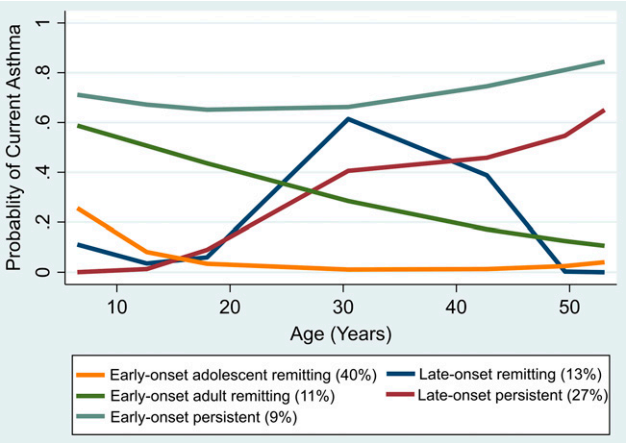

Figure 1. Longitudinal asthma phenotypes from ages 7–53 years (ever-asthma sample): probability of current asthma at each time point.

We examined associations between each asthma phenotype and TAHS childhood factors and adult outcomes, using never asthma as the reference category. Linear regression was used for continuous outcomes, logistic regression for binary outcomes, and multinomial logistic regression for nominal outcomes. Models were adjusted for a minimum set of confounders selected using directed acyclic graphs. Interactions between the longitudinal phenotypes and adult smoking and weight status were tested. In a *post hoc* analysis, we also examined the association of each phenotype with SNPs in 45 genes known to be associated with asthma or atopic sensitization. Methods for the genotyping process are provided in the online supplement (*see* Methods E5). We used a complete case analysis approach for tests of associations between the asthma phenotypes and early-life exposures and adult outcomes. Analyses were performed using Stata version 16 (StataCorp) with a GBTM plug-in (26).

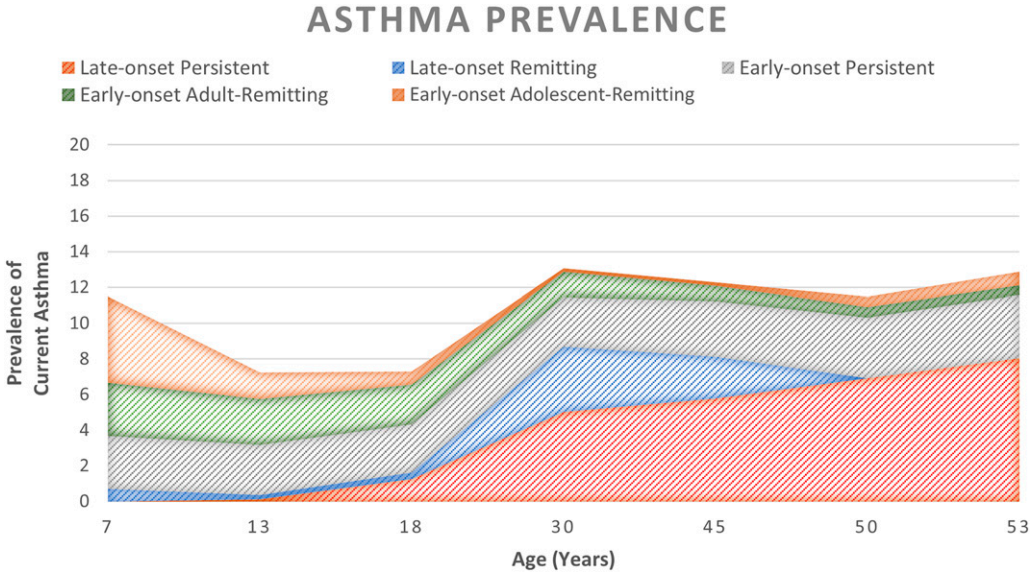

Figure 2. Contribution of each phenotype to asthma prevalence at each time point from ages 7–53 years (whole sample).

Table 1. Characteristics of the Longitudinal Asthma Phenotypes

	Never Asthma ($n = 1,743$)	Early-Onset Adolescent-Remitting ($n = 822$)	Early-Onset Adult-Remitting ($n = 95$)	Early-Onset Persistent ($n = 123$)	Late-Onset Remitting ($n = 110$)	Late-Onset Persistent ($n = 356$)
Childhood characteristics at age 7 yr						
Female	867 (50%)	413 (50%)	28 (29%)*	56 (46%)	67 (61%)†	224 (63%)*
Weight status						
Normal	1,422 (85%)	685 (85%)	72 (81%)	101 (84%)	93 (85%)	286 (84%)
Underweight	68 (4%)	22 (3%)	4 (4%)	4 (3%)	3 (3%)	10 (3%)
Overweight or obese	192 (12%)	96 (11%)	13 (14%)	15 (13%)	13 (12%)	43 (13%)
Socioeconomic status						
First quintile (highest)	438 (26%)	178 (23%)	17 (18%)	33 (29%)	27 (26%)	83 (25%)
Second quintile	132 (8%)	55 (7%)	5 (5%)	11 (10%)	8 (8%)	25 (7%)
Third quintile	453 (27%)	249 (32%)	26 (28%)	29 (25%)	28 (27%)	105 (31%)
Fourth quintile	449 (27%)	206 (26%)	30 (33%)	28 (24%)	25 (24%)	85 (25%)
Fifth quintile (lowest)	191 (11%)	91 (12%)	14 (15%)	14 (12%)	16 (15%)	37 (11%)
Smoking status at major follow-up time points						
Age 7 yr (parental)	1,094 (64%)	548 (68%)†	66 (70%)	88 (73%)	63 (59%)	244 (70%)†
Age 13 yr (personal)	35 (2%)	49 (7%)*	5 (5%)	4 (4%)	3 (3%)	14 (4%)†
Age 45 yr (personal)	393 (23%)	192 (23%)	22 (23%)	33 (27%)	35 (32%)†	108 (31%)‡
Age 53 yr (personal)	268 (15%)	127 (15%)	17 (18%)	20 (16%)	19 (17%)	83 (23%)*
BMI ($kg \cdot m^{-2}$) at major follow-up time points						
Age 7 yr	16.0 (1.5)	16.1 (1.4)	16.0 (1.6)	16.0 (1.4)	16.0 (1.2)	16.2 (1.6)†
Age 13 yr	18.9 (2.5)	19.1 (2.4)	18.7 (3.0)	20.0 (3.6)	19.1 (1.6)	19.4 (2.8)
Age 45 yr	27.0 (5.3)	28.3 (6.1)‡	27.7 (4.6)	28.7 (5.8)†	27.6 (4.6)	29.5 (7.3)*
Age 53 yr	28.2 (10.4)	29.0 (9.1)†	28.1 (5.0)	29.5 (6.1)	28.2 (4.8)	30.2 (6.6)*
Reproductive history (female subjects only)						
Age at menarche	13.0 (1.6)	12.9 (1.7)	12.4 (1.5)	12.7 (2.0)	13.2 (1.7)	12.8 (1.8)
Age at menopause	52.8 (2.3)	52.6 (3.0)	52.0 (4.0)	51.8 (4.1)	51.6 (5.6)	52.1 (3.0)
Menarche (age < 12 yr)	117 (14%)	74 (18%)†	8 (29%)†	13 (23%)†	12 (18%)	42 (19%)
Hormonal contraceptive (ever)	765 (89%)	371 (90%)	23 (82%)	51 (91%)	61 (91%)	196 (88%)
Pregnancy (ever)	762 (88%)	357 (86%)	22 (76%)	51 (91%)	62 (93%)	198 (88%)

Definition of abbreviation: BMI = body mass index.
Data are *n* (%) or mean (SD). The reference group was never asthma. Reproductive data were available for 1,637 (99%) of the female sample. Overweight and obese status was defined using age- and sex-specific thresholds from Cole and colleagues (41). Groups were compared using logistic regression for dichotomous variables, multinominal logistic regression for nominal variables, and linear regression for continuous variables.
*$P < 0.001$.
†$P < 0.05$.
‡$P < 0.01$.

Results

Of the original 8,583 TAHS participants, 3,249 (38%) had asthma status defined for at least the three whole-cohort follow-up time points at ages 7, 43, and 53 years. Of these, 1,506 (46%) reported ever asthma for at least one follow-up visit and formed the ever-asthma sample. The remaining 1,743 (54%) participants formed the reference never-asthma sample. The participants included had similar baseline characteristics to those not included, except for more female participants, more with childhood allergies and lung diseases, and fewer with smoking parents (*see* Table E1).

Longitudinal Asthma Phenotypes

The best-fitting model identified five longitudinal asthma phenotypes within the ever-asthma sample (Figure 1). On the basis of age of onset and age of remission over the follow-up period, these asthma phenotypes were labeled early-onset adolescent-remitting (40% of the ever-asthma sample), early-onset adult-remitting (11%), early-onset persistent (9%), late-onset remitting (13%), and late-onset persistent (27%). The mean posterior probability for each cluster in the final model ranged from 0.60 to 0.85, indicating reasonable model accuracy. In an assessment of model stability across different five-class models (*see* Methods E3), the most stable clusters were the early-onset persistent (posterior probability = 0.85 to 0.87), late-onset persistent (0.66–0.86), and early-onset adult-remitting (0.65–0.84) phenotypes. Posterior probabilities for early-onset adolescent-remitting (0.55–0.78) and late-onset remitting (0.50–0.60) asthma were comparatively lower across all models, indicating higher uncertainty in the allocation of participants to these groups.

The prevalence of current asthma stratified by phenotype at each time point is shown in Figure 2. At age 7 years, the overall prevalence of current asthma in the total population was 11.5%, composed primarily of the three early-onset phenotypes

Table 2. Adjusted Associations between Longitudinal Asthma Phenotypes and Childhood Factors

	Early-Onset Adolescent-Remitting ($n = 822$)	Early-Onset Adult-Remitting ($n = 95$)	Early-Onset Persistent ($n = 123$)	Late-Onset Remitting ($n = 110$)	Late-Onset Persistent ($n = 356$)
Childhood characteristics at age 7 yr					
Female	1.02 (0.86–1.20)	0.42 (0.27–0.66)*	0.84 (0.59–1.22)	1.57 (1.06–2.34)†	1.71 (1.36–2.17)*
Ever eczema	2.02 (1.57–2.59)*	4.00 (2.47–6.48)*	7.12 (4.67–10.84)*	1.71 (0.97–3.00)	1.90 (1.35–2.66)*
Ever allergic rhinitis	2.81 (2.17–3.64)*	8.23 (5.15–13.16)‡	10.22 (6.66–15.67)*	1.22 (0.62–2.42)	1.85 (1.28–2.68)‡
Ever food allergy	1.94 (1.39–2.70)*	2.86 (1.48–5.53)*	4.83 (2.85–8.17)*	0.77 (0.28–2.16)	1.55 (0.97–2.48)
Ever bronchitis	2.95 (2.46–3.55)*	8.22 (4.50–15.00)*	16.13 (8.07–32.35)*	1.65 (1.09–2.48)†	1.37 (1.08–1.76)†
Ever pneumonia	2.18 (1.70–2.79)*	3.98 (2.46–6.43)*	4.66 (3.03–7.17)*	1.78 (1.00–3.18)†	1.45 (1.00–2.09)†
Weight					
Normal	Ref	Ref	Ref	Ref	Ref
Underweight	0.69 (0.42–1.14)	1.36 (0.47–3.88)	1.05 (0.37–2.96)	0.76 (0.23–2.47)	0.79 (0.40–1.56)
Overweight or obese	1.00 (0.76–1.32)	1.49 (0.78–2.85)	1.04 (0.57–1.93)	0.90 (0.47–1.73)	1.01 (0.70–1.47)
Breastfeeding					
Breastfed only	Ref	Ref	Ref	Ref	Ref
Bottle only	1.11 (0.89–1.39)	1.39 (0.81–2.38)	1.27 (0.80–2.01)	0.80 (0.46–1.40)	0.80 (0.46–1.40)
Breast and bottle	1.04 (0.85–1.28)	1.21 (0.73–2.00)	0.61 (0.37–1.02)	1.11 (0.70–1.74)	1.22 (0.90–1.67)
Parental characteristics at age 7 yr					
Maternal asthma	2.14 (1.60–2.86)*	3.59 (2.07–6.25)*	3.14 (1.86–5.30)*	2.50 (1.40–4.49)‡	2.28 (1.57–3.32)*
Paternal asthma	1.69 (1.27–2.25)*	4.07 (2.42–6.83)*	5.84 (3.77–9.06)*	2.50 (1.43–4.35)‡	1.36 (0.90–2.05)
Maternal smoking	1.29 (1.08–1.55)‡	1.13 (0.72–1.77)	1.14 (0.75–1.72)	1.06 (0.69–1.64)	1.10 (0.85–1.42)
Paternal smoking	1.04 (0.87–1.24)	1.12 (0.71–1.74)	1.41 (0.94–2.12)	0.87 (0.58–1.32)	1.34 (1.04–1.72)†

Definition of abbreviation: Ref = reference.
Data are relative risk ratio (95% confidence interval). The reference group was never asthma. Groups were compared using logistic regression for dichotomous variables and multinominal logistic regression for nominal variables. For eczema, allergic rhinitis, food allergy, and bronchitis, models were adjusted for sex, parental asthma, childhood socioeconomic status, parental smoking, and breastfeeding. For pneumonia and pleurisy, the model was adjusted for sex, childhood socioeconomic status, parental smoking, and breastfeeding. For childhood weight status, the model was adjusted for sex, childhood socioeconomic status, parental smoking, breastfeeding, and childhood pneumonia and pleurisy. For breastfeeding, the model was adjusted for parental asthma, childhood socioeconomic status, and parental smoking. For parental asthma, the model was adjusted for parental smoking and childhood socioeconomic status. For parental smoking, models were adjusted for parental asthma and childhood socioeconomic status.
*$P < 0.001$.
†$P < 0.05$.
‡$P < 0.01$.

(adolescent-remitting, 4.8%; adult-remitting, 3.0%; persistent, 3.0%). Between childhood and middle age, current asthma prevalence ranged from 11.5% to 13.1%, except in adolescence, when prevalence was lower (7.2–7.3%) because of remission of the early-onset adolescent-remitting phenotype. After adolescence, the prevalence of current asthma increased in line with the emerging late-onset phenotypes, peaking by age 30 years (13.1%). Thereafter, asthma prevalence remained stable, and remission of the early-onset adult-remitting and late-onset remitting phenotypes was offset by an increasing prevalence of late-onset persistent asthma.

Characteristics of the Longitudinal Asthma Phenotypes

The early-onset adult-remitting phenotype had more male subjects ($P < 0.001$); the early-onset adolescent-remitting and early-onset persistent phenotypes had equal male-to-female sex ratios (Table 1); and in contrast, the late-onset remitting ($P = 0.02$) and late-onset persistent ($P < 0.001$) phenotypes had more female subjects. Compared with never asthma, three asthma phenotypes were characterized by increased exposure to cigarette smoke at different time points: for early-onset adolescent-remitting asthma and late-onset remitting asthma, cigarette smoke exposure was more common when subjects were most symptomatic (ages 7 and 13 years for early-onset adolescent-remitting and age 45 years for late-onset remitting). For the late-onset persistent phenotype, cigarette smoke exposure and higher body mass index were more common at multiple time points from ages 7–53 years.

For female reproductive history, early menarche (<12 yr) was more common among the three early-onset asthma phenotypes compared with the never asthma reference ($P < 0.05$ for all). Hormonal contraceptive use (ever) and history of pregnancy (ever) were reported at similar rates among all five longitudinal phenotypes.

Childhood Risk Factors

We identified differential associations between childhood factors and the longitudinal phenotypes when compared with never asthma (Table 2). All phenotypes were independently associated with maternal asthma, childhood bronchitis, and pneumonia, and except for late-onset remitting asthma, all phenotypes were also associated with childhood eczema, allergic rhinitis, and food allergy. These associations were much stronger for the early-onset persistent and early-onset adult-remitting phenotypes. We found that maternal smoking was an independent risk factor for early-onset adolescent-remitting asthma ($P = 0.01$), whereas paternal smoking was an

Table 3. Adjusted Associations between Longitudinal Asthma Phenotypes and Spirometric Outcomes at Age 53

	Early-Onset, Adolescent-Remitting ($n = 822$)	Early-Onset Adult-Remitting ($n = 95$)	Early-Onset Persistent ($n = 123$)	Late-Onset Remitting ($n = 110$)	Late-Onset Persistent ($n = 356$)
Pre-BD lung function (% predicted)					
FEV_1	−1.7 (−4.1 to 0.8)	−4.6 (−10.7 to 1.5)	−14.8 (−20.3 to −9.3)*	−4.2 (−9.5 to 1.2)	−10.6 (−14.0 to 7.2)*
FVC	−0.3 (−3.0 to 2.3)	−2.6 (−9.4 to 4.3)	−7.6 (−13.8 to −1.5)†	−2.4 (−8.3 to 3.6)	−6.5 (−10.2 to 2.7)‡
FEV_1:FVC ratio	−1.0 (−1.7 to −0.4)‡	−2.2 (−3.9 to −0.6)‡	−6.6 (−8.0 to −5.1)*	−1.8 (−3.2 to −0.3)†	−3.8 (−4.6 to −2.9)*
Post-BD lung function (% predicted)					
FEV_1	−2.3 (−4.4 to −0.3)†	−4.6 (−9.8 to 0.7)	−12.7 (−17.3 to −8.0)*	−4.0 (−8.6 to 0.5)	−8.8 (−11.7 to −6.0)*
FVC	−1.3 (−3.5 to 0.9)	−2.5 (−8.0 to 3.1)	−5.5 (−10.5 to −0.4)†	−1.8 (−6.7 to 3.1)	−4.9 (−8.0 to −1.8)‡
FEV_1:FVC ratio	−1.1 (1.84 to −0.3)‡	−2.1 (−4.0 to −0.2)†	−7.6 (−9.4 to −5.9)*	−2.3 (−4.0 to −0.6)‡	−4.2 (−5.2 to −3.1)*
Spirometric COPD, OR (95% CI)	2.00 (1.13 to 3.56)†	3.61 (1.30 to 10.02)†	8.73 (4.10 to 18.55)*	1.86 (0.54 to 6.35)	6.69 (3.81 to 11.73)*

Definition of abbreviations: BD = bronchodilator; CI = confidence interval; COPD = chronic obstructive pulmonary disease; OR = odds ratio.
Data are mean difference (95% CI) except as indicated. The reference group was never asthma. Groups were compared using logistic regression for dichotomous outcomes and linear regression for continuous outcomes. Models were adjusted for sex, parental asthma, parental smoking, childhood socioeconomic status, childhood pneumonia and pleurisy, and childhood body mass index.
*$P < 0.001$.
†$P < 0.05$.
‡$P < 0.01$.

independent risk factor for late-onset persistent asthma ($P = 0.02$).

We identified modest associations between SNPs in several asthma-related genes and the longitudinal phenotypes (*see* Table E2). SNPs in the HLA-DR-DQ (rs6903608) and filaggrin (rs41370446) genes were associated with a slightly increased risk of early-onset adolescent-remitting asthma, whereas an SNP in the TLR6 (Toll-like receptor 6) (rs1039559) gene was protective. SNPs in the IL4R (IL-4 receptor) region (rs2057768 and rs4787948) were associated with early-onset adult-remitting asthma, SNPs in the HLA-DR-DR gene (rs9268614) and TGFBR2 (transforming growth factor β receptor 2) gene (rs11924422) were associated with early-onset persistent asthma, SNPs in CD14 (cluster of differentiation 14) gene (rs2569190 and rs2915863) were associated with late-onset remitting asthma, and an SNP in IRF2 (IFN regulatory factor 2) gene (rs724528) was associated with late-onset persistent asthma.

Clinical Outcomes: Lung Function and COPD

We also identified differential associations between the longitudinal phenotypes and spirometric outcomes at age 53 years (Table 3). Although all asthma phenotypes were associated with pre- and post-BD spirometric changes consistent with obstructive deficits, the magnitude of the deficits were far greater for persistent asthma (both early-onset and late-onset). We identified a multiplicative interaction between the effects of persistent asthma and personal smoking on pre- and post-BD FEV_1:FVC ratio at age 53 years (Table 4).

All longitudinal phenotypes, excluding late-onset remitting asthma, were associated with an increased risk of spirometrically defined COPD at age 53 years. Consistent with the spirometric findings, the highest odds of developing COPD were observed for early-onset persistent (odds ratio, 8.73 [95% confidence interval (CI), 4.10–18.55]) and late-onset persistent asthma (odds ratio, 6.69 [95% CI, 3.81–11.73]).

For the relationship between asthma phenotypes and FEV_1 trajectories (22), we found that early-onset persistent and late-onset persistent asthma were associated with three abnormal lung function trajectories (Table 5). These trajectories were characterized by subnormal FEV_1 in childhood and subnormal maximally attained FEV_1 in early adulthood. Among

Table 4. Interaction between Longitudinal Phenotypes and Smoking Status on FEV_1:FVC Ratio at Age 53 Years

	Smoking Status	Pre-BD FEV_1:FVC Ratio	*P* Value for Interaction	Post-BD FEV_1:FVC Ratio	*P* Value for Interaction
Never asthma (control)	Nonsmoker	Ref	—	Ref	—
	Smoker	−2.9 (−3.9 to −2.0)*	—	−4.9 (−6.1 to −3.8)*	—
Early-onset persistent	Nonsmoker	−6.0 (−7.5 to −4.5)*	—	−7.6 (−8.5 to −5.0)*	—
	Smoker	−13.1 (−16.6 to −9.5)*	0.05	−19.9 (−24.3 to −15.5)*	<0.001
Late-onset persistent	Nonsmoker	−2.6 (−3.5 to −1.6)*	—	−2.6 (−3.8 to −1.5)*	—
	Smoker	−9.4 (−11.0 to −7.7)*	<0.001	−13.7 (−15.8 to −11.6)*	<0.001

Definition of abbreviations: BD = bronchodilator; Ref = reference.
Data are mean difference (95% confidence interval). Groups were compared using linear regression. Models were adjusted for sex, parental asthma, parental smoking, childhood socioeconomic status, childhood pneumonia and pleurisy, and childhood body mass index.
*$P < 0.001$.

these, the strongest associations were observed with a trajectory ("early below average, accelerated decline") also characterized by accelerated FEV_1 decline during adulthood (early-onset persistent: relative risk ratio, 28.98 [95% CI, 12.48–67.27]; late-onset persistent: RRR, 10.04 [95% CI, 5.13–19.63]). Although to a lesser extent, the three remitting phenotypes also appeared to be associated with these same lung function trajectories. However, these associations did not always reach statistical significance (Table 5).

Clinical Outcomes: Adult Comorbidities

Late-onset persistent asthma was associated with multiple nonrespiratory comorbidities at age 53 years, including mental health disorders (anxiety and depression), cardiovascular risk factors (diabetes and high cholesterol) and gastroesophageal reflux disease (GERD) (Table 6). Similarly, late-onset remitting asthma was associated with high cholesterol, depression, and GERD. In contrast, the early-onset phenotypes were associated with anxiety (early-onset adult-remitting), GERD (early-onset persistent), or both anxiety and GERD (early-onset adolescent-remitting). None of the phenotypes was associated with hypertension.

Discussion

This study is the first to characterize longitudinal asthma phenotypes from childhood to middle age. Using a data-driven approach, on the basis of respiratory histories collected at seven time points from ages 7–53 years, we identified five distinct asthma phenotypes distinguished by age of asthma onset and remission. This study extends the current framework of longitudinal asthma phenotypes (limited in previous studies to ages in the mid-20 s) to the mid-50 s. In this study, we described two novel phenotypes: early-onset adult-remitting and late-onset remitting asthma. We also found that longitudinal asthma phenotypes were differentially associated with childhood factors and adult outcomes.

Several studies have now characterized asthma-wheeze phenotypes over limited periods from childhood to early adulthood in prospective cohorts, including LCA and GBTM analyses of the population-based BAMSE (Barn/Child, Allergy, Milieu, Stockholm, Epidemiology) birth cohort (10) (follow-up 1–24 years, $n = 4{,}089$), Pelotas birth cohort (13) (follow-up 4–22 years, $n = 5{,}249$), and Study Team for Early Life Asthma Research (STELAR) consortium of five United Kingdom birth cohorts (follow-up from birth to 18 years, $n = 7{,}719$) (11).

Table 5. Association between Longitudinal Asthma Phenotypes and Lifetime Lung Function (FEV_1) Trajectories

	Early-Onset Adolescent-Remitting (*n* = 602)	Early-Onset Adult-Remitting (*n* = 69)	Early-Onset Persistent (*n* = 90)	Late-Onset Remitting (*n* = 88)	Late-Onset Persistent (*n* = 248)
Persistently high	1.09 (0.77–1.53)	0.41 (0.12–1.41)	1.07 (0.41–2.80)	1.14 (0.54–2.41)	1.03 (0.61–1.76)
Average	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)	1 (Ref)
Early low, accelerated growth, normal decline	1.36 (0.91–2.02)	2.35 (0.99–5.53)	1.10 (0.31–3.91)	0.92 (0.34–2.47)	1.00 (0.51–1.94)
Below average	1.49 (1.16–1.91)*	1.13 (0.59–2.17)	2.03 (1.06–3.89)†	1.63 (0.94–2.81)	2.02 (1.40–2.92)‡
Persistently low	1.80 (1.05–3.06)†	2.47 (0.86–7.13)	5.47 (2.14–14.00)‡	1.84 (0.60–5.60)	5.34 (2.96–9.66)‡
Early below average, accelerated decline	2.02 (1.01–4.02)†	3.22 (0.87–11.91)	28.98 (12.48–67.27)‡	4.95 (1.70–14.47)*	10.04 (5.13–19.63)‡

Definition of abbreviation: Ref = reference.
Data are relative risk ratio (95% confidence interval). The reference group was never asthma. Lung function trajectory data were available for 2,255 (69%) of the study sample. Groups were compared using multinominal logistic regression. Models were adjusted for sex, parental asthma, parental smoking, childhood socioeconomic status, childhood pneumonia and pleurisy, and childhood body mass index.
*$P < 0.01$.
†$P < 0.05$.
‡$P < 0.001$.

Table 6. Adjusted Associations between Longitudinal Asthma Phenotypes and Nonrespiratory Comorbidities at Age 53 Years

Comorbidities (Ever)	Early-Onset Adolescent-Remitting ($n = 822$)	Early-Onset Adult-Remitting ($n = 95$)	Early-Onset Persistent ($n = 123$)	Late-Onset Remitting ($n = 110$)	Late-Onset Persistent ($n = 356$)
Hypertension	1.08 (0.89–1.32)	0.89 (0.53–1.49)	1.29 (0.84–1.97)	0.73 (0.43–1.21)	1.20 (0.92–1.58)
Diabetes	1.40 (0.99–1.99)	1.29 (0.55–3.06)	1.74 (0.87–3.45)	1.83 (0.89–3.78)	1.81 (1.16–2.82)*
High cholesterol	1.09 (0.88–1.34)	1.36 (0.82–2.23)	1.25 (0.80–1.97)	1.97 (1.27–3.05)*	1.42 (1.07–1.89)†
GERD	1.44 (1.08–1.91)†	1.60 (0.83–3.11)	2.33 (1.38–3.95)*	2.99 (1.79–5.01)‡	1.89 (1.31–2.71)*
Anxiety	1.40 (1.12–1.76)*	1.75 (1.02–3.03)†	1.30 (0.78–2.15)	1.19 (0.70–2.03)	1.62 (1.20–2.18)*
Depression	1.11 (0.89–1.38)	1.20 (0.69–2.09)	1.55 (0.99–2.42)	1.89 (1.21–2.95)*	1.69 (1.28–2.23)‡

Definition of abbreviation: GERD = gastroesophageal reflux disease.
Data are odds ratio (95% confidence interval). The reference group was never asthma. Comparisons between groups were assessed using logistic regression. Models were adjusted for sex, parental smoking, childhood socioeconomic status, and childhood body mass index.
*$P < 0.01$.
†$P < 0.05$.
‡$P < 0.001$.

These studies have identified four similar longitudinal wheeze phenotypes: never or infrequent, early transient, early persistent, and late-onset wheeze. In our TAHS cohort, the present asthma phenotypes followed similar trajectories up to age 18 years but later diverged on the basis of persistence or remission of asthma symptoms during adulthood. Consequently, we identified two additional remitting asthma-wheeze phenotypes between childhood and middle age. Importantly, it should be noted that our GBTM analysis was conducted within an ever-asthma sample rather than an unselected cohort, as used in previous studies. This approach was chosen so that distinct subgroups could be identified without the interference of a large never-asthma subgroup, which constituted 80%, 71%, and 54% of the BAMSE, Pelotas, and STELAR cohorts, respectively.

Recently, a secondary analysis of the STELAR consortium cohorts applied a novel partition-around-medoids (PAM) clustering approach to multidimensional wheeze variables on the basis of six wheeze characteristics and identified an additional "intermittent wheeze" phenotype (12), but this was not evident in the present study. The PAM approach appeared to reduce within-class heterogeneity compared with a conventional LCA model on the basis of binary (yes or no) wheeze data. Although differences in statistical approach (GBTM vs. PAM) likely explain the absence of this phenotype within our model, it is also possible that longer periods between follow-up time points in TAHS (seven time points from ages 7–53 yr) compared with the STELAR cohorts (five time points from ages 1–18 yr) may have limited our ability to identify this phenotype.

The findings of our multivariable analyses suggest that the longitudinal phenotypes identified are relevant from both etiological and clinical perspectives. Although most phenotypes shared common childhood risk factor profiles, there was evidence of differential associations among them. Familial factors, childhood allergies, and childhood lung conditions appeared to play a greater role in the natural history of early-onset and persistent phenotypes and consequently may hold prognostic value. These findings are consistent with those from prior studies of early-life factors associated with early-onset versus late-onset asthma (27), and persistence versus remission of asthma (28, 29), including previous analyses conducted in TAHS. We also found some evidence that phenotypes were associated with different asthma-related genetic polymorphisms, although this is of uncertain clinical relevance.

Our study provides new insights into the relationship between asthma and lung function across the life course into middle age. In particular, our findings add to growing evidence indicating that even remitted asthma is an important yet often underrecognized cause of lung function impairments in adulthood (30–32). All three remitting phenotypes were associated with significant obstructive deficits in middle age, and both early-onset remitting phenotypes were also associated with an increased risk of established COPD. This is consistent with a recent prospective study by Miura and colleagues (30), in which remitted childhood asthma was shown to be an independent risk factor of accelerated lung function decline in middle-aged adults. These findings raise concerns regarding the optimal follow-up and management of individuals with apparently remitted asthma, who represented an important >30% of the general population at age 53 years in TAHS (27). This highlights a need to identify high-risk subgroups at least in early adult life.

Our study is unique in its comparison of longitudinal asthma phenotypes and lung function trajectories, both characterized from ages 7–53 years. We found that the spirometric deficits associated with persistent asthma phenotypes were at least in part related to abnormal lung function trajectories characterized by subnormal FEV_1 in childhood, subnormal maximally attained FEV_1 in early adulthood, and, in some cases, accelerated FEV_1 decline during adulthood. Consistent with other studies, we showed that the effects of persistent asthma (both early onset and late onset) were exacerbated by adult personal smoking with a multiplicative interaction (33–35). Our findings reinforce the importance of smoking cessation and good asthma control in preserving lung function across the life course in individuals with asthma. This is supported by findings of a recent systematic review showing that inhaled corticosteroid use attenuates the adverse effects of asthma on lung function (36), with different effects in children and adults.

Of the phenotypes described in this study, late-onset persistent asthma was associated with the most nonrespiratory comorbidities in middle age, including multiple cardiovascular risk factors, mental

ill health, and GERD. Biological mechanisms proposed to underlie associations of asthma with cardiovascular disease include systemic inflammation and T-helper cell type 1 inflammatory responses (37, 38) and, for mental health disorders, chronic illness reactions, use of systemic steroids, and T-helper cell type 2-inflammatory responses (39, 40). Shared risk factors such as personal smoking and obesity are likely also involved and were characteristics of the late-onset persistent phenotype, though we did not identify statistical evidence for a direct interaction.

Our study has a number of major advantages. The comprehensive respiratory data collected at seven time points from childhood to middle age in TAHS allowed us to extend the current framework of longitudinal asthma phenotypes from the mid-20 s in previous studies to the mid-50 s in TAHS. The population-based nature of TAHS also allowed us to examine the phenotype-specific prevalence of current asthma at each time point and to examine associations with a range of childhood, lifetime, and adult characteristics.

However, there were also several limitations. First, as data on current asthma at seven different time points were used to characterize our longitudinal phenotypes, participants with asthma symptoms occurring between follow-up time points (e.g., relapsing-remitting asthma) may have been misclassified. In addition, the interval between follow-up time points in TAHS was also longer compared with other prospective cohorts (10, 11, 13).

Second, our phenotypes were characterized using data at seven time points from ages 7–53 years, including at age 53 years when outcomes (COPD and comorbidities) were assessed. This approach limited our ability to determine the temporality (and thus causality) of the relationship between asthma phenotypes and clinical outcomes.

Third, although we aimed to examine the association between asthma phenotypes and early-life exposures and adult outcomes, we did not test for between-phenotype differences in these analyses. The small sample sizes for some phenotypes may have also resulted in a lack of statistical power within these groups.

Fourth, we did not statistically adjust for multiple testing in our analyses (e.g., via Bonferroni or Šidák corrections) and instead considered biological plausibility in the interpretation of our results. Replication of our analyses in other cohorts is also required to further examine the stability and generalizability of the identified phenotypes.

Finally, our use of self-reported data to determine asthma status is another potential limitation. However, these definitions have been validated with sensitivity and specificity of 80% (58–93%) and 97% (90–99%) against respiratory physician assessments (23), respectively.

Conclusions

This study is the first to characterize longitudinal asthma phenotypes over the life course from childhood to middle age. Using a data-driven GBTM approach, we identified five distinct phenotypes distinguished by age of asthma onset and asthma remission, of which two remitting phenotypes are novel. These phenotypes were differentially associated with childhood risk factors and adult outcomes. We would emphasize that asthma at any age should be taken seriously and treatment titrated to achieve good clinical control. Clinicians should also be aware that clinically remitted asthma may be an important risk factor for COPD in later life. Future research should focus on linking longitudinal asthma phenotypes with biological pathways and further exploring genetic associations. Studies should also determine whether long-term preventive treatment and smoking cessation can alter disease trajectory and improve outcomes for patients with asthma. ■

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