Table 2 Association of food taste with weight increase in the past, JPHC Study

	Men				*Women*			
	Dislike	*Neither dislike nor like*	*Like*	*Trend P*	*Dislike*	*Neither dislike nor like*	*Like*	*Trend P*
Rich and heavy taste								
No. of participants	2880	7066	3497		3638	8812	3210	
⩾5 kg increase between 20 years old and baseline								
No. of participants	1375	3801	2123		1999	5189	2027	
Area- and age-adjusted OR (95% CI)	1 (Reference)	1.16 (1.06–1.26)	1.45 (1.31–1.60)	<0.001	1 (Reference)	1.12 (1.04–1.21)	1.28 (1.16–1.41)	<0.001
Fully adjusted OR (95% CI)[a]	1 (Reference)	1.13 (1.04–1.24)	1.45 (1.31–1.61)	<0.001	1 (Reference)	1.11 (1.03–1.21)	1.28 (1.16–1.41)	<0.001
Sweet taste								
No. of participants	3304	6715	3424		1758	8069	5833	
⩾5 kg increase between 20 years old and baseline								
No.	1755	3633	1911		981	4665	3569	
Area- and age-adjusted OR (95% CI)	1 (Reference)	1.04 (0.95–1.13)	1.07 (0.97–1.18)	0.18	1 (Reference)	1.09 (0.98–1.21)	1.24 (1.11–1.38)	<0.001
Fully adjusted OR (95% CI)[a]	1 (Reference)	0.99 (0.90–1.07)	1.00 (0.91–1.11)	0.93	1 (Reference)	1.08 (0.97–1.20)	1.22 (1.09–1.36)	<0.001

Abbreviations: CI, confidence interval; OR, odds ratio. [a]Adjusted for age, study area (Okinawa or other), smoking (never, former or current) and exercise (<1 per week or ⩾1 per week) at baseline.

(1.09–1.36) for women. Among men, there was no difference in odds ratios according to the taste preference for sweets. These associations were fundamentally unchanged after further adjustment for energy intake and, for rich and heavy taste, fat energy ratio (data not shown). In addition, a stratified analysis revealed no measurable difference in results according to age group (data not shown).

Body weight changes during the period from the baseline to the 10-year survey in relation to taste preferences are presented in Table 3. There were significant differences in body weight change in association with the preference for sweet tastes; the age-, area- and body weight-adjusted means (s.e.) of body weight changes for the 'dislike', 'neither' and 'like' groups were −0.05 (0.08), 0.26 (0.05) and 0.34 (0.07) kg in men, and 0.08 (0.09), 0.23 (0.04) and 0.24 (0.05) kg in women, respectively. These relationships were materially unchanged in a fully adjusted model and after further adjustment for energy intake or fat energy ratio (data not shown). In a stratified analysis by age, the association with sweet taste preference was evident in the age of 40s, but it was less clear in the age of 50s (data not shown). In contrast, there were no significant differences in weight change in relation to the rich and heavy taste preference.

Discussion

Using data from a large-scale cohort study of Japanese subjects, we analyzed the relationships between taste preferences and changes in body weight during adulthood. There was a significant positive association between weight increase from age 20 years to middle age, and a preference for rich and heavy taste in both men and women, and for a sweet taste preference only in women. A significant difference in weight increase after 10 years from middle age was observed between the 'dislike' and the 'neither' or 'like' groups, for the sweet but not the rich and heavy taste preference.

Our search of the literature yielded no reports on the relation between rich and heavy taste and changes in body weight. Therefore, we discuss these findings regarding the rich and heavy taste preference by comparing our results with those for a preference of fat-rich food, because foods described as having a rich and heavy taste are often cooked with a large amount of oil, fat and seasoning. Several cross-sectional studies have examined the relationship between a fatty taste preference and BMI or body weight; the preference for fat has been shown to be associated with levels of adiposity in primarily normal weight[16,21] and in almost overweight or obesity,[12,22] and also in dietary restraint[23] and/or disinhibition.[24] Consistent with these reports, we observed a clearly increasing BMI trend in relation to the rich and heavy taste preference at baseline. Only one longitudinal study to date has investigated the longitudinal relationship between fat preference and changes in BMI.[16]

Table 3 Changes in body weight during the 10-year follow-up period

	Men				*Women*			
	Dislike	*Neither dislike nor like*	*Like*	*Trend P*	*Dislike*	*Neither dislike nor like*	*Like*	*Trend P*
Rich and heavy taste								
No. of participants	2880	7066	3497		3638	8812	3210	
Changes in body weight for 10 years (kg)[a]	0.11 (0.08)	0.27 (0.05)	0.15 (0.07)	0.873	0.17 (0.06)	0.27 (0.04)	0.13 (0.07)	0.762
Changes in body weight for 10 years (kg)[b]	0.11 (0.08)	0.27 (0.05)	0.15 (0.07)	0.864	0.17 (0.06)	0.26 (0.04)	0.14 (0.07)	0.766
Sweet taste								
No. of participants	3304	6715	3424		1758	8069	5833	
Changes in body weight for 10 years (kg)[a]	−0.05 (0.08)	0.26* (0.05)	0.34* (0.07)	<0.001	0.08 (0.09)	0.23* (0.04)	0.24* (0.05)	0.218
Changes in body weight for 10 years (kg)[b]	−0.04 (0.08)	0.26* (0.05)	0.33* (0.07)	<0.001	0.10 (0.09)	0.23* (0.04)	0.24* (0.05)	0.307

[a]Adjusted for age, study area (Okinawa or other) and body weight at baseline. [b]Adjusted for age, study area (Okinawa or other), body weight, smoking (never, former or current) and exercise (< 1 per week or ⩾ 1 per week) at baseline. Values except for numbers are means (s.e.). *P-value < 0.01 (compared with dislike).

However, that study failed to detect 3-year changes in BMI and waist circumference among fat preference groups in either men or women, a finding compatible with our results for the 10-year follow-up period.

Contrary to the null association with the rich and heavy taste preference during the follow-up period, this preference was significantly associated with an increased odds ratio of a large weight increase (more than 5 kg) from age 20 years to the baseline survey. This may be ascribed to age differences in fat intake. According to the National Nutrition Survey in Japan,[25] the fat energy ratio is nearly 30% in the 20s but it decreases with advancing age in both men and women. Younger adults who like the rich and heavy taste are more likely to consume large amounts of fatty foods than their middle-aged or older counterparts. Therefore, the gap in the fat energy ratio among rich and heavy taste preference groups narrows with increasing age.

Another study identified a positive correlation between the hedonic response to a sweet solution measured at baseline and after weight gain.[26] In our study, the preference for the sweet taste was associated with weight gain during the period from age 20 years to the baseline survey in women, but not in men, although the sweet preference was associated with weight gain during the period from the baseline to the 10-year survey in both men and women. According to the National Nutrition Survey in Japan,[25] men 30–69 years of age consume much smaller amounts of snacks than women of comparable ages. This may be one reason for the lack of an association between the sweet taste preference and weight gain from age 20 years until middle age in men.

In our study, fat intake and the fat energy ratio did not differ greatly, according to rich and heavy taste preference at baseline, although the frequency of eating oily foods was higher among people who liked the rich and heavy taste than among those who did not. People who tend to underreport dietary intake are more likely to be obese.[27] In our study, people who liked the rich and heavy taste tended to have a greater weight than those who did not, and thus probably underreported their intake of fat when they answered the dietary questionnaire. Alternatively, a food frequency questionnaire cannot capture detailed intakes of foods, especially the intakes of fat, oil and sugar that are added during preparing or having a meal. In this respect, taste preferences may provide complementary information. Preference measures are less cognitively demanding;[12,28] the questions are relatively easy to answer, and might be less biased by cognitive control on reporting dietary intake (that is, dietary restraint). Food preference assessment appeals to people who respond to health screening, because it requires minimal concentration and cognitive processing.[12]

Our study has several strengths. First, we examined the relationships between two taste preferences and weight change using a longitudinal design. Second, the number of the subjects of our study was large, with approximately 30 000 subjects being followed. Third, we controlled for lifestyle factors including diet, exercise and smoking that

may confound the taste preference–weight change association. Our study also has a few limitations. First, the taste preference was determined only at the time of the baseline survey. However, we believe that taste preferences would not change greatly during adulthood. Second, height and weight were not measured, instead being self-reported. However, the BMI based on self-reported data was previously shown to be highly correlated with the measured BMI.[17] Third, weight change from age 20 years to the baseline survey was based on recall at baseline.

In conclusion, this study of a Japanese population showed a preference for the rich and heavy taste to be associated with weight gain between the age of 20 years and middle age in both men and women, and that the preference for a sweet taste was a predictor of weight gain among adult women and middle-aged or older men. A population approach to weight control is advocated, according to the taste preference for rich and heavy taste in subjects in their 20s or younger for both sexes, and for the sweet taste after middle age for women.

Conflict of interest

The authors declare no conflict of interest.

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Appendix

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ARTICLE

Calcium, vitamin D and dairy intake in relation to type 2 diabetes risk in a Japanese cohort

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Abstract
Aims/hypothesis Calcium and vitamin D have been implicated in the development of type 2 diabetes, but epidemiological evidence is limited. We examined prospectively the relation of calcium and vitamin D intake to type 2 diabetes risk in a Japanese cohort.
Methods Participants were 59,796 middle-aged and older men and women, who participated in the Japan Public Health Center-based Prospective Study and had no history of type 2 diabetes or other serious diseases. Dietary intake of calcium and vitamin D were estimated using a validated food frequency questionnaire. Logistic regression was used to assess the association between intake of these nutrients and self-reported newly diagnosed type 2 diabetes.
Results During a 5 year follow-up, 1,114 cases of type 2 diabetes were documented. Overall, calcium intake was not associated with a significantly lower risk of type 2 diabetes; the multivariable odds ratio for the highest vs lowest quartiles was 0.93 (95% CI 0.71–1.22) in men and 0.76 (95% CI 0.56–1.03) in women. However, among participants with a higher vitamin D intake, calcium intake was inversely associated with diabetes risk; the odds ratio for the highest vs lowest intake categories was 0.62 (95% CI 0.41–0.94) in men and 0.59 (95% CI 0.38–0.91) in women. Dairy food intake was significantly associated with a lower risk of type 2 diabetes in women only.
Conclusions/interpretation Calcium and vitamin D may not be independently associated with type 2 diabetes risk. Our finding suggesting a joint action of these nutrients against type 2 diabetes warrants further investigation.

Keywords Calcium · Cohort studies · Type 2 diabetes · Vitamin D

Abbreviations
25-OHD 25-Hydroxyvitamin D
JPHC Japan Public Health Center-based Prospective Study

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Introduction

The number of people with type 2 diabetes has been increasing worldwide, with an estimated prevalence of 2.8% in 2000 and 4.4% in 2030 [1]. According to community-based studies, the prevalence of diabetes in Japan has rapidly increased during the past two decades [2]. Insight into the role of dietary factors in the development of diabetes may contribute to its prevention.

In experimental studies, calcium and vitamin D have been shown to improve pancreatic beta cell function and peripheral insulin sensitivity [3–5]. In humans, evidence on this issue so far is mainly derived from cross-sectional studies as reviewed [6], while findings from prospective studies are limited and inconsistent. Two cohort studies found a moderate, but not statistically significant association between dietary calcium intake and the risk of diabetes after adjustments for other dietary factors [7, 8], although the association with supplemental intake was statistically significant. A high intake of dairy foods, a major food source of calcium, has also been shown to be associated with a lower risk of type 2 diabetes [7–10]. Similarly, vitamin D intake from supplement [7] or supplement plus diet [11], but not from diet alone was associated with a lower incidence of diabetes. As regards blood vitamin D, a prospective study in Finland showed an inverse association between serum 25-hydroxyvitamin D (25-OHD) concentrations and the risk of type 2 diabetes [12]. However, in a large-scale randomised controlled trial in US American women [13], calcium plus vitamin D_3 supplementation did not reduce the risk of developing diabetes over 7 years of follow-ups. Given the scarcity and inconsistency of prospective evidence [6], it is unclear whether these nutrients prevent type 2 diabetes.

To the best of our knowledge, there are no reports on the relation between both calcium and vitamin D intake, and the incidence of type 2 diabetes in the Japanese population, which consumes, on average, a relatively low amount of calcium [14]. We therefore examined the associations of calcium, vitamin D and dairy foods intake with the risk of type 2 diabetes in a large-scale cohort of the Japanese population. Since calcium and vitamin D have been hypothesised to act jointly, rather than independently, in reducing the risk of diabetes [7], we also explored their combined effect on the risk of type 2 diabetes.

Methods

Study cohort The Japan Public Health Center-based Prospective Study (JPHC) was established in 1990 for cohort I and in 1993 for cohort II. Details of the study design have been described elsewhere [15]. The participants of cohort I included residents, aged 40 to 59 years, in five Japanese Public Health Center areas (Iwate, Akita, Nagano, Okinawa and Tokyo); the participants of cohort II included residents, aged 40 to 69 years, in six Public Health Center areas (Ibaraki, Niigata, Kouchi, Nagasaki, Okinawa and Osaka). Study participants were informed about the objectives of the study and those who responded to the survey questionnaire were regarded as consenting to participate in the study. This study was approved by the institutional review board of the National Cancer Center, Tokyo, Japan.

Questionnaire surveys A questionnaire survey was conducted at baseline and at the 5- and 10-year follow-ups. Information on medical history and health-related lifestyles, including smoking, drinking and dietary habits, was obtained in each survey. In the present analysis, we used data from the 5-year survey, which was carried out in 1995 for cohort I and in 1998 for cohort II, as baseline. We did this because the questionnaire used for that survey contained more comprehensive information on food intake than that used for the first survey.

Participants Within the study population at baseline (n= 140,420), we excluded residents of two areas (Tokyo and Osaka) because of the differences in recruitment criteria. Of the remaining 116,672 individuals, 95,373 (82%) responded to the baseline survey. Of these, 80,128 (84%) completed a questionnaire at the 5-year survey, which provided the baseline of the present analysis. Of these, 71,075 (89%) responded to a questionnaire at the 10-year follow-up. We excluded individuals with a history of stroke, cardiovascular disease, cancer, chronic liver disease or kidney disease (n= 10,694) at the first and 5-year follow-up surveys. We also excluded those with >3 and <3 standard deviations of energy intake (n=585). As a result, 59,796 individuals (25,877 men, 33,919 women) were analysed.

Food frequency questionnaire The food frequency questionnaire used for the 5-year follow-up survey included questions about 147 food and beverage items with standard portions/units and eating frequency. Nine response options were available for eating frequency: rarely, one to two times/month, 1 to 2 days/week, 3 to 4 days/week, 5 to 6 days/week, once a day, two to three times/day, four to six times/day and ≥7 times/day. Slightly different options were used for beverage intake: rarely, 1 to 2 days/week, 3 to 4 days/week, 5 to 6 days/week, once a day, two to three times/day, four to six times/day, seven to nine times/day and ≥10 times/day. A standard portion size was specified for each food item and the respondents were asked to choose their usual portion from among three categories: less than half, same and more than 1.5 times the standard portion. We calculated the average daily intake of nutrients,

including calcium and vitamin D, by multiplying the frequency of the consumption of each food by its nutrient content per serving and totalling the nutrient intake for all food items. In Japan, vitamin D fortification of dairy products was not a common practice at the time of survey. The validity of the dietary calcium and vitamin D intake was assessed in a sub-sample of the cohort by comparing the estimated intake according to the questionnaire with that based on dietary records [16]. The Spearman's correlation coefficients of the energy-adjusted intake of calcium and vitamin D between the questionnaire and the dietary records were 0.54 and 0.77 for the men in cohort I, 0.68 and 0.56 for the men in cohort II, 0.45 and 0.43 for the women in cohort I and 0.68 and 0.52 for the women in cohort II, respectively [16].

Ascertainment of diabetes mellitus In the 10-year follow-up questionnaire, study participants were asked if they had ever been diagnosed as having diabetes and, if so, when the initial diagnosis had been made. Because the 5-year survey was used as baseline in the present study, only participants who were subsequently diagnosed (i.e. after 1995 for cohort I and after 1998 for cohort II) were regarded as incident cases during the follow-up. We did not obtain information on the type of diabetes; however, considering the minimum age of the study population (45 years old at baseline [5-year survey]), we reasonably assumed that most reported cases were type 2 diabetes. To assess the validity of self-reported diabetes, we examined a series of medical records of some study participants in three districts of the study areas, finding that 94% of the self-reported cases of diabetes were confirmed by medical records [17]. We also examined the sensitivity of self-reported diabetes among JPHC cohort I participants for whom data on plasma glucose were available from the 1990 health check-up. Of the 6,118 participants with plasma glucose data, 248 had self-reported diabetes. Of the 5,870 participants who did not have self-reported diabetes, 49 participants (0.83%) had diabetes based on a single measurement and according to the diagnostic standards commonly used in Japan at that time (1990), i.e.: (1) fasting plasma glucose ≥7.8 mmol/l; and (2) casual plasma glucose ≥11 mmol/l [18]. Taking into account the above-mentioned positive predictive value, the sensitivity and specificity of self-reported diabetes were 82.9% and 99.7%, respectively.

Statistical analysis Analyses were performed on men and women, separately. Dietary intakes of calcium and vitamin D were adjusted for total energy intake using the residual method [19]. Baseline characteristics were presented according to quartiles of dietary calcium and vitamin D intake, and their trend associations assessed using a linear regression analysis for continuous variables or a logistic regression for categorical variables, with the median value of calcium or vitamin D intake in each category assigned to the corresponding category. A logistic regression analysis was used to assess the associations of the dietary intake of calcium, vitamin D and dairy food with the incidence of type 2 diabetes. The odds ratios and 95% CIs were calculated for each quartile of intake using the lowest consumption category as a reference. All logistic regression analyses were adjusted for age (year; continuous) and study area (nine Public Health Centers). The multivariate analyses were additionally adjusted for the following nine factors: (1) BMI (<21, 21–22.9, 23–24.9, 25–26.9 or ≥27 kg/m^2); (2) family history of diabetes mellitus (yes or no); (3) smoking status (none, past, current smoking <20 cigarettes/day or current smoking ≥20 cigarettes/day); (4) alcohol intake (men: none, <150, 150–299, 300–449 or ≥450 g ethanol per week; women: none, <150, 150–299 or ≥300 g ethanol per week); (5) history of hypertension (yes or no); (6) exercise frequency (less than once/week or once or more times per week); (7) coffee consumption (none, less than daily, 1 cup/day, ≥2–3 cups/day); (8) energy-adjusted magnesium intake (mg; continuous); and (9) total energy intake (kJ; continuous). The above analyses were also performed for selected foods containing high amounts of calcium: total dairy products, milk, cheese and yogurt. The analysis for calcium was stratified according to vitamin D intake (less than median or median or greater) to assess whether vitamin D had a modifying effect on the association between calcium and diabetes risk. Similarly, we examined the above associations according to BMI (<25 or ≥25 kg/m^2), smoking status (non-smokers or current smokers) and drinking status (non-drinkers or current drinkers), since these variables are known to be associated with the risk of type 2 diabetes and might modify nutrient–diabetes associations. An interaction term of two exposure variables was created and added in the model to assess a statistical interaction. Tests for trends were assessed by assigning the median intake value of each quartile of nutrients or food intake in each category. All p values were two sided; statistical significance was determined at $p<0.05$.

Results

During the 5-year follow-up period, 1,114 participants were newly diagnosed with diabetes (634 men [2.4%], 480 women [1.4%]). Table 1 shows the potential confounders according to dietary calcium and vitamin D intake at baseline. The dietary intake of calcium was positively associated with age and sports participation in both sexes, but was inversely associated with current smoking and heavy alcohol drinking in both sexes, and with BMI and

Table 1 Baseline characteristics according to quartiles of energy-adjusted dietary intakes of calcium and vitamin D

Characteristic	Men (quartiles of intake)					Women (quartiles of intake)				
	Lowest	Second	Third	Highest	*p* value, trend	Lowest	Second	Third	Highest	*p* value, trend
Calcium										
Age, years	55 (8)	56 (8)	57 (8)	58 (8)	<0.001	57 (8)	57 (8)	57 (8)	58 (8)	<0.001
BMI (kg/m^2)	23.6 (2.9)	23.6 (2.8)	23.5 (2.8)	23.6 (2.8)	0.33	23.7 (3.2)	23.5 (3.1)	23.5 (3.0)	23.4 (3.0)	<0.001
Family history of diabetes (%)	5.6	6.6	5.9	6.1	0.03	5.5	5.8	6.1	6.1	0.003
Current smokers (%)	53.8	50.5	45.2	37.9	<0.001	7.0	4.5	3.5	3.5	<0.001
Alcohol intake ≥150 g/week (%)	67.6	55.8	47.8	34.0	<0.001	4.6	2.4	1.4	1.0	<0.001
Sports ≥1 time/week (%)	16.3	19.2	22.2	26.6	<0.001	14.7	19.0	21.3	25.7	<0.001
Antihypertensive medication (%)	21.9	21.7	22.3	23.0	0.005	22.1	22.1	23.3	23.3	0.197
Coffee ≥1 cup/day (%)	31.4	34.1	32.0	30.4	0.97	38.9	35.8	33.5	31.5	<0.001
Dietary intake (median)										
Calcium (mg/day)	254	356	457	629	<0.001	356	487	608	810	<0.001
Vitamin D (μg/day)	7.7	9.7	10.3	10.9	<0.001	8.3	9.7	10.4	10.1	<0.001
Magnesium (mg/day)	245	286	307	331	<0.001	248	281	298	314	<0.001
Dairy products (median) (g)	21	68	180	260	<0.001	39	124	214	304	<0.001
Calcium supplement use (%)	0.1	0.2	0.2	0.1	0.34	0.5	0.4	0.6	0.7	0.07
Vitamin D										
Age (years)	56 (8)	56 (8)	57 (8)	58 (8)	<0.001	58 (8)	56 (8)	57 (8)	58 (7)	<0.001
BMI (kg/m^2)	23.7 (2.9)	23.6 (2.8)	23.5 (2.8)	23.4 (2.8)	<0.001	23.7 (3.2)	23.5 (3.1)	23.4 (3.0)	23.5 (3.1)	<0.001
Family history of diabetes (%)	5.7	5.8	6.3	6.5	<0.001	4.9	6.5	6.5	5.6	0.046
Current smokers (%)	46.8	47.2	46.8	46.6	<0.001	4.7	4.5	4.6	4.6	<0.001
Alcohol intake ≥150 g/week (%)	57.4	52.9	50.6	44.5	<0.001	2.8	2.4	2.5	1.8	<0.001
Sports ≥1 time/week (%)	21.0	22.2	21.1	19.9	0.01	20.7	21.0	20.4	18.8	<0.001
Antihypertensive medication (%)	20.5	21.5	22.8	24.1	0.02	23.4	20.9	21.9	24.7	0.01
Coffee ≥1 cup/day (%)	37.6	34.4	30.5	25.6	<0.001	41.9	38.7	33.0	26.2	<0.001
Dietary intake (median)										
Calcium (mg/day)	348	403	423	439	<0.001	495	548	565	568	<0.001
Vitamin D (μg/day)	4.7	8.1	11.5	18.0	<0.001	4.8	8.1	11.4	17.4	<0.001
Magnesium (mg/day)	265	284	298	315	<0.001	264	278	289	301	<0.001
Dairy products (median) (g)	70	121	130	114	0.54	123	195	200	164	<0.001
Calcium supplement use (%)	0.2	0.2	0.1	0.1	0.10	0.6	0.7	0.4	0.4	0.02

Data are means (SD) unless otherwise indicated

Intake of calcium, vitamin D and magnesium were adjusted for total energy intake

coffee consumption among women. The dietary intake of vitamin D was positively associated with age in both sexes, but was inversely associated with BMI, heavy alcohol intake, sports participation and coffee consumption in both sexes, and with calcium supplement use among women.

In the analysis with adjustments for age and area only, we observed a statistically significant inverse association between dietary calcium intake and the risk of type 2 diabetes in women (Table 2). The odds ratio comparing the highest vs lowest quartile group of calcium intake was 0.74 (95% CI 0.57–0.96; p=0.039 for trend) among women. The association was slightly attenuated and no longer statistically significant after further adjustment for other potential confounders. The multivariable odds ratio for the highest vs lowest quartiles of calcium intake was 0.76 (95% CI 0.56–1.03; p=0.095 for trend) among women. The exclusion of calcium supplement users from the analysis (n=25,836 for men, n=33,735 for women) did not notably alter the results; the odds ratio was 0.77 (95% CI 0.56–1.04; p=0.116 for trend) among women. There was no association between calcium intake and the risk of diabetes in men. Vitamin D intake alone was not appreciably associated with the risk of type 2 diabetes either in men or in women. Additional adjustment of saturated fat intake did not appreciably alter these results (data not shown).

In women, the intake of dairy foods was significantly inversely associated with the risk of type 2 diabetes. In models with adjustment of age and area only, the odds ratios for the highest vs lowest intake category were 0.65 (95% CI 0.49–0.88; p=0.007 for trend), 0.79 (95% CI 0.64–0.97; p=0.02 for trend), 0.94 (95% CI 0.68–1.30; p= 0.71 for trend) and 0.72 (95% CI 0.55–0.93; p=0.04 for

Table 2 ORs of type 2 diabetes according to quartiles of energy-adjusted dietary intake of calcium and vitamin D

Intake per quartile and sex	At risk (n)	Cases (n)	Age- and area-adjusted OR (95% CI)	Multivariable OR (95% CI)*
Calcium				
Men				
Lowest	6,469	174	1.00	1.00
Second	6,469	143	0.82 (0.66–1.03)	0.83 (0.66–1.05)
Third	6,470	162	0.93 (0.75–1.16)	0.97 (0.76–1.24)
Highest	6,469	155	0.89 (0.71 1.11)	0.93 (0.71 1.22)
p value for trend			0.52	0.95
Women				
Lowest	8,479	134	1.00	1.00
Second	8,480	118	0.88 (0.69–1.14)	0.90 (0.70–1.18)
Third	8,480	126	0.94 (0.73–1.20)	0.95 (0.73–1.25)
Highest	8,480	102	0.74 (0.57–0.96)	0.76 (0.56–1.03)
p value for trend			0.039	0.095
Vitamin D				
Men				
Lowest	6,469	156	1.00	1.00
Second	6,469	182	1.20 (0.96–1.49)	1.17 (0.93–1.46)
Third	6,470	145	0.96 (0.76–1.21)	0.93 (0.73–1.18)
Highest	6,469	151	1.01 (0.79–1.28)	0.96 (0.74–1.23)
p value for trend			0.58	0.35
Women				
Lowest	8,479	139	1.00	1.00
Second	8,480	104	0.76 (0.58–0.98)	0.77 (0.59–1.00)
Third	8,480	105	0.76 (0.58–0.99)	0.76 (0.57–1.00)
Highest	8,480	132	0.94 (0.72–1.23)	0.88 (0.67–1.16)
p value for trend			0.94	0.67

*Adjusted further for age (continuous), area (nine Public Health Center areas), BMI (<21, 21–22.9, 23–24.9, 25–26.9 or ≥27 kg/m^2), family history of diabetes mellitus (yes or no), smoking status (none, past, current smoking <20 or ≥20 cigarettes/day), alcohol intake (men: none, <150, 150–299, 300–449 or ≥450 g ethanol/week; women: none, <150, 150–299 or ≥300 g ethanol/week), history of hypertension (yes or no), exercise frequency (less than once/week or ≥once/week), consumption of coffee (less than daily, 1–3 cups/day or ≥4 cups/day), energy-adjusted magnesium (continuous) and total energy (continuous)

trend) for total dairy products, milk, cheese and yogurt, respectively. In multivariable analyses, these associations were attenuated. No significant association between dairy product intake and the risk of diabetes was observed in men (Table 3). We repeated the above analyses without adjustment for intake of magnesium, a component of dairy foods, but the results were not materially changed (data not shown).

In a stratified analysis according to vitamin D intake, the inverse association between calcium intake and the risk of diabetes was more pronounced among participants who consumed a median or greater amount of vitamin D; the odds ratios (95% CI) for the highest vs lowest quartiles of calcium intake were 0.62 (0.41–0.94; p=0.050 for trend) in men and 0.59 (0.38–0.91; p=0.043 for trend) in women (Table 4). In contrast, calcium intake was not associated with the risk of diabetes in either sex in the lower vitamin D intake group. p for interaction between calcium (continuous) and vitamin D (dichotomous) was 0.02 and 0.06 for men and women, respectively. In stratified analyses according to BMI, smoking status or alcohol intake, the associations with calcium or vitamin D were not notably different between the stratified subgroups (data not shown).

Discussion

In this large-scale cohort of Japanese adults, intake of calcium and vitamin D was not associated with a significantly lower risk of type 2 diabetes. However, both in men and women there was a clear decreasing trend of type 2 diabetes risk with increasing dietary intake of calcium among persons with a higher vitamin D intake. Dairy food intake was inversely associated with the risk of type 2 diabetes in women, but not in men. To our knowledge, this is the first prospective study in a Japanese population to show an association between both calcium and vitamin D intake and the risk of type 2 diabetes.

Although calcium intake was not clearly associated with risk of type 2 diabetes, there was a suggestion of an inverse association in women. This finding appears to be consistent with results from studies in US American women showing a marginally significant inverse association with dietary calcium intake in multivariable analyses [7, 8]. A notable finding in our study is that a distinct inverse association between calcium and the risk of diabetes was observed in the higher, but not in the lower vitamin D intake subgroup.

Table 3 ORs of type 2 diabetes according to the intake of dairy products, milk, cheese and yogurt

Intake (g/day) per product group	Men			Women		
	At risk (n)	Cases (n)	Multivariable OR (95% CI)*	At risk (n)	Cases (n)	Multivariable OR (95% CI)*
Dairy products						
<50	8,776	217	1.00	7,674	136	1.00
50–<150	6,016	141	0.99 (0.79–1.23)	8,154	113	0.82 (0.64–1.07)
150–<300	7,772	189	1.04 (0.85–1.28)	11,958	160	0.82 (0.64–1.04)
≥300	3,313	87	1.18 (0.90–1.56)	6,133	71	0.71 (0.51–0.98)
p value for trend			0.21			0.054
Milk						
<50	12,102	304	1.00	12,485	191	1.00
50–<100	732	19	1.07 (0.66–1.72)	1,282	23	1.29 (0.83–2.01)
100–<200	4,463	98	0.90 (0.71–1.13)	6,349	98	1.08 (0.84–1.39)
≥200	8,580	213	1.02 (0.85–1.24)	13,803	168	0.87 (0.70–1.09)
p value for trend			0.88			0.16
Cheese						
0	13,085	326	1.00	16,939	253	1.00
0.1–<5	10,390	261	1.08 (0.91–1.29)	13,570	182	1.08 (0.88–1.33)
≥5	2,402	47	0.88 (0.64–1.21)	3,410	45	1.12 (0.80–1.57)
p value for trend			0.39			0.56
Yogurt						
0	15,820	386	1.00	12,551	209	1.00
0.1–<60	7,528	193	1.14 (0.95–1.37)	14,100	186	0.85 (0.69–1.05)
≥60	2,529	55	1.01 (0.75–1.36)	7,268	85	0.77 (0.58–1.01)
p value for trend			0.94			0.13

*Adjusted variables as in Table 2 (footnote)

Table 4 Multivariable odds ratios of type 2 diabetes according to quartiles of calcium intake, stratified by median intake of vitamin D

Quartiles of calcium intake per vitamin D intake	Men			Women		
	At risk (*n*)	Cases (*n*)	Multivariable OR (95% CI)*	At risk (*n*)	Cases (*n*)	Multivariable OR (95% CI)*
Low vitamin D (<median)						
Lowest	4,166	107	1.00	5,053	73	1.00
Second	3,218	71	0.86 (0.63–1.19)	4,195	63	1.14 (0.79–1.63)
Third	2,870	73	1.01 (0.72–1.41)	3,762	56	1.12 (0.76–1.66)
Highest	2,684	87	1.31 (0.92–1.89)	3,949	51	0.94 (1.62–1.43)
p value for trend			0.08			0.70
High vitamin D (≥median)						
Lowest	2,303	67	1.00	3,426	61	1.00
Second	3,251	72	0.76 (0.53–1.08)	4,285	55	0.70 (0.48–1.02)
Third	3,600	89	0.87 (0.61–1.25)	4,718	70	0.79 (0.54–1.15)
Highest	3,785	68	0.62 (0.41–0.94)	4,531	51	0.59 (0.38–0.91)
p value for trend			0.050			0.043

*Adjustment variables, see Table 2 (footnote)

p=0.02 and p=0.06 for interaction of calcium (continuous) and vitamin D (dichotomous), men and women respectively

This is in line with the hypothesis that calcium and vitamin D act jointly to protect against type 2 diabetes. In a prospective study among US American nurses [7], a combined daily intake of >1,200 mg of calcium and >800 IU of vitamin D was associated a 33% lower risk of type 2 diabetes compared with a daily intake of ≤600 mg and ≤400 IU respectively. Although the lowest risk was observed in persons with a combined high intake of calcium and vitamin D, the benefit of the two nutrients appears to be additive in the US study.

We found a marginally significant risk reduction associated with the highest intake of calcium and dairy products in women, but not in men. This sex-related difference in association could be ascribed to chance, but another explanation is possible. Thus in the present cohort, women consumed greater amounts of calcium and dairy products than men, with median daily calcium intake at 404 mg for men and 546 mg for women and that for dairy products at 111 g for men and 171 g for women. If apparent risk reduction is observed only above a certain intake level, comparatively lower intake of calcium and dairy products in men than in women could explain the observed discrepancy in association.

A few intervention studies have examined the effects of the combined intake of calcium and vitamin D on type 2 diabetes, but their results have been inconsistent. Specifically, supplementation with 400 IU of vitamin D and 1,000 mg of calcium did not reduce the risk of type 2 diabetes over a 7-year follow-up among participants with normal and impaired fasting glucose levels [13]. In another trial of 221 elderly persons with normal glucose tolerance, combined supplementation with 700 IU of vitamin D and 500 mg of calcium citrate malate had no effect on glycaemia or insulin resistance during a 3-year follow-up, compared with the placebo group [20]. In that study, however, the administration of calcium and vitamin D supplements significantly attenuated the increase in fasting glycaemia and insulin resistance among participants with impaired fasting glucose, compared with control participants [20].

Regarding the intake of dairy foods, we found statistically significant inverse associations with the risk of type 2 diabetes in age- and area-adjusted analyses in women, but the association was attenuated after multivariable adjustments. An inverse association with type 2 diabetes has been reported for the intake of dairy foods in men [9] and women [7], for the intake of low-fat dairy foods in women [8, 10] and for yogurt intake in men [9] and women [10]. Our study did not find a risk reduction associated with milk intake, a finding consistent with the results of American studies [9, 10], although one study [9] reported a lower risk of type 2 diabetes with low-fat milk intake.

Vitamin D intake was not independently associated with the risk of type 2 diabetes in our study. Two prospective studies have shown an inverse association with supplemental [7] and total [11] vitamin D intake, but not with dietary vitamin D intake. A possible explanation for the lack of association with dietary vitamin D in our study and in others is the fact that sunlight-induced cutaneous synthesis of vitamin D also contributes to systemic vitamin D levels [4]. Consequently, dietary vitamin D intake alone may not explain the overall vitamin D status. Data from the present study population do not enable us to examine the

contribution of dietary vitamin D intake to circulating 25-OHD concentrations, an indicator of systemic vitamin D status. However, a study of Japanese women, which was conducted in winter [21], showed that persons who frequently consumed fish, a rich source of vitamin D, had higher mean blood 25-OHD concentrations than those who consumed fish infrequently. Thus, dietary vitamin D intake could be used in ranking systemic vitamin D status at least when the amount of sunlight-induced cutaneous synthesis of vitamin D is low.

The precise mechanisms whereby calcium and vitamin D exert glucose-lowering effects are not clear. Calcium is essential for insulin-mediated intracellular processes. Intracellular calcium levels are tightly controlled within a narrow range to maintain insulin signalling [22]. Calcium deficiency leads to the secretion of parathyroid hormone and increases calcium inflow from the extracellular fluid into intracellular regions, resulting in cellular calcium overload and impaired insulin sensitivity [5, 23]. In epidemiological studies, calcium intake was positively associated with insulin sensitivity [24–26]. Vitamin D is also involved in insulin regulation [3, 4]. 1,25-Dihydroxyvitamin D_3, an active form of circulating vitamin D, binds to the vitamin D receptor on pancreas beta cells and enhances insulin receptor expression, resulting in improved insulin sensitivity [27, 28]. Vitamin D deficiency has also been shown to impair insulin secretion in experimental studies [3, 4]. Moreover, because vitamin D facilitates calcium absorption in the intestines [29], vitamin D and calcium may act synergistically to reduce the risk of type 2 diabetes. Dairy foods rich in calcium may decrease the risk of diabetes through calcium-related mechanisms. In addition, milk protein induces the release of insulinogenic amino acids and the peptide hormone incretin, both of which augment insulin secretion [30].

Japanese patients with type 2 diabetes are on average leaner than white counterparts, which might reflect differences in insulin secretion and sensitivity between the two ethnic groups [31]. A multi-ethnic study of US American women [32] found that Japanese-Americans had lower beta cell function than non-Hispanic whites, suggesting a need to improve beta cell function as well as insulin sensitivity in order to prevent type 2 diabetes in the Japanese. If calcium and vitamin D have beneficial effects on beta cell function and insulin sensitivity, sufficient intake of these nutrients may have a large impact on reducing the risk of type 2 diabetes among Japanese.

The major strengths of our study include its prospective design, large sample size and the use of a validated food frequency questionnaire. However, several study limitations should also be mentioned. First, the incidence of diabetes was ascertained on the basis of self-reported information obtained from the participants. According to a validation study, self-reported diabetes exhibited a fairly good agreement with documented diabetes on the basis of medical records (94%), while sensitivity (82.6%) and specificity (99.7%) of self-reported diabetes were also high. Second, the dietary intake of calcium and vitamin D was only measured at one time-point and thus may not reflect long-term exposure. Third, we were unable to distinguish regular from low-fat dairy foods, two categories that may have different effects on the risk of diabetes. Fourth, we did not consider sunlight-induced cutaneous synthesis of vitamin D. Studies involving the measurement of blood 25-OHD, a marker of systemic vitamin D exposure, could reveal the association between vitamin D and the risk of type 2 diabetes more precisely. Finally, significant results obtained in subgroup analysis may be due to chance and thus should be interpreted with caution.

In conclusion, the present study provided no clear evidence to support an independent role of calcium and vitamin D in the development of type 2 diabetes. An inverse association between calcium intake and type 2 diabetes risk in persons with a higher vitamin D intake suggests that these nutrients may act jointly, rather than independently, in lowering risk of type 2 diabetes. This possibility warrants further investigation.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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ORIGINAL ARTICLE

Weight change and all-cause, cancer and cardiovascular disease mortality in Japanese men and women: the Japan Public Health Center-Based Prospective Study

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Background: It is unclear whether weight change during adulthood influences subsequent mortality in Asian populations, who have a relatively lean body mass.
Objective: To assess the relation of weight change over 5 years to all-cause, cancer and cardiovascular disease mortality among Japanese men and women.
Design: Subjects were 36 220 men and 44 091 women aged between 45 and 75 years without a history of serious disease at baseline. Weight change was calculated as the difference of body weight between two surveys with a 5-year interval.
Results: During 699 963 person-years of follow-up, we identified 4232 deaths of all-cause, 1872 cancer deaths and 1021 cardiovascular deaths. The relation between weight change and all-cause mortality was reverse J-shaped. Multivariate hazard ratios (95% confidence interval) for weight loss of 5 kg or more versus weight change of less than 2.5 kg were 1.62 (1.45–1.81) in men and 1.76 (1.51–2.05) in women, whereas those for weight gain of 5 kg or more were 1.40 (1.22–1.59) in men and 1.25 (1.02–1.54) in women. These associations remained statistically significant even after the exclusion of deaths in the first 3 years of follow-up. The weight change–mortality association was pronounced in underweight persons or in nonsmoking men. The risk of cancer mortality increased in both men and women who lost weight by 5 kg or more. With regard to cardiovascular disease, mortality risk tended to increase with weight loss both in men and women, whereas its increase with weight gain was observed only in women.
Conclusions: A large weight change, both loss and gain, was associated with an increased risk of mortality. Weight loss and gain may be predictors of early death in apparently healthy adult Japanese.
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Keywords: cancer; cardiovascular diseases; cohort studies; Japan; mortality; weight change

Introduction

Obesity, because of its causal link to hypertension, diabetes mellitus, cardiovascular disease and certain cancers,[1,2] is an increasing public health problem worldwide.[2–4] The relation between body mass index (BMI) and all-cause mortality is J-,[5–7] or U-shaped,[5,8,9] with both obesity and underweight being associated with increased mortality. However, the findings based on a single point-in-time measurement of BMI may not be used to predict the effect of weight change on future health events. Specifically, weight loss in overweight persons or weight gain in underweight persons may or may not be beneficial in reducing mortality risk. Therefore, it would be important to clarify the association of weight change over a time period with subsequent mortality risk.

Weight loss has been related to an increased risk of all-cause mortality in many,[10–19] but not all,[20–22] studies. The relation with weight gain and mortality has been inconsistent; some studies found an increased mortality

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among persons who experienced weight gain[16] or excess weight gain,[11] whereas others showed no association with weight gain.[10,12–15,17,20–22] However, these studies were relatively small in size (number of subjects less than 10 000[10,12,14,15,17,18,20–22]), included only elderly people (65 years old and above[10,12,15,17]), assessed short-term weight change (within 2 years[10,15,21]) and did not report cause-specific mortality.[10,12,15,17,19] Moreover, most of the studies were conducted among Western populations[10,12–14,16–18,20–22] and the evidence regarding this issue is sparse among Asian populations,[15,19] who have a relatively low BMI. The aim of this study was to investigate the relation of weight change over a 5-year period to subsequent mortality from all-cause, cancer and cardiovascular disease using data of a large-scale population-based cohort study in Japan.

Methods

Study population

The Japan Public Health Center-Based Prospective Study (JPHC) was launched in 1990 for cohort I and in 1993 for cohort II.[23] The subjects were residents of 11 public health centers who were 40–69 years old at each baseline survey. The Institutional Review Board of the National Cancer Center, Japan approved this study.

Of 140 025 eligible subjects, 113 268 (80.9%) responded to the questionnaire survey at baseline (1990–1995) and, of these, 90 700 (80.1%) also responded to the 5-year follow-up survey (1995–2000). We excluded 7204 subjects who reported cancer, cerebrovascular disease, myocardial infarction or chronic liver disease at baseline or at 5-year follow-up and also excluded 3392 subjects with a BMI of less than 14 kg m^{-2}, 40 kg m^{-2} or more, or missing on weight or height. After a further exclusion of 155 subjects who reported to have lost or gained weight of more than 20 kg from baseline to 5-year follow-up, a total of 80 311 subjects (36 220 men and 44 091 women) remained for the analysis.

Body mass index and weight change

At baseline and 5-year follow-up, participants completed a self-administered questionnaire which included queries on height, body weight, medical history, smoking, alcohol consumption, physical activity, diet and other lifestyle factors. Weight change was calculated as the difference of body weight between the two surveys. BMI was calculated as weight in kilograms divided by squared height in meters. Subjects were categorized into five groups: $\geqslant$5 kg loss, 2.5–4.9 kg loss, <2.5 kg change (stable), 2.5–4.9 kg gain and $\geqslant$5 kg gain. Among the study participants whose anthropometric data were also obtained from health checkups (11 274 men and 21 196 women), Spearman's rank correlation coefficients between self-reported BMI and the measured one were 0.89 and 0.90 for men and women, respectively.

Follow-up and outcome

Subjects were followed up for residence status or vital status through the residential registry. Cause of death was confirmed by death certification with permission and was defined according to the tenth revision of the International Classification of Disease (ICD-10). The principal outcome of this study was all-cause, cancer (ICD-10: C00-D48) and cardiovascular disease mortality (ICD-10: I00-I99). Cardiovascular disease mortality was subdivided into heart disease (ICD-10: I20-I25 and I30-I52) and cerebrovascular disease (ICD-10: I60-I69).

Statistical analysis

Person-year of follow-up was calculated for each person from the date of response to the 5-year follow-up questionnaire, date of death or 31 December 2005, whichever came first. The confounding variables considered were age (year, continuous), study area (11 areas), BMI (<21, 21 to <23, 23 to <25, 25 to <27 or $\geqslant$27 kg m^{-2}), smoking (lifetime nonsmoker, former smoker or current smoker with a consumption of <20 or $\geqslant$20 cigarettes per day), alcohol consumption (nondrinker, occasional drinker or drinker with a consumption of <150, 150–299, 300–449 or $\geqslant$450 g ethanol per day for men; and nondrinker, occasional drinker or drinker with a consumption of <150 or $\geqslant$150 g ethanol per day for women), leisure-time physical activity (<1 time per month, 1–3 times per month or $\geqslant$1 time per week), history of hypertension (yes or no) and history of diabetes mellitus (yes or no). Dummy variables were created for missing data.

Cox proportional hazard regression analysis was used to estimate hazard ratios and 95% confidence intervals (CI) of mortality for each weight change category, taking the group of individuals with stable weight (<2.5 kg change) as the reference. The multivariate model was adjusted for age, study area, baseline BMI, smoking, alcohol consumption, leisure-time physical activity, history of hypertension and history of diabetes mellitus. We repeated the analysis after exclusion of deaths in the first 3 years of follow-up. We also analyzed data by baseline BMI (<22 kg m^{-2} (underweight), 22 to <25 kg m^{-2} (normal weight) and $\geqslant$25 kg m^{-2} (overweight)), smoking (current smoker and nonsmoker in men only) or age (<60 and $\geqslant$60 years old). In the analysis by baseline BMI, we used the group of individuals who had normal weight at baseline and showed <2.5 kg change at the 5-year follow-up survey as the reference group. All analyses were performed using Statistical Analysis System (SAS) version 9.1 (SAS Institute, Cary, NC, USA).

Results

During 699 963 person-years of follow-up (mean 8.7 years), we identified 4232 deaths of all-cause, 1872 cancer deaths and 1021 cardiovascular deaths. Table 1 shows the characteristics of the study population at the 5-year follow-

Table 1 Characteristics according to weight change categories at the 5-year follow-up survey

	Men					*Women*				
	≥5 kg loss	*2.5–4.9 kg loss*	*2.4 kg loss–2.4 kg gain*	*2.5–4.9 kg gain*	*≥5 kg gain*	*≥5 kg loss*	*2.5–4.9 kg loss*	*2.4 kg loss–2.4 kg gain*	*2.5–4.9 kg gain*	*≥5 kg gain*
No of subjects	3211	3307	22 232	3926	3544	3239	3906	29 108	4766	3072
Age (years), mean (s.d.)	57.7 (7.9)	57.6 (7.9)	56.5 (7.8)	55.3 (7.6)	55.4 (7.8)	58.9 (8.0)	58.5 (8.0)	56.8 (7.8)	55.0 (7.7)	55.4 (7.8)
Weight (kg), mean (s.d.)	60.7 (9.7)	61.8 (8.6)	62.7 (8.5)	66.3 (8.4)	69.4 (9.1)	51.5 (8.5)	52.1 (7.7)	53.5 (7.3)	56.7 (7.2)	60.6 (8.3)
BMI at baseline ($kg\,m^{-2}$), mean (s.d.)	25.2 (3.0)	24.2 (2.7)	23.3 (2.7)	23.2 (2.7)	23.0 (2.8)	25.6 (3.4)	24.0 (3.1)	23.2 (2.9)	23.0 (2.9)	23.1 (3.3)
BMI at 5-year survey ($kg\,m^{-2}$), mean (s.d.)	22.5 (3.0)	23.0 (2.7)	23.3 (2.7)	24.4 (2.7)	25.5 (3.0)	22.5 (3.4)	22.7 (3.1)	23.2 (3.0)	24.4 (2.9)	26.0 (3.4)
Weight change[a] (kg), mean (s.d.)	−7.5 (3.1)	−3.4 (0.5)	0.1 (1.3)	3.3 (0.5)	7.1 (2.7)	−7.4 (3.0)	−3.4 (0.5)	0.1 (1.3)	3.3 (0.5)	6.9 (2.6)
Weight change[b] (%), mean (s.d.)	−11.1 (4.5)	−5.2 (1.0)	0.1 (2.1)	5.4 (1.1)	11.7 (5.2)	−12.7 (5.1)	−6.2 (1.2)	0.2 (2.4)	6.4 (1.3)	13.3 (5.8)
BMI $\geq 25\,kg\,m^{-2}$ (%)	18.8	20.8	24.8	37.1	51.8	20.4	21.6	26.4	40.2	58.2
Smoking (%)										
Never	33.5	34.0	35.6	35.3	32.2	91.8	92.3	94.0	93.8	91.9
Past	17.7	16.9	17.5	20.5	23.0	1.2	1.0	1.0	1.3	1.6
Current	48.8	49.1	46.8	44.2	44.8	7.0	6.7	5.0	4.9	6.5
Alcohol consumption (%)										
<1 day per week	38.9	33.6	30.3	32.2	35.5	90.7	87.8	86.6	84.6	86.3
≥1 day per week	61.1	66.4	69.7	67.8	64.5	9.3	12.2	13.4	15.4	13.7
Leisure-time physical activity (%)										
<1 day per month	61.5	58.8	56.9	57.3	62.5	71.4	68.2	65.7	67.5	71.4
1–3 days per month	15.9	17.4	20.5	20.5	18.0	8.7	9.3	11.5	10.4	9.2
≥1 day per week	22.6	23.9	22.6	22.2	19.5	19.8	22.4	22.8	22.1	19.4
History of hypertension (%)	20.2	20.7	17.4	16.6	17.0	26.7	23.0	19.3	17.0	20.1
History of diabetes mellitus (%)	14.3	10.5	5.5	4.4	4.7	9.0	6.6	2.7	2.2	3.2

Abbreviation: BMI, body mass index. [a]Difference of body weight between baseline and 5-year follow-up survey. [b]The weight change was expressed as percentage: ((weight at the 5-year follow-up survey−weight at baseline)/weight at baseline) × 100.

up survey (at the start of follow-up) according to the weight change between baseline and 5-year survey. Between the two surveys, 61.4% of men and 66% of women had a stable weight (<2.5 kg change). Both men and women who lost weight tended to be older, were less likely to be an alcohol drinker and had a higher BMI at baseline and a history of hypertension and diabetes mellitus. Men who gained weight were more likely to be past smokers, whereas those who lost weight were more likely to be current smokers.

Table 2 shows the hazard ratios of all-cause and cause-specific mortality according to weight change. In both men and women, there was a reverse J-shaped association, with a weight loss of 2.5 kg or more and a weight gain of 5 kg or more being significantly related to an increased risk of all-cause mortality. Multivariate-adjusted hazard ratios (95% CI) of all-cause mortality for weight loss of 5 kg or more versus stable weight were 1.62 (1.45–1.81) in men and 1.76 (1.51–2.05) in women. The corresponding values for weight gain of 5 kg or more were 1.40 (1.22–1.59) and 1.25 (1.02–1.54). After exclusion of deaths in the first 3 years of follow-up, the association with weight loss was attenuated but remained statistically significant in men, whereas there was no material change in women.

Among subjects whose weight was stable (<2.5 kg change) over the 5 years between baseline and the 5-year survey, the multivariate-adjusted hazard ratios (95% CI) of all-cause mortality for increasing BMI levels at the 5-year survey (<19, 19 to <21, 21 to <23, 23 to <25, 25 to <27, 27 to <30 and $\geq 30\,kg\,m^{-2}$) were 1.8 (1.4–2.2), 1.3 (1.2–1.6), 1.1 (1.0–1.3), 1.0 (reference), 1.0 (0.8–1.1), 0.7 (0.6–1.0) and 0.9 (0.5–1.6) in men and 2.0 (1.5–2.7), 1.3 (1.0–1.6), 1.4 (1.1–1.7), 1.0 (reference), 1.3 (1.1–1.7), 1.3 (1.0–1.7) and 1.2 (0.7–1.8) in women.

Weight loss was significantly associated with an increased risk of cancer mortality in both men and women (Table 2). Multivariate-adjusted hazard ratios (95% CI) for weight loss of 5 kg or more were 1.78 (1.51–2.10) in men and 1.61 (1.28–2.04) in women. Although the risk was attenuated after exclusion of early deaths, the increased risk of cancer mortality associated with weight loss of 5 kg or more remained statistically significant. Weight gain was not measurably related to cancer mortality. The risk of cardiovascular disease mortality increased in men who lost weight and in women who either lost or gained weight. However, multivariate adjustment and exclusion of early deaths substantially attenuated the association with weight loss, whereas it strengthened the association with weight gain in women. When the analysis was carried out separately for heart disease and cerebrovascular disease, a significant increase in heart disease mortality was observed in men who lost weight by 2.5 kg or more and in women who gained weight by 5 kg or more, whereas cerebrovascular disease mortality did not significantly differ by the levels of weight change in both men and women.

Table 2 Multivariate-adjusted hazard ratios and 95% confidence intervals of deaths according to weight change categories

	Men					*Women*				
	≥5 kg loss	*2.5–4.9 kg loss*	*2.4 kg loss–2.4 kg gain*	*2.5–4.9 kg gain*	*≥5 kg gain*	*≥5 kg loss*	*2.5–4.9 kg loss*	*2.4 kg loss–2.4 kg gain*	*2.5–4.9 kg gain*	*≥5 kg gain*
Person-year of follow-up	26495	27759	192947	34458	30900	27839	33519	256179	42588	27280
All-cause										
No of deaths	421	315	1498	242	281	221	176	842	132	104
Adjusted HR[a]	1.62	1.26	1.00	1.08	1.40	1.76	1.30	1.00	1.11	1.25
95% CI	1.45–1.81	1.12–1.43	Reference	0.94–1.24	1.22–1.59	1.51–2.05	1.10–1.53	Reference	0.92–1.34	1.02–1.54
Adjusted HR[b]	1.43	1.25	1.00	1.13	1.29	1.70	1.19	1.00	1.13	1.31
95% CI	1.25–1.63	1.09–1.44	Reference	0.97–1.32	1.11–1.51	1.42–2.03	0.98–1.45	Reference	0.91–1.39	1.03–1.65
Cancer										
No of deaths	188	126	666	104	110	88	71	425	57	37
Adjusted HR[a]	1.78	1.17	1.00	1.03	1.22	1.61	1.13	1.00	0.89	0.83
95% CI	1.51–2.10	0.97–1.42	Reference	0.84–1.27	0.99–1.50	1.28–2.04	0.88–1.46	Reference	0.67–1.17	0.59–1.18
Adjusted HR[b]	1.53	1.19	1.00	1.12	1.15	1.45	0.98	1.00	0.88	0.82
95% CI	1.25–1.88	0.95–1.48	Reference	0.89–1.40	0.91–1.47	1.11–1.91	0.72–1.32	Reference	0.64–1.20	0.55–1.20
Cardiovascular disease										
No of deaths	79	97	349	58	66	56	47	202	35	32
Adjusted HR[a]	1.25	1.64	1.00	1.10	1.34	1.58	1.32	1.00	1.33	1.66
95% CI	0.97–1.60	1.31–2.05	Reference	0.83–1.46	1.02–1.76	1.17–2.15	0.96–1.81	Reference	0.92–1.90	1.13–2.44
Adjusted HR[b]	1.17	1.64	1.00	1.10	1.07	1.42	1.22	1.00	1.45	1.93
95% CI	0.88–1.57	1.27–2.12	Reference	0.80–1.51	0.76–1.50	0.98–2.07	0.82–1.80	Reference	0.96–2.19	1.25–2.99
Heart disease										
No of deaths	48	57	185	29	33	28	19	86	17	14
Adjusted HR[a]	1.40	1.81	1.00	1.03	1.26	1.60	1.14	1.00	1.62	1.82
95% CI	1.01–1.94	1.34–2.43	Reference	0.70–1.53	0.86–1.84	1.04–2.49	0.69–1.88	Reference	0.96–2.75	1.02–3.25
Adjusted HR[b]	1.45	2.00	1.00	1.07	1.10	1.48	1.04	1.00	1.71	2.14
95% CI	1.00–2.10	1.44–2.80	Reference	0.68–1.69	0.69–1.77	0.86–2.56	0.56–1.95	Reference	0.91–3.20	1.07–4.27
Cerebrovascular disease										
No of deaths	24	29	143	20	27	21	22	99	16	16
Adjusted HR[a]	0.94	1.20	1.00	0.94	1.38	1.38	1.36	1.00	1.13	1.53
95% CI	0.60–1.46	0.80–1.78	Reference	0.58–1.50	0.90–2.11	0.85–2.24	0.85–2.17	Reference	0.67–1.93	0.89–2.64
Adjusted HR[b]	0.83	1.05	1.00	1.09	0.99	1.04	1.22	1.00	1.20	1.66
95% CI	0.49–1.41	0.65–1.70	Reference	0.67–1.78	0.58–1.69	0.56–1.93	0.70–2.13	Reference	0.66–2.17	0.91–3.05

Abbreviations: CI, confidence interval; HR, hazard ratio. [a]Adjusted for age (year), study area (11 areas), body mass index (<21, 21 to <23, 23 to <25, 25 to <27 and ≥27 kg m^{-2}), smoking (never, past, current with a consumption of <20 or ≥20 cigarettes per day), alcohol consumption (nondrinker, occasional drinker, drinkers with a consumption of <150, 150–299, 300–449 or ≥450 g ethanol per week for men and nondrinker, occasional drinker, drinkers with a consumption of <150 or ≥150 g ethanol per week for women), leisure-time physical activity (<1 time per month, 1–3 times per month, ≥1 time per week), history of hypertension (yes or no) and history of diabetes mellitus (yes or no). [b]Further excluded deaths within the first 3 years of follow-up.

An increased risk of all-cause mortality associated with weight loss of 5 kg or more was observed irrespective of initial BMI, but was pronounced in lean persons (Figure 1). Compared with subjects who had normal weight at baseline (BMI: 18.5–24.9 kg m^{-2}) and experienced a little weight change at the 5-year survey (<2.5 kg), the multivariate-adjusted hazard ratios (95% CI) for underweight subjects who lost weight by 5 kg or more were 2.85 (2.31–3.53) in men and 3.62 (2.65–4.95) in women; for overweight persons; the corresponding hazard ratios were 1.42 (1.18–1.70) in men and 1.82 (1.45–2.28) in women. Weight gain was related to an increased risk of all-cause mortality among underweight subjects but not among normal weight or overweight persons. An increased risk of cancer mortality associated with weight loss was observed irrespective of the initial BMI in both men and women, although the association was pronounced in underweight men (hazard ratio = 2.66, 95% CI: 1.92, 3.68). With regard to cardiovascular disease mortality, the association with weight change did not differ by initial BMI in men, whereas it was more evident among underweight subjects in women.

In men, an increased risk of all-cause, cancer and cardiovascular disease mortality associated with weight loss was observed in both nonsmokers and current smokers but was more pronounced in nonsmokers (Table 3). However, an increase risk of cancer, cardiovascular disease and cerebrovascular disease mortality with weight gain was observed in nonsmokers but not in current smokers. In the analysis by age, an increased risk of cardiovascular disease mortality in relation to weight loss and weight gain was observed in older men only; the association with weight loss reflected an increased risk of coronary heart disease mortality, whereas

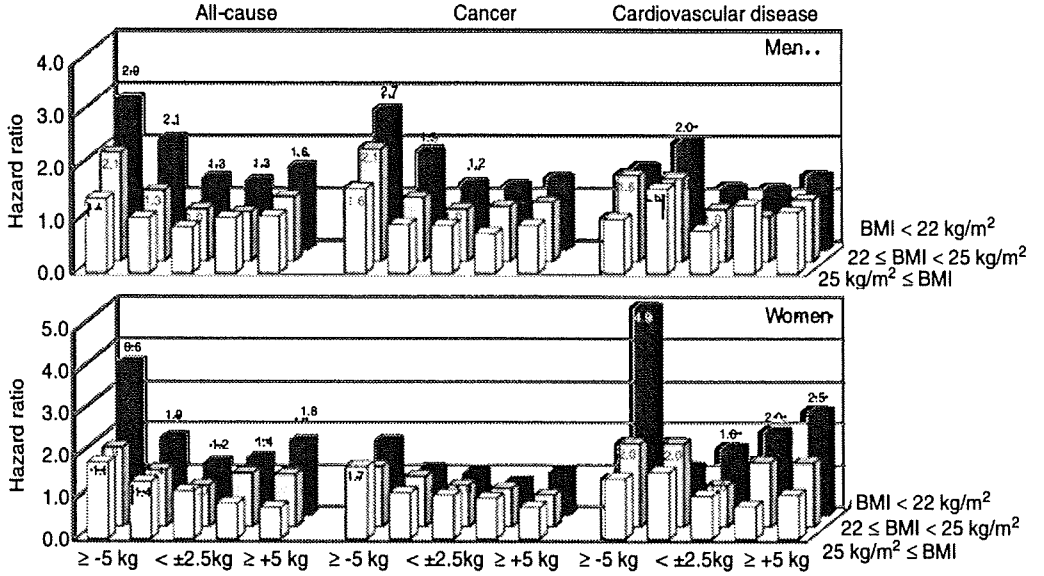

Figure 1 Multivariate-adjusted hazard ratio (a group of individuals with normal weight at baseline and stable weight for 5 years was used as reference. Hazard ratio was adjusted for age (years), study area (11 areas), smoking (never, past, current with a consumption of <20 or ≥20 cigarettes per day), alcohol consumption (nondrinker, occasional drinker, drinkers with a consumption of <150, 150–299, 300–449 or ≥450 g ethanol per week for men; and nondrinker, occasional drinker, drinkers with a consumption of <150 or ≥150 g ethanol per week for women), leisure-time physical activity (<1 time per month, 1–3 times per month, ≥1 time per week), history of hypertension (yes or no) and history of diabetes mellitus (yes or no)) of deaths according to weight change categories and initial body mass index. Abbreviation: BMI, body mass index.

that with weight gain was due to increased mortality of cerebrovascular disease. In contrast, an increased risk of cardiovascular disease mortality with weight change was more evident in the younger age group in women.

Discussion

In this large-scale population-based prospective study in Japanese men and women, the relation between weight change over a 5-year period and all-cause mortality was reverse J-shaped, with both loss and gain in weight of 5 kg or more being related to an increased risk of all-cause mortality. The association was observed irrespective of sex, age, baseline BMI and smoking status and remained significant even after adjustment for covariates. The risk of cancer mortality increased in both men and women who lost weight by 5 kg or more. Weight loss in men and women and weight gain in women were related to an increased risk of cardiovascular disease mortality.

The observed weight loss–mortality association in this study, as well as in many other studies,[10–19] may be accounted for preexisting disease and smoking, factors affecting both body weight and mortality. However, this idea has been supported by only few studies.[20,22] Many other studies found an increased mortality with weight loss even after excluding subjects with preexisting disease[12,13,16–19] or deaths in the early period of follow-up.[13,14,18,19] Similarly, an increased mortality risk among weight losers has been observed with adjustment for smoking status[12,14,17,18] or in nonsmokers.[13,16,19] In the present analytic cohort comprising only persons without serious disease, the association between weight loss and mortality remained statistically significant even after excluding deaths in the first 3 years of follow-up and was observed in both nonsmokers and smokers. Our data argue against the possibility that the weight loss–mortality association is attributed to preexisting disease or smoking.

With regard to weight gain, previous findings are conflicting. In a 1993 review of 11 studies, Andres *et al.*[11] concluded that the risk of overall mortality increased in persons who gained excessive weight, whereas it decreased in those who experienced moderate weight gain. Our finding that an increased mortality risk associated with weight gain of 5 kg or more agrees with the review. In contrast, several recently published studies have shown no association with weight gain.[10,12–15,17,20–22] We have no clear explanation for the discrepancy, but the effect of weight gain on mortality may differ according to sex, age, race, cause of death, period of weight change assessed and period of follow-up.

The association between weight change and mortality may be modified by the initial BMI levels. However, we observed an increased risk of mortality with weight loss even in overweight subjects, a finding compatible with the results of several studies showing increased mortality irrespective of the initial BMI levels.[13,14,16–18,24] We also observed an increased risk of mortality after weight gain even in underweight subjects. Data were limited regarding this point, but in one study,[16] weight gain was related to an

Table 3 Multivariate-adjusted hazard ratios and 95% confidence intervals of deaths according to weight change categories and smoking status or age categories

	Men				*Men*				*Women*			
	Nonsmoker		*Current smoker*		*< 60 year*		*⩾ 60 year*		*< 60 year*		*⩾ 60 year*	
	HR[a]	*95% CI*	*HR*[a]	*95% CI*	*HR*[b]	*95% CI*	*HR*[b]	*95% CI*	*HR*[b]	*95% CI*	*HR*[b]	*95% CI*
All-cause												
⩾5 kg loss	1.76	1.50–2.07	1.50	1.28–1.75	1.68	1.40–2.02	1.58	1.37–1.82	1.87	1.44–2.43	1.68	1.39–2.03
2.5–4.9 kg loss	1.36	1.14–1.63	1.21	1.02–1.43	1.12	0.91–1.40	1.34	1.15–1.55	1.40	1.07–1.84	1.23	1.00–1.51
2.4 kg loss–2.4 kg gain	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
2.5–4.9 kg gain	0.96	0.78–1.18	1.20	0.99–1.45	1.16	0.94–1.41	1.02	0.84–1.23	0.93	0.70–1.23	1.26	0.99–1.61
⩾5 kg gain	1.56	1.30–1.87	1.25	1.02–1.52	1.27	1.03–1.57	1.49	1.26–1.76	1.29	0.96–1.75	1.14	0.85–1.53
Cancer												
⩾5 kg loss	2.13	1.68–2.70	1.48	1.16–1.88	1.92	1.45–2.54	1.69	1.38–2.08	1.60	1.10–2.34	1.64	1.21–2.21
2.5–4.9 kg loss	1.40	1.06–1.83	1.05	0.80–1.37	1.11	0.78–1.56	1.20	0.95–1.51	1.05	0.70–1.58	1.18	0.86–1.63
2.4 kg loss–2.4 kg gain	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
2.5–4.9 kg gain	0.86	0.62–1.19	1.22	0.93–1.61	1.16	0.84–1.59	0.95	0.72–1.26	0.72	0.47–1.08	1.07	0.74–1.57
⩾5 kg gain	1.39	1.04–1.85	1.05	0.77–1.44	1.21	0.86–1.69	1.23	0.95–1.60	0.88	0.55–1.40	0.76	0.45–1.27
Cardiovascular disease												
⩾5 kg loss	1.44	0.99–2.10	1.22	0.87–1.71	1.14	0.74–1.75	1.32	0.97–1.80	1.84	1.04–3.29	1.43	1.00–2.04
2.5–4.9 kg loss	1.96	1.39–2.75	1.46	1.07–1.99	1.04	0.66–1.64	1.98	1.52–2.59	1.37	0.74–2.54	1.27	0.88–1.85
2.4 kg loss–2.4 kg gain	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
2.5–4.9 kg gain	1.34	0.90–2.00	0.89	0.59–1.36	1.20	0.80–1.80	1.00	0.67–1.47	1.25	0.70–2.25	1.32	0.83–2.10
⩾5 kg gain	1.94	1.34–2.79	0.97	0.63–1.49	1.21	0.79–1.86	1.43	1.00–2.03	1.86	1.02–3.40	1.46	0.88–2.41
Heart disease												
⩾5 kg loss	1.77	1.09–2.89	1.33	0.86–2.07	1.14	0.64–2.02	1.56	1.05–2.32	4.07	1.89–8.77	1.09	0.63–1.87
2.5–4.9 kg loss	2.16	1.36–3.45	1.66	1.11–2.48	1.20	0.68–2.13	2.16	1.52–3.08	1.07	0.32–3.61	1.10	0.63–1.91
2.4 kg loss–2.4 kg gain	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
2.5–4.9 kg gain	1.21	0.66–2.21	0.88	0.50–1.55	0.94	0.51–1.73	1.12	0.67–1.88	1.77	0.70–4.48	1.49	0.78–2.85
⩾5 kg gain	1.56	0.88–2.78	1.14	0.67–1.93	1.52	0.89–2.60	1.05	0.60–1.82	2.10	0.75–5.83	1.63	0.80–3.32
Cerebrovascular disease												
⩾5 kg loss	1.25	0.66–2.35	0.76	0.40–1.44	0.92	0.43–1.94	0.95	0.55–1.64	0.43	0.10–1.81	1.70	1.00–2.90
2.5–4.9 kg loss	1.80	1.04–3.12	0.84	0.46–1.55	0.72	0.31–1.67	1.46	0.92–2.32	1.57	0.73–3.39	1.29	0.72–2.31
2.4 kg loss–2.4 kg gain	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference	1.00	Reference
2.5–4.9 kg gain	1.24	0.66–2.31	0.76	0.37–1.58	1.28	0.70–2.37	0.59	0.27–1.28	1.15	0.53–2.48	1.05	0.50–2.21
⩾5 kg gain	2.05	1.20–3.52	0.87	0.41–1.82	0.74	0.33–1.66	1.85	1.12–3.07	1.50	0.65–3.47	1.46	0.71–2.99

Abbreviations: CI, confidence interval; HR, hazard ratio. [a]Adjusted for age (year), study area (11 areas), body mass index (<21, 21 to <23, 23 to <25, 25 to <27 and ⩾27 kg m^{-2}), alcohol consumption (nondrinker, occasional drinker, drinkers with a consumption of <150, 150–299, 300–449 or ⩾450 g ethanol per week for men and nondrinker, occasional drinker, drinkers with a consumption of <150 or ⩾150 g ethanol per week for women), leisure-time physical activity (<1 time per month, 1–3 times per month, ⩾1 time per week), history of hypertension (yes or no) and history of diabetes mellitus (yes or no). [b]Further adjusted for smoking (never, past, current with a consumption of <20 or ⩾20 cigarettes per day).

increased risk of mortality among both nonoverweight and overweight groups. These findings may suggest that weight loss and gain predict an increased mortality risk irrespective of initial BMI levels.

Limited evidence is available regarding the relation of weight change to risk of cause-specific mortality. Three studies among Western populations have examined overall cancer mortality in association with weight change, but the results are all null.[16,20,21] In our study, however, weight loss was significantly associated with an increased risk of cancer mortality. In our previous report, the risk of cancer mortality significantly increased in underweight subjects,[9] and this association was replicated in the present analysis among subjects with stable weight over a 5-year period. These findings from the JPHC Study indicate that both weight loss and underweight are important predictors of an increased risk of cancer mortality in Japanese. In contrast, we did not observe any association between weight gain and cancer mortality except for nonsmoking men. This finding seems to contradict the established association between obesity and cancer.[25,26] However, several Western studies[16,20,21] have reported no increase in cancer mortality with weight gain. Japanese differ substantially from Western populations not only in the prevalence of obesity but also in the type of major cancers. For example, stomach cancer and esophageal cancer (squamous cell carcinoma), the risks of which have been shown to increase among persons with a low BMI,[26] are much more common in Japan than in Western countries.[27] This could be an explanation why the present finding, especially for weight loss, was not compatible with those derived from Western studies.

Obesity is a known risk factor for cardiovascular disease,[28] and overweight was a significant predictor of cardiovascular disease mortality in the JPHC Study.[9] It may thus be

reasonable to expect that the risk of cardiovascular disease increased with weight gain and decreased with weight loss. However, existing data are not fully compatible with the idea. For instance, some studies[21,22] have reported a suggestion of an increased risk of cardiovascular disease mortality with weight gain, whereas some others[13,14,20] did not detect such an association. In this study, increased mortality of cardiovascular disease with weight gain was observed in women, nonsmoking men and older men. The finding of an increased risk of cardiovascular disease mortality with weight loss in men and younger women is unexpected, although similar findings have been documented in several studies.[13,14,18,20] It is not clear why the association between weight change and cardiovascular disease mortality differed by sex in this study. Given the similarity of the result for nonsmoking men and overall women (Table 3), 95% of whom were nonsmokers (Table 1), we speculate that smoking status may have modified the weight change–mortality association.

There are several plausible mechanisms to explain the association between weight gain and cardiovascular disease mortality. Weight gain increases the risk of diabetes mellitus[29,30] and hypertension,[31] worsens a profile of cardiovascular disease risk factors,[32] and induces inflammation.[33] However, the mechanism for the weight loss–cardiovascular disease association is unclear. Depression may partly account for the link due to its potential effects on both weight and mortality of cardiovascular disease.[34] Moreover, weight loss in the elderly is mainly caused by muscle loss,[35,36] which could deteriorate the risk factors for cardiovascular disease.[37] With regard to cancer, insulin is hypothesized to be involved in the pathogenesis of several cancers through effects on insulin-like growth factors[38] and could link obesity to cancer but this mechanism may be less likely to work in Japanese because of their low ability to secrete insulin.[39] There is biological evidence that supports the observed positive association with weight loss. A biomarker study showed that weight loss was associated with increased oxidative DNA damage,[40] which is hypothesized to have a major role in carcinogenesis.[41] In addition, weight loss may increase the risk of cancer because of its adverse effects on immune function.[42]

As large weight loss is one clinical condition of frailty,[43] the observed weight loss–mortality association could be explained in this context. Frailty is a state of increased vulnerability to stressors resulting from decreased physiological reserves and dysregulation of multiple physiological systems, and limited capacity to maintain homeostasis and to respond to internal and external stresses.[44] In fact, an increased risk associated with frailty was observed for various health outcomes, including falls, disability, hospitalization and mortality.[43] Although frailty itself may not be a direct cause of early death, deterioration of organ systems resulting from frailty could increase mortality risk.[45] Some studies have shown that frail persons, compared with nonfrail persons, had higher levels of markers of inflammation,[43] a condition that has been linked to cancer and cardiovascular disease.[46,47]

The strengths of this study are large sample size, population-based prospective design and few subjects being lost to follow-up (0.6%). Death registration in Japan, which we used to identify the cause of death, is believed to be complete. Moreover, we excluded subjects with serious disease and adjusted for or stratified by important confounding variables. To minimize the effect of potential occult disease, analysis was also carried out with further exclusion of deaths occurring in the first 3 years of follow-up. This study also had some limitations. First, we had no information about whether weight loss is intentional or unintentional. Intentional weight loss has been related to lower mortality, whereas unintentional weight loss has been related to higher mortality.[48,49] If we could exclude subjects with intentional weight loss, the association between weight loss and mortality would become stronger. Second, as we did not measure body composition, we did not know whether weight loss represented fat loss or muscle loss. However, it may not be feasible to measure body composition in a large sample. Third, although we extensively excluded subjects who reported serious diseases and deaths in the first 3 years of follow-up and adjusted for covariates including BMI at baseline and smoking status, we cannot completely rule out the possibility of occult disease and bias due to residual confounding. Fourth, we used self-reported weight and height. However, we confirmed that the self-reported BMI was highly correlated with the measured one. Finally, the present finding for weight loss should not be applied to clinical settings in which obese patients are instructed to decrease weight by health professionals.

Obesity and weight gain have been increasingly recognized as a major health issue,[1] but less attention has been paid to the adverse health outcome associated with underweight and weight loss except for populations that are subject to malnutrition. In the present finding among Japanese, who are on an average much thinner than Westerners, large weight change, either gain or loss, predicted subsequent mortality risk, with weight loss conferring greater risk than weight gain. More research is required to clarify the impact of intentional weight loss on subsequent morbidity and mortality and elucidate the mechanisms linking weight change and mortality risk.

Conflict of interest

The authors declare no conflict of interest.

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