Risk Factors of Severe COPD Exacerbation in Chinese Adults: A Prospective Study

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Summary

Background: Severe exacerbation is the predominant cause of COPD hospitalization. We investigated sex-specific risk factors of severe exacerbation, and to explore the potential interactions of regions, smoking status, and age.

Methods: The present study included 13,641 males and 13,051 females with spirometry-defined COPD at baseline from China Kadoorie Biobank. Hazard ratios (HR) and 95% confidence intervals (CIs) of risk factors with severe exacerbation were estimated using Cox model.

Results: During a median of 11.5 years follow-up, 5,967 cases of COPD hospitalization were recorded. GOLD stage, tobacco smoking, and underweight were positively associated with COPD hospitalization in both sexes. Stronger associations were observed in females than in males, the corresponding HRs for males and females were 1.87 (1.73, 2.03) and 2.47 (2.24, 2.72) respectively for a history of respiratory diseases, and 1.46 (1.33, 1.60) and 1.65 (1.46, 1.87) for coughing frequently and coughing up sputum after getting up in the morning for ≥3 months. Higher risks were found among urban residents, noncurrent smokers, and patients <60 years old.

Conclusions: Our findings may help clinicians and the public to identify COPD patients at high risk of exacerbation requiring hospitalization and take targeted measures in time.

Keywords: COPD; exacerbations; hospitalization; risk factor; sex difference

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of death and disability worldwide[1]. In China, the prevalence of spirometry-defined COPD is estimated to be 8.6% in adults more than 20 years old, with 99.9 million prevalent cases[2]. COPD patients often experience worsening symptoms <14 days, called exacerbation[3], which is the predominant cause of COPD hospitalization due to the worse lung function, emerging morbidity, and poor prognosis[4,5]. Therefore, identifying risk factors associated with severe exacerbation can contribute to its prevention and treatment, thus substantially reducing clinical implications and disease burden.

A growing body of evidence suggested that various respiratory-related and demographic factors might influence the risk of moderate-to-severe COPD exacerbations, such as the severity of airflow limitation, symptomatic burden, age, sex, BMI, and smoking[6,7]. However, it is still not clear whether other factors could increase the risk of COPD exacerbation, such as household air pollution[8] and central obesity[9]. It is noteworthy that COPD is characterized by distinct sex heterogeneity in terms of epidemiology, diagnosis, and physiologic and psychologic impairments[10,11]. Furthermore, a number of studies revealed a significant association between sex and moderate-to-severe COPD exacerbations, although the results were inconsistent[6,7]. However, few studies explored the potential effects of sex in modifying the association of other potential risks, such as socio-demographic characteristics, lifestyle factors, and household air pollution. Similarly, the potential modifiable effects of age and smoking were also unclear.

Four studies with limited sample sizes were conducted among the Chinese population, but failed to explore comprehensively the risk factors of severe COPD exacerbation by sex, age, regions, and smoking status[12–15]. The present study based on the China Kadoorie Biobank (CKB), aimed to investigate comprehensively the sex-specific associations of respiratory, demographic, and lifestyle factors with severe

COPD exacerbation, and then to explore the potential interactions of age, regions (urban or rural), and smoking status.

Method

Study population

Details of the CKB design, survey methods, and participant characteristics have been described previously[16,17]. Briefly, a total of 512,724 participants aged 30-79 years were recruited from ten geographically diverse regions across China, including five urban areas (Harbin, Qingdao, Suzhou, Liuzhou, and Haikou) and five rural areas (Gansu, Henan, Sichuan, Zhejiang, and Hunan) between June 2004 and July 2008. The study areas were selected according to multiple factors such as disease pattern, exposure to potential risk factors, and feasibility of long-term follow-up.

The China Kadoorie Biobank (CKB) complies with all the required ethical standards for medical research on human subjects. Ethical approvals were granted and have been maintained by the relevant institutional ethical research committees in the UK and China, which was in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants included in the study.

Identification of participants

Trained technicians measured forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) to the nearest 0.01 L by handheld Micro Spirometer (MSO1; CareFusion Crop, Basingstoke, UK). To ensure the accuracy of lung function, participants practiced exhalations under the technician's guidance, after which two standard measurements were recorded. The highest values of FEV1 and FVC were used in the analyses. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD), FEV1/FVC ratio <0.7 was considered airflow limitation. The severity of airflow limitation was further divided into four levels by the proportion of FEV1 to the predicted value, i.e., mild (≥80%, GOLD 1), moderate (50%-<80%, GOLD 2), severe (30%-<50%, GOLD 3), and very severe (<30%, GOLD 4)[18]. Predicted values were obtained from the Global Lung Initiative (GLI) reference equations for northeast Asian (Harbin, Qingdao, Gansu, and Henan) and southeast Asian (Suzhou, Liuzhou, Haikou, Sichuan, Zhejiang, and Hunan) population[19].

From August to October 2008, the CKB study randomly selected 5% of participants (n=19,788) to conduct a resurvey, using almost the same procedures as the baseline survey. Lung function was available for 15,722 participants. The Spearman correlation coefficients were 0.91 for FEV1 and FVC values between the baseline survey and the resurvey (1.4 years for median interval of the two surveys) [17].

The present study included participants with airflow limitation defined as FEV1/FVC ratio <0.7 (n=27,485). Given the absence of applying bronchodilators before the lung function tests, we excluded participants with self-reported asthma (n=793) to avoid possible misclassification. Finally, a total of 26,692 participants, including 13,641 males and 13,051 females, were left in the analyses.

Data collection

Baseline information was collected by trained staff, including a laptop-based questionnaire, anthropometric measurements, and a 10-ml non-fasting blood sample. The baseline questionnaire collected information on socio-demographic characteristics (age, sex, education level, marital status, and household income), lifestyle behaviors (smoking, passive smoking, alcohol consumption, diet, household air pollution, and physical activity), and disease history (respiratory symptoms, asthma, tuberculosis, chronic bronchitis or emphysema, diabetes, coronary heart disease (CHD), stroke or transient ischemic attack (TIA), etc.). As for respiratory symptoms, participants were asked the following questions: ‘During the past 12 months, have you usually had the following symptoms? (i) Cough frequently; (ii)

Cough up sputum after getting up in the morning'. If yes, the frequency of each symptom (<3 or ≥3 months) was further asked. The electronic questionnaire embedded functions to avoid missing items and possible logic errors. Except for lung function, a range of anthropometric measurements, such as height, weight, and waist circumference, were assessed by trained technicians with calibrated instruments and standard protocols. Baseline variables showed good reproducibility[17].

Ascertainment of COPD hospitalizations

All participants were followed up for disease surveillance, hospitalization events, and mortality statistics by linking to China's Disease Surveillance Points (DSP) system, national health insurance database, local residential, and annual active follow-up. All death and hospitalization events were coded by trained staff blinded to baseline information according to the International Classification of Diseases, 10th Revision (ICD-10). We defined severe COPD exacerbation as hospitalization due to COPD (ICD-10: J41-J44), which was consistent with the definition of the Global Initiative for Chronic Obstructive Lung Disease[18]. We followed up with participants until the incidence, death, loss to follow-up, or December 31, 2018, whichever came first. To verify the accuracy of diagnosis, medical records of 1,069 randomly selected COPD cases were retrieved and adjudicated by professional physicians, and 85% were confirmed[20].

Statistical analysis

All main analyses were conducted among males and females, respectively. Baseline characteristics were described as mean for continuous variables using linear regression models and percentages for categorical variables using logistic models, adjusting for age and study areas. Poisson regression models were used to calculate the incidence of COPD hospitalization. According to previous studies, we carefully selected potential risk factors of severe COPD exacerbation, including respiratory-related factors and non-respiratory factors (demographic and lifestyle factors)[6,7]. The respiratory-related factors included GOLD stages (four levels), a prior history of respiratory diseases (emphysema, bronchitis, or tuberculosis: yes, no), and a history of respiratory symptoms (cough frequently or cough up sputum after getting up in the morning: no, <3 months, ≥3 months with one symptom, ≥3 months with two symptoms). Socio-demographic and lifestyle factors included marital status (married, not married), education level (illiterate and primary school, middle and high school, college or university), household income (<10,000, 10,000-19,999, ≥20,000 yuan/year), smoking status (never or occasional, former, current and 1-14, 15-24, ≥25 cig/d), alcohol drinking (non-weekly drinker, former weekly drinker, current weekly drinker, current daily drinker), consumption of fresh fruit and red meat (less than daily, daily), physical activity (sex- and age-specific tertiles of metabolic equivalent of task), BMI (<18.5, 18.5-23.9, 24.0-27.9, ≥28.0 kg/m^2), waist circumference (not central obesity: <90 cm for males and <85 cm for females; central obesity: ≥90 cm for males and ≥85 cm for females)[21], passive smoking (never or ever lived with smoker), and household air pollution due to cook or heat in winter (never cook/heat or cook/heat with clean fuel, cook/heat with solid fuel). All risk factors were simultaneously included in the Cox proportional hazard regression models, with stratification of age at risk (5-year groups) and study regions (10 regions). The proportional hazards assumptions of Cox models were not violated via Schoenfeld residuals. The *P* values of interaction between sex and the above potential risk factors were calculated by likelihood ratio tests, with adjusted significant level of 0.003 by using the Bonferroni method. For the factors with significant interaction, their product terms with sex were included in the models for subsequent analyses.

Several sensitivity analyses were conducted to test the robustness of our results: (1) using the lower limit of normal (LLN) criterion to include participants with airflow limitation at baseline, and excluding participants with FEV1/FVC ratio >1; (2) further excluding participants with major diseases at baseline, including CVD, diabetes, depression, and anxiety.

We also conducted subgroup analyses to examine whether the associations between potential risk factors and COPD hospitalization were significantly different between different regions (urban or rural areas), age groups (<60 or ≥60 years), and smoking status (noncurrent or current smokers). The *P* values of interaction were also calculated by likelihood ratio tests.

All *P* values were two-sided, and the statistical level was set at 0.003 for interaction tests and at 0.05 for other tests. All analyses were performed using Stata (version 17.0, StataCorp), and figures were drawn by R (version 4.1.3).

Results

Among 26,692 participants with spirometry-defined COPD (FEV1/FVC <0.7), the mean age was 59.1±10.7 years, 51.1% were females, and 31.7% resided in urban areas. Compared with females, males with COPD tended to have higher education level and household income, to smoke and drink alcohol daily, and to report respiratory symptoms (all *P* values of sex difference were <0.001), while females were more likely to be exposed to second-hand smoke and household air pollution(*P*<0.001) (Table 1).

During a median of 11.5 (interquartile range 7.8-13.1) years follow-up, we documented 5,967 cases of COPD hospitalization. Among potential risk factors, the GOLD stage, tobacco smoking, and underweight were positively associated with COPD hospitalization in both sexes (Table 2, Figure 1, and Table S1). In males, the HRs of GOLD stages increased in dose-response manner (*P* for trend <0.001), and the corresponding HRs for level 2-4 were 2.48 (2.11, 2.92), 6.11 (5.19, 7.19), and 10.52 (8.78, 12.60) compared with level 1; the HR for current smokers with ≥25 cig/d was 1.55 (1.37, 1.76) compared with never or occasional smokers; and underweight males had an HR of 1.38 (1.27, 1.51) compared with males with normal BMI. In females, similar associations between these three factors and COPD hospitalization were also found (*P* for sex difference >0.003). While the positive association between a history of respiratory diseases or symptoms and COPD hospitalization were stronger in females than in males (*P* for sex difference <0.003) (Table 2). The HRs of a history of respiratory diseases were 1.87 (1.73, 2.03) and 2.47 (2.24, 2.72) for males and females, respectively. Compared with those without respiratory symptoms, the risk of COPD hospitalization increased with the duration and number of respiratory symptoms (*P* for trend <0.001). Participants who cough frequently and cough up sputum after getting up in the morning for ≥3 months had a 46% higher risk in males and a 65% higher risk in females (*P* for sex difference <0.003). Additionally, we observed negative association between daily intake of red meat and COPD hospitalization only in females (HR=0.87; 95% CI=0.76, 0.99; *P* for sex difference <0.003) (Figure 1 and Table S1). Sensitivity analyses confirmed the robustness of our results (Table S2 and S3).

In the subgroup analyses, higher risks were found among urban residents than rural residents for GOLD stages, and among noncurrent smokers for GOLD stages and respiratory symptoms, as well as among those <60 years old in respect of all three respiratory-related factors (*P* for interaction <0.003) (Figure 2). For demographic characteristics and lifestyle behavior, associations differed across regions for smoking, alcohol drinking, red meat consumption, and BMI (*P* for interaction <0.003). We also found significant interaction between smoking status and household air pollution (*P* for interaction <0.003). No significant interaction was observed between age and non-respiratory factors. (Table S4).

Discussion

Based on a large prospective cohort of Chinese adults, the present study comprehensively examined the associations between various factors and severe COPD exacerbation, and investigated effect modification on associations of respiratory, demographic, and lifestyle factors across sex, age, regions, and smoking status.

In the present study, we confirmed the existing evidence on the association between GOLD stages ≥2, severe respiratory symptoms, a history of respiratory diseases, tobacco smoking, and underweight and risk of severe exacerbation. A multicenter study reported an increase of 1.74 (1.53-1.97) in HR per GOLD stage increase for COPD exacerbation during the first year of follow-up[22]. As for respiratory symptoms, our results were consistent with a cross-sectional study conducted in France, which found chronic cough and sputum production increased the number of severe exacerbations requiring hospitalizations[23]. Therefore, patients with severe COPD should pay more attention to preventing exacerbation. Other respiratory diseases might also exacerbate COPD progression. Emphysema is a primary cause of abnormal lung function of COPD and could increase with the GOLD stages[24]. COPD patients with chronic bronchitis had an increased risk of frequent exacerbations, with an OR of 4.0 (2.7-5.9)[25]. Besides, existing studies consistently identified smoking and underweight were risk factors of COPD exacerbations[6,7]. A possible mechanism might lie in the high inflammation levels[26,27].

Besides, our study also observed the interactions of potential risk factors and age, regions, and smoking status in severe COPD exacerbation. Previous studies found smoking and older age were risk factors of COPD exacerbations[6,7]. However, the subgroup analyses in the present study found that patients <60 years old and never or previously smoker had higher risk of severe COPD exacerbation. This might be attributed to the relatively lower risk of control groups for the two populations. As for rural or urban regions, more researches are warranted to confirm our results. Overall, our findings suggested more attention should be paid to patients who resided in urban areas, had age <60 years, and never or previously smoked.

The present study benefited from large sample size, long follow-up period, and comprehensive information to detect the risk factors of severe COPD exacerbation. However, inevitably, several limitations exist. First, a bronchodilator was not used before measuring lung function, which might underestimate lung function and make it difficult to distinguish COPD and asthma. However, we excluded participants with asthma to reduce the possibility of misclassification. Second, the information on predictors was collected at baseline, and it’s hard to depict the possible changes during follow-up. Third, the lack of information caused us not to analyze a prior history of exacerbation, the strongest risk factor of severe COPD exacerbation[6]. Therefore, potential confounding effects cannot be avoided.

In summary, the present study provides important epidemiological evidence of risk factors for severe COPD exacerbation in China. GOLD stages ≥2, severe respiratory symptoms, a history of respiratory diseases, tobacco smoking, and underweight were risk factors of severe exacerbation for both males and females. More attention should be paid to urban residents, patients <60 years old, and non-current smokers. Our findings may help clinicians to identify COPD patients who are more likely to experience exacerbation requiring hospitalization and thereby administer targeted treatment.

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Availability of data and materials

Details of how to access China Kadoorie Biobank data and details of the data release schedule are available from www.ckbiobank.org/site/Data+Access.

Author contributions

CQY conceptualised and designed the paper; LML, ZMC, and JSC, as members of the CKB steering committee, designed and supervised the conduct of the whole study, obtained funding, and together with JL, DJYS, PP, LY, YPC, HDD, YP, and XMY acquired the data. WY and YBL analyzed the data and drafted the manuscript. All authors contributed to and approved the final manuscript. CQY is the study guarantor.

Ethics approval and consent to participate

The China Kadoorie Biobank (CKB) complies with all the required ethical standards for medical research on human subjects. Ethical approvals were granted and have been maintained by the relevant institutional ethical research committees in the UK and China, which was in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants included in the study.

Consent for publication

Not applicable.

Competing interests

The authors have declared that no competing interest exists.

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Table 1 Baseline characteristics of participants by sex.

Characteristic	Males (n=13,641)	Females (n=13,051)	*P* for sex difference
Socio-demographic characteristics			
Age, years	60.5±10.0	57.7±11.2	<0.001
Urban area, %	29.0	34.5	<0.001
Married, %	88.4	79.8	<0.001
Middle school and higher, %	34.7	20.8	<0.001
Income ≥20,000 yuan/year, %	30.5	26.8	<0.001
Lifestyle factors			
Current daily smoker, %	75.1	9.7	<0.001
Passive smoker, %	67.3	84.3	<0.001
Current daily drinker, %	24.5	2.0	<0.001
Consuming meat daily, %	23.6	17.6	<0.001
Consuming fresh fruit daily, %	9.8	13.4	<0.001
Household air pollution, %	50.0	67.9	<0.001
Physical activity, MET h/day	19.6±15.0	17.6±12.3	<0.001
Anthropometric measures			
BMI, kg/m^2	22.0±3.1	22.8±3.6	<0.001
Waist circumference, cm	78.1±9.8	77.1±10.1	0.015
Respiratory-related index			
FEV_1, L	1.7±0.6	1.2±0.5	<0.001
FEV_1 % predicted	61.4±19.9	62.8±19.7	<0.001
GOLD stages, %			0.042
1	18.3	20.2	
2	52.2	52.7	
3	23.0	22.2	
4	6.6	4.9	
Respiratory symptoms[2], %			<0.001
No	73.5	83.1	
<3 months	9.4	7.8	
≥3 months (one symptom)	5.9	3.6	
≥3 months (two symptoms)	11.2	5.4	
History of respiratory diseases[1], %	16.8	13.0	<0.001
Severe exacerbation, %	25.0	19.3	<0.001

Baseline characteristics were adjusted for age and study area as appropriate. Figures in the table were mean± standard deviation for continuous variables and percentages for categorical variables.

FEV1=forced expiratory volume in 1 second, GOLD=the Global Initiative for Chronic Obstructive Lung Disease, MET h/day=metabolic equivalent of task hours per day.

[1] Respiratory diseases included self-reported emphysema/bronchitis and tuberculosis.

[2] Respiratory symptoms included cough frequently and cough up sputum after getting up in the morning.

Table 2 Adjusted HR for respiratory-related factors and severe exacerbation in patients with COPD by sex.

	Males (n=13,641)		**Females (n=13,051)**		$P_{interaction}$
	Events (incidence rate)	HR (95% CI)	Events (incidence rate)	HR (95% CI)	
GOLD stages					0.888
1	172 (7.6)	1.00 (Ref)	124 (5.1)	1.00 (Ref)	
2	1,256 (19.5)	2.48 (2.11, 2.92)	911 (14.1)	2.56 (2.12, 3.09)	
3	1,497 (55.8)	6.11 (5.19, 7.19)	1,018 (36.2)	5.47 (4.51, 6.62)	
4	619 (109.1)	10.52 (8.78, 12.60)	370 (68.3)	8.82 (7.13, 10.91)	
P_{trend}		<0.001		<0.001	
History of respiratory diseases[1]					<0.001
No	2,227 (22.2)	1.00 (Ref)	1,564 (14.7)	1.00 (Ref)	
Yes	1,317 (71.4)	1.87 (1.73, 2.03)	859 (59.6)	2.47 (2.24, 2.72)	
Respiratory symptoms[2]					<0.001
No	2,112 (23.8)	1.00 (Ref)	1,617 (16.2)	1.00 (Ref)	
<3 months	430 (38.8)	1.19 (1.07, 1.32)	282 (30.2)	1.31 (1.15, 1.49)	
≥3 months (one symptom)	289 (48.4)	1.44 (1.27, 1.63)	139 (34.1)	1.53 (1.28, 1.83)	
≥3 months (two symptoms)	713 (59.2)	1.46 (1.33, 1.60)	385 (50.3)	1.65 (1.46, 1.87)	
P_{trend}		<0.001		<0.001	

The incidence rates of severe exacerbation were calculated as severe exacerbation cases divided by follow-up time (/1,000 person-years), with adjustment for age and study areas. Multivariate Cox models were adjusted above respiratory-related confounders and other potential risk factors (marital status, educational level, household income, tobacco smoking, alcohol drinking, fresh fruit consumption, red meat consumption, physical activity, BMI, waist circumference, passive smoking, cook pollution, heat pollution in winter, and history of cardiovascular diseases and diabetes), with stratification of age and study areas. The adjusted significant level of interaction was set at 0.003 by using the Bonferroni method.

[1] Respiratory diseases included self-reported emphysema/bronchitis and tuberculosis.

[2] Respiratory symptoms included cough frequently and cough up sputum after getting up in the morning.

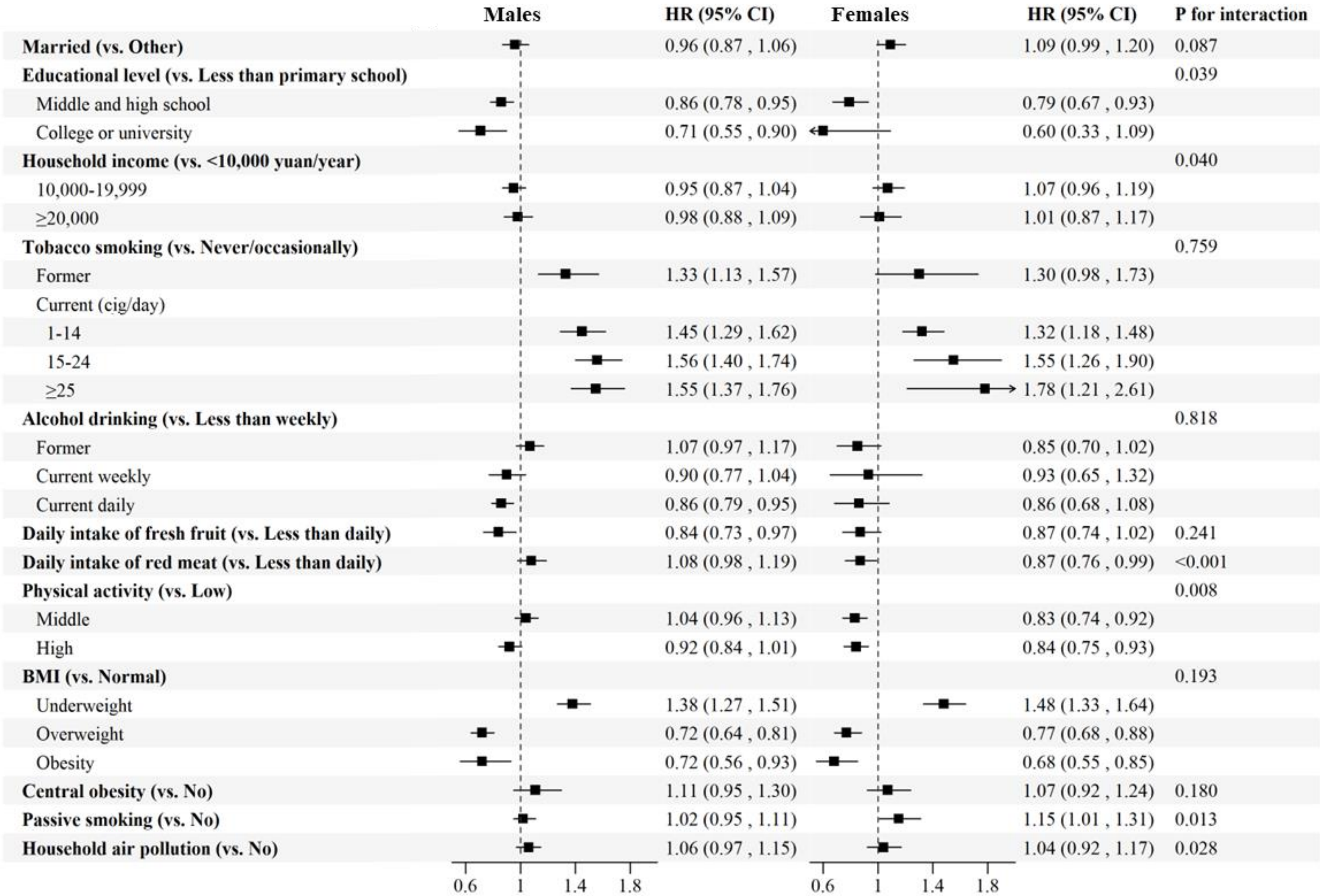

Figure 1 Adjusted HR for demographic and lifestyle factors and severe exacerbation in patients with COPD by sex.

Multivariate Cox models were adjusted above potential risk factors and respiratory-related confounders (GOLD stages, respiratory symptoms, a history of respiratory diseases), with stratification of age and study areas. The adjusted significant level of interaction was set at 0.003 by using the Bonferroni method.

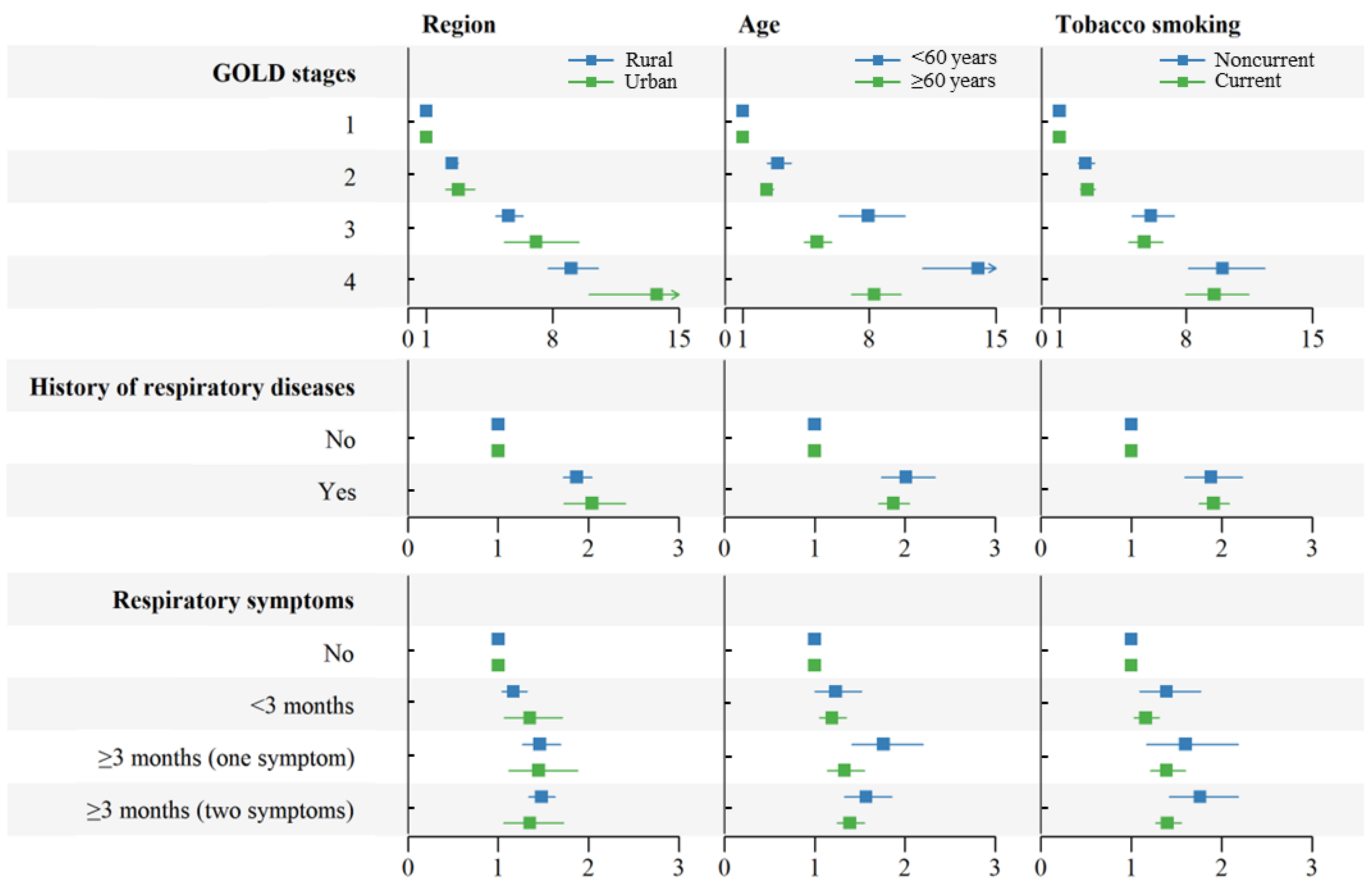

Figure 2 Subgroup analyses of respiratory-related factors and severe exacerbation in patients with COPD.

Multivariate Cox models were stratified of age and study areas, and adjusted above respiratory-related confounders, other potential risk factors (marital status, educational level, household income, tobacco smoking, alcohol drinking, fresh fruit consumption, red meat consumption, physical activity, BMI, waist circumference, passive smoking, cook pollution, heat pollution in winter, and history of cardiovascular diseases and diabetes), and the product terms of sex with red meat consumption, a history of respiratory diseases, and respiratory symptoms. Respiratory diseases included self-reported emphysema or bronchitis or tuberculosis. Respiratory symptoms included cough frequently and cough up sputum after getting up in the morning. *P* values for interaction were all <0.001 except regions with a history of any respiratory diseases and respiratory symptoms (*P* >0.05), and region with GOLD stages and tobacco smoking with GOLD stages (*P* = 0.002).