## Title

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# Associations of overweight and obesity with the risk of cardiovascular disease according to metabolic risk factors among middle-aged Japanese workers: The Aichi Workers' cohort study

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ABSTRACT

*Background:* The association between obesity and cardiovascular disease (CVD) remains unclear, particularly for those with established CVD risk factors. We analyzed follow-up data from the Aichi Workers' Cohort Study. We studied the association between the degree of obesity and risk of CVD and its subtypes specifically among individuals with hypertension, hyper-low-density lipoprotein (LDL)-cholesterolemia, or diabetes.

*Methods:* Pooled data of 8972 adults (7076 men and 1896 women) who were recruited between 2002 and 2008 were used in the current analysis. We used multivariable Cox proportional hazard model to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the associations between the degree of obesity assessed with body mass index (BMI) and the risk of CVD and its subtypes, i.e., coronary heart disease (CHD) and stroke.

*Results:* During a median of 12 years, there were 197 CVDs (80 CHDs and 117 strokes). BMI $\geq$ 27.5 compared to 21.0–22.9 kg/m$^2$ was positively and significantly associated with the risks of CVD, CHD, and total stroke. Hypertension, hyper-LDL-cholesterolemia, and diabetes mediated 15.9%, 5.8%, and 8.7% of obesity-CVD associations, respectively, and 28.3% by their combination. In the stratified analyses by the presence of risk factors, BMI $\geq$ 25.0 (overweight/obesity) compared to BMI $<$ 25 kg/m$^2$ was associated with a higher risk of CVD in those with and without hypertension, but only with hyper-LDL-cholesterolemia, and without diabetes.

*Conclusions:* Overweight/obesity was associated with the risk of CVD and its subtypes. About 30% of the risk was explained by hypertension, hyper-LDL-cholesterolemia, and diabetes, of which hypertension accounted for approximately the half of the explained risk. However, overweight/obesity increased the risk of CVD even in those without hypertension. These findings highlight the importance of controlling and preventing overweight/obesity regardless of chronic disease status.

## Introduction

Obesity is known to increase the risk of cardiovascular diseases (CVD), a major cause of death worldwide [1]. However, the associations of overweight and obesity defined by body mass index (25 $\leq$ BMI $<$ 30, BMI $\geq$ 30 kg/m$^2$, respectively) with increased risk of CVD [2–6] are not necessarily consistent [7–10]. Namely, longitudinal studies among European populations reported no association between obesity and myocardial infarction (MI) [7] or coronary heart disease (CHD) [8]. Other prospective studies among Spanish and Korean populations reported no association between BMI and the risk of ischemic [9] or hemorrhagic strokes [9,10]. Among the Japanese population, mixed

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results were reported for the associations of BMI with CVD, in which BMI was not associated with MI in women [11] or with hemorrhagic stroke [12]. Further, some of the previous studies in Japan had limitations including a lack of information about alcohol drinking, physical activity, and medication use [5,13].

In addition, higher adiposity often accompanies established CVD risk factors such as hypertension, dyslipidemia, and diabetes, which would mediate its effect on CVD risk to varying degrees according to studies. For example, a previous study reported that these risk factors totally mediated the association of BMI with CVD [8]. On the contrary, another study reported that there remained an independent effect of obesity on the risk of CVD not mediated by these factors [11,14]. In addition to the inconsistencies regarding the presence of mediation, its degree has not been widely explored.

Furthermore, it is not well known whether the possible effect of overweight/obesity on CVD risk would be exaggerated in those with the established risk factors. Although an increased risk of cardioembolic stroke related to overweight/obesity in those with hypertension [15] or that of CHD in those with diabetes [16] have been reported, the majority of previous studies assessed CVD risk for the combinations of obesity and risk factors in reference to healthy individuals [7,12,15-18]. From preventive medicine perspective in a clinical setting, it would be important to estimate the risk of overweight/obesity in those with such risk factors so that clinicians could provide appropriate health counseling related to overweight/obesity.

This study aims to explore the association between the degree of BMI and the risk of CVD and its subtypes in middle-aged workers from a metropolitan area in Japan. This study also estimated the degree of mediation by a set of established risk factors for the association between overweight/obesity and explored the potential effect modification by the presence of hypertension, hyper-low-density lipoprotein (LDL)-cholesterolemia, or diabetes.

## Methods

### *Study population*

The Aichi Workers' Cohort Study, initiated in 1997, is an ongoing longitudinal epidemiological study on chronic diseases, including diabetes and CVD. Participants were civil servants aged between 35 and 66 years in Aichi prefecture, an urban and suburban area located in central Japan [19–22]. The current study pooled data from three consecutive baseline surveys conducted in 2002 (n = 5413), 2005 (n = 2369), and 2008 (n = 1190). The following participants were excluded: those with (1) histories of CVD (n = 104) or cancer (n = 40); (2) less than one-year follow-up (n = 250), leaving 8972 (men= 7076, women= 1896) participants for the current study.

### *Definition and classification of baseline variables*

Information on lifestyles, disease history, and medication use were collected through a self-administered questionnaire from each survey. Body weight was measured to the nearest 0.1 kg, and height was measured to the nearest 0.1 cm. BMI was calculated as body weight (kg) divided by the square of height ($m^2$). Blood pressure was obtained in the seated position after at least 5 min' rest. Venous blood samples were drawn after the subjects fasted for eight hours or overnight.

BMI was grouped into 5 categories: < 21, 21–22.9 (reference), 23.0–< 25, 25.0–< 27.5, and ≥ 27.5 kg/$m^2$. Current smoking status was dichotomized as non-smoker or current smoker. Alcohol consumption was estimated from the number of days of alcohol drinking and the amount of alcohol consumed per occasion. It was grouped into the low (< 40 g/day for men and < 20 g/day for women) and high (≥ 40 g/day for men and ≥ 20 g/ day for women) consumption groups. Physical activity was evaluated by the number of days per month participants engaged in moderate to vigorous exercise (leisure-time physical activity) which lasted at least 60 min. Hypertension was defined as systolic blood pressure (SBP) ≥ 140 mmHg, diastolic blood pressure (DBP) ≥ 90 mmHg, and/or the use of anti-hypertensive medications. Diabetes was defined as fasting blood glucose (FBG) ≥ 126 mg/dL and/or the use of glucose-lowering medications. Hyper-LDL-cholesterolemia was defined as LDL cholesterol (LDL-C) ≥ 140 mg/dL or the use of cholesterol-lowering or other medications for dyslipidemia [23]. Blood level of high-density lipoprotein cholesterol (HDL-C) was also obtained in the health check-up.

### *Follow-up*

Participants were followed through March 2019. The person-years of follow-up were calculated from baseline to the date of CVD incidence, the date of censoring, or the end of follow-up, whichever came first. Participants were censored when they died or retired, except for those who agreed to provide information about their health statuses after retirement (approximately 52.1% of the retired participants).

### *Ascertainment of CHD and stroke, and classification of stroke types*

We ascertained the incidence of CVD events using multiple sources. First, participants biennially completed a self-administered questionnaire about their medical histories including CHD and stroke subtypes. For those with positive histories, they were asked to provide contact information of their attending physicians so that we could make inquiries for confirmation. Approximately 87.2% of participants responded to at least one biennial follow-up survey through 2015. In the current analysis, CHD included myocardial infarction and unstable angina followed by percutaneous coronary intervention. A diagnosis of myocardial infarction was made according to the modified World Health Organization MONICA Project (monitoring trends and determinants in cardiovascular disease) [24] criteria, in which we also included cardiac troponin as a marker of cardiac injury. In addition, confirmation of acute coronary artery occlusion by angiography or of abnormal cardiac wall motion that correspond to the clinical findings was employed as the definition. Incidence of stroke was confirmed by a physician using the following definition: sudden diffuse or focal neurological deficit due to cerebrovascular disorder, which persists for a minimum of 24 hours. Definite stroke cases must have computed tomography or magnetic resonance imaging findings that are consistent with the signs and symptoms. A stroke was classified into ischemic stroke, intracerebral hemorrhage, subarachnoid hemorrhage, and stroke of unknown type. Cases that were not confirmed by the physicians were deemed as probable ones.

Second, the incidence was also ascertained through the worksite's healthcare division which deals with workers' sick leave information. These cases were classified as definite because the sick leave application usually accompanies medical certificates. Fatal cases were determined using this channel as well. Finally, CVD cases were identified through a brief questionnaire administered during annual mandatory health check-up. Since these cases could not be confirmed by the medical record, they were considered probable cases. Sources of probable cases consist of a brief questionnaire during annual health checkup (n = 77), sick leave information (n = 2), and physicians' report that deemed them as probable (n = 10).

Retirees were followed up using a biennial self-administered questionnaire only. The next of kin of the participants was asked to provide details if the participants were deceased or were unable to respond. Details of the histories of the retirees were also confirmed by their physicians when it was possible.

### *Statistical analysis*

Missing data observed in the following variables were imputed using multiple imputation by chained equations using the R package "mice":

physical activity (n = 467, 5.2%), smoking (n = 320, 3.6%), alcohol intake (n = 373, 4.2%), SBP and DBP (n = 1, 0.01%), LDL-C (n = 112, 1.3%), HDL-C (n = 53, 0.6%) and diabetes (n = 57, 0.6%). Ten datasets were created and analyzed, and the estimates from each dataset were pooled. A fixed seed was used for the random number generator during multiple imputation to ensure the reproducibility of the findings.

Differences in baseline variables other than age and sex according to BMI categories were assessed using analysis of covariance (ANCOVA) with adjustment for age and sex. Cox proportional hazard model was used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CIs) of baseline BMI categories for the incidence of CVD, CHD, stroke, and stroke subtypes. Model 1 was adjusted for age (continuous), sex, current smoking, alcohol consumption, physical activity, and survey year. Model 2 was additionally SBP, HDL-C, LDL-C, antihypertensive medication, dyslipidemia medication, and diabetes. The proportional hazard assumption was confirmed using Schoenfeld residuals test and log-log survival curve (Supplementary Figure 1). The degree of mediation by hypertension, hyper-LDL-cholesterolemia, and diabetes was examined using SAS PROC CAUSALMED. Non-linear relationships between BMI with CVD, CHD, and total stroke were explored using multivariable-adjusted restricted cubic spline analyses with four knots at the 5th, 35th, 65th, and 95th percentiles of BMI distribution. To avoid the potential influence of outliers in spline analysis, we trimmed BMI at the 99th percentile.

In order to examine potential differences in the associations of overweight/obesity with the risk of CVD according to the presence/absence of hypertension, hyper-LDL-cholesterolemia, or diabetes, stratified analyses by these conditions were performed. The multivariable model included age, sex, current smoking, alcohol consumption, physical activity, survey year, and HDL-C as well as other conditions (i.e., hyper-LDL-cholesterolemia and diabetes in case of hypertension-stratified analysis). Test of interaction was conducted by including the multiplicative term of overweight/obesity and the condition being examined.

A series of sensitivity analyses were performed to ensure the robustness of the findings including analysis. Restricted to only definite cases while censoring probable events at the date of the occurrence, analysis that censored all the participants at retirement or at 60 years, analysis restricted to men, and complete case analysis restricted to those without missing data.

All the statistical analyses were performed using R and SAS software. A two-sided p-value $< 0.05$ indicated statistical significance.

## Results

Age, the proportions of men, current smoking, excessive alcohol drinking, and the number of days engaging in exercise at baseline differed significantly across BMI categories within both before and after imputation datasets (Table 1). Overweight/obese individuals (BMI $\geq$ 25.0 kg/m$^2$) compared to BMI$<$ 25.0 kg/m$^2$ were more likely to be current smokers, hypertensive, diabetic, and on medications for risk factors. Overweight/obesity was also associated with higher levels of SBP, DBP, LDL-C, FBG, and lower levels of HDL-C.

During a median of 12-year follow-up, there were 197 CVDs including 80 CHDs and 117 strokes that consisted of 55 ischemic strokes, 24 intracerebral hemorrhage, 13 subarachnoid hemorrhage, and 25 strokes of unknown subtypes. The definite events (108, 55.0%) consisted of 39 (48.8%) CHDs, 69 (59.0%) total strokes, 41 (74.5%) ischemic strokes, and 19 (79.2%) intracerebral hemorrhage.

Compared to subjects with BMI 21.0–22.9 kg/m$^2$, those with BMI= 25.0–$<$ 27.5 or BMI $\geq$ 27.5 kg/m$^2$ showed a significantly increased risk of CVD with the Model 1 HRs of 2.05 (95% CI: 1.35–3.10) and 3.08 (95%

**Table 1**
Baseline characteristics according to BMI categories before and after the multiple imputation, Aichi Workers' Cohort, 2002–2008.

| | Before imputation | | | | | | | After imputation | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Body mass index, kg/m$^2$ | | | | | | | Body mass index, kg/m$^2$ | | | | | | |
| | All | < 21.0 | 21.0–22.9 | 23.0–< 25 | 25.0–< 27.5 | ≥ 27.5 | | All | < 21.0 | 21.0–22.9 | 23.0–< 25 | 25.0–< 27.5 | ≥ 27.5 | |
| Median | 22.7 | 19.8 | 22.0 | 23.9 | 25.9 | 28.7 | | 22.7 | 19.8 | 22.0 | 23.9 | 25.9 | 28.7 | |
| Variables | N = 8972 | N = 2284 | N = 2530 | N = 2194 | N = 1414 | N = 550 | p-value | N = 8972 | N = 2284 | N = 2530 | N = 2194 | N = 1414 | N = 550 | p-value |
| Age, years | 46.7 | 45.3 | 46.7 | 47.7 | 47.6 | 46.6 | < 0.001 | 46.7 | 45.3 | 46.7 | 47.7 | 47.6 | 46.6 | < 0.001 |
| Men, (%) | 78.9 | 60.6 | 80.0 | 87.3 | 90.4 | 86.2 | < 0.001 | 78.9 | 60.6 | 80.0 | 87.3 | 90.4 | 86.2 | < 0.001 |
| Physical activity, days/ month | 6.4 | 5.8 | 6.2 | 6.9 | 6.8 | 6.2 | < 0.001 | 6.3 | 5.8 | 6.2 | 6.9 | 6.7 | 5.3 | 0.001 |
| Current smoking, (%) | 26.9 | 23.9 | 26.4 | 27.8 | 28.8 | 33.7 | < 0.001 | 26.9 | 23.9 | 26.3 | 27.9 | 28.9 | 33.3 | < 0.001 |
| Alcohol drinking, (High-risk %) | 10.7 | 9.5 | 11.3 | 10.5 | 12.8 | 9.1 | 0.017 | 10.7 | 9.6 | 11.2 | 10.3 | 12.8 | 9.4 | 0.030 |
| Systolic blood pressure, mmHg | 124.9 | 118.8 | 123.8 | 126.9 | 130.3 | 134.4 | < 0.001 | 124.9 | 118.8 | 123.8 | 126.9 | 130.3 | 134.4 | < 0.001 |
| Diastolic blood pressure, mmHg | 77.4 | 72.5 | 76.4 | 79.0 | 81.9 | 84.8 | < 0.001 | 77.4 | 72.5 | 76.4 | 79.0 | 81.9 | 84.8 | < 0.001 |
| Hypertension, (%) | 21.5 | 10.0 | 17.6 | 24.2 | 33.4 | 46.6 | < 0.001 | 21.5 | 10.0 | 17.6 | 24.2 | 33.4 | 46.6 | < 0.001 |
| Antihypertensive medication, (%) | 6.4 | 2.0 | 5.1 | 7.52 | 10.4 | 15.3 | < 0.001 | 6.4 | 2.0 | 5.1 | 7.52 | 10.4 | 15.3 | < 0.001 |
| HDL cholesterol, mg/dL | 58.4 | 66.6 | 60.0 | 54.8 | 51.9 | 48.7 | < 0.001 | 58.5 | 66.7 | 60.0 | 54.8 | 51.9 | 48.7 | < 0.001 |
| LDL cholesterol, mg/dL | 124.6 | 115.0 | 123.0 | 128.3 | 133.6 | 134.0 | < 0.001 | 124.5 | 114.9 | 122.9 | 128.2 | 133.5 | 134.1 | < 0.001 |
| Dyslipidemia medication, (%) | 2.9 | 0.9 | 2.4 | 2.8 | 5.0 | 8.0 | < 0.001 | 2.9 | 0.9 | 2.4 | 2.8 | 5.0 | 8.0 | < 0.001 |
| Fasting blood glucose, mg/dL | 95.3 | 92.0 | 94.2 | 96.2 | 98.2 | 102.0 | < 0.001 | 94.1 | 92.4 | 92.9 | 94.1 | 95.9 | 100.5 | < 0.001 |
| Diabetes, (%) | 5.3 | 3.8 | 3.9 | 5.9 | 6.4 | 12.8 | < 0.001 | 5.2 | 3.8 | 3.9 | 5.8 | 6.4 | 12.7 | < 0.001 |

Notes: p-values for categorical variables were from the chi-square test and for continuous variables were from the analysis of variance.

CI: 1.91–5.00), respectively (Table 2). The categories-specific HRs as well as the association of BMI on the continuous scale (HR: 1.09, 95% CI: 1.04–1.14) with CVD risk remained significant in Model 2. Participants with BMI= 25.0–< 27.5 and BMI ≥ 27.5 kg/m$^2$ compared to BMI of 21.0–22.9 kg/m$^2$ showed a significantly increased risk of CHD with HRs of 2.12 (95% CI: 1.11–4.05) and 3.92 (95% CI: 1.93–7.96) in Model 1. Although these estimates became attenuated in Model 2 with HRs of 1.31 (95% CI: 0.67–2.55) and 1.60 (95% CI: 0.75–3.43), the continuous association remained statistically significant (HR: 1.10, 95% CI: 1.03–1.18). The results of spline analysis showed that the risk of CHD gradually increased and statistically significant in BMI ranges higher than 27.5 kg/m$^2$ (Fig. 1).

Similarly, subjects with BMI = 25.0–< 27.5 or BMI ≥ 27.5 kg/m$^2$ compared to those with BMI of 21.0–22.9 kg/m$^2$ showed a significantly increased risk of total stroke with the Model 1 HRs of 1.99 (95% CI: 1.15–3.44) and 2.47 (95% CI: 1.25–4.90), respectively. And the association was significantly attenuated in Model 2 with HRs of 1.72 (95% CI: 0.98–3.03) and 1.84 (95% CI: 0.90–3.80), but the continuous association remained significant (HR: 1.07, 95% CI: 1.00–1.15). Although the continuous association of BMI with ischemic stroke was significant (HR: 1.10, 95% CI:1.00—1.21), the similar association was not observed for intracerebral hemorrhage.

According to the mediation analyses, 15.9% (p = 0.003), 5.8% (p = 0.068), and 8.7% (p = 0.003) of the BMI association with CVD were mediated by hypertension, hyper-LDL-cholesterolemia, and diabetes, respectively (Table 3). Collectively, these factors mediated approximately 28.3% of the observed association.

Overweight/obesity was associated with an increased risk of CVD in subjects with (HR=1.68; 95% CI: 1.06–2.66) or without (HR=1.67; 95% CI: 1.10–2.54) hypertension (interaction p = 0.71, Table 4). Although statistical interaction was not significant, overweight/obesity was associated with CVD risk only in subjects with hyper-LDL-cholesterolemia (HR: 1.89; 95% CI: 1.21–2.96) and in subjects without diabetes (HR: 1.71; 95% CI: 1.23–2.39).

A series of sensitivity analyses including definite events analysis (Supplementary Table 1), analysis that censored everyone at the retirement age (Supplementary Table 2), male-only analysis (Supplementary Table 3), and analysis using subjects without missing values (Supplementary Table 4) yielded essentially similar findings.

## Discussion

In this prospective cohort study, we assessed the associations of BMI with the risk of CVD among middle-aged Japanese civil servants without a history of CVD at baseline. We observed a positive linear relationship of BMI with the risk of CVD, CHD, and total and ischemic stroke. Approximately 30% of the association between BMI and CVD was explained by hypertension, hyper-LDL-cholesterolemia, and diabetes. The association of BMI with CVD (direct effect) remained significant after incorporating the indirect effect through these mediators. Even though there are no statistical interactions, subjects with hypertension or hyper-LDL cholesterolemia who also have overweight/obesity had significantly higher risks of CVD compared to non-overweight/obese counterparts indicating the importance of weight control advice or interventions in clinical settings.

The present finding for CHD would be consistent with a previous case-control study among the Japanese population, the Japan Epidemiology Collaboration on Occupational Health (J-ECOH) Study (mean BMI, case: 25.3 kg/m$^2$, control: 23.7 kg/m$^2$), which reported that the highest tertile of BMI (≥24.5 kg/m$^2$) was associated with around 3-time higher risk of myocardial infarction compared to the lowest tertile (<22.2 kg/m$^2$) and that the association attenuated after the adjustment for hypertension, diabetes, and dyslipidemia in men. Also, it would be consistent with an individual data meta-analysis of 16 Japanese cohorts

**Table 2**
Hazard ratios (HRs) and 95% confidence intervals (CIs) for the association of BMI categories with the incidence of CVD and its subtypes, Aichi Workers' Cohort, 2002–2019.

| | | | Crude | | Model 1 | | Model 2 | |
|---|---|---|---|---|---|---|---|---|
| Outcome | BMI (kg/m$^2$) | n/Person-years | HRs (95% CIs) | p-value | HRs (95% CIs) | p-value | HRs (95% CIs) | p-value |
| Cardiovascular disease | < 21.0 | 21/24597 | **0.56 (0.33–0.96)** | **0.033** | 0.69 (0.40–1.17) | 0.17 | 0.81 (0.47–1.39) | 0.44 |
| | 21.0–22.9 | 41/26998 | Ref | | Ref | | Ref | |
| | 23.0– < 25 | 56/23176 | **1.59 (1.06–2.38)** | **0.025** | 1.44 (0.96–2.16) | 0.080 | 1.22 (0.81–1.85) | 0.335 |
| | 25.0–< 27.5 | 51/14861 | **2.27 (1.49–3.43)** | **< 0.001** | **2.05 (1.35–3.10)** | **0.001** | **1.55 (1.01–2.37)** | **0.044** |
| | ≥ 27.5 | 28/5726 | **3.23 (1.99–5.23)** | **< 0.001** | **3.08 (1.90–5.00)** | **< 0.001** | **1.80 (1.08 –3.02)** | **0.026** |
| | Continuous scale | 197/95358 | **1.15 (1.11–1.18)** | **< 0.001** | **1.15 (1.10–1.19)** | **< 0.001** | **1.09 (1.04–1.14)** | **0.002** |
| Coronary heart disease | < 21.0 | 5/24597 | **0.32 (0.12–0.89)** | **0.030** | 0.41 (0.15–1.13) | 0.083 | 0.54 (0.20–1.52) | 0.240 |
| | 21.0–22.9 | 17/26998 | Ref | | Ref | | Ref | |
| | 23.0– < 25 | 21/23176 | 1.44 (0.75–2.75) | 0.27 | 1.29 (0.67–2.47) | 0.45 | 0.98 (0.50 –1.89) | 0.942 |
| | 25.0–< 27.5 | 22/14861 | **2.35 (1.24–4.48)** | **0.010** | **2.12 (1.11 –4.05)** | **0.023** | 1.31 (0.67–2.55) | 0.419 |
| | ≥ 27.5 | 15/5726 | **4.17 (2.06–8.46)** | **0.000** | **3.92 (1.93–7.96)** | **< 0.001** | 1.60 (0.75–3.43) | 0.220 |
| | Continuous scale | 80/95358 | **1.18 (1.13–1.23)** | **< 0.001** | **1.19 (1.13–1.25)** | **< 0.001** | **1.10 (1.03–1.18)** | **0.016** |
| Total stroke | < 21.0 | 16/24597 | 0.73 (0.39–1.39) | 0.334 | 0.88 (0.46–1.67) | 0.690 | 0.94 (0.49–1.81) | 0.854 |
| | 21.0–22.9 | 24/26998 | Ref | | Ref | | Ref | |
| | 23.0– < 25 | 35/23176 | **1.69 (1.00–2.87)** | **0.048** | 1.55 (0.91–2.61) | 0.104 | 1.44 (0.84–2.45) | 0.182 |
| | 25.0–< 27.5 | 29/14861 | **2.20 (1.27–3.80)** | **0.005** | **1.99 (1.15–3.44)** | **0.015** | 1.72 (0.98–3.03) | 0.059 |
| | ≥ 27.5 | 13/5726 | **2.55 (1.29–5.05)** | **0.008** | **2.47 (1.25–4.90)** | **0.010** | 1.84 (0.90–3.80) | 0.096 |
| | Continuous scale | 117/95358 | **1.12 (1.06–1.18)** | **< 0.001** | **1.11 (1.05–1.17)** | **0.001** | **1.07 (1.00–1.15)** | **0.046** |
| Ischemic stroke | < 21.0 | 3/24597 | **0.24 (0.06–0.84)** | **0.027** | 0.30 (0.08–1.07) | 0.062 | 0.36 (0.10–1.30) | 0.115 |
| | 21.0–22.9 | 14/26998 | Ref | | Ref | | Ref | |
| | 23.0– < 25 | 16/23176 | 1.33 (0.64–2.77) | 0.44 | 1.17 (0.56–2.44) | 0.68 | 1.01 (0.48–2.14) | 0.978 |
| | 25.0–< 27.5 | 15/14861 | 1.95 (0.92–4.11) | 0.079 | 1.69 (0.80 –3.58) | 0.17 | 1.27 (0.59–2.78) | 0.532 |
| | ≥ 27.5 | 7/5726 | 2.35 (0.93–5.96) | 0.071 | 2.34 (0.92–5.95) | 0.074 | 1.44 (0.53–3.92) | 0.461 |
| | Continuous scale | 55/95358 | **1.15 (1.09–1.23)** | **< 0.001** | **1.16 (1.08–1.25)** | **< 0.001** | **1.10 (1.00–1.21)** | **0.048** |
| Intracerebral hemorrhage | < 21.0 | 3/24597 | 0.82 (0.17–4.07) | 0.80 | 1.02 (0.19– 5.32) | 0.98 | 0.88 (0.15–5.14) | 0.868 |
| | 21.0–22.9 | 4/26998 | Ref | | Ref | | Ref | |
| | 23.0– < 25 | 10/23176 | 2.91 (0.84–10.02) | 0.087 | 2.65 (0.74–9.51) | 0.12 | 2.91 (0.74–11.48) | 0.112 |
| | ≥ 25.0 | 7/20587 | 2.29 (0.62–8.51) | 0.20 | 2.11 (0.55–8.15) | 0.26 | 2.39 (0.54–10.51) | 0.213 |
| | Continuous scale | 24/95358 | 1.09 (0.96–1.24) | 0.16 | 1.07 (0.92–1.24) | 0.34 | 1.10 (0.93–1.30) | 0.24 |

Abbreviations: BMI, body mass index; HR, hazard ratio; CVD, cardiovascular diseases; Ref, reference category; n, number of events
Model 1 includes age, sex, smoking, alcohol drinking, physical activity, and year of the survey. Model 2 includes variables in Model 1, systolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, diabetes, antihypertensive medication, and dyslipidemia medication.

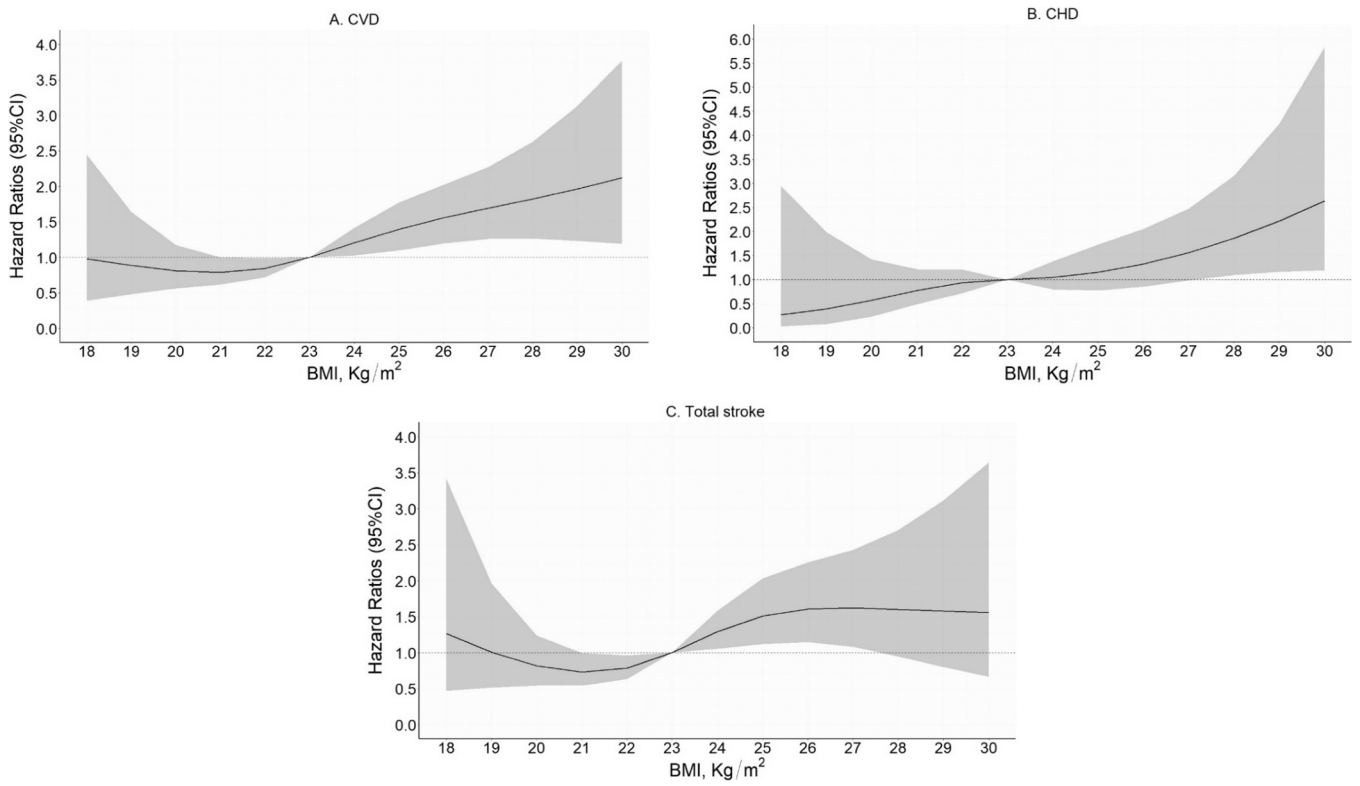


**Fig. 1.** Restricted cubic spline curve showing BMI associations with incidence of CVD, CHD, and total stroke. A, cardiovascular disease (CVD): B, coronary heart disease (CHD): C, total stroke. The solid line represents the hazard ratio of the outcome, and the gray area represents the 95% confidence interval (CI). BMI was trimmed at the 99th percentile. Models are adjusted for age, sex, smoking, alcohol drinking, physical activity, diabetes, hypertension medication, dyslipidemia medication, systolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and survey year.

**Table 3**
Changes in the coefficients of continuous BMI in the mediation analyses by hypertension, hyper-LDL-cholesterolemia, and diabetes, Aichi Workers' Cohort, 2002–2019.

| Mediator | Model 1 | Model 1 +mediator (s) | Change in coefficients | Proportion mediated | p-value |
|---|---|---|---|---|---|
| Hypertension | 0.138 | 0.116 | 0.022 | 15.9% | 0.003 |
| Hyper-LDL-cholesterolemia | | 0.130 | 0.008 | 5.8% | 0.068 |
| Diabetes | | 0.126 | 0.012 | 8.7% | 0.003 |
| All mediators | | 0.099 | 0.039 | 28.3% | 0.001 |

Model 1 includes age, sex, smoking, alcohol drinking, physical activity, year of the survey, and high-density lipoprotein cholesterol.

which reported that BMI $\geq$ 27.5 kg/m$^2$ compared to BMI $<$ 21.0 kg/m$^2$ had a 2-time higher risk of myocardial infarction in men even after adjusting for systolic blood pressure, total cholesterol, history of diabetes, and HDL-C [11]. The Swedish Annual Level of Living Survey (SALLS) study reported that BMI $\geq$ 30 – $<$ 60 kg/m$^2$ compared to BMI $\geq$ 14 – $<$ 25 kg/m$^2$ had a 1.4-time increased risk of CHD after adjusting for diabetes, hypertension, and dyslipidemia [3]. A pooled analysis of 97 prospective cohorts reported that per 5 kg/m$^2$ increase in BMI increased the risk of CHD by 15% independent of potential mediators (i.e. blood pressure, dyslipidemia, diabetes) [25].

Our findings for total and ischemic stroke, namely, continuous BMI being positively associated with the risk of total and ischemic stroke even after taking account of mediators would be consistent with the previous studies in Japan and other countries. The Hisayama Study reported a significant positive linear association between BMI and ischemic stroke in men (HR: 5.59; 95% CI: 2.09–14.91) independent of lifestyles, SBP, diabetes, total cholesterol (TC), HDL-C, triglycerides (TG) [12]. The Japan Public Health Center-based Prospective (JPHC) Study (mean BMI: 23.6 kg/m$^2$) reported a positive linear association between baseline BMI and risk of ischemic stroke across its subtypes except for large-artery occlusive stroke in men, independent of lifestyles and histories of hypertension, dyslipidemia, and diabetes mellitus [15]. The JMDC Claims Database retrospective study in Japanese population (median BMI: 23.2 in men and 21.0 kg/m$^2$ in women) reported around 15% higher risk of stroke and 20% higher risk of ischemic stroke for subjects with BMI of 25.0–29.9 kg/m$^2$ compared to BMI of 18.5–24.9 kg/m$^2$, after adjusting for lifestyle factors, hypertension, diabetes and dyslipidemia [13]. Further, a systematic review and meta-analysis reported an increased risk of total and ischemic stroke, especially in men with higher BMI [26]. The Atherosclerosis Risk in Communities (ARIC) Study from the US (median BMI: 28.0 kg/m$^2$) reported a significant positive linear association between BMI and the risks of non-lacunar and cardioembolic stroke before taking account of mediators (i.e. SBP, diabetes, HDL-C) while the association with lacunar stroke was weak even before adjusting for mediators [2]. By contrary, the EPIC Spanish cohort study (mean BMI: 28.3 kg/m$^2$) reported null association between overweight and obesity defined by BMI $>$ 30 kg/m$^2$ with the risk of total and ischemic stroke compared to BMI of (18.5–25 kg/m$^2$) after considering only lifestyle factors [9].

Unlike previous studies [27,28] we did not find an association between BMI and the risk of intracerebral hemorrhage. The lack of association might be due to the small number of intracerebral hemorrhage

**Table 4**
Hazard ratios and 95% confidence intervals for the associations of overweight/obesity with the incidence of cardiovascular disease according to the presence of hypertension, hyper-LDL-cholesterolemia, and diabetes, Aichi Workers' Cohort, 2002–2019.

| | BMI < 25 kg/m$^2$ | BMI ≥ 25 kg/m$^2$ | p-value | p for interaction |
|---|---|---|---|---|
| **Hypertension (+)** | | | | 0.71 |
| Number of cases/N | 38/1203 | 43/728 | | |
| Incidence rate | 3.3 | 6.0 | | |
| Model 1 | Ref | **1.95 (1.25–3.06)** | **0.004** | |
| Model 1 + HDLC+hypr-LDL-cholesterolemia+diabetes | Ref | **1.68 (1.06–2.66)** | **0.029** | |
| **Hypertension** (-) | | | | |
| Number of cases/N | 80/5804 | 36/1236 | | |
| Incidence rate | 1.3 | 2.7 | | |
| Model 1 | Ref | **1.88 (1.26–2.81)** | **0.002** | |
| Model 1 + HDLC+hypr-LDL-cholesterolemia+diabetes | Ref | **1.67 (1.10–2.54)** | **0.015** | |
| **Hyper-LDL-cholesterolemia (+)** | | | | 0.21 |
| Number of cases/N | 42/1905 | 46/847 | | |
| Incidence rate | 2.1 | 5.3 | | |
| Model 1 | Ref | **2.52 (1.64–3.87)** | **< 0.001** | |
| Model 1 + HDLC+hypertension+diabetes | Ref | **1.89 (1.21–2.96)** | **0.006** | |
| **Hyper-LDL-cholesterolemia (-)** | | | | |
| Number of cases/N | 75/5042 | 31/1100 | | |
| Incidence rate | 1.4 | 2.6 | | |
| Model 1 | Ref | **1.63 (1.07–2.50)** | **0.023** | |
| Model 1 + HDLC+hypertension+diabetes | Ref | 1.42 (0.91–2.22) | 0.115 | |
| **Diabetes (+)** | | | | 0.64 |
| Number of cases/N | 16/280 | 12/150 | | |
| Incidence rate | 6.3 | 9.5 | | |
| Model 1 | Ref | 1.48 (0.66–3.37) | 0.321 | |
| Model 1 + HDLC+hypertension+hyper-LDL-cholestelemia | Ref | 1.16 (0.48–2.79) | 0.725 | |
| **Diabetes (-)** | | | | |
| Number of cases/N | 102/6647 | 66/1795 | | |
| Incidence rate | 1.4 | 3.4 | | |
| Model 1 | Ref | **2.15 (1.57–2.94)** | **< 0.001** | |
| Model 1 + HDLC+hypertension+hyper-LDL-cholestelemia | Ref | **1.71 (1.23–2.39)** | **0.001** | |

Abbreviations: BMI, body mass index; HDLC, high-density lipoprotein cholesterol; N, the number of participants in each body mass index category.
Model 1 includes age, sex, smoking, alcohol drinking, physical activity, and year of the survey.

events; however, some previous studies may support our results. The Multicenter Study on Cerebral Hemorrhage in Italy reported a null association between obesity defined by BMI> 30 kg/m$^2$ with the incidence of intracerebral hemorrhage after adjusting for potential moderators [29]. The JMDC Claims Database retrospective study found that overweight (BMI 25.0–29.9 kg/m$^2$) and obesity (BMI ≥ 30 kg/m$^2$) were not associated with the risk of hemorrhagic stroke in women (13).

As is indicated by the existence of no interaction, overweight/obesity was associated with an increased risk of CVD among those with and without hypertension suggesting the vital importance of weight and blood pressure control in any circumstances. However, overweight/obesity was significantly associated with CVD risk independent of other risk factors only in subjects with hyper-LDL-cholesterolemia although the interaction was not statistically significant. This would imply the importance of weight control advice especially in clinical settings. In contrast, overweight/obesity was not associated with CVD risk in subjects with diabetes. The finding that overweight/obesity was associated with CVD risk in the hypertensive would be consistent with the Asia Cohort Consortium [30]. The Korean National Health Insurance Service cohort study also reported that general obesity was associated with the incidence of myocardial infarction and ischemic stroke among individuals with and without hypertension or dyslipidemia[31]. The finding that statistically significant association between overweight/obesity and CVD was observed only among subjects without diabetes would be consistent with the Korean National Health Insurance Service cohort study [31] but was inconsistent with a previous study that reported that diabetic individuals with overweight and obesity had an increased risk of CHD compared to those without overweight or obesity [16,32,33]. Our use of BMI instead of a measure of abdominal obesity may be related to the null finding as the Korean National Health Insurance Service cohort study reported a significant positive association between abdominal obesity (not general obesity) and CVD incidence in those with diabetes [31]. Also, the number of CVD cases in diabetic participants of our study may not be sufficient to draw a meaningful conclusion. Other reasons may be that diabetic subjects even without overweight/obesity would carry significantly increased risk of CVD. In addition, subjects with diabetes may lose weight when the condition progresses.

This study confirmed that overweight and obesity were positively and significantly associated with the risk of CVD. As Japan experienced a steady increase in the mean BMI in the last four decades, especially in men [34], there would be an urgent need to address the rising trend in mean BMI to prevent CVD [35].

The strength of this study is that BMI was not self-reported but measured in middle-aged workers from a metropolitan area in Japan. Second, we were able to explore the association of overweight and obesity with the risk of CVD in those with major metabolic risk factors separately, especially for hyper-LDL-cholesterolemia which was not reported before among middle-aged Japanese workers. This study has some limitations. First, we used a single measurement of BMI at baseline; therefore, the relationships between BMI, CHD, and stroke might be underestimated owing to random error resulting from the measurement of BMI. Second, we did not have a measure of abdominal obesity in this study. As in the Korean National Health Insurance Service cohort study, we might have obtained different results if we had used such measurements instead of BMI. Third, there was a small number of incident cases of intracerebral hemorrhage and we could not capture the effect of BMI on this outcome. Fourth, medication use at baseline was self-reported, therefore, possible under-reporting may introduce bias although we previously reported high accuracy of self-report [36].

## Conclusion

Overweight and obesity were positively and significantly associated with CVD, CHD, total stroke, and ischemic stroke. It would be important to control overweight and obesity to reduce the risk of CVD in Japanese.

## Ethical statement

Participants provided a written informed consent to use their annual health checkups data for research. The study protocol was approved by the Ethics Review Committees of Nagoya University School of Medicine (2007–0504), Japan.

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## Author agreement

All the authors have read the manuscript and agreed on the publication.

## CRediT authorship contribution statement

**Yoshihisa Nakano:** Writing – review & editing, Investigation. **Chifa Chiang:** Writing – review & editing, Investigation. **Young Jae Hong:** Writing – review & editing, Investigation. **Zean Song:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Yuanying Li:** Writing – review & editing, Investigation. **Abubakr Al-shoaibi:** Writing – original draft, Formal analysis, Data curation, Conceptualization. **Hiroshi Yatsuya:** Writing – review & editing, Supervision, Project administration, Investigation, Funding acquisition, Conceptualization. **Koji Tamakoshi:** Writing – review & editing, Supervision. **Atsuhiko Ota:** Writing – review & editing, Supervision. **Matsunaga Masaaki:** Writing – review & editing, Investigation. **Yoshihisa Hirakawa:** Writing – review & editing, Investigation.

## Declaration of Competing Interest

All authors declare no competing interests.

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## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.orcp.2024.02.006.

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