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TITLE PAGE

Title

Spirometry and survival in large UK cohorts of lifelong non-smokers

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Author contributions

The study was conceived by DS. Design and analysis of the Health Survey for England and Scottish Health Surveys modelling was conducted by RG. Design and analysis of the UK Biobank modelling was conducted by DS. Both authors contributed to interpretation of the findings and writing of the manuscript. The corresponding author DS has full access to all the data included in these analyses and is the guarantor of this manuscript.

Conflict of interests

There are no conflicts of interest to declare for either RG or DS.

Data sharing statement

No additional data are available.

ABSTRACT

Background. Reduced lung function is an established predictor of all-cause mortality. We sought to verify this among lifelong non-smokers from large UK national surveys.

Methods. In UK Biobank, among 149,343 white never-smokers aged 40–69 years at entry, 2401 deaths occurred over a mean 6·5 years follow-up. In the Health Surveys for England (HSE) 1995, 1996, 2001 and Scottish Health Surveys (SHS) 1998 and 2003 combined there were 500 deaths among 6579 white never-smokers aged 40–69 at entry, followed for a mean 14·3 years. Standard deviation (z) scores for forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC) were related to deaths from all causes, circulatory disease and cancers using proportional hazards models adjusted for age, sex, height, socio-economic status, region and survey.

Results. In the HSE-SHS dataset, decreasing z-scores for FEV1 and FVC were each associated to a similar degree with increased all-cause mortality (hazard ratios per SD decrement 1·17, 95%CI 1·09–1·25 for zFEV1 and 1·19, 1·10–1·28 for zFVC). This was replicated in Biobank (HRs per SD 1·21, 1·17–1·26 and 1·24, 1·19–1·29, respectively). In HSE-SHS, zFEV1 and zFVC were also associated to similar degrees with mortality from circulatory diseases. These associations were stronger in Biobank. For cancer mortality, the hazard ratios were more consistent between the cohorts. Spirometric indices predicted mortality at least as strongly as systolic blood pressure and body mass index.

Conclusions. These results emphasise the importance of promoting lung health in the general population, even among lifelong non-smokers.

ARTICLE SUMMARY

Strengths and limitations of this study

- This study is one of the largest studies in the world showing the effect of lung function on mortality in lifelong non-smokers, made possible by the recent availability of data from UK Biobank.
- Results from Biobank are corroborated by findings from health surveys in England and Scotland, which are more representative of the national population and have been followed over a longer period for mortality outcome.
- Both data sources show that better lung function predicts greater survival from a range of causes at least as strongly as systolic blood pressure and body mass index, emphasising the potential importance of promoting lung health in the general population, even in those who have never smoked.
- This analysis was restricted to fatal outcomes but the recent linkage of hospital admissions and primary care consultations to the UK Biobank cohort will allow associations of reduced lung function with incidence and case-fatality to be investigated in future.

140 character conclusion from the manuscript for Twitter feed

Lung health is important, even among lifelong non-smokers. Blowing tests predict survival chances as strongly as blood pressure and obesity.

INTRODUCTION

Four decades of epidemiological research have consistently shown that reduced levels of ventilatory function, measured as one-second forced expiratory volume (FEV1) or forced vital capacity (FVC) are associated with shorter survival in the general population.[1-7] Few studies have reported specifically on lifelong non-smokers,[3,4] a group who form the minority of most populations surveyed hitherto, but are set to become more common in future as smoking becomes less prevalent in higher income countries.

In this report, we compare the relationship of lung function measures (FEV1 and FVC) to subsequent mortality in UK Biobank and in the Health Surveys for England and Scottish Health Surveys. Biobank is the largest spirometric study ever performed in the UK and included a relatively high proportion of never-smokers. The national health surveys, although based on smaller numbers of subjects, recruited a wider age range, have a longer period of follow-up, higher response rates and are more representative of the general UK population than Biobank. The two sources are therefore complementary, in terms of precision and generalisability.

This paper focuses upon findings for white lifelong non-smokers. Corresponding results for white former smokers and current smokers are included in the online supplement for completeness.

METHODS

Health Surveys for England and Scottish Health Surveys

Results were combined from the Health Surveys for England 1995, 1996 and 2001,[8-10] and the Scottish Health Surveys 1998 and 2003,[11-12] the years when spirometry was included in the protocol. These surveys aimed to recruit a representative sample of British adults through

household sampling within selected parliamentary constituencies throughout England or Scotland. Participants were visited at home. Response rates ranged from 60% to 76% across the five surveys. The proportion of those visited who performed usable spirometry ranged from 63% to 84%.

Spirometry was performed using hand-held pneumotachograph spirometers (Vitalograph Escort) with the best results of FEV1 and FVC recorded from three technically satisfactory blows. No flow-volume curves or reproducibility criteria were available for assessment. Valid lung function measurements were available for 6,579 lifelong non-smokers aged 40-69 years and 1,429 aged 70 or more at the start of follow-up.

Deaths occurring up to April 2013 were available for analysis in the Health Surveys for England,[13] and deaths up to December 2011 were linked in the Scottish Health Surveys.[14] Combining all five surveys, there were 500 deaths among never-smokers aged 40-69 at recruitment over a mean follow-up period of 14·3 years. Deaths from respiratory disease, circulatory disease, cancer and all other causes were coded using ICD9 (460-519, 390-459, 140-208, all others, respectively) and ICD10 (chapters J, I, C, all others, respectively).

Smoking history was self-reported. Socio-economic status was measured at the level of the household, based on the social class of the head of the household. Nation (England or Scotland), region (within England) and survey year were included as additional covariates.

UK Biobank

This study recruited 502,682 volunteers aged 40-69 years in 22 recruitment centres throughout England, Wales and Scotland during 2006-2010, following invitations to 9 million people.[15] Spirometry was performed using a hand-held pneumotachograph spirometer (Pneumotrac 6800) from which volume-time arrays were stored for each blow.[16]

81% of the cohort performed two blows with acceptable start and measures of FEV1 reproducible within 250mL. This was considered the most inclusive sample of "usable spirograms". When end-blow quality was also considered, 58% of the cohort had evidence of a good plateau and both FEV1 and FVC reproducible within 150mL, the criteria recommended by the ATS/ERS Task Force on Standardisation of Spirometry.[17] This subgroup of 58% was considered to be the "best quality" spirograms, among which to evaluate the relative importance of FEV1 and FVC as predictors of mortality.

The present analysis is based on deaths occurring up to mid-August 2015, a mean follow-up period of 6·5 years. There were 2,401 deaths among 149,343 lifelong non-smokers aged 40-69 of white ethnicity who performed "usable spirograms". Deaths from respiratory disease, circulatory disease, cancer and all other causes were coded using ICD10 (chapters J, I, C, all others, respectively).

Smoking history was self-reported. Socio-economic status was measured at the level of residential area, using the Townsend deprivation index, grouped into quartiles for analysis. Biobank recruitment centre was used as an additional covariate to adjust for possible regional differences.

Adjustment of spirometric measures for gender, age and height

The Global Lung Initiative (GLI) 2012 reference equations for white ethnic groups[18] were used in both sets of data to standardise FEV1 and FVC for age, sex and height. The GLI equations generate a "z-score" which represents the relative position of an individual among the distribution predicted for lifelong non-smokers with no history of lung disease of the same gender, age and height. This allows for the spread of predicted values to differ by age, height and gender, expressing the relative ranking of an individual in terms of a standard

deviation (z) score. For each individual in the analysis, there were three z-scores, corresponding to their relative ranking for FEV1 (zFEV1), FVC (zFVC) and the ratio FEV1/FVC (zFEVFVC). Outlying observations were excluded by restricting all the analyses in both datasets to values of zFEV1 and zFVC within the range -5 to +5 SD units.

Modelling of mortality

The relationship of spirometric indices to subsequent mortality was modelled by proportional hazards (Cox) regression, which estimates the relative increase in mortality rate (hazard ratio) for a unit change in each explanatory variable. The z-scores are expressed on a standard deviation scale, so hazard ratios for zFEV1 and zFVC are expressed per SD decrement (ie. an increase in risk for a decrease in lung function). A typical range of z-scores among lifelong non-smokers would be 4SD units. A hazard ratio of 1·2 per SD decrement corresponds approximately to a twofold difference in mortality rate across the 4SD range.

Due to the high correlation between zFEV1 and zFVC, we modelled the effect of zFEV1 both alone and jointly with zFEVFVC; and similarly for zFVC.

All proportional hazards models were restricted to white participants and adjusted for sex, age, standing height, socio-economic status and region. Analyses of the national health surveys were additionally adjusted for survey year.

RESULTS

All-cause mortality

Table 1 compares the hazard ratios for age-sex-height-adjusted FEV1 and FVC in relation to all-cause mortality in the combined Health Survey for England (HSE) and Scottish Health Surveys (SHS) dataset, and UK Biobank (UKB), among participants aged 40-69 years at entry. All "usable spirograms" from Biobank were included in this comparison, because no additional quality control had been applied in the national health surveys 1995-2003.

Table 1 **All-cause mortality in white lifelong non-smokers aged 40-69 at entry in national health surveys (HSE and SHS) and in UK Biobank**

		HSE-SHS white lifelong non-smokers, 40-69 at entry			*Biobank white lifelong non-smokers, 40-69 at entry*		
Timing of death	***Cause of death***	***Total N (deaths)***	***zFEV1 HR(95%CI)***	***zFVC HR(95%CI)***	***Total N (deaths)***	***zFEV1 HR(95%CI)***	***zFVC HR(95%CI)***
Any time	All causes	6579 (500)	1.17 (1.09-1.25)	1.19 (1.10-1.28)	149343 (2401)	1.21 (1.17-1.26)	1.24 (1.19-1.29)
Within 5 years	All causes	6579 (103)	1.35 (1.17-1.56)	1.35 (1.16-1.57)	149343 (1599)	1.23 (1.17-1.28)	1.26 (1.20-1.32)
After 5 years	All causes	6476 (397)	1.12 (1.03-1.21)	1.14 (1.05-1.24)	147744 (802)	1.18 (1.11-1.26)	1.21 (1.13-1.29)
Any time	Respiratory	6579 (34)	1.72 (1.34-2.21)	1.61 (1.25-2.08)	149343 (69)	1.86 (1.53-2.27)	2.15 (1.77-2.61)
Any time	Circulatory	6579 (130)	1.21 (1.06-1.38)	1.22 (1.06-1.40)	149343 (431)	1.41 (1.30-1.53)	1.47 (1.35-1.60)
Any time	Cancer	6579 (241)	1.10 (1.00-1.22)	1.12 (1.01-1.24)	149343 (1535)	1.08 (1.03-1.13)	1.10 (1.05-1.15)
Any time	Other non-respiratory	6579 (105)	1.15 (0.98-1.34)	1.20 (1.03-1.41)	149343 (366)	1.46 (1.33-1.59)	1.45 (1.32-1.59)

Spirometric indices (FEV1 and FVC) are modelled as z-scores derived from the Global Lung Initiative 2012 reference equations for whites.
All hazard ratios are expressed per SD decrement in z-score, adjusted for age, sex, height, socio-economic status, geographical region and survey year.

When each spirometric index was modelled singly, all associations were highly statistically significant ($p<0{\cdot}0001$). Among lifelong non-smokers in both cohorts, FEV1 and FVC displayed similar strengths of association with all-cause mortality. Among current smokers, however, FEV1 was the stronger predictor in both datasets (Supplementary e-Tables 1 and 2).

Table 1 also shows the most direct comparison between the two datasets, based on all-cause mortality within 5 years. Although the associations of spirometric indices with these earlier deaths were stronger in HSE-SHS than in UKB, the difference between the cohorts was not statistically significant. Associations with deaths after 5 years are less comparable between the datasets, due to the shorter period of follow-up in UKB.

Stronger associations of FEV1 and FVC with earlier deaths than with later mortality from all causes were also evident among former smokers and current smokers, although the differences were more marked in HSE-SHS than in UKB (e-Tables 1 and 2).

Influence of spirogram quality

Table 2 presents the results for all causes of death among Biobank participants with "best quality" spirograms, for comparison with those obtained from the full set of "usable spirograms". The pattern and magnitude of the results among the former subset are very similar to the overall UKB results.

Table 2 **Comparison of mutually adjusted spirometric indices to predict all-cause mortality in national health surveys (all spirograms) and in UK Biobank (comparing all usable spirograms with best quality spirograms)**

		HSE-SHS white lifelong non-smokers, 40-69 at entry			*Biobank white lifelong non-smokers, 40-69 at entry*		
Subset analysed	***z-score in model (plus covariates)***	***Total N (deaths)***	***HR(95%CI) alone***	***HR (95%CI) joint***	***Total N (deaths)***	***HR(95%CI) alone***	***HR (95%CI) joint***
All usable spirograms	FEV1 alone	6579 (500)	1.17 (1.09-1.25)		149343 (2401)	1.21 (1.17-1.26)	
	FEV1 adj FEV/FVC			1.20 (1.11-1.29)			1.26 (1.21-1.31)
	FEV/FVC adj FEV1			0.94 (0.87-1.01)			0.90 (0.85-0.94)
All usable spirograms	FVC alone	6579 (500)	1.19 (1.10-1.28)		149343 (2401)	1.24 (1.19-1.29)	
	FVC adj FEV/FVC			1.19 (1.11-1.28)			1.24 (1.19-1.29)
	FEV/FVC adj FVC			1.02 (0.95-1.10)			1.02 (0.97-1.07)
Best quality spirograms	FEV1 alone		(No data)		102945 (1583)	1.23 (1.18-1.29)	
	FEV1 adj FEV/FVC						1.29 (1.23-1.36)
	FEV/FVC adj FEV1						0.86 (0.81-0.91)
Best quality spirograms	FVC alone		(No data)		102945 (1583)	1.29 (1.23-1.35)	
	FVC adj FEV/FVC						1.29 (1.23-1.35)
	FEV/FVC adj FVC						0.98 (0.93-1.04)

Spirometric indices (FEV1, FVC and FEV1/FVC ratio) are modelled as z-scores derived from the Global Lung Initiative 2012 reference equations for whites.
All hazard ratios are expressed per SD decrement in z-score, adjusted for age, sex, height, socio-economic status, geographical region and survey year.

The covariate-adjusted hazard ratios for all-cause mortality comparing the "best quality" group to the remainder were: 0·94 (95%CI 0·86–1·02) among lifelong non-smokers, HR 1·02 (0·96–1·09) among former smokers and HR 0·94 (0·85–1·04) among current smokers. None of these hazard ratios are statistically significant, despite very large numbers of subjects included each comparison.

Choice of spirometric index

Among lifelong non-smokers, adding FEV1/FVC ratio to a model including FVC did not contribute additional information, whereas adding FEV1/FVC ratio to a model including FEV1 did improve the fit of the model significantly (Table 2). This pattern was evident in both HSE-SHS and UKB, and among the subset of UKB participants with "best quality" spirograms.

Cause-specific mortality

Table 1 also presents the association of spirometric indices (modelled singly) with respiratory, circulatory, cancer and other causes of death. The strength of association with FEV1 and FVC was greatest for respiratory mortality and weakest for cancer deaths. This applied in both datasets, but the hazard ratios for respiratory, circulatory and other causes of death were substantially greater in UKB than in HSE-SHS. The results in the two cohorts are more similar for cancer mortality.

Within UKB, results for cause-specific mortality were generally consistent between the "best" subgroup and the fuller dataset (e-Table 3). FVC emerged as the more influential

predictor of non-respiratory mortality and this was confirmed in the subset with good quality spirometry. The same pattern also applied to respiratory mortality among never-smokers (Table 1) although these results should be interpreted with caution due to the small number of respiratory deaths among lifelong non-smokers, particularly among those with good quality spirograms (e-Table 3).

Comparisons by subgroups of age and sex

Supplementary e-Table 2 shows that within UK Biobank there were slightly stronger associations of mortality with both FEV1 and FVC among male never-smokers, and among female current smokers, but the general pattern of results was similar in both sexes.

Supplementary e-Table 2 also compares the results for all-cause mortality among younger (aged 40-59) and older (aged 60-69) UKB participants. The hazard ratios in all smoking groups were consistent between these two age subgroups.

Supplementary e-Table 4 compares the spirometric associations with all-cause and cause-specific mortality among HSE and SHS participants aged 40-69 and 70 or more at entry. Again, the pattern of results was consistent between these age groups in all smoking subgroups.

Comparisons by prior disease history in UK Biobank

Table 3 compares the spirometric associations with all-cause mortality in Biobank participants with and without a history of respiratory disease at the baseline spirometric examination.

Table 3 **Comparison of spirometric prediction of mortality among subjects with and without prior disease history at entry in UK Biobank**

		Biobank age 40-69, white lifelong non-smokers without a history of the condition at entry			*Biobank age 40-69, white lifelong non-smokers with a history of the condition at entry*		
Condition at entry	***Cause of death***	***Total N (deaths)***	***zFEV1 HR(95%CI)***	***zFVC HR(95%CI)***	***Total N (deaths)***	***zFEV1 HR(95%CI)***	***zFVC HR(95%CI)***
Respiratory disease	All causes	130798 (2081)	1.21 (1.16-1.26)	1.22 (1.17-1.27)	18545 (320)	1.23 (1.12-1.35)	1.33 (1.21-1.47)
Circulatory disease	Circulatory disease	109141 (189)	1.40 (1.23-1.59)	1.40 (1.23-1.60)	40202 (242)	1.35 (1.20-1.51)	1.43 (1.27-1.60)
Cancer	Cancer	137742 (978)	1.05 (0.99-1.11)	1.06 (1.00-1.12)	11601 (557)	1.10 (1.02-1.18)	1.13 (1.04-1.22)

Spirometric indices (FEV1 and FVC) are modelled as z-scores derived from the Global Lung Initiative 2012 reference equations for whites.
All hazard ratios are expressed per SD decrement in z-score, adjusted for age, sex, height, socio-economic status and geographical region (recruitment centre).

In the 18,545 (12%) white never-smokers with "usable spirograms" who had a history of diagnosed respiratory disease (of which 90% reported asthma), FVC was a stronger predictor of all-cause mortality than FEV1. Among the subgroup without a respiratory history, results were similar to the full cohort.

Lung function also emerged as a significant predictor of circulatory mortality among those with and without a prior history of heart attack, angina, stroke, thrombosis or hypertension (Table 3). This pattern was confirmed among former smokers and current smokers (e-Table 5).

Finally, the association of FEV1 and FVC with cancer mortality was shown to be stronger in those with a prior cancer diagnosis (Table 3), though was not statistically significant, despite the large sample size, among those with no cancer history at the spirometric examination. However, this finding is confined to the lifelong non-smokers: both FEV1 and FVC were more strongly and significantly associated with cancer death among former smokers and current smokers with no cancer history (e-Table 5). Cancer mortality among participants with a history of cancer at entry was strongly and significantly associated with both FEV1 and FVC in all three smoking subgroups (e-Table 5).

Comparison of spirometry with other predictors of mortality

Figure 1 (data in e-Table 6) compares the relative mortality across quartiles of body mass index, systolic blood pressure and FVC z-score, for all non-respiratory deaths and for deaths from circulatory disease, among white lifelong non-smokers in HSE-SHS and in UK Biobank. A similar pattern emerged in both cohorts, with differentials in mortality across

quartiles of zFVC being at least as great as those across quartiles of body mass index or systolic blood pressure.

DISCUSSION

A broadly coherent picture emerges from this comparison of UK national cohorts. Lung function, even if measured imperfectly, consistently predicts non-respiratory mortality from a range of causes. This applies even among lifelong non-smokers, so confounding by the amount or duration of active smoking is not the sole explanation.

Previous studies of lifelong non-smokers have been of limited size: 662 males and 2048 females in the Copenhagen City Heart Study,[3] and 3562 male London civil servants in the Whitehall Study.[4] UK Biobank offers a spirometric study of lifelong non-smokers of unprecedented size, but its 5·5% participation rate may have compromised its generalisability. Assembling data from five UK national health surveys produced a cohort larger than the previous publications[3,4] in which the generalisability of Biobank results could be tested. The similar pattern of results in HSE-SHS and UKB suggests that the key findings are generalisable.

An analysis of the Athersclerosis Risk in Communities (ARIC) cohort[7] suggested that FVC should be considered as a more predictive spirometric index than FEV1. However, this conclusion was drawn from a cohort of mixed smoking habits. In our study of lifelong non-smokers, we confirmed that FVC (rather than FEV1) is the index of greater importance in determining survival in middle-aged never-smokers. However, among current smokers, FEV1 emerged as the more influential predictor. This may be because the FEV1/FVC ratio declines with both the dose and duration of smoking, and these also increase mortality risk.

The ability to perform good quality spirometry is an integrated assessment of physical and cognitive function and therefore might be considered a predictor of mortality in its own right. In the US Six Cities study, excessively variable spirometric performance was an indicator of poor health and associated with shorter survival.[19] In contrast, the mortality experience of Biobank participants who produced "best quality" spirograms did not differ greatly from that of their peers who produced "usable" but not "best quality" blows.

In clinical practice, particularly in primary care, quality control of spirometry is unlikely to be much better than in the national health surveys where lung function was tested by a trained research nurse in the home setting. Therefore, while the results from the Biobank "best quality" subgroup are of confirmatory interest, the more inclusive results for all "usable spirograms" may be more generally relevant.

This analysis was restricted to fatal outcomes and therefore cannot distinguish between an influence of reduced ventilatory function on disease incidence and an effect on case-fatality. The association with cancer mortality was weaker among those with no cancer diagnosis at entry, suggesting an effect primarily on case-fatality. In contrast, the association of spirometric indices with circulatory mortality was equally strong in those with and without a prior history of circulatory disease. The recent linkage of hospital admissions and primary care consultations to the UK Biobank cohort will allow associations with incidence and case-fatality to be investigated more directly in future.

In both cohorts, age-sex-height-adjusted lung function emerged as a stronger predictor of non-respiratory mortality than either systolic blood pressure or body mass index, which are, respectively, the 2nd and 6th most influential causes worldwide of loss of healthy lifespan, as measured by disability-adjusted life-years.[20] It is therefore puzzling to find U-shaped or J-shaped relationships of these two cardiovascular risk factors with non-respiratory mortality,

but the similar patterns of results in Biobank and the national health surveys suggests that this is not a unique feature of either of these British cohorts.

Specifically for circulatory disease mortality, FEV1 and FVC were as strongly predictive as body mass index, and more strongly predictive than systolic blood pressure. Therefore, spirometry may deserve consideration as an addition to cardiovascular risk scoring algorithms in future. More generally, however, these results emphasise the potential importance of promoting and protecting lung health in the general population, even among lifelong non-smokers with no history of respiratory disease.

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Ethical approval

This is a secondary analysis of anonymised data from national health surveys, each of which obtained ethics committee approval for their fieldwork,[8-12,15] but no specific ethical approval was required for this data analysis.

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Figure 1 title

Hazard ratios for death from all non-respiratory causes, and from circulatory diseases, by quartile of age-sex-height-adjusted forced vital capacity (zFVC), systolic blood pressure (SBP) and body mass index (BMI) among white lifelong non-smokers aged 40-69 at entry in national health surveys (HSE and SHS) and in UK Biobank

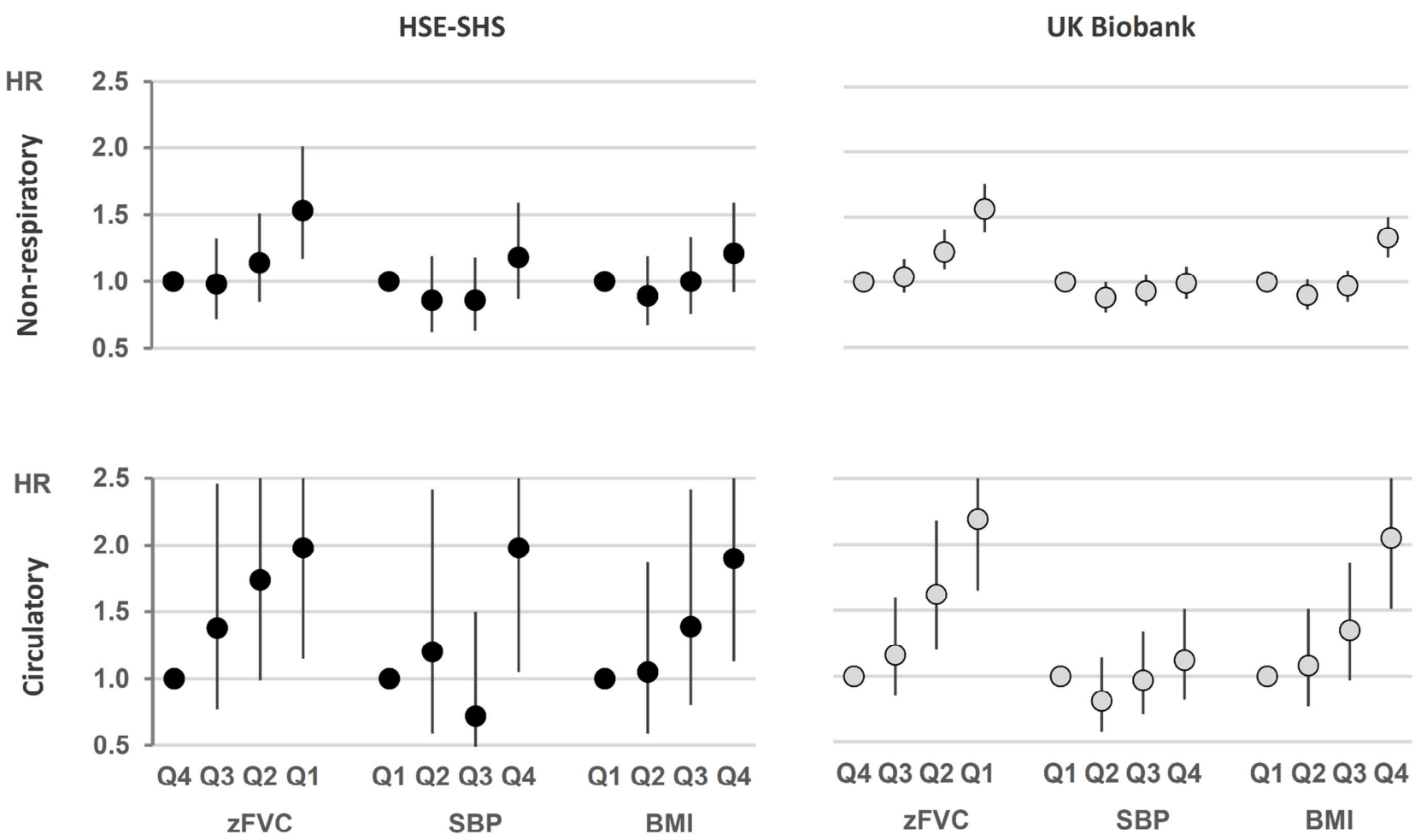
Figure 1 footnote

Hazard ratios are adjusted for age, sex, height, socio-economic status, region and survey year. The reference category (HR=1) is the highest quartile (Q4) for zFVC and the lowest quartile (Q1) for SBP and BMI.

Figure 1 data

Included in supplementary e-Table 6

Figure 1



Hazard ratios are adjusted for age, sex, height, socio-economic status, region and survey year.

SUPPLEMENTARY MATERIAL

Title

Spirometry and survival in large UK cohorts of lifelong non-smokers

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e-Table 1 **Relationship of spirometric indices to mortality before and after 5 years among younger and older subjects, by smoking habit, in the Health Surveys for England and Scottish Health Surveys**

		HSE-SHS age 40-69 at entry, white ethnicity			*HSE-SHS age 70+ at entry, white ethnicity*		
Timing of death	***Smoking history***	***Total N (deaths)***	***zFEV1 HR (95%CI)***	***zFVC HR (95%CI)***	***Total N (deaths)***	***zFEV1 HR (95%CI)***	***zFVC HR (95%CI)***
All deaths	Never smokers	6579 (500)	1.17 (1.09-1.25)	1.19 (1.10-1.28)	1429 (783)	1.24 (1.17-1.32)	1.22 (1.15-1.29)
	Former smokers	9403 (1212)	1.33 (1.28-1.39)	1.31 (1.25-1.37)	3083 (1883)	1.23 (1.19-1.28)	1.20 (1.16-1.25)
	Current smokers	6640 (1271)	1.30 (1.24-1.35)	1.20 (1.15-1.26)	909 (666)	1.36 (1.28-1.46)	1.23 (1.16-1.31)
Deaths within 5 years	Never smokers	6579 (103)	1.35 (1.17-1.56)	1.35 (1.16-1.57)	1429 (217)	1.37 (1.23-1.54)	1.38 (1.24-1.54)
	Former smokers	9403 (288)	1.43 (1.32-1.55)	1.49 (1.37-1.63)	3083 (590)	1.33 (1.25-1.41)	1.28 (1.20-1.36)
	Current smokers	6640 (332)	1.31 (1.21-1.43)	1.24 (1.15-1.35)	909 (250)	1.33 (1.20-1.48)	1.19 (1.08-1.32)
Deaths after 5 years	Never smokers	6476 (397)	1.12 (1.03-1.21)	1.14 (1.05-1.24)	1212 (566)	1.19 (1.11-1.28)	1.15 (1.07-1.24)
	Former smokers	9115 (924)	1.29 (1.23-1.36)	1.25 (1.19-1.32)	2493 (1293)	1.19 (1.14-1.24)	1.17 (1.12-1.22)
	Current smokers	6308 (939)	1.29 (1.23-1.36)	1.18 (1.12-1.25)	659 (416)	1.38 (1.27-1.50)	1.25 (1.15-1.36)

Spirometric indices (FEV1, FVC and FEV1/FVC ratio) are modelled as z-scores derived from the Global Lung Initiative 2012 reference equations for whites.
All hazard ratios are expressed per SD decrement in z-score, adjusted for age, sex, height, socio-economic status, geographical region and survey year.

e-Table 2 **Relationship of spirometric indices to all-cause mortality before and after 5 years, among males and females, and among younger and older subjects, by smoking habit, in UK Biobank**

Biobank age 40-69, white ethnicity, all usable spirograms

Subjects and timing of death	*Smoking history*	*Total N (deaths)*	*zFEV1 HR (95%CI)*	*zFVC HR (95%CI)*
All subjects, deaths within 5 years	Never smokers	149343 (1599)	1.23 (1.17-1.28)	1.26 (1.20-1.32)
	Former smokers	191627 (2998)	1.40 (1.36-1.45)	1.40 (1.35-1.45)
	Current smokers	38514 (1112)	1.39 (1.32-1.46)	1.29 (1.22-1.36)
All subjects, deaths after 5 years	Never smokers	147744 (802)	1.18 (1.11-1.26)	1.21 (1.13-1.29)
	Former smokers	188629 (1430)	1.33 (1.27-1.39)	1.32 (1.25-1.38)
	Current smokers	37402 (564)	1.37 (1.28-1.47)	1.30 (1.20-1.40)
Males, all deaths	Never smokers	56924 (1143)	1.24 (1.18-1.31)	1.28 (1.21-1.35)
	Former smokers	89542 (2714)	1.39 (1.34-1.43)	1.39 (1.34-1.44)
	Current smokers	19909 (1096)	1.36 (1.30-1.43)	1.27 (1.21-1.34)
Females, all deaths	Never smokers	92419 (1258)	1.18 (1.12-1.24)	1.20 (1.14-1.27)
	Former smokers	102085 (1714)	1.37 (1.31-1.43)	1.34 (1.28-1.40)
	Current smokers	18605 (580)	1.42 (1.33-1.52)	1.33 (1.23-1.43)
Age 40-59 at entry, all deaths	Never smokers	90676 (872)	1.23 (1.16-1.31)	1.25 (1.17-1.33)
	Former smokers	101171 (1161)	1.36 (1.29-1.43)	1.37 (1.30-1.45)
	Current smokers	25584 (692)	1.39 (1.31-1.48)	1.27 (1.19-1.36)
Age 60-69 at entry, all deaths	Never smokers	58667 (1529)	1.20 (1.15-1.26)	1.23 (1.18-1.29)
	Former smokers	90456 (3267)	1.39 (1.35-1.43)	1.37 (1.33-1.42)
	Current smokers	12930 (984)	1.38 (1.31-1.45)	1.31 (1.24-1.39)

Spirometric indices (FEV1 and FVC) are modelled as z-scores derived from the Global Lung Initiative 2012 reference equations for whites.
All hazard ratios are expressed per SD decrement in z-score, adjusted for age, sex, height, socio-economic status and geographical region (recruitment centre).

e-Table 3 **Comparison of best quality spirograms with all usable spirograms to predict all-cause and cause-specific mortality, by smoking habit, in UK Biobank**

		Biobank age 40-69, white ethnicity, best spirograms			*Biobank age 40-69, white ethnicity, usable spirograms*		
Cause of death	***Smoking history***	***Total N (deaths)***	***zFEV1 HR (95%CI)***	***zFVC HR (95%CI)***	***Total N (deaths)***	***zFEV1 HR (95%CI)***	***zFVC HR (95%CI)***
All causes	Never smokers	102945 (1583)	1.23 (1.18-1.29)	1.29 (1.23-1.35)	149343 (2401)	1.21 (1.17-1.26)	1.24 (1.19-1.29)
	Former smokers	134173 (3043)	1.39 (1.35-1.44)	1.40 (1.35-1.45)	191627 (4428)	1.38 (1.35-1.42)	1.37 (1.33-1.41)
	Current smokers	26105 (1079)	1.39 (1.32-1.46)	1.30 (1.23-1.38)	38514 (1676)	1.38 (1.33-1.44)	1.29 (1.24-1.35)
Respiratory diseases	Never smokers	102945 (48)	2.07 (1.63-2.62)	2.22 (1.76-2.80)	149343 (69)	1.86 (1.53-2.27)	2.15 (1.77-2.61)
	Former smokers	134173 (140)	2.52 (2.20-2.88)	2.28 (1.98-2.63)	191627 (197)	2.46 (2.20-2.76)	2.26 (2.01-2.54)
	Current smokers	26105 (66)	2.93 (2.37-3.62)	2.44 (1.99-3.00)	38514 (106)	2.52 (2.15-2.96)	2.08 (1.76-2.45)
Circulatory diseases	Never smokers	102945 (269)	1.46 (1.31-1.62)	1.57 (1.41-1.76)	149343 (431)	1.41 (1.30-1.53)	1.47 (1.35-1.60)
	Former smokers	134173 (590)	1.56 (1.46-1.68)	1.66 (1.54-1.79)	191627 (860)	1.58 (1.49-1.67)	1.64 (1.54-1.74)
	Current smokers	26105 (219)	1.43 (1.28-1.60)	1.45 (1.28-1.63)	38514 (366)	1.41 (1.30-1.54)	1.38 (1.26-1.52)
Cancer	Never smokers	102945 (1023)	1.10 (1.04-1.16)	1.13 (1.07-1.20)	149343 (1535)	1.08 (1.03-1.13)	1.10 (1.05-1.15)
	Former smokers	134173 (1907)	1.27 (1.22-1.32)	1.25 (1.20-1.31)	191627 (2762)	1.25 (1.21-1.30)	1.23 (1.18-1.27)
	Current smokers	26105 (624)	1.27 (1.19-1.36)	1.18 (1.09-1.27)	38514 (937)	1.28 (1.22-1.36)	1.20 (1.13-1.27)
Other non-respiratory diseases	Never smokers	102945 (243)	1.44 (1.29-1.61)	1.51 (1.35-1.69)	149343 (366)	1.46 (1.33-1.59)	1.45 (1.32-1.59)
	Former smokers	134173 (406)	1.43 (1.31-1.56)	1.49 (1.36-1.63)	191627 (609)	1.41 (1.32-1.51)	1.43 (1.33-1.55)
	Current smokers	26105 (170)	1.36 (1.20-1.55)	1.25 (1.08-1.44)	38514 (267)	1.36 (1.23-1.51)	1.25 (1.12-1.39)

Spirometric indices (FEV1 and FVC) are modelled as z-scores derived from the Global Lung Initiative 2012 reference equations for whites.
All hazard ratios are expressed per SD decrement in z-score, adjusted for age, sex, height, socio-economic status and geographical region (recruitment centre).

e-Table 4 **Relationship of spirometric indices to all-cause and cause-specific mortality among younger and older subjects, by smoking habit, in the Health Surveys for England and Scottish Health Surveys**

		HSE-SHS age 40-69 at entry, white ethnicity			*HSE-SHS age 70+ at entry, white ethnicity*		
Cause of death	***Smoking history***	***Total N (deaths)***	***zFEV1 HR (95%CI)***	***zFVC HR (95%CI)***	***Total N (deaths)***	***zFEV1 HR (95%CI)***	***zFVC HR (95%CI)***
All causes	Never smokers	6579 (500)	1.17 (1.09-1.25)	1.19 (1.10-1.28)	1429 (783)	1.24 (1.17-1.32)	1.22 (1.15-1.29)
	Former smokers	9403 (1212)	1.33 (1.28-1.39)	1.31 (1.25-1.37)	3083 (1883)	1.23 (1.19-1.28)	1.20 (1.16-1.25)
	Current smokers	6640 (1271)	1.30 (1.24-1.35)	1.20 (1.15-1.26)	909 (666)	1.36 (1.28-1.46)	1.23 (1.16-1.31)
Respiratory diseases	Never smokers	6579 (34)	1.72 (1.34-2.21)	1.61 (1.25-2.08)	1429 (118)	1.82 (1.54-2.14)	1.65 (1.41-1.93)
	Former smokers	9403 (185)	1.97 (1.77-2.19)	1.71 (1.53-1.91)	3083 (347)	1.65 (1.52-1.79)	1.46 (1.34-1.59)
	Current smokers	6640 (355)	1.70 (1.56-1.84)	1.40 (1.29-1.52)	909 (221)	1.90 (1.69-2.13)	1.50 (1.34-1.67)
Circulatory diseases	Never smokers	6579 (130)	1.21 (1.06-1.38)	1.22 (1.06-1.40)	1429 (299)	1.26 (1.13-1.39)	1.28 (1.16-1.41)
	Former smokers	9403 (390)	1.37 (1.28-1.48)	1.39 (1.28-1.50)	3083 (745)	1.20 (1.13-1.27)	1.22 (1.15-1.29)
	Current smokers	6640 (380)	1.26 (1.17-1.36)	1.22 (1.12-1.32)	909 (212)	1.21 (1.08-1.35)	1.20 (1.07-1.34)
Cancer	Never smokers	6579 (241)	1.10 (1.00-1.22)	1.12 (1.01-1.24)	1429 (166)	1.08 (0.95-1.23)	1.09 (0.96-1.24)
	Former smokers	9403 (509)	1.18 (1.10-1.26)	1.14 (1.06-1.22)	3083 (448)	1.19 (1.10-1.28)	1.14 (1.05-1.22)
	Current smokers	6640 (532)	1.21 (1.13-1.29)	1.09 (1.02-1.17)	909 (197)	1.20 (1.07-1.34)	1.08 (0.96-1.21)
Other non-respiratory diseases	Never smokers	6579 (105)	1.15 (0.98-1.34)	1.20 (1.03-1.41)	1429 (208)	1.11 (0.98-1.25)	1.04 (0.92-1.17)
	Former smokers	9403 (204)	1.22 (1.10-1.35)	1.32 (1.18-1.48)	3083 (435)	1.11 (1.03-1.20)	1.08 (1.00-1.17)
	Current smokers	6640 (210)	1.11 (1.00-1.24)	1.15 (1.03-1.28)	909 (117)	1.20 (1.03-1.40)	1.11 (0.95-1.29)

Spirometric indices (FEV1 and FVC) are modelled as z-scores derived from the Global Lung Initiative 2012 reference equations for whites.
All hazard ratios are expressed per SD decrement in z-score, adjusted for age, sex, height, socio-economic status, geographical region and survey year.

e-Table 5 **Spirometric prediction of mortality among subjects with and without a history of selected diseases at entry, by smoking habit, in UK Biobank**

		Biobank age 40-69, white, no history of condition			*Biobank age 40-69, white, with history of condition*		
Condition and cause of death	***Smoking history***	***Total N (deaths)***	***zFEV1 HR (95%CI)***	***zFVC HR (95%CI)***	***Total N (deaths)***	***zFEV1 HR (95%CI)***	***zFVC HR (95%CI)***
Respiratory disease at entry, all deaths	Never smokers	130798 (2081)	1.21 (1.16-1.26)	1.22 (1.17-1.27)	18545 (320)	1.23 (1.12-1.35)	1.33 (1.21-1.47)
	Former smokers	166259 (3711)	1.36 (1.32-1.40)	1.34 (1.30-1.38)	25368 (717)	1.48 (1.39-1.57)	1.48 (1.39-1.58)
	Current smokers	33491 (1352)	1.32 (1.26-1.38)	1.21 (1.15-1.27)	5023 (324)	1.53 (1.39-1.68)	1.48 (1.35-1.63)
Circulatory disease at entry, circulatory death	Never smokers	109141 (189)	1.40 (1.23-1.59)	1.40 (1.23-1.60)	40202 (242)	1.35 (1.20-1.51)	1.43 (1.27-1.60)
	Former smokers	131593 (281)	1.39 (1.26-1.54)	1.40 (1.26-1.57)	60034 (579)	1.59 (1.48-1.70)	1.64 (1.52-1.77)
	Current smokers	27843 (162)	1.32 (1.16-1.50)	1.29 (1.12-1.48)	10671 (204)	1.42 (1.26-1.59)	1.36 (1.20-1.54)
Cancer at entry, cancer death	Never smokers	137742 (978)	1.05 (0.99-1.11)	1.06 (1.00-1.12)	11601 (557)	1.10 (1.02-1.18)	1.13 (1.04-1.22)
	Former smokers	174917 (1898)	1.21 (1.16-1.26)	1.18 (1.13-1.23)	16710 (864)	1.32 (1.25-1.40)	1.30 (1.22-1.38)
	Current smokers	35573 (738)	1.29 (1.22-1.37)	1.18 (1.10-1.26)	2941 (199)	1.24 (1.11-1.39)	1.28 (1.12-1.45)

Spirometric indices (FEV1 and FVC) are modelled as z-scores derived from the Global Lung Initiative 2012 reference equations for whites.
All hazard ratios are expressed per SD decrement in z-score, adjusted for age, sex, height, area-based socio-economic measure and geographical region (recruitment centre)..

e-Table 6 **Mortality from all non-respiratory causes, and from circulatory diseases, by quartile of systolic blood pressure, body mass index and spirometric indices among white lifelong non-smokers aged 40-69 at entry in national health surveys (HSE and SHS) and in UK Biobank**

		Non-respiratory mortality				*Circulatory mortality*			
Risk factor	***Quartile***	***HSE-SHS HR (95%CI) (based on 427 deaths)***		***Biobank HR (95%CI) (based on 2256 deaths)***		***HSE-SHS HR (95%CI) (based on 129 deaths)***		***Biobank HR (95%CI) (based on 403 deaths)***	
SBP	Q1 (low)	1.00	(reference)	1.00	(reference)	1.00	(reference)	1.00	(reference)
	Q2	0.86	(0.62-1.19)	0.88	(0.77-1.00)	1.20	(0.59-2.42)	0.81	(0.58-1.14)
	Q3	0.86	(0.63-1.18)	0.93	(0.82-1.06)	0.72	(0.34-1.50)	0.97	(0.71-1.34)
	Q4 (high)	1.18	(0.87-1.59)	0.99	(0.87-1.12)	1.98	(1.05-3.72)	1.12	(0.82-1.51)
BMI	Q1 (low)	1.00	(reference)	1.00	(reference)	1.00	(reference)	1.00	(reference)
	Q2	0.89	(0.67-1.19)	0.90	(0.79-1.02)	1.05	(0.59-1.87)	1.08	(0.77-1.51)
	Q3	1.00	(0.76-1.33)	0.97	(0.85-1.09)	1.39	(0.80-2.42)	1.35	(0.97-1.86)
	Q4 (high)	1.21	(0.92-1.59)	1.34	(1.19-1.50)	1.90	(1.13-3.22)	2.05	(1.51-2.79)
zFEV1	Q4 (high)	1.00	(reference)	1.00	(reference)	1.00	(reference)	1.00	(reference)
	Q3	0.98	(0.72-1.32)	1.10	(0.98-1.25)	1.73	(0.93-3.22)	0.97	(0.71-1.33)
	Q2	1.20	(0.90-1.59)	1.13	(1.00-1.27)	2.13	(1.16-3.89)	1.29	(0.96-1.73)
	Q1 (low)	1.41	(1.07-1.86)	1.54	(1.37-1.73)	2.24	(1.25-4.04)	1.99	(1.52-2.61)
zFVC	Q4 (high)	1.00	(reference)	1.00	(reference)	1.00	(reference)	1.00	(reference)
	Q3	0.98	(0.72-1.32)	1.04	(0.92-1.18)	1.38	(0.77-2.46)	1.16	(0.85-1.60)
	Q2	1.14	(0.85-1.51)	1.23	(1.10-1.40)	1.74	(0.99-3.04)	1.62	(1.20-2.18)
	Q1 (low)	1.53	(1.17-2.01)	1.56	(1.38-1.75)	1.98	(1.15-3.40)	2.19	(1.65-2.92)

Spirometric indices (FEV1 and FVC) are modelled as z-scores derived from the Global Lung Initiative 2012 reference equations for whites.
All hazard ratios are adjusted for age, sex, height, socio-economic status, geographical region and survey year.

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Ventilatory function as a predictor of mortality in lifelong non-smokers: evidence from large British cohort studies

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TITLE PAGE

Title

Ventilatory function as a predictor of mortality in lifelong non-smokers: evidence from large British cohort studies

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Author contributions

The study was conceived by DS. Design and analysis of the Health Survey for England and Scottish Health Surveys modelling was conducted by RG. Design and analysis of the UK Biobank modelling was conducted by DS. Both authors contributed to interpretation of the findings and writing of the manuscript. The corresponding author DS has full access to all the data included in these analyses and is the guarantor of this manuscript.

Conflict of interests

There are no conflicts of interest to declare for either RG or DS.

Data sharing statement

No additional data are available.

ABSTRACT

Background. Reduced ventilatory function is an established predictor of all-cause mortality in general population cohorts. We sought to verify this in lifelong non-smokers, among whom confounding by active smoking can be excluded, and investigate associations with circulatory and cancer deaths.

Methods. In UK Biobank, among 149,343 white never-smokers aged 40–69 years at entry, 2401 deaths occurred over a mean 6·5 years follow-up. In the Health Surveys for England (HSE) 1995, 1996, 2001 and Scottish Health Surveys (SHS) 1998 and 2003 combined there were 500 deaths among 6579 white never-smokers aged 40–69 at entry, followed for a mean 13·9 years. Standard deviation (z) scores for forced expiratory volume in the first second (FEV1) and forced vital capacity (FVC) were derived using Global Lung Initiative 2012 reference equations. These z-scores were related to deaths from all causes, circulatory disease and cancers using proportional hazards models adjusted for age, sex, height, socio-economic status, region and survey.

Results. In the HSE-SHS dataset, decreasing z-scores for FEV1 and FVC were each associated to a similar degree with increased all-cause mortality (hazard ratios per unit decrement 1·17, 95%CI 1·09–1·25 for zFEV1 and 1·19, 1·10–1·28 for zFVC). This was replicated in Biobank (HRs 1·21, 1·17–1·26 and 1·24, 1·19–1·29, respectively). zFEV1 and zFVC were less strongly associated with mortality from circulatory diseases in HSE-SHS (HR 1·22, 1·06–1·40 for zFVC) than in Biobank (HR 1·47, 1·35–1·60 for zFVC). For cancer mortality, hazard ratios were more consistent between cohorts (for zFVC: HRs 1·12, 1·01–1.24 in HSE-SHS and 1.10, 1·05–1.15 in Biobank). The strongest associations were with respiratory mortality (for zFVC: HRs 1·61, 1·25–2·08 in HSE-SHS and 2·15, 1·77–2·61 in Biobank).

Conclusions. Spirometric indices predicted mortality more strongly than systolic blood pressure or body mass index, emphasising the importance of promoting lung health in the general population, even among lifelong non-smokers.

ARTICLE SUMMARY

Strengths and limitations of this study

- UK Biobank offers a spirometric study of lifelong non-smokers of unprecedented size, but the low participation rate may have compromised its generalisability.
- Assembling data from five national health surveys of England or Scotland produced a cohort of never-smokers, larger than in previously published studies, in which the generalisability of Biobank results could be tested.
- Within Biobank, the large numbers permitted subgroup analyses by sex, age, obesity and pre-existing disease, of sufficient statistical power to exclude important interaction effects. These within-cohort comparisons provide further reassurance about generalisability of associations between reduced ventilatory function and mortality.
- Mortality associations among the subset of Biobank participants whose spirograms met internationally recommended criteria for acceptability and reproducibility were very similar to the results among the full Biobank cohort, suggesting that the key findings are robust to inclusion or exclusion of participants with suboptimal spirometry.
- In common with previous studies of this issue, this analysis was restricted to fatal outcomes and therefore cannot distinguish between an association of reduced ventilatory function with disease incidence and an influence on case-fatality.

INTRODUCTION

Four decades of epidemiological research have consistently shown that reduced levels of ventilatory function, measured as one-second forced expiratory volume (FEV1) or forced vital capacity (FVC) are associated with higher all-cause mortality rates and therefore shorter survival in the general population.[1-7] Few studies have reported specifically on lifelong non-smokers,[3,4] a group who form the minority of most populations surveyed hitherto, but are set to become more common in future as smoking becomes less prevalent in higher income countries.

Most publications have focused on FEV1, but a recent analysis[7] of asymptomatic participants in the multi-ethnic Atherosclerosis Risk in Communities (ARIC) study reported that all-cause mortality was strongly associated with diminished FVC, after adjustment for FEV1, but not the other way around, and there was no association between survival and the ratio of FEV1 to FVC. This conclusion was based on a combined analysis of smokers and non-smokers.

In this report, we compare the relationship of lung function measures (FEV1 and FVC) to subsequent mortality in UK Biobank and in the Health Surveys for England and Scottish Health Surveys. Biobank is the largest spirometric study ever performed in the UK and included a relatively high proportion of never-smokers. The national health surveys, although based on smaller numbers of subjects, recruited a wider age range, have a longer period of follow-up, higher response rates and are more representative of the general UK population than Biobank. The two sources are therefore complementary, in terms of precision and generalisability.

This paper focuses upon findings for white lifelong non-smokers, among whom confounding by frequency or duration of active smoking can be excluded. We investigate associations of spirometric indices with total mortality and with major groups of causes of death; compare FEV1 and FVC as independent predictors of all-cause mortality, and evaluate the possibility

of reverse causation. We also compare results from UK Biobank with those from the national health survey participants of a similar age at spirometric examination, to establish how widely generalisable are the findings from Biobank. Corresponding results for white former smokers and current smokers are included in the online supplement for completeness, and described briefly in the text.

METHODS

Health Surveys for England and Scottish Health Surveys

Data were combined from the Health Surveys for England 1995, 1996 and 2001,[8-10] and the Scottish Health Surveys 1998 and 2003,[11-12] the years when spirometry was included in the protocol. These surveys aimed to recruit a representative sample of British adults through household sampling within selected parliamentary constituencies throughout England or Scotland. Participants were visited at home. Response rates ranged from 60% to 76% across the five surveys. The proportion of those visited who performed usable spirometry ranged from 63% to 84%.

Spirometry was performed using hand-held pneumotachograph spirometers (Vitalograph Escort) with the best results of FEV1 and FVC recorded from three technically satisfactory blows. No flow-volume curves or reproducibility criteria were available for assessment. Valid lung function measurements were available for 6,579 lifelong non-smokers aged 40-69 years and 1,429 aged 70 or more at the start of follow-up, all of white ethnicity.

Deaths occurring up to April 2013 were available for analysis in the Health Surveys for England,[13] and deaths up to December 2011 were linked in the Scottish Health Surveys.[14] Combining all five surveys, there were 500 deaths among white never-smokers aged 40-69 at recruitment over a mean follow-up period of 13·9 years. Deaths from respiratory disease,

circulatory disease, cancer and all other causes were coded using ICD9 (460-519, 390-459, 140-208, all others, respectively) and ICD10 (chapters J, I, C, all others, respectively).

Smoking history was self-reported. Socio-economic status was measured at the level of the household, based on the social class of the head of the household. Nation (England or Scotland), region (within England) and survey year were included as additional covariates.

UK Biobank

This study recruited 502,682 volunteers aged 40-69 years in 22 recruitment centres throughout England, Wales and Scotland during 2006-2010, following invitations to 9 million people.[15] Spirometry was performed using a hand-held pneumotachograph spirometer (Pneumotrac 6800) from which volume-time arrays were stored for each blow.[16]

81% of the cohort performed two blows with acceptable start and measures of FEV1 reproducible within 250mL. This was considered the most inclusive sample of "usable spirograms". When end-blow quality was also considered, 58% of the cohort had evidence of a good plateau and both FEV1 and FVC reproducible within 150mL, the criteria recommended by the ATS/ERS Task Force on Standardisation of Spirometry.[17] This subgroup of 58% was considered to be the "best quality" spirograms, among which to evaluate the relative importance of FEV1 and FVC as predictors of mortality.

The present analysis is based on deaths occurring up to mid-August 2015, a mean follow-up period of 6·5 years. There were 2,401 deaths among 149,343 lifelong non-smokers aged 40-69 of white ethnicity who performed "usable spirograms". Deaths from respiratory disease, circulatory disease, cancer and all other causes were coded using ICD10 (chapters J, I, C, all others, respectively).

Smoking history was self-reported. Socio-economic status was measured at the level of residential area, using the Townsend deprivation index, grouped into quartiles for analysis. Biobank recruitment centre was used as an additional covariate to adjust for possible regional differences.

Adjustment of spirometric measures for gender, age and height

The Global Lung Initiative (GLI) 2012 reference equations for white ethnic groups[18] were used in both sets of data to standardise FEV1 and FVC for age, sex and height. The GLI-2012 equations generate a "z-score" which represents the relative position of an individual among the distribution predicted for lifelong non-smokers with no history of lung disease of the same gender, age and height. This allows for the spread of predicted values to differ by age, height and gender, expressing the relative ranking of an individual in terms of a standard deviation (z) score. For each individual in the analysis, there were three GLI-2012 z-scores, corresponding to their relative ranking for FEV1 (zFEV1), FVC (zFVC) and the ratio FEV1/FVC (zFEVFVC). Outlying observations were excluded by restricting all the analyses in both datasets to values of zFEV1 and zFVC within the range -5 to +5 z-score units. This exclusion removed 0.2% of UK Biobank participants, 0.5% of participants in the national health surveys aged 40-69 and 0.3% of national health survey participants aged 70 or more.

Modelling of mortality

The relationship of spirometric indices to subsequent mortality was modelled by proportional hazards (Cox) regression, which estimates the relative increase in mortality rate (hazard ratio) for a unit change in each explanatory variable. The z-scores are expressed on a standard deviation scale, so hazard ratios for zFEV1 and zFVC are expressed per unit decrement (ie. an

increase in risk for a decrease in lung function). A typical range of z-scores among lifelong non-smokers would be four units. A hazard ratio of 1·2 per unit decrement corresponds approximately to a twofold difference in mortality rate across this range.

Due to the high correlation between zFEV1 and zFVC among lifelong non-smokers (0.88 in Biobank, 0.80 in national health survey participants aged 40-69), we modelled the association of mortality with zFEV1 both alone and jointly with zFEVFVC; and similarly for zFVC. Among never smokers, the correlations between zFEV1 and zFEVFVC (0.35 in Biobank, 0.36 in the national surveys) and between zFVC and zFEVFVC (-0.13 in Biobank, -0.20 in the national surveys) were weak enough to avoid major collinearity in the joint models. The significance of the hazard ratio for zFEVFVC when modelled jointly with zFEV1 was used to assess whether zFVC predicted mortality independent of zFEV1, and *vice versa* when zFEVFVC was modelled jointly with zFEV1.

All proportional hazards models were restricted to white participants and adjusted for sex, age, standing height, socio-economic status and region. Analyses of data from the five national health surveys were additionally adjusted for survey year as a categorical variable. Since each survey was conducted in a different year, inclusion of survey year in the model is closely equivalent to a fixed-effect meta-analysis of the results from each of the five surveys. In a more formal two-stage individual participant meta-analysis for all-cause mortality in lifelong non-smokers, there was no substantial or significant heterogeneity of hazard ratios among the five national health surveys (I^2 = 0.0%, p = 0.775 for zFEV1; I^2 = 10.5%, p = 0.346 for zFVC). Therefore, for simplicity of presentation we report results for the five national surveys combined, but analyse UK Biobank separately because one of our objectives is to investigate how closely these two sets of results correspond. Heterogeneity between hazard ratios for the pooled national surveys and UK Biobank was assessed by testing the significance of the difference between the corresponding log-hazard-ratios from these two datasets.

The assumption of proportionality of hazards was assessed by log-log plots and by fitting zFEV1 or zFVC as a time-dependent covariate in the model. No strong or statistically significant evidence of time-dependence emerged for all-cause mortality among lifelong non-smokers. Nevertheless, results for all-cause mortality were partitioned at 5 years of follow-up for two reasons. Firstly, because the minimum duration of follow-up in UK Biobank was 4.87 years, so virtually all of that cohort had been followed for 5 years or more, allowing a more direct comparison with results from the national health surveys, all of which had been followed for more than 5 years. A second reason for partitioning at 5 years was to address the possibility of reverse causation (impaired spirometric performance due to pre-existing conditions which lead to early death). Reverse causation was also investigated by analysing mortality in subgroups with no prior history of respiratory disease, circulatory disease, or cancer.

RESULTS

Participant characteristics

Supplementary e-Table 1 summarises the numbers of participants, duration of follow-up and deaths from all causes and subgroups of cause, in each dataset, by sex, age and smoking history.

All-cause mortality

Table 1 compares the hazard ratios for age-sex-height-adjusted FEV1 and FVC in relation to all-cause mortality in the combined Health Survey for England (HSE) and Scottish Health Surveys (SHS) dataset, and UK Biobank (UKB), among participants aged 40-69 years at entry. All “usable spirograms” from Biobank were included in this comparison, because no additional quality control had been applied in the national health surveys 1995-2003.

Table 1 **All-cause mortality in white lifelong non-smokers aged 40-69 at entry in national health surveys (HSE and SHS) and in UK Biobank, in relation to GLI-2012 z-scores for FEV1 and FVC**

		HSE-SHS white lifelong non-smokers, 40-69 at entry			*Biobank white lifelong non-smokers, 40-69 at entry*		
Timing of death	***Cause of death***	***Total N (deaths)***	***zFEV1 HR(95%CI)***	***zFVC HR(95%CI)***	***Total N (deaths)***	***zFEV1 HR(95%CI)***	***zFVC HR(95%CI)***
Any time	All causes	6579 (500)	1.17 (1.09-1.25)	1.19 (1.10-1.28)	149343 (2401)	1.21 (1.17-1.26)	1.24 (1.19-1.29)
Within 5 years	All causes	6579 (103)	1.35 (1.17-1.56)	1.35 (1.16-1.57)	149343 (1599)	1.23 (1.17-1.28)	1.26 (1.20-1.32)
After 5 years	All causes	6476 (397)	1.12 (1.03-1.21)	1.14 (1.05-1.24)	147744 (802)	1.18 (1.11-1.26)	1.21 (1.13-1.29)
Any time	Respiratory	6579 (34)	1.72 (1.34-2.21)	1.61 (1.25-2.08)	149343 (69)	1.86 (1.53-2.27)	2.15 (1.77-2.61)
Any time	Circulatory	6579 (130)	1.21 (1.06-1.38)	1.22 (1.06-1.40)	149343 (431)	1.41 (1.30-1.53)	1.47 (1.35-1.60)
Any time	Cancer	6579 (241)	1.10 (1.00-1.22)	1.12 (1.01-1.24)	149343 (1535)	1.08 (1.03-1.13)	1.10 (1.05-1.15)
Any time	Other non-respiratory	6579 (105)	1.15 (0.98-1.34)	1.20 (1.03-1.41)	149343 (366)	1.46 (1.33-1.59)	1.45 (1.32-1.59)

Spirometric indices (FEV1 and FVC) are modelled as z-scores derived from the Global Lung Initiative 2012 reference equations for whites.
All hazard ratios are expressed per unit decrement in z-score, adjusted for age, sex, height, socio-economic status, geographical region and survey year.

When each spirometric index was modelled singly, all associations were highly statistically significant (p<0·0001). Among lifelong non-smokers in both cohorts, FEV1 and FVC displayed similar strengths of association with all-cause mortality (Table 1). Among former smokers, FEV1 was the stronger predictor in HSE-SHS but FEV1 and FVC showed similar strength of association with all-cause mortality in UKB. Among current smokers in both datasets, FEV1 was a stronger predictor of all-cause mortality than FVC (e-Tables 2-4).

Table 1 also shows the most direct comparison between the two datasets, based on all-cause mortality within 5 years. Although the associations of spirometric indices with these earlier deaths were stronger in HSE-SHS than in UKB, the differences between the cohorts were not statistically significant (p=0.23 for FEV1, p=0.39 for FVC). Associations with deaths after 5 years are less comparable between the datasets, due to the shorter period of follow-up in UKB.

Stronger associations of FEV1 and FVC with earlier deaths than with later mortality from all causes were also evident among former smokers and current smokers, although the differences were more marked in HSE-SHS than in UKB (e-Tables 2 and 3). Formal tests for time-dependence of the hazard ratio (HR) for all-cause mortality found statistically significant reduction in HR with increasing follow-up time (t) only among ex-smokers (p = 0.00032 for zFEV1*t in UKB, p = 0.021 for zFEV1*t in HSE-SHS, p = 0.000006 for zFVC*t in UKB, p = 0.001 for zFVC*t in HSE-SHS). Among never-smokers and current smokers in both datasets, the reduction in HR with increasing follow-up was small (a relative reduction of 1% per year) and non-significant (p>0.05) for both FEV1 and FVC.

These analyses confirm that the modelling assumption of proportionality of hazards over the duration of follow-up is valid, at least for lifelong non-smokers, in both datasets.

Table 2 **Comparison of mutually adjusted spirometric indices to predict all-cause mortality in national health surveys (all spirograms) and in UK Biobank (comparing all usable spirograms with best quality spirograms)**

		HSE-SHS white lifelong non-smokers, 40-69 at entry			*Biobank white lifelong non-smokers, 40-69 at entry*		
Subset analysed	***z-score in model (plus covariates)***	***Total N (deaths)***	***HR(95%CI) alone***	***HR (95%CI) joint***	***Total N (deaths)***	***HR(95%CI) alone***	***HR (95%CI) joint***
All usable spirograms	FEV1 alone	6579 (500)	1.17 (1.09-1.25)		149343 (2401)	1.21 (1.17-1.26)	
	FEV1 adj FEV/FVC			1.20 (1.11-1.29)			1.26 (1.21-1.31)
	FEV/FVC adj FEV1			0.94 (0.87-1.01)			0.90 (0.85-0.94)
All usable spirograms	FVC alone	6579 (500)	1.19 (1.10-1.28)		149343 (2401)	1.24 (1.19-1.29)	
	FVC adj FEV/FVC			1.19 (1.11-1.28)			1.24 (1.19-1.29)
	FEV/FVC adj FVC			1.02 (0.95-1.10)			1.02 (0.97-1.07)
Best quality spirograms	FEV1 alone		(No data)		102945 (1583)	1.23 (1.18-1.29)	
	FEV1 adj FEV/FVC						1.29 (1.23-1.36)
	FEV/FVC adj FEV1						0.86 (0.81-0.91)
Best quality spirograms	FVC alone		(No data)		102945 (1583)	1.29 (1.23-1.35)	
	FVC adj FEV/FVC						1.29 (1.23-1.35)
	FEV/FVC adj FVC						0.98 (0.93-1.04)

Spirometric indices (FEV1, FVC and FEV1/FVC ratio) are modelled as z-scores derived from the Global Lung Initiative 2012 reference equations for whites.
All hazard ratios are expressed per unit decrement in z-score, adjusted for age, sex, height, socio-economic status, geographical region and survey year.

Influence of spirogram quality

Table 2 presents the results for all causes of death among Biobank participants with "best quality" spirograms, for comparison with those obtained from the full set of "usable spirograms". The pattern and magnitude of the results among the former subset are very similar to the overall UKB results.

The covariate-adjusted hazard ratios for all-cause mortality comparing the "best quality" group to the remainder were: 0·94 (95%CI 0·86–1·02) among lifelong non-smokers, HR 1·02 (0·96–1·09) among former smokers and HR 0·94 (0·85–1·04) among current smokers. None of these hazard ratios are statistically significant, despite very large numbers of subjects included each comparison.

Choice of spirometric index

Among lifelong non-smokers, adding FEV1/FVC ratio to a model including FVC did not contribute additional information, whereas adding FEV1/FVC ratio to a model including FEV1 did improve the fit of the model significantly (Table 2). This pattern was evident in both HSE-SHS and UKB, and among the subset of UKB participants with "best quality" spirograms.

Cause-specific mortality

Table 1 also presents the association of spirometric indices (modelled singly) with respiratory, circulatory, cancer and other causes of death among lifelong non-smokers. The strength of association with FEV1 and FVC was greatest for respiratory mortality and weakest for cancer deaths. This applied in both datasets, but the hazard ratios for respiratory, circulatory and other causes of death were greater in UKB than in HSE-SHS. The results in the two cohorts are more

similar for cancer mortality. The heterogeneity of hazard ratios between the two datasets was statistically significant only for FVC in relation to circulatory mortality (p = 0.025), and for both FEV1 (p = 0.009) and FVC (p = 0.042) in relation to causes of death other than respiratory, circulatory or cancer among never-smokers. Within UKB, results for cause-specific mortality were generally consistent between the "best spirogram" subgroup and the fuller dataset, in all smoking subgroups (e-Table 4).

Comparisons by subgroups of age and sex

Supplementary e-Table 3 shows that within UK Biobank the general pattern of results was similar in both sexes. There was no statistically significant effect modification by sex for either spirometric index in any smoking subgroup ($p \geq 0.10$ for each interaction test).

Supplementary e-Table 3 also compares the results for all-cause mortality among younger (aged 40-59) and older (aged 60-69) UKB participants. The hazard ratios in all smoking groups were consistent between these two age subgroups and there were no statistically significant age interactions for either spirometric index ($p > 0.40$).

Supplementary e-Table 5 compares the spirometric associations with all-cause and cause-specific mortality among HSE and SHS participants aged 40-69 and 70 or more at entry. The pattern for all-causes was consistent between these age groups in never-smokers and current smokers ($p > 0.2$), but there were significant age interactions among ex-smokers ($p < 0.006$).

Supplementary e-Table 3 compares the results for all-cause mortality among obese and non-obese Biobank participants. Although the pattern of results was generally consistent between these categories in all smoking subgroups, a statistically significant difference in the hazard ratio for FVC occurred among current smokers (p=0.022). Other interactions with obesity were non-significant ($p \geq 0.10$).

Table 3 **Comparison of spirometric prediction of mortality among subjects with and without prior disease history at entry in UK Biobank**

		Biobank age 40-69, white lifelong non-smokers without a history of the condition at entry			*Biobank age 40-69, white lifelong non-smokers with a history of the condition at entry*		
Condition at entry	***Cause of death***	***Total N (deaths)***	***zFEV1 HR(95%CI)***	***zFVC HR(95%CI)***	***Total N (deaths)***	***zFEV1 HR(95%CI)***	***zFVC HR(95%CI)***
Respiratory disease	All causes	130798 (2081)	1.21 (1.16-1.26)	1.22 (1.17-1.27)	18545 (320)	1.23 (1.12-1.35)	1.33 (1.21-1.47)
Circulatory disease	Circulatory disease	109141 (189)	1.40 (1.23-1.59)	1.40 (1.23-1.60)	40202 (242)	1.35 (1.20-1.51)	1.43 (1.27-1.60)
Cancer	Cancer	137742 (978)	1.05 (0.99-1.11)	1.06 (1.00-1.12)	11601 (557)	1.10 (1.02-1.18)	1.13 (1.04-1.22)

Spirometric indices (FEV1 and FVC) are modelled as z-scores derived from the Global Lung Initiative 2012 reference equations for whites.
All hazard ratios are expressed per unit decrement in z-score, adjusted for age, sex, height, socio-economic status and geographical region (recruitment centre).

Comparisons by prior disease history in UK Biobank

Table 3 compares the spirometric associations with all-cause mortality in Biobank participants with and without a history of respiratory disease at the baseline spirometric examination. In the 18,545 (12%) white never-smokers with "usable spirograms" who had a history of diagnosed respiratory disease (of which 90% reported asthma), FVC was a stronger predictor of all-cause mortality than FEV1. Among the subgroup without a respiratory history, results were similar to the full cohort.

Lung function also emerged as a significant predictor of circulatory mortality among those with and without a prior history of heart attack, angina, stroke, thrombosis or hypertension (Table 3). This pattern was confirmed among former smokers and current smokers (e-Table 6).

Finally, the association of FEV1 and FVC with cancer mortality was shown to be stronger in those with a prior cancer diagnosis (Table 3), but it was not statistically significant, despite the large sample size, among those with no cancer history at the spirometric examination. However, this finding is confined to the lifelong non-smokers: both FEV1 and FVC were more strongly and significantly associated with cancer death among former smokers and current smokers with no cancer history (e-Table 6). Cancer mortality among participants with a history of cancer at entry was strongly and significantly associated with both FEV1 and FVC in all three smoking subgroups (e-Table 6).

Comparison of spirometry with other predictors of mortality

Figure 1 (data in e-Table 7) compares the relative mortality across quartiles of body mass index, systolic blood pressure and FVC z-score, for all deaths and for deaths from circulatory disease, among white lifelong non-smokers in HSE-SHS and in UK Biobank. A similar pattern emerged

for all-cause mortality in both cohorts, with differentials in mortality across quartiles of zFVC being at least as great as those across quartiles of body mass index or systolic blood pressure.

DISCUSSION

Principal findings

A broadly coherent picture emerges from this comparison of UK national cohorts. Ventilatory function, even if measured imperfectly, consistently predicted both respiratory deaths and non-respiratory mortality from a range of causes. This was found even among lifelong non-smokers, so confounding by the amount or duration of active smoking is not the sole explanation. Both for all-cause mortality, and more specifically for circulatory disease mortality, FEV1 and FVC were as strongly predictive as body mass index, and more strongly predictive than systolic blood pressure.

Strengths and weaknesses of this study

UK Biobank offers a spirometric study of lifelong non-smokers of unprecedented size, but its 5·5% participation rate may have compromised its generalisability. Assembling data from five UK national health surveys produced a cohort of never-smokers, larger than the combined number of participants in previous publications[3,4] in which the generalisability of Biobank results could be tested. The similar pattern of results in HSE-SHS and UKB suggests that the key findings are generalisable, at least to the British population.

Within Biobank, the large numbers permitted subgroup analyses by sex, age, obesity and pre-existing disease, of sufficient statistical power to exclude important interaction effects. These

within-cohort comparisons provide further reassurance about the generalisability of the principal findings among lifelong non-smokers.

Although only 58% of the Biobank cohort performed spirometry which fulfilled internationally recommended criteria for acceptability and reproducibility,[17] the results in this subgroup were very similar to those among the full set of Biobank participants who performed "usable" spirometry. Those results were, in turn, consistent with the findings from national health surveys where the acceptability and reproducibility of spirometry was not formally assessed in the field. These within-cohort and cross-cohort comparisons suggest that the principal findings are robust to inclusion or exclusion of participants with suboptimal spirometric performance.

In common with previous studies of this topic, our analysis was restricted to fatal outcomes and therefore cannot distinguish between an influence of reduced ventilatory function on disease incidence and an effect on case-fatality. The association with cancer mortality was weaker among those with no cancer diagnosis at entry, suggesting an association primarily with case-fatality. In contrast, the association of spirometric indices with circulatory mortality was equally strong in those with and without a prior history of circulatory disease. The recent linkage of hospital admissions and primary care consultations to the UK Biobank cohort will allow associations with incidence and case-fatality to be investigated more directly in future.

Comparison with other studies

Previous studies of lifelong non-smokers have been of limited size: 662 males and 2048 females in the Copenhagen City Heart Study, of whom 195 died during 10 years of follow-up,[3] and 3562 male London civil servants in the Whitehall Study, of whom 408 died over a period of 18 years.[4] The Whitehall cohort was subsequently followed for 33-35 years, accumulating 1545 deaths among 3083 lifelong non-smokers.[19] In the analyses we present here, there are

almost twice this number of deaths among lifelong non-smokers, despite a shorter follow-up period, due to the much larger sample size at entry, particularly in UK Biobank.

The two publications from the Whitehall cohort[4,19] compared FEV1 and height as predictors of all-cause and cause-specific mortality among never-smokers. The first[4] found that FEV1 predicted mortality independent of height, but height did not predict survival independent of FEV1. The second[19] found that FEV1 and height were similarly related both to mortality and to a range of other risk factors, concluding that both FEV1 and height may be markers of early life exposures of relevance to longevity.

Published analyses of the Whitehall cohort[4,19] assessed only FEV1 but not FVC. In the Copenhagen study,[3] the association of all-cause mortality among never-smokers was slightly stronger and more statistically significant with FVC than with FEV1 (both spirometric indices analysed as percent predicted for age, sex and height). However, no formal comparison was made between the mortality risks associated with the two indices. An analysis of mortality over an average follow-up period of 13.7 years among 7,489 45-64-year-old participants in the United States ARIC cohort[7] suggested that FVC should be considered as a more predictive spirometric index than FEV1, but this conclusion was drawn from a cohort of mixed smoking habits.

In our study of lifelong non-smokers, we confirmed that FVC (rather than FEV1) is the index of greater importance in determining survival in middle-aged never-smokers. In contrast, among current smokers, FEV1 emerged as the more influential predictor. This may be because the FEV1/FVC ratio declines with both the dose and duration of smoking, and these also increase mortality risk.

The ability to perform good quality spirometry is an integrated assessment of physical and cognitive function and therefore might be considered a predictor of mortality in its own right.

In the US Six Cities study, excessively variable spirometric performance was an indicator of poor health and associated with shorter survival.[20] In contrast, the mortality experience of Biobank participants who produced "best quality" spirograms did not differ greatly from that of their peers who produced "usable" but not "best quality" blows.

Possible implications

In clinical practice, particularly in primary care, quality control of spirometry is unlikely to be much better than in the national health surveys where lung function was tested by a trained research nurse in the home setting. Therefore, while the results from the Biobank "best quality" subgroup are of confirmatory interest, the more inclusive results for all "usable spirograms" may be more generally relevant.

In both cohorts, age-sex-height-adjusted lung function emerged as a stronger predictor of all-cause mortality than either systolic blood pressure or body mass index, which are, respectively, the 2nd and 6th most influential causes worldwide of loss of healthy lifespan, as measured by disability-adjusted life-years.[21] It is therefore puzzling to find U-shaped or J-shaped relationships of mortality with these two cardiovascular risk factors, but the similar patterns of results in Biobank and the national health surveys suggests that this is not a unique feature of either of these British cohorts.

Specifically for circulatory disease mortality, FEV1 and FVC were as strongly predictive as body mass index, and more strongly predictive than systolic blood pressure. Therefore, spirometry may deserve consideration as an addition to cardiovascular risk scoring algorithms in future.

Conclusion

More generally, these results emphasise the potential importance of promoting and protecting lung health in the general population, even among lifelong non-smokers with no history of respiratory disease.

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Ethical approval

This is a secondary analysis of anonymised data from national health surveys, each of which obtained ethics committee approval for their fieldwork,[8-12,15] but no specific ethical approval was required for this data analysis.

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Figure 1 title

Hazard ratios for death from all causes, and from circulatory diseases, by quartile of age-sex-height-adjusted forced vital capacity (zFVC), systolic blood pressure (SBP) and body mass index (BMI) among white lifelong non-smokers aged 40-69 at entry in national health surveys (HSE and SHS) and in UK Biobank

Figure 1 footnote

Hazard ratios are adjusted for age, sex, height, socio-economic status, region and survey year. The reference category (HR=1) is the highest quartile (Q4) for zFVC and the lowest quartile (Q1) for SBP and BMI. Whiskers represent the 95% confidence interval for each hazard ratio.

Figure 1 data

Included in supplementary e-Table 7

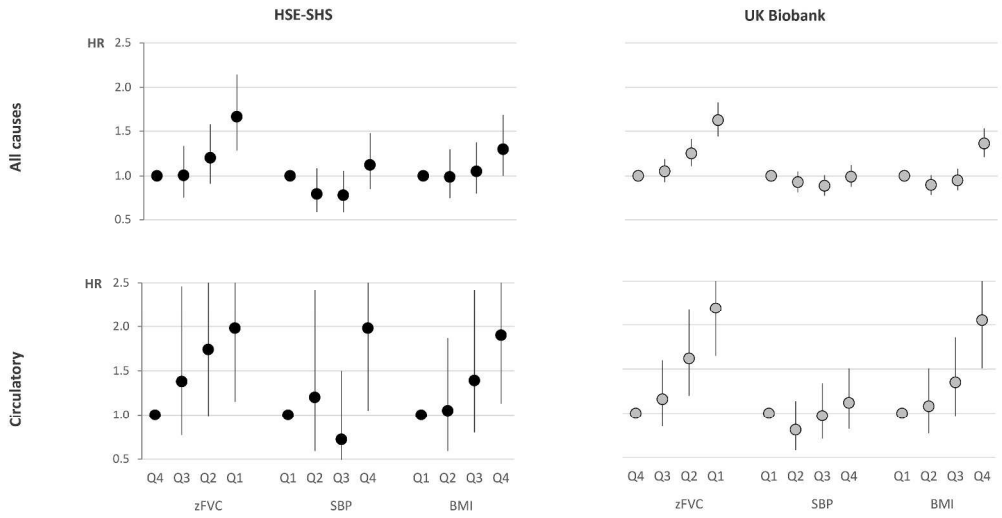

Figure 1 title: Hazard ratios for death from all causes, and from circulatory diseases, by quartile of age-sex-height-adjusted forced vital capacity (zFVC), systolic blood pressure (SBP) and body mass index (BMI) among white lifelong non-smokers aged 40-69 at entry in national health surveys (HSE and SHS) and in UK Biobank.

Figure 1 footnote: Hazard ratios are adjusted for age, sex, height, socio-economic status, region and survey year. The reference category (HR=1) is the highest quartile (Q4) for zFVC and the lowest quartile (Q1) for SBP and BMI. Whiskers represent the 95% confidence intervals for each hazard ratio.

Figure 1 data: Included in supplementary e-Table 7.

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SUPPLEMENTARY MATERIAL

Title

Ventilatory function as a predictor of mortality in lifelong non-smokers: evidence from large British cohort studies

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e-Table 1 **Descriptive characteristics of participants in the Health Surveys for England and Scottish Health Surveys, and in UK Biobank**

		HSE-SHS age 40-69 at entry, white ethnicity		*HSE-SHS age 70+ at entry, white ethnicity*		*UK Biobank age 40-69 at entry, white ethnicity*	
Characteristic	***Smoking history***	***Males***	***Females***	***Males***	***Females***	***Males***	***Females***
Number of subjects included in Cox regression models	Never smokers	2343	4236	345	1084	56924	92419
	Former smokers	3336	3243	753	676	89542	102085
	Current smokers	3430	3149	813	616	19909	18605
Mean follow-up period (years)	Never smokers	13.75	13.93	12.26	13.03	6.52	6.54
	Former smokers	14.41	14.35	12.87	13.84	6.46	6.50
	Current smokers	14.46	14.11	13.39	13.52	6.47	6.54
All deaths	Never smokers	178	322	195	588	1143	1258
	Former smokers	758	455	1072	811	2714	1714
	Current smokers	732	539	406	260	1096	580
Respiratory deaths	Never smokers	13	21	30	88	41	28
	Former smokers	117	68	220	127	131	66
	Current smokers	190	165	142	79	69	37
Circulatory deaths	Never smokers	51	79	63	236	270	161
	Former smokers	272	118	415	330	668	192
	Current smokers	255	125	126	86	278	88
Cancer deaths	Never smokers	80	161	56	110	640	895
	Former smokers	290	219	283	165	1530	1232
	Current smokers	283	249	132	65	555	382
Other non-respiratory deaths	Never smokers	37	68	50	158	192	174
	Former smokers	123	81	212	223	385	224
	Current smokers	114	96	61	56	194	73

e-Table 2 **Relationship of spirometric indices to mortality before and after 5 years among younger and older subjects, by smoking habit, in the Health Surveys for England and Scottish Health Surveys**

		HSE-SHS age 40-69 at entry, white ethnicity			*HSE-SHS age 70+ at entry, white ethnicity*		
Timing of death	***Smoking history***	***Total N (deaths)***	***zFEV1 HR (95%CI)***	***zFVC HR (95%CI)***	***Total N (deaths)***	***zFEV1 HR (95%CI)***	***zFVC HR (95%CI)***
All deaths	Never smokers	6579 (500)	1.17 (1.09-1.25)	1.19 (1.10-1.28)	1429 (783)	1.24 (1.17-1.32)	1.22 (1.15-1.29)
	Former smokers	9403 (1212)	1.33 (1.28-1.39)	1.31 (1.25-1.37)	3083 (1883)	1.23 (1.19-1.28)	1.20 (1.16-1.25)
	Current smokers	6640 (1271)	1.30 (1.24-1.35)	1.20 (1.15-1.26)	909 (666)	1.36 (1.28-1.46)	1.23 (1.16-1.31)
Deaths within 5 years	Never smokers	6579 (103)	1.35 (1.17-1.56)	1.35 (1.16-1.57)	1429 (217)	1.37 (1.23-1.54)	1.38 (1.24-1.54)
	Former smokers	9403 (288)	1.43 (1.32-1.55)	1.49 (1.37-1.63)	3083 (590)	1.33 (1.25-1.41)	1.28 (1.20-1.36)
	Current smokers	6640 (332)	1.31 (1.21-1.43)	1.24 (1.15-1.35)	909 (250)	1.33 (1.20-1.48)	1.19 (1.08-1.32)
Deaths after 5 years	Never smokers	6476 (397)	1.12 (1.03-1.21)	1.14 (1.05-1.24)	1212 (566)	1.19 (1.11-1.28)	1.15 (1.07-1.24)
	Former smokers	9115 (924)	1.29 (1.23-1.36)	1.25 (1.19-1.32)	2493 (1293)	1.19 (1.14-1.24)	1.17 (1.12-1.22)
	Current smokers	6308 (939)	1.29 (1.23-1.36)	1.18 (1.12-1.25)	659 (416)	1.38 (1.27-1.50)	1.25 (1.15-1.36)

Spirometric indices (FEV1, FVC and FEV1/FVC ratio) are modelled as z-scores derived from the Global Lung Initiative 2012 reference equations for whites.
All hazard ratios are expressed per unit decrement in z-score, adjusted for age, sex, height, socio-economic status, geographical region and survey year.

e-Table 3 **Relationship of spirometric indices to all-cause mortality before and after 5 years, among males and females, and among younger and older subjects, by smoking habit, in UK Biobank**

Biobank age 40-69, white ethnicity, all usable spirograms

Subjects and timing of death	*Smoking history*	*Total N (deaths)*	*zFEV1 HR (95%CI)*	*zFVC HR (95%CI)*
All subjects, deaths within 5 years	Never smokers	149343 (1599)	1.23 (1.17-1.28)	1.26 (1.20-1.32)
	Former smokers	191627 (2998)	1.40 (1.36-1.45)	1.40 (1.35-1.45)
	Current smokers	38514 (1112)	1.39 (1.32-1.46)	1.29 (1.22-1.36)
All subjects, deaths after 5 years	Never smokers	147744 (802)	1.18 (1.11-1.26)	1.21 (1.13-1.29)
	Former smokers	188629 (1430)	1.33 (1.27-1.39)	1.32 (1.25-1.38)
	Current smokers	37402 (564)	1.37 (1.28-1.47)	1.30 (1.20-1.40)
Males, all deaths	Never smokers	56924 (1143)	1.24 (1.18-1.31)	1.28 (1.21-1.35)
	Former smokers	89542 (2714)	1.39 (1.34-1.43)	1.39 (1.34-1.44)
	Current smokers	19909 (1096)	1.36 (1.30-1.43)	1.27 (1.21-1.34)
Females, all deaths	Never smokers	92419 (1258)	1.18 (1.12-1.24)	1.20 (1.14-1.27)
	Former smokers	102085 (1714)	1.37 (1.31-1.43)	1.34 (1.28-1.40)
	Current smokers	18605 (580)	1.42 (1.33-1.52)	1.33 (1.23-1.43)
Age 40-59 at entry, all deaths	Never smokers	90676 (872)	1.23 (1.16-1.31)	1.25 (1.17-1.33)
	Former smokers	101171 (1161)	1.36 (1.29-1.43)	1.37 (1.30-1.45)
	Current smokers	25584 (692)	1.39 (1.31-1.48)	1.27 (1.19-1.36)
Age 60-69 at entry, all deaths	Never smokers	58667 (1529)	1.20 (1.15-1.26)	1.23 (1.18-1.29)
	Former smokers	90456 (3267)	1.39 (1.35-1.43)	1.37 (1.33-1.42)
	Current smokers	12930 (984)	1.38 (1.31-1.45)	1.31 (1.24-1.39)
BMI<30kg/m^2, all deaths	Never smokers	113932 (1628)	1.17 (1.11-1.22)	1.19 (1.14-1.25)
	Former smokers	142418 (2893)	1.35 (1.30-1.39)	1.32 (1.27-1.37)
	Current smokers	29638 (1266)	1.37 (1.30-1.43)	1.27 (1.21-1.33)
BMI≥30kg/m^2, all deaths	Never smokers	33367 (696)	1.19 (1.11-1.27)	1.18 (1.10-1.27)
	Former smokers	46624 (1403)	1.36 (1.30-1.43)	1.37 (1.30-1.44)
	Current smokers	8326 (365)	1.49 (1.36-1.63)	1.44 (1.31-1.59)

Spirometric indices (FEV1 and FVC) are modelled as z-scores derived from the Global Lung Initiative 2012 reference equations for whites.
All hazard ratios are expressed per unit decrement in z-score, adjusted for age, sex, height, socio-economic status and geographical region (recruitment centre).

e-Table 4 **Comparison of best quality spirograms with all usable spirograms to predict all-cause and cause-specific mortality, by smoking habit, in UK Biobank**

		Biobank age 40-69, white ethnicity, best spirograms			*Biobank age 40-69, white ethnicity, usable spirograms*		
Cause of death	***Smoking history***	***Total N (deaths)***	***zFEV1 HR (95%CI)***	***zFVC HR (95%CI)***	***Total N (deaths)***	***zFEV1 HR (95%CI)***	***zFVC HR (95%CI)***
All causes	Never smokers	102945 (1583)	1.23 (1.18-1.29)	1.29 (1.23-1.35)	149343 (2401)	1.21 (1.17-1.26)	1.24 (1.19-1.29)
	Former smokers	134173 (3043)	1.39 (1.35-1.44)	1.40 (1.35-1.45)	191627 (4428)	1.38 (1.35-1.42)	1.37 (1.33-1.41)
	Current smokers	26105 (1079)	1.39 (1.32-1.46)	1.30 (1.23-1.38)	38514 (1676)	1.38 (1.33-1.44)	1.29 (1.24-1.35)
Respiratory diseases	Never smokers	102945 (48)	2.07 (1.63-2.62)	2.22 (1.76-2.80)	149343 (69)	1.86 (1.53-2.27)	2.15 (1.77-2.61)
	Former smokers	134173 (140)	2.52 (2.20-2.88)	2.28 (1.98-2.63)	191627 (197)	2.46 (2.20-2.76)	2.26 (2.01-2.54)
	Current smokers	26105 (66)	2.93 (2.37-3.62)	2.44 (1.99-3.00)	38514 (106)	2.52 (2.15-2.96)	2.08 (1.76-2.45)
Circulatory diseases	Never smokers	102945 (269)	1.46 (1.31-1.62)	1.57 (1.41-1.76)	149343 (431)	1.41 (1.30-1.53)	1.47 (1.35-1.60)
	Former smokers	134173 (590)	1.56 (1.46-1.68)	1.66 (1.54-1.79)	191627 (860)	1.58 (1.49-1.67)	1.64 (1.54-1.74)
	Current smokers	26105 (219)	1.43 (1.28-1.60)	1.45 (1.28-1.63)	38514 (366)	1.41 (1.30-1.54)	1.38 (1.26-1.52)
Cancer	Never smokers	102945 (1023)	1.10 (1.04-1.16)	1.13 (1.07-1.20)	149343 (1535)	1.08 (1.03-1.13)	1.10 (1.05-1.15)
	Former smokers	134173 (1907)	1.27 (1.22-1.32)	1.25 (1.20-1.31)	191627 (2762)	1.25 (1.21-1.30)	1.23 (1.18-1.27)
	Current smokers	26105 (624)	1.27 (1.19-1.36)	1.18 (1.09-1.27)	38514 (937)	1.28 (1.22-1.36)	1.20 (1.13-1.27)
Other non-respiratory diseases	Never smokers	102945 (243)	1.44 (1.29-1.61)	1.51 (1.35-1.69)	149343 (366)	1.46 (1.33-1.59)	1.45 (1.32-1.59)
	Former smokers	134173 (406)	1.43 (1.31-1.56)	1.49 (1.36-1.63)	191627 (609)	1.41 (1.32-1.51)	1.43 (1.33-1.55)
	Current smokers	26105 (170)	1.36 (1.20-1.55)	1.25 (1.08-1.44)	38514 (267)	1.36 (1.23-1.51)	1.25 (1.12-1.39)

Spirometric indices (FEV1 and FVC) are modelled as z-scores derived from the Global Lung Initiative 2012 reference equations for whites.
All hazard ratios are expressed per unit decrement in z-score, adjusted for age, sex, height, socio-economic status and geographical region (recruitment centre).

e-Table 5 **Relationship of spirometric indices to all-cause and cause-specific mortality among younger and older subjects, by smoking habit, in the Health Surveys for England and Scottish Health Surveys**

		HSE-SHS age 40-69 at entry, white ethnicity			*HSE-SHS age 70+ at entry, white ethnicity*		
Cause of death	***Smoking history***	***Total N (deaths)***	***zFEV1 HR (95%CI)***	***zFVC HR (95%CI)***	***Total N (deaths)***	***zFEV1 HR (95%CI)***	***zFVC HR (95%CI)***
All causes	Never smokers	6579 (500)	1.17 (1.09-1.25)	1.19 (1.10-1.28)	1429 (783)	1.24 (1.17-1.32)	1.22 (1.15-1.29)
	Former smokers	9403 (1212)	1.33 (1.28-1.39)	1.31 (1.25-1.37)	3083 (1883)	1.23 (1.19-1.28)	1.20 (1.16-1.25)
	Current smokers	6640 (1271)	1.30 (1.24-1.35)	1.20 (1.15-1.26)	909 (666)	1.36 (1.28-1.46)	1.23 (1.16-1.31)
Respiratory diseases	Never smokers	6579 (34)	1.72 (1.34-2.21)	1.61 (1.25-2.08)	1429 (118)	1.82 (1.54-2.14)	1.65 (1.41-1.93)
	Former smokers	9403 (185)	1.97 (1.77-2.19)	1.71 (1.53-1.91)	3083 (347)	1.65 (1.52-1.79)	1.46 (1.34-1.59)
	Current smokers	6640 (355)	1.70 (1.56-1.84)	1.40 (1.29-1.52)	909 (221)	1.90 (1.69-2.13)	1.50 (1.34-1.67)
Circulatory diseases	Never smokers	6579 (130)	1.21 (1.06-1.38)	1.22 (1.06-1.40)	1429 (299)	1.26 (1.13-1.39)	1.28 (1.16-1.41)
	Former smokers	9403 (390)	1.37 (1.28-1.48)	1.39 (1.28-1.50)	3083 (745)	1.20 (1.13-1.27)	1.22 (1.15-1.29)
	Current smokers	6640 (380)	1.26 (1.17-1.36)	1.22 (1.12-1.32)	909 (212)	1.21 (1.08-1.35)	1.20 (1.07-1.34)
Cancer	Never smokers	6579 (241)	1.10 (1.00-1.22)	1.12 (1.01-1.24)	1429 (166)	1.08 (0.95-1.23)	1.09 (0.96-1.24)
	Former smokers	9403 (509)	1.18 (1.10-1.26)	1.14 (1.06-1.22)	3083 (448)	1.19 (1.10-1.28)	1.14 (1.05-1.22)
	Current smokers	6640 (532)	1.21 (1.13-1.29)	1.09 (1.02-1.17)	909 (197)	1.20 (1.07-1.34)	1.08 (0.96-1.21)
Other non-respiratory diseases	Never smokers	6579 (105)	1.15 (0.98-1.34)	1.20 (1.03-1.41)	1429 (208)	1.11 (0.98-1.25)	1.04 (0.92-1.17)
	Former smokers	9403 (204)	1.22 (1.10-1.35)	1.32 (1.18-1.48)	3083 (435)	1.11 (1.03-1.20)	1.08 (1.00-1.17)
	Current smokers	6640 (210)	1.11 (1.00-1.24)	1.15 (1.03-1.28)	909 (117)	1.20 (1.03-1.40)	1.11 (0.95-1.29)

Spirometric indices (FEV1 and FVC) are modelled as z-scores derived from the Global Lung Initiative 2012 reference equations for whites.
All hazard ratios are expressed per unit decrement in z-score, adjusted for age, sex, height, socio-economic status, geographical region and survey year.

e-Table 6 **Spirometric prediction of mortality among subjects with and without a history of selected diseases at entry, by smoking habit, in UK Biobank**

		Biobank age 40-69, white, no history of condition			*Biobank age 40-69, white, with history of condition*		
Condition and cause of death	***Smoking history***	***Total N (deaths)***	***zFEV1 HR (95%CI)***	***zFVC HR (95%CI)***	***Total N (deaths)***	***zFEV1 HR (95%CI)***	***zFVC HR (95%CI)***
Respiratory disease at entry, all deaths	Never smokers	130798 (2081)	1.21 (1.16-1.26)	1.22 (1.17-1.27)	18545 (320)	1.23 (1.12-1.35)	1.33 (1.21-1.47)
	Former smokers	166259 (3711)	1.36 (1.32-1.40)	1.34 (1.30-1.38)	25368 (717)	1.48 (1.39-1.57)	1.48 (1.39-1.58)
	Current smokers	33491 (1352)	1.32 (1.26-1.38)	1.21 (1.15-1.27)	5023 (324)	1.53 (1.39-1.68)	1.48 (1.35-1.63)
Circulatory disease at entry, circulatory death	Never smokers	109141 (189)	1.40 (1.23-1.59)	1.40 (1.23-1.60)	40202 (242)	1.35 (1.20-1.51)	1.43 (1.27-1.60)
	Former smokers	131593 (281)	1.39 (1.26-1.54)	1.40 (1.26-1.57)	60034 (579)	1.59 (1.48-1.70)	1.64 (1.52-1.77)
	Current smokers	27843 (162)	1.32 (1.16-1.50)	1.29 (1.12-1.48)	10671 (204)	1.42 (1.26-1.59)	1.36 (1.20-1.54)
Cancer at entry, cancer death	Never smokers	137742 (978)	1.05 (0.99-1.11)	1.06 (1.00-1.12)	11601 (557)	1.10 (1.02-1.18)	1.13 (1.04-1.22)
	Former smokers	174917 (1898)	1.21 (1.16-1.26)	1.18 (1.13-1.23)	16710 (864)	1.32 (1.25-1.40)	1.30 (1.22-1.38)
	Current smokers	35573 (738)	1.29 (1.22-1.37)	1.18 (1.10-1.26)	2941 (199)	1.24 (1.11-1.39)	1.28 (1.12-1.45)

Spirometric indices (FEV1 and FVC) are modelled as z-scores derived from the Global Lung Initiative 2012 reference equations for whites.
All hazard ratios are expressed per unit decrement in z-score, adjusted for age, sex, height, area-based socio-economic measure and geographical region (recruitment centre)..

e-Table 7 **Mortality from all causes, and from circulatory diseases, by quartile of systolic blood pressure, body mass index and spirometric indices among white lifelong non-smokers aged 40-69 at entry in national health surveys (HSE and SHS) and in UK Biobank**

		All-cause mortality				*Circulatory mortality*			
Risk factor	***Quartile***	***HSE-SHS HR (95%CI) (based on 495 deaths)***		***Biobank HR (95%CI) (based on 2319 deaths)***		***HSE-SHS HR (95%CI) (based on 129 deaths)***		***Biobank HR (95%CI) (based on 403 deaths)***	
SBP	Q1 (low)	1.00	(reference)	1.00	(reference)	1.00	(reference)	1.00	(reference)
	Q2	0.80	(0.59-1.09)	0.93	(0.82-1.05)	1.20	(0.59-2.42)	0.81	(0.58-1.14)
	Q3	0.78	(0.58-1.06)	0.89	(0.78-1.01)	0.72	(0.34-1.50)	0.97	(0.71-1.34)
	Q4 (high)	1.12	(0.85-1.48)	0.99	(0.88-1.12)	1.98	(1.05-3.72)	1.12	(0.82-1.51)
BMI	Q1 (low)	1.00	(reference)	1.00	(reference)	1.00	(reference)	1.00	(reference)
	Q2	0.99	(0.75-1.3)	0.90	(0.79-1.01)	1.05	(0.59-1.87)	1.08	(0.77-1.51)
	Q3	1.05	(0.8-1.37)	0.95	(0.84-1.08)	1.39	(0.80-2.42)	1.35	(0.97-1.86)
	Q4 (high)	1.30	(1-1.68)	1.36	(1.21-1.53)	1.90	(1.13-3.22)	2.05	(1.51-2.79)
zFEV1	Q4 (high)	1.00	(reference)	1.00	(reference)	1.00	(reference)	1.00	(reference)
	Q3	0.95	(0.71-1.27)	1.12	(0.99-1.26)	1.73	(0.93-3.22)	0.97	(0.71-1.33)
	Q2	1.20	(0.91-1.58)	1.15	(1.01-1.30)	2.13	(1.16-3.89)	1.29	(0.96-1.73)
	Q1 (low)	1.56	(1.2-2.01)	1.60	(1.43-1.79)	2.24	(1.25-4.04)	1.99	(1.52-2.61)
zFVC	Q4 (high)	1.00	(reference)	1.00	(reference)	1.00	(reference)	1.00	(reference)
	Q3	1.01	(0.76-1.34)	1.05	(0.93-1.19)	1.38	(0.77-2.46)	1.16	(0.85-1.60)
	Q2	1.20	(0.92-1.58)	1.25	(1.11-1.41)	1.74	(0.99-3.04)	1.62	(1.20-2.18)
	Q1 (low)	1.66	(1.29-2.14)	1.62	(1.44-1.82)	1.98	(1.15-3.40)	2.19	(1.65-2.92)

Spirometric indices (FEV1 and FVC) are modelled as z-scores derived from the Global Lung Initiative 2012 reference equations for whites.
All hazard ratios are adjusted for age, sex, height, socio-economic status, geographical region and survey year.

bmjopen-2016-015381 – Authors' response to comments – Annex 3

Title Ventilatory function as a predictor of mortality in lifelong non-smokers: evidence from large British cohort studies

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STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract "Cohort" included in the title
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found. See page 3.
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported Text (pages 5-6) explains the reason for focusing on lifelong non-smokers.
Objectives	3	State specific objectives, including any prespecified hypotheses. Text (p5) explains the rationale for comparing findings from two longitudinal data sources.
Methods		
Study design	4	Present key elements of study design early in the paper. The longitudinal potential of each data source (national health surveys and UK Biobank) is introduced at the start of the relevant section of the methods (text p6-7).
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection. Separately specified for national health surveys (p6) and UK Biobank (p7).
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up. Separately specified for national health surveys (p6) and UK Biobank (p7)
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed. Not applicable.
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable. Cause of death coding (outcome) and spirometric assessment (main exposure of interest) are specified. Potentially confounding covariates adjusted for in all models are described briefly (p7-8). Effect modification is addressed by stratified analyses. All analyses are restricted to participants of white ethnicity due to uncertainty about the most appropriate method of adjustment of spirometry for age, sex and height in non-whites, and the small and diverse nature of the minority ethnic groups in both data sources.
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group. Spirometric methods are separately specified for national health surveys and UK Biobank (p6-7).

Bias	9	Describe any efforts to address potential sources of bias. Possible lack of generalisability in UK Biobank is dealt with by comparing results to national health surveys which are more representative of the UK population. Possible influence of spirogram quality is addressed by a supplementary analysis in UK Biobank, restricting to better quality spirograms (p13-14). The major confounding effect of active smoking is excluded by focusing on lifelong non-smokers in both cohorts. However, findings for former and current smokers are shown in supplementary tables (e-Tables 1-6) for completeness.
Study size	10	Explain how the study size was arrived at. This is a secondary analysis of national surveys. Both data sources are of fixed size, determined by the original (baseline) surveys which were not specifically designed to answer our study question. Thus, the sample size was not determined by a statistical power calculation. However, we note that both sources are larger than all previous studies of spirometry and survival among lifelong non-smokers (see discussion, p19-20).
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why. The same method of adjustment of spirometric measures for age, sex and height was applied to both cohorts and this is described in a specific section of the methods (p8).
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding Modelling approaches are described in a subsection of the methods (p8-10).
		(*b*) Describe any methods used to examine subgroups and interactions Subgroups defined by time of death, cause of death, spirogram quality, age, sex, and presence of respiratory disease, circulatory disease or cancer at baseline examination are described in the results section (tables 1-3) and supplementary tables.
		(*c*) Explain how missing data were addressed Response rates at the original (baseline) examination are specified in the methods section (p6-7). We have no information on mortality rates among the non-participants.
		(*d*) If applicable, explain how loss to follow-up was addressed Not addressed, as mortality ascertainment is complete in both data sources except for participants who emigrate from the UK, which will be very few.
		(*e*) Describe any sensitivity analyses. The comparison of findings between cohorts, and the analysis of Biobank participants with better quality spirometry, attempt to confirm the generalisability of key findings. The modelling assumption of proportionality of hazards throughout the follow-up period is tested specifically in each cohort and smoking subgroup (p12). Alternative approaches to pooling the results from the five national health surveys were explored (see annex 2 in response to reviewers and the text at p9).
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed. Specified briefly for each data source in the methods (p6-7).
		(b) Give reasons for non-participation at each stage. No information is available on reasons for non-participation. Non-participation in spirometry due to ill-health can be a potential source of bias. However, we were able to compare the mortality experience of Biobank participants who performed higher and lower quality spirometry. This showed no substantial difference (results, p14).

		(c) Consider use of a flow diagram. Considered but not included for sake of brevity.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders. References (8-16, p21-23) are supplied to the baseline surveys on which this longitudinal follow-up were based.
		(b) Indicate number of participants with missing data for each variable of interest. Proportions of each cohort with usable spirometry are specified (p6-7).
		(c) Summarise follow-up time (eg, average and total amount). Described in the abstract and in the methods, separately for each data sources p6-7) and in supplementary e-Table 1.
Outcome data	15*	Report numbers of outcome events or summary measures over time. Numbers of deaths from each cohort are summarised in the abstract and are specified in all tables, along with the corresponding hazard ratio and the number of subjects included in each model.
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included. Each table lists the covariates included. All results (hazard ratios) are presented with 95% confidence intervals. We do not consider it appropriate to present unadjusted estimates, but when modelling FEV1 and FEV/FVC ratio jointly, we present results before and after inclusion of the ratio, and similarly for FVC adjusted for FEV/FVC ratio. This is explained in the methods (p9).
		(*b*) Report category boundaries when continuous variables were categorized. Not applicable to our tabulated analyses, which are presented per unit change in z-score.
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period. We do not consider this to be relevant to our paper as the periods of follow-up differ substantially between the cohorts and the baseline mortality risk varies considerably with age. On pages 8-9 we interpret hazard ratios per z-score unit decrement in lung function in terms of mortality change across a 4 unit range typical of the z-scores encountered in lifelong non-smokers.
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses. Described in the results (especially pages 15 and 17). Supplementary tables include the corresponding results for former smokers and current smokers.
Discussion		
Key results	18	Summarise key results with reference to study objectives. Done - see pages 18-19.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias. Limitations and potential biases are evaluated in the discussion (p18-19).
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence. Results from previous studies of lifelong non-smokers are discussed (p19-20) and spirometry as a predictor of mortality is set into context by comparison with systolic blood pressure and body mass index (p21). The possibility that the association with mortality represents a predictive relationship with case-fatality, rather than disease incidence, is addressed in the discussion (p19, referring to results in Biobank participants without disease at entry examination – table 3).
Generalisability	21	Discuss the generalisability (external validity) of the study results. One main objective of this paper is to establish the generalisability of results (within the UK, at least) by comparison of two complementary data sources. See p18-19.

Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based. See p22.