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Changes in lung function in European adults born between 1884 and 1996 and implications for the diagnosis of lung disease: a cross-sectional analysis of ten population-based studies

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Summary

Background During the past century, socioeconomic and scientific advances have resulted in changes in the health and physique of European populations. Accompanying improvements in lung function, if unrecognised, could result in the misclassification of lung function measurements and misdiagnosis of lung diseases. We therefore investigated changes in population lung function with birth year across the past century, accounting for increasing population height, and examined how such changes might influence the interpretation of lung function measurements.

Methods In our analyses of cross-sectional data from ten European population-based studies, we included individuals aged 20–94 years who were born between 1884 and 1996, regardless of previous respiratory diagnoses or symptoms. FEV_1, forced vital capacity (FVC), height, weight, and smoking behaviour were measured between 1965 and 2016. We used meta-regression to investigate how FEV_1 and FVC (adjusting for age, study, height, sex, smoking status, smoking pack-years, and weight) and the FEV_1/FVC ratio (adjusting for age, study, sex, and smoking status) changed with birth year. Using estimates from these models, we graphically explored how mean lung function values would be expected to progressively deviate from predicted values. To substantiate our findings, we used linear regression to investigate how the FEV_1 and FVC values predicted by 32 reference equations published between 1961 and 2015 changed with estimated birth year.

Findings Across the ten included studies, we included 243 465 European participants (mean age 51·4 years, 95% CI 51·4–51·5) in our analysis, of whom 136 275 (56·0%) were female and 107 190 (44·0%) were male. After full adjustment, FEV_1 increased by 4·8 mL/birth year (95% CI 2·6–7·0; p<0·0001) and FVC increased by 8·8 mL/birth year (5·7–12·0; p<0·0001). Birth year-related increases in the FEV_1 and FVC values predicted by published reference equations corroborated these findings. This height-independent increase in FEV_1 and FVC across the last century will have caused mean population values to progressively exceed previously predicted values. However, the population mean adjusted FEV_1/FVC ratio decreased by 0·11 per 100 birth years (95% CI 0·09–0·14; p<0·0001).

Interpretation If current diagnostic criteria remain unchanged, the identified shifts in European values will allow the easier fulfilment of diagnostic criteria for lung diseases such as chronic obstructive pulmonary disease, but the systematic underestimation of lung disease severity.

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Introduction

Across the last century, substantial socioeconomic changes and scientific advances have resulted in changes in the health[1] and physique[2,3] of European populations. Such changes in physical norms over time need to be recognised for physical measurements to be interpreted appropriately. The appropriate interpretation of lung function measurements is important for the diagnosis of lung diseases, particularly chronic obstructive pulmonary disease (COPD),[4,5] but also asthma[6] and interstitial lung disease.[7] For COPD, FEV_1 and forced vital capacity (FVC) measurements are used to confirm the presence of airflow obstruction, defined as an FEV_1/FVC ratio of less than the lower limit of normal or less than 0·70.[4] The severity of COPD is graded by the severity of FEV_1 impairment, determined by comparing observed values with predicted normal values.[4] Thus, the diagnosis and grading of COPD relies partly on understanding what constitutes normal lung function.

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Research in context

Evidence before this study

We searched PubMed for articles published in English between database inception and Jan 17, 2021, using the search terms ("cohort effects" OR "secular trends") AND ("lung function" OR "pulmonary function" OR "FEV_1" OR "FVC" OR "height"). Height is a major determinant of lung function, and European population height has increased with advancing birth year across most of the 20th century. This increase has been attributed to improved growth due to improvements in diet, health care, and lifestyle. Although our search found multiple (>30) studies examining changing European population height with time, we found only one study investigating cohort effects on European population lung function. The study included 6148 Dutch individuals born before 1950 and aged 20–54 years whose lung functions were measured from 1965 to 1990. The study showed that progressive height-adjusted lung function increased with advancing birth year, at least until the mid-20th century. However, a subsequent larger international study that collected data between 1978 and 2009 and included 43 032 White individuals aged 2–95 years across 30 centres reported no convincing ongoing birth cohort effects and proposed that this finding reflected the stabilisation of socioeconomic conditions in these countries.

Added value of this study

Our European population study included a much larger sample (243 465 individuals) and covered a wider range of birth years (1884–1996) and measurement years (1965–2016) than previous similar studies. These data allowed us to identify increases in mean FEV_1 and forced vital capacity (FVC) that occurred independently of height in the European population across more than a century of birth years. We corroborated these findings using published reference equations, and showed that these changes result in the progressive deviation of lung function from previously predicted values. We also found that the FEV_1/FVC ratio decreased over the study period.

Implications of all the available evidence

Physiologically, height-independent changes in lung function could indicate that socioeconomic change has been accompanied by beneficial changes in thoracic geometry, muscle strength, or alveoli number in the European population. Clinically, these changes in lung function with time will have led lung function predictions to increasingly underestimate mean lung function among healthy Europeans, and therefore underestimate the degree of lung function impairment associated with lung diseases such as chronic obstructive pulmonary disease (COPD). Although clinicians consider many factors when diagnosing lung diseases, the concurrent decrease in the FEV_1/FVC ratio, perhaps attributable to increasing height and dysanaptic pulmonary growth, will also have led to easier fulfilment of COPD diagnostic criteria. This study highlights the need to update reference equations for populations from high-income European countries to better reflect current normal values and raises issues regarding the application of reference equations to longitudinal lung function data.

Reference equations derived from cross-sectional studies of healthy, non-smoking adults are used to predict normal lung function.[8,9] However, in cross-sectional studies, decreasing participant age corresponds to advancing birth year. Consequently, these studies are particularly susceptible to cohort effects, in which differences associated with age reflect differing environmental exposures across successive birth years. For example, the dietary, infectious disease, health care, and air pollution exposures of a 20-year-old European born in the 1920s are likely to differ substantially from those of a 20-year-old European born in the 1980s. The previous impacts of cohort effects have been illustrated by the progressive increase in lung function in Dutch individuals born across the first half of the 20th century.[10] These effects explain why the rate of decline in lung function across adulthood estimated from early cross-sectional studies exceeded that observed in subsequent longitudinal studies.[11,12]

Whether cohort effects continue to impact lung function in historically high-income countries is unclear. Reviewing data collected between 1978 and 2009, one major international study found little impact on lung function, attributing this finding to the stabilisation of socioeconomic conditions.[13] However, other studies show that the height of European populations has continued to increase with birth year across much of the 20th century, suggesting ongoing cohort effects.[2,3,14] These changes have been attributed to improving diets, health care, and lifestyle,[10,14] resulting in better growth during childhood and adolescence.[2] Hypothesised transgenerational inheritance of exposure effects[14,15] might also implicate a role for changing parental exposures.[16]

As a major determinant of thoracic volume, such increases in height would be expected to result in increasing average lung function.[8,9] However, reference equations predict lung function for each individual according to their height and should therefore accommodate increases in population lung function driven purely by increasing population height.[8,9] Nevertheless, height-independent increases in lung function—eg, due to changes in chest geometry, an increasing number of alveoli, or enhanced muscle physique—could cause normal population values to progressively diverge from previously predicted values. Unrecognised, this divergence could lead to the increasingly inappropriate interpretation of lung function values, and the misclassification or misdiagnosis of diseases such as COPD.

We hypothesised that the lung volumes of people in high-income European countries have increased with

advancing birth year in excess of the change expected to accompany increasing population height over the past century. We therefore aimed to analyse observational data from ten major European population-based studies, and 32 published reference equations, to investigate how FEV_1 and FVC have changed with advancing birth year after accounting for increasing height. We then aimed to explore how the changes with birth year could affect the diagnostic interpretation of FEV_1, FVC, and FEV_1/FVC ratios.

Methods

Study design and participants

In our cross-sectional analysis, we included men and women aged 20–94 years who were enrolled, with the intention of completing longitudinal follow-up, in ten central and northern European general population representative studies participating in the European Respiratory Society Chronic Airway Diseases Early Stratification (CADSET) Clinical Research Collaboration (table 1).[17] We did not exclude individuals with previous respiratory diagnoses or symptoms. Details of the research methods of the included studies, including recruitment, data collection, and lung function measurements, are available in the appendix (pp 3–11). Each included study obtained written informed consent from participants and ethical approval from the relevant regulatory boards.

Data extraction

For each individual, we used their date of birth and date of spirometry measurement to calculate their age at the time of spirometry measurement. For each individual, pre-bronchodilator FEV_1 (mL), FEV_1 in percentages of predicted normal values, sex, smoking status (ever smoker *vs* never smoker), cumulative tobacco consumption (pack-years), height (m), and weight (kg) were included. We included only individuals who provided complete data. Each individual contributed data only once, at the first point in time when these cross-sectional data were recorded. Nine studies also provided pre-bronchodilator FVC (mL), FVC in percentages of predicted normal values, and FEV_1/FVC ratio. The Vlagtwedde-Vlaardingen study[18] measured vital capacity, rather than FVC, so participants in this study were excluded from analyses reliant on FVC values. Individual percentages of predicted normal values were calculated according to Global Lung Function Initiative 2012 reference equations.[8] Ever smokers were defined as those who had smoked at least one cigarette per day for at least 1 year before the date of spirometry measurement. Those who had not smoked at least one cigarette per day for at least 1 year before the date of spirometry measurement were considered never smokers. Pack-years were calculated as the mean number of cigarettes smoked daily multiplied by the number of years smoked divided by 20.

Each study provided summary data (means with SEs) stratified by sex, smoking status, birth cohort, and age group. We defined nine birth cohorts (pre-1920, 1920–29, 1930–39, 1940–49, 1950–59, 1960–69, 1970–79, 1980–89, and 1990–99) and seven age groups (20–29 years, 30–39 years, 40–49 years, 50–59 years, 60–69 years, 70–79 years, and 80–94 years). The oldest age group spanned 15 years rather than 10 years because of the low sample size in this age group.

We searched PubMed without language restrictions for studies detailing reference equations predicting FEV_1 and FVC for 50-year-old White (Caucasian) adults in Europe, North America, or Australia published between database inception and Jan 7, 2021, using the search terms ("spirometry" OR "lung function") AND "reference equation". Equations were also identified from published reviews. We chose these regions so that included reference equations would be based on White adults from high-income countries. For each reference equation, we used the midpoint year of the study's reported measurement period to estimate the year of lung function measurement. Where the measurement period was unreported, we instead used the year of manuscript submission, or, if unavailable, the year of publication. We estimated the birth year of 50-year-olds included in each study by subtracting 50 years from the estimated measurement year.

Statistical analysis

We explored how birth year influenced both lung function (FEV_1 and FVC) and height with age among women and men, and never smokers and ever smokers. This approach was repeated for central and northern European studies separately (see appendix p 24 for the groupings) to check for replication in never smokers in two geographical regions.

To identify whether lung function increased with birth year, independent of increasing height, we used meta-regression (also known as meta-analysis regression) using stratified summary estimates, with SEs, from each study. Meta-regression is a meta-analysis technique that relates statistical heterogeneity between study effect sizes to variables available in the studies by use of regression-based techniques.[19] Within these meta-regression models, we progressively adjusted for variables potentially associated with lung function and birth year: sex, smoking status, study (using an indicator variable), and stratum mean age, height, weight, and pack-years recorded when lung function was measured.[20] For each meta-regression analysis, we calculated R^2 and residual I^2. R^2 describes the between-study variance explained by the included covariates and I^2 describes the proportion residual of between-study variation explained by heterogeneity versus sampling variation. In sensitivity analyses, we stratified models by age (<50 years *vs* ≥50 years) and, separately, we accounted for clustering of estimates using an extended mixed-effects framework for meta-analysis.[21] We also repeated our analyses while excluding a small number of individuals for whom height was asked and not measured.

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For more on **CADSET** see https://www.cadset.org/

See **Online** for appendix

Furthermore, we explored whether including non-linear terms for age, height, and birth year improved model fit.

As appropriate, we used each reference equation to calculate predicted FEV_1 and FVC values for 50-year-old women and men using the mean height (and mean weight, when required) of never smokers in our study. Linear regression, with heteroskedasticity robust SEs, was used to evaluate whether the predicted values of FEV_1 and FVC changed according to participant birth year. In a sensitivity analysis, we excluded reference equations derived from studies that might have included ever smokers (ie, reference equations that did not explicitly predict lung function for never smokers).

	Included participants, n	Age range, years	Measurement year range	Birth year range
Overall	243 465	20–94	1965–2016	1884–1996
Vlagtwedde-Vlaardingen (Netherlands)	5997	20–74	1965–89	1901–53
Copenhagen City Heart Study (Denmark)	17 636	20–93	1976–2003	1884–1981
European Community Respiratory Health Study (Austria, Belgium, Denmark, Estonia, France, Germany, Iceland, Ireland, the Netherlands, Norway, Sweden, Switzerland, and the UK)	10 359	20–47	1991–95	1945–73
HUNT (Norway)	4431	20–92	1995–2008	1906–88
Copenhagen General Population Study (Denmark)	106 140	20–94	2003–15	1911–94
Lifelines (Netherlands)	81 978	20–90	2006–13	1920–93
OLIN (Sweden)	661	21–86	2008–10	1922–86
Rotterdam Study (Netherlands)	5471	51–94	2009–14	1915–60
West Sweden Asthma Study (Sweden)	991	21–77	2009–12	1933–88
LEAD (Austria)	9801	20–82	2011–16	1931–96

Studies are ordered chronologically according to the earliest measurement date contributed to this study. Details and references for the studies can be found in the appendix (pp 3–7). Corresponding graphical representations of the included age range, measurement year range, and birth year range are available in the appendix (pp 32–33).

Table 1: **Characteristics of the included studies**

Using estimates from our meta-regression models, we investigated how mean population lung function values would, with time, be expected to progressively deviate from predictions based on previous cross-sectional measurements. According to Global Lung Function Initiative 2012 reference equations, we plotted FVC for men of four ages (30 years, 50 years, 70 years, and 90 years) with a height of 1·81 m. We took these values to represent mean population values for never smoking White individuals in 1994 (the estimated midpoint year of the Global Lung Function Initiative 2012 measurements). Using results from our meta-regression models, we estimated the height-independent increase in FVC across 20 years and plotted the impact of this change with time from 1994 (both with age and measurement year). These calculated values were then plotted as the percentage of predicted values with time. To visually compare these theorised patterns with observed patterns, we plotted both the percentage of predicted FEV_1 and FVC observed among never smokers within our study.

To investigate whether the FEV_1/FVC ratio changed with birth year, we used meta-regression and calculated R^2 and residual I^2, accounting for age, sex, smoking status, and study. We stratified this model by sex and smoking status. To explore how changes in the FEV_1/FVC ratio might relate to differences in height, weight, and pack-years, we further adjusted this model for these variables in sensitivity analyses.

Analyses were done with SPSS, version 22, and STATA, version 14. For all tests, a p value of less than 0·05 was considered statistically significant.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

	Overall (n=243 465)	Women (n=136 275)		Men (n=107 190)	
		Never smoker (n=62 589 [45·9%])	Ever smoker (n=73 686 [54·1%])	Never smoker (n=40 611 [37·9%])	Ever smoker (n=66 579 [62·1%])
Mean age, years	51·4 (51·4–51·5)	50·0 (49·9–50·2)	51·8 (51·7–51·9)	48·5 (48·4–48·7)	54·1 (53·9–54·2)
Mean pack-years, years	10·0 (9·9–10·0)	NA	13·8 (13·7–13·9)	NA	21·2 (21·1–21·4)
Mean height, m	1·72 (1·72–1·72)	1·67 (1·67–1·67)	1·66 (1·66–1·66)	1·81 (1·81–1·81)	1·79 (1·79–1·79)
Mean weight, kg	77·2 (77·1–77·2)	70·9 (70·8–71·0)	70·8 (70·7–70·9)	85·4 (85·3–85·6)	85·1 (85·0–85·2)
Mean BMI, kg/m²	25·9 (25·9–25·9)	25·5 (25·5–25·5)	25·6 (25·5–25·6)	26·2 (26·1–26·2)	26·6 (26·6–26·6)
Mean FEV_1, mL	3183 (3179–3186)	2828 (2823–2833)	2688 (2683–2693)	4019 (4011–4026)	3554 (3547–3561)
Mean predicted FEV_1%	95·1 (95·0–95·2)	97·2 (97·1–97·4)	93·9 (93·8–94·1)	98·1 (97·9–98·2)	92·5 (92·4–92·7)
Participants who also had available FVC data, n	237 468	60 734	72 524	40 241	63 969
Mean FVC, mL	4127 (4123–4132)	3599 (3594–3605)	3503 (3497–3509)	5139 (5130–5148)	4699 (4691–4707)
Mean predicted FVC%	98·3 (98·2–98·3)	99·7 (99·6–99·8)	98·4 (98·3–98·5)	99·1 (99·0–99·2)	96·2 (96·1–96·3)
Mean FEV_1/FVC ratio	0·77 (0·77–0·77)	0·79 (0·79–0·79)	0·77 (0·77–0·77)	0·78 (0·78–0·78)	0·76 (0·76–0·76)

Data are n (%) or mean (95% CI) , calculated by combining the relevant means and SEs provided by each included study, unless otherwise specified. Details on ethnicity and race can be found in the appendix (p 8). BMI=body-mass index. FVC=forced vital capacity. NA=not applicable.

Table 2: **Participant demographics**

Results

Across the ten population-based studies, we included 243 465 European participants aged 20–94 years (mean age 51·4 years, 95% CI 51·4–51·5) in our analysis, of whom 136 275 (56·0%) were female and 107 190 (44·0%) were male (table 1). Included participants were born between 1884 and 1996, and their lung function, height, smoking behaviour, and weight were measured between 1965 and 2016. As expected, mean FEV_1, FVC, and height were lower in women than in men, and mean FEV_1 and FVC were higher in never smokers than in ever smokers (table 2). Graphical representations of mean FEV_1, FVC, and height according to age, stratified by sex and smoking status, are available in the appendix (p 21).

We observed a stepwise increase in FEV_1 across successive birth cohorts, irrespective of sex or smoking status (figure 1). This pattern persisted when never smokers in studies from central Europe and studies from northern Europe were examined separately (appendix p 24), suggesting that the association was not driven by data from one study or country. We identified similar stepwise increments in FVC and height with advancing birth cohorts (ie, from pre-1920 to 1990–99; appendix p 23), patterns that persisted when individuals from central and northern studies were examined separately (appendix pp 25–26).

After adjusting for age and study, we found that FEV_1 increased by 13·3 mL/birth year (95% CI 5·5–21·2; p=0·0009) and FVC increased by 22·7 mL/birth year (10·4–35·1; p=0·0003; figure 2). After adjusting for age, study, height, sex, smoking status, pack-years, and weight, FEV_1 increased by 4·8 mL/birth year (95% CI 2·6–7·0; p<0·0001) and FVC increased by 8·8 mL/birth year (5·7–12·0; p<0·0001). Results were similar after stratifying by sex and smoking status; however, the increase in FEV_1 in male never smokers was not statistically significant (figure 2). Stratifying the models by age produced similar birth year-related increments in FEV_1 and FVC in both younger and older adults (appendix p 37). Sensitivity analyses excluding the 661 (0·3%) individuals for whom height was asked rather than measured) and separately accounting for clustering within studies provided similar results to the main analysis (appendix p 27). Including non-linear terms for age, height, and birth year yielded even larger changes with advancing birth year than when including linear terms, but left our conclusions unchanged (appendix p 36).

We used 32 reference equations published between 1961 and 2015 to examine the association between birth year and lung function (figure 3; appendix pp 12–20). Advancing measurement year directly corresponds to advancing birth year. The estimated birth year of 50-year-olds enrolled in these studies ranged from 1910 to 1960 (appendix pp 12–15). Overall, we calculated 31 predictions of FEV_1 and 24 predictions of FVC for 50-year-old men, and 27 predictions of FEV_1 and 23 predictions of FVC for 50-year-old women (appendix p 20). For a 50-year-old female participant with a height of 1·67 m (the mean height of female never-smoking participants in our study), predicted FEV_1 increased by 9·0 mL/birth year and predicted FVC increased by 13·0 mL/birth year (figure 3). For a 50-year-old male participant with a height of 1·81 m (the mean height of male never-smoking participants in our study), predicted FEV_1 increased by 13·2 mL/birth year and predicted FVC increased by 16·2 mL/birth year (figure 3). Even after the exclusion of eight reference equations that might have included ever smokers in a sensitivity analysis, change in predicted FEV_1 and FVC per birth year remained statistically significant and of a similar size in both men and women (figure 3).

An increase in FVC of 13·7 mL/birth year, as reported in figure 2 for male never smokers, would be expected to cause a progressive deviation from the FVC values predicted by Global Lung Function Initiative 2012 reference equations, equating to an increase of 274 mL after 20 birth years (figure 4A–C). This change would favour a progressive increase in the percentage of predicted FVC values with age (figure 4D). As the midpoint of the data collection period (1978–2011) for the Global Lung Function Initiative 2012 predictions was 1994, birth cohort effects should lead to the progressive underestimation of values measured

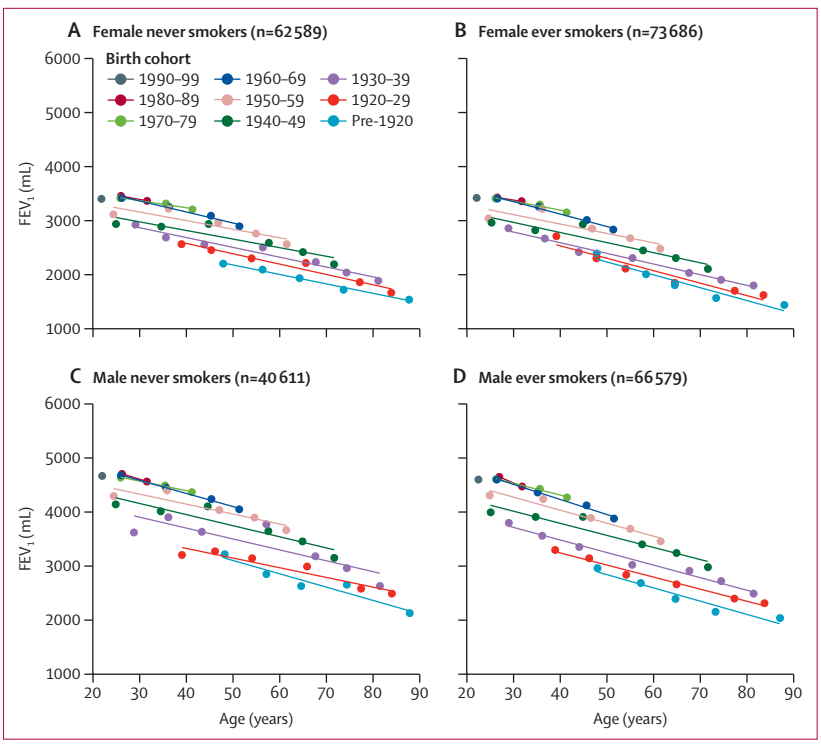

Figure 1: **Relationship between FEV_1 and age by birth cohort**
(A) Female never smokers. (B) Female ever smokers. (C) Male never smokers. (D) Male ever smokers. Each marker shows the mean FEV_1 value among individuals belonging to that subgroup (defined by both their birth cohort and age at measurement). Data from these subgroups are plotted according to their mean age. Linear trendlines are shown. Each individual appears once only (they each contribute to one timepoint within one panel only).

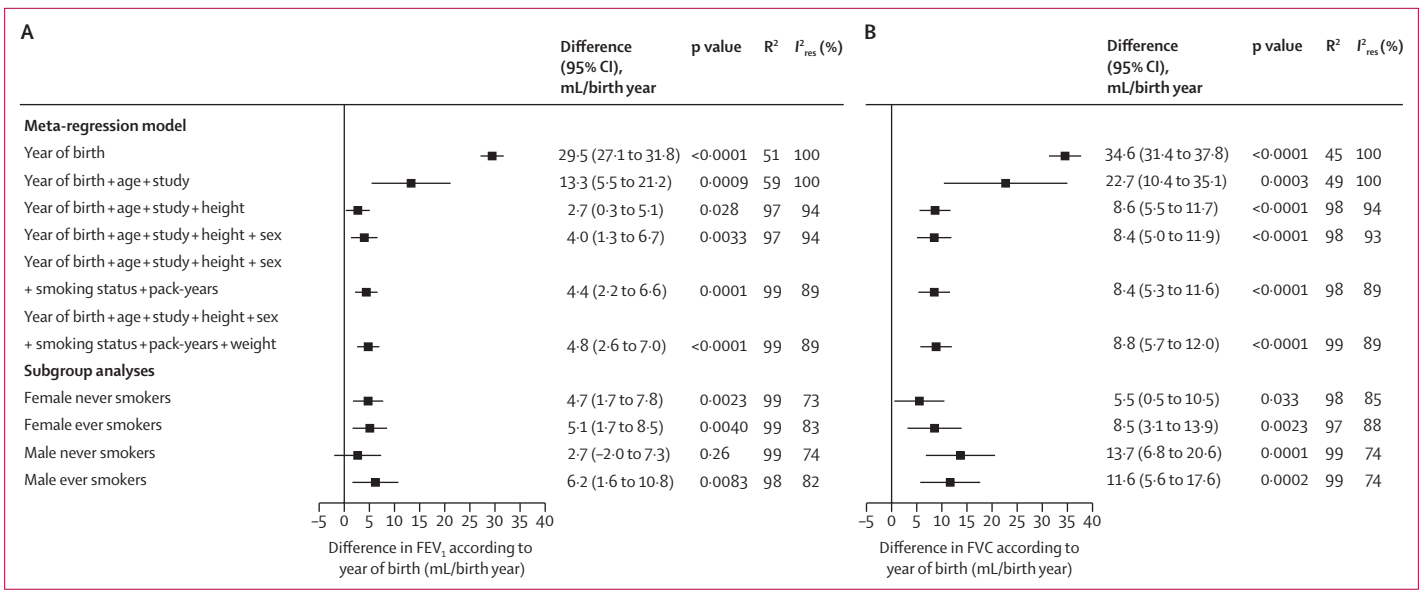

Figure 2: **Difference in FEV_1 and FVC according to birth year in a meta-regression model**
The FEV_1 model (A) included data from ten population-based studies (comprising 243 465 participants) and the FVC model (B) included data from nine of the ten population-based studies (comprising 237 468 participants). Subgroup analyses show the final fully adjusted model stratified according to sex and smoking status. FVC=forced vital capacity. I^2_{res}=residual I^2.

after 1994 and the overestimation of values measured before 1994.

We show the relationship observed in our study between birth year and the percentage of predicted FEV_1 (figure 4E) or the percentage of predicted FVC (figure 4F) among never smokers. The patterns we observed in the percentage of predicted FEV_1 (figure 4E) and the percentage of predicted FVC (figure 4F) with birth year in male and female never smokers were similar to the theorised patterns in figure 4D. Similar patterns were also observed among ever-smokers (appendix pp 28–29).

The population mean FEV_1/FVC ratio decreased steadily with advancing birth year, irrespective of smoking status (figure 5A). After adjusting for age, study, sex, and smoking status, the FEV_1/FVC ratio decreased by 0·11 per 100 birth years (figure 5B). Overall, results were similar in sensitivity analyses adjusted for height, weight, and pack-years and stratified by sex and smoking status (appendix pp 30–31). If this pattern continues, our model estimates that the mean FEV_1/FVC ratio among 65-year-old, never smoking European men will decrease from 0·77 (95% CI 0·77–0·77) in 1995 to 0·70 (0·69–0·72) in 2060 (65 years after birth in 1930 and 1995, respectively).

Discussion

Using data from 243 465 European adults born between 1884 and 1996, we have shown that mean FEV_1 and FVC increased with time, partly due to increasing population height. However, after adjusting for height, age, study, sex, smoking status, pack-years, and weight, FEV_1 still increased by 4·8 mL/birth year and FVC increased by 8·8 mL/birth year. These findings were supported by a corresponding height-independent increase in predicted lung function values across 32 reference equations published between 1961 and 2015. We expect that these changes will cause current reference equations to increasingly underestimate normal lung function, thereby underestimating disease severity among individuals with lung diseases such as COPD. By contrast, the FEV_1/FVC ratio decreased by 0·11 per 100 birth years, favouring the easier fulfilment of current COPD diagnostic criteria over time. In addition to affecting diagnostic accuracy, such cohort effects could undermine current approaches towards interpreting longitudinal lung function data.

Height is a major determinant of lung function. We found that, although increasing population height across successive birth cohorts was accompanied by increasing mean lung function, the increases in lung function exceeded those expected due to observed increases in height. This finding indicates a changing relationship between height and lung function.[11] One physiological explanation is that standing height, although widely used as a proxy for thoracic cavity size, does not account for differences in musculature, alveoli number, or thoracic geometry.[22] Changes in these factors across successive birth years, in response to improving environments, diets, and health care, could have driven increases in lung function not explained by increasing height.

Irrespective of the physiological cause, progressive height-independent increases in lung function will have important diagnostic consequences because of their effect on the accuracy of predicted values. Height-independent increases in lung function would cause normal population values to progressively deviate from predictions made by reference equations (eg, the highly

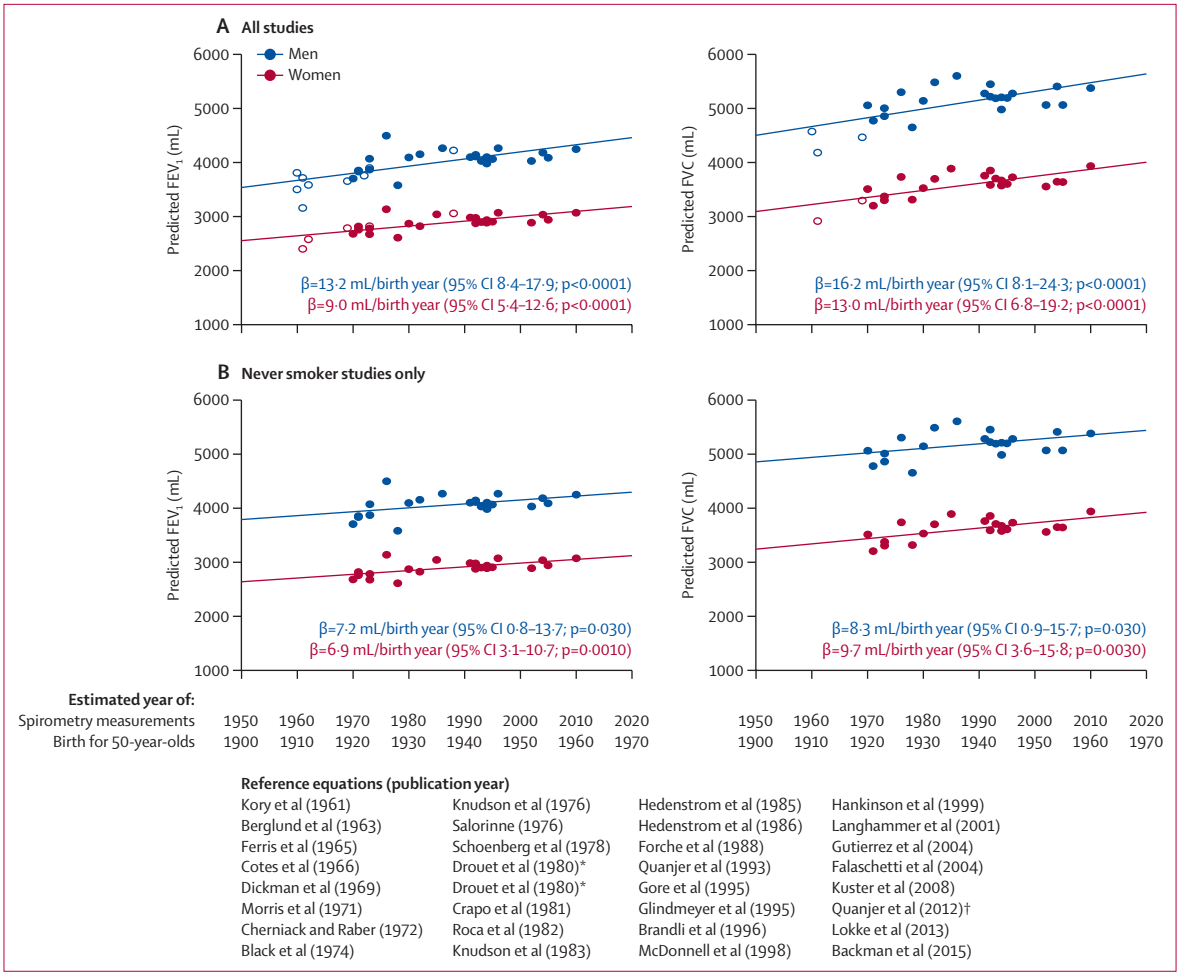

Figure 3: **Influence of birth year on FEV_1 and FVC predicted by published reference equations**
(A) All studies. (B) Studies of never smokers only (excluding the eight studies that might have included ever smokers). Open circles represent all studies. Solid circles represent studies that included never smokers only. References for the reference equations are in the appendix (pp 14–15). FVC=forced vital capacity. *These studies included distinct study populations. †Part of the Global Lung Function Initiative.

refined Global Lung Function Initiative 2012 reference equations)[8,13] over time. We observed an increase in FVC of 13·7 mL/birth year among male never smokers, amounting to an increase of 274 mL across 20 birth years. We expect this change to cause the mean FVC trajectory to deviate from the curve predicted by the Global Lung Function Initiative 2012 reference equations, manifesting as a progressive underestimation of values measured after 1994 (the midpoint of the data collection period for the reference equations) and an overestimation of values measured before 1994. The striking similarities we found between the expected and the observed effects of birth year on the percentage of predicted FEV_1 and FVC values support this hypothesis. The Global Lung Function Initiative 2012 reference equations are the best available, but the cohort effects we have identified could lead them to underestimate current normal European lung function, perhaps explaining why more recent European population-based data indicate supra-normal average lung function values.[23] These cohort effects could also cause clinicians to underestimate the severity of well known respiratory diseases, such as COPD, and under-recognise the impacts of emerging adverse exposures, such as electronic cigarettes or the COVID-19 pandemic.

Although FEV_1 and FVC increased with advancing birth year, we found that the FEV_1/FVC ratio decreased. This finding is a predictable mathematical consequence of both height-dependent and height-independent increases in lung function. The FEV_1/FVC ratio is known to decrease with increasing height.[8] Furthermore, we observed a height-independent increase in FVC (8·8 mL/birth year) that exceeded the corresponding FEV_1 increase (4·8 mL/birth year), favouring further reduction of the FEV_1/FVC ratio. The failure of FEV_1 to keep up with increasing FVC suggests that increasing flow volumes are accompanied by increasing resistance to flow, as FEV_1 is more susceptible than is FVC to changes in airway resistance. This increasing resistance could reflect disproportionate tracheobronchial growth

relative to parenchymal growth during lung development—an occurrence known as dysanapsis.[24–26] Dysanapsis arises because the tracheobronchial tree forms early in fetal development, whereas parenchymal tissue continues to form post-partum, thereby introducing the potential for unmatched growth.[24] If progressively improving parenchymal growth led to larger lung volumes and greater airflow without matched

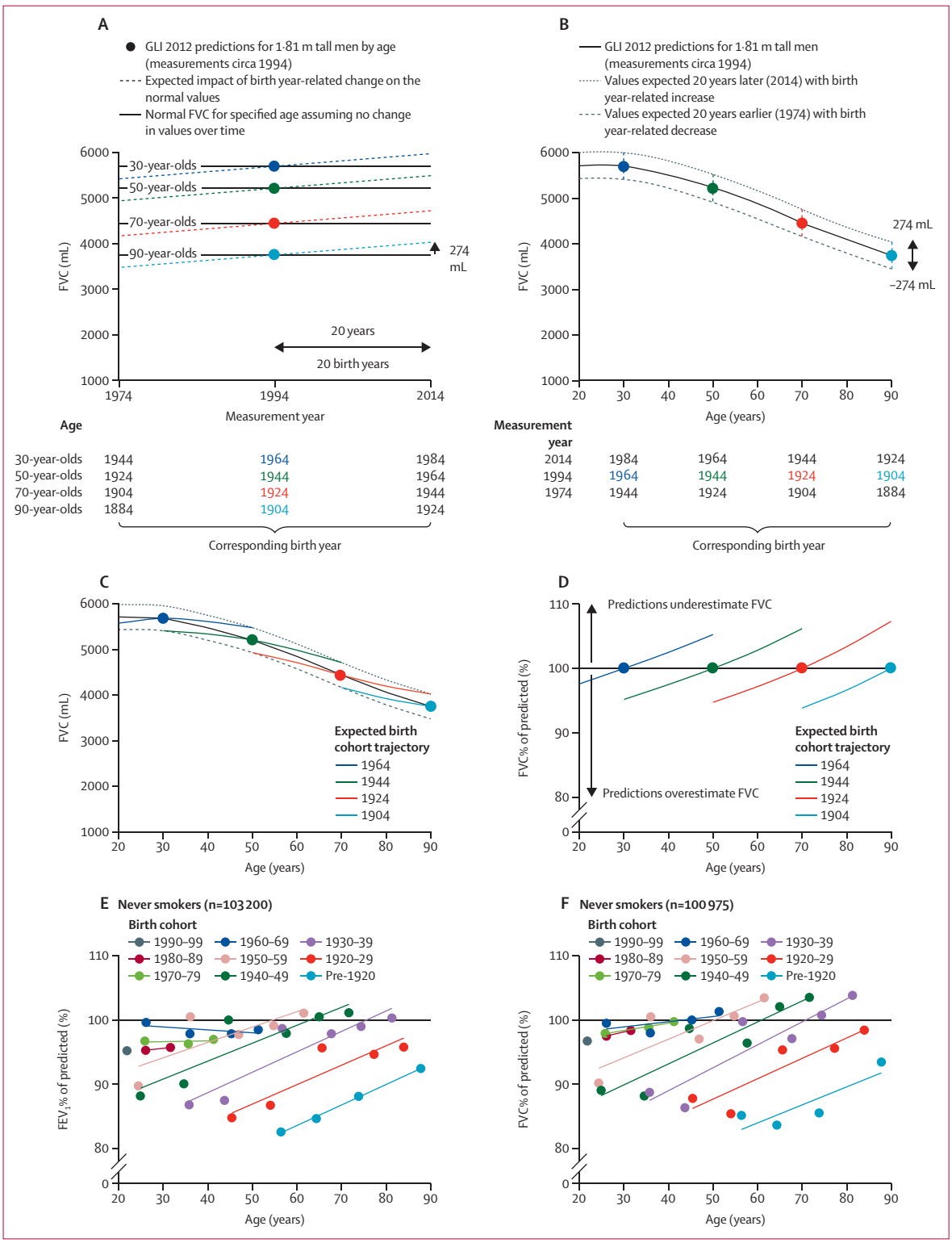

Figure 4: **Comparison between calculated theoretical and observed birth cohort effects on the interpretation of lung function values**

The expected impact over time (measurement year; A) and with age (B) of a height-independent increase in FVC of 13·7 mL/birth year for White male never smokers with a height of 1·81 m (the mean height for male never-smoking participants) predicted by GLI 2012 reference equations. (C) The expected trajectories between 1974 and 2014 in FVC of the four White male never-smoking theoretical birth cohorts as they age, accounting for an increase in FVC of 13·7 mL/birth year. (D) The expected trajectories between 1974 and 2014 in FVC of the four White male never-smoking theoretical birth cohorts as they age, accounting for an increase in FVC of 13·7 mL/birth year, as a percentage of GLI 2012 predicted values. The observed impact of birth cohort on percentage of predicted FEV_1 (E) and FVC (F), using individual participant-level percentages of GLI 2012 predicted values in male and women never smokers, shown according to age. Corresponding graphs for ever smokers can be found in the appendix (pp 28–29). FVC=forced vital capacity. GLI=Global Lung Function Initiative.

increases in airway diameter, airway resistance would increase, potentially decreasing the FEV_1/FVC ratio.

Changes in the mean population FEV_1/FVC ratio with time pose a diagnostic challenge for clinicians, especially in the diagnosis of COPD. An obstructive FEV_1/FVC ratio is required to confirm a diagnosis of COPD, with obstruction defined as either a ratio of less than 0·70 or less than the lower limit of normal based on Global Lung Function Initiative 2012 predictions.[4] If the mean European population FEV_1/FVC ratio is decreasing, as we suggest, it will become progressively easier for individuals to fulfil the diagnostic criteria for COPD. Indeed, if current trends continue, our model estimates that 0·70 will be the mean FEV_1/FVC ratio among 65-year-old, never smoking European men in 2060. If this change is due to shifting physiological norms, rather than increasing disease prevalence or severity, it could lead to the overdiagnosis of COPD, resulting in harm.

A key message from this study is that the persistence of cohort effects is causing current lung function reference equations to become progressively outdated, even within high-income countries. Updating these equations to reflect new population norms would improve the interpretation of individual measurements. These results also have implications for the interpretation of longitudinal lung function data. To understand how chronic respiratory disease develops across life and to identify abnormal lung function trajectories that lead to disease,[27] longitudinal lung function data are often interpreted by use of reference equations derived from cross-sectional data.[28,29] This approach could be problematic if the persistence of cohort effects causes longitudinal trajectories to progressively deviate from the trajectories predicted by cross-sectional studies, as our results suggest. Of note, the deviations we report are consistent with trends previously identified from longitudinal data.[30] By highlighting these effects, we hope to contribute towards the development of a more accurate picture of how respiratory health versus disease develops.

In addition to age, height, and sex, ethnicity is considered a major determinant of lung function. Unfortunately, our predominantly White European study sample precludes delineation of the influence of ethnicity and race on lung function.[31] Variation in lung function with ethnicity leads current reference equations to predict lower FEV_1 and FVC values, but often higher FEV_1/FVC ratios, for non-White ethnicities, relative to their White counterparts.[8] Historical inequalities linked to ethnicity and race, both within and across countries, might contribute substantially to differences in lung function currently attributed to ethnicity. If this is the case, societal change might help to close this gap, perhaps exemplified by the increases in lung function seen in children in Hong Kong relative to their White UK counterparts.[32] Attributing lower normal lung function simply to ethnicity could risk accepting the current manifestations of historical inequalities as normal.

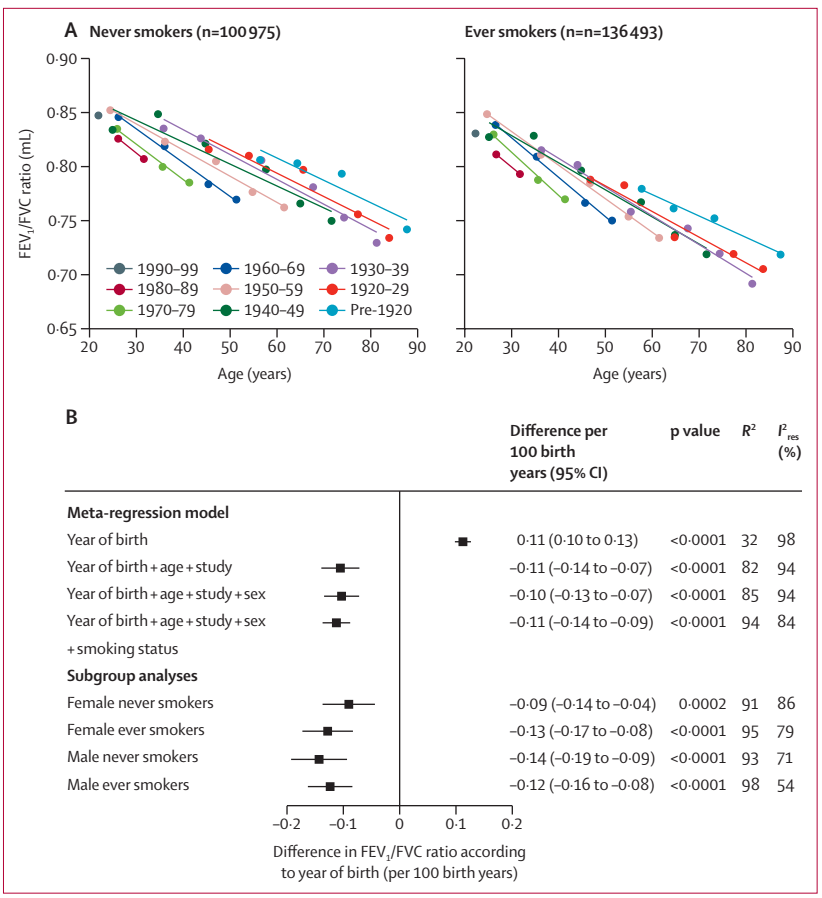

Figure 5: **Change in FEV_1/FVC ratio with advancing birth cohort**
(A) Relationship between FEV_1/FVC ratio and advancing age according to birth cohort, stratified by smoking status. Each marker shows the mean FEV_1/FVC ratio according to the mean age of subpopulations defined by both birth year and age at measurement. Linear trendlines are shown. (B) Meta-regression model examining the influence of birth year on FEV_1/FVC ratio, independent of age, study, sex, and smoking status. The model progressively adjusts for age, study, sex, and smoking status. FVC=forced vital capacity. I^2_{res}=residual I^2.

Similarly, the use of locally derived reference values to interpret lung function in lower-income countries might also risk labelling any population-level effects of historically lower income as normal. Therefore, although personalised predictions using ethnic, socioeconomic, or geographical background help to identify important functional variations within specific groups, they also risk reinforcing existing structural inequalities.

Our study has several strengths. First, we included data from ten high-quality studies that are representative of general populations, and did not exclude individuals with previous respiratory diagnoses or symptoms, which might explain our slightly lower-than-predicted lung function values. Our cross-sectional study design might also have reduced survival bias derived from sample attrition by improving the representation of populations from earlier eras, meaning that included individuals should better represent those surviving to similar ages within the wider population. Increasing European life expectancy across the past century could mean that some

individuals included in later studies would not have survived to participate in earlier studies had they been born in earlier eras. However, given the known inverse correlation between lung function and survival, the increasing survival of sicker individuals would probably favour a reduction, rather than an increase, in mean population lung function.

Our study also has several limitations. Our analysis was limited to variables recorded across the included studies, and we were unable to directly explore other changes over time (eg, changes in thoracic cage dimension or sitting height). Previous studies suggest that increasing height with socioeconomic improvement is largely due to increasing leg length, rather than increasing thorax height.[22,33] Our adjustments for height, as a proxy for thoracic cage size, might therefore have underestimated the contribution of height-independent improvements in lung function. Although our approach of reporting mean gains in lung function across all birth cohorts was somewhat supported by the stepwise changes identified, lung function increases appeared visually smaller among more recent birth cohorts, suggesting that these birth cohorts might also relate differently to Global Lung Function Initiative 2012 predictions compared with their predecessors. Therefore, variation in cohort effects on lung function across birth cohorts could be a useful topic of further study, especially as growth in European height might now be slowing.[34] Limitations in adjusting for period effects—effects caused by changes during a particular period of time that uniformly influence all ages and birth cohorts—alongside age and birth cohort are well documented.[10] However, given the uniform, stepwise changes between birth cohorts across the age range examined, we believe that cohort, rather than period, effects more plausibly explain our findings. Our observational study design means we cannot exclude residual confounding from unmeasured confounders. However, residual confounding from measurement errors in height and time variables—the variables that explained most of the variation in our models—seems unlikely given the precision with which they were measured. Although minor variation in research techniques existed between studies, we do not believe that this would explain our results. Improved spirometer technology, protocol standardisation, and quality control could have contributed to increasing lung function values,[35] but would not explain the wider cohort effects observed (eg, on height) or avoid the need to update normal references to better interpret current measurements.

Several further factors support the validity of our findings. First, cohort effects persisted after stratification by geographical region (central *vs* northern Europe), indicating that they were not driven by data from a single study or country. Second, sensitivity analyses, such as excluding the single study that recorded asked height rather than measured height (contributing 0·3% of our study sample), left our findings unchanged. Third, adjusting our models for contributing study did not change our findings. Finally, our analyses of values from published lung function reference equations from different eras corroborate our overall findings.

In conclusion, European population mean FEV_1 and FVC have increased with advancing birth year across the past century. These increases appeared to exceed the expected impact of increasing height and have led mean population FEV_1 and FVC to progressively deviate from, and be underestimated by, currently predicted values. By contrast, the mean FEV_1/FVC ratio decreased over this period. We believe that these two changes will have resulted in the easier fulfilment of COPD diagnostic criteria and the progressive underestimation of disease severity. Our study highlights the need to update reference equations for populations from high-income European countries to better reflect current normal values and to re-evaluate our approach to interpreting longitudinal lung function data.

Contributors

JPA conceptualised the study and formulated the original manuscript draft and figures. JPA, LEGWV, and JV contributed towards conceptualisation and methodology. JPA and SA did the statistical analysis. SA formulated and contributed to the construction of the meta-regression models. JPA, SA, YÇ, LEGWV, and JV contributed to writing the manuscript. SA, YÇ, DJ, SAAV, AL, M-KB, RB-K, SH, OCB, JMV, NO, RF, MvdB, HMB, HB, ER, LL, SRAW, BIN, and BL contributed to the curation, preparation, and contribution of data from the respective population-based studies. JMV and HMB are principal investigators of the Vlagtwedde-Vlaardingen study. PL is a principal investigator of the Copenhagen City Heart Study. DJ is a principal investigator of the European Community Respiratory Health Study. AL is a principal investigator of the HUNT study. BGN is a principal investigator of the Copenhagen General Population Study. MvdB is a principal investigator of the Lifelines study. ER is a principal investigator of the OLIN study. GB is a principal investigator of lung diseases within the Rotterdam Study. BL is a principal investigator of the West Sweden Asthma Study. OCB, SH, M-KB, and RB-K are principal investigators of the Austrian LEAD study. JPA and SA had accessed and verified the data contributed by the respective studies. JPA, LEGWV, and SA accessed the data derived from published reference studies. JAW, RF, GCD, and AA set up and lead CADSET, a pan-European, multicentre Clinical Research Collaboration endorsed by the European Respiratory Society. GCD and RF contributed towards the Clinical Research Collaboration registry curation and administration. This study was done by Working Group 3 of the CADSET Clinical Research Collaboration, which is co-led by JPA, LEGWV, and JV. All authors contributed to the scientific content of the manuscript, critically reviewed it, and approved the final version. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

JPA has received speaker fees from Pulmonx, travel costs from Boehringer Ingelheim to deliver a lecture, and travel costs from GlaxoSmithKline to attend an advisory board meeting. YÇ received personal fees from Boehringer Ingelheim, AstraZeneca, and Sanofi Genzyme. HB has received payment from AstraZeneca and Boehringer Ingelheim for presentations made at scientific meetings. MvdB has received institutional research grants from GlaxoSmithKline, Roche, Genentech, and Novartis. GB has received honoraria from AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Novartis, Sanofi, and TEVA. OCB has received grants or contracts, consulting fees, and payment or honoraria from AstraZeneca, Abbvie, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Menarini, MSD, Novartis, Roche, Takeda, and TEVA for lectures, presentations, speakers

bureaus, manuscript writing, or educational events. RF has received research grants from GlaxoSmithKline, Menarini, AstraZeneca, ISC-III, and the Spanish Health Service, consulting fees from GlaxoSmithKline, and honoraria from Chiesi Farmaceutici. SH has received grants or contracts, consulting fees, and payment or honoraria from AstraZeneca, Abbvie, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Menarini, MSD, Novartis, Roche, Takeda, and TEVA for lectures, presentations, speakers bureaus, manuscript writing, or educational events. AL has received payment for lectures from Boehringer Ingelheim and travel costs from Novartis and AstraZeneca to attend meetings, has participated in an AstraZeneca advisory board, has contributed to the Norwegian Primary Care Respiratory Group, and has been a member of the Norwegian Health Directorate. BL has received grants from AstraZeneca and ThermoFisher and has participated in a Sanofi advisory board. SAAV has received support from AstraZeneca to attend meetings. SRAW has received travel grants from GlaxoSmithKline. PL has received institutional grants, personal consulting fees, and personal lecture fees from AstraZeneca, GlaxoSmithKline, and Boehringer Ingelheim. GCD has received institutional grants from Genentech and AstraZeneca, book chapter royalties from Elsevier, and payment from AstraZeneca and Novartis for participation in advisory boards. JAW has received institutional grants from GlaxoSmithKline, AstraZeneca, Chiesi Farmaceutici, Boehringer Ingelheim, Novartis, and Genentech, and has participated in a Virtus data and safety monitoring board. JV is supported by the National Institute for Health Research Manchester Biomedical Research Centre, has received a research grant from Boehringer Ingelheim, honoraria from AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, and Novartis for presentations at meetings, and honoraria from AstraZeneca, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline, Novartis, and TEVA for participation in advisory boards, is a member of the Panel for Clinical and Translational Research for the Novo Nordisk Foundation, has chaired the Asthma UK Research Review Panel, and is a member of the Medical and Chemicals Technical Options Committee for the Montreal Protocol, the UN Environment Programme. LEGWV has received institutional grants from AstraZeneca, personal payments from AstraZeneca, GlaxoSmithKline, Boehringer, Linde, Novartis, Menarini, and Zambon for lectures, presentations, speakers bureaus, manuscript writing, or educational events, personal payments from AstraZeneca, GlaxoSmithKline, and Boehringer Ingelheim for participation on data safety monitoring boards or advisory boards, and payment from Chiesi Farmaceutici for medical writing. All other authors declare no competing interests.

Data sharing

The data we present have been collected across ten independent population-based studies. To produce this study, investigators from these studies have collaborated through the European Respiratory Society CADSET Clinical Research Collaboration. Each cohort study overseas the governance of their datasets. Therefore, requests regarding access to individual participant data should be directed to the relevant study. Contact details for these studies and details of their collected data are available through the CADSET website (https://www.cadset.org/).

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