Associations between life-course FEV_1/FVC trajectories and respiratory symptoms up to middle age: analysis of data from two prospective cohort studies

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Summary

Background Life-course lung function trajectories leading to airflow obstruction, as measured by impaired FEV_1/FVC (forced vital capacity), precede the onset of chronic obstructive pulmonary disease (COPD). We aimed to investigate whether individuals on impaired FEV_1/FVC trajectories have an increased burden of respiratory symptoms, including those who do not meet the spirometric criteria for COPD.

Methods We analysed serial life-course data from two population-based cohort studies separately, which included respiratory symptoms and spirometry: the Tasmanian Longitudinal Health Study (TAHS, Australia) cohort was recruited at age 6–7 years and followed up until middle age (mean age 53 years; range 51–55); and the Coronary Artery Risk Development in Young Adults (CARDIA, USA) cohort was recruited at a mean age of 25 years (range 18–30) and followed up to a mean age of 55 years (range 47–64). Participants' symptom profiles at ages 53 and 55 years were derived by latent class analysis. Symptom profiles were compared across pre-bronchodilator FEV_1/FVC trajectories derived by group-based modelling, then restricted to those without COPD defined by post-bronchodilator airflow obstruction (FEV_1/FVC <5th percentile) at ages 51–55 years and 47–64 years.

Findings Six FEV_1/FVC trajectories previously derived for TAHS were replicated in CARDIA. Optimal models identified five symptom profiles in TAHS (n=2421) and six in CARDIA (n=3153). For both cohorts, the most impaired FEV_1/FVC trajectory (early low, rapid decline in TAHS; low peak, rapid decline in CARDIA) was associated with predominant wheeze (multinomial odds ratio [mOR] 6·71 [95% CI 4·10–10·90] in TAHS and 9·90 [4·52–21·70] in CARDIA) and nearly all respiratory symptoms (4·95 [2·52–9·74] and 14·80 [5·97–36·60]) at age 51–55 years in TAHS and age 47–64 years in CARDIA, compared with the average trajectory. Among individuals belonging to the three most impaired trajectories, the associations with predominant wheeze increased with worsening FEV_1/FVC impairment and persisted when considering only those without spirometry-defined COPD. Additionally, for those belonging to the two rapid decline trajectories, both wheezing and usual phlegm or bronchitis were reported by 54 (20%) of 265 participants younger than 14 years in TAHS and by 31 (25%) of 123 participants aged 30 years or younger in CARDIA.

Interpretation In two independent cohorts that collected similar data, people on impaired FEV_1/FVC trajectories often had a longstanding history of both wheeze and phlegm or bronchitis, and wheeze was the predominant symptom in individuals aged 47–64 years among those who had not already progressed to COPD.

Funding National Health and Medical Research Council (Australia); The University of Melbourne; Clifford Craig Medical Research Trust; Victorian, Queensland & Tasmanian Asthma Foundations; Royal Hobart Hospital Research Foundation; Helen MacPherson Smith Trust; GlaxoSmithKline; National Heart, Lung, and Blood Institute of the US National Institutes of Health.

Introduction

Chronic obstructive pulmonary disease (COPD) is the third leading cause of global mortality and the seventh leading cause of poor health worldwide.[1] Chronic respiratory symptoms predict adverse outcomes, including accelerated lung function decline,[2] acute exacerbations, hospital admission, and mortality, even in the absence of post-bronchodilator airflow obstruction.[3–6] These symptoms can occur before the FEV_1/FVC (forced vital capacity) ratio falls below traditional spirometric cutoffs for diagnosis of COPD and well before a clinical diagnosis of COPD is made. In COPD, symptom burden increases with disease severity as patients age, and more symptoms predict worse health outcomes.[3] Yet symptoms often occur

Lancet Respir Med 2024

Published Online November 27, 2024 https://doi.org/10.1016/S2213-2600(24)00265-0

See Online/Comment https://doi.org/10.1016/S2213-2600(24)00337-0

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Research in context

Evidence before this study

We searched PubMed using the keywords "trajectory*", "FEV", "FVC", and "FEV_1/FVC", from database inception to Oct 4, 2023 for previous population-based analyses investigating lung function trajectories and symptoms. The articles we found focused only on FEV_1 trajectories, which can reflect both obstructive and restrictive processes with diverse underlying disease mechanisms. No previous population-based analysis had examined the history of respiratory symptoms in parallel with obstructive FEV_1/FVC lung function trajectories and related these trajectories to mutually exclusive symptom profiles in middle age. Furthermore, a physiological definition of pre-chronic obstructive pulmonary disease (pre-COPD; ie, some evidence of the disease process but not yet meeting diagnostic spirometric criteria for COPD) based on the FEV_1/FVC ratio has yet to be established, and potential links with respiratory symptoms when using such a definition have not previously been described.

Added value of this study

By bringing together longitudinal data from two independent population-based cohort studies, the Tasmanian Longitudinal Health Study (TAHS, Australia) and Coronary Artery Risk Development in Young Adults (CARDIA, USA), and analysing these data separately, we found that symptomatic COPD occurred in at least one in 25 participants aged 51–55 years in TAHS and aged 47–64 years in CARDIA. In a replication analysis, we independently found that especially participants belonging to the two most impaired trajectories that featured rapid FEV_1/FVC decline commonly reported wheezing and usual phlegm or bronchitis from childhood (TAHS) and early adulthood (CARDIA). We also found that the three most impaired trajectories were associated with this predominant wheeze symptom profile at a mean age of 53 years in TAHS and a mean age of 55 years in CARDIA; furthermore, these associations were stronger for worse impairments in FEV_1/FVC. Additionally, impaired FEV_1/FVC trajectories were associated with predominant wheeze even when considering only those who had a rapid rate of FEV_1/FVC decline but had not yet reached the diagnostic spirometric criterion for COPD.

Implications of all the available evidence

New knowledge that symptomatic COPD (or COPD with co-existent asthma) occurs somewhat frequently in adults aged 47–64 years strengthens the rationale to arrange objective testing (eg, pre-bronchodilator and post-bronchodilator spirometry) in the diagnostic work-up when a patient of this demographic presents to primary care with respiratory symptoms. Furthermore, a predominant wheeze symptom profile in those on rapidly declining FEV_1/FVC trajectories who do not yet have spirometry-defined COPD might reflect the first stages of small airway obstruction (ie, trajectory-defined pre-COPD) and could foreshadow future COPD. Having wheeze as a key symptom outcome would enable clinical trials to establish the disease-modifying potential of new and repurposed therapies at a younger age, when interventions could still modify the course of disease.

years before a clinical diagnosis is made.[7] Consideration for spirometry testing has been recommended to actively find individuals aged 35–40 years or older who have respiratory symptoms or risk factors for the disease, or both, to promote good lung health earlier in the life course.

People with impaired lung function trajectories[8–10] who go on to develop COPD are also at increased risk of premature death.[11] These findings have prompted *Lancet* Commissioners and others to advocate for proactive detection of at-risk adults at a younger age.[12] People who develop established COPD by their early fifties represent the most susceptible subgroup,[13] although most individuals who develop COPD have not yet been diagnosed at this point, and so identifying these individuals and offering them secondary preventive interventions could slow their disease progression and thereby reduce the burden of disease.[12] However, how respiratory symptoms relate to COPD-related lung function trajectories across the life course for individuals within the general population has not previously been studied. It is also unknown which respiratory symptom or combination of symptoms (ie, symptom profiles) should especially alert primary care clinicians to include pre-bronchodilator and post-bronchodilator spirometry in the diagnostic work-up of patients in the community aged 30–64 years who might already have or be at risk of developing COPD.

Using data from two independent, prospective cohorts from Australia and the USA that serially measured lung function and respiratory symptoms up to the sixth decade of life, we aimed to develop FEV_1/FVC trajectories and document the timing of key respiratory symptoms (eg, wheeze and phlegm) across the life course in the most impaired trajectories; to identify combinations of symptoms (symptom profiles) in middle age and investigate relationships with FEV_1/FVC trajectories; and to identify which symptom profiles at 47–64 years are associated with a new physiological definition of individuals who have a rapidly declining FEV_1/FVC trajectory but do not yet have spirometry-defined COPD.

Methods

Study cohorts and participants

The Tasmanian Longitudinal Health Study (TAHS) is a prospective whole-of-population cohort, comprising individuals who were born in 1961 and went to school in urban and rural Tasmania, Australia, in 1968. Participants were first enrolled at age 6–7 years (n=8583) and followed up serially with spirometry at mean ages of 7, 13, 20, 45, 50, and 53 years, including post-bronchodilator

measurements at age 45 years (n=1389) and 53 years (range 51–55; n=2719).[10,14] A stratified 1:1 sample of participants with or without childhood asthma in 1968 was surveyed at age 31 years (n=2000).[14] For the present analysis, those enrolled were assignable to both a symptom profile and FEV_1/FVC trajectory (n=2421). As previously published,[8] the trajectories included: average; early high, normal decline; early low, catch-up, normal decline; early low, normal decline; early normal, rapid decline; and early low, rapid decline. Missing lung function data have been previously reported.[8,10]

The Coronary Artery Risk Development in Young Adults (CARDIA) study enrolled 5115 healthy Black and White non-Hispanic individuals aged 18–30 years in 1985–86 from four cities in the USA that were non-mining areas. Spirometry measurements were collected at mean ages of 25 (baseline), 27, 30, 35, 45, and 55 years, with post-bronchodilator testing done at a mean age of 55 years (range 47–64; 2015–16, n=3172), alongside respiratory symptom questionnaires, with missing data previously reported.[2] For the present analysis, those studied were assignable to both a symptom profile and FEV_1/FVC trajectory (n=3153).

TAHS was approved by human ethics review committees at all participating institutions, principally the Universities of Melbourne (040375) and Tasmania (H0012710). For CARDIA, institutional review board approval was obtained at each study site. Written informed consent was obtained from all participants at each follow-up of the cohort studies at each study site.

Derivation of FEV_1/FVC trajectories and definition of COPD in both cohorts

Participants underwent spirometry at each timepoint and Z scores were derived with Global Lung Function Initiative (GLI) reference values.[15] Six pre-bronchodilator FEV_1/FVC trajectories derived from group-based trajectory modelling (GBTM) from TAHS participants aged 7–53 years have been published.[8,10] This methodology was used to independently derive pre-bronchodilator FEV_1/FVC trajectories from CARDIA at mean ages of 25, 27, 30, 35, 45, and 55 years (appendix pp 3–4); GBTM was similarly applied to Z scores of pre-bronchodilator FEV_1/FVC at these six timepoints, which estimated the population prevalence of each trajectory group and the posterior probability of each individual belonging to each subgroup. An eight-trajectory model (not shown) was deemed optimal on the basis of established criteria; however, a six-trajectory model was chosen given CARDIA was the replication cohort (appendix p 3).

Spirometry-defined COPD, synonymous with post-bronchodilator airflow obstruction at the 53-year TAHS and 55-year CARDIA study follow-ups, was defined by a post-bronchodilator FEV_1/FVC lower than the lower limit of predicted normal (ie, Z score <–1·645).[15]

Ten respiratory symptoms at the mean ages of 53 years and 55 years and their harmonisation across TAHS (age 53 years) and CARDIA (age 55 years) are summarised in the appendix (p 5). The survey questions encompassed wheeze apart from a cold, duration and frequency of cough and phlegm, as well as colds that travelled to the chest, and dyspnoea on exertion. To identify distinct symptom profiles, latent class analysis was applied for each cohort independently. The parameters behind model selection based on established criteria are outlined in the appendix (p 6). Notably, although the seven-class model in TAHS had the lowest Akaike information criterion (AIC) and Bayesian information criterion (BIC), the five-class model was chosen given its near-lowest BIC, group membership higher than 4·0%, and similar clinicial interpretability.

Other descriptive variables, including wheeze and phlegm over time, are summarised in the appendix (pp 7–8).

Statistical analysis

Analyses were carried out with Stata (version 17) and with complete cases. χ^2 comparisons were made for categorical data and analysis of variance (ANOVA) for continuous data. The prevalence (or weighted prevalence) of wheeze and phlegm or bronchitis by FEV_1/FVC trajectory at each timepoint was presented across the life course and patterns between cohorts described. Similarly, the age at which participants first reported wheezing and phlegm or bronchitis, or both, was summarised into the following categories: younger than 14 years (TAHS), 18–30 years (CARDIA), older than 30 years (CARDIA), and 40–55 years (TAHS; appendix p 7). Unadjusted multinomial regression methods were used to summarise patterns between the FEV_1/FVC trajectories and respiratory symptom profiles, and forest plots were used to assess results for consistency. Sensitivity analyses excluded participants with obesity, coronary artery disease, chronic heart failure, some occupational exposures, and self-reported asthma (ever) at age 53 or 55 years. Effect modification by smoking status and inhaled corticosteroid (ICS) use was examined if sufficient numbers were available, and results stratified if the interaction p value was less than 0·10.

See Online for appendix

Role of the funding source

The funders of the two studies had no role in study design, data collection, data analysis, data interpretation, writing of the manuscript, or the decision to submit the manuscript for publication. The conduct of the current study was encompassed within the original ethics approvals for TAHS and CARDIA. No funding was sought or required independently of the original studies.

Results

Of 2421 TAHS participants, 116 (5%) met spirometric criteria for COPD at a mean age of 53 years (range 51–55). Of these, 95 (82%) concurrently reported one or more respiratory symptoms, which represented 4% of the total

	Total (n=2421)	Latent symptom profile at mean age 53 years					p value*
		Minimal (n=1852)	Predominant wheeze (n=179)	Predominant productive cough (n=114)	Predominant dry cough (n=189)	Nearly all respiratory symptoms (n=87)	
Mean age, years	52·7 (0·8)	52·7 (0·8)	52·8 (0·8)	52·9 (0·8)	52·7 (0·8)	53·0 (0·9)	0·64
Sex at birth							0·64
Female	1249 (52%)	947 (51%)	99 (55%)	57 (50%)	104 (55%)	42 (48%)	..
Male	1172 (48%)	905 (49%)	80 (45%)	57 (50%)	85 (45%)	45 (52%)	..
FEV_1/FVC trajectory (age 7–53 years)							<0·0001
Average	1200 (50%)	970 (52%)	69 (39%)	58 (51%)	87 (46%)	38 (44%)	..
Early high, normal decline	392 (16%)	336 (18%)	18 (10%)	10 (9%)	32 (17%)	7 (8%)	..
Early low, catch-up, normal decline	86 (4%)	72 (4%)	4 (2%)	4 (4%)	6 (3%)	1 (1%)	..
Early low, normal decline	442 (19%)	326 (18%)	40 (22%)	21 (18%)	38 (20%)	19 (22%)	..
Early normal, rapid decline	124 (5%)	81 (4%)	16 (9%)	9 (8%)	12 (6%)	9 (10%)	..
Early low, rapid decline	136 (6%)	67 (4%)	32 (18%)	12 (11%)	14 (7%)	13 (15%)	..
Spirometry-defined COPD†	116 (5%)	50 (3%)	25 (14%)	14 (12%)	13 (7%)	14 (17%)	<0·0001
Post-bronchodilator FEV_1/FVC (Z scores)	0·24 (0·8)	0·12 (0·8)	−0·43 (1·1)	−0·24 (1·1)	−0·10 (1·1)	−0·5 (1·0)	<0·0001
Reduced D_Lco (n<LLN)	83 (4%)	47 (3%)	5 (3%)	8 (8%)	12 (7%)	11 (14%)	<0·0001
Self-reported asthma (ever), age 53 years	515 (21%)	267 (15%)	115 (64%)	31 (28%)	64 (34%)	38 (44%)	<0·0001
Doctor diagnosis reported	475 (20%)	249 (13%)	106 (59%)	27 (24%)	57 (30%)	36 (41%)	<0·0001
Asthma inhaler use in past 12 months	284 (12%)	89 (5%)	88 (54%)	26 (23)	43 (24%)	27 (34%)	<0·0001
ICS use in past 12 months	157 (7%)	56 (3%)	45 (26%)	10 (9%)	25 (13%)	21 (24%)	<0·0001
Asthma or wheezing at age 7 years‡	353 (15%)	250 (14%)	50 (28%)	20 (18%)	19 (10%)	14 (16%)	<0·0001
Asthma or wheezing at age 31 years‡§	111 (14%)	59 (10%)	27 (38%)	12 (29%)	9 (26%)	4 (18%)	<0·0001
Self-reported coronary artery disease	60 (2%)	36 (2%)	8 (4%)	6 (5%)	7 (4%)	3 (3%)	0·036
Mean BMI, kg/m²	28·6 (5·5)	28·2 (5·2)	30·2 (6·6)	30·1 (6·7)	29·3 (5·9)	29·4 (6·3)	<0·0001
Obesity (BMI ≥30 kg/m²)	791 (33%)	553 (30%)	77 (43%)	51 (45%)	77 (40%)	33 (38%)	<0·0001
Occupational exposure							0·18
Low exposure to mineral dust	522 (23%)	394 (22%)	33 (20%)	24 (22%)	43 (23%)	28 (33%)	..
High exposure to mineral dust	595 (26%)	447 (25%)	56 (34%)	27 (24%)	43 (23%)	22 (26%)	..
Low exposure to vapours, gases, dusts, and fumes	836 (36%)	644 (37%)	52 (31%)	48 (43%)	61 (33%)	31 (36%)	..
High exposure to vapours, gases, dusts, and fumes	875 (38%)	656 (37%)	71 (43%)	43 (39%)	67 (36%)	38 (45%)	..
Self-reported non-smoker	1045 (43%)	844 (46%)	58 (33%)	37 (32%)	81 (42%)	25 (29%)	..
Ever-smoker							<0·0001
Past smoker	992 (41%)	781 (42%)	84 (47%)	46 (40%)	60 (32%)	21 (24%)	..
Current smoker	382 (16%)	226 (12%)	36 (20%)	31 (27%)	48 (25%)	41 (47%)	..
Median pack-years	17 (3–27)	11 (2–24)	12 (3–31)	18 (5–33)	20 (7–36)	27 (7–46)	<0·0001
Maternal smoking at child age 7 years‡	788 (33%)	596 (33%)	47 (27%)	46 (40%)	65 (36%)	34 (41%)	0·053
Paternal smoking at child age 7 years‡	1351 (58%)	1045 (58%)	101 (59%)	70 (64%)	95 (54%)	51 (63%)	0·44

Data are n (%), mean (SD), or median (IQR). TAHS=Tasmanian Longitudinal Health Study. FVC=forced vital capacity. COPD=chronic obstructive pulmonary disease. D_Lco=diffusing capacity of the lung for carbon monoxide. LLN=lower limit of normal. ICS=inhaled corticosteroid. *χ^2 tests for categorical data and ANOVA for continuous data. †Defined by post-bronchodilator FEV_1/FVC less than the lower limit of predicted normal, using Global Lung Function Initiative reference values. ‡Data are from age 53 years, except for parent-report from the 1968 survey as indicated; asthma is defined as at least two episodes of wheezing by age 7 years. §The 1991–92 survey was enriched for asthma in a 1:1 stratified sample of n=2000, thus reweighted prevalence estimates (%) are presented.

Table 1: **Characteristics of participants belonging to each symptom profile in the TAHS cohort**

analytical sample. Of 3153 CARDIA participants, 199 (6%) met spirometric criteria for COPD at a mean age of 55 years (range 47–65). Of these, 142 (71%) concurrently reported one or more respiratory symptoms, which represented 5% of the total analytical sample. More descriptive details of these cohorts are summarised in the appendix (p 9).

Regarding the symptom profiling in TAHS, those with missing trajectory data had a marginally higher proportion of participants reporting one or more symptoms at a mean age of 53 years than those reporting no symptoms (59·9% [95% CI 57·0–62·7] *vs* 56·6% [54·6–58·6]). In CARDIA, the proportion of participants reporting one or more symptoms at a mean age of 55 years was similar to those reporting no symptoms, but slightly lower than in TAHS (52·1% [95% CI 44·8–59·3] *vs* 49·4% [47·7–51·2]). Among those with trajectory data, 0·1–0·5% of data for each symptom were missing in TAHS (ie, 3–10 observations), and 0·4% were missing in CARDIA (ie, 13–15 observations; data not shown).

The optimal symptom latent class analysis in TAHS produced five distinct profiles: predominant wheeze, predominant productive cough, predominant dry cough,[16] nearly all respiratory symptoms, and minimal (reference; table 1, figure 1; appendix p 10). The symptom profiles in CARDIA were similar but also included some chesty colds (figure 1; appendix p 11). This six-class model in CARDIA resembled the less-optimal seven-class model in TAHS, which additionally partitioned participants reporting predominant dry cough into those with and without wheeze (appendix pp 12–13). A moderate probability of dyspnoea was observed for all symptom profiles other than minimal, and thus was not a defining feature of any profile (figure 1).

At a mean age of 53 years in TAHS, there was significant variation in pre-bronchodilator FEV_1/FVC trajectory; post-bronchodilator FEV_1/FVC Z score; spirometry-defined COPD; diffusing capacity of the lung for carbon monoxide less than the lower limit of normal; self-reported asthma, including doctor-diagnosed asthma; inhaler use in the past 12 months, including inhaled corticosteroids; self-reported asthma at age 7 years and age 31 years; BMI and obesity; and smoking status and pack-year history across symptom profiles (all p<0·0001; table 1). There was also modest variation in self-reported coronary artery disease (p=0·036) and maternal smoking at age 7 years (p=0·053; table 1). At a mean age of 55 years in CARDIA, there was significant variation in female predominance; race; pre-bronchodilator FEV_1/FVC trajectory; post-bronchodilator FEV_1/FVC Z score; spirometry-defined COPD; centrilobular emphysema; self-reported asthma; inhaler use, including inhaled corticosteroids at a mean age of 25 years and 55 years; adjudicated chronic heart failure; BMI and obesity; and smoking status and pack-year history across symptom profiles (all p<0·0001; table 2). Colds that usually go to the chest were commonly reported by both cohorts, even by those belonging to the minimal symptom profile (514 [28%] of 1852 in TAHS and 409 [19%] of 2118 in CARDIA; data not shown).

Based on previously published pre-bronchodilator FEV_1/FVC trajectories in TAHS,[8] 1222 (51%) of 2421 TAHS participants belonged to the average (reference) trajectory and 709 (29%) belonged to the three most impaired trajectories, which included 114 (98%) cases of spirometry-defined COPD at a mean age of 53 years (appendix pp 14–16). For those belonging to the early normal, rapid decline trajectory (n=127), the mean post-bronchodilator FEV_1/FVC Z score was –1·2 (0·7) SD and 26 (21%) had spirometry-defined COPD. For those belonging to the early low, rapid decline trajectory (n=138), the mean post-bronchodilator FEV_1/FVC Z score was –1·8 (0·7) SD and 76 (56%) had spirometry-defined COPD. Compared with those who belonged to normal decline trajectories, more of those belonging to both rapid decline FEV_1/FVC trajectories self-reported greater smoking histories, asthma, inhaler use including ICS, occupational exposure or exposures, and one or more respiratory symptoms at a mean age of 53 years (appendix pp 14–15).

	Predominant wheeze		Predominant productive cough		Predominant dry cough		Nearly all respiratory symptoms		Minimal (reference)		Some chesty colds*	
	TAHS	CARDIA	TAHS	CARDIA	TAHS	CARDIA	TAHS	CARDIA	TAHS	CARDIA	TAHS	CARDIA
Usual cough†	0·2606	0·0023	0·5507	0·0196	0·9957	0·9990	0·9990	0·9989	0·1034	0·0047	..	0·0024
Cough most days (≥3 months per year)	0·0001	0·0000	0·0634	0·0001	0·8290	0·7197	0·8625	0·7950	0·0000	0·0000	..	0·0000
Chronic cough (≥2 years)	0·0002	0·0000	0·0007	0·0001	0·9113	0·7587	0·9672	0·7604	0·0000	0·0000	..	0·0000
Usual phlegm‡	0·1292	0·0047	0·9987	0·9992	0·0651	0·0191	0·9855	0·9990	0·0233	0·0001	..	0·0298
Phlegm most days (≥3 months per year)	0·0000	0·0000	0·4580	0·6805	0·0000	0·0001	0·8321	0·8520	0·0000	0·0000	..	0·0000
Chronic phlegm (≥2 years)	0·0001	0·0001	0·4634	0·8535	0·0002	0·0001	0·9650	0·8106	0·0000	0·0000	..	0·0000
Colds usually go to the chest	0·5876	0·6955	0·6516	0·5125	0·5144	0·5716	0·7950	0·7508	0·2782	0·1708	..	0·4298
Current wheeze without a cold	0·8393	0·5850	0·3530	0·3252	0·2359	0·4071	0·5852	0·5989	0·0263	0·0104	..	0·0840
Wheeze with breathlessness	0·7448	0·7275	0·2215	0·3060	0·2040	0·2481	0·4170	0·4556	0·0173	0·0441	..	0·0058
Shortness of breath after exercise	0·6591	0·4649	0·4162	0·4075	0·2938	0·4554	0·4947	0·6715	0·0994	0·0594	..	0·4512

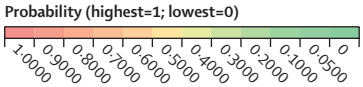

Figure 1: **Probability of having each symptom within each latent symptom class**
The heatmap shows data from adults in the TAHS (aged 51–55 years) and CARDIA (aged 47–64 years) cohorts. *Some chesty colds was a latent symptom profile of the six-class and seven-class models that were less optimal than the five-class model in TAHS. †Usual cough was defined by an affirmative response to the question "Do you usually cough when you do not have a cold?" in TAHS or "Do you usually have a cough?" in CARDIA. ‡Usual phlegm was defined by an affirmative response to the question "Do you usually have phlegm in your chest when you do not have a cold?" in TAHS or "Do you usually bring up phlegm from your chest? Exclude clearing of throat" in CARDIA. TAHS=Tasmanian Longitudinal Health Study. CARDIA=Coronary Artery Risk Development in Young Adults.

Fewer participants in the replication cohort (CARDIA, n=3153) than in TAHS belonged to the three most impaired FEV_1/FVC trajectories (443 [14%] in CARDIA *vs* 709 [29%] in TAHS), which included 159 (80%) of 198 cases of spirometry-defined COPD at a mean age of 55 years (appendix pp 16–18). The proportions of these cases in the normal peak, early rapid decline FEV_1/FVC trajectory and the low peak, persistent rapid decline FEV_1/FVC trajectory were higher in CARDIA than in TAHS (49 [98%] of 50 *vs* 45 [63%] of 71), and corresponded to lower mean Z scores (–2·4 SD *vs* –3·4 SD; appendix p 16–17). Compared with TAHS (appendix pp 14–15), the proportion currently smoking in the most impaired trajectory was the same (19 [38%] of 51 *vs* 52 [38%] of 138), otherwise fewer had smoked and their pack-year history was lower in CARDIA (appendix pp 17–18). Compared with normal decline trajectories, more of those belonging to these rapid decline trajectories smoked and self-reported asthma, inhaler use, and one or more respiratory symptoms in middle age (appendix pp 17–18); this was more pronounced in CARDIA than in TAHS. Of these two trajectories, those belonging to the most impaired low peak, persistent rapid decline trajectory included a higher prevalence of participants of Black racial origin, severe COPD, and centrilobular emphysema, and only five (10%) of 51 participants reported using ICS therapies (appendix pp 17–18).

When symptom onset was stratified by age group (figure 2; appendix p 19), wheeze alone was the most common symptom for those who first reported symptoms after the age of 30 years in CARDIA (and >40 years in TAHS), especially among those on the most impaired

	Total (n=3153)	Latent symptom profile at mean age 55 years						p value*
		Minimal (n=2118)	Predominant wheeze (n=244)	Predominant productive cough (n=168)	Predominant dry cough (n=147)	Nearly all respiratory symptoms (n=134)	Some chesty colds (n=342)	
Mean age, years	55·1 (3·6)	55·2 (3·6)	55·2 (3·6)	55·3 (3·6)	55·0 (3·6)	54·9 (3·7)	55·1 (3·6)	0·99
Sex at birth								<0·0001
Female	1810 (57%)	1138 (54%)	165 (68%)	87 (52%)	103 (70%)	73 (54%)	244 (71%)	..
Male	1343 (43%)	980 (46%)	79 (32%)	81 (48%)	44 (30%)	61 (46%)	98 (29%)	..
Race								<0·0001
Black	1495 (47%)	919 (43%)	118 (48%)	102 (61%)	76 (52%)	72 (54%)	208 (61%)	..
White	1658 (53%)	1199 (57)	126 (52%)	66 (39%)	71 (48%)	62 (46%)	134 (39%)	..
FEV_1/FVC trajectory (age 25–55 years)								<0·0001
Average	1265 (40%)	855 (40%)	93 (38%)	64 (38%)	65 (44%)	40 (30%)	148 (43%)	..
Above average	366 (12%)	267 (13%)	14 (6%)	17 (10%)	20 (14%)	8 (6%)	40 (12%)	..
Below average	1079 (34%)	747 (35%)	68 (28%)	48 (29%)	48 (33%)	50 (37%)	118 (35%)	..
Persistently low	320 (10%)	206 (10%)	39 (16%)	26 (15%)	11 (8%)	16 (12%)	22 (6%)	..
Normal peak, rapid decline	72 (2·3%)	30 (<1%)	16 (7%)	7 (4%)	1 (1%)	11 (8%)	7 (2%)	..
Low peak, rapid decline	51 (1·6%)	13 (1%)	14 (6%)	6 (4%)	2 (1%)	9 (7%)	7 (2%)	..
Spirometry-defined COPD†	198 (6·3%)	79 (4%)	37 (15%)	16 (10%)	10 (7%)	33 (25%)	23 (7%)	<0·0001
Post-bronchodilator FEV_1/FVC (Z scores)	–0·35 (1·0)	–0·27 (0·9)	–0·74 (1·2)	–0·57 (1·1)	–0·27 (1·0)	–1·0 (1·4)	–0·2 (1·1)	<0·0001
Centrilobular emphysema	113 (4%)	47 (3%)	8 (4%)	16 (11%)	6 (5%)	27 (23%)	9 (3%)	<0·0001
Self-reported asthma (ever)	498 (16%)	163 (8%)	159 (65%)	49 (29%)	35 (24%)	47 (35%)	45 (13%)	<0·0001
Asthma inhaler use at age 55 years	290 (9%)	47 (2%)	102 (42%)	33 (20%)	28 (19%)	53 (40%)	27 (8%)	<0·0001
ICS use reported	144 (5%)	37 (2%)	39 (16%)	20 (12%)	16 (11%)	20 (15%)	12 (4%)	<0·0001
Asthma inhaler use at age 25 years‡	124 (4%)	45 (2%)	49 (20%)	11 (7%)	4 (3%)	5 (4%)	10 (3%)	<0·0001
Adjudicated coronary artery disease (up to 2020)‡	71 (2%)	44 (1%)	4 (2%)	6 (4%)	3 (2%)	7 (5%)	7 (2%)	0·19
Adjudicated chronic heart failure (up to 2020)‡	41 (1%)	12 (1%)	6 (3%)	7 (4%)	3 (2%)	4 (3%)	9 (3%)	<0·0001
Mean BMI, kg/m²	30·5 (7·2)	29·2 (6·2)	32·5 (8·5)	32·4 (7·9)	33·2 (8·3)	30·1 (8·0)	34·6 (8·1)	<0·0001
Obesity (BMI ≥30 kg/m²)	1449 (46%)	834 (39%)	140 (57%)	89 (53%)	83 (56%)	64 (48%)	239 (70%)	<0·0001
Self-reported non-smoker	1982 (64%)	1452 (69%)	150 (62%)	82 (49%)	77 (53%)	32 (25%)	189 (56%)	..
Ever-smoker								<0·0001
Past smoker	715 (23%)	459 (22%)	57 (24%)	42 (25%)	27 (18%)	31 (24%)	99 (29%)	..
Current smoker	424 (14%)	190 (9%)	35 (14%)	42 (25%)	42 (29%)	65 (51%)	50 (15%)	..
Median pack-years	10 (3–21)	9 (3–17)	9 (3–18)	16 (9–30)	15 (6–25)	22 (12–35)	13 (4–22)	<0·0001

Data are n (%), mean (SD), or median (IQR). CARDIA=Coronary Artery Risk Development in Young Adults. FVC=forced vital capacity. COPD=chronic obstructive pulmonary disease. ICS=inhaled corticosteroid. *χ^2 tests for categorical data and ANOVA for continuous data. †Defined by post-bronchodilator FEV_1/FVC Z score less than 1·645 SD with Global Lung Function Initiative reference values. ‡At mean age 55 years, except for asthma inhalers at baseline (year 0) and adjudicated heart outcomes as indicated.

Table 2: **Characteristics of participants belonging to each symptom profile in the CARDIA cohort**

(ie, rapid decline) FEV_1/FVC trajectories. Similarly, the rapid decline FEV_1/FVC trajectories were enriched for both wheeze and bronchitis in TAHS participants aged younger than 14 years (54 [20%] of 265 *vs* 289 [12%] of 2421), and for both wheeze and usual phlegm in CARDIA participants aged 30 years or younger (31 [25%] of 123 *vs* 344 [11%] of 3153), symptoms that might have been concurrent. This corresponds with 94 (35%) of 265 TAHS participants aged younger than 14 years (childhood measurement) and 56 (45%) of 123 CARDIA participants (young adult measurements) who reported at least one symptom (figure 2). Individual symptom history by trajectory is illustrated in the appendix (pp 20–21).

Of the latent respiratory symptom profiles, the three trajectories that featured early low FEV_1/FVC or rapid decline, or both, in adulthood were associated with predominant wheeze, compared with the average trajectory (figure 3). The increasing odds ratios corresponded with worsening impairment, such that there was minimal overlap between the 95% CIs of the most and third-most impaired trajectories. This pattern was consistent across TAHS and CARDIA.

The two rapid decline FEV_1/FVC trajectories were significantly associated with nearly all respiratory symptoms at a mean age of 53 or 55 years, although the associations were stronger for participants of CARDIA than those of TAHS (figure 3). For both cohorts, the most impaired early low, rapid decline trajectory in TAHS and low peak, persistent rapid decline trajectory in CARDIA were also associated with the following symptom profiles: predominant productive cough (TAHS, multinomial odds ratio [mOR] 3·00 [95% CI 1·53–5·85]; CARDIA, 6·17 [2·26–16·8]; appendix pp 22–23); predominant dry cough (TAHS, 2·32 [1·26–4·31]; appendix p 22); and some chesty colds (CARDIA, 3·11 [1·22–7·93], TAHS, 2·55 [1·24–5·23]; appendix pp 23–24). In CARDIA only, the second-most and third-most impaired trajectories were also associated with predominant productive cough (appendix p 23).

When considering only those who had not yet developed COPD (appendix p 16), other than the most impaired FEV_1/FVC trajectory in CARDIA, which contained too few participants, significant associations remained between the three most impaired trajectories and predominant wheeze in a similar pattern of increasing odds with worsening FEV_1/FVC impairment for both cohorts (appendix pp 25–27). This was observed even when excluding those with obesity, coronary artery disease, or chronic heart failure (appendix pp 28–29). Associations with nearly all respiratory symptoms were underpowered (appendix pp 26–27).

When considering only those who did not self-report having asthma, the most impaired FEV_1/FVC trajectory remained associated with predominant wheeze (TAHS [n=64], mOR 3·77 [95% CI 1·50–9·50]; CARDIA [n=23], 5·03 [1·03–24·50]; appendix pp 28–29). Associations with nearly all respiratory symptoms were unchanged (data not shown).

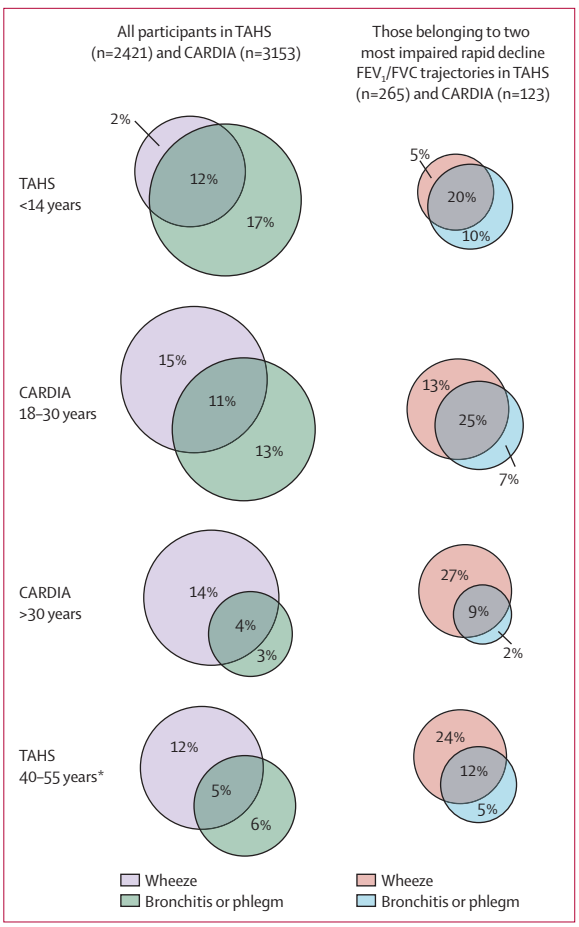

***Figure 2*: Timing of first symptom in all participants and those belonging to the two most impaired rapid decline FEV_1/FVC trajectories**
Charts are not scaled between columns; scale within columns is based on numbers and is approximate only. The corresponding numbers from which the percentages have been derived are presented in the appendix (p 19). In TAHS, bronchitis was defined at age 6–7 years by two or more bronchitic episodes in the past year, compared with one or more episodes at age 13–14 years (see appendix p 7 for definitions). CARDIA=Coronary Artery Risk Development in Young Adults. FVC=forced vital capacity. TAHS=Tasmanian Longitudinal Health Study. *Age gap between 14–40 years, as interval follow-ups were enriched for asthma.

When considering only those in TAHS who were not exposed to vapours, dusts, gases, and fumes, and mineral dusts more specifically, the most impaired FEV_1/FVC trajectory remained associated with predominant wheeze (vapours, dusts, gases, and fumes [n=44], mOR 4·99 [95% CI 1·84–13·5]; mineral dusts [n=78], 4·95 [2·30–10·7]; data not shown). Associations with nearly all respiratory symptoms were underpowered (data not shown).

When assessing effect modification by smoking, there was an interaction between the effects of FEV_1/FVC trajectories and smoking status on symptom profiles in TAHS ($p_{interaction}$=0·073) but not in CARDIA ($p_{interaction}$=0·23). In TAHS, among those who never smoked or previously smoked, associations with predominant wheeze were of similar or greater magnitude, as were the associations

with predominant productive cough and nearly all respiratory symptoms in former smokers (appendix pp 30–31). For those who were current smokers, associations with predominant wheeze and nearly all respiratory symptoms were attenuated, whereas the association with predominant dry cough was greater (appendix p 32). Other associations were not reported due to low numbers.

In TAHS and CARDIA, there were no interactions by self-reported asthma ($p_{interaction}$=0·52 for TAHS *vs* $p_{interaction}$=0·20 for CARDIA) nor any sex differences ($p_{interaction}$=0·78 *vs* $p_{interaction}$=0·17). There was insufficient evidence of a significant modifying effect by ICS use in TAHS ($p_{interaction}$=0·22), and there were too few participants in a low peak, rapid decline trajectory using ICS therapies to perform this analysis in CARDIA (appendix p 18).

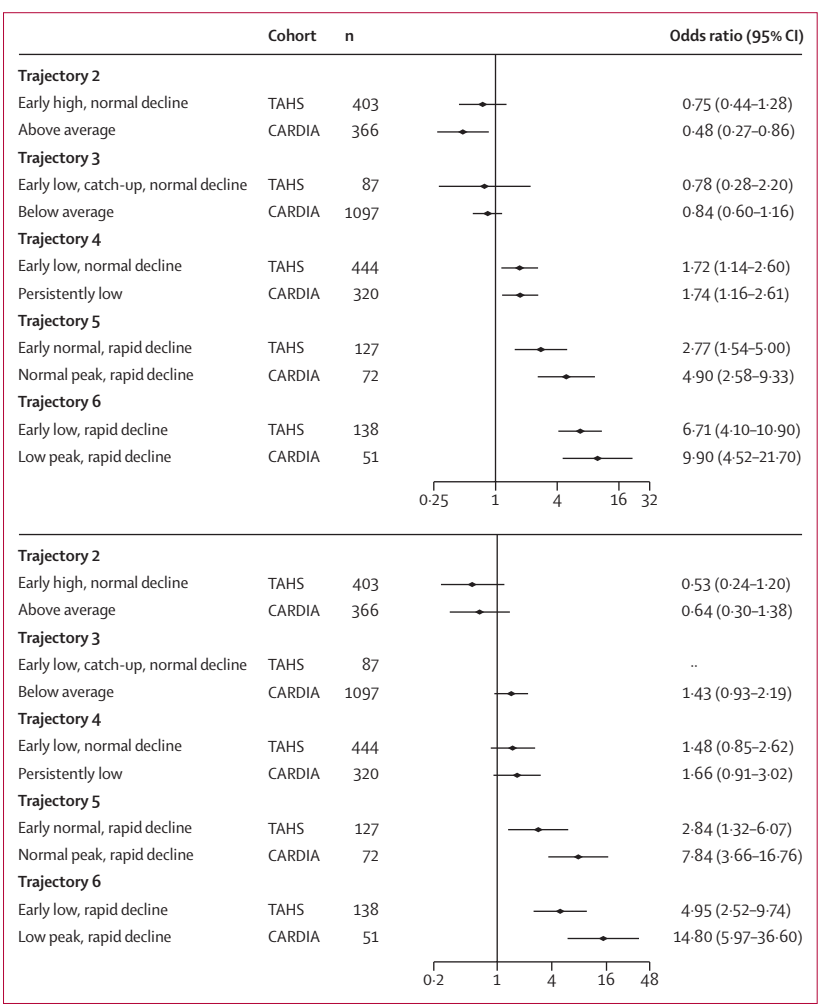

Figure 3: **Associations between pre-bronchodilator FEV_1/FVC trajectories and predominant wheeze (top panel) and nearly all respiratory symptoms (bottom panel) at mean age 53 and 55 years (replication of TAHS by CARDIA)**

The reference or average trajectories for TAHS (n=1222) and CARDIA (n=1265) are omitted as the odds ratio is 1. The order of the numbers refers to the next least impaired FEV_1/FVC trajectory (2) to the most impaired trajectory (6) for both cohorts, as illustrated in the appendix (p 4). There were fewer than four TAHS participants belonging to trajectory 3 and nearly all respiratory symptoms so this category is omitted from the forest plot. CARDIA=Coronary Artery Risk Development in Young Adults. FVC=forced vital capacity. TAHS=Tasmanian Longitudinal Health Study.

Discussion

Using prospectively collected, population-based data starting from childhood (TAHS) or early adulthood (CARDIA), we have shown that respiratory symptoms occur commonly in adults, mainly in their fifties, who have the most impaired lung function trajectories. For many, respiratory symptoms were present decades earlier. Specifically, among participants with a rapid FEV_1/FVC decline in adulthood, wheeze alone was the most common first symptom for participants aged 30–40 years or older, most of whom were not using ICS therapies. By contrast, both wheezing and usual phlegm or bronchitis were reported by 20% of these susceptible participants by age 14 years in TAHS and by 25% of susceptible participants by age 30 years in CARDIA.

Additionally, we estimated that at least one in 25 participants were both symptomatic and already fulfilled spirometry criteria for COPD (or COPD with co-existent asthma) in their early to mid-fifties, which is a novel finding. Moreover, there were consistent associations between the most impaired FEV_1/FVC trajectory and all wheeze, cough, or phlegm symptom profiles, including chesty colds, with little evidence to suggest that these symptom associations were driven by current smoking. Although wheezing often co-existed with other symptoms, wheeze in the absence of other symptoms gave a specific symptom profile that had the strongest associations with the most impaired trajectories. This association persisted for the most impaired trajectory even when considering only participants without self-reported asthma or relevant occupational exposures. So, although this study did not focus on the cause of impaired FEV_1/FVC, it reinforced the view that typical respiratory symptoms, especially wheezing, should be a red flag to prompt primary care clinicians to arrange objective testing such as pre-bronchodilator and post-bronchodilator spirometry in the diagnostic work-up of a symptomatic individual aged 35–40 years or older.[17]

Furthermore, after excluding those at the highest risk, we found that predominant wheeze was also the only symptom profile to be associated with those on an early low or rapid decline FEV_1/FVC trajectory, or both, but not yet meeting the spirometric criteria for COPD (or COPD with co-existent asthma). Thus, we propose that an impaired FEV_1/FVC trajectory is an important physiological consideration when developing a clinically operational definition of (more rapidly progressive) pre-COPD.[5]

To date, no population-based cohort analyses have uncovered distinct respiratory symptom profiles in middle age and related these to obstructive lung function trajectories across the life course. Previously in the CARDIA study, cough, phlegm, and wheeze persisting for more than 2 years in adults aged 18–30 years was

associated with a more rapid rate of lung function decline over the next 25 years.[2] However, this analysis was not informative in terms of respiratory symptoms in middle age—a time when more patients first present for evaluation. Another CARDIA-related analysis found that lower FEV_1 trajectories were associated with an increased risk of emphysema, but did not assess directly related symptoms.[9]

Although the participants of TAHS and CARDIA had comparable symptom data and post-bronchodilator spirometry assessed in their fifties, there were distinct differences in their geographical location, race and ethnicity profiles, and age of baseline data collection; this diversity is a study strength given that the independent findings were consistent across cohorts. Our findings are novel since TAHS had developed trajectories of FEV_1, FVC, and FEV_1/FVC from childhood, with the most impaired FEV_1 trajectories (early below average, accelerated decline; and persistently low) linked to respiratory symptoms in middle age;[10] however, neither the symptom history nor their profiles according to FEV_1/FVC trajectories had been described.[8] Children with persistently low FEV_1 into young adulthood were more likely to have wheeze and asthma in the Manchester Asthma and Allergy Study (MAAS), Avon Longitudinal Study of Parents and Children (ALSPAC), and Australia Perth Infant Asthma Follow-up (PIAF) studies,[18] but these cohort studies investigated neither other respiratory symptoms nor their association with FEV_1/FVC trajectories.

By leveraging our prospective datasets, we have confirmed that people on impaired FEV_1/FVC trajectories can have a history of respiratory symptoms originating even in childhood. Early detection of COPD is now widely promoted as an important public health strategy[12,17] to implement timelier disease-modifying strategies for younger adults (aged <50 years).[13,17] However, adults with spirometry-defined COPD in their early to mid-fifties often have few COPD-related symptoms in their early to mid-forties.[19] Nonetheless, an accurate diagnosis that is objectively confirmed should be sought to inform indicated treatments, as trials of inhaled dual-bronchodilator therapy have so far provided little evidence to support its use in people who smoke and have symptoms but no spirometric evidence of COPD.[20,21]

Our study suggests that adults with predominant wheeze and nearly all respiratory symptoms in their fifties might benefit more from diagnostic spirometry to investigate potential COPD than those who predominantly have cough, with or without phlegm. This finding complements results from our risk prediction model, developed with TAHS data and externally validated in the European Community Respiratory Health Survey.[19] This work found that wheezing attacks or asthma in adults in their early to mid-forties predicted spirometry-defined COPD 10 years later much more strongly than cough, phlegm, or dyspnoea, which suggested that the predictive ability of the latter symptoms was lower at this age.[19] The concept of few symptoms at this age was highlighted in the 2022 *Lancet* Commission on COPD.[12]

Separately, the concept of pre-COPD is a relatively new entity akin to pre-diabetes and pre-heart failure, in which there is some abnormality on objective testing that does not yet meet predefined diagnostic thresholds.[5] However, unlike pre-diabetes, we have confirmed that our proposed definition of pre-COPD can be symptomatic.[3–5] Pre-COPD that progresses towards COPD is poorly defined, especially as a physiological cutoff of the FEV_1/FVC ratio[22] is not yet widely accepted. Our findings suggest that many younger middle-aged adults (especially those in their fifties) who report wheezing are on an impaired FEV_1/FVC trajectory, which places them at high risk either of already having spirometry-defined COPD, or of developing it, which provides a rationale to add rapid decline FEV_1/FVC trajectories to the existing pre-COPD framework.[5]

Unlike wheeze, interestingly, dyspnoea per se was not a dominant feature of any of the symptom profiles in this age group, although it is usually a feature of advanced COPD. Thus, we hypothesise that wheezing better reflects the first stages of airway obstruction developing in the small airways as the core disease process.[23] We also propose that wheezing is the most specific respiratory symptom reflecting active disease of the small airways, which, at least when defined by CT imaging, has been shown to be associated with accelerated FEV_1 decline, including in patients at risk of developing COPD, defined as stage 0 in the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[24] Given the potential for diagnostic confusion with asthma,[25,26] we and others advocate for objective testing and monitoring of wheezing patients with spirometry over a period of 7–10 years,[27] in which post-bronchodilator measurements are important to define COPD and document the extent of bronchodilator reversibility. Pro-actively detecting symptomatic individuals on rapidly declining FEV_1/FVC trajectories might aid recruitment of such individuals into much needed clinical trials to establish the disease-modifying potential of new and repurposed therapies.[28] Furthermore, we suggest that wheeze be documented as a key symptom outcome in future large-scale intervention COPD trials.

Of the study's major strengths, first, we used two parallel prospective cohorts that were aligned for both participants' age and the serial but independent collection of respiratory data. Second, we used data-driven latent class analysis and GBTM techniques to create distinct symptom profiles and trajectories of obstructive lung function that were very similar across cohorts, rather than studying symptoms in isolation. Third, we were able to assess symptoms in adults mainly in their fifties, at an age when interventional strategies might still have the potential to provide substantial benefit. Fourth, although our trajectory modelling used pre-bronchodilator spirometry, which was available at all timepoints, we used post-bronchodilator spirometry to classify COPD at the last follow-up, and our main findings persisted after excluding those with self-reported asthma.

Our study also had some limitations. Although we could describe the proportions of participants who reported taking inhaled therapies, disentangling the associations among those who were steroid naive, adherent or non-adherent to inhaled corticosteroids or long-acting bronchodilators, or both, was beyond the scope of this study, but is an important area for future research. Similarly, the final datapoint of the FEV_1/FVC trajectory was measured concurrently with the symptoms at mean ages of 53 years (TAHS) and 55 years (CARDIA), so causality cannot be inferred, and it is clinically plausible that the symptoms could be due to any underlying lung condition associated with an impaired FEV_1/FVC.

Although the prevalence of spirometry-defined COPD was derived before race-neutral equations were widely advocated, the ratio of FEV_1 to FVC used to define post-bronchodilator airflow obstruction probably varies little by race or ethnicity when using the GLI reference equations.[29,30] Although COPD severity based on FEV_1 could be underestimated especially among Black participants in CARDIA,[31] our trajectories related Z scores of FEV_1/FVC to one another over time, which largely sidesteps this issue.[29] Conversely, study attrition might have selected out those with more symptoms and overestimated the prevalence and associations in the general community. Finally, Australia in particular has a relatively high prevalence of chronic cough, asthma, and allergies in the community, so although our findings are broadly generalisable to both White and Black populations in high-income countries, they require replication in other racial and ethnic populations and geographical areas as these data become available.

In summary, we have shown that respiratory symptoms are common in people on impaired FEV_1/FVC trajectories, many of whom developed early-onset COPD or young COPD by the time they were in their fifties.[20] We found that these individuals with early-onset COPD and more rapidly progressive pre-COPD often had a history of wheeze and phlegm that started decades earlier. We propose that wheezing might indicate the first stages of airway obstruction and is a likely prognostic feature for future risk of COPD. More work on identifying symptomatic patients on an impaired FEV_1/FVC trajectory via objective testing is needed.

Contributors

JLP, DSB, MM, CP, GRW, and SCD were responsible for the study concept and design. SCD, EHW, MJA, GSH, and BRT were responsible for acquisition of data for TAHS. AA, DRJ, RK, and GRW were responsible for acquisition of data for CARDIA. JLP, DSB, and DV had access to and verified the data, and conducted the statistical analyses. JLP, DSB, CP, DV, GRW, and SCD were responsible for interpretation of main data. SSK, MKH, AJL, CJL, WWL, JVP, RSJE, CVS, GSH, DJT, AA, DRJ, MJA, EHW, and RK contributed at progress meetings. JLP, DSB, CP, and DV were responsible for drafting of the manuscript. All authors contributed to critical revision of the manuscript for important intellectual content. SCD, EHW, MJA, JLP, and GSH obtained funding for TAHS. RK, GRW, DRJ, and AA obtained funding for CARDIA. JLP, CP, AA, and NSI provided administrative, technical, and material support. SCD, GRW, and RK were responsible for supervision of the study. All authors had full access to data analysis and the results of the study, and were responsible for the decision to submit the manuscript for publication.

Declaration of interests

JLP holds research grants from GlaxoSmithKline and AstraZeneca for unrelated research. DSB holds a research grant from GlaxoSmithKline for unrelated research. CP reports personal fees from Verona Pharma and research support paid to their institution from AstraZeneca. MKH reports personal fees from GlaxoSmithKline, AstraZeneca, Boehringer Ingelheim, Cipla, Chiesi, Novartis, Pulmonx, Teva Pharmaceutical Industries, Verona Pharma, Merck, Mylan, Sanofi, DevPro Biopharma, Aerogen, Polarian, Regeneron, Amgen, Roche, RS Biotherapeutics, Apreo Health, UpToDate, Altesa Biopharma, Norton Publishing, Penguin Random House, Medscape, the National Association of Colleges and Employers, Medwiz, and Integrity; research support paid to their institution from Novartis, Sunovion, Nuvaira, Sanofi, AstraZeneca, Boehringer Ingelheim, Gala Therapeutics, Biodesix, the COPD Foundation, and the American Lung Association; data and safety monitoring board funds paid to their institution from Novartis and Medtronic; and stock options from Meissa Vaccines and Altesa BioScience. RSJE holds research grants from Boehringer Ingelheim, Lung Biotechnology, and Insmed for unrelated research; has undertaken unrelated consultancy for LeukoLab and Mount Sinai; has received personal fees from Chiesi; is a co-founder and equity holder of Quantitative Imaging Solutions, an image analytics company; and has a patent pending unrelated to the current work. AJL has received grant funding from GlaxoSmithKline and Sanofi Regeneron, and has received an investigational product (EpiCeram) free of charge from Primus Pharmaceuticals, all for unrelated research. CJL holds a research grant from GlaxoSmithKline for unrelated research. WWL has received personal fees from the Clinical Education Alliance. BRT has been a medical advisor for Chiesi Pharmaceuticals, GlaxoSmithKline, and Mundipharma. MJA holds research grants from GlaxoSmithKline, Pfizer, Boehringer Ingelheim, and Sanofi Regeneron for unrelated research; has undertaken an unrelated consultancy for Sanofi; has received a speaker's fee from GlaxoSmithKline; and has served on a data safety and monitoring board for the Woolcock Institute of Medical Research. EHW holds a research grant from GlaxoSmithKline for unrelated research. GRW has received personal fees from Actelion, Vertex Pharmaceuticals, Intellia Therapeutics, and Janssen Pharmaceuticals; grants from the US Department of Defense and Boehringer Ingelheim; and consulting fees from Apogee Therapeutics, AstraZeneca, Intellia Therapeutics, Pieris Therapeutics, Regeneron, Sanofi, Pulmonx, Janssen Pharmaceuticals, and CSL Behring; is a co-founder and equity holder of Quantitative Imaging Solutions, an image analytics company; and reports that their spouse is an employee of Biogen. RK has received grants to their institution from AstraZeneca, PneumRx/BTG, and Spiration, and personal fees from GlaxoSmithKline, AstraZeneca, CVS Caremark, and CSA Medical, all outside the submitted work. SCD holds research grants from GlaxoSmithKline, AstraZeneca, and Sanofi Regeneron for unrelated research. DV, SSK, JVP, NSI, CVS, DJT, GSH, MM, AA, and DRJ declare no competing interests.

Data sharing

TAHS is a cohort study with data that have been prospectively collected since 1968 and will be an ongoing resource for future epidemiological analyses. Data collection, protocols, and the data dictionary have been detailed on the TAHS website (https://www.tahs.com.au) and in the TAHS cohort profile paper (Matheson et al, 2017). The raw individual participant data collected over the duration of the study have not been made widely available. However, expressions of interest can be discussed with the corresponding author or the principal investigator on an individual basis. CARDIA is a cohort study with data that have been prospectively collected since 1985 and will be an ongoing resource for future epidemiological analyses. Data collection, protocols, and the data dictionary are detailed on the website of CARDIA and CARDIA-Lung (https://www.cardia.dopm.uab.edu/exam-materials2/data-collection-forms). Access to the raw de-identified individual participant data that underlie the results reported in this Article (ie, text, tables, figures, and appendices) can be discussed with the principal investigator of CARDIA-Lung on an individual basis. Expressions of interest can also be requested here: https://biolincc.nhlbi.nih.gov/studies/cardia/.

Acknowledgments

CARDIA is conducted and supported by the US National Heart, Lung, and Blood Institute (NHLBI) in collaboration with the University of Alabama at Birmingham (grants 75N92023D00002 and 75N92023D00005), Northwestern University (grant 75N92023D00004), University of Minnesota (grant 75N92023D00006), Kaiser Foundation Research Institute (grant 75N92023D00003), and Johns Hopkins University School of Medicine (grant HHSN268200900041C). CARDIA is also partially supported by the Intramural Research Program of the National Institute on Aging and an intra-agency agreement between the US National Institute on Aging and NHLBI (grant AG0005). Additional funding has been provided by the US National Institutes of Health (NIH)-NHLBI grant R01 HL122477 (CARDIA Lung Study). This manuscript has been reviewed by CARDIA for scientific content. TAHS was supported by the National Health and Medical Research Council (NHMRC) of Australia (NHMRC project grant schemes 299901 and 1021275) and an NHMRC European collaborative grant scheme (1101313) as part of Ageing Lungs in European Cohorts funded by the EU Horizon 2020 research and innovation programme under grant agreement 633212. TAHS was also supported by The University of Melbourne; Clifford Craig Medical Research Trust; Victorian, Queensland & Tasmanian Asthma Foundations; Royal Hobart Hospital Research Foundation; Helen MacPherson Smith Trust; and GlaxoSmithKline. The TAHS-affiliated authors thank the TAHS participants and the TAHS investigators who were not co-authors of this manuscript for their assistance with obtaining funds and data collection. They thank the respiratory scientists who collected data in the lung function laboratories of Tasmania, Victoria, Queensland, and New South Wales; the research interviewers, data entry operators, and research officers; and the Archives Office of Tasmania for providing data from the 1968 and 1974 TAHS questionnaires and copies of the school medical records. The co-authors acknowledge members of the AUSCULTATE collaboration (Australia-US Collaboration to Understand Lung disease Trajectories And Timely Endpoints) who were not co-authors of this manuscript. Finally, the co-authors also thank the data manager from the University of Alabama at Birmingham for their assistance in providing the data from CARDIA.

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