Title page

Title

Paternal pre-pubertal passive smoke exposure is related to impaired lung function trajectories from childhood to middle age in their offspring

Word count: 20/20

Authors' names

Jiacheng Liu,[1] Jennifer L. Perret,[1,2] Caroline J. Lodge,[1] Don Vicendese,[1,3,4] Gayan Bowatte,[1,5] Adrian J. Lowe,[1,4] N. Sabrina Idrose,[1,4] Peter A. Frith,[6,7] Richard R. Wood-Baker,[8] Gita D. Mishra,[9] John W. Holloway,[10,11] Cecilie Svanes,[12,13] Michael J. Abramson,[14] E. Haydn Walters,[1,8] Shyamali C. Dharmage,[1,4*] Dinh S. Bui,[1*]

Author affiliations

1. Allergy and Lung Health Unit, Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Australia.
2. Institute for Breathing and Sleep, Department of Respiratory and Sleep Medicine, Austin Health, Heidelberg, Australia.
3. School of Computing, Engineering and Mathematical Sciences, La Trobe University, Melbourne, Australia.
4. Murdoch Children's Research Institute, Melbourne, Australia.
5. Department of Basic Sciences, Faculty of Allied Health Sciences, University of Peradeniya, Peradeniya, Sri Lanka.
6. College of Medicine and Public Health, Flinders University, Adelaide, Australia.
7. Respiratory Medicine, Repatriation General Hospital, Daw Park, Australia.
8. School of Medicine, University of Tasmania, Hobart, Australia.
9. Australian Women and Girls' Health Research Centre, School of Public Health, The University of Queensland, Brisbane, Australia.
10. Human Development and Health, Faculty of Medicine, University of Southampton, Southampton, UK.

11. NIHR Southampton Biomedical Research Center, University Hospitals Southampton, Southampton, UK.
12. Department of Occupational Medicine, Haukeland University Hospital, Bergen, Norway.
13. Centre for International Health, Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway.
14. School of Public Health & Preventive Medicine, Monash University, Melbourne, Australia.

* Equal last author

Corresponding author

Professor Shyamali C. Dharmage

Allergy and Lung Health Unit, Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne.

Level 3, 207 Bouverie Street, Carlton, VIC 3053, Australia.

Email: s.dharmage@unimelb.edu.au

Tel: +61 3 8344 0737 Fax: +61 3 9349 5815

Manuscript word count

3,500/3,500

ORCID

Jiacheng Liu: 0000-0002-5663-0154

Jennifer L. Perret: 0000-0001-7034-0615

Caroline J. Lodge: 0000-0002-2342-3888

Don Vicendese: 0000-0002-0176-0314

Gayan Bowatte: 0000-0002-9577-9752

Adrian J. Lowe: 0000-0002-4691-8162

N. Sabrina Idrose: 0000-0002-7079-3670

Peter A. Frith: 0000-0003-3265-0131

Richard R. Wood-Baker: He does not have an ORCID number.

Gita D. Mishra: 0000-0001-9610-5904

John W. Holloway: 0000-0001-9998-0464
Cecilie Svanes: 0000-0001-8512-5192
Michael J. Abramson: 0000-0002-9954-0538
E. Haydn Walters: 0000-0002-0993-4374
Shyamali C. Dharmage: 0000-0001-6063-1937
Dinh S. Bui: 0000-0002-4388-784X

ABSTRACT

Introduction Paternal pre-pubertal passive smoke exposure may increase the risk of childhood asthma. However, its association with impaired lung function trajectories at risk of chronic obstructive pulmonary disease in offspring was not investigated. We assessed the association between paternal pre-pubertal passive smoke exposure and lung function from childhood to middle age in their offspring.

Methods Data were analysed from 890 father-offspring from the Tasmanian Longitudinal Health Study (TAHS). The offspring were probands in the original cohort who have undergone spirometry at six-time points from ages 7 to 53 years. Lung function (FEV_1, FVC, and FEV_1/FVC) trajectories were previously derived using group-based trajectory modelling. Fathers reported their own passive smoke exposure before age 15 years. Multinomial logistic regressions assessed associations between paternal pre-pubertal passive smoke exposure and lung function trajectories in offspring. Potential mediation and interactions were assessed for active paternal smoking, offspring passive smoke exposure and respiratory illnesses during childhood, and subsequent active smoking.

Results Paternal pre-pubertal passive smoke exposure was associated with the Below Average FEV_1 (adjusted multinomial odds ratio [aMOR] 1.56; 95% CI 1.05-2.31) and Early Low-Rapid Decline FEV_1/FVC trajectories (aMOR 2.30; 1.07-4.94) in offspring. The association with the Below Average FEV_1 trajectory was augmented for offspring exposed to childhood passive smoke (aMOR 2.36; 1.34-4.13; *p-interaction* 0.053). Observed associations partly mediated through smoking and respiratory illnesses in fathers and offspring (each contributing <15%).

Conclusion Paternal pre-pubertal passive smoke exposure was associated with impaired lung function trajectories in offspring, which highlights the adverse impact of smoking on multiple generations.

Word count: 250/250

Key words Tobacco and the lung, COPD epidemiology

Key messages

What is already known on this topic

Paternal adverse exposure before their own completing puberty, such as pre-pubertal passive smoke exposure, was associated with childhood asthma by age 7 years in their offspring. However, its long-term association with lifetime lung function trajectories in the offspring was not investigated.

What this study adds

Paternal pre-pubertal passive smoke exposure was associated with impaired lung function trajectories at risk of chronic obstructive pulmonary disease in their offspring. This association was further exacerbated when offspring also experienced passive smoke exposure during their own childhood.

How this study might affect research, practice or policy

Passive smoke exposure before completing puberty may intergenerationally impair lung function in future generations and this information about intergenerational impacts can inform public health messages about the harms of passive smoke exposure.

INTRODUCTION

Chronic lung diseases, especially chronic obstructive pulmonary disease (COPD), are significant public health problems. COPD is now globally the third leading cause of death,[1] accounting for approximately 3.2 million deaths annually.[2] The burden of COPD is projected to increase in the coming decades given the overarching aging trend and high prevalence of exposure to relevant risk factors, such as tobacco smoking and air pollution.[3] Nonetheless, besides smoking avoidance and cessation, effective prevention for COPD is still a challenge,[4] which is largely due to insufficient knowledge of other modifiable risk factors and susceptibility windows.

COPD is usually diagnosed when lung function deficits reach a threshold, i.e. fixed airflow limitation, but there are many years of progressive airway damage before this occurs.[5] The lungs may be particularly vulnerable during one or more susceptibility windows throughout the lifespan.[6] In contrast to using lung function at a single time point to predict COPD development, emerging research has identified distinct lung function trajectories based on multiple time points since childhood or early adulthood.[7-9] This has highlighted several disadvantaged groups who have impaired lung growth, do not reach maximum lung function in early adulthood and/or have more rapid lung function decline, resulting in an increased risk of developing COPD in middle age.[5] Specifically, the Tasmanian Longitudinal Health Study (TAHS) has identified three distinct impaired lifetime lung function trajectories from ages 7 to 53 years which together accounted for 75% of subsequent COPD burden.[8] These findings have led to substantial interest in identifying patients during pre-COPD stage by tracking their longitudinal lung function trajectories. Moreover, to reduce

the burden of COPD, it is crucial to identify the determinants of impaired pre-COPD lung function trajectories.[10]

Multiple risk factors throughout the lifespan may increase the risk of lung function deficits and subsequent COPD and associations have been documented between both early life (e.g. passive or second-hand tobacco smoke exposure and childhood respiratory illnesses) and also adult risk factors (e.g. active smoking and respirable occupational hazards).[6,8-10] Recently, there has been increasing interest in intergenerational transmission of exposure to risk factors.[11] Some emerging evidence has suggested maternal passive smoke exposure during their own intrauterine life as a risk factor for childhood asthma in their offspring.[12-15] Active paternal smoking before age 15 years (pre-puberty) increased the risk of childhood asthma and early lung function deficits in their offspring.[16,17] The association between active paternal pre-pubertal smoking and asthma even persisted into adulthood in their offspring.[18] Our preliminary analysis extended from active smoking to passive smoke exposure during paternal pre-puberty and identified an association between this paternal smoke exposure and childhood asthma in their offspring.[19] Thus, we hypothesised that the intergenerational association of passive smoke exposure before paternal completing puberty might persist well into offspring adulthood, impairing their lifetime lung function trajectory.

This study aimed to assess: 1) associations between paternal pre-pubertal passive smoke exposure and lung function trajectories from childhood to middle age and development of COPD by age 53 years in their offspring; and, 2) to what extent any such associations were mediated through or

153 modified by other factors in fathers and offspring.

154

155 **METHODS**

156 **Study cohort**

157 This study was based on the TAHS, which commenced in 1968 (baseline) and recruited 8,583
158 probands (denoted as "offspring" in this paper) who were born in 1961 and were attending schools in
159 Tasmania, Australia.[20] A total of 8,022 (93.5%) such offspring underwent spirometry. Parents
160 completed a comprehensive baseline respiratory health-based survey for themselves and their
161 offspring. Thereafter, follow-up studies were initiated when the offspring were aged 13, 18, 43, 50,
162 and 53 years, which included spirometry and surveys for demographics and respiratory
163 symptoms/diseases. Of 7,243 parents who were alive and could be traced in 2010, a total of 5,111
164 (70.6%) were resurveyed. Of 5,097 parents with valid data, 2,096 were fathers.

165

166 **Exposure measurement**

167 Paternal pre-pubertal passive smoke exposure was ascertained in the *2010 TAHS Parents Postal*
168 *Survey*. Fathers of the offspring responded to the questions, "Did your father smoke when you were
169 less than 5 years?", "Did your father smoke when you were aged 5-15 years?", "Did your mother
170 smoke when you were less than 5 years?" and "Did your mother smoke when you were aged 5-15
171 years?". Fathers with an affirmative answer to passive smoke exposure during any one of these
172 periods to either of their own parents were labelled as exposed.

Outcome measurement

Pre-bronchodilator lung function parameters of offspring, including forced expiratory volume in the first second (FEV_1), forced vital capacity (FVC), and FEV_1/FVC, were measured at six time points according to the American Thoracic Society and European Respiratory Society criteria.[21] Offspring *lung function trajectories* from their ages 7 to 53 years (7, 13, 18, 45, 50, and 53) had been previously modelled in the TAHS using group-based trajectory modelling. Specifically, six FEV_1 trajectories, five FVC trajectories, and six FEV_1/FVC trajectories had been reported (figure 1).[8,9] Spirometry-defined COPD in parents' offspring at age 53 years was defined as a post-bronchodilator FEV_1/FVC less than the lower limit of normal.[8]

Statistical analyses

The adjustment for socio-economic indexes for area - the index of relative socio-economic disadvantage (SEIFA-IRSD) scores of parents in adjusted model 1 was guided by a Directed Acyclic Graph that suggested a minimal sufficient adjustment set of confounders.[22] SEIFA-IRSD scores of parents were adjusted for as a proxy for paternal socio-economic status (methods S1-S2, figure S1). Furthermore, paternal lifetime history of asthma/wheeze was adjusted as a proxy for potential genetic risk factors,[23] and paternal age at baseline in adjusted model 2.[17] Variance Inflation Factor (VIF) was used to assess multicollinearity among the exposure of interest (paternal pre-pubertal passive smoke exposure) and confounders (SEIFA-IRSD scores of parents, paternal lifetime history of asthma/wheeze, and paternal age at baseline). Statistical significance for multicollinearity was

194 defined as a VIF value above 5.[24] Multinomial logistic regressions then estimated the associations
195 between paternal pre-pubertal passive smoke exposure and lung function trajectories from ages 7 to
196 53 years in their offspring. Results were presented as multinomial odds ratios (MOR) and when
197 adjusted as aMOR. The adjusted models were fitted using father-offspring pairs with complete data
198 on the exposure, outcomes, and confounders. Logistic regressions assessed the associations between
199 the paternal exposure and spirometry-defined COPD at age 53 years in their offspring.

200

201 Causal mediation analysis was conducted using the *medeff* programme to estimate the proportion of
202 the total effect mediated through different pathways. *Medeff*, based on methods by Imai et al.,
203 provides robust standard errors with confidence intervals to assess mediation for each potential
204 mediator.[25,26] Mediation was considered significant if the 95% confidence interval did not include
205 0%. Joint mediation was also of interest. Since *medeff* does not support this, the *KHB* method was
206 used instead,[27] although it does not provide confidence intervals. It was speculated that paternal pre-
207 pubertal passive smoke exposure might partly contribute to unhealthy lifestyles, including active
208 paternal smoking, offspring passive smoke exposure during childhood (by age 7 years) due to active
209 parental smoking, and active offspring smoking by middle age (53 years). Paternal pre-pubertal
210 passive smoke exposure might also lead to early-life disadvantages, such as offspring preterm birth,
211 low birthweight, and respiratory illnesses, including childhood asthma/wheeze, bronchitis, food
212 allergy, and pneumonia/pleurisy. These disadvantages might then influence the offspring lung
213 function trajectory.[19,28]

214

Likelihood ratio test assessed whether the inclusion of an interaction term between the exposure and a potential effect modifier improved model fit in multinomial logistic regressions.[29] The null hypothesis of no effect modification was tested. Effect modifiers considered in this analysis were active paternal smoking, offspring sex at birth, respiratory illnesses during childhood, passive smoke exposure during childhood, and active smoking by middle age. Statistical significance for associations and interactions was defined as *p*-values lower than 0.05 and 0.10, respectively. If the test for interaction between the exposure and a potential effect modifier was significant, the analysis was stratified by this effect modifier.

To exclude the influence of offspring asthma, a sensitivity analysis was conducted by excluding offspring who reported asthma/wheeze by age 53 years to assess the association between paternal pre-pubertal passive smoke exposure and offspring lung function trajectories. To assess the influence of missing confounder data, another sensitivity analysis was conducted using multiple imputation (methods S3).

To compare included and excluded father-offspring pairs, chi-squared or t-tests were used for their characteristics. Definitions of confounders, mediators and effect modifiers are provided in the supplementary (methods S4). All analyses were carried out using STATA version 18 (StataCorp, College Station, TX, USA).

RESULTS

Characteristics of participants

In this analysis, a total of 890 father-offspring pairs with data on paternal pre-pubertal passive smoke exposure and lung function data of offspring at age 53 years were included (figure S2). The prevalence of paternal pre-pubertal passive smoke exposure was 68.7%. The prevalence of offspring childhood passive smoke exposure was 56.5%. Forty nine percent of the offspring had a history of active smoking by middle age. A total of 5.1% of offspring had developed spirometry-defined COPD by middle age (table 1).

Compared to the offspring not included in the analyse, those included had similar characteristics except that those included had a lower prevalence of childhood passive smoke (56.5% vs. 72.1%, $p < 0.001$) and a lower prevalence of active smoking by middle age (49.0% vs. 59.0%, $p < 0.001$). In addition, compared to the fathers excluded, those included in the analyse were younger at the baseline in 1968 (34.7±5.3 years vs. 37.2±7.1, $p < 0.001$) and socio-economically advantaged (SEIFA-IRSD 994.0±44.0 scores vs. 989.9±45.5, $p = 0.016$). There was also some evidence suggesting that the fathers included in the analysis had a slightly lower prevalence of pre-pubertal passive smoke exposure compared to those excluded (68.7% vs. 72.8%, $p = 0.053$) (table S1).

Associations between paternal pre-pubertal passive smoke exposure and lung function trajectories and spirometry-defined COPD in their offspring

The VIFs for SEIFA-IRSD scores of parents, paternal lifetime history of asthma/wheeze, and paternal age at baseline were all 1.01 or less, indicating no significant multicollinearity. After adjusting for SEIFA-IRSD scores of parents, paternal lifetime history of asthma/wheeze, and paternal age at baseline, paternal pre-pubertal passive smoke exposure was associated with increased odds of having the Below Average FEV_1 trajectory (aMOR 1.56; 95% CI 1.05-2.31; $p = 0.028$) in their offspring (table 2). No significant associations were found for FVC trajectories (table S2). For the FEV_1/FVC trajectories, after adjustments, paternal pre-pubertal passive smoke exposure was also associated with the Early Low-Rapid Decline FEV_1/FVC trajectory (aMOR 2.30; 95% CI 1.07-4.94; $p = 0.033$) in their offspring (table 3). The associations for Early Low-Normal Decline FEV_1/FVC trajectory in offspring were found only in the crude model but became non-significant in the adjusted models (table 3). Aside from significant associations identified for the Below Average FEV_1 and the Early Low-Rapid Decline FEV_1/FVC trajectories, there were trends for paternal pre-pubertal passive smoke exposure to be associated with increased odds of other impaired trajectories. However, the *p*-values were well above the traditional cut-off of 0.05 and even above 0.1 suggesting the evidence was weak. Furthermore, a moderate association was shown between the paternal exposure and spirometry-defined COPD at age 53 years in their offspring, but the association was non-significant after adjustments (adjusted odds ratio [aOR] 2.06; 95% CI 0.93-4.55; $p = 0.073$) (table S3).

Mediation analyses: proportions of mediations between paternal pre-pubertal passive smoke exposure and impaired lung function trajectories in their offspring

For the total effect between paternal pre-pubertal passive smoke exposure and the Below Average

FEV_1 trajectory in their offspring, active paternal smoking, active offspring smoking and childhood passive smoke exposure contributed 13.7% (95% CI 7.7-59.5%), 13.4% (95% CI 7.6-52.4%), and 10.9% (95% CI 6.0-47.4%), respectively (figure 2). The other mediators examined, namely offspring asthma/wheeze, bronchitis, and pneumonia/pleurisy during childhood demonstrated limited mediations (each contributing $\leq$2.0%). Offspring preterm birth, low birthweight, and childhood food allergy did not show mediations. Jointly, all mediators accounted for 14.1% of the total effect.

For the association with offspring Early Low-Rapid Decline FEV_1/FVC trajectory, offspring childhood asthma accounted for 14.8% (95% CI 7.6-73.7%). Their childhood passive smoke exposure and active paternal smoking contributed 12.4% (95% CI 6.4-57.7%) and 11.3% (95% CI 6.0-53.5%), respectively (figure 3). Other mediators examined, as above, demonstrated limited mediations (each contributing <7%). Jointly, all mediators accounted for 10.1% of the total effect.

Interactions: paternal pre-pubertal passive smoke exposure and potential effect modifiers

Substantial interactions were observed between paternal pre-pubertal passive smoke exposure and potential effect modifiers, including offspring passive smoke exposure (*p-interaction* = 0.053), pneumonia/pleurisy (*p-interaction* = 0.008), and food allergy during childhood (*p-interaction* = 0.071) (table S4). Specifically, the association between the relevant paternal smoke exposure and offspring risk of developing the Below Average FEV_1 trajectory was especially pronounced in the offspring who also experienced passive smoke exposure during childhood (aMOR 2.36; 95% CI 1.34-4.13; $p = 0.003$) compared to those who did not (aMOR 0.90; 95% CI 0.51-1.60; $p = 0.73$) (table S5).

297

298 Furthermore, stratified analysis revealed that the association between the paternal exposure and the
299 Below Average FEV_1 trajectory in offspring was more evident in offspring without childhood
300 pneumonia/pleurisy (aMOR 1.96; 95% CI 1.26-3.04; $p = 0.003$) (table S6). Similarly, the association
301 between the paternal exposure and Early Low-Rapid Decline FEV_1/FVC trajectory in offspring was
302 more evident in offspring without childhood food allergy (aMOR 3.85; 95% CI 1.45-10.19; $p = 0.007$)
303 (table S7). There were no statistically significant interactions between paternal pre-pubertal smoke
304 exposure and active paternal smoking, offspring sex at birth or their having asthma/wheeze and/or
305 bronchitis during childhood or actively smoking by middle age (all *p-interaction* > 0.1) (table S4).

306

307 **Sensitivity analyses**

308 After excluding offspring who reported a history of asthma/wheeze by age 53 years, the association
309 for the Below Average FEV_1 trajectory remained evident (aMOR 2.07; 95% CI 1.24-3.46; $p = 0.005$)
310 (table S8). For the Early Low-Rapid Decline FEV_1/FVC trajectory, the point estimates remained
311 similar between the original and sensitivity analyses (2.30 vs. 2.42), but the 95% confidence intervals
312 widened in the sensitivity analysis (aMOR 2.42; 95% CI 0.51-11.43; $p = 0.27$) (table S9). The upper
313 bound of the 95% CI still suggested some signal, while the wide CI indicated limited power.

314

315 After applying multiple imputation, the associations remained evident for both the Below Average
316 FEV_1 trajectory (aMOR 1.56; 95% CI 1.08-2.27; $p = 0.018$) and the Early Low-Rapid Decline

317 FEV_1/FVC trajectory (aMOR 2.64; 95% CI 1.24-5.60; p = 0.011) (table S10). Similar results in
318 complete-case and imputed analyses support the robustness of observed associations.

319

320 **DISCUSSION**

321 This is the first study to provide evidence for adverse association between pre-pubertal passive smoke
322 exposure in fathers and impaired lung function trajectories from childhood to middle age in their
323 offspring, prior to their clinical manifestation of COPD (pre-COPD). We found that paternal pre-
324 pubertal smoke exposure was associated with increased odds of developing the Below Average FEV_1
325 and the Early Low-Rapid Decline FEV_1/FVC trajectories for their offspring. These associations were
326 not substantially mediated through active smoking or respiratory illnesses in fathers or offspring.
327 However, the adverse association of the paternal passive smoke exposure on the Below Average FEV_1
328 trajectory in their offspring was augmented by passive smoke exposure during offspring childhood.

329

330 This study extends the scope of intergenerational research by extending the focus from active paternal
331 pre-pubertal smoking to indirectly including active grandparental smoking, exploring its association
332 with long-term lung function from childhood to middle age in the offspring. We are unable to directly
333 compare this study with previous research, because ours is the first to investigate passive smoke
334 exposure before paternal completing puberty on lung function by offspring middle age. However, our
335 findings are in line with studies investigating the association between active pre-pubertal smoking
336 and early-life lung function or asthma. According to the findings from European Community
337 Respiratory Health Survey (ECRHS), which included 274 fathers and their offspring, active paternal

smoking during pre-puberty was associated with reduced FEV_1 levels at a median age of 28 years in their offspring.[17] Some studies have reported evidence of associations between active paternal smoking during pre-puberty and offspring asthma from childhood to adult life.[16,18]

The inheritance of smoking behaviours and/or epigenetic mechanisms may explain the observed associations. This study found wide 95% confidence intervals with high upper bound (>50%) for mediation by some mediators, such as active paternal smoking and offspring passive smoke exposure. Therefore, inheritance of smoking behaviours, could link paternal passive smoke exposure to impaired lung function in offspring. A parental history of active smoking increased the odds of adolescent offspring becoming active smokers by 2.8-fold.[30] Moreover, active smoking is a known risk factor for respiratory illnesses in smokers and their offspring.[31] However, our analysis also suggested that point estimates for mediation by each mediator were modest (<15%). This implied that the remaining association may be a direct effect of paternal pre-pubertal passive smoke exposure on the impaired lung function trajectories of their offspring. A similar direct effect was reported for active paternal smoking during pre-puberty and epigenetics have been proposed as potential mechanisms.[17] Pre-puberty represents a specific vulnerable window for males, during which exposure to harmful substances may induce epigenetic dysregulations of developing sperm cells and modify repair mechanisms through modifications in reactive oxygen species levels in sperm precursors.[32] Such epigenetic modifications may be heritable and result in DNA methylation abnormalities in offspring cord blood,[32] which link to their lung function development.[33]

Our findings indicated that the association between paternal pre-pubertal passive smoke exposure and their offspring risk of having impaired lung function trajectories was augmented in those offspring who experienced additional passive smoke exposure during childhood, and the association was attenuated in the offspring without such childhood exposure. These results are in line with the potentially reversible nature of epigenetic modifications described in humans, with partial reversibility of the methylome after interventions, including exercise and smoking cessation for more than three months.[34,35]

In the rest of the stratified analysis, our results demonstrated pronounced associations in offspring without pneumonia/pleurisy or food allergy during childhood. Given that early-onset pneumonia and food allergy are important contributors to lung function deficits,[8,28] their impact could potentially mask the influence of paternal pre-pubertal passive smoke exposure on offspring lung function. However, the pronounced associations in offspring without these respiratory illnesses suggest that paternal pre-pubertal passive smoke exposure may still be associated with lung function deficits in their offspring.

The major strength of this study was that the TAHS is a longitudinal cohort study with unique lung function data at six waves from ages 7 to 53 years, allowing examination of lung function trajectories. Furthermore, pre-pubertal health has been found to significantly affect future life outcomes.[36,37] Our discoveries advance preventive approaches for addressing lung function deficits in future generations by targeting adverse exposures during their paternal pre-puberty stage. The rich data collected on

active paternal smoking, offspring passive smoke exposure, respiratory illnesses, and active smoking enabled a thorough analysis of potential mediators and effect modifiers. More importantly, our findings are novel as this is the first study to investigate and provide evidence for adverse association of paternal pre-pubertal passive smoke exposure, rather than just active smoking on impaired lung function of offspring by middle age. This is of importance from a public health perspective, as passive smoke exposure affects about 63% of adolescents,[38] which is significantly higher than the approximately 7% affected by active smoking.[39]

This study has some limitations. Fathers with asthma/wheeze might have recall bias regarding pre-pubertal passive smoke exposure, potentially overestimating the associations observed. However, prior studies suggest high consistency between adult offspring and parental reports of parental smoking during offspring childhood.[40] Thus, recall bias was unlikely to have significantly influenced the associations observed. The prevalence of paternal pre-pubertal passive smoke exposure was slightly lower among included fathers than those excluded, likely introducing bias toward the null. Post-bronchodilator lung function was first measured in offspring in their fifth decade, while pre-bronchodilator data from ages 7 to 53 were used to develop lung function trajectories.[8,9] Differences between pre- and post-bronchodilator trajectories warrant further investigation. TAHS lacks data on paternal lung function and genetics, preventing assessment of familial aggregation as a potential mechanism. Offspring childhood passive smoke exposure was defined as at least one parent smoking six days per week. This might have misclassified moderate/light smokers as non-smokers, limiting our ability to detect mediation. Most fathers exposed to pre-pubertal passive smoke had continuous exposure from birth to age 15 years, making it difficult to isolate effects of specific exposure windows.

The use of a TAHS subset might limit the generalisability of findings.

In conclusion, this study revealed that paternal pre-pubertal passive smoke exposure was associated with impaired pre-COPD lung function trajectories across first six decades of their offspring lives, including the Below Average FEV_1 and Early Low-Rapid Decline FEV_1/FVC trajectories. These findings suggest that smoking may adversely affect lung function not only in smokers but also in their children and grandchildren. The association of such paternal exposure was augmented when offspring were also exposed to passive smoke during childhood, highlighting an opportunity for intervention. Fathers exposed to tobacco smoke during pre-puberty may still reduce risk for future generations by avoiding smoking around their children. The weaker associations observed for other impaired lung function trajectories should be interpreted with caution.

Table 1. Characteristics of the offspring and their fathers

	Offspring of fathers (n = 890)
Birthweight (kg), mean (SD)	3.3 (0.6)
Missing, n	194
Height at age 53 years (cm), mean (SD)	170.1 (8.7)
Missing, n	3
Weight at age 53 years (kg), mean (SD)	82.2 (17.1)
Missing, n	3
Sex at birth, male, n (%)	433 (48.7)
Birthplace	
Tasmania, Australia, n (%)	804 (90.7)
Other Australian state or territory, n (%)	45 (5.1)
UK, NZ, SA, Canada or USA, n (%)	28 (3.2)
Other overseas country, n (%)	9 (1.0)
Missing, n	4
Passive smoke exposure by age 7 years, n (%)	500 (56.5)
Missing, n	5
Active smoking by age 53 years, n (%)	436 (49.0)
Missing, n	1
Spirometry-defined COPD at age 53 years*, n (%)	45 (5.1)
	Fathers (n = 890)
Age at baseline when offspring aged 7 years (years), mean (SD)	34.7 (5.3)
Missing, n	12
SEIFA-IRSD (scores), mean (SD)	994.0 (44.0)
Missing, n	94
Pre-pubertal passive smoke exposure, n (%)	611 (68.7)
Active smoking	
Never smoked, n (%)	347 (39.7)
Smoking debuted before age 15 years, n (%)	113 (12.9)
Smoking debuted after age 15 years, n (%)	415 (47.4)
Missing, n	15
Lifetime history of asthma/wheeze, n (%)	147 (16.8)
Missing, n	13

* Spirometry-defined COPD was defined as a post-bronchodilator FEV_1/FVC ratio less than the lower limit of normal at age 53 years.

Kg, kilogram; SD, standard deviation; cm, centimetre; UK, United Kingdom; NZ, New Zealand; SA, South Africa; USA, United States of America; COPD, chronic obstructive pulmonary disease; SEIFA-IRSD, socio-economic indexes for areas - the index of relative socio-economic disadvantage; FEV_1/FVC, ratio of forced expiratory volume in the first second to forced vital capacity.

Table 2. Associations between paternal pre-pubertal passive smoke exposure and FEV_1 trajectories from ages 7 years to 53 years in their offspring

Paternal pre-pubertal passive smoke exposure	**n./total n. (%)***	**Crude model** MOR (95% CI) *p*-value	**Adjusted model 1** aMOR (95% CI) *p*-value	**Adjusted model 2** aMOR (95% CI) *p*-value
	Trajectory: *Average (n = 337)*			
Not exposed	121/253 (47.83)	Base outcome (ref.)		
Exposed	216/564 (38.30)			
	Trajectory: *Early Below Average-Accelerated Decline (n = 37)*			
Not exposed	10/253(3.95)			
Exposed	27/564 (4.79)	1.51 (0.71-3.23) 0.29	1.68 (0.76-3.71) 0.20	1.59 (0.71-3.56) 0.26
	Trajectory: *Early Low-Normal Decline (Persistently Low) (n = 46)*			
Not exposed	12/253 (4.74)			
Exposed	34/564 (6.03)	1.59 (0.79-3.18) 0.19	1.54 (0.74-3.20) 0.25	1.46 (0.69-3.09) 0.32
	Trajectory: *Below Average (n = 233)*			
Not exposed	62/253 (24.51)			
Exposed	171/564 (30.32)	**1.55 (1.07-2.23)** **0.020**	**1.50 (1.02-2.20)** **0.040**	**1.56 (1.05-2.31)** **0.028**
	Trajectory: *Early Low-Catch Up-Normal Decline (Early Low-Accelerated Growth-Normal Decline) (n = 66)*			
Not exposed	21/253 (8.30)			
Exposed	45/564 (7.98)	1.20 (0.68-2.11) 0.53	1.18 (0.66-2.09) 0.57	1.15 (0.63-2.08) 0.65
	Trajectory: *Early High-Normal Decline (Persistently High) (n = 98)*			
Not exposed	27/253 (10.67)			
Exposed	71/564 (12.59)	1.47 (0.90-2.42) 0.13	1.48 (0.86-2.52) 0.16	1.45 (0.84-2.50) 0.18

MORs, aMORs, and *p*-values from multinomial logistic regressions. Statistically significant MORs, aMORs, and *p*-values were reported in bold.

Adjusted model 1: adjustment for SEIFA-IRSD scores of parents.

Adjusted model 2: Model 1 plus further adjustment for paternal lifetime history of asthma/wheeze and paternal age at baseline.

* Numbers of each trajectory in each exposure category.

FEV_1, forced expiratory volume in the first second; aMOR, adjusted multinominal odds ratio; 95% CI, 95% confidence interval; SEIFA-IRSD, socio-economic indexes for areas - the index of relative socio-economic disadvantage.

Table 3. Associations between paternal pre-pubertal passive smoke exposure and FEV_1/FVC trajectories from ages 7 years to 53 years in their offspring

Paternal pre-pubertal passive smoke exposure	**n./total n. (%)***	**Crude model** MOR (95% CI) *p*-value	**Adjusted model 1** aMOR (95% CI) *p*-value	**Adjusted model 2** aMOR (95% CI) *p*-value
	Trajectory: *Average (n = 414)*			
Not exposed	147/253 (58.10)	Base outcome (ref.)		
Exposed	267/563 (47.42)			
	Trajectory: *Early Low-Rapid Decline (n = 53)*			
Not exposed	9/253 (3.56)			
Exposed	44/563 (7.82)	**2.69 (1.28-5.67) 0.009**	**2.42 (1.14-5.14) 0.022**	**2.30 (1.07-4.94) 0.033**
	Trajectory: *Early Normal-Rapid Decline (n = 43)*			
Not exposed	16/253 (6.32)			
Exposed	27/563 (4.80)	0.93 (0.48-1.78) 0.83	0.94 (0.47-1.88) 0.86	0.84 (0.41-1.69) 0.62
	Trajectory: *Early Low-Normal Decline (n = 146)*			
Not exposed	37/253 (14.62)			
Exposed	109/563 (19.36)	**1.62 (1.06-2.48) 0.025**	1.39 (0.90-2.16) 0.14	1.35 (0.86-2.12) 0.19
	Trajectory: *Early Low-Catch Up-Normal Decline (n = 25)*			
Not exposed	5/253 (1.98)			
Exposed	20/563 (3.55)	2.20 (0.81-5.99) 0.12	1.96 (0.71-5.40) 0.19	2.32 (0.76-7.05) 0.14
	Trajectory: *Early High-Normal Decline (n = 135)*			
Not exposed	39/253 (15.42)			
Exposed	96/563 (17.05)	1.36 (0.89-2.07) 0.16	1.24 (0.79-1.94) 0.35	1.22 (0.77-1.92) 0.40

MORs, aMORs, and *p*-values from multinomial logistic regressions. Statistically significant MORs, aMORs, and *p*-values were reported in bold.

Adjusted model 1: adjustment for SEIFA-IRSD scores of parents.

Adjusted model 2: Model 1 plus further adjustment for paternal lifetime history of asthma/wheeze and paternal age at baseline.

* Numbers of each trajectory in each exposure category.

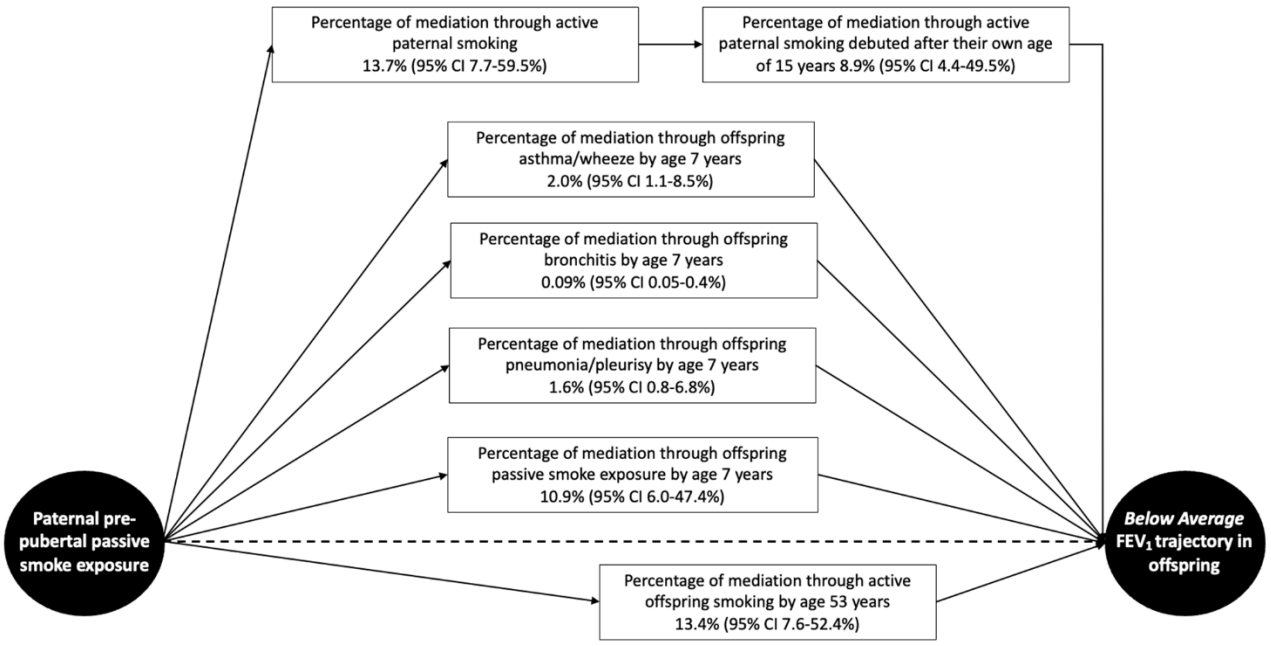
FEV_1/FVC, ratio of forced expiratory volume in the first second to forced vital capacity; aMOR, adjusted multinominal odds ratio; 95% CI, 95% confidence interval; SEIFA-IRSD, socio-economic indexes for areas - the index of relative socio-economic disadvantage.

FEV_1 trajectories	FVC trajectories	FEV_1/FVC trajectories
Average (reference trajectory)	*Average (reference trajectory)*	*Average (reference trajectory)*
Early Below Average-Accelerated Decline	*Early Low-Normal Decline*	*Early Low-Rapid Decline*
Early Low-Normal Decline (Persistently Low)	*Early Low-Catch Up-Normal Decline*	*Early Normal-Rapid Decline*
Below Average	*Early High-Normal Decline*	*Early Low-Normal Decline*
Early Low-Catch Up-Normal Decline (Early Low-Accelerated Growth-Normal Decline)	*Early Very High-Normal Decline*	*Early Low-Catch Up-Normal Decline*
Early High-Normal Decline (Persistently High)		*Early High-Normal Decline*

This figure illustrates the lung function trajectories analysed in the study. Each trajectory was separately derived based on z-scores at offspring ages 7, 13, 18, 45, 50, and 53 years in previous analyses.[8,9]

FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; FEV_1/FVC, ratio of forced expiratory volume in the first second to forced vital capacity.

Figure 1. Illustration of offspring lung function trajectories



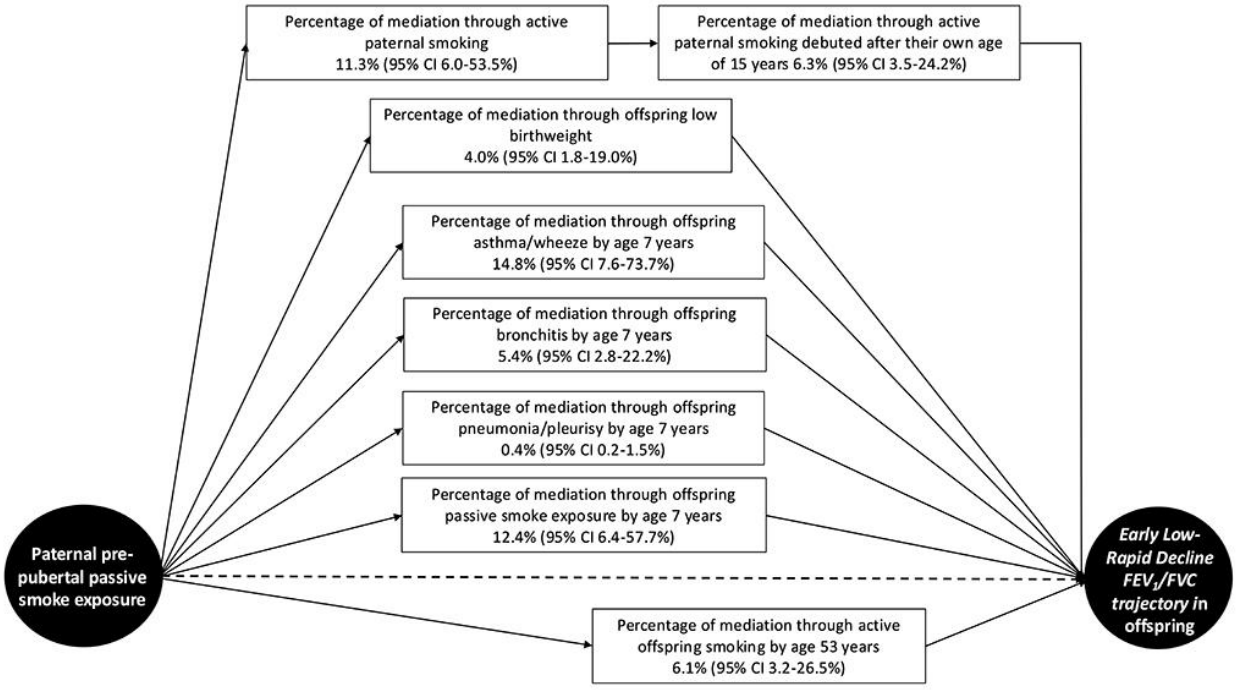
This figure illustrates the percentage of mediation for each mediator, assessed individually using the *medeff* programme.[25,26] A solid unidirectional path represents the indirect effect through a mediator, while a dashed unidirectional path indicates the potential direct effect.

Analyses were adjusted for SEIFA-IRSD scores of parents, paternal lifetime history of asthma/wheeze, and paternal age at baseline.

Analyses were also conducted for active paternal smoking debuted before their own age of 15 years, offspring preterm birth, low birthweight, and food allergy by age 7 years; however, no evidence of mediation was found. Therefore, these variables are not illustrated in this figure.

FEV_1, forced expiratory volume in the first second; 95% CI, 95% confidence interval; SEIFA-IRSD, socio-economic indexes for areas - the index of relative socio-economic disadvantage.

Figure 2. Mediations of the association between paternal pre-pubertal passive smoke exposure and Below Average FEV_1 trajectory from ages 7 years to 53 years in their offspring



This figure illustrates the percentage of mediation for each mediator, assessed individually using the *medeff* programme.[25,26] A solid unidirectional path represents the indirect effect through a mediator, while a dashed unidirectional path indicates the potential direct effect.

Analyses were adjusted for SEIFA-IRSD scores of parents, paternal lifetime history of asthma/wheeze, and paternal age at baseline.

Analyses were also conducted for active paternal smoking debuted before their own age of 15 years, offspring preterm birth, and food allergy by age 7 years; however, no evidence of mediation was found. Therefore, these variables are not illustrated in this figure.

FEV_1/FVC, ratio of forced expiratory volume in the first second to forced vital capacity; 95% CI, 95% confidence interval; SEIFA-IRSD, socio-economic indexes for areas - the index of relative socio-economic disadvantage.

Figure 3. Mediations of the association between paternal pre-pubertal passive smoke exposure and Early Low-Rapid Decline FEV_1/FVC trajectory from ages 7 years to 53 years in their offspring

Contributorship Statement

SCD, PAF, RRW-B, MJA, JLP, and EHW designed the follow-ups of the Tasmanian Longitudinal Health Study since 2000, acquired funding and/or the data. JL conceived and designed this study, analysed and interpreted the data, and prepared the initial draft of the manuscript. JLP, CJL, and DV interpreted the data and modified the manuscript. SCD and DSB co-conceived and co-designed the study, interpreted the data and modified the manuscript, and provided supervision of JL. GB, AJL, NSI, GDM, JWH, and CS modified the manuscript. All authors critically reviewed the manuscript for important intellectual content and approved the final version for submission. SCD is the guarantor of the manuscript.

Funding Statement

This study was based on the Tasmanian Longitudinal Health Study, which was supported by funds from the National Health and Medical Research Council (NHMRC) of Australia under NHMRC project grant scheme (#299901, #454425, #566391, #628513, and #1021275) and NHMRC European collaborative grant scheme (#1101313) as part of ALEC (Ageing Lungs in European Cohorts funded by the European Union's Horizon 2020 research and innovation programme under grant agreement #633212); The University of Melbourne; Clifford Craig Medical Research Trust of Tasmania; the Victorian, Queensland & Tasmanian Asthma Foundations; The Royal Hobart Hospital; Helen MacPherson Smith Trust; and GlaxoSmithKline. No award/grant numbers for these funders. JL is supported by the China Scholarship Council - University of Melbourne PhD Scholarship (File No. 202208240007-1087369). JLP (APP ID: 2026519), CJL (APP ID: 2008019), SCD (APP ID: 1193993), and DSB (APP ID: 2008436) are supported by the NHMRC of Australia. AJL is supported by the Faculty of Medicine, Dentistry and Health Sciences, The University of Melbourne (no award/grant number). The funding sources had no role in the conception, design, or conduct of the study; the acquisition, analysis, or interpretation of the data; the preparation, review, or approval of the manuscript; or the decision to submit it for publication. The corresponding author SCD had full access to all data and had the final responsibility for the decision to submit the manuscript for publication.

Competing of Interests

JLP, CJL, AJL, MJA, and SCD have received an investigator-initiated grant from GlaxoSmithKline (GSK) for unrelated research. JLP and SCD also hold a similar grant from AstraZeneca. AJL has received an investigational product (EpiCeram™) free of charge from Primus Pharmaceuticals for use in unrelated research. AJL and SCD have also received grant funding from Sanofi Regeneron for unrelated research. MJA holds investigator-initiated grants from Pfizer, Boehringer-Ingelheim and Sanofi for unrelated research. He has undertaken an unrelated consultancy for Sanofi and received a speaker's fee from GSK. The rest of the authors declare that they have no conflicts of interest.

Ethics approval

This study was based on the Tasmanian Longitudinal Health Study, which was approved by Human Ethics Review Committees at The Universities of Melbourne (040375), Tasmania (040375.1, H0012710), New South Wales (08094), The Alfred Hospital (1118/04), and Royal Brisbane and Women's Hospital Health Service District (2006/037). Written informed consent was obtained from all participants.

Data sharing

Individual participant data can be provided upon request to anyone with a suitable proposal. The proposal will be reviewed by the steering committee of the Tasmanian Longitudinal Health Study (TAHS). Requests can be directed to Shyamali C. Dharmage, the principal investigator of the TAHS and the corresponding author of this paper. Individual deidentified data for all TAHS participants may be provided.

Acknowledgements

The authors gratefully acknowledge the participants of the Tasmanian Longitudinal Health Study (TAHS). We thank all TAHS investigators for their assistance with obtaining funds and data collection. We acknowledge all the respiratory scientists who collected data in lung function laboratories in

Tasmania, Victoria, Queensland and New South Wales; the research interviewers, data entry operators and research officers. Finally, we thank the Archives Office of Tasmania for providing data from the 1968 TAHS questionnaires.

AI use statement

No AI tools were used in the preparation of this manuscript. However, to improve visual communication, four images in the visual abstract were generated using OpenAI's DALL·E model (GPT-4o), illustrating paternal pre-pubertal passive smoke exposure, offspring childhood passive smoke exposure, lung function testing, and COPD. This disclosure has been included in the visual abstract.

References

1. GBD 2016 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* 2017;390:1345-1422.
2. Viegi G, Maio S, Fasola S, *et al*. Global Burden of Chronic Respiratory Diseases. *J Aerosol Med Pulm Drug Deliv* 2020;33:171-177.
3. Adeloye D, Song P, Zhu Y, *et al*. Global, regional, and national prevalence of, and risk factors for, chronic obstructive pulmonary disease (COPD) in 2019: a systematic review and modelling analysis. *Lancet Respir Med* 2022;10:447-458.
4. Abramson MJ, Koplin J, Hoy R, *et al*. Population-wide preventive interventions for reducing the burden of chronic respiratory disease. *Int J Tuberc Lung Dis* 2015;19:1007-18.
5. Melén E, Faner R, Allinson JP, *et al*. Lung-function trajectories: relevance and implementation in clinical practice. *Lancet* 2024;403:1494-1503.
6. Postma DS, Bush A, van den Berge M. Risk factors and early origins of chronic obstructive pulmonary disease. *Lancet* 2015;385:899-909.
7. Lange P, Celli B, Agustí A, *et al*. Lung-Function Trajectories Leading to Chronic Obstructive Pulmonary Disease. *N Engl J Med* 2015;373:111-22.
8. Bui DS, Lodge CJ, Burgess JA, *et al*. Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life. *Lancet Respir Med* 2018;6:535-544.
9. Dharmage SC, Bui DS, Walters EH, *et al*. Lifetime spirometry patterns of obstruction and restriction, and their risk factors and outcomes: a prospective cohort study. *Lancet Respir Med* 2023;11:273-282.
10. Dharmage SC, Faner R, Agustí A. Treatable traits in pre-COPD: Time to extend the treatable traits paradigm beyond established disease. *Respirology* 2024;29:551-562.
11. Svanes C, Holloway JW, Krauss-Etschmann S. Preconception origins of asthma, allergies and lung function: The influence of previous generations on the respiratory health of our children. *J Intern Med* 2023;293:531-549.
12. Li YF, Langholz B, Salam MT, *et al*. Maternal and grandmaternal smoking patterns are associated with early childhood asthma. *Chest* 2005;127:1232-41.
13. Magnus MC, Håberg SE, Karlstad Ø, *et al*. Grandmother's smoking when pregnant with the mother and asthma in the grandchild: the Norwegian Mother and Child Cohort Study. *Thorax* 2015;70:237-43.
14. Lodge CJ, Bråbäck L, Lowe AJ, *et al*. Grandmaternal smoking increases asthma risk in grandchildren: A nationwide Swedish cohort. *Clin Exp Allergy* 2018;48:167-174.
15. Bråbäck L, Lodge CJ, Lowe AJ, *et al*. Childhood asthma and smoking exposures before conception-A three-generational cohort study. *Pediatr Allergy Immunol* 2018;29:361-368.
16. Svanes C, Koplin J, Skulstad SM, *et al*. Father's environment before conception and asthma risk in his children: a multi-generation analysis of the Respiratory Health In Northern Europe study. *Int J Epidemiol* 2017;46:235-245.
17. Accordini S, Calciano L, Johannessen A, *et al*. Prenatal and prepubertal exposures to tobacco smoke in men may cause lower lung function in future offspring: a three-generation study using a causal modelling approach. *Eur Respir J* 2021;58:2002791.
18. Accordini S, Calciano L, Johannessen A, *et al*. A three-generation study on the association of tobacco smoking with asthma. *Int J Epidemiol* 2018;47:1106-1117.
19. Liu J, Bowatte G, Pham J, *et al*. Pre-pubertal smoke exposure of fathers and increased risk of offspring asthma: a possible transgenerational effect. *Eur Respir J* 2022;60:2200257.

20. Matheson MC, Abramson MJ, Allen K, *et al*. Cohort Profile: The Tasmanian Longitudinal Health STUDY (TAHS). *Int J Epidemiol* 2017;46:407-408i.
21. Miller MR, Hankinson J, Brusasco V, *et al*. Standardisation of spirometry. *Eur Respir J* 2005;26:319-38.
22. Textor J, van der Zander B, Gilthorpe MS, *et al*. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. *Int J Epidemiol* 2016;45:1887-1894.
23. Willis-Owen SAG, Cookson WOC, Moffatt MF. The Genetics and Genomics of Asthma. *Annu Rev Genomics Hum Genet* 2018;19:223-246.
24. Sheather SA. A modern approach to regression with R. New York: Springer; 2009.
25. Imai K, Keele L, Tingley D. A general approach to causal mediation analysis. *Psychol Methods* 2010;15:309-34.
26. Hicks R, Tingley D. Causal Mediation Analysis. *The Stata Journal* 2011;11:605–619.
27. Kohler U, Karlson KB, Holm A. Comparing Coefficients of Nested Nonlinear Probability Models. *The Stata Journal* 2011;11:420–438.
28. Peters RL, Soriano VX, Lycett K, *et al*. Infant food allergy phenotypes and association with lung function deficits and asthma at age 6 years: a population-based, prospective cohort study in Australia. *Lancet Child Adolesc Health* 2023;7:636-647.
29. VanderWeele TJ, Knol MJ. A Tutorial on Interaction. *Epidemiol. Methods* 2014;3:33–72.
30. Gilman SE, Rende R, Boergers J, *et al*. Parental smoking and adolescent smoking initiation: an intergenerational perspective on tobacco control. *Pediatrics* 2009;123:e274-81.
31. Agache I, Ricci-Cabello I, Canelo-Aybar C, *et al*. The impact of exposure to tobacco smoke and e-cigarettes on asthma-related outcomes: Systematic review informing the EAACI guidelines on environmental science for allergic diseases and asthma. *Allergy* 2024;79:2346-2365.
32. Soubry A, Hoyo C, Jirtle RL, *et al*. A paternal environmental legacy: evidence for epigenetic inheritance through the male germ line. *Bioessays* 2014;36:359-71.
33. Mukherjee N, Arathimos R, Chen S, *et al*. DNA methylation at birth is associated with lung function development until age 26 years. *Eur Respir J* 2021;57:2003505.
34. Denham J, O'Brien BJ, Harvey JT, *et al*. Genome-wide sperm DNA methylation changes after 3 months of exercise training in humans. *Epigenomics* 2015;7:717-31.
35. Tsaprouni LG, Yang TP, Bell J, *et al*. Cigarette smoking reduces DNA methylation levels at multiple genomic loci but the effect is partially reversible upon cessation. *Epigenetics* 2014;9:1382-96.
36. Hannon E, Anselimus SM, Bardikoff N, *et al*. Why cities matter for adolescent mental health and wellbeing. *Lancet* 2024;403:708-710.
37. Zhang Y, Qi H, Hu C, *et al*. Association between early life famine exposure and risk of metabolic syndrome in later life. *J Diabetes* 2022;14:685-694.
38. Ma C, Heiland EG, Li Z, *et al*. Global trends in the prevalence of secondhand smoke exposure among adolescents aged 12-16 years from 1999 to 2018: an analysis of repeated cross-sectional surveys. *Lancet Glob Health* 2021;9:e1667-e1678.
39. Hammer B, Kadalayil L, Boateng E, *et al*. Preconceptional smoking alters spermatozoal miRNAs of murine fathers and affects offspring's body weight. *Int J Obes (Lond)* 2021;45:1623-1627.
40. Pape K, Svanes C, Malinovschi A, *et al*. Agreement of offspring-reported parental smoking status: the RHINESSA generation study. *BMC Public Health* 2019;19:94.

Supplementary Material

Paternal pre-pubertal passive smoke exposure is related to impaired lung function trajectories from childhood to middle age in their offspring

Jiacheng Liu, Jennifer L. Perret, Caroline J. Lodge, Don Vicendese, Gayan Bowatte, Adrian J. Lowe, N. Sabrina Idrose, Peter A. Frith, Richard R. Wood-Baker, Gita D. Mishra, John W. Holloway, Cecilie Svanes, Michael J. Abramson, E. Haydn Walters, Shyamali C. Dharmage, and Dinh S. Bui

Correspondence to: Professor Shyamali C. Dharmage. Allergy and Lung Health Unit, Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, The University of Melbourne, Melbourne, Australia (email: s.dharmage@unimelb.edu.au).

Table of Contents

Supplementary Methods

Methods S1. Identification of minimum set of potential confounders

The Directed Acyclic Graph (DAG) illustrated the hypothesised causal relationships between variables, which we used to guide the identification of minimum set of potential confounders in the analyses.[1] Variables and their potential associations (depicted by an arrow) included in the DAG model were based on prior (expert) knowledge and existing literature. The following DAG model (figure S1) for this analysis was developed using DAGitty v3.0 software.[1] Multicollinearity between variables was subsequently assessed for the regression models.

According to the following DAG model, the socio-economic status of paternal grandparents (labelled as "PGP_social_class") was represented by a pink circle with a pink border, indicating that it was identified as a potential confounder of the association between the exposure (paternal pre-pubertal passive smoke exposure) and the primary outcomes (offspring impaired lung function trajectories from ages 7 to 53 years). Although the socio-economic status of paternal grandparents was not measured in the Tasmanian Longitudinal Health Study (TAHS), adjusting for paternal socio-economic status (labelled as "P_social_class"; represented by a white circle with a black border) could block potential biasing pathways. The socio-economic indexes for area - the index of relative socio-economic disadvantage (SEIFA-IRSD) score was then adjusted for as a proxy for paternal socio-economic status in this analysis. The use of SEIFA-IRSD scores was preferred because it was independently developed by the Australian Bureau of Statistics (ABS) and included a wide range of variables comprehensively representing socio-economic status, such as income, educational level, employment, occupation, housing and family structure.[2,3] Unlike the data we collected in the TAHS, which might reflect only specific aspects of socio-economic status, such as occupation or educational level, SEIFA-IRSD scores provided a broader measure of social and economic disadvantage. This made SEIFA-IRSD score possibly a more reliable measure of socio-economic status.

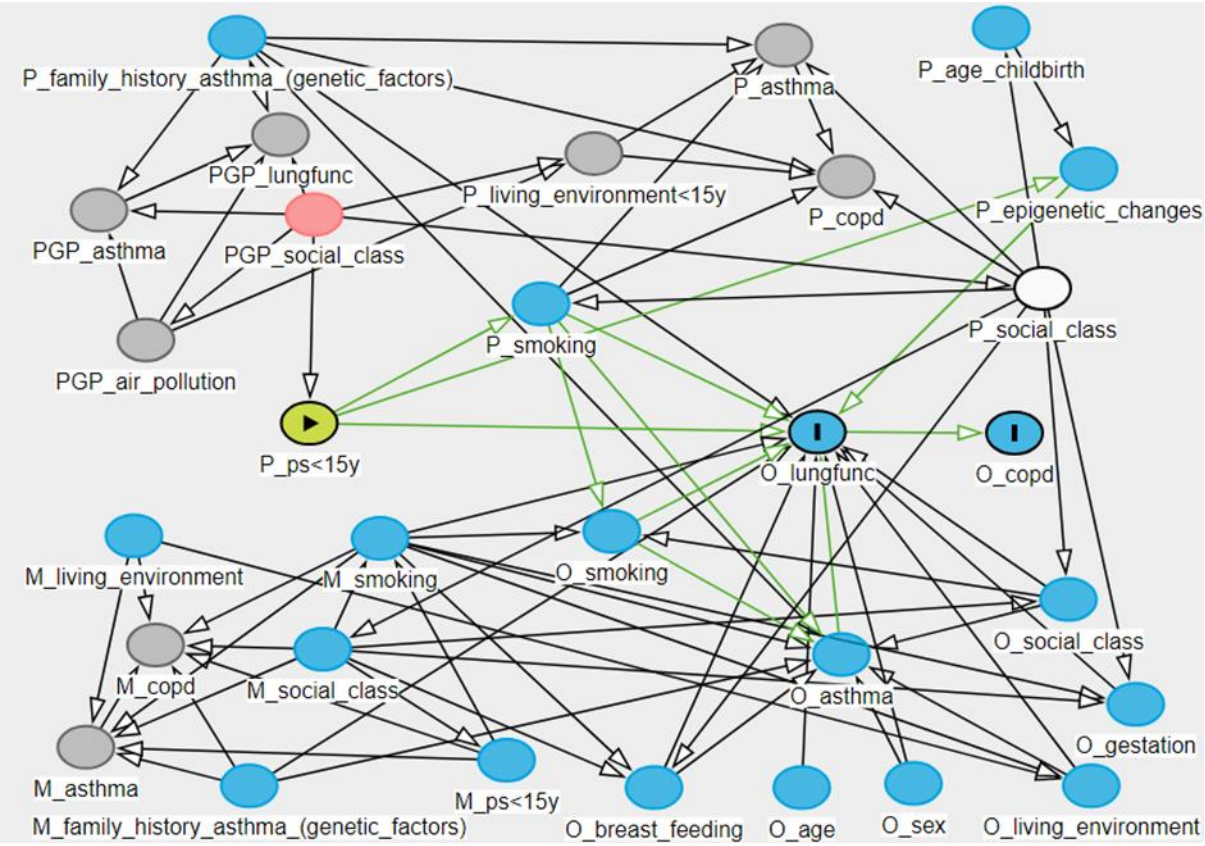


Figure S1. DAG for minimum set of potential confounders in the father-offspring pairs

Legends: A variable represented by a green circle with a black border, containing a black triangle: the exposure of interest in this analysis; A variable represented by a blue circle with a black border, containing the "I": the outcome of interest in this analysis; A variable represented by a blue circle with a blue border: an ancestor of outcome; A variable represented by a pink circle with a pink border: an ancestor of both exposure and outcome; A variable represented by a white circle with a black border: an variable adjusted in the analysis to block biasing pathway(s); A variable represented by a grey circle with a grey border: other variable; A path represented by a green line with an unidirectional arrow: a causal path.

P_family_history_asthma_(genetic_factors), family history of genetic factors of asthma and impaired lung function in the paternal ancestors; PGP_lungfunc, impaired lung function of paternal grandparents; PGP_asthma, history of asthma of paternal grandparents; PGP_social_class, socio-economic status of paternal grandparents; PGP_air_pollution, air pollution exposure of paternal grandparents; P_ps<15y, paternal pre-pubertal passive smoke exposure; P_smoking, active paternal smoking; P_living_environment<15y, paternal pre-pubertal living environment; P_asthma, paternal asthma; P_copd, paternal COPD; P_age_childbirth, paternal age at childbirth; P_epigenetic_changes, paternal epigenetic changes in sperm precursor cells due to pre-pubertal passive smoke exposure; P_social_class, paternal socio-economic status; M_family_history_asthma_(genetic_factors), family history of genetic factors of asthma and impaired lung function in the maternal ancestors; M_ps<15, maternal pre-pubertal passive smoke exposure; M_asthma, maternal asthma; M_copd, maternal COPD; M_social_class, maternal socio-economic status; M_living_environment, maternal living environment; M_smoking, active maternal smoking; O_lungfunc, offspring impaired lung function trajectory; O_copd, offspring COPD; O_smoking, active offspring smoking; O_social_class, offspring socio-economic status; O_asthma, offspring asthma; O_gestation, offspring gestational age; O_breastfeeding, offspring breast feeding status; O_age, offspring age; O_sex, offspring sex at birth; O_living_environment, offspring living environment.

Methods S2. Development of SEIFA-IRSD scores

The initial socio-economic indexes for area - the index of relative socio-economic disadvantage (SEIFA-IRSD) scores were derived by Australian Bureau of Statistics (ABS) in 1986, summarising socio-economic conditions of the residents in a particular area based on their income, educational level, employment, occupation, housing and family structure.[2,3] A lower SEIFA-IRSD score represents disadvantaged socio-economic status.

In the analysis, the probands (denoted as "offspring" in this paper) of the TAHS were assigned an IRSD based on their postcode provided in their survey. As the survey dates do not align exactly with the ABS Census dates, where the SEIFA data used to calculate IRSD was generated, the closest available Census data was used. Where the SEIFA data had more than one IRSD assigned for the same postcode, a weighted IRSD was calculated proportional to the population in each sub-postcode.

1. **SEIFA Data extracted from ABS website:**
    a. 2011 data: https://www.abs.gov.au/websitedbs/censushome.nsf/home/seifa

    b. 1986, 1991,1996, 2001, 2006, 2001 data: https://www.abs.gov.au/websitedbs/censushome.nsf/home/seifapast?opendocument&navpos=260

    c. 2016 Data available here but not extracted as no surveys to be matched to
2. **Prepare SEIFA data for merging into the TAHS data:**
    a. For each year relevant, rename variables to standard names:
        i. SEIFA_IRSD_YYYY
        ii. SEIFA_IRSAD_YYYY
        iii. Postcode
        iv. Pop
    b. As postcodes have been split into multiple areas (i.e. multiple lines (sub-postcodes) & SEIFA values for the same postcode) for the years 1986 – 1996, a weighted SEIFA score was allocated to each postcode, by:
        i. Calculating the total postcode population by summing all the populations in rows with the same postcode
        ii. Calculating the weighted SEIFA value for a sub-postcode

iii. Summing all the weighted sub-postcode SEIFA values together to get the overall SEIFA value for the postcode.

Example of SEIFA weighted variable creation:

Creating weighted SEIFA values

postcode	population	SEIFA	population proportion	weighted SEIFA	postcode SEIFA
3000	10,000	1,000	0.333	333.3333	1,200
3000	10,000	1,200	0.333	400.0000	1,200
3000	10,000	1,400	0.333	466.6667	1,200
3001	5,000	500	0.2	100	900
3001	20,000	1,000	0.8	800	900

Deduplicate to:

postcode	SEIFA_IRSD_YYYY
3000	1200
3001	900

3. **Merge in SEIFA values to the TAHS dataset**
    a. The created SEIFA variables from each year's ABS are merged into the existing the TAHS data using the closest postcode possible.

Methods S3. Sensitivity analysis using multiple imputation

To assess the potential influence of missing data in confounders, a sensitivity analysis was conducted using multiple imputation by chained equations (MICE) under the missing-at-random (MAR) assumption. The proportion of missing data in the fully adjusted models was relatively low (up to ~11%), making imputation appropriate. The following methodological considerations were applied in line with guidance by White *et al*.[4]:

1. For reproducibility, we used a number of imputations approximately equal to the fraction of missing information × 100. For our data (~11% missing), this yielded 11 imputations, which we conservatively increased to 20.

2. To avoid inflating standard errors, the primary outcomes, offspring impaired lung function trajectories, were not imputed. Furthermore, these trajectories were derived from observed spirometric z-scores across multiple follow-ups.[5,6] If no lung function was recorded, no trajectory could be constructed. Given this structure and the reliance on observed data for valid trajectory derivation, imputation was not appropriate.

3. The exposure variable, paternal pre-pubertal passive smoke exposure, had missingness due to "don't know" responses. This reflects recall limitations rather than MAR conditional on observed data. Therefore, imputation in such cases was considered inappropriate.

4. Continuous confounders, SEIFA-IRSD scores and paternal age at baseline, were imputed using linear regression models. Due to the right skew, paternal age was log-transformed prior to imputation to better approximate normality. After imputation, the variable was back-transformed to the original scale for use in the multinomial logistic regressions.

5. The binary variable, paternal lifetime asthma/wheeze, was imputed using the logistic regression model.

6. Estimates and standard errors were combined across imputations using Rubin's Rules.[7]

Confounder	Total (n)	Complete data (n)	Incomplete data (n)
SEIFA-IRSD scores of parents	890	796	94 (10.6%)
Paternal lifetime history of asthma/wheeze	890	877	13 (1.5%)
Paternal age at baseline	890	878	12 (1.3%)

SEIFA-IRSD, socio-economic indexes for areas - the index of relative socio-economic disadvantage.

Methods S4. Questionnaire definitions of variables

Variables	Questions	Participants responded to the questions (*Survey*)
	Paternal variables	
Age at baseline when offspring aged 7 years	"Age ☐☐"	Fathers self-reported (*1968 TAHS questionnaire_Baseline study*)
Pre-pubertal passive smoke exposure (i.e. passive smoke exposure before age 15 years)	"Did your father smoke... When you were less than 5 years? o No o Yes o Don't know When you were aged 5-15 years? o No o Yes o Don't know" "Did your mother smoke... When you were less than 5 years? o No o Yes o Don't know When you were aged 5-15 years? o No o Yes o Don't know" *Definition in this analysis:* • No (i.e. four negative responses were provided regarding passive smoke exposure from their own parents) • Yes (i.e. an affirmative answer to passive smoke exposure during any one of these periods to either of their own parents)	Fathers self-reported (*2010 TAHS Parents Postal Survey*)
Active smoking	"In your lifetime, have you smoked at least 100 cigarettes or equal amount of cigars, pipes, or any other tobacco product? o No o Yes" "How old were you when you started smoking? ☐☐ (age in years)" *Definition in this analysis:* • Never smoked • Smoking debuted before age 15 years • Smoking debuted after age 15 years	Same as above

Lifetime history of asthma/wheeze	"Have you, at any time in your life, suffered from attacks of asthma or wheezy breathing (Regard asthma and wheezy breathing as being much the same for this question.)? o No o Yes"	Same as above
Offspring variables		
Gestational age	"How long were you pregnant before delivery of this child (in weeks)? ☐☐ "	Parents reported (*2010 TAHS Parents Postal Survey*)
Preterm birth	"How long were you pregnant before delivery of this child (in weeks)? ☐☐ " *Definition in this analysis:* • Term birth (i.e. gestational age of at least 37 weeks) • Preterm birth (i.e. gestational age of less than 37 weeks) Term birth was defined as a gestational age of at least 37 weeks. Preterm birth was defined as a gestational age of less than 37 weeks.[6]	Same as above
Birthweight	"What was this child's birth weight? ☐☐"	Same as above
Low birthweight	"What was this child's birth weight? ☐☐" *Definition in this analysis:* • Normal birthweight (i.e. at least 2.5 kg) • Low birthweight (i.e. less than 2.5 kg) Normal birthweight was defined as a birth weight of at least 2.5 kg. Low birthweight was defined as a birth weight of less than 2.5 kg.[6]	Same as above
Birthplace	"Where was he/she born? o Tasmania o Other Australian State o United Kingdom, New Zealand, South Africa, Canada, United States of America o Other overseas country Please name ☐☐"	Parents reported (*1968 TAHS questionnaire_Baseline study*)
Passive smoke exposure by age 7 years (i.e. passive smoke exposure during childhood)	"Do you smoke every day (or six days out of seven)? o No o Yes" *Definition in this analysis:* • No (i.e. neither the father nor the mother smoked every day [or six days out of seven] when the offspring was 7 years old) • Yes (i.e. at least one parent smoked every day [or six days out of seven] when the offspring was 7 years old)	Same as above

Asthma/wheeze by age 7 years (i.e. childhood asthma/wheeze)	"Has he/she at any time in his/her life suffered from attacks of asthma or of wheezy breathing? Note: Please regard 'asthma' and 'wheezy breathing' as being much the same thing for this survey; we do not ask you to try to tell the difference. o No o Yes"	Same as above
Bronchitis by age 7 years (i.e. childhood bronchitis)	"Has he/she at any time in his/her life suffered from attacks of bronchitis or attacks of cough with sputum (phlegm) in the chest ("loose" or "rattly" cough)? Note: Please regard 'bronchitis', 'cough with sputum (phlegm) in the chest' and 'loose or rattly cough' as being much the same thing for this survey; we do not ask you to try to tell the difference. o No o Yes"	Same as above
Food allergy by age 7 years (i.e. childhood food allergy)	"Have you been told by a doctor that he/she is allergic to any foods or medicines? o No o Yes"	Same as above
Pneumonia/pleurisy by age 7 years (i.e. childhood pneumonia/pleurisy)	"Have you ever been told by a doctor that he/she had pneumonia or pleurisy? o No, Never o Yes, Once or twice o Yes, More than twice" *Definition in this analysis:* • No (i.e. never) • Yes (i.e. once or twice or more than twice)	Same as above
Active smoking by age 53 years (i.e. active offspring smoking by middle age)	"In your lifetime, have you smoked at least 100 cigarettes or equal amounts of cigarettes? o No o Yes"	Offspring self-reported (*2012-2016 TAHS Men's Questionnaire_ 6th decade study & 2012-2016 TAHS Women's Questionnaire_ 6th decade study*)
Asthma/wheeze by age 53 years (i.e. offspring asthma/wheeze by middle age)	"Have you, at anytime in your life, suffered from attacks of asthma of wheezy breathing? (Regard asthma and wheezy breathing as being much the same thing for this question.) o No o Yes"	Same as above

TAHS, the Tasmanian Longitudinal Health Study.

Supplementary Tables and Figures

Table S1. Comparison of the characteristics of the offspring and their fathers included and excluded in this analysis

	Offspring of fathers in this analysis	Offspring of fathers excluded	*p*-value*
Birthweight (kg), mean (SD)	3.3 (0.6)	3.3 (0.6)	0.14
Height at age 53 years (cm), mean (SD)	170.1 (8.7)	169.8 (10.3)	0.42
Weight at age 53 years (kg), mean (SD)	82.2 (17.1)	82.6 (18.2)	0.52
Sex at birth, male, n (%)	433 (48.7)	3,960 (51.5)	0.11
Birthplace			
Tasmania, Australia, n (%)	804 (90.7)	6,720 (90.4)	0.58
Other Australian state or territory, n (%)	45 (5.1)	446 (6.0)	
UK, NZ, SA, Canada or USA, n (%)	28 (3.2)	214 (2.9)	
Other overseas country, n (%)	9 (1.0)	57 (0.8)	
Passive smoke exposure by age 7 years, n (%)	500 (56.5)	5,035 (72.1)	**< 0.001**
Active smoking by age 53 years, n (%)	436 (49.0)	1,601 (59.0)	**< 0.001**
Spirometry-defined COPD at age 53 years†, n (%)	45 (5.1)	94 (5.3)	0.81
	Fathers in this analysis	Fathers excluded	*p*-value*
Age at baseline when offspring aged 7 years (years), mean (SD)	34.7 (5.3)	37.2 (7.1)	**< 0.001**
SEIFA-IRSD (scores), mean (SD)	994.0 (44.0)	989.9 (45.5)	**0.016**
Pre-pubertal passive smoke exposure, n (%)	611 (68.7)	702 (72.8)	0.053
Active smoking			
Never smoked, n (%)	347 (39.7)	428 (37.5)	0.41
Smoking debuted before age 15 years, n (%)	113 (12.9)	168 (14.7)	
Smoking debuted after age 15 years, n (%)	415 (47.4)	546 (47.8)	
Lifetime history of asthma/wheeze, n (%)	147 (16.8)	210 (18.0)	0.46

Chi-squared tests were performed for categorical variables to compare included and excluded father-offspring pairs (i.e. offspring sex at birth, birthplace, passive smoke exposure by age 7 years, active smoking by age 53 years, spirometry-defined COPD at age 53 years, paternal pre-pubertal passive smoke exposure, active paternal smoking, and paternal lifetime history of asthma/wheeze).

T-tests were performed for continuous variables to compare included and excluded father-offspring pairs (i.e. offspring birthweight, height at age 53 years, weight at age 53 years, paternal age at baseline when offspring aged 7 years, and SEIFA-IRSD scores of parents).

The percentages of birthplace among the offspring of fathers excluded from this analysis do not sum to 100.0% because of rounding.

* *P*-values between the offspring or their fathers included in this analysis and the rest of TAHS with the corresponding data. Statistically significant *p*-values were reported in bold.

† Spirometry-defined COPD was defined as a post-bronchodilator FEV_1/FVC ratio less than the lower limit of normal at age 53 years.

Kg, kilogram; SD, standard deviation; cm, centimetre; UK, United Kingdom; NZ, New Zealand; SA, South Africa; USA, United States of America; COPD, chronic obstructive pulmonary disease; SEIFA-IRSD, socio-economic indexes for areas - the index of relative socio-economic disadvantage; TAHS, the Tasmanian Longitudinal Health Study; FEV_1/FVC, ratio of forced expiratory volume in the first second to forced vital capacity.

Table S2. Associations between paternal pre-pubertal passive smoke exposure and FVC trajectories from ages 7 years to 53 years in their offspring

Paternal pre-pubertal passive smoke exposure	**n./total n. (%)***	**Crude model** MOR (95% CI) *p*-value	**Adjusted model 1** aMOR (95% CI) *p*-value	**Adjusted model 2** aMOR (95% CI) *p*-value
	Trajectory: *Average (n = 484)*			
Not exposed	151/264 (57.20)	Base outcome (ref.)		
Exposed	333/583 (57.12)			
	Trajectory: *Early Low-Normal Decline (n = 120)*			
Not exposed	35/264 (13.26)			
Exposed	85/583 (14.58)	1.10 (0.71-1.71) 0.67	1.14 (0.72-1.80) 0.59	1.18 (0.74-1.90) 0.49
	Trajectory: *Early Low-Catch Up-Normal Decline (n = 21)*			
Not exposed	9/264 (3.41)			
Exposed	12/583 (2.06)	0.60 (0.25-1.47) 0.27	0.71 (0.28-1.78) 0.47	0.75 (0.29-1.98) 0.56
	Trajectory: *Early High-Normal Decline (n = 205)*			
Not exposed	63/264 (23.86)			
Exposed	142/583 (24.36)	1.02 (0.72-1.46) 0.90	1.02 (0.70-1.49) 0.92	0.99 (0.67-1.45) 0.94
	Trajectory: *Early Very High-Normal Decline (n = 17)*			
Not exposed	6/264 (2.27)			
Exposed	11/583 (1.89)	0.83 (0.30-2.29) 0.72	0.84 (0.31-2.33) 0.74	0.85 (0.30-2.39) 0.76

MORs, aMORs, and *p*-values from multinomial logistic regressions.

Adjusted model 1: adjustment for SEIFA-IRSD scores of parents.

Adjusted model 2: Model 1 plus further adjustment for paternal lifetime history of asthma/wheeze and paternal age at baseline.

* Numbers of each trajectory in each exposure category.

FVC, forced vital capacity; aMOR, adjusted multinominal odds ratio; 95% CI, 95% confidence interval; SEIFA-IRSD, socio-economic indexes for areas - the index of relative socio-economic disadvantage.

Table S3. Associations between paternal pre-pubertal passive smoke exposure and spirometry-defined COPD at age 53 years in their offspring

Paternal pre-pubertal passive smoke exposure	**Cases/total (%)**	**Crude model** OR (95% CI) *p*-value	**Adjusted model 1** aOR (95% CI) *p*-value	**Adjusted model 2** aOR (95% CI) *p*-value
	Spirometry-defined COPD*			
Not exposed	8/279 (2.87)	1	1	1
Exposed	37/611 (6.06)	**2.18 (1.00-4.75) 0.049**	2.09 (0.95-4.57) 0.066	2.06 (0.93-4.55) 0.073

ORs, aORs, and *p*-values from logistic regressions. Statistically significant OR and *p*-value were reported in bold.

Adjusted model 1: adjustment for SEIFA-IRSD scores of parents.

Adjusted model 2: Model 1 plus further adjustment for paternal lifetime history of asthma/wheeze and paternal age at baseline.

* Spirometry-defined COPD was defined as a post-bronchodilator FEV_1/FVC ratio less than the lower limit of normal at age 53 years.

COPD, chronic obstructive pulmonary disease; aOR, adjusted odds ratio; 95% CI, 95% confidence interval; SEIFA-IRSD, socio-economic indexes for areas - the index of relative socio-economic disadvantage; FEV_1/FVC, ratio of the forced expiratory volume in the first second to the forced vital capacity.

Table S4. Interactions between paternal pre-pubertal passive smoke exposure and potential effect modifiers

Outcomes	FEV_1 trajectories in offspring	FEV_1/FVC trajectories in offspring
Potential effect modifiers	*p*-value for interaction*	
Active paternal smoking (never smoked/smoking debuted before age 15 years/smoking debuted after age 15 years)	0.35	0.20
Offspring sex at birth (male/female)	0.28	0.44
Offspring asthma/wheeze by age 7 years (no/yes)	0.85	0.70
Offspring bronchitis by age 7 years (no/yes)	0.98	0.69
Offspring food allergy by age 7 years (no/yes)	0.60	**0.071**
Offspring pneumonia/pleurisy by age 7 years (no/yes)	**0.008**	0.98
Offspring passive smoke exposure by age 7 years (no/yes)	**0.053**	0.43
Active offspring smoking by age 53 years (no/yes)	0.19	0.33

P-values from likelihood ratio tests. Statistically significant *p*-values were reported in bold.

* Analyses were adjusted for SEIFA-IRSD scores of parents, paternal lifetime history of asthma/wheeze, and paternal age at baseline.

FEV_1, forced expiratory volume in the first second; FEV_1/FVC, ratio of forced expiratory volume in the first second to forced vital capacity; SEIFA-IRSD, socio-economic indexes for areas - the index of relative socio-economic disadvantage.

Table S5. Associations between paternal pre-pubertal passive smoke exposure and FEV_1 trajectories from ages 7 years to 53 years in their offspring, stratified by offspring passive smoke exposure by age 7 years

Paternal pre-pubertal passive smoke exposure	**n./total n. (%)***	**Adjusted model** aMOR (95% CI) *p*-value	**n./total n. (%)***	**Adjusted model** aMOR (95% CI) *p*-value
	Interaction for the overall model p = **0.053**			
	Stratum 1: offspring *without* exposure to passive smoke by age 7 years (n = 352)		Stratum 2: offspring *with* exposure to passive smoke by age 7 years (n = 462)	
	Trajectory: *Average (n = 161)*		Trajectory: *Average (n = 174)*	
Not exposed	60/127 (47.24)	Base outcome (ref.)	60/125 (48.00)	Base outcome (ref.)
Exposed	101/225 (44.89)		114/337 (33.83)	
	Trajectory: *Early Below Average-Accelerated Decline (n = 14)*		Trajectory: *Early Below Average-Accelerated Decline (n = 23)*	
Not exposed	2/127 (1.57)		8/125(6.40)	
Exposed	12/225 (5.33)	3.26 (0.70-15.28) 0.13	15/337 (4.45)	1.05 (0.39-2.83) 0.92
	Trajectory: *Early Low-Normal Decline (Persistently Low) (n = 16)*		Trajectory: *Early Low-Normal Decline (Persistently Low) (n = 30)*	
Not exposed	5/127 (3.94)		7/125 (5.60)	
Exposed	11/225 (4.89)	0.85 (0.25-2.86) 0.79	23/337 (6.82)	1.91 (0.71-5.11) 0.20
	Trajectory: *Below Average (n = 93)*		Trajectory: *Below Average (n = 140)*	
Not exposed	34/127 (26.77)		28/125 (22.40)	
Exposed	59/225 (26.22)	0.90 (0.51-1.60) 0.73	112/337 (33.23)	**2.36 (1.34-4.13) 0.003**
	Trajectory: *Early Low-Catch Up-Normal Decline (Early Low-Accelerated Growth-Normal Decline) (n = 38)*		Trajectory: *Early Low-Catch Up-Normal Decline (Early Low-Accelerated Growth-Normal Decline) (n = 28)*	
Not exposed	15/127 (11.81)		6/125 (4.80)	
Exposed	23/225 (10.22)	0.83 (0.38-1.80) 0.64	22/337 (6.53)	1.83 (0.68-4.89) 0.23
	Trajectory: *Early High-Normal Decline (Persistently High) (n = 30)*		Trajectory: *Early High-Normal Decline (Persistently High) (n = 67)*	
Not exposed	11/127 (8.66)		16/125 (12.80)	
Exposed	19/225 (8.44)	0.85 (0.34-2.15) 0.73	51/337 (15.13)	1.77 (0.88-3.55) 0.11

The *p*-value for interaction in the overall model from a likelihood ratio test. aMORs and corresponding *p*-values from multinomial logistic regressions. Statistically significant aMOR and corresponding *p*-value were reported in bold.

Adjusted model: adjustment for SEIFA-IRSD scores of parents, paternal lifetime history of asthma/wheeze, and paternal age at baseline.

* Numbers of each trajectory in each exposure category.

FEV_1, forced expiratory volume in the first second; aMOR, adjusted multinominal odds ratio; 95% CI, 95% confidence interval; SEIFA-IRSD, socio-economic indexes for areas - the index of relative socio-economic disadvantage.

Table S6. Associations between paternal pre-pubertal passive smoke exposure and FEV_1 trajectories from ages 7 years to 53 years in their offspring, stratified by offspring pneumonia/pleurisy by age 7 years

Paternal pre-pubertal passive smoke exposure	**n./total n. (%)***	**Adjusted model** aMOR (95% CI) *p*-value	**n./total n. (%)***	**Adjusted model** aMOR (95% CI) *p*-value
	Interaction for the overall model p = **0.008**			
	Stratum 1: offspring *without* pneumonia/pleurisy by age 7 years (n = 696)		Stratum 2: offspring *with* pneumonia/pleurisy by age 7 years (n = 115)	
	Trajectory: *Average (n = 292)*		Trajectory: *Average (n = 42)*	
Not exposed	112/220 (50.91)	Base outcome (ref.)	8/31 (25.81)	Base outcome (ref.)
Exposed	180/476 (37.82)		34/84 (40.48)	
	Trajectory: *Early Below Average-Accelerated Decline (n = 30)*		Trajectory: *Early Below Average-Accelerated Decline (n = 6)*	
Not exposed	9/220 (4.09)		0/31 (0.00)	
Exposed	21/476 (4.41)	1.53 (0.64-3.64) 0.34	6/84 (7.14)	NA
	Trajectory: *Early Low-Normal Decline (Persistently Low) (n = 43)*		Trajectory: *Early Low-Normal Decline (Persistently Low) (n = 3)*	
Not exposed	11/220 (5.00)		1/31 (3.23)	
Exposed	32/476 (6.72)	1.60 (0.73-3.53) 0.24	2/84 (2.38)	0.42 (0.03-5.81) 0.52
	Trajectory: *Below Average (n = 187)*		Trajectory: *Below Average (n = 45)*	
Not exposed	47/220 (21.36)		15/31 (48.39)	
Exposed	140/476 (29.41)	**1.96 (1.26-3.04) 0.003**	30/84 (35.71)	0.38 (0.13-1.15) 0.087
	Trajectory: *Early Low-Catch Up-Normal Decline (Early Low-Accelerated Growth-Normal Decline) (n = 61)*		Trajectory: *Early Low-Catch Up-Normal Decline (Early Low-Accelerated Growth-Normal Decline) (n = 5)*	
Not exposed	18/220 (8.18)		3/31 (9.68)	
Exposed	43/476 (9.03)	1.44 (0.76-2.70) 0.26	2/84 (2.38)	0.09 (0.008-1.07) 0.057
	Trajectory: *Early High-Normal Decline (Persistently High) (n = 83)*		Trajectory: *Early High-Normal Decline (Persistently High) (n = 14)*	
Not exposed	23/220 (10.45)		4/31 (12.90)	
Exposed	60/476 (12.61)	1.65 (0.91-2.99) 0.10	10/84 (11.90)	0.58 (0.13-2.64) 0.48

The *p*-value for interaction in the overall model from a likelihood ratio test. aMORs and corresponding *p*-values from multinomial logistic regressions. Statistically significant aMOR and corresponding *p*-value were reported in bold.

Adjusted model: adjustment for SEIFA-IRSD scores of parents, paternal lifetime history of asthma/wheeze, and paternal age at baseline.

* Numbers of each trajectory in each exposure category.

FEV_1, forced expiratory volume in the first second; aMOR, adjusted multinominal odds ratio; 95% CI, 95% confidence interval; NA, results were not available due to no observation in "not exposed" group; SEIFA-IRSD, socio-economic indexes for areas - the index of relative socio-economic disadvantage.

Table S7. Associations between paternal pre-pubertal passive smoke exposure and FEV_1/FVC trajectories from ages 7 years to 53 years in their offspring, stratified by offspring food allergy by age 7 years

Paternal pre-pubertal passive smoke exposure	**n./total n. (%)***	**Adjusted model** aMOR (95% CI) *p*-value	**n./total n. (%)***	**Adjusted model** aMOR (95% CI) *p*-value
	Interaction for the overall model p = **0.071**			
	Stratum 1: offspring *without* food allergy by age 7 years (n = 748)		Stratum 2: offspring *with* food allergy by age 7 years (n = 67)	
	Trajectory: *Average (n = 378)*		Trajectory: *Average (n = 36)*	
Not exposed	134/228 (58.77)	Base outcome (ref.)	13/25 (52.00)	Base outcome (ref.)
Exposed	244/520 (46.92)		23/42 (54.76)	
	Trajectory: *Early Low-Rapid Decline (n = 45)*		Trajectory: *Early Low-Rapid Decline (n = 8)*	
Not exposed	5/228 (2.19)		4/25 (16.00)	
Exposed	40/520 (7.69)	**3.85 (1.45-10.19) 0.007**	4/42 (9.52)	0.38 (0.06-2.23) 0.28
	Trajectory: *Early Normal-Rapid Decline (n = 37)*		Trajectory: *Early Normal-Rapid Decline (n = 6)*	
Not exposed	14/228 (6.14)		2/25 (8.00)	
Exposed	23/520 (4.42)	0.77 (0.36-1.66) 0.51	4/42 (9.52)	1.61 (0.23-11.28) 0.63
	Trajectory: *Early Low-Normal Decline (n = 138)*		Trajectory: *Early Low-Normal Decline (n = 7)*	
Not exposed	36/228 (15.79)		1/25 (4.00)	
Exposed	102/520 (19.62)	1.24 (0.79-1.97) 0.35	6/42 (14.29)	NA
	Trajectory: *Early Low-Catch Up-Normal Decline (n = 24)*		Trajectory: *Early Low-Catch Up-Normal Decline (n = 1)*	
Not exposed	4/228 (1.75)		1/25 (4.00)	
Exposed	20/520 (3.85)	2.30 (0.75-7.02) 0.15	0/42 (0.00)	NA
	Trajectory: *Early High-Normal Decline (n = 126)*		Trajectory: *Early High-Normal Decline (n = 9)*	
Not exposed	35/228 (15.35)		4/25 (16.00)	
Exposed	91/520 (17.50)	1.28 (0.79-2.08) 0.31	5/42 (11.90)	0.75 (0.16-3.58) 0.72

The *p*-value for interaction in the overall model from a likelihood ratio test. aMORs and corresponding *p*-values from multinomial logistic regressions. Statistically significant aMOR and corresponding *p*-value were reported in bold.

Adjusted model: adjustment for SEIFA-IRSD scores of parents, paternal lifetime history of asthma/wheeze, and paternal age at baseline.

* Numbers of each trajectory in each exposure category.

FEV_1/FVC, ratio of forced expiratory volume in the first second to forced vital capacity; aMOR, adjusted multinominal odds ratio; 95% CI, 95% confidence interval; NA, results were not available due to limited observations; SEIFA-IRSD, socio-economic indexes for areas - the index of relative socio-economic disadvantage.

Table S8. Associations between paternal pre-pubertal passive smoke exposure and FEV_1 trajectories from ages 7 years to 53 years in their offspring, excluding offspring who reported a history of asthma/wheeze by age 53 years

Paternal pre-pubertal passive smoke exposure	**n./total n. (%)***	**Crude model** MOR (95% CI) *p*-value	**Adjusted model 1** aMOR (95% CI) *p*-value	**Adjusted model 2** aMOR (95% CI) *p*-value
	Trajectory: *Average (n = 226)*			
Not exposed	84/163 (51.53)	Base outcome (ref.)		
Exposed	142/351 (40.46)			
	Trajectory: *Early Below Average-Accelerated Decline (n = 8)*			
Not exposed	4/163 (2.45)			
Exposed	4/351 (1.14)	0.59 (0.14-2.43) 0.47	0.58 (0.14-2.43) 0.46	0.59 (0.14-2.47) 0.47
	Trajectory: *Early Low-Normal Decline (Persistently Low) (n = 21)*			
Not exposed	7/163 (4.29)			
Exposed	14/351 (3.99)	1.18 (0.46-3.05) 0.73	1.19 (0.43-3.32) 0.74	1.06 (0.37-3.07) 0.91
	Trajectory: *Below Average (n = 142)*			
Not exposed	34/163 (20.86)			
Exposed	108/351 (30.77)	**1.88 (1.17-3.01)** **0.009**	**1.91 (1.16-3.14)** **0.011**	**2.07 (1.24-3.46)** **0.005**
	Trajectory: *Early Low-Catch Up-Normal Decline (Early Low-Accelerated Growth-Normal Decline) (n = 50)*			
Not exposed	15/163 (9.20)			
Exposed	35/351 (9.97)	1.38 (0.71-2.68) 0.34	1.38 (0.70-2.71) 0.35	1.26 (0.63-2.51) 0.51
	Trajectory: *Early High-Normal Decline (Persistently High) (n = 67)*			
Not exposed	19/163 (11.66)			
Exposed	48/351 (13.68)	1.49 (0.82-2.71) 0.19	1.72 (0.89-3.31) 0.11	1.67 (0.86-3.24) 0.13

MORs, aMORs, and *p*-values from multinomial logistic regressions. Statistically significant MORs, aMORs, and *p*-values were reported in bold.

Adjusted model 1: adjustment for SEIFA-IRSD scores of parents.

Adjusted model 2: Model 1 plus further adjustment for paternal lifetime history of asthma/wheeze and paternal age at baseline.

* Numbers of each trajectory in each exposure category.

FEV_1, forced expiratory volume in the first second; aMOR, adjusted multinominal odds ratio; 95% CI, 95% confidence interval; SEIFA-IRSD, socio-economic indexes for areas - the index of relative socio-economic disadvantage.

Table S9. Associations between paternal pre-pubertal passive smoke exposure and FEV_1/FVC trajectories from ages 7 years to 53 years in their offspring, excluding offspring who reported a history of asthma/wheeze by age 53 years

Paternal pre-pubertal passive smoke exposure	**n./total n. (%)***	**Crude model** MOR (95% CI) *p*-value	**Adjusted model 1** aMOR (95% CI) *p*-value	**Adjusted model 2** aMOR (95% CI) *p*-value
	Trajectory: *Average (n = 280)*			
Not exposed	100/163 (61.35)	Base outcome (ref.)		
Exposed	180/350 (51.43)			
	Trajectory: *Early Low-Rapid Decline (n = 15)*			
Not exposed	2/163 (1.23)			
Exposed	13/350 (3.71)	3.61 (0.80-16.32) 0.095	2.83 (0.61-13.11) 0.18	2.42 (0.51-11.43) 0.27
	Trajectory: *Early Normal-Rapid Decline (n = 20)*			
Not exposed	7/163 (4.29)			
Exposed	13/350 (3.71)	1.03 (0.40-2.67) 0.95	1.04 (0.38-2.88) 0.94	0.88 (0.31-2.51) 0.82
	Trajectory: *Early Low-Normal Decline (n = 83)*			
Not exposed	22/163 (13.50)			
Exposed	61/350 (17.43)	1.54 (0.89-2.66) 0.12	1.24 (0.70-2.18) 0.46	1.16 (0.65-2.06) 0.62
	Trajectory: *Early Low-Catch Up-Normal Decline (n = 14)*			
Not exposed	3/163 (1.84)			
Exposed	11/350 (3.14)	2.04 (0.56-7.47) 0.28	1.67 (0.44-6.33) 0.45	1.67 (0.44-6.37) 0.46
	Trajectory: *Early High-Normal Decline (n = 101)*			
Not exposed	29/163 (17.79)			
Exposed	72/350 (20.57)	1.38 (0.84-2.26) 0.20	1.42 (0.84-2.39) 0.19	1.37 (0.80-2.34) 0.26

MORs, aMORs, and *p*-values from multinomial logistic regressions.

Adjusted model 1: adjustment for SEIFA-IRSD scores of parents.

Adjusted model 2: Model 1 plus further adjustment for paternal lifetime history of asthma/wheeze and paternal age at baseline.

* Numbers of each trajectory in each exposure category.

FEV_1/FVC, ratio of forced expiratory volume in the first second to forced vital capacity; aMOR, adjusted multinominal odds ratio; 95% CI, 95% confidence interval; SEIFA-IRSD, socio-economic indexes for areas - the index of relative socio-economic disadvantage.

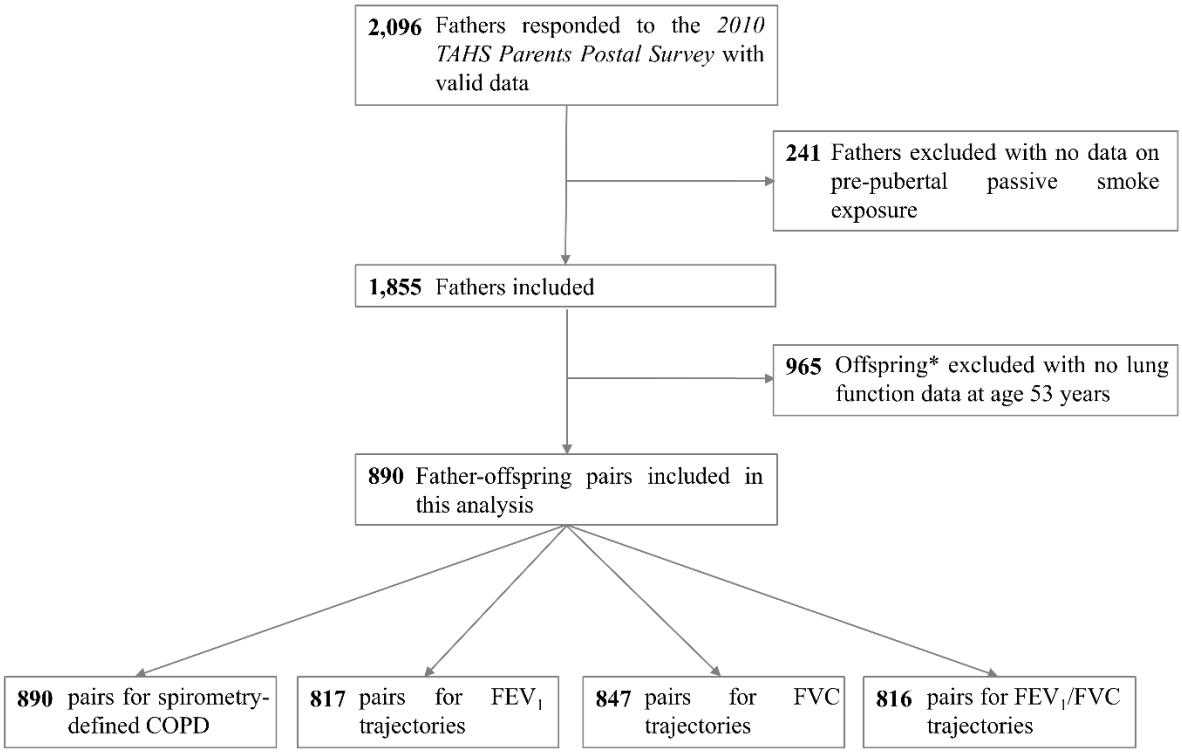
Table S10. Comparison of adjusted associations from unimputed and imputed data

Association	Crude model MOR (95% CI) *p*-value	Unimputed adjusted model aMOR (95% CI) *p*-value	Imputed adjusted model aMOR (95% CI) *p*-value
Between paternal pre-pubertal passive smoke exposure and the *Below Average* FEV_1 trajectories in their offspring	**1.55 (1.07-2.23)** **0.020**	**1.56 (1.05-2.31)** **0.028**	**1.56 (1.08-2.27)** **0.018**
Between paternal pre-pubertal passive smoke exposure and the *Early Low-Rapid Decline* FEV_1/FVC trajectories in their offspring	**2.69 (1.28-5.67)** **0.009**	**2.30 (1.07-4.94)** **0.033**	**2.64 (1.24-5.60)** **0.011**

MORs, aMORs, and *p*-values from multinomial logistic regressions. Associations from the crude models, the unimputed (complete-case) adjusted models, and the imputed (multiple imputation) adjusted models are presented. Statistically significant MORs, aMORs, and *p*-values were reported in bold.

Adjusted model: adjustment for SEIFA-IRSD scores of parents, paternal lifetime history of asthma/wheeze, and paternal age at baseline.

FEV_1, forced expiratory volume in the first second; FEV_1/FVC, ratio of forced expiratory volume in the first second to forced vital capacity; aMOR, adjusted multinominal odds ratio; 95% CI, 95% confidence interval; SEIFA-IRSD, socio-economic indexes for areas - the index of relative socio-economic disadvantage.



* The offspring in this analysis were the probands in the Tasmanian Longitudinal Health Study (TAHS).

COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; FEV_1/FVC, ratio of forced expiratory volume in the first second to forced vital capacity.

Figure S2. Illustration of sample selection

References

1. Textor J, van der Zander B, Gilthorpe MS, *et al*. Robust causal inference using directed acyclic graphs: the R package 'dagitty'. *Int J Epidemiol* 2016;45:1887-1894.
2. Moad D, Tapley A, Fielding A, *et al*. Socioeconomic status of practice location and Australian GP registrars' training: a cross-sectional analysis. *BMC Med Educ* 2022;22:285.
3. Maher S, Kabir A, Behary J, *et al*. New South Wales data linkage study reveals a shift in HCC mortality risk: Time for broader strategies. *Cancer Epidemiol* 2024;93:102690.
4. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Stat Med* 2011;30:377-99.
5. Bui DS, Lodge CJ, Burgess JA, *et al*. Childhood predictors of lung function trajectories and future COPD risk: a prospective cohort study from the first to the sixth decade of life. *Lancet Respir Med* 2018;6:535-544.
6. Dharmage SC, Bui DS, Walters EH, *et al*. Lifetime spirometry patterns of obstruction and restriction, and their risk factors and outcomes: a prospective cohort study. *Lancet Respir Med* 2023;11:273-282.
7. Rubin DB. Multiple imputation for nonresponse in surveys. New York: John Wiley & Sons; 1987.

Paternal pre-pubertal passive smoke exposure is related to impaired lung function trajectories from childhood to middle age in their offspring

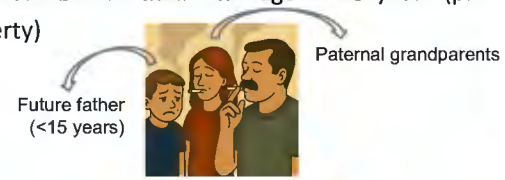
Liu J, *et al*. *Thorax* 2025. DOI: 10.1136/thorax-2024-222482

Methods

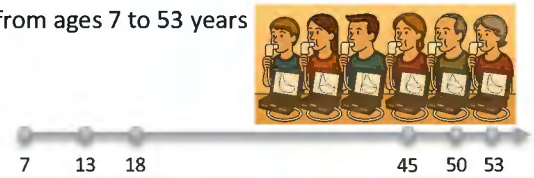
Participants: 890 father-offspring pairs from the Tasmanian Longitudinal Health Study (TAHS)

TAHS
Tasmanian Longitudinal Health Study

Exposure: Paternal passive (second-hand) smoke exposure before their own age of 15 years (pre-puberty)



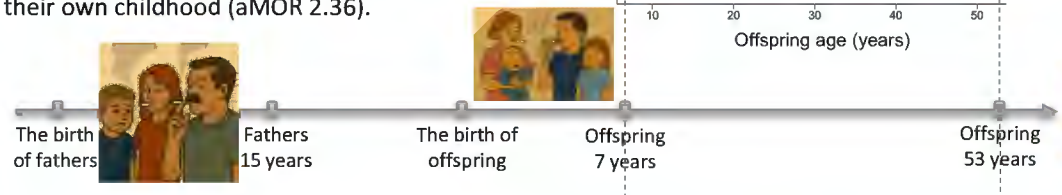
Primary outcomes: Offspring impaired lung function trajectories (FEV_1, FVC and FEV_1/FVC) from ages 7 to 53 years



Findings

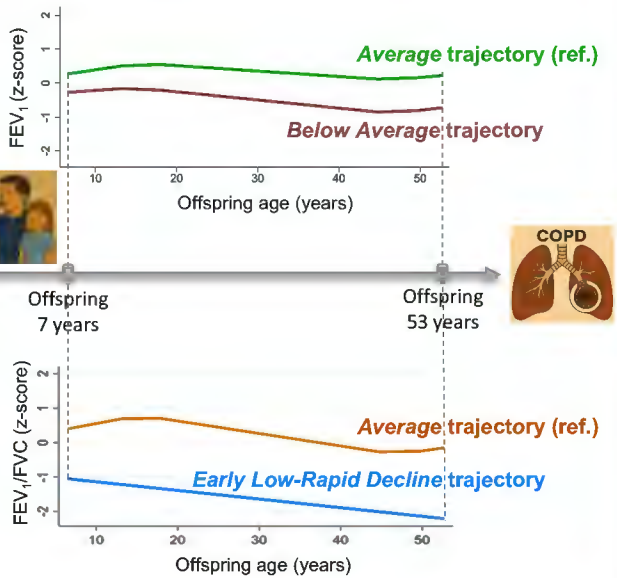
Paternal pre-pubertal passive smoke exposure was associated with the ***Below Average*** FEV_1 trajectory in their offspring (aMOR 1.56).

This association was stronger among offspring who were also exposed to passive smoke during their own childhood (aMOR 2.36).



Paternal pre-pubertal passive smoke exposure was associated with the ***Early Low-Rapid Decline*** FEV_1/FVC trajectory in their offspring (aMOR 2.30).

Lung function trajectories overtime in offspring



aMOR, adjusted multinominal odds ratio.

Four images in this visual abstract were conceptualised by Liu J. and generated using OpenAI's DALL·E model (GPT-4o), illustrating paternal pre-pubertal passive smoke exposure, offspring passive smoke exposure during childhood, lung function testing, and COPD.

Conclusion

These findings highlight potential intergenerational links between passive smoke exposure and impaired lung function trajectories at risk of COPD.