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Body mass index and chronic obstructive pulmonary disease-related mortality: a nationally representative prospective study of 220 000 men in China

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Accepted 15 February 2010

Background Low body mass index (BMI) is associated with chronic obstructive pulmonary disease (COPD) in populations where many are overweight. Substantial uncertainty remains about the relationship in populations with lower mean BMI levels, and about the relevance to it of the effects of smoking or of reverse causality.

Methods A nationally representative prospective cohort study included 221 194 Chinese men aged 40–79 years in 1990–91, who were followed up for 15 years or to the age of 80 years. Hazard ratios for COPD-related mortality vs baseline BMI were adjusted for age, smoking, drinking and other factors. To reduce reverse causality, main analyses excluded all men with prior history of any respiratory diseases or abnormal lung function at baseline, leaving 2960 COPD-related deaths (16% of all deaths).

Results The mean baseline BMI was 21.7 kg/m². There was a highly significant inverse association between BMI and COPD-related mortality among men without any apparent impairment of lung function. Approximately 90% of men had a baseline BMI <25 kg/m², and among them, 5 kg/m² lower BMI was associated with 31% (95% confidence interval 18–45%) higher COPD-related mortality. The excess risk persisted after restricting the analysis to never-smokers or excluding the first 5 years of follow-up.

Conclusions Low BMI is associated with increased COPD mortality in a relatively lean adult male population in China where COPD is one of the most common causes of death.

Keywords Body mass index, smoking, prospective study, chronic obstructive pulmonary disease, mortality

Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of death and disability worldwide,¹ with more than 200 million affected individuals and approximately 3 million annual deaths.² In China, COPD causes about 1.3 million deaths every year³ and the prevalence of spirometric-detected COPD in people aged ≥ 40 years has been reported to be 8%, with three-quarters of those affected having clinically manifest disease.⁴ Despite this high disease burden, epidemiological evidence about the aetiology of COPD in China is limited.⁵

In Western populations, where cigarette smoking has persisted for many decades, smoking is responsible for most COPD deaths.^{6,7} In China, the situation is different, with only about half of the male COPD deaths in the 1980s being attributable to smoking,⁸ and with high rates even among individuals who have never smoked, especially in certain inland rural regions.^{4,9,10} It has been suggested that, in addition to smoking, other factors such as particular types of indoor air pollution, chronic infection and malnutrition may also contribute significantly to risk of the disease.^{1,11–14}

Several hospital-based studies have shown that low body mass index (BMI; weight in kilograms divided by the square of the height in metres) is an independent prognostic factor for both long-term survival following diagnosis of COPD^{15–20} and disease severity.²¹ In cross-sectional studies, COPD is more prevalent among lean people.^{6,22–25} Recent data from large prospective cohort studies have also shown that low BMI is associated with COPD. However, most such studies have been in European-origin populations where the prevalence of COPD is relatively low, especially among non-smokers, and few have low BMI persistently throughout childhood and adult life.^{26–29} Furthermore, most such studies have included only small number of deaths and did not control appropriately for smoking or for the effects of pre-existing disease on BMI (reverse causality).²⁹ We report a 15-year prospective study of the association between BMI and COPD mortality in a nationally representative cohort of 220 000 men in China recruited during 1990–91, including 148 000 current smokers and 59 000 never-smokers.

Materials and methods

Baseline survey

Details of the study design, participants and baseline survey methods have been reported previously.^{30,31} Briefly, the study involves 45 areas (23 urban and 22 rural) randomly selected from China's 145 Disease Surveillance Points (DSPs). The DSP system was established in the mid-1980s to provide a nationally representative sample of mortality statistics for the entire country.^{32,33} A typical surveillance point

covers a defined population of approximately 50 000–100 000 residents in four to eight geographically defined administrative units (i.e. catchment area of urban street committees or clusters of rural villages). During 1990–91, all men aged ≥ 40 years from two or three randomly selected units within each of the 45 areas were invited to participate in the survey, and $\sim 80\%$ of invitees attended. In survey clinics set up for the study, trained health workers administered a standardized questionnaire, which included education, occupation, tobacco use, alcohol consumption, dietary patterns, exposure to indoor air pollution, self-reported medical history and health status. Physical measurements included blood pressure (BP), height, weight and peak expiratory flow rate. Waist and hip circumference and subsequent weight changes were not measured.

Follow-up for cause-specific mortality

The vital status of each study participant was monitored regularly by DSP staff through their death registries previously established in these areas. In addition, active confirmation of vital status was done annually through local residential committees. Causes of death were sought chiefly from official death certificates, supplemented, if necessary, by review of medical records.³² The underlying cause of each death was coded centrally by DSP staff in Beijing, without knowledge of the baseline information, using the ninth revision of the International Classification of Disease (ICD-9). In the few deaths without any recent medical attention, standard procedures were used by local DSP staff to determine the probable cause from symptoms or signs described by family members.³² COPD-related death was defined as death from chronic bronchitis, emphysema, asthma, bronchiectasis, other COPD, or pulmonary heart disease (ICD-9 codes 490–496 and 415–417).

Since it is often difficult to assign an underlying cause reliably for death in old age, all analyses were restricted to deaths occurring between age 40 and 79 years, with censoring when men reached 80 years of age, died from other causes or moved away from the original study area during follow-up. This report is based on follow-up data to 1 January 2006 among the 221 194 men who were aged 40–79 years and had baseline BMI in the range of 10–50 kg/m².

Statistical analysis

Cox proportional hazards models were used to calculate hazard ratios (HRs), with BMI as the exposure variable and COPD-related death as the outcome. All analyses were stratified by area (45 strata) and by 5-year age group at risk, and were adjusted simultaneously for education, tobacco use (never, former, current), alcohol consumption (at least weekly, not), regular exposure to indoor domestic or occupational air pollution from coal or biomass (yes, no), and

consumption of certain food stuffs (times/week), such as meat, vegetables and fruit. Baseline BMI was divided into five categories, with cut-off points at 18.5, 20, 22.5 and 25 kg/m². The HR for COPD-related mortality was calculated for each BMI category, with the BMI category of 20.0–22.5 kg/m² as the reference group. The 95% confidence interval (CI) for each log HR was estimated using the ‘floating absolute risk’ method,³⁴ which facilitates many different comparisons and tests for trend between different BMI categories, rather than just pair-wise comparisons between one arbitrarily chosen reference group and each of the other categories. Trend tests were conducted treating BMI as a continuous variable in the Cox model. The analyses were done in SAS version^{9.1} (SAS Institute Inc., Cary, NC, USA) under Windows XP.

Results

For the 221 194 participants (mean baseline age 54.3 years), overall mean BMI was 21.7 (standard deviation 2.7) kg/m², with 9.2% being underweight (BMI <18.5 kg/m²), and 11.1% being either overweight (BMI 25 to <30 kg/m², 10.3%) or obese (BMI ≥30 kg/m², 0.8%). The mean age-adjusted BMI was higher among urban than among rural men (23.1 vs 21.2 kg/m²). After adjusting for area and age, it was strongly positively related to BP (Table 1), with similar gradients for smokers and never-smokers (data not shown). Men with high BMI were slightly better educated, and somewhat more likely to drink alcohol. The prevalence of smoking was strongly inversely associated with BMI, but among current smokers, the mean number of cigarette smoked per

Table 1 Baseline characteristics of participants and standardized mortality rate from COPD-related disease by BMI category, all men aged 40–79 years at baseline

Baseline characteristics ^a	All	BMI categories (kg/m ²)				
		<18.5	18.5–19.9	20–22.4	22.5–24.9	≥25
Total population	221 194	20 338	37 748	89 079	49 418	24 611
Mean BMI (kg/m ²)	21.7	17.6	19.4	21.3	23.5	26.9
Mean age (years)	54.3	59.0	55.4	53.4	53.1	54.4
Living in urban area (%)	27.2	17.9	15.5	19.3	35.6	64.4
Mean weight (kg)	59.0	48.4	53.0	57.8	63.4	72.3
Mean height (cm)	164.5	165.5	165.1	164.7	163.9	163.5
Mean SBP (mm Hg)	124.1	119.4	121.3	123.4	125.8	131.2
Mean peak flow (l/min)	395.2	360.8	381.9	397.7	406.8	412.1
Education ≥6 years (%)	33.1	32.8	31.4	32.3	34.3	36.6
Ex-smokers (%)	6.3	6.1	5.2	5.5	6.8	9.8
Current smokers (%)	67.1	72.3	71.6	68.7	63.7	56.8
Number of cigarettes/day	11.9	11.6	11.6	11.9	12.1	12.3
Age started smoking (years)	22.2	22.0	22.1	22.2	22.4	22.7
Regular alcohol drinking (%)	33.5	30.6	31.9	33.7	34.6	35.1
Exposure to indoor air pollution (%)	10.9	11.1	10.9	10.7	11.0	11.1
Intake of meat (times/week)	3.5	3.3	3.3	3.4	3.6	3.8
Intake of vegetable (times/week)	13.8	13.7	13.7	13.7	13.8	13.9
Intake of fruit (times/week)	1.3	1.2	1.2	1.3	1.4	1.6
History of major chronic disease (%)	19.4	27.7	21.0	17.7	17.2	20.2
Prior respiratory disease (%)	15.9	24.6	17.9	14.6	13.6	14.5
Chronic respiratory symptoms (%)	28.4	36.6	30.8	27.0	25.4	29.0
Self-reported poor health status (%)	7.3	13.5	8.4	6.6	5.5	6.6
Mortality from COPD ^b						
Number of deaths	8769	1860	1980	3244	1264	421
Mortality rate /100 000	255.6	490.9	301.1	235.1	194.5	189.2

^aExcept for locality and age, all other characteristics were adjusted for individual area and age by 5-year age group, by direct standardization to the whole study population.

^bMortality rates were standardized to the geographic area and the 5-year age group structure in the study population aged 40–79 years.

SBP, systolic BP.

day was not associated with BMI (which implies that, among smokers, the dose of tobacco per kilogram of body weight was inversely related to BMI). Men with low BMI were more likely to report a prior history of disease at baseline (Table 1).

During the 15-year follow-up, 40 907 died before 80 years of age, 8769 (21.4%) from COPD-related conditions. Of the remainder, 34 165 (1% per annum) were lost to follow-up, mainly because of demolition of whole neighbourhoods for redevelopment. Those lost to follow-up did not differ significantly from those not in the main baseline characteristics such as age, SBP, BMI or prevalence of ever-smoking.³¹ The standardized COPD mortality rate was more than twice as high among men with than without a history of respiratory disease at baseline (540 vs 203 per 100 000, respectively). It was also about twice as high among rural than urban men (290 vs 156 respectively), and higher among ever-smokers than among never-smokers (265 vs 223 respectively). Overall,

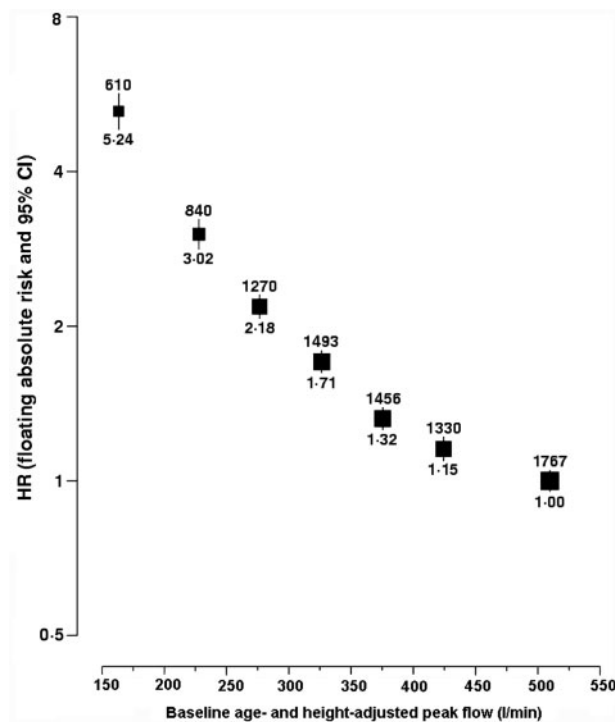


Figure 1 HRs for death from COPD-related disease vs baseline age- and height-adjusted peak flow (l/min) among men aged 40–79 years. Analyses were stratified by area and age, and adjusted simultaneously for education, tobacco, alcohol, exposure to indoor domestic or occupational air pollution and dietary patterns. The HRs are plotted on a floating absolute scale. Each square has an area inversely proportional to the standard error (SE) of the log risk. Vertical lines indicate the corresponding 95% CIs ($HR \times \exp \pm 1.96SE$). Numbers above CIs are of deaths and those below CIs are the HRs

there was a highly significant inverse association between BMI and COPD-related mortality, with the death rate in the lowest BMI group ($<18.5 \text{ kg/m}^2$) being 2.5-fold that in the highest group ($\geq 25 \text{ kg/m}^2$) (Table 1).

Peak expiratory flow rate was strongly inversely associated with COPD-related mortality (Figure 1). This inverse association was particularly steep among men with impaired lung function at baseline [i.e. a diagnosis of prior tuberculosis (TB), chronic bronchitis, asthma, emphysema or pulmonary heart disease; self-reported chronic respiratory symptoms (i.e. cough or shortness of breath); or in the lowest quintile of age- and height-adjusted peak expiratory flow rate] (Figure 2). Among these participants, each 5 kg/m^2 lower baseline BMI was associated with 118% (95% CI 104–134%) higher risk of COPD-related death for BMI $<25 \text{ kg/m}^2$, whereas in men without impaired lung function, the increase in risk was shallower [30% (17–44%)]. Exclusion of the first 5 years

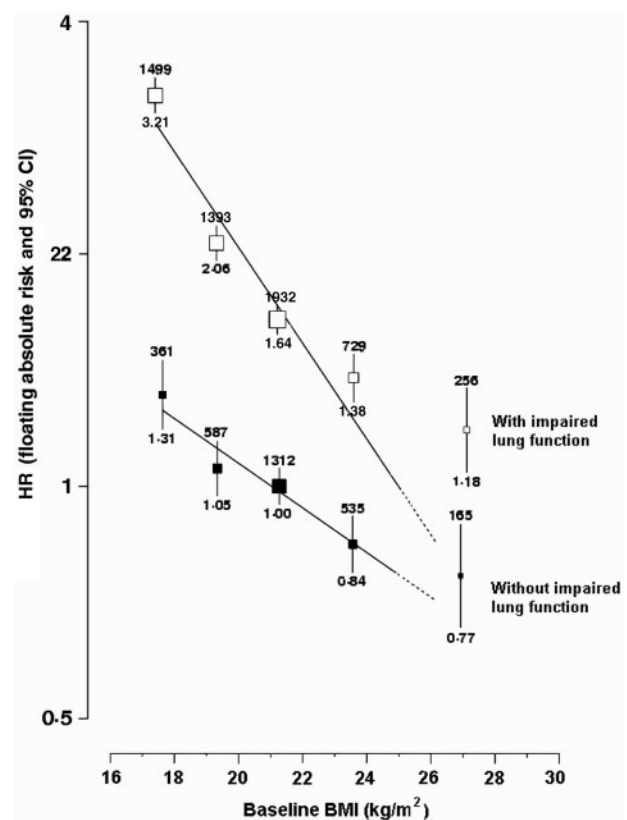


Figure 2 HRs for death from COPD-related disease vs baseline BMI among men aged 40–79 years (i) with impaired lung function at baseline (white squares) and (ii) without impaired lung function at baseline (black squares). Conventions as in Figure 1; trends were fitted by linear regression through mean BMI for each category among men with baseline BMI $<25 \text{ kg/m}^2$

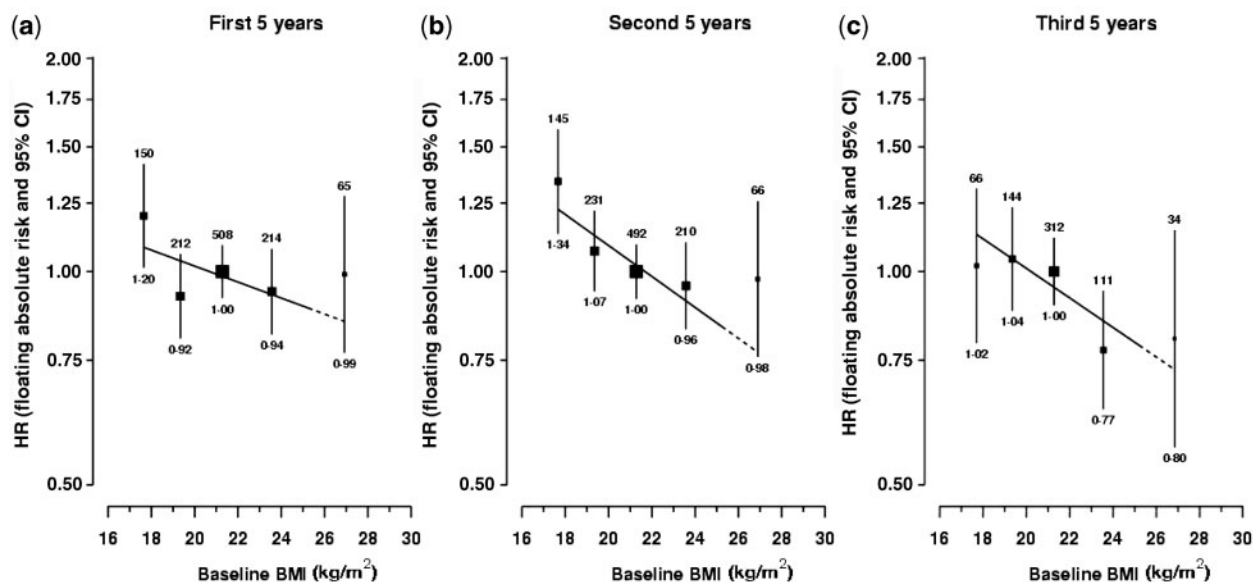


Figure 3 HRs for death from COPD-related disease vs baseline BMI among men aged 40–79 years with no prior respiratory disease or impaired lung function at baseline in (a) the first 5 years, (b) the second 5 years and (c) the third 5 years of follow-up. Conventions as in Figures 1 and 2

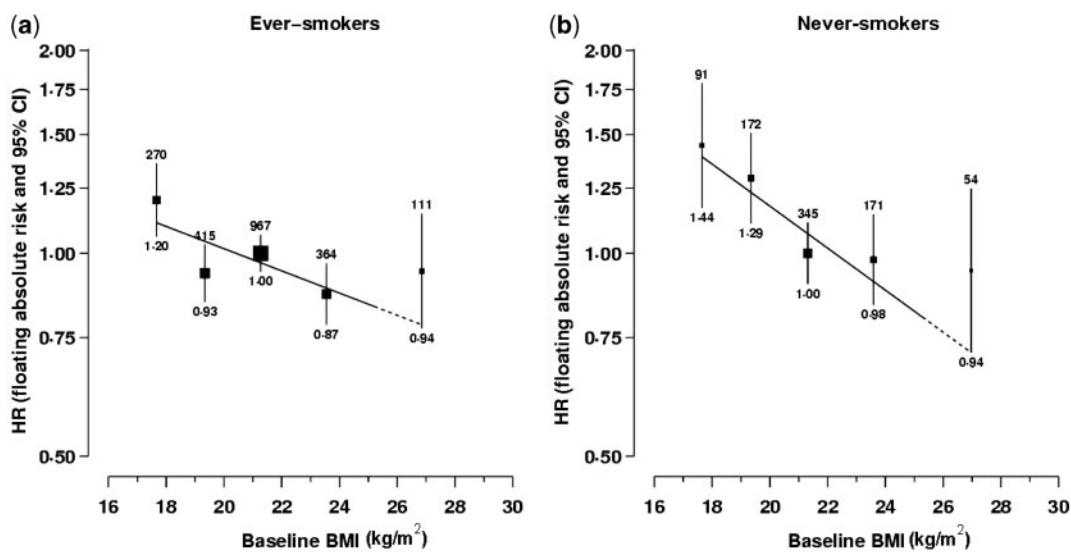


Figure 4 HRs for death from COPD-related disease vs baseline BMI among men aged 40–79 years with no prior respiratory disease or impaired lung function at baseline in (a) ever-smokers and (b) never-smokers. Conventions as in Figures 1 and 2

of follow-up did not materially alter these relationships [94% (76–113%) higher risk per 5 kg/m² lower BMI for men with impaired lung function vs 34% (17–53%) for men without it]. To limit the effects of reverse causality, those with impaired lung function at baseline were excluded from subsequent analyses.

Among men without any apparent impairment of lung function, the relationship of BMI with the COPD HR was similar during different periods of follow-up ($P=0.4$ for heterogeneity among the three follow-up periods, Figure 3). Moreover, further exclusion of those who reported poor health status at baseline did not materially change the association (data

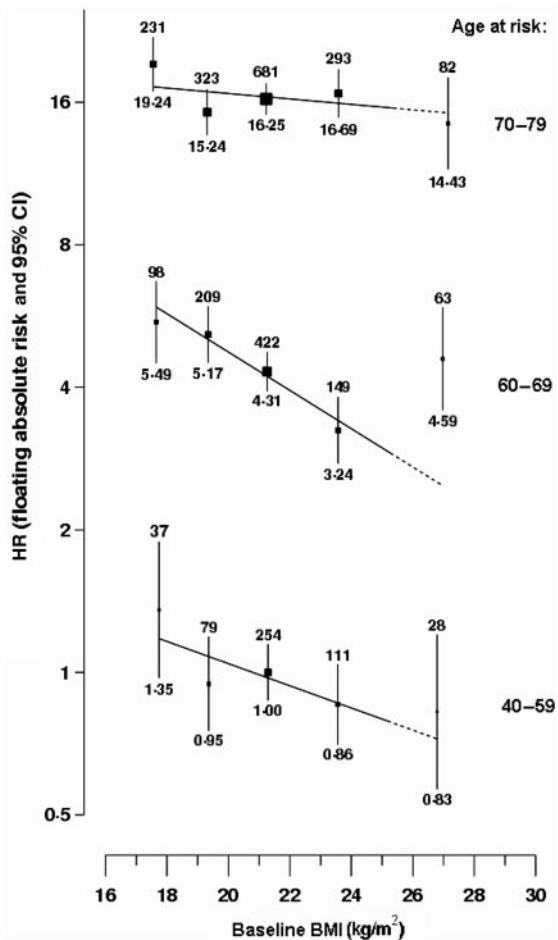


Figure 5 HRs for death from COPD-related disease vs baseline BMI among men with no prior respiratory disease or impaired lung function at baseline, by age at risk. Conventions as in Figures 1 and 2

not shown). The inverse association between BMI and COPD-related mortality was slightly more extreme in never-smokers than in ever-smokers (Figure 4). Among ever-smokers, each 5 kg/m² lower BMI was associated with 24% (10–40%) higher risk at BMI <25 kg/m², whereas among never-smokers, each 5 kg/m² lower BMI was associated with 49% (22–82%) higher risk. After further exclusion of the first 5 years of follow-up, the association was not altered, with each 5 kg/m² lower BMI associated with 29% (11–51%) and 52% (15–99%) higher risks among ever- and never-smokers, respectively.

Figure 5 shows the association of BMI with COPD-related death separately for different age groups. The inverse association appeared to be somewhat steeper at age <70 years than at age 70–79 years ($P < 0.05$ for heterogeneity test). Among men with BMI <25 kg/m², there was little evidence that the strength of the association was significantly modified

by other factors such as locality, level of education, alcohol drinking or exposure to indoor air pollution (Figure 6).

In the study, COPD accounts of 87% of all respiratory deaths, with a further 595 (6%) deaths from TB. For TB mortality, a significant inverse association with BMI was also seen, with HRs of 2.6, 1.6, 1.0, 0.7 and 0.3 for men with BMI <18.5, 18.5–20, 20–22.5, 22.5 and ≥ 25 kg/m² respectively. Below 25 kg/m², each 5-kg/m² lower BMI was associated with 237% (95% CI 170–319%) higher TB mortality.

Discussion

This is one of the largest prospective studies of the relationship between BMI and COPD-related mortality in a relatively lean population, and it involved a nationally representative population of Chinese men with nearly 9000 COPD-related deaths. In this population, ~90% of men had baseline BMI <25 kg/m² (as opposed to <50% in many Western countries^{35,36}). Among those who did, there was a highly significant inverse relationship between BMI and COPD-related mortality, with each 5-kg/m² lower BMI associated with 30% higher mortality. The association was largely independent of age, smoking and other factors, and the extent to which the association could be biased by reverse causality was limited by exclusion of all who had evidence of impaired lung function at baseline.

Several prospective studies both in Western and in East Asian populations have reported an inverse association between BMI and COPD.^{27–29,37} There were differences between those studies in the strengths of the relationships, which may be partly due to difference in the completeness of control for reverse causality by prior disease and for confounding by smoking. Moreover, most previous studies have smaller numbers of COPD cases, especially at lower levels of BMI, so the shape of the association between BMI and COPD mortality may have been more susceptible to the play of chance. For example, in the recently published European Prospective Investigation into Cancer and Nutrition among 360 000 participants, only 637 respiratory deaths (4% of total deaths) were recorded after 10 years of follow-up.²⁸ In that study, there was a strong inverse association between baseline BMI and respiratory mortality, with the risk among men with BMI <18.5 kg/m² 6.5 times that among men with BMI 23.5–25.0 kg/m². It was, however, not clear to what extent the excess risk at low BMI could be attributed to reverse causality, for the analysis did not exclude those with prior respiratory disease. In a recently published collaborative meta-analysis of BMI and cause-specific mortality among 900 000 individuals in 57 prospective studies [the Prospective Studies Collaboration (PSC)], mostly in population of European origin,²⁹ COPD mortality

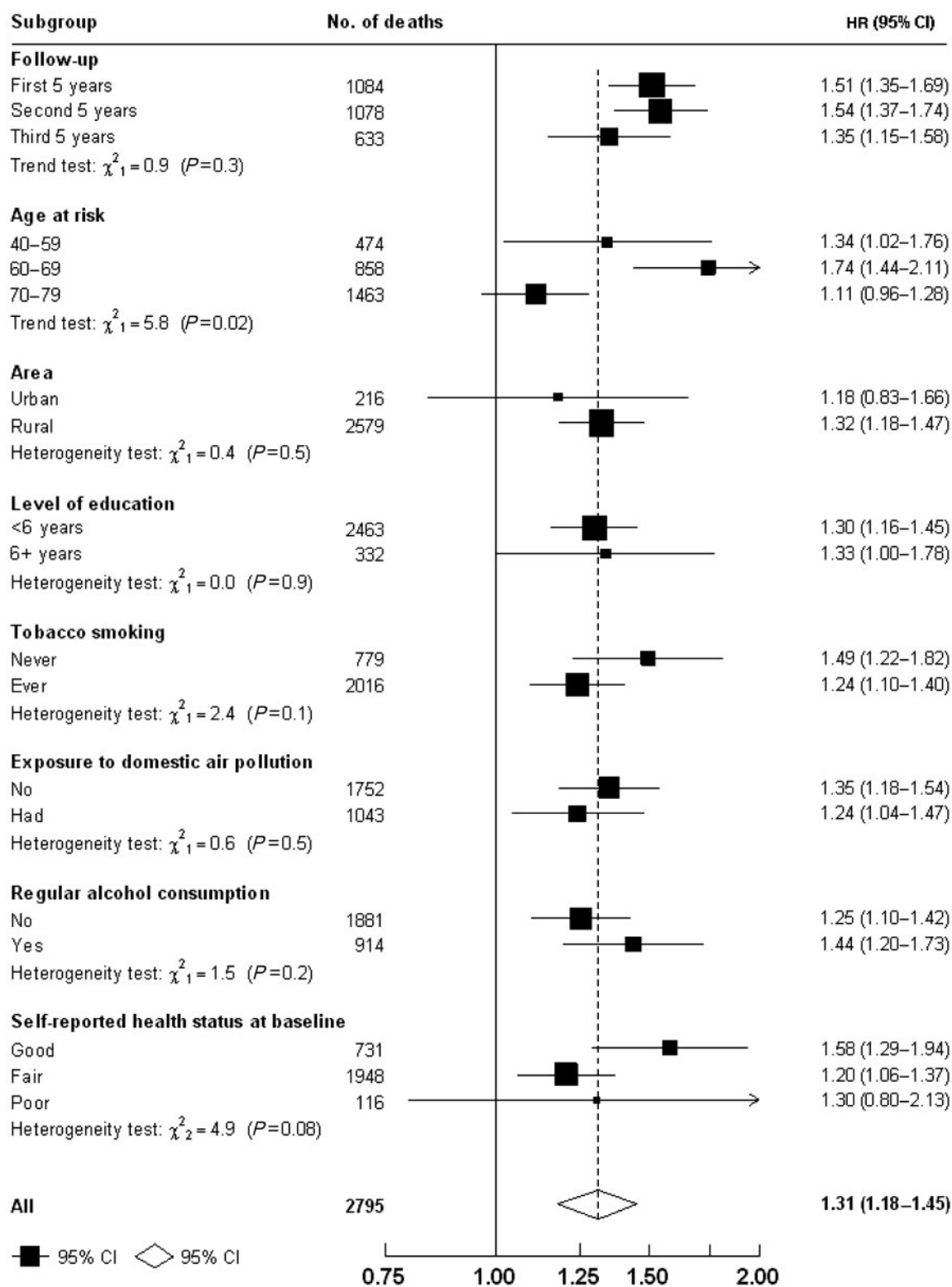


Figure 6 HRs for death from COPD-related disease per 5-kg/m² lower BMI among men with baseline BMI <25.0 kg/m² and with no prior respiratory disease or impaired lung function at baseline. Each closed square represents an HR with area inversely proportional to the variance of log HR. The dotted vertical line indicates the overall HR; the open diamond indicates it and its 95% CI.

(1958 deaths) was strongly inversely associated with BMI, with each 5-kg/m² lower BMI associated with a 4-fold increased risk within the BMI range of 15–25 kg/m². In the PSC, COPD was defined as in the present study, with the exception of pulmonary heart disease, but the PSC could not exclude people with COPD or abnormal lung function at baseline, which may help to explain why the inverse association with COPD mortality was much more extreme than in the present study. Moreover, smoking is much more strongly associated with COPD in Western populations than in Chinese populations,⁸ and so is the relationship between smoking and BMI.²⁹ Thus confounding by some aspect of smoking may have been more substantial than in the present study, further inflating the excess risk associated with low BMI.

The overall findings are generally consistent with limited data from other prospective studies in Asian populations.^{38–40} In a large prospective study of 170 000 adult Chinese,³⁹ 10.8% men and 12.5% women were underweight at baseline, and there were 2470 COPD-related deaths after ~8 years of follow-up. As in the present study, smoking was only weakly associated with COPD mortality, and BMI was strongly inversely associated with COPD-related mortality, with a risk ratio of 2.7 (95% CI 2.3–3.0) comparing underweight with other men. However, no information was available in that study about pre-existing disease or lung function at baseline, so control for reverse causality bias was chiefly by exclusion of the first few years of follow-up.

In the present study, potential biases related to reverse causality from prior disease and confounding by smoking have been limited. A reliable diagnosis of COPD is usually based on a typical history of persistent progressive symptoms, and a confirmatory spirometric test.⁴¹ In China, only about one-third of those with spirometric evidence of COPD had ever been clinically diagnosed.^{4,42} Moreover, many patients with COPD die from other causes, with less than half having COPD certified as the underlying cause of death.³⁹ To help reduce potential under-reporting of COPD as cause of death, we used COPD-related mortality as our main endpoint for analysis, which included not only COPD deaths, but also those with asthma and pulmonary heart disease as the underlying causes of death. This definition was compatible with that used in another large COPD-related study in China³⁹ and in the PSC.²⁷ Due to lack of a more complex spirometry measurement at baseline, we used the measured peak flow rate as an indicator of pulmonary function. Though not ideal, it should have helped identify undiagnosed cases of serious COPD at baseline.⁴³ In addition to excluding those with any prior respiratory disease or abnormal lung function at baseline, data were also examined separately among ever- and never-smokers and by different

periods of follow-up. The strong inverse relationship of BMI to COPD-related mortality persisted even after excluding the first 10 years of follow-up, and was present not only among smokers but also among never-smokers.

Still, however, it may not be causal. COPD can lead to weight loss over a prolonged period of time and many of the patients with prior COPD, despite exclusion of those with prior disease, with impaired lung function, or dying in the first 5 years of follow-up, may still not have been properly identified, so the residual inverse association could still have been mainly due to reverse causality. On the other hand, some close correlate of low BMI, such as malnutrition, might itself cause or aggravate COPD.⁴⁴ Clinic-based studies suggest that low BMI is an independent prognostic factor of poor long-term survival following diagnosis of COPD.^{19,45} There is also evidence that low body weight could predispose to an increased risk of chronic infection such as pulmonary TB,^{46,47} a disease which was also shown in this study to be strongly inversely related to BMI. If chronic respiratory infections also play a role in the aetiology of COPD,⁴⁸ it may help to understand the possible biological mechanism underlying the inverse relationship between BMI and COPD death. Newly established large blood-based prospective studies in China⁴⁹ may help resolve this. Although other measures of body composition (e.g. waist to hip ratio or percentage body fat)^{15,25,50–52}; some instrumental variable like offspring BMI⁵³ or some direct measure of low physical activity might have been helpful, they were not available in the present study.

The recent large increase in male cigarette consumption⁵⁴ in China may eventually lead to a substantial increase in COPD.^{4,42,55} Conversely, if some close correlate of low BMI increases COPD through mechanisms yet to be elucidated, then the recent rise in mean BMI in the population as a result of decreased undernutrition could decrease future COPD rates. At present, however, COPD is a major cause of premature death and disability in China and low BMI is an intriguingly unexplained correlate of it.

Funding

Chinese Ministry of Health; UK Medical Research Council, British Heart Foundation, Cancer Research UK; the World Bank loan to China; the Canadian International Development Research Centre.

Acknowledgements

The authors thank the study participants and the China DSP staff.

Conflicts of interest: None declared.

KEY MESSAGES

- Low BMI is associated with increased risk of COPD mortality in a relatively lean adult male population, in which about 90% had BMI < 25 kg/m² in 1990–91.
- After excluding all who had history of chronic respiratory diseases or impaired lung function at baseline, each 5 kg/m² lower BMI was associated with 31% (95% CI: 18%–45%) higher COPD-related mortality.
- The excess risk associated with low BMI persisted after restricting the analysis to never smokers or excluding the first 5 years of follow-up.
- In this study, COPD accounted for more than 20% of all the deaths. The study only relates BMI levels in 1990 to COPD mortality around year 2000; it does not directly relate the current or future BMI levels to future mortality.

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