The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Original Article

J Atheroscler Thromb, 2023; 30: 335-347. http://doi.org/10.5551/jat.63415

Trends for the Association between Body Mass Index and Risk of Cardiovascular Disease among the Japanese Population: The Circulatory Risk in Communities Study (CIRCS)

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Aim: This study aimed to investigate whether the impact of body mass index (BMI) on the risk of cardiovascular disease (CVD) has changed among the 1960s, 1970s, 1980s, 1990s, and early 2000s in Japan.

Methods: The study population consisted of residents in Japan aged 40–69 years who had no history of CVD. The baseline surveys have been conducted every year since 1963. We defined the first, second, third, fourth, and fifth cohorts as 1963–1969 (n=4,248), 1970–1979 (n=6,742), 1980–1989 (n=12,789), 1990–1999 (n=12,537), and 2000–2005 (n=9,140) respectively. The participants were followed up for a median of 15 years for each cohort to determine the incidence of CVD. We classified them into four categories (BMI <21.0, 21.0–<23.0, 23.0–<25.0, and ≥ 25.0 kg/m^2).

Results: From 1963–1969 to 2000–2005, the prevalence of BMI ≥ 25.0 increased over time. Compared with BMI 23.0–<25.0, the age-, sex- and community-adjusted hazard ratios (95% confidence interval [CIs]) of CVD for BMI ≥ 25.0 were 1.10 (0.77–1.57), 0.89 (0.68–1.18), 1.03 (0.85–1.26), 1.28 (1.04–1.58), and 1.36 (1.04–1.78) in the first, second, third, fourth, and fifth cohorts, respectively. The corresponding population attributable fractions were 2.0% (nonsignificant), –2.6% (nonsignificant), 0.9% (nonsignificant), 7.6%, and 10.9%. Further adjustment for systolic blood pressure and antihypertensive medication use in the fourth and fifth cohorts attenuated the associations, which may reflect that blood pressure may mediate the BMI-CVD association.

Conclusion: The proportion of CVD attributable to overweight/obesity has increased during the periods between 1963–1969 and 2000–2005. The significant associations between overweight/obesity and risk of CVD after the 1990s were mediated by blood pressure levels.

See editorial vol. 30: 323-325

Key words: Body mass index, Cardiovascular disease, Population attributable fraction, Cohort study

Introduction

In Western countries, overweight (body mass index [BMI] ≥ 25 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) were associated with increased risk of cardiovascular disease (CVD)[1-6]. In Japan, the age-adjusted prevalence of overweight/obesity was much lower than that in Western countries, i.e., 32.6%

among men and 19.9% among women in Japan in 2019 [7], whereas that in 2017–2018 was 73.1% in the United States[8]. The impact of overweight/obesity on CVD was less attributable than hypertension, diabetes, or dyslipidemia in the Japanese population[9]. The prevalence of overweight and obesity worldwide has been increasing, especially in developing countries[10, 11]. Urbanization accompanied by rapid economic growth has caused changes in people's lifestyles, including increased fat intake and reduced physical activity[12-14], leading to the increased prevalence of overweight/obesity. The number of people that are overweight/obese worldwide is projected to increase to approximately 3.3 billion by 2030 from approximately 1.3 billion in 2005 [15]. In East Asian countries, the prevalence of overweight/obesity has increased with economic growth. In Korean men and Chinese men and women, the prevalence of overweight/obesity increased from 10.6%–24.8% in the 1990s to 32.3%–42.4% in the 2010s[16, 17]. In Japan, rapid economic growth was achieved from the 1960s to the 1980s, and the crude prevalence of overweight/obesity among men increased from 17.8% in 1980 to 33.0% in 2019, whereas among women, the prevalence was not materially changed[7, 18].

Aim

In this context, we sought to investigate whether the impact (relative and attributable risks) of BMI on the risk of CVD changed from the 1960s to 2000s in Japan, which experienced rapid economic growth.

Methods

Study Population

The study population included residents aged 40–69 years who lived in four communities of the Circulatory Risk in Communities Study (CIRCS)[19]: (community 1) Ikawa, Akita Prefecture; (community 2) Minami-Takayasu District of Yao City, Osaka Prefecture; (community 3) Noichi, Kochi Prefecture; and (community 4) Kyowa District of Chikusei City, Ibaraki Prefecture. The CIRCS is an ongoing dynamic community-based cohort study that started since 1963 [19]. According to the availability of the data, we defined the first cohort (1963–1969 for community 1, 1964–1969 for community 2, and 1969 for community 3), second cohort (1970–1979 for community 1, 1970–1974 and 1976–1979 for community 2, and 1970–1979 for community 3), third cohort (1980–1989 for communities 1–3 and 1981–1989 for community 4); fourth cohort (1990–1999 for communities 1–4); and fifth cohort (2000–2005 for communities 1–4). The numbers of persons who participated in the baseline survey in the first, second, third, fourth, and fifth cohorts were 5,001 (2,223 men and 2,778 women), 7,595 (3,099 men and 4,496 women), 14,158 (5,787 men and 8,371 women), 13,866 (5,409 men and 8,457 women), and 10,092 (3,770 men and 6,322 women), respectively. After excluding the participants with a history of heart disease or stroke, or with missing information on BMI at the baseline survey, we analyzed data from 4,248 (1,909 men and 2,339 women), 6,742 (2,754 men and 3,988 women), 12,789 (5,240 men and 7,549 women), 12,537 (4,867 men and 7,670 women), and 9,140 (3,347 men and 5,793 women) individuals, respectively.

Baseline Survey

The height (with stocking on) and weight (wearing of light clothing) were measured, and the BMI at baseline was calculated as weight (kg) divided by the square of height (m^2). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured on the right arm by trained physicians or nurses using a standard mercury sphygmomanometer employing standard epidemiological methods after the participant has rested for 5 min in the sitting position[20]. The serum total cholesterol and serum glucose levels were measured using standardized methods at the laboratory of the Osaka Center for Cancer and Cardiovascular Disease Prevention or Ibaraki Health Service Association.

We conducted a face-to-face interview to obtain information on the use of medication. Information on the history of diabetes was obtained from 1975. Diabetes mellitus was defined as a fasting serum glucose level ≥ 126 mg/dL, non-fasting serum glucose level ≥ 200 mg/dL, or the use of glucose-lowering medication.

Follow-up Survey of Incidence of Cardiovascular Disease

CVD follow-up surveys were conducted from the time of baseline survey until the end of 1980 for the first cohort, end of 1988 for the second cohort,

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Received: December 9, 2021 Accepted for publication: May 20, 2022

end of 1999 for the third cohort, end of 2007 for the fourth cohort, and end of 2019 in Ikawa, 2018 in Minami-Takayasu District, 2009 in Noichi, and 2015 in Kyowa District for the fifth cohort. The median follow-up years were 15.0, 14.7, 15.1, 15.1, and 15.1, respectively. Incident CVD was defined as first-ever stroke and coronary heart disease (CHD). Details of the CVD registration system in CIRCS were described in our previous report[19]. In brief, we extracted information on the possible cases of incident CVD from the death certificate, national health insurance claim, report by local physicians, public health nurses and community health volunteers, annual cardiovascular risk surveys, and/or household visited surveys. To confirm the epidemiological diagnosis of CVD, all suspected patients or their families were called, visited, or invited to take part in a cardiovascular risk survey to obtain a history of the incidence. In addition, we reviewed medical records at local clinics and hospitals.

Stroke was diagnosed through neurological symptoms with rapid onset and that persisted at least 24 h after onset or until death. CHD (definite myocardial infarction, possible myocardial infarction, definite angina pectoris, and sudden cardiac death) was diagnosed based on the modified World Health Organization criteria[21]. Definite myocardial infarction was diagnosed through the following two conditions: (1) typical severe chest pain that persisted for 30 min or more and (2) appearance of abnormal Q or QS wave on the electrocardiogram or consistent change in myocardial enzyme value. The patients who had a symptom of (1) but not (2) were diagnosed with possible myocardial infarction. Definite angina pectoris was diagnosed through repeated episodes of chest pain when exerting effort, especially when walking, usually disappearing rapidly after the cessation of effort or the use of sublingual nitroglycerin. Sudden cardiac death was defined as death within 1 h from onset, except for other obvious causes of death. Finally, several physician-epidemiologists determined the incidence of stroke or CHD using the same diagnostic criteria of CVD, blinded to the data from the cardiovascular risk survey.

Statistical Analysis

In the present study, we stratified the participants into four categories (<21.0, $21.0–<23.0$, $23.0–<25.0$, and ≥ 25.0 kg/m^2) and used $23.0–<25.0$ as the reference. The person-years for each individual were calculated as the follow-up period from the time at baseline survey until the occurrence of CVD, death, emigration from the community, or end of follow-up. For the CVD subtype analysis, the person-years for the people who developed both stroke and CHD during the follow-up were calculated until the occurrence of stroke if the stroke was the outcome or that of CHD if CHD was the outcome. The absolute risk (age- and sex-adjusted incidence rate/1000 person-years) was adjusted with the direct method using the STDRATE procedure (version 9.4 SAS Institute, Cary, NC, USA). The sum of person-years from cohorts 1 to 5 for each group combining age categories (40–49, 50–59, and 60–69 years) and sex was set as the reference for the direct method. Age- (years), sex-, and community-adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated according to the BMI categories using Cox proportional hazards model compared with the reference category. The population attributable fraction (PAF) was calculated using the formula: PAF = pdi × [(HR–1)/HR], where pdi denotes the proportion of the cases of each BMI category to the total cases, and HR indicates age-, sex-, and community-adjusted HR of each BMI category with 95% CI for PAF[22, 23]. To consider the effect of aging from cohorts 1 to 5 on the results, we conducted stratified analyses by age categories (40–49, 50–59, and 60–69 years).

Two approaches were applied to examine mediation on the association between overweight/obesity and risk of CVD when the association was statistically significant. First, we added serum total cholesterol (quartiles in each cohort), history of diabetes, and blood pressure (continuous SBP and antihypertensive medication use) separately to the age-, sex-, and community-adjusted HR model to determine whether the association between overweight/obesity and risk of CVD was attenuated through mediation. Second, we calculated the magnitude of mediating effect *via* traditional mediation analysis using the following formula[24]: the percentage of mediation effect = (HR with the basic model–HR with adjustment model)/(HR with the basic model–1) × 100. HR with the basic model indicates the age-, sex-, and community-adjusted HR, and HR with adjustment model added each mediator separately to the basic model.

We conducted all analyses using SAS (version 9.4 SAS Institute, Cary, NC, USA). *P* values less than 0.05 in a two-sided test were regarded as statistically significant.

The CIRCS protocol was approved by the Ethics Committee of Osaka Center for Cancer and Cardiovascular Disease Prevention, Osaka University, and University of Tsukuba.

Results

After a median of approximately 15 years of

follow-up for each cohort, the incident cases for the first, second, third, fourth, and fifth cohorts were 274 CVDs (226 strokes and 52 CHDs), 444 CVDs (351 strokes and 99 CHDs), 752 CVDs (571 strokes and 192 CHDs), 612 CVDs (451 strokes and 181 CHDs), and 338 CVDs (235 strokes and 110 CHDs), respectively.

As presented in **Table 1**, the proportions of BMI 23.0–<25.0 and ≥ 25.0 increased from cohorts 1 to 5, whereas those of BMI <21.0 and 21.0–<23.0 decreased in the same period, i.e., from 29.1% to 22.7% for <21.0, from 29.1% to 23.9% for 21.0–<23.0, from 21.0% to 24.4% for 23.0–<25.0, and from 20.7% to 29.0% for BMI ≥ 25.0. The mean SBP, DBP, serum total cholesterol, and proportion of antihypertensive medication use tended to be higher for the higher BMI categories in all cohorts. The proportion of history of diabetes tended to be higher for the higher BMI categories in cohort 5. In each BMI category, the serum total cholesterol level increased from cohorts 1 to 5.

Table 2 presents the HRs (95% CIs) and PAFs of CVD according to the BMI categories in five cohorts. Compared with the persons with BMI 23.0–<25.0, the age-, sex-, and community-adjusted HRs (95% CIs) and PAFs of CVD for BMI ≥ 25.0 increased from cohorts 1 to 5. The age-, sex-, and community-adjusted HRs (95% CIs, PAFs) of CVD for BMI ≥ 25.0 were 1.10 (0.77–1.57, 2.0% [nonsignificant]), 0.89 (0.68–1.18, –2.6% [nonsignificant]), 1.03 (0.85–1.26, 0.9% [nonsignificant]), 1.28 (1.04–1.58, 7.6%), and 1.36 (1.04–1.78, 10.9%) in cohorts 1, 2, 3, 4, and 5, respectively. Regarding the subtypes of CVD, there was an increasing trend for HRs and PAFs of stroke for BMI ≥ 25.0 **(Table 3)**. The corresponding HRs (95% CIs, PAFs) of stroke were 1.23 (0.83–1.83, 4.3% [nonsignificant]), 0.83 (0.61–1.13, –4.5% [nonsignificant]), 1.22 (0.97–1.53, 5.5% [nonsignificant]), 1.25 (0.98–1.60, 6.7% [nonsignificant]), and 1.42 (1.03–1.97, 12.6%). For CHD, the HRs for BMI ≥ 25.0 were higher in cohorts 4 and 5, but those were not statistically significant (HRs: 1.30 [95% CIs: 0.89–1.88] in cohort 4 and 1.35 [0.85–2.15] in cohort 5; **Table 4**). The HRs and PAFs of BMI ≥ 25.0 for incident CVD and stroke tended to increase from cohorts 1 to 5 in all age categories, especially among individuals aged 40–49 years. We could not calculate the HRs and PAFs of CHD among those aged 40–49 years in cohort 5 because of the small number of CHD cases **(Supplemental Tables 1, 2, 3).**

Table 5 presents the mediation effects of the selected risk factors on the associations between overweight/obesity and risks of CVD and stroke. The HRs of CVD and stroke for BMI ≥ 25.0 compared with BMI 23.0–<25.0 were almost unchanged after further adjustment for serum total cholesterol or history of diabetes. When we adjusted further for blood pressure levels (SBP and antihypertensive medication use), those associations were attenuated and no longer statistically significant. The percentage of the mediation effect of blood pressure level on overweight/obesity-CVD risk was 37% in cohort 4 and 21% in cohort 5, whereas that on overweight/obesity-stroke risk was 32% in cohort 5.

Discussion

We found that the prevalence of overweight/obesity increased and that the HRs and PAFs of BMI ≥ 25.0 kg/m^2 for total CVD, more specifically stroke, increased between the 1960s and early 2000s in the Japanese populations. Similar but nonsignificant trends were observed for CHD, particularly due to the small number of cases. The excessive risks of CVD for BMI ≥ 25.0 kg/m^2 in cohorts 4 and 5 were attenuated and no longer statistically significant after adjustment for blood pressure levels, which may reflect that blood pressure may mediate the BMI-CVD association.

We noted two reasons for the increase in the PAF of CVD for BMI ≥ 25.0 kg/m^2. First, the absolute risk of stroke in the reference group (BMI 23.0–<25.0 kg/m^2) dramatically decreased from 4.4/1000 person-years in cohort 1 to 1.5/1000 person-years in cohort 5. Our previous observation revealed that the major contributors to the reduced risk of stroke were decreased blood pressure levels, followed by increased serum cholesterol levels from very low levels, partly reflecting improved nutritional status[25, 26]. The prevalence of hypertension without overweight/obesity was much higher than that of hypertension with overweight/obesity in both men and women aged 40–69 in the 1960s[27]. Economic development contributed to a reduction in sodium intake and in extremely strenuous labor as farm work due to the use of farming machines[26]. The community-wide health screening system was established in 1982, and residents aged ≥ 40 years could receive health check-ups to prevent CVD along with universal health insurance[25]. Community-based health education also contributed to the decline in sodium intake and increased proportion of antihypertensive medication use[25, 26]. The increased saturated fat intakes caused the rise in serum total cholesterol from the very low levels (mean, 157 mg/dL in men and 163 mg/dL in women) to the moderate levels (179 mg/dL in men and 192 mg/dL in women), which might contribute in part to the decline in intraparenchymal hemorrhage

Table 1. Mean values (standard deviation) and proportions of cardiovascular risk factors at baseline according to body mass index (BMI) categories for 5 baseline periods from 1963 to 2005

	BMI (kg/m²)			
	<21.0	21.0-<23.0	23.0-<25.0	≥ 25.0
First cohort (1963-1969)				
No. at risk	1237	1238	892	881
Proportion, %	29.1	29.1	21.0	20.7
Age, years	53.2 (8.5)	51.8 (8.2)	51.6 (8.2)	52.4 (7.9)
Male, %	45.6	52.7	45.5	32.6
Systolic blood pressure, mmHg	132.7 (21.9)	135.7 (23.3)	139.7 (23.8)	142.4 (23.4)
Diastolic blood pressure, mmHg	77.9 (11.6)	79.6 (12.3)	82.8 (12.8)	84.6 (12.2)
Anti-hypertensive medication use, %	2.6	2.9	5.0	7.4
Serum total cholesterol, mg/dl	169.4 (32.6)	170.2 (33.4)	174.7 (35.3)	188.1 (39.2)
History of diabetes, %	-	-	-	-
Second cohort (1970-1979)				
No. at risk	2023	1786	1418	1515
Proportion, %	30.0	26.5	21.0	22.5
Age, years	53.1 (9.0)	51.7 (8.8)	51.3 (8.5)	51.6 (8.5)
Male, %	43.0	46.9	41.5	30.2
Systolic blood pressure, mmHg	132.2 (20.8)	135.5 (21.8)	136.4 (19.7)	140.9 (20.1)
Diastolic blood pressure, mmHg	77.9 (11.4)	80.6 (12.1)	82.2 (11.6)	85.0 (11.6)
Anti-hypertensive medication use, %	6.6	7.3	9.9	14.5
Serum total cholesterol, mg/dl	180.3 (31.7)	183.5 (32.0)	186.1 (33.2)	193.0 (34.7)
History of diabetes, %	-	-	-	-
Third cohort (1980-1989)				
No. at risk	3142	3365	3004	3278
Proportion, %	24.6	26.3	23.5	25.6
Age, years	52.8 (9.0)	51.5 (8.7)	51.7 (8.5)	52.4 (8.4)
Male, %	42.8	43.0	41.5	36.6
Systolic blood pressure, mmHg	130.1 (21.2)	133.0 (20.7)	135.9 (20.1)	140.9 (20.6)
Diastolic blood pressure, mmHg	76.6 (11.9)	79.2 (11.7)	81.7 (11.5)	85.1 (11.8)
Anti-hypertensive medication use, %	6.7	8.8	11.8	18.4
Serum total cholesterol, mg/dl	182.9 (33.2)	189.2 (34.0)	194.6 (35.4)	199.8 (36.3)
History of diabetes, %	3.9	3.7	4.6	5.8
Fourth cohort (1990-1999)				
No. at risk	2905	3220	3049	3363
Proportion, %	23.2	25.7	24.3	26.8
Age, years	52.9 (9.4)	52.9 (9.0)	53.3 (8.8)	53.8 (8.7)
Male, %	35.1	38.0	42.4	39.6
Systolic blood pressure, mmHg	128.1 (20.3)	131.0 (20.0)	135.3 (19.8)	139.6 (20.3)
Diastolic blood pressure, mmHg	76.5 (11.2)	78.9 (11.4)	81.7 (11.6)	84.9 (11.8)
Anti-hypertensive medication use, %	6.1	8.3	11.4	18.0
Serum total cholesterol, mg/dl	193.5 (34.7)	197.4 (35.0)	202.9 (35.9)	208.5 (35.8)
History of diabetes, %	3.2	2.9	4.6	6.0
Fifth cohort (2000-2005)				
No. at risk	2074	2185	2233	2648
Proportion, %	22.7	23.9	24.4	29.0
Age, years	53.9 (9.0)	55.3 (8.4)	56.2 (8.1)	56.3 (8.3)
Male, %	25.5	35.3	41.6	42.3
Systolic blood pressure, mmHg	125.4 (18.3)	130.2 (18.2)	134.9 (18.2)	138.9 (18.6)
Diastolic blood pressure, mmHg	76.4 (10.8)	79.6 (10.9)	82.3 (10.9)	85.1 (11.3)
Anti-hypertensive medication use, %	6.9	10.0	15.2	21.3
Serum total cholesterol, mg/dl	206.4 (35.8)	210.9 (36.2)	215.3 (35.8)	216.2 (35.1)
History of diabetes, %	3.7	4.9	5.9	7.0

Table 2. Hazard ratios (HRs), 95% confidence intervals (CIs) and population-attributable fractions (PAFs) for cardiovascular disease according to body mass index (BMI) categories for 5 baseline periods from 1963 to 2005

	BMI (kg/m²)			
	< 21.0	21.0 - < 23.0	23.0 - < 25.0	≥ 25.0
First cohort (1963-1969)				
Person-years	17530	17362	12570	12355
No. at risk	1237	1238	892	881
No. cases	55	97	62	60
Age- and sex-adjusted incident rate/1000 person-years	3.0	5.8	5.7	5.5
Age-, sex- and community-adjusted HR	0.59 (0.41-0.85)	1.08 (0.79-1.49)	1.00	1.10 (0.77-1.57)
PAF (%)	-13.9 (-24.2 to -4.4)	2.7 (-8.7 to 12.9)	-	2.0 (-5.9 to 9.2)
Second cohort (1970-1979)				
Person-years	28582	24856	19308	20887
No. at risk	2023	1786	1418	1515
No. cases	131	112	105	96
Age- and sex-adjusted incident rate/1000 person-years	4.4	4.6	6.2	5.7
Age-, sex- and community-adjusted HR	0.69 (0.54-0.90)	0.75 (0.58-0.98)	1.00	0.89 (0.68-1.18)
PAF (%)	-13.0 (-23.0 to -3.8)	-8.4 (-16.6 to -0.7)	-	-2.6 (-9.2 to 3.5)
Third cohort (1980-1989)				
Person-years	44860	48701	43843	48012
No. at risk	3142	3365	3004	3278
No. cases	170	178	190	214
Age- and sex-adjusted incident rate/1000 person-years	3.7	3.9	4.6	4.7
Age-, sex- and community-adjusted HR	0.80 (0.65-0.99)	0.85 (0.69-1.04)	1.00	1.03 (0.85-1.26)
PAF (%)	-5.6 (-11.0 to -0.5)	-4.3 (-9.8 to 0.8)	-	0.9 (-4.7 to 6.2)
Fourth cohort (1990-1999)				
Person-years	39078	44269	41966	45827
No. at risk	2905	3220	3049	3363
No. cases	114	136	151	211
Age- and sex-adjusted incident rate/1000 person-years	2.9	3.0	3.5	4.5
Age-, sex- and community-adjusted HR	0.83 (0.65-1.06)	0.88 (0.70-1.11)	1.00	1.28 (1.04-1.58)
PAF (%)	-3.8 (-8.9 to 1.0)	-3.0 (-8.7 to 2.4)	-	7.6 (1.1 to 13.7)
Fifth cohort (2000-2005)				
Person-years	27520	29819	30431	35493
No. at risk	2074	2185	2233	2648
No. cases	59	53	86	140
Age- and sex-adjusted incident rate/1000 person-years	2.2	1.6	2.2	3.3
Age-, sex- and community-adjusted HR	0.98 (0.70-1.36)	0.70 (0.50-0.99)	1.00	1.36 (1.04-1.78)
PAF (%)	-0.4 (-6.4 to 5.3)	-6.7 (-13.2 to -0.5)	-	10.9 (1.1 to 19.8)

PAF was calculated using age-, sex-, and community-adjusted HR.

occurrence[26]. On the other hand, the reduction of stroke incidence rate for BMI ≥ 25.0 kg/m² from cohorts 1 to 5 was smaller (from 4.7/1000 person-years to 2.4/1000 person-years) than that of the reference category. A possible reason for this finding is that an adverse impact of overweight/obesity on hypertension remained, while other factors associated with overweight/obesity such as elevated systemic inflammation[28] might increase overtime.

According to a pooled analysis of the population in East Asia (Japan, Korea, China, Taiwan, and Singapore), high BMI was a risk factor for mortality from CVD, CHD, and stroke[29]. In the Japan Public Health Center-based Prospective Study (JPHC), compared with BMI 23.0–<25.0 kg/m², men with BMI ≥ 30.0 kg/m² had 1.8 times higher risk of CHD, and women with BMI ≥ 30.0 kg/m² had 2.2 to 2.5 times higher risks of total, intraparenchymal hemorrhagic, and ischemic strokes after adjustment for history of hypertension and diabetes[30, 31]. In the Japan Arteriosclerosis Longitudinal Study (JALS) that consolidated 16 Japanese cohorts in Japan, including

Table 3. Hazard ratios (HRs), 95% confidence intervals (CIs) and population-attributable fractions (PAFs) for stroke according to body mass index (BMI) categories for 5 baseline periods from 1963 to 2005

	BMI (kg/m²)			
	<21.0	21.0 - <23.0	23.0 - <25.0	≥ 25.0
First cohort (1963-1969)				
Person-years	17567	17406	12622	12372
No. at risk	1237	1238	892	881
No. cases	46	80	48	52
Age- and sex-adjusted incident rate/1000 person-years	2.6	4.9	4.4	4.7
Age-, sex- and community-adjusted HR	0.64 (0.43-0.96)	1.15 (0.81-1.65)	1.00	1.23 (0.83-1.83)
PAF (%)	-11.4 (-22.6 to -1.2)	4.7 (-7.7 to 15.6)	-	4.3 (-4.3 to 12.2)
Second cohort (1970-1979)				
Person-years	28699	24951	19394	20993
No. at risk	2023	1786	1418	1515
No. cases	101	88	87	75
Age- and sex-adjusted incident rate/1000 person-years	3.4	3.7	5.1	4.2
Age-, sex- and community-adjusted HR	0.65 (0.49-0.87)	0.72 (0.53-0.96)	1.00	0.83 (0.61-1.13)
PAF (%)	-15.6 (-27.1 to -5.2)	-10.0 (-19.4 to -1.4)	-	-4.5 (-12.0 to 2.6)
Third cohort (1980-1989)				
Person-years	45044	48941	44131	48197
No. at risk	3142	3365	3004	3278
No. cases	127	134	133	177
Age- and sex-adjusted incident rate/1000 person-years	2.8	3.0	3.2	3.9
Age-, sex- and community-adjusted HR	0.86 (0.68-1.10)	0.91 (0.72-1.16)	1.00	1.22 (0.97-1.53)
PAF (%)	-3.6 (-9.6 to 2.1)	-2.3 (-8.4 to 3.5)	-	5.5 (-1.0 to 11.6)
Fourth cohort (1990-1999)				
Person-years	39193	44444	42175	46156
No. at risk	2905	3220	3049	3363
No. cases	92	101	108	150
Age- and sex-adjusted incident rate/1000 person-years	2.3	2.2	2.5	3.1
Age-, sex- and community-adjusted HR	0.92 (0.70-1.22)	0.91 (0.69-1.19)	1.00	1.25 (0.98-1.60)
PAF (%)	-1.7 (-7.8 to 4.0)	-2.3 (-8.9 to 3.9)	-	6.7 (-0.9 to 13.7)
Fifth cohort (2000-2005)				
Person-years	27642	29919	30580	35791
No. at risk	2074	2185	2233	2648
No. cases	45	33	57	100
Age- and sex-adjusted incident rate/1000 person-years	1.7	0.9	1.5	2.4
Age-, sex- and community-adjusted HR	1.12 (0.76-1.66)	0.66 (0.43-1.02)	1.00	1.42 (1.03-1.97)
PAF (%)	2.1 (-5.3 to 9.0)	-7.1 (-14.6 to -0.1)	-	12.6 (0.5 to 23.2)

PAF was calculated using age-, sex-, and community-adjusted HR.

CIRCS, compared with BMI <21.0 kg/m², men with BMI ≥ 27.5 kg/m² had 1.5 to 2.1 times higher risks of total CVD, total stroke, ischemic CVD, and myocardial infarction independent of SBP and serum total cholesterol[32]. In women, BMI was positively associated with the risk of total stroke after adjustment for SBP and serum total cholesterol (*P* for trend=0.021).

The HRs of CVD and stroke associated with high BMI were attenuated after adjustment for blood pressure, but not serum total cholesterol or history of diabetes. In the Women's Health Study, the multivariable HR of stroke for BMI ≥ 35.0 kg/m² compared with BMI <20.0 kg/m² was attenuated and no longer statistically significant after adjustment for history of hypertension[3]. In JALS, the excessive risks of total CVD and stroke for BMI ≥ 27.5 kg/m² compared with BMI <21.0 kg/m² were substantially attenuated after adjustment for SBP[32].

The strengths of this study are as follows: (1) sufficient follow-up period to consider the trend in BMI and the HR and PAF of incident CVD, (2) an

Table 4. Hazard ratio (HRs), 95% confidence intervals (CIs) and population-attributable fractions (PAFs) for coronary heart disease according to body mass index (BMI) categories for 5 baseline periods from 1963 to 2005

	BMI (kg/m²)			
	< 21.0	21.0 - < 23.0	23.0 - < 25.0	≥ 25.0
First cohort (1963-1969)				
Person-years	17623	17649	12747	12519
No. at risk	1237	1238	892	881
No. cases	11	18	14	9
Age- and sex-adjusted incident rate/1000 person-years	0.6	1.0	1.2	0.9
Age-, sex- and community-adjusted HR	0.51 (0.23-1.14)	0.88 (0.44-1.76)	1.00	0.75 (0.32-1.74)
PAF (%)	-20.0 (-47.1 to 2.1)	-4.9 (-34.7 to 18.3)	-	-5.9 (-24.0 to 9.6)
Second cohort (1970-1979)				
Person-years	28938	25234	19724	21184
No. at risk	2023	1786	1418	1515
No. cases	31	25	20	23
Age- and sex-adjusted incident rate/1000 person-years	1.0	0.9	1.1	1.5
Age-, sex- and community-adjusted HR	0.88 (0.50-1.55)	0.88 (0.49-1.59)	1.00	1.21 (0.66-2.21)
PAF (%)	-4.4 (-25.5 to 13.2)	-3.4 (-20.7 to 11.4)	-	4.0 (-9.6 to 15.9)
Third cohort (1980-1989)				
Person-years	45491	49446	44503	48978
No. at risk	3142	3365	3004	3278
No. cases	47	47	59	39
Age- and sex-adjusted incident rate/1000 person-years	1.0	1.0	1.4	0.9
Age-, sex- and community-adjusted HR	0.70 (0.48-1.04)	0.72 (0.49-1.05)	1.00	0.62 (0.41-0.93)
PAF (%)	-10.3 (-22.2 to 0.4)	-9.8 (-21.5 to 0.8)	-	-12.6 (-23.5 to -2.6)
Fourth cohort (1990-1999)				
Person-years	39498	44805	42569	46671
No. at risk	2905	3220	3049	3363
No. cases	28	39	48	66
Age- and sex-adjusted incident rate/1000 person-years	0.7	0.9	1.1	1.4
Age-, sex- and community-adjusted HR	0.68 (0.43-1.08)	0.82 (0.54-1.25)	1.00	1.30 (0.89-1.88)
PAF (%)	-7.3 (-16.3 to 1.0)	-4.8 (-15.3 to 4.8)	-	8.3 (-4.3 to 19.4)
Fifth cohort (2000-2005)				
Person-years	27706	30033	30752	36075
No. at risk	2074	2185	2233	2648
No. cases	15	21	29	45
Age- and sex-adjusted incident rate/1000 person-years	0.6	0.6	0.7	1.0
Age-, sex- and community-adjusted HR	0.77 (0.41-1.44)	0.84 (0.48-1.47)	1.00	1.35 (0.85-2.15)
PAF (%)	-4.1 (-14.0 to 5.0)	-3.7 (-16.0 to 7.3)	-	10.6 (-7.2 to 25.3)

PAF was calculated using age-, sex-, and community-adjusted HR.

almost-complete CVD surveillance, and (3) the use of standardized methods for physical examinations, including measurements of weight, height, and blood pressure level.

This study has several limitations. First, we used data of weight only at the baseline for each cohort, which may have caused regression dilution bias, because of temporal changes and random errors in the measurement of weight. We calculated the regression dilution rate[33] among persons who participated at both baseline and 1–5 years after the baseline surveys. The differences in the mean values of BMI between the top and bottom categories reduced from baseline to 1–5 years after baseline in all cohorts, i.e., from 7.7 to 7.2 kg/m² in cohort 1 (n=2,285), from 7.8 to 7.4 kg/m² in cohort 2 (n=4,681), from 7.8 to 7.3 kg/m² in cohort 3 (n=9,554), from 7.7 to 7.4 kg/m² in cohort 4 (n=10,281), and from 7.8 to 7.5 kg/m² in cohort 5 (n=7,538). Based on this, we estimated that the regression dilution rates were 0.93, 0.95, 0.94, 0.96, and 0.96, respectively. Therefore, the regression dilution effect-adjusted HRs should have been 4% to 8% higher

Table 5. Mediation effects of selected risk factors on the associations between overweight/obesity and risks of cardiovascular disease and stroke

	CVD			Stroke		
	BMI (kg/m²)		Percentage of mediation effect (%)	BMI (kg/m²)		Percentage of mediation effect (%)
	23.0 - <25.0	≥ 25.0		23.0 - <25.0	≥ 25.0	
Fourth cohort (1990-1999)						
Age-, sex- and area-adjusted HR	1.00	1.28 (1.04-1.58)	-	-	-	-
+ Total cholesterol	1.00	1.27 (1.03-1.56)	5	-	-	-
+ History of diabetes	1.00	1.26 (1.03-1.56)	6	-	-	-
+ Systolic blood pressure and antihypertensive medication use	1.00	1.18 (0.95-1.45)	37	-	-	-
Fifth cohort (2000-2005)						
Age-, sex- and area-adjusted HR	1.00	1.36 (1.04-1.78)	-	1.00	1.42 (1.03-1.97)	-
+ Total cholesterol	1.00	1.37 (1.05-1.79)	-3	1.00	1.44 (1.04-1.99)	-4
+ History of diabetes	1.00	1.36 (1.04-1.78)	-1	1.00	1.43 (1.03-1.97)	-1
+ Systolic blood pressure and antihypertensive medication use	1.00	1.29 (0.98-1.69)	21	1.00	1.28 (0.92-1.79)	32

CVD; cardiovascular disease, BMI; body mass index, CI; confidence interval, HR; hazard ratio.

than our study result. Second, we did not conduct sex-specific analyses due to the small sample size. Although the interaction of sex and BMI categories in relation to the incident CVD was not significant in this study, previous studies demonstrated that the association between overweight/obesity and risk of CVD was different between men and women[30-32]. In the JPHC study, the BMI–stroke association was observed only in women, and the BMI–CHD association was only noted in men. In JALS, the BMI–stroke association was observed in both men and women, and the BMI–myocardial infarction association was noted only in men.

Conclusion

In conclusion, the proportion of cardiovascular disease attributable to overweight/obesity has slightly increased between 1963–1969 and 2000–2005. The significant associations between overweight/obesity and risk of CVD after the 1990s were mediated by blood pressure levels.

Acknowledgements

The authors thank the healthcare staffs of surveyed communities, and the Osaka Center for Cancer and Cardiovascular Disease Prevention. The full list of the CIRCS Investigators are listed in Ref. 19.

Sources of Funding

This research was partly supported, by a Grant-in-Aid from the Ministry of Health, Labour and Welfare, Health and Labour Sciences Research Grants, Japan (19-FA1-008 and 20-FA1-002), and the Japan Society for the Promotion of Science (Scientific Research B [19H03901]).

Conflict of Interest

None.

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Supplemental Table 1. Hazard ratios (HRs), 95% confidence intervals (CIs), and population-attributable fractions (PAFs) of body mass index (BMI) ≥ 25.0 kg/m² versus BMI 23.0-<25.0 kg/m² for cardiovascular disease, stratified by age categories

	40-49 years			50-59 years			60-69 years		
	Total	BMI (kg/m²)		Total	BMI (kg/m²)		Total	BMI (kg/m²)	
		23.0 - <25.0	≥ 25.0		23.0 - <25.0	≥ 25.0		23.0 - <25.0	≥ 25.0
First cohort (1963-1969)									
Person-years	25672	5924	4921	20973	4120	4943	13173	2526	2491
No. at risk	1788	413	348	1474	291	346	986	188	187
No. of cases	57	12	16	93	20	22	124	30	22
Age-, sex- and area-adjusted HR	-	1.00	1.94 (0.91-4.13)	-	1.00	1.09 (0.59-2.01)	-	1.00	0.80 (0.46-1.40)
PAF	-	-	13.6 (-3.5 to 28.0)	-	-	1.9 (-12.9 to 14.8)	-	-	-4.4 (-16.1 to 6.1)
Second cohort (1970-1979)									
Person-years	41477	8962	9507	30237	6602	7078	21918	3744	4302
No. at risk	3004	661	694	2100	465	491	1638	292	330
No. of cases	79	24	12	143	33	33	222	48	51
Age-, sex- and area-adjusted HR	-	1.00	0.51 (0.25-1.01)	-	1.00	0.98 (0.60-1.59)	-	1.00	0.99 (0.67-1.47)
PAF	-	-	-14.8 (-30.3 to -1.2)	-	-	-0.5 (-12.5 to 10.2)	-	-	-0.2 (-9.8 to 8.6)
Third cohort (1980-1989)									
Person-years	80455	19633	20146	61934	14849	16810	43027	9361	11055
No. at risk	5519	1355	1354	4160	994	1134	3110	655	790
No. of cases	144	44	42	281	72	90	327	74	82
Age-, sex- and area-adjusted HR	-	1.00	0.89 (0.59-1.37)	-	1.00	1.15 (0.84-1.57)	-	1.00	0.98 (0.71-1.34)
PAF	-	-	-3.5 (-17.4 to 8.8)	-	-	4.1 (-5.7 to 12.9)	-	-	-0.6 (-8.9 to 7.1)
Fourth cohort (1990-1999)									
Person-years	65991	15989	15807	53850	13487	15721	51299	12490	14299
No. at risk	4841	1154	1169	3825	951	1132	3871	944	1062
No. of cases	82	19	38	195	50	75	335	82	98
Age-, sex- and area-adjusted HR	-	1.00	2.00 (1.15-3.47)	-	1.00	1.35 (0.94-1.93)	-	1.00	1.07 (0.80-1.44)
PAF	-	-	23.2 (3.7 to 38.7)	-	-	10.0 (-2.6 to 20.9)	-	-	1.9 (-6.7 to 9.9)
Fifth cohort (2000-2005)									
Person-years	33860	7062	8484	44668	11563	12733	44735	11806	14276
No. at risk	2430	502	621	3192	820	909	3518	911	1118
No. of cases	26	3	15	82	22	33	230	61	92
Age-, sex- and area-adjusted HR	-	1.00	4.01 (1.16-13.85)	-	1.00	1.35 (0.78-2.31)	-	1.00	1.23 (0.89-1.71)
PAF	-	-	43.3 (5.4 to 66.0)	-	-	10.3 (-10.2 to 27.0)	-	-	7.6 (-4.7 to 18.4)

PAF was calculated using age-, sex-, and community-adjusted HR.

Supplemental Table 2. Hazard ratios (HRs), 95% confidence intervals (CIs), and population-attributable fractions (PAFs) of body mass index (BMI) ≥ 25.0 kg/m² versus BMI 23.0-<25.0 kg/m² for stroke, stratified by age categories

	40-49 years			50-59 years			60-69 years		
	Total	BMI (kg/m²)		Total	BMI (kg/m²)		Total	BMI (kg/m²)	
		23.0 - <25.0	≥ 25.0		23.0 - <25.0	≥ 25.0		23.0 - <25.0	≥ 25.0
First cohort (1963-1969)									
Person-years	25701	5932	4929	21007	4123	4952	13259	2567	2491
No. at risk	1788	413	348	1474	291	346	986	188	187
No. of cases	42	9	12	82	16	20	102	23	20
Age-, sex- and area-adjusted HR	-	1.00	2.04 (0.86-4.89)	-	1.00	1.26 (0.65-2.44)	-	1.00	0.94 (0.51-1.73)
PAF	-	-	14.6 (-5.6 to 30.9)	-	-	5.0 (-10.6 to 18.3)	-	-	-1.3 (-14.5 to 10.3)
Second cohort (1970-1979)									
Person-years	41572	8981	9507	30395	6648	7134	22070	3765	4352
No. at risk	3004	661	694	2100	465	491	1638	292	330
No. of cases	61	21	10	105	23	26	185	43	39
Age-, sex- and area-adjusted HR	-	1.00	0.48 (0.22-1.02)	-	1.00	1.10 (0.63-1.94)	-	1.00	0.83 (0.53-1.28)
PAF	-	-	-18.0 (-36.7 to -1.8)	-	-	2.3 (-11.9 to 14.7)	-	-	-4.5 (-15.2 to 5.2)
Third cohort (1980-1989)									
Person-years	80711	19746	20206	62236	14929	16854	43367	9457	11137
No. at risk	5519	1355	1354	4160	994	1134	3110	655	790
No. of cases	103	28	31	220	53	80	248	52	66
Age-, sex- and area-adjusted HR	-	1.00	1.02 (0.61-1.70)	-	1.00	1.39 (0.98-1.97)	-	1.00	1.12 (0.78-1.61)
PAF	-	-	0.5 (-16.1 to 14.7)	-	-	10.3 (-1.0 to 20.2)	-	-	2.8 (-6.8 to 11.5)
Fourth cohort (1990-1999)									
Person-years	66121	16015	15878	54148	13570	15836	51699	12589	14441
No. at risk	4841	1154	1169	3825	951	1132	3871	944	1062
No. of cases	54	13	25	140	35	55	257	60	70
Age-, sex- and area-adjusted HR	-	1.00	1.89 (0.97-3.71)	-	1.00	1.36 (0.89-2.08)	-	1.00	1.04(0.73-1.46)
PAF	-	-	21.8 (-3.3 to 40.8)	-	-	10.4 (-4.8 to 23.4)	-	-	0.9 (-8.8 to 9.8)
Fifth cohort (2000-2005)									
Person-years	33908	7062	8514	44908	11633	12834	45117	11885	14444
No. at risk	2430	502	621	3192	820	909	3518	911	1118
No. of cases	19	3	11	47	11	20	169	43	69
Age-, sex- and area-adjusted HR	-	1.00	2.94 (0.82-10.54)	-	1.00	1.62 (0.77-3.37)	-	1.00	1.26 (0.86-1.85)
PAF	-	-	38.2 (-12.6 to 66.1)	-	-	16.2 (-11.4 to 37.0)	-	-	8.5 (-6.1 to 21.2)

PAF was calculated using age-, sex-, and community-adjusted HR.

Supplemental Table 3. Hazard ratios (HRs), 95% confidence intervals (CIs), and population-attributable fractions (PAFs) of body mass index (BMI) ≥ 25.0 kg/m² versus BMI 23.0-<25.0 kg/m² for coronary heart disease, stratified by age categories

	40-49 years			50-59 years			60-69 years		
	Total	BMI (kg/m²)		Total	BMI (kg/m²)		Total	BMI (kg/m²)	
		23.0 - <25.0	≥25.0		23.0 - <25.0	≥25.0		23.0 - <25.0	≥25.0
First cohort (1963-1969)									
Person-years	25804	5960	4963	21276	4184	5019	13458	2603	2537
No. at risk	1788	413	348	1474	291	346	986	188	187
No. of cases	16	3	5	11	4	2	25	7	2
Age-, sex- and area-adjusted HR	-	1.00	2.15 (0.51-9.11)	-	1.00	0.48 (0.09-2.61)	-	1.00	0.35 (0.07-1.73)
PAF	-	-	16.7 (-20.8 to 42.6)	-	-	-20.0 (-72.8 to 16.7)	-	-	-14.6 (-36.0 to 3.5)
Second cohort (1970-1979)									
Person-years	41747	9069	9558	30707	6714	7193	22627	3941	4434
No. at risk	3004	661	694	2100	465	491	1638	292	330
No. of cases	19	3	2	41	11	9	39	6	12
Age-, sex- and area-adjusted HR	-	1.00	0.72 (0.12-4.32)	-	1.00	0.82 (0.34-1.98)	-	1.00	2.14 (0.80-5.73)
PAF	-	-	-4.1 (-28.7 to 15.8)	-	-	-4.9 (-28.8 to 14.5)	-	-	16.4 (-6.6 to 34.4)
Third cohort (1980-1989)									
Person-years	80981	19775	20287	63069	15126	17246	44368	9601	11445
No. at risk	5519	1355	1354	4160	994	1134	3110	655	790
No. of cases	42	17	11	66	20	11	84	22	17
Age-, sex- and area-adjusted HR	-	1.00	0.65 (0.30-1.38)	-	1.00	0.49 (0.24-1.03)	-	1.00	0.70 (0.37-1.32)
PAF	-	-	-14.4 (-41.6 to 7.7)	-	-	-17.2 (-36.0 to -1.0)	-	-	-8.7 (-25.3 to 5.8)
Fourth cohort (1990-1999)									
Person-years	66269	16066	15937	54610	13649	16051	52664	12854	14683
No. at risk	4841	1154	1169	3825	951	1132	3871	944	1062
No. of cases	29	6	14	59	18	21	93	24	31
Age-, sex- and area-adjusted HR	-	1.00	2.33 (0.89-6.07)	-	1.00	1.10 (0.59-2.07)	-	1.00	1.18 (0.69-2.02)
PAF	-	-	27.6 (-7.4 to 51.1)	-	-	3.3 (-20.6 to 22.5)	-	-	5.2 (-12.6 to 20.1)
Fifth cohort (2000-2005)									
Person-years	34013	7077	8570	44980	11649	12860	45572	12026	14646
No. at risk	2430	502	621	3192	820	909	3518	911	1118
No. of cases	7	0	4	36	11	14	67	18	27
Age-, sex- and area-adjusted HR	-	1.00	-	-	1.00	1.13 (0.51-2.50)	-	1.00	1.31 (0.72-2.38)
PAF	-	-	-	-	-	4.6 (-29.0 to 29.4)	-	-	9.5 (-13.8 to 28.0)

PAF was calculated using age-, sex-, and community-adjusted HR.