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Body mass index and mortality from lung cancer in smokers and nonsmokers: A nationally representative prospective study of 220,000 men in China

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Low body mass index (BMI) has been associated with increased risk of lung cancer. However, the nature of the association, especially in populations with relatively low BMI, is less well characterized, as is the relevance to it of smoking. A nationally representative prospective cohort study included 217,180 Chinese men aged 40–79 years in 1990–91 who had no prior history of cancer and were followed up for 15 years. Standardized hazard ratios (HRs) were calculated for lung cancer mortality by baseline BMI. The mean baseline BMI was 21.7 kg/m^2, and 2,145 lung cancer deaths were recorded during 15 years of follow-up. The prevalence of smoking was strongly inversely associated with BMI, but no apparent relationship was seen between amount smoked (or other measures of smoking intensity) and BMI among smokers. Overall there was a strong inverse association between BMI and lung cancer mortality ($p < 0.0001$ for trend) after excluding the first 3 years of follow-up. This association appeared to be confined mainly to current smokers, with no apparent relationship in nonsmokers ($p < 0.001$ for difference between slopes). Among current smokers, the inverse association appeared to be log-linear, with each 5 kg/m^2 lower BMI associated with a 35% (95% confidence interval: 24–46%; $p < 0.0001$) higher lung cancer mortality, and it persisted after excluding those who had reported poor health status or history of any disease or respiratory symptoms at baseline. In this relatively lean Chinese male population, low BMI was strongly associated with increased risk of lung cancer only among current smokers.

Key words: body mass index; smoking; lung cancer; cohort study; mortality

Lung cancer is among the commonest types of cancer throughout China, causing some 400,000 deaths annually. During the last few decades the disease rate has risen steadily, especially among males, as a consequence of the recent large increase in cigarette consumption.[1,2] Despite the rise in smoking-related diseases, the emerging tobacco hazard in China remains at an early stage due to the delayed effect of increase in cigarette consumption, with only about 12% of male adult deaths being attributed to smoking during the 1990s, a proportion similar to that in the USA during the early 1950s.[3] Currently about two-thirds of men aged 15 or over in China smoke, compared to fewer than 5% of women.[3,4] Although there is little variation in the smoking prevalence between different regions of China, the absolute lung cancer rate varies considerably, with the nonsmoker lung cancer rate in some parts of China being about 10 times greater than that among US nonsmokers.[3] This suggests that factors other than smoking contribute significantly to disease risk in the population.[3,5,6]

Several observational studies have examined the relationship between lung cancer and body mass index (BMI), an indirect but useful measure of body fatness.[7–23] Most of these studies have shown BMI to be inversely associated with the risk of lung cancer, with particularly high excess risk among very lean people (BMI < 18.5 kg/m^2). Questions remain, however, about the nature of the association, particularly the relevance to it of smoking. Some studies have attributed the inverse association of BMI and lung cancer risk entirely to incomplete control of confounding by smoking and/or of reverse causality due to pre-existing disease,[7,9,10,14,15,22,23] whereas others have found no such evidence and purported to show that leanness itself may lead to increased risk of lung cancer.[13,18]

Most previous studies were conducted in populations in whom many are overweight or obese and did not record enough events among people with lower levels of BMI to determine the shape of the association reliably, particularly when analyzed separately in smokers and nonsmokers. There is little reliable epidemiological evidence of the association between BMI and lung cancer in countries such as China, where mean BMI is relatively low and few have smoked cigarettes persistently because of early adulthood. We report the association between BMI and lung cancer mortality in a 15-year prospective study of about 220,000 Chinese men aged 40–79 years recruited during 1990–91, of whom 67% were current smokers and 27% were lifelong nonsmokers.

Material and methods

Study population

Detailed information about study design, survey methods and participants has been published previously.[24,25] In brief, the original study cohort included 225,721 men recruited from 45 areas throughout China. These 45 areas were chosen at random from the 145 Disease Surveillance Points (DSPs), which were established in the mid-1980s and intended to provide a nationally representative sample of mortality statistics for the entire country.[26] A typical surveillance point covers a defined population of about 50,000–100,000 residents in 4–8 geographically defined units (either urban street committees or groups of rural villages).[27] During 1990–91, all men aged 40 years or above in 2 or 3 randomly selected residential units (urban street committees or rural communes) from each of the 45 areas were invited to participate in the survey, to assess mainly the prevalence of smoking (and other exposures) and its long-term effects on cause-specific mortality. No women were included in the study, as very few smoked. About 80% of invitees attended the survey clinics and were interviewed by trained health workers using a standardized questionnaire to collect information on education, occupation, smoking, alcohol and tea consumption, indoor air pollution, diet, medical history and self-reported health status. Height, weight, blood pressure and peak expiratory flow rate were measured, but no blood sample was collected. Changes in weight or smoking patterns after the baseline survey were not sought.

Conflicts of interest: None declared.

Abbreviations: BMI, Body Mass Index; CDC, Centre for Disease Control; CI, confidence interval; DSP, Disease Surveillance Point; HR, hazard ratio; ICD, International Classification of Disease; SBP, systolic blood pressure.

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Annual follow-up for cause-specific mortality

After the baseline survey, the vital status of each participant was monitored on a regular basis by local DSP staff through the established death registries in these areas, with additional active confirmation obtained annually from local residential committees.[27] Causes of death were sought chiefly from official death certificates, supplemented (if necessary) by a review of medical records. The underlying cause of death was coded in the central DSP office at the China Centre for Disease Control (China CDC) in Beijing, without knowledge of the survey information and using the ninth revision of the International Classification of Disease (ICD-9). In the few cases, in which death had occurred without medical attention, standard procedures were used by local DSP staff to determine the probable cause from symptoms or signs described by family members.[27] As it is often difficult to assign an underlying cause reliably to deaths in old age, all analyses are restricted to deaths occurring at ages 40–79 years, with censoring of live subjects at age 80 or on moving from original study area. The present report is of follow-up to January 1, 2006 (an average of 15 years) among the 217,180 men who, at the baseline survey, were aged 40–79 years, had valid BMI data (10–50 kg/m^2) and had no reported history of cancer.

Statistical analysis

Cox proportional hazards model was used to calculate hazard ratios (HRs), with BMI (or smoking) as the exposure variable and lung cancer death as the outcome variable.[28] All analyses were stratified by study area, 5-year age group and self-reported health status (good or poor) at baseline. BMI was categorized into 5 groups using cut-off points of 18.5, 20.0, 22.5 and 25.0 kg/m^2, with the main analyses also adjusted simultaneously for smoking status (never/former/current), education level (illiterate, primary school, middle school, college or university) and alcohol drinking (nondrinker, drinking alcohol <15, 15–29, 30–44, 45–59, ≥60 units/week). Adjustments were also made for exposure to indoor and occupational air pollution and dietary intake of fruit and meat, all of which have been identified previously as potential risk factors for lung cancer in China.[29]

HRs for lung cancer mortality were calculated for each BMI category, with BMI category of 20.0–22.5 kg/m^2 as the reference group (HR of 1.0). For each log HR, the 95% confidence interval (CI) was estimated using the "floating absolute risk" method,[30] which facilitates comparisons between many different categories, rather than pair-wise comparisons with the arbitrarily chosen reference category. Trend tests were conducted for the BMI analysis using the mean value for each BMI category as a continuous variable in the model. Departure from log-linearity was tested by a likelihood ratio test between this model and that with BMI group as a categorical variable. SAS version 9.1 under Windows XP was used for modeling.

Results

For the 217,180 men included in the present analyses, the overall mean BMI was 21.7 kg/m^2 (SD 2.7), with 9.2% of men being underweight (<18.5 kg/m^2) and 11.2% being either overweight (25–30 kg/m^2, 10.3%) or obese (≥30 kg/m^2, 0.8%). The ratio of urban to rural participants recruited in the study was similar to that for China as a whole (30%:70%), with the age-standardized BMI being higher in urban than in rural men (23.1 *vs.* 21.2 kg/m^2). After adjustment for age and area, BMI was strongly positively related to systolic blood pressure (SBP), each 2.5 kg/m^2 higher BMI being associated with about 3 mmHg higher SBP. These gradients were similar for smokers and nonsmokers. Men with higher BMI tended to be slightly better educated, less likely to report poor-health status at baseline or to be current smokers, but more likely to be ex-smokers and to consume alcohol. Although the prevalence of smoking was strongly inversely related to BMI, there was no apparent relationship between the mean amount smoked per day and BMI among current smokers, nor any relationship between mean age began smoking and BMI (Table I). Compared to lifelong nonsmokers, current smokers were slightly younger, less well educated and much more likely to drink alcohol, but the overall relationships between BMI and other baseline variables were similar for smokers and nonsmokers (Table I).

During about 15 years of follow-up, 40,636 participants died at ages 40–79 years. Deaths included 9,014 (22.2%) from cancer, of which 2,145 (70 per 100,000 person years) were attributed to lung cancer (ICD-9: 162). The age and area standardized lung cancer mortality rate was higher in urban (87 per 100,000) than in rural men (63 per 100,000), and higher among ever smokers (80 per 100,000) than among never smokers (44 per 100,000). After further adjustment for other factors, the overall hazard ratio for lung cancer among current smokers was 1.77 (95% CI: 1.67–1.87), being higher in urban (HR = 2.28, 95% CI: 2.06–2.52) than in rural men (HR = 1.57, 95% CI: 1.47–1.67; Table II). Among current smokers, the proportion who smoked cigarettes only was much higher in urban (63%) than did in rural areas (33%), but in both areas there was a significant positive dose-response relationship between lung cancer risk and amount smoked, with the overall combined HRs being 1.32, 1.59, 1.97 and 2.02, respectively, for those who smoked <10, 10–19, 20–29 and 30 or more grams of tobacco per day (p for trend <0.0001). Furthermore, men who began smoking at a younger age were at greater risk of lung cancer than those who began later, with HRs of 2.05, 1.90 and 1.34, respectively, for those who began smoking at age <20, 20–24 and 25+ years (p for trend <0.0001). Again, the HRs associated with amount smoked and age began smoking were more extreme in urban than in rural men (Table II).

There was a strong inverse association between BMI and lung cancer mortality, the age-standardized mortality rate being highest (102 per 100,000) among men with BMI < 18.5 kg/m^2 (Table I). After adjustment for smoking and various other potential confounding factors (education, alcohol consumption, exposure to indoor air-pollution and self-reported dietary intakes) as well as excluding the first 3 years of follow-up, there remained a strong inverse association between baseline BMI and lung cancer risk (p for trend <0.0001; Fig. 1). Figure 1 suggests that the association between BMI and lung cancer risk is log-linear, each 5 kg/m^2 lower baseline BMI being associated with 20% (95% CI: 5–35%) higher lung cancer mortality. Exclusion of men with a history of any pre-existing diseases (involving a total of 17 common non-neoplastic conditions such as IHD, stroke, chronic lung disease) or with self-reported poor health status at baseline did not alter the relationship significantly (data not shown).

To assess potential modifying effects of smoking, analyses were done separately for smokers and nonsmokers. Among current smokers, lung cancer mortality (1,311 deaths after excluding the first 3 years of follow-up) increased progressively with decreasing BMI in a log-linear fashion [p for trend <0.0001; Fig. 2(a)], each 5 kg/m^2 lower BMI being associated with 35% (95% CI: 24–46%; p < 0.0001) higher lung cancer mortality. In contrast, among the lifelong nonsmokers (with 309 lung cancer deaths after excluding the first 3 years of follow-up), there was no apparent association between BMI and lung cancer mortality [p for trend >0.05, Fig. 2(b)]. This difference in relationship of BMI with lung cancer mortality between current smokers and nonsmokers was significant (p < 0.001 for difference between slopes). Among ex-smokers, no association was seen between BMI and lung cancer mortality, but the number of deaths involved was small (158).

Among current smokers, the relationship was not significantly modified after taking account of the follow-up period, age at risk, area of residence, education, regular alcohol consumption and smoking intensity (type of smoking, amount smoked and age began smoking; Fig. 3). After restricting analyses to a subset of apparently "healthy" smokers (613 deaths), who had reported neither poor health status nor history of pre-existing disease or respiratory symptoms (*e.g.*, chronic cough or shortness of breath) at

TABLE I – BASELINE CHARACTERISTICS AND MORTALITY FROM LUNG CANCER BY BMI CATEGORY AMONG MEN AGED 40–79 YEARS AT BASELINE

Characteristics	Overall	BMI categories (kg/m^2)				
		<18.5	18.5–19.9	20.0–22.4	22.5–24.9	≥25.0
Number of participants	217,180	19,880	37,019	87,472	48,582	24,227
All participants						
Urban locality (%)[1]	27.2	17.9	15.5	19.3	35.6	64.5
Age (year)[1]	54.2	58.9	55.4	53.4	53.0	54.4
BMI (kg/m^2)	21.7	17.6	19.4	21.3	23.5	26.9
Weight (kg)	59.0	48.4	53.0	57.8	63.4	72.3
Height (cm)	164.5	165.5	165.1	164.7	163.9	163.5
SBP (mm Hg)	124.0	119.5	121.2	123.4	125.8	131.2
Education >6 years (%)	33.1	32.8	31.4	32.4	34.3	36.7
Alcohol drinking (%)	33.5	30.5	31.9	33.7	34.6	35.1
Self-reported poor health status (%)	7.2	13.2	8.3	6.5	5.4	6.6
Smoking status (%)						
Never	26.6	21.6	23.3	25.7	29.5	33.3
Past	6.2	6.0	5.2	5.5	6.7	9.8
Current	67.1	72.4	71.6	68.8	63.7	56.9
Amount smoked (g/day)	20.8	20.5	20.8	21.0	20.9	20.7
Age began smoking (year)	22.2	22.0	22.1	22.2	22.4	22.7
Never smokers						
Age (year)[1]	54.6	59.2	55.8	53.8	53.6	55.1
BMI (kg/m^2)	22.1	17.6	19.4	21.3	23.6	27.0
SBP (mm Hg)	124.9	120.0	121.5	123.5	126.2	132.0
Alcohol drinking (%)	18.1	14.2	16.4	17.6	18.9	21.6
Education >6 years (%)	38.2	36.1	35.9	38.0	39.3	40.1
Self-reported poor health status (%)	6.4	12.9	7.4	5.8	4.9	6.1
Current smokers						
Age (year)[1]	53.7	58.3	55.0	52.9	52.3	52.9
BMI (kg/m^2)	21.5	17.6	19.4	21.2	23.5	26.8
SBP (mm Hg)	123.3	119.2	120.9	123.0	125.1	130.2
Alcohol drinking (%)	39.7	36.0	37.3	39.8	41.8	43.0
Education >6 years (%)	30.0	30.6	28.9	29.1	30.8	33.5
Self-reported poor health status (%)	6.7	11.7	7.7	6.0	5.0	6.0
Death from lung cancer						
Number of deaths	2,145	262	418	780	465	220
Mortality rate per 100,000[2]	69.7	102.2	86.6	66.5	65.6	68.7

[1]Except for percentage of urban locality and mean age, all other variables were adjusted for individual area and age by 5 year age group by direct standardization to the study population.–[2]Mortality rates are standardized to the geographic area and the 5 year age group structures in the study population aged 40–79 years.

TABLE II – STANDARDIZED HAZARD RATIOS FOR LUNG CANCER MORTALITY BY SMOKING STATUS, AMONG MEN AGED 40–79 YEARS AT BASELINE

	Overall		Urban		Rural	
	No. of deaths	HR (95% CI)[1]	No. of deaths	HR (95% CI)[1]	No. of deaths	HR (95% CI)[1]
All men						
Never smoker[2]	393	1.00 (0.90, 1.11)	119	1.00 (0.83, 1.20)	274	1.00 (0.89, 1.13)
Ex-smoker	158	1.44 (1.23, 1.69)	82	1.45 (1.17, 1.81)	76	1.63 (1.30, 2.05)
Current smoker	1,594	1.77 (1.67, 1.87)	490	2.28 (2.06, 2.52)	1,104	1.57 (1.47, 1.67)
Current smokers						
Type of tobacco smoked						
Never smoker[2]	393	1.00 (0.90, 1.11)	119	1.00 (0.83, 1.21)	274	1.00 (0.89, 1.13)
Noncigarette	485	1.69 (1.52, 1.87)	41	2.90 (2.09, 4.01)	444	1.50 (1.35, 1.67)
Partly cigarettes	237	1.92 (1.67, 2.20)	20	1.77 (1.13, 2.78)	217	1.81 (1.57, 2.09)
Cigarettes only	872	1.77 (1.63, 1.91)	429	2.25 (2.04, 2.49)	443	1.49 (1.34, 1.66)
Amount smoked (g/day)						
Never smoker[2]	393	1.00 (0.90, 1.11)	119	1.00 (0.83, 1.21)	274	1.00 (0.88, 1.13)
1–9	143	1.32 (1.12, 1.56)	51	1.57 (1.19, 2.07)	92	1.22 (0.99, 1.50)
10–19	474	1.59 (1.45, 1.74)	115	1.82 (1.51, 2.18)	359	1.48 (1.33, 1.64)
20–29	629	1.97 (1.82, 2.14)	235	2.77 (2.43, 3.16)	394	1.65 (1.49, 1.83)
≥30	347	2.02 (1.81, 2.26)	89	3.02 (2.44, 3.74)	258	1.72 (1.51, 1.95)
Age began smoking (years)						
Never smoker[2]	393	1.00 (0.90, 1.11)	119	1.00 (0.83, 1.21)	274	1.00 (0.88, 1.13)
≥25	353	1.34 (1.21, 1.49)	137	1.77 (1.49, 2.09)	216	1.15 (1.01, 1.32)
20–24	674	1.90 (1.76, 2.05)	182	2.39 (2.07, 2.77)	492	1.69 (1.55, 1.85)
<20	567	2.05 (1.88, 2.24)	171	2.99 (2.55, 3.50)	396	1.73 (1.56, 1.91)

[1]Hazard ratio estimated by Cox regression model, which was stratified by age, area and baseline self-reported health status and adjusted for education, alcohol, intake of fruit and meat, body mass index, indoor or occupational pollution. The 95% confidence interval (95% CI) is estimated using the “floating absolute risk” method. Missing values were excluded from the analyses.–[2]Never smoker was used as reference group for all comparisons.

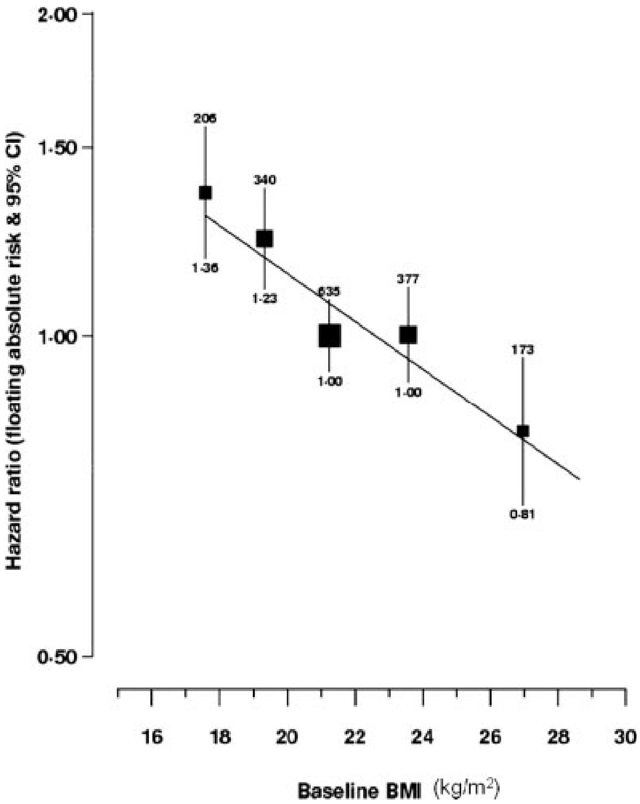

FIGURE 1 – Standardized lung cancer hazard ratio *versus* BMI among men aged at 40–79 years with no history of cancer at baseline, excluding the first 3 years follow-up. The hazard ratios (HR) are plotted on a floating absolute scale. Each closed square has an area inversely proportional to the effective variance of log HR. Vertical lines indicate the 95% confidence intervals, figures above which are numbers of lung cancer deaths (at ages 40–79 years) and those below are the HRs. The trend line was fitted by linear regression through the mean BMI for each category.

baseline, the inverse association between BMI and lung cancer risk persisted, the HRs being 1.19, 1.00 and 0.89, respectively, for men with BMI < 20, 20–22.5 (reference group) and >22.5 kg/m^2 (p for trend <0.01). In this subset of men, there was again no evidence of any interaction between smoking intensity and the inverse association of BMI with lung cancer mortality ($p > 0.05$ for interaction across 4 categories of smoking intensity, Table III).

Discussion

This is one of the largest prospective studies in China of the association between BMI, smoking and the risk of lung cancer mortality, involving a national random sample of adult males and a large number of lung cancer deaths. In this cohort, about two-thirds of men were current smokers, among whom the risk of lung cancer was significantly elevated compared to never smokers. Only 11% of the men were overweight or obese at baseline, (compared to more than 50% in the USA and UK at the same age,[31,32]) and among them the risk of lung cancer mortality was significantly lower than among those with lower BMI. The strong inverse association between BMI and lung cancer mortality was largely confined to current smokers, with no apparent association observed among lifelong nonsmokers.

A number of prospective studies have previously reported on the relationship between smoking and lung cancer in Chinese populations. Although most of them were relatively small and tended to involve particular areas of China, they have demonstrated consistently that smoking is a major cause of lung cancer, with the relative risk generally being in the range of 2.0–3.5[3,6,29,33–37] among those born before 1950. This is a much more modest result than that reported in studies of Western populations where the prolonged use of cigarettes has persisted for several decades. There is further evidence that the relative risk of lung cancer (as well as many other conditions) is less extreme in rural than in urban areas of China where there has been more prolonged use of cigarettes during the past few decades.[3] The present prospective study in a large national random sample that further confirms these early findings. The relatively lower disease risks currently associated with smoking in Chinese populations reflect primarily the fact that

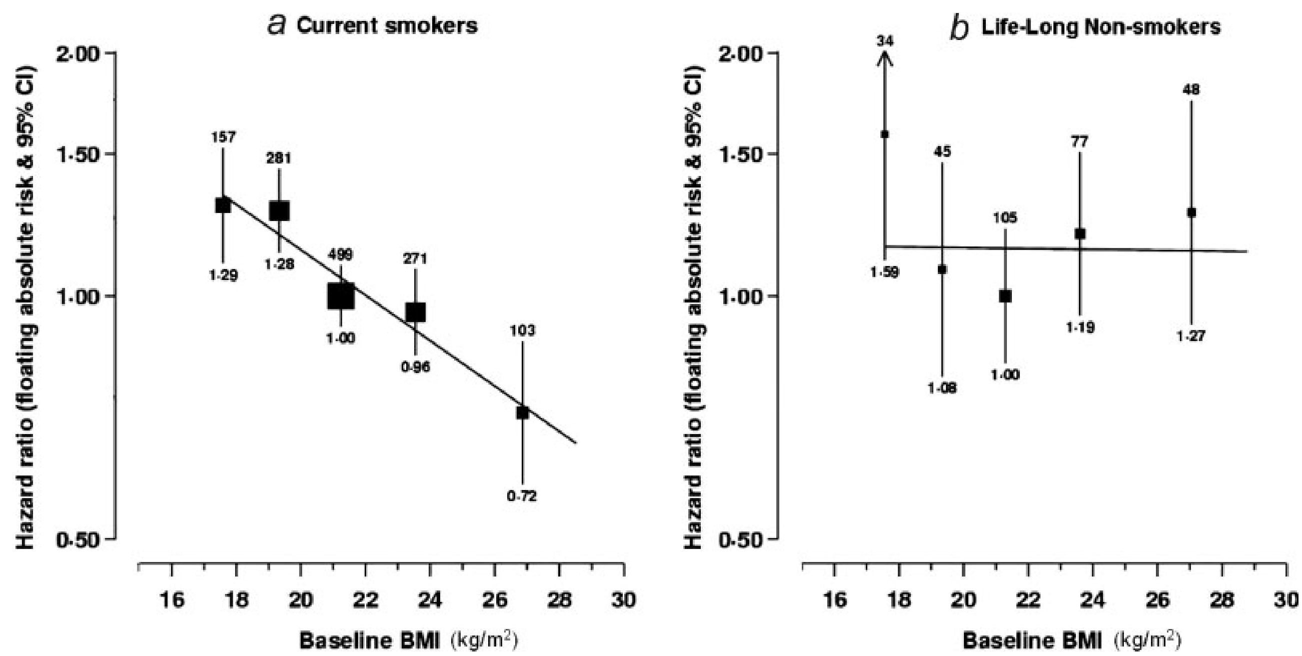

FIGURE 2 – Standardized lung cancer hazard ratio *versus* BMI, in (a) current-smokers and (b) life-long nonsmokers. Population and conventions are as in Figure 1.

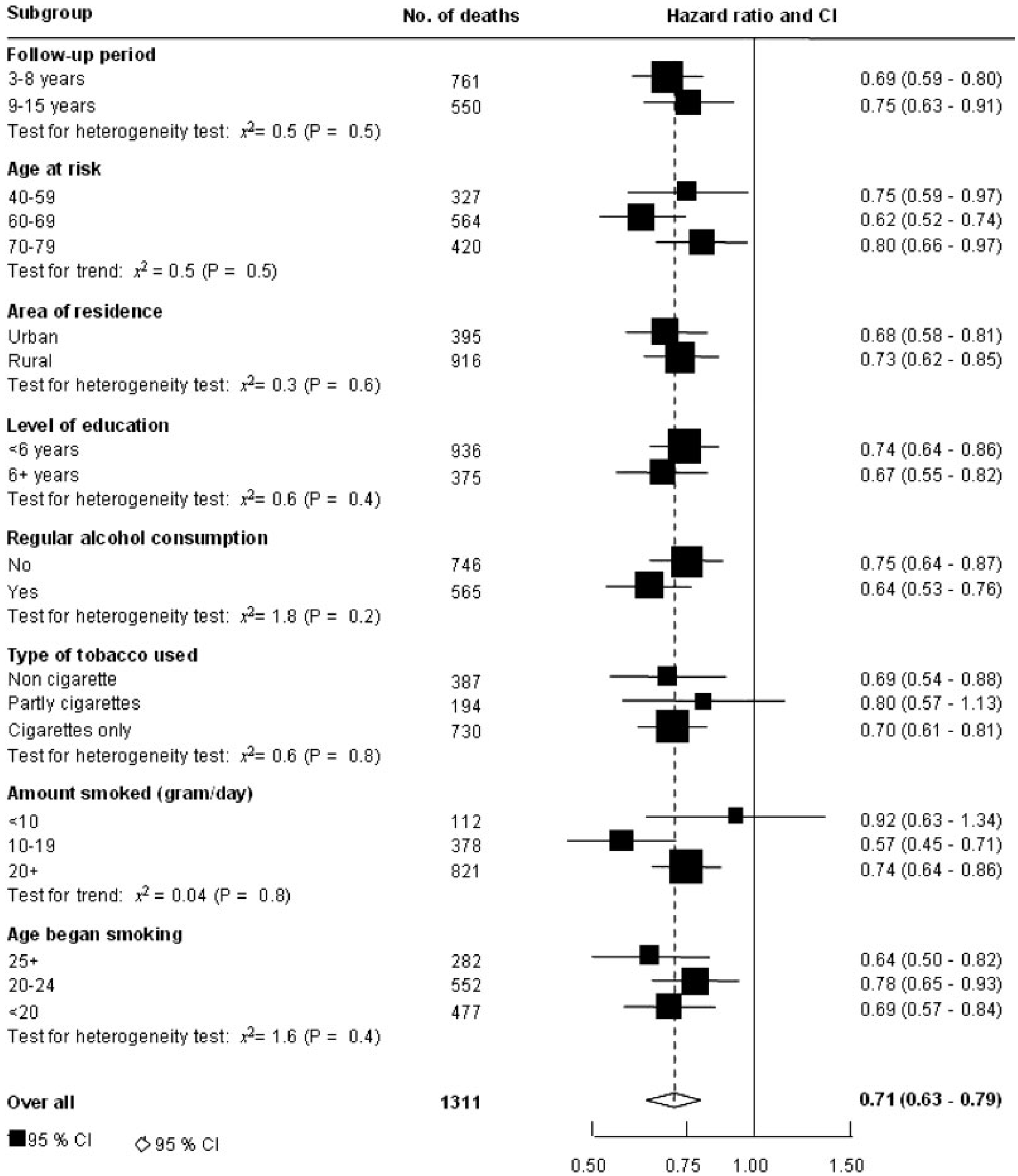

Figure 3 – Standardized lung cancer hazard ratio associated with 5 kg/m^2 higher BMI among current smokers who were aged 40–79 years and had no history of cancer at baseline, excluding the first 3 years follow-up. Each closed square represents a hazard ratio (HR) with the area inversely proportional to the variance of log HR. The dotted vertical line indicates the overall HR, and the open diamond indicates it and its 95% CI.

Chinese adults, especially those born before 1950, may not have smoked persistently in the past and/or may have smoked forms of tobacco with lower risk than cigarettes. Although the relative risk of lung cancer among smokers is modest, the absolute risks are not, given the high absolute rate of lung cancer among never smokers. In the present study, the mortality rate from lung cancer among life-long nonsmokers was 44.5 per 100,000, more than double that typically seen in many Western populations.[38] Until very recently, few Chinese smokers would have stopped smoking, and of those that did, many would have quitted because of illness.

TABLE III – STANDARDIZED HAZARD RATIOS FOR LUNG CANCER MORTALITY BY BASELINE BMI AND AMOUNT SMOKED, AMONG CURRENT SMOKERS WHO WERE AGED 40–79 YEARS AND HAD REPORTED NO POOR HEALTH STATUS NOR HISTORY OF ANY DISEASE OR RESPIRATORY SYMPTOMS AT BASELINE

BMI (kg/m^2)		Amount smoked (g/day)			
		<10	10–19	20–29	≥30
<20.0	No. of deaths	15	54	63	47
	HR (95% CI)[2]	1.66 (0.91, 1.48)	1.72 (1.31, 2.26)	1.91 (1.48, 2.45)	2.20 (1.63, 2.96)
20.0–22.5	No. of deaths	18	92	102	54
	HR (95% CI)[2]	1.00 (0.63, 1.60)[1]	1.61 (1.31, 1.99)	1.70 (1.39, 2.07)	1.58 (1.20, 2.09)
>22.5	No. of deaths	18	41	80	29
	HR (95% CI)[2]	1.05 (0.65, 1.68)	0.94 (0.69, 1.29)	1.96 (1.56, 2.47)	1.47 (1.02, 2.13)

[1]Men who had BMI between 20.0 and 22.5 kg/m^2 and smoked <10 g/day was used as the reference group.–[2]Hazard ratios were adjusted for education, consumption of alcohol, intakes of fruit and meat, exposure to domestic or occupational air pollution and stratified by age and area. The 95% confidence interval (95% CI) was estimated using the "floating absolute risk" method. Missing values were excluded from the analyses.

So, although no information was available about changes in smoking habits among study participants, it is unlikely that using only baseline smoking data would have materially affected the risk ratio estimation from smoking in the present study cohort.

The relationship between BMI and lung cancer has been investigated previously in more than a dozen prospective studies, and most of them were consistent in demonstrating an inverse association between BMI and lung cancer risk.[12,13,15,18,19,22,23] Questions remain, however, about the nature of the observed relationship, especially about the relevance of differences in smoking patterns. Smokers tend to be lean and at increased risk of not only lung cancer but also many other conditions and are likely to gain weight after cessation. It is, therefore, possible that incomplete or inappropriate control for smoking history or pre-existing disease, both of which may contribute significantly to low body weight, could result in a spurious association between BMI and lung cancer. Consequently, the most appropriate way of minimizing potential confounding effects of smoking is to examine the relationship separately for smokers and nonsmokers, rather than attempting, as did most previous studies, to adjust for smoking in multivariate analyses. Indeed, a few studies found that the inverse association between BMI and lung cancer appeared to differ significantly between smokers and nonsmokers,[14,15,22,23] although this was not fully supported by findings in other studies.[18,20]

Most previous studies were conducted in Western populations with a relatively small proportion of apparently healthy adults having low BMI (say <20 kg/m^2), and many yielded insufficient deaths at these lower levels of BMI, especially when analyzed separately by smoking status, to determine the associations reliably. Hence the shape of the associations may have been particularly susceptible to random fluctuations. The situation is quite different in the present study, where about 90% of men had BMI <25 kg/m^2 at baseline, and a large number of lung cancer deaths were recorded, so the association between BMI and the disease can be assessed reliably, not only overall but also separately for smokers and nonsmokers. The study showed that the observed inverse association between BMI and lung cancer mortality persisted after taking account of smoking and other potential confounding factors as well as various measures of pre-existing disease. When the analyses were done separately by smoking status, the strongly inverse association of BMI with lung cancer mortality was confined mainly to current smokers, with no apparent relationship among lifelong nonsmokers. The results of the present study are largely compatible with those from a few large prospective studies in Eastern and Western populations. In a large prospective study of more than a million adults in South Korea, there was a significant inverse association between BMI and lung cancer risk in men, with the strength of the association differing significantly between smokers and nonsmokers. However, the study simply compared the men who were obese (*i.e.*, BMI > 30 kg/m^2) with those having normal BMI (23–25 kg/m^2), and provided no further information about the shape of the association across the whole range of BMI in smokers and nonsmokers.[19] In the large USA ACS-II cohort study involving some 900,000 adults,[14] about 60% of male participants were overweight or obese (*i.e.*, BMI ≥ 25 kg/m^2), and overall there was a significant inverse association between self-reported BMI and lung cancer mortality. No significant association was seen among either male or female lifelong nonsmokers without pre-existing disease reported, though the numbers of lung cancer deaths in these subgroups were relatively small (199 men, 408 women).

In the present study, the inverse association between BMI and lung cancer mortality among current smokers was not altered by further adjustment for smoking intensity or other variables (indoor and occupational air pollution, and dietary factors), nor was it much affected by the exclusion of men with any prior disease or poor health status at baseline. Nevertheless, it remains possible that some residual confounding by smoking factors, such as intensity, degree of inhaling, use of filters, cessation or by some hypothetical interaction between smoking and other causative factors for lung cancer, is causing the observed association among the smokers. Further consideration of such possible residual confounding in other studies (such as the large USA ACS-II cohort study which has not reported separate analyses among smokers[14]) might help establish the nature of the association.

The present study involves a large number of lung cancer deaths, so its findings are statistically reliable. Although it is possible that the inverse association between BMI and lung cancer death observed among smokers could be due to residual confounding by smoking factors, it is also possible that low BMI may interact with smoking somehow to increase the risk of lung cancer death. It has been suggested that the association of BMI with lung cancer may vary with different histological types of the disease,[9,39] but this cannot be assessed in the present study.

Among current smokers in the present study, the mean amount smoked per day was not associated with BMI despite the strong inverse association between prevalence of smoking and BMI in the overall population. This implies that the dose of tobacco per kilogram of body weight is higher among smokers with low BMI than those with high BMI. This is consistent with observations in a number of other studies that, for a given amount smoked, the salivary levels of cotinine, the major metabolite of nicotine, are significantly higher among lean smokers than among those with high BMI.[40–42] The reasons for this difference are not entirely clear but could be due to greater nicotine intake per cigarette and/or by lower metabolic clearance of cotinine associated with leanness. There was also evidence that smokers with low BMI tended to have higher levels of 8-hydroxydeoxyguanosine, a marker of oxidative DNA damage, compared to smokers having normal or higher BMI,[43] which could have been caused by increased exposure to carcinogens from smoking. Future studies using specific biomarkers (*e.g.*, cotinine) for better characterization of smoking intensity[44] as well as genetic markers for obesity [such as fat-mass and obesity associated (FTO) gene][45] or for lung cancer[46] may help to elucidate the nature of the inverse association between BMI and lung cancer risk among smokers. Moreover, although BMI is the most commonly used measure for obesity, substantial differences in percentages of fat and fat-free mass can exist between individuals with the same BMI. Unfortunately, no other anthropometric data, such as waist and hip circumferences or bioimpedance, were available in the present study.

In summary, the present large prospective study has confirmed the fundamental importance of smoking as a major cause of lung cancer among Chinese men. Although the risk ratio of lung cancer for smokers is currently much lower than that typically seen in Western populations, the absolute risk of the disease associated with smoking is not, given the high background rate of the disease in the population, and it is likely to increase substantially in the future owing to the delayed effects from the recent large increase in cigarette consumption in China. The inverse association between BMI and lung cancer risk observed in current smokers is largely unexplained and warrants further investigation. During recent decades, the mean BMI in the Chinese population has risen steadily as a result of changes in dietary patterns and physical activities. Further increase in the prevalence of overweight and obesity in China is likely to result in increased mortality from cardiovascular disease and other conditions, especially when combined with widespread use of cigarettes. This could well offset any advantageous effects on lung cancer of improved population nutrition, even assuming a causal association between low BMI and lung cancer.

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