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All-cause and cause-specific mortality from restrictive and obstructive spirometric patterns in Chinese adults with and without dyspnea: Guangzhou Biobank Cohort Study

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Short title: mortality from restrictive and obstructive spirometric patterns with dyspnea

Abstract

Objective To study whether abnormal spirometric patterns were associated with differential mortality in Chinese adults with and without dyspnea.

Methods Guangzhou Biobank Cohort Study (GBCS) participants were classified by spirometric patterns and presence of dyspnea into 6 groups: normal spirometry (NS), restriction on spirometry (ROS) and airflow obstruction (AO), each with and without dyspnea. Adjusted hazard ratios (aHRs) were calculated for mortality using Cox models.

Results Among 16777 subjects, 1595 (9.5%) had ROS, 1036 (6.2%) had AO and1009 (6.0%) had dyspnea. A total of 1993 deaths (11.9%) occurred during 11-year follow-up. Using NS without dyspnea as reference, NS with dyspnea was significantly associated with increased cardiovascular mortality risk (aHRs 1.61 (95% confidence interval (CI) 1.18-2.19); ROS with and without dyspnea were associated with increased risks of all-cause (aHRs 1.46 (95% CI 1.28-1.66) and 1.81(95% CI 1.33-2.47)) and cardiovascular mortality (aHRs 1.89 (95% CI 1.55-2.31) and 1.85 (95% CI 1.12-3.03)), but not of lung cancer mortality (aHRs 1.33 (95% CI 0.91-1.94) and 1.35 (95% CI 0.49-3.70)); AO with and without dyspnea were associated with increased risks of all-cause (aHRs 1.59 (95% CI 1.36-1.86) and 2.36 (95% CI 1.77-3.15)), cardiovascular (aHRs 1.43 (95% CI 1.08-1.90) and 1.61(95% CI 0.91-2.82)) and lung cancer mortality (aHRs 1.91 (95% CI 1.29-2.84)and 3.01(95% CI 1.46-6.23)). These associations did not vary by sex or smoking status (all P-values for interaction >0.05).

Conclusion: Both ROS and AO, with and without dyspnea, were associated with increased all-cause and cardiovascular disease mortality. The increased risk of all-cause was greater and that of cardiovascular mortality was lower for AO than ROS. AO showed significantly increased risk of lung cancer but ROS did not. (272 words)

Introduction

Chronic obstructive pulmonary disease (COPD), characterised by airflow obstruction (AO), is the third leading cause of mortality worldwide[1]. The China Pulmonary Health (CPH) study reported an overall COPD prevalence of 8.6% among adults aged 20 years or older during 2012-2015, estimated to affect about 100 million Chinese[2]. Restriction on spirometry (ROS) is also associated with increased mortality risk[3-8]. The prevalence of ROS varied from 6.5% to 21.0% in United States populations[9-16], and from 8.0% to 12.3% in Asian populations[17, 18]. A few cohort studies have compared the risks of mortality from AO and ROS, but the results were inconsistent. Some studies found that both AO and ROS were associated with higher risk of all-cause mortality compared to those with normal lung function[3, 6, 7, 9, 11, 19, 20], while other studies showed that only ROS, but not AO, was significantly associated with all-cause and cardiovascular mortality[5], or that only recurrent AO was associated with higher lung cancer mortality[6].

A nationally representative survey of adults by the Chinese Centre for Disease Control and Prevention showed that around two-thirds of COPD patients were asymptomatic[21]. Among respiratory symptoms, the level of dyspnea has been found to be superior in predicting mortality in those with COPD[22, 23] and in the general population[24-28].

We studied the relationships between abnormal spirometric patterns and dyspnea with subsequent all-cause and cause-specific mortality in a cohort of Chinese adults after 11-year follow-up.

Methods

Study participants

The Guangzhou Biobank Cohort Study (GBCS) is a three-way collaboration among the Guangzhou No. 12 Hospital, the Universities of Hong Kong and Birmingham. The cohort study was set up in 2003-8, inviting members of the Guangzhou Health and Happiness Association for the Respectable Elders' (GHHARE) to take part. GHHARE is a community social and welfare association with branches throughout Guangzhou. GHHARE is open for membership to any permanent Guangzhou residents aged 50 years or older. GBCS recruited 30430 members of GHHARE who agreed to take part. Members were not eligible if they were non-ambulatory, were receiving chemotherapy or radiotherapy for cancer, or dialysis for renal failure[29]. Due to cultural reasons, female members were more likely to respond and were over-represented in the GBCS. GBCS study was approved by Guangzhou Medical Ethics Committee of the Chinese Medical Association. All participants gave written informed consent before participation. Trained interviewers used a standardized computer-based questionnaire to collect information on demographic characteristics, education level, smoking status, childhood and adulthood exposure to passive smoking at home, passive smoking exposure at work, occupational dust and fume exposure, daily cooking oil fume exposure, installed fume extraction system, and personal disease history of hypertension, diabetes mellitus (DM), cancer and cardiovascular disease (CVD). Standard physical examination included assessment of body weight, height, waist circumference and blood pressure using

validated instruments. Blood glucose, white blood cell count and lipids were assayed after an

overnight (>8 hours) fast. Dyslipidaemia was defined as plasma triglycerides ≥1.7 mmol/L,

high-density lipoprotein (HDL)-cholesterol <1.00 mmol/L in men and <1.30 mmol/L in

women, or self-reported use of lipid-lowering medication. Hypertension was defined as

systolic blood pressure ≥140mmHg, diastolic blood pressure ≥90mmHg, or self-reported use

of antihypertensive medication. DM was defined as fasting glucose ≥7.0 mmol/L and/or

self-reported DM.

Exposure indicators

Spirometry was done with a pneumotachograph (Chestgraph HI-701, Chest MI Inc, Tokyo,

Japan) in phase I recruitment from September 2003 to October 2004, a turbine flowmeter

(Cosmed microQuark, Rome, Italy) in phase II recruitment from April 2005 to May 2006 and

two ultrasonic flowmeters (ndd Medical Technologies Easy-on PC; Zurich, Switzerland) in

phase Ⅲrecruitment from September 2006 to January 2008. Details of the methods have

been reported elsewhere[30, 31]. Briefly, the pulmonary function test with at least three

manoeuvres was conducted in a standing position following standard procedures, and the best

measure of forced expiratory volume in 1 sencond (FEV_1) and forced vital capacity (FVC)

were recorded. Predicted values and the fifth percentile of FEV_1 and FVC were derived using

the equations developed by Ip and colleagues for Chinese populations[32]. We used a

numerical quality-check algorithm developed according to European Respiratory Society

recommendations and criteria[33] to classify tests for reliability and validity. The remaining

results were assessed by visual inspection of flow-volume and volume-time curves.

Spirometry outcomes were classified into 3 categories: normal spirometry (NS): FEV_1/FVC

ratio ≥lower limits of normal (LLN, the fifth percentile of FEV_1 and FVC by Ip [32]) and

FVC % predicted (% predicted=observed/predicted x100%) ≥LLN; AO: FEV_1/ FVC ratio

<LLN and ROS: FEV$_1$/ FVC ratio ≥LLN and FVC % predicted <LLN. For comparability with other studies, spirometry outcomes were also classified based on the fixed ratio criteria for sensitivity analysis: NS: FEV$_1$/FVC ≥0.70, FVC% predicted ≥0.80; AO: FEV$_1$/FVC <0.70 and ROS: FEV$_1$/FVC ≥0.70, FVC% predicted <0.80.

The British modified Medical Research Council (mMRC) dyspnea questionnaire has been prioritised by the Global initiative for COPD (GOLD) for assessing COPD exacerbation and mortality, and was therefore used in this study. The presence of dyspnea was defined as mMRC dyspnea scale >2 (felt shortness of breath while walking with other people of the same age or after walking a few minutes on level ground, during dressing or undressing, or at rest).

Participants were classified into 6 mutually exclusive groups according to spirometric patterns and presence of dyspnea: NS without dyspnea as the reference group, NS with dyspnea, ROS without dyspnea, ROS with dyspnea, AO without dyspnea and AO with dyspnea.

Study outcomes

Vital status of participants on 31st December 2017 and the date and the underlying causes of death were obtained using record linkage with the Guangzhou Centre for Disease Control and Prevention (GZCDC). Follow-up duration was calculated from the date of first visit until the date of death or December 2017 for survivors. Causes of death were coded by trained nosologist in each hospital according to the International Classification of Disease, 10th Revision (ICD-10). ICD-10 I00–I99 was classified as cardiovascular mortality and C34 as lung cancer mortality. Cross-checking of past medical history against verbal autopsy (VA)

was conducted to improve the quality of coding. VA has been shown to yield reasonably reliable estimates of the broad cause of death in adults in China[34].

Statistical analysis

The baseline demographic and clinical characteristics were analyzed by the mean ($\pm$standard deviation (SD)) for continuous values and as percentages of the total number of subjects in the groups for categorical variables. Continuous variables were analyzed using one way analysis of variance (ANOVA) for three groups. Categorical variables were compared using chi-square test. Plots of the log–log survival curves were used to assess the proportional hazards assumptions. Cox proportional hazard models were used to calculate the adjusted hazard ratio (aHR) of all-cause and cause-specific mortality for ROS and AO with and without dyspnea. Age, sex, waist circumference, education ($\leqslant$primary, middle school and $\geqslant$ college), smoking (never, former, current smokers with 0-29 pack-years and current smokers with 30+ pack-years), childhood and adulthood exposure to passive smoking at home, passive smoking exposure at work, occupational dust and fume exposure, daily cooking oil fume exposure, installed fume extraction system, white blood cell count, hyperlipidemia, hypertension, DM and history of CVD and cancer were included in the models. 10 multiple imputations were performed using chained equation to predict missing data based on all other variables, and the HRs of each imputed data set were estimated and combined to produce an overall estimate of HR using the Rubin rule[35]. Interactions between the spirometric patterns and the presence of dyspnea were assessed, and stratified analysis by spirometric patterns and dyspnea was conducted in line with GOLD recommendation[22] and biological plausibility that both indexes were reported to have independent impact on mortality[9, 26]. Sex and smoking status interactions were assessed and stratified analyses were conducted separately. We further performed sensitivity analyses for spirometric patterns based on the

fixed ratio criteria. All tests of significance were 2-tailed, with P <0.05 as statistically significant. All analyses were performed using Stata / SE 15.0 (StataCorp LP, 4905 Lakeway Drive, College Station, TX77845 USA).

Results

After excluding 13278 GBCS participants with invalid spirometry measurements, 194 participants with missing vital status data and181 participants with missing dyspnea data, we included 16777 subjects with valid exposure and outcome indicators in the present study (Figure 1). The mortality of the participants included in this study (11.9%) was slightly lower than that of those excluded (15.2%). The mean age ($\pm$SD) of included participants was 61.4 ($\pm$7.3) years, and 1009 (6.0%) of them had >=Grade 2 dyspnea. 1595 (9.5%) participants had ROS and 1036 (6.2%) had AO based on LLN criteria. Table 1 shows that participants with ROS and AO were older and had lower education level and higher prevalence of dyspnea and general obesity than those with NS. Those with ROS had longer waist circumference, lower high density lipoprotein cholesterol, higher white blood cell count, and higher prevalence of central obesity, hypertension and DM than those with AO and NS. They also had higher prevalence of CVD than those with NS. Participants with AO were more likely to have ever smoked, had lower triglyceride, lower prevalence of hyperlipidemia and higher prevalence of underweight than those with ROS and NS.

We recorded 1993 (11.9%) deaths during an average of 11.1($\pm$2.2)-year follow-up, including 699 cardiovascular and 252 lung cancer deaths. Compared to the reference group of NS without dyspnea, NS with dyspnea was significantly associated with increased cardiovascular mortality risk (aHR 1.61 (95% confidence interval (CI) 1.18-2.19), while ROS with and without dyspnea were associated with increased all-cause (aHRs 1.46 (95% CI 1.28-1.66) and

1.81(95% CI 1.33-2.47) respectively) and cardiovascular (aHRs 1.89 (95% CI 1.55-2.31) and 1.85 (95% CI 1.12-3.03)) mortality risks. There was no significant association with lung cancer mortality risk (aHRs 1.33 (95% CI 0.91-1.94) and 1.35 (95% CI 0.49-3.70)). AO with and without dyspnea were associated with increased all-cause (aHRs 1.59 (95% CI 1.36-1.86) and 2.36 (95% CI 1.77-3.15) respectively), cardiovascular (aHRs 1.43 (95% CI 1.08-1.90) and 1.61(95% CI 0.91-2.82)) and lung cancer (aHRs 1.91 (95% CI 1.29-2.84) and 3.01(95% CI 1.46-6.23)) mortality risks (Figure 1-2).

The interaction term between the spirometric patterns and the presence of dyspnea was non-significant for all-cause, cardiovascular and lung cancer mortality, with the P values for interaction ranging from 0.18 to 0.44. In the whole cohort, ROS was associated with higher risk of all-cause (aHR 1.47, 95% CI 1.31-1.66) and cardiovascular mortality (aHR 1.81, 95% CI 1.50-2.19), but not with lung cancer mortality (aHR 1.33, 95% CI 0.93-1.91). AO was associated with higher risk of all-cause (aHR 1.68, 95% CI 1.46-1.94), cardiovascular (aHR 1.40, 95% CI 1.08-1.82) and lung cancer mortality (aHR 2.07, 95% CI 1.45-2.97). Dyspnea was associated with higher risk of all-cause (aHR 1.36, 95% CI 1.17-1.59) and cardiovascular mortality (aHR 1.43, 95% CI 1.12-1.82), but not with lung cancer mortality (aHR 1.23, 95% CI 0.79-1.94). Stratified analyses showed similar relationships between abnormal spirometric patterns and mortality in participants with and without dyspnea (Appendix table 1). The association between dyspnea and mortality varied in different spirometric patterns: it remained significant only in those with AO for all-cause mortality and in those with NS for cardiovascular mortality (Appendix table 2).

There were no significant interactions by sex or smoking status, and the P values for interaction ranging from 0.40 to 0.97. The stratified analyses showed similar tendencies

(Appendix figure 3-4). Sensitivity analyses based on fixed ratio criteria showed similar patterns (Appendix figure 1-2 and 5-6).

Discussion

We found that ROS, AO and dyspnea were all independently associated with increased all-cause and cardiovascular mortality risk in a cohort of older Chinese after 11-year follow-up. Presence of dyspnea combined with spirometric abnormality increased mortality risk. AO with and without dyspnea had greater increased risks for all-cause mortality but lower risks for cardiovascular mortality than ROS. Furthermore, AO, but not ROS nor dyspnea, was associated with significantly increased risk for lung cancer mortality.

COPD is the third leading cause of mortality worldwide[1], but its impact on cardiovascular mortality remains controversial. ROS is still under-diagnosed and underestimated in clinical settings. Several population studies including the National Health and Nutrition Examination surveys (NHANES)[9, 10] , the Atherosclerosis Risk in Communities (ARIC)[20] , COPD Gene[12], the Cardiovascular Health Study (CHS)[11] , Health Aging, and Body Composition (Health ABC)[13] , the Multi-Ethnic Study of Atherosclerosis (MESA)-Lung[14], Jackson Heart Study[15], the Tucson Epidemiological Study of Airway Obstructive Disease (TESAOD)[16], Singapore Longitudinal Ageing Studies (SLAS)[17] and Korea National Health and Nutrition Examination Survey (KNHANES)[18] have shown that the prevalence of ROS were similar to that of AO, varying from 6.5% to 21.0%. ROS was also reported to be associated with increased risks of co-morbidity and mortality[3-8]. The associations of both AO and ROS with all-cause mortality in general population were compared by a few previous studies[3, 5, 6, 9, 11, 20, 36], but only two studies reported the risks of cause-specific mortality, and the results were inconsistent[5, 6]. The Yamagata study

showed that ROS, instead of AO, was an independent predictor of all-cause and cardiovascular mortality[5]. On the other hand, the TESAOD study found recurrent and inconsistent ROS and recurrent AO, but not inconsistent AO, were associated with cardiovascular mortality[6]. In keeping with our findings, the TESAOD study also reported that only recurrent AO was associated with higher risk of lung cancer mortality[6].

The precise mechanisms to explain these findings are unknown, but chronic muscle wasting, systematic inflammation and oxidative stress in COPD patients may be responsible for the increased all cause and CVD mortality risks[37, 38]. On the other hand, the higher percentage of smokers and older age of participants with AO are also the risk factors for lung cancer, which may explain the observed relationship. The demographic and clinical characteristics of ROS such as higher percentage of obesity, hypertension and DM were also risk factors for cardiovascular disease, and these might be responsible for the higher risk of cardiovascular mortality for ROS. Nevertheless, such risks remained significant after controlling for all these variables, indicating the independent associations of abnormal spirometric patterns regardless of these risk factors.

An interesting finding of our study was that the mortality risk associated with dyspnea varied by spirometric patterns. Dyspnea was reported to be independently associated with increased all-cause and cardiovascular mortality[24, 25]. Our study showed similar associations and further found dsypnea was not associated with lung cancer mortality.
Vlagtwedde/Vlaardingen study showed the all-cause and cardiovascular mortality risks associated with dyspnea were highest seen in subjects with an above median $FEV_1\%$ predicted than that for those with a below median $FEV_1\%$ predicted[24]. The ARIC study showed that respiratory symptoms predicted higher mortality in those with normal pulmonary

function[20]. Stratified analyses in our study showed increased cardiovascular mortality risk in those with normal spirometry, but the increased all-cause mortality risk only remained significant in those with AO. The ARIC study used a wide definition of respiratory symptoms including having cough, sputum production, wheezing and dyspnea. The percentages of symptomatic participants ranged from 20.6% to 81.9% in different spirometric patterns[20]. In contrast, the proportion with dyspnea ranged from 5.0% to 18.5% in our study and may explain some of the contrasting findings[20] . Nevertheless, our findings suggested that a combination of symptom and spirometric abnormality could identify subjects with higher mortality risk more accurately.

The 13th Five-year Plan for Sanitation and Health of the People's Republic China promotes spirometry screening as a regular health test. Nevertheless, the United States Preventive Services Task Force (USPSTF) review and recommendations[39], the United Kingdom National screening committee and GOLD[22] recommend against spirometry screening for COPD in asymptomatic patients because of inadequate evidence of its efficiency for directing clinical decisions or improving outcomes. Our study did not provide evidence of clinical benefit of spiromtry screening, but it demonstrated that AO in itself is associated with poorer outcome, indicating there is potential to early intervention.

Our study had several strengths. It was based on a large population-based cohort of approximately 17000 older Chinese with 11-year follow-up. Of 9 studies exploring similar questions, only two had about 15000 participants[20, 36], while the sample size of other studies ranged from 1265 to 5542[3-6, 11, 19]. Only 3 studies had followed their participants for more than 22 years[4, 6, 9]. Most previous studies had adjusted for shared risk factors including age, sex, BMI and smoking[3-6, 11, 19, 20, 36], but none of them had more

information on other risk factors such as education level, dust and fume exposure, passive smoking exposure, inflammation, central obesity, hypertension, CVD, DM and cancer. The availability of such comprehensive data on risk factors for sensitivity analysis and adjustment was a strength. We also examined a range of outcomes, including all-cause, cardiovascular and lung cancer mortality. In contrast, most previous studies had only examined all-cause mortality and only 2 included cardiovascular mortality and lung cancer mortality[5, 6] . Furthermore, we used LLN as our primary measure for defining spirometric abnormalities, to minimize potential misclassification of subjects with normal pulmonary function. Nevertheless our findings were robust to alternative fixed ratio definitions of spirometric abnormality. We found that a surrogate outcome including both spirometry, a physiology measurement, and dyspnea, a patient-centred measurement, is associated with higher risk of mortality. This is consistent with American Thoracic Society and European Respiratory Society recommendations for COPD patients[40], but is seldom applied to general population. Only 2 previous studies had studied the mortality risk for a combination of both measurements[9, 20].

However, our study had some limitations. First, the definition of restriction was based on FVC instead of total lung capacity. Sub-maximal inspiratory effort could lead to low FVC, which might lead to overinclusion of the number of participants with reduced lung volume. However, plethysmography, the only conclusive test to identify truly restricted subjects is not feasible to use in large population studies. Second, ROS could resolve and relapse inconsistently over time. We used spirometry at baseline, but not longitudinal data to classify spirometric patterns. Several serial follow-up spirometry tests can better identify cases with persistent ROS. The TESAOD study for example, classified participants with ROS at baseline into consistent or inconsistent ROS groups based on the presence of ROS at least

half, or less than half of follow-up surveys respectively, which we were not able to replicate. However, they found similar mortality risk in both groups[6]. Third, we did not have post-bronchodilator lung function data so could not identify those with reversible AO. Nevertheless, those with self-reported asthma have been excluded to minimize inclusion of post-bronchodilator spirometry. Among previous studies exploring the association between spirometric patterns and mortality, only SaRA study performed post-bronchodilator spirometry[3]. Fourth, 16777 participants included in our study had lower mortality overall than 13653 participants who were excluded, mainly due to invalid spirometry. Patients with more severe AO are likely to be overrepresented in those with invalid spirometry, so potential for selection bias and underestimation of the effect size could not be fully ruled out.

Conclusions

Our cohort study of older Chinese in the community showed that AO with and without dyspnea had greater increased mortality risks for all-cause but lower risks for cardiovascular disease than ROS with and without dyspnea. AO showed significantly increased risk of lung cancer but ROS did not. The associations of dyspnea with mortality varied by spirometric patterns. These findings emphasize the value of combining dyspnea symptom and pulmonary function in assessing respiratory health and predicting mortality outcomes. Screening with spirometry in asymptomatic subjects is not recommended in international guidelines because of inadequate evidence of health benefits. However, our study showed that even among those with no dyspnea symptom, the presence of AO is associated with higher all cause and lung cancer mortality risk than those with no spirometric abnormality. Our findings demonstrate that AO in itself is associated with poorer outcomes, so there might be potential to intervene. Furthermore, preliminarily assessment of respiratory health in the general population with the easy-to-use mMRC dyspnea questionnaires before performing spirometry might be an

efficient method to identify people with higher risk of mortality who could be targeted for interventions.

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Table 1. Baseline demographic and clinical characteristics by spirometric patterns

	Normal spirometry	Restriction on spirometry	Airflow obstruction	P value
N	14146	1595	1036	
Male, n (%)	3651 (25.8)	445 (27.9)	295 (28.5)	0.06
Age, years, mean±SD	61.0±7.2	63.7±7.2[a]	63.7±7.6[a]	<0.001
Education, n (%)		[a]	[a]	<0.001
≤ Primary	5480 (38.8)	846 (53.1)	533 (51.5)	
Junior middle	7379 (52.2)	642 (40.1)	425 (41.0)	
≥ Senior middle	1284 (9.1)	106 (6.7)	78 (7.5)	
Waist circumference, cm, mean±SD	78.3±8.8	81.8±9.8[a,b]	77.4±9.4[a]	<0.001
Central obesity, n (%)	4583 (32.4)	756 (47.4)[a,b]	322 (31.1)	<0.001
BMI, kg/m², mean±SD	23.8±3.2	24.3±3.7[a,b]	22.9±3.6[a,]	<0.001
BMI groups, n (%)		[a,b]	[a,]	<0.001
Underweight	537 (3.8)	77 (4.8)	102 (9.9)	
Normal	5274 (37.3)	526 (33.0)	462 (44.6)	
Overweight	6958 (49.2)	750 (47.1)	389 (37.6)	
Obesity	1369 (9.7)	240 (15.1)	83 (8.0)	
IPAQ, n (%)[£]		[a]		<0.001
Low	669 (6.5)	41 (3.9)	44 (5.5)	
Middle	2957 (28.9)	370 (35.2)	242 (30.1)	
High	6604 (64.6)	640 (60.9)	518 (64.4)	
Smoking status, n (%)		[a,b]	[a,]	<0.001
Never	11629 (82.5)	1242 (78.0)	722 (70.0)	
Former	1128 (8.0)	172 (10.8)	155 (15.0)	
Current (0-29 pack-years)	373 (2.7)	23 (1.4)	42 (4.1)	
Current (≥30 pack-years)	962 (6.8)	156 (9.8)	113 (11.0)	
Passive smoking exposure, n (%)				
Childhood home exposure	8417 (59.8)	908 (57.1)	588 (57.1)	0.04
Adulthood home exposure	7542 (53.6)	873 (54.8)	523 (50.7)	0.12
Work exposure	7362 (52.4)	784 (49.3)	529 (51.4)	0.06
Occupational exposure, n (%)				
Dust exposure	5088 (36.1)	637 (40.1)	407 (39.5)	0.001
Fume exposure	3869 (27.5)	441 (27.8)	286 (27.8)	0.95
Cooking oil fume exposure, n (%)				
Daily cooking	13887 (98.9)	1561 (98.6)	1021 (99.5)	0.07
Fume extraction system	9634 (68.8)	1064 (67.4)	637 (62.3)	<0.001
Triglyceride, mmol/L	1.73±1.32	1.79±1.31[b]	1.56±1.00 [a]	<0.001
HDL-cholesterol, mmol/L, mean±SD	1.66±0.41	1.63±0.39[a,b]	1.69±0.40 [a]	<0.001
LDL-cholesterol, mmol/L, mean±SD	3.35±0.71	3.26±0.75[a]	3.25±0.67[a,]	<0.001
Fasting glucose, mmol/L, mean±SD	5.69±1.58	6.07±2.18[b]	5.62±1.50[a]	<0.001
Systolic blood pressure, mmHg, mean±SD	129±22	135±23[a,b]	130±23	<0.001
Diastolic blood pressure, mmHg, mean±SD	73±11	75±12[a,b]	72±11	<0.001
White blood cell count,	6.3±1.6	6.7±1.6[a,b]	6.5±1.7[a]	<0.001

10^9/L, mean±SD				
History of CVD, n (%)	650 (4.6)	98 (6.1)[a]	53 (5.1)	0.02
History of cancer, n (%)	253 (1.8)	38 (2.4)[a]	19 (1.8)	0.25
Co-morbidity, n (%)				
Hyperlipidemia	7295 (52.1)	844 (53.8)	485 (47.1)	0.002
Hypertension	5650 (40.0)	824 (51.7)[a,b]	421 (40.7)	<0.001
Type 2 Diabetes mellitus	1574 (11.2)	289 (18.2)[a,b]	108 (10.5)	<0.001
Dyspnoea, n (%)	737 (5.2)	143 (9.0)[a]	129 (12.5)[a]	<0.001
FEV$_1$% predicted, %, mean±SD	98.7±14.1	67.7±11.5[a]	68.0±21.1[a]	<0.001
FVC% predicted, %, mean±SD	95.9±13.3	64.0±9.9[a,b]	84.6±23.0[a,]	<0.001
FEV$_1$/FVC, %, mean±SD	80.4±5.5	81.5±7.6[a,b]	61.5±8.2[a,]	**<0.001**
Mortality, n (%)				
All-cause mortality	1424 (10.1)	336 (21.1)	233 (22.5)	<0.001
Cardiovascular mortality	481 (3.4)	150 (9.4)	68 (6.6)	<0.001
Lung cancer mortality	177 (1.3)	37 (2.3)	38 (3.7)	<0.001

SD, standard deviation; BMI, body mass index; IPAQ, International Physical Activity Questionnaire; HDL, high density lipoprotein; LDL, low density lipoprotein; CVD, cardiovascular disease; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; LLN, lower limits of normal;

% predicted= (observed/predicted) *100%

Central obesity: waist circumference ≥90 cm in men or ≥80 cm in women

Underweight: BMI < 18.5 kg/m^2 Normal: 18.5 ≤BMI < 24 kg/m^2 Overweight: 24 ≤BMI < 28 kg/m^2 Obesity: BMI ≥28 kg/m^2

Normal spirometry: FEV$_1$/FVC ≥LLN, FVC% predicted ≥LLN

Restriction on spirometry: FEV$_1$/FVC ≥LLN, FVC% predicted <LLN

Airflow obstruction: FEV$_1$/FVC <LLN

Dyspnoea: the British modified Medical Research Council dyspnoea scale ≥2

£: only 12085 participants with valid data

a: P <0.05 versus normal spirometry
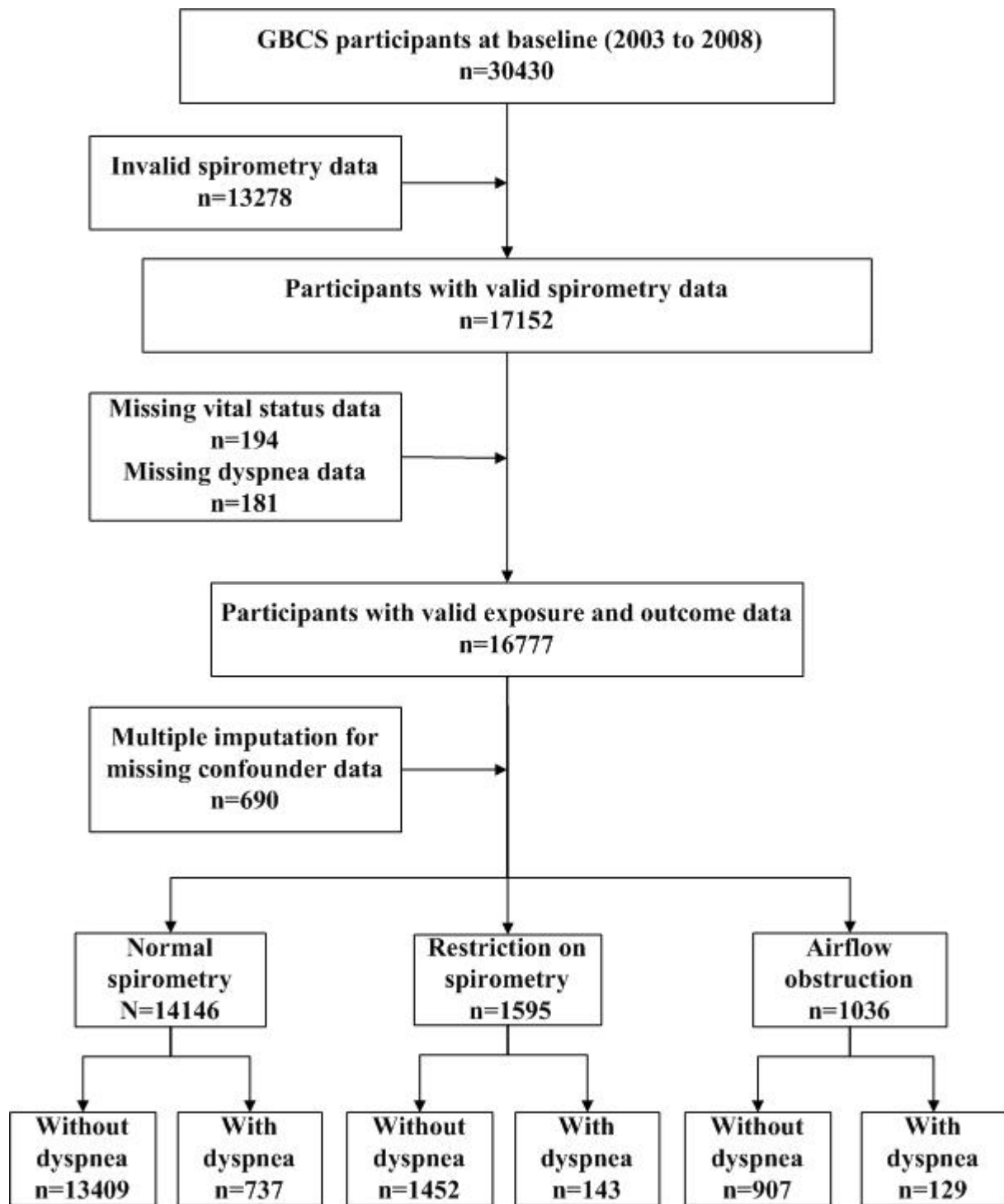
b: P <0.05 versus airflow obstruction

Figure 1 Flow diagram of participants

GBCS, Guangzhou Biobank Cohort Study; LLN, lower limits of normal
Normal spirometry: $FEV_1/FVC \geq LLN$, FVC% predicted $\geq LLN$
Restrictive on spirometry: $FEV_1/FVC \geq LLN$, FVC% predicted $< LLN$
Airflow obstruction: $FEV_1/FVC < LLN$
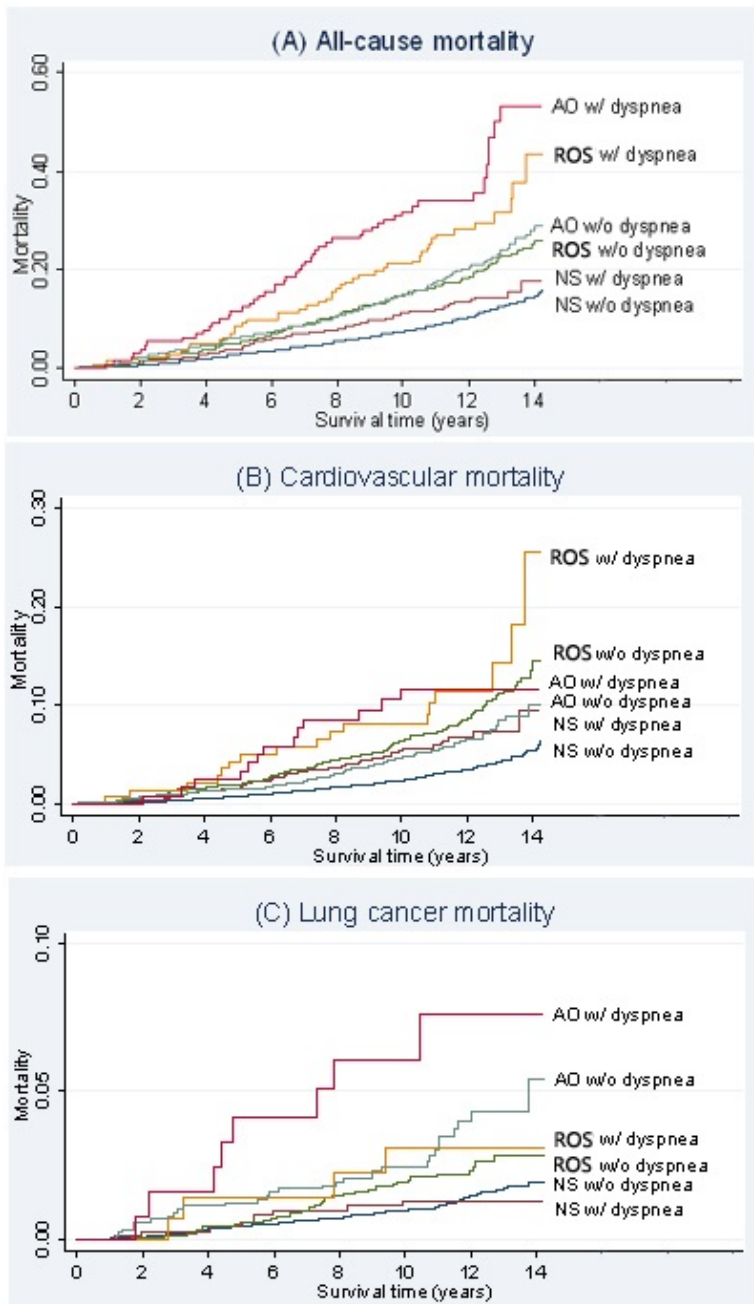Dyspnoea: the British modified Medical Research Council dyspnoea scale ≥ 2

Figure 1 Kaplan-Meier analysis of subjects with NS, ROS and AO with or without dyspnea for all-cause, cardiovascular and lung cancer mortality.

NS, normal spirometry; w/, with; w/o, without; ROS, restriction on spirometry; AO, airflow obstruction.

NS: FEV1/FVC ≥LLN, FVC% predicted ≥LLN

ROS: FEV1/FVC ≥LLN, FVC% predicted <LLN

AO: FEV1/FVC <LLN

Log-rank test for all-cause mortality, P <0.001

Log-rank test for cardiovascular mortality, P <0.001

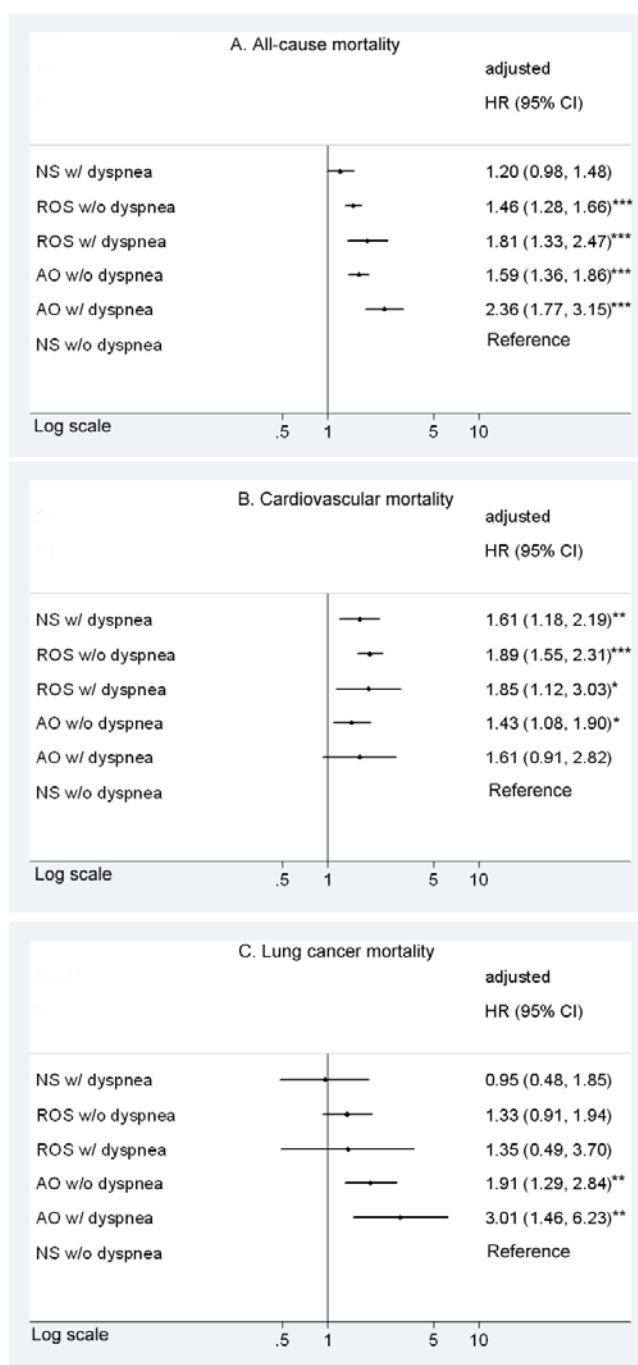Log-rank test for lung cancer mortality, P <0.001

Figure 2. Adjusted hazard ratio (HR) of mortality from Cox proportional hazard models by spirometric patterns and presence of dyspnea.

Reference group: subjects with normal spirometry and without dyspnea (risk of 1).

Models adjusted for sex, age, waist circumference, education, smoking status with pack-year, childhood and adulthood exposure to passive smoking at home, passive smoking exposure at work, occupational dust and fume exposure, daily cooking oil fume exposure, installed fume extraction system, white blood cell count, hyperlipidemia, hypertension, diabetes mellitus and history of cardiovascular disease and cancer.

NS, normal spirometry; w/, with; w/o, without; ROS, restriction on spirometry; AO, airflow obstruction.

NS: $FEV_1/FVC \geq LLN$, FVC% predicted $\geq LLN$

ROS: FEV$_1$/FVC ≥LLN, FVC% predicted <LLN
AO: FEV$_1$/FVC <LLN
*: P <0.05; **: P<0.01; ***: P<0.001.

Appendix table 1 Mortality rate (per 10000 person-years) and risk of all-cause and cause-specific mortality (from Cox proportional hazard models) in the whole cohort and stratified by presence of dyspnea

	Person-years	All-cause mortality		Cardiovascular mortality		Lung cancer mortality	
		Rate	HR (95% CI)	Rate	HR (95% CI)	Rate	HR (95% CI)
All							
NS	157267	90.5	1.00	30.6	1.00	11.3	1.00
ROS	17954	187.1	1.47 (1.31-1.66)***	83.5	1.81 (1.50-2.19)***	20.6	1.33 (0.93-1.91)
AO	11084	210.2	1.68 (1.46-1.94)***	61.4	1.40 (1.08-1.82)*	34.3	2.07 (1.45-2.97)***
Without dyspnea							
NS	149233	89.0	1.00	29.1	1.00	11.3	1.00
ROS	16425	178.4	1.45 (1.28-1.65)***	81.0	1.88 (1.54-2.29)***	20.1	1.31 (0.90-1.91)
AO	9830	186.2	1.59 (1.36-1.85)***	56.0	1.42 (1.07-1.88)*	30.5	1.90 (1.28-2.83)**
With dyspnea							
NS	8033	119.5	1.00	57.3	1.00	11.2	1.00
ROS	1529	281.2	1.89 (1.28-2.81)**	111.2	1.49 (0.81-2.77)	26.2	1.93 (0.51-7.21)
AO	1254	398.9	1.94 (1.33-2.83)**	103.7	1.01 (0.52-1.99)	63.8	4.81 (1.56-14.86)**

Adjusted for sex, age, waist circumference, education, smoking status with pack-year, childhood and adulthood exposure to passive smoking at home, passive smoking exposure at work, occupational dust and fume exposure, daily cooking oil fume exposure, installed fume extraction system, white blood cell count, hyperlipidemia, hypertension, diabetes mellitus and history of cardiovascular disease and cancer.
HR, hazard ratio; NS, normal spirometry; ROS, restriction on spirometry; AO, airflow obstruction; w/, with; w/o, without.
NS: FEV$_1$/FVC ≥LLN, FVC% predicted ≥LLN
ROS: FEV$_1$/FVC ≥LLN, FVC% predicted <LLN
AO: FEV$_1$/FVC <LLN
P for dyspnea interaction: (1) all-cause mortality: 0.38; (2) cardiovascular mortality: 0.18; (3) lung cancer mortality: 0.44.
*: P <0.05; **: P <0.01; ***: P <0.001.

Appendix table 2 Mortality rate (per 10000 person-years) and risk of all-cause and cause-specific mortality (from Cox proportional hazard models) in the whole cohort and stratified by spirometric patterns

	Person-years	All-cause mortality		Cardiovascular mortality		Lung cancer mortality	
		Rate	HR (95% CI)	Rate	HR (95% CI)	Rate	HR (95% CI)
All							
w/o dyspnea	175489	102.8	1.00	35.5	1.00	13.2	1.00
w/ dyspnea	10816	174.7	1.36 (1.17-1.59)***	70.3	1.43 (1.12-1.82)**	19.4	1.23 (0.79-1.94)
NS							
w/o dyspnea	149233	89.0	1.00	29.1	1.00	11.3	1.00
w/ dyspnea	8033	119.5	1.17 (0.95-1.44)	57.3	1.55 (1.14-2.11)**	11.2	0.94 (0.48-1.84)
ROS							
w/o dyspnea	16425	178.4	1.00	81.0	1.00	20.1	1.00

w/ dyspnea	1529	281.2	1.38 (0.98-1.93)	111.2	1.10 (0.65-1.88)	26.2	1.21 (0.41-3.61)
AO						
w/o dyspnea	9830	186.2	1.00	56.0	1.00	30.5	1.00
w/ dyspnea	1254	398.9	1.57 (1.12-2.19)[**]	113.7	1.37 (0.72-2.63)	63.8	1.46 (0.62-3.39)

Adjusted for sex, age, waist circumference, education, smoking status with pack-year, childhood and adulthood exposure to passive smoking at home, passive smoking exposure at work, occupational dust and fume exposure, daily cooking oil fume exposure, installed fume extraction system, white blood cell count, hyperlipidemia, hypertension, diabetes mellitus and history of cardiovascular disease and cancer.

HR, hazard ratio; NS, normal spirometry; ROS, restriction on spirometry; AO, airflow obstruction; w/, with; w/o, without.
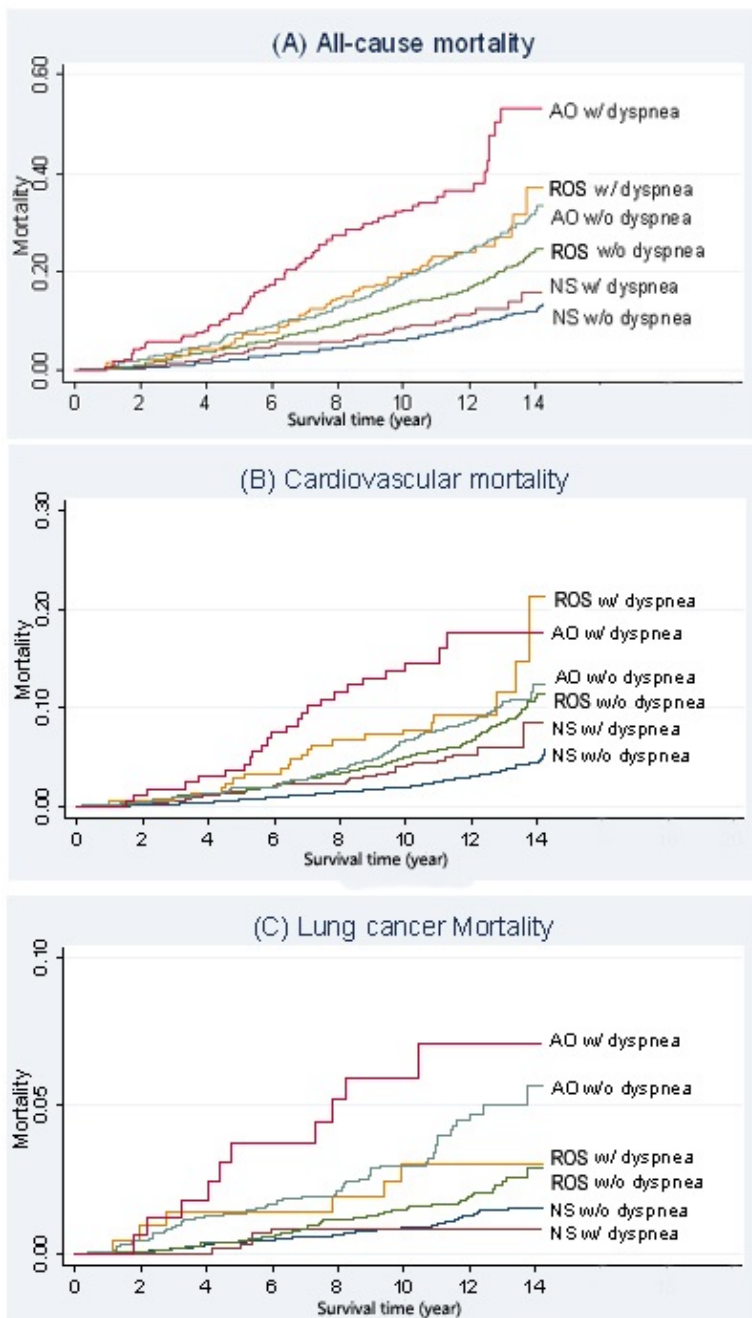
NS: $FEV_1/FVC \geq LLN$, FVC% predicted $\geq LLN$

ROS: $FEV_1/FVC \geq LLN$, FVC% predicted $< LLN$

AO: $FEV_1/FVC < LLN$

P for spirometry interaction: (1) all-cause mortality: 0.38; (2) cardiovascular mortality: 0.18; (3) lung cancer mortality: 0.44.

*: $P < 0.05$; **: $P < 0.01$; ***: $P < 0.001$

Appendix figure 1 Kaplan-Meier analysis of subjects with NS, ROS and AO based on fixed ratio criteria with or without dyspnea for all-cause, cardiovascular and lung cancer mortality. NS, normal spirometry; w/, with; w/o, without; ROS, restriction on spirometry; AO, airflow obstruction.
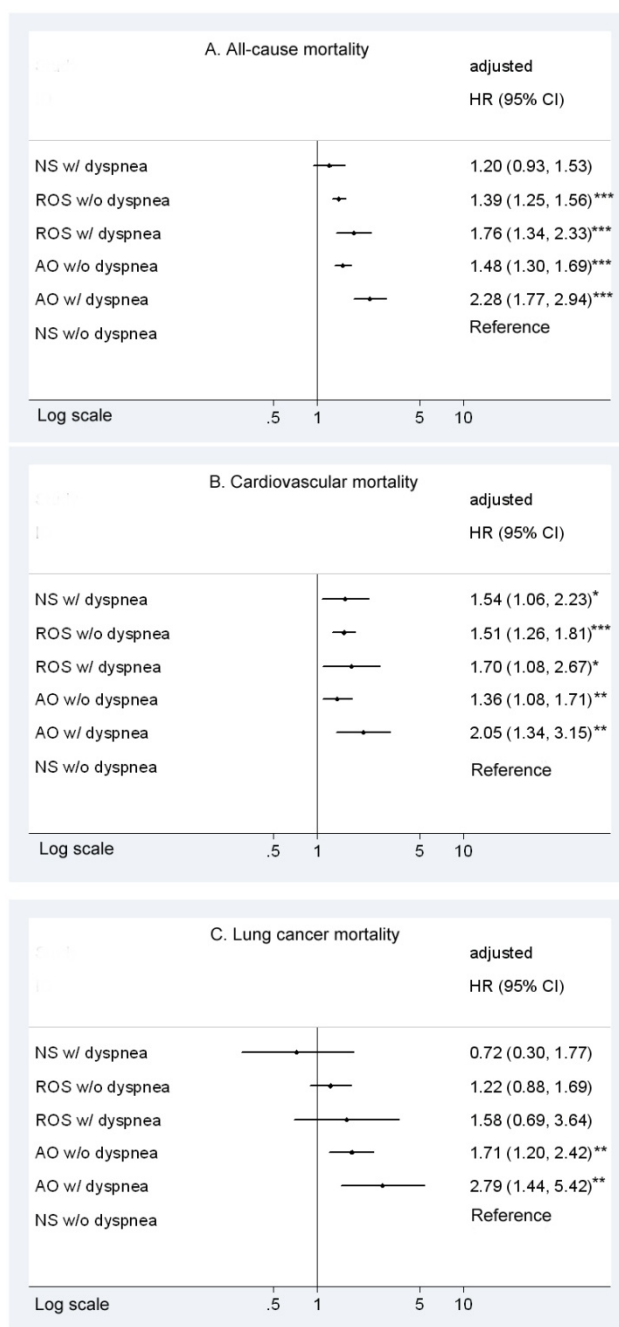
NS: $FEV_1/FVC \geq 0.70$, FVC% predicted ≥ 0.80
ROS: $FEV_1/FVC \geq 0.70$, FVC% predicted < 0.80
AO: $FEV_1/FVC < 0.70$
Log-rank test for all-cause mortality, P <0.001
Log-rank test for cardiovascular mortality, P <0.001
Log-rank test for lung cancer mortality, P <0.001

Appendix figure 2. Adjusted hazard ratio (HR) of mortality from Cox proportional hazard models by spirometric patterns based on fixed ratio criteria and presence of dyspnea.
Reference group: normal spirometry and without dyspnea (risk of 1).
Models adjusted for sex, age, waist circumference, education, smoking status with pack-year, childhood and adulthood exposure to passive smoking at home, passive smoking exposure at work, occupational dust and fume exposure, daily cooking oil fume exposure, installed fume extraction system, white blood cell count, hyperlipidemia, hypertension, diabetes mellitus and history of cardiovascular disease and cancer.
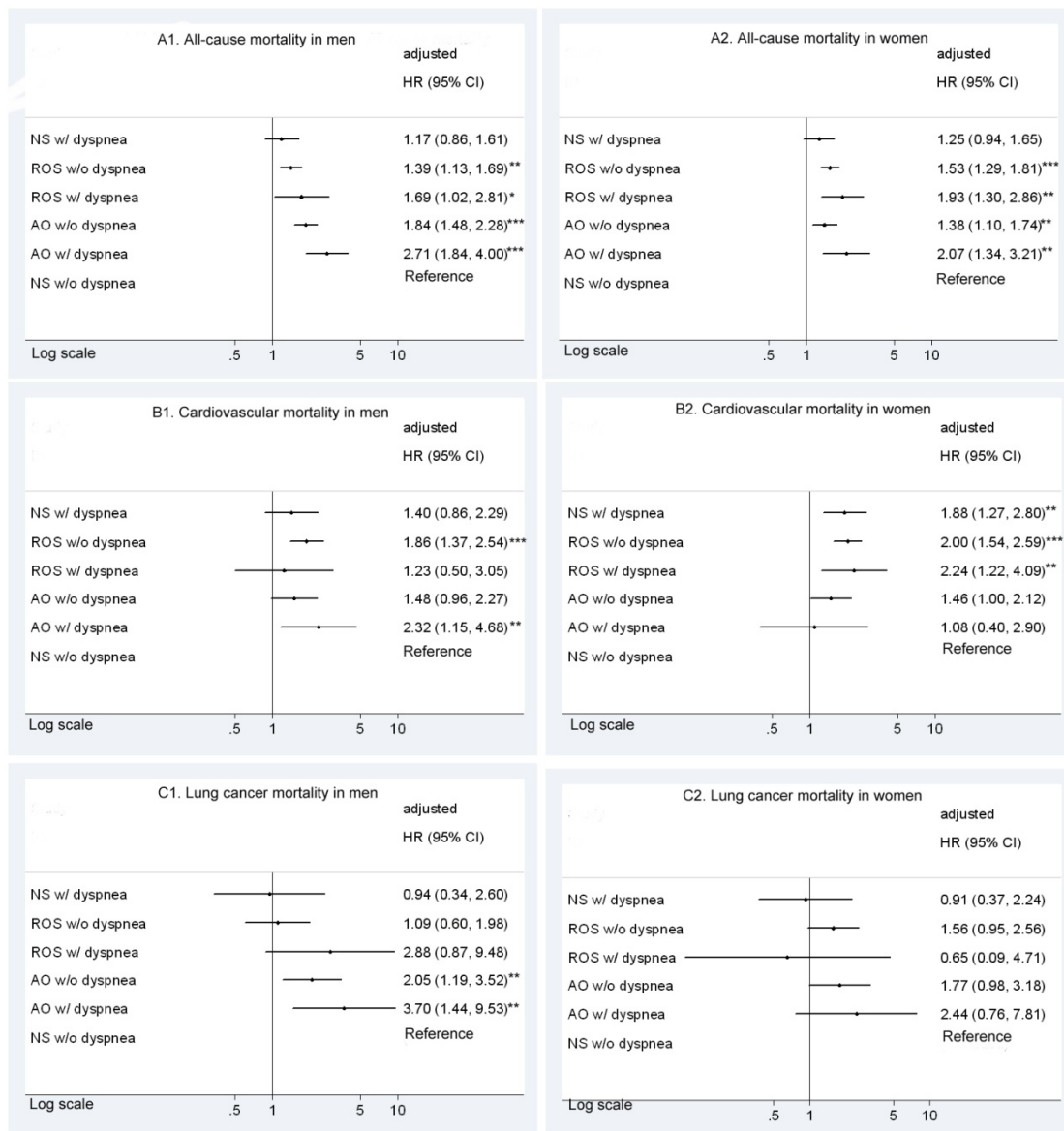NS, normal spirometry; w/, with; w/o, without; ROS, restriction on spirometry; AO, airflow obstruction.
NS: $FEV_1/FVC \geq 0.70$, FVC% predicted ≥ 0.80
ROS: $FEV_1/FVC \geq 0.70$, FVC% predicted < 0.80
AO: $FEV_1/FVC < 0.70$
*: P <0.05; **: P<0.01; ***: P<0.001.

Appendix figure 3. Adjusted hazard ratio (HR) of mortality from Cox proportional hazard models by spirometric patterns and presence of dyspnea in men and women.

Reference group: normal spirometry and without dyspnea (risk of 1).

Models adjusted for age, waist circumference, education, smoking status with pack-year, childhood and adulthood exposure to passive smoking at home, passive smoking exposure at work, occupational dust and fume exposure, daily cooking oil fume exposure, installed fume extraction system, white blood cell count, hyperlipidemia, hypertension, diabetes mellitus and history of cardiovascular disease and cancer.

NS, normal spirometry; w/, with; w/o, without; ROS, restriction on spirometry; AO, airflow obstruction.
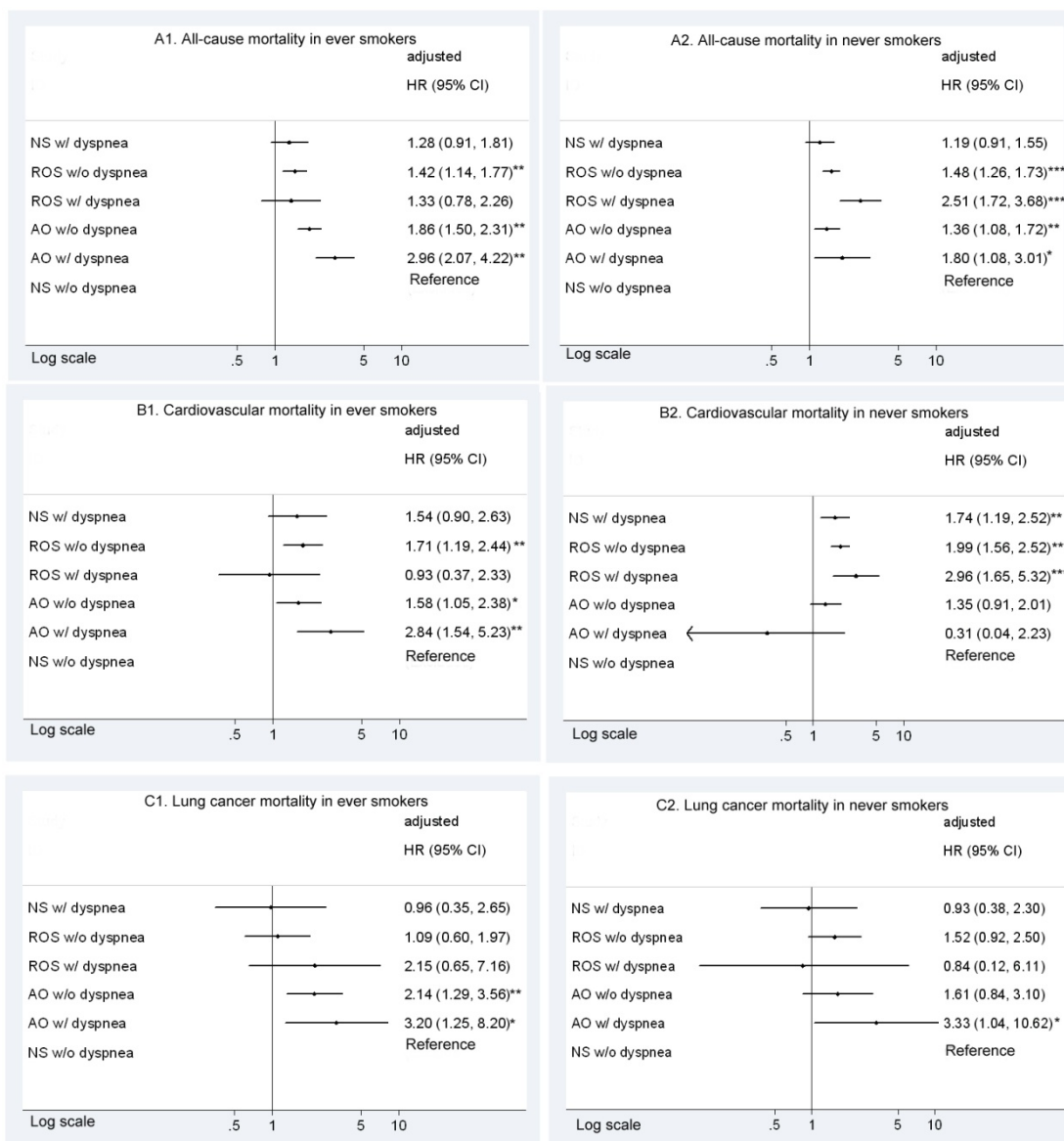
NS: $FEV_1/FVC \geq LLN$, FVC% predicted $\geq LLN$

ROS: $FEV_1/FVC \geq LLN$, FVC% predicted $< LLN$

AO: $FEV_1/FVC < LLN$

P for sex interaction: (1) all-cause mortality: 0.50; (2) cardiovascular mortality: 0.57; (3) lung cancer mortality: 0.46.

*: P <0.05; **: P<0.01; ***: P<0.001.

Appendix figure 4. Adjusted hazard ratio (HR) of mortality from Cox proportional hazard models by spirometric patterns and presence of dyspnea in ever and never smokers.

Reference group: normal spirometry and without dyspnea (risk of 1).

Models adjusted for sex, age, waist circumference, education, childhood and adulthood exposure to passive smoking at home, passive smoking exposure at work, occupational dust and fume exposure, daily cooking oil fume exposure, installed fume extraction system, white blood cell count, hyperlipidemia, hypertension, diabetes mellitus and history of cardiovascular disease and cancer.

NS, normal spirometry; w/, with; w/o, without; ROS, restriction on spirometry; AO, airflow obstruction.
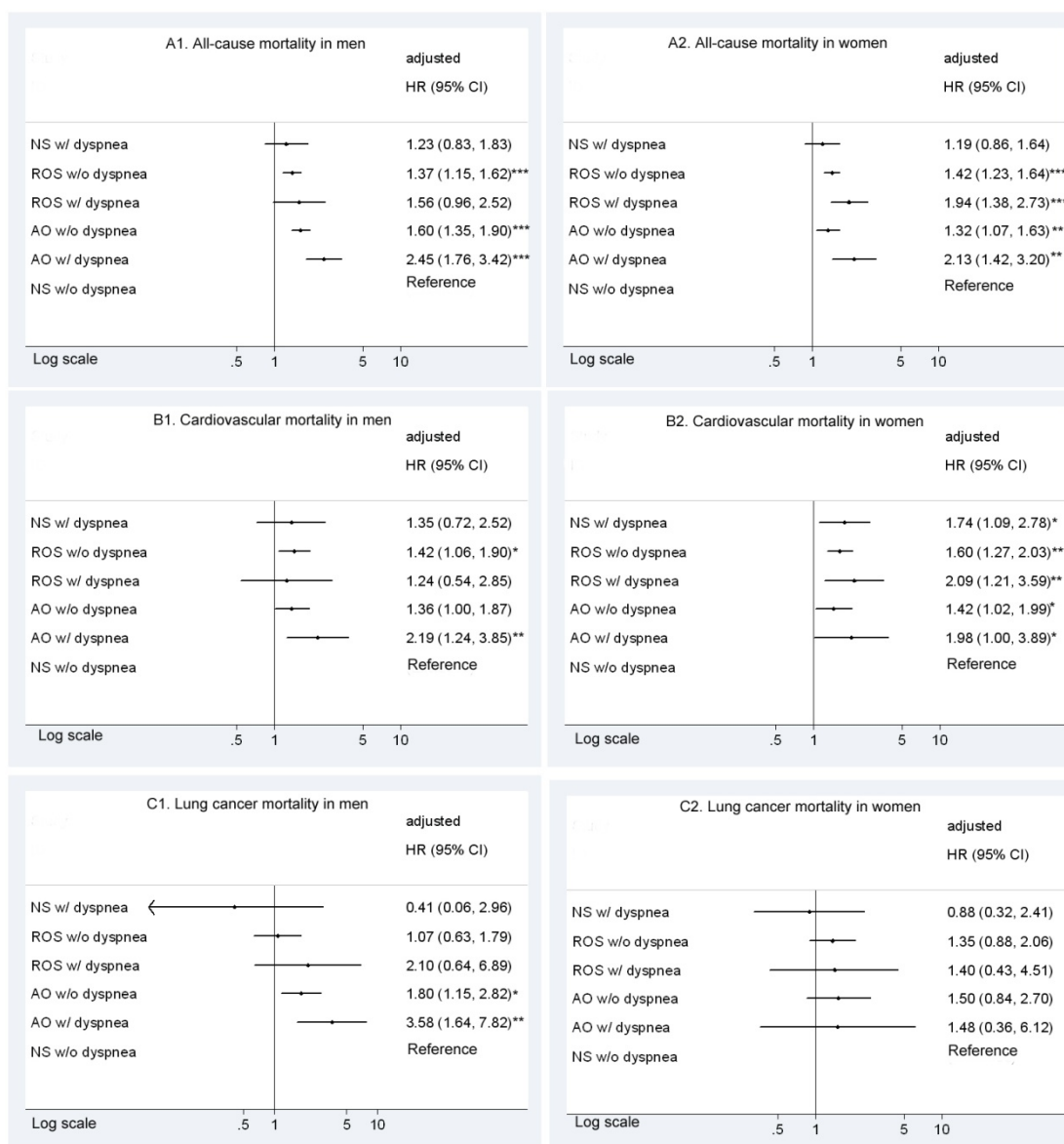
NS: $FEV_1/FVC \geq LLN$, FVC% predicted $\geq LLN$

ROS: $FEV_1/FVC \geq LLN$, FVC% predicted $<LLN$

AO: $FEV_1/FVC <LLN$

P for sex interaction: (1) all-cause mortality: 0.97; (2) cardiovascular mortality: 0.40; (3) lung cancer mortality: 0.41.

*: P <0.05; **: P<0.01; ***: P<0.001

Appendix figure 5. Adjusted hazard ratio (HR) of mortality from Cox proportional hazard models by spirometric patterns based on fixed ratio criteria and presence of dyspnea in men and women.

Reference group: normal spirometry and without dyspnea (risk of 1).

Models adjusted for age, waist circumference, education, smoking status with pack-year, childhood and adulthood exposure to passive smoking at home, passive smoking exposure at work, occupational dust and fume exposure, daily cooking oil fume exposure, installed fume extraction system, white blood cell count, hyperlipidemia, hypertension, diabetes mellitus and history of cardiovascular disease and cancer.

NS, normal spirometry; w/, with; w/o, without; ROS, restriction on spirometry; AO, airflow obstruction.
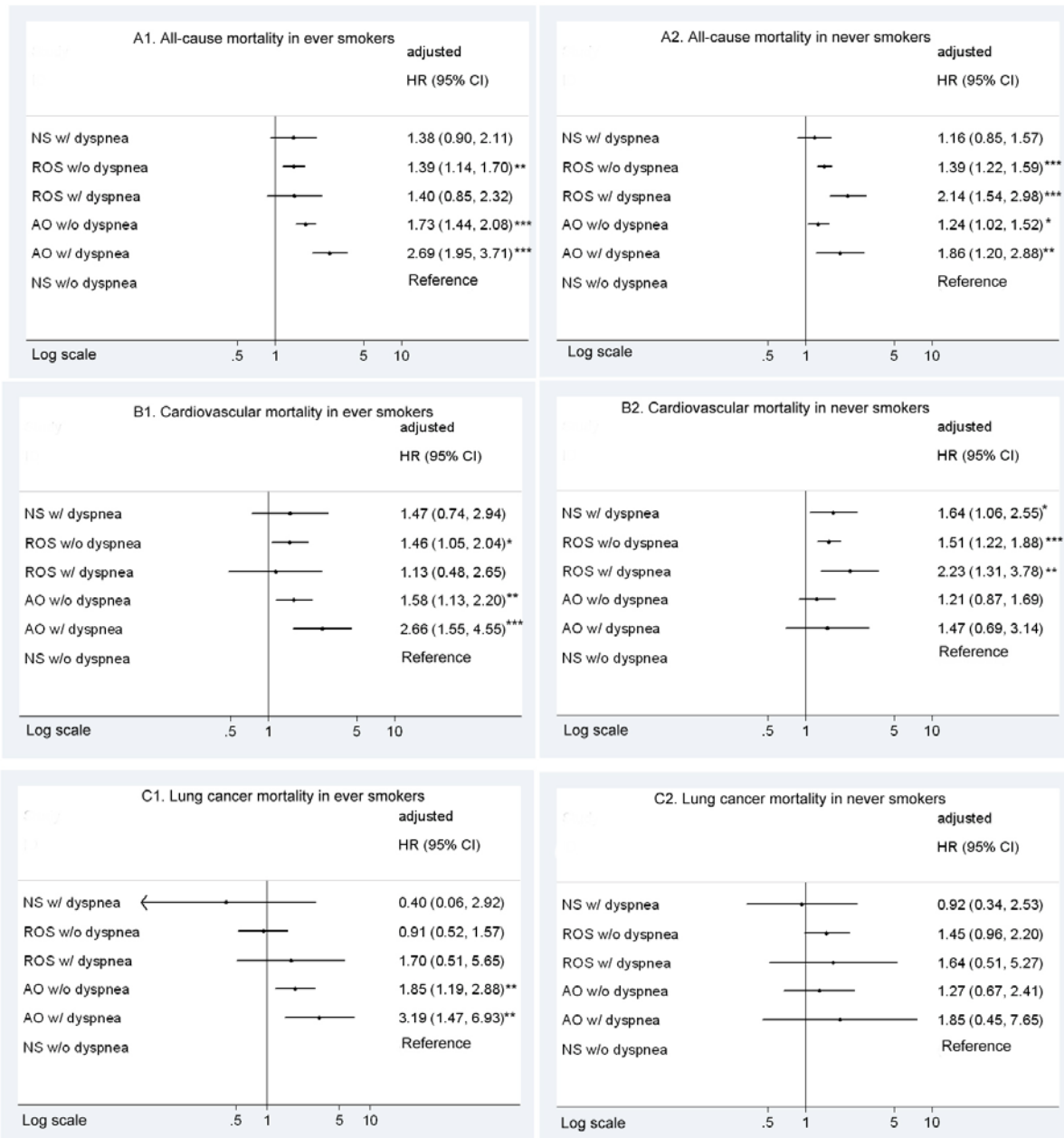
NS: $FEV_1/FVC \geq 0.70$, FVC% predicted ≥ 0.80

ROS: $FEV_1/FVC \geq 0.70$, FVC% predicted <0.80

AO: $FEV_1/FVC <0.70$

P for sex interaction: (1) all-cause mortality: 0.92; (2) cardiovascular mortality: 0.18; (3) lung cancer mortality: 0.32.

*: P <0.05; **: P<0.01; ***: P<0.001.

Appendix figure 6. Adjusted hazard ratio (HR) of mortality from Cox proportional hazard models by spirometric patterns based on fixed ratio criteria and presence of dyspnea in ever and never smokers.

Reference group: normal spirometry and without dyspnea (risk of 1).

Models adjusted for sex, age, waist circumference, education, childhood and adulthood exposure to passive smoking at home, passive smoking exposure at work, occupational dust and fume exposure, daily cooking oil fume exposure, installed fume extraction system, white blood cell count, hyperlipidemia, hypertension, diabetes mellitus and history of cardiovascular disease and cancer.

NS, normal spirometry; w/, with; w/o, without; ROS, restriction on spirometry; AO, airflow obstruction.

NS: $FEV_1/FVC \geq 0.70$, FVC% predicted ≥ 0.80

ROS: $FEV_1/FVC \geq 0.70$, FVC% predicted < 0.80

AO: $FEV_1/FVC < 0.70$

P for sex interaction: (1) all-cause mortality: 0.67; (2) cardiovascular mortality: 0.26; (3) lung

cancer mortality: 0.68.
*: P <0.05; **: P<0.01; ***: P<0.001