Original research

Predictive value of lung function measures for cardiovascular risk: a large prospective cohort study

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ABSTRACT

Introduction Although lung function measures are associated with cardiovascular disease (CVD), the added predictive values of these measures remain unclear.

Methods From the UK Biobank, 308 415 participants free of CVD with spirometry parameters were included. The CVD outcomes included were defined by QRISK3, the American College of Cardiology/American Heart Association (ACC/AHA) and the European Systematic Coronary Risk Evaluation (SCORE) prediction models, respectively. Cox proportional hazard models were used to estimate the associations of lung function measures with CVD outcomes. The predictive capability was determined by the decision curve analyses.

Results Over a median follow-up of 12.5 years, 21 885 QRISK3 events, 12 843 ACC/AHA events and 2987 SCORE events were recorded. The associations of spirometry parameters with CVD outcomes were L-shaped. Restrictive and obstructive impairments were associated with adjusted HRs of 1.84 (95% CI: 1.65 to 2.06) and 1.72 (95% CI: 1.55 to 1.90) for SCORE CVD, respectively, compared with normal spirometry. Similar associations were seen for QRISK3 CVD (restrictive vs normal, adjusted HR: 1.30, 95% CI: 1.25 to 1.36; obstructive vs normal, adjusted HR: 1.20, 95% CI: 1.15 to 1.25) and ACC/AHA CVD (restrictive vs normal, adjusted HR: 1.39, 95% CI: 1.31 to 1.47; obstructive vs normal, adjusted HR: 1.26, 95% CI: 1.19 to 1.33). Using models that integrated non-linear forced expiratory volume in 1 s led to additional 10-year net benefits per 100 000 persons of 25, 43 and 5 for QRISK3 CVD at the threshold of 10%, ACC/AHA CVD at 7.5% and SCORE CVD at 5.0%, respectively.

Conclusion Clinicians could consider spirometry indicators in CVD risk assessment. Cost-effectiveness studies and clinical trials are needed to put new CVD risk assessment into practice.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Lung function impairments, respiratory diseases and spirometry parameters are associated with a higher risk of cardiovascular diseases (CVDs). However, whether these lung function measures provide additional prediction values for CVD risk prediction remains unclear.

WHAT THIS STUDY ADDS

⇒ The addition of lung function indicators in non-fatal and fatal CVD risk prediction models, especially forced expiratory volume in 1 s and forced vital capacity, offered a slight improvement for 10-year CVD risk prediction.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study indicates that clinicians could consider lung function measures in CVD risk assessment and consider improving lung function as a target for CVD prevention. However, further evidence is needed using cost-effectiveness analysis or clinical trial design to determine the performance of new CVD risk models that integrate spirometry measures in clinical practice.

INTRODUCTION

Observational studies show that impaired lung function and subclinical impairments are associated with a higher risk of cardiovascular disease (CVD).[1–5] Furthermore, Mendelian randomisation studies suggest that reduced forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) are independently and causally associated with coronary artery disease and reverse causations are not found.[6 7] Preventing lung function impairment and reducing exacerbation of chronic obstructive pulmonary disease (COPD) may contribute to CVD prevention.[8] Therefore, lung function parameters could be used as potential predictors and prevention targets for CVD. Spirometry tests are recommended for confirmation of COPD screening among symptomatic and/or at-risk individuals in primary care.[9] This further provides the possibility to add spirometry measures for CVD risk evaluation. On the other hand, the benefit of CVD prevention may increase the cost-effectiveness of spirometry tests. Considering the sequelae in respiratory and cardiovascular systems following COVID-19, accurate CVD risk prediction integrated with lung function surveillance is more practical and is essential to avoid excess future CVD events.[10 11] However, whether lung function impairment screening by spirometry contributes to CVD risk assessment in the general population remains uncertain.

Currently, several fatal and non-fatal CVD prediction models that integrated with conventional CVD risk factors are used for primary prevention and health promotion, including the QRISK3 risk score,[12] the American College of Cardiology/American Heart Association (ACC/AHA) CVD risk score[13] and the European Systematic Coronary Risk Evaluation (SCORE) CVD risk score.[14] However,

lung function measures do not feature in the aforementioned CVD risk prediction models. The lack of data from a single large cohort with consistent phenotyping of multiple exposures and events limits research on this topic. This issue requires better evidence to inform clinical care.

In this study, by investigating the UK Biobank, we aimed to (1) detect the changes in predictive discrimination of CVD risk prediction models with lung function measures and impairment patterns compared with the original CVD risk prediction models; (2) compare the predicted value of lung function parameters to determine the most suitable measures in CVD risk evaluation.

METHODS

Population

Data of this study were from the UK Biobank, one of the largest open cohorts, with half a million participants aged 37–73 years recruited from 22 assessment centres across England, Wales and Scotland from 2006 to 2010. Details of this cohort were described elsewhere.[15] Briefly, the sociodemographic characteristics, lifestyle factors, family histories and medical histories were collected via a touchscreen questionnaire or a verbal interview at the assessment centre from 2006 to 2010. Physical measures and biological sampling, including spirometry tests, were also conducted at recruitment. The medical histories of participants were derived from the first occurrence dates of diseases before the recruitment. The first occurrences of diseases were generated from hospital admission records, death register records and self-report questionnaires.[16] The UK Biobank received ethics approval from the North West Multicenter Research Ethics Committee (reference number 11/NW/03820). People were followed to get their health outcomes with their consent. In this study, we excluded participants who withdrew consent (n=141), those diagnosed with CVDs at baseline (n=18 989), those without valid spirometry data (n=122 619), those with missing values in variables for the calculation of lung function parameters using the Global Lung Function Initiative (GLI) 2012 equations (n=1847) and those who had missing values in conventional CVD risk factors (n=50 496). After exclusions, a total of 308 415 participants were included (online supplemental figure S1). Baseline characteristics and CVD factors among participants with and without spirometry data are listed in online supplemental table S1. The inclusion criteria for the current analyses were similar to those used in the development of the original CVD prediction models.

Lung function and chronic respiratory disease status

Breath spirometry was tested using the Vitalograph Pneumotrac 6800 spirometer by trained healthcare technicians and nurses in UK Biobank assessment centres following the UK Biobank procedure manual.[17] Participants were asked to record two blows (lasting for at least 6 s) within about 6 min. The third blow was required if the results of the first two blows were unacceptable (defined as a ≥5% difference). A blow was deemed valid if: (1) the extrapolated volume at the start of the test is excessive, (2) the time to peak flow is excessive, (3) an adequate plateau at the end of the test does not exist, (4) cough was detected during the manoeuvre, (5) the test is less than 6 s, (6) the test was explicitly not accepted by the investigator or (7) the test was explicitly rejected by the investigator. The highest values for spirometry parameters from acceptable and valid blows were used in analyses.[18]

The lung function parameters evaluated in this study include FEV_1, FVC, peak expiratory flow (PEF) and FEV_1/FVC ratio. Further, absolute spirometry measurements (FEV_1, FVC) were converted to % predicted values based on demographic data (age, height, gender and ethnicity) using the GLI-2012 equation.[19] Lung function impairment patterns were classified into clinically meaningful groups: normal spirometry (both the FEV_1/FVC ratio and FVC at or above the lower limits of normal (LLN)), obstructive impairment (FEV_1/FVC<LLN) and restrictive impairment (FEV_1/FVC≥LLN and FVC<LLN).[20] LLNs for spirometry parameters were calculated using the GLI-2012 equations. The GLI R-macro was used for the GLI-2012 equation calculations.[21]

In addition, chronic respiratory disease status at baseline was included as a new predictor. Chronic respiratory disease was defined as having COPD (International Classification of Diseases ICD-10 code: J41–J44) or asthma (ICD-10 code: J45–J46) at baseline determined by self-report, hospital inpatient data and death data.

Outcomes defined

Data on health outcomes were from the linkage to hospital admission records and death registry records. There were three main outcomes considered in this study according to current CVD prediction models. (1) Composite QRISK3 CVD events used as outcomes in the QRISK3 prediction model, including fatal or non-fatal coronary heart disease, ischaemic stroke or transient ischaemic attack (ICD-10 code: G45, I20–24 and I63–64)[12]; (2) composite ACC/AHA CVD events, a composite of fatal and non-fatal CVD that reflects the ACC/AHA guideline prediction score including death from CVD (ICD-10 code: I20–25 and I60–64) or hospitalisation for CVD (ICD-10 code: I21, I22 and I60–64)[13] and (3) fatal SCORE CVD events, fatal CVD as defined by primary cause of death from events included in the SCORE clinical guidelines (ICD-10 code: I10–15, I44–51, I20–25 and I61–73).[14]

Covariates

The conventional risk factors at recruitment included in each risk prediction model were used to calculate individual CVD risk scores in this study. In the QRISK3 prediction model, risk factors include age, sex, systolic blood pressure (SBP), smoking (current, previous or never), ethnicity (white, black, south Asian or mixed/others), Townsend Deprivation Index (TDI) (index of deprivation based on postcode), total cholesterol to high-density lipoprotein cholesterol (HDL-C) ratio, body mass index (BMI), family history of CVD, hypertension, rheumatoid arthritis, atrial fibrillation, chronic kidney disease stages 3–5, migraine, steroid use, systemic lupus erythematosus, atypical antipsychotic medication use, serious psychological disorders, antihypertensive medication use and cholesterol-lowering medication use. In ACC/AHA or SCORE risk models, risk factors include age, sex, ethnicity (white, black, South Asian or mixed/other), smoking (current, previous or never), total cholesterol, HDL-C, SBP, diastolic blood pressure, antihypertensive medication use and cholesterol-lowering medication use.

Statistical analysis

Descriptive characteristics of all participants according to lung function impairment patterns were presented as means with SDs or medians with IQRs for continuous variables and frequencies with percentages for categorical variables.

The follow-up duration started at the date of the spirometry assessment and ended with the first date of hospitalisation for non-fatal CVD, the date of death, the date lost to follow-up

Table 1 Baseline characteristics of participants according to lung function impairment patterns (N=3 08 415)

Characteristics	All participants (N=3 08 415)	Normal spirometry (n=2 58 408)	Restrictive impairment (n=21 999)	Obstructive impairment (n=28 008)
Age, years, mean (SD)	56.15 (8.05)	56.22 (8.01)	55.21 (8.14)	56.29 (8.23)
Male, no (%)	142 304 (46.1)	117 294 (45.4)	10 960 (49.8)	14 050 (50.2)
White, no (%)	293 928 (95.3)	248 474 (96.2)	19 113 (86.9)	26 341 (94.0)
Townsend Deprivation Index at recruitment, median (IQR)	−2.24 (−3.70, 0.30)	−2.33 (−3.74, 0.10)	−1.64 (−3.39, 1.38)	−1.67 (−3.43, 1.34)
Smoking status, no (%)				
Never	168 660 (54.7)	144 628 (56.0)	12 238 (55.6)	11 794 (42.1)
Previous	108 050 (35.0)	91 188 (35.3)	7043 (32.0)	9819 (35.1)
Current	31 705 (10.3)	22 592 (8.7)	2718 (12.4)	6395 (22.8)
Body mass index, kg/m^2, mean (SD))	27.33 (4.65)	27.24 (4.50)	29.54 (5.68)	26.48 (4.57)
Systolic blood pressure, mmHg, mean (SD)	137.82 (18.44)	137.71 (18.38)	139.40 (18.71)	137.60 (18.66)
Diastolic blood pressure, mmHg, mean (SD)	82.42 (10.03)	82.36 (9.99)	83.86 (10.26)	81.78 (10.08)
Total cholesterol, mmol/L, mean (SD)	5.75 (1.12)	5.77 (1.11)	5.60 (1.16)	5.67 (1.11)
HDL-C, mmol/L, mean (SD)	1.46 (0.38)	1.47 (0.38)	1.35 (0.36)	1.47 (0.39)
Total cholesterol-to-HDL-C ratio, mean (SD)	4.14 (1.12)	4.13 (1.11)	4.36 (1.18)	4.06 (1.12)
Family history of CVD, no (%)	172 038 (55.8)	145 057 (56.1)	12 103 (55.0)	14 878 (53.1)
Antihypertensive medication use, no (%)	56 381 (18.3)	45 385 (17.6)	5788 (26.3)	5208 (18.6)
Cholesterol-lowering medication, no (%)	44 531 (14.4)	35 943 (13.9)	4553 (20.7)	4035 (14.4)
Chronic respiratory diseases, no (%)	37 403 (12.1)	25 348 (9.8)	3163 (14.4)	8892 (31.7)
Lung function indicators				
FVC, L, mean (SD)	3.76 (1.00)	3.86 (0.95)	2.72 (0.70)	3.66 (1.15)
FEV_1, L, mean (SD)	2.84 (0.79)	2.97 (0.74)	2.10 (0.57)	2.26 (0.79)
PEF, L/min, mean (SD)	414.86 (125.83)	432.58 (120.34)	335.58 (105.90)	313.66 (117.69)
FEV_1/FVC, mean (SD)	0.76 (0.07)	0.77 (0.05)	0.77 (0.05)	0.61 (0.07)
FEV_1 % predicted, mean (SD)	92.68 (16.70)	97.02 (13.08)	67.48 (9.23)	72.38 (18.47)
FVC % predicted, mean (SD)	96.63 (15.49)	99.39 (12.76)	69.10 (8.06)	92.73 (20.22)

CVD, cardiovascular disease; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; HDL-C, high-density lipoprotein cholesterol; PEF, peak expiratory flow.

or the end of follow-up (30 September 2021 for England, 19 September 2021 for Scotland and 31 May 2016 for Wales), whichever came first. The crude event incidence rates and 95% CIs according to lung function impairment patterns were calculated using Poisson regression models. Cox proportional hazard models were used to estimate HRs and 95% CIs for CVD outcomes adjusted for 10-year individual CVD risk scores calculated from three aforementioned prediction models. Restricted cubic spline (RCS) models with four knots at the 5th, 35th, 65th and 95th percentiles were used to evaluate the non-linear relationships between spirometry parameters and CVD outcomes adjusted for individual risk scores.[22] A non-linearity test used the likelihood ratio to compare the model that comprised the linear term with the model that comprised both the linear and the cubic spline terms. The reference points in the RCS models were the medians for FEV_1 (2.76 L), FVC (3.64 L) and PEF (400.00 L/min) and clinically relevant reference points for FEV_1/FVC (0.70), FEV1 % predicted (80%) and FVC % predicted (100%).[23] For sensitivity analyses of non-linear relationships, generalised additive models (GAM) were used. The generalised cross-validation criterion was used to solve the optimal effective degree of freedom used in each model. The change in Harrell's concordance statistic (C-statistic) was used to estimate the added discriminative ability of non-linear spirometry indicators and lung function impairment category to the original prediction models.[24 25] In addition to the changes in C-statistic, the decision curve analysis (DCA) was used to assess the clinical utility.[26 27] The DCA was used to evaluate and compare the net benefits of models with and without lung function measures for 10-year CVD risk prediction from a clinical utility perspective.[28 29] The net benefits of the 10-year CVD risk prediction models with and without lung function measures were calculated at the thresholds of 10.0%, 7.5% and 5.0% for QRISK3, ACC/AHA and SCORE models, respectively.[12–14] Locally weighted scatterplot smoothing (LOESS) was used to derive the smooth decision curves. For internal validation, the changes in the C- statistics and net benefits were recalculated in two randomly assigned subdatasets with 70% and 30% of the total participants.

For sensitivity analysis, we imputed the variates for the GLI-2012 equations with the means for continuous variables (height) and indicators for missing category variables (ethnicity). Multiple imputations with five replications were used to impute other predictors with missing values based on a chained equation method. The missing cases and proportions of covariates are listed in online supplemental table S2. In subgroup analysis, we investigated the magnitudes of the association between lung function impairment patterns with CVD outcomes and the model performances among participants in different age groups (<60 and ≥60 years) and sexes (females and males).

Statistical analyses were conducted using Stata (V.15, StataCorp) and R (V.4.2.0). All tests were two-sided with a significance level of 0.05.

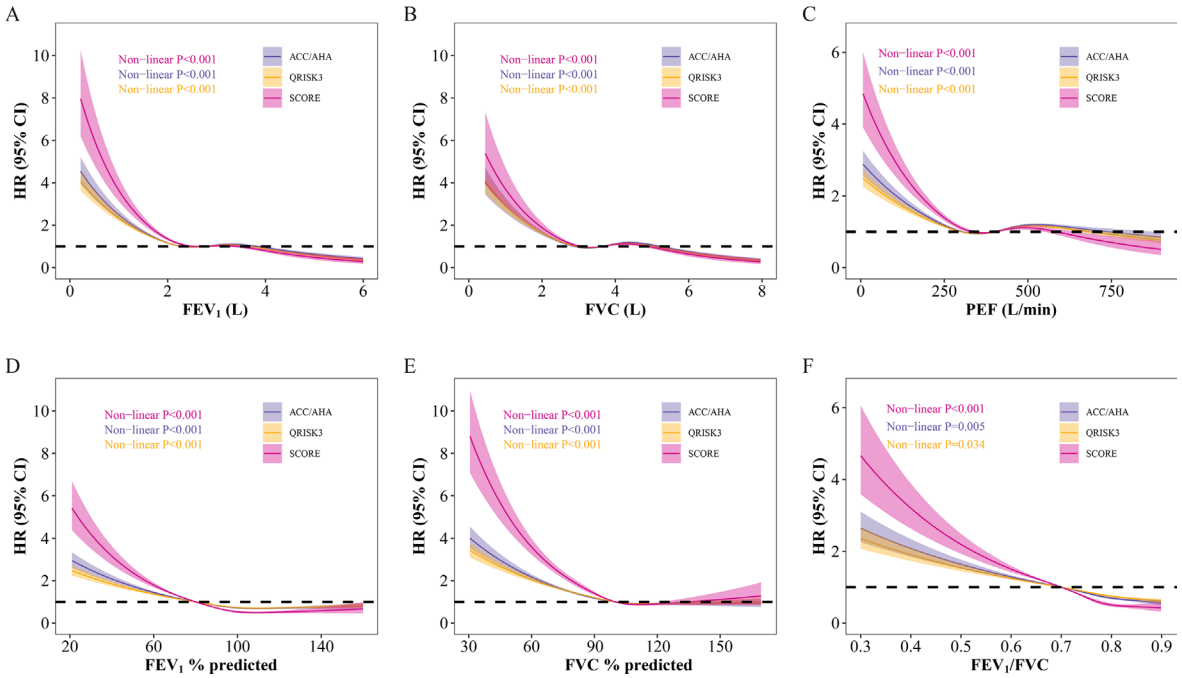


Figure 1 The non-linear associations of spirometry indicators with composite CVD and fatal CVD outcomes according to restrictive cubic splines. Composite QRISK3 CVD outcome is defined based on the QRISK3 prediction model. Composite ACC/AHA CVD outcome is defined based on the American College of Cardiology/American Heart Association (ACC/AHA) CVD risk score. SCORE fatal CVD outcome is defined based on the European Systematic Coronary Risk Evaluation (SCORE) CVD risk score. The reference points are the medians for FEV_1 (2.76 L), FVC (3.64 L), PEF (400 L/min) and clinically significant reference points for FEV_1/FVC (0.7), FEV1 % predicted (80%) and FVC % predicted (100%). Individual risk scores from three prediction models are adjusted in each model. Risk factors in the QRISK3 model include age, sex, systolic blood pressure, smoking, ethnicity, Townsend Deprivation Index, total cholesterol to high-density lipoprotein cholesterol ratio, body mass index, family history of CVD, hypertension, rheumatoid arthritis, atrial fibrillation, chronic kidney disease stages 3–5, migraine, steroid use, systemic lupus erythematosus, atypical antipsychotic medication use, serious psychological disorders, antihypertensive medications and cholesterol-lowering medication use. In ACC/AHA or SCORE risk models, covariates include age, sex, ethnicity, smoking, total cholesterol, high-density lipoprotein cholesterol, systolic and diastolic blood pressure, antihypertensive medications and cholesterol-lowering medication use. FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; PEF, peak expiratory flow.

RESULTS

Of 308 415 people without CVD at baseline and complete data on covariates included in this study, 21 885 developed QRISK3 composite CVD events, 12 843 developed ACC/AHA composite CVD events and 2987 developed SCORE fatal CVD events over a median follow-up of 12.5 (IQR: 11.8–13.2) years. The analysis sample comprised 142 304 (46.1%) males, and the mean age was 56.15 (±8.05) years. The mean values of FVC, FEV_1, PEF and FEV1/FVC were 3.76±1.00 L, 2.84±0.79 L, 414.86±125.83 L/min and 0.76±0.07, respectively. Of all participants included, 21 999 (7.1%) were classified as restrictive impairment, and 28 008 (9.1%) were classified as obstructive impairment. The baseline characteristics of participants according to lung function impairment patterns are listed in table 1. Participants with normal spirometry were more likely to be females, whites, non-smokers, have lower TDI (less deprived), higher total cholesterol, higher HDL-C, higher probability of family history of CVD, lower probability of antihypertensive medication use and cholesterol-lowering medication use. The baseline risk characteristics of participants according to the CVD status at the end of follow-up are listed in online supplemental table S3. All spirometry parameters were correlated as shown in online supplemental figure S2. The strongest correlation was detected between FEV_1 and FVC (r=0.95), and the weakest correlation was detected between FEV_1/FVC ratio and FVC (r=0.01). The distributions of spirometry parameters were plotted in online supplemental figure S3.

According to RCS splines (figure 1 and online supplemental figure S4), the associations of spirometry parameters with fatal and non-fatal CVD were reversed L-shape. Lower spirometry measures were associated with higher risks of all CVD outcomes, whereas higher lung function parameters did not show higher protective effects. The magnitudes of effects for fatal SCORE CVD outcome were stronger, followed by composite ACC/AHA CVD and composite QRISK3 CVD. The non-linear splines using GAM showed similar L-shapes (plateaus or decrease of HRs at extreme lower ranges), as well as the RCS splines among 360 758 participants with imputed missing values in covariates (online supplemental figures S5 and S6).

Participants with chronic respiratory diseases had 15% (95% CI: 11% to 19%), 15% (95% CI: 9% to 21%) and 28% (95% CI: 16% to 42%) higher risks of composite QRISK3 CVD, composite ACC/AHA CVD and fatal SCORE CVD, respectively, after adjusting for predicted individual risks calculated from the original prediction models (figure 2 and online supplemental table S4). Compared with normal spirometry, restrictive and obstructive impairment were associated with HRs of 2.20 (95% CI: 1.97 to 2.46) and 1.93 (95% CI: 1.74 to 2.13) for fatal SCORE CVD after adjusting for age and sex (figure 2). After adjusting for predicted individual CVD risk calculated using the original SCORE prediction model, the effect sizes were attenuated (adjusted HR: 1.84 (95% CI: 1.65 to 2.06) for restrictive impairment and adjusted HR: 1.72 (95% CI: 1.55 to 1.90) for obstructive impairment). Similar associations were observed for

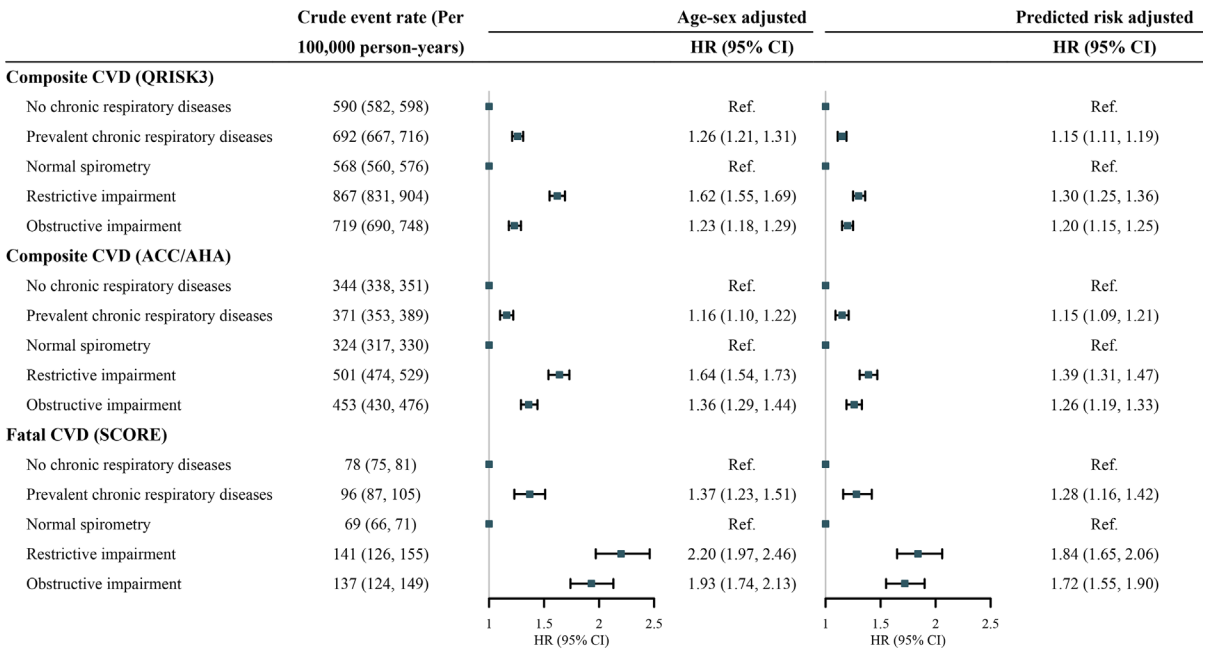


Figure 2 The association of lung function impairment with composite CVD and fatal CVD outcomes. Composite QRISK3 CVD outcome is defined based on the QRISK3 prediction model. Composite ACC/AHA CVD outcome is defined based on the American College of Cardiology/American Heart Association (ACC/AHA) CVD risk score. SCORE fatal CVD outcome is defined based on the European Systematic Coronary Risk Evaluation (SCORE) CVD risk score. Individual CVD risk scores were calculated from three prediction models. Risk factors in the QRISK3 model include age, sex, systolic blood pressure, smoking, ethnicity, Townsend Deprivation Index, total cholesterol to high-density lipoprotein cholesterol ratio, body mass index, family history of CVD, hypertension, rheumatoid arthritis, atrial fibrillation, chronic kidney disease stages 3–5, migraine, steroid use, systemic lupus erythematosus, atypical antipsychotic medication use, serious psychological disorders, antihypertensive medications and cholesterol-lowering medication use. In ACC/AHA or SCORE risk models, covariates include age, sex, ethnicity, smoking, total cholesterol, high-density lipoprotein cholesterol, systolic and diastolic blood pressure, antihypertensive medications and cholesterol-lowering medication use. CVD, cardiovascular disease.

composite ACC/AHA CVD and composite QRISK3 CVD, while the effect sizes were larger for fatal SCORE CVD outcomes. The magnitudes of these associations were slightly increased among the 360 758 participants with imputed missing values in covariates (online supplemental table S5). Significant interactions were identified between chronic respiratory disease status, lung function impairment and sex for composite QRISK3 CVD and composite ACC/AHA CVD (online supplemental table S6). The effect sizes were larger among females. The associations were consistent among participants aged <60 years and those aged ≥60 years, except for prevalent chronic respiratory diseases, which were associated with a higher risk of composite ACC/AHA CVD among participants aged ≥60 years (online supplemental table S7).

Conventional risk factors in the original models yielded a C-statistic of 0.7385 (95% CI: 0.7355 to 0.7416) composite QRISK3 CVD, a C-statistic of 0.7303 (95% CI: 0.7263 to 0.7344) composite ACC/AHA CVD and a C-statistic of 0.7969 (95% CI: 0.7895 to 0.8043) fatal SCORE CVD using data from the UK Biobank (online supplemental table S8). All lung function measures significantly improved the discrimination, with the largest improvement seen with non-linear FEV_1 (C-statistic change: +0.0018 for composite QRISK3 CVD, +0.0033 for composite ACC/AHA CVD) or non-linear FEV_1 % predicted (+0.0065 for fatal SCORE CVD). The changes in the C-statistics were largely consistent with results among 360 758 participants with imputed missing values (online supplemental table S9) and in the two validation datasets (baseline characteristics: online supplemental table S10, results of C-statistics: online supplemental tables S11 and S12) except for the addition of chronic respiratory diseases.

According to the decision curve analysis within 10 years, all models that integrated lung function measures had higher net benefits than the original models (table 2). At the recommended thresholds, using the model that integrated non-linear FEV_1 led to a net increase of 25 more true-positive (TP) composite QRISK3 events, 43 more TP composite ACC/AHA events and 5 more TP fatal SCORE events per 100 000 participants without an increase in the number of false-positive cases compared with the original models. From the false-positive reduction perspective, using the new models that integrate non-linear FEV_1 would lead to the equivalent of 224, 391 and 48 fewer redundant interventions per 1 00 000 patients, respectively, in participants who would not develop CVD within 10 years. In addition, this would lead to no increase in the number of untreated future CVD cases. The largest advantage of net benefit was observed with the model that integrated with non-linear FEV_1 and non-linear FVC. The results were consistent in sensitivity analysis among 360 758 participants with imputed missing values and two internal validation subsets (online supplemental tables S13–S15). The advantage of net benefit of SCORE model was not shown among females (online supplemental tables S16 and S17). The advantages of net benefits of models that integrated with lung measures were much higher among participants aged 60 and older (online supplemental tables S18 and S19).

Figure 3 shows the decision curves for CVD prediction models that integrated non-linear FEV_1 or non-linear FVC. Across the likely threshold probability (1–15% for QRISK3, 1–10% for ACC/AHA and 1–8% for SCORE), CVD prediction models with non-linear FEV_1 and non-linear FVC showed slightly higher net

Table 2 Net benefits of models for composite CVD and fatal CVD 10-year risk prediction

Model	Net benefit*	Advantage of model	
		Advantage of net benefit per 100 000 participants	Reduction in avoidable false positive cases per 100 000 participants
Composite CVD (QRISK3)			
Original model	0.00850		
+ FEV_1	0.00875	25	224
+ FVC	0.00874	24	212
+ FEV_1 % predicted	0.00872	21	192
+ FVC % predicted	0.00872	22	196
+ Lung function category	0.00864	14	127
+ PEF	0.00859	9	80
+ Chronic respiratory diseases	0.00854	3	31
+ FEV_1/FVC	0.00856	6	55
Composite CVD (ACC/AHA)			
Original model	0.00168		
+ FEV_1	0.00212	43	391
+ FVC	0.00205	36	327
+ FEV_1 % predicted	0.00194	26	234
+ FVC % predicted	0.00200	31	282
+ Lung function category	0.00181	12	110
+ PEF	0.00189	20	184
+ Chronic respiratory diseases	0.00173	5	46
+ FEV_1/FVC	0.00175	7	63
Fatal CVD (SCORE)			
Original model	0.00005		
+ FEV_1	0.00011	5	48
+ FVC	0.00012	7	63
+ FEV_1 % predicted	0.00011	5	47
+ FVC % predicted	0.00011	6	51
+ Lung function category	0.00007	1	12
+ PEF	0.00008	2	20
+ Chronic respiratory diseases	0.00006	0	3
+ FEV_1/FVC	0.00007	1	12

The threshold of 'high' and 'low' classification for the three prediction models are 10.0% (QRISK3), 7.50% (ACC/AHA) and 5.0% (SCORE). Composite QRISK3 CVD outcome is defined based on the QRISK3 prediction model. Composite ACC/AHA CVD outcome is defined based on the American College of Cardiology/American Heart Association (ACC/AHA) CVD risk score. SCORE fatal CVD outcome is defined based on the European Systematic Coronary Risk Evaluation (SCORE) CVD risk score. The lung function category includes normal spirometry (reference), restrictive impairment and obstructive impairment. Other spirometry indicators are added to the prediction models as non-linear parameters.

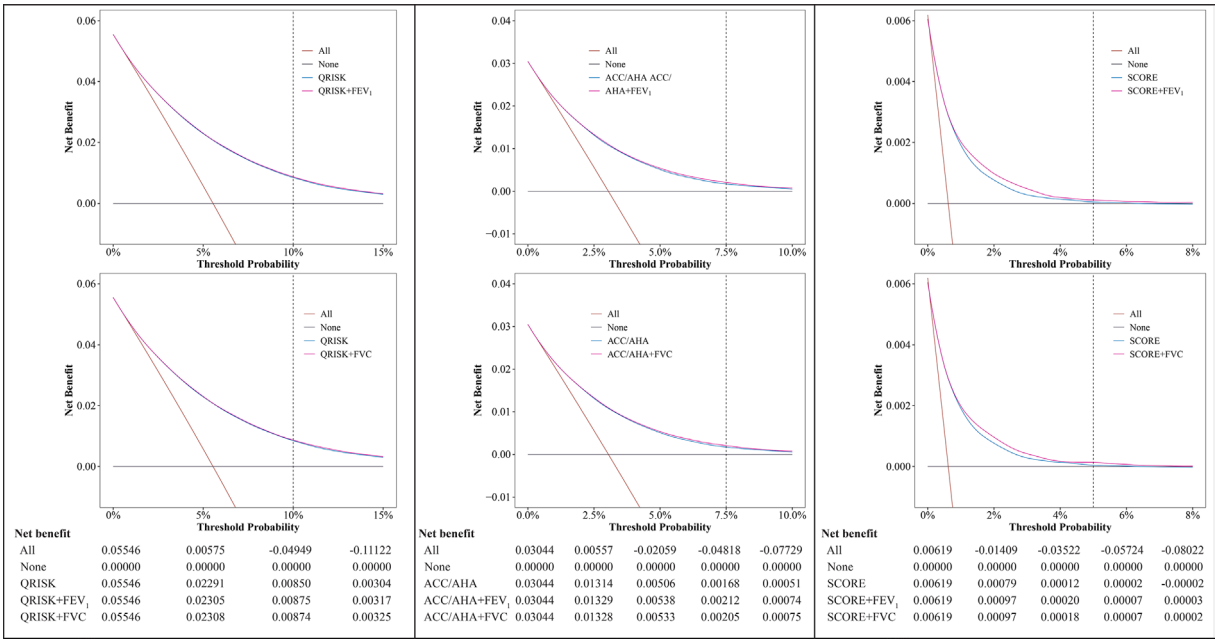
*Net benefit for 10-year CVD risk is calculated as (TP−wFP)/N, where TP is true-positive count, FP is false-positive count, N is the total count of participants, w is the weight of the relative harm of a false-positive and a false-negative result, which is calculated as (1−p)/p, where p is the threshold probability mentioned above (10.0% for QRISK3, 7.50% for ACC/AHA and 5.0% for SCORE). The net benefits under treat all strategy are −0.04949 for composite QRISK3 CVD, −0.04254 for composite ACC/AHA CVD and −0.04611 for fatal SCORE CVD at these thresholds.

CVD, cardiovascular disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow.

benefits than the original models. The figure of unsmoothed, original DCA curves is listed in online supplemental figure S7). The nomograms of three CVD prediction models that integrated with non-linear FEV_1 or non-linear FVC are listed in online supplemental figures S8–S13).

DISCUSSION

With this large and comprehensive UK Biobank cohort, our study evaluated the additional prediction values of spirometry parameters for CVD risk prediction. Over a median of 12.5 years of follow-up, lung function impairments and lower spirometry parameters were associated with higher risks of non-fatal and fatal CVD outcomes after adjusting for the predicted 10-year CVD risk score. The associations of spirometry parameters with CVD outcomes tended to be L-shaped. The addition of some spirometry parameters could improve the discrimination of the original prediction models, with the largest improvement seen with FEV_1. From a clinical utility perspective, the addition of FEV_1 and FVC could lead to higher net benefits. Our study suggests that spirometry parameters, especially FEV_1 and EVC, could serve as risk factors for the identification of high-risk individuals of composite and fatal CVD events for primary prevention.



Net benefit

All	0.05546	0.00575	-0.04949	-0.11122
None	0.00000	0.00000	0.00000	0.00000
QRISK	0.05546	0.02291	0.00850	0.00304
QRISK+FEV$_1$	0.05546	0.02305	0.00875	0.00317
QRISK+FVC	0.05546	0.02308	0.00874	0.00325

Net benefit

All	0.03044	0.00557	-0.02059	-0.04818	-0.07729
None	0.00000	0.00000	0.00000	0.00000	0.00000
ACC/AHA	0.03044	0.01314	0.00506	0.00168	0.00051
ACC/AHA+FEV$_1$	0.03044	0.01329	0.00538	0.00212	0.00074
ACC/AHA+FVC	0.03044	0.01328	0.00533	0.00205	0.00075

Net benefit

All	0.00619	-0.01409	-0.03522	-0.05724	-0.08022
None	0.00000	0.00000	0.00000	0.00000	0.00000
SCORE	0.00619	0.00079	0.00012	0.00002	-0.00002
SCORE+FEV$_1$	0.00619	0.00097	0.00020	0.00007	0.00003
SCORE+FVC	0.00619	0.00097	0.00018	0.00007	0.00002

Figure 3 Decision curve analysis of three prediction models that integrated with lung function impairment or parameters for 10-year composite CVD and fatal CVD risks. Composite QRISK3 CVD outcome is defined based on the QRISK3 prediction model. Composite ACC/AHA CVD outcome is defined based on the American College of Cardiology/American Heart Association (ACC/AHA) CVD risk score. SCORE fatal CVD outcome is defined based on the European Systematic Coronary Risk Evaluation (SCORE) CVD risk score. FEV_1 and FVC are added to the prediction models as non-linear parameters. The tables of net benefits listed under the figures are derived from decision curve analyses. The decision curves were smoothed using the locally weighted scatterplot smoothing (LOESS) method. The y-axis shows the net benefit for 10-year CVD risk prediction. The net benefit is calculated as (TP−wFP)/N, where TP is true-positive count, FP is false-positive count, N is the total count of participants, w is the weight of the relative harm of a false-positive and a false-negative result, which is calculated as (1−p)/p, where p is the x-axis. The dashed vertical lines are the threshold of 'high' and 'low' classification for the three original prediction models (10.0% for QRISK3, 7.50% for ACC/AHA and 5.0% for SCORE). CVD, cardiovascular disease; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s.

Consistent with previous studies, our study supports the association of lung function with fatal and non-fatal CVD. According to the Coronary Artery Risk Development in Young Adults study, per 10-unit decrement in FEV_1 % predicted and per 10-unit decrement FVC % predicted were associated with an 18% and a 19% higher risk of future cardiovascular events, respectively, independent of classic cardiovascular risk factors.[30] Restricted spirometry was associated with a 54% higher risk of CVD after adjusting for cardiometabolic risk factors.[3] Subclinical reductions in FEV_1/FVC and FVC % predicted differentially associated with cardiac function and heart failure risk in late life.[31] A previous study showed that the highest quintile of FEV_1 and FVC were related to a 30% and 21% risk reduction, respectively, of cardiovascular risk among patients with COPD.[32] Moreover, our results also show that the association of lung function impairment with fatal CVD is stronger than composite CVD outcomes. This suggests that lung function indicators are more sensitive to fatal CVD risk prediction than non-fatal CVD.

According to the L-shaped associations of spirometry indicators with CVD risk, we found that impaired lung function was associated with higher risks of fatal and non-fatal CVD, but better lung function was not related to lower CVD risks. This evidence supports the high-risk/symptomatic screening strategy of COPD case-finding.[8] COPD screening might provide the foundation and data resources for spirometry tests, which might also benefit CVD risk assessment. Lambe *et al*[9] suggested that regular systematic case-finding for COPD is likely to be cost-effective in the long term. However, the aforementioned study did not take into account the reduction of comorbidities, such as CVD, as a potential benefit, which might underestimate the cost-effectiveness of screening. What's more, a study suggested that the greater effectiveness of spirometry screening exists in identifying and targeting people who had undiagnosed COPD or subclinical lung function impairments and early prevention and detection of signs of lung damage were needed.[33] Thus, lung function measures could be taken into consideration when assessing CVD risk and considered as potential targets for reducing CVD burden. However, further studies are needed to confirm the specific high-risk populations for lung function tests.

Accurate prediction of CVD risk is essential in clinical practice to target high-risk populations for healthy lifestyle promotion and cholesterol-lowering or blood pressure-lowering treatment. According to our results, by adding non-linear FEV_1 into the 10-year CVD risk prediction models, 25, 43 and 5 more TP CVD events per 100 000 participants would be identified without increases in the number of false-positive cases compared with the original prediction models. From the false-positive reduction perspective, redundant interventions in participants who have no CVD risk within 10 years could be avoided. Although these improvements seem modest, a large number of high-risk people would be identified accurately, leading to intervention to prevent or delay CVD events, when multiplying these values by the huge population receiving CVD risk assessment. Moreover, avoidable interventions for non-CVD cases would be reduced to save healthcare budgets. To date, over 758 million people worldwide have had COVID-19,[34] and long-term respiratory complications might follow and require persistent respiratory follow-up.[10] Thus, it is of great importance to consider adding lung function measures into CVD risk scores to prevent an excess future CVD burden.[11] However, according to the DCA curves, the

net benefits of new prediction models that integrated with lung function measures might be modest and might not offset the cost of staff and devices. Thus, cost-effectiveness studies and clinical trials are still needed for confirmation of the performance of CVD risk assessments based on these models in clinical practice.

There are several potential mechanisms underlying these associations. Lung function impairment would increase levels of oxidative stress and systemic inflammation,[35 36] which would affect the vascular endothelium function and cause structural changes in the endothelium contributing to the formation and complication of atherosclerotic lesions.[37] Moreover, impaired lung function might indicate undiagnosed or preclinical COPD, which could induce higher levels of haematocrit and haemoglobin, and could predispose to CVD by elevation in the plasma viscosity.[38 39] According to a two-sample bidirectional Mendelian randomisation study, FEV_1 and FVC tend to be causal risk factors for CVD, and no strong evidence for reverse causation was discovered.[7] More mechanisms underlying the associations of spirometry parameters with CVD need to be studied.

Our study contributes to improving the discriminations of current CVD risk prediction models by adding lung function indicators and suggesting FEV_1 and FVC as better risk factors among all spirometry parameters. Several studies have discussed the improvement of current CVD risk prediction models. Welsh *et al*[40] suggested that although people with diagnosed or undiagnosed baseline diabetes had higher risks of CVD, the addition of circulating hemoglobin A1c in prediction models did not increase reclassification. Previous studies indicated that lipoprotein (a), grip strength, usual walking pace, and grip strength and walking pace combined could improve the identification of high-risk individuals of CVD.[41 42] Lung function measures could result in similar and even better discriminations for CVD risk prediction. Moreover, spirometry is a reproducible and objective measurement of lung function. The conduction of spirometry is non-invasive, readily available and easily performed in any healthcare setting, which could be an advantage for accurate CVD risk prediction.[43]

Strength and limitations

To the best of our knowledge, the present study is the largest study to assess the prediction value of lung function parameters on CVD outcomes adjusted for all conventional risk factors. This study used comprehensive and standard cohort data from the UK Biobank. The C-statistics of CVD risk models and the baseline characteristics of participants in our study were comparable with those in the original prediction models. Thus, our results were reliable. However, there are several limitations in the present study. Participants in the UK Biobank were healthier than the general population, which might cause healthy volunteer bias. Due to the L-shaped non-linear associations between spirometry parameters and CVD risk, better performance of additional prediction value is likely in the general population. Secular trends in lung function might be a more valuable indicator for CVD prediction,[44] but these data were not accessible in the UK Biobank. Our results should be generalised with caution since no external validation was performed. Further studies using other cohorts and other designs are needed.

CONCLUSION

This study suggests that lung function impairments (restrictive and obstructive) and lower spirometry parameters are associated with composite and fatal CVD outcomes after adjusting for all conventional risk factors. The associations of spirometry parameters with CVD outcomes (composite QRISK3 CVD, composite ACC/AHA CVD and fatal SCORE CVD) tended to be L-shaped. The association was strongest for fatal SCORE CVD. All spirometry parameters could improve discrimination of the prediction models, with the largest improvement seen with FEV_1. Models that integrate FEV_1 and FVC offered additional net benefits compared with the original models. Therefore, FEV_1 and FVC could serve as risk factors in the identification of high-risk individuals with composite and fatal CVD events and be a target for primary prevention and treatment.

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