



HAL
open science

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

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

► **To cite this version:**

Ling Yang, Maigeng Zhou, Margaret Smith, Gonghuan Yang, Richard - Peto, et al.. Body mass index and COPD-related mortality: A nationally representative prospective study of 220 000 men in China. International Journal of Epidemiology, 2010, 10.1093/ije/DYQ051 . hal-00586460

HAL Id: hal-00586460

<https://hal.science/hal-00586460>

Submitted on 16 Apr 2011

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

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

Journal:	<i>International Journal of Epidemiology</i>
Manuscript ID:	IJE-2009-11-0979.R1
Manuscript Type:	Original Article
Date Submitted by the Author:	04-Feb-2010
Complete List of Authors:	Yang, Ling; Univ. of Oxford, CTSU Zhou, Maigeng; China CDC, Center of public health surveillance and information service Smith, Margaret; Univ. of Oxford, CTSU Yang, Gonghuan; China CDC, Center of public health surveillance and information service Peto, Richard; Univ. of Oxford, CTSU Boreham, J; University of Oxford, CTSU Chen, ZM; Univ. of Oxford, CTSU
Key Words:	body mass index, smoking, prospective study, COPD, mortality

1
2
3
4 **Body mass index and COPD-related mortality: A nationally**
5
6 **representative prospective study of 220 000 men in China**
7
8
9

10
11
12
13 Ling Yang¹, Maigeng Zhou², Margaret Smith¹, Gonghuan Yang², Richard Peto¹, Jun
14
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
40
41
42
43
44
45
46
47
48
49

50 Word counts:

51 Abstract: 219

52 Text (excluding abstract, reference, tables, footnotes, figure legends): 3087
53
54
55
56
57
58
59
60

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

1
2
3
4 smoking or for the effects of pre-existing disease on BMI (the reverse causality).²⁹ We
5
6 report a 15-year prospective study of the association between BMI and COPD mortality
7
8 in a nationally representative cohort of 221,000 men in China recruited during 1990-91,
9
10 including 148,000 current smokers and 59,000 never-smokers.
11

12 13 14 **MATERIALS AND METHODS**

15 16 17 ***Baseline survey***

18
19
20 Details of the study design, participants and baseline survey methods have been
21
22 reported previously.^{30;31} Briefly, the study involves 45 areas (23 urban and 22 rural)
23
24 which were randomly selected from China's 145 Disease Surveillance Points (DSPs).
25
26 The DSP system was established in the mid-1980s to provide a nationally
27
28 representative sample of mortality statistics for the entire country.^{32;33} A typical
29
30 surveillance point covers a defined population of about 50,000-100,000 residents in 4-8
31
32 geographically defined units (ie, urban street committees or clusters of rural villages).
33
34 During 1990-91, all men aged 40 years or over from two or three randomly selected
35
36 units within each of the 45 areas were invited to participate in the survey, and about
37
38 80% of invitees attended. In the survey clinics set up for the study, trained health
39
40 workers administered a standardized questionnaire, which included education,
41
42 occupation, tobacco, alcohol, dietary pattern, exposure to indoor air pollution, self-
43
44 reported medical history and health status. Physical measurements included blood
45
46 pressure, height, weight and peak expiratory flow rates. Waist and hip circumferences
47
48 and subsequent weight changes were not measured.
49
50
51
52
53
54
55

56 57 ***Follow-up for cause-specific mortality***

58
59 The vital status of each study participant was monitored regularly by DSP staff through
60
their death registries previously established in these areas. In addition, active

1
2
3
4 confirmation of vital status was done annually through local residential committees.
5
6 Causes of death were sought chiefly from official death certificates, supplemented, if
7
8 necessary, by review of medical records.³² The underlying cause of each death was
9
10 coded centrally by DSP staff in Beijing, without knowledge of the baseline information,
11
12 using the ninth revision of the International Classification of Disease (ICD-9). In the few
13
14 deaths without any recent medical attention, standard procedures were used by local
15
16 DSP staff to determine the probable cause from symptoms or signs described by family
17
18 members.³² COPD-related death was defined as death from chronic bronchitis,
19
20 emphysema, asthma, bronchiectasis, other chronic obstructive pulmonary disease, or
21
22 pulmonary heart disease (ICD-9 codes 415-417 and 490-496).
23
24
25
26
27

28 Since it is often difficult to assign an underlying cause reliably for death in old age, all
29
30 analyses were restricted to deaths occurring between age 40-79, with censoring when
31
32 men reached 80 years of age, died from other causes or moved away from the original
33
34 study area during follow-up. This report is based on follow-up data to 1,1,2006 among
35
36 the 221,194 men who were aged 40-79 years and had baseline BMI in the range of 10-
37
38 50 kg/m².
39
40
41
42

43 ***Statistical analysis***

44
45
46 Cox proportional hazards models were used to calculate hazard ratios (HRs), with BMI
47
48 as the exposure variable and COPD-related death as the outcome. All analyses were
49
50 stratified by area (45 strata) and by 5-year age group at risk, and were adjusted
51
52 simultaneously for education, tobacco (never, former, current), alcohol (at least
53
54 weekly/not), regular exposure to indoor domestic or occupational air pollution from coal
55
56 or biomass (yes/no), and consumption of certain food stuffs (times/week), such as meat,
57
58 vegetable and fruit. Baseline BMI was divided into five categories, with cut-off points at
59
60

1
2
3
4 18.5, 20, 22.5 and 25 kg/m². The HR for COPD-related mortality was calculated for
5
6 each BMI category, with the BMI category of 20.0-22.5 kg/m² as the reference group.
7
8 The 95% confidence interval (CI) for each log HR was estimated using the 'floating
9
10 absolute risk' method.³⁴ This facilitates many different comparisons and tests for trend
11
12 between different BMI categories, rather than just pair-wise comparisons between one
13
14 arbitrarily chosen reference group and each of the other categories. Trend tests were
15
16 conducted treating BMI as a continuous variable in the Cox model. The analyses were
17
18 done in SAS version 9.1 under Windows XP.
19
20
21
22
23

24 RESULTS

25
26 For the 221,194 participants (mean baseline age of 54.3 years), overall mean BMI was
27
28 21.7 (SD 2.7) kg/m², with 9.2% being underweight (BMI <18.5 kg/m²), and 11.1% being
29
30 either overweight (BMI 25 to <30 kg/m², 10.3%) or obese (BMI ≥30 kg/m², 0.8%). The
31
32 mean age-adjusted BMI was higher among urban than among rural men (23.1 vs 21.2
33
34 kg/m²). After adjusting for area and age, it was strongly positively related to blood
35
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
39
40 likely to drink alcohol. The prevalence of smoking was strongly inversely associated with
41
42 BMI, but among current smokers, the mean number of cigarette smoked per day was
43
44 not associated with BMI (which implies that, among smokers, the dose of tobacco per
45
46 kilogram of body weight was inversely related to BMI). Men with low BMI were more
47
48 likely to report a prior history of disease at baseline. (table 1)
49
50
51
52
53

54
55 During the 15-year follow-up, 40,907 died before age 80, of which 8,769 (21.4%) were
56
57 due to COPD-related conditions. Of the remainder, 34,165 (1% per annum) were lost to
58
59 follow-up, mainly because of demolition of neighborhood for redevelopment. Those lost
60

1
2
3
4 did not differ significantly from those not in the main baseline characteristics such as
5
6 age, SBP, BMI, prevalence of ever-smoking.³¹ The standardized COPD mortality rate
7
8 was more than twice as high among men with a history of respiratory disease as among
9
10 men without it (540 vs 203 per 100,000). It was also about twice as high among rural
11
12 men as among urban men (290 vs 156), and higher among ever-smokers than among
13
14 never-smokers (265 vs. 223). Overall there was a highly significant inverse association
15
16 between BMI and COPD-related mortality, with the death rate in the lowest BMI group
17
18 (<18.5 kg/m²) being 2.5 fold that in the highest group (≥25 kg/m²) (table 1).
19
20
21

22
23
24 In the study, the peak expiratory flow rate was strongly inversely associated with the
25
26 COPD-related death (figure 1). However, the inverse association between BMI and
27
28 COPD-related death was particularly steep among men with impaired lung function at
29
30 baseline, defined as having pre-existing respiratory diseases (i.e. TB, chronic bronchitis,
31
32 asthma, emphysema or pulmonary heart disease), or self-reported chronic respiratory
33
34 symptoms (ie cough or shortness of breath) or being in the lowest quintile of age- and
35
36 height-adjusted peak expiratory flow rate) (figure 2). Among these participants, each 5
37
38 kg/m² lower baseline BMI was associated with 118% (95%CI: 104%-134%) higher risk
39
40 of COPD-related death for BMI <25 kg/m²), while in men without impaired lung function,
41
42 the increased risk was much less extreme (30% [17%-44%]). The exclusion of the first 5
43
44 years of follow-up did not materially alter the relationships (94% [76%-113%] higher risk
45
46 per each 5 kg/m² lower BMI for men with impaired lung function versus 34% [17%-53%]
47
48 higher risk for men without it). To help minimize the effects of reverse causality, those
49
50 with impaired lung function at baseline were excluded from subsequent analyses.
51
52
53
54
55
56

57
58 Among men without any apparent impairment of lung function, the relationship of BMI
59
60 with COPD mortality varies little at different periods of follow-up (p=0.4 for heterogeneity

1
2
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.
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27

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).
34
35
36
37
38
39
40
41
42

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.
48
49
50
51
52
53
54
55
56
57
58
59
60

DISCUSSION

1
2
3
4 This is one of the largest prospective studies of the relationship between BMI and
5
6 COPD-related mortality in a relatively lean population, and it involved a nationally
7
8 representative population of Chinese men with nearly 9,000 COPD-related deaths. In
9
10 this population, approximately 90% of men had baseline BMI < 25 kg/m² (as opposed to
11
12 less than 50% in many Western countries^{35;36}), and among them there was a highly
13
14 significant inverse relationship between BMI and COPD-related mortality with each 5
15
16 kg/m² lower BMI associated with 30% higher mortality. The association was largely
17
18 independent of age, smoking and other factors, and the extent to which the association
19
20 could be biased by reverse causality was greatly limited by exclusion of all who had
21
22 evidence of impaired lung function at baseline.
23
24
25
26
27

28
29 Several prospective studies both in Western and in East Asian populations have
30
31 reported an inverse association between BMI and COPD.^{27-29;37} There were differences
32
33 in the strength of the relationship between these studies, which may be partly due to
34
35 difference in the completeness of control for reverse causality by prior disease and for
36
37 confounding by smoking. Moreover, most previous studies have not individually
38
39 recorded large numbers of COPD cases, especially at lower levels of BMI, so the shape
40
41 of the association between BMI and COPD may be particularly susceptible to the play of
42
43 chance. For example, in the recently published European Prospective Investigation into
44
45 Cancer and Nutrition (EPIC) among 360,000 participants, only 637 respiratory deaths
46
47 (4% of total deaths) were recorded after 10 years of follow-up.²⁸ In that study, there was
48
49 a strong inverse association between baseline BMI and respiratory mortality, with the
50
51 risk among men with BMI < 18.5 kg/m² being 6.5 times that among men with BMI 23.5-
52
53 25.0 kg/m². However, it was not clear to what extent the excess risk at low BMI could be
54
55 attributed to reverse causality, for the analysis did not exclude those with prior
56
57 respiratory disease. In a recently published collaborative meta-analysis of BMI and
58
59
60

1
2
3
4 cause-specific mortality among 900,000 individuals in 57 prospective studies (the
5
6 Prospective Studies Collaboration (PSC), mostly in Western Europe and North
7
8 America),²⁹ COPD mortality (1,958 deaths) was strongly inversely associated with BMI,
9
10 with each 5 kg/m² lower BMI associated with a four-fold increased risk within the BMI
11
12 range of 15-25 kg/m². Above BMI 25 kg/m², there appeared to be a weakly positive
13
14 relationship between BMI and COPD mortality. In the PSC, COPD was defined similarly
15
16 as in the present study, with the exception of pulmonary heart disease, but it could not
17
18 exclude people with COPD at baseline, nor those with abnormal lung function.
19
20 Consequently, reverse causality was controlled for mainly by excluding the early period
21
22 of follow-up,²⁹ which may help to explain why the inverse association with COPD
23
24 mortality was much more extreme in PSC than in this study. On the other hand,
25
26 smoking is much more strongly associated with COPD in Western populations than in
27
28 Chinese,⁸ and so is the relationship between smoking and BMI.²⁹ This suggests that
29
30 confounding by smoking may be more substantial in the Western studies than in the
31
32 present study of Chinese, and failure to control it effectively could potentially inflate the
33
34 excess risk associated with low BMI.
35
36
37
38
39
40
41

42
43 The overall findings of the present study are generally consistent with limited data from
44
45 other prospective studies in Asian populations where the rate of COPD is relatively high
46
47 and many people have relatively low BMI persistently throughout childhood and adult
48
49 life.³⁸⁻⁴⁰ In a large prospective study of 170,000 adult Chinese,³⁹ 10.8% men and 12.5%
50
51 women were underweight at baseline, and there were 2,470 COPD-related deaths after
52
53 about 8 years of follow-up. As in the present study, smoking was found to be only
54
55 weakly associated with COPD mortality, with RR of 1.2 for men who had smoked for at
56
57 least 20 pack-years compared with never-smokers. Among men, BMI was inversely
58
59 associated with COPD-related mortality, with RR of 2.7 (95% CI: 2.3-3.0) among
60

1
2
3
4 underweight men compared with those who were not. However, no information was
5
6 available in that study about history of pre-existing disease or measured lung function at
7
8 baseline, so the control for potential reverse causality bias was limited chiefly to the
9
10 exclusion of the first few years of follow-up.
11
12

13
14 In the present study, potential biases related to reverse causality from prior disease and
15
16 confounding by smoking have been dealt with rigorously. A reliable diagnosis of COPD
17
18 is usually based on a typical history of persistent progressive symptoms, existence of an
19
20 appropriate risk factor (such as smoking), and a confirmatory spirometric test.⁴¹ In China,
21
22 only about a third of patients with spirometric evidence of COPD had ever been
23
24 clinically diagnosed, and less than 10% had been tested with spirometry.^{4;42} Moreover,
25
26 patients with COPD are often likely to die from other causes, with less than half having
27
28 COPD certified as the underlying cause of death.³⁹ To help reduce potential under-
29
30 reporting of COPD as cause of death, we used COPD-related mortality as our main
31
32 endpoint for analysis, which included not only COPD deaths, but also those with asthma
33
34 and pulmonary heart disease as the underlying causes of death. This definition was
35
36 compatible with that used in another large COPD-related study in China³⁹ and in PSC
37
38²⁷. Due to lack of spirometry measurement at baseline, we used the measured peak
39
40 flow rate as an indicator of pulmonary function. Though not ideal, it should have helped
41
42 to identify effectively undiagnosed cases of COPD at baseline.⁴³ In addition to excluding
43
44 those with any prior respiratory disease or abnormal lung function at baseline, data
45
46 were also examined separately among ever- and never-smokers and by different
47
48 periods of follow-up. The strong inverse relationship of BMI to risk of COPD-related
49
50 death persisted even after excluding the first 10 years of follow-up, and was present not
51
52 only among smokers but also among never-smokers. So, the relationship is not likely to
53
54
55
56
57
58
59
60

1
2
3
4 be accounted for by chance, by prior disease affecting BMI at baseline, or by residual
5
6 confounding by smoking. It may, however, not necessarily be causal.
7
8

9
10 The inverse relationship between BMI and risk of COPD-related death could represent a
11
12 combination of various factors. COPD can lead to weight loss over a prolonged period
13
14 of time and many of the patients with COPD, despite exclusion of those with prior
15
16 disease, with impaired lung function, or first 5 years of follow-up, may still not be
17
18 properly identified, so it is still possible that the inverse association observed could still
19
20 have been mainly due to reverse causality. On the other hand, some close correlate of
21
22 low BMI, such as malnutrition, could itself cause COPD, or increase its progression and,
23
24 consequently, mortality.⁴⁴ Clinical-based studies showed that low BMI is an independent
25
26 prognostic factor of poor long-term survival following diagnosis of COPD.^{19;45} There is
27
28 also evidence that low body weight could predispose to an increased risk of chronic
29
30 infection such as pulmonary TB,^{46;47} a disease which was also shown in this study to be
31
32 strongly inversely related to BMI. If chronic respiratory infections also play a role in the
33
34 aetiology of COPD,⁴⁸ it may help to understand the possible biological mechanism
35
36 underlying the inverse relationship between BMI and COPD death. Newly established
37
38 large blood-based prospective studies in China⁴⁹ will eventually provide good evidence
39
40 on it. It has been suggested that other measures of body composition (eg waist and hip
41
42 ratio, percentage body fat)^{15;25;50-52} or instrumental variable like offspring BMI⁵³ might
43
44 provide better assessment for disease association, and that low physical activity may
45
46 also help to identify those with underlying disease that generate the association with
47
48 COPD. However, no such measurements were available in the present study.
49
50
51
52
53
54
55

56
57 The recent large increase in cigarette consumption⁵⁴ in China may eventually lead to a
58
59 substantial increase in the risk of COPD in the population, especially among men.^{4;42;55}
60

On the other hand, if low BMI were causally associated with increased risk of COPD

1
2
3
4 through mechanisms yet to be elucidated, then the recent rise in mean BMI in the
5
6 population as a result of improved living standards could potentially lead to decreased
7
8 risk of COPD in the future. This may counterbalance to some extent the likely increase
9
10 in the disease rate from increased exposure to smoking, even though the extent and
11
12 time scale of these changes needs to be closely monitored in future studies.
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

For Review Only

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Funding and Acknowledgements

This work was supported by the Chinese Ministry of Health; the UK Medical Research Council, British Heart Foundation and Cancer Research UK; the World Bank loan to China; and the Canadian International Development Research Centre. We thank the China DSP staff for their continuing effort and cooperation with long-term follow-up of study participants.

Conflicts of Interest

None declared

For Review Only

Figures Legends

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
- (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 $<25 \text{ kg/m}^2$ 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.

- 1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
- (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.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure 1

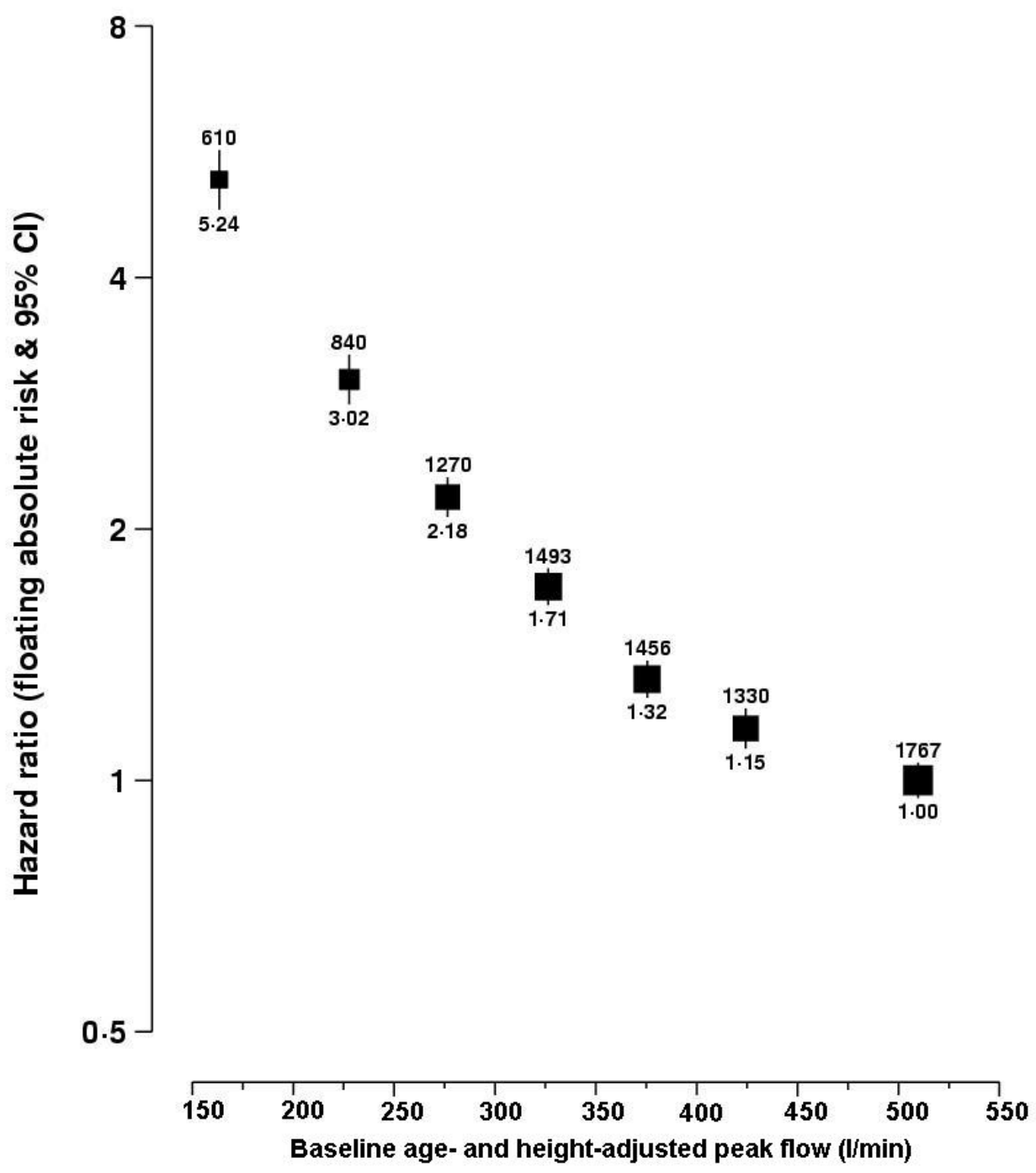
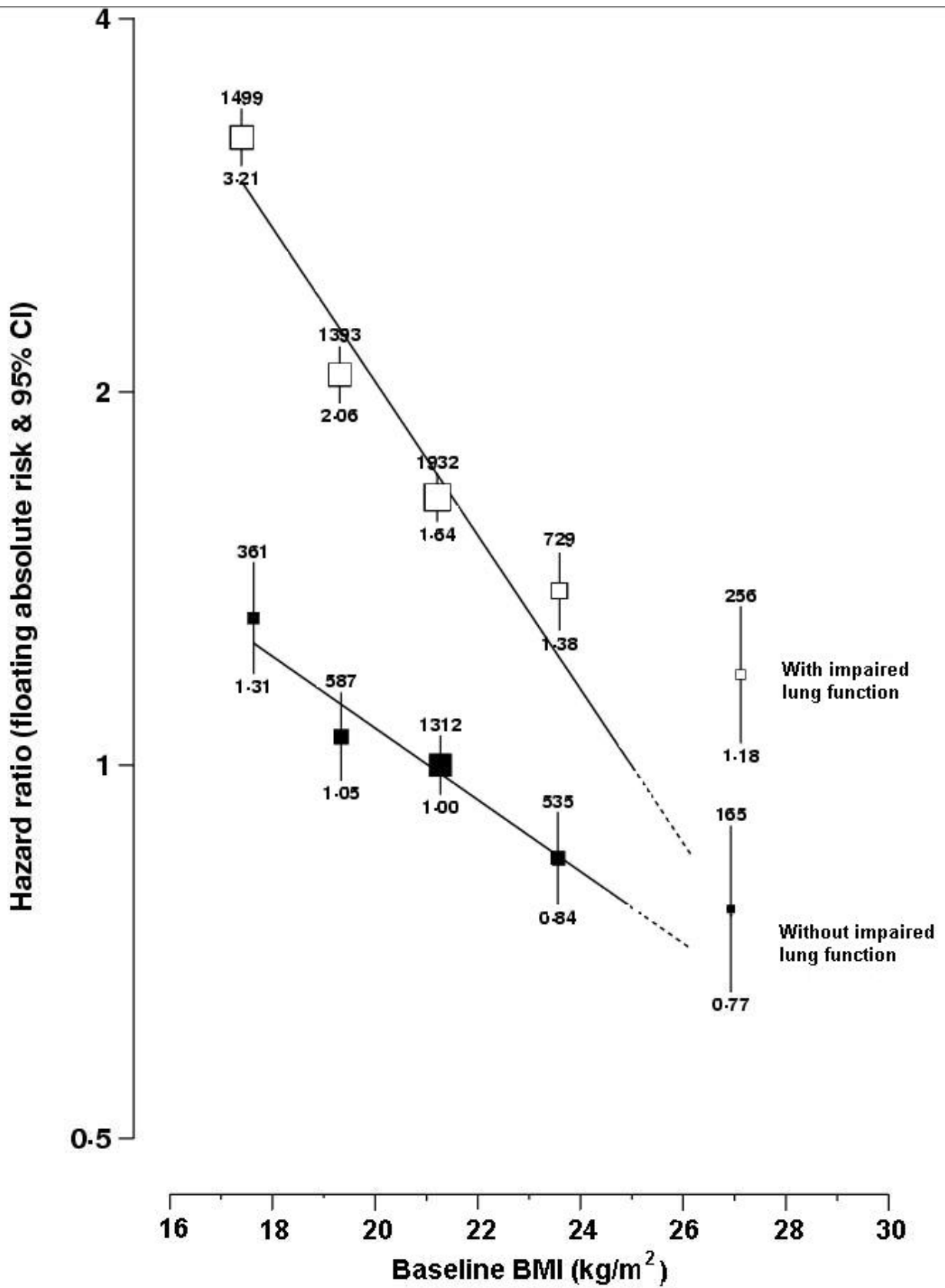


Figure 2



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47

Figure 3

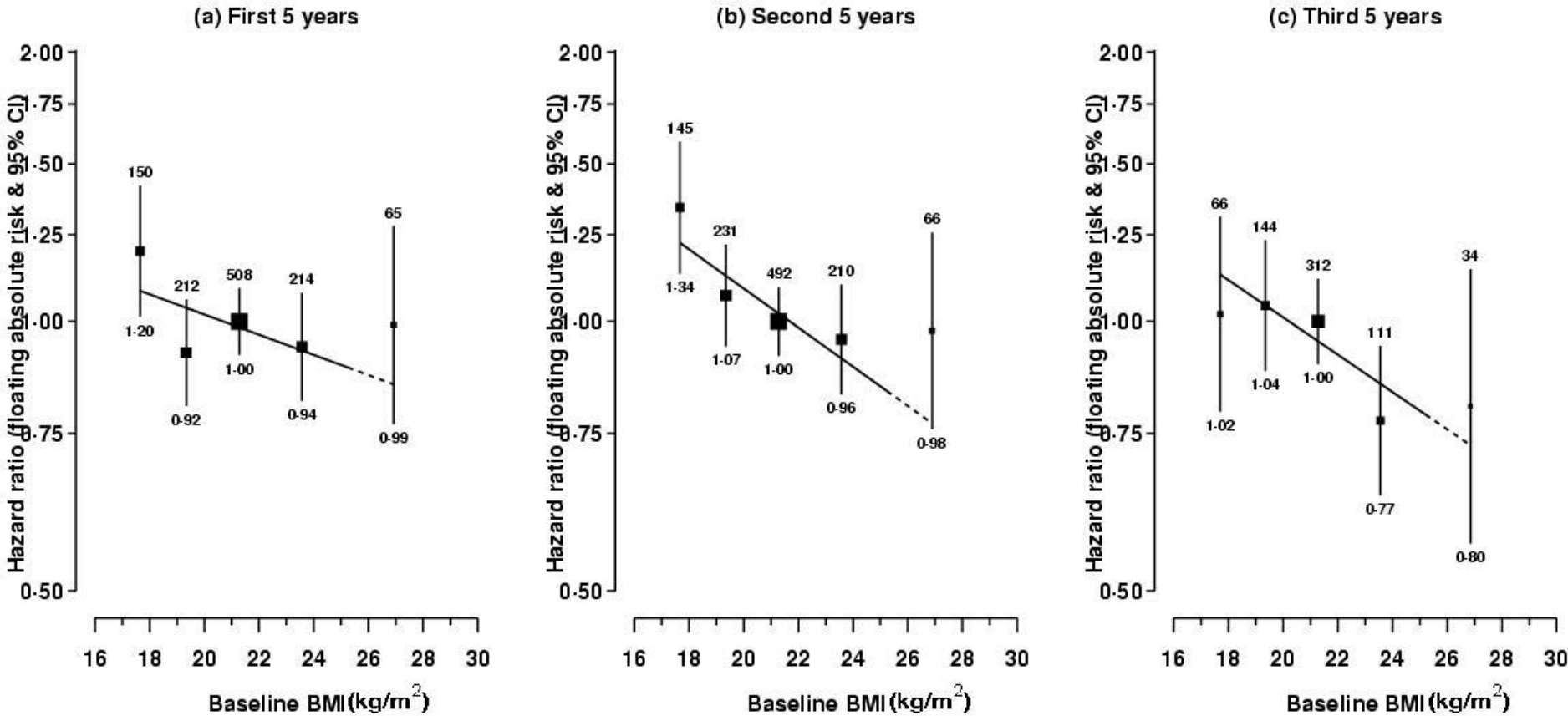
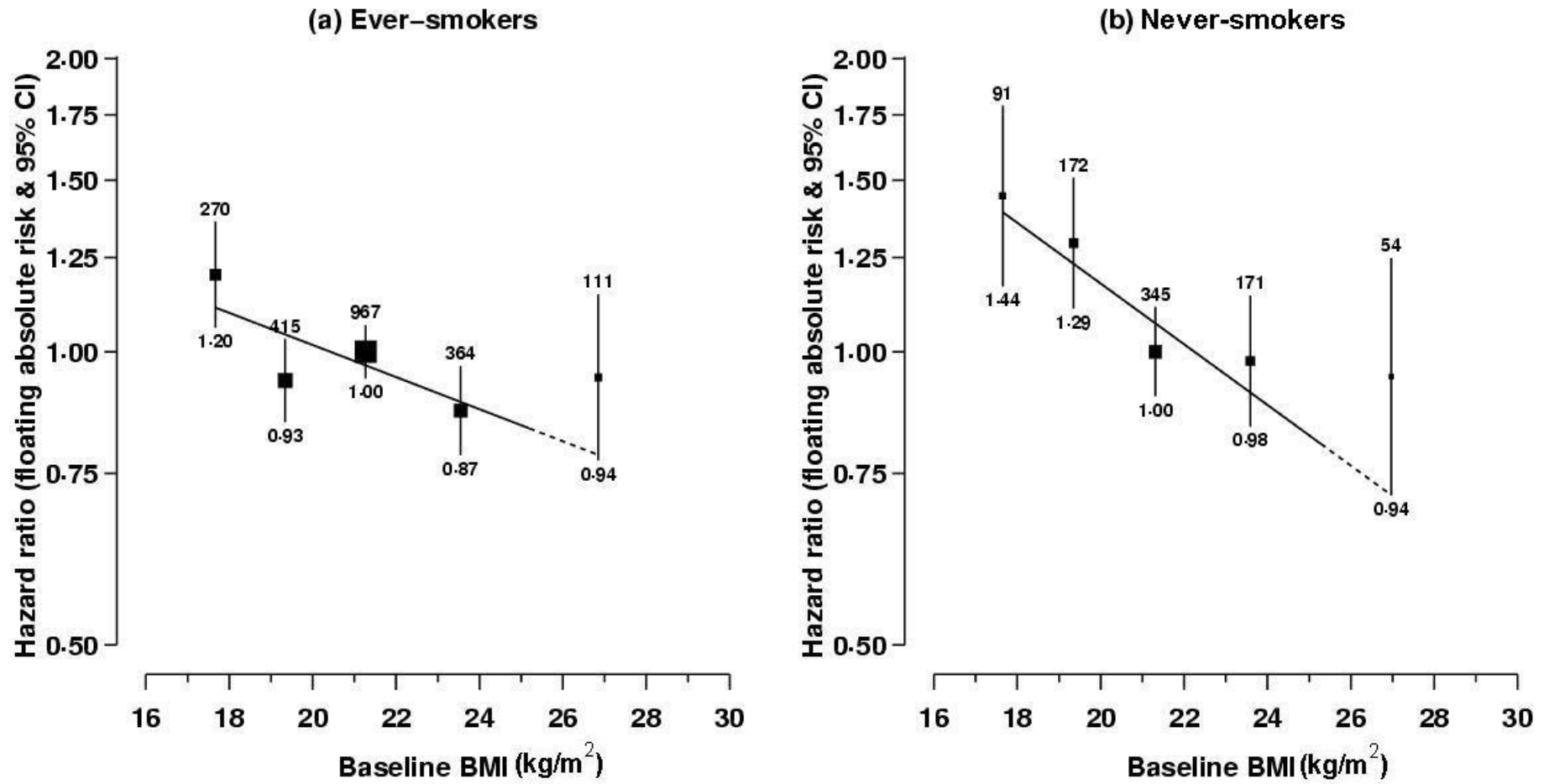


Figure 4



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

Figure 5

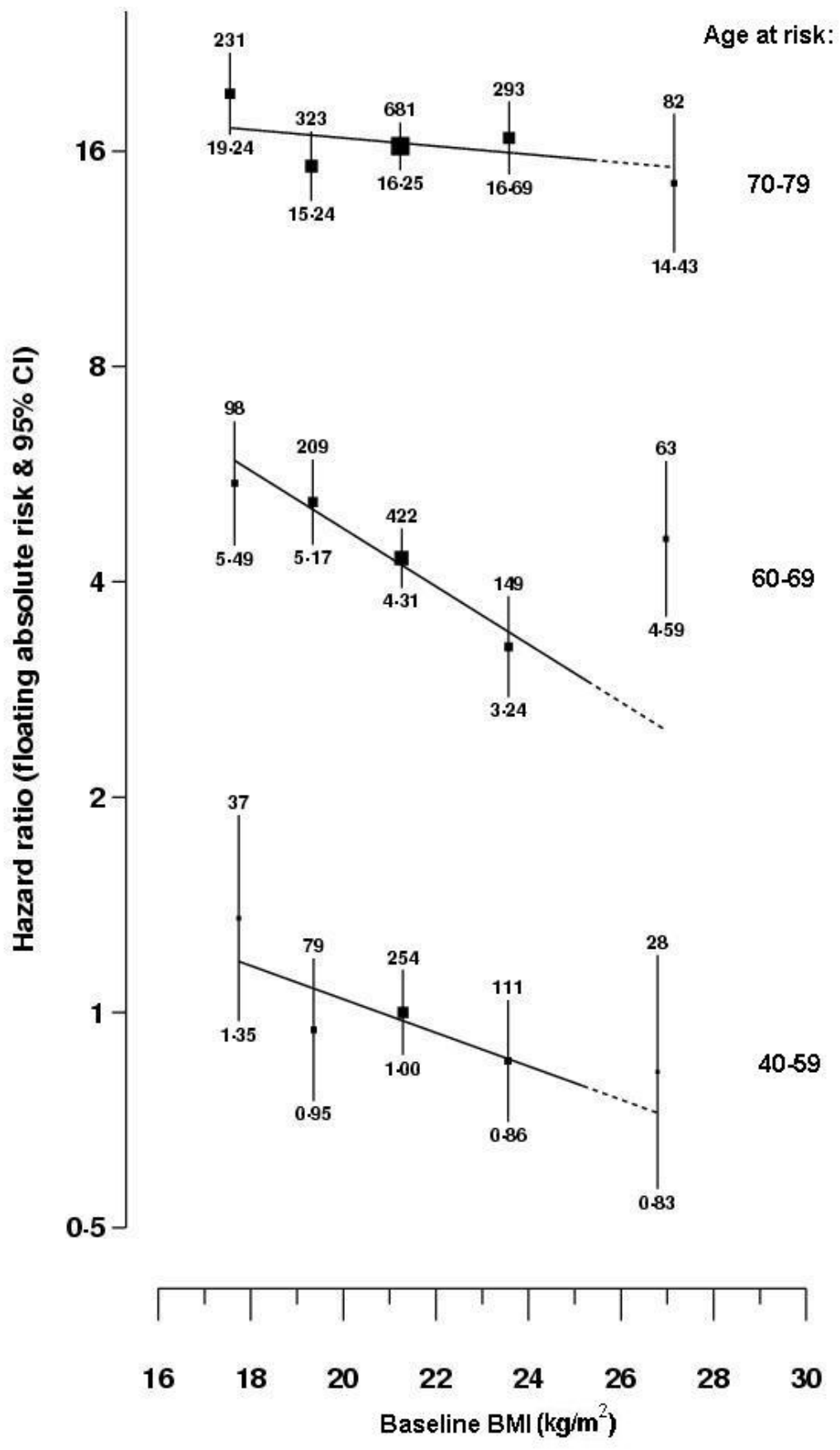
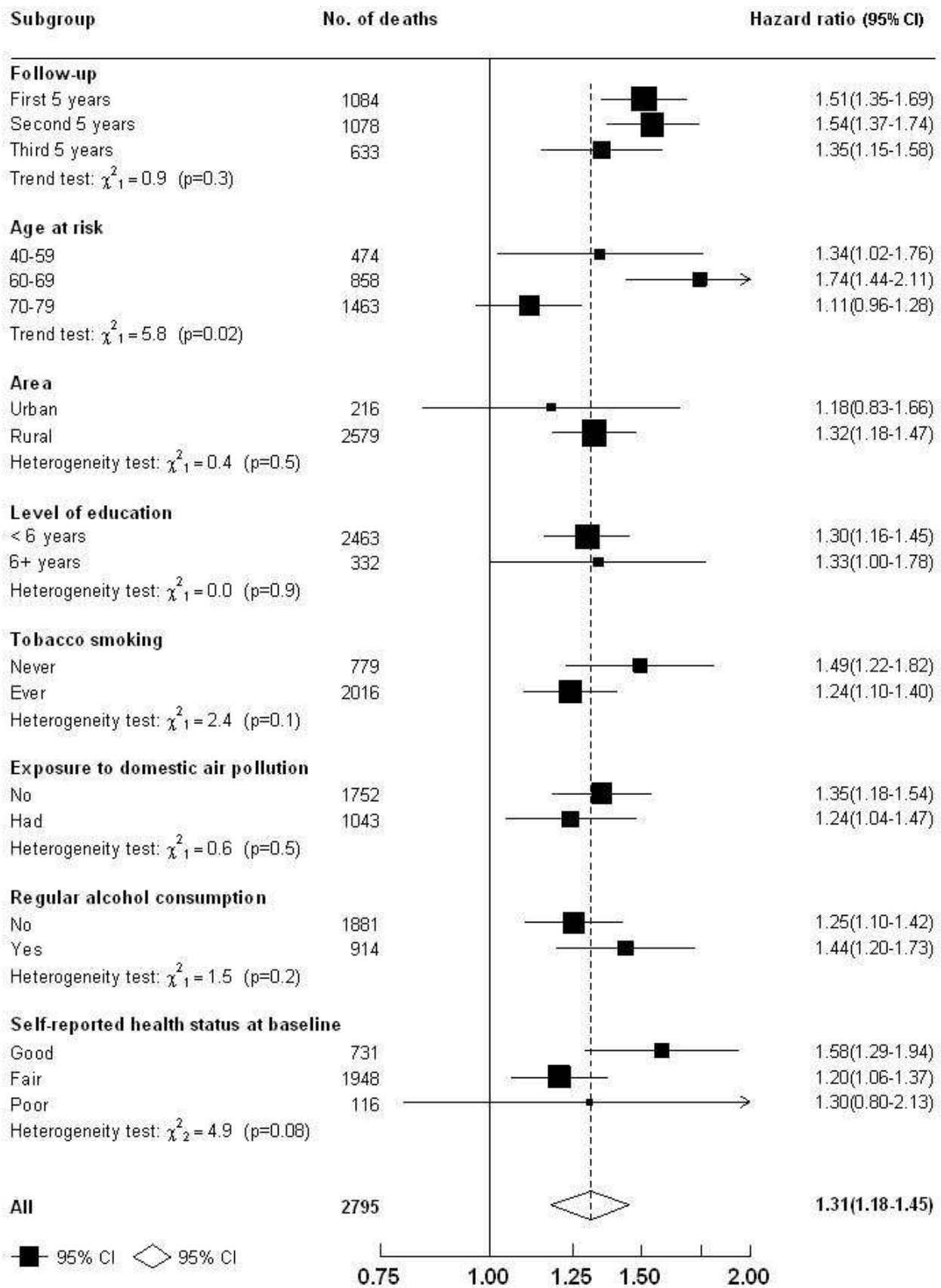


Figure 6



Reference

1. Viegi G, Scognamiglio A, Baldacci S, Pistelli F, and Carrozzi L. Epidemiology of chronic obstructive pulmonary disease (COPD). *Respiration*. 2001; 68: 4-19.
2. <http://www.who.int/respiratory/copd/en/>. Accessed in May 2008.
3. <http://www.who.int/healthinfo/statistics/bodgbdddeathdalyestimates.xls>. Accessed in May 2008.
4. Zhong N, Wang C, Yao W, Chen P, Kang J, Huang S, Chen B, Wang C, Ni D, Zhou Y, Liu S, Wang X, Wang D, Lu J, Zheng J, and Ran P. Prevalence of chronic obstructive pulmonary disease in China: a large, population-based survey. *Am J Respir Crit Care Med*. 2007;176(8): 753-760.
5. Chan-Yeung M, Ait-Khaled N, White N, Ip MS, and Tan WC. The burden and impact of COPD in Asia and Africa. *Int J Tuberc Lung Dis*. 2004; 8(1): 2-14.
6. Celli BR, Halbert RJ, Nordyke RJ, and Schau B. Airway obstruction in never smokers: results from the Third National Health and Nutrition Examination Survey. *Am J Med*. 2005; 118(12): 1364-1372.
7. Doll R, Peto R, Boreham J, and Sutherland I. Mortality in relation to smoking: 50 years' observations on male British doctors. *BMJ*. 2004; 328(7455):1519.
8. Liu BQ, Peto R, Chen ZM, Boreham J, Wu YP, Li JY, Campbell TC, and Chen JS. Emerging tobacco hazards in China: 1. Retrospective proportional mortality study of one million deaths. *BMJ*. 1998; 317:1411-1422.
9. Chen JS, Campbell TC, Li JY, Peto R. Diet, life-style and mortality in China. Oxford: Oxford University Press, Cornell University Press, and People's Medical Publishing House; 1990.
10. Chen JS, Peto R, Pan WH, Liu BQ, Campbell TC, Boreham J, Parpia B, Cassano P, and Chen ZM. Mortality, Biochemistry, Diet and Lifestyle in Rural China: Geographic Study of the Characteristics of 69 Counties in Mainland China and 16 Areas in Taiwan. Oxford University Press. 2006. Oxford,
11. Chen JC and Mannino DM. Worldwide epidemiology of chronic obstructive pulmonary disease. *Curr Opin Pulm Med*. 1999; 5(2): 93-99.
12. Buist AS, McBurnie MA, Vollmer WM, Gillespie S, Burney P, Mannino DM, Menezes AM, Sullivan SD, Lee TA, Weiss KB, Jensen RL, Marks GB, Gulsvik A, and Nizankowska-Mogilnicka E. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. *Lancet*. 2007; 370(9589): 741-750.
13. Brug J, Schols A, Mesters I. Dietary change, nutrition education and chronic obstructive pulmonary disease. *Patient Educ Couns* 2004; 52: 249-257.
14. de la Iglesia F, Diaz JL, Pita S, Nicolas R, Ramos V, Pellicer C, and Diz-Lois F. Peak expiratory flow rate as predictor of inpatient death in patients with chronic

- 1
2
3 obstructive pulmonary disease. *South Med J.* 2005; 98(3): 266-272.
4
5
6 15. Vestbo J, Prescott E, Almdal T, Dahl M, Nordestgaard BG, Andersen T, Sorensen
7 TI, and Lange P. Body mass, fat-free body mass, and prognosis in patients with
8 chronic obstructive pulmonary disease from a random population sample: findings
9 from the Copenhagen City Heart Study. *Am J Respir Crit Care Med.* 2006; 173(1):
10 79-83.
11
12 16. Menezes AM, Jardim JR, Perez-Padilla R, Camelier A, Rosa F, Nascimento O,
13 and Hallal PC. Prevalence of chronic obstructive pulmonary disease and
14 associated factors: the PLATINO Study in Sao Paulo, Brazil. *Cad Saude Publica.*
15 2005; 21(5): 1565-1573.
16
17 17. Landbo C, Prescott E, Lange P, Vestbo J, and Almdal TP. Prognostic value of
18 nutritional status in chronic obstructive pulmonary disease. *Am J Respir Crit Care*
19 *Med.* 1999; 160(6): 1856-1861.
20
21 18. Montes de Oca M, Talamo C, Perez-Padilla R, Jardim JR, Muino A, Lopez MV,
22 Valdivia G, Pertuze J, Moreno D, Halbert RJ, and Menezes AM. Chronic
23 obstructive pulmonary disease and body mass index in five Latin America cities:
24 The PLATINO study. *Respir Med.* 2008; 102(5): 642-650.
25
26 19. Schols AM, Slangen J, Volovics L, and Wouters EF. Weight loss is a reversible
27 factor in the prognosis of chronic obstructive pulmonary disease. *Am J Respir Crit*
28 *Care Med.* 1998; 157(6): 1791-1797.
29
30 20. Prescott E, Almdal T, Mikkelsen KL, Tofteng CL, Vestbo J, Lange P. Prognostic
31 value of weight change in chronic obstructive pulmonary disease: results from the
32 Copenhagen City Heart Study. *Eur Respir J* 2002; 20: 539-544.
33
34 21. Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, Pinto
35 Plata V, and Cabral HJ. The body-mass index, airflow obstruction, dyspnea, and
36 exercise capacity index in chronic obstructive pulmonary disease. *N Engl J Med.*
37 2004; 350(10): 1005-1012.
38
39 22. Ran PX, Wang C, Yao WZ, Chen P, Kang J, Huang SG, Chen BY, Wang CZ, Ni
40 DT, Zhou YM, Liu SM, Wang XP, Wang DL, Lu JC, Zheng JP, and Zhong NS. A
41 study on the correlation of body mass index with chronic obstructive pulmonary
42 disease and quality of life. *Zhonghua Jie He He Hu Xi Za Zhi.* 2007; 30(1): 18-22.
43
44 23. Johannessen A, Omenaas ER, Bakke PS, and Gulsvik A. Implications of
45 reversibility testing on prevalence and risk factors for chronic obstructive
46 pulmonary disease: a community study. *Thorax.* 2005; 60(10): 842-847.
47
48 24. Nemery B, Moavero NE, Brasseur L, and Stanescu DC. Smoking, lung function,
49 and body weight. *Br Med J (Clin Res Ed).* 1983; 286(6361): 249-251.
50
51 25. Steuten LM, Creutzberg EC, Vrijhoef HJ, and Wouters EF. COPD as a
52 multicomponent disease: inventory of dyspnoea, underweight, obesity and fat free
53 mass depletion in primary care. *Prim Care Respir J.* 2006; 15(2): 84-91.
54
55 26. Watson L, Vonk JM, Lofdahl CG, Pride NB, Pauwels RA, Laitinen LA, Schouten
56
57
58
59
60

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60

JP, and Postma DS. Predictors of lung function and its decline in mild to moderate COPD in association with gender: results from the Euroscop study. *Respir Med.* 2006; 100(4): 746-753.

27. Harik-Khan RI, Fleg JL, and Wise RA. Body mass index and the risk of COPD. *Chest.* 2002; 121(2): 370-376.
28. Pischon T, Boeing H, Hoffmann K, Bergmann M, Schulze MB, Overvad K, van der Schouw YT., Spencer E, Moons KG, Tjonneland A, Halkjaer J, Jensen MK, Stegger J, Clavel-Chapelon F, Boutron-Ruault MC, Chajes V, Linseisen J, Kaaks R, Trichopoulou A, Trichopoulos D, Bamia C, Sieri S, Palli D, Tumino R, Vineis P, Panico S, Peeters PH, May AM, Bueno-de-Mesquita HB, van Duijnhoven FJ, Hallmans G, Weinehall L, Manjer J, Hedblad B, Lund E, Agudo A, Arriola L, Barricarte A, Navarro C, Martinez C, Quiros JR, Key T, Bingham S, Khaw KT, Boffetta P, Jenab M, Ferrari P, and Riboli E. General and abdominal adiposity and risk of death in Europe. *N Engl J Med.* 2008; 359(20): 2105-2120.
29. Prospective Studies Collaboration. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. *Lancet.* 2009; 373(9669): 1083-1096.
30. Niu SR, Yang GH, Chen ZM, Wang JL, Wang GH, He XZ, Schoepff H, Boreham J, Pan HC, and Peto R. Emerging tobacco hazards in China: 2. Early mortality results from a prospective study. *BMJ.* 1998; 317:1423-1424.
31. Chen Z, Yang G, Zhou M, Smith M, Offer A, Ma J, Wang L, Pan H, Whitlock G, Collins R, Niu S, and Peto R. Body mass index and mortality from ischaemic heart disease in a lean population: 10 year prospective study of 220,000 adult men. *Int J Epidemiol.* 2006; 35:141-150.
32. Yang GH, Murray CJL, and Zhang Z. Exploring adult mortality in China: levels patterns and causes. Hua Xia Press. 1991. Beijing.
33. Chinese Academy of Preventative Medicine. Annual Report on Chinese Diseases Surveillance Points. Hua Xia Press. 1991. Beijing.
34. Easton DF, Peto J, Babiker AG. Floating absolute risk: an alternative to relative risk in survival and case-control analysis avoiding an arbitrary reference group. *Stat Med.* 1991; 10: 1025-1035.
35. Flegal KM, Graubard BI, Williamson DF, and Gail MH. Cause-specific excess deaths associated with underweight, overweight, and obesity. *JAMA.* 2007; 298(17): 2028-2037.
36. Seidell JC. The epidemiology of obesity. In Bjorntorp P, ed. *International Textbook of Obesity*, pp 23-9. Chichester: John Wiley, 2001.
37. Guerra S, Sherrill DL, Bobadilla A, Martinez FD, and Barbee RA. The relation of body mass index to asthma, chronic bronchitis, and emphysema. *Chest.* 2002; 122(4): 1256-1263.
38. Jee SH, Sull JW, Park J, Lee SY, Ohrr H, Guallar E, and Samet JM. Body-mass

- 1
2
3 index and mortality in Korean men and women. *N Engl J Med*. 2006; 355(8): 779-
4 787.
5
6
7 39. Reilly KH, Gu D, Duan X, Wu X, Chen CS, Huang J, Kelly TN, Chen J, Liu X, Yu L,
8 Bazzano LA, and He J. Risk factors for chronic obstructive pulmonary disease
9 mortality in Chinese adults. *Am J Epidemiol*. 2008; 167(8): 998-1004.
10
11 40. Sauvaget C, Ramadas K, Thomas G, Vinoda J, Thara S, and Sankaranarayanan
12 R. Body mass index, weight change and mortality risk in a prospective study in
13 India. *Int J Epidemiol*. 2008; 37(5):990-1004.
14
15 41. Calverley PM and Walker P. Chronic obstructive pulmonary disease. *Lancet*. 2003;
16 362(9389): 1053-1061.
17
18 42. Sin DD and Tan WC. Breaking down the "Great Wall" of COPD care in China. *Am*
19 *J Respir Crit Care Med*. 2007; 176(8): 732-733.
20
21 43. Pauwels RA and Rabe KF. Burden and clinical features of chronic obstructive
22 pulmonary disease (COPD). *Lancet*. 2004; 364(9434): 613-620.
23
24 44. Schwartz, D. B. Malnutrition in chronic obstructive pulmonary disease. *Respir*
25 *Care Clin N Am*. 12(4), 521-531. 2006.
26
27 45. Ringbaek TJ, Viskum K, and Lange P. BMI and oral glucocorticoids as predictors
28 of prognosis in COPD patients on long-term oxygen therapy. *Chron Respir Dis*.
29 2004;1(2): 71-78.
30
31 46. Schaible UE and Kaufmann SH. Malnutrition and infection: complex mechanisms
32 and global impacts. *PLoS Med*. 2007; 4(5): e115.
33
34 47. Lonroth, K., Williams, B. G., Cegielski, P., and Dye, C. A consistent log-linear
35 relationship between tuberculosis incidence and body mass index. *Int J Epidemiol*.
36 2009.
37
38 48. Chapman KR, Mannino DM, Soriano JB, Vermeire PA, Buist AS, Thun MJ,
39 Connell C, Jemal A, Lee TA, Miravittles M, Aldington S, and Beasley R.
40 Epidemiology and costs of chronic obstructive pulmonary disease. *Eur Respir J*.
41 2006; 27(1): 188-207.
42
43 49. Chen Z, Lee L, Chen J, Collins R, Wu F, Guo Y, Linksted P, and Peto R. Cohort
44 profile: the Kadoorie Study of Chronic Disease in China (KSCDC). *Int J Epidemiol*.
45 2005; 34(6): 1243-1249.
46
47 50. Eisner MD, Blanc PD, Sidney S, Yelin EH, Lathon PV, Katz PP, Tolstykh I,
48 Ackerson L, and Iribarren C. Body composition and functional limitation in COPD.
49 *Respir Res*. 2007; 8: 7.
50
51 51. Schols AM, Broekhuizen R, Weling-Scheepers CA, and Wouters EF. Body
52 composition and mortality in chronic obstructive pulmonary disease. *Am J Clin*
53 *Nutr* 2005; 82: 53-59.
54
55 52. Wannamethee SG, Shaper AG, and Whincup PH. Body fat distribution, body
56
57
58
59
60

composition, and respiratory function in elderly men. *Am J Clin Nutr.* 2005; 82(5): 996-1003.

53. Davey Smith, G., Sterne, J. A., Fraser, A., Tynelius, P. , Lawlor, D. A., and Rasmussen, F. The association between BMI and mortality using offspring BMI as an indicator of own BMI: large intergenerational mortality study. *BMJ* 339, b5043. 2009.
54. Zhang H and Cai B. The impact of tobacco on lung health in China. *Respirology.* 2003; 8(1): 17-21.
55. Mathers CD and Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med.* 2006; 3(11): e442.

For Review Only