

## Preplanned Studies

# The Association Between Preserved Ratio Impaired Spirometry and Mortality — 10 CKB Study Areas, China, 2004–2022

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## Summary

### What is already known about this topic?

China has the world's most significant public health and economic burden of chronic respiratory disease. However, the association between preserved ratio impaired spirometry (PRISm) and mortality risk is unknown.

### What is added by this report?

The PRISm group exhibited a 37% higher risk of all-cause mortality than the normal group, and the risks of death from cardiovascular diseases, neoplasms, respiratory diseases, and infectious and parasitic diseases were also increased in PRISm. Moreover, the presence of respiratory symptoms or disease was associated with an increased risk of mortality in PRISm.

### What are the implications for public health practice?

It is imperative to enhance public awareness of PRISm and to implement measures to facilitate the regression of PRISm toward normal lung function.

Preserved ratio impaired spirometry (PRISm) is a non-obstructive spirometry phenotype described as a transient state associated with the progression of chronic obstructive pulmonary disease (COPD) (1). The prevalence of COPD is increasing in China (2). Previous studies excluded PRISm from respiratory studies (3), while recent studies on PRISm have predominantly been conducted in Western or high-income countries (1), leaving the significance of this lung function pattern in China uncertain. To address these gaps, this study analyzed the association between PRISm and all-cause and cause-specific mortality based on the China Kadoorie Biobank (CKB), a large-scale prospective cohort. Elevated risks of mortality from all-cause, cardiovascular, neoplastic, respiratory, and infectious and parasitic diseases were observed in PRISm, with rates comparable to those observed in obstructive spirometry. PRISm should be given more attention to avoid its progression to COPD.

The CKB, which has been reported previously (4), recruited 512,724 participants aged 30 to 79 from 10 areas across China at baseline from 2004 to 2008. All individuals underwent interviewer-administered questionnaires, physical measurements, and spirometry tests by trained technicians according to standard operating procedures. In the present study, participants with previously self-reported physician-diagnosed ischemic heart disease, stroke, cancer, or asthma at baseline, lost to follow-up shortly after baseline, with an FEV<sub>1</sub>/FVC ratio >1.0, or missing data for covariates were omitted from the study, leaving 484,301 participants.

For baseline spirometry, the higher of two measurements for both FEV<sub>1</sub> and FVC was used to calculate the FEV<sub>1</sub>/FVC ratio. Predicted FEV<sub>1</sub> was calculated using the Global Lung Function Initiative 2012 equations for the Southeast Asian and Northeast Asian populations (5). Normal lung function was defined as an FEV<sub>1</sub>/FVC ratio ≥0.7 and FEV<sub>1</sub> ≥80% predicted, PRISm as an FEV<sub>1</sub>/FVC ratio ≥0.7 and FEV<sub>1</sub> <80% predicted, and obstructive spirometry as an FEV<sub>1</sub>/FVC ratio <0.7.

Mortality data were obtained from official residential records and the Disease Surveillance Points system, supplemented by annual door-to-door investigations among those not linked to the database. Based on the International Classification of Disease, 10th Revision (ICD-10), the outcomes comprised death from all causes and cause-specific mortality, including circulatory diseases (ICD-10: I00–I99), neoplasms (C00–D48), respiratory diseases (J00–J99), infectious and parasitic diseases (A00–B99), ischemic heart disease (I20–I25), intracerebral hemorrhage (I61), ischemic stroke (I63), lung cancer (C34), COPD (J41–J44), pneumonia (J12–J18), and respiratory tuberculosis (A15–A16). Participants were censored upon death, loss to follow-up, or December 31, 2022, whichever occurred first.

Baseline variable means and prevalences were calculated for normal, PRISm, and obstructive

spirometry groups using linear regression for continuous variables and logistic regression for categorical variables, adjusted for age, sex, and 10 study areas when appropriate. Mortality rates per 100,000 person-years for each group were standardized to the age structure of the 7<sup>th</sup> National Population Census data (2020). For all-cause mortality, stratified Cox proportional hazards regression was used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs). A proportional subdistribution hazards regression model for cause-specific mortality was fitted to account for competing risks from other causes. All analyses were stratified by age (in 5-year groups), sex, and 10 study areas, and adjusted for education, occupation, household income, marital status, alcohol consumption, smoking status, passive smoking status, physical activity levels, primary cooking and heating fuel use, consumption frequency of fresh fruits, fresh vegetables, and meat, general obesity, and abdominal obesity. The proportional hazards assumption was verified using Schoenfeld residuals. Associations between mortality and PRISm were analyzed after stratification by the presence of self-reported cough or sputum, ever-smoking, physician-diagnosed bronchitis or emphysema, and tuberculosis at baseline. Subgroup analyses were conducted across sex, age ( $\geq 60$  years or not), and region (urban/rural).

Competing-risk analysis was performed using SAS (version 9.4, SAS Institute Inc, Cary, NC, USA), and all other statistical analyses were performed using R (version 4.3.1, R Foundation for Statistical Computing, Vienna, Austria). All tests were two-tailed, and  $P < 0.05$  were considered statistically significant.

The study included 484,301 participants with a mean age of 51.5 [standard deviation (SD)=10.5] years at baseline, 59.1% women, and 32.3% ever-smokers. At baseline, 117,210 (24.2%) had PRISm, with a mean FEV<sub>1</sub> % predicted of 83.9%. Compared with the normal group, individuals with PRISm or an obstructive spirometry pattern were more likely to be older, male, current or former smokers, reside in rural areas, have a lower socioeconomic level, and report poorer self-rated health status (Table 1).

During a median follow-up of 16.0 years, 73,288 deaths were documented, and the corresponding all-cause age-standardized mortality rates for normal, PRISm, and obstructive spirometry were 1,070.5, 1,574.4, and 1,943.3 per 100,000 person-years, respectively. Compared with the normal group, PRISm had a higher adjusted all-cause ( $HR=1.37$ , 95% CI: 1.35, 1.40), circulatory disease [subdistribution hazard

ratio (SHR)=1.36, 95% CI: 1.33, 1.40], neoplasm (SHR=1.07, 95% CI: 1.04, 1.11), and infectious and parasitic disease (SHR=1.47, 95% CI: 1.24, 1.73) mortality, comparable to those observed in obstructive spirometry (Table 2). For respiratory disease mortality, the SHR in PRISm was 2.45 (95% CI: 2.30, 2.60), lower than those with obstructive spirometry (SHR=5.05, 95% CI: 4.73, 5.39). For disease-specific deaths, PRISm was associated with a higher risk of death from ischemic heart disease (SHR=1.37, 95% CI: 1.31, 1.42), intracerebral hemorrhage (SHR=1.31, 95% CI: 1.25, 1.38), ischemic stroke (SHR=1.30, 95% CI: 1.20, 1.40), lung cancer (SHR=1.26, 95% CI: 1.19, 1.34), COPD (SHR=3.06, 95% CI: 2.84, 3.31), pneumonia (SHR=1.47, 95% CI: 1.28, 1.68), and respiratory tuberculosis (SHR=2.63, 95% CI: 1.82, 3.82).

When stratified by respiratory symptoms of PRISm individuals, those with frequent coughing or sputum ( $HR=1.62$ , 95% CI: 1.57, 1.68) and self-reported prior bronchitis or emphysema ( $HR=1.81$ , 95% CI: 1.72, 1.91) had a much higher risk of all-cause mortality. However, the risk of all-cause mortality in the PRISm group did not appear to be substantially affected by smoking or passive smoking status (Figure 1). Analyses of sex, age, and regional subgroups of PRISm mortality risk did not show large differences (Supplementary Table S1, available at <https://weekly.chinacdc.cn/>).

## DISCUSSION

Based on a large prospective cohort, this study explored the health effects of PRISm in the Chinese population, examining a comprehensive spectrum of mortality risks. The PRISm group exhibited a 1.4-fold higher risk of all-cause mortality. Risks of cause-specific death were also increased in the PRISm group; however, respiratory disease mortality in the PRISm group was lower than in the obstructive spirometry group, suggesting the reversibility of airflow obstruction development in PRISm. Moreover, respiratory-related symptoms and diseases were associated with an increased mortality risk, which could help identify high-risk individuals in the PRISm population.

A systematic review, including eight population-based cohort studies up to 2023, found that PRISm was associated with a 1.7-fold, 1.6-fold, and 2.0-fold increased risk of all-cause, cardiovascular, and respiratory mortality, respectively (1). These results were slightly higher than our findings; however, the

TABLE 1. Characteristics of China Kadoorie Biobank participants by obstruction state at baseline of 2004–2008.

| Characteristics                             | Normal         | PRISm          | Obstructive spirometry |
|---|----------------|----------------|------------------------|
| No. of participants                         | 341,975 (70.6) | 117,210 (24.2) | 25,116 (5.2)           |
| FEV <sub>1</sub> /FVC [%, mean (SD)]        | 86.3 (5.8)     | 83.9 (5.9)     | 64.4 (5.8)             |
| FEV <sub>1</sub> % predicted [%, mean (SD)] | 96.1 (11.1)    | 69.8 (11.3)    | 62.0 (11.2)            |
| Sociodemographic characteristics            |                |                |                        |
| Age, years [mean (SD)]                      | 50.5 (10.4)    | 53.0 (10.6)    | 58.8 (10.4)            |
| Women                                       | 59.5           | 59.9           | 50.8                   |
| Urban                                       | 44.9           | 40.5           | 29.0                   |
| South                                       | 64.8           | 46.4           | 72.8                   |
| Education >6 years                          | 50.4           | 46.1           | 45.1                   |
| Farmer or worker                            | 57.5           | 57.9           | 58.7                   |
| Household income ≥20,000 yuan/year          | 43.9           | 40.3           | 35.7                   |
| Married                                     | 91.3           | 90.4           | 89.1                   |
| Lifestyle factors                           |                |                |                        |
| Ever smoking                                | 31.8           | 32.8           | 36.3                   |
| Ever passive smoking                        | 75.5           | 75.7           | 73.8                   |
| Currently drinking                          | 15.3           | 14.7           | 14.2                   |
| Daily intake of fresh fruit                 | 18.6           | 17.1           | 16.8                   |
| Daily intake of fresh vegetables            | 94.9           | 94.3           | 94.4                   |
| >4 days/week intake meat                    | 47.6           | 46.8           | 43.9                   |
| Physical activity, MET-h/d [mean (SD)]      | 21.7 (12.2)    | 21.2 (12.5)    | 21.3 (12.3)            |
| BMI, kg/m <sup>2</sup> [mean (SD)]          | 23.6 (3.3)     | 23.8 (3.4)     | 22.5 (3.3)             |
| Abdominal obesity                           | 22.2           | 28.3           | 15.8                   |
| Personal medical history                    |                |                |                        |
| Self-rated poor health                      | 8.3            | 10.5           | 13.9                   |
| Hypertension                                | 32.7           | 37.5           | 30.5                   |
| Diabetes                                    | 5.2            | 6.1            | 4.4                    |
| Emphysema or bronchitis                     | 1.4            | 3.4            | 8.9                    |
| Frequent coughing                           | 6.9            | 9.6            | 15.0                   |
| Frequent expectoration                      | 6.2            | 8.5            | 13.0                   |

Note: Values are reported as % unless otherwise indicated and adjusted for age, sex, and study areas when appropriate. All *P* values for comparisons between groups were < 0.001, except for ever passive smoking (*P*=0.009). Lung function category definitions: normal (FEV<sub>1</sub>/FVC ratio ≥0.7 and FEV<sub>1</sub> ≥80%), PRISm (FEV<sub>1</sub>/FVC ratio ≥0.7 and FEV<sub>1</sub> <80%), and obstructive spirometry (FEV<sub>1</sub>/FVC ratio <0.7). Abbreviation: PRISm=preserved ratio impaired spirometry; FEV<sub>1</sub>=forced expiratory volume in one second; FVC=forced vital capacity; SD=standard deviation; MET-h/d=metabolic equivalents of task per hour per day; BMI=body mass index; CVD=cardiovascular disease.

review neglected the competing risks from other causes of death, leading to overestimation of the *HR*s. Evidence for disease-specific mortality risk is scarce due to the need for long-term follow-up and large sample sizes. Only one study reported that PRISm was associated with a 1.5-fold increased risk of death from stroke or heart disease (6). This study is the first to show that PRISm is associated with an increased risk of death from lung cancer, pneumonia, COPD, and respiratory tuberculosis. However, no modification effect was observed between smoking or passive

smoking and the association between PRISm and mortality. Nonetheless, previous studies have shown smoking to be a strong risk factor for PRISm and its progression to airflow obstruction (7,8), suggesting that smoking cessation should be prioritized when managing PRISm to prevent premature death.

This study has several limitations. First, like other population-based epidemiologic studies (7,9), spirometry without postbronchodilator testing may overestimate the prevalence of both PRISm and obstructive spirometry. Participants with self-reported

TABLE 2. Associations of PRISm and Obstructive Spirometry with all-cause and cause-specific mortality in China Kadoorie Biobank, 2004–2022.

| Cause of death                    | Normal           | PRISm             | Obstructive spirometry |
|-----------------------------------|------------------|-------------------|------------------------|
| All causes                        |                  |                   |                        |
| No. of deaths (mortality rate)    | 40,099 (1,070.5) | 23,791 (1,574.4)  | 9,398 (1,943.3)        |
| HR (95% CI)                       | 1.00             | 1.37 (1.35, 1.40) | 1.59 (1.56, 1.63)      |
| Circulatory diseases              |                  |                   |                        |
| No. of deaths (mortality rate)    | 16,091 (473.7)   | 10,916 (738.0)    | 3,340 (676.2)          |
| SHR (95% CI)                      | 1.00             | 1.36 (1.33, 1.40) | 1.22 (1.18, 1.27)      |
| Ischemic heart disease            |                  |                   |                        |
| No. of deaths (mortality rate)    | 6,008 (181.1)    | 4,254 (293.2)     | 1,157 (250.0)          |
| SHR (95% CI)                      | 1.00             | 1.37 (1.31, 1.42) | 1.22 (1.14, 1.30)      |
| Intracerebral haemorrhage         |                  |                   |                        |
| No. of deaths (mortality rate)    | 3,726 (96.7)     | 2,938 (186.6)     | 881 (169.7)            |
| SHR (95% CI)                      | 1.00             | 1.31 (1.25, 1.38) | 1.29 (1.19, 1.39)      |
| Ischemic stroke                   |                  |                   |                        |
| No. of deaths (mortality rate)    | 1,808 (61.0)     | 1,198 (84.5)      | 329 (64.8)             |
| SHR (95% CI)                      | 1.00             | 1.30 (1.20, 1.40) | 1.02 (0.90, 1.15)      |
| Neoplasms                         |                  |                   |                        |
| No. of deaths (mortality rate)    | 13,982 (316.1)   | 6,188 (374.5)     | 2,231 (461.3)          |
| SHR (95% CI)                      | 1.00             | 1.07 (1.04, 1.11) | 1.09 (1.04, 1.14)      |
| Lung cancer                       |                  |                   |                        |
| No. of deaths (mortality rate)    | 3,416 (77.4)     | 1,843 (111.8)     | 692 (134.8)            |
| SHR (95% CI)                      | 1.00             | 1.26 (1.19, 1.34) | 1.35 (1.24, 1.48)      |
| Respiratory diseases              |                  |                   |                        |
| No. of deaths (mortality rate)    | 2,013 (69.6)     | 2,607 (188.5)     | 2,389 (481.3)          |
| SHR (95% CI)                      | 1.00             | 2.45 (2.30, 2.60) | 5.05 (4.73, 5.39)      |
| COPD                              |                  |                   |                        |
| No. of deaths (mortality rate)    | 1,148 (39.6)     | 2,009 (146.1)     | 2,130 (426.8)          |
| SHR (95% CI)                      | 1.00             | 3.06 (2.84, 3.31) | 6.81 (6.29, 7.38)      |
| Pneumonia                         |                  |                   |                        |
| No. of deaths (mortality rate)    | 582 (21.2)       | 380 (27.6)        | 125 (26.7)             |
| SHR (95% CI)                      | 1.00             | 1.47 (1.28, 1.68) | 1.32 (1.08, 1.63)      |
| Infectious and parasitic diseases |                  |                   |                        |
| No. of deaths (mortality rate)    | 445 (10.8)       | 275 (16.8)        | 101 (22.3)             |
| SHR (95% CI)                      | 1.00             | 1.47 (1.24, 1.73) | 1.68 (1.33, 2.11)      |
| Respiratory tuberculosis          |                  |                   |                        |
| No. of deaths (mortality rate)    | 59 (1.5)         | 69 (4.9)          | 48 (10.2)              |
| SHR (95% CI)                      | 1.00             | 2.63 (1.82, 3.82) | 4.08 (2.69, 6.19)      |
| Other diseases                    |                  |                   |                        |
| No. of deaths (mortality rate)    | 7,568 (200.3)    | 3,805 (256.6)     | 1,337 (302.2)          |
| SHR (95% CI)                      | 1.00             | 1.23 (1.18, 1.28) | 1.15 (1.08, 1.22)      |

Note: The mortality rate is per 100,000 person-years and is age-standardized based on the 7<sup>th</sup> National Population Census data (2020). For cause-specific mortality, other causes of mortality were considered as competing risks, and SHRs were calculated. HRs and SHRs were stratified by age (in 5-year intervals), sex, and study areas, and adjusted for education, occupation, household income, marital status, alcohol consumption, smoking status, passive smoking status, physical activity levels, cooking and heating fuel usage, consumption frequency of fresh fruits, fresh vegetables, meat, and general and abdominal obesity. Lung function category definitions: normal ( $FEV_1/FVC$  ratio  $\geq 0.7$  and  $FEV_1 \geq 80\%$ ), PRISm ( $FEV_1/FVC$  ratio  $\geq 0.7$  and  $FEV_1 < 80\%$ ), and obstructive spirometry ( $FEV_1/FVC$  ratio  $< 0.7$ ).

Abbreviation: PRISm=preserved ratio impaired spirometry; COPD=chronic obstructive pulmonary disease; HR=hazard ratio; SHR=subdistribution hazard ratio; CI=confidence interval;  $FEV_1$ =forced expiratory volume in one second; FVC=forced vital capacity.

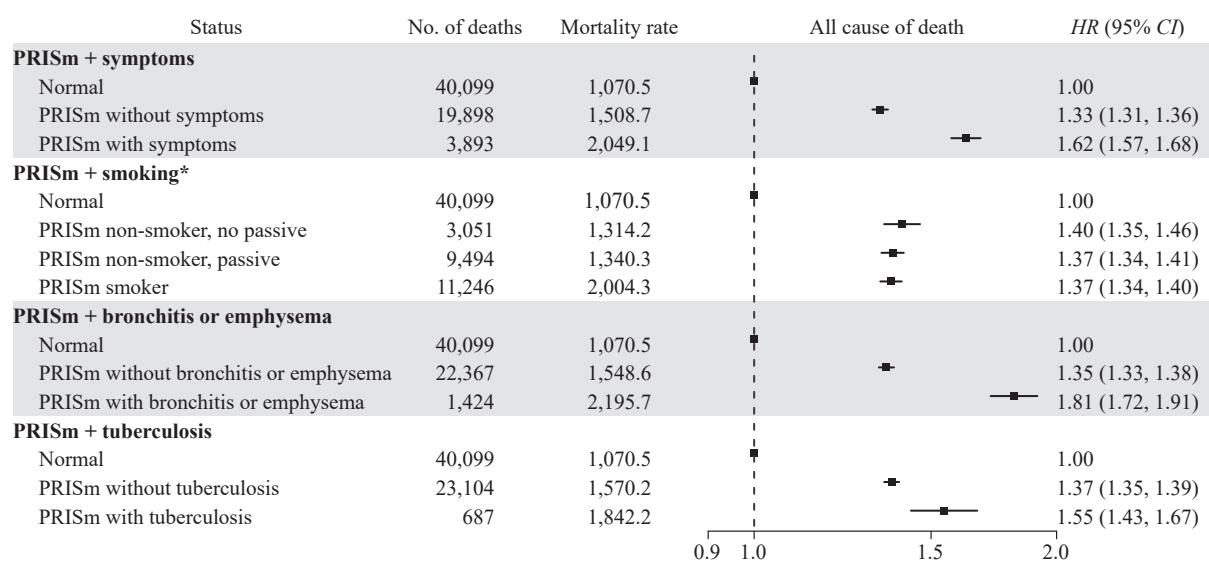


FIGURE 1. Associations of PRISm with symptoms, smoking, bronchitis or emphysema, tuberculosis at baseline with all-cause mortality in China Kadoorie Biobank, 2004–2022.

Note: The mortality rate is per 100,000 person-years and is age-standardized based on the 7<sup>th</sup> National Population Census data (2020). HRs were stratified by age (in 5-year intervals), sex, and study areas, and adjusted for education, occupation, household income, marital status, alcohol consumption, smoking status, passive smoking status, physical activity levels, cooking and heating fuel usage, consumption frequency of fresh fruits, fresh vegetables, meat, and general and abdominal obesity. Symptoms were defined as frequent coughing or sputum. PRISm was defined as FEV<sub>1</sub>/FVC ratio  $\geq 0.7$  and FEV<sub>1</sub> <80%.

Abbreviation: PRISm=preserved ratio impaired spirometry; HR=hazard ratio; CI=confidence interval.

\*PRISm individuals were grouped according to whether they never/occasionally smoked or smoked regularly, and whether they were passively exposed to smoke.

asthma at baseline were excluded to minimize such misclassification bias. Despite the potential misclassification, this study indicated that pre-bronchodilator testing is crucial and can provide significant insights, especially in resource-limited settings. Second, PRISm was employed as a single-time measurement of exposure. Given the high variability in spirometry-measured lung function observed within individuals over time (7,10), this study could not examine the relationship between longitudinal PRISm trajectories and mortality risk. Third, the generalization of results to other populations should be made with caution, as the CKB cohort sample is not nationally representative.

This study identified an elevated risk of all-cause and cause-specific mortality from PRISm in China, including circulatory, neoplasm, respiratory, and infectious and parasitic disease mortality. This finding indicates the necessity of enhancing public awareness of PRISm and taking action to prevent its progression to COPD.

**Conflicts of interest:** No conflicts of interest.

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## SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE S1. Subgroup analysis of PRISm with all-cause and chapter-specific mortality in China Kadoorie Biobank, 2004–2022.

| Subgroup  |                  | All causes   | Circulatory diseases | Neoplasms    | Respiratory diseases | Infectious and parasitic diseases | Other        |
|-----------|------------------|--------------|----------------------|--------------|----------------------|-----------------------------------|--------------|
| Sex       |                  |              |                      |              |                      |                                   |              |
| Men       | No. of deaths    | 13,033       | 5,637                | 3,711        | 1,526                | 185                               | 1,974        |
|           | (mortality rate) | (1893.3)     | (825.7)              | (507.2)      | (231.5)              | (25.8)                            | (303.1)      |
|           | HR               | 1.37         | 1.32                 | 1.11         | 2.38                 | 1.58                              | 1.18         |
|           | (95% CI)         | (1.34, 1.40) | (1.28, 1.37)         | (1.06, 1.15) | (2.20, 2.58)         | (1.28, 1.93)                      | (1.12, 1.25) |
| Women     | No. of deaths    | 10,758       | 5,279                | 2,477        | 1,081                | 90                                | 1,831        |
|           | (mortality rate) | (1258.6)     | (636.4)              | (258.3)      | (140.9)              | (9.6)                             | (213.3)      |
|           | HR               | 1.37         | 1.40                 | 1.03         | 2.55                 | 1.29                              | 1.29         |
|           | (95% CI)         | (1.34, 1.41) | (1.35, 1.46)         | (0.98, 1.08) | (2.32, 2.80)         | (0.98, 1.70)                      | (1.21, 1.37) |
| Age       |                  |              |                      |              |                      |                                   |              |
| <60 years | No. of deaths    | 8,400        | 3,278                | 2,751        | 588                  | 144                               | 1,639        |
|           | (mortality rate) | (569.5)      | (219.3)              | (184.1)      | (38.8)               | (10.6)                            | (116.7)      |
|           | HR               | 1.39         | 1.56                 | 1.07         | 3.50                 | 1.67                              | 1.37         |
|           | (95% CI)         | (1.35, 1.43) | (1.49, 1.63)         | (1.02, 1.12) | (3.08, 3.98)         | (1.33, 2.09)                      | (1.29, 1.46) |
| ≥60 years | No. of deaths    | 15,391       | 7,638                | 3,437        | 2,019                | 131                               | 2,166        |
|           | (mortality rate) | (4449.4)     | (2221.9)             | (919.1)      | (616.5)              | (34.8)                            | (657.1)      |
|           | HR               | 1.36         | 1.29                 | 1.08         | 2.15                 | 1.24                              | 1.13         |
|           | (95% CI)         | (1.33, 1.39) | (1.25, 1.33)         | (1.03, 1.13) | (2.01, 2.30)         | (0.98, 1.57)                      | (1.10, 1.20) |
| Region    |                  |              |                      |              |                      |                                   |              |
| Urban     | No. of deaths    | 8,687        | 3,711                | 2,685        | 752                  | 83                                | 1,456        |
|           | (mortality rate) | (1098.2)     | (472.2)              | (324.7)      | (99.8)               | (13.0)                            | (188.5)      |
|           | HR               | 1.34         | 1.36                 | 1.08         | 2.03                 | 1.31                              | 1.30         |
|           | (95% CI)         | (1.31, 1.38) | (1.30, 1.42)         | (1.03, 1.13) | (1.83, 2.25)         | (1.00, 1.73)                      | (1.21, 1.38) |
| Rural     | No. of deaths    | 15,104       | 7,205                | 3,503        | 1,855                | 192                               | 2,349        |
|           | (mortality rate) | (2192.7)     | (1082.4)             | (435.2)      | (315.9)              | (23.3)                            | (335.8)      |
|           | HR               | 1.39         | 1.36                 | 1.07         | 2.74                 | 1.56                              | 1.19         |
|           | (95% CI)         | (1.36, 1.42) | (1.32, 1.41)         | (1.02, 1.11) | (2.54, 2.96)         | (1.27, 1.91)                      | (1.13, 1.25) |

Note: The mortality rate is per 100,000 person-years and is age-standardized based on the 7<sup>th</sup> National Population Census data (2020). HRs were stratified by age-at-risk (in 5-year intervals), sex, and study areas, and adjusted for education, occupation, household income, marital status, alcohol consumption, smoking status, passive smoking status, physical activity levels, cooking and heating fuel usage, and consumption frequency of fresh fruits, fresh vegetables, meat, general obesity, and abdominal obesity. For cause-specific mortality, a proportional subdistribution hazards regression model was fitted to account for competing risks from other causes.

Abbreviation: PRISm=preserved ratio impaired spirometry; HR=hazard ratio; CI=confidence interval.