Weight change during middle age and risk of stroke and coronary heart disease: The Japan Public Health Center–based Prospective Study

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Tables/Figures (≤5): 4 Tables/ 1 Figure

Supplementary Tables: 7

Abstract

Background and aims: The impact of weight changes in middle age on the incidence of cardiovascular disease has not been well elucidated. We investigated whether a 5-year weight change was associated with risk of stroke and coronary heart disease (CHD) in middle-aged individuals.

Methods: We analyzed data of 74,928 participants aged 40–69 years who provided responses to the baseline and 5-year follow-up questionnaires in the Japan Public Health Center–based Prospective Study. Weight change was calculated by subtracting self-reported weight at baseline from that at 5-year follow-up. Stroke and CHD events were confirmed by reviewing hospital records.

Results: During 997,406 person-years of follow-up, we documented 3,975 stroke and 914 CHD events. The multivariable HRs of stroke for losing ≥5 kg compared to stable weight (change ≤2 kg) was 1.17 (95% CI, 1.01–1.37) in men versus 1.33 (1.13-1.57) for losing ≥5 kg and 1.61 (1.36–1.92) for gaining ≥5 kg in women (U-shaped association). These associations did not change after the exclusion of early events. The multivariable HR of CHD for gaining ≥5 kg was 1.22 (0.95–1.58) in men. After exclusion of early events within another 5 years, that positive association became stronger [multivariable HR 1.34 (1.00–1.82)].

Conclusions: Weight gain during middle age was associated with an increased risk of stroke in women and an increased risk of CHD in men. Weight loss was associated with an increased risk of stroke in both men and women.

Keywords: Weight change; Stroke; Coronary heart disease; Prospective cohort study; Population study

Introduction

Although obesity is a known risk factor for cardiovascular disease (CVD) and guidelines recommend sustained weight reduction in overweight/obese individuals [1-3], the relationship between weight change during middle age and incident CVD has not been fully elucidated. Increasing efforts have been made to assess the relationship between weight change and CVD incidence. Weight change in early to middle age was reportedly associated with an increased risk of CVD [4]. Two recent studies examined the associations between short- and long-term weight change and cardiovascular health, but the results were inconsistent regarding short-term weight changes during middle age [5, 6]. Although previous findings were reported mostly in the United States, where overweight/obesity has been prevalent and continuously increases [7], previous findings may not be simply extrapolated to Asian populations because the prevalence of overweight/obesity is not so high in Asian countries including Japan compared to that in the US and European countries and their body fat distributions differ from those of Caucasians [8]. Also, the case-mix of stroke and coronary heart disease (CHD) varies according to countries [9], possibly due to the difference in ethnicities or lifestyles. In our prior study, the association of weight change during middle age with risk of incident stroke was examined in which weight gain was associated with increased risk of stroke

in women while the association was weak in men [10]. Accumulation of incident cases by the continued follow-up enabled us to examine the sex-specific associations with incident risk of CHD or subtypes of ischemic stroke. Therefore, we investigated the association of incident stroke and CHD with weight change during middle age in a large long-term population-based prospective cohort study in Japan.

Materials and Methods

Study design and population

The Japan Public Health Center-based prospective (JPHC) study comprised a population-based sample of 140,420 Japanese adults aged 40–69 years. The study design was described in detail previously [11]. In brief, this study consisted of cohorts I and II. Cohort I was started in 1990, enrolling 61,595 residents aged 40–59 years from five public health center (PHC) areas across Japan. Cohort II was established in 1993, enrolling 78,825 residents aged 40–69 years from six other PHC areas. A self-administered questionnaire mailed to all participants at baseline and every 5 years after baseline until 15 years of follow-up was achieved to obtain information regarding anthropometry; medical history; and lifestyle including smoking status, alcohol intake, and physical activity.

The JPHC Study protocol received approval from the National Cancer Center, Tokyo, Japan (approval no.: 13-021), and Osaka University, Osaka, Japan (approval no.: 2001-021). Informed consent was obtained when the participant responded to the baseline questionnaire, in which the study purpose and follow-up methods were described and explained.

Of 140,420 participants in the JPHC study, we excluded participants from two PHC areas due to the unavailability of CVD incidence data and differences in inclusion criteria (n = 23,524) as well as ineligible participants (non-Japanese nationality, emigration occurring before the start of follow-up, age missing, duplicate registration, and study refusal) (n = 252). We also excluded participants who did not respond to the baseline or 5-year follow-up questionnaires (n = 35,712), those who reported a history of CVD or any cancer at baseline or those who developed CVD or any cancer from baseline to 5-year follow-up survey (n = 2,340 for CVD, n = 1,062 for any cancer), and those who had body mass index (BMI) less than 14 kg/m^2 or ≥40 kg/m^2 at baseline or in the 5-year follow-up survey owing to possible unreliable reporting (n = 2,602). Finally, 74,928 participants (34,358 men and 40,570 women) were recruited in the study (Figure 1).

Assessment of weight changes and potential confounding factors

We used self-reported height and weight, both of which had sufficiently high validity in the JPHC study, the Spearmen correlation coefficients between the self-reported and measured BMI estimates were 0.89 in men and 0.91 in women for cohort I and 0.91 in men and 0.92 in women for cohort II [12, 13]. The mean BMIs (standard deviations) [interquartile range] were 23.5 (2.9) [21.4-25.2] for self-reported and 23.5 (3.0) [21.4-25.4] for measured ones among participants for analysis in the current study. Weight change was calculated by subtracting weight at baseline from that at the 5-year follow-up survey and was classified into the following five categories: loss ≥ 5 kg; loss 3–4 kg; stable (change ≤ 2 kg); gain 3–4 kg; and gain ≥ 5 kg.

As potential confounding factors, we also asked smoking status, alcohol intake, physical activity, and histories of dyslipidemia, hypertension and diabetes mellitus in the baseline questionnaire. Histories of dyslipidemia, hypertension, or diabetes mellitus were asked as following: 'Have the following conditions been diagnosed by physicians?' and 'Do you currently take medicines prescribed by physicians for the following diseases?', and participants chose their responses from the disease list including dyslipidemia, hypertension, diabetes mellitus and other chronic diseases.

Follow-up survey

To identify stroke and CHD incidence, all major hospitals with facilities for treating patients with acute stroke and CHD located in the study areas were registered. The medical records in the registered hospitals were reviewed regularly by physicians blinded to the baseline and follow-up survey data.

According to the National Survey of Stroke criteria [14], patients were diagnosed with stroke when participants developed apparent focal symptoms and confirmed with computed tomography scan, magnetic resonance imaging, or autopsy findings. As stroke subtypes, we classified intraparenchymal or subarachnoid hemorrhage as hemorrhagic stroke and thrombotic or embolic stroke as ischemic stroke. Thrombotic stroke was cerebral infarction at the locations of basal ganglia, brain stem, thalamus, internal capsule, cerebral white matter, or cortical areas without the evidence of embolism. Embolic stroke depended on clinical diagnosis with the presence of an embolus in the brain or hemorrhagic infarction and/or a possible source of embolus such as moderate or severe valvular heart disease, atrial fibrillation, or intracardiac thrombus. CHD was diagnosed as myocardial infarction and sudden cardiac death (death within 1 hour from event onset) according to the criteria of the MONICA project [15], which requires apparent chest pain and evidence from electrocardiograms, cardiac biomarkers,

and/or autopsy. The final diagnosis for stroke, its types and CHD was made by the consensus of an independent review board consisting three to four physician-epidemiologists.

Participants lost to follow-up were censored at the last confirmed date of their presence in the study area. Residence and survival were ascertained annually by review of private registries in the municipality. Residency and death registrations are required by law in Japan.

Statistical analysis

Person-years of follow-up for each participant was calculated from the date of the 5-year follow-up survey to the date of the first endpoint diagnosis of stroke or CHD, death, move from the study area, or end of the follow-up (end of 2009 for cohort I, end of 2012 for cohort II).

Hazard ratios (HRs) and their 95% confidence intervals (CIs) were calculated using Cox proportional hazards models. The proportional hazard assumption was confirmed by including product terms of weight change (continuous) and person-year (continuous) and was not violated for each outcome. To test for a linear or U-shaped trend across the weight change categories, we assigned median weight change values in

each category and included a continuous variable of exposure for the linear trend and squared continuous variable of exposure for the U-shaped trend. We adjusted for baseline survey values of age (continuous), BMI (continuous), PHC areas (nine total), smoking status (never smoker; former smoker; current smoker ≤19, 20–29, ≥30 cigarettes/day; or missing), hypertension (yes, no, or missing), diabetes mellitus (yes, no, or missing), dyslipidemia (yes, no, or missing), physical activity (<1 day/month, 1–3 days/month, 1–6 days/week, almost every day, or missing), and alcohol intake (non-drinker; occasional drinker; drinker of ethanol intake 1–149, 150–299, 300–499, and ≥450 g/week; or missing). Missing covariate values were adjusted for using a dummy variable. First, we adjusted for age, second, adjusted further for BMI, and then adjusted further for smoking status, physical activity, and alcohol intake, and PHC areas. The final model was adjusted further for hypertension, diabetes mellitus, and dyslipidemia. We also performed the analyses stratified by initial BMI (<25 or ≥25 kg/m^2). We tested statistical interactions for sex and BMI (<25 or ≥25 kg/m^2) by using a cross-product term. To evaluate the delayed impact of a short-term weight change, we examined the association excluding early-onset occurring 5 years from the start of the follow-up. Statistical analyses were conducted using SAS software, version 9.4 (SAS Institute, Inc., USA). For all analyses, two-sided values of $p < 0.05$ were considered to indicate

182 statistical significance.

183

184 **Results**

185 Table 1 shows age-adjusted means and proportions of baseline characteristics according
186 to weight change category. The range of weight change was -35 to 44 kg for men and -
187 39 to 35 kg for women. Weight change was inversely associated with age, initial BMI,
188 prevalence of hypertension, and diabetes mellitus in both men and women. In men,
189 heavy alcohol drinkers were more likely to lose weight. The characteristics of
190 participants for analysis were similar to those in baseline survey (Supplementary Table
191 S1).

192 During 997,406 person-years of follow-up, we documented 914 CHD events
193 (655 men, 259 women) and 3,975 strokes (2,278 men, 1,697 women), including 2,445
194 ischemic strokes (1,503 men, 942 women) and 1,511 hemorrhagic strokes (764 men,
195 747 women). The cases of subtypes of ischemic and hemorrhagic stroke were 1,911
196 thrombotic strokes (1,156 men, 755 women), 534 embolic strokes (347 men, 187
197 women), 1,080 intraparenchymal hemorrhages (623 men, 457women) and 431
198 subarachnoid hemorrhages (141 men, 290 women).

199 Table 2 shows the HRs for incident stroke according to weight change over the

5 years compared with stable weight (≤2 kg). Among men, a weight loss of ≥5 kg was associated with a higher risk of total stroke: the multivariable HR of total stroke was 1.17 (95% CI, 1.01–1.37) for losing ≥5 kg weight. The excess risks of stroke subtypes associated with weight loss of ≥5 kg were similarly observed, but the associations did not reach statistical significance, probably due to an insufficient sample size (Table 3 and Supplementary Table S2). Among women, weight change and the risks of total stroke and its subtypes had a U-shaped association (Tables 2 and 3), and that association was stronger for ischemic stroke (either thrombotic or embolic stroke) than for hemorrhagic stroke (either intraparenchymal or subarachnoid hemorrhage) (Tables 3 and Supplementary Table S2). After the exclusion of early events, though the results were based on smaller number of events, the association between weight change and risks of total stroke and its subtypes did not change substantially in both men and women (Supplementary Table S3). The U-shaped association for total stroke was also observed in BMI-adjusted and BMI-specific incidence rates (Supplementary Table S4).

Table 4 shows the HRs for incident CHD according to weight change over the 5 years compared with stable weight (≤2 kg). The age-adjusted HR of CHD was higher for a weight gain of ≥5 kg in men, but that association was no longer statistical significance after adjustment for potential confounding factors. After excluding early

events occurring within 5 years of follow-up, the HR of CHD for weight gain of ≥5 kg became pronounced and statistically significant in men [multivariable HR 1.34 (95% CI, 1.00–1.82), $p<0.05$]. In women, weight change was not associated with risk of CHD (Supplementary Table S3).

When we performed the analyses stratified by initial BMI (<25 or ≥25 kg/m^2), the results were similar to those of the main analyses of the outcomes (Supplementary Tables S5 and S6).

When we altered the exposure from weight change to BMI change, we observed similar results (Supplementary Table S7).

Discussion

This study addressed the prospective association of body weight change during middle age with CVD outcomes in the general population. In this large prospective cohort study, a U-shaped association of weight change during middle age and incident stroke was observed in women. In men, weight loss ≥ 5 kg was associated with an increased risk of stroke. Weight gain of ≥ 5 kg was associated with an increased risk of CHD in men after the exclusion of early events.

The association between weight change and subsequent risk of total CVD was examined in several previous studies, which reported a U-shaped association [16, 17].

237 However, limited studies separately examined the associations of weight change with
238 stroke [6, 10] and CHD [6, 13, 18, 19]. Regarding stroke risk, long-term weight gain
239 since young to middle adulthood was positively associated [6, 20, 21], but the
240 association with short-term weight change in middle age was inconsistent. In the
241 Atherosclerosis Risk In Communities (ARIC) study, among 15,792 US men and women
242 aged 45–64 years with mean BMI 27.6 kg/m^2, the association with weight gain (≥10%)
243 over 3 years was not positive (HR 0.75, 95% CI 0.39–1.43), while weight loss (≥3%)
244 was associated with an increased risk (HR 1.45, 1.10–1.92) compared to weight
245 maintenance (≤3%) during 3-year follow-up [6]. In the Singaporean Chinese Health
246 Study (SCHS), however, among 36,338 Singaporean Chinese men and women aged 45–
247 74 years with mean BMI 23.0 kg/m^2, both weight gain (≥10%) and weight loss (≥10%)
248 over a mean period of 5.7 years were associated with an increased risk of stroke (HR
249 1.25, 0.98–1.60 and 1.35, 1.07–1.69, respectively) compared to stable weight (≤5%)
250 during a mean follow-up period of 14.2 years [22]. In previous JPHC report with a
251 median follow-up of 7.9 years, weight gain was associated with an increased risk of
252 stroke in women [10]. While the reason for the elevated risk of stroke among the weight
253 loss group is unclear, weight loss due to underlying diseases or sarcopenia has been
254 discussed as being among these reasons [23]. In this study, age, BMI, and the

255 prevalence of hypertension and diabetes mellitus were higher in the weight loss of ≥5 kg
256 group than in the stable weight group. The possible confounding by some underlying
257 diseases or sarcopenia cannot be excluded.

258 Regarding CHD outcome, long-term weight gain since early life (5 years) or
259 young adulthood (18–25 years) to middle adulthood was associated with a higher risk
260 [6, 19, 20] and prior JPHC report also observed similar results in men [13], but the
261 associations for short-term weight gain during middle age were inconclusive among
262 previous studies. Among 6,445 British men aged 40–59 years with mean BMI 25.6
263 kg/m^2 without a history of CHD, the relative risk of heart attack for weight gain (>10%)
264 over a 5-year period compared to that for stable weight (≤4%) was 1.45 (0.97–2.13)
265 over a 6.5-year follow-up [18]. In the Honolulu Heart Program (HHP), however, among
266 6,176 Japanese-American men with a mean age of 54 years and mean BMI 22.0 kg/m^2,
267 weight gain (>2.5 kg) over a mean period of 6.1 years compared to stable weight (≤1
268 kg) was not associated with risk of CHD (relative risk 1.10, 0.84–1.46) during a
269 maximum follow-up period of 17 years [19]. In the SCHS, the HR of CHD was 1.11
270 (0.93-1.34) for weight gain (≥10%) [22]. In the ARIC study, weight gain (≥10%) was
271 not associated with risk of CHD (HR 1.06, 0.70–1.61) [6]. In the present study, the
272 association for weight gain became pronounced when we excluded the event within the

first five years, supporting that the adverse effect of weight gain may be apparent with some delay. In the ARIC study, the positive association for weight gain was relatively weak among previous studies because the 3-year follow-up may be too short to observe the adverse effect [6]. Regarding weight loss, the positive association was observed in the SCHS, in which the HR of CHD was 1.23 (1.04–1.45) for weight loss (≥10%) [22]. Similarly, in the ARIC, weight loss (≥3%) was associated with an elevated CHD risk (HR 1.46, 1.18–1.81) [6]. In the British study, the relative risk of heart attack for weight loss (>10%) was 1.79 (0.98–3.25) [18]. In the HHP, weight loss (>2.5 kg) was not associated with risk of CHD (relative risk 1.25, 0.98–1.60) [19]. The lack of association for weight loss in our study might be due to differences in BMI distributions and the CVD outcomes (either mortality or incidence). The mean BMI was higher in ARIC (27.6 kg/m^2) and British (25.6 kg/m^2) compared to other studies (22.0-23.5 kg/m^2). The outcome in SCHC was mortality, while that in other studies was incidence. To confirm the impact of weight change in middle age on stroke and CHD, further researches, especially randomized controlled trials, are needed.

In this study, weight gain was associated with an increased risk of CHD only in men. Even at similar BMI, men had a larger visceral fat area and a smaller subcutaneous fat area than women [24]. Estrogen exerts cardiovascular protective effects through

291 altering serum lipid concentrations and improving endothelial function in the coronary
292 artery [25].

293 The major strengths of our study are its prospective design, long follow-up
294 period, and large sample size representative of the general population. However, the
295 present study has several potential limitations. First, we used self-reported height and
296 weight values, and we cannot eliminate a possibility of misclassification due to
297 reporting errors. However, the validity of BMI calculated from self-reported height and
298 weight was confirmed in the present study. Second, we did not assess measures of
299 adiposity other than BMI, such as waist-to-hip ratio; hence, we do not know whether the
300 weight changes were due to changes in lean mass or fat mass. Third, the change in risk
301 factors over time were not considered and a surrogate measure (i.e., weight change) may
302 not sufficiently capture the exposure to underlying risk profiles. Fourth, due to the
303 observational study design, causality between weight changes and the risk of CVD
304 cannot be adequately addressed, partly due to residual confounding. Finally, our cohort
305 comprises Japanese individuals, thus limiting the generalizability of our findings to
306 other ethnicities.

307 In this large long-term prospective cohort study, weight gain during middle age
308 was associated with an increased risk of stroke in women, and with an increased risk of

CHD in men, while weight loss was associated with an increased risk of stroke in both men and women. Our findings suggest that a weight change during middle age – either gain and loss – may be a clinical clue of an increased risk of CVD.

Conflict of interest

KK is an employee of Takeda Pharmaceutical Co. Ltd. The authors declare no conflict of interest with respect to this research study and paper.

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Author contributions

KK conceived the idea for the study. KK, IM and HI designed the work. All authors acquired data and played an important role in interpreting the results. KK and IM analyzed the data. KK drafted the manuscript. IM, KY, YK, IS, HY, NS, HI and ST critically revised the manuscript. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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Figure Legends

Figure 1. Flowchart of Cohort Selection

Table 1. Age-adjusted means and proportions of baseline characteristics according to weight change over 5 years

	Weight change over 5 years					
	Loss of ≥5 kg	Loss of 3-4 kg	Stable (≤2 kg)	Gain 3-4 kg	Gain ≥5 kg	*p* for trend[a]
Men						
Number	3196	3173	20936	3620	3433	
Age, years	53.6	53.2	52.1	50.9	51.0	<0.001
BMI, kg/m^2	25.2	24.1	23.3	23.2	22.9	<0.001
BMI at 5-year survey, kg/m^2	22.3	22.9	23.3	24.5	25.6	<0.001
Weight, kg	67.8	64.9	62.5	62.8	62.0	<0.001
Weight at 5-year survey, kg	60.3	61.5	62.5	66.1	69.3	<0.001
Current smokers, %	52.8	51.9	49.9	50.8	55.8	0.81

Alcohol intake ≥300 g/week, %	31.6	30.9	31.4	29.4	28.2	<0.001
Sports ≥1 day/week, %	17.6	18.7	18.6	18.6	17.9	0.47
Hypertension, %	22.0	22.6	18.0	16.6	16.5	<0.001
Diabetes mellitus, %	9.6	9.0	5.4	5.6	5.6	<0.001
Dyslipidemia, %	1.7	1.5	1.4	1.1	0.8	0.004
Women						
Number	3147	3590	26596	4324	2913	
Age, years	54.9	54.3	52.5	50.7	51.2	<0.001
BMI, kg/m^2	25.6	24.1	23.3	23.1	23.1	<0.001
BMI at 5-year survey, kg/m^2	22.2	22.6	23.3	24.5	26.1	<0.001
Weight, kg	58.7	55.6	53.6	53.4	53.5	<0.001

Weight at 5-year survey, kg	51.2	52.2	53.6	56.7	60.6	<0.001
Current smokers, %	6.4	5.3	4.4	4.5	6.7	0.03
Alcohol intake ≥300 g/week, %	0.8	1.0	0.9	0.9	1.1	0.85
Sports ≥1 day/week, %	16.7	17.2	17	16.2	15.4	0.82
Hypertension, %	24.2	20.6	16.6	15	17.3	<0.001
Diabetes mellitus, %	5.1	4.4	2.4	2.3	3.2	<0.001
Dyslipidemia, %	2.1	2.7	2.1	1.9	2.3	0.24

[a] Linear regression for continuous variables and logistic regression for categorical variables.

BMI, body mass index

438 Table 2. Sex-specific age-adjusted and multivariable HRs and 95% CIs of total stroke according to weight change over 5 years

	Weight change over 5 years						
	Loss of ≥5 kg	Loss of 3-4 kg	Stable (≤2 kg)	Gain 3-4 kg	Gain ≥5 kg	*p* for linear	*p* for quadratic
Men							
No. at risk	3196	3173	20936	3620	3433		
Person-years	38365	39953	273128	47259	44170		
No. of cases	270	235	1356	203	214		
Incidence per 10,000 person-year	70.4	58.8	49.6	43.0	48.4		
Age-adjusted HR	1.30 (1.13-1.50)	1.06 (0.91-1.23)	Reference	0.95 (0.82-1.17)	1.01 (0.86-1.17)	0.003	0.02

Age and BMI-adjusted HR	1.21 (1.08-1.43)	1.03 (0.89-1.20)	Reference	0.95 (0.81-1.11)	1.02 (0.87-1.19)	0.03	0.04
Multivariable HR[a]	1.19 (1.04-1.38)	1.03 (0.89-1.20)	Reference	0.96 (0.83-1.12)	1.00 (0.86-1.17)	0.05	0.11
Multivariable HR[b]	1.17 (1.01-1.37)	1.00 (0.86-1.16)	Reference	0.96 (0.82-1.12)	0.99 (0.85-1.15)	0.08	0.20
Women							
No. at risk	3147	3590	26596	4324	2913		
Person-years	40854	48035	367181	59336	39125		
No. of cases	203	190	981	154	169		
Incidence per 10,000 person-year	49.7	39.6	26.7	26.0	43.2		
Age-adjusted HR	1.54 (1.31-1.80)	1.30 (1.11-1.53)	Reference	1.12 (0.94-1.33)	1.69 (1.42-2.01)	0.58	<0.001
Age and BMI-adjusted HR	1.38 (1.17-1.62)	1.25 (1.07-1.47)	Reference	1.13 (0.95-1.35)	1.71 (1.44-2.04)	0.51	<0.001

Multivariable HR[a]	1.35 (1.15-1.60)	1.26 (1.07-1.48)	Reference	1.12 (0.94-1.33)	1.67 (1.41-1.99)	0.56	<0.001
Multivariable HR[b]	1.33 (1.13-1.57)	1.26 (1.07-1.48)	Reference	1.11 (0.93-1.32)	1.61 (1.36-1.92)	0.64	<0.001
p for sex interaction			<0.001				

[a] Adjusted further for smoking status, physical activity, alcohol intake, and public health center areas.

[b] Adjusted further for hypertension, diabetes mellitus, and dyslipidemia.

CI, confidence interval; HR, hazard ratio

445 Table 3. Sex-specific age-adjusted and multivariable HRs and 95% CIs of ischemic and hemorrhagic strokes according to weight change

446 over 5 years

	Weight change over 5 years						
	Loss of ≥5 kg	Loss of 3-4 kg	Stable (≤2 kg)	Gain 3-4 kg	Gain ≥5 kg	*p* for linear	*p* for quadratic
Men							
No. at risk	3196	3173	20936	3620	3433		
Person-years	38365	39953	273128	47259	44170		
Ischemic stroke							
No. of cases	185	158	889	141	130		

Incidence per 10,000 person-year	48.2	39.5	32.5	29.8	29.4		
Age-adjusted HR	1.34 (1.13-1.58)	1.05 (0.87-1.25)	Reference	1.03 (0.85-1.23)	0.95 (0.78-1.16)	0.01	0.07
Age and BMI-adjusted HR	1.26 (1.06-1.49)	1.01 (0.85-1.22)	Reference	1.03 (0.86-1.24)	0.97 (0.80-1.18)	0.06	0.14
Multivariable HR[a]	1.20 (1.01-1.43)	1.00 (0.84-1.21)	Reference	1.04 (0.86-1.24)	0.95 (0.78-1.16)	0.10	0.31
Multivariable HR[b]	1.17 (0.98-1.39)	0.97 (0.80-1.16)	Reference	1.03 (0.86-1.24)	0.93 (0.77-1.14)	0.16	0.49
Hemorrhagic stroke							
No. of cases	82	77	461	62	82		
Incidence per 10,000 person-year	21.4	19.3	16.9	13.1	18.6		
Age-adjusted HR	1.20 (0.94-1.54)	1.10 (0.85-1.41)	Reference	0.82 (0.62-1.08)	1.09 (0.85-1.40)	0.22	0.16

Age and BMI-adjusted HR	1.18 (0.92-1.52)	1.09 (0.84-1.40)	Reference	0.82 (0.62-1.08)	1.10 (0.86-1.41)	0.29	0.19
Multivariable HR[a]	1.15 (0.89-1.48)	1.10 (0.85-1.41)	Reference	0.83 (0.63-1.09)	1.09 (0.85-1.40)	0.35	0.25
Multivariable HR[b]	1.14 (0.89-1.47)	1.08 (0.84-1.39)	Reference	0.83 (0.63-1.09)	1.09 (0.84-1.39)	0.37	0.28
Women							
No. at risk	3147	3590	26596	4324	2913		
Person-years	40854	48035	367181	59336	39125		
Ischemic stroke							
No. of cases	123	114	527	81	97		
Incidence per 10,000 person-year	30.1	23.7	14.4	13.7	24.8		
Age-adjusted HR	1.71 (1.39-2.11)	1.40 (1.14-1.73)	Reference	1.16 (0.92-1.47)	1.91 (1.52-2.39)	0.46	<0.001

Age and BMI-adjusted HR	1.48 (1.20-1.83)	1.34 (1.08-1.65)	Reference	1.18 (0.93-1.49)	1.95 (1.56-2.45)	0.60	<0.001
Multivariable HR[a]	1.45 (1.17-1.79)	1.34 (1.08-1.65)	Reference	1.17 (0.92-1.48)	1.94 (1.55-2.44)	0.55	<0.001
Multivariable HR[b]	1.42 (1.15-1.75)	1.33 (1.07-1.64)	Reference	1.16 (0.91-1.46)	1.84 (1.47-2.32)	0.61	<0.001
p for sex interaction			<0.001				
Hemorrhagic stroke							
No. of cases	79	76	451	71	70		
Incidence per 10,000 person-year	19.3	15.8	12.3	12.0	17.9		
Age-adjusted HR	1.31 (1.01-1.69)	1.18 (0.92-1.52)	Reference	1.04 (0.81-1.35)	1.40 (1.07-1.84)	0.84	0.003
Age and BMI-adjusted HR	1.23 (0.95-1.60)	1.16 (0.90-1.49)	Reference	1.05 (0.81-1.36)	1.41 (1.07-1.85)	0.82	0.01
Multivariable HR[a]	1.21 (0.93-1.58)	1.18 (0.91-1.51)	Reference	1.03 (0.80-1.34)	1.35 (1.02-1.77)	0.98	0.02

Multivariable HR[b]	1.20 (0.92-1.57)	1.18 (0.91-1.52)	Reference	1.03 (0.79-1.34)	1.31 (1.00-1.73)	0.97	0.03
p for sex interaction			<0.001				

[a] Adjusted further for smoking status, physical activity, and alcohol intake, and public health center areas.

[b] Adjusted further for hypertension, diabetes mellitus, and dyslipidemia.

CI, confidence interval; HR, hazard ratio

453 Table 4. Sex-specific age-adjusted and multivariable HRs and 95% CIs of CHD according to weight change over 5 years

	Weight change over 5 years						
	Loss of ≥5 kg	Loss of 3-4 kg	Stable (≤2 kg)	Gain 3-4 kg	Gain ≥5 kg	*p* for linear	*p* for quadratic
Men							
No. at risk	3196	3173	20936	3620	3433		
Person-years	38365	39953	273128	47259	44170		
No. of cases	62	79	373	68	73		
Incidence per 10,000 person-year	16.2	19.8	13.7	14.4	16.5		
Age-adjusted HR	1.07 (0.81-1.42)	1.34 (1.05-1.73)	Reference	1.18 (0.91-1.53)	1.34 (1.04-1.73)	0.41	0.07

Age and BMI-adjusted HR	0.97 (0.73-1.29)	1.28 (0.99-1.64)	Reference	1.18 (0.91-1.54)	1.38 (1.07-1.77)	0.11	0.15
Multivariable HR[a]	0.88 (0.66-1.18)	1.24 (0.97-1.60)	Reference	1.14 (0.88-1.48)	1.20 (0.96-1.60)	0.14	0.64
Multivariable HR[b]	0.87 (0.65-1.16)	1.20 (0.93-1.55)	Reference	1.13 (0.87-1.46)	1.22 (0.95-1.58)	0.13	0.76
Women							
No. at risk	3147	3590	26596	4324	2913		
Person-years	40854	48035	367181	59336	39125		
No. of cases	29	27	163	24	16		
Incidence per 10,000 person-year	7.1	5.6	4.4	4.0	4.1		
Age-adjusted HR	1.33 (0.89-1.99)	1.10 (0.73-1.66)	Reference	1.06 (0.69-1.65)	1.09 (0.65-1.83)	0.41	0.27
Age and BMI-adjusted HR	1.20 (0.80-1.82)	1,07 (0.71-1.61)	Reference	1.06 (0.69-1.66)	1.11 (0.66-1.86)	0.72	0.39

Multivariable HR[a]	1.15 (0.76-1.74)	1.04 (0.69-1.57)	Reference	1.07 (0.69-1.66)	1.09 (0.64-1.84)	0.82	0.49
Multivariable HR[b]	1.10 (0.72-1.66)	1.00 (0.67-1.51)	Reference	1.03 (0.67-1.60)	0.99 (0.59-1.66)	0.78	0.80
p for sex interaction			0.66				

[a] Adjusted further for smoking status, physical activity, and alcohol intake, and public health center areas.

[b] Adjusted further for hypertension, diabetes mellitus, and dyslipidemia.

CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio