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A century of increasing lung function and its implications for the diagnosis of lung disease: Results from 243,465 European adults across ten population-based studies

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140 content of the manuscript, critically reviewed it and approved the final version.

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144 Research Collaboration (https://www.cadset.org). Each cohort study overseas the governance of their datasets.
145 Therefore, requests regarding access to individual participant data should be directed to the relevant study. Contact
146 details for these studies and details of their collected data are available through the CADSET Website:
147 https://www.cadset.org/.

148

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A century of increasing lung function and its implications for the diagnosis of lung disease: Results from 243,465 European adults across ten population-based studies

ABSTRACT

Background: During the last century, socioeconomic and scientific advances changed the health and physique of European populations. Accompanying improvements in lung function, if unrecognised, could lead us to misclassify lung function measurements, and hence diseases such as Chronic Obstructive Pulmonary Disease (COPD). We investigated how population lung function changed with birth year across the last century and how such change may influence lung function interpretation.

Methods: We included 243,465 Europeans from ten population-based studies, aged 20-95 years, born between 1884 and 1996. Forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC), were measured between 1965 and 2016. We used meta-regression to investigate how FEV_1, FVC and the FEV_1/FVC ratio changed with birth year. 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: Average European FEV_1 and FVC values increased substantially with birth year across the last century. After accounting for height, smoking behaviour, and other co-factors, FEV_1 increased by 4.8 mL/birth year (95% confidence interval [CI]:2.6-7.0; P<0.0001) and FVC by 8.8 mL/birth year (95% CI:5.7-12.0; P<0.0001). We found corroboratory birth year-related increases in the FEV_1 and FVC values predicted by published reference equations. Whereas FEV_1 and FVC increased with advancing birth year, the FEV_1/FVC ratio decreased by 0.11 per 100 birth years (95% CI:0.09-0.14; P<0.0001).

Interpretation: Average height adjusted European FEV_1 and FVC increased with birth year across the last century, causing population values to progressively exceed previously predicted values. Concurrently, the FEV_1/FVC ratio decreased. If current diagnostic parameters remain unchanged, the identified shifts in European values will allow the easier fulfilment of diagnostic criteria for COPD, but the systematic underestimation of lung disease severity.

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RESEARCH IN CONTEXT

Evidence before this study:

We searched PubMed on 17th January 2021, using the terms ("cohort effects" OR "secular trends") AND ("lung function" OR "FEV_1" OR "FVC" OR "height"). Height is a major determinant of lung function, and average European height has increased with advancing birth year across most of the twentieth century. This increase has been attributed to improved growth due to improvements in diet, healthcare, and lifestyle. We found evidence that European height-adjusted lung function also increased with advancing birth year, at least until the mid-twentieth century. However, it was less clear if birth cohort effects have continued to impact European lung function. One major study, using data collected in high income countries between 1978 and 2011, found no evidence of cohort effects on height-adjusted lung function and the authors proposed this reflected the stabilisation of socioeconomic conditions in these countries. To substantiate our population-based findings, we also analysed the FVC and/or FEV_1 values predicted by published reference equations for 50-year-old Caucasians from Europe, North America, or Australia. To find these equations, we searched PubMed using the terms: ("spirometry" OR "lung function") AND "reference equation". Equations were also identified from published reviews. We identified 32 reference equation studies, published between 1961 and 2015.

Added value of this study:

Relative to previous comparable studies, this study includes a much larger study sample, of 243,465 individuals, and covers a wider range of birth years, between 1884-1996. These data allow us, for the first time, to show how European forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) increased independent of height across a century of birth years. We corroborate these findings using published reference equations, and we show how these changes will have led European lung function to progressively deviate from previously predicted values. This study also indicates that the FEV_1/FVC ratio has decreased over this time.

Implications of all the available evidence:

We show that, even after adjustment for increasing height, European FEV_1 and FVC increased with birth year across the last century, causing a deviation from previously predicted values and the persistence of birth cohort effects upon current European population lung function. During this time, the FEV_1/FVC ratio has fallen. Physiologically, these height-independent changes may indicate that socioeconomic change has been accompanied by beneficial changes in thoracic geometry, muscle strength or alveoli number within the population. Clinically, these changes in lung function over time will have led lung function predictions to increasingly underestimate average 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). While clinicians consider many factors when diagnosing lung diseases, the concurrent decrease in the FEV_1/FVC ratio will make it easier for individuals to meet the criteria used to diagnose COPD. This study highlights the need to update reference equations for populations from high-income countries to better reflect current "normal values" and raises issues regarding the application of reference equations to longitudinal lung function data.

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INTRODUCTION

Across the last century, dramatic socioeconomic changes and scientific advancements have changed the health[1] and physique[2,3] of European populations. To appropriately interpret physical measurements, we need to recognise how physical norms have shifted over time. The appropriate interpretation of lung function measurements are important for the diagnosis of lung diseases, particularly Chronic Obstructive Pulmonary Disease (COPD),[4,5] but also asthma[6] and interstitial lung disease.[7] When clinicians diagnose COPD, they use forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) measurements to confirm the presence of airflow obstruction, defined as an FEV_1/FVC ratio below the lower limit of normal (LLN) or less than 0.70.[4] COPD severity is then graded by the severity of FEV_1 impairment, determined by comparing observed values with predicted "normal" values.[4] Thus, COPD diagnosis and grading partly relies upon knowing what constitutes "normal" lung function.

To predict "normal" lung function we use reference equations, derived from cross-sectional studies of healthy non-smoking adults.[8,9] However, within cross-sectional studies, decreasing subject age corresponds to advancing birth year. Consequently, these studies are particularly susceptible to "cohort effects", where differences associated with age reflect differing environmental exposures across successive birth years. For example, the dietary, infectious disease, healthcare, and air pollution exposures of a 20-year-old European born in the 1920s are likely to differ substantially from their counterparts born in the 1980s. The previous impacts of cohort effects have been illustrated by the progressive rise in the lung function of Dutch individuals born across the first half of the 20th century,[10] and, they explain why the rate of lung function decline estimated from early cross-sectional studies exceeded the decline rate observed in subsequent longitudinal studies.[11,12]

The extent to which cohort effects currently impact lung function within 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 to the stabilisation of socioeconomic conditions.[13] However, other studies show that European population height has continued to increase with birth year across much of the twentieth century, suggesting ongoing cohort effects,[2,3] and, as a major determinant of thoracic volume, such increases in height should have driven up average lung function.[8,9] That said, reference equations predict lung function for each

individual according to their height and therefore such predictions should accommodate increases in population lung function driven purely by increasing population height.[8,9] However, height-independent increases in lung function, for example due to increasingly favourable 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 as birth year advanced across the last century, lung volumes in high-income countries increased in excess of the change expected to accompany increasing height. We therefore analysed observational data from ten major European population-based studies, and 32 published reference equations, to investigate how FEV_1 and FVC has changed with advancing birth year after accounting for increasing height. We then explore how the changes observed with birth year could impact the diagnostic interpretation of FEV_1, FVC and FEV_1/FVC ratio values.

METHODS

Study design and sample:

We included males and females aged 20-95 years, enrolled with the intention of longitudinal follow-up in central and northern European general population representative studies participating in the European Respiratory Society CADSET clinical research collaboration.[14] Table 1A lists the collaborating studies. Details of their research methods are available in the online supplement (Tables S1-S3).

For each individual, we used date of birth and date of spirometry measurement to calculate age. For each individual, pre-bronchodilator FEV_1 (millilitres), FEV_1 in percent of predicted normal, sex, ever-smoker status, cumulative tobacco consumption (pack-years), height (metres) and weight (kilograms) were included. We only included individuals providing complete data. Each individual contributed data once only, at the first point in time when these data were recorded. Nine studies also provided pre-bronchodilator FVC (millilitres), FVC in percent of predicted normal and FEV_1 /FVC ratio. The Vlagtwedde-Vlaardingen study measured vital capacity (VC), rather than FVC, and so these individuals were excluded from analyses reliant on FVC values.[15] Individual percent of predicted values were calculated according to Global Lung Initiative (GLI) 2012 reference equations.[8] Ever-smokers were defined as those who had smoked at least one cigarette for at least one year by the date of spirometry

measurement. 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 standard errors) stratified by sex, ever-smoking status, birth period and age band. We defined nine birth periods (pre-1920, 1920-1929, 1930-1939, 1940-1949, 1950-1959, 1960-1969, 1970-1979, 1980-1989, and 1990-1999) and seven age bands (20-29, 30-39, 40-49, 50-59, 60-69, 70-79, and 80-95 years); the oldest age band spanned 15 rather than 10 years due to lower sample sizes in this older age group.

Influence of birth year on FEV_1 and FVC:

We explored how birth year influenced both lung function and height with age among female and male, never and ever-smokers. This approach was repeated for central and northern European studies separately to check for replication within two geographical regions.

To determine if lung function increased with birth year, independent of increasing height, we used meta-regression (also known as meta-analysis regression) using appropriately stratified summary estimates, with standard errors, from each study. Meta-regression is a meta-analysis technique that relates statistical heterogeneity between study effect sizes to variables available in the studies using regression-based techniques.[16] Within these meta-regression models we progressively adjusted for variables potentially associated with lung function and birth year, including sex, ever-smoking status, study (using an indicator variable) and stratum average age, height, sex, weight and pack years recorded when lung function was measured.[17] In sensitivity analyses, we further accounted for clustering of estimates using an extended mixed-effects framework for meta-analysis.[18] We also explored if including non-linear terms age, height, and birth year improved model fit.

Influence of birth year upon the FEV_1 and FVC values predicted by published reference equations:

To substantiate our finding of a height-independent change in lung function with increasing birth year in high-income countries, we sought published reference equations predicting FEV_1 and FVC for 50-year-old Caucasians in Europe, North America, or Australia. We chose these regions so that included reference equations would be based upon Caucasians from high-income countries. For each reference equation included in this supportive analysis, we used the mid-year of their reported measurement period to estimate the year when they measured lung function. Where the measurement period was unreported, we instead used the year of manuscript submission/publication. We estimated the birth year of 50-year-olds included within each study by subtracting 50

years from the estimated measurement year. As appropriate, we used each reference equation to calculate predicted FEV_1 and FVC values for 50-year-old females and/or males using the average height of our never-smokers sample: (females:1.67m; males:1.81m), and weight when required (females:71kg; males:85kg). Linear regression, using heteroskedasticity robust standard errors, was used to determine if the predicted value of FEV_1 and FVC changed according to participant birth year. As a sensitivity analysis, we excluded reference equations derived from studies potentially including ever-smokers.

Influence of birth year on the FEV_1/FVC ratio

To investigate if the FEV_1/FVC ratio changed with birth year within our study, we used meta-regression, accounting for year of birth, age, sex, ever-smoker status, and pack years. We stratified this model for sex and ever-smoker status. To explore how these changes may relate to differences in height and weight we further adjusted this model for these variables.

Analyses were performed using SPSS version 22 (IBM Corporation, Armonk, NY, USA), and STATA version 14 (Stata Corporation, Texas, USA). For all tests $P<0.05$ was considered statistically significant.

RESULTS

Study sample:

We included 243,465 Europeans (56% female) aged 20-95 years (mean age 51.4 years) from ten population-based studies (Table 1A). Those included were born between 1884 and 1996, and their lung function and height was measured between 1965 and 2016. Table 1B shows demographics according to sex and smoking status. As expected, FEV_1, FVC, and height were lower in females than males, and FEV_1 and FVC were higher in never-smokers than ever-smokers. Mean FEV_1, FVC, and height according to age are available in the online supplement (Figure S1).

Influence of birth year on FEV_1 and FVC

Figure 1 shows a stepwise increment in FEV_1 across successive birth cohorts, irrespective of sex or smoking status. This pattern persists when examining studies from central and northern European studies separately (Figure S3), suggesting the association is not driven by data from one study or country. Similar stepwise increments in FVC and height are shown in Figure S2.

Figure 2 shows results from the meta-regression examining how FEV_1 and FVC values changed with advancing birth year. After adjusting for age and study, we found FEV_1 increased by 13.3 mL/birth year (95% CI:5.5 to 21.2; P=0.0009) and FVC by 22.7 mL/birth year (95%CI:10.4 to 35.1; P=0.0003). Significant lung function increments persisted even after adjusting for height, sex, smoking history, and weight; FEV_1 increased by 4.8 mL/birth year (95% CI:2.6 to 7.0; P<0.0001) and FVC by 8.8 mL/birth year (95% CI:5.7 to 12.0; P<0.0001). Results were overall similar after stratifying by sex and ever-smoking status for both FEV_1 and FVC. Accounting for clustering within studies provided similar results (Figure S4). Including non-linear terms for age, height, and birth year yielded more extreme results but left our conclusions unchanged (Figure S12).

Influence of birth year upon the FEV_1 and FVC values predicted by published reference equations:

We included 32 reference equations published between 1961 and 2015 (Figure 3 and Tables S4-S6). The estimated birth year of 50-year-olds enrolled in these studies ranged from 1910 to 1960 (Table S4). Overall, we included 31 predictions of male FEV_1; 24 predictions of male FVC; 27 predictions of female FEV_1; and 23 predictions of female FVC.

Figure 3 shows linear regressions examining how the predicted values of FEV_1 and FVC vary according to the estimated birth year of a 50-year-old subject. For a 50-year-old, 1.67 m tall female subject, FEV_1 predicted increased by 9.0 mL/birth year (95% CI:5.4 to 12.6; P<0.0001) and FVC predicted increased by 13.0 mL/birth year (95% CI:6.8 to 19.2; P<0.0001). Corresponding increases for a 50-year-old, 1.81 m tall male subject were 13.2 mL/birth year (95% CI:8.4 to 17.9; P<0.0001) and 16.2 mL/birth year (95% CI:8.1 to 24.3; P<0.0001), respectively. Since eight of the 32 reference equations were not explicity predicting values for never-smokers, they may have included smokers. However, even after excluding these eight reference equations there remained statistically significant change, of comparable magnitude, among both males and females.

Expected and observed impact of advancing birth year upon percent of predicted values

Figure 4 illustrates how height-independent increases in lung function with advancing birth year would be expected to impact the interpretation of lung function values. Panels A to C (in Figure 4) show that an increase in FVC of 13.7 mL/birth year, as reported in Figure 2, would be expected to cause a progressive deviation from the FVC values predicted by GLI 2012. Panel D indicates that this change would favour a progressive increase in percent of predicted values with age. We take GLI 2012 predictions as representing normal population lung function in 1994 because this was the mid-point of their data collection period (1978-2011). For comparison with

panel D, panels E and F shows the relationship observed between percent of predicted lung function (FEV_1 and FVC) and birth year among never-smokers in this study (Figures S5-65 show data from ever-smokers).

Influence of birth year on the FEV_1/FVC ratio

Figure 5A suggests that the population mean FEV_1/FVC ratio has decreased steadily with advancing birth year, irrespective of smoking status. The forest plot in Figure 5B shows meta-regression examining how the FEV_1/FVC ratio changes with advancing birth year. After adjusting for age, study, sex, and smoking history, we found that the FEV_1/FVC ratio decreased by 0.11 per 100 birth years (95% CI:0.09 to 0.14; P<0.001). Overall, results were similar in sensitivity analyses adjusted for height and weight with stratification by sex and smoking status (Figures S7S8). If this pattern continues, our model estimates that mean FEV_1/FVC ratio among the 65-year-old never-smoking European males will decrease from 0.77 (95% CI:0.77 to 0.77) in 1995 to 0.70 (95% CI:0.69 to 0.72) in 2060 (65 years following their birth in 1930 and 1995 respectively).

DISCUSSION

Using data from 243,465 European adults born between 1884 and 1996, we show that average FEV_1 and FVC have increased over time, partly due to increasing population height. However, after adjusting for height, FEV_1 still increased by 4.8 mL/birth year and FVC increased by 8.8 mL/birth year. These findings are supported by a similar rate of height-independent increase in predicted lung function values across 32 reference equations published between 1961 and 2015. As time passes, these changes will lead current reference equations to increasingly underestimate “normal” lung function, thereby underestimating disease severity among those with, for example, COPD. In contrast, we find that the FEV_1/FVC ratio has decreased over time by 0.11 per 100 birth years, favouring the easier fulfilment of current COPD diagnostic criteria. Besides impacting diagnostic accuracy, such cohort effects may undermine current approaches towards interpreting longitudinal lung function data.

Increasing European population height across the last century indicates that cohort effects have continued to influence the body dimensions of populations from these high-income countries.[2,3,19] This change has been attributed to improving diet, healthcare and lifestyle,[10,19] resulting in better growth during childhood and adolescence.[2] Hypothesised transgenerational inheritance of exposure effects[19,20] may also implicate a role for change in parental exposures.[21] However, few studies examine how advancing birth year, and the accompanying

increase in height, impact population lung function.[10] We address this through a large study spanning a century of birth years.

We find that increasing population height across successive birth cohorts was accompanied by increasing average lung function. Height is a major determinant of lung function and the trajectories suggested by Figures 1 and S2 fit with the achievement of progressively greater height and consequently larger lung volumes by early adulthood. However, the increases found in lung function over time exceed those expected due to the observed increases in height (Figure 2). This 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 environment, diet and healthcare, may drive the increases in lung function not explained by increasing height.

Irrespective of the physiological cause, progressive height-independent increases in lung function will have had important diagnostic consequences due to their impact on the accuracy of predicted values. "Normal" lung function values are predicted using reference equations, derived from measurements made during a specific period in time. For example, the highly refined GLI 2012 reference equations were derived from measurements made between 1978 and 2011.[8,13] Height-independent increases in lung function would, over time, cause "normal" population values to progressively deviate from predictions made by these equations. We observed an increase in FVC of 13.7 mL/birth year among male never-smokers, amounting to 274 mL across 20 birth years. Figure 4 A-D shows how this change would be expected to cause the average FVC trajectory to deviate from the curve predicted by GLI 2012. This would manifest as a progressive underestimation of future "normal" values and an overestimation of preceding "normal" values. The striking similarities between the expected and the observed impacts of birth year on percent of predicted FEV_1 and FVC values (Figure 4D-F), appears to support this hypothesis. The GLI 2012 reference equations are the best available, but the cohort effects we identify would lead them to underestimate current "normal" European lung function, perhaps explaining why recent European population-based studies report supra-normal average lung function values.[23] This would also lead clinicians to underestimate the severity of well-known respiratory diseases, such as COPD, and under-recognise the impacts of emerging adverse exposures, such as e-cigarettes or the COVID-19 pandemic.

Whereas FEV_1 and FVC increased with advancing birth year, we found that the FEV_1/FVC ratio decreased. This decrease in the FEV_1/FVC ratio with advancing birth year 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] Further, we observe a height-independent FVC increase which exceeds the corresponding FEV_1 increase (8.8 versus 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 implies that increasing flow volumes are accompanied by increasing resistance to flow, as FEV_1 is more susceptible to changes in airway resistance than FVC. This increasing resistance could reflect disproportionate tracheobronchial growth relative to parenchymal growth during lung development, a phenomenon known as dysanapsis.[24-26] Dysanapsis arises because the tracheobronchial tree forms early in foetal 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 increases in airway diameter, airway resistance would increase, potentially decreasing the FEV_1/FVC ratio.

Change in average population FEV_1/FVC ratio over time poses a diagnostic challenge for clinicians, especially with regards to COPD diagnosis. An "obstructive" FEV_1/FVC ratio is required to confirm COPD diagnosis, with some defining obstruction as a ratio less than 0.70 and others as less than the lower limit of normal (LLN) based upon GLI 2012 predictions.[4] If the average 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 males by the year 2060. If this is due to shifting physiological norms, rather than increasing disease, it could lead to the over-diagnosis 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 help us to better interpret individual measurements being made today. However, there are also fundamental implications regarding the interpretation of longitudinal lung function data. Understanding how chronic disease develops across life is a major scientific frontier, and in respiratory medicine the major focus remains upon identifying those abnormal lung function trajectories which lead to disease.[27] To this end, longitudinal lung function data are often interpreted using reference equations derived from cross-sectional data.[28,29] Our study shows this approach as potentially problematic because the persistence of cohort effects will cause longitudinal trajectories to progressively deviate from the trajectories predicted by cross-sectional studies. Of note, the trajectory 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.

Alongside age, height and sex, ethnicity is considered a major determinant of lung function. Unfortunately, our predominantly Caucasian study sample precludes us from attempting to delineate how ethnicity and race, together with genetic variation and environmental exposures, influence lung function.[31] Lung function variation with ethnicity leads current reference equations to predict lower FEV_1 and FVC, but often higher FEV_1/FVC ratios, for non-Caucasian ethnicities, relative to their Caucasian counterparts.[8] However, our data highlight the potentially long-lasting after-effects of environment upon Caucasians, even Caucasians from historically affluent countries. Therefore, historical inequalities, linked to ethnicity and race, both within and across countries, may contribute substantially to those differences in lung function currently attributed to ethnicity. Encouragingly, societal change may help close this gap, as seen recently in Asia.[32] Arguably, attributing lower "normal" lung function simply to "ethnicity" risks accepting the current manifestations of historical inequalities as "normal" function. Similarly, using locally derived reference values to interpret lung function within lower income countries may also risk labelling any population-level impacts of historically lower income as "normal". Therefore, while "personalised" predictions using ethnic, socioeconomic, or geographic background may help us better recognise important functional variation within specific groups they also risk reinforcing existing structural inequalities.

Our inclusion of data from ten high-quality studies, representative of general populations, is a major study strength, and not excluding individuals with prior respiratory diagnoses or symptoms explains our slightly lower than predicted lung function values. Arguably, our cross-sectional study design also reduces survival bias derived from sample attrition by improving the representation of populations from earlier eras, meaning those included should better represent those surviving to similar ages within the wider population. Increasing European life expectancy across the last century, may mean that some individuals included in later studies would not have survived to participate in earlier studies had they have been born in earlier eras. However, given the known inverse correlation between lung function and survival, the increasing survival of sicker individuals would likely favour a reduction, rather than the shown increase, in average population lung function.

Our examination was limited to variables recorded across the included studies, and we were unable to directly explore, for example, change in thoracic cage dimension or sitting height. This is important because prior studies suggest that increasing height with socioeconomic improvement is largely due to increasing leg length not

increasing thorax height.[22,33] If so, our adjustments for height, as a proxy for thoracic cage size, may underestimate the contribution of height-independent lung function gains.

While our approach of reporting average gains across all birth cohorts is somewhat supported by the stepwise changes suggested in Figures 1 and S2, we note that across our more recent birth cohorts, lung function increases appear visually smaller, and these birth cohorts may also relate differently to GLI 2012 predictions than their predecessors. Therefore, variation in cohort effects upon lung function across the different birth cohorts could be a useful further topic of study, especially as growth in European height may now be slowing.[34]

Limitations in adjusting for period effects alongside age and birth cohort are well documented.[10] We would argue 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 error in height and time variables, variables which explained most variation in our models, seems unlikely given the precision with which they were measured. Although minor variation in research technique existed between different studies, we cannot see how these would explain our results. Improved spirometer technology, protocol standardisation standardization and quality control could have contributed to increasing values,[35] but would not explain the wider cohort effects observed (e.g., upon height) or avoid the need to update normal references to better interpret measurements made today. Several further factors support the validity of our findings. First, cohort effects persisted after stratification by geographical region, indicating they were not driven by data from a single study or country. Second, sensitivity analyses, e.g., excluding the single study which 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 summary, European average FEV_1 and FVC has increased with advancing birth year across the last century. These increases appear to exceed the expected impact of increasing height. This has led average population FEV_1 and FVC to progressively deviate from, and be underestimated by, currently predicted values. In contrast, over this time the average FEV_1/FVC ratio has decreased. Clinicians consider many factors when diagnosing lung diseases, but these two changes will have led to the easier fulfilment of COPD diagnostic criteria but the progressive underestimation of disease severity. This study highlights the need to update reference equations for populations from high-income countries to better reflect current “normal values” due to the ongoing impact of cohort effects, and to re-evaluate our approach towards interpreting longitudinal data.

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508 **TABLES AND FIGURES**

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510 **TABLE 1: Details of the study sample included.**

511 **Table 1A:** Sample size, age range, measurement year range and birth year range, overall and according to each
512 participating study. Studies are ordered chronologically according to the earliest measurement date they
513 contribute. A corresponding graphical representation of the included age, measurement year and birth year ranges
514 is shown in Figures S9 and S10

515 **Table 1B:** Demographics of the included sample, overall and then stratified by both sex and ever-smoker status.
516 Values shown are means with 95% confidence intervals calculated by combining the relevant means and standard
517 errors provided by each study show in Table 1A.

A		Number included	Age range (years)	Measurement year range (year)	Birth year range (year)
OVERALL		**243465**	**20-94**	**1965-2016**	**1884-1996**
INDIVIDUAL STUDIES	Vlagtwedde Vlaardingen	5997	20-74	1965-1989	1901-1953
	Copenhagen City Heart Study	17636	20-93	1976-2003	1884-1981
	European Community Respiratory Health Study	10359	20-47	1991-1995	1945-1973
	HUNT	4431	20-92	1995-2008	1906-1988
	Copenhagen General Population Study	106140	20-94	2003-2015	1911-1994
	Lifelines	81978	20-90	2006-2013	1920-1993
	OLIN	661	21-86	2008-2010	1922-1986
	Rotterdam Study	5471	51-94	2009-2014	1915-1960
	West Sweden Asthma Study	991	21-77	2009-2012	1933-1988
	LEAD	9801	20-82	2011-2016	1931-1996

B	OVERALL	Females (56%)		Males (44%)	
		Never-smoker (46%)	Ever-smoker (54%)	Never-smoker (38%)	Ever-smoker (62%)
Number included	**243465**	**62589**	**73686**	**40611**	**66579**
Mean age (years)	51.4 (+/-0.1)	50.0 (+/-0.1)	51.8 (+/-0.1)	48.5 (+/-0.1)	54.1 (+/-0.1)
Mean pack years	10.0 (+/-0.1)	n/a	13.8 (+/-0.1)	n/a	21.2 (+/-0.2)
Mean height (m)	1.72 (+/-0.0004)	1.67 (+/-0.0005)	1.66 (+/-0.0005)	1.81 (+/-0.0007)	1.79 (+/-0.0006)
Mean weight (kg)	77.2 (+/-0.1)	70.9 (+/-0.1)	70.8 (+/-0.1)	85.4 (+/-0.1)	85.1 (+/-0.1)
Mean BMI (kg/m^2)	25.9 (+/-0.02)	25.5 (+/-0.04)	25.6 (+/-0.03)	26.2 (+/-0.04)	26.6 (+/-0.03)
Mean FEV_1 (mL)	3183 (+/-4)	2828 (+/-5)	2688 (+/-5)	4019 (+/-8)	3554 (+/-7)
Mean FEV_1 % predicted	95.1 (+/-0.1)	97.2 (+/-0.1)	93.9 (+/-0.1)	98.1 (+/-0.1)	92.5 (+/-0.1)
Number with FVC data also	**237468**	**60734**	**72524**	**40241**	**63969**
Mean FVC (mL)	4127 (+/-4)	3599 (+/-6)	3503 (+/-6)	5139 (+/-9)	4699 (+/-8)
Mean FVC % predicted	98.3 (+/-0.1)	99.7 (+/-0.1)	98.4 (+/-0.1)	99.1 (+/-0.1)	96.2 (+/-0.1)
Mean FEV_1/FVC	0.77 (+/-0.0003)	0.79 (+/-0.001)	0.77 (+/-0.001)	0.78 (+/-0.001)	0.76 (+/-0.001)

(95% Confidence Interval); n/a indicates not applicable

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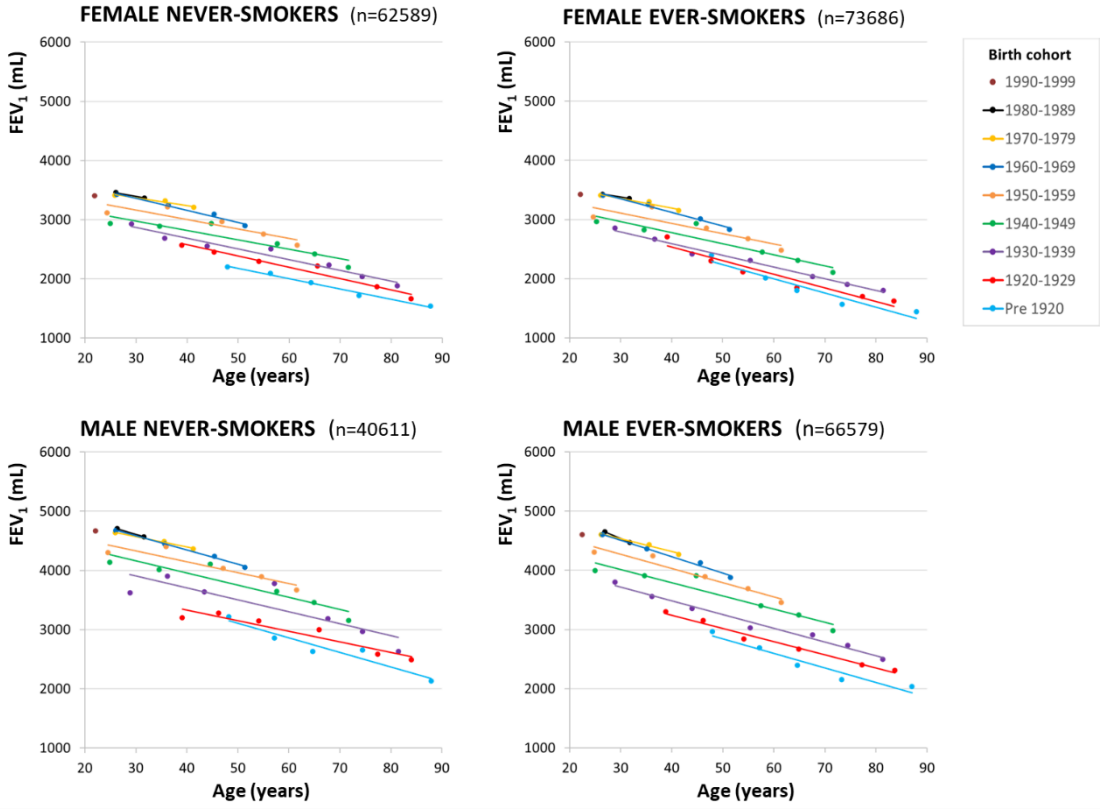
FIGURE 1: The relationship between FEV_1 (y-axis) with advancing age (x-axis) according to birth cohort (legend).

Each marker shows the mean value (y-axis) among individuals belonging to that sub-group (defined by both their birth cohort and age at measurement). The key defines the distinct birth cohorts. The age bands are described in the methods section. Data from these sub-groups are plotted according to their mean age (x-axis). Linear trendlines are shown.

The upper and lower panels show females and males, respectively. The left and right panels show never and ever-smokers, respectively. Each individual appears once only (they each contribute to one time point within one panel only). The number included in each panel is as shown. See also Figure S2.



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535 **FIGURE 2: Difference in FEV_1 and FVC according to year of birth in a meta-regression model.**

536 Estimates show change in lung function (mL) per year of birth increase. Each model is adjusted, as shown, for
537 covariates considered relevant (age, study, height, sex, ever-smoking status, pack years and weight). In the final
538 adjusted model, FEV_1 and FVC increased by 4.8 mL/birth year (95%CI: 2.6 to 7.0; P<0.0001) and 8.8 mL/birth
539 year (95%CI: 5.7 to 12.0; P<0.0001) respectively, independent of age, height, sex, ever-smoking status, pack
540 years and weight. The FEV_1 and FVC models include data from 10 population-based studies (243,465
541 participants) and 9 studies (237,468 participants) respectively. Subgroup analyses show the final fully adjusted
542 model stratified according to sex and ever-smoking status. For each meta-regression analysis, we show the
543 calculated R^2 and residual I^2. R^2 describes the between-study variance explained by the included covariates and I^2
544 describes the proportion residual of between-study variation explained due to heterogeneity versus sampling
545 variation. Stratifying by age yielded results in younger and older (Figure S13).

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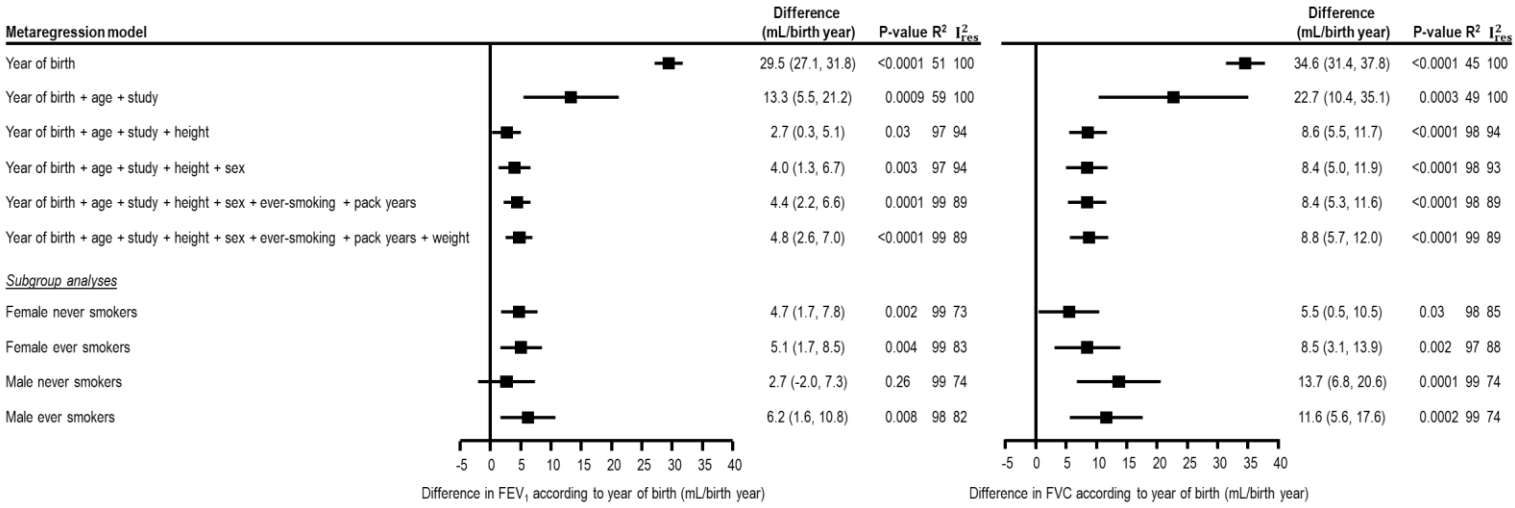

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FIGURE 3: The influence of birth year on the FEV_1 and FVC values predicted by published reference equations:

Each of the listed reference equations were used to calculate predicted FEV_1 and FVC values for 50-year-old females and males (as applicable) using the average height and, where applicable, average weight, of never-smokers in our study (Female: height 1.67m, weight 71kg; Male: height 1.81m, weight 85kg). For each reference equation, the study measurement date was estimated, using the mid-year of the study measurement period. If this was unreported, we instead used the year of manuscript submission and if this was unavailable, we used publication year. Birth year was then estimated by subtracting 50 years from the estimated year of measurement.

The resulting predicted values are plotted according to estimated year of birth (upper panel: FEV_1; lower panel: FVC). The equations show the results of linear regression analysis. Female values are shown in red. Male values are shown in blue. The left panels include all 32 equations. The right panels exclude the 8 studies which may have included ever-smokers (open circles) (See also Tables S4-S6)).

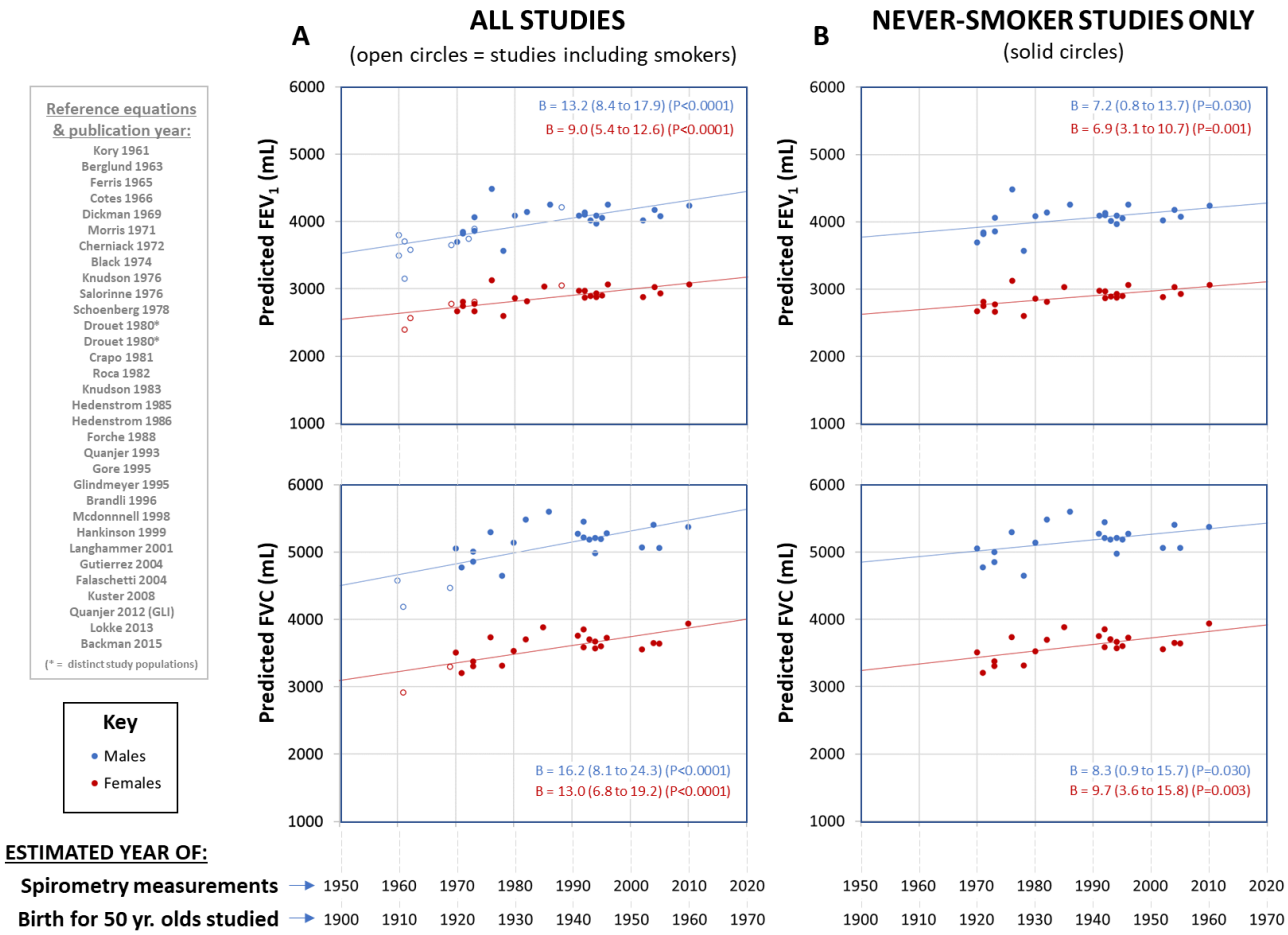

FIGURE 4: Comparison between the calculated theoretical (A-D) and observed (E-F) impact of birth cohort effects upon lung function interpretation using percent of predicted values.

A: Shows how the height-independent 13.7 mL/birth year increase in FVC we report for never-smoking males (Figure 2) would be expected to cause "normal" population FVC values to deviate, over time, from those predicted by GLI 2012 reference equations. Circular markers show the GLI 2012 predicted FVC values for 1.81m tall Caucasian men at four ages (● 30-year-olds; ● 50-year-olds; ● 70-year-olds; ● 90-year-olds). These reflect "normal" population values in 1994, the approximated year of the measurements used to derive GLI 2012 predictions. In the absence of birth cohort effects, the "normal" values at these ages would remain constant over time (dashed black line). The x-axis shows that, for each age line, advancing measurement year corresponds directly to advancing birth year. In our study, FVC increased by 13mL/birth year, equating to an increase of 274mL after 20 birth years. This would lead "normal" values to progressively deviate from the values observed in 1994, as per the dashed coloured lines (colour according to age)

B: Here, data from panel A is plotted according to age instead of the year of measurement. The central dashed black line plots GLI 2012 predicted FVC (derived from measurements circa 1994). The two additional curves show the curve expected twenty years earlier (in 1974) and twenty years later (in 2014) incorporating a 274mL decrease and increase, respectively. Again, the x-axis shows that, for each dashed coloured age line, advancing measurement year directly corresponds to advancing birth year.

C: Using the data from panel B, we plot the expected course of four birth cohorts as they age, accounting for the 13.7mL per birth year increase in FVC. The solid lines represent cohorts from the following birth years: 1964 (dark blue), 1944 (green), 1924 (red) and 1904 (light blue) as they age over time . This shows how the persistence of birth cohort effects will have caused ageing birth cohorts to transect the FVC curve predicted by GLI 2012 (and other such cross-sectional studies).

D: Translates the data from panel C into percent of GLI 2012 predicted values. This panel shows how the birth cohort effects found should lead to the progressive underestimation of values measured after 1994, and the overestimation of values measured prior to 1994.

E and F (FEV_1 and FVC respectively): Show, from our current study, the observed relationship between percent of predicted lung function (using individual subject-level percent of GLI predicted values) according to age and

592 birth cohort. The patterns observed within panels E and F bear strong resemblance to the theorised pattern shown

593 in panel D. Linear trendlines are shown. See also Figures S5-6 and S14.

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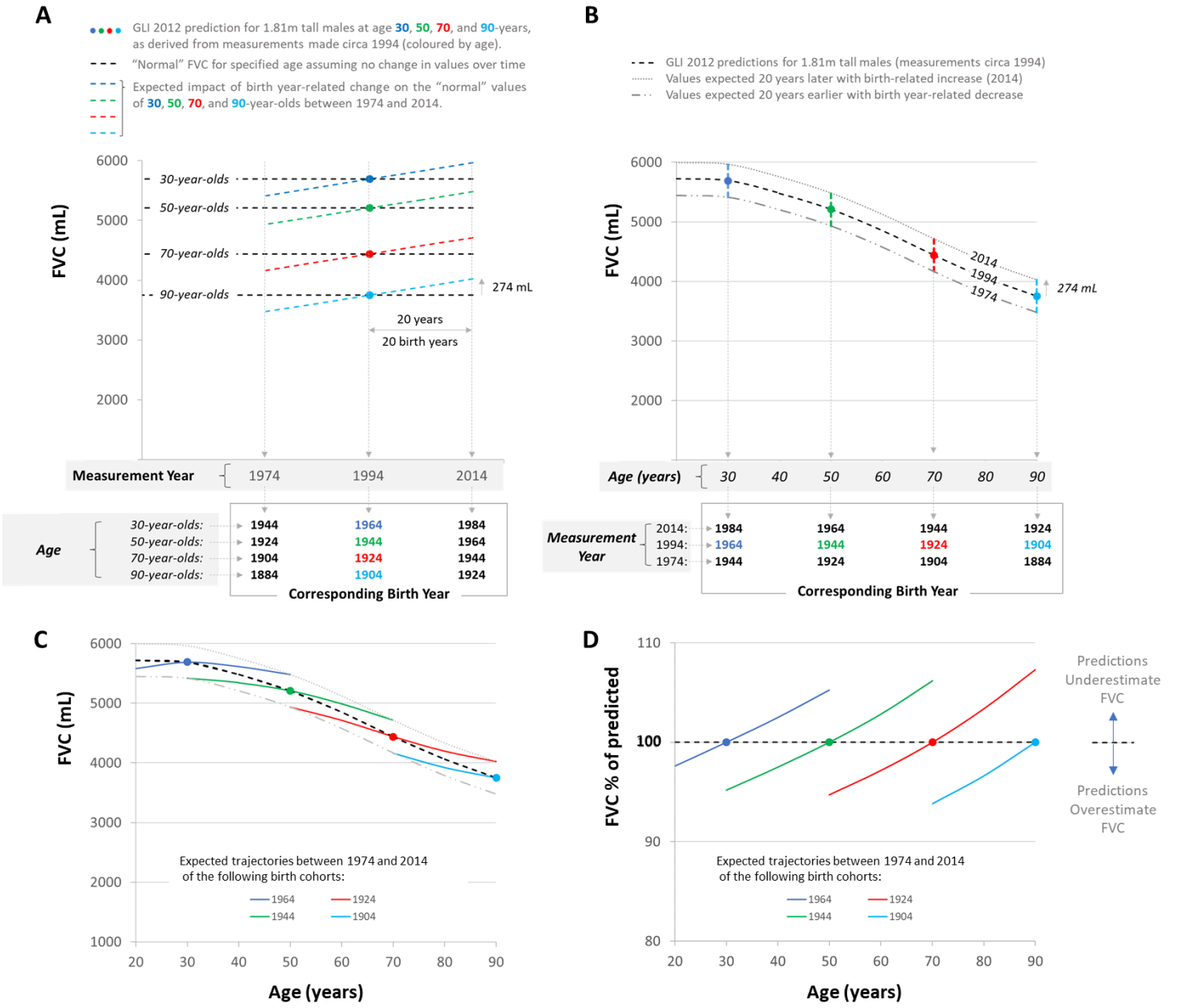
Calculated theoretical impact of 13.7 ml/birth year increase of FVC on percent FVC predicted values:



Observed impact of birth cohort on FEV_1 and FVC percent predicted values within this study:

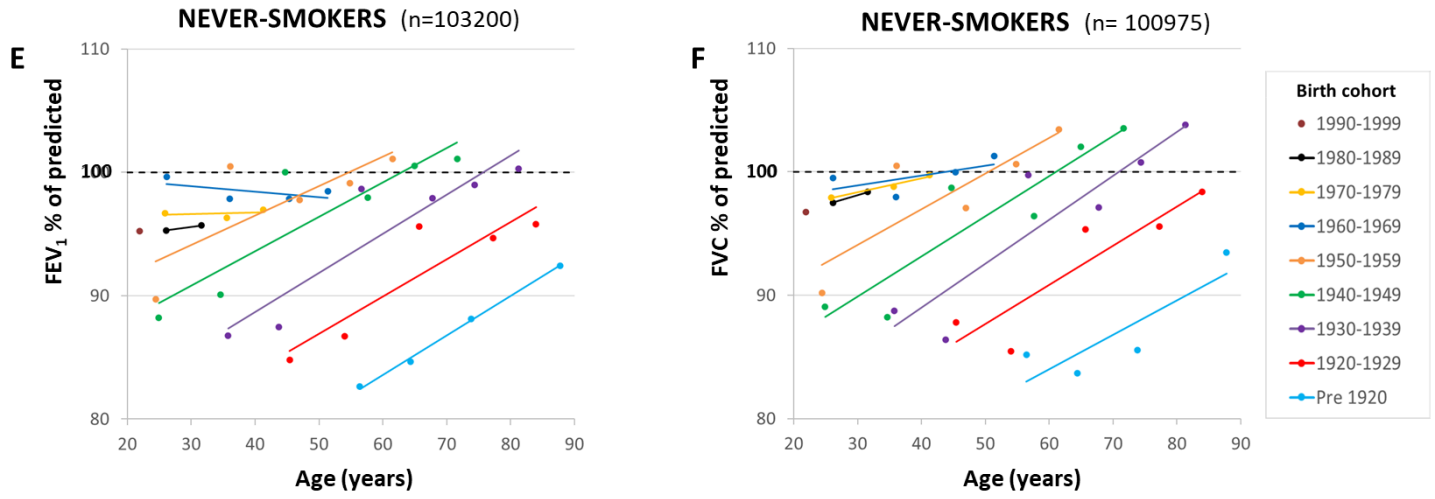
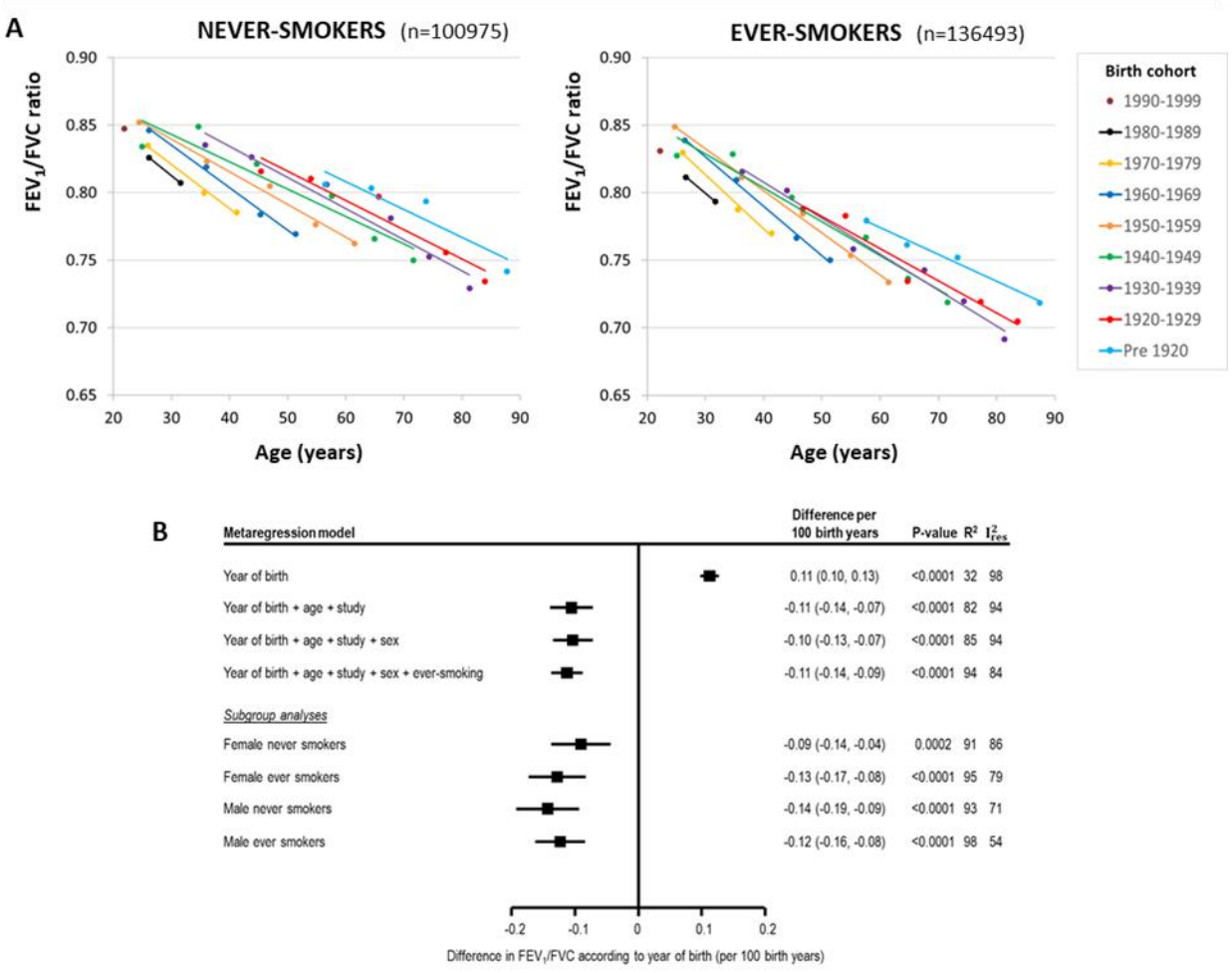


FIGURE 5: FEV_1 /FVC ratio change with advancing birth cohort.

A: The relationship between FEV_1/FVC ratio with advancing age according to birth cohort. The left and right panels show never and ever-smokers respectively. Each marker shows the mean FEV_1/FVC ratio (y-axis) according to mean age (x-axis) of sub-populations defined by both birth year and age at measurement. The key defines the birth cohorts, and the age bands are described in the methods section. Linear trendlines are shown.

B: Meta-regression model examining how birth year influenced FEV_1/FVC ratio, independent of age and smoking. For simplicity estimates show FEV_1/FVC ratio change across 100 birth years. The model progressively adjusts for age, ever-smoking, and pack years. The fully adjusted model demonstrates a decrease in FEV_1/FVC ratio by 0.11 (95%CI: 0.09 to 0.14; P<0.0001) per 100 birth years. The model is subsequently stratified by sex and ever-smoker status. For each meta-regression analysis, we show the 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 due to heterogeneity versus sampling variation. For results of additional adjustment for height and weight see Supplementary material.



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. HB has received payment from AstraZeneca and Boehringer Ingelheim for presentations made at scientific meetings. MVDB has received institutional research grants from GlaxoSmithKline LLC, Roche, Genentech and Novartis. GB has received honoraria from AstraZeneca, Boehringer-Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Sanofi and TEVA. OCB has received grants/contracts, consulting fees and payment/honoraria from AstraZeneca, Abbvie, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline LLC, Menarini, MSD, Novartis, Roche, Takeda, TEVA for lectures/presentations/speakers bureaus/manuscript writing/educational events. RF has received research grants from GlaxoSmithKline LLC, Menarini, AstraZeneca, ISC-III and the Spanish Health Service, with consulting fees from GlaxoSmithKline LLC and honoraria from Chiesi. SH has received grants/contracts, consulting fees and payment/honoraria from AstraZeneca, Abbvie, Boehringer Ingelheim, Chiesi Farmaceutici, GlaxoSmithKline LLC, Menarini, MSD, Novartis, Roche, Takeda, TEVA for lectures/presentations/speakers bureaus/manuscript writing/educational events. AL has received payment for lectures from Boehringer Ingelheim, travel costs from Novartis and Astra Zeneca to attend meetings, has participated in an Astra Zeneca advisory board, has contributed to the Norwegian Primary Care Respiratory Group and has been a member of the Norwegian Health Directorate. BL received grants from Astra Zeneca and ThermoFisher, and has participated in a Sanofi advisory board. SAV 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 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, Boehringer Ingelheim, Novartis and Genentech and participated in a Virtus Data and Safety Monitoring Board. JV has received a research grant from Boehringer-Ingelheim, honoraria from AstraZeneca, Boehringer-Ingelheim, Chiesi, GlaxoSmithKline and Novartis for presentations at meetings, has received honoraria from AstraZeneca, Boehringer-Ingelheim, Chiesi, 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, UNEP. LEGWV has received institutional grants from AstraZeneca, has received personal payments from AstraZeneca, GlaxoSmithKline, Boehringer, AGA/Linde, Novartis, Menarini and

Zambon for lectures/presentations/speakers bureaus/manuscript writing or educational events, has received personal payments from AstraZeneca, GlaxoSmithKline and Boehringer-Ingelheim for participation on data safety monitoring/advisory boards, and has received payment from Chiesi for medical writing. SA, YC, DJ, MKB, RBK, LL, BIN, EN, JMV, BN, NO, and AA declare no conflicts of interest.

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