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Peak flow as a predictor of cause-specific mortality in China: results from a 15-year prospective study of ~170 000 men

Margaret Smith,[1]* Maigeng Zhou,[2] Lijun Wang,[2] Richard Peto,[1] Gonghuan Yang[3] and Zhengming Chen[1]

[1]Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), Nuffield Department of Clinical Medicine, University of Oxford, UK, [2]National Center for Chronic and Non-communicable Disease Control and Prevention, Chinese Center for Disease Control and Prevention, Beijing, People's Republic of China and [3]Chinese Center for Disease Control and Prevention, Beijing, People's Republic of China

*Corresponding author. Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), Richard Doll Building, University of Oxford, Old Road campus, Roosevelt Drive, Oxford, OX3 7LF, UK. E-mail: margaret.smith@ctsu.ox.ac.uk

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Background Forced expiratory volume in one second (FEV_1) is inversely associated with mortality in Western populations, but few studies have assessed the associations of peak expiratory flow (PEF) with subsequent cause-specific mortality, or have used populations in developing countries, including China, for such assessments.

Methods A prospective cohort study followed ~170 000 Chinese men ranging in age from 40–69 years at baseline (1990–1991) for 15 years. In the study, height-adjusted PEF (h-PEF), which was uncorrelated with height, was calculated by dividing PEF by height. Hazard ratios (HR) for cause-specific mortality and h-PEF, adjusted for age, area of residence, smoking, and education, were calculated through Cox regression analyses.

Results Of the original study population, 7068 men died from respiratory causes (non-neoplastic) and 22 490 died from other causes (including 1591 from lung cancer, 5469 from other cancers, and 10 460 from cardiovascular disease) before reaching the age of 85 years. Respiratory mortality was strongly and inversely associated with h-PEF. For h-PEF $\geqslant$ 250 L/min, the association was log-linear, with a hazard ratio (HR) of 1.29 (95% CI: 1.25–1.34) per 100 L/min reduction in h-PEF. The association was stronger but not log-linear for lower values of h-PEF. Mortality from combined other causes was also inversely associated with h-PEF, and the association was log-linear for all values of h-PEF, declining with follow-up, with HRs per 100 L/min reduction in h-PEF of 1.13 (1.10–1.15), 1.08 (1.06–1.11), and 1.06 (1.03–1.08) in three consecutive 5-year follow-up periods. Specifically, lower values of h-PEF were associated with higher mortality from cardiovascular disease and lung cancer, but not from other cancers.

Conclusions A lower value of h-PEF was associated with increased mortality from respiratory and other causes, including lung cancer and

cardiovascular disease, but its associations with the other causes of death declined across the follow-up period.

Keywords Peak expiratory flow rate, prospective studies, mortality, respiratory-tract disease, cardiovascular disease, lung cancer, COPD, China

Background

Many prospective observational studies have found a strong inverse association between indices of baseline lung function, based on forced expiratory volume in one second (FEV_1), and subsequent all-cause mortality,[1–5] even >20 years after the initial measurement of FEV_1.[2–5] Similar studies of cause-specific mortality have shown that impaired lung function does not only predict mortality from non-neoplastic respiratory disease, but also mortality from a range of other specific conditions including lung cancer,[1,6–8] coronary heart disease (CHD),[1–3,9,10] and stroke.[1,2,9,11,12] Although the mechanisms underlying some of these associations are not fully understood, lung function may still be a useful screening tool for assessing individual general health.[1,13,14]

Relatively few studies have investigated associations of peak expiratory flow (PEF) with long-term cause-specific mortality.[13,15–18] However, PEF can be measured rapidly with an inexpensive and easily used hand-held device, possibly making it particularly useful as an indicator of health status in populations with limited access to healthcare. Measurements of the PEF and FEV_1 of the same individual are highly correlated with one another, but the intra-subject variability of PEF is somewhat greater than that of FEV_1. However, PEF tends not to properly reflect airway obstruction, and a low value of PEF may also indicate restrictive lung disease or tuberculosis.[19–21] Consequently, PEF may have slightly different associations with subsequent cause-specific mortality than may FEV_1[16] and prospective studies of PEF and subsequent outcomes are therefore needed to fully establish its value for screening and disease detection.

Furthermore, almost all prospective studies of lung function and subsequent mortality have been conducted on Western populations. We know of only one such published study on the population of a developing country,[22] and none in China, where the general patterns of mortality differ from those in Western populations. Moreover, chronic obstructive pulmonary disease (COPD) is often under-diagnosed in China, particularly in rural areas,[23,24] and although smoking is the main risk factor for this disease, other risk factors contribute significantly to its prevalence.[23-25] We therefore conducted a detailed analysis of the associations of PEF with cause-specific mortality over 15 years of follow-up in ~170 000 Chinese men who took part in a nationally representative prospective study.

Methods

Baseline survey

The design of the study has been described in detail elsewhere.[26] Forty-five areas (23 urban and 22 rural) were chosen at random from China's 145 Disease Surveillance Points (DSPs), which were originally established to provide nationally representative mortality statistics. During 1990–1991, 225 721 men aged ⩾40 years were recruited from two or three geographically defined units in each of the 45 selected areas (each unit consisting of a group of rural villages or a set of streets covered by a street committee).

Various physical measurements of each participant were made by trained health workers. These measurements included PEF [as the maximum of three readings made with a mini-Wright peak flow meter (range 60–800 L/min)], height, weight, and systolic blood pressure (SBP) (as the mean of two readings). A standardized questionnaire was used to collect detailed information related to socio-economic status (e.g. level of education); lifestyle factors (e.g. smoking); and a medical history, including physician-made diagnoses of specific chronic diseases (tuberculosis, coronary heart disease (CHD), stroke, peptic ulcer, kidney disease, cirrhosis, chronic hepatitis, cancer, emphysema, chronic bronchitis, asthma, and pulmonary heart disease) prior to the study baseline; and self-reported respiratory symptoms (frequent coughing or coughing up of mucus in the morning, shortness of breath when walking with other people of similar age at normal speed). Participants reporting a physician's diagnosis of one or more of chronic bronchitis, emphysema, pulmonary heart disease or asthma were defined as having COPD at the study baseline. Asthma was considered jointly with COPD because of the difficulties in its accurate diagnosis, and pulmonary heart disease is a common outcome of COPD in China.[27]

Follow-up

The vital status of each participant was followed by local DSP staff members through the death registries in each study area, together with annual active confirmation by local residential committees. The underlying cause of each death was sought from official death certificates, supplemented with information from medical records, and was coded according to the Ninth Revision of the WHO International Classification of Disease (ICD-9). The codes used were categorized as respiratory (including pulmonary

heart disease, but excluding cancers) (010–018, 137, 415–417, 460–519), and combined non-respiratory causes, with the latter group further subdivided into neoplastic (including cancers of the respiratory tract) (140–208), cardiovascular (390–414, 420–459, 798) and other causes (Supplementary Table S1, available as Supplementary data at *IJE* online). No attempt was made to further subdivide respiratory deaths because COPD is often poorly diagnosed in China,[23,24] although most respiratory deaths recorded in the present study (87%) were attributed to COPD.

Statistical analysis

The data analysis in the study was confined to 200 533 men aged 40–69 years at baseline who resided in 44 of the original 45 study areas (no follow-up data were received after 2001 from one area), who were followed to either 1 January 2006 or their 85th birthday (whichever came first), so that all surviving participants potentially contributed to ~15 years of follow-up. Men with missing PEF data or a recorded PEF outside the meter range (178 men), or missing values for other variables used in the study (a further 125 men), were also excluded from all analyses. Of the remaining participants a further 28 295 had a history of chronic disease other than COPD (i.e. tuberculosis, CHD, stroke, peptic ulcer, kidney disease, cirrhosis, chronic hepatitis or cancer), and were included only in a supplementary analysis, leaving 171 935 men who were included in the main study.

Peak expiratory flow was standardized to be uncorrelated with height by dividing it by height,[28] with the result then corrected to the mean population height by multiplying it by 1.65 m. The lack of correlation of PEF with height was checked empirically after this standardisation. This height-standardised PEF (h-PEF) was divided into 8 categories (with cut points of 200, 250, 300, 350, 400, 450, and 500 L/min) or 4 categories (with cut points of 250, 350 and 450 L/min), depending on the number of deaths in each category in a particular analysis.

Cox proportional hazard models, with time in follow-up as the time scale, and stratified by area, were then used to examine the associations of categorical baseline h-PEF with respiratory or non-respiratory mortality. The highest h-PEF category was used as the reference category in all data analyses. The 95% confidence interval (CI) for the hazard ratio (HR) of each categorical h-PEF group was estimated through the 'floating absolute risk' method, which allows comparisons of any pair of groups rather than with an arbitrarily chosen reference group alone.[29,30]

Initial analyses, with respiratory or combined non-respiratory mortality as end points, were done separately according to 5-year follow-up period, to assess the predictive ability of h-PEF over follow-up time, and were also done for each 10-year category of baseline age to assess whether associations were similar within each age category. Further Cox regression models, adjusted for baseline age (5-year categories) and area (strata), were used to investigate the effects of further adjustment for never/ever smoking, <6 years of education/ ⩾6years education, or body-mass index (BMI), defined as weight (kg) divided by the square of height (m^2). Individuals with physician-diagnosed COPD or shortness of breath were excluded from some analyses, to investigate the effect of baseline respiratory disease on the HR.

We also estimated the associations of specific causes of mortality with categorical h-PEF and continuous h-PEF. Confounding by smoking and education was assessed by comparing the hazard ratios (HRs) in models restricted to specific levels of these two variables. All statistical analyses were done with SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

The overall mean baseline age of the 171 935 men included in the study was 52.1 years; the mean (SD) h-PEF of this study population was 405 (103) L/min, 12.0% reported a history of COPD, 10.0% reported a history of shortness of breath, and a further 14.7% had other respiratory symptoms without shortness of breath (Table 1). Mean h-PEF declined consistently with age at baseline and, within each 10-year age group at baseline, a lower h-PEF was strongly associated with less education, living in a rural area, underweight, shortness of breath, and a previous diagnosis of COPD. Conversely, a higher h-PEF was associated with overweight. Lower h-PEF was only associated with smoking prevalence in the two uppermost groups for age. There was little or no trend in the prevalence of hypertension or cough in relation to h-PEF (Table 1).

After a maximum 14.5 years of follow-up (mean 12.0 years), 24 500 men were lost to follow-up (mean age 51.7 years, mean (SD) h-PEF 423(109) L/min) and 30 181 had died before their 85th birthday. Of these deaths, 7068 (23%) were from respiratory and 22 490 (75%) were from non-respiratory causes. A further 623 deaths (2%) involved ill-defined or unknown causes (these were not considered in further analyses). Within each 10-year baseline age group, the crude death rates from both respiratory and non-respiratory causes were strongly inversely associated with h-PEF (Supplementary Table S2, available as Supplementary data at *IJE* online). These inverse associations were also found within all combinations of 5-year follow-up period and 10-year baseline age group (Figure 1).

There was no statistical evidence of an interaction of baseline age with non-respiratory mortality over the entire range of values of h-PEF, nor for an interaction with respiratory mortality for values of h-PEF ⩾ 250 L/min. However, the association of h-PEF with mortality varied with the follow-up period

Table 1 Characteristics of the population at baseline by category of height-adjusted peak flow and age at baseline

Age (years)	Category of h-PEF (L/min)	*n*	%	Mean (SD) h-PEF (L/min)	Ever smoker (%)	Education <6 years (%)	Rural resident (%)	BMI < 18.5 kg/m² (%)	BMI ⩾ 25 kg/m² (%)	SBP ⩾ 140 mmHg (%)	COPD[a] (%)	Shortness of breath[b] (%)	Cough[c] (%)
40–69	Overall	171 935	100	405 (103)	73.8	67.4	76.8	7.5	10.8	14.9	12.0	10.0	14.7
40–49	Overall	74 328	43.2	437 (94)	73.7	58.8	78.1	4.9	10.3	7.2	7.7	5.8	13.8
	<250	2477	1.4	208	71.9	66.0	76.5	9.4	7.6	9.5	20.1	15.5	13.7
	250–349	9720	5.7	309	73.7	67.7	83.9	7.3	7.9	8.2	11.5	9.0	13.3
	350–449	27 335	15.9	404	73.9	64.1	84.1	5.2	7.6	7.0	7.3	5.6	13.4
	⩾450	34 796	20.2	515	73.7	51.7	71.8	3.6	13.2	6.9	6.0	4.4	14.4
	P trend[d]				0.5	<0.0001	<0.0001	<0.0001	<0.0001	0.001	<0.0001	<0.0001	<0.0001
50–59	Overall	58 504	34.0	400 (99)	74.1	69.6	75.7	7.6	11.7	16.2	13.1	10.5	15.3
	<250	4272	2.5	200	78.3	79.2	78.8	16.2	7.8	17.7	33.6	27.6	15.6
	250–349	12 614	7.3	307	75.7	78.2	83.7	9.7	7.7	16.3	16.3	13.6	15.5
	350–449	23 134	13.5	400	75.1	73.1	80.4	7.2	10.2	15.4	11.0	8.8	15.2
	⩾450	18 484	10.8	508	70.9	57.0	63.7	4.7	17.1	16.6	8.9	6.7	15.3
	P trend[d]				<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	1.0	<0.0001	<0.0001	0.7
60–69	Overall	39 103	22.7	352 (103)	73.4	80.6	76.0	12.2	10.6	27.4	18.7	17.0	15.6
	<250	6592	3.8	195	77.2	85.9	77.9	20.7	7.5	29.3	37.0	34.3	15.5
	250–349	11 983	7.0	301	74.2	85.1	83.2	13.7	7.7	27.0	19.0	18.0	15.7
	350–449	13 603	7.9	397	73.4	80.0	76.2	9.7	11.2	26.8	13.9	12.1	15.8
	⩾450	6925	4.0	500	68.2	68.8	61.1	6.2	17.5	27.5	10.3	8.2	14.9
	P trend[d]				<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.04	<0.0001	<0.0001	0.4

BMI, body-mass index; COPD, chronic obstructive pulmonary disease; h-PEF, height-adjusted peak expiratory flow; SBP, systolic blood pressure; SD, standard deviation.
[a]Physician-made diagnosis of chronic bronchitis, emphysema, pulmonary heart disease, or asthma before baseline measurement.
[b]When walking with other people of own age at normal speed.
[c]Coughing frequently or coughing up of mucus from chest upon arising in the morning, but without reporting shortness of breath.
[d]*P* trend, calculated as *P*-value of the Wald χ^2 for the variable in a logistic regression on h-PEF as a continuous variable.

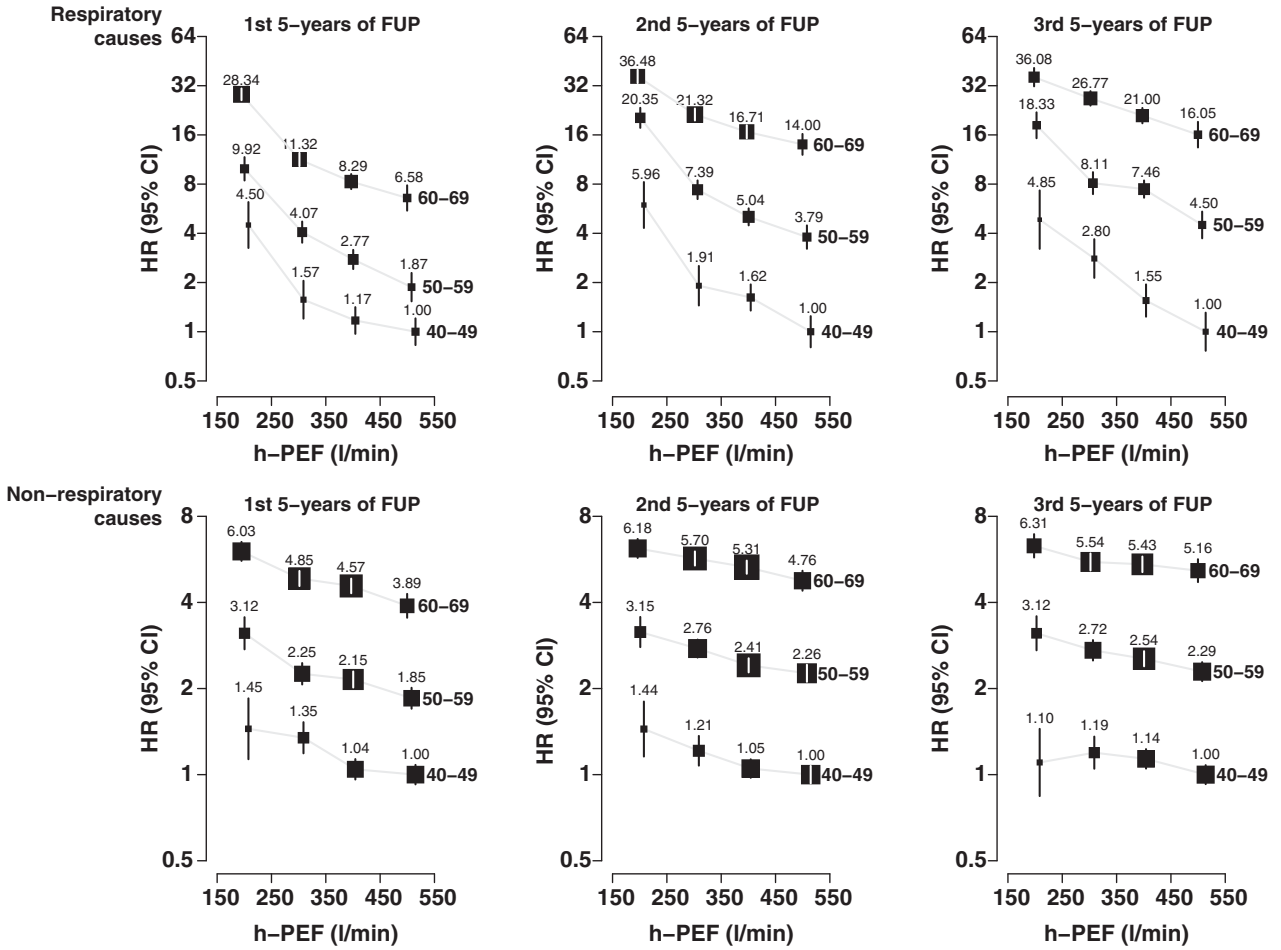

Figure 1 All-cause mortality by category of height-adjusted peak flow (h-PEF) (L/min), 10-year baseline age group and follow-up period (FUP). Baseline age groups used were 40–49, 50–59, and 60–69 years. Hazard ratios (HR) are adjusted for area. Area of square is inversely proportional to floated variance of log HR. Error bars indicate 95% confidence interval (CI). Numbers above error bars are HRs

(Figure 1). In further analyses that were also adjusted for baseline age, additional adjustment for smoking and education slightly attenuated all associations (Table 2). Further adjustment for BMI resulted in little change in associations of h-PEF with mortality from combined non-respiratory causes (Table 2), but did slightly attenuate the associations of h-PEF with respiratory mortality. However, because weight-loss can be a result of COPD, BMI was not routinely included in further models. Consequently, all further analyses were adjusted for smoking and years of education as well as baseline age (in 5-year categories) and area of residence (strata), but were done separately according to follow-up period.

In the first 5-years of follow-up, the exclusion of individuals with COPD or shortness of breath at baseline considerably reduced the HR for respiratory disease in the category of h-PEF $\leqslant$250 L/min, from 4.20 to 1.97 (Table 2). The HRs in other categories of h-PEF and at later follow-up intervals, beyond 5 years, were reduced to a lesser extent. After similar exclusions for COPD or shortness of breath, the HRs for combined non-respiratory mortality were also slightly reduced in the lowest category of h-PEF and in the first 5-years of follow-up, but there was almost no effect in higher categories of h-PEF.

The HRs for respiratory mortality in the category of h-PEF<250 L/min were much higher in the first and second 5-year follow-up periods than would be expected from a log-linear association ($P < 0.0001$) (Figure 2). However, for h-PEF $\geqslant$ 250 L/min, the association was approximately log-linear and was consistent over 15 years of follow-up (Figure 3). A decrease in h-PEF of 100 L/min was associated with a 29% (95% CI: 25%–34%) greater rate of respiratory mortality. The exclusion of individuals with COPD or shortness of breath at baseline attenuated this association, yielding an excess mortality of 19% (14%–24%) per 100 L/min h-PEF.

Associations of h-PEF with mortality from combined non-respiratory causes were approximately log-linear throughout the observed range of values of h-PEF

Table 2 Hazard ratios with 95% confidence intervals for all respiratory and all non-respiratory mortality by category of height-adjusted peak flow at baseline and by 5-year follow-up period

		h-PEF ⩽250 L/min		h-PEF 250–349 L/min		h-PEF 350–449 L/min		h-PEF ⩾450 L/min		*P* for
Model and cause of death	**FUP**	Deaths *N*	HR (95% CI)	Deaths *N*	HR (95% CI)	Deaths *N*	HR (95% CI)	Deaths *N*	HR (95% CI)	trend[a]
Adjusted for baseline age and area										
Respiratory	1	746	4.20 (3.89–4.54)	669	1.73 (1.61–1.87)	668	1.27 (1.18–1.37)	332	1.00 (0.89–1.12)	<0.0001
	2	670	3.25 (3.00–3.52)	812	1.68 (1.57–1.80)	847	1.30 (1.21–1.39)	405	1.00 (0.90–1.11)	<0.0001
	3	376	2.75 (2.47–3.05)	590	1.79 (1.65–1.94)	668	1.47 (1.36–1.58)	285	1.00 (0.89–1.13)	<0.0001
Non-respiratory	1	955	1.47 (1.37–1.57)	1800	1.19 (1.14–1.25)	2583	1.11 (1.07–1.15)	1633	1.00 (0.95–1.05)	<0.0001
	2	1016	1.26 (1.18–1.35)	2252	1.16 (1.11–1.21)	3240	1.06 (1.03–1.10)	2190	1.00 (0.96–1.05)	<0.0001
	3	717	1.21 (1.12–1.31)	1644	1.10 (1.05–1.16)	2645	1.08 (1.04–1.12)	1815	1.00 (0.95–1.05)	<0.0001
Adjusted for baseline age, area, smoking and education										
Respiratory	1	746	4.10 (3.80–4.43)	669	1.70 (1.57–1.83)	668	1.25 (1.16–1.35)	332	1.00 (0.89–1.12)	<0.0001
	2	670	3.16 (2.92–3.42)	812	1.64 (1.53–1.76)	847	1.27 (1.19–1.36)	405	1.00 (0.90–1.11)	<0.0001
	3	376	2.69 (2.42–2.99)	590	1.76 (1.62–1.91)	668	1.44 (1.34–1.56)	285	1.00 (0.89–1.13)	<0.0001
Non-respiratory	1	955	1.44 (1.34–1.53)	1800	1.17 (1.12–1.23)	2583	1.10 (1.06–1.14)	1633	1.00 (0.95–1.05)	<0.0001
	2	1016	1.23 (1.15–1.31)	2252	1.14 (1.09–1.19)	3240	1.05 (1.01–1.08)	2190	1.00 (0.96–1.05)	<0.0001
	3	717	1.19 (1.10–1.28)	1644	1.08 (1.03–1.14)	2645	1.06 (1.03–1.11)	1815	1.00 (0.95–1.05)	0.0005
Adjusted for baseline age, area, smoking, education and BMI[b]										
Respiratory	1	746	3.60 (3.33–3.90)	669	1.58 (1.47–1.71)	668	1.21 (1.12–1.31)	332	1.00 (0.89–1.12)	<0.0001
	2	670	2.88 (2.66–3.12)	812	1.56 (1.45–1.67)	847	1.23 (1.15–1.32)	405	1.00 (0.90–1.11)	<0.0001
	3	376	2.56 (2.30–2.85)	590	1.70 (1.57–1.84)	668	1.42 (1.31–1.53)	285	1.00 (0.89–1.13)	<0.0001
Non-respiratory	1	955	1.41 (1.31–1.50)	1800	1.16 (1.11–1.22)	2583	1.09 (1.05–1.13)	1633	1.00 (0.95–1.05)	<0.0001
	2	1016	1.23 (1.15–1.31)	2252	1.14 (1.09–1.19)	3240	1.05 (1.01–1.08)	2190	1.00 (0.96–1.05)	<0.0001
	3	717	1.20 (1.11–1.30)	1644	1.10 (1.04–1.15)	2645	1.07 (1.03–1.11)	1815	1.00 (0.95–1.05)	0.0001
Adjusted for basleline age, area, smoking and education, and excluding those who reported COPD[c] or shortness of breath[d]										
Respiratory	1	190	1.97 (1.70–2.28)	377	1.35 (1.21–1.49)	494	1.22 (1.12–1.33)	261	1.00 (0.88–1.14)	<0.0001
	2	219	1.67 (1.45–1.91)	504	1.31 (1.20–1.43)	648	1.19 (1.10–1.28)	338	1.00 (0.89–1.12)	<0.0001
	3	170	1.97 (1.68–2.30)	394	1.61 (1.45–1.78)	510	1.40 (1.29–1.53)	236	1.00 (0.87–1.14)	<0.0001
Non-respiratory	1	495	1.34 (1.22–1.47)	1298	1.14 (1.08–1.21)	2101	1.09 (1.04–1.13)	1414	1.00 (0.94–1.06)	<0.0001
	2	578	1.18 (1.09–1.29)	1710	1.14 (1.09–1.20)	2712	1.05 (1.01–1.09)	1915	1.00 (0.95–1.05)	<0.0001
	3	446	1.16 (1.0–1.28)	1296	1.10 (1.04–1.17)	2282	1.08 (1.04–1.13)	1610	1.00 (0.95–1.05)	0.003

BMI, body-mass index; FUP, follow-up period; h-PEF, height-adjusted peak expiratory flow; HR, hazard ratio.
[a]*P* for trend is the *P* value for the Wald χ^2 of categorical PEF modelled as a continuous variable with values 1,2,3,4.
[b]Categories of BMI: <18.5, 18.5–19.9, 20.0–22.4, 22.5–25.0, ⩾25.0 kg/m^2.
[c]Physician-made diagnosis of chronic bronchitis, emphysema, pulmonary heart disease or asthma prior to baseline.
[d]When walking with other people of own age at normal speed.

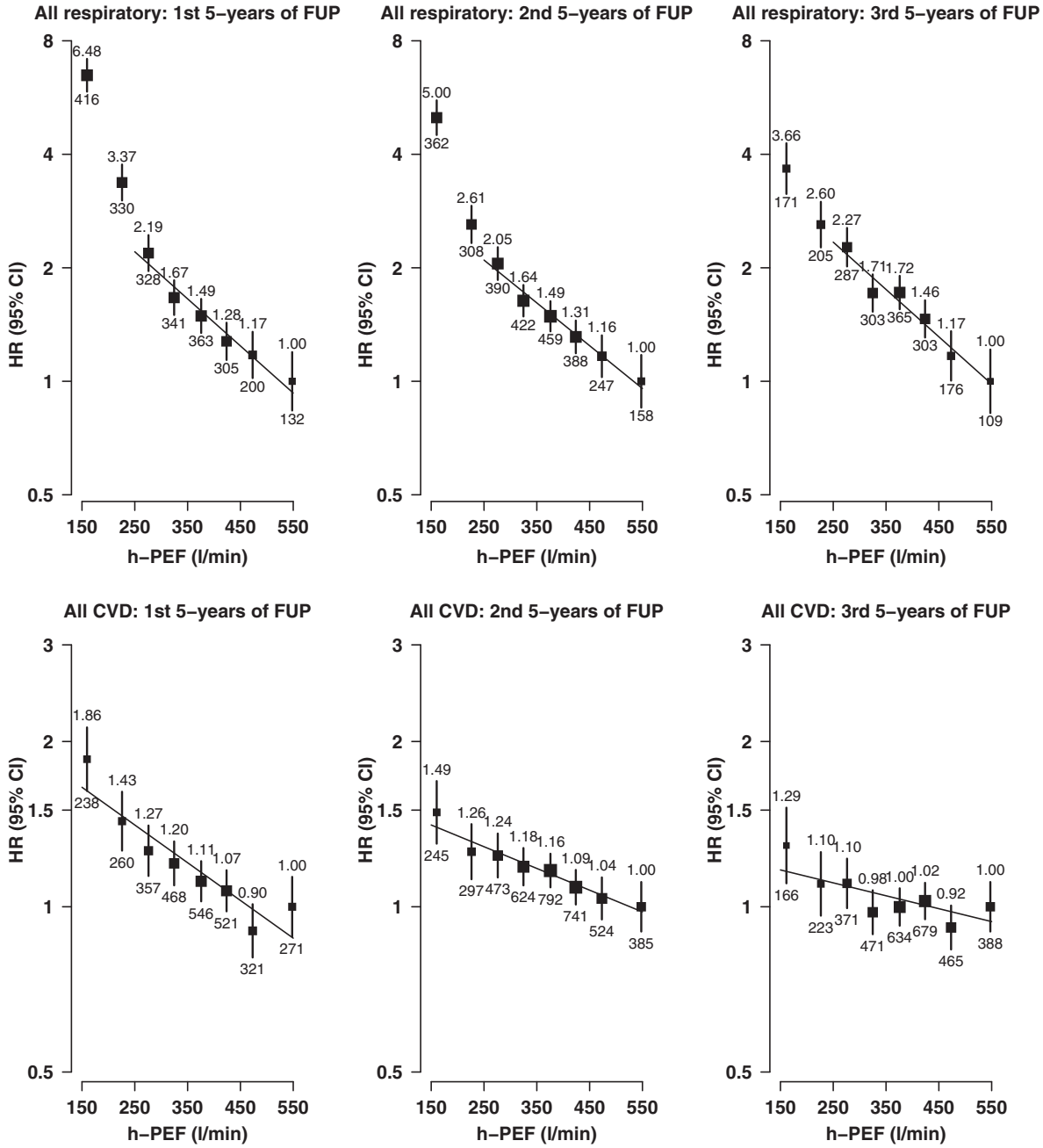

Figure 2 Mortality from respiratory and cardiovascular disease (CVD) by category of height-adjusted peak flow (h-PEF) (L/min) and follow-up period (FUP). Hazard ratios (HR) are adjusted for area, baseline age, smoking, and education. Area of square is inversely proportional to floated variance of log HR. Error bars indicate 95% confidence interval (CI). Numbers above error bars are HRs, numbers below error bars are numbers of deaths

(Figure 1), although there was some statistical evidence of departure from log-linearity in the first 5-year follow-up period ($P = 0.02$), particularly for cardiovascular disease ($P = 0.0007$) (Figure 2, and Supplementary Table S3, available as Supplementary data at *IJE* online). Throughout the entire range of h-PEF, a 100 L/min decrease in h-PEF was associated with a 13% greater mortality from combined non-respiratory causes in the first 5-year follow-up period, but this declined to 8% in the second and 6% in the third 5-year follow-up period (P for trend = 0.001) (Figure 3). Peak flow also predicted death from a wide range of specific causes (Figure 3, and Supplementary Table S3, available as Supplementary data at *IJE* online).

Mortality from all cardiovascular disease was strongly associated with h-PEF (Figure 2). In the three consecutive 5-year follow-up periods in the

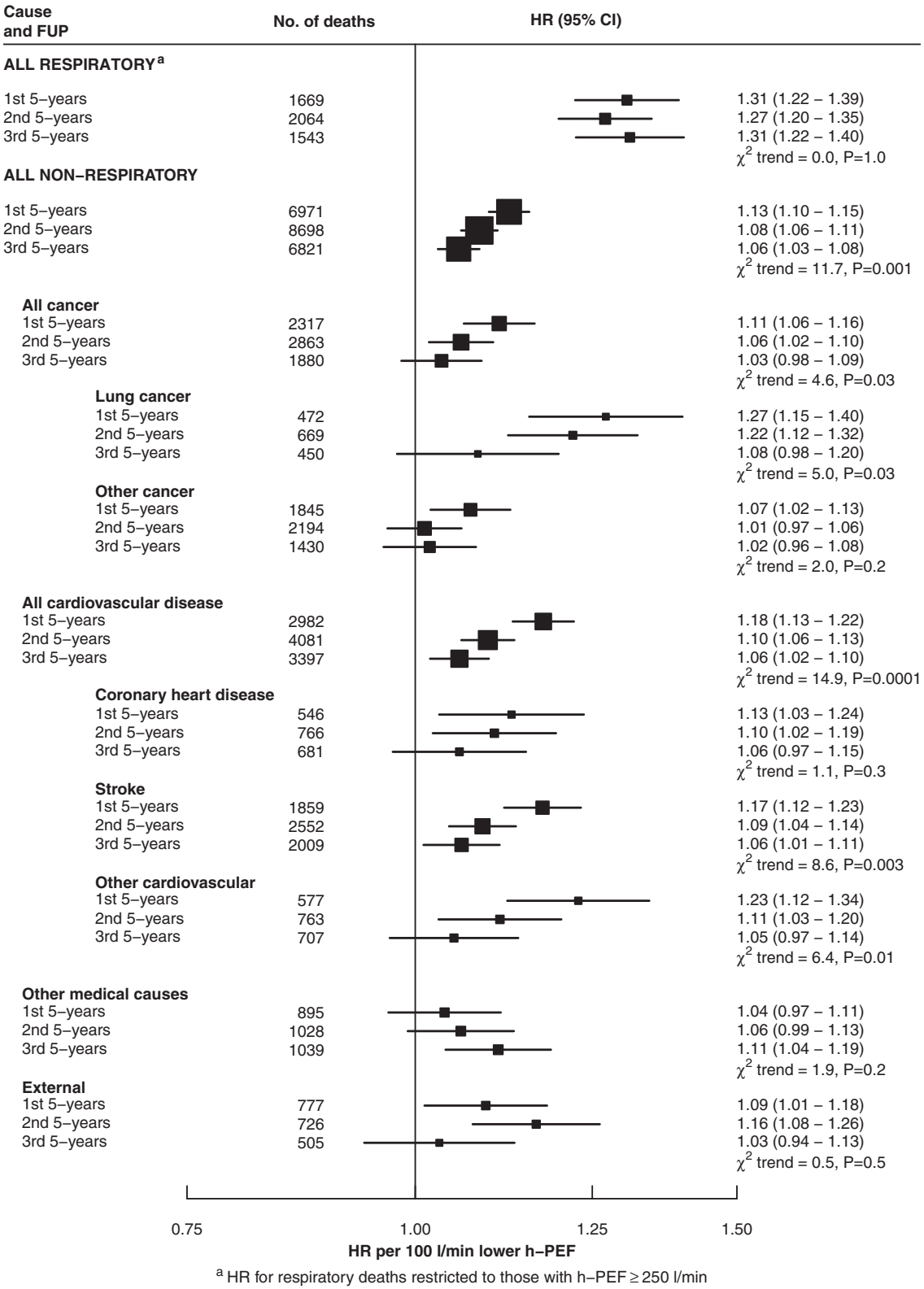

Figure 3 Cause-specific hazard ratios (HR) for a 100 L/min decrease in height-adjusted peak expiratory flow (h-PEF) (L/min) by 5-year follow up period (FUP). HRs are adjusted for 5-year baseline age group, area, smoking, and education. Area of square is inversely proportional to floated variance of log HR. Error bars indicate 95% confidence intervals (CI)

Table 3 Hazard ratios for selected causes of death, per 100 L/min decrease in height-adjusted peak expiratory flow at baseline, by 5-year follow-up period and smoking status at baseline

		Never smokers		Ever smokers		
Cause of death	**FUP**	Deaths (*N*)	HR (95% CI)[a]	Deaths (*N*)	HR (95% CI)[a]	*P*[b]
All respiratory[c]	1	392	1.22 (1.07–1.38)	1277	1.34 (1.24–1.44)	0.2
	2	436	1.32 (1.17–1.49)	1628	1.26 (1.18–1.34)	0.5
	3	284	1.36 (1.17 - 1.58)	1259	1.30 (1.21–1.40)	0.6
All non-respiratory	1	1720	1.09 (1.03–1.14)	5251	1.14 (1.11–1.17)	0.08
	2	1963	1.09 (1.04–1.14)	6735	1.08 (1.06–1.11)	0.9
	3	1543	1.07 (1.02–1.13)	5278	1.05 (1.02–1.08)	0.5
Lung cancer	1	91	1.27 (1.04–1.56)	381	1.27 (1.14–1.41)	1.0
	2	120	1.35 (1.14–1.61)	549	1.19 (1.09–1.30)	0.2
	3	85	1.22 (0.99–1.51)	365	1.05 (0.94–1.17)	0.2
Coronary heart disease	1	141	1.04 (0.88–1.23)	405	1.16 (1.05–1.28)	0.3
	2	165	1.23 (1.06–1.43)	601	1.07 (0.98–1.17)	0.09
	3	169	1.16 (0.99–1.35)	512	1.03 (0.93–1.13)	0.2
Stroke	1	440	1.12 (1.02–1.24)	1419	1.19 (1.13–1.26)	0.3
	2	585	1.04 (0.96–1.13)	1967	1.10 (1.05–1.16)	0.2
	3	463	1.10 (1.00–1.20)	1546	1.05 (0.99–1.11)	0.4
External	1	209	0.99 (0.86–1.14)	568	1.13 (1.04–1.23)	0.1
	2	169	1.25 (1.07–1.45)	557	1.14 (1.04–1.25)	0.3
	3	106	0.92 (0.76–1.12)	399	1.06 (0.96–1.18)	0.2

CI, confidence interval; FUP, follow-up period; HR, hazard ratio.
[a]Hazard ratios were adjusted for area, baseline age and years of education.
[b]*P* for interaction between height-adjusted peak expiratory flow and smoking status determined from the Wald χ^2 for the interaction term.
[c]Analysis confined to men with height-adjusted peak expiratory flow $\geqslant$ 250 L/min for all respiratory causes of death as the association with respiratory mortality was approximately log-linear above this value of height-adjusted peak expiratory flow.

study, a decrease in h-PEF of 100 L/min was associated with an 18%, 10%, and 6% higher mortality, respectively, from all cardiovascular disease (*P* for trend = 0.0001) (Figure 3). Associations of h-PEF with CHD, stroke, and other cardiovascular causes of death were similar, although the trend for CHD mortality over the 15-year follow-up period was not statistically significant. The exclusion of individuals with physician-diagnosed COPD or shortness of breath at baseline had very little effect on cardiovascular mortality, resulting in 15% (10%–21%), 11% (7%–15%), and 6% (1%–10%) higher cardiovascular mortality, respectively, in each successive 5-year follow-up period for every 100 L/min decrease in h-PEF.

Lung cancer was responsible for most of the observed inverse association of all cancer with h-PEF. In the first and second 5-year follow-up periods, mortality from lung cancer was respectively 27% and 22% higher per 100 L/min decrease in h-PEF, but was only 8% higher (not significantly different from zero) in the remainder of the 15-year follow-up, (*P* for trend = 0.03) (Figure 3). In contrast, the corresponding excess mortality for all other cancers was only 7%, 1%, and 2%, respectively, in the three follow-up periods, (not significantly different from zero in the last two follow-up periods) (Figure 3). After the exclusion of individuals with physician-diagnosed COPD or shortness of breath at baseline, excess lung cancer mortality was reduced to 16% (95% CI 3%–32%), 13% (3%–25%), and 2% (−9–16%), respectively, per 100 L/min decrease in h-PEF in each of the three successive 5-year follow-up periods.

There were also inverse associations of h-PEF with lung cancer, stroke, and CHD within categories of smoking and years of education, and no statistical evidence that the strengths of these associations

Table 4 Hazard ratios for selected causes of death, per 100 L/min decrease in height-adjusted peak expiratory flow at baseline, by 5-year follow-up period and socio-economic status (years of education)

		⩽6 Years of education		⩾6 Years education		
Cause of death	**FUP**	Deaths (*n*)	HR (95% CI)[a]	Deaths (*n*)	HR (95% CI)[a]	*P*[b]
All respiratory[c]	1	1457	1.30 (1.21–1.39)	212	1.36 (1.15–1.60)	0.6
	2	1809	1.25 (1.17–1.33)	255	1.40 (1.21–1.63)	0.2
	3	1341	1.29 (1.20–1.39)	202	1.41 (1.19–1.68)	0.3
All non-respiratory	1	5608	1.12 (1.08–1.15)	1363	1.17 (1.11–1.23)	0.1
	2	6892	1.07 (1.05–1.10)	1806	1.13 (1.07–1.18)	0.1
	3	5513	1.05 (1.02–1.08)	1308	1.10 (1.04–1.16)	0.1
Lung cancer	1	343	1.24 (1.11–1.39)	129	1.35 (1.14–1.60)	0.4
	2	484	1.17 (1.06–1.28)	185	1.36 (1.18–1.57)	0.1
	3	329	1.08 (0.96–1.21)	121	1.08 (0.90–1.31)	1.0
Coronary heart disease	1	401	1.09 (0.98–1.21)	145	1.24 (1.05–1.45)	0.2
	2	568	1.09 (0.99–1.19)	198	1.16 (1.01–1.33)	0.4
	3	529	1.02 (0.93–1.13)	152	1.17 (1.00–1.38)	0.1
Stroke	1	1544	1.19 (1.13–1.25)	315	1.12 (1.00–1.24)	0.3
	2	2130	1.08 (1.03–1.13)	422	1.12 (1.02–1.23)	0.5
	3	1683	1.05 (0.99–1.10)	326	1.14 (1.02–1.27)	0.2
External	1	628	1.09 (1.00–1.18)	149	1.12 (0.95–1.32)	0.8
	2	583	1.14 (1.04–1.24)	143	1.28 (1.08–1.51)	0.2
	3	408	1.03 (0.93–1.14)	97	1.03 (0.84–1.27)	1.0

CI, confidence interval; FUP, 5-year follow-up period HR, hazard ratio.
[a]Hazard ratios were adjusted for area, baseline age, and years of education.
[b]*P* for interaction between height-adjusted peak expiratory flow and smoking status determined from the Wald χ^2 for the interaction term.
[c]Analysis confined to men with height-adjusted peak expiratory flow ⩾ 250 L/min for all respiratory causes of death as the association with respiratory mortality was approximately log-linear above this value of height-adjusted peak expiratory flow.

were significantly modified by smoking (Table 3) or years of education (Table 4).

Discussion

The strengths of this study are its large size, nationally representative population sample, and long follow-up period, enabling associations of PEF with cause-specific mortality to be analysed in detail. In common with prospective studies of FEV_1 in Western populations we found that mortality from respiratory causes and from a wide range of specific non-respiratory causes, including lung cancer,[1,6–8] CHD,[1–3,9,10] and stroke,[1,2,9,11,12] was associated with lung function.

Associations in the single study of FEV_1 and cause-specific mortality that was also based on the population of a developing country (India)[22] can be compared with the associations found in our study on the basis of HR per SD decline in lung function. In that study, the associations of FEV_1 with respiratory and cardiovascular mortality and all cancer were slightly higher than in our study, but persons with histories of chronic disease were not excluded. That study did not have enough deaths from lung cancer to make good comparisons. A limited number of other studies of PEF and subsequent cause–specific mortality also found associations with cardiovascular events[15,17,18] and lung-cancer mortality,[15] but these studies were small, with relatively short follow-up periods, elderly populations at baseline, and varying indices of PEF, preventing comparisons of the strengths of associations of PEF with cause-specific mortality with those found in our study.

In our study, 23% of deaths were attributed to respiratory causes, which is much greater than the 5%–15% typically reported in similar studies of Western populations,[1,2,5,9,15,31] and most of these were attributed to COPD on the death certificates.

Chronic obstructive pulmonary disease is usually characterised by a gradual decline in lung function, yet in our study, deaths attributed to COPD occurred in the first 5-year follow-up period in participants with apparently normal baseline values of h-PEF. These deaths may therefore actually have been caused by acute respiratory infections,[32] or may indicate that PEF poorly indicated airflow obstruction at baseline.[19,20] Unsurprisingly, respiratory mortality was very strongly associated with low values of h-PEF, and particularly with values of h-PEF <250 L/min. In accord with the findings in other studies,[1] and with respiratory failure being the main cause of death in severe COPD,[32] the association was strongest in participants with a physician diagnosis of COPD or with shortness of breath at baseline. However, there was also a 29% increase in respiratory mortality per 100 L/min decrease in h-PEF that was consistent over the 15 years of follow-up and over the entire range of values of h-PEF ⩾250 L/min. Even after the exclusion of individuals known to have respiratory disease at baseline, about half of the association remained, suggesting that the measurement of PEF may be a useful means of screening for persons at risk for future respiratory disease.

Several explanations have been proposed for the associations of lung function with non-respiratory–associated mortality. First, lung function, and particularly PEF, is well correlated with indicators of general physical and cognitive health.[15,33,34] Other explanations include pre-existing disease at baseline; residual confounding; and systemic effects of COPD.[15,32] That low h-PEF was associated with mortality from all of the specific causes investigated in our study supports the view that it may be correlated with general health status. Associations were stronger in the 28 295 participants who were excluded from the main analyses in our study because of a history of chronic disease other than COPD (Supplementary Table S4, available as Supplementary data at *IJE* online), and undiagnosed disease at baseline could therefore have contributed to the observed associations of PEF with mortality in the study population. However, with the notable exception of the association of PEF with cancers other than lung cancer, most other associations of PEF with mortality persisted after the first 5-year follow-up period, and are therefore probably not completely explained by reverse causality. Associations of PEF with non-respiratory mortality are also unlikely to be explained by confounding by smoking or low socio-economic status, both of which are important risk factors for COPD in China.[24,25] Excluding persons with COPD at the study baseline did not affect associations of cardiovascular mortality with h-PEF, but did reduce those of lung cancer mortality, suggesting that COPD at baseline is associated with lung cancer but not with cardiovascular disease in the study population. However, baseline COPD was defined as a self-reported, physician-made diagnosis, and was probably also considerably under-diagnosed.

A puzzling feature of our findings is the attenuation of associations of PEF with non-respiratory disease in later stages of the follow-up period. Other published studies have found associations of mortality with FEV_1 to be highly consistent over lengthy follow-up periods,[1,3,11] but we know of no comparable studies using PEF. It is unlikely that reverse causality would have contributed much to the attenuation of associations of PEF with non-respiratory disease after the first 5-year follow-up period, but minor departure from log-linearity in some of the associations in early stages of the follow-up period would have contributed to this. Baseline PEF might predict future respiratory decline less well than FEV_1, but then we would also expect to have seen attenuation in associations of PEF with respiratory mortality. A weakness of the present study was that we had only the highest of the three measurements that were made of PEF, and no data on repeatability and no estimates of the decline in PEF in individuals with which to test this hypothesis.

A few small studies,[35] including one in China,[36] have assessed the utility of PEF as a screening tool for COPD. Our study suggests that further such assessments of the utility of PEF should be conducted. Such a screening tool might be particularly useful in China, where late diagnosis of COPD adds considerably to the burden of this disease.[23] Spirometry is not always practicable, particularly in rural areas, and a recent survey in China found that only 35% of persons found to have spirometrically defined COPD had previously had a diagnosis of the disease.[24]

Studies of Western populations have found that PEF also provides a useful assessment of general health status and is predictive of future hospitalizations and mortality.[13,14] In our study, cardiovascular mortality accounted for a further 35% of all deaths and was also strongly associated with a lower PEF in the 5 years after its measurement, even after the exclusion of individuals with known cardiovascular disease. Because PEF was also not strongly associated with SBP, the possibility of using PEF as part of a health-assessment to screen for individuals likely to develop cardiovascular disease, as well as identifying those at risk of respiratory disease, should be considered. Because associations of PEF with non-fatal events may differ from its associations with mortality, further studies of PEF and incident disease are needed in China.

Supplementary Data

Supplementary data are available at *IJE* online.

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KEY MESSAGES

- In the Chinese population of this study, PEF was inversely associated with subsequent mortality from a range of causes, including death from non-neoplastic respiratory disease, cardiovascular diseases, and lung cancer, but not other cancers.
- Inverse associations of PEF with lung cancer and cardiovascular disease were not explained by confounding with smoking or socio-economic status, or by existing disease at baseline.
- In contrast to studies of Western populations that have found consistent associations of PEF with lung cancer and cardiovascular disease mortality over long periods of follow-up, these were attenuated over 15 years of follow-up in the present study.
- The association of PEF with subsequent respiratory mortality was present, even after the exclusion of persons known to have COPD or reporting shortness of breath at baseline. Therefore measurement of PEF may be a useful means of screening for persons at risk for future respiratory disease.

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