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RESEARCH

Association between body mass index and cardiovascular disease mortality in east Asians and south Asians: pooled analysis of prospective data from the Asia Cohort Consortium

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Abstract

Objective To evaluate the association between body mass index and mortality from overall cardiovascular disease and specific subtypes of cardiovascular disease in east and south Asians.

Design Pooled analyses of 20 prospective cohorts in Asia, including data from 835 082 east Asians and 289 815 south Asians. Cohorts were identified through a systematic search of the literature in early 2008, followed by a survey that was sent to each cohort to assess data availability.

Setting General populations in east Asia (China, Taiwan, Singapore, Japan, and Korea) and south Asia (India and Bangladesh).

Participants 1 124 897 men and women (mean age 53.4 years at baseline).

Main outcome measures Risk of death from overall cardiovascular disease, coronary heart disease, stroke, and (in east Asians only) stroke subtypes.

Results 49 184 cardiovascular deaths (40 791 in east Asians and 8393 in south Asians) were identified during a mean follow-up of 9.7 years. East Asians with a body mass index of 25 or above had a raised risk of death from overall cardiovascular disease, compared with the reference range of body mass index (values 22.5-24.9; hazard ratio 1.09 (95% confidence interval 1.03 to 1.15), 1.27 (1.20 to 1.35), 1.59 (1.43 to 1.76), 1.74 (1.47 to 2.06), and 1.97 (1.44 to 2.71) for body mass index ranges 25.0-27.4, 27.5-29.9, 30.0-32.4, 32.5-34.9, and 35.0-50.0, respectively). This association was similar for risk of death from coronary heart disease and ischaemic stroke; for haemorrhagic stroke, the risk of death was higher at body mass index values of 27.5 and above. Elevated risk of death from cardiovascular disease was also observed at lower categories of body mass index (hazard ratio 1.19 (95% confidence interval 1.02 to 1.39) and 2.16 (1.37 to 3.40) for body mass index ranges 15.0-17.4 and <15.0, respectively), compared with the reference range. In south Asians, the association between body mass index and mortality from cardiovascular disease was less pronounced than that in east Asians. South Asians had an increased risk of death observed for coronary heart disease only in individuals with a body mass index greater than 35 (hazard ratio 1.90, 95% confidence interval 1.15 to 3.12).

Conclusions Body mass index shows a U shaped association with death from overall cardiovascular disease among east Asians: increased risk of death from cardiovascular disease is observed at lower and higher ranges of body mass index. A high body mass index is a risk factor for mortality from overall cardiovascular disease and for specific diseases, including coronary heart disease, ischaemic stroke, and haemorrhagic stroke in east Asians. Higher body mass index is a weak risk factor for mortality from cardiovascular disease in south Asians.

Introduction

Cardiovascular disease (CVD) is the leading cause of death globally.[1] CVD incidence is predicted to increase steadily over the next few decades.[2] Between 1990 and 2020, the increase in death from coronary heart disease (CHD) is expected to be 120% in women and 137% in men in low and middle income countries, and 29% and 48%, respectively, among high income countries. A similar pattern for increases in stroke mortality is predicted.[3] Asian countries in general have higher rates of stroke mortality—especially death from haemorrhagic stroke—than Western countries, although these rates have decreased in Japan and urban areas in China.[4 5] With regard to CHD, east Asian countries have a lower mortality than Western countries, whereas south Asian countries have a higher mortality.[4]

Cardiovascular risk factors including hypertension, diabetes, tobacco use, dyslipidaemia, and overweight are traditionally derived from studies conducted in Europe and North America. Owing to differing experiences at various stages of epidemiological transition and urbanisation—with varied life expectancy, diverse demographic profiles, as well as differences in environmental and genetic risk factors—the relations between these risk factors and CVD mortality may differ between Asian and Western societies.[6] Migrant studies show that Japanese Americans have higher CHD rates and lower stroke rates[7 8] than Japanese people living in Japan.[9] Likewise, increased risk of CHD has been reported in migrant south Asians.[10] Among south Asians, those who migrated from rural to urban areas of their native countries also have a greater prevalence of obesity and lower level of physical activity than those who resided in rural areas.[11 12]

Overweight and obesity are increasingly globally. Many Asian populations used to be physically active with a low body mass index (BMI), but the region now has some of the world's highest rates of obesity.[1] Several meta-analyses have been conducted to evaluate associations between BMI and stroke and CHD mortality,[13-17] based mostly on studies in Western populations. Several prospective studies of BMI and CVD risk have been conducted in east Asians.[18-20] However, no data have been available to compare east and south Asians for any potential differences in the associations of BMI with CVD risk. In

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Web appendix: Supplementary material

addition, data on BMI in relation to subtypes of stroke are limited. There is increasing evidence that obesity is a risk factor for ischaemic stroke.[21-25] However, excess weight has not been recognised as an established risk factor for stroke and generally has not been included in the overall estimation of stroke risk.[26-28] The association between BMI and haemorrhagic stroke is less clear. Most studies in Western populations have shown no[21 29-32] or an inverse[24 33 34] association, but several cohort studies have reported a J or U shaped curve in Japanese and Korean populations.[25 35-39] Large prospective studies that better characterise the shape of the association between BMI and mortality for specific CVD in Asian populations could improve our understanding, awareness, treatment, and control of this major group of diseases.

There are several methodological issues in examining the association between excess adiposity and CVD. Firstly, weight loss resulting from illness may distort the relation between leanness and health because of the bias often referred to as reverse causation.[40-42] Studies that did not exclude individuals with history of disease, or that had a short follow-up, are more prone to reverse causality.[41 43] Secondly, cigarette smoking—an established risk factor for CVD that is related to low BMI—may confound the relation between BMI and CVD mortality.[41 42] Recent studies in Western populations have attempted to tackle these methodological challenges, using offspring BMI as an indicator of own BMI or a Mendelian randomisation approach.[44 45] However, these methods have not been extended to assess non-linear associations. Owing to limited sample size, few studies have explored the extent to which the association between BMI and CVD mortality differs by smoking status and in individuals without a history of CVD among Asian populations. In addition, studies in Asian populations are needed to evaluate potential mediation by risk factors such as hypertension and diabetes, or potential effect modification by age of the association between BMI and CVD risk.

We conducted a pooled analysis using data from 20 prospective cohorts, involving more than 1.1 million participants from east and south Asia with comparable BMI data in the Asia Cohort Consortium, to characterise the shape of the association between BMI and CVD mortality. The analyses included a large sample size, allowing us to examine, in detail, the risk of CVD subtypes across a wide distribution of BMI.

Methods

The Asia Cohort Consortium

Details of the Asia Cohort Consortium have been presented elsewhere.[46-48] Briefly, the Asia Cohort Consortium is an international collaboration committed to the study of environmental exposures and genetics in the aetiology of disease. Cohorts were identified through a systematic search of the literature in early 2008, followed by a survey that was sent to each cohort to assess data availability.[48] The Asia Cohort Consortium includes more than 20 cohorts representing Japan, China, Korea, India, Taiwan, Bangladesh, and Singapore. There were no different ethnicities within each cohort. For the present study, we included people from 20 cohorts with baseline data for BMI, age, sex, and smoking status, and follow-up data for deaths from any cause (table 1⇓).

Data for baseline BMI (calculated based on measured or self reported height and weight, table 1), sex, age, date of birth, cigarette smoking, alcohol drinking, and information on specific CVD risk factors (including history of hypertension, diabetes, stroke, and CHD at baseline) were collected from all cohorts using structured questionnaires. Each cohort collected data for follow-up time and cause specific deaths (using ICD-7 (international classification of diseases, 7th revision), ICD-8, ICD-9, or ICD-10) through linkage to death registry or active follow-up.

All data were transferred and harmonised at the Asia Cohort Consortium coordinating centre at the Fred Hutchinson Cancer Research Center. Harmonisation involved several rounds of discussions to ensure that variables were correctly interpreted and extracted. Data were checked for illogical or missing values and queries sent back for clarification. The distributions of individual variables were explored to identify false or implausible values. All personal identifiers were removed, but study specific identification numbers were retained to facilitate all queries back to the individual cohorts.

Outcomes of interest included: cardiovascular disease (using ICD-10 codes I00-I99; ICD-9 codes 390-459), which was further categorised into coronary heart disease (ICD-10 codes I20-I25; ICD-9 codes 410-414) and stroke (ICD-10 codes I60-I69; ICD-9 codes 430-438); as well as subtypes of stroke, including ischaemic stroke and haemorrhagic stroke (web table 1).

Statistical analyses

Descriptive analyses were first conducted to describe the characteristics of each cohort. To examine the shape of the relation of BMI and mortality from overall cardiovascular disease, CHD, total stroke, ischaemic stroke, and haemorrhagic stroke, we estimated hazard ratios and 95% confidence intervals based on Cox proportional hazards regression models that combined studies in an individual-participant-data meta-analysis.[65-69] To reduce the likelihood of reverse causation, all analyses excluded people and deaths with fewer than three years of follow-up.

The primary analysis consisted of a Cox model for analysis of individual participant data, stratified by cohort to account for possible differences among cohorts in the baseline hazard.[65] In the models, the effect of BMI on mortality was taken to be cohort specific, assuming that the log hazard ratio for BMI had a fixed effect component in each cohort that was common to all cohorts and a cohort-specific random effect that was normally distributed with mean zero. Hazard ratios for mortality from CVD and its subtypes were estimated in relation to BMI levels separately for east Asians (China, Taiwan, Singapore, Korea, and Japan), south Asians (Bangladesh and India), overall, and in men and women separately. We used the BMI range 22.5-24.9 (based on analyses of all cause mortality)[48] as the reference. We also established 10 levels of BMI levels in total (<15.0, 15.0-17.4, 17.5-19.9, 20.0-22.4, 22.5-24.9, 25.0-27.4, 27.5-29.9, 30.0-32.4, 32.5-34.9, and ≥35.0). Because data for stroke subtypes from south Asian cohorts were limited, separate analyses for ischaemic stroke and haemorrhagic stroke were conducted for east Asians only.

Potential confounders included baseline age (<40, 40-49, 50-59, 60-69, 70-79, and ≥80 years), sex (except for stratified analyses by sex), cigarette smoking (never *v* ever), alcohol consumption (never *v* ever), educational attainment (no formal education, primary, secondary, trade/technical, university degree, postgraduate degree, other), marital status (single, married, separated, widowed, divorced), and urban residence. Because several cohorts did not collect information on marital status and educational attainment at baseline, people with missing data for these two variables were coded using dummy variables, allowing their inclusion in the analyses under a “missing at random” assumption. We also did sensitivity analyses to compare adjusted and unadjusted results among people with non-missing values.

These results were similar to the main analyses and are therefore not shown.

We also conducted analyses using conventional BMI in three categories: 15-18.4 (low), 18.5-24.9 (normal), and 25 and above (high).[70] Individuals with a BMI value lower than 15 were excluded from subgroup analyses to be more comparable with other studies.[18 19 71] To evaluate the influence of specific potential confounders and mediators, analyses were conducted—excluding individuals with a history of CHD or stroke at baseline—for the overall population and in never smokers, and by baseline smoking status (ever, current, former, and never). Additional stratified analyses by baseline age (<53 *v* ≥53 years; the median age of the east and south Asians combined) were conducted to evaluate whether the influence of BMI was similar in different age groups. Because diabetes and hypertension are considered intermediate risk factors on the causal pathway between BMI and CVD,[20 71 72] we conducted separate models stratifying on, or adjusting for, these variables.

Results

From 20 cohorts, there were a total of 1 124 897 participants and 49 184 CVD deaths (table 1). This group included 835 082 participants and 40 791 CVD deaths in east Asians, and 289 815 participants and 8393 CVD deaths in south Asians. Mean BMI in the cohorts was 22.8, with cohort specific means ranging from 19.8 in Bangladesh to 24.0 in the Community-based Cancer Screening Project study in Taiwan. Mean BMI was 23.1 in east Asians and 22.0 in south Asians. Participants were, on average, 53.4 years old at baseline, with a mean follow-up of 9.7 years. Across all studies, 535 451 (47.6%) were men, and 386 965 (34.4%) were ever smokers at baseline. The enrolment period started after 1980 for all cohorts except the Radiation Effects Research Foundation cohort, which recruited participants from 1963. CHD mortality accounted for 29.3% (n=14 411) of total CVD mortality, ranging from 17.6% (n=31) in Bangladesh to 62.8% (n=2643) in the Trivandrum cohort. Stroke accounted for 41.9% (n=20 608) of total CVD mortality, ranging from 19.6% (n=785) in Mumbai to 61.7% (n=1040) in Shanghai.

All the analyses on BMI and CVD mortality excluded participants and deaths with fewer than three years of follow-up (n=17 026). In east Asians, we observed a U shaped association between BMI and overall CVD mortality (table 2⇓, fig 1⇓). Elevated risk of death was observed for overall CVD at BMI value 25 and above, compared with the reference range of 22.5-24.9 (hazard ratios 1.09 (95% confidence interval 1.03 to 1.15), 1.27 (1.20 to 1.35), 1.59 (1.43 to 1.76), 1.74 (1.47 to 2.06), and 1.97 (1.44 to 2.71) for BMI ranges of 25.0-27.4, 27.5-29.9, 30.0-32.4, 32.5-34.9, and 35.0-50.0, respectively). Adjusted hazard ratios were lowest at BMI range 20.0-22.4 for death from overall CVD, total stroke, and stroke subtypes, and lowest at BMI range 17.5-19.9 for deaths from CHD. Elevated hazard ratios were observed in all BMI categories greater than 24.9 for CVD, CHD, and ischaemic stroke. Compared with the BMI reference range of 22.5-24.9, we noted greater hazard ratios for death from CHD and ischaemic stroke, starting at range 25.0-27.4 (1.14, 1.04 to 1.24, for CHD; 1.21, 1.07 to 1.37, for ischaemic stroke). The risk of death from total stroke and haemorrhagic stroke was elevated, starting at BMI range 27.5-29.9, with a positive, dose-response association continuing across higher BMI categories.

In the low BMI range (<17.5), BMI had an inverse relationship with total CVD mortality. These individuals were more likely to die from CVD than those with BMI values in the reference range of 22.5-24.9 (BMI<15.0, hazard ratio 2.16 (95% confidence interval 1.37 to 3.40); BMI 15.0-17.4, 1.19 (1.02 to 1.39); table 2). Very low BMI (<15.0) was associated with increased risk of death from all CVD subtypes, although none of the estimates was statistically significant. Stratified analyses by sex showed similar patterns of the associations, with a stronger association observed in men (web table 2).

In south Asians, we observed a positive association between high BMI categories (>24.9) and cardiovascular death, although this relation was not statistically significant and was substantially weaker than in east Asians (table 3⇓, fig 1). Individuals with a lower BMI had a reduced risk of death from CVD. This risk was lowest for individuals with BMI values in ranges 15.0-17.4 and 17.5-19.9, compared with those with values in the reference range 22.5-24.9 (table 3).

We observed a similar pattern for death from CHD. BMI was positively related to the risk of death from CHD in individuals with BMI values above 24.9. A weaker association was observed in south Asians than in east Asians, with hazard ratios ranging from 1.07 to 1.18—except for the highest BMI range of 35.0-50.0, with a hazard ratio of 1.90 (95% confidence interval 1.15 to 3.12; table 3). This hazard ratio was similar in east Asians (1.88 (1.08 to 3.27), table 2). BMI values below 20 were associated with about a 20% reduced risk for death from CHD. On the other hand, we saw no association between BMI and stroke mortality in south Asians across the other BMI categories. Stratified analyses by sex showed similar patterns (web table 3).

We also examined CVD mortality in three BMI categories: 15-18.4 (low), 18.5-24.9 (normal), and 25 and above (high) in east Asians. East Asians with normal BMI values showed a 20% increased risk of death from CVD compared with those with higher BMI values (fig 2⇓). The positive association was similar among never, ever, and current smokers, but it was weaker among former smokers. Excluding participants with a history of CHD or stroke did not change the strength of association appreciably. A greater risk of death from CVD was associated with high BMI among individuals who were younger than 53 at baseline (hazard ratio 1.38 (95% confidence interval 1.20 to 1.58)) than among individuals aged 53 and older (1.17 (1.10 to 1.25)). The estimate did not change appreciably with additional adjustment for baseline diabetes status. On the other hand, adjustment for baseline hypertension status attenuated the association (1.07 (1.00 to 1.15)).

A stronger association was observed for CHD than for overall CVD (fig 2). High BMI values (≥25) were associated with a 38% higher risk of death from CHD, and the difference in risk was greater among individuals younger than 53 years (hazard ratio 1.62 (95% confidence interval 1.33 to 1.97)). The higher risk was attenuated, but remained statistically significant after adjusting for baseline hypertension status and remained apparent for individuals both with and without hypertension at baseline.

A weaker association was observed for stroke than for overall CVD. High BMI was associated with a 14% increase in risk of death from overall stroke, 28% from ischaemic stroke, and 9% from haemorrhagic stroke (fig 2). The higher risk for total stroke and stroke subtypes associated with higher BMI was seen in never smokers and individuals younger than 53 years, although the association for haemorrhagic stroke in those younger than 53 years was not statistically significant. Adjustment for hypertension at baseline attenuated the risk, especially the risk of haemorrhagic stroke. High BMI was not related to a statistically significant higher risk of death from haemorrhagic stroke in individuals who were older, ever-smokers, or hypertensive at baseline.

Compared with normal BMI values (range 18.5-24.9), low BMI (15-18.4) was associated with an increased risk of death from overall CVD (fig 3⇓). The higher risk of death from overall CVD was observed in all subgroups and persisted after adjustment for hypertension. There was insufficient evidence indicating that low BMI was related to the risk of death from CHD, overall, or in subgroups. The higher risk of stroke associated with low BMI was seen only in individuals who were ever smokers or hypertensive at baseline. Associations for stroke subtypes were weak or absent.

We did similar analyses in south Asians (figs 4⇓ and 5⇓), and observed weaker associations than in east Asians. High BMI values (≥25) were associated with an 8% and18% increased risk of death from overall CVD and CHD, respectively (fig 4). The positive association remained in never smokers, but was weaker after excluding individuals with a history of CVD, and was attenuated after adjustment for hypertension status at baseline. Low BMI values (15-18.4) in south Asians was associated with a 10% and 14% reduced risk of death from overall CVD and CHD (fig 5), respectively, and the association remained similar in never smokers and in individuals free of CHD and stroke at baseline. The data did not suggest that high or low BMI was related to the risk of death from stroke in south Asians.

Discussion

Principal findings of the study

In this pooled analysis of prospective cohorts involving 1.1 million participants, we observed a U shaped association between BMI and risk of death from CVD in east Asians. An increased risk of death was observed in all BMI values greater than 24.9 for overall CVD, CHD, and ischaemic stroke, and values greater than 27.4 for overall stroke and haemorrhagic stroke, as well as values lower than 17.5 for overall CVD. The increased risk of death from overall CVD associated with high BMI (>24.9) in east Asians was stronger among individuals younger than 53 years. This increased risk was seen among never smokers, individuals free of CVD at baseline, and individuals without hypertension. Adjustment for hypertension attenuated the risk, especially the risk of death from stroke. In south Asians, the association between BMI and death from CVD seemed weak.

Comparison with other studies

In the Prospective Studies Collaboration (PSC), which included mostly cohorts from Western countries, BMI was positively and roughly log-linearly related to CHD mortality throughout the BMI range of 20-40, with the lowest risk observed at about 20-22.5.[71] Similarly, in the Emerging Risk Factors Collaboration, with data on fatal and non-fatal CVD endpoints from more than 220 000 individuals in cohorts predominantly from Europe and the United States, a dose-response association was observed between BMI and risk of CVD, CHD, and ischaemic stroke, in those with BMI of 20 or higher.[73] In east Asians, we observed a similar positive association for CHD mortality in the upper BMI range, with the lowest risk noted at the same BMI range of 20-22.4. However, these data did not suggest a dose-response relationship for BMI values above 30. The PSC showed a positive association in the upper BMI range (values 25-50) for death from ischaemic and haemorrhagic stroke; stroke mortality was flat across the lower BMI range of 15-25.[71] The pattern was similar in our analyses for east Asians.

Several meta-analyses or pooled analyses of cohort studies have assessed the association between BMI and CVD mortality in east Asians. However, few studies have evaluated the strength and shape of the association in more specific categories of BMI and for subtypes of CVD. In the Asia Pacific Cohort Studies Collaboration (APCSC), including data from 245 881 east Asians, every five unit increase in BMI was associated with a hazard ratio of 1.36 (95% confidence interval 1.17 to 1.59) for CHD mortality,[74] but there was no association with mortality from either ischaemic stroke (1.07, 0.87 to 1.37) or haemorrhagic stroke (0.95, 0.79 to 1.14).[74] However, BMI was considered as a continuous variable across all levels. In a study that included 1 213 829 Koreans,[18] the risk of death from CVD rose steadily with increasing BMI values from 18. In a 2012 study of 220 000 Chinese men, a 61% and 48% increase in stroke and CHD mortality, respectively, was observed for every five unit increase in the upper BMI range (23.5 to 35), whereas no association was observed in the lower range (15 to 23.5).[19]

Taken together, the body of literature suggests that the relation between high BMI and CVD mortality is thus largely similar in east Asians and Western populations. This is also consistent with findings from a comparison between east Asians and populations in Australia and New Zealand.[74] Although the data in the present study are largely consistent with previous studies in east Asians, we also show that higher BMI is an important risk factor, not only for CHD mortality but also for death from ischaemic stroke and haemorrhagic stroke in east Asians.

A 2013 meta-analysis of 97 studies encompassing 2.88 million individuals, mostly from cohorts in Western countries, reported a higher risk of death from any cause associated with obesity (BMI ≥30) and a slightly lower risk (hazard ratio 0.94 (95% confidence interval 0.91 to 0.96)) for overweight people (BMI 25-30), compared with people within a normal BMI range of 18.5-25.[75] In our previous pooled analyses of 1.1 million people in 19 cohorts in Asia, risk of death from any cause was also not elevated in east Asians with a BMI value between 25.1 and 27.5. However, we observed an increased risk in east Asians with a BMI 27.6-30.0 or above,[48] but no excess risk associated with BMI higher than 25 in south Asians. As discussed, in east Asians and Westerners, consistently higher risk of death from CVD mortality was observed in all BMI categories greater than 25, and those with BMI values between 20 and 22.4 had the lowest risk. These data suggest that the association between higher BMI and mortality differs by race and causes of death, and that overweight may be a more important risk factor for CVD mortality. Given that CVD is the leading cause of death, global conclusions and recommendations for all groups and all diseases seems inadvisable.

We also observed a higher risk in individuals with a BMI value lower than 17.5. Individuals with markedly low (<16) or moderately low (16-16.9) values of BMI were excluded from previous large cohort studies of Korean and Chinese as well as from pooled analyses of Western cohorts.[18 19 71] The Emerging Risk Factors Collaboration showed an increased risk of fatal and non-fatal CHD in individuals with BMI values less than 20, but all subsequent analyses were restricted to those with a value of 20 or higher.[73] In the APCSC, as mentioned earlier, BMI was considered as a continuous variable across all levels, and this analysis did not detect any increase in risk for BMI values lower than 17.5.[74] Several smaller individual cohort studies in Japan and China have reported that BMI values of less than 18 or 18.5 were related to an increased risk of death from overall CVD,[37] CHD,[37 76] total stroke,[35 37] ischaemic stroke,[36] and haemorrhagic stroke.[35 37]

A low BMI may indicate a low level of circulating total cholesterol or triglycerides, which has been related to increased risk of haemorrhagic stroke in several cohort studies.[77-80] A low

BMI may also indicate other anthropometric measures such as a small thigh circumference (a risk factor for cardiovascular and coronary heart disease recently identified in a Danish cohort[81]) or a low amount of total fat free mass, which has been related to total mortality.[82 83] However, we did not have data on lipid profile or other anthropometric measures to assess whether the high risk associated with low BMI can be attributable to these factors. Given that leanness is more prevalent in Asian populations than in Western populations, additional research using superior measures of amount and distribution of body fat are needed.

Evidence suggests that Asian Indians have more fat—both total and abdominal—for a given BMI than Europeans.[84 85] It has been shown that south Asians have a higher risk of diabetes at a lower BMI than white populations.[86] Given the effect of fat and diabetes on CVD, a stronger association between BMI and CVD mortality in south Asians than in Europeans would have been expected. On the contrary, we found a weaker association between BMI and CVD mortality in south Asians. Individual cohorts from south Asia reported similar findings,[62 87] and our pooled analyses, with a large sample size and sufficient numbers in each BMI category, probably exclude lack of power as an explanation. The finding is also consistent with data from a previous study that suggested that a BMI values greater than 25 were associated with low population attributable fraction of CHD and stroke (<1%).[88] In previous analyses, we also observed a very weak association of higher BMI with the risk of death from any cause, respiratory disease, or cancer in south Asians[31]; therefore, the issue of competing risks does not explain the weak association between BMI and CVD mortality in south Asians.

In the present study, the lowest risk of death among south Asians from overall CVD and CHD was observed at the BMI range of 15.0-19.9, lower than the range of 20.0-22.4 associated with the lowest risk among east Asians (table 3). Although using BMI cut-off points based on race or ethnicity is not appropriate for overall mortality,[31] evidence of their consideration for cause specific mortality is inconclusive. Taken together, our data stress that future studies including other anthropometric measures (such as waist circumference, thigh circumference, or waist to hip ratio) will be particularly important in assessing CVD risk in south Asians. Furthermore, BMI values associated with CVD mortality in east Asians and Western populations may not apply to south Asians.

We found that, in east Asians, higher BMI was associated with elevated risk of death from CVD in never smokers as well as individuals free of hypertension, CHD, and stroke at baseline. The pooled analyses of Western cohorts found that the positive association of BMI and CVD mortality can be largely accounted for by blood pressure, lipid profile, and diabetes.[71] Consistent with this, the adjustment for baseline hypertension status attenuated the association between BMI and death from CVD in our study. We calculated the mediation proportion[89] and estimated that 62.3%, 35.7%, and 92.4% of the association of higher BMI with the risk of death from overall CVD, CHD, and stroke, respectively, could be attributed to hypertension in east Asians. Adjustment for diabetes status, on the other hand, did little to attenuate the positive association. The elevated risk associated with higher BMI was also greater among individuals younger than 53 years, as opposed to those aged 53 and older, a finding also consistent with data from Western cohorts.[71] The weaker association in individuals aged 53 and over is probably a result of the weaker correlation between BMI and cholesterol or blood pressure at these older ages.[71] Taken together, our data suggest that hypertension control is critical among east Asians to prevent CVD mortality that is associated with a high BMI, especially in middle age.

Strengths and limitations of the study

We were able to include data on a wider range of BMI values than previous studies and a large number of CVD events—including stroke—which is rare in individual cohorts. This allowed us to examine the risk of CVD subtypes across much finer categories of BMI. We were also able to conduct subgroup analyses by smoking status and history of CVD and assess potential mediation by hypertension and diabetes.

However, the present study had several limitations. Firstly, as mentioned previously, although it can be assumed that individuals with a high BMI have an elevated fat mass, BMI does not distinguish between weight associated with muscle and weight associated with fat. We could not evaluate the influence of waist circumference or waist-to-hip ratio on CVD mortality, because the information was available from only four east Asian cohorts and none of the south Asian cohorts included in the present study. Nonetheless, BMI can be considered the most useful, albeit crude, measure of obesity at the population level.

Secondly, we used mortality data, not incidence data. The use of death certificates may involve some misclassification in deaths due to different stroke subtypes. However, such errors are not likely to been affected by BMI levels. Widespread use of computed tomography scans in Japanese local hospitals since the 1980s and routine use of computed tomography and magnetic resonance imaging in Korea have probably made the diagnosis of stroke subtypes based on death certificates sufficiently accurate.[90] A validation study in China has shown that the registration system has good sensitivity in diagnosing stroke.[91] Non-fatal CVD events remained unidentified and were therefore misclassified as non-cases. Although we believe that any misclassification of CVD deaths is unlikely to have been affected by BMI levels, we cannot predict the exact direction or extent of the potential bias with certainty. Future large studies that include incidence data are needed.

Nonetheless, our findings are also in line with data from the pooled analyses of 33 cohorts in Asia-Pacific region with a much smaller sample size that included incidence data.[20] Similar to other studies of BMI and CVD mortality,[71] history of diabetes and hypertension were measured at baseline only and were based on self reported data in some cohorts, which could underestimate the mediating effects of hypertension and diabetes.

Finally, as with all observational studies, we cannot exclude the possibility of unmeasured or residual confounding. Specifically, higher BMI is related to higher educational status, better living conditions, and better nutrition in south Asians. Although we controlled for educational attainment in the analyses, potential negative residual confounding due to socioeconomic status may remain and partly account for the weak association between BMI and CVD mortality in south Asians.

Possible implications and future research

We observed an increased risk of death from CVD in all BMI values greater than 24.9 as well as values lower than 17.5 in east Asians. In east Asians, higher BMI was a risk factor for mortality from all subtypes of CVD—including CHD, ischaemic stroke, and haemorrhagic stroke, particularly in middle age; the association for stroke was largely explained by baseline hypertension. In south Asians, a much weaker association was observed than in east Asians. The findings stress the important role of higher BMI in the increasing rates of death from CVD in Asia, which could be managed by policy and prevention strategies. However, additional research with more refined anthropometric measures is needed to better explain the elevated risk observed at low BMI and the apparently weak association among south Asians.

Contributors: YC, JDP, and WZ designed the study. PB, WZ, JDP, and ZF obtained funding. WKC, MT, and DM analysed the data. YC, JDP, WZ, and PB wrote the paper. RV, EG, JEL, WG, BR, DM, RS, MT, ZF, and JH helped interpret the results. DG, PCG, KR, MI, ST, AT, Y-TG, J-MY, X-OS, KO, IT, MK, HT, YN, C-JC, RW, K-YY, Y-OA, HA, W-HP, C-SC, MSP, CS, SS, GY, W-PK, Y-BX, WO, TW, YS, KM, S-LY, SKP, D-HK, FP, S-YC, DK, WZ, and JH contributed data. JDP is the study guarantor.

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Data sharing: no additional data available.

Declaration of transparency: The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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What is already known on this topic

Higher body mass index has been shown to be associated with increased risk of death in east Asians but not among south Asians

Higher body mass index has been related to an elevated risk of death from cardiovascular disease in Western populations

What this study adds

Higher body mass index is a risk factor for mortality from overall cardiovascular disease, coronary heart disease, ischaemic stroke, and haemorrhagic stroke in east Asians, especially in middle aged men and women

Very low body mass index is also associated with an increased risk of death from cardiovascular disease in east Asians

Higher body mass index is a weak risk factor for death from cardiovascular disease in south Asians

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Tables

Table 1| Characteristics of participating cohorts

Cohort and size	Enrolment period	Mean follow-up (years)	Mean age (years) at baseline	Mean BMI	Male sex (%)	Ever smokers (%)	CVD deaths			
							Total No	Stroke related (%)	CHD related (%)	Other (%)
East Asians (n=835 082)	**1963-2006**	**11.0**	**54.63**	**23.1**	**47.9**	**40.0**	**40 791**	**45.2**	**23.4**	**31.4**
China (mainland)										
CHEFS[49] (n=154 791)	1990-92	7.3	55.40	22.6*	48.9	37.9	8106	48.4	15.5	36.1
SCS[50] (n=18 100)	1986-89	16.5	55.26	22.2	100.0	57.3	1686	61.7	26.6	11.7
SMHS[51] (n=61 501)	2001-06	3.2	54.88	23.7*	100.0	69.6	297	47.1	33.7	19.2
SWHS[52] (n=74 942)	1996-2000	8.7	52.13	24.0*	0.0	2.8	804	56.3	22.0	21.6
Taiwan										
CBCSP[53] (n=23 820)	1991-92	15.4	47.35	24.0*	50.3	28.9	558	46.6	28.5	24.9
CVDFACTS[54] (n=5160)	1990-93	15.0	47.08	23.7*	44.1	24.8	220	54.1	22.7	23.2
Singapore Chinese Health Study† (n=63 257)	1993-99	11.6	56.51	23.1	44.2	30.6	3708	27.5	56.9	15.6
Korea										
KMCC[55] (n=16 013)	1993-2004	6.59	55.6	23.7	39.7	36.4	330	55.45	22.7	21.82
Seoul Male Cohort Study (n=14 533)	1992-93	14.8	49.20	23.4	100	77.2	155	43.23	34.8	21.94
Japan										
Three Prefecture Cohort Study Aichi[56] (n=33 529)	1985	11.7	56.42	22.1	47.0	50.7	2209	39.3	18.4	42.3
JACC[57] (n=86 682)	1988-90	12.8	57.59	22.8	41.8	38.6	3981	46.2	20.2	33.6
JPHC1[58] (n=43 096)	1990-92	14.6	49.59	23.6	47.9	40.2	888	45.3	21.4	33.3
JPHC2[58] (n=56 572)	1992-95	11.6	54.27	23.5	47.4	40.1	1372	41.2	25.3	33.4
Three Prefecture Cohort Study Miyagi[59] (n=31 345)	1984	11.5	57.32	23.3	44.6	43.0	2662	48.7	19.2	32.2
Miyagi Cohort Study[59] (n=47 605)	1990	12.9	52.14	23.6	48.0	50.0	705	43.7	25.4	30.9
Ohsaki National Health Insurance[60] (n=51 253)	1995	9.9	60.51	23.5	47.9	48.6	2432	46.8	21.8	31.4
RERF cohort[61] (n=52 883)	1963-93	22.0	51.82	22.0	38.7	43.8	10 678	45.1	20.1	34.9
South Asians (n=289 815)	**1991-2002**	**6.4**	**49.72**	**22.0**	**49.3**	**21.7**	**8393**	**26.1**	**58.3**	**15.7**
India										
Mumbai Cohort Study[62] (n=146 827)	1991-97	5.3	50.82	22.3*	59.6	18.9	4008	19.6	55.3	25.1
TOCS trial[63] (n=131 242)	1995-2002	7.6	49.62	21.8*	38.5	23.5	4209	32.3	62.8	4.9
Bangladesh (HEALS)[64] (n=11 746)	2000-02	6.7	37.06	19.8*	42.9	35.5	176	24.4	17.6	58.0
Total (east and south Asians) (n=1 124 897)	**1963-2006**	**9.7**	**53.42**	**22.8**	**47.6**	**34.4**	**49 184**	**41.9**	**29.3**	**28.8**

HEALS=Health Effects of Arsenic Longitudinal Study; CHEFS=China National Hypertension Survey Epidemiology Follow-up Study; SCS=Shanghai Cohort Study; SMHS=Shanghai Men's Health Study; SWHS=Shanghai Women's Health Study; CBCSP=Community-based Cancer Screening Project study; CVDFACTS=CardioVascular Disease risk FACtor Two-township Study; KMCC=Korea Multi-center Cancer Cohort; JACC=Japan Collaborative Cohort Study; JPHC=Japan Public Health Center-based Prospective Study on Cancer and Cardiovascular Diseases; RERF=Radiation Effects Research Foundation cohort; TOCS=Trivandrum Oral cancer Screening trial.

Table 1 (continued)

Cohort and size	Enrolment period	Mean follow-up (years)	Mean age (years) at baseline	Mean BMI	Male sex (%)	Ever smokers (%)	CVD deaths			
							Total No	Stroke related (%)	CHD related (%)	Other (%)

*BMI estimated using weight and height measured at enrolment. For other studies, weight and height were self reported.

†Included only people from the two major dialect groups of Chinese in Singapore—that is, the Hokkien and Cantonese, who originated from the contiguous provinces of Fujian and Guangdong in the southern part of China, respectively.

Table 2| **Association between BMI and CVD mortality in east Asians**

Cause and No of CVD deaths	Body mass index at baseline									
	<15.0	15.0-17.4	17.5-19.9	20.0-22.4	22.5-24.9	25.0-27.4	27.5-29.9	30.0-32.4	32.5-34.9	35.0-50.0
All participants (n=820 439)										
No of participants per BMI category	2032	21 687	111 144	229 861	243 602	136 344	52 456	16 668	4210	2435
CVD (n=38 738)										
No of deaths per BMI category	372	2375	7274	10 422	9711	5121	2160	841	245	217
Hazard ratio (95% CI)	2.16 (1.37 to 3.40)	1.19 (1.02 to 1.39)	1.06 (0.95 to 1.17)	0.94 (0.89 to 0.98)	Reference	1.09 (1.03 to 1.15)	1.27 (1.20 to 1.35)	1.59 (1.43 to 1.76)	1.74 (1.47 to 2.06)	1.97 (1.44 to 2.71)
CHD (n=9142)										
No of deaths per BMI category	58	401	1352	2324	2724	1358	562	252	72	39
Hazard ratio (95% CI)	1.7 (0.86 to 3.37)	0.88 (0.71 to 1.10)	0.85 (0.72 to 0.99)	0.87 (0.79 to 0.95)	Reference	1.14 (1.04 to 1.24)	1.34 (1.19 to 1.52)	1.93 (1.52 to 2.46)	2.34 (1.70 to 3.22)	1.88 (1.08 to 3.27)
Stroke (n=17 501)										
No of deaths per BMI category	138	922	3388	4747	4310	2365	1023	392	102	114
Hazard ratio (95% CI)	2.05 (0.75 to 5.61)	1.12 (0.88 to 1.42)	1.10 (0.96 to 1.27)	0.92 (0.87 to 0.98)	Reference	1.07 (0.98 to 1.16)	1.24 (1.14 to 1.36)	1.57 (1.38 to 1.79)	1.51 (1.08 to 2.12)	1.92 (1.43 to 2.57)
Ischaemic stroke (n=5771)										
No of deaths per BMI category	50	300	1062	1602	1368	841	330	140	41	37
Hazard ratio (95% CI)	1.51 (0.71 to 3.23)	1.16 (0.89 to 1.5)	1.05 (0.90 to 1.22)	0.92 (0.84 to 1.01)	Reference	1.21 (1.07 to 1.37)	1.25 (1.02 to 1.52)	2.00 (1.63 to 2.45)	2.00 (1.33 to 3.01)	1.71 (1.14 to 2.58)
Haemorrhagic stroke (n=6758)										
No of deaths per BMI category	41	337	1284	1871	1643	887	443	170	39	43
Hazard ratio (95% CI)	1.37 (0.91 to 2.07)	1.05 (0.9 to 1.23)	1.12 (0.91 to 1.38)	0.99 (0.90 to 1.09)	Reference	1.00 (0.90 to 1.11)	1.28 (1.12 to 1.47)	1.58 (1.27 to 1.95)	2.08 (1.41 to 3.08)	2.7 (1.44 to 5.05)

Analyses for the calculation of hazard ratios were adjusted for baseline age, sex, cigarette smoking, alcohol consumption, educational attainment, marital status, urban residence, and baseline status of cancer. All analyses excluded first three years of follow-up.

Table 3| **Association between BMI and CVD mortality in south Asians**

Cause and No of CVD deaths	Body mass index at baseline									
	<15.0	15.0-17.4	17.5-19.9	20.0-22.4	22.5-24.9	25.0-27.4	27.5-29.9	30.0-32.4	32.5-34.9	35.0-50.0
All participants (n=287 432)										
No of participants per BMI category	6754	31 185	59 396	68 885	58 517	35 894	16 199	6988	2251	1363
CVD (n=8190)										
No of deaths per BMI category	329	1085	1750	2028	1553	864	333	166	45	37
Hazard ratio (95% CI)	0.95 (0.79 to 1.14)	0.85 (0.76 to 0.95)	0.90 (0.82 to 0.99)	0.97 (0.89 to 1.06)	Reference	1.03 (0.93 to 1.15)	1.01 (0.87 to 1.18)	1.14 (0.92 to 1.42)	0.95 (0.64 to 1.41)	1.27 (0.81 to 1.97)
CHD (n=4806)										
No of deaths per BMI category	180	579	972	1215	951	536	215	106	26	26
Hazard ratio (95% CI)	0.83 (0.64 to 1.07)	0.78 (0.67 to 0.9)	0.83 (0.74 to 0.94)	0.96 (0.86 to 1.07)	Reference	1.07 (0.93 to 1.23)	1.18 (0.98 to 1.43)	1.17 (0.88 to 1.55)	1.15 (0.71 to 1.87)	1.90 (1.15 to 3.12)
Stroke (n=2083)										
No of deaths per BMI category	78	313	504	516	366	197	66	27	9	7
Hazard ratio (95% CI)	0.95 (0.68 to 1.33)	0.89 (0.72 to 1.10)	0.97 (0.81 to 1.16)	0.97 (0.81 to 1.15)	Reference	0.97 (0.77 to 1.22)	0.83 (0.59 to 1.15)	0.93 (0.57 to 1.50)	0.81 (0.33 to 1.97)	0.48 (0.12 to 1.95)

Analyses for the calculation of hazard ratios were adjusted for baseline age, sex, cigarette smoking, alcohol consumption, educational attainment, marital status, urban residence, and baseline status of cancer. All analyses excluded first three years of follow-up.

Figures

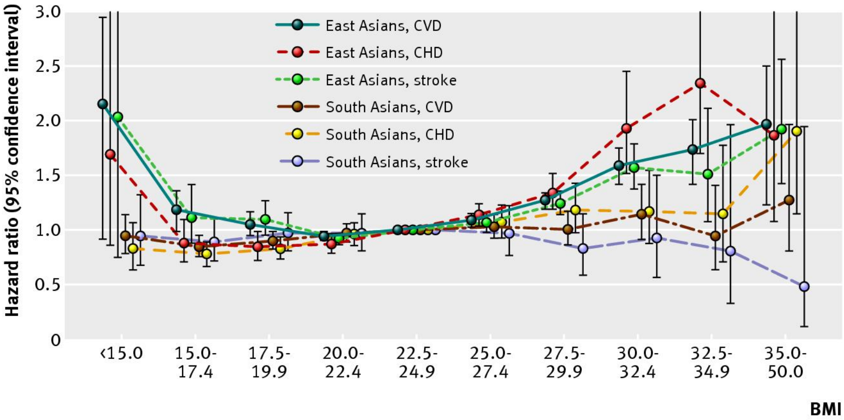

Fig 1 Association between BMI and CVD mortality in east Asians and south Asians. Analyses for the calculation of hazard ratios were adjusted for baseline age, sex, cigarette smoking, alcohol consumption, educational attainment, marital status, urban residence, and baseline status of cancer. All analyses excluded first three years of follow-up

CVD diseases and subgroups	Total No of deaths	No of cases in high BMI	Hazard ratio (95% CI)
CVD			
Overall	38 366	8584	1.20 (1.11 to 1.29)
Overall with baseline CVD data*	24 525	6138	1.16 (1.06 to 1.26)
Excluding baseline stroke or CHD*	20 543	4933	1.16 (1.05 to 1.27)
Never smokers	18 173	4736	1.24 (1.14 to 1.35)
Excluding baseline stroke or CHD*	10 046	2758	1.19 (1.09 to 1.31)
Current smokers	13 781	2463	1.25 (1.19 to 1.32)
Past smokers	4214	902	1.07 (0.95 to 1.22)
Baseline age <53 years	5939	1526	1.38 (1.20 to 1.58)
Baseline age ≥53 years	33 156	7252	1.17 (1.10 to 1.25)
Adjusting for diabetes	38 366	8584	1.18 (1.09 to 1.27)
Adjusting for hypertension	38 366	8584	1.07 (1.00 to 1.15)
Baseline hypertension	16 173	4583	1.00 (0.93 to 1.07)
No baseline hypertension	19 349	3537	1.15 (1.06 to 1.26)
CHD			
Overall	9084	2283	1.38 (1.29 to 1.47)
Overall with baseline CVD data*	6203	1728	1.33 (1.23 to 1.45)
Excluding baseline stroke or CHD*	4963	1327	1.33 (1.21 to 1.46)
Never smokers	3969	1155	1.39 (1.26 to 1.52)
Excluding baseline stroke or CHD*	2282	690	1.34 (1.18 to 1.53)
Current smokers	3486	732	1.46 (1.31 to 1.61)
Past smokers	1186	299	1.20 (0.93 to 1.56)
Baseline age <53 years	1360	407	1.62 (1.33 to 1.97)
Baseline age ≥53 years	7905	1926	1.32 (1.23 to 1.42)
Adjusting for diabetes	9084	2283	1.33 (1.24 to 1.42)
Adjusting for hypertension	9084	2283	1.23 (1.15 to 1.32)
Baseline hypertension	3781	1196	1.12 (1.01 to 1.23)
No baseline hypertension	4765	988	1.35 (1.23 to 1.49)
Stroke			
Overall	17 363	3996	1.14 (1.03 to 1.26)
Overall with baseline CVD data*	10 967	2826	1.07 (0.95 to 1.21)
Excluding baseline stroke or CHD*	9130	2264	1.08 (0.94 to 1.24)
Never smokers	8484	2313	1.22 (1.10 to 1.36)
Excluding baseline stroke or CHD*	4590	1332	1.18 (1.04 to 1.33)
Current smokers	6147	1092	1.15 (1.00 to 1.31)
Past smokers	1739	360	1.05 (0.90 to 1.22)
Baseline age <53 years	2708	714	1.34 (1.12 to 1.60)
Baseline age ≥53 years	14 999	3378	1.12 (1.02 to 1.23)
Adjusting for diabetes	17 363	3996	1.13 (1.01 to 1.27)
Adjusting for hypertension	17 363	3996	1.01 (0.91 to 1.11)
Baseline hypertension	7963	2281	0.92 (0.82 to 1.03)
No baseline hypertension	8134	1510	1.12 (1.02 to 1.24)
Ischaemic stroke			
Overall	5721	1389	1.28 (1.11 to 1.48)
Overall with baseline CVD data*	4706	1216	1.18 (0.99 to 1.41)
Excluding baseline stroke or CHD*	2652	703	1.21 (1.02 to 1.42)
Never smokers	2749	764	1.27 (1.11 to 1.45)
Excluding baseline stroke or CHD*	1269	386	1.20 (1.02 to 1.40)
Current smokers	1905	376	1.52 (1.33 to 1.73)
Past smokers	641	152	1.35 (1.00 to 1.82)
Baseline age <53 years	628	186	1.86 (1.52 to 2.26)
Baseline age ≥53 years	5195	1235	1.24 (1.08 to 1.42)
Adjusting for diabetes	5721	1389	1.26 (1.08 to 1.46)
Adjusting for hypertension	5721	1389	1.13 (0.98 to 1.31)
Baseline hypertension	2616	816	1.12 (0.99 to 1.28)
No baseline hypertension	2638	501	1.26 (1.10 to 1.45)
Haemorrhagic stroke			
Overall	6717	1582	1.09 (0.97 to 1.23)
Overall with baseline CVD data*	3378	936	1.04 (0.88 to 1.22)
Excluding baseline stroke or CHD*	4109	1007	1.02 (0.82 to 1.26)
Never smokers	3328	945	1.17 (1.01 to 1.36)
Excluding baseline stroke or CHD*	2108	618	1.12 (0.93 to 1.35)
Current smokers	2492	435	1.01 (0.82 to 1.25)
Past smokers	557	124	1.01 (0.77 to 1.32)
Baseline age <53 years	1551	381	1.18 (1.00 to 1.40)
Baseline age ≥53 years	5324	1245	1.08 (0.97 to 1.21)
Adjusting for diabetes	6717	1582	1.10 (0.96 to 1.27)
Adjusting for hypertension	6717	1582	0.96 (0.85 to 1.08)
Baseline hypertension	3165	911	0.82 (0.69 to 0.98)
No baseline hypertension	3159	602	1.08 (0.95 to 1.22)

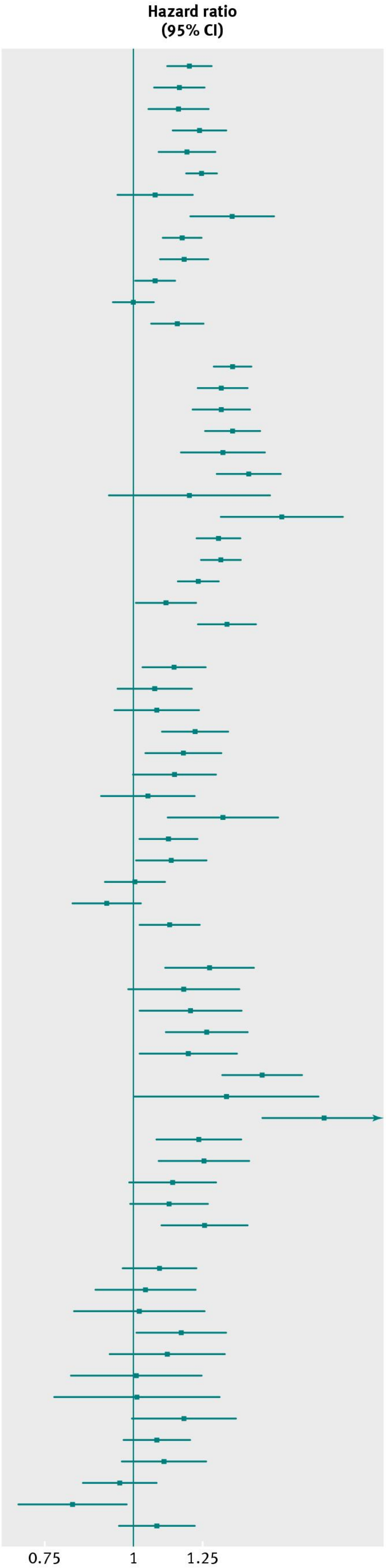

Fig 2 Subgroup analyses for the association between high BMI values (≥25) and CVD mortality in east Asians. Hazard ratios were estimated in comparison to normal BMI values (18.5-24.9), with adjustments for baseline age, sex, cigarette smoking, alcohol consumption, educational, marital status, urban residence, and baseline status of cancer, except for the stratifying variable. All analyses excluded first three years of follow-up. *Analyses excluded people with missing information

on history of CVD and data from the Radiation Effects Research Foundation cohort, three Prefecture Cohort Study Aichi, and Shanghai Cohort Study, which did not have data on previous diagnoses of CHD and stroke

CVD diseases and subgroups	Total No of deaths	No of cases in low BMI	Hazard ratio (95% CI)
CVD			
Overall	38 366	4744	1.19 (1.05 to 1.34)
Overall with baseline CVD data*	24 525	2682	1.28 (1.12 to 1.46)
Excluding baseline stroke or CHD*	20 543	2387	1.29 (1.15 to 1.45)
Never smokers	18 173	2197	1.17 (1.04 to 1.32)
Excluding baseline stroke or CHD*	10 046	1143	1.29 (1.13 to 1.46)
Current smokers	13 781	1801	1.15 (1.01 to 1.30)
Past smokers	4214	475	1.27 (1.09 to 1.47)
Baseline age <53 years	5939	485	1.27 (1.00 to 1.61)
Baseline age ≥53 years	33 156	4331	1.18 (1.05 to 1.33)
Adjusting for diabetes	38 366	4744	1.21 (1.07 to 1.37)
Adjusting for hypertension	38 366	4744	1.27 (1.12 to 1.45)
Baseline hypertension	16 173	1546	1.35 (1.14 to 1.59)
No baseline hypertension	19 349	2656	1.25 (1.12 to 1.39)
CHD			
Overall	9084	833	1.03 (0.85 to 1.26)
Overall with baseline CVD data*	6203	441	1.11 (0.84 to 1.48)
Excluding baseline stroke or CHD*	4963	367	1.09 (0.81 to 1.45)
Never smokers	3969	362	1.15 (0.89 to 1.48)
Excluding baseline stroke or CHD*	2282	158	1.18 (0.79 to 1.78)
Current smokers	3486	324	0.91 (0.73 to 1.15)
Past smokers	1186	88	1.21 (0.73 to 2.02)
Baseline age <53 years	1360	77	1.04 (0.72 to 1.48)
Baseline age ≥53 years	7905	769	1.04 (0.85 to 1.28)
Adjusting for diabetes	9084	833	1.08 (0.88 to 1.33)
Adjusting for hypertension	9084	833	1.11 (0.91 to 1.35)
Baseline hypertension	3781	254	1.08 (0.79 to 1.46)
No baseline hypertension	4765	480	1.07 (0.91 to 1.26)
Stroke			
Overall	17 363	1952	1.11 (0.94 to 1.31)
Overall with baseline CVD data*	10 967	1049	1.19 (0.97 to 1.47)
Excluding baseline stroke or CHD*	9130	905	1.21 (0.99 to 1.48)
Never smokers	8484	877	1.00 (0.84 to 1.18)
Excluding baseline stroke or CHD*	4590	414	1.08 (0.86 to 1.35)
Current smokers	6147	779	1.21 (1.00 to 1.46)
Past smokers	1739	181	1.15 (0.93 to 1.42)
Baseline age <53 years	2708	207	1.09 (0.84 to 1.42)
Baseline age ≥53 years	14 999	1781	1.14 (0.95 to 1.37)
Adjusting for diabetes	17 363	1952	1.13 (0.95 to 1.33)
Adjusting for hypertension	17 363	1952	1.20 (1.00 to 1.43)
Baseline hypertension	7963	743	1.20 (1.09 to 1.33)
No baseline hypertension	8134	981	1.17 (0.94 to 1.46)
Ischaemic stroke			
Overall	5721	613	1.06 (0.92 to 1.23)
Overall with baseline CVD data*	4706	468	1.09 (0.86 to 1.38)
Excluding baseline stroke or CHD*	2652	231	1.18 (0.92 to 1.51)
Never smokers	2749	271	0.97 (0.83 to 1.13)
Excluding baseline stroke or CHD*	1269	104	1.06 (0.83 to 1.36)
Current smokers	1905	238	1.11 (0.91 to 1.36)
Past smokers	641	64	1.44 (1.03 to 2.02)
Baseline age <53 years	628	55	1.18 (0.86 to 1.60)
Baseline age ≥53 years	5195	565	1.06 (0.92 to 1.23)
Adjusting for diabetes	5721	613	1.08 (0.93 to 1.27)
Adjusting for hypertension	5721	613	1.14 (0.99 to 1.31)
Baseline hypertension	2616	193	1.07 (0.89 to 1.29)
No baseline hypertension	2638	336	1.19 (0.94 to 1.51)
Haemorrhagic stroke			
Overall	6717	733	1.05 (0.87 to 1.27)
Overall with baseline CVD data*	3378	279	1.18 (0.94 to 1.47)
Excluding baseline stroke or CHD*	4109	421	1.19 (0.94 to 1.50)
Never smokers	3328	371	0.93 (0.77 to 1.13)
Excluding baseline stroke or CHD*	2108	182	0.97 (0.73 to 1.30)
Current smokers	2492	318	1.33 (0.96 to 1.84)
Past smokers	557	55	1.10 (0.72 to 1.68)
Baseline age <53 years	1551	108	1.13 (0.84 to 1.53)
Baseline age ≥53 years	5324	640	1.08 (0.88 to 1.34)
Adjusting for diabetes	6717	733	1.08 (0.89 to 1.31)
Adjusting for hypertension	6717	733	1.16 (0.94 to 1.43)
Baseline hypertension	3165	319	1.28 (1.08 to 1.53)
No baseline hypertension	3159	354	1.18 (0.92 to 1.50)

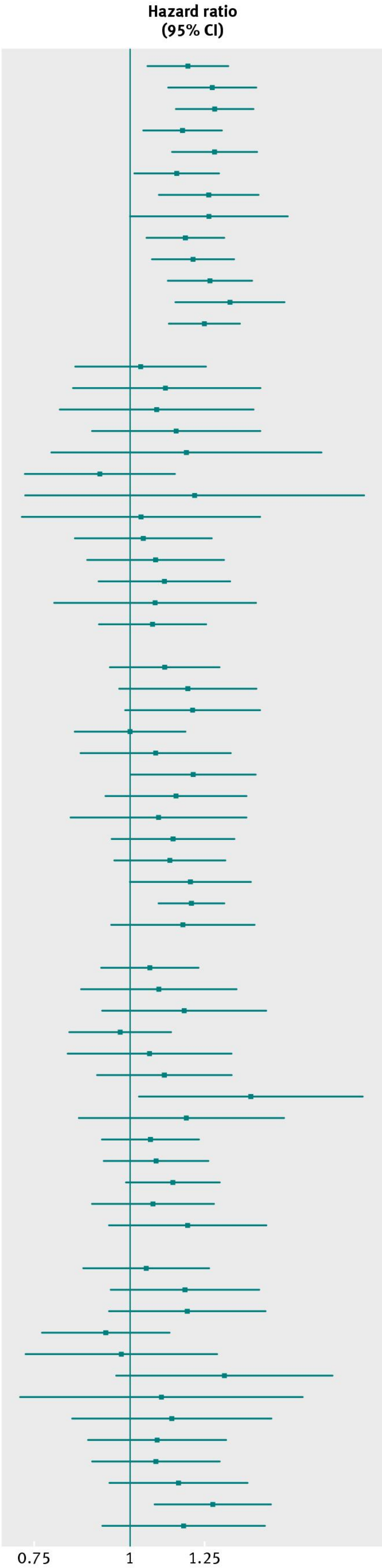

Fig 3 Subgroup analyses for the association between low BMI values (15-18.4) and CVD mortality in east Asians. Hazard ratios were estimated in comparison to normal BMI (18.5-24.9), with adjustments for baseline age, sex, cigarette smoking, alcohol consumption, educational attainment, marital status, urban residence, and baseline status of cancer, except for the stratifying variable. All analyses excluded first three years of follow-up. *Analyses excluded people with missing information

on history of CVD and data from the Radiation Effects Research Foundation cohort, three Prefecture Cohort Study Aichi, and Shanghai Cohort Study, which did not have data on previous diagnoses of CHD and stroke

CVD diseases and subgroups	Total No of deaths	No of cases in high BMI	Hazard ratio (95% CI)
CVD			
Overall	7861	1445	1.08 (1.00 to 1.17)
Overall with baseline CHD/stroke data*	3936	1034	1.07 (0.95 to 1.20)
Excluding baseline stroke or CHD*	3740	540	1.06 (0.94 to 1.19)
Never smokers	5227	1116	1.10 (1.00 to 1.20)
Excluding baseline stroke or CHD*	2257	403	1.09 (0.95 to 1.26)
Current smokers	2164	257	1.08 (0.91 to 1.29)
Past smokers	469	72	0.92 (0.64 to 1.33)
Baseline age <53 years	1432	313	1.10 (0.93 to 1.30)
Baseline age ≥53 years	6534	1160	1.08 (0.99 to 1.18)
Adjusting for diabetes	7861	1445	1.06 (0.97 to 1.16)
Adjusting for hypertension*	4009	583	0.93 (0.83 to 1.05)
CHD			
Overall	4626	909	1.18 (1.07 to 1.30)
Overall with baseline CHD/stroke data*	2492	598	1.12 (0.97 to 1.29)
Excluding baseline stroke or CHD*	2341	367	1.11 (0.96 to 1.29)
Never smokers	2892	673	1.18 (1.05 to 1.33)
Excluding baseline stroke or CHD*	1289	262	1.14 (0.95 to 1.36)
Current smokers	1454	187	1.19 (0.98 to 1.46)
Past smokers	1733	236	1.12 (0.72 to 1.74)
Baseline age <53 years	926	204	1.12 (0.91 to 1.38)
Baseline age ≥53 years	3775	728	1.22 (1.09 to 1.36)
Adjusting for diabetes	4626	909	1.15 (1.03 to 1.28)
Adjusting for hypertension*	2494	393	0.99 (0.86 to 1.14)
Stroke			
Overall	2005	306	0.93 (0.79 to 1.10)
Overall with baseline CHD/stroke data*	1234	361	0.95 (0.76 to 1.18)
Excluding baseline stroke or CHD*	1207	144	0.94 (0.76 to 1.18)
Never smokers	1443	251	0.94 (0.78 to 1.13)
Excluding baseline stroke or CHD*	831	116	0.96 (0.75 to 1.23)
Current smokers	482	42	0.93 (0.61 to 1.41)
Past smokers	80	13	0.83 (0.33 to 2.10)
Baseline age <53 years	269	59	1.16 (0.79 to 1.71)
Baseline age ≥53 years	1753	248	0.88 (0.73 to 1.06)
Adjusting for diabetes	2005	306	0.90 (0.75 to 1.07)
Adjusting for hypertension*	1238	151	0.82 (0.66 to 1.02)

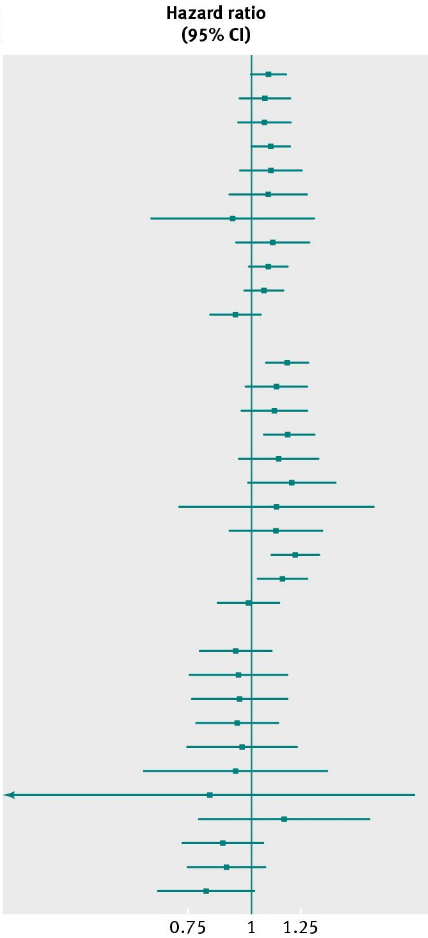

Fig 4 Subgroup analyses for the association between high BMI values (≥25) and CVD mortality in south Asians. Hazard ratios were estimated in comparison to normal BMI (18.5-24.9), with adjustments for baseline age, sex, cigarette smoking, alcohol consumption, educational attainment, marital status, urban residence, and baseline status of cancer, except for the stratifying variable. All analyses excluded first three years of follow-up. *Analyses excluded people with missing information on history of CVD and data from Mumbai cohort, which did not have information on previous diagnoses of stroke, CHD, and hypertension

CVD diseases and subgroups	Total No of deaths	No of cases in low BMI	Hazard ratio (95% CI)
CVD			
Overall	7861	1744	0.90 (0.84 to 0.98)
Overall with baseline CHD/stroke data*	3936	578	0.89 (0.81 to 0.99)
Excluding baseline stroke or CHD*	3740	985	0.90 (0.82 to 1.00)
Never smokers	5227	1015	0.93 (0.84 to 1.03)
Excluding baseline stroke or CHD*	2257	507	0.96 (0.84 to 1.10)
Current smokers	2164	617	0.82 (0.72 to 0.94)
Past smokers	469	112	1.32 (0.95 to 1.85)
Baseline age <53 years	1432	294	1.02 (0.86 to 1.22)
Baseline age ≥53 years	6534	1466	0.88 (0.80 to 0.95)
Adjusting for diabetes	7861	1744	0.97 (0.90 to 1.06)
Adjusting for hypertension*	4009	1055	1.00 (0.91 to 1.11)
CHD			
Overall	4626	943	0.86 (0.78 to 0.95)
Overall with baseline CHD/stroke data*	2492	393	0.86 (0.76 to 0.98)
Excluding baseline stroke or CHD*	2341	571	0.88 (0.77 to 1.00)
Never smokers	2892	490	0.85 (0.74 to 0.99)
Excluding baseline stroke or CHD*	1289	256	0.92 (0.76 to 1.11)
Current smokers	1454	385	0.83 (0.71 to 0.97)
Past smokers	1733	68	1.56 (1.00 to 2.45)
Baseline age <53 years	926	173	0.94 (0.76 to 1.17)
Baseline age ≥53 years	3775	780	0.84 (0.75 to 0.95)
Adjusting for diabetes	4626	943	0.97 (0.87 to 1.08)
Adjusting for hypertension*	2494	598	0.95 (0.84 to 1.08)
Stroke			
Overall	2005	500	0.92 (0.80 to 1.06)
Overall with baseline CHD/stroke data*	1234	149	0.94 (0.80 to 1.11)
Excluding baseline stroke or CHD*	1207	353	0.93 (0.79 to 1.10)
Never smokers	1443	316	0.96 (0.80 to 1.14)
Excluding baseline stroke or CHD*	831	209	0.98 (0.79 to 1.20)
Current smokers	482	169	0.85 (0.65 to 1.10)
Past smokers	80	15	0.93 (0.42 to 2.06)
Baseline age <53 years	269	61	1.30 (0.88 to 1.91)
Baseline age ≥53 years	1753	442	0.87 (0.75 to 1.02)
Adjusting for diabetes	2005	500	0.97 (0.84 to 1.13)
Adjusting for hypertension*	1238	363	1.08 (0.91 to 1.27)

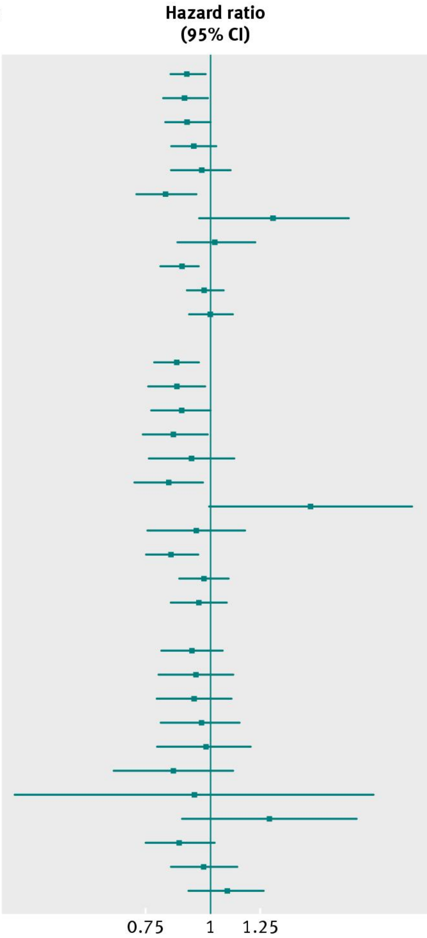

Fig 5 Subgroup analyses for the association between low BMI values (15-18.4) and CVD mortality in south Asians. Hazard ratios were estimated in comparison to normal BMI (18.5-24.9), with adjustments for baseline age, sex, cigarette smoking, alcohol consumption, educational attainment, marital status, urban residence, and baseline status of cancer, except for the stratifying variable. All analyses excluded first three years of follow-up. *Analyses excluded people with missing information on history of CVD and data from Mumbai cohort, which did not have information on previous diagnoses of stroke, CHD, and hypertension