

1 Childhood predictors and adult COPD risk of lung function trajectories: a prospective
2 cohort study from the first to the sixth decade
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46 **Panel: Research in context**

47 **Evidence before this study**

48 While there is evidence that accelerated lung function decline is associated with COPD development,
49 the relationship between the full expression of lung function, encompassing an individual's lifetime
50 trajectory capturing both growth and decline, and COPD, has never been reported. We searched for
51 articles in PubMed up to July 28, 2017 using the search terms: "lung function", "growth", "decline",
52 "pattern*" and "trajector*". From 266 identified papers, only two classified lung function
53 trajectories based on more than 2 repeated lung function measurements. However, one was
54 restricted to participants with childhood asthma and both were unable to capture the lung function
55 decline phase due to duration of the follow-up (maximum age at last measurement being 32 years).
56 Additionally, it is critical to understand how child and adult factors interact to determine
57 membership of healthy as well as adverse lifetime trajectories to inform lifetime preventive
58 strategies and promote lung health. Such evidence does not currently exist.

59 **Added value of this study**

60 Our findings of associations between distinct lung function trajectories and risk of *COPD* provide
61 novel insights into the role of lifetime lung function trajectories in the aetiology of COPD, and show
62 the potential for interventions promoting healthy lung function and lessening COPD risk. Our study is
63 the first to model lung function trajectories from childhood to the sixth decade of life in a general

64 population. We identified six distinct trajectories. Three trajectories exhibiting lower lung function in
65 childhood with subsequent normal or accelerated decline had increased the risk of COPD, and
66 collectively accounted for most COPD cases. Most importantly, moderate/severe COPD cases (GOLD
67 stage 2 or more) arose only from these three trajectories. Early life factors including allergic
68 diseases, lung infections, parental asthma and maternal smoking predicted three unfavourable lung
69 function trajectories. Personal smoking amplified the effect of maternal smoking on belonging to the
70 worst lung function trajectory.

71 **Implications of all the available evidence**

72 Reducing maternal smoke exposure and personal smoking, and encouraging immunization, are
73 identified as public health targets to prevent adverse lung function trajectories and reduce future
74 COPD burden. Clinicians and patients with asthma should be made aware of the potential long-term
75 implications of non-optimal asthma control throughout life, and this should be investigated in future
76 intervention trials.

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81 **SUMMARY**

82 **Background**

83 Lifetime lung function is related to quality of life and longevity. Over the lifespan, individuals follow
84 different lung function trajectories. It is important to identify these trajectories, their determinants
85 and outcomes but no study has done this beyond the fourth decade.

86 **Methods**

87 We modelled trajectories of forced expiratory volume in 1 second (FEV₁) measured at 7, 13, 18, 45,
88 50 and 53 years (n=2438). The trajectories identified were then related to childhood factors and
89 Chronic Obstructive Pulmonary Disease (COPD) risk.

90 **Findings**

91 Six trajectories were identified: “early below average, accelerated decline” (4%, n=97), “persistently
92 low” (5.6%, n=136), “below average” (31.6%, n=772), “persistently high” (12.1%, n=293), “early low,
93 accelerated growth, normal decline” (8%, n=196), and “average” (38.7%, n=944). The first three
94 trajectories had increased risk of COPD at age 53 compared with the average group: OR 35(95%CI
95 19.5-64); 9.5(4.5-20.6); and 3.7(1.9-6.9) respectively. Early-life predictors of the three trajectories
96 included childhood asthma, bronchitis, pneumonia, hayfever, eczema, parental asthma, and
97 maternal smoking. Personal smoking and active adult asthma increased the impact of maternal
98 smoking and childhood asthma respectively on the “early below average, accelerated decline”
99 trajectory.

100 **Interpretation**

101 We identified six potential FEV₁ trajectories, two of which were novel. Three trajectories
102 contributed 75% of COPD burden and were associated with modifiable early-life exposures
103 whose impact was aggravated by adult factors. We postulate that reducing maternal
104 smoking; encouraging immunization; and avoiding personal smoking, especially in those

105 with smoking parents and/or low childhood lung function, may minimize COPD risk.
106 Clinicians and asthmatic patients should be made aware of the potential long-term
107 implications of non-optimal asthma control for lung function trajectory throughout life, and
108 this should be investigated in future intervention trials.

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113 Trust; and GlaxoSmithKline.

114 **INTRODUCTION**

115 Lifetime lung function is related to quality of life and longevity. Recent studies highlight that low lung
116 function, especially low forced expiratory volume in 1 second (FEV₁) in early adulthood is associated
117 with incidence of respiratory, cardiovascular, and metabolic abnormalities, and all-cause mortality.^{1,2}
118 Over the lifespan, lung function progresses through different growth and decline phases^{3,4} and
119 individuals have unique lifetime lung function trajectories based on these phases. Trajectories may
120 have different risk factors and different consequences for chronic lung disease risk, particularly
121 chronic obstructive pulmonary disease (COPD), the expected third largest cause of death globally by
122 2030.⁵ Insights into how lung function trajectories develop over the lifespan are important for lung
123 disease prediction, prevention and management.

124 Repeated lung function measurements from childhood into late adulthood are needed to identify
125 lifetime lung function trajectories but data are sparse. Among the few studies with longitudinal lung
126 function measurements, only two studies^{6,7} have published lung function trajectories based on more
127 than two time points, one being restricted to subjects with childhood asthma.⁷ However, both were
128 unable to capture the decline phase, vital for lung health outcomes in later life, as they had data only
129 to the fourth decade. While there is evidence that both maximally attained FEV₁ and its decline are
130 associated with the COPD development⁸, the relationship between the full expression of lung
131 function, encompassing an individual's trajectory capturing both growth and decline, and COPD, has
132 never been reported. Furthermore, it is critical to understand how childhood and adult factors
133 interact to determine membership of healthy as well as adverse lifetime trajectories.

134 Despite inter-individual variation in lung function trajectories within a general population, there may
135 be distinct subpopulations following similar FEV₁ trajectories. The Tasmanian Longitudinal Health
136 Study (TAHS), a population-based cohort study with multiple assessments of lung function, provided
137 an opportunity to investigate lung function trajectories into the sixth decade. We aimed to: (1)
138 characterize population FEV₁ trajectories from the first to the sixth decade; (2) investigate their

139 childhood predictors and interaction with adult asthma and personal smoking; (3) relate trajectories
140 to COPD risk.

141 **METHODS**

142 **Study design and data collection**

143 Six waves of TAHS⁹ were used. TAHS began in 1968 when 8,583 Tasmanian children born in 1961 and
144 attending school in Tasmania were enrolled. At age 7 (baseline), the children underwent a clinical
145 examination including pre-bronchodilator (BD) spirometry and parents completed a questionnaire.
146 Follow-up assessments were conducted at 13, 18, 45 and 50 years with pre-BD spirometry
147 measured. In the most recent follow-up in 2015, when the participants were 53 years old, all those
148 from the original cohort who were alive and had up-to-date contact details were invited to attend a
149 clinical study. Pre- and post-BD spirometry were performed in 2,689 participants. Those with at least
150 two waves of lung function data at age 7 and 53 comprised the study population (n=2438) (see
151 supplement).

152 **Lung function measurements**

153 Pre- and post-BD spirometry was conducted according to the American Thoracic Society and
154 European Respiratory Society joint guidelines.¹⁰ Spirometry z-scores were derived from the Global
155 Lung Initiative (GLI) reference equations¹¹ which have been validated in an Australian population.¹²

156 **Definition of variables (see supplement)**

157 Childhood factors (asthma, bronchitis, eczema, hayfever, food allergy, pneumonia, breast feeding,
158 weight status, parental asthma and parental smoking) were defined using the information provided
159 by parents in 1968. COPD was defined as post-BD FEV₁/FVC < Lower Limit of Normal (LLN) at 53 years.
160 Other adulthood factors were defined using information provided by participants at age 53 years.

161 **Statistical analysis**

162 *Identification of lung function trajectories*

163 Pre-BD FEV₁ z-scores at six time points (7, 13, 18, 45, 50 and 53 years) were analysed using group-
164 based trajectory modelling (GBTM) to identify distinct subgroups of individuals whose
165 measurements followed a similar pattern over time.¹³ GBTM estimated the population prevalence of
166 each lung function trajectory subgroup, and the posterior probability of each individual belonging to
167 each subgroup. Parameter values determining models with an increasing number of trajectories
168 were derived using maximum likelihood estimation to determine the best fitting model (see
169 Supplement).^{14,15} This method allows handling of missing data for each individual, and produces
170 asymptotically unbiased parameter estimates. As well as model fit, interpretation of trajectories was
171 also considered in the selection of the final model. Assignment of a single trajectory subgroup to
172 each individual was based on the modal method (the highest posterior probability for that
173 individual).

174 *Investigating factors associated with identified lung function trajectories*

175 We first examined the association between each childhood predictor and the six-category trajectory
176 variable using multinomial logistic regression. Childhood predictors were retained based on a 5
177 degree-of-freedom likelihood ratio test. Then we employed two modelling approaches in parallel: In
178 the first, we used logistic regression to investigate associations between each childhood predictor
179 and lung function trajectories, where each trajectory was compared with the “average” trajectory -
180 the “non-disease” group. For each childhood predictor, a specific minimal sufficient set of potential
181 confounders was selected based on causal diagrams (Directed Acyclic Graphs [DAGs]).¹⁶ Interactions
182 between parental and personal smoking, childhood asthma and adult active asthma were tested.
183 Using the likelihood ratio test, an interaction term with p-value < 0.1 was retained in the final model.
184 For comparison, we used a second approach in which all childhood predictors with a p-value < 0.15,
185 computed using likelihood ratio test, were included in a single multivariable multinomial logistic
186 regression model adjusted simultaneously for all childhood predictors. The results of these two
187 approaches were almost similar, thus only results for the first were presented. Associations between

188 lung function trajectories as a predictor and COPD at 53 years were investigated using logistic
189 regression; in case of groups with sparse data (for COPD cases), penalized maximum likelihood
190 logistic regression was used to reduce bias in estimates of regression coefficients.¹⁷ Population-
191 attributable fractions of COPD were estimated for trajectories.¹⁸ All analyses were performed using
192 Stata 13.0 (Stata Corp, College Station, TX, USA) with a GBTM plug-in.¹⁵

193 **Ethics**

194 The study was approved by the Human Ethics Review Committees of all relevant institutions. Written
195 informed consent was obtained from all participants.

196 **Role of the funding source**

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

200 **RESULTS**

201 **Baseline characteristics of participants**

202 Of 8583 participants from the original cohort, 2438 with longitudinal lung function data were analysed.
203 The participants included had similar baseline characteristics to those not included except for more
204 females and more eczema, and fewer smoking parents (Table S1 in supplement). Those included and
205 those deceased by 53 years also had similar baseline characteristics (Table S2).

206 **Lung function trajectories**

207 The best fitting model identified six lung function trajectories (Figure 1). The average membership
208 probability of individuals in each trajectory exceeded 0.7, suggesting good model adequacy.¹⁹ Based
209 on lung function at age 7 years and growth and decline rates, trajectories were given the following
210 labels: “average” (38.7%; n=944), “early below average, accelerated decline” (4%; n=97), “persistently

211 low" (5.6%; n=136), "early low, accelerated growth, normal decline" (8.0%; n=196), "persistently high"
212 (12.0%; n=293), and "below average" (31.6%; n=772) (see supplement). The "average" trajectory had
213 lung function consistently around the population mean over time. The means of the raw values of
214 FEV₁ at six time points among trajectories are presented in Figure S1. In a sensitivity analysis, exclusion
215 of the data point with the smallest number of observations (at 18 years) yielded six very similar lung
216 function trajectories (Figure S2).

217 **Childhood factors and lung function trajectories**

218 Prevalence of childhood factors among lung function trajectories are shown in Table 1. Adjusted
219 associations between these factors and lung function trajectories compared to the average
220 trajectory are presented (Table 2). Individuals with the "early below average, accelerated decline"
221 trajectory were more likely to have childhood asthma (OR 3.1: 95%CI 1.9-5.2), bronchitis (2.0: 1.2-
222 3.2), hayfever (2.0: 1.2-3.4), pneumonia (2.0: 1.2-3.5), and a heavy smoking mother (2.5: 1.1-5.9).
223 The "persistently low" trajectory was associated with childhood asthma (OR 1.7: 95%CI 1.2-2.7),
224 particularly frequent asthma symptoms (4.2: 2.2-7.8) and early asthma onset (2.0:1.1-3.4), eczema
225 (1.8: 1.1-3.0), and parental asthma (1.8: 1.1-2.9). A modest association was seen between this
226 trajectory and food allergy (1.8: 0.94-3.4), and childhood underweight (2.2:0.95-5.2). There were
227 synergistic effects between childhood asthma and eczema (p=0.07) and hayfever (p=0.06).
228 Participants with childhood asthma, eczema and hayfever had a 4.9 (1.9-12) fold risk increase for the
229 "persistently low" trajectory.

230 Having the "below average" trajectory was associated with childhood pneumonia (OR 1.3: 95%CI
231 1.0-1.8). The effects of the childhood factors on the three trajectories listed above were
232 independent of adult personal smoking.

233 Females and underweight children were more likely to have an "early low, accelerated growth,
234 normal decline" trajectory (OR 1.7: 95%CI 1.2-2.3 and 2.6:1.3-5.2, respectively). The effect of

235 underweight on this trajectory became non-significant when weight gain between 7-11 years was
236 added to the model (OR 2.0:0.9-4.5).

237 No significant associations were observed between childhood factors and the “persistently high”
238 trajectory.

239 **The interactions of adult asthma and smoking with childhood factors, and lung function** 240 **trajectories**

241 The prevalences of adult active asthma and personal smoking are presented in Table 3. Adult active
242 asthma and personal smoking were independently associated with three trajectories: “early below
243 average, accelerated decline”, “below average” and “persistently low” (Table S3).

244 We observed a significant interaction between heavy maternal smoking and personal smoking
245 defined using pack-years ($p < 0.001$) for the risk of belonging to the “early below average, accelerated
246 decline” trajectory. The adverse impact of maternal smoking increased with increasing personal
247 smoking (Figure S3).

248 There was evidence of interaction between childhood asthma and adult active asthma for the risk of
249 the “early below average, accelerated decline” trajectory ($p = 0.08$) with the effect of childhood
250 asthma mainly evident in participants with adult active asthma.

251 **Lung function trajectories (based on pre-BD FEV1) and COPD (based on post-BD measures) at 53** 252 **years**

253 At 53 years, those in the “early below average, accelerated decline” trajectory had the highest
254 prevalence of COPD (46%), followed by the “persistently low” trajectory (12.5%) and the “below
255 average” trajectory (6%) (Figure 2). Compared with the “average” trajectory, these three trajectories
256 had 35 (95%CI 19.5-64), 9.5 (4.5-20.6), and 3.7 (1.9-6.9) fold increased risk of COPD respectively
257 (Table S4). The distribution of COPD cases among trajectories is presented in Figure S4. The

258 population-attributable fractions for the three trajectories “early below average, accelerated
259 decline”, “persistently low”, and “below average” in relation to COPD were 35·4%, 12·6% and 27·2%,
260 respectively. For moderate/severe COPD (an addition of $FEV_1 < 80\%$ predicted values), all cases only
261 arose from three trajectories, “early below average, accelerated decline”, “below average” and
262 “persistently low”.

263 We replicated the analysis by defining COPD using the $FEV_1/FVC < 0.7$ and findings were not
264 materially different to those using LLN (table S5). We found similar results using a clinical definition
265 of COPD (see supplement) (Table S6).

266 **DISCUSSION**

267 Our study is unique in that it is the first to characterize lung function trajectories in a large general
268 population sample from early childhood to the sixth decade. This is of considerable importance
269 because understanding lifetime lung function is crucial for population-based interventions to
270 promote advantaged trajectories and prevent disadvantaged ones. We identified six distinct FEV_1
271 trajectories including two novel trajectories, namely, “early below average, accelerated decline” and
272 “early low, accelerated growth, normal decline”. These two trajectories contradict the notion that
273 lung function established in childhood tracks through life. Three of the six trajectories had increased
274 risk of developing COPD by middle-age, namely, “early below average, accelerated decline”, “below
275 average”, and “persistently low”. Seventy-five percent of COPD cases at 53 years was attributable to
276 these three trajectories. Most importantly, moderate/severe COPD cases arose only from these
277 three trajectories. Childhood asthma, bronchitis, pneumonia, hayfever, eczema, parental asthma
278 and maternal smoking during childhood increased the risk of these three trajectories. We showed
279 that aggravation of the impact of childhood risk factors by adult personal smoking and active asthma
280 lead to our newly established “early below average, accelerated decline” trajectory.

281 To date only two published studies^{6,7} have identified lung function trajectories. Both were unable to
282 incorporate the adult decline phase, as they had data only into early adulthood. McGeachie and

283 colleagues⁷ described four FEV₁ trajectories from age 7 to 26 years in 684 asthmatics. This study
284 provided novel insights into how lung function changed over time in asthmatics, but cannot be
285 compared with our population-based results. Furthermore, we used an unsupervised modelling
286 method, which facilitates capture of distinct groups with similar trajectories. The population-based
287 Tucson Children's Respiratory Study⁶ modelled lung function from 11 to 32 years in 599 participants
288 identifying only a persistently low and a normal trajectory. The reasons they identified fewer
289 trajectories than our analysis may include smaller sample size and shorter follow-up.

290 Using similar statistical methodology to ours, a study from two population-based birth cohorts
291 (MAAS and ALSPAC) published in this issue of the journal, found four FEV₁trajectories between ages
292 5 and 24 years (persistently high, average, below average and persistently low).²⁰ We also found
293 these trajectories, and identified two further trajectories. Our study's ability to tease out more
294 trajectories may be explained by our larger sample size and follow-up into the decline phase.

295 COPD risk attributed to our identified trajectories provides insight into potential origins of and
296 pathways to COPD. The "below average" and "persistently low" trajectories representing a pathway
297 to COPD with mostly childhood origins contributed half the COPD cases in our study. This was
298 supported by Lange and colleagues⁸ who found half of their participants with COPD had normal
299 adult lung function decline, but lower baseline lung function in early adulthood. Yet our "early below
300 average, accelerated decline" group carried the highest risk of COPD, and although representing only
301 4% of our study sample, contributed substantially to COPD cases (a population-attributable fraction
302 of 35.4%). These findings highlight the importance of preventing both early life adverse exposures
303 that may lead to poorer lung growth and adult risk factors contributing to accelerated decline.²¹⁻²³

304 We believe we are the first to establish the early life factors determining FEV₁ trajectories into the
305 sixth decade. Previous studies have investigated early life factors only on single phases of lung
306 function trajectories i.e. impaired growth²⁴⁻²⁹ or accelerated decline.³⁰⁻³² Maternal smoking, allergic
307 diseases, and pneumonia increased the risk of the "early below average, accelerated decline"

308 trajectory. Interestingly, personal smoking and adult asthma modified the effect of maternal
309 smoking and childhood asthma on being in the “early below average, accelerated decline”
310 trajectory. A similar interaction related to smoking had been identified in other studies examining
311 lung function deficits^{33,34} and decline.³² Together, these findings suggest that maternal smoking not
312 only adversely affected early lung function, but predisposed children to more rapid lung function
313 decline if they later smoked. Expressed another way, personal smoking not only accelerated FEV₁
314 decline but also amplified the impact of early life exposure to tobacco smoke on lung function,
315 possibly by preventing recovery from early acquired deficits.³⁵ Similarly, our findings highlight the
316 potential role of lifelong asthma control in promoting lung health and preventing COPD.

317 Our “persistently low” trajectory was associated with asthma, eczema, food allergy, parental asthma
318 and childhood underweight. Additionally, asthma in combination with either eczema or hayfever had
319 a multiplicative rather than additive effect on the risk of following this trajectory. Consistent with
320 our findings, the MAAS and ALSPAC study (published in this issue of the journal) found that the
321 “persistently low” trajectory was associated with asthma/wheeze and allergic sensitization.²⁰
322 Similarly, Lodrup Carlsen and colleagues reported a persistently impaired lung function pattern from
323 birth to 16 years in asthma with eczema and hayfever.³⁶ These findings suggest that arresting the
324 atopic march, believed to drive these early allergic comorbidities, may help prevent subsequent
325 adverse lung function and COPD. In addition, the association between parental asthma and the
326 “persistently low” trajectory in our study suggests a role for genetic factors as evident in the MAAS
327 and ALSPAC study.¹⁷

328 We found that those with early low lung function tracked as either “persistently low” or “early low,
329 accelerated growth, normal decline”. This split of the early low lung function group is supported by
330 the Perth Infant Asthma Follow-up study (PIAF) published in this issue of the journal.¹⁷ While some
331 infants with poor lung function in the PIAF continued in the low FEV₁ trajectory, the majority had
332 improvement in their lung function through adolescence and moved to the normal or above average
333 FEV₁ trajectories. Our “early low, accelerated growth, normal decline” trajectory may be related to

334 birth weight, given weight “catch-up” was reported in children with low birth weight and those with
335 catch-up growth showed improved lung function.³⁷ We did not have full birth weight information to
336 explore this effect. However, we found that childhood underweight predicted the “early low,
337 accelerated growth, normal decline” and the “persistently low” trajectories. Interestingly, unlike the
338 “persistently low” trajectory, the association between childhood underweight and “early low,
339 accelerated growth, normal decline” trajectory became non-significant when controlled for weight
340 gain between 7 and 11 years. This suggests that childhood underweight followed by accelerated
341 weight gain may be related to accelerated lung growth in this group. Another difference between
342 these trajectories was that the “persistently low” trajectory had more than double the prevalence of
343 persistent childhood asthma. It is possible that while the two trajectories had similar early acquired
344 lung function deficits, persistent asthma prevented the catch-up in the “persistently low” trajectory.

345 Early below average and accelerated decline” trajectory had the highest prevalence and intensity of
346 smoking. Thus, this trajectory resembles the lung function pattern among “susceptible smokers” as
347 originally framed by Fletcher and Peto.³ While the “below average” group had similar lung function
348 to the “early below average, accelerated decline” group up to age 20 years, it had much lower rates
349 of personal smoking, which may have prevented an accelerated decline in lung function. In contrast,
350 the prevalence and intensity of smoking were extremely low in the three best trajectories i.e.
351 “persistently high”, “early low, accelerated growth, normal decline”, and “average”. These are likely
352 to reflect the lung function trajectories in non-smokers.

353 Evidence of a link between low lung function in early adulthood and prevalence and incidence of
354 respiratory, cardiovascular, and metabolic abnormalities, and all-cause mortality has been recently
355 reported.^{1,2} Our findings also support some of these associations. In addition to the significantly
356 higher prevalence of respiratory conditions (table 3), the three unfavourable lung function
357 trajectories had higher prevalences of diabetes and obstructive sleep apnoea, compared with the
358 average trajectory (table S7). Higher prevalences of hypertension and heart attack/myocardial
359 infarction were also seen for the “below average” and “persistently low” trajectories. Together, our

360 findings and others highlight the significant burden of comorbidity associated with low lung function,
361 and indicate the importance of early identification of this high-risk group.

362 Identification of lifetime lung function trajectories in a general population, their determinants and
363 consequences, has been a fundamental but challenging question for respiratory experts for decades.
364 An ideal longitudinal study with a large sample size, multiple waves of lung function measurement
365 spanning from early life through old age, and with perfect follow-up would fully explore this
366 question, but the ideal study does not exist. Most current longitudinal studies have a limited sample
367 sizes with limited repeated lung function measurements. To date, with its population-based design,
368 large sample size and long follow-up period, TAHS provides the best existing data with which to
369 answer this question. Over six decades, we have lung function measurements from childhood to
370 middle age which enable good classification of trajectories over these periods. We acknowledge that
371 not having sufficient lung function data around age 18 years is a key weakness which may mean that
372 we have missed trajectory transitions around peak lung function. However, the lack of sufficient data
373 at this peak lung function period would be unlikely to significantly affect trajectories in childhood
374 and middle age. In a sensitivity analysis, when the data point at 18 years was excluded, we still
375 identified six similar lung function trajectories. We encourage researchers to develop long term
376 studies of large birth cohorts with repeated lung function from infancy to old age to replicate our
377 findings and provide a more comprehensive picture of lung function over the entire life course.
378 However, given logistic difficulties, results from such studies would not be available for decades.

379 Besides the uniqueness of our data, the use of GBTM was a strength. This data driven technique
380 enabled us to explore potential unknown lung function trajectories which were not based on any a
381 priori hypotheses. Most of the identified trajectories were similar to those found in other cohorts
382 (Tucson, MAAS and ALSPAC). Moreover, the identified shapes and associations between risk factors
383 and trajectories further support their biological plausibility.

384 A limitation of this study is that GLI equations were not available in 1968 and equipment changed
385 over time. This could lead to an imperfect fit of GLI equations at different times, but this would have
386 little effect on the relative positions between trajectories. Of note, the last measurement in our
387 study is at an age when the burden of COPD is just starting to emerge as most patients with COPD
388 are diagnosed in their sixties. The effect of adverse lung function trajectories on COPD risk may
389 become clearer in future follow-ups of this study when COPD prevalence will be higher.

390 To identify trajectories from early life to the sixth decade, the analysis was restricted to those who
391 were alive and continuing to participate in the study at age 53; hence there is a high attrition rate.
392 Importantly however, the death rate for TAHS participants by age 53, was small (4.7%) and
393 consistent with Australian population statistics.³⁸ Most importantly, comparisons of childhood lung
394 function and characteristics between participants and: those deceased and; non-participants
395 showed minimal differences. If attrition was differential across trajectories, it would influence the
396 lung function trajectory prevalence estimates and generalisability of these estimates however this
397 issue is unlikely to affect the patterns or the associations between these trajectories and the
398 predictors/outcomes observed.

399 Diagnosis of childhood asthma is difficult, and there is conceptual ambiguity concerning the exact
400 nature of asthma, which is likely to be an umbrella term for a range of conditions. Children with
401 abnormal lung development may present with asthma-like symptoms, while airway inflammation
402 associated with asthma may lead to reduced lung function. The possibility of these bidirectional
403 associations between poor lung development and childhood asthma has been raised³⁹, but it
404 remains unclear which occurs first. Future cohort studies with lung function measured at birth and
405 close follow-up for asthma diagnosis may help elucidate this issue.”

406 Our findings have clinical and public health implications. Visual presentations of lung function
407 trajectory scenarios may be useful in educational programs on the dangers of smoking. Routine
408 spirometry measurements in school students to identify those with low lung function may help early

409 identification of high risk groups for whom early interventions such as avoidance of smoking and
410 hazardous occupational exposures can be implemented. Although not directly tested, our findings
411 raise the possibility that reducing maternal smoke exposure; encouraging immunization; and
412 avoiding personal smoking, especially for those with smoking parents and those with low childhood
413 lung function; would promote healthy lung function trajectories and lessen COPD risk. Clinicians and
414 patients with asthma should be made aware of the potential long-term implications of non-optimal
415 asthma control throughout life, and these should be investigated in future intervention trials.

416 **CONCLUSION**

417 This world-first characterization of lung function change from the first to the sixth decade
418 revealed six distinct trajectories which may represent population patterns. In our model,
419 most COPD, especially when more severe, was attributable to three trajectories exhibiting
420 lower lung function in childhood with either subsequent normal or accelerated decline. Our
421 findings suggest that early life factors including allergic diseases, lung infections, parental
422 asthma and maternal smoking influence the three unfavourable lung function trajectories.
423 Personal smoking may amplify the effect of maternal smoking and adult asthma may
424 amplify the effect of childhood asthma to determine membership of the worst lung function
425 trajectory.

426 **Authors' contributions**

427 Study concept and design: S.C.D., E.H.W., G.G.G; M.J.A. Acquisition of data: S.C.D., E.H.W., M.C.M;
428 J.A.B, P.S.T, S.M, Analysis and interpretation of data: D.S.B., S.C.D., J.A.B, M.C.M. Drafting of the
429 manuscript: D.S.B., S.C.D., J.A.B., M.C.M. Critical revision of the manuscript for important intellectual
430 content: all authors. Statistical analysis: D.S.B, S.C.D., J.A.B. Obtained funding: S.C.D., E.H.W., M.J.A,
431 S.M.

432

433 **Conflicts of interest**

434 Authors have no conflicts of interest

435

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444

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454

455 **Figure legends**

456 **Figure 1.** Trajectories of lung function (FEV₁ z-score) from 7 to 53 years of age. The six trajectories
457 represent the latent growth patterns of lung function.

458 **Figure 2.** Prevalence of COPD among six lung function trajectories at 53 years (%).

Table 1: Childhood characteristics of participants according to lung function trajectories from 1st to 6th decade (% (n))

	Lung function trajectory groups					
	Early below average, accelerated decline	Persistently low	Early low, accelerated growth, normal decline	Persistently high	Below average	Average
	(n=97)	(n=136)	(n=196)	(n=293)	(n=772)	(n=944)
Childhood characteristics (at 7 years)						
Male sex	52/97 (53%)	72/136 (53%)	73/196 (37%)*	126/293 (43%)	392/772 (51%)	465/944 (49%)
Ever asthma	36/97 (37%)*	38/135 (28%)*	32/196 (16%)	48/291 (16%)	137/766 (18%)	137/940 (14%)
Asthma phenotype						
Transient	3/96 (3.1%)	8/133 (6%)	8/193 (4.2%)	16/287 (5.6%)	36/758 (4.8%)	39/935 (4.2%)
Late onset	11/96 (11.5%)	7/133 (5.3%)	7/193 (3.6%)	12/287 (4.2%)	43/758 (5.8%)	43/935 (4.6%)
Persistent	21/96 (22%)	21/133 (15.8%)	14/193 (7.3%)	16/287 (5.6%)	50/758 (6.6%)	50/935 (5.4%)
Ever bronchitis	68/97 (70%)*	75/135 (55%)	97/196 (49%)	132/291 (45%)	386/765 (50%)	449/942 (47%)
Ever eczema	18 (18)*	27/123 (20%)*	24/195 (12%)	28/291 (10%)	75/765 (10%)	98/937 (10%)

Ever hay fever	26/94 (28%*	18/134 (13%)	28/194 (14%)	32/287 (11%)	106/763 (14%)	117/932 (13%)
Ever food allergy	11/96 (11%)	17/134 (13%)*	14/196 (7%)	21/291 (7%)	55/762 (7 %)	60/940 (6%)
Ever pneumonia/pleurisy	21/96 (22%)*	19/134 (14%)	18/196 (9%)	29/287 (10%)	120/760 (16%)*	116/931 (12%)
Weight status at 7 years						
Underweight	3/95 (3%)	7/134 (5%)	13/196 (7%)*	5/290 (2%)	30/766 (4%)	25/937 (3%)
Normal	77/95 (81%)	116/134 (87%)	165/196 (84%)	241/290 (83%)	665/766 (87%)	803/937 (85%)
Overweight	15/95 (16%)	11/134 (8%)	18/196 (9%)	44/290 (15%)	71/766 (9%)	109/937 (12%)
Breast feeding						
Breast fed only	36/97 (37%)	56/134 (42%)	73/195 (37%)	136/290 (47%)	309/763 (41%)	427/941 (45%)
Breast and bottle	32/97 (33%)	36/136 (27%)	66/195 (34%)	95/290 (33%)	248/763 (33%)	293/941 (31%)
Socio-economic status						
1 st (highest)	18/94 (19.2%)	28/123 (22.8%)	45/182 (24.7%)	74/278 (26.6%)	185/732 (25.3%)	226/908 (24.9%)
2 nd	7/94 (7.5%)	14/123 (11.4%)	11/182 (6%)	17/278 (6.1%)	47/732 (6.4%)	73/908 (8%)
3 rd	32/94 (34%)	34/123 (27.6%)	53/182 (29.1%)	80/278 (28.8%)	210/732 (29.9%)	276/908 (30.4%)

4 th	29/94 (30.8%)	30/123 (24.4%)	53/182 (29.1%)	78/278 (28%)	190/732 (26%)	248/908 (27.3%)
5 th	8/94 (8.5%)	17/123 (13.8%)	20/282 (11%)	29/278 (10.4%)	91/732 (12.4%)	85/908 (9.4%)
Parental characteristics						
Parental asthma	19/94 (20%)	37/131 (28%)*	30/189 (16%)	58/283 (21%)	155/740 (21%)	156/915 (17%)
Maternal smoking						
Light/moderate smoking	34/94 (36%)*	38/131 (29%)	51/189 (27%)	67/282 (24%)	226/740 (30%)	255/913 (28%)
Heavy smoking	9/94 (10%)*	7/131 (5%)	7/189 (4%)	15/282 (5%)	37/740 (5%)	36/913 (4%)
Paternal smoking						
Light/moderate smoking	37/90 (41%)	58/127 (46%)	62/174 (36%)	110/270 (41%)	269/697 (39%)	304/867 (35%)
Heavy smoking	20/90 (22%)	19/127 (15%)	35/174 (20%)	48/270 (18%)	135/697 (19%)	162/867 (19%)
FEV ₁ at 7 years, mean (\pm SD)						
z-score	-0.23 (\pm 0.64)*	-1.66 (\pm 0.6)*	-1.57(\pm 0.57)*	1.15 (\pm 0.7)*	-0.33 (\pm 0.62)*	0.31 (\pm 0.6)
% predicted	97 (\pm 8)*	79 (\pm 8)*	80.2 (\pm 7)*	114 (\pm 9.3)*	96 (\pm 8)*	104 (\pm 8)

FEV ₁ /FVC at 7 years, mean (±SD) (%)	88.4 (±0.1)	87.7 (±0.1)	87.3 (±0.1)	92.6 (±0.1)	90.7 (±0.1)	92 (±0.1)
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* significant difference from the “average” trajectory ($p < 0.05$)

Table 2: Associations between childhood clinical factors and each of lung function trajectories compared to the “average” trajectory

	Lung function trajectory groups - OR (95%CI)				
	Early below average, accelerated decline	Persistently low	Early low, accelerated growth, normal decline	Persistently high	Below average
Asthma†	3·1 (1·9;5·2)**	1·7 (1·1;2·7)*	1·1 (0·7;1·8)	1·2 (0·8;1·8)	1·1 (0·8;1·5)
Frequent asthma at 7 years †					
Never asthma	1	1	1	1	1
Infrequent	2·7 (1·5;4·9)**	0·9 (0·5;1·8)	0·9 (0·5;1·6)	1·1 (0·7;1·8)	0·9 (0·6;1·3)
Frequent	4·4 (2·1;9·1)***	4·1 (2·2;7·8)***	1·7 (0·8;3·5)	1·3 (0·7;2·5)	1·4 (0·9;2·2)
Asthma onset †					
Never asthma	1	1	1	1	1
<3 years	3·1 (1·7;5·5)***	2·0 (1·1;3·4)*	1·1 (0·6;2·0)	1·3 (0·8;2·0)	1·1 (0·8;1·5)

≥3 years	3.2 (1.4;7.0)**	1.2 (0.5;2.9)	1.0 (0.4,2.3)	0.8 (0.4;1.8)	1.0 (0.6;1.7)
Bronchitis†	2.0 (1.2;3.2)**	1.1 (0.7;1.6)	1.1 (0.7;1.4)	0.9 (0.7;1.2)	1.1 (0.9;1.3)
Frequent bronchitis at 7 years †					
Never bronchitis	1	1	1	1	1
Infrequent	1.9 (1.1;3.1)*	1.1 (0.7;1.6)	1.0 (0.7;1.3)	0.9 (0.7;1.2)	1.0 (0.8;1.3)
Frequent	2.5 (1.3;4.8)**	1.2 (0.6;2.2)	1.2 (0.7;2.1)	0.9 (0.6;1.5)	1.3 (0.9;1.8)
Pneumonia/pleurisy †	2.0 (1.2;3.5)**	1.1 (0.6;1.9)	0.6 (0.4;1.1)	0.8 (0.5;1.3)	1.3 (1.0;1.8)*
Eczema 	1.3 (0.7;2.3)	1.8 (1.1;3.0)*	1.3 (0.8;2.3)	1.1 (0.6;1.6)	0.9 (0.6;1.3)
Hay fever 	2.0 (1.2;3.4)**	0.9 (0.5;1.6)	1.4 (0.8;2.2)	0.7 (0.5;1.1)	1.0 (0.8;1.4)
Food allergy 	1.5 (0.7;3.1)	1.8 (0.94;3.4)	1.2 (0.6;2.3)	1.3 (0.8;2.2)	1.2 (0.8;1.8)
Parental asthma ¶	1.2 (0.7;2.1)	1.8 (1.1;2.9)*	0.9 (0.5;1.4)	1.4 (0.9;2.0)	1.2 (0.9;1.6)
Maternal smoking §					
Light/moderate smoking	1.3 (0.8;2.2)	1.0 (0.7;1.6)	0.8 (0.5;1.2)	0.7 (0.5;1.0)	1.0 (0.8;1.2)
Heavy smoking	2.5 (1.1;5.9)*	1.7 (0.7;4.0)	1.0 (0.4;2.4)	1.5 (0.8;2.9)	1.3 (0.8;2.2)
Paternal smoking §					

Light/moderate smoking	1.3 (0.7;2.1)	1.6 (0.9;2.5)	1.0 (0.7;1.5)	1.4 (0.9;1.9)	1.2 (0.9;1.5)
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Heavy smoking	1.2 (0.6;2.1)	1.0 (0.6;1.8)	1.0 (0.6;1.6)	1.1 (0.7;1.6)	1.1 (0.8;1.5)
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Breast feeding Δ

Bottle only	1	1	1	1	1
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Breast only	0.7 (0.4;1.2)	0.7 (0.5;1.1)	0.7 (0.5;1.1)	1.1 (0.7;1.5)	0.8 (0.6;1.0)
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Bottle & breast	0.9 (0.5;1.6)	0.7 (0.4;1.1)	0.9 (0.6;1.4)	1.1 (0.8;1.7)	0.9 (0.7;1.2)
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Weight status at 7 years ∇

Underweight	1.3 (0.4;4.2)	2.2 (0.95;5.2)	2.6 (1.3;5.2)**	0.7 (0.3;1.8)	1.5 (0.8;2.5)
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Overweight	1.6 (0.9;2.8)	0.6 (0.3;1.2)	0.8 (0.5;1.4)	1.3 (0.9;2.0)	0.8 (0.6;1.1)
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Sex

Female	0.8 (0.5;1.2)	0.8 (0.6;1.2)	1.7 (1.2;2.3)*	1.2 (0.9;1.5)	0.9 (0.8;1.1)
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*P<0.05; ** p<0.001; *** p<0.001

†For asthma, model adjusted for parental asthma, childhood pneumonia/pleurisy, infantile eczema, parental smoking, sex, breast feeding and childhood SES.

‡For bronchitis, model adjusted for childhood asthma, childhood pneumonia/pleurisy, infantile eczema, parental smoking and childhood SES.

† For pneumonia/pleurisy, model adjusted for breast feeding and childhood SES.

||For eczema, hay fever and food allergy, models adjusted for childhood asthma, parental asthma, parental smoking, sex and childhood SES.

¶ For parental asthma, models adjusted for sex, parental smoking and childhood SES.

§ For parental smoking, models adjusted for parental asthma, childhood asthma and childhood SES.

Δ For breast feeding, model adjusted for parental asthma, parental smoking and childhood SES.

√ For childhood weight status, model adjusted for childhood pneumonia/pleurisy, sex, breast feeding and childhood SES.

Table 3: Clinical characteristics at 53 years according to lung function trajectories from 1st to 6th decade

Characteristics	Lung function trajectory groups					
	Early below average, accelerated decline (n=97)	Persistently low (n=136)	Early low, accelerated growth, normal decline (n=196)	Persistently high (n=293)	Below average (n=772)	Average (n=944)
COPD	44/95 (46%)*	17/136 (12.5%)*	1/194 (0.5%)	1/289 (0.4%)	44/765 (6%)*	12/936 (1.3%)
Active asthma at 53 years	56/97 (58%)*	53/135 (39%)*	35/196 (18%)	41/291 (14%)	179/771 (23%)*	153/944 (16%)
Atopic asthma	28/97 (29%)	21/135 (15.6%)	18/196 (9.2%)	12/291 (4%)	77/771 (10%)	69/944 (7.3%)
Non-atopic asthma	28/97 (29%)	32/135 (23.4%)	17/196 (8.8%)	29/291 (10%)	103/771 (13%)	84/944 (8.7%)
Asthma-COPD phenotypes						
Neither	21/95 (22%)	79/135 (58%)	159/194 (82%)	246/287 (86%)	557/764 (73%)	774/936 (83%)
Asthma alone	30/95 (32%)*	39/135 (29%)*	34/194 (18%)	40/287 (14%)	163/764 (21%)	150/936 (16%)
COPD alone	19/95 (20%)*	3/135 (2.2%)	0/194 (0%)	1/287 (0.4%)	30/764 (4%)	9/936 (1%)

Overlap	25/95 (26%)*	14/135 (10.4%)*	1/194 (0.5%)	0/287 (0%)	14/764 (1.8%)	3/936 (0.3%)
Chronic cough	41/96 (42.7%)*	40/135 (29.6%)	35/196 (17.8%)	46/291 (15.8%)*	198/770 (26%)	219/941 (23.2%)
Chronic sputum production	32/95 (33.7%)*	32/133 (24%)*	16/196 (8.2%)	20/291 (6.8%)	95/769 (12.3%)	96/942 (10.2%)
Shortness of breath at rest in last year	17/96 (17.7%)*	16/133 (12%)*	13/195 (6.7%)	11/292 (3.8%)	61/768 (8%)	59/938 (6.3%)
Shortness of breath after exercise in last year	50/97 (51.6%)*	53/134 (40%)*	20/195 (10.3%)	34/292 (11.6%)	136/769 (17.7%)*	117/940 (12.5%)
Wheezing in last year	57/97 (58.8%)*	54/135 (40%)*	28/196 (14.3%)	33/293 (11.3%)	184/768 (24%)*	140/942 (14.9%)
Pre BD lung function at 53 years †						
FEV ₁ , z-score	-2.35 (±0.59)*	-1.61 (±0.52)*	0.30 (±0.51)	1.35 (±0.58)*	-0.81 (±0.46)*	0.29 (±0.52)
FEV ₁ , % predicted	67.1 (±8.7)*	77.7 (±7.4)*	104 (±6.8)	112 (±7.5)*	88.9 (±6.4)*	104 (±6.8)
FEV ₁ /FVC, %	66.5 (±0.1)*	73 (±0.1)*	79.8 (±0.1)	79.5 (±0.1)	75.6 (±0.1)*	78.5 (±0.1)
Post BD lung function at 53 years †						
FEV ₁ , z-score	-1.94 (±0.65)*	-1.28 (±0.57)*	0.45 (±0.54)	1.54 (±0.57)*	-0.5 (±0.62)*	0.5 (±0.55)
FEV ₁ , % predicted	73 (±9.3)*	82.4 (±8.0)*	106 (±7.3)	120 (±7.5)*	93 (±8.2)*	107 (±7.3)

FEV ₁ /FVC, %	68.9 (±0.1)*	75.6 (±0.1)*	81.8 (±0.1)	81.6 (±0.1)	78.1 (±0.1)*	80.7 (±0.1)
Use of medicines (inhaler, oral or injection) for breathing problems in the prior year	41/88 (47%)*	38/132 (29%)*	15/191 (8%)	21/290 (7%)	103/755 (%)*	79/933 (8.5%)
Smoking status at 53 years						
Never	22/96 (23%)*	63/134 (47%)	91/195 (47%)	142/291 (49%)	319/765 (42%)*	470/936 (50%)
Past	43/96 (45%)	43/134 (32%)	87/195 (44%)	123/291 (42%)	294/765 (38%)	346/936 (37%)
Current	31/96 (32%)*	28/134 (21%)*	17/195 (9%)	26/291 (9%)	152/765 (20%)*	120/936 (13%)
Pack-years, median (IQR)	13.5 (0-29)*	0.43 (0-19.5)*	0 (0-10)	0 (0-6)	0.6 (0-18.3)*	0 (0-9)

t mean (± SD)

* significant difference from the “average” trajectory ($p < 0.05$)

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