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Ling Yang, Maigeng Zhou, Margaret Smith, Gonghuan Yang, Richard - Peto, J Boreham, Zm Chen

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Body mass index and COPD-related mortality: A nationally representative prospective study of 220 000 men in China

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4 **Body mass index and COPD-related mortality: A nationally**
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6 **representative prospective study of 220 000 men in China**
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13 Ling Yang¹, Maigeng Zhou², Margaret Smith¹, Gonghuan Yang², Richard Peto¹, Jun
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15 Wang², Jillian Boreham¹, Yisong Hu², Zhengming Chen¹
16
17
18

- 19
20
21 1. Clinical Trial Service Unit & Epidemiological Studies Unit (CTSU), Richard Doll
22 Building, Old Road Campus, University of Oxford, Oxford OX3 7LF, UK
23
24 2. Center of Public Health Surveillance and Information Service, Chinese Center for
25 Disease Control and Prevention, Beijing 102206, P.R. China
26
27
28
29

30 Correspondence to:

31
32
33 CTSU
34 Richard Doll Building,
35 Old Road Campus,
36 University of Oxford, Oxford OX3 7LF,
37 United Kingdom,
38 Email: ling.yang@ctsu.ox.ac.uk
39
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Abbreviations

COPD: Chronic Obstructive Pulmonary Disease

BMI: Body Mass Index

DSP: Disease Surveillance Point

CDC: Centre for Disease Control

ICD: International Classification of Disease

HR: Hazard Ratio

CI: Confidence Interval

WHO: World Health Organization

EPIC: European Prospective Investigation into Cancer and Nutrition

PSC: Prospective Studies Collaboration

Summary

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.

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. Hazard ratios of COPD-related death relating to 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 2,960 COPD-related deaths (16% of total 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% CI: 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 risk of 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; COPD; mortality

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a leading cause of mortality and disability world-wide,¹ with an estimate of over 200 million affected individuals and about 3 million annual deaths.² In China, COPD causes about 1.3 million deaths each year³ and the prevalence of spirometric-detected COPD in people aged 40 years or above 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 aetiology of COPD in China is limited.⁵

In Western populations, where cigarette smoking has persisted for many decades, smoking is responsible for most of COPD deaths.^{6;7} In China, the situation is quite different, with only about half of the male COPD deaths being attributable to smoking⁸, and the disease rate is high 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 some 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 meters) is an independent prognostic factor for both long-term survival following diagnosis of COPD¹⁵⁻²⁰ 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 Western 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 small number of deaths and did not control appropriately for

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3 smoking or for the effects of pre-existing disease on BMI (the reverse causality).²⁹ We
4 report a 15-year prospective study of the association between BMI and COPD mortality
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6 in a nationally representative cohort of 221,000 men in China recruited during 1990-91,
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8 including 148,000 current smokers and 59,000 never-smokers.
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13 **MATERIALS AND METHODS**

14 ***Baseline survey***

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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)
which were 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 about 50,000-100,000 residents in 4-8
geographically defined units (ie, urban street committees or clusters of rural villages).
During 1990-91, all men aged 40 years or over from two or three randomly selected
units within each of the 45 areas were invited to participate in the survey, and about
80% of invitees attended. In the survey clinics set up for the study, trained health
workers administered a standardized questionnaire, which included education,
occupation, tobacco, alcohol, dietary pattern, exposure to indoor air pollution, self-
reported medical history and health status. Physical measurements included blood
pressure, height, weight and peak expiratory flow rates. Waist and hip circumferences
and subsequent weight changes were not measured.

56 ***Follow-up for cause-specific mortality***

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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

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4 confirmation of vital status was done annually through local residential committees.
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6 Causes of death were sought chiefly from official death certificates, supplemented, if
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8 necessary, by review of medical records.³² The underlying cause of each death was
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10 coded centrally by DSP staff in Beijing, without knowledge of the baseline information,
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12 using the ninth revision of the International Classification of Disease (ICD-9). In the few
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14 deaths without any recent medical attention, standard procedures were used by local
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16 DSP staff to determine the probable cause from symptoms or signs described by family
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18 members.³² COPD-related death was defined as death from chronic bronchitis,
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20 emphysema, asthma, bronchiectasis, other chronic obstructive pulmonary disease, or
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22 pulmonary heart disease (ICD-9 codes 415-417 and 490-496).
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28 Since it is often difficult to assign an underlying cause reliably for death in old age, all
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30 analyses were restricted to deaths occurring between age 40-79, with censoring when
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32 men reached 80 years of age, died from other causes or moved away from the original
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34 study area during follow-up. This report is based on follow-up data to 1,1,2006 among
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36 the 221,194 men who were aged 40-79 years and had baseline BMI in the range of 10-
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38 50 kg/m².
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43 ***Statistical analysis***

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46 Cox proportional hazards models were used to calculate hazard ratios (HRs), with BMI
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48 as the exposure variable and COPD-related death as the outcome. All analyses were
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50 stratified by area (45 strata) and by 5-year age group at risk, and were adjusted
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52 simultaneously for education, tobacco (never, former, current), alcohol (at least
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54 weekly/not), regular exposure to indoor domestic or occupational air pollution from coal
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56 or biomass (yes/no), and consumption of certain food stuffs (times/week), such as meat,
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58 vegetable and fruit. Baseline BMI was divided into five categories, with cut-off points at
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4 18.5, 20, 22.5 and 25 kg/m². The HR for COPD-related mortality was calculated for
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6 each BMI category, with the BMI category of 20.0-22.5 kg/m² as the reference group.
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8 The 95% confidence interval (CI) for each log HR was estimated using the 'floating
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10 absolute risk' method.³⁴ This facilitates many different comparisons and tests for trend
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12 between different BMI categories, rather than just pair-wise comparisons between one
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14 arbitrarily chosen reference group and each of the other categories. Trend tests were
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16 conducted treating BMI as a continuous variable in the Cox model. The analyses were
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18 done in SAS version 9.1 under Windows XP.
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24 RESULTS

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26 For the 221,194 participants (mean baseline age of 54.3 years), overall mean BMI was
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28 21.7 (SD 2.7) kg/m², with 9.2% being underweight (BMI <18.5 kg/m²), and 11.1% being
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30 either overweight (BMI 25 to <30 kg/m², 10.3%) or obese (BMI ≥30 kg/m², 0.8%). The
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32 mean age-adjusted BMI was higher among urban than among rural men (23.1 vs 21.2
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34 kg/m²). After adjusting for area and age, it was strongly positively related to blood
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36 pressure (table 1), with similar gradients for smokers and never-smokers (data not
37
38 shown). Men with high BMI were slightly better educated, and were somewhat more
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40 likely to drink alcohol. The prevalence of smoking was strongly inversely associated with
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42 BMI, but among current smokers, the mean number of cigarette smoked per day was
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44 not associated with BMI (which implies that, among smokers, the dose of tobacco per
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46 kilogram of body weight was inversely related to BMI). Men with low BMI were more
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48 likely to report a prior history of disease at baseline. (table 1)
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55 During the 15-year follow-up, 40,907 died before age 80, of which 8,769 (21.4%) were
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57 due to COPD-related conditions. Of the remainder, 34,165 (1% per annum) were lost to
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59 follow-up, mainly because of demolition of neighborhood for redevelopment. Those lost
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4 did not differ significantly from those not in the main baseline characteristics such as
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6 age, SBP, BMI, prevalence of ever-smoking.³¹ The standardized COPD mortality rate
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8 was more than twice as high among men with a history of respiratory disease as among
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10 men without it (540 vs 203 per 100,000). It was also about twice as high among rural
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12 men as among urban men (290 vs 156), and higher among ever-smokers than among
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14 never-smokers (265 vs. 223). Overall there was a highly significant inverse association
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16 between BMI and COPD-related mortality, with the death rate in the lowest BMI group
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18 (<18.5 kg/m²) being 2.5 fold that in the highest group (≥25 kg/m²) (table 1).
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24 In the study, the peak expiratory flow rate was strongly inversely associated with the
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26 COPD-related death (figure 1). However, the inverse association between BMI and
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28 COPD-related death was particularly steep among men with impaired lung function at
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30 baseline, defined as having pre-existing respiratory diseases (i.e. TB, chronic bronchitis,
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32 asthma, emphysema or pulmonary heart disease), or self-reported chronic respiratory
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34 symptoms (ie cough or shortness of breath) or being in the lowest quintile of age- and
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36 height-adjusted peak expiratory flow rate) (figure 2). Among these participants, each 5
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38 kg/m² lower baseline BMI was associated with 118% (95%CI: 104%-134%) higher risk
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40 of COPD-related death for BMI <25 kg/m²), while in men without impaired lung function,
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42 the increased risk was much less extreme (30% [17%-44%]). The exclusion of the first 5
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44 years of follow-up did not materially alter the relationships (94% [76%-113%] higher risk
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46 per each 5 kg/m² lower BMI for men with impaired lung function versus 34% [17%-53%]
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48 higher risk for men without it). To help minimize the effects of reverse causality, those
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50 with impaired lung function at baseline were excluded from subsequent analyses.
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58 Among men without any apparent impairment of lung function, the relationship of BMI
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60 with COPD mortality varies little at different periods of follow-up (p=0.4 for heterogeneity

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3 among the three follow-up periods, figure 3). Moreover, further exclusion of the small
4 number of individuals who reported poor health status at baseline did not materially
5 change the association (data not shown). The inverse association between BMI and
6 COPD-related mortality was slightly more extreme in never-smokers than in ever-
7 smokers (figure 4). Among ever-smokers, each 5 kg/m² lower BMI was associated with
8 24% (10%-40%) higher risk at BMI<25 kg/m², whereas among never-smokers, each 5
9 kg/m² lower BMI was associated with 49% (22%-82%) higher risk. After further
10 exclusion of the first 5 years of follow-up, the association was not altered, with each 5
11 kg/m² lower BMI associated with 29% (11%-51%) and 52% (15%-99%) higher risks
12 among ever- and never-smokers respectively.
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28 Figure 5 shows the association of BMI with COPD-related death separately for different
29 age groups. The inverse association appeared to be somewhat steeper at age <70 than
30 at age 70-79 years ($p<0.05$ for heterogeneity test). Among men with BMI<25 kg/m²,
31 there was little evidence that the strength of the association was significantly modified
32 by other factors such as locality, level of education, alcohol drinking or exposure to
33 indoor air-pollution (figure 6).
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43 In the study, COPD accounts of 87% of all respiratory deaths, with a further 595 (6%)
44 deaths from TB. For TB mortality, a significant inverse association with BMI was also
45 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,
46 22.5 and ≥ 25 kg/m² respectively. At BMI <25 kg/m², each 5 kg/m² lower BMI was
47 associated with 237% (95%CI: 170%-319%) higher TB mortality.
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DISCUSSION

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4 This is one of the largest prospective studies of the relationship between BMI and
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6 COPD-related mortality in a relatively lean population, and it involved a nationally
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8 representative population of Chinese men with nearly 9,000 COPD-related deaths. In
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10 this population, approximately 90% of men had baseline BMI < 25 kg/m² (as opposed to
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12 less than 50% in many Western countries^{35;36}), and among them there was a highly
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14 significant inverse relationship between BMI and COPD-related mortality with each 5
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16 kg/m² lower BMI associated with 30% higher mortality. The association was largely
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18 independent of age, smoking and other factors, and the extent to which the association
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20 could be biased by reverse causality was greatly limited by exclusion of all who had
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22 evidence of impaired lung function at baseline.
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28 Several prospective studies both in Western and in East Asian populations have
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30 reported an inverse association between BMI and COPD.^{27-29;37} There were differences
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32 in the strength of the relationship between these studies, which may be partly due to
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34 difference in the completeness of control for reverse causality by prior disease and for
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36 confounding by smoking. Moreover, most previous studies have not individually
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38 recorded large numbers of COPD cases, especially at lower levels of BMI, so the shape
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40 of the association between BMI and COPD may be particularly susceptible to the play of
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42 chance. For example, in the recently published European Prospective Investigation into
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44 Cancer and Nutrition (EPIC) among 360,000 participants, only 637 respiratory deaths
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46 (4% of total deaths) were recorded after 10 years of follow-up.²⁸ In that study, there was
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48 a strong inverse association between baseline BMI and respiratory mortality, with the
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50 risk among men with BMI < 18.5 kg/m² being 6.5 times that among men with BMI 23.5-
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52 25.0 kg/m². However, it was not clear to what extent the excess risk at low BMI could be
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54 attributed to reverse causality, for the analysis did not exclude those with prior
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56 respiratory disease. In a recently published collaborative meta-analysis of BMI and
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4 cause-specific mortality among 900,000 individuals in 57 prospective studies (the
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6 Prospective Studies Collaboration (PSC), mostly in Western Europe and North
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8 America),²⁹ COPD mortality (1,958 deaths) was strongly inversely associated with BMI,
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10 with each 5 kg/m² lower BMI associated with a four-fold increased risk within the BMI
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12 range of 15-25 kg/m². Above BMI 25 kg/m², there appeared to be a weakly positive
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14 relationship between BMI and COPD mortality. In the PSC, COPD was defined similarly
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16 as in the present study, with the exception of pulmonary heart disease, but it could not
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18 exclude people with COPD at baseline, nor those with abnormal lung function.
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20 Consequently, reverse causality was controlled for mainly by excluding the early period
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22 of follow-up,²⁹ which may help to explain why the inverse association with COPD
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24 mortality was much more extreme in PSC than in this study. On the other hand,
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26 smoking is much more strongly associated with COPD in Western populations than in
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28 Chinese,⁸ and so is the relationship between smoking and BMI.²⁹ This suggests that
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30 confounding by smoking may be more substantial in the Western studies than in the
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32 present study of Chinese, and failure to control it effectively could potentially inflate the
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34 excess risk associated with low BMI.
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43 The overall findings of the present study are generally consistent with limited data from
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45 other prospective studies in Asian populations where the rate of COPD is relatively high
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47 and many people have relatively low BMI persistently throughout childhood and adult
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49 life.³⁸⁻⁴⁰ In a large prospective study of 170,000 adult Chinese,³⁹ 10.8% men and 12.5%
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51 women were underweight at baseline, and there were 2,470 COPD-related deaths after
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53 about 8 years of follow-up. As in the present study, smoking was found to be only
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55 weakly associated with COPD mortality, with RR of 1.2 for men who had smoked for at
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57 least 20 pack-years compared with never-smokers. Among men, BMI was inversely
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59 associated with COPD-related mortality, with RR of 2.7 (95% CI: 2.3-3.0) among
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4 underweight men compared with those who were not. However, no information was
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6 available in that study about history of pre-existing disease or measured lung function at
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8 baseline, so the control for potential reverse causality bias was limited chiefly to the
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10 exclusion of the first few years of follow-up.
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14 In the present study, potential biases related to reverse causality from prior disease and
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16 confounding by smoking have been dealt with rigorously. A reliable diagnosis of COPD
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18 is usually based on a typical history of persistent progressive symptoms, existence of an
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20 appropriate risk factor (such as smoking), and a confirmatory spirometric test.⁴¹ In China,
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22 only about a third of patients with spirometric evidence of COPD had ever been
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24 clinically diagnosed, and less than 10% had been tested with spirometry.^{4;42} Moreover,
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26 patients with COPD are often likely to die from other causes, with less than half having
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28 COPD certified as the underlying cause of death.³⁹ To help reduce potential under-
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30 reporting of COPD as cause of death, we used COPD-related mortality as our main
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32 endpoint for analysis, which included not only COPD deaths, but also those with asthma
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34 and pulmonary heart disease as the underlying causes of death. This definition was
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36 compatible with that used in another large COPD-related study in China³⁹ and in PSC
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38²⁷. Due to lack of spirometry measurement at baseline, we used the measured peak
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40 flow rate as an indicator of pulmonary function. Though not ideal, it should have helped
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42 to identify effectively undiagnosed cases of COPD at baseline.⁴³ In addition to excluding
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44 those with any prior respiratory disease or abnormal lung function at baseline, data
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46 were also examined separately among ever- and never-smokers and by different
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48 periods of follow-up. The strong inverse relationship of BMI to risk of COPD-related
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50 death persisted even after excluding the first 10 years of follow-up, and was present not
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52 only among smokers but also among never-smokers. So, the relationship is not likely to
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4 be accounted for by chance, by prior disease affecting BMI at baseline, or by residual
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6 confounding by smoking. It may, however, not necessarily be causal.
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10 The inverse relationship between BMI and risk of COPD-related death could represent a
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12 combination of various factors. COPD can lead to weight loss over a prolonged period
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14 of time and many of the patients with COPD, despite exclusion of those with prior
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16 disease, with impaired lung function, or first 5 years of follow-up, may still not be
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18 properly identified, so it is still possible that the inverse association observed could still
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20 have been mainly due to reverse causality. On the other hand, some close correlate of
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22 low BMI, such as malnutrition, could itself cause COPD, or increase its progression and,
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24 consequently, mortality.⁴⁴ Clinical-based studies showed that low BMI is an independent
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26 prognostic factor of poor long-term survival following diagnosis of COPD.^{19;45} There is
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28 also evidence that low body weight could predispose to an increased risk of chronic
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30 infection such as pulmonary TB,^{46;47} a disease which was also shown in this study to be
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32 strongly inversely related to BMI. If chronic respiratory infections also play a role in the
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34 aetiology of COPD,⁴⁸ it may help to understand the possible biological mechanism
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36 underlying the inverse relationship between BMI and COPD death. Newly established
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38 large blood-based prospective studies in China⁴⁹ will eventually provide good evidence
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40 on it. It has been suggested that other measures of body composition (eg waist and hip
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42 ratio, percentage body fat)^{15;25;50-52} or instrumental variable like offspring BMI⁵³ might
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44 provide better assessment for disease association, and that low physical activity may
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46 also help to identify those with underlying disease that generate the association with
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48 COPD. However, no such measurements were available in the present study.
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57 The recent large increase in cigarette consumption⁵⁴ in China may eventually lead to a
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59 substantial increase in the risk of COPD in the population, especially among men.^{4;42;55}
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On the other hand, if low BMI were causally associated with increased risk of COPD

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4 through mechanisms yet to be elucidated, then the recent rise in mean BMI in the
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6 population as a result of improved living standards could potentially lead to decreased
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8 risk of COPD in the future. This may counterbalance to some extent the likely increase
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10 in the disease rate from increased exposure to smoking, even though the extent and
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12 time scale of these changes needs to be closely monitored in future studies.
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Conflicts of Interest

None declared

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Figures Legends

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- (1) **Figure 1. Hazard ratios for death from COPD-related diseases versus baseline age- and height-adjusted peak flow (l/min) among men aged 40-79.** 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 hazard ratios (HRs) are plotted on a floating absolute scale. Each closed square has an area inversely proportional to the effective variance of the log HR. Vertical lines indicate the 95% confidence intervals. Numbers above confidence intervals are deaths and those below confidence intervals are hazard ratios.
- (2) **Figure 2. Hazard ratios for death from COPD-related diseases versus baseline BMI among men aged 40-79: (1) with impaired lung function and (2) without impaired lung function at baseline.** Conventions as in Figure 1, and the trend line was fitted by linear regression through mean BMI for each category among men with baseline BMI <25 kg/m² in each subgroup.
- (3) **Figure 3. Hazard ratios for death from COPD-related diseases versus baseline BMI among men aged 40-79 with no prior respiratory disease or impaired lung function at baseline, in (a) the first 5 years, (b) the second 5 years, (c) the third 5 years of follow-up.** Conventions as in Figures 1 and 2.

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- (4) **Figure 4. Hazard ratios for death from COPD-related diseases versus baseline BMI among men aged 40-79 with no prior respiratory disease or impaired lung function at baseline, in those who were (a) Ever-smokers and (b) Life-long non-smokers.** Conventions as in Figures 1 and 2.
- (5) **Figure 5. Hazard ratios for death from COPD-related diseases versus 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.
- (6) **Figure 6. Hazard ratios for death from COPD-related diseases 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 a hazard ratio (HR) with the area inversely proportional to the variance of log HR. The dotted vertical line indicates the overall HR, and open diamonds indicates it and its 95% CI.

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 *	All	BMI Categories (kg/m ²)				
		<18.5	18.5-19.9	20-22.4	22.5-24.9	≥25
Total population	221194	20338	37748	89079	49418	24611
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
Smoking status (%)						
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
No. of cigarettes per 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 †						
No. of deaths	8769	1860	1980	3244	1264	421
Mortality rate /100,000	255.6	490.9	301.1	235.1	194.5	189.2

* Except 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.

† Mortality rates were standardized to the geographic area and the 5 year age group structure in the study population aged 40-79.

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Figure 1

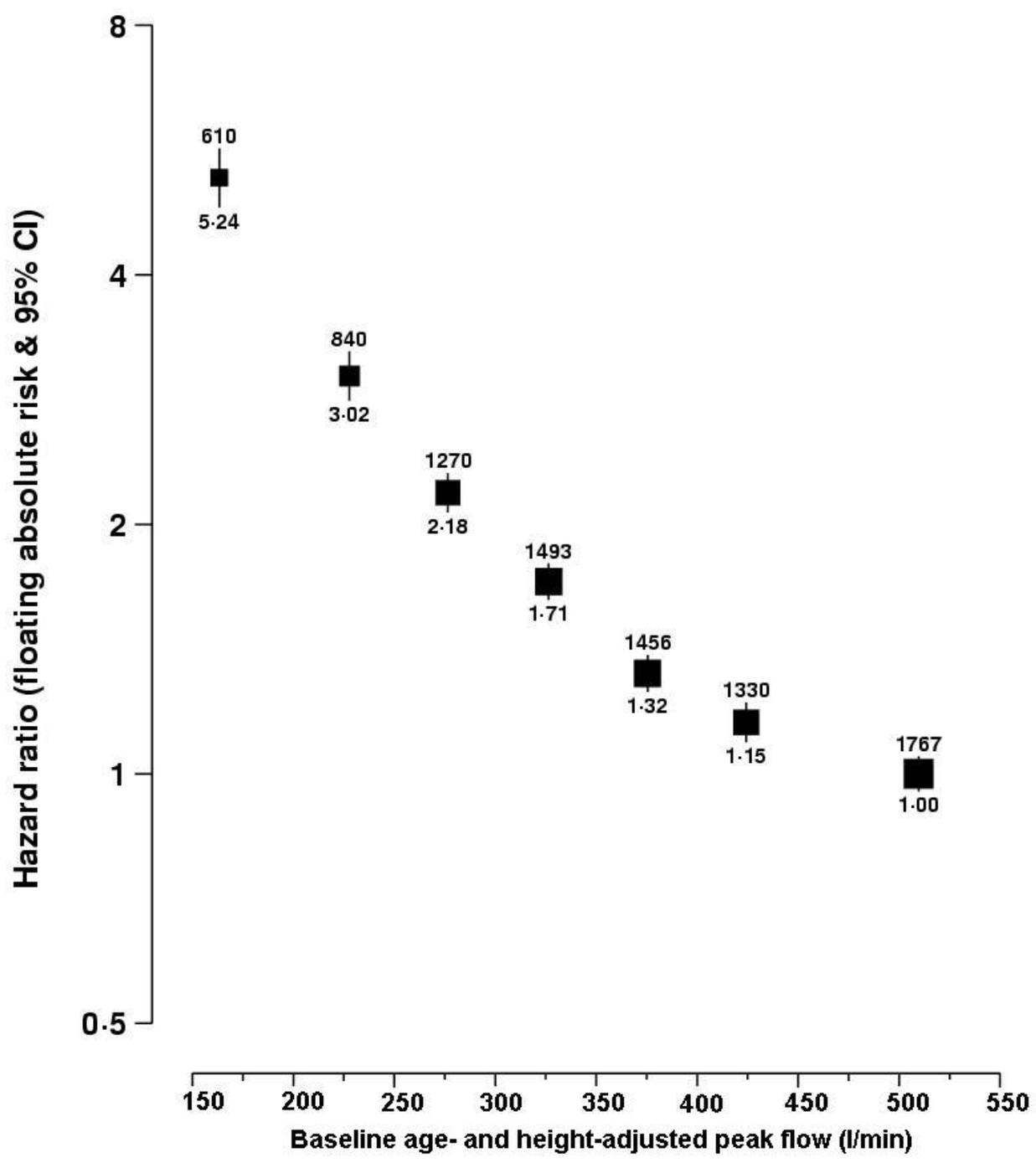


Figure 2

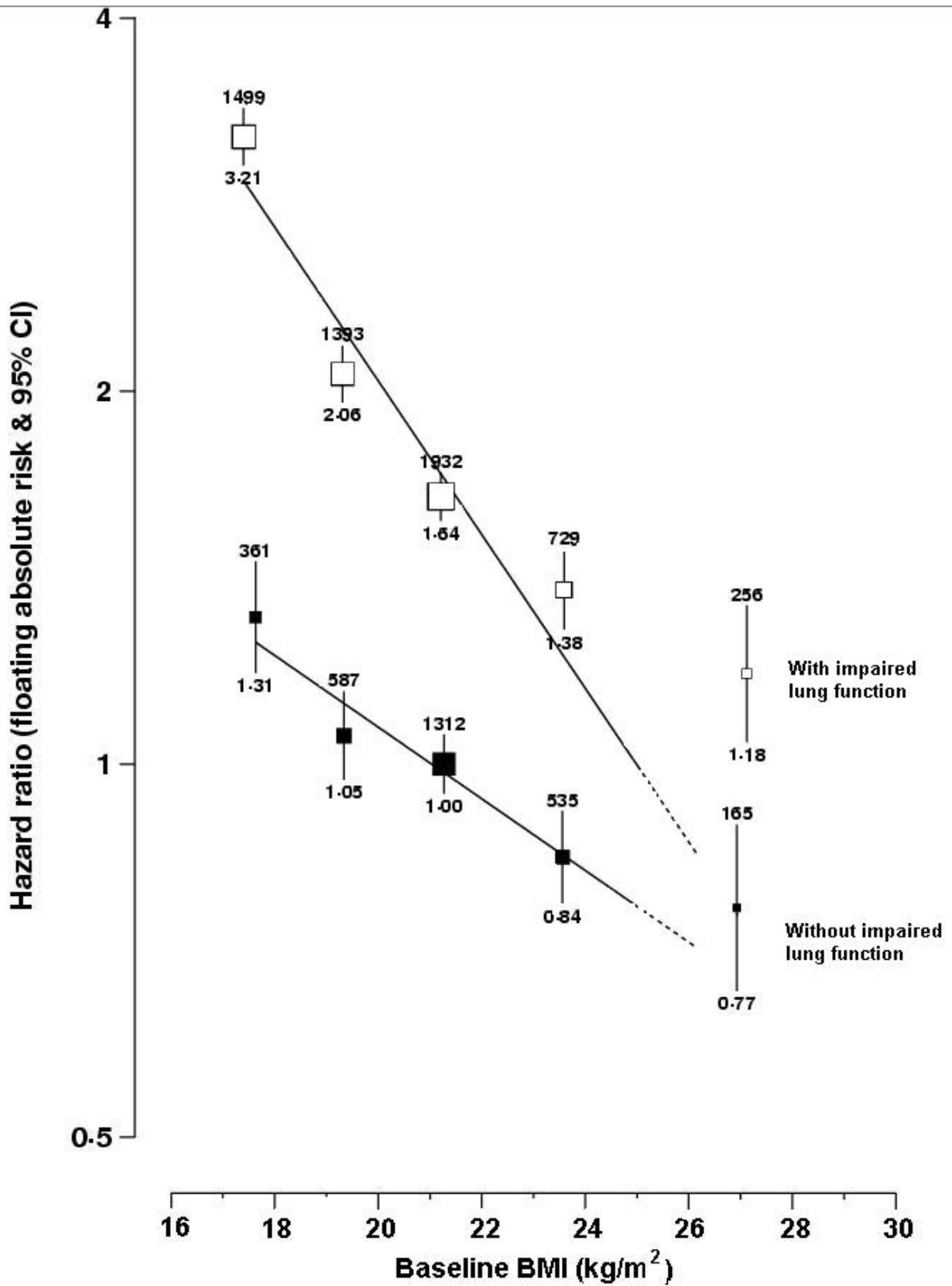


Figure 3

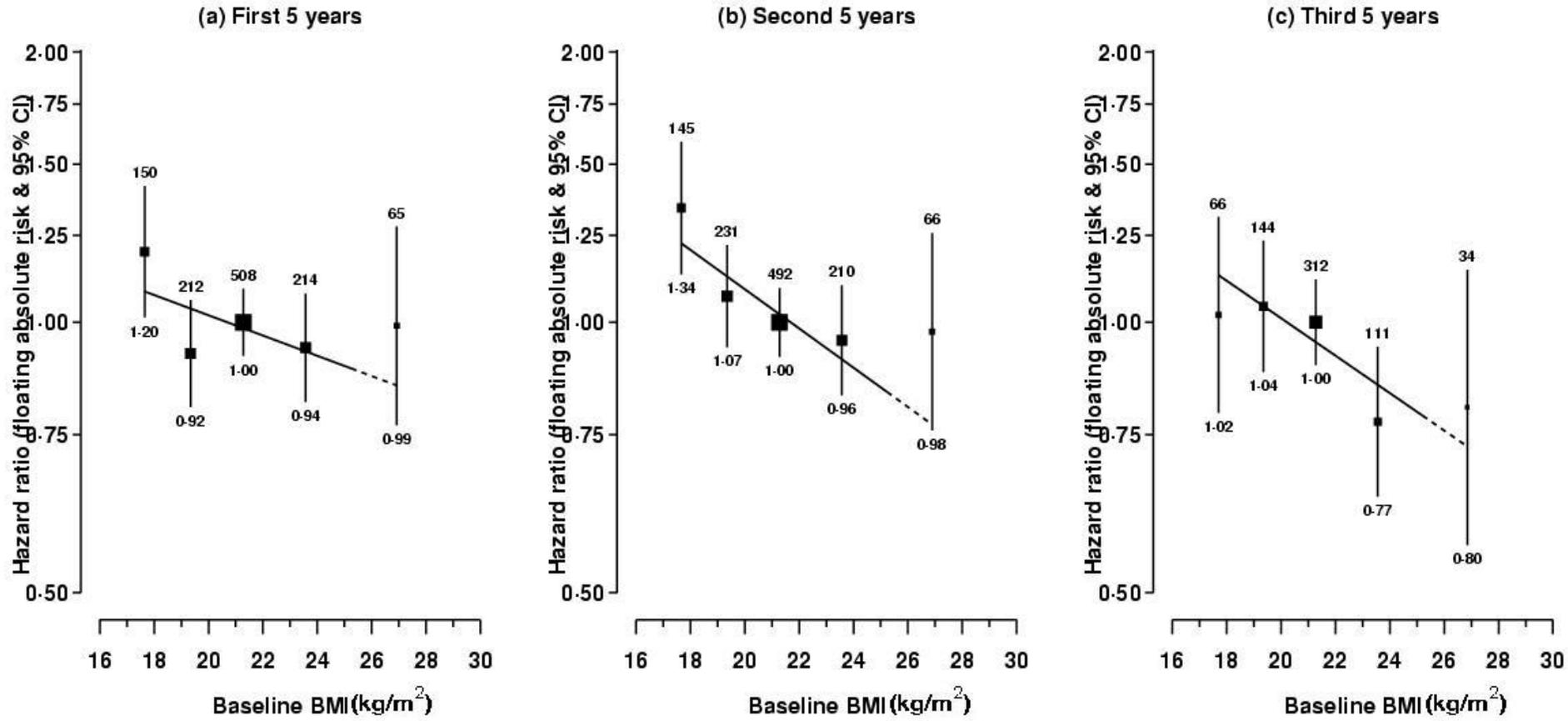
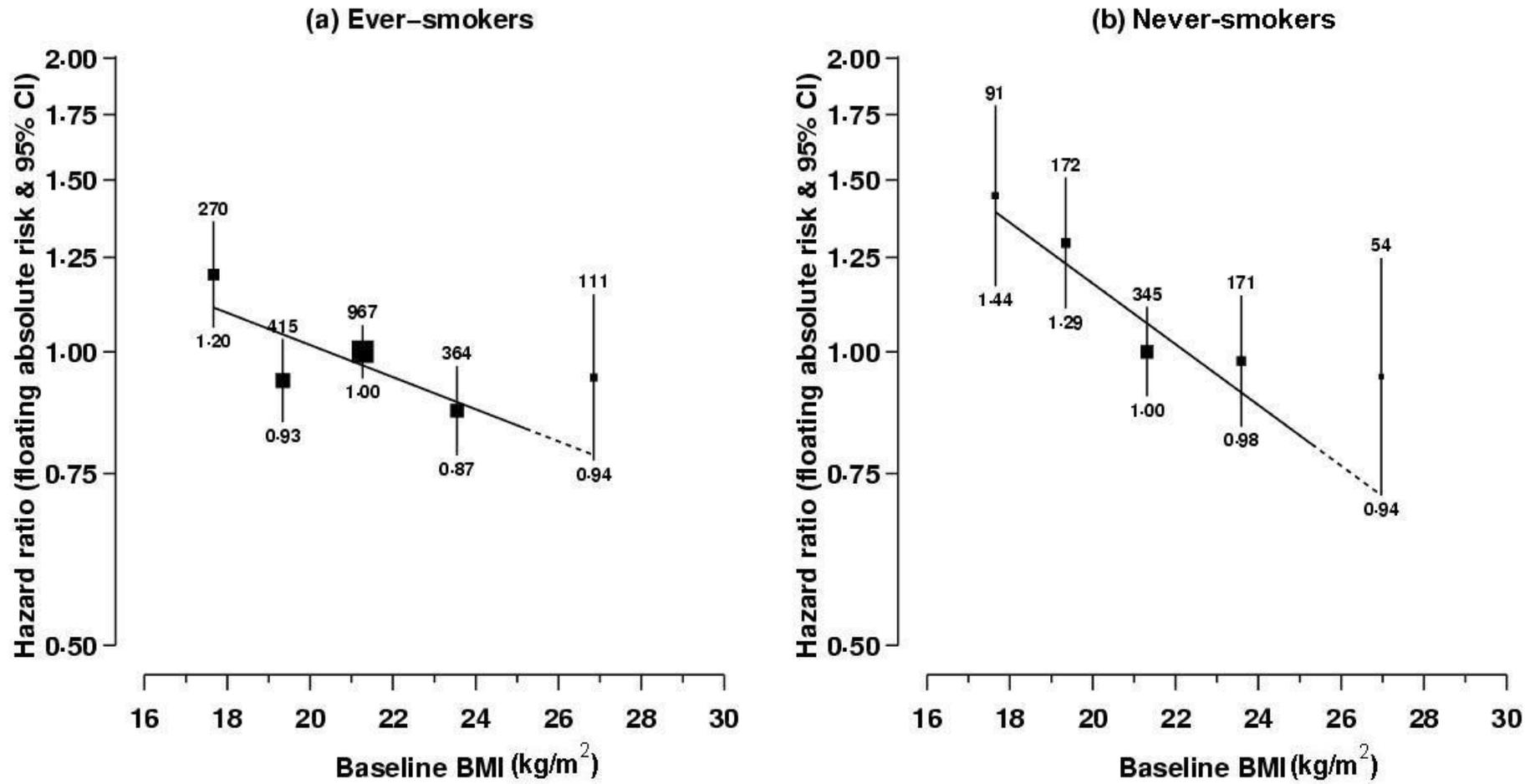


Figure 4



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Figure 5

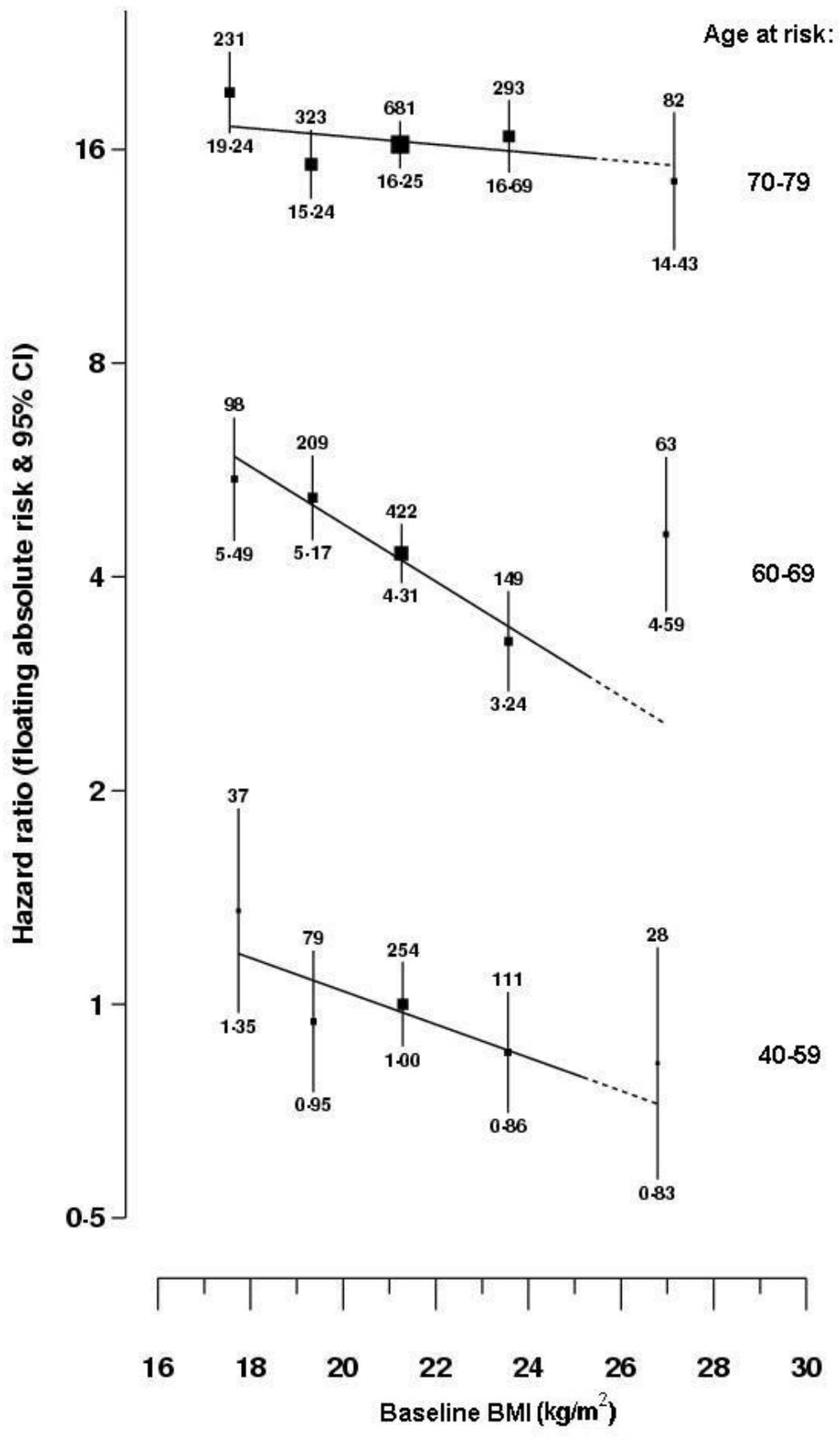
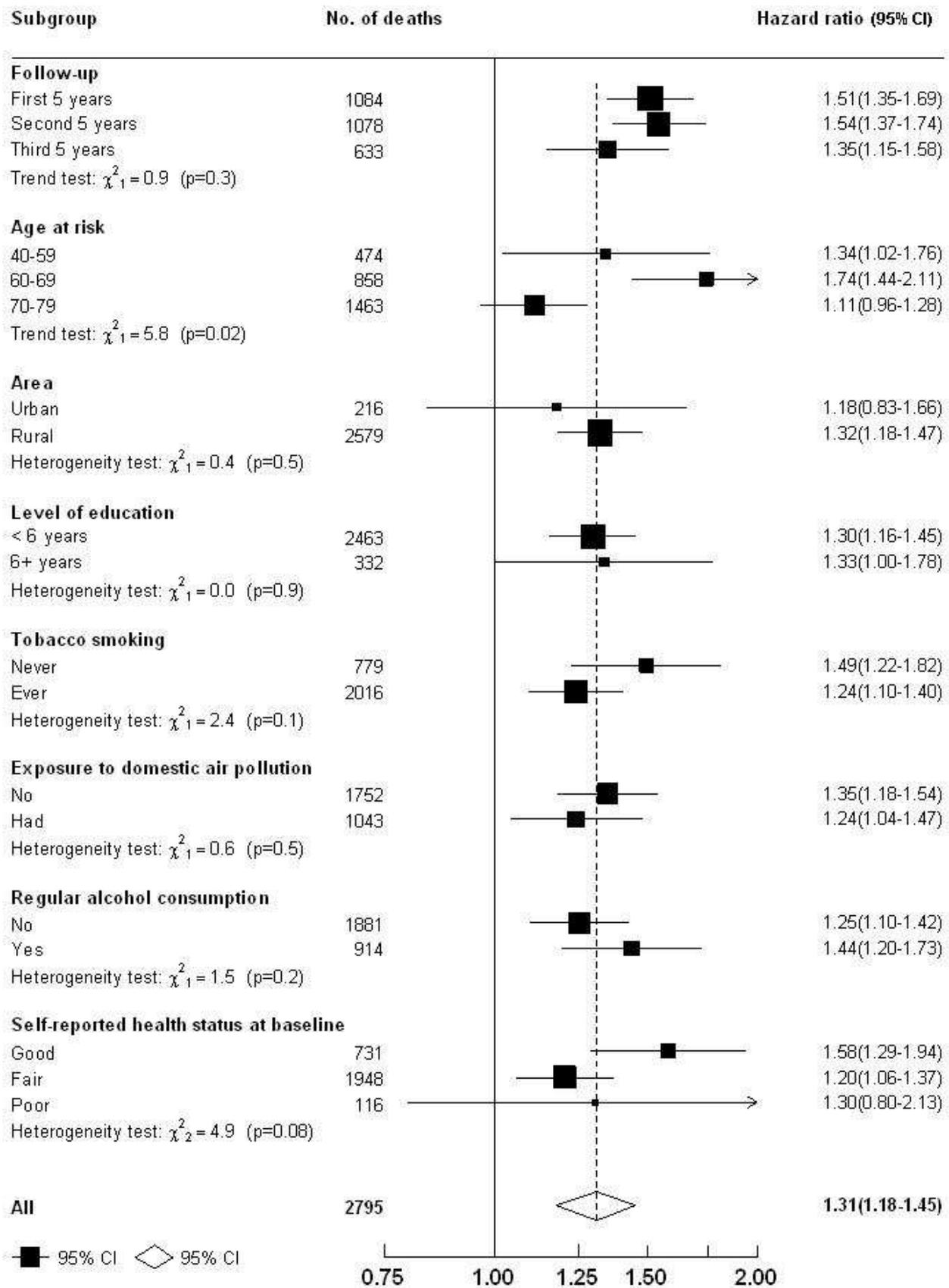


Figure 6



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