Trajectories of asthma and allergies from 7 years to 53 years and associations with lung function and extrapulmonary comorbidity profiles: a prospective cohort study

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Summary

Background Longitudinal trajectories of asthma and allergies from childhood to adulthood might be differentially associated with lung function and chronic obstructive pulmonary disease (COPD), but associations with extrapulmonary comorbidities have not been well investigated. We aimed to assess these trajectories and examine their associations with lung function outcomes and profiles of comorbidities.

Methods In this prospective cohort study, data for asthma and related allergic conditions (ie, eczema, hay fever, and food allergy) were prospectively collected from the Tasmanian Longitudinal Health Study for participants aged 7–53 years originally recruited in Tasmania, Australia. All surviving individuals in the database with contact details were invited in the most recent follow-up (mean age 53 years). There were no exclusion criteria. With use of latent class analysis, we identified longitudinal trajectories of asthma and allergic conditions from 7–53 years, and profiles of self-reported extrapulmonary conditions recorded at 53 years. The associations between asthma and allergy trajectories and morbidity profiles and lung function at 53 years were investigated with regression models.

Findings Between Sept 3, 2012, and Nov 8, 2016, of 6128 individuals invited, 3609 (58·9%) individuals were enrolled. We identified five asthma and allergy trajectories: minimal and least asthma and allergies (n= 1767 [49·0%]); late-onset hay fever, no asthma (n=1065 [29·5%]); early-onset remitted asthma and allergies (n=236 [6·5%]); late-onset asthma and allergies (n=317 [8·8%]); and early-onset persistent asthma and allergies (n=224 [6·2%]); and four profiles of extrapulmonary morbidities: minimal or least disease (n=2206 [61·1%]); dominant mental health disorders (n=861 [23·9%]); dominant cardiovascular diseases or risks (n=424 [11·7%]); and multiple disorders (n=117 [3·2%]). The late-onset asthma and allergies trajectory was predominantly associated with the multiple disorders profile (relative risk ratio 3·3 [95% CI 1·9–5·9]), whereas the other asthma and allergy trajectories were associated only with the dominant mental health disorders profile. Both spirometrically defined and clinical COPD were most strongly associated with the early-onset persistent asthma and allergies trajectory (odds ratio [OR] 5·3 [95% CI 3·2–8·6]) and also with the late-onset asthma and allergies trajectory (OR 3·8 [2·4–6·1]).

Interpretation Distinct longitudinal trajectories of asthma and allergic disease from childhood to 53 years are associated with different profiles of extrapulmonary comorbidities and varying risk of COPD. These findings can inform a personalised approach in clinical guidelines and management focusing on treatable traits. Comorbidity profiles are a new target for early identification and intervention.

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Introduction

Asthma and related allergic diseases are important personal and public health challenges, given their high prevalence and burden, with asthma affecting more than 339 million people worldwide as of 2018.[1] Asthma is heterogeneous in its natural history with variable age of onset, severity, persistence, and relationships to other allergic diseases. Asthma often coexists with other allergic diseases (ie, hay fever, eczema, and food allergies), in both children and adults, with hay fever being especially prevalent with cases exceeding 50% in individuals with asthma.[2,3] Such heterogeneity might create diverse longitudinal trajectories of asthma and allergies over the life course.

The burden of lifetime asthma stems from both long-term lung function deficits and comorbidities. Asthma is associated with numerous comorbidities, some of the most prevalent being gastro-oesophageal reflux disease (GERD), cardiovascular, metabolic, musculoskeletal, and psychological conditions.[1] Extrapulmonary comorbidities

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Research in context

Evidence before this study

Asthma is heterogeneous in its natural history with a variable age of onset, severity, persistence, and relationship to other allergic diseases (eg, eczema, hay fever, and food allergy) and chronic obstructive pulmonary disease (COPD). Asthma is also frequently a component in individuals with multimorbidities, particularly in older individuals aged 60 years and older. Understanding of longitudinal trajectories of asthma in combination with other allergies, and the link between these trajectories and comorbidities, is essential for tailored treatment and management of asthma itself, as well as for reducing the burden of multimorbidity. We searched for articles in PubMed from database inception until Feb 10, 2020, using the search terms "asthma", "allerg*", "comorbidit*", "multimorbidit*", "pattern*", and "trajector*". We included studies that identified longitudinal trajectories of asthma and allergic diseases based on repeated measurements and investigated comorbidities among these trajectories. There were no language restrictions. We found no studies that have investigated profiles of comorbidities and their associations with longitudinal trajectories of asthma and allergic disease.

Added value of this study

To our knowledge, with use of data-driven techniques, we are the first to characterise four profiles of extrapulmonary comorbidities. The comorbidities were differentially associated with longitudinal trajectories of asthma and allergies based on repeated measurements from the first to the sixth decade of life for an unselected community population sample. The late-onset asthma and allergies trajectory was associated with multiple comorbidities and dominant cardiovascular comorbidity profiles, highlighting new inflammatory paradigms responsible for asthma and multimorbidities. The other asthma and allergy trajectories were solely associated with the dominant mental health comorbidity profile. The identified trajectories also had specific associations with lung function deficits and risk of COPD. Although the early-onset persistent asthma and allergies trajectory was associated with the highest risk of COPD, the late-onset asthma and allergies trajectory also had an increased risk but to a lesser extent.

Implications of all the available evidence

Our findings are important from a clinical perspective. They can inform a personalised approach in clinical guidelines and management focusing on treatable traits. Longitudinal phenotypes, comorbid allergic diseases, and other extrapulmonary comorbidities should be considered together in the management of individuals with asthma. The findings also highlight avenues with the potential to reduce the burden of COPD and multimorbidity in the general population.

compound the already substantial burden of asthma on the health-care system, patients, and carers.[1] Extrapulmonary comorbidities are also gaining increasing interest in the context of so-called treatable traits, a new paradigm for management of chronic airway diseases.[4] It is quite possible that profiles of comorbidities could vary depending on longitudinal trajectories of asthma and allergies, but we currently have a poor understanding of such potential relationships.

See Online for appendix

Trajectories of asthma and lung function outcomes have been previously reported, but have mainly focused on trajectories from childhood to the mid-20s. Some of these early life studies have used a manual classification to identify asthma trajectories,[5,6] while others[7,8] have used data-driven approaches that recognise dynamic changes in disease status and have helped identify new longitudinal patterns of wheeze and asthma. To our knowledge, only two respiratory studies spanning from childhood to the sixth decade of life have investigated changes in asthma or wheeze status. The WHEASE study[9,10] followed up a small number of participants (n=330) at four timepoints until the age of 61 years, after initially recruiting three groups of children (ie, children with asthma, wheezy bronchitis, and controls) aged 10–15 years. The MESCA followed five small groups of children (n=484; children with mild wheezy bronchitis, wheezy bronchitis, asthma, severe asthma, and controls) up to the age of 50 years.[11–13] Both MESCA and WHEASE were seminal longitudinal studies on asthma and they have provided insights into the long-term outcomes of childhood asthma and wheeze, especially when severe. However, these studies focused on the change of asthma or wheeze status (persistence and remission) from baseline to each follow-up for predefined recruitment groups (appendix p 1). They did not use latent modelling techniques, which include variable sequential phenotype changes over time to develop longitudinal asthma or wheeze trajectories for the whole population. Moreover, while asthma and allergies are closely linked and known to occur frequently together or manifest sequentially, longitudinal trajectories of asthma and concurrent allergic diseases over the life course are not well defined.

Understanding longitudinal trajectories of asthma and allergic diseases from childhood to adulthood will help in several ways. Different trajectories might have different underlying causes, pathophysiological processes and prognoses, and might need specific preventive treatment, or management strategies. While childhood asthma, especially severe asthma, has been associated with reduced adult lung function,[9,11] investigation of longitudinal trajectories of asthma and allergic diseases could provide more insight into the phenotypic influence of lifetime asthma and allergy on the causes of lung function deficits and chronic obstructive pulmonary disease (COPD). Exploring the potential association of longitudinal trajectories of asthma and allergic diseases with specific profiles of extrapulmonary comorbidities in later life can help

untangle the burden of multimorbidity that starts to increase in the sixth decade of life.

These investigations could help identify at-risk groups, and guide optimal primary care, clinical surveillance, and clinical interventions. Addressing these knowledge gaps requires large cohorts with comprehensive data over the life course. The Tasmanian Longitudinal Health Study (TAHS) provides a unique opportunity given that it has extensive data for respiratory health and related factors at different life stages. In this study, we aimed to identify and characterise longitudinal trajectories of asthma and related allergic diseases from childhood to middle-age (7–53 years); examine their associations with lung function outcomes, especially COPD, and with profiles of common extrapulmonary comorbidities at 53 years.

Methods

Study design and participants

In this prospective cohort study, we used data from the TAHS, collected at ages 7, 13, 45, and 53 years (appendix p 10). Study methods have been reported in detail elsewhere.[14] In brief, TAHS began in 1968 when 8583 Tasmanian children born in 1961 (probands) and attending school in Tasmania were enrolled in a respiratory health study. Parents completed a questionnaire for the child who then underwent a clinical examination and pre-bronchodilator spirometry. The next follow-up was in 1974 when probands had a mean age of 13 years. The original cohort was traced and 7380 participants (85·6%) completed a respiratory questionnaire. In 2002 (mean age 45 years) the original cohort was traced and 5729 participants (78·4% of those traced) completed a postal questionnaire. In 2012, surviving participants (mean age 53 years) from the original cohort with contact details (n=6128, 71% of the original cohort) were invited to attend a clinical study. Between 2012 and 2016, 3609 (58·9%) of those invited participated. Of those, 2689 participants (74·5%) had pre-bronchodilator and post-bronchodilator spirometry. The same protocol was applied at all sites in accordance with American Thoracic Society/European Respiratory Society criteria for acceptable and repeatable spirometry.[15] All laboratories participated in quality control. The study was approved by the human ethics review committees of all relevant institutions. Written informed consent was obtained from all participants.

Procedures

Current asthma at age 7, 13, 45, and 53 years was defined by an affirmative response to both questions: "Have you, at any time in your life, suffered from attacks of asthma or wheezy breathing?" and "Have you had an attack of asthma or wheezy breathing in the last 12 months?". These questions have been previously validated.[16] Definitions of eczema, hay fever, and food allergy are detailed in the appendix (p 3).

COPD was defined spirometrically as post-bronchodilator FEV_1/forced vital capcity (FVC) less than the lower limit of normal derived from Global Lung Initiative reference equations for white people.[17] A clinical definition of COPD was defined as post-bronchodilator FEV_1/FVC less than the lower limit of normal plus at least one of the key indicators (shortness of breath at rest or after exercise, chronic cough, or chronic sputum production; a history of smoking ≥10 pack years; occupational exposure to vapour, gas, dust, or fumes; a family history of COPD).[18] A fixed cut point of 0·7 for FEV_1/FVC, which is very close to the lower limit of normal in this age group, was used in sensitivity analyses.

At the follow-up at 53 years, participants responded to the question "has a doctor ever told you that you have/had any of the following conditions?". From the response options, we selected potential extrapulmonary comorbidities including anxiety, depression, diabetes, GERD, angina or heart attack, hypertension, high blood cholesterol or lipids, arthritis, thyroid problems, and cancer. In addition, obstructive sleep apnoea as defined by a separate question "has your doctor ever told you that you have or had obstructive sleep apnoea?" was included. These conditions were selected in this analysis because of their potential link to asthma and respiratory health.[1,19–22] Other conditions from the response options, including coeliac disease, Crohn's disease, lupus, multiple sclerosis, transient ischaemic attack or stroke, and type 1 diabetes, were not included in this analysis because of their low prevalence in this study or weak evidence for a link with asthma. Profiles of these extrapulmonary multimorbidites were defined as those conditions that clustered in classes defined by latent class analysis (LCA). These clusters were considered to be comorbidity clusters when associations were considered with trajectories of asthma and allergies. Definitions of other variables are shown in the appendix (pp 3–4).

Statistical analysis

Based on the available information, asthma and allergy trajectories were defined with use of LCA on the basis of the following dichotomous variables: current asthma at 7, 13, 45, and 53 years; eczema at 7 and 53 years; hay fever at 7 and 53 years; food allergy at 7 and 53 years; being allergic to animals at 53 years; and being allergic to plants at 53 years.[23] In LCA, two sets of variables were estimated: conditional probabilities (ie, probability of having each allergic variable within a known class) and posterior probabilities (ie, probability of membership of each class for a given participant). Models with an increasing number of classes were fitted to determine the best fit model from the Bayesian information criterion and Akaike information criterion. Missing data for indicator variables were treated as missing at random. The LCA model with maximum likelihood estimation allows for handling of missing data for each individual. Assignment of a single trajectory group to each individual was based

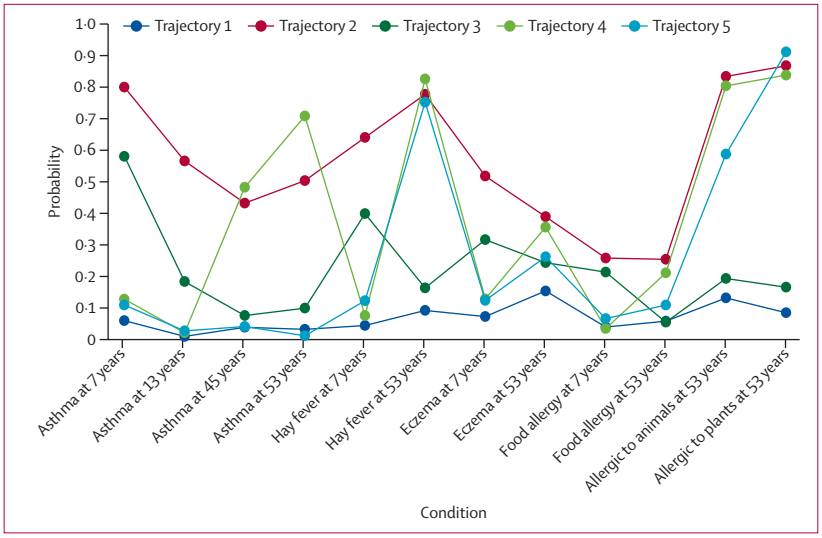

Figure 1: **Longitudinal trajectories of asthma and allergic diseases.**
Probability of having each condition in the five trajectories (latent classes) from the latent class analysis model. Trajectory 1: minimal or least asthma and allergies (reference; n=1767 [49·0%]). Trajectory 2: early-onset persistent asthma and allergies (n=224 [6·2%]). Trajectory 3: early-onset remitted asthma and allergies (n=236 [6·5%]). Trajectory 4: late-onset asthma and allergies (n=317 [8·8%]). Trajectory 5: late-onset hay fever, no asthma (n=1065 [29·5%]).

	Asthma and allergy trajectories				
	Minimal or least asthma and allergies	Early-onset persistent asthma and allergies	Early-onset remitted asthma and allergies	Late-onset asthma and allergies	Late-onset hay fever, no asthma
Asthma at 7 years	0·059	0·80	0·58	0·13	0·11
Asthma at 13 years	0·0084	0·57	0·18	0·020	0·026
Asthma at 45 years	0·037	0·43	0·074	0·48	0·040
Asthma at 53 years	0·031	0·50	0·098	0·71	0·010
Hay fever at 7 years	0·043	0·64	0·40	0·073	0·12
Hay fever at 53 years	0·09	0·78	0·16	0·83	0·75
Eczema at 7 years	0·071	0·52	0·32	0·13	0·12
Eczema at 53 years	0·15	0·39	0·24	0·35	0·26
Food allergy at 7 years	0·038	0·26	0·21	0·033	0·065
Food allergy at 53 years	0·057	0·25	0·05	0·21	0·11
Allergic to animals at 53 years	0·13	0·83	0·19	0·80	0·59
Allergic to plants at 53 years	0·083	0·87	0·16	0·84	0·91

Probability and colour coding

0 0·1 0·2 0·3 0·4 0·5 0·6 0·7 0·8 0·9 1·0

Figure 2: **Probability of each indicator variable across five asthma and allergy trajectories**
Data show conditional probabilities (ie, probability of having each indicator variable within a known class) from the latent class analysis model.

on the modal method (the highest posterior probability for that individual). The mean membership probability of individuals in each trajectory was used to assess model adequacy. For comparison, we used the proportional assignment method with regression models weighted by membership probability; the findings were essentially unchanged.

Characteristics of participants were compared between different asthma and allergy trajectories and the reference trajectory, using χ^2 tests, or one-way ANOVA where appropriate. Multivariable linear and logistic regressions were done to investigate the associations between the identified asthma and allergy trajectories and lung function and COPD at 53 years, adjusting for sex, age, height, obesity status, socioeconomic status, and personal smoking. Interactions between trajectories and personal smoking and sex were tested using the likelihood ratio test and strata specific estimates were reported if the p value for the interaction was less than 0·1.

LCA was also used to identify profiles (latent classes) of 11 doctor-diagnosed extrapulmonary conditions (ie, anxiety, depression, cancer, diabetes, GERD, angina or heart attack, hypertension, high blood cholesterol or lipids, arthritis, thyroid problems, or obstructive sleep apnoea). The model with four classes was identified as the best fit. The association between lifetime trajectories of asthma and allergies and profiles of comorbidity were examined using multinomial logistic regression, adjusting for sex, age, socioeconomic status, obesity, and smoking status.

Analyses were done in Stata, version 14.1 and Mplus, version 7.4.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Sept 3, 2012, and Nov 8, 2016, of 6128 individuals invited, we analysed data from 3609 participants who attended the last follow-up at 53 years and previously also had three follow-ups done at ages 7, 13, and 45 years. Just more than half (1845 [51·1%]) of the participants were women (appendix p 6). By age 7 years, 627 (17·4%) participants had self-reported asthma, 509 (14·2%) had eczema, 490 (13·8%) had hay fever, and 270 (7·5%) had food allergy. At 53 years, more than half (2029 [56·2%]) of the participants were smokers (626 [17·3%] current and 1403 [38·9%] former); the prevalence of current asthma was 13·1%, current eczema was 22·7%, current hay fever was 40·1%, and current food allergy was 9·9%. More than a third (1355 [37·8%]) of participants reported allergies to animals, and almost half (1604 [44·9%]) to plants at 53 years. Among those reporting allergies to animals, 397 (29·3%) had a positive skin prick test to cat allergen. Among those reporting allergies to plants, 843 (52·6%) had a positive skin prick test to rye grass or mixed grass allergens.

Regarding the prevalence of the asthma and allergy trajectories identified by LCA, the best fit LCA model delineated five trajectory groups (figures 1, 2). The mean membership probability of individuals in each trajectory ranged from 0·85 to 0·97, indicating good model adequacy. The trajectories were labelled based on age at onset, and

	Minimal or least asthma and allergies (reference; n=1767)	Early-onset persistent asthma and allergies (n=224)	Early-onset remitted asthma and allergies (n=236)	Late-onset asthma and allergies (n=317)	Late-onset hay fever, no asthma (n=1065)
Adulthood characteristics at 53 years					
Sex					
Female	857 (48·5%)	92 (41·1%)	88 (37·3%)	203 (64·0%)	604 (56·7%)
Male	910 (51·5%)	132 (58·9%)*	148 (62·7%)†	114 (36·0%)‡	461 (43·3%)‡
Smoking status					
Never	747 (42·3%)	111 (49·6%)*	89 (37·7%)	126 (39·7%)	505 (47·4%)†
Past	680 (38·5%)	82 (36·6%)	99 (41·9%)	124 (39·1%)	417 (39·2%)
Current	340 (19·2%)	31 (13·8%)	48 (20·3%)	67 (21·1%)	143 (13·4%)
Heavy alcohol use	386/1762 (21·9%)	43 (19·2%)	70/234 (29·9%)	62/313 (19·8%)	203/1059 (19·2%)
Frequent alcohol use	229/1763 (13·0%)	35 (15·6%)	36/234 (15·4%)	40/313 (12·8%)	149/1059 (14·1%)
Obesity	547/1755 (31·2%)	78/222 (35·1%)	86 (36·4%)	140/315 (44·5%)†	305/1053 (29·0%)
Atopy	442/1114 (39·7%)	127/140 (90·7%)†	84/151 (55·6%)†	148/210 (70·5%)†	444/662 (67·1%)†
Mean CC16 concentration	7·5 (3·7)	7·9 (4·3)	7·5 (4·4)	6·5 (3·9)*	7·7 (3·7)
Median CC16 concentration	6·6 (4·7–9·2)	6·3 (5·0–10·0)	6·5 (4·6–9·3)	5·5 (3·9–8·2)†	7·0 (4·9–9·4)
Mean CRP concentration	4·8 (6·4)	4·2 (5·1)	4·7 (6·5)	5·9 (6·9)*	4·3 (6·3)
Median CRP concentration	2·8 (1·3–5·9)	2·3 (0·9–5·9)	2·9 (1·4–6·2)	4·0 (1·5–8·2)†	2·4 (1·1–5·0)
SES					
1	546/1763 (31·0%)	93 (41·5%)	69 (29·2%)	102/313 (32·6%)	390/1057 (36·9%)
2	238/1763 (13·5%)	25 (11·2%)	32 (13·6%)	36/313 (11·5%)	166/1057 (15·7%)
3	597/1763 (33·9%)	63 (28·1%)	94 (39·8%)	104/313 (33·2%)	322/1057 (30·5%)
4	185/1763 (10·5%)	15 (6·7%)	16 (6·8%)	25/313 (8·0%)	72/1057 (6·8%)
5	197/1763 (11·2%)	28 (12·5%)	25 (10·6%)	46/313 (14·7%)	107/1057 (10·1%)
Asthma severity					
Mild persistent	9 (0·5%)	40 (17·9%)	2 (0·9%)	48 (15·1%)	6 (0·6%)
Moderate to severe persistent	9 (0·5%)	30 (13·4%)	7 (3·0%)	62 (19·6%)	4 (0·4%)
Inhaled steroid last year	30 (1·7%)	73 (32·6%)†	14 (5·9%)	109 (34·4%)†	22 (2·1%)
Childhood characteristics at 7 years					
Childhood SES					
1	429 (24·3%)	66 (29·5%)	57 (24·2%)	76 (24·0%)	270/1061 (25·4%)
2	122 (6·9%)	21 (9·4%)	17 (7·2%)	15 (4·7%)	93/1061 (8·8%)
3	487 (27·6%)	56 (25·0%)	73 (30·9%)	98 (30·9%)	312/1061 (29·4%)
4	493 (27·9%)	55 (24·6%)	57 (24·2%)	90 (28·4%)	278/1061 (26·2%)
5	236 (13·4%)	26 (11·6%)	32 (13·6%)	38 (12·0%)	108/1061 (10·2%)
Maternal smoking	625 (35·4%)	74 (33·0%)	90 (38·1%)	116 (36·6%)	333 (31·3%)
Paternal smoking	1033 (58·5%)	134 (59·8%)	146 (61·9%)	202 (63·7%)	580 (54·5%)
Maternal asthma	118 (6·7%)	56 (25·0%)†	47 (19·9%)†	45 (14·2%)†	109/1062 (10·3%)†
Paternal asthma	138 (7·8%)	54 (24·1%)†	54 (22·9%)†	37 (11·7%)*	122 (11·5%)†
Pneumonia or pleurisy by 7 years	191 (10·8%)	67 (29·9%)†	71 (30·1%)†	44 (13·9%)	117 (11·0%)
Overweight at 7 years	180 (10·2%)	22 (9·8%)	33 (14·0%)	42 (13·2%)	121 (11·4%)
Mean birth weight, kg	3·35 (0·6)	3·36 (0·5)	3·35 (0·6)	3·31 (0·6)	3·32 (0·5)
Mean gestational age, weeks	39·3 (1·9)	39·1 (2·1)	39·2 (1·9)	39·3 (1·8)	39·3 (1·9)

Data are n (%), n/N (%), median (IQR), or mean (SD). Denominators are shown where data are missing. SES categories range from 1 to 5 with 1 being the highest category. SES=socioeconomic status. CRP=C-reactive protein. *p<0·05; †p<0·01; and ‡p<0·001 compared with the reference group.

Table 1: **Adult and childhood characteristics of five asthma and allergy trajectories**

persistence or remission of asthma and allergies over time. Minimal or least asthma and allergies (1767 [49·0%] of 3609) was characterised by having the lowest prevalence for all allergic variables from 7–53 years, and this group was considered as the reference group in all comparisons. Late-onset hay fever, no asthma (1065 [29·5%]) was

	Minimal or least asthma and allergies	Early-onset persistent asthma and allergies	Early-onset remitted asthma and allergies	Late-onset asthma and allergies	Late-onset hay fever, no asthma
Pre-bronchodilator					
Mean FEV_1, mL	(ref)	−310 (−386 to −233)‡	−95 (−175 to −15)*	−237 (−304 to −170)‡	15 (−26 to 56)
Mean FVC, mL	(ref)	−163 (−251 to −74)‡	−44 (−137 to 48)	−155 (−233 to −77)‡	7 (−41 to 55)
Mean FEV_1/FVC, %	(ref)	−4·7% (−5·7 to −3·7)‡	−1·2% (−2·3 to −0·2)*	−2·9% (−3·8 to −2·1)‡	0·1% (−0·4 to 0·7)
Post-bronchodilator					
Mean FEV_1, mL	(ref)	−268 (−343 to −193)‡	−107 (−185 to −28)†	−192 (−258 to −126)‡	14 (−26 to 55)
Mean FVC, mL	(ref)	−87 (−172·0 to −1·5)*	−63 (−153 to 27)	−99 (−175 to −24)*	16 (−30 to 63)
Mean FEV_1/FVC, %	(ref)	−4·5% (−5·4 to −3·6)‡	−1·0% (−2·0 to −0·1)*	−2·5% (−3·4 to −1·7)‡	0·1% (−0·4 to 0·6)
Spirometric COPD, OR	1 (ref)	5·3 (3·2 to 8·6)‡	2·2 (1·2 to 3·9)†	3·8 (2·4 to 6·1)‡	0·98 (0·6 to 1·5)
Clinical COPD, OR	1 (ref)	5·9 (3·2 to 11·0)‡	2·6 (1·3 to 5·2)†	3·6 (2·0 to 6·3)†	0·95 (0·6 to 1·6)

Data are mean difference (95% CI) or OR (95% CI). Model adjusted for sex, age, height, smoking status, obesity status, and socioeconomic status. COPD=chronic obstructive pulmonary disease. FVC=forced vital capacity. *p<0·05; †p<0·01; and ‡p<0·001.

Table 2: **Associations between trajectories of asthma and allergies and lung function and COPD at 53 years**

characterised by a high probability of hay fever in adulthood and allergy to animals and plants, but no asthma. Late-onset asthma and allergies (317 [8·8%]) was characterised by a high probability of asthma, hay fever, and reported allergy to animals and plants in adulthood. Early-onset remitted asthma and allergies (236 [6·5%]) was characterised by asthma and other allergic diseases in early life (eczema, hay fever, food allergy) remitting in adulthood. Early-onset persistent asthma and allergies (224 [6·2%]) was characterised by a high probability of having early-onset persistent asthma, hay fever, eczema, and food allergy from 7–53 years. The sensitivity analysis using the International Study of Asthma and Allergies in Childhood definition of eczema yielded similar asthma and allergy trajectories (data not shown).

All asthma and allergy groups were more likely to be atopic at 53 years and have parents with asthma, with the early-onset persistent asthma and allergies group having the strongest associations, when compared with the reference group (minimal or least asthma and allergies; table 1). The early-onset classes were more likely to be men, whereas the late-onset classes were more likely to be women. The late-onset asthma and allergies group was more likely to be obese and have higher C-reactive protein and lower CC16 (also known as CC10, club cell secretory protein, and uteroglobin) concentrations than the reference group. The early-onset persistent asthma and allergies group had a lower prevalence of personal smoking than the reference group. A high prevalence of inhaled steroids at 53 years was observed in both the early-onset persistent asthma and allergies and the late-onset asthma and allergies groups. In addition, the two early-onset asthma and allergy groups had a higher prevalence of reported pneumonia in early childhood (table 1). The early-onset persistent asthma and allergies group had lower childhood lung function than the reference group (appendix p 7).

Associations between asthma and allergy trajectories and lung function and COPD at 53 years were seen. Lung function data at 53 years were available for most (2689 of 3609) participants. The early-onset persistent asthma and allergies trajectory was most strongly associated with lung function deficits (–268 mL [95% CI –343 to –193] for post-bronchodilator FEV_1 and –4·5% [–5·4 to –3·6] for post-bronchodilator FEV_1/FVC) and increased risk of COPD (odds ratio [OR] 5·3 [95% CI 3·2 to 8·6]), followed by the late-onset asthma and allergies trajectory (–192 mL [–258 to –126] for post-bronchodilator FEV_1, –2·5% [–3·4 to –1·7] for post-bronchodilator FEV_1/FVC and OR 3·8 [2·4 to 6·1] for COPD), when compared with the reference trajectory (table 2). The early-onset remitted asthma and allergies trajectory was also associated with a lesser reduction in FEV_1 (–107 mL [95% CI –185 to –28]) and FEV_1/FVC (–1·0% [–2·0 to –0·1]) than the early-onset persistent asthma and allergies and the late-onset asthma and allergies trajectories. By contrast, the late-onset hay fever, no asthma trajectory was not significantly associated with reductions in lung function or COPD. The late-onset asthma and allergies and early-onset persistent asthma and allergies trajectories were additionally associated with reduced FVC but the effect size was smaller than for FEV_1. Results were similar for both pre-bronchodilator and post-bronchodilator spirometry (table 2). For COPD, findings were similar for both spirometrically defined and clinically defined disease, and whether a fixed cutoff of 0·7 or the lower limit of normal for FEV_1/FVC was used. Results from repeating these analyses with the proportional assignment method were similar to those from the modal assignment method.

We identified four profiles of extrapulmonary multimorbidities (figure 3). Minimal or least diseases (2206 [61·1%] of 3608) was characterised by the lowest probability for all diseases, so this group was considered as the reference group in all analyses. Dominant mental health disorders (861 [23·9%]) was characterised by high probabilities for anxiety and depression. Dominant

cardiovascular diseases or risks (424 [11·7%]) was characterised by high probabilities for hypertension and high blood cholesterol or lipid concentrations. Multiple disorders (117 [3·2%]) was characterised by a combination of these and more—ie, high probabilities for anxiety, depression, hypertension, high blood cholesterol or lipids, diabetes, GERD, and obstructive sleep apnoea.

Associations between lifetime asthma and allergy trajectories and profiles of extrapulmonary comorbidity at 53 years were as follows. The late-onset asthma and allergies trajectory was the most affected by multimorbidity, being associated with all three multimorbidity profiles: multiple disorders (relative risk ratio [RRR] 3·3 [95% CI 1·9–5·9]), dominant cardiovascular diseases or risks (RRR 1·5 [1·1–2·2]), and dominant mental health disorders (RRR 2·3 [1·7–3·0]; table 3). The other asthma and allergy trajectories were associated only with the dominant mental health disorders profile and even then to a lesser extent. There was also some evidence of an association between the multiple disorders profile and the early-onset persistent asthma and allergies trajectory with a point estimate RRR of 1·9, but CIs crossed one (0·8–4·1). Although obesity (body-mass index ≥30) was more prevalent in the late-onset asthma and allergies trajectory, the above associations were independent of obesity at 53 years, measured by body-mass index as a categorical (obese *vs* non-obese) or continuous variable. The prevalence of individual comorbidities among asthma and allergy trajectories is summarised in the appendix (p 8).

Discussion

To our knowledge, this study is the first to investigate associations of profiles of extrapulmonary comorbidities with different longitudinal trajectories of asthma and allergic diseases from childhood to middle-age. With use of a data-driven method, we identified five trajectories. We found associations between individual trajectories and specific profiles of extrapulmonary comorbidities. The late-onset asthma and allergies trajectory was associated with multiple comorbidities independent of obesity. Conversely, the early-onset persistent asthma and allergies and early-onset remitted asthma and allergies trajectories were particularly associated with the dominant mental health disorders profile. Trajectories of asthma and allergic diseases were also differentially associated with lung function outcomes in middle-age. The early-onset persistent asthma and allergies trajectory had the strongest associations with pre-bronchodilator and post-bronchodilator spirometric deficits and risk of COPD. The late-onset asthma and allergies trajectory had similar associations but to a slightly lesser extent.

We believe that our findings on the specific relationships of longitudinal asthma and allergy trajectories with profiles of extrapulmonary comorbidities and lung function in later life are novel and important. Although it was not known whether profiles of comorbidities differed by trajectories of asthma, it has been recognised that asthma is often associated with an increased prevalence of mental health disorders, GERD, obstructive sleep apnoea, cardiovascular diseases, and diabetes.[19] The identified specific relationships suggest either common underlying mechanisms, such as shared genetic or environmental exposures or a possible causal relationship between asthma and allergy trajectories and comorbidities and lung function deterioration. These possibilities now need to be investigated further, but at least these new paradigms provide a starting point for understanding common disease mechanisms and establishing potential avenues of preventive intervention for later-onset asthma or allergy-related comorbidities.

We found that both early-onset and late-onset asthma and allergy trajectories were associated with common mental health disorders (the dominant mental health disorders profile). This important and novel finding provides insights into the link between these burdensome common chronic diseases. Our findings also highlight the need for further focused research. These associations

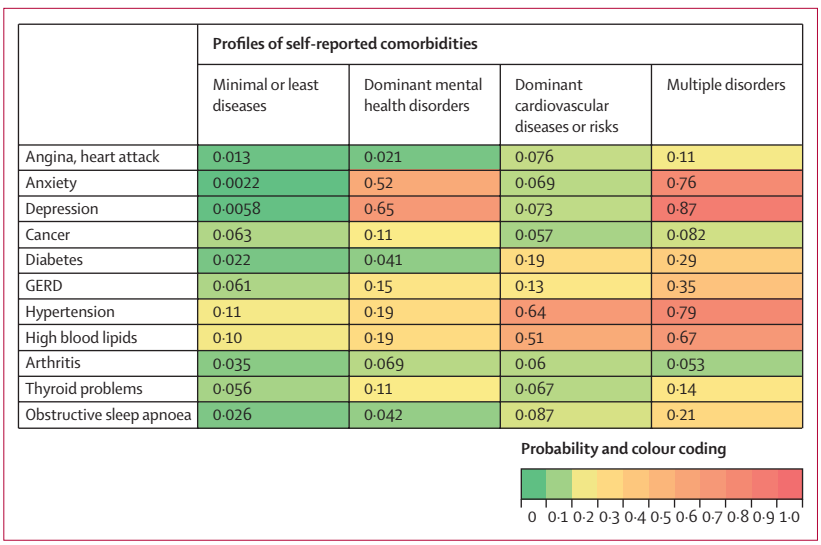

Figure 3: **Probability of each indicator variable across four profiles of comorbidities**
Data show conditional probabilities (ie, probability of having each indicator variable within a known class) from the latent class analysis model. Indicator variables (at mean age 53 years). GERD=gastro-oesophageal reflux disease.

	Multiple disorders	Dominant mental health disorders	Dominant cardiovascular diseases or risks
Minimal asthma and allergies	1 (ref)	1 (ref)	1 (ref)
Early-onset persistent asthma and allergies	1·9 (0·8–4·1)	1·6 (1·2–2·3)†	1·2 (0·8–1·8)
Early-onset remitted asthma and allergies	1·6 (0·7–3·5)	1·7 (1·2–2·4)†	1·3 (0·8–1·9)
Late-onset asthma and allergies	3·3 (1·9–5·9)‡	2·3 (1·7–3·0)‡	1·5 (1·1–2·2)*
Late-onset hay fever, no asthma	1·6 (0·9–2·5)	1·2 (1·0–1·4)*	0·9 (0·7–1·2)

Data are relative risk ratio (95% CI). Adjusted for sex, age, socioeconomic status, smoking status, and obesity status. *p<0·05; †p<0·01; and ‡p<0·001.

Table 3: **Association between lifetime trajectories of asthma and allergies and profiles of comorbidities**

might be partly explained by several factors, including the stress of living with a chronic illness such as asthma (particularly if poorly controlled), the use of systemic corticosteroids, reduction of daily activity and exercise, and possibly poor sleep quality. All of these factors might contribute to depression.[24] An alternative mechanism could involve sleep disordered breathing disruption secondary to asthma and allergies, particular in more severe asthma.[25] Alteration of immune system capabilities could be a shared pathway between asthma and mental health disorders, with growing evidence for the involvement of innate and adaptive immunity in the pathology of mental health disorders.[26] Thus, enhancement and periodic exacerbations of type 2 T helper (Th) cell responses might contribute to the higher prevalence of both mental health disorders in patients with asthma,[24] and asthma in patients with major depressive disorders.[27] Moreover, shared risk factors might play a role in the association between asthma trajectories and mental health disorders. Studies from 2019 have provided evidence for significant positive genetic correlations between these conditions.[28,29]

Similarly, there are potential mechanisms that might contribute to the association between the late-onset asthma trajectory and the dominant cardiovascular diseases or risks profile in our analysis.[30] Systemic inflammation through dominant Th1 rather than Th2 responses is one hypothesis,[31,32] which could link asthma, atherosclerosis, and coronary artery disease to a shared underlying inflammatory pathogenesis.[33] In animal models, the extent of atherosclerosis and coronary artery disease is reduced when the Th1 pathway is inhibited pharmacologically[34] or genetically.[35] Additionally, animal studies have reported that systemic inflammation associated with asthma and allergies could adversely affect cardiovascular function and increase myocardial vulnerability,[36] with increased neutrophil infiltration during acute ischaemia.[37] Our study found some support for systemic inflammation potentially influencing cardiovascular risk with the late-onset asthma and allergies trajectory, which had the greatest general systemic comorbidities, having higher concentrations of the circulating inflammation marker C-reactive protein and lower concentrations of anti-inflammatory CC16.

Understanding the interplay between asthma and extrapulmonary comorbidities is the subject of important research and clinical interest. Comorbidities might affect asthma severity and asthma control, and need to be considered in asthma management, especially given that over time the presence of multiple comorbidities might further affect the severity of asthma with advancing age. Importantly, an integrated or holistic strategy is now needed to tackle the burden of asthma and its comorbidity profiles in people aged 60 years and older. This strategy is also important in the context of polypharmacy resulting from multimorbidity with inherent risks of drug interactions and adverse effects of some disease-specific drugs on other comorbid conditions. Fortunately, guidelines for asthma management are increasingly addressing the important issue of comorbidities.[1] Further, given the complexity of asthma with other chronic diseases, a new treatable traits paradigm for disease management has been promoted.[4] This paradigm highlights the necessary role of a personalised patient management plan based on a multidimensional assessment including comorbidities as well as the primary complaint.[4] Moreover, understanding profiles of related comorbidities might provide insights into the need for targeted clinical investigation, and research into related causes of both asthma and these other conditions.

Our findings provide additional insights into the link between asthma and allergies over time, and lung function deficits and COPD. Although we found an increased risk of COPD in both early-onset persistent and late-onset trajectories of asthma, we highlight that this risk was strongest for the early-onset persistent asthma and allergies trajectory. This result aids our understanding of the phenotypic difference between early-onset and late-onset asthma.[38] Although not directly tested here, the associations of both early-onset persistent and late-onset asthma allergy trajectories with COPD suggest there might be a role for achieving good control of asthma and allergies throughout the life course in the prevention of COPD. There is some evidence that inhaled corticosteroid use might have some beneficial effects on long-term lung function decline in people with asthma.[39]

As a data-driven approach, any LCA model also requires interpretation to establish the number of classes. In this study, in which five classes were determined, the mean membership probability of individuals in each trajectory was notably high (range 0·85–0·97), indicating good model adequacy. The differential relationship between asthma and allergy trajectories and comorbidities in this study supports the validity of the model. In addition, trajectories of asthma and allergy identified in this study are clinically interpretable, further attesting to their validity. However, it is important that our findings are validated with data from other population-based longitudinal studies in the future, if and when this comparison becomes feasible.

This study has major strengths, including the large population-based sample, longitudinal data from the first to sixth decades of life, and the use of a data-driven clustering technique. Thus, prospectively collected data on asthma and allergies from childhood to middle-age in TAHS has provided us with a unique opportunity to examine longitudinal trajectories of asthma and allergies.

Our study had several limitations. Although the inclusion of variables at 53 years in the model was essential for identifying longitudinal trajectories of asthma and allergies, this method might have partly influenced the associations with 53-year respiratory outcomes. However, the link between early-onset and remitted trajectory and lung function at 53 years suggests

that the trajectories are sufficiently robust to detect biologically plausible signals. The uneven distribution of variables across timepoints, with some additional variables at 53 years is a limitation. Additional variables including allergies to plants and animals were included in the questionnaire at 53 years. However, we highlight that data for asthma were included at all timepoints and data for allergic diseases were included for both 7 years and 53 years, thus ensuring the representation of both childhood and adulthood in establishing longitudinal trajectories. Although the use of self-reported asthma is a limitation in this study, our questions have been validated against respiratory physician assessment.[16] As we defined current eczema through participants' self-reported medication use, untreated cases might have been misclassified. However, the sensitivity analysis using the International Study of Asthma and Allergies in Childhood definition of eczema yielded similar asthma and allergy trajectories. Lung function data were available for most of the sample, and further, the prevalences of trajectories of asthma and allergies are similar between those with and those without lung function data; thus the observed association was unlikely to be affected. Missing data for some indicator variables included in the LCA model are a limitation. However, the missingness was small (<1·6%) and likely to be at random, a type of missingness that is allowed by the LCA model with maximum likelihood estimation. Finally, information on the timing of onset of comorbidities was not available, which hinders understanding of temporality and the assessment of causality. The forthcoming planned follow-up of TAHS participants into their seventh decade will enable us to further explore this issue.

We have identified novel longitudinal trajectories of asthma and allergic diseases from childhood to middle-age. Notably, these trajectories were associated with differential profiles of extrapulmonary comorbidities. Participants in all longitudinal asthma and allergy trajectories had a higher risk of mental health disorders, while those belonging to the late-onset asthma and allergies trajectory were especially at risk of multiple extrapulmonary comorbidities. Those with early-onset persistent asthma and allergies had the highest risk of lung function deficits and COPD. These findings can help refine a personalised approach in clinical guidelines related to treatable traits of asthma, in which profiles of comorbidity become a new target. The findings also suggest potential high-risk groups that should be targeted for intense monitoring to reduce the burden of both lung function deficits and extrapulmonary comorbidities among people with asthma. Finally, our findings propose new inflammatory paradigms responsible for asthma and multimorbidities.

Contributors

SCD, EHW, MJA, CJL, DSB, GG, and JH were responsible for study concept and design. SCD, EHW, GSH, PT, MJA, and BT were responsible for acquisition of data. DSB, SCD, CJL, EHW, JLP, DT, BE, GSH, JP, FC, RC, GB, AL, and JG-A were responsible for analysis and interpretation of data. DSB, SCD, CJL, and EHW were responsible for statistical analysis. DSB, SCD, CJL, and EHW were responsible for drafting of the manuscript. All authors were responsible for critical revision of the manuscript for important intellectual content. SCD, EHW, GSH, PT, and MJA obtained funding.

Declaration of interests

We declare no competing interests.

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Supplementary appendix

This appendix formed part of the original submission. We post it as supplied by the authors.

Supplement to: Bui D S, Lodge C J, Perret J L, et al Trajectories of asthma and allergies from 7 years to 53 years and associations with lung function and extrapulmonary comorbidity profiles: a prospective cohort study. *Lancet Respir Med* 2020; published online November 17. http://dx.doi.org/10.1016/S2213-2600(20)30413-6.

Trajectories of asthma and allergies from 7 to 53 years and their relationship with middle-aged lung function and extra-pulmonary comorbidity profiles: a prospective cohort study

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Supplement

Selection of the LCA model:

models with an increasing number of classes were fitted. Bayesian Information Criterion (BIC) and Akaike Information Criterion (AIC) were used to assess model fit, with the lowest values indicating best model fit. In addition, interpretation of classes was also considered if necessary. The model with 5 classes was found to be the best fit (Table S7) and were clinically interpretable. Thus, it was selected as the final model.

Table S1. Comparison of major studies on asthma trajectories that span from childhood to young-middle age and lung function

Studies (ref)	**Recruitment at baseline**	**Time span**	**Approach to define asthma groups**	**Lung function outcomes investigated**
TAHS (The current manuscript)	95% of students aged 7 years in Tasmania (n=8583)	Repeatedly followed 7 times from age 7 to 53 years	• Identified longitudinal trajectories of asthma (**asthma and/or wheeze), eczema, hayfever and food allergy from 7 to 53** years in the whole population • Method used: **latent class analysis**	• Investigated the association between asthma and allergy trajectories and lung function and comorbidities in middle age
MAS (Phelan PD, et al. J Allergy Clin Immunol 2002; Tai A, et al. J Allergy Clin Immunol 2014)	School based survey of students aged 7 years, 4 random stratified groups selected for the follow-up: -Mild wheezy bronchitis (n=74) -Wheezy bronchitis (n=104) -Asthma (n=113) -Controls (n=105)	Repeatedly followed 7 times from age 7 to 50 years	• Only **followed five recruitment groups** • **DID NOT** model dynamic longitudinal trajectories of asthma and allergic diseases for the whole population.	• Reported and compared lung function between five baseline predefined groups at each follow up

	At 10 years, an additional severe asthma group (n=83) was added			
WHEAS (Godden DJ, et al Am J Respir Crit Care Med 1994; Tagiyeva N, et al Am J Respir Crit Care Med 2016	3 groups of children aged 10-15 years from a population sample selected for the follow-up: -Wheezy bronchitis (n=167) -Asthma (n=121) Controls (n=2223 – only random sample invited to attend follow-up)	Repeatedly followed 4 times from age 10 to 61 years	• Only **followed recruitment groups** • **DID NOT** identify dynamic longitudinal trajectories of asthma or allergic diseases for the whole population	• Investigated the association between predefined childhood asthma/wheeze groups and lung function at each follow up
Dunnedin study (Sears MR, et al N Engl J Med 2003)	Birth cohort (n=1037)	Repeatedly followed 7 times from age 9 to 26 years	• Identified **longitudinal trajectories of asthma (asthma and/or wheeze) from 9 to 26** years in the whole population • Method used: manual **classification** • **DID NOT** include other allergic disease in identify longitudinal trajectories	• Investigated the association between asthma trajectories and **lung function by 26 years**

Table S2. Definition of variables in childhood.

Variables	Definition
Eczema by 7 years	a positive response to either "Dose he/she have infantile (baby) eczema?" or "Has he/she ever had eczema in the creases of elbows, wrists, or knees?"
Hayfever by 7 years	a positive response to the question: "Does he/she get attacks of hay fever?" [1,2].
Food allergy by 7 years	a positive response to the question: "Have you been told by a doctor that he/she is allergic to any foods?"
Childhood lung infections	a positive response to the question "Have you ever been told by a doctor that he/she had pneumonia or pleurisy?"
Maternal and paternal smoking	defined by parents' responses to the question "Do you smoke every day (or six days out of seven)?"
Maternal and paternal asthma	defined by parents' responses to the question "Have you ever had asthma or attacks of wheezing like asthma?"
Childhood socio-economic status	classified by the occupation of the father of the participant and divided into 5 categories according to the Australian Standard Classification of Occupations [3]

Table S3. Definition of variables at 53 years.

Variables	Definition
Current eczema at 53 year	an affirmative response to both questions: "Have you ever had eczema or any kind of skin allergy?" and "Have you used any medicines including creams and ointments for rash or eczema during the last 12 months?" In addition, the International Study of Asthma and Allergy in Children (ISAAC) definition of eczema [4] was used in the sensitivity analysis.
Current hay fever at 53 years	an affirmative response to both questions: "Have you ever had hay fever or nasal allergies (that is sneezing, running or blocked nose when you do not have a cold or the flu)?" and "Have you had this problem in the last 12 months?"
Current food allergy at 53 years	An affirmative response to both questions "Have you ever had any food allergies" and "Are you still allergic to it?".
Personal smoking	self-reported and included three categories: never, past and current
Obesity at the age of 53 years	BMI≥30kg/m^2, and calculated conventionally from measured height and weight.
Serum C-reactive protein (CRP)	measured from blood samples collected at 53 years.
Club Cell protein (CC16)	measured from blood samples collected at 53 years.
Current inhaled steroid usage	a report of using inhaled steroids "to help breathing in the last 12 months" at 53 years.
Allergic to animals at 53 years	a report of allergic symptoms (start to cough; start to wheeze; get a feeling of tightness in the chest; start to feel short of breath; get a runny or stuffy nose or start to sneeze; or get itchy or watery eyes) when the participant is "near animals, such as cats, dogs, or horses; near feathers, including pillows, quilts or doonas".
Allergic to plants at 53 years	a report of allergic symptoms (start to cough; start to wheeze; get a feeling of tightness in the chest; start to feel short of breath; get a runny or stuffy nose or start to sneeze; or get itchy or watery eyes) when the participant is "near trees, grass or flowers, or when there is a lot of pollen about".

Atopy at 53 years	a positive skin prick test (≥ 3mm diameter wheal) to one or more of twelve allergens (house dust mite, cat, *Hormodendrum, Alternaria, Penicillium, Aspergillus*, rye grass, mixed grasses, egg white, peanut, shellfish, cow's milk).
Socio-economic status at 53 years	the occupation of the participant and grouped into five categories according to Australian Standard Classification of Occupations [3].

Table S4. Characteristics of the participants (N=3609)

Characteristics	
Age, mean (SD)	52.9 (0.9)
Male sex, N(%)	1764 (48.9)
Smoking status at 53 years, N(%)	
Never	1580 (43.8)
Past	1403 (38.9)
Current	626 (17.3)
Obesity at 53 years, N(%) ł	1156 (32.3)
Current eczema at 53 years, N(%)	819 (22.7)
Current asthma at 53 years, N(%)	472 (13.1)
Current hayfever at 53 years, N(%)	1447 (40.1)
Current food allergy at 53 years, N(%) ł	354 (9.9)
Allergic to animals at 53 years, N(%) ł	1355 (37.8)
Allergic to plants at 53 years, N(%) ł	1604 (44.9)
Atopy, N(%)*	1255 (55.3)
SES at 53 years, N(%)	
1st (highest)	1200 (33.4)
2nd	497 (13.8)
3rd	1180 (32.8)
4th	313 (8.7)
5th	403 (11.2)
Asthma at 7 years, N(%)	627 (17.4)
Asthma at 13 years, N(%)	245 (6.8)
Asthma at 45 years, N(%) ł	402 (11.3)
Eczema by 7 years, N(%) ł	509 (14.2)
Hay fever by 7 years, N(%)ł	490 (13.8)
Food allergy by 7 years, N(%)	270 (7.5)

*Data are available for a subsample (n=2277). Ł Missing data for hayfever at 7 years (n=56), eczema at 7 years (n=21); asthma at 45 years (n=44), allergic to animals (n=22) and allergic to plants (n=36), food allergy at 53 years (n=31), obesity at 53 years (n=28) and SES at 53 years (n=16)

Table S5. Childhood lung function among five trajectories of asthma-allergy

	Asthma-allergy trajectories				
	Minimal asthma & allergies (Ref)	Early onset persistent asthma & allergies	Early onset, remitted asthma & allergies	Late onset asthma & allergies	Late onset hayfever, no asthma
Childhood lung function					
FEV_1, L (SD)	1.35 (0.2)	1.32 (0.2)	1.31 (0.2)	1.31 (0.2)	1.33 (0.2)
FVC, L (SD)	1.46 (0.2)	1.49 (0.2)	1.45 (0.2)	1.44 (0.2)	1.46 (0.2)
FEV_1, % predicted (SD)	99.8 (15)	97.0 (14)*	97.8 (15)	98.1 (12)	98.9 (12.8)
FVC, % predicted (SD)	97.4 (15)	98.3 (13)	96.4 (13)	96.9 (12)	97.0 (12)
FEV_1/FVC, % (SD)	91.2 (5.5)	88.5 (7.2)***	90.4 (6.4)	90.5 (5.5)	91.1 (5.6)
Lifetime lung function trajectories from 7 to 53 years ł					
Normal, %	40.3	28.9	31.5	34.4	40.8
Low, %	31.2	28.9	33.6	34.4	31.7
Very low, %	4.8	12.6	11.2	8.3	3.5
Catch -up, %	8.2	6.3	5.6	5.5	9.3
High, %	13.3	8.2	12.6	6.4	12.5
Accelerated decline, %	2.2	15	5.6	11.1	2

*:p<0.05; **p<0.01; ***p<0.001 compared to the reference group; ł Lung function trajectories from 7 to 53 years [5]

Table S6 . Prevalence of individual comorbidities at 53 years among five asthma-allergy trajectories

	Asthma-allergy trajectories				
	Minimal asthma & allergies (Ref)	Early onset persistent asthma & allergies	Early onset, remitted asthma & allergies	Late onset asthma & allergies	Late onset hayfever, no asthma
Angina, heart attack, %	3.7	2.7	4.7	3.2	1.5
Anxiety, %	15.1	18.3	**21.3***	**28.7*****	**18.9****
Cancer, %	7.1	6.7	9.8	9.8	7.1
Depression, %	19.2	**26.3***	**24.7***	**34.0*****	**22.7***
Diabetes, %	6.6	9.4	7.2	**11.3****	5.0
Hypertension, %	24.8	23.2	29.9	28.7	24.2
High cholesterol, %	21.0	23.2	22.1	28.1	22.8
Arthritis, %	4.2	4.5	**7.7***	**8.8****	4.9
TIA or stroke, %	0.7	0.5	0	**3.1*****	0.6
GERD, %	8.6	**15.6****	8.5	**16.7****	**12.8****
OSA, %	4.4	7.2	6.0	**8.7****	3.8
Anxiety score (GAD7) , %	2.98	3.71	3.62	4.62	3.35
No: 0-4	75	70	71	**62.7*****	**71.5***
Mild: 5-9	17.5	20.6	18.4	18.9	19.4
Moderate/Severe: >=10	7.5	9.2	10.5	18.3	9.1
Depression score (PHQ-9) , %					
No: (0-4)	79.7	**73.3***	**73.8***	**63.4****	77.4
Mild:5-9	13.9	21.2	14.9	22.1	16.5
Moderate/severe:>=10	6.4	5.5	11.3	14.5	6.1

*p<0.05; **p<0.01; ***p<0.001 compared to the reference group

Table S7. Model fit criteria for LCA models with different classes

LCA models	**Fit criteria***	
	AIC	**BIC**
3 classes	2188.6	2423.8
4 classes	1994.1	2309.8
5 classes	1873.9	2270.2
6 classes	1891.7	2328.4

* Lower AIC and BIC indicate better model fit

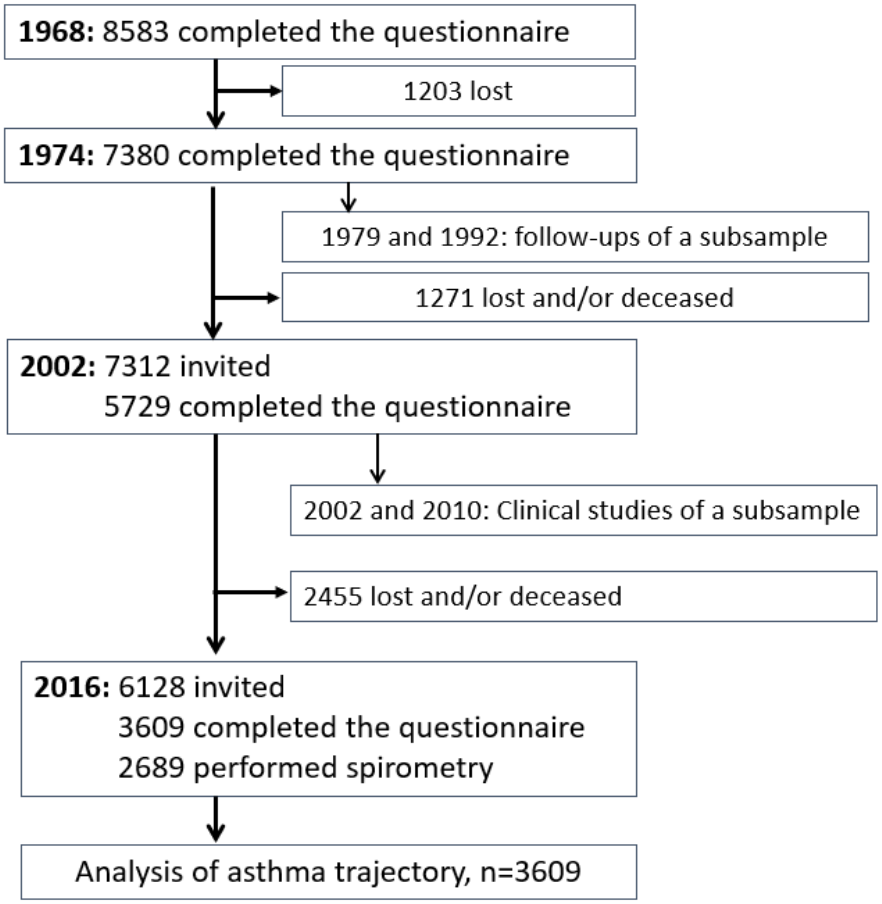
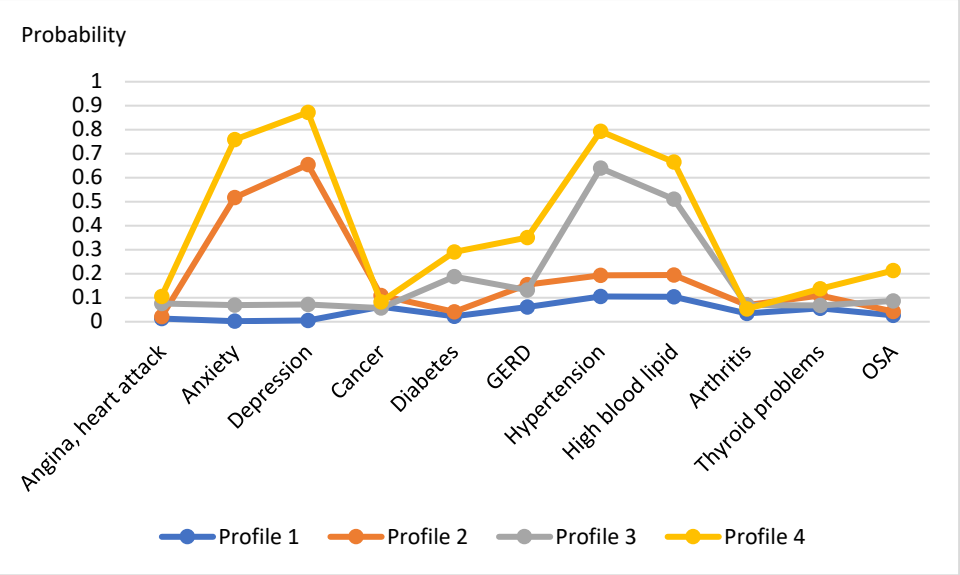


Fig S1. Flow chart of TAHS and sample selection for this analysis.



Profile 1: Minimal/least diseases (N=2206, 61.1%)
Profile 2: Dominant mental health disorders (N=861, 23.9%)
Profile 3: Dominant cardiovascular diseases/risks (N=424, 11.7%).
Profile 4: Multiple disorders (N=117, 3.3%)

Fig S2. Profiles of comorbidities at 53 years. The figure shows probability (y axis) of having each condition (x axis) in the comorbidity mix within the for four profiles

Reference

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4. Ding Z, Wang K, Li J, Tan Q, Tan W, Guo G. Association between glutathione S-transferase gene M1 and T1 polymorphisms and chronic obstructive pulmonary disease risk: A meta-analysis. *Clinical genetics* 2019; **95**(1): 53-62.
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