Spirometric patterns in young and middle-aged adults: a 20-year European study

Spirometric patterns in young and middle aged adults. A 20-year European study

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ABSTRACT

Background

Understanding the natural history of abnormal spirometric patterns at different stages of life is critical to identify and optimize preventive strategies. We aimed to describe characteristics and risk factors of restrictive and obstructive spirometric patterns occurring before 40 years (young onset) and between 40 and 61 years (mid-adult onset).

Methods

We used data from the population-based cohort of the European Community Respiratory Health Survey (ECRHS). Pre-bronchodilator FEV_1 and FVC were assessed longitudinally at baseline (ECRHS1, 1993-1994) and again 20-years later (ECRHS3, 2010-2013). Spirometry patterns were defined as: restrictive if FEV_1/FVC≥LLN and FVC<10th percentile, obstructive if FEV_1/FVC<LLN, or normal otherwise. Five spirometry patterns were derived depending on whether participants never developed restrictive/obstructive (normal), developed restrictive/obstructive at baseline (young-onset) or at last follow-up (mid-adult onset). Characteristics and risk factors associated with these patterns were described and assessed using multi-level multinomial logistic regression analysis adjusting for age, sex, sample (random or symptomatic) and centre.

Results

Among 3502 participants (mean age=30·4 [SD 5.4] at ECRHS1, 50·4 [SD 5.4] at ECRHS3), 2293 (65%) had a normal, 371 (11%) a young restrictive, 301 (9%) a young obstructive, 187 (5%) a mid-adult onset restrictive, and 350 (10%) a mid-adult onset obstructive spirometric pattern. Being lean/underweight in childhood and young adult-life was associated with the occurrence of the young spirometric restrictive pattern (RRR=1·61 95% confidence interval (CI)=1·21-2·14, and RRR=2·43 95%CI=1·80-3·29; respectively), so were respiratory infections before 5 years (RRR=1·48, 95%CI=1·05-2·08). Main determinants for young obstructive, mid-adult restrictive, and mid-adult obstructive patterns were asthma, obesity, and smoking, respectively.

Conclusion

Spirometric patterns with onset in young and mid-adult life were associated with distinct characteristics and risk factors.

Take home message

What is already known on this topic

Abnormal spirometric restrictive and obstructive patterns occurring throughout a life course are likely resulting from different trajectories of lung function growth and decline. Risk factors vary between restrictive and obstructive patterns.

What this study adds

Characteristics and risk factors for restrictive and obstructive spirometric patterns differ profoundly based on whether their onset occurs in young versus mid-adult life.

How this study might affect research, practice or policy

These differences in relation to the onset of spirometric patterns should be taken into account by future studies addressing possible prevention and treatment strategies of abnormal spirometric patterns.

INTRODUCTION

Lung function impairment, detected by spirometry, can be classified into two main abnormal phenotypes: the obstructive pattern (defined by reduced levels of the ratio of Forced Expiratory Volume in 1 sec (FEV_1) to the Forced Vital Capacity (FVC)) and the restrictive spirometric pattern, also referred to as Preserved Ratio Impaired Spirometry (PRISm)[1] (characterized by reduced levels of both FEV_1 and FVC, while FEV_1/FVC remains within normal ranges).[2, 3] The obstructive pattern has been extensively studied and is routinely diagnosed in current practice, whereas the restrictive spirometric pattern has been under-recognized despite being prevalent and associated with higher morbidity and mortality, reduced physical activity and worse quality of life compared to normal pattern.[2-8]

Recent studies have conclusively shown that the obstructive pattern can develop in adult life through two main trajectories: one characterized by an accelerated decline of FEV_1 and FEV_1/FVC in adulthood, after lung function reached its peak by young adult life; the other by lung function deficits that are already established in young adulthood, before entering the declining phase.[9-11] Little is known on whether spirometric restriction also develops following distinct trajectories, especially FVC trajectories. A recent study has shown that a low FVC trajectory that starts low from early life is associated with true restriction at age 45 years as measured by complex lung function measures[12]. However, this study did not use the above standard definition of restrictive spirometry pattern in its longitudinal analysis.

Using data from a longitudinal European cohort, we aimed to describe characteristics and risk factors of both restrictive and obstructive spirometric patterns occurring before 40 years (young onset) and after 40 years (mid-adult onset). Understanding the natural history and risk factors associated with these patterns can lead to identify possible preventive strategies and time windows in life when these strategies can be most effective.

MATERIAL AND METHODS

Study Design

The European Community Respiratory Health Study (ECRHS) has been described elsewhere.[13] Briefly, ECRHS is a multi-centre cohort involving 46 centres in 25 countries, across Europe and Australia. Between 1991-1993, participants aged 20 to 44 years were

138 randomly selected from the population and complemented with a sample of subjects with
139 asthma-related symptoms (ECRHS1). Two follow-up surveys took place approximately 10 years
140 (ECRHS2) and 20 years (ECRHS3) later. All participants answered a detailed questionnaire and
141 underwent a clinical visit at each occasion, where spirometry and blood sample collection
142 were performed. Overall, the response rate at the last follow-up was 53%.[14]

143 The current study used longitudinal data collected at baseline (ECRHS1) and at the last follow-
144 up (ECRHS3). Only participants aged < 40 years at baseline and participants aged ≥ 40 at the
145 last follow-up were included in this study in order to have complete separation between
146 spirometric patterns assessed in "young" (ECRHS1, age 20 to 39) and "mid-adult" (ECRHS3,
147 aged 40 to 61) life (Figure 1).

148 Written informed consent was obtained from all participants and, in each participating centre,
149 the study was approved by the appropriate institutional ethics committees.

150

151 **Lung function measurement**

152 Pre-bronchodilator lung function was used to determine spirometric patterns at each survey.
153 Measurements reproducible within 150mL from at least two of a maximum of five correct
154 manoeuvers were included, following the American Thoracic Society (ATS)
155 recommendations.[15] Details of the spirometers used in each centre are provided
156 elsewhere.[16] Since 2005 the ATS and the European Respiratory Society have recommended
157 the use of lower limit of normal (LLN) for FEV_1/FVC to define airway obstruction in
158 epidemiological studies.[17] In contrast, no consensus exists on how to define spirometric
159 restriction[18], although some studies[19] have used definitions based on the lowest 10th
160 percentile of FVC to maximize sample size. Previously used ECRHS-specific equations[7] were
161 used to calculate the LLN for FEV_1/FVC and the 10th percentile for FVC. The *a-priori* spirometric
162 patterns were then defined as:

163 - Normal spirometry if FEV_1/FVC ≥ LLN and FVC ≥ 10th percentile both at baseline and
164 follow-up

165 - Young onset restrictive spirometric pattern if FEV_1/FVC ≥ LLN and FVC < 10th percentile
166 at baseline

167 - Young onset obstructive spirometric pattern if FEV_1/FVC < LLN at baseline

- Mid-adult onset restrictive spirometric pattern if $FEV_1/FVC \geq LLN$ and $FVC < 10^{th}$ percentile at follow-up, while being normal at baseline
- Mid-adult onset obstructive spirometric pattern if $FEV_1/FVC < LLN$ at follow-up, while being normal at baseline.

Characteristics and risk factors collected at baseline (ECRHS1)

Early life risk factors, reported by the participants at ECRHS1, included the following parental, infancy, and childhood factors: maternal/paternal asthma, parental education, maternal age at birth, maternal smoking in pregnancy, parental smoking, history of respiratory infections before 5 years, childhood asthma, living in city or rural place during childhood.

Young adult risk factors referred to characteristics assessed at ECRHS1 when participants were 20 to 39-yrs old and included: smoking status and pack-years, asthma in the last 12 months (defined as ever had asthma plus any of the following occurring in the last 12 months: use of asthma medication, having asthma attack or having had shortness of breath), atopy (any positive specific IgE (cat, house dust mite, grass) >0.35 ug/ml), and Body Mass Index (BMI). BMI was categorized into low (<20 kg/m^2), normal (20 to <25 kg/m^2), overweight (25 to <30 kg/m^2) and obese (≥ 30 kg/m^2).[20]

Change between ECRHS1 and ECRHS3

BMI, smoking status and pack-years were available both at ECRHS1 and ECRHS3. Longitudinal categories of BMI were classified as persistent underweight, persistent normal, persistent overweight, underweight to normal, underweight/normal to overweight/obesity and a decrease in BMI. Because only 68 participants had a BMI category in ECRHS1 greater than their BMI category in ECRHS3, they were all included in the "decrease in BMI category" group. Longitudinal categories of smoking were classified as never, ex-smokers (if they were smokers before ECRHS1), quitters (if they quitted between ECRHS1 and ECRHS3) and late starters (if they started after ECRHS1).

Participant characteristics collected at ECRHS3

Additionally, at ECRHS3, participants were asked about their body silhouettes at age 8, the time of puberty and age 30. This tool has been previously validated[21] in this cohort. Among the 9 body silhouettes (from scale 1 (extremely lean) to scale 9 (extremely obese)),

198 participants were asked to tick the figural scale that best described their body silhouette at
199 that age. This scale was then categorised into 4 groups in order to have sufficient numbers in
200 each group and according to the best trade-off for obesity definition[21] (category 1: lean, 2 to
201 3: normal, 4: overweight, 5 to 9: obese). Longitudinal categories for changes in body silhouette
202 between the ages of 8 and 30 years were also generated, with methods similar to those
203 described for the longitudinal categories of BMI.

204 Participants' characteristics evaluated at ECRHS3 were chronic conditions (diagnosis of chronic
205 bronchitis, heart disease, hypertension, stroke, diabetes, depression and ankylosing spondylitis
206 or psoriatic arthritis), dyspnea, body composition (fat-mass and fat-free mass, derived from
207 bioelectrical impedance analysis using validated equations[22]) and physical activity. Z-score
208 for fat-mass and fat-free-mass were standardised on sex, height and height-squared. Low,
209 normal and high categories were further derived according to 10th percentiles. Lowest tertile
210 of total Mets-min per week[23] was used to describe physical activity levels.

211

212 **Statistical analysis**

213 Adjusted mean levels of FEV_1, FVC and FEV_1/FVC over age were graphically represented after
214 estimating margins from 3-levels (level 1: visit, level 2: participant, level 3: centre) mixed
215 models with lung function as the dependent variable while adjusting for age, age squared (to
216 capture acceleration of decline over time), sex and spirometric pattern, and interactions
217 between age*sex, spirometric pattern*age, spirometric pattern*age-squared. We
218 complemented these figures by providing figures of unadjusted mean lung function levels by
219 survey and sex according to spirometric patterns (supplemental Figure 1).

220 The two groups of potential risk factors ("early-life" and "young adult-life", as described
221 above) for the spirometric patterns were considered in the analysis. Associations between
222 spirometric patterns and subject characteristics (at ECRHS3) as well as risk factors were first
223 tested by bivariate analysis (chi-squared test and anova test).

224 For each risk factor, relative risk ratios (RRR) were estimated using 2-level multinomial logistic
225 regressions with normal trajectory as the reference, while adjusting for age, sex, sample (to
226 control for possible differences in risk factors and outcomes between the random and
227 symptomatic samples) and centre (level 2, as a random effect).[24] A final multivariate

228 multinomial logistic regression model was also run retaining independent variables with p-
229 value<0.1.

230 A series of sensitivity analyses were performed to assess the robustness of the results to
231 assumptions about definitions and confounding. We (1) excluded participants from the
232 symptomatic sample (n=457), (2) excluded any asthmatic at baseline (n=375), (3) used GLI
233 equations rather than study-specific equations to define the spirometric patterns, and (4)
234 excluded participants with an increase in FVC between ECRHS1 and ECRHS3 (n=377). All
235 analyses were done using Stata 16 (StataCorp, Texas, USA).

236

237 **Role of the funding source**

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

241

242 **RESULTS**

243 In the present study, 3502 participants with data at both ECRHS1 (mean age=30·4, sd=5·4) and
244 ECRHS3 (mean age= 50·4, sd=5·4) were included (Figure 1). Participants not included (lost to
245 follow-up) were more likely to be younger, male and smoker at baseline, and to report more
246 respiratory symptoms (supplementary Table 1). In total, 2293 (65%) had normal spirometry,
247 371 (11%) a young onset restrictive, 301 (9%) a young onset obstructive, 187 (5%) a mid-adult
248 onset restrictive, and 350 (10%) a mid-adult onset obstructive spirometric patterns.

249

250 **Lung function trajectories from mixed linear regression models**

251 Mean FEV_1 levels at age 20 years were lowest among participants in both young onset
252 restrictive and obstructive spirometric patterns and both groups followed a similar trend with
253 FEV_1 deficits tracking over time (Figure 2a). The mean rates of FEV_1 and FVC decline during the
254 study follow-up were 34 and 26 ml/yr respectively, but they differed substantially across
255 spirometric pattern groups. While participants with mid-adult onset spirometric patterns (both
256 restrictive and obstructive) had FEV_1 levels close to normal at age 20, their decline was faster
257 than for subjects with normal spirometry. In contrast, FVC showed very similar levels and

258 decline for normal, young onset obstructive, and mid-adult onset obstructive spirometric
259 patterns, while levels at age 20 were lowest for the participants with a young onset restrictive
260 spirometry and decline was fastest for the participants with a mid-adult onset restrictive
261 spirometry (Figure 2b). Mean FEV_1/FVC was constantly lower over age for subjects in the
262 young onset obstructive, while a steeper decline was observed for those with mid-adult onset
263 obstructive compared to the normal spirometry (Figure 2c). These observations were
264 confirmed when actual unadjusted means were graphically represented according to sex
265 (supplementary Figure 1).

266

267 **Participants characteristics at follow-up**

268 Participants in the young onset abnormal patterns were more likely to be underweight and to
269 have a low fat-free mass Z-score at follow-up compared to the normal pattern (Table 1). 43%
270 of those in the mid-adult restrictive pattern were obese (compared to 19% in the normal
271 pattern). Smoking was more frequent in the mid-adult onset obstructive spirometry.
272 Respiratory symptoms and diagnosis were more frequent in the abnormal patterns compared
273 to normal spirometry as were cardiovascular and metabolic diseases. Ankylosing
274 spondylitis/psoriatic arthritis was more frequent in the mid-adult onset restrictive spirometry.

275

276 **Risk factors associated with spirometric trajectories**

277 Early-life risk factors were found to be consistently related with the young onset spirometric
278 patterns (Table 2, upper part). Maternal and paternal asthma as well as childhood asthma
279 were most frequent among participants with young obstructive spirometry compared to
280 normal. A positive history of respiratory infections before age 5 years was more frequent both
281 in subjects with young onset restrictive (14%) and obstructive (18%) patterns than in subjects
282 with the normal spirometry (10%), while the leanest silhouette at age 8 was more frequent in
283 the young onset restrictive pattern compared to other patterns.

284 Among young adult risk factors (Table 2, bottom part), compared to the normal spirometry,
285 leanest silhouette at age 30 and underweight at ECRHS1 were highest in the young onset
286 restrictive pattern, whereas both the obese silhouettes at age 30 and obesity at ECRHS1 were
287 highest in the mid-adult onset restrictive pattern. The proportion of underweight and obese
288 participants were also higher in the young onset obstructive spirometry compared to normal

289 pattern. Cigarette smoking was the strongest risk factor for the mid-adult onset obstructive
290 pattern, with a proportion of 71% smokers (versus 54% in the normal pattern) and a median of
291 12 pack-years (versus 7 pack-years in the normal pattern). Proportion of current asthma in
292 young adult-life was remarkably higher in the young obstructive (28%) than in the normal
293 pattern (5%) and appeared somewhat increased in the mid-adult onset obstructive (10%)
294 pattern.

295 These associations were largely confirmed in multinomial models adjusted for age, sex, sample
296 and centre (Table 3). A history of respiratory infections before age 5 was associated with both
297 young onset patterns (RRR=1·5 and 2·0 for the young onset restrictive and obstructive pattern,
298 respectively). Reporting the leanest silhouette at age 8 and 30 years and being underweight in
299 young adult-life increased significantly the risk for the young onset restrictive spirometry (RRR:
300 1·6, 2·5, and 2·4, respectively). When these three risk factors were mutually adjusted for each
301 other, their RRRs, particularly those for reporting the leanest silhouette at age 8 and for being
302 underweight in young adult-life, remained consistent: 1·6, 1·9, and 2·4, respectively. Former
303 smokers showed 32% reduced risk for the young restrictive pattern compared to the normal
304 pattern. Atopy was associated with a 114% increased risk for the young obstructive
305 spirometry, while participants with current asthma in young adult-life were nearly 7 times
306 more likely to be in the young onset obstructive than the normal group.

307 Maternal asthma was the only early-life risk factor associated with the mid-adult onset
308 obstructive pattern, whereas current smokers in young adult life had a 130% increased risk for
309 developing this mid-adult onset obstructive pattern. Reporting the heaviest body silhouettes
310 and being obese in young adult-life increased the risk of the mid-adult onset restrictive pattern
311 (RRRs: 2·3 for both risk factors).

312 When we tested for possible sex differences in the association between being underweight
313 and the young onset spirometric restrictive pattern, while the effects of having the leanest
314 body silhouette appeared to be stronger in females than males, comparable RRRs were
315 observed for the association between low BMI at ECRHS1 and the young onset restrictive
316 pattern in the two sexes (see supplementary Table 2 for analyses stratified by sex). Of note, in
317 a final analysis including all significant predictors in a single mutually adjusted model, reporting
318 the leanest body silhouette at ages 8 and 30 as well as having low BMI at ECRHS1 remained all
319 independently associated with the young onset restrictive spirometric pattern (supplementary
320 Table 3).

321

322 **Changes in risk factors between young and mid-adult**

323 Table 4 shows changes and longitudinal categories of risk factors between ECRHS1 and ECRHS3
324 by spirometric patterns. Compared with the normal pattern, participants in the mid-adult
325 onset restrictive pattern were more likely not only to be overweight/obese at both surveys
326 (25% versus 32%, respectively) but also to become overweight/obese at ECRHS3 (35% versus
327 47%). These results were in line with those on changes in body silhouette categories between
328 ages 8-30 years (supplementary Table 4) and with the remarkably higher increase in BMI
329 between ECRHS1 and ECRHS3 in the mid-adult onset restrictive group (median BMI change:
330 4·7 [Interquartile Range:5.3]) than in any of the other patterns (medians between 2·8 and 3·0).
331 In contrast, participants in the mid-adult onset obstructive spirometry had the highest pack-
332 years increase ($p<0.001$), and they were about twice as likely to be persistent smokers (33%)
333 than participants in the other spirometric patterns (16-18%). Of note, no appreciable
334 differences in smoking were found between participants in the normal and those in the mid-
335 adult onset restrictive spirometry.

336

337 In sensitivity analysis, estimates were mostly similar to those from the main analysis. Excluding
338 the symptomatic sample did not change the results (supplementary Table 5). Excluding
339 asthmatics at ECRHS1 reduced the estimates for parental and childhood asthma, while the
340 other associations remained similar to those from main analysis (supplementary Table 6).
341 Using GLI-equations reduced the number of individuals with abnormal spirometry
342 (supplementary Table 7) but estimates were consistent with those observed in our main
343 analysis. Estimates remained similar when excluding subjects with FVC value at baseline lower
344 than FVC value at follow-up (supplementary Table 8).

345

346 **DISCUSSION**

347 This study describes the characteristics and risk factors of spirometric patterns from age 20 to
348 60 years in a large mostly European population. As expected by definition, we observed that
349 young onset spirometric patterns were characterized by lung function deficits that were
350 established by young adult-life, whereas an accelerated decline of lung function was the main

351 characteristic of mid-adult onset spirometric patterns. Most importantly, we found that
352 distinct risk factors were associated with young versus mid-adult onset spirometric patterns.

353

354 Most previous studies have investigated spirometric patterns among older individuals when
355 respiratory diseases arise more frequently but the effects of early adult deficits versus
356 accelerated decline of lung function cannot be distinguished.[1, 7, 25] It is only recently that
357 the full trajectories from young to older age have received more attention.[11, 26]. Our work
358 fills the gap by contrasting the restrictive and obstructive spirometric patterns between young
359 and mid-adult life.

360

361 On one hand, as expected, main risk factors for the young onset obstructive pattern were early
362 life factors (parental, childhood asthma and respiratory infections before 5 years), while for
363 the mid-adult onset obstructive pattern they were adult exposures, such as the amount of
364 tobacco smoked. These results are very much in line with previous studies on trajectories for
365 COPD.[9, 27] Wang et al.[27] reported parental asthma, childhood asthma and respiratory
366 infections as risk factors for airflow limitation by young adult life. The role of early life origins
367 as well as smoking on development of obstructive lung diseases has been widely described
368 before.[25, 27-29]

369

370 On the other hand, the contributions of different risk factors to the trajectories of the
371 restrictive spirometry patterns remain largely unknown. We found that reporting the leanest
372 body silhouette in childhood and being underweight in young adult life were independently
373 related to the young onset restrictive spirometry pattern, while on the contrary, obesity and
374 weight-gain were strongly associated with the mid-adult onset restrictive spirometry. These
375 results expand the growing evidence that spirometric restriction arising in young adults may be
376 a different phenotype than the restrictive spirometry pattern observed in older adults.[30] It
377 was particularly striking that being underweight was the most consistent risk factor for the
378 young restrictive pattern while it had no effect among individuals with mid-adult onset
379 spirometric restriction. This finding is in line with growing literature showing childhood
380 underweight[19] and/or having a persistently low BMI at an early age[31] strongly predict the
381 development of spirometric restriction in young adult life. Wang and colleagues found

underweight to be related with restrictive spirometry while early-life risk factors related to obstructive patterns.[32]

Each individual is believed to follow their own lung function trajectory which is likely influenced by a wide range of host factors and exposures starting early in life (including in utero) as well as throughout childhood and adult life after lungs have reached their full growth. It is therefore expected that different risk factors may interfere with growth or decline at different ages. This has been described in a large cross-sectional study.[30]

The reasons why individuals who are underweight in childhood and young adult-life are more likely to develop the young restrictive spirometric pattern are yet to be understood. Trajectories of low BMI from childhood into young adult-life can result from developmental growth deficits (acquired in-utero or in childhood), which have been found recently to be associated with spirometric restriction in young adults.[19] Such growth deficits may affect the lungs as well as other organs and systems, a hypothesis consistent with the increased comorbidities associated with spirometric restriction observed in this and previous studies.[1, 2, 5, 12] The early origins of young spirometric restriction are also supported by the association of this spirometric pattern with a positive report of respiratory infections in the first 5 years of life, although the possibilities of recall bias and reverse causation (i.e., the possibility that children with small lungs are more susceptible to respiratory infections in the first place) cannot be ruled out. Interestingly, the majority of participants with young spirometric restriction who were underweight in ECRHS1 moved to a higher BMI category at follow-up. However, the young onset spirometric pattern was still associated with a prevalence of low fat-free mass that was twice as high as that of the normal pattern.

Obesity, on the contrary, is a known risk factor for the restrictive spirometric pattern and lower FVC levels in older adults, possibly through fat-induced inflammation, altered respiratory mechanics, and/o reduced physical activity.[20, 23] In our study, while BMI showed a U-shaped relation to the young spirometric restriction with both the underweight and obese categories being at increased risk, BMI was linearly associated with the mid-adult onset spirometric restriction with only obese individuals being at increased risk. Most importantly,

413 the increase in BMI over the years was a strong predictor for mid-adult onset spirometric
414 restriction.

415

416 The main limitations of our analysis are that, as in all longitudinal studies with long follow-up
417 periods, we cannot discard the possibility of attrition bias. Most risk factors were assessed
418 using questionnaires and early life factors were assessed retrospectively, which are likely
419 subject to some misclassification. Pre-bronchodilator spirometry was used, therefore
420 participants with obstructive patterns could have had either irreversible or reversible
421 obstruction. One recent study showed that risk factors for the two phenotypes can be
422 different.[27] However, in previous studies risk factors for young spirometric restriction were
423 confirmed after removing individuals with bronchodilator response.[19] We also acknowledge
424 that our study could not differentiate participants with true lung restriction (which needs
425 measurement of total lung capacity) from those with spirometric restriction alone. Spirometric
426 restriction could occur for air trapping and other reasons not necessarily related to lung
427 impairment (among which comorbidities, pain, poor physical conditions etc). However, even
428 when true restriction is absent, the reasons for low FVC should be determined.[2, 3] Likewise,
429 our study was not designed to describe the natural course of abnormal spirometric patterns
430 (i.e. how individuals with young/mid-adult onset evolved over time). Future studies should
431 look into this to understand the natural history of individuals with young abnormal spirometry
432 as they age.

433

434 Among the strengths of this study, ECRHS is a large longitudinal population-based cohort that
435 has a long follow-up (>20-years) and is representative of the general population in Europe. This
436 study is the first one to look at distinct trajectories at young and older ages, filling the gap
437 between studies looking at spirometric patterns in younger or older individuals only. We
438 provided a series of sensitivity analysis to ensure that our results were robust to the chosen
439 definition of spirometric patterns and to the inclusion of asthmatics and additional subjects
440 with respiratory symptoms at baseline. Obesity, one of the main determinants of spirometric
441 patterns, was assessed using different measures (clinically measured weight and height (BMI),
442 body-silhouettes, and fat mass) and at different times giving more comprehensive results and
443 providing insight into the temporal sequence of exposures and outcomes.
444

445 In conclusion, in a large longitudinal study across Europe, we found that characteristics and
446 risk factors for restrictive and obstructive spirometric patterns differ profoundly based on
447 whether their onset occurs in young versus mid-adult life. Being underweight in childhood and
448 young adult-life was strongly associated with the occurrence of the young spirometric
449 restrictive pattern, while asthma was the main risk factor for the young obstructive pattern. In
450 contrast, adult life risk factors, especially smoking and obesity (and weight gain), were
451 associated with mid-adult onset patterns (obstructive and restrictive, respectively). To be fully
452 effective, prevention efforts will need to target both fostering lung function development in
453 childhood and reducing lung function decline in adult life. In this context, identifying specific,
454 abnormal lung function trajectories will be critical to understand and disentangle the best
455 windows of opportunity to prevent future lung impairments and diseases.
456

457 **Authors' contributions**

458 Study concept and design: SG, JMA, AEC. Data collection and coordination: SA, SDC, BL, LC, SC,
459 PD, BF, TG, AGC, CJ, RJ, JMM, DN, LPG, IP, NPH, CR, GS, CS, KT, IU, IH, JMA, JGA, DJ. Analysis
460 and interpretation of data: AEC, MH, SDC, SG. Drafting of the manuscript: AEC, SG. Critical
461 revision of the manuscript for important intellectual content: all authors.

462

463 **Conflicts of interest**

464 Authors have no conflicts of interest

465

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472 principal investigators for the European Community Respiratory Health Survey are reported in

473 the Supplementary Appendix 1.

Table 1. Participant characteristics in mid-adult life (i.e., as assessed at the ECRHS3 survey) according to spirometric patterns

	Normal	**Young onset restrictive**	**Young onset obstructive**	**Mid-adult onset restrictive**	**Mid-adult onset obstructive**	***P*-val**
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	
Age, mean (sd)	50·4 (5·4)	*49·7 (5·4)	*51·2 (5·2)	50·2 (5·5)	50·9 (5·5)	0·003
Sex, Female	1,277 (55·7%)	184 (49·6%)	159 (52·8%)	105 (56·1%)	178 (50·9%)	0·121
Education						0·141
Low	166 (7·4%)	19 (5·2%)	26 (9·3%)	13 (7·3%)	38 (11·2%)	
Medium	764 (34·3%)	129 (35·6%)	102 (36·4%)	68 (38·0%)	108 (31·8%)	
High	1,3 (58·3%)	214 (59·1%)	152 (54·3%)	98 (54·7%)	194 (57·1%)	
BMI		*	*	*		<0·001
Low	85 (3·7%)	21 (5·7%)	20 (6·7%)	3 (1·6%)	12 (3·4%)	
Normal	833 (36·5%)	128 (34·7%)	94 (31·3%)	36 (19·6%)	133 (38·2%)	
Overweight	923 (40·5%)	130 (35·2%)	105 (35·0%)	66 (35·9%)	143 (41·1%)	
Obese	439 (19·3%)	90 (24·4%)	81 (27·0%)	79 (42·9%)	60 (17·2%)	
Fat-Free Mass (Z-score) ‡		*	*	*		<0·001
Low	87 (5·1%)	29 (10·2%)	14 (6·6%)	5 (4·2%)	20 (7·2%)	
Normal	1,478 (86·8%)	228 (80·3%)	171 (80·7%)	90 (75·0%)	242 (87·1%)	
High	137 (8·0%)	27 (9·5%)	27 (12·7%)	25 (20·8%)	16 (5·8%)	
Fat Mass (Z-score) ‡			*	*		<0·001
Low	107 (6·3%)	17 (6·0%)	21 (9·9%)	4 (3·3%)	11 (4·0%)	
Normal	1,461 (85·8%)	236 (83·1%)	167 (78·8%)	84 (70·0%)	241 (86·7%)	
High	134 (7·9%)	31 (10·9%)	24 (11·3%)	32 (26·7%)	26 (9·4%)	
Smoking status					*	<0·001

Never	1,028 (45·0%)	175 (47·6%)	127 (42·3%)	87 (46·5%)	109 (31·3%)	
Ex-smoker	803 (35·2%)	115 (31·3%)	113 (37·7%)	65 (34·8%)	113 (32·5%)	
Current smoker	453 (19·8%)	78 (21·2%)	60 (20·0%)	35 (18·7%)	126 (36·2%)	
Pack-years, median (IQR)	0·1 (14·0)	0 (19·0)	0·6 (17·0)	0 (16·5)	*12·9 (30·0)	<0·001
Among smokers, median (IQR)	14 (19·5)	*18·9 (24·3)	17·0 (24·0)	16·7 (20·5)	*24·0 (23·0)	<0·001
Asthma last 12mo.	163 (7·1%)	*53 (14·4%)	*103 (34·3%)	12 (6·5%)	*64 (18·7%)	<0·001
Wheezing last 12 mo.	493 (21·5%)	*120 (32·3%)	*150 (49·8%)	*50 (26·7%)	*124 (35·4%)	<0·001
Dyspnea last 12 mo.	76 (3·3%)	*23 (6·2%)	*27 (9·0%)	*13 (7·0%)	16 (4·6%)	<0·001
Chronic bronchitis	105 (5·0%)	25 (7·1%)	*36 (14·5%)	12 (7·0%)	*33 (9·8%)	0·165
Comorbidities						
Heart disease	36 (1·7%)	9 (2·6%)	6 (2·4%)	6 (3·5%)	*14 (4·2%)	0·040
Hypertension	395 (17·3%)	72 (19·5%)	54 (18·0%)	*54 (29·2%)	67 (19·3%)	0·002
Stroke	13 (0·6%)	4 (1·1%)	2 (0·7%)	*6 (3·2%)	2 (0·6%)	0·003
Diabetes	67 (3·2%)	*21 (6·0%)	12 (4·8%)	*15 (8·7%)	*19 (5·7%)	0·001
Depression	352 (15·4%)	68 (18·5%)	57 (19·1%)	36 (19·5%)	68 (19·5%)	0·104
†Ank spondylitis/psoariatic arthr.	39 (1·9%)	12 (3·4%)	4 (1·6%)	*12 (6·9%)	11 (3·3%)	<0·001
Low physical activity#	574 (33·9%)	113 (38·8%)	60 (30·8%)	*60 (42·6%)	85 (34·0%)	0·094

sd: standard deviation. BMI: Body Mass Index. IQR: Interquartile Range. mo:month. *P* -value from chi^2 test (categorical), Kruskal Wallis test (continuous) * *P*-value <0·05 when comparing the corresponding spirometry pattern to the normal pattern. †ankylosing spondylitis or psoariatic arthritis ‡ low if z-score< 10th percentile, high if z-score> the 90th percentile #physical activity was defined as the lowest tertile of total Mets per week.

Table 2. Risk factors distribution according to spirometric patterns

	Normal	**Young onset restrictive**	**Young onset obstructive**	**Mid-adult onset restrictive**	**Mid-adult onset obstructive**	***P-value***
	No. %	% No.	No. %	% No.	No. %	
Early-life risk factors						
Maternal age at birth						0·756
≤25 years	672 (34·1%)	100 (33·3%)	91 (38·7%)	57 (37·7%)	102 (34·1%)	
26-31 years	697 (35·4%)	103 (34·3%)	81 (34·5%)	50 (33·1%)	97 (32·4%)	
≥32 years	599 (30·4%)	97 (32·3%)	63 (26·8%)	44 (29·1%)	100 (33·4%)	
Mother education						0·964
Minimum school leaving age	1,353 (65·5%)	227 (66·2%)	164 (67·2%)	115 (68·0%)	215 (65·5%)	
Secondary school past min age	453 (21·9%)	80 (23·3%)	54 (22·1%)	35 (20·7%)	71 (21·6%)	
College or university	260 (12·6%)	36 (10·5%)	26 (10·7%)	19 (11·2%)	42 (12·8%)	
Father education						0·329
Minimum school leaving age	1,121 (55·0%)	169 (50·4%)	129 (54·0%)	85 (51·5%)	167 (51·9%)	
Secondary school past min age	526 (25·8%)	86 (25·7%)	57 (23·8%)	46 (27·9%)	98 (30·4%)	
College or university	393 (19·3%)	80 (23·9%)	53 (22·2%)	34 (20·6%)	57 (17·7%)	
Smoking pregnancy						0·738
No	1,723 (76·0%)	276 (76·0%)	225 (75·5%)	133 (71·5%)	263 (76·5%)	
During childhood	416 (18·3%)	67 (18·5%)	59 (19·8%)	44 (23·7%)	67 (19·5%)	
During pregnancy	129 (5·7%)	20 (5·5%)	14 (4·7%)	9 (4·8%)	14 (4·1%)	
Parental smoking status						0·918
None	678 (30·7%)	117 (33·2%)	88 (30·2%)	57 (32·0%)	98 (28·9%)	

1 parent smoked	1,127 (51·1%)	175 (49·7%)	144 (49·5%)	85 (47·8%)	178 (52·5%)	
2 parents smoked	400 (18·1%)	60 (17·0%)	59 (20·3%)	36 (20·2%)	63 (18·6%)	
Maternal asthma	121 (5·3%)	28 (7·5%)	*30 (10·1%)	14 (7·6%)	*34 (9·9%)	0·001
Paternal asthma	186 (8·3%)	34 (9·3%)	*44 (15·1%)	18 (10·2%)	37 (10·7%)	0·004
Delivered by Caesarean section	71 (3·1%)	10 (2·7%)	12 (4·0%)	6 (3·3%)	5 (1·5%)	0·406
Living place <5 years old						0·078
Farm/rural	628 (32·0%)	88 (29·5%)	66 (27·8%)	40 (26·5%)	98 (32·3%)	
Small town	405 (20·6%)	44 (14·8%)	43 (18·1%)	27 (17·9%)	59 (19·5%)	
Suburb/city	930 (47·4%)	*166 (55·7%)	128 (54·0%)	84 (55·6%)	146 (48·2%)	
Childhood asthma†	86 (3·8%)	18 (4·9%)	*43 (14·3%)	7 (3·7%)	*24 (6·9%)	<0·001
Respiratory Infection before 5 years	209 (9·7%)	*47 (13·6%)	*51 (18·4%)	17 (9·8%)	42 (13·0%)	<0·001
Body silhouette at 8 years		*				0·006
1	931 (48·4%)	183 (58·5%)	121 (51·9%)	66 (42·6%)	161 (51·1%)	
2	386 (20·1%)	54 (17·3%)	40 (17·2%)	40 (25·8%)	64 (20·3%)	
3	284 (14·8%)	26 (8·3%)	27 (11·6%)	21 (13·5%)	42 (13·3%)	
4	172 (8·9%)	23 (7·3%)	20 (8·6%)	9 (5·8%)	16 (5·1%)	
5 to 9	151 (7·8%)	27 (8·6%)	25 (10·7%)	19 (12·3%)	32 (10·2%)	
Body silhouette at puberty						0·059
1	361 (21·0%)	81 (27·2%)	55 (26·3%)	19 (14·1%)	67 (23·0%)	
2	610 (35·5%)	102 (34·2%)	73 (34·9%)	49 (36·3%)	104 (35·7%)	
3	383 (22·3%)	48 (16·1%)	35 (16·7%)	37 (27·4%)	61 (21·0%)	
4	233 (13·5%)	41 (13·8%)	25 (12·0%)	15 (11·1%)	30 (10·3%)	
5 to 9	133 (7·7%)	26 (8·7%)	21 (10·0%)	15 (11·1%)	29 (10·0%)	

Young adult life risk factors						
Body silhouette at 30 years		*		*	*	<0·001
1	63 (3·3%)	24 (7·5%)	13 (5·6%)	3 (1·9%)	13 (4·2%)	
2	375 (19·4%)	48 (15·1%)	48 (20·7%)	20 (12·7%)	85 (27·2%)	
3	690 (35·6%)	108 (34·0%)	75 (32·3%)	45 (28·7%)	102 (32·6%)	
4	474 (24·5%)	77 (24·2%)	48 (20·7%)	43 (27·4%)	66 (21·1%)	
5 to 9	334 (17·3%)	61 (19·2%)	48 (20·7%)	46 (29·3%)	47 (15·0%)	
BMI at ECRHS1[‡]		*	*	*		<0·001
Low	284 (12·4%)	80 (21·6%)	50 (16·6%)	19 (10·2%)	55 (15·7%)	
Normal	1,41 (61·5%)	176 (47·6%)	160 (53·2%)	105 (56·1%)	215 (61·4%)	
Overweight	495 (21·6%)	87 (23·5%)	66 (21·9%)	46 (24·6%)	69 (19·7%)	
Obese	102 (4·5%)	27 (7·3%)	25 (8·3%)	17 (9·1%)	11 (3·1%)	
Smoking status at ECRHS1[‡]		*			*	<0·001
Never	1,025 (46·1%)	178 (50·1%)	119 (42·2%)	88 (48·4%)	102 (29·4%)	
Ex-smoker	430 (19·4%)	49 (13·8%)	57 (20·2%)	34 (18·7%)	62 (17·9%)	
Current smoker	767 (34·5%)	128 (36·1%)	106 (37·6%)	60 (33·0%)	183 (52·7%)	
Pack-years at ECRHS1[‡], median (IQR)	0·8 (8·0)	0 (8·0)	*2 (11·5)	0·8 (8· 5)	*5·8 (15·0)	<0·001
Pack-years at ECRHS1[‡] in ever smokers, median (IQR)	7·2 (12·7)	8·1 (11·7)	*10·4 (13·0)	8·2 (11·2)	*12 (12·7)	<0·001
Atopy at ECRHS1[$]	586 (29·3%)	106 (34·0%)	*122 (49·0%)	44 (26·7%)	105 (32·3%)	<0·001
Asthma last 12 months at ECRHS1[‡]	109 (4·8%)	*31 (8·4%)	*85 (28·4%)	12 (6·4%)	*35 (10·0%)	<0·001

Information for all risk factors was collected at ECRHS1, with the exception of information on body silhouette at 8 years, at puberty and at 30 years, which was recalled at ECRHS3.

sd: standard deviation; IQR: Interquartile Range. *P* -value from chi-squared test (categorical) and Kruskal Wallis test (continuous) * *P*-value <0·05 when comparing corresponding spirometry pattern to the group with normal spirometry after adjustment for age and sex. [†] Childhood asthma defined as first asthma attack occurring before 11 years old. [$] Atopy (yes if at least 1 Spe-IgE was >0·35 ng/ml, measured at ECRHS1)

Table 3. Association between early-life and young adult-life risk factors and spirometric patterns

	Young onset restrictive	**Young onset obstructive**	**Mid-adult onset restrictive**	**Mid-adult onset obstructive**
	RRR 95%CI	RRR 95%CI	RRR 95%CI	RRR 95%CI
Early-life risk factors				
Maternal asthma	1·48 (0·96-2·28)	**1·77 (1·15-2·72)**	1·46 (0·82-2·59)	**1·84 (1·23-2·76)**
Paternal asthma	1·15 (0·78-1·69)	**1·72 (1·20-2·48)**	1·25 (0·75-2·09)	1·25 (0·85-1·82)
Childhood asthma	1·22 (0·72-2·08)	**3·36 (2·22-5·07)**	0·98 (0·44-2·17)	1·60 (0·99-2·60)
Resp. Infect. <5yrs	**1·48 (1·05-2·08)**	**1·97 (1·40-2·77)**	1·01 (0·60-1·70)	1·34 (0·94-1·92)
Body silhouette at 8yrs†				
1	**1·61 (1·21-2·14)**	1·25 (0·90-1·73)	0·80 (0·55-1·16)	1·04 (0·79-1·37)
2 and 3	1	1	1	1
4	1·12 (0·68-1·84)	1·18 (0·69-2·01)	0·56 (0·27-1·16)	0·59 (0·34-1·04)
5 to 9	1·47 (0·92-2·36)	1·62 (0·98-2·67)	1·40 (0·81-2·42)	1·30 (0·84-2·01)
Young adult risk factors				
Body silhouette at 30yrs†				
1	**2·52 (1·52-4·16)**	1·70 (0·90-3·21)	0·77 (0·23-2·52)	1·11 (0·60-2·06)
2 and 3	1	1	1	1
4	1·11 (0·83-1·50)	0·87 (0·61-1·25)	1·48 (0·99-2·21)	0·80 (0·59-1·08)
5 to 9	1·20 (0·87-1·66)	1·30 (0·90-1·87)	**2·32 (1·55-3·46)**	0·80 (0·57-1·13)
BMI at ECRHS1				
Low	**2·43 (1·80-3·29)**	**1·67 (1·18-2·38)**	0·87 (0·52-1·45)	1·38 (0·99-1·92)
Normal	1	1	1	1
Overweight	**1·37 (1·03-1·82)**	1·06 (0·77-1·45)	1·30 (0·90-1·88)	0·84 (0·63-1·13)
Obese	**2·20 (1·39-3·48)**	**1·81 (1·12-2·93)**	**2·34 (1·34-4·08)**	0·64 (0·34-1·23)
Smoking status at ECRHS1				
Never-smoker	1	1	1	1
Ex-smoker	**0·68 (0·48-0·96)**	1·09 (0·77-1·54)	0·93 (0·61-1·42)	1·40 (1·00-1·98)
Current smoker	0·95 (0·74-1·22)	1·12 (0·84-1·49)	0·91 (0·65-1·28)	**2·32 (1·78-3·01)**
Atopy at ECRHS1	1·20 (0·92-1·60)	**2·14 (1·63-2·83)**	0·89 (0·62-1·28)	1·10 (0·85-1·43)
Asthma last 12 mo. at ECRHS1	**1·84 (1·17-2·89)**	**6·94 (4·81-10·01)**	1·38 (0·71-2·68)	**1·74 (1·12-2·70)**

RRR: Relative Risk Ratio from multinomial logistic regression adjusted for age, sex and symptomatic sample. Centre was included as random effect. The group with normal spirometry was the reference group. 95%CI: 95% confidence interval. Resp. Infect.: history of respiratory infection before 5 years. BMI: Body Mass Index. †recalled at ECRHS3

Table 4. Changes and longitudinal categories of risk factors from young to mid-adult life by spirometric patterns

	Normal	**Young onset restrictive**	**Young onset obstructive**	**Mid-adult onset restrictive**	**Mid-adult onset obstructive**	***P-value***
	No. (%)	No. (%)	No. (%)	No. (%)	No. (%)	
BMI longitudinal categories		*	*	*	*	<0·001
Persistent underweight	60 (2·6%)	18 (4·9%)	17 (5·7%)	3 (1·6%)	8 (2·3%)	
Persistent normal weight	632 (27·7%)	75 (20·4%)	64 (21·3%)	24 (13·0%)	87 (25·0%)	
Persistent Overweight/obese	564 (24·8%)	108 (29·3%)	90 (30·0%)	59 (32·1%)	77 (22·1%)	
Underweight to normal	175 (7·7%)	48 (13·0%)	30 (10·0%)	11 (6·0%)	44 (12·6%)	
Underweight/normal to overweight/obese	796 (34·9%)	112 (30·4%)	96 (32·0%)	86 (46·7%)	126 (36·2%)	
Decrease in BMI category	51 (2·2%)	7 (1·9%)	3 (1·0%)	1 (0·5%)	6 (1·7%)	
Δ BMI[†], median (IQR)	2·87 (±3·2)	2·79 (±3·7)	3·01 (±3·9)	*4·72 (±5·3)	2·85 (±3·3)	<0·001
Smoking longitudinal categories					*	<0·001
Never	933 (42·0%)	162 (46·0%)	110 (39·0%)	80 (44·0%)	94 (27·2%)	
Ex-smoker	383 (17·3%)	39 (11·1%)	50 (17·7%)	31 (17·0%)	53 (15·4%)	
Quitters	465 (20·9%)	76 (21·6%)	65 (23·0%)	37 (20·3%)	72 (20·9%)	
Late smokers	78 (3·5%)	13 (3·7%)	9 (3·2%)	6 (3·3%)	11 (3·2%)	
Persistent smokers	361 (16·3%)	62 (17·6%)	48 (17·0%)	28 (15·4%)	115 (33·3%)	
Δ pack-years, median (IQR) [‡]	0 (3·2)	*0 (7·7)	0 (3·0)	0 (3·6)	*0·3 (14·0)	<0·001
Δ pack-years (ever smokers), median (IQR) [‡]	2·2 (11·2)	*6·5 (18·9)	0·9 (10·7)	2·6 (11·0)	*8·8 (17·9)	<0·001

IQR : Interquartile Range. [†]difference between BMI measured at ECRHS3 and ECRHS1· [‡]difference in pack-years of smoking between ECRHS3 and ECRHS1. * *P*-value <0·05 when comparing corresponding spirometric pattern to the group with normal spirometry.

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FIGURES

Figure 1. Flow-chart. Blue boxes refer to the spirometric pattern groups included in analyses.

Figure 2. Predicted mean with 95% Confidence Intervals of FEV_1 (a), FVC (b), and FEV_1/FVC (c) from mixed linear regression models including age, age^2, sex, spirometric trajectories, and their interactions with age.