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## ORIGINAL ARTICLE

# Taste preferences and body weight change in Japanese adults: the JPHC Study

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**Objective:** Limited data are available with regard to longitudinal changes in body weight by food taste preference. Here, we examined the associations between taste preferences and weight change in adults for a large-scale cohort study in Japan.  
**Design:** Longitudinal analysis of data from a population-based cohort study, the Japan Public Health Center-based Prospective Study (JPHC Study).

**Subjects:** A total of 29 103 middle-aged men and women, who participated in a JPHC Study and returned questionnaires on lifestyle and diet, including taste preferences, at both baseline and the 10th year of follow-up.

**Measurements:** We assessed the relations of preferences for rich and heavy taste and a sweet taste to weight changes between the age of 20 years and baseline and those during the 10-year follow-up period.

**Results:** Preferences for rich and heavy taste and for sweet taste were significantly positively associated with weight increases between the age of 20 years and baseline ( $P$  for trend  $<0.001$ ); the fully adjusted odds ratios (95% confidence interval) comparing the 'like' versus 'dislike' groups with a preference for rich and heavy taste were 1.45 (1.31–1.24) for men and 1.28 (1.16–1.41) for women, whereas that for a sweet taste preference was 1.22 (1.09–1.36) for women. As regards weight change during the 10 years of follow-up, subjects who liked the sweet taste and those who neither liked nor disliked this taste experienced a significantly greater increase than those who disliked it in both men and women. There was no such difference for rich and heavy taste.

**Conclusion:** These results suggest that food taste preferences may be an important predictor of weight changes in adults. Taste preferences need to be considered when counseling patients to achieve weight control.

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**Keywords:** overweight; taste preference; longitudinal studies; Japan

## Introduction

Obesity is known to be a risk factor for a wide range of diseases including cardiovascular disease and some cancers, and its prevention must be given high priority in modern society.<sup>1</sup> Energy imbalance is the most fundamental explanation for the current worldwide epidemic of obesity. Frequent intakes of energy dense foods,<sup>2,3</sup> saturated fat<sup>4</sup> and

sweetened beverages<sup>5,6</sup> have been linked to the increasing risk of obesity, whereas greater intakes of dietary fiber,<sup>7</sup> and fruits and vegetables<sup>8</sup> have been shown to be protective against obesity. Food selection may be determined by various factors, including knowledge, preference and environment.<sup>9</sup> Among these, taste preferences are formed in the early stage of life<sup>10</sup> and may have a marked influence on the choice of foods throughout an individual's lifetime.<sup>11</sup> As it is difficult to estimate energy intake over a long period of time, taste preferences may provide additional information on dietary habits that cannot easily be ascertained by a standard dietary assessment.<sup>12</sup>

Compatible with the worldwide trend, the prevalence of obesity in Japan has also been increasing.<sup>13,14</sup> Traditionally, the Japanese diet is characterized by an essentially simple

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<sup>6</sup>See Appendix

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taste, with a minimum amount of oil being used in cooking, although it contains a large amount of salt.<sup>15</sup> Owing to the westernization of lifestyles, fatty and sweetened foods have become much more readily available in Japan. In such a food environment, it may be that persons who have a preference for fatty foods or sweets have a greater risk of developing obesity or overweight than those who do not. However, there is little actual evidence linking weight change with taste preferences.<sup>16</sup>

The objective of this study was to investigate weight increases during adulthood in association with two types of taste preference: one for a rich and heavy taste, and the other for a sweet taste. These associations were examined using data from a large-scale population-based cohort study in Japan.

## Subjects and methods

### *The JPHC Study*

The data used in this study were derived from the Japan Public Health Center-based Prospective Study (JPHC Study) Cohort I, a large-scale, population-based cohort study of residents in 15 administrative areas covered by a total of five public health centers in Ninohe (Iwate prefecture), Yokote (Akita prefecture), Saku (Nagano prefecture), Ishikawa (Okinawa prefecture) and Katsushika-kita (Tokyo metropolitan area). These PHC areas were selected to represent the extent of variation in the mortality rate of stomach cancer based on our previous ecological study.<sup>17</sup> Most of the centers are located in rural areas. The Japanese inhabitants were identified by the population registries maintained by the local municipalities.<sup>18</sup> The target age of the JPHC Study Cohort I was between 40 and 59 years at the baseline survey, which was carried out mainly in 1990. A self-administered questionnaire was distributed to study participants at the baseline, 5th- and 10th-year follow-up surveys. The design of the JPHC Study has been reported in detail elsewhere.<sup>19</sup> This study was approved by the human ethics review committees of the National Cancer Center.

### *Assessment of taste preference and lifestyles*

Items included in the baseline questionnaire were socio-demographic factors, medical history, health-related lifestyle factors, as well as height and weight, and any increase in weight of more than 5 kg from age 20 years to baseline (yes or no). Diet was assessed by using a 44-item food frequency questionnaire, and energy intake (kcal), fat intake (g), and energy ratios of protein, fat and carbohydrate were estimated. The validation of this food frequency questionnaire was reported previously.<sup>20</sup> Taste preferences for foods were obtained by asking whether they liked the rich and heavy taste (*kotteri* in Japanese) and whether they liked the sweet taste. *Kotteri* is a word that all Japanese would know, indexing a taste as common as sweet or sour, and described as a rich and heavy taste in the *Kojien*, one of the most

popular Japanese dictionaries. The questioning sentence used was as follows: '*Kotteri to shita ryori wa suki desu ka?*' (Do you like rich and heavy food?) The possible responses to each taste preference were 'dislike', 'neither dislike nor like (hereafter 'neither')' and 'like.' At the 10-year survey, body height and weight were also self-reported. Body mass index (BMI) was calculated as weight in kilograms divided by square height in meters. Of JPHC Study participants at baseline, 5575 men and 9736 women attended health check-up and provided measured data on height and weight;<sup>17</sup> the Spearman's correlation coefficients between BMI based on self-reported data and that on measured data were 0.89 and 0.91 for men and women, respectively.

### *Study subjects*

Overall, a total of 50 245 residents (82%) returned the baseline questionnaire. In total, 37 860 (75%) people responded to the follow-up study conducted 10 years after the baseline. For this analysis, we excluded the 1648 subjects in the Tokyo-Katsushika public health center because individuals surveyed in these areas were limited to those aged 40 or 50 years, or were selected from among participants in a health check-up program. Furthermore, we excluded 7109 subjects who had a self-reported BMI <14 or >40 kg m<sup>-2</sup> or who had data missing from the baseline and/or 10-year follow-up survey. We also excluded the following subjects: those with any self-reported serious illness (cancer, cerebrovascular disease, myocardial infarction, chronic liver disease or angina pectoris) at baseline; those who did not answer baseline survey questions on taste preferences, smoking history, alcohol drinking, exercise habit, oil use and weight change from age 20 years to present and those whose energy intake was <900 or >4000 kcal for men and <800 or >3600 kcal for women. These exclusions left 29 103 subjects (13 443 men and 15 660 women) who were appropriate for the final analysis. Among subjects who had valid data on BMI and taste preference at baseline, those who remained in the analysis were slightly younger than those excluded from the analysis; mean (s.d.) age of the former and latter groups, respectively, was 49.1 (5.9) and 51.2 (5.7) years in men and 49.4 (5.8) and 50.4 (5.8) years in women. There was little difference in BMI and taste preferences between the two groups.

### *Analyses*

All analyses were done in a sex-specific manner. We compared baseline characteristics of study subjects according to taste preferences, and their trend associations were assessed by using a linear regression analysis for continuous variables or a logistic regression analysis for categorical variables, with values of 1–3 assigned to categories of taste preference. Logistic regression analysis was used to estimate the odds ratio of having a more than 5 kg weight increase between age of 20 years and the baseline for each taste preference, using the answer 'dislike' as the reference. Two

types of adjustments were made; first, age and study area (Okinawa or other); second, age, study area, smoking (never, former or current) and exercise ( $1 <$  per week or  $1 \geq$  per week) at baseline. Study area was adjusted for because of a large difference in obesity levels between Okinawa and other areas.<sup>13</sup> The relationships between taste preferences and changes in body weight from baseline to the 10-year survey were examined by analysis of covariance. Two types of adjustments were made; first, age, study area (Okinawa or other) and body weight at baseline; second, age, study area, body weight, smoking (never, former or current) and exercise ( $1 <$  per week or  $1 \geq$  per week) at baseline. Trend associations were assessed with ordinal numbers 1–3 assigned to categories of taste preference. All analyses were performed using SPSS (Version 15.0, SPSS Inc, Chicago, IL, USA).

## Results

Table 1 shows the baseline characteristics of the subjects. The mean BMI increased in the order of groups responding 'dislike', 'neither' and 'like' to the questions about taste

preferences, respectively, in both tastes. There were no differences in energy intake, protein energy ratio, fat energy ratio, carbohydrate energy ratio or exercise among the three groups for either taste. The proportion of persons with frequent consumption of oily foods increased in the order of 'dislike', 'neither' and 'like' for the rich and heavy taste among both men and women.

Table 2 shows the odds ratio of having a more than 5 kg weight increase between age 20 years and the baseline survey for each taste preference in those answering 'dislike', as the reference group, according sex. There was a significant positive association between a preference for rich and heavy taste and the risk of weight increase for both men and women, and between preference for sweet taste and the risk only for women, with adjustment for age and study area ( $P$  for trend  $<0.001$ ). The association did not fundamentally change after further adjustment for other potential confounding variables ( $P$  for trend  $<0.001$ ). The fully adjusted odds ratios (95% confidence interval) comparing the 'like' versus 'dislike' groups with a preference for rich and heavy taste were 1.45 (1.31–1.61) for men and 1.28 (1.16–1.41) for women, whereas that for a sweet taste preference was 1.22

Table 1 Baseline characteristics: JPHC Study

	Men				Women			
	Dislike	Neither dislike nor like	Like	Trend P	Dislike	Neither dislike nor like	Like	Trend P
<i>Rich and heavy taste</i>								
No. of participants	2880	7066	3497		3638	8812	3210	
Age (years)	49.5 (5.8)	49.1 (6.0)	48.6 (5.8)		50.1 (5.7)	49.5 (5.8)	48.4 (5.8)	
People living in Okinawa (%)	13.9	23.5	29.5	$<0.001$	14.2	21.3	29.0	$<0.001$
Body height (cm)	163.8 (6.0)	164.0 (6.0)	164.5 (6.1)	$<0.001$	151.5 (5.2)	151.8 (5.2)	151.9 (5.2)	0.004
Body weight (kg)	61.7 (8.0)	63.4 (8.3)	65.2 (8.7)	$<0.001$	53.4 (7.5)	54.1 (7.2)	55.3 (7.7)	$<0.001$
Body mass index ( $\text{kg m}^{-2}$ )	23.0 (2.6)	23.5 (2.7)	24.1 (2.8)	$<0.001$	23.2 (3.1)	23.5 (3.0)	24.0 (3.1)	$<0.001$
Current smoking (%)	53.7	49.5	52.9	0.733	5.3	3.8	5.8	0.436
Alcohol drinking (%) <sup>a</sup>	61.5	59.6	59.8	0.188	6.8	6.1	7.1	0.672
Exercise (%) <sup>b</sup>	16.2	18.3	19.0	0.006	14.5	14.7	13.2	0.134
Energy intake (kcal per day) <sup>c</sup>	2223 (591)	2169 (583)	2194 (602)	0.100	1436 (339)	1457 (333)	1474 (365)	$<0.001$
Protein energy ratio (%)	12.0 (2.1)	12.0 (2.0)	11.9 (2.1)	$<0.001$	14.9 (2.2)	14.8 (2.0)	14.7 (2.1)	$<0.001$
Fat energy ratio (%)	14.2 (4.9)	14.7 (4.8)	14.9 (4.9)	$<0.001$	19.6 (5.3)	20.3 (5.1)	20.5 (5.1)	$<0.001$
Carbohydrate energy ratio (%)	62.8 (8.9)	62.7 (8.6)	61.9 (8.8)	$<0.001$	63.2 (7.0)	62.7 (6.5)	62.2 (6.9)	$<0.001$
Fat (g)	34.2 (13.6)	34.6 (12.6)	35.3 (13.0)	0.001	31.4 (12.1)	32.9 (11.6)	33.6 (11.9)	$<0.001$
Oily foods (%) <sup>d</sup>	52.7	66.8	76.8	$<0.001$	59.3	72.4	79.8	$<0.001$
<i>Sweet taste</i>								
No. of participants	3304	6715	3424		1758	8069	5833	
Age (years)	48.6 (5.8)	49.1 (5.9)	49.4 (5.9)		49.6 (5.9)	49.5 (5.8)	49.1 (5.8)	
People living in Okinawa (%)	20.0	22.3	27.2	$<0.001$	20.5	20.1	23.0	0.001
Body height (cm)	164.3 (6.0)	164.1 (6.0)	163.9 (6.1)	0.005	151.4 (5.2)	151.7 (5.2)	151.9 (5.2)	$<0.001$
Body weight (kg)	63.4 (8.3)	63.5 (8.4)	63.7 (8.8)	0.227	53.3 (7.5)	53.9 (7.3)	54.8 (7.5)	$<0.001$
Body mass index ( $\text{kg m}^{-2}$ )	23.5 (2.6)	23.6 (2.7)	23.7 (2.9)	0.001	23.3 (3.1)	23.4 (3.0)	23.7 (3.0)	$<0.001$
Current smoking (%)	60.7	49.9	45.0	$<0.001$	11.1	4.2	3.0	$<0.001$
Alcohol drinking (%) <sup>a</sup>	80.2	61.1	38.5	$<0.001$	15.2	6.1	4.3	$<0.001$
Exercise (%) <sup>b</sup>	17.5	18.5	17.7	0.840	15.8	15.1	13.0	$<0.001$
Energy intake (kcal per day) <sup>c</sup>	2226 (586)	2187 (586)	2149 (601)	$<0.001$	1464 (375)	1453 (336)	1456 (339)	0.699
Protein energy ratio (%)	11.7 (2.2)	12.0 (2.0)	12.2 (2.0)	$<0.001$	14.6 (2.3)	14.9 (2.1)	14.7 (2.1)	0.103
Fat energy ratio (%)	14.0 (4.8)	14.7 (4.8)	15.2 (5.0)	$<0.001$	19.6 (5.6)	20.3 (5.0)	20.1 (5.1)	0.038
Carbohydrate energy ratio (%)	59.3 (9.0)	62.7 (8.5)	65.3 (8.0)	$<0.001$	61.8 (8.0)	62.6 (6.6)	63.1 (6.5)	$<0.001$

Abbreviations: BMI, body mass index ( $\text{kg m}^{-2}$ ). <sup>a</sup>Alcohol drinking: drinking more than three times per week. <sup>b</sup>Exercise: exercising more than once a week. <sup>c</sup>Energy intake from alcohol is included. <sup>d</sup>Oily foods: consuming oily foods more than three times per week. Values except for percentages are means (s.d.).

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	
<b>Rich and heavy taste</b>										
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) <sup>a</sup>	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	
<b>Sweet taste</b>										
No. of participants	3304	6715	3424			1758	8069	5833		
≥ 5 kg increase between 20 years old and baseline										
No. of participants	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) <sup>a</sup>	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. <sup>a</sup>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<sup>16,21</sup> and in almost overweight or obesity,<sup>12,22</sup> and also in dietary restraint<sup>23</sup> and/or disinhibition.<sup>24</sup> 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.<sup>16</sup>

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
<b>Rich and heavy taste</b>								
No. of participants	2880	7066	3497		3638	8812	3210	
Changes in body weight for 10 years (kg) <sup>a</sup>	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) <sup>b</sup>	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
<b>Sweet taste</b>								
No. of participants	3304	6715	3424		1758	8069	5833	
Changes in body weight for 10 years (kg) <sup>a</sup>	-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) <sup>b</sup>	-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

<sup>a</sup>Adjusted for age, study area (Okinawa or other) and body weight at baseline. <sup>b</sup>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,<sup>25</sup> 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.<sup>26</sup> 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,<sup>25</sup> 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.<sup>27</sup> 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,<sup>12,28</sup> 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.<sup>12</sup>

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.<sup>17</sup> 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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## 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 epidemi-

ological 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.

**Electronic supplementary material** The online version of this article (doi:10.1007/s00125-009-1554-x) contains a list of the members of the Japan Public Health Center-based Prospective Study Group, which is available to authorised users.

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

### Abbreviations

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

## 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<sub>3</sub> 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  $\geq 7$  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  $\geq 10$  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  $\geq 7.8$  mmol/l; and (2) casual plasma glucose  $\geq 11$  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  $\geq 27$  kg/m<sup>2</sup>); (2) family history of diabetes mellitus (yes or no); (3) smoking status (none, past, current smoking  $<20$  cigarettes/day or current smoking  $\geq 20$  cigarettes/day); (4) alcohol intake (men: none,  $<150$ , 150–299, 300–449 or  $\geq 450$  g ethanol per week; women: none,  $<150$ , 150–299 or  $\geq 300$  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,  $\geq 2$ –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  $\geq 25$  kg/m<sup>2</sup>), 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)				p value, trend
	Lowest	Second	Third	Highest	Lowest	Second	Third	Highest	
<b>Calcium</b>									
Age, years	55 (8)	56 (8)	57 (8)	58 (8)	57 (8)	57 (8)	57 (8)	58 (8)	<0.001
BMI (kg/m <sup>2</sup> )	23.6 (2.9)	23.6 (2.8)	23.5 (2.8)	23.6 (2.8)	23.5 (3.1)	23.5 (3.1)	23.5 (3.0)	23.4 (3.0)	0.33
Family history of diabetes (%)	5.6	6.6	5.9	6.1	5.5	5.8	6.1	6.1	0.03
Current smokers (%)	53.8	50.5	45.2	37.9	7.0	4.5	3.5	3.5	<0.001
Alcohol intake ≥150 g/week (%)	67.6	55.8	47.8	34.0	4.6	2.4	1.4	1.0	<0.001
Sports ≥1 time/week (%)	16.3	19.2	22.2	26.6	14.7	19.0	21.3	25.7	<0.001
Antihypertensive medication (%)	21.9	21.7	22.3	23.0	22.1	22.1	23.3	23.3	0.005
Coffee ≥1 cup/day (%)	31.4	34.1	32.0	30.4	38.9	35.8	33.5	31.5	0.97
<b>Dietary intake (median)</b>									
Calcium (mg/day)	254	356	457	629	356	487	608	810	<0.001
Vitamin D (µg/day)	7.7	9.7	10.3	10.9	8.3	9.7	10.4	10.1	<0.001
Magnesium (mg/day)	245	286	307	331	248	281	298	314	<0.001
Dairy products (median) (g)	21	68	180	260	39	124	214	304	<0.001
Calcium supplement use (%)	0.1	0.2	0.2	0.1	0.5	0.4	0.6	0.7	0.34
<b>Vitamin D</b>									
Age (years)	56 (8)	56 (8)	57 (8)	58 (8)	58 (8)	56 (8)	57 (8)	58 (7)	<0.001
BMI (kg/m <sup>2</sup> )	23.7 (2.9)	23.6 (2.8)	23.5 (2.8)	23.4 (2.8)	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	4.9	6.5	6.5	5.6	0.046
Current smokers (%)	46.8	47.2	46.8	46.6	4.7	4.5	4.6	4.6	<0.001
Alcohol intake ≥150 g/week (%)	57.4	52.9	50.6	44.5	2.8	2.4	2.5	1.8	<0.001
Sports ≥1 time/week (%)	21.0	22.2	21.1	19.9	20.7	21.0	20.4	18.8	<0.001
Antihypertensive medication (%)	20.5	21.5	22.8	24.1	23.4	20.9	21.9	24.7	0.01
Coffee ≥1 cup/day (%)	37.6	34.4	30.5	25.6	41.9	38.7	33.0	26.2	<0.001
<b>Dietary intake (median)</b>									
Calcium (mg/day)	348	403	423	439	495	548	565	568	<0.001
Vitamin D (µg/day)	4.7	8.1	11.5	18.0	4.8	8.1	11.4	17.4	<0.001
Magnesium (mg/day)	265	284	298	315	264	278	289	301	<0.001
Dairy products (median) (g)	70	121	130	114	123	195	200	164	<0.001
Calcium supplement use (%)	0.2	0.2	0.1	0.1	0.6	0.7	0.4	0.4	0.10

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 trend).

**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 ( <i>n</i> )	Cases ( <i>n</i> )	Age- and area-adjusted OR (95% CI)	Multivariable OR (95% CI)*
<b>Calcium</b>				
<b>Men</b>				
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)
<i>p</i> value for trend			0.52	0.95
<b>Women</b>				
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)
<i>p</i> value for trend			0.039	0.095
<b>Vitamin D</b>				
<b>Men</b>				
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)
<i>p</i> value for trend			0.58	0.35
<b>Women</b>				
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)
<i>p</i> 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  $\geq 27$  kg/m<sup>2</sup>), family history of diabetes mellitus (yes or no), smoking status (none, past, current smoking <20 or  $\geq 20$  cigarettes/day), alcohol intake (men: none, <150, 150–299, 300–449 or  $\geq 450$  g ethanol/week; women: none, <150, 150–299 or  $\geq 300$  g ethanol/week), history of hypertension (yes or no), exercise frequency (less than once/week or  $\geq$ once/week), consumption of coffee (less than daily, 1–3 cups/day or  $\geq 4$  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 ( <i>n</i> )	Cases ( <i>n</i> )	Multivariable OR (95% CI)*	At risk ( <i>n</i> )	Cases ( <i>n</i> )	Multivariable OR (95% CI)*
<b>Dairy products</b>						
<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)
<i>p</i> value for trend			0.21			0.054
<b>Milk</b>						
<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)
<i>p</i> value for trend			0.88			0.16
<b>Cheese</b>						
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)
<i>p</i> value for trend			0.39			0.56
<b>Yogurt</b>						
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)
<i>p</i> 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 ( <i>n</i> )	Cases ( <i>n</i> )	Multivariable OR (95% CI)*	At risk ( <i>n</i> )	Cases ( <i>n</i> )	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)
<i>p</i> 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)
<i>p</i> 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<sub>3</sub>, 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,<sup>1,2</sup> is an increasing public health problem worldwide.<sup>2–4</sup> The relation between body mass index (BMI) and all-cause mortality is

J-<sup>5–7</sup> or U-shaped,<sup>5,8,9</sup> 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,<sup>10–19</sup> but not all,<sup>20–22</sup> 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<sup>16</sup> or excess weight gain,<sup>11</sup> whereas others showed no association with weight gain.<sup>10,12–15,17,20–22</sup> However, these studies were relatively small in size (number of subjects less than 10 000<sup>10,12,14,15,17,18,20–22</sup>), included only elderly people (65 years old and above<sup>10,12,15,17</sup>), assessed short-term weight change (within 2 years<sup>10,15,21</sup>) and did not report cause-specific mortality.<sup>10,12,15,17,19</sup> Moreover, most of the studies were conducted among Western populations<sup>10,12–14,16–18,20–22</sup> and the evidence regarding this issue is sparse among Asian populations,<sup>15,19</sup> 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.<sup>23</sup> 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<sup>-2</sup>, 40 kg m<sup>-2</sup> 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:  $\geq 5$  kg loss, 2.5–4.9 kg loss,  $< 2.5$  kg change (stable), 2.5–4.9 kg gain and  $\geq 5$  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  $\geq 27$  kg m<sup>-2</sup>), smoking (lifetime nonsmoker, former smoker or current smoker with a consumption of  $< 20$  or  $\geq 20$  cigarettes per day), alcohol consumption (nondrinker, occasional drinker or drinker with a consumption of  $< 150$ , 150–299, 300–449 or  $\geq 450$  g ethanol per day for men; and nondrinker, occasional drinker or drinker with a consumption of  $< 150$  or  $\geq 150$  g ethanol per day for women), leisure-time physical activity ( $< 1$  time per month, 1–3 times per month or  $\geq 1$  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<sup>-2</sup> (underweight), 22 to  $< 25$  kg m<sup>-2</sup> (normal weight) and  $\geq 25$  kg m<sup>-2</sup> (overweight)), smoking (current smoker and nonsmoker in men only) or age ( $< 60$  and  $\geq 60$  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-