Does Body Mass Index Impact on the Relationship Between Systolic Blood Pressure and Cardiovascular Disease?

Meta-Analysis of 419 488 Individuals From the Asia Pacific Cohort Studies Collaboration

Rumi Tsukinoki, PhD; Yoshitaka Murakami, PhD; Rachel Huxley, DPhil; Takayoshi Ohkubo, MD; Xianghua Fang, MD; Il Suh, MD; Hirotugu Ueshima, MD; Tai-Hing Lam, MD; Mark Woodward, PhD; and on behalf of the Asia Pacific Cohort Studies Collaboration

Background and Purpose—Elevated blood pressure and excess body mass index (BMI) are established risk factors for cardiovascular disease (CVD) but controversy exists as to whether, and how, they interact.

Methods—The interactions between systolic blood pressure and BMI on coronary heart disease, ischemic and hemorrhagic stroke and CVD were examined using data from 419 448 participants (≥30 years) in the Asia-Pacific region. BMI was categorized into 5 groups, using standard criteria, and systolic blood pressure was analyzed both as a categorical and continuous variable. Cox proportional hazard models, stratified by sex and study, were used to estimate hazard ratios, adjusting for age and smoking and the interaction was assessed by likelihood ratio tests.

Results—During 2.6 million person-years of follow-up, there were 10 877 CVD events. Risks of CVD and subtypes increased monotonically with increasing systolic blood pressure in all BMI subgroups. There was some evidence of a decreasing hazard ratio, per additional 10 mm Hg systolic blood pressure, with increasing BMI, but the differences, although significant, are unlikely to be of clinical relevance. The hazard ratio for CVD was 1.34 (95% CI, 1.32–1.36) overall with individual hazard ratios ranging between 1.28 and 1.36 across all BMI groups. For coronary heart disease, ischemic stroke, and hemorrhagic stroke, the overall hazard ratios per 10 mm Hg systolic blood pressure were 1.24, 1.46, and 1.65, respectively.

Conclusions—Increased blood pressure is an important determinant of CVD risk irrespective of BMI. Although its effect tends to be weaker in people with relatively high BMI, the difference is not sufficiently great to warrant alterations to existing guidelines. (Stroke. 2012;43:1478-1483.)

Key Words: body mass index ■ interaction ■ pooled analysis ■ stroke subtypes ■ systolic blood pressure

Elevated blood pressure1–2 and excess weight3–5 are established major risk factors for cardiovascular disease (CVD). The global prevalence of hypertension is estimated at >1 billion6 and the number categorized as overweight (body mass index [BMI] in excess of 25 kg/m²) is 1.1 billion.4 According to the Global Burden of Disease Study, blood pressure (BP) and BMI combined account for >60% of the global burden of CVD.7 These 2 risk factors frequently coexist due, in part, to a causal positive relationship between BMI and BP.

However, current estimates of effects of BP and BMI on risk of coronary heart disease (CHD) and stroke are based on the assumption that there is no interaction between them despite evidence to the contrary. Previous findings from some early cohort studies suggested that BMI modifies the relationship between BP and subsequent risk of CHD in an antagonistic fashion, that is, that the relationship between BP and vascular risk is diminished with increasing BMI.8–13 From this, it was hypothesized that lean hypertensive men are especially vulnerable to mortality from CHD.8–11 Subsequent
cohorts have produced inconsistent reports with some studies, most notably the large Swedish study of young male conscripts, reporting a synergistic effect of BMI on the relationship between BP and CVD risk, whereas other studies have reported no evidence of an interaction, antagonistic or otherwise.

Discrepancies in earlier observations regarding an interaction between BMI and BP on subsequent risk of CVD may have partly arisen from differences in participant characteristics (such as age) as well as methodological challenges, including limited statistical power to reliably detect an interaction and differences in the statistical methods used to explore this issue. Moreover, the relationships between both BP and BMI with CHD and stroke subtype differ, but no study has yet had adequate power to examine the possible interaction between these 2 risk factors separately for the major subtypes of stroke (ischemic and hemorrhagic).

In the current study, we attempted to overcome these limitations by investigating the joint relationship between systolic BP (SBP) and BMI on CVD and then separately for CHD, ischemic, and hemorrhagic stroke using individual participant data from the Asia Pacific Cohort Studies Collaboration (APCSC). This Collaboration contains a large number of CHD and stroke events with an unusually high number of hemorrhagic strokes and a wide range of BP and BMI levels.

Methods

Identification of Studies and Collection of Data
APCSC is an overview, using individual participant data, of prospective cohort studies from the Asia-Pacific region. The design and methods of the APCSC have been previously described in detail. All studies in APCSC had follow-up for at least 5000 person-years and recorded date of birth (or age), sex, and BP at baseline and date of death (or the age at death) during follow-up. Studies were excluded from APCSC if enrollment was dependent on having a particular condition or a risk factor. For this report, only participants aged >30 years with information on both SBP and BMI at study entry were included in the analysis. BP was generally measured at rest in the seated position using a standard mercury sphygmomanometer. Because the association between SBP and CVD is stronger than that for other BP indices, SBP was used as the BP index in this report. Height and weight were measured by standard methods and BMI was calculated as weight (kg) divided by squared height (m²). Participants at extreme ends of the BMI spectrum (<12 or >60 kg/m²) were excluded from the analysis. Smoking status was dichotomized into current/not current smoker.

Outcomes

All studies reported deaths by underlying cause; a subset of studies also reported nonfatal CVD events. Most studies used database linkages to identify deaths, whereas others also included scheduled follow-up visits or examined hospital records, particularly to identify nonfatal events, defined as those that did not result in death within 28 days. Outcomes were classified according to the Ninth Revision of International Classification of Disease: 410–414, hemorrhagic stroke (431.0–432.9), ischemic stroke (433.0–434.9), and CVD (390–459). Because most studies identified events using record linkage, verification of stroke was not routinely reported. All data provided were checked for completeness and consistency and recoded, when necessary, to maximize comparability across cohorts. Summary reports were referred back to the principal investigators of each collaborating study for review and confirmation.

Statistical Methods

Stratified Cox proportional hazard models were used to examine the joint effects of SBP and BMI on CVD. Baseline hazards were allowed to be different by sex and cohort by using these variables as strata in the Cox models. Age and smoking status were included as confounders in the models. For the primary analysis, BMI was categorized according to 5 groups that are used clinically to determine an individual’s weight status following the World Health Organization criteria for Asia-Pacific populations: 12.0 ≤ BMI < 18.5, underweight; 18.5 ≤ BMI < 23.0, normal; 23.0 ≤ BMI < 25.0, high normal; 25.0 ≤ BMI < 30.0, overweight; and 30.0 ≤ BMI < 60.0 kg/m², obese. In a secondary analysis, BMI was classified according to 5 equal-sized groups to facilitate a more equal distribution of events in the population.

Repeat measurements of SBP taken after a median of 4 years were available for 67,210 participants. These repeated measures were used to estimate the regression dilution attenuation coefficients for SBP using a linear mixed regression model that accounted for the heterogeneity of variance between studies and within-subject correlation. Hazard ratios (HR; 95% CIs) for all outcomes were estimated by analyzing SBP as both a continuous (per 10-mm Hg increase) and categorical variable (SBP < 120; 120 ≤ SBP < 140, 140 ≤ SBP < 160, and SBP ≥ 160 mm Hg) within each category of BMI. We also examined the joint relationships between SBP and BMI by comparing the HRs of cardiovascular events across the 20 groups defined by the 4 SBP and 5 BMI categories relative to the reference group set at the lowest SBP and normal weight values (SBP < 120 mm Hg and 18.5 ≤ BMI < 23.0 kg/m²). The interaction between SBP and BMI on cardiovascular outcomes was assessed using likelihood ratio tests.

Results

Baseline Data
Overall, 39 cohorts with individual data from 419,488 (78% Asian; 41% female) individuals contributed to this analysis (online-only Supplemental Table I). Mean SBP at baseline varied, between studies, from 120.3 to 157.1 mm Hg and mean BMI varied from 21.5 to 26.9 kg/m². Both risk factors tended to be higher in those cohorts sourced from Australia or New Zealand compared with those from Asia.

Outcomes
Overall, there were 2,619,241 person-years of follow-up (mean follow-up, 6.2 years). The mean follow-up was 5.5 years and 8.9 years in cohorts from Asia and Australia–New Zealand, respectively. During follow-up, there were 10,877 CVD events (59% in Asia, 34% women, 71% fatal). Of these, there were 7,010 strokes (1993 ischemic, 1508 hemorrhagic, and 3509 unclassified strokes) and 3,867 CHD events.

The Impact of BMI on the SBP–CVD Association
The age and smoking-adjusted HR for CVD increased continuously with increasing SBP irrespective of BMI category (Figure 1); overall, for every 10-mm Hg increase in SBP, there was a 34% (95% CI, 32%–36%) increase in the risk of CVD (Figure 2). Irrespective of how BMI was classified (either according to the World Health Organization criteria or by fifths of the population), there was evidence to suggest that the association was slightly, but significantly, attenuated with increasing BMI such that the most obese individuals had the lowest risk of CVD per unit increase in SBP (Figure 2;
online-only Supplemental Figure I). Left-censoring had no material impact of the results (online-only Supplemental Figure II). Compared with individuals with a normal weight and SBP/H11021/120 mm Hg, the risk of CVD was 4 times as high in obese individuals with SBP/H11350/160 mm Hg (HR, 4.4; 95% CI, 3.9–5.1; Figure 3).

The Impact of BMI on the SBP–CHD Association

Across all categories of BMI, the age and smoking-adjusted HRs for CHD rose with increasing levels of SBP (Figure 1); overall, for every 10-mm Hg increase in SBP, there was a 24% (95% CI, 21%–27%) increase in the risk of CHD (Figure 2). Like with total CVD, the association was not consistent across BMI with evidence to indicate a diminution in the relationship between SBP and risk of CHD as BMI increased throughout the normal to overweight range (probability value for interaction=0.01). In obese individuals, although the HR was elevated, the 95% CIs were wide due to a relatively small number of events. When BMI was classified by fifths (as opposed to the World Health Organization criteria), a more linear attenuation in the relationship between SBP and CHD risk became apparent (P for interaction=0.01; online-only Supplemental Figure I). The relationship remained largely unchanged after left-censoring (online-only Supplemental Figure II). Compared with individuals with normal weight and SBP <120 mm Hg, the risk of CHD was 4 times as high in obese individuals with SBP ≥160 mm Hg (HR, 4.1; 95% CI, 3.3–5.1; Figure 3).

The Impact of BMI on the SBP–Ischemic Stroke Association

The age and smoking-adjusted HRs for ischemic stroke increased continuously with increasing SBP irrespective of BMI category (Figure 1); overall, for every 10-mm Hg increase in SBP, there was a 46% (95% CI, 41%–51%) increase in the risk of ischemic stroke (Figure 2). The relationship between SBP and ischemic stroke was constant across a wide range of BMI values (Figure 2). It was significantly weaker among those classified as obese, although this was most likely a chance finding due to the small
number of events because there was no indication of an interaction with BMI when examined by population fifths (P for interaction = 0.24; online-only Supplemental Figure I) or after left-censoring (online-only Supplemental Figure II). Compared with individuals with a normal weight and SBP < 120 mm Hg, the risk of ischemic stroke was nearly 6 times as high in obese individuals with SBP > 160 mm Hg (HR, 5.9; 95% CI, 4.2–8.3; Figure 3).

The Impact of BMI on the SBP–Hemorrhagic Stroke Association
Irrespective of BMI category, the age and smoking-adjusted HRs for hemorrhagic stroke rose steeply, and continuously, as SBP increased (Figure 1). The HR for hemorrhagic stroke risk associated with a 10-mm Hg increase in SBP level was consistent across the BMI categories with no evidence of interaction (HR, 1.65; 95% CI, 1.59–1.71; P for interaction = 0.18; Figure 2). These findings remained unchanged in analyses in which BMI was classified by population fifths (online-only Supplemental Figure I) or after left-censoring (online-only Supplemental Figure II). Compared with individuals with a normal weight and SBP < 120 mm Hg, the risk of hemorrhagic stroke was greater in each of the other BMI categories than in the obese group, although given the small numbers of events on which this subgroup analysis is based (n = 37 hemorrhagic stroke events in those with BMI < 18.5 kg/m² and n = 38 in 18.5 < BMI < 22.9 kg/m²), caution in interpreting this result is warranted.

Discussion
These analyses, based on prospective data from >400 000 individuals, demonstrate the strong role of BP in determining future risk of CHD and stroke across all levels of BMI. Irrespective of an individual’s BMI, increases in SBP above levels of 120 mm Hg are associated, in a dose–response pattern, with a concomitant increase in the risk of CVD, CHD, and both ischemic and hemorrhagic stroke.

Findings from this study suggest that for incident CVD and CHD, but not stroke, the magnitude of the excess risk associated with changes in SBP diminished with increasing BMI such that the relationship between SBP and CHD risk was actually weaker among overweight individuals compared with the leanest individuals. Although the antagonistic interactions were statistically significant, the actual differences in BP-related CHD and CVD risk by BMI category were small and are unlikely to translate into meaningful clinical differences. These findings are consistent with some earlier reports.
that reported an antagonistic effect of BMI on the BP-related risk of CHD or CVD. For example, the Tecumseh Community Health Study,9 Israeli Ischemic Heart Study10 and Whitehall Study13 all reported a greater excess risk from higher SBP among lean individuals compared with those of ideal weight. In contrast, the Honolulu Heart Program,16 the British Regional Heart Study,17 and the Swedish Young Male Cohort Study14 did not report any effect modification on the risk of CHD.

Limited sample size and short study duration of study follow-up resulting in a small number of events are likely to have generated random noise within any 1 study. Given that the magnitude of any interaction between BMI and SBP on subsequent risk of CVD is likely to be rather modest, a large number of cardiovascular events across the BMI spectrum is required to reliably detect it. Thus, an insufficient number of events within the extreme World Health Organization categories of BMI may explain some of the less robust associations from the current study.

The precise biological mechanisms that may mediate the antagonistic effect of BMI on SBP and CVD risk may also potentially be due to confounding by cigarette smoking. Individuals who currently smoke or have quit smoking tend to have lower BMIs and an increased risk of death compared with never-smokers,12 which could therefore distort the relationship between BMI and mortality. However, like in the present study, the excess risk for CHD among lean hypertensives remains. A second possible explanation for the antagonistic effect is the existence of preclinical illness at baseline resulting in “reverse causality.” Compared with other subgroups, lean hypertensives could be disproportionately more affected by underlying disease.12 In the present study, to try to minimize the possibility of “reverse causation,” the data were left-censored by 2 years. Overall, this made little material difference to the study findings, although the possibility remains that 2 years was not a sufficiently long enough period of time to completely eliminate those individuals with pre-existing illness.

The current analysis has both strengths and limitations. The large sample size allowed a more reliable examination of the impact of BMI on SBP-related cardiovascular risk than had

Figure 3. Hazard ratios, stratified by study and sex and adjusted for age and smoking status, for cardiovascular outcomes by systolic blood pressure (SBP) and body mass index (BMI) categories. The reference group has the lowest SBP and normal weight (SBP <120 mm Hg and BMI 18.5–25.0 kg/m²). A, coronary heart disease; B, ischemic stroke; C, hemorrhagic stroke; D, cardiovascular disease.
previously been possible. It also enabled the use of a stratified Cox model, which included 4 SBP categories and 5 BMI categories and their interaction terms and confounders. Unlike previous studies that used a separate Cox model for each category of BMI,\textsuperscript{14,15} our combined model is more statistically appropriate for the investigation of interactions between risk factors and disease outcomes. We were also able to adjust for the possible confounding effect of cigarette smoking and for error in the measurement of SBP by correcting for regression dilution error. Moreover, this is the first comprehensive study showing the interaction between SBP and BMI on CHD and stroke subtypes. The major weaknesses of the study include the lack of standard methods of data collection across the cohorts and a possible misclassification of events, particularly with respect to stroke subtype, which requires verification, by imaging or through autopsy data, which was not always possible.

The rationale for undertaking this study was largely because current hypertension and stroke guidelines\textsuperscript{20} separate roles of SBP and BMI in determining vascular risk without considering the existence of an interaction. Because the main CVD risk algorithms\textsuperscript{29,30} do not include a term for the SBP by BMI interaction, this could result in a slight overestimation of CVD risk among overweight subjects. However, we find that the magnitude of the interaction is modest and hence such an omission is unlikely to have major implications for current risk scores. Moreover, given that trial data indicate that the reduction in major cardiovascular risks with BP-lowering therapy is consistent across categories of BMI,\textsuperscript{31} we conclude that current hypertension and stroke guidelines do not require modification for error in the measurement of SBP by correcting for the possible confounding effect of cigarette smoking and for the interaction between SBP and BMI.

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**Disclosures**

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**References**


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SUPPLEMENTAL MATERIAL

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Appendix: List of the Asia Pacific Cohort Studies Collaboration (APCSC)


Table S1. Baseline characteristics of the studies

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<th>SBP (mmHg)</th>
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Tsukinoki R et al.: the APCSC
CISCH, Capital Iron and Steel Hospital; EGAT, Electricity Generating Authority of Thailand; KMIC, Korean Medical Insurance Corporation; NHS, National Health Survey; Longitudinal Study of Aging, Australian Longitudinal Study of Aging; National Heart Foundation, Australian National Heart Foundation.
Figure S1: Hazard ratios, stratified by study and sex and adjusted for age and smoking status, for cardiovascular outcomes associated with a 10mmHg increase in usual systolic blood pressure among equal fifths of body mass index (BMI). Bars show 95% confidence intervals. The diamonds show overall results, all BMI categories. The vertical diagonal of the diamond indicate the estimate and the horizontal diagonal indicates the 95% confidence intervals.
Figure S2: Hazard ratios, stratified by study and sex and adjusted for age and smoking status, for cardiovascular outcomes associated with a 10mmHg increase in usual systolic blood pressure among body mass index (BMI) categories after left-censoring by two years. Body mass index (BMI) was categorized as in Figure 2. Bars show 95% confidence intervals. The diamonds show overall results, all BMI categories. The vertical diagonal of the diamond indicate the estimate and the horizontal diagonal indicates the 95% confidence intervals.
肥満指数は収縮期血圧と心管疾患の関係に影響を及ぼすか？—アジア太平洋コホート共同研究に登録した 419,488 例の被験者のメタ解析

Does Body Mass Index Impact on the Relationship Between Systolic Blood Pressure and Cardiovascular Disease?—Meta-Analysis of 419,488 Individuals From the Asia Pacific Cohort Studies Collaboration

Rumi Tsukinoki, PhD1,2; Yoshitaka Murakami, PhD1,3; Rachel Huxley, DPhil4; Takayoshi Ohkubo, MD5; Xianghua Fang, MD6; Il Suh, MD7; Hirotsugu Ueshima, MD5; Tai-Hing Lam, MD8; Mark Woodward, PhD1; and on behalf of the Asia Pacific Cohort Studies Collaboration

1 Professorial Unit, The George Institute for Global Health, University of Sydney, Sydney, Australia; 2 Department of Preventive Medicine and Epidemiology, National Cerebral and Cardiovascular Center, Osaka, Japan; 3 Department of Medical Statistics, Shiga University of Medical Science, Shiga, Japan; 4 Division of Epidemiology and Public Health, University of Minnesota, Minneapolis, MN; 5 Department of Health Science, Shiga University of Medical Science, Shiga, Japan; 6 Department of Epidemiology and Social Medicine, Xuanwu Hospital, Capital Medical University, Beijing, China; 7 Department of Preventive Medicine, Yonsei University College of Medicine, Seoul, Korea; 8 Department of Community Medicine, University of Hong Kong, People's Republic of China

背景および目的：血圧上昇と高すぎる肥満指数（BMI）は心管管疾患（CVD）の確立された危険因子であるが、それらが相互に作用しているのか、またどのように作用しているのかについては見解が一致していない。

方法：収縮期血圧と BMI の相互作用が冠動脈疾患、虚血性および出血性脳卒中ならびに CVD に及ぼす影響を、アジア太平洋地域の被験者（年齢 30 歳以上）419,488 例から得られたデータを用いて検討した。BMI は標準的な基準を用いて 5 群に分類し、収縮期血圧をカテゴリー変数および連続変数の両方として解析した。性別および試験で層別化した Cox 比例ハザードモデルを用いて、年齢および喫煙について補正したハザード比を推定し、尤度比検定によって相互作用を評価した。

結果：260 万人・年の追跡期間中に、10,877 件の CVD イベントが発生した。CVD およびサブタイプのリスクはすべての BMI サブグループにおいて、収縮期血圧の上昇とともに単調に増加した。収縮期血圧の 10 mmHg 上昇ごとのハザード比が、BMI の上昇とともに低下するというエビデンスがある程度得られ、その差は有意であるものの、臨床上重要である可能性は低い。全体の CVD のハザード比は 1.34 (95% CI: 1.32 ~ 1.36) であり、各ハザード比はすべての BMI 群を通じて 1.28 ~ 1.36 の範囲であった。冠動脈疾患、虚血性脳卒中および出血性脳卒中については、収縮期血圧 10 mmHg あたりの全体のハザード比はそれぞれ 1.24, 1.46 および 1.65 であった。

結論：血圧上昇は、BMI とは無関係に、CVD のリスクの重要な決定因子である。その影響は BMI が相対的に高い集団で顕著な傾向があるが、その差は既存のガイドラインの変更が必要なほど大きいかはないと考えられた。

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