$FEF_{25–75\%}$ trajectories from age 7 to 53 years, associations with childhood and parental preconception factors, and midlife COPD risk: a prospective cohort study

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Summary

Background Existing trajectory studies have emphasised large-airway indices, but chronic obstructive pulmonary disease (COPD) might originate in smaller airways. This study aimed to investigate mid-to-small-airway function trajectories, their associated factors, and COPD risk.

Methods In this prospective cohort study, probands (referred to throughout as offspring) were recruited to the Tasmanian Longitudinal Health Study from local schools across Tasmania, Australia at age 7 years. Pre-bronchodilator mean forced expiratory flow between 25% and 75% of the forced vital capacity ($FEF_{25–75\%}$) of offspring was measured at age 7 years as a proxy measure of mid-to-small-airway function. Parents completed a comprehensive respiratory health survey on themselves and their offspring. Offspring were followed up at mean ages of 13, 18, 45, 50, and 53 years. Follow-up included pre-bronchodilator spirometry, demographic surveys, lifestyle factors, respiratory symptoms, and illnesses. Post-bronchodilator spirometry was measured at mean ages of 45 and 53 years. Parents were later approached to complete the 2010 Tasmanian Longitudinal Health Study Parents Postal Survey, which collected information on parental preconception factors, including exposures during their own childhood and adolescence. Group-based trajectory modelling was used to identify $FEF_{25–75\%}$ trajectories. Regression models were used to assess associations of $FEF_{25–75\%}$ trajectories with childhood and parental preconception factors, and with COPD risk by age 53 years.

Findings Between Feb 23, 1968, and Nov 8, 2016, 2314 offspring from the Tasmanian Longitudinal Health Study were included. Six $FEF_{25–75\%}$ trajectories were identified: persistently low (144 [6·2%]); early normal-reduced growth-rapid decline (168 [7·3%]); early below average-reduced growth (740 [32·0%]); early low-accelerated growth (80 [3·5%]); average (976 [42·2%]; reference); and persistently high (206 [8·9%]). Three impaired trajectories across the lifespan were associated with COPD: persistently low (adjusted odds ratio 112 [95%CI 42–304]), early normal-reduced growth-rapid decline (41 [15–112]), and early below average-reduced growth (3·1 [1·0–9·2]) trajectories. Factors associated with impaired trajectories included no breastfeeding, the presence of asthma or wheeze, allergic rhinitis, and pneumonia or pleurisy during childhood, maternal asthma or wheeze, and parental smoking before conception. The persistently high trajectory was associated with parental preconception microbial-related exposures (ie, fathers sharing a childhood bedroom with three or more siblings and maternal cat keeping before completing puberty).

Interpretation $FEF_{25–75\%}$ across the life course, particularly from early life, could be more relevant to COPD than previously recognised. Several childhood and novel parental preconception factors were associated with $FEF_{25–75\%}$ trajectories, although causality cannot be inferred due to no clear temporality of these associations. Our findings on the relationship between $FEF_{25–75\%}$ and COPD should be interpreted as life-course associations rather than as predictive. As COPD was rare in the average trajectory, the magnitude of effect estimates could be inflated.

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Introduction

Chronic obstructive pulmonary disease (COPD) is one of the top three global non-communicable diseases,[1] and its burden continues to rise globally.[2] This rise could be partly due to insufficient understanding of susceptibility windows, modifiable risk factors, and limited primary care awareness of COPD.

Studies have shown that large-airway dysfunction, such as reduced growth, an accelerated decline of FEV_1 and FEV_1/forced vital capacity (FVC), or a combination of the two, is associated with COPD by age 53 years.[3,4] Notably, COPD can originate from a series of pathological changes occurring throughout the whole airways, particularly within the small airways.[5] However, small airways are

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Research in context

Evidence before this study

Established evidence has suggested that impaired lung function trajectories over the life course are associated with chronic obstructive pulmonary disease (COPD) by age 53 years. Existing trajectory studies have focused on large-airway indices, especially FEV_1 and FEV_1/forced vital capacity (FVC). Notably, COPD might also originate in the small airways, the "silent zone", in which substantial damage can occur before the disease clinically manifests. The mean forced expiratory flow between 25% and 75% of the FVC ($FEF_{25–75\%}$) primarily reflects airflow in the mid-portion of forced expiration, providing a more detailed assessment of the more distal and smaller airways than reflected by FEV_1. However, whether longitudinal $FEF_{25–75\%}$ trajectories are differentially associated with COPD risk compared with large-airway indices is unknown. We searched PubMed from database inception to Jan 31, 2026, using the keywords "FEF25-75", "MMEF", "mid-expiratory flow", "trajector*", and "COPD". No studies had derived life-course $FEF_{25–75\%}$ trajectories and assessed their association with COPD risk. Evidence was also absent on whether adverse childhood and parental preconception exposures linked to large-airway dysfunction are similarly associated with mid-to-small-airway dysfunction.

Added value of this study

This study extends knowledge by highlighting the potential role of $FEF_{25–75\%}$, despite known intra-individual variability, as a clinically relevant life-course marker of airway function when assessed longitudinally. It also suggests that $FEF_{25–75\%}$ trajectories could capture aspects of COPD risk not fully reflected by large-airway indices such as FEV_1. In addition, this study extends knowledge by showing that parental preconception factors, including factors from their own childhood and adolescence, are associated with offspring $FEF_{25–75\%}$ trajectories.

Implications of all the available evidence

These findings suggest that $FEF_{25–75\%}$ impairment across the life course, including from early life, could be relevant to understanding the risk of COPD. Incorporating $FEF_{25–75\%}$ alongside commonly used spirometric measures could provide additional insight into airway dysfunction. The observed links with parental preconception exposures suggest the potential importance of intergenerational associations. Together, these findings support a life-course approach to prevention, while recognising that these associations do not imply causality.

often referred to as the "silent zone" because extensive damage can occur before spirometric dysfunction and overt disease clinically manifest.[5] Such potential for undetected small-airway impairment underscores the need for measures other than FEV_1 and FEV_1/FVC to aid early detection and prevention of small-airway dysfunction.

During forced expiration, the flow-limiting segment moves peripherally into progressively smaller airways as lung volume falls.[6] The mean forced expiratory flow between 25% and 75% of the FVC ($FEF_{25–75\%}$) primarily reflects airflow in the mid-portion of forced expiration, when smaller airways increasingly contribute to flow limitation, and $FEF_{25–75\%}$ overlaps with small-airway function. For this reason, reduced $FEF_{25–75\%}$ has been used as a proxy measure for dysfunction in small airways.[7] However, the use of $FEF_{25–75\%}$ has been debated because it is dependent on FVC,[8] which itself can be influenced by gas trapping and suboptimal effort. $FEF_{25–75\%}$ has also been criticised for greater intra-individual variability than other spirometric measures.[8] Historically, there has been uncertainty around whether this measure adds clinical utility beyond FEV_1.[9] Moreover, published analyses of $FEF_{25–75\%}$ have been largely cross-sectional or limited to short-term follow-up.[10] Whether distinct longitudinal trajectories of $FEF_{25–75\%}$ existed and whether impaired trajectories were differentially associated with COPD risk is unknown. Thus, characterising long-term $FEF_{25–75\%}$ trajectories is novel from a smaller-airway perspective and could help identify sustained early impairment relevant to subsequent COPD. The Tasmanian Longitudinal Health Study (TAHS) measured lung function repeatedly in probands from age 7 to 53 years.[11] Although single timepoint measurements of $FEF_{25–75\%}$ could be influenced by variability, modelling repeated measures over time allows identification of sustained patterns across the lifespan and assessment of the longitudinal value of this spirometric index.

Emerging evidence suggests that adverse parental preconception exposures are intergenerationally associated with lung function impairment in their offspring.[12] The preconception period includes not only the immediate time parents spent preparing for pregnancy, but also antecedent years before, extending into their completion of puberty (approximately age 15 years) and childhood.[12] Nonetheless, studies on preconception exposures, including ours, predominantly focused on a few factors and their associations with large-airway indices.[13,14] To the best of our knowledge, no previous study has investigated the associations between adverse parental preconception exposures and longitudinal changes in smaller airways in their offspring. To address these research gaps, this study aimed to: derive population-based $FEF_{25–75\%}$ trajectories from the ages of 7 to 53 years; assess their associations with spirometry-defined COPD by the age of 53 years; and investigate their associations with childhood factors and preconception factors in parents.

Methods

Study design and data collection

In this prospective cohort study, data from the TAHS were used, which commenced in 1968 (baseline).[11] The

probands, referred to throughout this Article as offspring, of TAHS were recruited between Feb 23, 1968, and continued until the end of that year from Tasmania, Australia, at the age of 7 years from all local schools. Offspring underwent spirometry, while their parents completed a comprehensive respiratory health survey including information about themselves and their offspring. Offspring were followed up at the mean ages of 13, 18, 45, 50, and 53 years, including pre-bronchodilator spirometry and surveys addressing demographic information, lifestyle factors, respiratory symptoms, and illnesses. Post-bronchodilator spirometry was measured at mean ages of 45 and 53 years. In 2010, parents who were alive and traceable were invited to complete the TAHS Parents Postal Survey, which collected information on parental preconception factors. This study was based on the TAHS, which was approved by human ethics review committees at: The Universities of Melbourne (040375), Tasmania (040375·1, H0012710), and New South Wales (08094); The Alfred Hospital (1118/04); and the Royal Brisbane and Women's Hospital Health Service District (2006/037). Written informed consent was obtained from all participants.

Procedures

Pre-bronchodilator and post-bronchodilator spirometry followed the American Thoracic Society and European Respiratory Society guidelines.[15] Spirometry *Z* scores were generated based on the Global Lung Initiative reference equations,[16] previously validated in the Australasian population.[17]

Adult factors at age 53 years were collected through offspring self-reported information between 2012 and 2016 or via clinical assessments, such as BMI, active smoking, and respiratory symptoms (appendix pp 3–6). Offspring spirometry-defined COPD was defined as post-bronchodilator FEV_1/FVC less than the lower limit of normal by age 53 years.[3]

Childhood factors from birth to age 7 years were defined based on information provided by parents at baseline, including offspring factors of sex at birth, breastfeeding in the first 3 months, and the presence of asthma or wheeze, bronchitis, eczema, allergic rhinitis, food allergies, or pneumonia or pleurisy, and parental factors of the presence of asthma or wheeze, active smoking, and socioeconomic status (appendix pp 7–10). Height and weight at age 7 years were measured as part of the spirometry. The Socio-economic Indexes for Areas–Index of Relative Socioeconomic Disadvantage was used as a proxy for socioeconomic status.[18] Race and ethnicity data were not collected in the 1968 TAHS baseline survey as Tasmania had a mostly homogeneous population at that time.

Preconception factors in parents were defined based on information provided by parents in the 2010 TAHS Parents Postal Survey, including exposures occurring before their own age of 5 years (ie, living environment, number of siblings sharing the bedroom, serious respiratory infection, daycare centre attendance, and main type of heating at home) and 15 years (ie, passive smoke exposure, cat at home, carpet or rug in the bedroom, and ages of active smoking commencement and asthma or wheeze onset; appendix pp 11–13).

Statistical analyses

Offspring included in this analysis had pre-bronchodilator $FEF_{25–75\%}$ measurements taken at ages 7 years and 53 years, with any additional measurements at intermediate ages (ie, 13, 18, 45, and 50 years) also included. Offspring without $FEF_{25–75\%}$ measurements at both ages 7 and 53 years were excluded. Group-based trajectory modelling was used to analyse $FEF_{25–75\%}$ *Z* scores from age 7 to 53 years. Group-based trajectory modelling is a statistical method based on a finite mixture (latent class) modelling approach used to identify latent population subgroups of individuals that follow a similar pattern of change with age,[19] such as for lung function trajectories. Models with increasing numbers of trajectories were estimated using maximum likelihood estimation, which allowed inclusion of offspring with incomplete $FEF_{25–75\%}$ measurements at intermediate ages under the missing-at-random assumption.[20] Models were fitted iteratively, starting with two trajectories, and different polynomial orders of repeated $FEF_{25–75\%}$ measurements against age were tested for each model. The final model was selected based on optimal Bayesian Information Criterion in conjunction with biological plausibility. Model diagnostic criteria, including a minimum average posterior probability of assignment of 0·7, were also checked. Offspring were assigned to the trajectory with the highest posterior probability of membership (appendix p 14).

See Online for appendix

Associations between offspring $FEF_{25–75\%}$ trajectories and COPD by age 53 years were assessed using penalised maximum likelihood logistic regressions.[21] This method helps reduce bias in estimating regression coefficients, given the rarity of COPD cases in several $FEF_{25–75\%}$ trajectories. Models were adjusted for offspring sex at birth, active smoking, and socioeconomic status at age 53 years.[3] Adjusted predicted probabilities of COPD for each $FEF_{25–75\%}$ trajectory group were estimated from the adjusted logistic regression model using predictive margins.

Comparisons of adult, childhood, and parental preconception factors between each distinct $FEF_{25–75\%}$ trajectory and the reference $FEF_{25–75\%}$ trajectory were conducted using *t* tests, Wilcoxon rank-sum tests, or *Z* tests where appropriate. Multinomial logistic regressions were used to assess associations between childhood factors and $FEF_{25–75\%}$ trajectories, using adjustments consistent with a previous publication.[3] Multinomial logistic regressions were used to assess associations between preconception factors in parents and $FEF_{25–75\%}$ trajectories in their offspring. For each

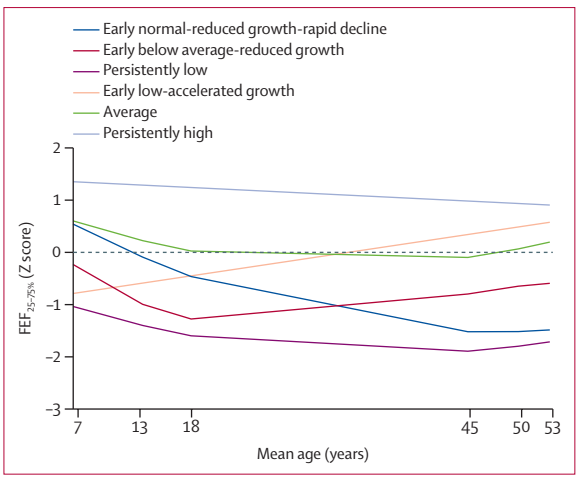

Figure: **$FEF_{25-75\%}$ trajectories from age 7 years to 53 years in offspring**
This figure illustrates six trajectories representing the latent growth patterns of $FEF_{25-75\%}$. $FEF_{25-75\%}$=mean forced expiratory flow between 25% and 75% of the forced vital capacity.

preconception factor, the minimal sufficient adjustment set of confounders was ascertained using a directed acyclic graph,[22] developed based on previous knowledge and existing literature (appendix pp 26–28). The specific sets of confounders are provided in the table legends. Adjusted models were fitted using father–offspring or mother–offspring pairs with complete data on exposures, outcomes, and confounders.

To evaluate the robustness of the selected model, alternative functional forms were assessed by comparing the trajectory shapes and group distributions. To minimise potential influence of early-onset COPD, associations between $FEF_{25-75\%}$ trajectories and COPD by age 53 years were re-assessed after restricting analyses to offspring without COPD by age 45 years. To evaluate the potential influence of missing covariate data, particularly in the analyses of parental preconception factors, a sensitivity analysis was conducted using multiple imputation (appendix p 15). All associations that were statistically significant (p value ≤0·05) in the complete-case analysis were re-assessed by using multiple imputation.

To assess potential selection bias, baseline characteristics were compared between included and excluded offspring using *t* tests or χ^2 tests. All analyses were performed using Stata (version 18.0) with a group-based trajectory modelling plug-in,[23] and R (version 4.2.2), including package *gmodels* (version 2.19.1).

Role of the funding source

The funders of the study had no role in study design, data collection, analysis, interpretation, writing of the manuscript, or the decision to submit.

Results

8022 (93·5%) of 8583 offspring underwent spirometry at age 7 years. Of the 8583 offspring, 2314 (27·0%) had $FEF_{25-75\%}$ measurements at both ages 7 and 53 years and comprised the analytical sample. There were 405 (4·7%) deaths before age 53 years among 8583 offspring. In 2010, of 7243 parents who were alive and traceable, 5111 (70·6%) completed the 2010 TAHS Parents Postal Survey (2096 fathers and 3001 mothers with valid data). Of these, 894 fathers and 1245 mothers had offspring with $FEF_{25-75\%}$ measurements at both ages 7 and 53 years and were included in the parent–offspring analyses (appendix p 29). The offspring included in this analysis had similar baseline characteristics to those who were excluded (6269 [73·0%]), except for a higher proportion being breastfed only, having childhood bronchitis, being socioeconomically advantaged, fewer males, and a lower prevalence of exposure to parental smoking (appendix p 16).

The selected model identified six $FEF_{25-75\%}$ trajectories (figure). The model fit parameters for different models, along with their justifications, are shown in the appendix (p 17). This model included three trajectories that were impaired across the lifespan. Based on $FEF_{25-75\%}$ at age 7 years and subsequent growth and decline patterns by age 53 years, trajectories were labelled as follows: average (n=976 [42·2%]); persistently low (144 [6·2%]); early normal-reduced growth-rapid decline (168 [7·3%]); early below average-reduced growth (740 [32·0%]); early low-accelerated growth (80 [3·5%]); and persistently high (206 [8·9%]; group prevalences do not add up to 100% because of rounding). The average trajectory consistently maintained lung function around the population mean (ie, *Z* score 0). Spaghetti plots of individual $FEF_{25-75\%}$ trajectories are shown in the appendix (p 30).

The prevalence of spirometry-defined COPD at age 53 years was highest in the persistently low trajectory (54 [37·5%] of 144 [95% CI 29·6–45·9]), followed by the early normal-reduced growth-rapid decline (35 [21·1%] of 166 [15·1–28·1]) and the early below average-reduced growth (11 [1·5%] of 730 [0·8–2·7]) trajectories. The average trajectory had a COPD prevalence of 0·4% (4 of 964 [0·1–1·1]). No COPD cases were found in the early low-accelerated growth (0 of 80 [0–4·5]) or the persistently high (0 of 201 [0–1·8]) trajectories (table 1).

Compared with the average trajectory, the persistently low (adjusted odds ratio 112 [95% CI 42–304]; p<0·0001), early normal-reduced growth-rapid decline (41 [15–112]; p<0·0001), and early below average-reduced growth (3·1 [1·0–9·2]; p=0·045) trajectories were associated with increased odds of COPD, after adjusting for offspring sex at birth, active smoking, and socioeconomic status at age 53 years (table 1). Adjusted predicted probabilities of COPD were 0·48% (95% CI 0·01–0·94; p=0·045) for the average trajectory, 34% (26–42; p<0·0001) for the persistently low, 16% (11–22; p<0·0001) for the early normal-reduced growth-rapid decline, and 1·55% (0·65–2·45; p=0·0008) for the early below average-reduced growth trajectory. Among 104 offspring who developed COPD by age 53 years, 54 (51·9%) belonged to the persistently low $FEF_{25-75\%}$ trajectory, 35 (33·7%) to the

early normal-reduced growth-rapid decline, 11 (10·6%) to the early below average-reduced growth, and four (3·8%) to the average trajectory (appendix p 31).

Adult factors by $FEF_{25–75\%}$ trajectories are presented in the appendix (pp 18–19). Compared with those belonging to the average trajectory, offspring belonging to the persistently low and the early normal-reduced growth-rapid decline trajectories were more likely to smoke and to have preserved ratio impaired spirometry and respiratory symptoms, including current asthma, breathing problems, and chronic cough. In contrast, offspring belonging to the early low-accelerated growth trajectory had a lower prevalence of current smoking (5·1% [4/79] *vs* 11·4% [110/969]; p=0·08; appendix p 18).

Distribution of offspring childhood factors are presented in the appendix (pp 20–21) and associations with $FEF_{25–75\%}$ trajectories are presented in table 2 and in the appendix (pp 32–33). The following factors were associated with the persistently low trajectory: asthma or wheeze with onset before age 3 years (adjusted multinomial odds ratio [aMOR] 2·64 [95% CI 1·51–4·63]; p=0·0007) or between ages 3 and 7 years (2·55 [1·25–5·19]; p=0·010), and frequent (at least one asthma attack every 3 months) at age 7 years (5·25 [2·79–9·88]; p<0·0001), allergic rhinitis (2·08 [1·28–3·37]; p=0·0029), and maternal asthma or wheeze (2·32 [1·42–3·79]; p=0·0007; table 2). The early normal-reduced growth-rapid decline trajectory was associated with asthma or wheeze onset between ages 3 and 7 years (2·28 [1·14–4·55]; p=0·019), pneumonia or pleurisy (1·60 [1·02–2·50]; p=0·040), and light-to-moderate maternal smoking (1·71 [1·19–2·44]; p=0·0033). Compared with exclusive bottle feeding, exclusive breastfeeding was associated with reduced odds of belonging to this rapid decline trajectory (0·55 [0·35–0·87]; p=0·011). The early below average-reduced growth trajectory was associated with asthma or wheeze onset before age 3 years (2·10 [1·47–2·99]; p<0·0001), and frequent (at least one episode every 3 months) bronchitis at age 7 years (1·46 [1·01–2·11]; p=0·043). The early low-accelerated growth trajectory was associated with asthma or wheeze onset before age 3 years (3·20 [1·56–6·58]; p=0·0016), bronchitis ever (1·70 [1·01–2·87]; p=0·048), and allergic rhinitis (1·90 [1·00–3·61]; p=0·050).

Distribution of preconception factors in fathers are presented in the appendix (p 22) and their associations with $FEF_{25–75\%}$ trajectories in their offspring are presented in table 3 and in the appendix (pp 34–35). The analyses were based on 894 father–offspring pairs. Exposure to wood or fossil fuel heating at home when fathers were younger than 5 years was associated with reduced odds of their offspring belonging to the early low-accelerated growth trajectory (aMOR 0·29 [95% CI 0·08–0·97]; p=0·045). The number of siblings sharing the bedroom when fathers were younger than 5 years was associated with increased odds of their offspring belonging to both the early normal-reduced growth-rapid decline (1·18 [0·94–1·48]; p=0·16) and the persistently high (1·30 [1·08–1·57]; p=0·0057) trajectories. Paternal sharing with one (1·98 [0·92–4·29]; p=0·083) or two siblings (2·61 [1·04–6·51]; p=0·040) was associated with increased odds of their offspring belonging to the early normal-reduced growth-rapid decline trajectory. However, paternal sharing with three or more siblings was associated with the persistently high trajectory in their offspring (2·44 [1·14–5·22]; p=0·021). Active smoking when fathers were younger than 15 years was associated with increased odds of their offspring belonging to the early normal-reduced growth-rapid decline trajectory (2·26 [1·00–5·10]; p=0·050).

	COPD cases/total (% [95% CI])	Crude model*, OR (95% CI); p value	Adjusted model*, aOR (95% CI); p value
Average (reference)	4/964 (0·4% [0·1–1·1])	1	1
Persistently low	54/144 (37·5% [29·6–45·9])	129 (48–344); <0·0001	112 (42–304); <0·0001
Early normal-reduced growth-rapid decline	35/166 (21·1% [15·1–28·1])	58 (21–156); <0·0001	41 (15–112); <0·0001
Early below average-reduced growth	11/730 (1·5% [0·8–2·7])	3·4 (1·1–10·2); 0·028	3·1 (1·0–9·2); 0·045
Early low-accelerated growth	0/80 (0–4·5)†	NA	NA
Persistently high	0/201 (0–1·8)†	NA	NA

ORs, aORs, and p values are from penalised maximum likelihood logistic regressions. The analyses were based on 2285 offspring with available data on both $FEF_{25–75\%}$ trajectories and spirometry-defined COPD. The adjusted model adjusted for offspring sex at birth, active personal smoking, and Socio-economic Indexes for Areas–Index of Relative Socioeconomic Disadvantage at age 53 years. aOR=adjusted odds ratio. COPD=chronic obstructive pulmonary disease. $FEF_{25–75\%}$=mean forced expiratory flow between 25% and 75% of the forced vital capacity. NA=results were not available due to no observations. OR=odds ratio. *Spirometry-defined COPD was defined as a post-bronchodilator FEV_1/forced vital capacity ratio less than the lower limit of normal at age 53 years. As COPD cases were rare in the average trajectory, penalised maximum likelihood logistic regression was used to reduce overfitting. Despite this, the ORs might remain inflated and should be interpreted with caution. †For trajectories with zero COPD cases, exact 95% CIs for the percentage of COPD cases/total were reported as 0 to the one-sided 97·5% upper bound.

Table 1: **Associations between offspring $FEF_{25–75\%}$ trajectories from age 7 to 53 years and their spirometry-defined COPD by age 53 years**

Alternative models produced largely comparable trajectory shapes and similar group distributions (appendix p 38). After restricting analyses to offspring without spirometry-defined COPD by age 45 years, the association between the persistently low $FEF_{25–75\%}$ trajectory and COPD by age 53 years remained evident, followed by the early normal-reduced growth-rapid decline trajectory (appendix

	Persistently low (n=144)	Early normal-reduced growth-rapid decline (n=168)	Early below average-reduced growth (n=740)	Early low-accelerated growth (n=80)	Persistently high (n=206)
Sex at birth (male as the reference)*					
Female	0·98 (0·69–1·39); 0·92	1·20 (0·87–1·67); 0·27	1·21 (1·00–1·46); 0·052	1·98 (1·23–3·19); 0·0048	1·38 (1·02–1·86); 0·039
Breastfeeding in the first 3 months (bottle only as the reference)†					
Breast only	0·84 (0·53–1·33); 0·45	0·55 (0·35–0·87); 0·011	0·92 (0·71–1·19); 0·52	0·65 (0·36–1·17); 0·15	1·06 (0·69–1·62); 0·80
Breast and bottle	0·63 (0·38–1·06); 0·079	1·04 (0·68–1·61); 0·85	0·85 (0·64–1·12); 0·25	0·65 (0·35–1·23); 0·19	1·16 (0·74–1·81); 0·53
BMI at age 7 years (normal BMI as the reference)‡					
Underweight (BMI <14·04 kg/m² for males and <13·82 kg/m² for females)	0·77 (0·23–2·59); 0·68	2·02 (0·92–4·40); 0·078	1·36 (0·79–2·34); 0·26	1·34 (0·39–4·54); 0·64	0·92 (0·35–2·43); 0·87
Overweight or obesity (BMI >17·71 kg/m² for males and >17·53 kg/m² for females)	1·10 (0·64–1·89); 0·73	0·78 (0·44–1·39); 0·40	0·77 (0·56–1·06); 0·11	0·90 (0·43–1·87); 0·78	1·17 (0·74–1·84); 0·51
Ever asthma or wheeze§	2·51 (1·56–4·04); 0·0001	1·64 (1·00–2·68); 0·048	1·74 (1·29–2·35); 0·0003	2·50 (1·33–4·73); 0·0047	0·92 (0·54–1·56); 0·75
Frequent asthma or wheeze at age 7 years (never asthma or wheeze as the reference)§					
Infrequent asthma or wheeze (less than one asthma attack every 3 months)	1·55 (0·82–2·91); 0·17	1·54 (0·86–2·74); 0·15	1·58 (1·11–2·24); 0·012	2·05 (0·94–4·48); 0·070	0·81 (0·42–1·56); 0·53
Frequent asthma or wheeze (at least one asthma attack every 3 months)	5·25 (2·79–9·88); <0·0001	1·96 (0·90–4·26); 0·090	2·20 (1·35–3·58); 0·0015	4·09 (1·65–10·13); 0·0024	1·14 (0·48–2·70); 0·76
Asthma or wheeze onset (never asthma or wheeze as the reference)§					
Onset before age 3 years	2·64 (1·51–4·63); 0·0007	1·38 (0·74–2·60); 0·31	2·10 (1·47–2·99); <0·0001	3·20 (1·56–6·58); 0·0016	1·31 (0·72–2·36); 0·37
Onset between ages 3 and 7 years	2·55 (1·25–5·19); 0·010	2·28 (1·14–4·55); 0·019	1·20 (0·73–1·99); 0·47	1·76 (0·59–5·26); 0·31	0·40 (0·12–1·33); 0·13
Ever bronchitis¶	1·16 (0·76–1·77); 0·48	1·05 (0·72–1·55); 0·79	1·18 (0·95–1·46); 0·15	1·70 (1·01–2·87); 0·048	1·06 (0·75–1·49); 0·73
Frequent bronchitis at age 7 years (never bronchitis as the reference)¶					
Infrequent bronchitis (less than one episode every 3 months)	1·10 (0·71–1·72); 0·67	0·99 (0·66–1·49); 0·97	1·14 (0·90–1·43); 0·28	1·68 (0·97–2·90); 0·063	1·03 (0·72–1·48); 0·87
Frequent bronchitis (at least one episode every 3 months)	1·61 (0·87–2·98); 0·13	1·28 (0·69–2·38); 0·43	1·46 (1·01–2·11); 0·043	2·32 (1·05–5·12); 0·037	1·39 (0·78–2·48); 0·27
Ever eczema‖	1·23 (0·71–2·14); 0·46	1·36 (0·82–2·28); 0·24	1·11 (0·81–1·54); 0·51	1·09 (0·52–2·30); 0·82	1·47 (0·92–2·38); 0·11
Ever allergic rhinitis‖	2·08 (1·28–3·37); 0·0029	1·51 (0·92–2·47); 0·10	0·99 (0·71–1·36); 0·93	1·90 (1·00–3·61); 0·050	0·88 (0·51–1·51); 0·64
Ever food allergy‖	1·34 (0·67–2·70); 0·41	1·02 (0·50–2·08); 0·95	1·37 (0·92–2·03); 0·12	1·25 (0·51–3·05); 0·63	1·40 (0·77–2·57); 0·27
Ever pneumonia or pleurisy**	1·55 (0·95–2·50); 0·076	1·60 (1·02–2·50); 0·040	1·27 (0·96–1·69); 0·098	0·83 (0·39–1·78); 0·64	0·92 (0·57–1·50); 0·74
Paternal asthma or wheeze††	1·37 (0·77–2·42); 0·28	1·18 (0·68–2·05); 0·56	1·27 (0·92–1·75); 0·14	1·15 (0·53–2·49); 0·72	1·27 (0·77–2·09); 0·35
Maternal asthma or wheeze‡‡	2·32 (1·42–3·79); 0·0007	0·88 (0·48–1·62); 0·68	1·22 (0·88–1·69); 0·24	0·86 (0·36–2·04); 0·73	0·78 (0·43–1·40); 0·40
Parental asthma or wheeze§§	1·89 (1·23–2·88); 0·0034	1·07 (0·68–1·67); 0·77	1·19 (0·92–1·54); 0·18	1·02 (0·55–1·91); 0·95	0·93 (0·61–1·44); 0·76
Active paternal smoking (never smoked as the reference)¶¶					
Light-to-moderate smoking	1·11 (0·73–1·70); 0·61	1·43 (0·98–2·09); 0·062	0·94 (0·75–1·18); 0·58	1·32 (0·78–2·24); 0·30	1·08 (0·76–1·53); 0·66
Heavy smoking	1·12 (0·67–1·88); 0·68	0·97 (0·59–1·62); 0·92	1·06 (0·80–1·39); 0·68	1·12 (0·57–2·21); 0·75	0·78 (0·49–1·25); 0·30
Active maternal smoking (never smoked as the reference)‖‖					
Light-to-moderate smoking	1·34 (0·90–1·99); 0·16	1·71 (1·19–2·44); 0·0033	1·24 (1·00–1·55); 0·054	1·18 (0·70–1·97); 0·53	1·00 (0·70–1·42); 0·99
Heavy smoking	0·79 (0·30–2·10); 0·64	1·31 (0·59–2·90); 0·50	1·15 (0·71–1·85); 0·57	0·59 (0·14–2·51); 0·47	0·97 (0·45–2·13); 0·95

Data are aMOR (95% CI); p value. aMORs and p values are from multinomial logistic regressions. The analyses were based on 2314 offspring. aMOR=adjusted multinomial odds ratio. $FEF_{25-75\%}$=mean forced expiratory flow between 25% and 75% of the forced vital capacity. SEIFA-IRSD=Socio-economic Indexes for Areas–Index of Relative Socio-economic Disadvantage. *No covariates were adjusted for. †The model was adjusted for paternal and maternal asthma or wheeze, active paternal and maternal smoking, and SEIFA-IRSD scores of parents. ‡The model was adjusted for offspring sex at birth, breastfeeding in the first 3 months, ever having pneumonia or pleurisy, and SEIFA-IRSD scores of parents. §The models were adjusted for offspring sex at birth, breastfeeding in the first 3 months, ever having pneumonia or pleurisy, ever having eczema, active paternal and maternal smoking, paternal and maternal asthma or wheeze, and SEIFA-IRSD scores of parents. ¶The models were adjusted for offspring ever having asthma or wheeze, pneumonia or pleurisy, ever having eczema, active paternal and maternal smoking, and SEIFA-IRSD scores of parents. ‖The models were adjusted for offspring sex at birth, ever having asthma or wheeze, active paternal and maternal smoking, paternal and maternal asthma or wheeze, and SEIFA-IRSD scores of parents. **The model was adjusted for offspring breastfeeding in the first 3 months and SEIFA-IRSD scores of parents. ††The model was adjusted for offspring sex at birth, active paternal smoking, and SEIFA-IRSD scores of parents. ‡‡The model was adjusted for offspring sex at birth, active maternal smoking, and SEIFA-IRSD scores of parents. §§The model was adjusted for offspring sex at birth, active paternal and maternal smoking, and SEIFA-IRSD scores of parents. ¶¶The model was adjusted for offspring ever having asthma or wheeze, paternal asthma or wheeze, and SEIFA-IRSD scores of parents. ‖‖The model was adjusted for offspring ever having asthma or wheeze, maternal asthma or wheeze, and SEIFA-IRSD scores of parents.

Table 2: **Associations between offspring childhood factors by age 7 years and each $FEF_{25-75\%}$ trajectory compared with the average trajectory**

p 24). After multiple imputation, the identified associations were broadly similar; however, some associations became weaker and less statistically significant although the direction of the identified associations remained unchanged (appendix p 25).

Discussion

Previous TAHS studies have focused on the large-airway indices, FEV_1 and FEV_1/FVC. Impaired lung function trajectories from age 7 to 53 years, particularly those with suboptimal growth, accelerated decline, or a combination

	Persistently low (n=66)	Early normal-reduced growth-rapid decline (n=55)	Early below average-reduced growth (n=288)	Early low-accelerated growth (n=32)	Persistently high (n=86)
Before fathers' own age of 5 years (ie, during childhood)					
Living environment (city as the reference)*					
Country town	0·86 (0·40–1·81); 0·68	1·73 (0·84–3·58); 0·14	0·90 (0·60–1·35); 0·61	1·82 (0·72–4·61); 0·21	1·47 (0·80–2·72); 0·22
Farm	1·88 (0·94–3·76); 0·076	1·08 (0·46–2·50); 0·86	1·22 (0·80–1·86); 0·35	0·84 (0·26–2·68); 0·77	1·47 (0·76–2·82); 0·25
Number of siblings sharing the bedroom (per one-sibling increase)*	1·14 (0·90–1·43); 0·28	1·18 (0·94–1·48); 0·16	1·04 (0·89–1·21); 0·63	0·89 (0·59–1·36); 0·60	1·30 (1·08–1·57); 0·0057
Number of siblings sharing the bedroom (no sibling as the reference)*					
One	1·63 (0·81–3·28); 0·17	1·98 (0·92–4·29); 0·083	1·16 (0·77–1·74); 0·47	0·66 (0·24–1·83); 0·42	1·21 (0·64–2·30); 0·56
Two	1·37 (0·53–3·55); 0·52	2·61 (1·04–6·51); 0·040	1·66 (1·00–2·77); 0·050	1·66 (0·58–4·77); 0·35	1·67 (0·76–3·65); 0·20
Three or more	1·96 (0·80–4·83); 0·14	1·71 (0·60–4·92); 0·32	0·88 (0·48–1·61); 0·67	0·34 (0·04–2·71); 0·31	2·44 (1·14–5·22); 0·021
Serious respiratory infection†	0·84 (0·18–3·97); 0·83	NA	1·18 (0·49–2·81); 0·71	1·62 (0·32–8·17); 0·56	0·78 (0·17–3·65); 0·76
Daycare centre attendance*	1·67 (0·74–3·76); 0·22	1·03 (0·38–2·79); 0·96	0·72 (0·39–1·30); 0·27	2·07 (0·72–5·97); 0·18	0·47 (0·16–1·39); 0·17
Wood or fossil fuel as the main type of heating at home (electric heating systems or others as the reference)*	0·51 (0·16–1·64); 0·26	2·00 (0·25–15·71); 0·51	0·78 (0·35–1·72); 0·54	0·29 (0·08–0·97); 0·045	1·74 (0·38–7·93); 0·47
Before fathers' own age of 15 years (ie, before completing puberty)					
Passive smoke exposure‡	1·64 (0·83–3·23); 0·16	0·91 (0·48–1·74); 0·78	1·07 (0·75–1·54); 0·70	0·52 (0·23–1·17); 0·11	0·76 (0·45–1·27); 0·29
Cat at home§	1·36 (0·73–2·50); 0·33	0·98 (0·52–1·86); 0·95	0·94 (0·66–1·33); 0·71	0·69 (0·28–1·70); 0·42	0·86 (0·51–1·44); 0·57
Carpet or rug in the bedroom§	0·86 (0·45–1·63); 0·64	0·92 (0·47–1·81); 0·81	0·68 (0·47–0·99); 0·046	1·58 (0·66–3·77); 0·30	0·84 (0·48–1·46); 0·53
Active smoking (never smoked as the reference)¶					
Commenced before age 15 years	1·99 (0·83–4·76); 0·12	2·26 (1·00–5·10); 0·050	1·36 (0·80–2·31); 0·26	0·39 (0·05–3·12); 0·37	0·62 (0·22–1·72); 0·36
Commenced after age 15 years	1·57 (0·82–2·99); 0·17	0·80 (0·40–1·62); 0·54	1·10 (0·77–1·58); 0·60	1·14 (0·48–2·73); 0·76	1·27 (0·75–2·17); 0·37
Asthma or wheeze (never asthma or wheeze as the reference)‖					
Onset before age 15 years	1·51 (0·31–7·46); 0·61	1·99 (0·40–9·92); 0·40	0·87 (0·28–2·72); 0·81	4·57 (0·88–23·84); 0·071	1·66 (0·43–6·50); 0·47
Onset after age 15 years	1·24 (0·56–2·74); 0·60	1·41 (0·61–3·30); 0·43	1·04 (0·63–1·72); 0·88	2·16 (0·75–6·25); 0·16	0·76 (0·32–1·77); 0·52

Data are aMOR (95% CI); p value. aMORs and p values are from multinomial logistic regressions. The analyses were based on 894 father–offspring pairs. aMOR=adjusted multinomial odds ratio. $FEF_{25–75\%}$=mean forced expiratory flow between 25% and 75% of the forced vital capacity. NA=results were not available due to limited observations. SEIFA-IRSD=Socio-economic Indexes for Areas–Index of Relative Socio-economic Disadvantage. *Models were adjusted for passive smoke exposure before age 15 years and SEIFA-IRSD scores of parents. †The model was adjusted for living environment, number of siblings sharing the bedroom (continuous), daycare centre attendance, and main type of heating at home before age 5 years, and cat at home and carpet or rug in the bedroom before age 15 years. ‡The model was adjusted for SEIFA-IRSD scores of parents. §Models were adjusted for passive smoke exposure before age 15 years and SEIFA-IRSD scores of parents. ¶The model was adjusted for passive smoke exposure before age 15 years. ‖The model was adjusted for passive smoke exposure before age 15 years, active smoking, and SEIFA-IRSD scores of parents.

Table 3: **Associations between preconception factors in fathers and each $FEF_{25–75\%}$ trajectory compared with the average trajectory in their offspring**

of the two, were associated with COPD by age 53 years.[3,4] This study extends these analyses with life-course trajectories, using $FEF_{25–75\%}$. This spirometric index reflects mid-to-small-airway function (hereafter termed smaller airways), smaller than the airways typically represented by FEV_1. Six distinct $FEF_{25–75\%}$ trajectories were identified. Three impaired trajectories over time (ie, persistently low, early normal-reduced growth-rapid decline, and early below average-reduced growth) together accounted for 96% of spirometry-defined COPD by age 53 years. Impaired trajectories were associated with childhood asthma or wheeze, allergic rhinitis, and maternal asthma or wheeze. Regarding parental preconception factors, both active paternal and maternal smoking before completing puberty were associated with their offspring belonging to the early normal-reduced growth-rapid decline trajectory. In contrast, microbial-related preconception exposures (ie, fathers sharing a childhood bedroom with three or more siblings and maternal cat keeping before completing puberty) were associated with the persistently high trajectory in their offspring.

Repeated $FEF_{25–75\%}$ measurements capture longitudinal variation in smaller-airway function that is not fully reflected by FEV_1, which primarily represents large-airway function. Given concerns about $FEF_{25–75\%}$ variability and its dependence on FVC, using repeated measures in trajectory modelling could mitigate the influence of single timepoint variability. In addition, the dependence of $FEF_{25–75\%}$ on FVC might be less pronounced in early COPD, when air trapping is limited. In this analysis, six $FEF_{25–75\%}$ trajectories broadly resembled previously reported FEV_1 trajectories.[3] Nonetheless, notable differences were found during the lung growth phase. For instance, the early below average-reduced growth $FEF_{25–75\%}$ trajectory diverged from the average trajectory from as early as age 7 years (our first measurement) and fell below a *Z* score of –1 before age 18 years. In contrast, the comparable below average FEV_1 trajectory remained largely parallel to the average FEV_1 trajectory until adolescence, with decline commencing only after age 18 years.[3] These findings suggest some differences between the life-course trajectory patterns of $FEF_{25–75\%}$

	Persistently low (n=81)	Early normal-reduced growth-rapid decline (n=89)	Early below average-reduced growth (n=404)	Early low-accelerated growth (n=38)	Persistently high (n=104)
Before mothers' own age of 5 years (ie, during childhood)					
Living environment (city as the reference)*					
Country town	0·97 (0·52–1·80); 0·92	1·42 (0·82–2·49); 0·21	0·79 (0·57–1·10); 0·16	0·31 (0·11–0·85); 0·023	0·80 (0·47–1·36); 0·41
Farm	1·29 (0·70–2·37); 0·41	1·05 (0·57–1·95); 0·87	0·89 (0·63–1·25); 0·51	0·66 (0·29–1·51); 0·33	0·84 (0·49–1·47); 0·55
Number of siblings sharing the bedroom (per one-sibling increase)*	1·01 (0·86–1·18); 0·90	1·00 (0·86–1·17); 1·00	0·92 (0·81–1·03); 0·15	0·89 (0·62–1·28); 0·53	1·00 (0·86–1·17); 1·00
Number of siblings sharing the bedroom (no sibling as the reference)*					
One	1·02 (0·55–1·90); 0·95	1·36 (0·75–2·48); 0·31	1·04 (0·75–1·46); 0·81	0·67 (0·29–1·59); 0·37	1·24 (0·70–2·18); 0·46
Two	0·85 (0·38–1·89); 0·69	1·36 (0·67–2·78); 0·40	0·98 (0·65–1·49); 0·93	0·88 (0·32–2·42); 0·81	1·03 (0·51–2·11); 0·93
Three or more	1·25 (0·53–2·93); 0·61	1·20 (0·51–2·83); 0·67	0·70 (0·41–1·19); 0·19	0·54 (0·12–2·52); 0·44	1·24 (0·55–2·79); 0·60
Serious respiratory infection†	1·36 (0·53–3·53); 0·52	0·50 (0·15–1·68); 0·26	0·85 (0·47–1·55); 0·60	0·46 (0·06–3·80); 0·47	0·69 (0·26–1·87); 0·47
Daycare centre attendance*	1·11 (0·50–2·48); 0·80	1·11 (0·52–2·37); 0·79	0·68 (0·41–1·12); 0·13	0·92 (0·27–3·19); 0·90	1·03 (0·50–2·12); 0·95
Wood or fossil fuel as the main type of heating at home (electric heating systems or others as the reference)*	0·54 (0·17–1·67); 0·28	0·63 (0·20–1·95); 0·42	0·70 (0·34–1·45); 0·34	0·50 (0·11–2·34); 0·38	0·75 (0·24–2·33); 0·62
Before mothers' own age of 15 years (ie, before completing puberty)					
Passive smoke exposure‡	1·18 (0·65–2·15); 0·58	1·01 (0·59–1·74); 0·96	0·99 (0·73–1·36); 0·97	0·97 (0·44–2·14); 0·94	0·84 (0·51–1·38); 0·50
Cat at home§	1·27 (0·74–2·19); 0·38	1·01 (0·62–1·65); 0·95	1·25 (0·93–1·68); 0·13	1·16 (0·55–2·47); 0·69	1·78 (1·08–2·91); 0·023
Carpet or rug in the bedroom§	1·05 (0·60–1·83); 0·87	0·89 (0·53–1·50); 0·66	0·83 (0·61–1·13); 0·24	0·68 (0·31–1·51); 0·34	0·66 (0·41–1·08); 0·096
Active smoking (never smoked as the reference)¶					
Commenced before age 15 years	2·97 (0·89–9·93); 0·077	4·24 (1·37–13·11); 0·012	1·18 (0·46–3·03); 0·74	NA	1·19 (0·25–5·61); 0·82
Commenced after age 15 years	1·51 (0·90–2·54); 0·12	2·33 (1·43–3·79); 0·0007	1·32 (0·98–1·78); 0·067	1·05 (0·50–2·21); 0·89	1·46 (0·91–2·33); 0·11
Asthma or wheeze (never asthma or wheeze as the reference)‖					
Onset before age 15 years	1·54 (0·50–4·71); 0·45	0·30 (0·04–2·28); 0·24	1·07 (0·53–2·15); 0·85	1·40 (0·31–6·36); 0·66	1·07 (0·35–3·26); 0·90
Onset after age 15 years	0·99 (0·45–2·21); 0·98	1·21 (0·62–2·37); 0·58	1·06 (0·69–1·62); 0·80	0·76 (0·22–2·61); 0·67	0·97 (0·48–1·95); 0·94

Data are aMOR (95% CI); p value. aMORs and p values are from multinomial logistic regressions. The analyses were based on 1245 mother–offspring pairs. aMOR=adjusted multinomial odds ratio. $FEF_{25–75\%}$=mean forced expiratory flow between 25% and 75% of the forced vital capacity. NA=results were not available due to limited observations. SEIFA-IRSD=Socio-economic Indexes for Areas–Index of Relative Socio-economic Disadvantage. *The models were adjusted for passive smoke exposure before age 15 years and SEIFA-IRSD scores of parents. †The model was adjusted for living environment, number of siblings sharing the bedroom (continuous), daycare centre attendance, and main type of heating at home before age 5 years, and cat at home and carpet or rug in the bedroom before age 15 years. ‡The model was adjusted for SEIFA-IRSD scores of parents. §The models were adjusted for passive smoke exposure before age 15 years and SEIFA-IRSD scores of parents. ¶The model was adjusted for passive smoke exposure before age 15 years. ‖The model was adjusted for passive smoke exposure before age 15 years, active smoking, and SEIFA-IRSD scores of parents.

Table 4: **Associations between preconception factors in mothers and each $FEF_{25–75\%}$ trajectory compared with the average trajectory in their offspring**

and FEV_1. Previous research found that reduced $FEF_{25–75\%}$ was associated with COPD over a 10-year follow-up and might be detectable earlier than reduced FEV_1 in older adults with a baseline mean age of 61·4 years (SD 10·5).[24] Taken together, these findings support the value of deriving $FEF_{25–75\%}$ trajectories across the lifespan.

Our findings advance knowledge of the associations between impaired airway function trajectories and COPD. The two most impaired $FEF_{25–75\%}$ trajectories showed strong associations with COPD, with the highest odds observed for the persistently low trajectory, followed by the early normal-reduced growth-rapid decline trajectory. This pattern suggests that persistent impairment from childhood was more strongly associated with COPD risk in relation to smaller-airway dysfunction than impairment emerging later during adolescence. Results were consistent after restricting analysis to offspring without COPD by age 45 years, reducing concern that associations were driven by early-onset COPD. For FEV_1, previous work suggested that COPD could arise either from low FEV_1 in early adulthood (before age 40 years) accompanied by normal decline, or from normal FEV_1 in early adulthood followed by rapid decline thereafter.[25] The relative odds of COPD for impaired FEV_1 trajectory groups were then quantified in TAHS. The early below average-accelerated decline trajectory showed the highest odds, followed by the persistently low trajectory,[3] suggesting that, adults with accelerated FEV_1 decline are a particularly high-risk subgroup for COPD. Although both persistently low and rapid decline trajectories were associated with increased COPD odds, their ranking of associations reversed between $FEF_{25–75\%}$ and FEV_1. This difference could suggest that large-airway and smaller-airway dysfunction might follow different pathophysiological pathways to COPD.

In relation to childhood factors, impaired $FEF_{25–75\%}$ trajectories differed by age of asthma or wheeze onset, suggesting asthma-related structural airway changes. Distinct patterns of association were observed for early-onset and later-onset asthma or wheeze. Early-onset asthma or wheeze before age 3 years was associated with

impaired $FEF_{25–75\%}$ trajectories during childhood, regardless of whether the trajectory remained persistently low or showed accelerated growth later in life. In contrast, later-onset asthma (ie, ages 3–7 years) was associated with persistent impairment (persistently low) or impairment commencing from adolescence (early normal-reduced growth-rapid decline). These patterns were less marked for FEV_1.[3] Mechanistically, asthma is especially characterised by increased thickness of the airway smooth muscle layer, which might contribute to airway narrowing.[26,27] Such airway remodelling in asthma could influence expiratory flow most marked in middle airways;[27] indeed, in children with asthma, $FEF_{25–75\%}$ has been shown to be a particularly sensitive marker of airway dysfunction, which was missed by FEV_1 alone.[28]

Furthermore, maternal history of asthma or wheeze, ascertained during offspring childhood, was associated with the persistently low $FEF_{25–75\%}$ trajectory in their offspring. This finding supports evidence of familial aggregation of impaired respiratory health. A twin study estimated the heritability of childhood asthma to be 82%.[29] Genetic loci associated with both asthma pathogenesis and airflow obstruction have been identified, including *ORMDL3* on chromosome 17q21; increased *ORMDL3* expression could lead to early airway remodelling in asthmatic mice.[30,31] We hypothesise that such mechanisms might also be relevant in humans.

This study identified novel associations for parental preconception factors. Paternal childhood bedroom sharing with a smaller sibship size (ie, one or two) and active smoking before completing puberty were associated with impaired $FEF_{25–75\%}$ trajectories in their offspring. These intergenerational associations support the Paternal Origins of Health and Disease. Having a private bedroom might reflect higher socioeconomic status and less household crowding, while sharing with siblings could increase microbial exposure. A murine study has shown that paternal preconception exposure to viral mimic (Poly I:C) altered sperm microRNA profiles and influenced innate immune responses in offspring.[32] Evidence in humans remains associative, but causality is supported in animal models and remains plausible in humans. Moreover, paternal smoking has been shown to alter sperm microRNA profiles in mice,[33] and is associated with offspring epigenetic profiles in humans, which could mechanistically explain observed association between paternal smoking in puberty and offspring lung function impairment.[34]

In contrast, paternal childhood bedroom sharing with a larger sibship size (ie, three or more) and maternal cat keeping before completing puberty were both associated with the persistently high trajectory in their offspring. Although mechanisms remain speculative, larger sibship size could reflect immune priming by enhanced ambient microbial exposures and microbial diversity that promote allergic-immune tolerance.[35] Supporting this hypothesis, cumulative daycare attendance exceeding 1800 h during the first year of life has been associated with a lower asthma risk.[36] Intergenerationally, paternal infections might be linked to offspring immune phenotype through epigenetic modifications.[37] Furthermore, pet exposures are surrogates for microbial exposures. Differences in bacterial taxa have been observed between homes of asthmatic and non-asthmatic children, some related to cat allergens.[38] Further, high cat allergen levels were associated with IgG4 responses without allergic sensitisation or asthma, suggesting another avenue to allergic-immune tolerance.[39] Maternal immune activation in mice reprogrammed their offspring's immunity through epigenetic modifications.[40]

Our previous analysis in TAHS found that, at age 45 years, those with combined large-airway and small-airway dysfunction, defined by reduced FEV_1/FVC and increased concavity of the maximal expiratory flow-volume curve, were at an increased risk of developing COPD.[41] Previous research has also suggested that small-airway dysfunction could arise earlier in the life course, and might precede symptoms or abnormalities on conventional spirometry.[42] By modelling $FEF_{25–75\%}$ trajectories from childhood to middle age, our study provides new insights into the life-course evolution of airway dysfunction and suggests that abnormalities in smaller-airway function might follow patterns that differ from those of predominantly large-airway function. Nonetheless, because the whole airway tree operates together, dysfunction in one section will, to some extent, be reflected across the entire system. Our analysis is also novel in its comprehensive assessment of factors during childhood and parental preconception. Understanding these factors could help inform early-life intervention strategies for vulnerable populations with a higher risk of COPD.

However, this study also has some limitations. The average (reference) trajectory had low prevalence of COPD (4/964), leading to near-complete separation between trajectories and producing high odds ratios for impaired trajectories. Although very strong associations were seen as expected because early low lung function persisted,[43] the magnitude of the odds ratios should be interpreted cautiously, and trajectory-specific COPD prevalence should be noted. Nonetheless, the large sample size in the average trajectory provides strong evidence of a qualitatively very low underlying COPD risk in this trajectory. The trajectory modelling included $FEF_{25–75\%}$ data up to age 53 years, while COPD was also assessed at age 53 years. Therefore, the observed associations should be interpreted as life-course associations rather than as predictive given that the trajectories and COPD were assessed over concurrent time periods. Shared familial and socioenvironmental factors, including adverse intrauterine exposures of offspring, might partly explain the observed preconception

and childhood associations. Parental preconception factors were recalled approximately 50 years after baseline and could not be verified using grandparent data. These factors might be subject to recall and survivor bias, and residual confounding could not be excluded. Survivor bias is possible because lung function at age 53 years was available only for a subset of the cohort. However, mortality before age 53 years was low (405 [4·7%] of 8583]),[3] limiting the impact of survival-related selection. Compared with those excluded, included offspring were more likely to have been breastfed and had less parental smoking exposure. As these factors are associated with more favourable early-life environments, our analytical sample is likely to be a somewhat advantaged subgroup and have lower incidence of impaired trajectories and COPD. However, the selection of an advantaged subgroup does not necessarily mean that the observed associations between these exposures and outcomes were biased.[44] The predominantly White TAHS population might further limit generalisability. Parental lung function was not measured, limiting assessment of familial predisposition.

For **data request instructions** see https://tahs.com.au/data-request/

Six life-course $FEF_{25–75\%}$ trajectories were identified, a measure that reflects smaller-airway function. Early impairment in $FEF_{25–75\%}$ from childhood or adolescence was associated with COPD in middle age. However, before recommending routine $FEF_{25–75\%}$ screening, its added value over FEV_1 measurement needs validation. The reported associations of childhood and parental preconception factors with $FEF_{25–75\%}$ trajectories are biologically plausible, but causality cannot be inferred. Further biological and clinical studies are needed to clarify the likely pathways. Our findings raise the possibility that identifying adverse preconception exposures in parents might help identify offspring who are susceptible to an increased risk of lung function impairment. Reducing adverse childhood exposures in these offspring could help mitigate subsequent lung function impairment and possibly benefit future generations.

Contributors

JL, CJL, JLP, DV, NSI, SOS, GRW, EHW, SCD, and DSB were responsible for the study concept and design. GB, GSH, RRW-B, DPJ, MJA, EHW, and SCD were responsible for acquisition of the data. JL, CJL, JLP, DV, NSI, DJT, EHW, SCD, and DSB were responsible for analysis and interpretation of the data. JL, DV, SCD, and DSB were responsible for the statistical analysis. JL, CJL, JLP, DV, NSI, EHW, SCD, and DSB were responsible for drafting of the manuscript. All authors contributed to interpretation of findings and were responsible for critical revision of the manuscript for important intellectual content and approved the submitted manuscript. CJL, JLP, GSH, MJA, EHW, and SCD obtained the study funding. All authors had direct access to the raw data. JL, DV, SCD, and DSB verified the data. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

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Data sharing

De-identified individual participant data can be provided upon request to anyone with a suitable proposal. Data request instructions are available online. Requests can be directed to the corresponding author, who is also the principal investigator of the Tasmanian Longitudinal Health Study. The proposal will be reviewed by the steering committee of the Tasmanian Longitudinal Health Study.

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