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Body Mass Index, Blood Pressure, and Mortality From Stroke
A Nationally Representative Prospective Study of 212 000 Chinese Men
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Background and Purpose—Despite previous investigations, substantial uncertainty remains about the relation between body mass index (BMI) and stroke, especially in populations with a relatively low BMI but a high stroke rate. Methods—A nationally representative prospective study of mortality included 212 000 Chinese men 40 to 79 years old without known cardiovascular disease in 1990 to 1991 who were followed up for 10 years. Standardized hazard ratios were calculated for stroke mortality by baseline systolic blood pressure (SBP) and BMI. Results—Mean SBP and BMI were 124 mm Hg and 21.7 kg/m², respectively. During 10 years of follow-up, 5766 stroke deaths were recorded. There were strong, positive relations between BMI and SBP and between SBP and stroke mortality, with a 3-mm Hg higher baseline SBP associated with a 5.6% (95% CI, 5.3% to 6.0%; P<0.00001) higher stroke mortality. The association between BMI and stroke mortality was, however, not linear, with the hazard increasing substantially only for BMI≥25 kg/m² (P<0.001 for nonlinearity). Approximately 90% of men had a baseline BMI<25 kg/m², and among them, BMI was not associated with stroke mortality despite its strong association with BP (which continued to a BMI<18 kg/m²). The relation with BMI was similar for ischemic and hemorrhagic stroke but appeared to be steeper among lifelong nonsmokers than among current smokers (P=0.01 for difference between slopes) despite similarly positive relations between BMI and SBP and between SBP and stroke risk in both smoking categories. Conclusions—High BMI was strongly associated with increased stroke mortality only among men who were overweight or obese. (Stroke. 2008;39:753-759.)

Key Words: blood pressure • body mass index • cohort study • mortality • stroke

Stroke is a leading cause of death and disability in China, despite the population being relatively lean and having a relatively low prevalence of hypertension, especially in rural areas.1 Higher body mass index (BMI) is strongly associated with higher blood pressure (BP), which can predispose to cardiovascular conditions such as ischemic heart disease and stroke. There is consistent evidence from prospective cohort studies in many populations that BMI is positively associated with ischemic heart disease,2 but its association with stroke is less well characterized. Some studies have reported a positive relation between BMI and stroke, chiefly for ischemic stroke,3–12 whereas others either have observed no such relation13–17 or have even reported an inverse association, at least for hemorrhagic stroke.10,18 Moreover, although many studies have indicated that those who are overweight (defined as a BMI of 25 to 30 kg/m²) or obese are at increased risk of stroke, there is substantial uncertainty about the shape and even the direction of the relation among those who are not9,11,14 and about the relevance to this relation of differences in age or smoking habit.4,10,17,18

Most previous studies were conducted in populations in which the mean BMI was relatively high but the stroke incidence in middle age was relatively low, by comparison with China. There is little reliable evidence of the relation between BMI and stroke in countries such as China, where BMI is relatively low and stroke mortality is much higher than ischemic heart disease mortality.1,19 We report a 10-year prospective study of the association between BMI and stroke mortality in a nationally representative cohort of 212 000 Chinese men recruited during 1990 to 1991, including 144 000 current smokers (68%) and 56 000 lifelong nonsmokers (26%).

Subjects and Methods Baseline Survey
Details of the study design, methods, and participants have been described previously.20,21 In brief, the original study population

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included 225,721 men. They were recruited in 45 areas across China, which were selected at random from the 145 Disease Surveillance Points (DSPs) that were established in the 1980s and are now coordinated nationally by the Chinese Centre for Disease Control (China CDC). These 145 DSPs cover ~1% of the total population in China and provide a nationally representative sample of mortality statistics for the entire country.22,23 During 1990 to 1991, all men aged 40 or older in 2 or 3 randomly selected residential units (urban street committees or rural communes) from each of these 45 areas were invited to participate in the survey. Approximately 80% of those invited attended the screening clinics and were interviewed by trained health workers using a standardized questionnaire about smoking and other exposures. Height, weight, BP, and peak expiratory flow rate were also measured, but no blood sample was collected. For BMI, information was available for all but 154 participants, but no information about weight or BP changes was collected after the baseline (1990–1991) survey.

Follow-Up for Cause-Specific Mortality

After the baseline survey, the vital status of each study participant was to be monitored passively through the death registries previously established in these regions, with active confirmation annually by local residential committees.22,23 Causes of death were sought chiefly from official death certificates, supplemented (if necessary) by a review of medical records. The underlying cause of each death was coded centrally by staff in the central DSP office in Beijing, who were blinded to the survey information and used the ninth revision of the International Classification of Disease (ICD-9). In the few cases where 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.20,23 Although computed tomography scanners were becoming widely available during the 1990s in large and medium-size hospitals throughout China, no information from such scans was sought (except insofar as their findings affected the official death certificate).

The 10,147 participants who reported a history of heart disease or stroke at baseline were excluded from the main analyses, because vascular disease itself could affect BP (reverse causality), but those with hypertension or diabetes were retained (because these could be mechanisms whereby obesity predisposes to stroke). The present report is based on follow-up to January 1, 2002 (ie, for an average of 10 years) among the 211,946 men who were 40 to 79 years old at the baseline survey and had no reported history of cardiovascular disease. Because it is often difficult to reliably assign an underlying cause of death at older ages, all analyses were restricted to deaths occurring at ages 40 to 79, with censoring when men reached 80 years of age (or moved away from the original study area).

Statistical Analysis

Hazard ratios (HRs) were estimated by a Cox proportional-hazards model, with either systolic BP (SBP) or BMI as the exposure variable and stroke death as the outcome.24 The analyses were stratified by individual area and by 5-year age group at risk and were adjusted simultaneously for baseline smoking (never/former/current), alcohol drinking (at least weekly, yes/no), and weekly number of units of alcohol consumed (as a covariate). For BP analyses, participants were divided into 8 categories of baseline SBP measure-
ments with 7 equally spaced cutpoints (from <110 to 170 mm Hg), whereas for BMI they were divided into 6 categories, with cutpoints (from 18.5 to 25 kg/m2) chosen as the reference groups with an HR of 1.0. For each log HR, the 95% CI was estimated by the “floating absolute risk” method,26 which facilitates comparisons between many different categories, rather than from pairwise comparisons with the arbitrarily chosen reference category.

In addition, HRs were also calculated by treating BMI as a continuous covariate in the Cox regression model. Departures from log linearity were examined by adding a quadratic term.27 The test of any interaction between smoking status and the effects of BMI on the log HR omitted the ex-smokers and used an age-, area-, and alcohol-adjusted Cox regression model, with BMI, smoking (lifelong nonsmoker or current smoker), and a BMI×smoking interaction term as covariates.

Results

Of the 211,946 men in the present analyses, 27,758 died at age 40 to 79 during ~10 years of follow-up, 12,558 survived to age 80, and 21,897 were lost to follow-up before age 80 (~1% loss per year, mainly because of demolition of entire residential areas for redevelopment). In a comparison of those who were lost to follow-up and those who were not, no material differences were seen (after adjustment for age and study area) in BMI, SBP, smoking prevalence, or other baseline characteristics.21 Of the recorded deaths, 5766 (20%) were attributed to stroke (ICD-9 430 to 438) and 1695 (6%) to ischemic heart disease (ICD-9 410 to 414). Of these stroke deaths, 570 were of unspecified etiology. Of the remaining stroke deaths (100%), 3609 (69%) were attributed to hemorrhagic stroke (ICD-9 431, 432), 1231 (24%) to ischemic stroke (ICD-9 433, 434), and 356 (7%) to subarachnoid hemorrhage. The proportion attributed to hemorrhagic stroke was slightly higher in middle than in old age (74% at age <60 vs 65% at age 70 to 79 years).

The overall mean BMI was 21.7 kg/m2 (SD 2.7) but was slightly lower at older ages. The age-adjusted BMI was lower among rural than among urban men (21.2 vs 23.1 kg/m2). After adjustment for age and area, BMI was strongly positively related to BP and, on average, each 2.5-kg/m2 higher BMI was associated with an ~3.0/1.5 mm Hg (systolic/dia-
stolic) higher BP (Table 1). These gradients were similar for smokers and nonsmokers. Men with higher BMI tended to be slightly better educated, less likely to be current smokers, and more likely to be ex-smokers and to consume alcohol. Although the prevalence of smoking was strongly inversely associated with BMI, the mean amount smoked per day was not associated with BMI among current smokers; hence, the dose of tobacco per kilogram of body weight was also inversely related to BMI. Participants with higher BMI were more likely to report a history of diabetes or hypertension at baseline.

Figure 1 shows the relation between baseline SBP and subsequent mortality from stroke. There was a strong, positive relation between SBP (as well as diastolic BP; data not shown) and stroke mortality, with no evidence of any threshold below which a lower SBP was no longer associated with lower stroke mortality. The relation appeared to be slightly steeper for an SBP >130 mm Hg than below it, but an average 3-mm Hg higher baseline SBP was typically associated with a 5.6% (95% CI, 5.3% to 6.0%; P<0.00001) higher stroke mortality. The strength of the relation was similar for both ischemic (5.3%; 95% CI, 4.6% to 6.2%) and hemorrhagic (6.0%; 95% CI, 5.6% to 7.1%) stroke mortality but appeared to be slightly steeper in urban (8.1%; 95% CI, 7.3% to 8.9%) than rural (5.2%; 95% CI, 4.8% to 5.6%) areas.
Despite the strong, positive, and approximately linear associations between baseline BMI and BP and between BP and stroke mortality, the relation between baseline BMI and stroke in the whole population was not linear (Table 2 and Figure 2). Stroke mortality increased progressively with BMI only at BMIs >25 kg/m² ($P<0.0001$ for test of nonlinearity across all 6 groups), with similar patterns for both ischemic and hemorrhagic stroke (Table 2) and in both urban and rural areas (data not shown). The relation was not materially altered by exclusion of the first 3 years of follow-up (Figure 2 vs Table 2), by exclusion of men with self-reported poor health status at baseline, by exclusion of those with self-reported hypertension and/or diabetes, or by further adjustment for any other factors (such as self-reported dietary intakes; data not shown).

To help assess any potential modifying effects, separate analyses were done according to smoking status at baseline. Both among lifelong nonsmokers and among current smokers (as well as ex-smokers; data not shown), BMI was strongly positively related to BP throughout the whole range of baseline BMI levels studied. There was also a strong, positive relation between baseline SBP and stroke mortality in both nonsmokers and smokers, with each 3-mm Hg higher baseline SBP being associated with a 6.7% (95% CI, 5.8% to 7.6%) and a 5.6% (95% CI, 5.2% to 6.1%) higher stroke mortality, respectively (Figure 3a). However, the relation between BMI and stroke mortality appeared to be steeper among lifelong nonsmokers than among current smokers ($P=0.01$ for test for difference between slopes).

Among the 56 000 lifelong nonsmokers, stroke mortality (based on 995 deaths) appeared to increase progressively with increasing levels of BMI in a log-linear fashion ($P=0.28$ for departure from log linearity), with no evidence of any threshold below which a lower BMI was no longer associated with a lower stroke mortality ($P<0.0001$ for trend; Figure 2).
Among nonsmokers, each 2.5-kg/m² higher baseline BMI was associated with an ≈16% (95% CI, 10% to 23%, \( P<0.0001 \)) higher stroke mortality throughout the range of BMI studied (18 to 30 kg/m²). The excess risk appeared to be somewhat greater for ischemic stroke (25%; 95% CI, 12% to 41%) than for hemorrhagic stroke (14%; 95% CI, 6% to 23%), but this difference was not statistically significant (\( P=0.2 \) for difference between slopes).

By contrast, among the 144 000 current smokers (2896 stroke deaths), there appeared to be a shallower and more irregular relation between BMI and stroke mortality (\( P=0.02 \) for nonlinearity), with the risk not starting to rise much until a BMI of 25 kg/m² (Figure 3b). Because smokers constituted two thirds of the whole study population, the pattern of the relation in the whole study population is largely similar to that among smokers (Figures 2 and 3b). Likewise, the relation with BMI appeared to be similar for both hemorrhagic and ischemic stroke (data not shown), and further adjustment for smoking intensity (eg, amount and duration) did not alter this relation, nor did adjustment for any other factors (such as self-reported dietary intakes).

Among the 12 000 ex-smokers (of whom 60% had stopped because of ill health), 412 subsequently died of stroke. The shape of the relation between BMI and stroke risk for these ex-smokers resembled that for lifelong nonsmokers more than that for current smokers, but the numbers were relatively small.

Among lifelong nonsmokers, simultaneous adjustment for SBP and diastolic BP measured once at baseline, as well as a history of hypertension and diabetes, attenuated the regression coefficient of the curve between BMI and stroke mortality by approximately two thirds (Figure 3c), with each 2.5-kg/m² higher baseline BMI being associated with only a marginally significant 6% (95% CI, 0% to 13%; \( P=0.046 \)) higher stroke mortality (compared with 16% without such adjustments). Because the self-correlation of repeated measurements of BP a few years apart is typically ≈0.5 to 0.6, long-term “usual” BP is likely to account for most or all of the association between BMI and stroke (see Discussion). Among current smokers, after simultaneous adjustment for these factors, the association with stroke appeared to be reversed, though not significantly.

**Discussion**

This is one of the largest prospective studies of the relation between BMI and mortality from stroke in a relatively lean population, and it involved a nationally representative population of Chinese men with substantial numbers of stroke deaths. In this population, BMI was strongly related to BP throughout the whole range of BMI levels studied. Similarly, BP was strongly related to stroke mortality, with no evidence of any threshold within the range of baseline SBP measurements studied (ie, ≈100 to 180 mm Hg). However, despite these two continuous relations, BMI was strongly associated with stroke mortality only in the range of BMI >25 kg/m². Most men in the study had a lower BMI than this, and among
them there was little relation of BMI to risk, which is not what would have been expected from the linear relations between BMI and BP and between BP and stroke mortality. To consider the BMI and stroke relation quantitatively, particularly the extent to which the relation is mediated through the effects of BP on stroke, further approximate correction is also needed for “regression dilution” bias (ie, for the random inaccuracy with which a single SBP measurement characterizes an individual’s long-term average, or “usual,” SBP). In the present study, analyses of SBP and stroke risk subdivided the single baseline SBP measurement into 8 categories, and the range of mean baseline measurements between the lowest (mean, \(\approx 100\) mm Hg) and highest (mean, \(\approx 180\) mm Hg) baseline SBP category was 80 mm Hg. Evidence from non-Chinese populations involving individuals with SBP measured on two separate occasions a few years apart suggests that the mean usual SBP values between the lowest and highest categories of baseline SBP measurements would probably be only \(\approx 50\) mm Hg (eg, mean \(\approx 110\) vs 160 mm Hg). Although no resurvey of the present population is available, this suggests that the slope of the relation of stroke mortality to usual SBP is considerably steeper than

Figure 3. Stroke mortality ratio vs (a) baseline SBP, (b) baseline BMI, and (c) baseline BMI after simultaneous adjustment for baseline SBP and diastolic BP, history of hypertension, and history of diabetes, in (left) lifelong nonsmokers and (right) current smokers. Population and conventions are as in Figure 2.
presented in Figure 1, particularly in the hypertensive range, for which the increase in stroke mortality could well be \( \approx 5\% \) per mm Hg usual SBP (as in European and North American studies).\(^5\) If this is true in this Chinese population, then BP could well account for most or all of the increase in stroke mortality with BMI in the overweight range (ie, \( >25 \text{ kg/m}^2 \)).

What remains unexplained is the striking lack of any apparent dependence of stroke mortality on BMI below the overweight range. There was a difference of \( 6/4 \text{ mm Hg} \) in SBP/diastolic BP between the first and fourth BMI groups in Figure 2 (which differ by \( 6 \text{ kg/m}^2 \) in BMI; Table 1), and this should, if other things were equal, correspond to a stroke mortality ratio of \( \approx 1.3 \), but it does not. Because our findings in this relatively narrow BMI range are appreciably subject to the play of chance, they should be considered together with the findings in other populations.

Several prospective studies have reported on the relation between BMI and stroke, but the findings have been inconsistent. Some have reported a positive linear association with total stroke,\(^5,8,10,12\) whereas others have reported no relation,\(^13,15,17\) a U- or J-shaped association,\(^9,11\) or even an inverse association.\(^18\) A few studies have also suggested that the relation may differ qualitatively between stroke subtypes, with positive associations for ischemic stroke and no association or even an inverse association for hemorrhagic stroke,\(^9,10,18\) but these findings have not been supported by other studies.\(^5,8,12\)

Studies in East Asian populations\(^8,12\) have, in general, found a positive association between BMI and ischemic stroke, although the association for hemorrhagic stroke was less definite below a BMI of \( 25 \text{ kg/m}^2 \). In a study of 230,000 Korean men with a mean BMI of \( 23.1 \text{ kg/m}^2 \), there was a positive association between BMI and the incidence of ischemic stroke (3296 cases) across the whole range of BMI, whereas for hemorrhagic stroke (1487 cases), there appeared to be little relation for a BMI \( <25 \text{ kg/m}^2 \).\(^5\) Likewise, in a meta-analysis of 33 prospective studies from the Asia-Pacific region involving 310,000 people and 3000 cases of stroke (25% from China),\(^12\) the mean baseline BMI was \( 23.6 \text{ kg/m}^2 \), and there was a positive relation between BMI and ischemic stroke throughout the whole range of BMI. However, the association with hemorrhagic stroke (851 cases) in that meta-analysis was mainly at high BMI levels. Given that much of the effect of BMI on stroke may be mediated through BP (which is associated about as strongly with ischemic as with hemorrhagic stroke),\(^5\) there is no priori reason to expect the association with BMI to differ qualitatively between ischemic and hemorrhagic stroke.

Previous studies have shown that the proportion of different subtypes of stroke differs significantly between Chinese and Western populations, with at least 30% of incident cases of stroke in China being hemorrhagic.\(^30\) Moreover, given the higher fatality rate for hemorrhagic than for ischemic stroke, most of the stroke deaths in China may be due to hemorrhage. In the present study, there were large number of stroke deaths, and two thirds were attributed to hemorrhagic stroke (and a further 7% to subarachnoid hemorrhage). Despite this, there was no evidence that the association with BMI differed significantly between hemorrhagic and ischemic stroke. These findings need to be interpreted with some caution, given the lack of information about computed tomography diagnoses of fatal strokes. In urban areas, a large proportion of incident stroke cases would have been hospitalized and diagnosed with computed tomography scanning,\(^30\) but only a quarter of the study population was urban and many fatal cases would not have been hospitalized before death.

Given the similarly strong relations between baseline BMI and SBP and between SBP and stroke death in both non-smokers and current smokers, the relation between BMI and stroke deaths might have been expected to be similar in non-smokers and smokers. Consequently, it is somewhat surprising that the observed relation between BMI and stroke should differ markedly between non-smokers and current smokers. It is possible that some residual confounding by smoking intensity, by the probability of smoking cessation, or by some hypothetical interaction between smoking and other causative factors for stroke is affecting the observed association between BMI and stroke risk in the current smokers. Alternatively, much of the apparent differences between the shapes of the relation for smokers and for nonsmokers in Figure 3b may well be due to the play of chance. Consideration of this apparent interaction in other studies (such as the meta-analysis of studies from the Asia-Pacific region, which has not reported analyses subdivided by smoking\(^12\)) could be useful to help confirm or refute it.

In summary, the present nationally representative study has confirmed, for China as a whole, where stroke is one of the most important causes of premature death and disability, the fundamental importance of BP and has found a substantial excess risk of stroke death among those who are overweight or obese (BMI \( >25 \text{ kg/m}^2 \)) that is largely accounted for by a higher BP. Among the 90% of men who were not overweight when the study began in 1990, however, BMI was not associated with excess stroke mortality (except perhaps in non-smokers). These findings suggest that, in the limited range \( <25 \text{ kg/m}^2 \), the effects of BMI on SBP may be counterbalanced by an inverse association between BMI and some other stroke risk factor(s).

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**Disclosures**

None.

**References**


