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Forced vital capacity paired with Framingham Risk Score for prediction of all-cause mortality

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ABSTRACT: Forced vital capacity (FVC) measures lung function and predicts coronary heart disease (CHD); whether it provides additive prediction over CHD risk factors has not been established. We examined whether FVC adds to the prediction of all-cause mortality provided by Framingham Risk Score (FRS) alone.

We examined 5,485 (61.1 million projected) nonsmoking adults from the USA who were aged 20–79 yrs. Subjects were from the Third National Health and Nutrition Examination Survey, were without obstructive lung disease, had FVC measurements and had ⩽12 yrs (mean 8.8 yrs) mortality follow-up. We performed Cox regression analysis to examine whether FVC and forced expiratory volume in 1 s (FEV_1) (categorised as low ⩽85% predicted, borderline 86–94% predicted and normal ⩾95% predicted) within FRS groups (10-yr risk of cardiovascular disease low <10%, intermediate 10–20%, high 20%) predict mortality. Receiver operator characteristic analysis examined whether FVC and FEV_1 added to the prediction provided by FRS.

Low-, intermediate- and high-risk FRS groups had 79.5% (n=4,361), 10.1% (n=555) and 10.4% (n=569) persons, respectively. Only the intermediate FRS group showed a graded increase in mortality (10.7, 18.2 and 42.8% per 1,000 person-yrs from highest to lowest FVC categories, respectively); those with low FVC had an almost three-fold greater risk of mortality (hazard ratio 2.64; $p<0.01$) than those with normal FVC. FVC provided incremental additive value for predicting mortality in addition to FRS for only this group (area under curve 0.65 *versus* 0.58; $p<0.05$). Similar results were obtained for FEV_1.

Evaluation of lung function may be useful to improve risk stratification in persons with intermediate CHD risk where it adds to prediction of mortality over global risk assessment.

KEYWORDS: Cardiovascular disease, epidemiology, lung function, mortality

In spite of the current evidence-based approach to cardiovascular disease (CVD) reduction, coronary heart disease (CHD) remains the leading cause of mortality in the industrialised world. Preventive strategies utilise risk assessment to identify those most likely to benefit from medical interventions to reduce the risk of CVD events [1].

The Framingham Risk Score (FRS) is a global risk algorithm using multiple risk factors, such as age, sex, smoking history, systolic blood pressure, total cholesterol and high-density lipoprotein cholesterol to estimate 10-yr CHD event risk in individuals not previously diagnosed with heart disease. While the assessment of risk with FRS is widely used, it is not entirely reliable in its ability to differentiate individuals regarding CVD events [2]. It is of interest to know whether various novel risk markers (such as C-reactive protein) or screening tests (such as coronary calcium scanning) can further add to prediction of CVD events in addition to global risk.

Previous studies have shown reduced pulmonary function to be a significant predictor of CVD [3–6], including CVD mortality [7]. There is also abundant literature describing a significant relationship between lung function and all-cause mortality [7–14]. Most of these studies included smokers in their samples and used forced expiratory volume in 1 s (FEV_1) as a measure of lung function. Smoking status was shown to be causally related to mortality. However, the link between poor lung function and mortality has also been reported in never-smokers [13, 14]. There is a lack of information on whether, in certain subgroups of patients, measures of pulmonary function may help improve prediction of CVD or all-cause mortality. Accordingly,

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TABLE 1 Descriptive statistics according to Framingham Risk Score (FRS) and sex

Variable	Overall	Male	Female	FRS groups		
				<10%	10–20%	>20%, or CVD or DM
Subjects n	5485	2503	2982	4361	555	569
Age yrs	43.0±16.8	43.4±16.9	42.7±16.7	37.6	66.0	62.1
Total cholesterol mg·dL^{-1}	203.6±43.4	203.7±42.1	203.5±44.4	198.0	225.8	225.3
HDL-C mg·dL^{-1}	51.8±14.9	47.1±12.9**	55.7±15.3	53.1	47.7	45.5
Systolic BP mmHg	122.4±18.0	125.7±16.0**	119.7±19.1	117.9	138.8	141.3
FVC % pred	104.0±19.1	103.9±18.7	104.2±19.4	104.4	104.7	100.6
FEV$_1$ % pred	102.5±19.0	102.0±18.9	103.0±19.1	103.1	101.4	98.8
Anti-HTN medication %	9.5	9.0	9.9	5.2**	27.7**	39.7**

Data are presented as mean±SD, unless otherwise stated. CVD: cardiovascular disease; DM: diabetes mellitus; HDL-C: high-density lipoprotein cholesterol; BP: blood pressure; FVC: forced vital capacity; % pred: % predicted; FEV$_1$: forced expiratory volume in 1 s; HTN: hypertension. **: $p<0.01$ indicates significant difference when compared across sex or ethnicity.

the objective of this study was to determine whether reduced pulmonary function, measured as forced vital capacity (FVC), can improve prediction of mortality over global risk assessment, and whether this may be limited to certain risk groups.

METHODS

We examined adults from the Third National Health and Nutrition Examination Survery, 1988–1994 (NHANES III) [15], who were from the USA and were aged 20–79 yrs (n=5,485, 61.1 million projected; 53% female). Subjects were never-smokers, had not been diagnosed with obstructive lung disease, had FVC measurements taken at baseline, and had follow-up for mortality to the year 2000 (see later). Never-smokers were based on self-report and cotinine levels >25 ng·mL^{-1} [16]. CVD was defined by self-report for stroke, congestive heart failure and myocardial infarction.

The FRS was derived from the National Cholesterol Education Program Adult Treatement Panel III algorithm [17]. FRS groups were defined by risk percentages (low <10%, intermediate 10–20%, high >20%). Subjects with pre-existing diabetes mellitus (DM) or CVD at baseline were assigned to the high-risk group.

Spirometric data were obtained following the 1979 and modified 1987 National Institute for Occupational Safety and Health (NIOSH) [18] and the American Thoracic Society (ATS) procedures. Predicted FVC and FEV$_1$ were calculated using equations developed by HANKINSON *et al.* [19]. Additional details of the NHANES methodology have been published.

Additionally, we used the NHANES III linked-mortality file which contains information on a mortality linkage conducted by the National Center for Health Statistics (NCHS). We linked NHANES III data to death certificate data found in the National Death Index (NDI). Follow-up data was from the time of NHANES III survey participation through December 31, 2000. Additional information on the probabilistic matching technique employed by NCHS can be found in the NHANES III [20].

Analysis of publically available nonidentifiable data, including the current study, does not fulfill the criteria for review by the Institutional Review Board of the University of California (Irvine, CA, USA) and is thus exempt from review.

Statistical analysis

The Chi-squared test of proportions and ANOVA were used to compare proportions and means, respectively, of risk factors across sex and ethnicity. Additionally, Cox proportional hazards regression was used to calculate hazard ratios (HR) for all-cause mortality in relation to FVC categories and according to age (using age groups of 20–34, 35–49, 50–65, 65–79 yrs) and sex-specific Z-scores for FVC. There was an insufficient number of deaths, however, to examine CHD and CVD mortality separately using FRS and FVC measurements. SAS version 9.1.3 (SAS Institute, Cary, NC, USA) and SUDAAN version 9.0.1 (Research Triangle Institute, Research Triangle Park, NC, USA) were used for statistical analysis as well as to obtain computations of weighted estimates for projection to the USA population. Area under the curve (AUC) was used to quantify whether combined FVC (using the Z-score transformed FVC) and FRS improved prediction of all-cause mortality in additon to that provided by FRS alone. AUC and the receiver operator characteristic (ROC) curves were computed by STATA version 10.0 (Stata Corporation, College Station, TX, USA).

RESULTS

The low, intermediate and high FRS groups comprised of 79.5% (n=4,361), 10.1% (n=555) and 10.4% (n=569) persons, respectively. Males had an approximately four percent greater 10-year risk of CHD estimated by FRS when compared to females ($p<0.01$). Caucasians had the highest 10-year risk of CHD at 5.5% compared to African-Americans at 3.1% and Mexican-Americans at 3.5% ($p<0.01$). There were no significant differences in the predicted FVC across sex. African-Americans had lowest predicted FVC when compared across ethnicity; Mexican-Americans had the highest ($p<0.01$). Table 1 shows mean values of Framingham risk factors, FVC and FEV$_1$ by sex across FRS groups (low, intermediate and high).

Figure 1 shows the proportions of persons within each FVC group according to FRS category. While in all FRS groups,

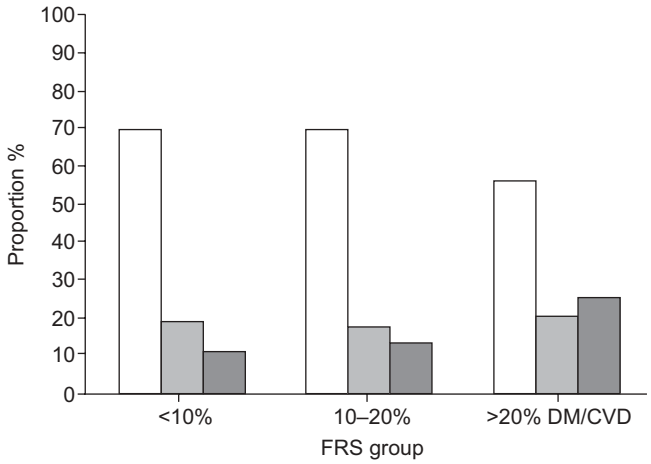

FIGURE 1. Proportions of individuals within Framingham Risk Score (FRS) groups (low <10%; intermediate 10–20%; and high >20%, or diabetes mellitus (DM) or cardiovascular disease (CVD)) according to forced vital capacity (FVC) categories (high ⩾95% (□), intermediate 86–94% (■) and low ⩽85% (■)). p<0.001 across FRS and FVC groups.

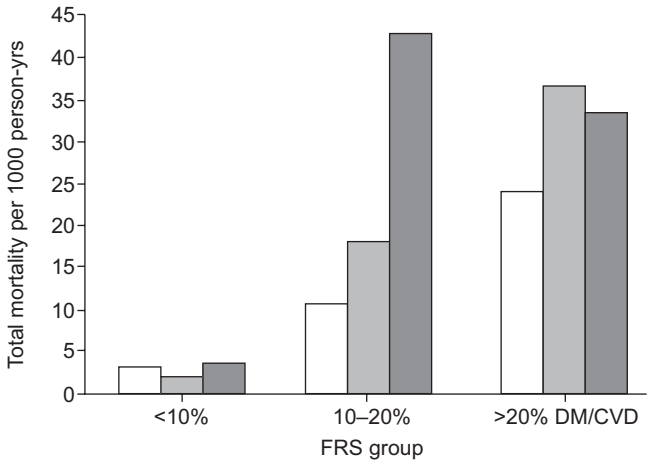

FIGURE 2. Total mortality per 1,000 person-yrs across Framingham Risk Score (FRS) groups (low <10%; intermediate 10–20%; and high >20%, or diabetes mellitus (DM) or cardiovascular disease (CVD)) stratified by forced vital capacity categories (high ⩾95% (□), intermediate 86–94% (■) and low ⩽85% (■)).

⩾60% of subjects had normal FVC, the proportion of subjects with low FVC was more than double in the high FRS risk group (24.5%) compared with the low FRS risk group (10.3%) (p<0.001 for FVC distribution across FRS categories).

Figure 2 shows the mortality rates (deaths per 1,000 person-yrs) across FRS groups stratified by FVC categories. The intermediate FRS group was the only group to show a progressive increase of mortality per 1,000 person-yrs (10.7, 18.2 and 42.8% from highest to lowest FVC categories, respectively). There was a lesser trend in the high-risk group and no evidence of a trend in the low FRS group. Analyses with FEV1 showed a similar stepwise increase in mortality in intermediate group and in the high risk group (data not shown).

Age-, sex- and ethnicity-adjusted Cox proportional hazards regression analyses examining mortality risk by FVC and FEV1 categories, stratified by FRS groups, showed a pattern of increase in HR for all-cause mortality within most FRS groups as FVC decreased. For those in the intermediate FRS group, subjects with FVC ⩽85% predicted had the highest HR for all-cause mortality at 2.64 (p<0.01 when compared to reference); those with high FRS and FVC ⩽85% predicted had an HR of 2.21 (p<0.05 when compared to reference) (table 2). FEV1 relationships with mortality were actually weaker, with only

TABLE 2 Hazard ratios (HRs) for all-cause mortality according to forced vital capacity (FVC) within Framingham Risk Score (FRS) groups adjusted for age, sex and ethnicity

FRS groups	Subjects n	FVC category % pred	HR (95% CI)	Mortality per 1000 person-yrs
Overall	5485	⩾95	1.00 (reference)	6.1 (200/3680)
		⩾86–94	1.55 (1.01–2.38)*	7.0 (54/883)
		⩽85	2.41 (1.63–3.58)***	10.6 (83/922)
		z-score	1.07 (1.02–1.12)**	
<10%	4361	⩾95	1.00 (reference)	3.1 (83/2947)
		86–94	1.30 (0.59–2.85)	2.2 (14/705)
		⩽85	1.72 (0.83–3.54)	3.6 (22/699)
		z-score	1.06 (1.01–1.12)*	
10–20%	555	⩾95	1.00 (reference)	10.7 (49/390)
		86–94	1.79 (0.73–3.94)	18.2 (13/84)
		⩽85	2.64 (1.28–5.43)**	42.8 (24/81)
		z-score	1.07(0.95–1.19)	
>20%, or DM or CVD	569	⩾95	1.00 (reference)	24.1 (68/333)
		86–94	1.48 (0.78–2.83)	36.7 (27/94)
		⩽85	2.21 (1.14–4.30)*	33.5 (37/142)
		z-score	1.17 (1.00–1.37)*	

Data are presented as % (n/N), unless otherwise stated. % pred: % predicted; DM: diabetes mellitus; CVD: cardiovascular disease. *: p<0.05 when compared to reference; **: p<0.01 when compared to reference; ***: p<0.001 when compared to reference.

TABLE 3 Analysis of receiver operator characteristic (ROC) curve for specific z-score for forced vital capacity (zFVC) within each Framingham Risk Score (FRS) group and overall

Model 1	AUC (95% CI)	Model 2	AUC (95% CI)	Model 1 *versus* model 2 p-value
Overall FRS	0.80 (0.77–0.82)	**Overall FRS and zFVC**	0.79 (0.76–0.82)	0.96
FRS <10%	0.66 (0.61–0.70)	**FRS <10% and zFVC**	0.67 (0.62–0.73)	0.27
FRS 10–20%	0.58 (0.51–0.64)	**FRS 10–20% and zFVC**	0.65 (0.59–0.71)	0.04
FRS >20%, or DM or CVD	0.69 (0.64–0.73)	**FRS >20%, or DM or CVD and zFVC**	0.70 (0.65–0.75)	0.31

AUC: area under ROC curve; DM: diabetes mellitus; CVD: cardiovascular disease.

those with FEV1 $\leqslant$85 noted as significant (HR 2.26; $p<0.01$) in the intermediate FRS group (data not shown).

ROC analysis showed that the addition of FVC with FRS only offered significant incremental prediction of mortality in the intermediate risk FRS group (AUC 0.64 *versus* 0.56; $p<0.05$). However, overall, the addition of FVC over FRS and the addition of FVC group over low or high FRS did not further increase prediction of mortality (table 3). Similar results were obtained for FEV1 (not shown).

DISCUSSION

Our results show the potential importance of pulmonary function assessment in risk stratification for mortality, particularly for those in the intermediate FRS group. Individuals in this risk group are often quite heterogenous and have treatment guidelines that are not always clear. Hence, there have been recommendations for the use of subclinical disease screening measures in intermediate-risk individuals, such as with coronary calcium scanning to be incorporated into risk stratification algorithms to refine the intensity of clinical management for key risk factors [21, 22]. Our study provides similar evidence that pulmonary function measures may be used to improve risk stratification in intermediate-risk individuals.

In our study, subjects with reduced lung function demonstrated a greater risk for all-cause mortality than those with normal pulmonary function, consistent with previous reports in which reduced FEV1 was related to a higher risk for mortality in mixed smoking and nonsmoking populations [7–14]. However, in this report, we have shown that FVC only adds to the prediction of mortality in the intermediate-FRS group. Cox regression analyses also show low *versus* high FVC to have the highest mortality risk (HR 2.64; $p<0.01$) in the intermediate-FRS group. Results were also consistent when examining FEV1 due to its high collinearity with FVC. This demonstrates FVC to be most effective in stratifying risk in persons with intermediate global risk of CHD. It is possible that FVC and FEV1 did not further add to mortality risk in high-FRS subjects because of the multiple comorbidities common to this group. Moreover, in low-FRS subjects, the fairly low mortality rates overall in this group may have made it more difficult to show an added impact of FVC or FEV1 to prediction of mortality in addition to risk factors.

Because of the higher risk we have identified, those with low FVC in the intermediate risk group, may be potential candidates for stratification into the next-highest risk category, in a manner that has been suggested for other measures of subclinical disease. For example, 12.6% of individuals in the intermediate group are possibly at a higher risk for mortality but lack the awareness of their risk when determined only by traditional (*e.g.* FRS) algorithms and could thus be considered for more aggressive clinical management, such as those at higher risk (*e.g.* CHD risk equivalents). These individuals had a mortality risk as high as or higher than many persons classified as high CHD-risk by FRS, or with previous diabetes or CVD.

In contrast to the recent study by SIN *et al.* [7], who reported that reduced FEV1 is a predictor of CVD mortality, our study only examined how reduced lung function may add to the prediction of mortality. Although the causal relationship is not clear, inflammation was considered as a possible causative factor. Recent reports showing the relation between the inflammatory markers of either fibrinogen or CRP to reduced lung function in prospective studies makes inflammation an intriguing mechanism [23–27].

Important strengths of our study design include the large sample of nonsmoking adults from the USA, aged 18–79 yrs, generalisable to the US population from the sample weighting available in NHANES. The well-standardised measurement of pulmonary function and FRS were also important strengths of our analysis. However, our study only examined all-cause mortality, as there was an insufficient number of CHD or CVD mortality events. Morbidity event data were not available either.

In conclusion, pulmonary function measures provide additive prediction for all-cause mortality when combined with traditional risk assessment using FRS, particularly in individuals at intermediate risk. The clinical implications of this finding can help assess risk more completely in individuals who are at intermediate risk are determined by the FRS algorithm.

STATEMENT OF INTEREST

None declared.

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