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ORIGINAL CONTRIBUTION

Low-fat dairy, but not whole-/high-fat dairy, consumption is related with higher serum adiponectin levels in apparently healthy adults

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Abstract
Purpose Although previous studies suggested that higher low-fat dairy consumption lower the risk of type 2 diabetes, the mediating factors are not well understood. Higher baseline adiponectin levels are related with a lower risk of type 2 diabetes. This study evaluated whether low-fat dairy is related with adiponectin in apparently healthy adults.
Methods We investigated a cross-sectional ($n = 938$) and one-year longitudinal ($n = 759$) relationship between low-fat and whole-/high-fat dairy (both including cow's milk and yogurt) and adiponectin. Dairy consumption was assessed with a validated food frequency questionnaire. Serum adiponectin was measured by using a specific sandwich enzyme-linked immunosorbent assay.
Results In the cross-sectional analysis, the geometric means (95 % confidence intervals [95 % CIs]) of log-transformed adiponectin related with the low-fat dairy categories were 7.27 (6.80–7.77) for the lowest category, 7.67 (7.09–8.31) for the middle category, and 8.40 (7.73–9.13) for the highest category ($p < 0.001$) after adjustment for potential confounders (including all lifestyle factors). In the longitudinal analysis, repeated-measures ANCOVA adjusted for confounding factors showed a significant time-by-categories (categories of low-fat dairy) interaction in the change of adiponectin. In contrast, no significant relationship was found between the whole-/high-fat dairy categories and adiponectin.
Conclusions This study has shown that higher consumption of low-fat dairy, but not of whole-/high-fat dairy, is related with higher levels of adiponectin and with the change of adiponectin level at the one-year follow-up. These results suggest that the consumption of low-fat dairy may have a beneficial effect on serum adiponectin levels.

Keywords Low-fat dairy · Adiponectin · Diabetes risk factors · Insulin resistance

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Introduction

Dairy products are complex mixtures of biochemical compounds and micronutrients; they are a good source of high-quality protein, several vitamins, bioactive peptides, oligosaccharides, organic acids, and minerals. Dairy drinks have nutritional value and offer health benefits not only to children but also to adults and the elderly [1, 2].

Although previous studies have demonstrated that higher low-fat dairy consumption is related with a lower risk of type 2 diabetes [3, 4], the mediating factors underlying this relationship have not been fully identified. Meanwhile, adiponectin (a circulating protein that has insulin-sensitizing effects on liver and other tissues) is down-regulated in obese individuals [5, 6], whereas it is secreted at high levels in the adipose tissues of lean individuals [7–9]. Furthermore, high adiponectin levels are related with a lower risk of type 2 diabetes [10]. It was, therefore, hypothesized that adiponectin may be a mechanism which mediates the relationships between dairy product consumption and type 2 diabetes. On the other

hand, prospective cohort studies have also suggested that low fat, but not whole fat, was related with a lower risk of type 2 diabetes [3, 4]. Although no definitive explanation exists for the inverse relationship found between low-fat dairy products and whole-fat dairy products, it is plausible that saturated fats in whole-fat dairy products somehow neutralize the beneficial effect of dairy consumption. Thus, it was also hypothesized that whole-/high-fat dairy and low-fat dairy products may have different regulatory effects on adiponectin. However, to the best of our knowledge, no epidemiological study has assessed the relationship between the consumption of low-fat dairy or whole-/high-fat dairy and adiponectin in the general population.

At present, we have designed a cross-sectional and one-year longitudinal study to investigate whether low-fat dairy or whole-/high-fat dairy consumption are related with circulating levels of adiponectin among apparently healthy adults.

Methods

Study population

The Oroshisho longitudinal study is composed of a dynamic cohort of adult employees working in Sendai Oroshisho Center (a general distribution center of multi-industry companies) in Sendai, Northern Japan. This study aims to investigate the risk factors for lifestyle-related illness or metabolic syndromes. The study was based on annual health examinations from 2008. A detailed description of the methods has been published elsewhere [11].

Both the 2008 and 2009 data were used in this study. In 2008 and 2009, there were 1,253 and 1,263 individuals, respectively, who had a received health examination; of these, 1,154 and 1,215 individuals, respectively, agreed to participate and provided informed consent for their data to be analyzed. The 2008 data were analyzed in the cross-sectional study, and the follow-up data were analyzed in the longitudinal study. The Institutional Review Board of the Tohoku University Graduate School of Medicine approved the study protocol.

Participants were excluded at baseline if they did not have dietary information ($n = 71$) or adiponectin measurement ($n = 5$); if they had a history of cardiovascular disease (CVD) ($n = 5$); or if they used antihypertensive ($n = 100$), lipid-lowering ($n = 15$), or antidiabetic agents ($n = 20$). These exclusions gave a final cross-sectional study population of 938 participants. Of those invited, 179 participants did not undergo health examinations in 2009, and data from 759 participants were used in the longitudinal analysis.

Assessment of dietary consumption

The participants were instructed to complete a brief, self-administered diet history questionnaire (BDHQ) that included questions on 75 food items along with their specified serving sizes [12]. The participants indicated their mean frequency of consumption of the food over the past month by checking one of the 7–8 frequency categories, ranging from "almost never" to "two or more times a day." The mean daily consumption of nutrients was calculated using an ad hoc computer program developed to analyze the questionnaire. The Japanese food composition table, 5th edition, was used as the nutrient database. The reproducibility and validity of the BDHQ have been described in detail elsewhere [12].

Participants indicated the mean frequency of consumption of dairy products (low-fat dairy and whole-/high-fat dairy: each one included cow's milk or yogurt) in terms of the specified serving size by selecting one of the seven frequency categories: almost never, <1 cup/week, 1 cup/week, 2–3 cups/week, 4–6 cups/week, 1 cup/day, and >2 cups/day. In the study region, the volume of a typical serving of dairy products is 150 mL in female and 173 mL in male [13]. Low-fat dairy or whole-/high-fat dairy consumptions (g/day) were separately classified into three categories: zero consumption, the remainders were divided into two groups based on a median daily consumption.

Measurement of serum adiponectin concentration

Serum adiponectin concentration was measured using a specific sandwich enzyme-linked immunosorbent assay (Otsuka Pharmaceutical, Tokyo, Japan). The detection limit of the assay was 23.4 pg/mL, the measurement range was 0.375–12.0 ng/mL, and the intra- and interassay coefficients of variation (CV) were less than 10 %.

Assessment of other variables

Blood pressure (BP) was measured twice from the upper left arm by using an automatic device (YAMASU605P; Kenzmedico, Saitama, Japan) after 5 min of rest in the sitting position. The mean of the 2 measurements was taken as the BP value.

Blood samples were collected in siliconized vacuum glass tubes containing sodium fluoride, for the analysis of fasting blood glucose (FBG), or containing no additives, for the analysis of lipids and adiponectin. FBG was measured by using enzymatic methods (Eerotec, Tokyo, Japan). The concentrations of triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were measured by enzymatic methods using appropriate kits (Sekisui Medical, Tokyo, Japan).

Anthropometric parameters (height and body weight) were recorded using a standard protocol. Body mass index (BMI) was calculated as weight in kilograms divided by squared height in meters (kg/m^2). Educational level was assessed by determining the last grade level. History of physical illness and current medication were noted as "yes" or "no." Information on age, sex, smoking status, and drinking status was obtained by conducting a questionnaire survey. The levels of physical activity (PA) were estimated using the International Physical Activity Questionnaire (including the validated Japanese version) [14]. Total daily PA (MET hours per week) was calculated [14], and PA was categorized into tertiles with a similar number of individuals.

Statistical analysis

All statistical analyses were performed using the Statistical Analysis System 9.2 edition (SAS Institute Inc., Cary, NC, USA). Because the distribution of all continuous variables was non-normal, the natural logarithm was applied to normalize the data before analysis of covariance (ANCOVA). For analysis, log-transformed adiponectin was used as a dependent variable, and dairy product consumption categories were used as independent variables. In the baseline analysis, differences among dairy product consumption categories were examined by ANCOVA for continuous variables and by multiple logistic regression analysis for proportional variables after adjustment for age and sex. For both cross-sectional and longitudinal analyses, ANCOVA and repeated-measures ANCOVA were used to examine the relationships between dairy product consumption categories and log-transformed adiponectin or the changes of adiponectin during the follow-up period, respectively, after adjustment for covariates: model 1, the variables adjusted for were age, sex, and BMI (in longitudinal analysis, additionally adjusted for baseline adiponectin); model 2, the variables adjusted for were those of model 1 plus PA (tertiles), smoking status, drinking status, and educational level (≥college); model 3, the variables adjusted for were those of model 2 plus the tertiles of total energy, dietary fiber, saturated fatty acid (SFA), n-3 polyunsaturated fatty acids (n-3 PUFA), vegetable, fruit intake, and other dairy product (low-fat or whole-/high-fat dairy categories); model 4, the variables adjusted for were those of model 3 plus SBP, FBG, TG, LDL-C, and HDL-C. Bonferroni-corrected p values were used for comparisons between dairy product consumption categories. The analyses of subgroups of study participants are important for evaluating the heterogeneity of the relationship across the levels of the baseline characteristic [15]. The appropriate statistical method for assessing the heterogeneity of the relationship begins with a statistical test for interaction [15]. In this study, interactions between dairy product consumption categories and confounders of log-transformed adiponectin, or the change of adiponectin, were tested by the addition of cross-product terms to the regression model. Furthermore, when multiple testing for interactions is performed, it is very important to think about the probability of a false positive finding [15]. However, in our current study, the interactions were not detected as significant for all confounders when using the customary criteria ($p < 0.05$). All tests were two-tailed, and $p < 0.05$ was defined as statistically significant.

Results

Cross-sectional analysis

Age- and sex-adjusted baseline characteristics according to categories of dairy products are shown in Table 1. Compared to individuals in the highest low-fat dairy consumption category, the lowest and/or middle category groups were younger and had lower consumption levels of total calories, calcium, total fat, SFA, n-3 PUFA, total protein, dietary fiber, vegetable, and fruit, with the lowest category group having lower levels of LDL and adiponectin ($p < 0.05$). The percentages of females and subjects who were everyday drinkers are significantly higher in the lowest category of low-fat dairy as compared to the highest category, but this result is reversed with sometime drinking subjects. Other than these results, no significant differences were observed between the categories of low-fat dairy consumption.

For the whole-/high-fat dairy groups, no significant relationship was observed between LDL, adiponectin or n-3 PUFA, and whole-/high-fat dairy categories. The percentage of subjects who were current smokers is significantly higher in the lowest category as compared to the highest category of whole-/high-fat dairy. Other relationships were similar to the categories of low-fat dairy consumption.

Table 2 shows the adjusted relationships between the categories of dairy products and adiponectin. In model 4, for the low-fat dairy categories, the adjusted geometric means (95 % confidence intervals [CIs]) of log-transformed adiponectin related with the low-fat dairy categories were 7.27 (6.80, 7.77) for the lowest category, 7.67 (7.09, 8.31) for the middle category, and 8.40 (7.73, 9.13) for the highest category ($p < 0.001$). The geometric mean of log-transformed adiponectin related with the highest low-fat dairy category was 15.5 % higher than that related with the lowest category (Bonferroni-corrected p value < 0.001). The tests for interaction between the categories of low-fat dairy consumption and other

Table 1 Age- and sex-adjusted baseline characteristics of the participants according to categories of dairy products ($n = 938$)

Low-fat dairy (range, g/day)	Category of dairy products			p value[a]
	0–0	8.0–54.9	58.9–375.9	
No. of participants	505	225	208	–
Age (years)	42.4 (41.5, 43.3)[b,c]	42.6 (41.3, 43.9)[c]	45.9 (44.5, 47.5)	<0.0001
Sex (female, %)	29.1[c]	23.6	17.3	<0.01
BMI (kg/m^2)	22.1 (21.8, 22.4)	22.4 (22, 22.9)	22.1 (21.6, 22.5)	0.40
SBP (mmHg)	121.1 (119.8, 122.5)	120.2 (118.3, 122.1)	118.9 (116.9, 120.9)	0.16
DBP (mmHg)	75.5 (74.5, 76.4)	75.5 (74.2, 76.9)	73.6 (72.2, 75)	0.06
Fasting blood sugar (mg/dl)	91.4 (90.4, 92.4)	91.4 (90, 92.9)	92 (90.4, 93.6)	0.79
TG (mg/dl)	85.1 (80.9, 89.4)	87.4 (81.2, 94.1)	88.2 (81.5, 95.3)	0.67
LDL (mg/dl)	112.6 (109.8, 115.6)[d]	115.1 (110.8, 119.6)	120.2 (115.4, 125.1)	0.02
HDL (mg/dl)	56.9 (55.7, 58.1)	56.6 (54.8, 58.4)	57.9 (56, 59.9)	0.55
Serum adiponectin concentration (μg/ml)	7.3 (6.9, 7.6)[d]	7.5(7, 8)	8.3 (7.8, 8.9)	<0.01
Total energy consumption (kcal/day)	1631.1 (1583.9, 1679.7)[c]	1636.7 (1567.6, 1708.8)[c]	1800.3 (1719.8, 1884.6)	<0.001
Calcium consumption (mg/day)	372.4 (356.9, 388.6)[c]	365.4 (343.3, 389)[c]	634.8 (594.1, 678.3)	<0.0001
Total fat (% of energy consumption)	24.9 (24.4, 25.5)[c, d]	23.5 (22.8, 24.3)[c]	26.5 (25.6, 27.4)	<0.0001
SFA (% of energy consumption)	6.3 (6.1, 6.5)[c,d]	5.8 (5.6, 6.1)[c]	6.9 (6.6, 7.2)	<0.0001
n-3 PUFA (% of energy consumption)	1.2 (1.2, 1.3)[c]	1.2 (1.1, 1.3)[c]	1.3 (1.3, 1.4)	<0.001
Total protein consumption (g/day)	54.0 (52.1, 56.0)[c]	53.1 (50.4, 55.9)[c]	66.7 (63.2, 70.5)	<0.0001
Dietary fiber (g/day)	9.1 (8.7, 9.5)[c]	9.1 (8.5, 9.7)[c]	11.1 (10.4, 11.9)	<0.0001
Vegetable consumption (g/day)	130.9 (121.1, 141.5)[d]	126.6 (113, 141.9)[d]	169.9 (150.6, 191.7)	<0.001
Fruit consumption (g/day)	18.8 (16.6, 21.3)[c,d]	26.6 (22.1, 31.9)[c]	38.8 (32, 47.1)	<0.0001
Tertile of physical activity (%)				
Middle (range 0.55–20.0 Mets·hours/week)	35.6	35.1	42.8	0.07
High (range >20.0 Mets·hours/week)	36.2	38.7	36.5	0.70
Smoker (%)				
Current smoker	45.9	48.9	42.8	0.17
Ex-smoker	12.1	11.6	11.5	0.92
Drinking status (%)				
Everyday	27.2[c]	24	24.5	0.02
Sometime	47.9[c]	53.3	55.3	0.02
Education (≥college, %)	25.2	27.6	33.7	0.10
Whole-fat dairy (range, g/day)	0–0	8.0–58.9	61.0–410.1	–
No. of participants	341	276	321	–
Age (years)	42.6 (41.5, 43.7)[c]	41.6 (40.4, 42.8)[c]	44.9 (43.8, 46.1)	<0.01
Sex (female, %)	17.9[c,d]	28.6	29.9	<0.001
BMI (kg/m^2)	21.9 (21.5, 22.3)	22.5 (22.1, 22.9)	22.1 (21.8, 22.5)	0.06
SBP (mmHg)	121 (119.4, 122.7)	120.6 (118.9, 122.3)	119.8 (118.3, 121.4)	0.55
DBP (mmHg)	75.1 (73.9, 76.3)	75.1 (73.9, 76.3)	75.1 (74, 76.2)	1.00
Fasting blood sugar (mg/dl)	92.1 (90.9, 93.4)	91.8 (90.5, 93.1)	90.8 (89.6, 92)	0.26
TG (mg/dl)	86.6 (81.3, 92.2)	85.8 (80.3, 91.6)	86.3 (81.2, 91.7)	0.98
LDL (mg/dl)	116.4 (112.7, 120.2)	113.9 (110.1, 117.9)	113.9 (110.3, 117.5)	0.52
HDL (mg/dl)	57.9 (56.3, 59.5)	55.8 (54.2, 57.4)	57.3 (55.8, 58.8)	0.13
Adiponectin (μg/ml)	7.4 (7, 7.9)	7.5 (7.1, 7.9)	7.6 (7.2, 8)	0.84
Total energy consumption (kcal/day)	1535.5 (1481, 1592)[c,d]	1631.8 (1570.8, 1695.2)[d]	1820.7 (1757.7, 1886)	<0.0001
Calcium consumption (mg/day)	326.4 (309.8, 344)[c,d]	365.9 (346.3, 386.7)[c]	563.3 (535.3, 592.9)	<0.0001
Total fat (% of energy consumption)	23.6 (22.9, 24.2)[c]	24.1(23.4, 24.8)[c]	26.9 (26.2, 27.7)	<0.0001
SFA (% of energy consumption)	5.5 (5.3, 5.7)[c,d]	5.9 (5.7, 6.1)[c]	7.5 (7.3, 7.7)	<0.0001
n-3 PUFA (% of energy consumption)	1.2 (1.2, 1.3)	1.2 (1.2, 1.3)	1.3 (1.2, 1.3)	0.84

Table 1 continued

Low-fat dairy (range, g/day)	Category of dairy products			*p* value[a]
	0–0	8.0–54.9	58.9–375.9	
Total protein consumption (g/day)	50.7 (48.5, 53)[c]	53.6 (51.1, 56.1)[c]	63.9 (61.2, 66.7)	<0.0001
Dietary fiber (g/day)	8.5 (8, 8.9)[c,d]	9.4 (8.9, 9.9)[c]	10.5 (10, 11.1)	<0.0001
Vegetable consumption (g/day)	116.7 (106, 128.6)[c]	132.6 (119.7, 146.8)[c]	162.2 (147.6, 178.2)	<0.0001
Fruit consumption (g/day)	15.5 (13.3, 18.1)[c,d]	26.6 (22.5, 31.3)	31.1 (26.7, 36.2)	<0.0001
Tertile of physical activity (%)				
Middle (range: 0.55–20.0 Mets·hours/week)	36.7	37.7	37.1	1.00
High (range ≥20.0 Mets·hours/week)	39	32.6	38.3	0.60
Smoker (%)				
Current smoker	54.6[c]	44.2	38.3	<0.01
Ex-smoker	10.9	12.7	12.2	0.68
Drinking status (%)				
Everyday	33.4[c,d]	19.6	24	<0.01
Sometime	44.0[c,d]	58.7	51.4	0.001
Education (≥college, %)	27.6	27.2	28	0.47

BMI body mass index, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *TG* triglyceride, *LDL* low-density lipoprotein cholesterol, *HDL* high-density lipoprotein cholesterol

[a] Analysis of covariance or logistic regression analysis adjusted for age and sex where appropriate

[b] Adjusted geometric mean (95 % confidence interval) (all such values)

[c] Significantly different from the highest category of dairy products (Bonferroni correction): $p < 0.05$

[d] Significantly different from middle category of dairy products (Bonferroni correction): $p < 0.05$

confounders in the final models were not statistically significant (data not shown). In contrast, no relationship was found between the categories of whole-/high-fat dairy consumption and adiponectin.

One-year longitudinal analysis

The characteristics of the longitudinal subsample ($n = 759$) by categories of low-fat or whole-/high-fat dairy consumption were generally similar to the full sample, except that no relationship was found between whole-/high-fat dairy consumption and the percentage of subjects who were everyday drinkers among the subsample (data not shown). Serum adiponectin levels increased more so over time in the highest low-fat dairy consumption categories than in lowest categories. Repeated-measures ANCOVA adjusted for confounding factors showed a significant time-by-categories (categories of low-fat dairy) interaction in follow-up adiponectin levels (Table 3). The tests for interaction between the categories of low-fat dairy consumption and other confounders in the final models were not statistically significant (data not shown). Similar to the results of the cross-sectional analysis, no relationship was found between the categories of whole-/high-fat dairy consumption and follow-up adiponectin measurements.

Discussion

This cross-sectional and longitudinal study has shown that consumption of low-fat dairy (including cow's milk and yogurt) is related with significantly higher adiponectin and with the change of adiponectin level at the one-year follow-up, while no relationship was observed with whole-/high-fat dairy. Similarly, a previous cross-sectional study has also indicated that a dietary pattern characterized by a high consumption of whole-grain cereals and low-fat dairy products is significantly positively related with adiponectin concentration in healthy women [16]. These results support the hypothesis that a moderate increase in the consumption of low-fat dairy products may have a beneficial effect on serum adiponectin levels in the general population.

Previous prospective studies indicated that higher low-fat dairy consumption was related with a lowered risk of type 2 diabetes [3, 4]. The current study indicated that higher low-fat dairy consumption was related with serum adiponectin levels and with the change of adiponectin. Because higher baseline adiponectin levels are related with a lower risk of type 2 diabetes in a dose–response manner [10], our results demonstrate that low-fat dairy consumption may reduce the risk of type 2 diabetes, due to serum adiponectin levels. Further study is needed to confirm these findings. On the other hand, in the complete opposite of

Table 2 Adjusted relationships of low-fat or whole-/high-fat dairy categories to the serum concentration of adiponectin ($n = 938$)

Low-fat dairy (range, g/day)	Category of dairy products			p value[a]
	0–0	8.0–54.9	58.9–375.9	
No. of participants	505	225	208	–
Model 1[b]	7.04 (6.75, 7.34)[f,g]	7.39 (6.96, 7.86)	8.06 (7.55, 8.60)	<0.01
Model 2[c]	6.60 (6.09, 7.16)[g]	6.92 (6.31, 7.58)	7.67 (7.01, 8.40)	<0.001
Model 3[d]	7.03 (6.45, 7.65)[g]	7.38 (6.69, 8.13)	8.16 (7.42, 8.98)	<0.001
Model 4[e]	7.27 (6.80, 7.77)[g]	7.67 (7.09, 8.31)	8.40 (7.73, 9.13)	<0.001
Whole-fat dairy (range, g/day)	0–0	8.0–58.9	61.0–410.1	–
No. of participants	341	276	321	–
Model 1[b]	7.15 (6.78, 7.53)	7.42 (7.02, 7.84)	7.38 (7.02, 7.77)	0.52
Model 2[c]	7.40 (6.88, 7.97)	7.73 (7.16, 8.35)	7.62 (7.08, 8.21)	0.47
Model 3[d]	7.27 (6.61, 7.99)	7.66 (6.97, 8.42)	7.60 (6.97, 8.30)	0.33
Model 4[e]	6.82 (6.23, 7.46)	7.16 (6.55, 7.83)	7.17 (6.60, 7.80)	0.27

[a] Analysis of covariance

[b] Adjusted for age, sex, and body mass index

[c] Additionally adjusted for physical activity, smoking status, drinking status, and educational levels

[d] Additionally adjusted for tertiles of total energy, dietary fiber, saturated fatty acid, n-3 polyunsaturated fatty acids, vegetable, fruit intake, and other dairy product (low-fat or whole-/high-fat dairy categories)

[e] Additionally adjusted for systolic blood pressure, blood glucose concentration, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol

[f] Adjusted geometric mean (95 % confidence interval) (all such values)

[g] Significantly different from highest category of dairy (Bonferroni correction): $p < 0.001$

Table 3 Adjusted relationships of low-fat or whole-/high-fat dairy categories to changes in the serum adiponectin concentration during one-year follow-up ($n = 759$)

Low-fat dairy (range, g/day)	Tertile of low-fat dairy (g/day)			p values (time × group)[a]			
	0–0	8.0–53.6	54.9–375.9	Model 1[b]	Model 2[c]	Model 3[d]	Model 4[e]
No. of participants	418	172	169				
Serum adiponectin concentration [medians (interquartile range)]							
Baseline	6.63 (4.51, 9.64)	6.54 (4.51, 9.31)	7.13 (4.99, 10.20)				
After one year	6.77 (4.97, 9.90)	6.76 (4.80, 9.20)	7.67 (5.50, 10.70)	0.03	0.03	0.02	0.02
Whole-fat dairy (range, g/day)	0–0	8.0–58.9	61.0–410.1				
No. of participants	281	222	256				
Serum adiponectin concentration [medians (interquartile range)]							
Baseline	6.24 (4.27, 8.86)	6.59 (4.83, 9.76)	7.02 (4.85, 10.75)				
After one year	6.59 (4.61, 9.50)	7.02 (5.26, 9.74)	7.48 (5.17, 10.80)	0.99	0.97	0.42	0.46

[a] Obtained by using repeated-measures analysis of covariance

[b] Adjusted for age, sex, body mass index, and baseline serum adiponectin levels

[c] Additionally adjusted for physical activity, smoking status, drinking status, and educational levels

[d] Additionally adjusted for tertiles of total energy, dietary fiber, saturated fatty acid, n-3 polyunsaturated fatty acids, vegetable, fruit intake, and other dairy product (low-fat or whole-/high-fat dairy categories)

[e] Additionally adjusted for systolic blood pressure, blood glucose concentration, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol

previous expectations based on the beneficial effects of adiponectin [17], several epidemiological studies have indicated that a higher longitudinal increase in adiponectin predicted increased mortality in older persons [18, 19]. Furthermore, several prospective cohort studies have also indicated that higher baseline levels of adiponectin were related with increased all-cause mortality and CVD mortality, and severity of congestive heart failure [20, 21]. Although an explanation was discussed that very high levels, much like longitudinal increases, may predominantly

signal and/or contribute to greater homeostatic dysregulation accounting for their adverse prognostic implications [18], the exact role of increased adiponectin production under pathophysiological conditions has not been fully identified. Thus, a long-term follow-up study is needed to explore how adiponectin's low-fat dairy intake-related increase is related to incidents of diabetes and/or CVD in the future.

Two intervention studies have investigated the effects of increased consumption of dairy products on adiponectin [22, 23]. Wennersberg et al. [22] investigated the effects of dairy products (including milk, yogurt or sour milk, cream, cheese, butter, and ice cream) on adiponectin among overweight men and women. However, this study gave no clear support to the hypothesis that increased consumption of dairy products increases the level of adiponectin. Another randomized study (by Zemel et al.) showed that a high-milk diet (including yogurt, fluid milk, and hard cheese) significantly increased the adiponectin level of obese individuals [23]. Although the reason for the discrepancy between these 2 studies is unclear, the differences in the kind of dairy products consumed and in subjects may provide a partial explanation. Furthermore, compared to those in Zemel et al.'s study, our subjects were a general population with less instances of obesity (BMI $\geq$ 30: $n = 27$ [2.7 %] and 21 [2.8 %], in cross-sectional and longitudinal study, respectively), and the positive relationship between low-fat dairy consumption and serum adiponectin levels has not changed (data not shown) even when excluding the subjects who were obese. These results have shown that low-fat dairy consumption not only has the therapeutic effect of increasing serum adiponectin levels among obese individuals (in Zemel et al.'s study), but also has a possible preventive effect in a general population based on this study's findings. Further, in general, a preventative effect is more important to human health than treatment, and therefore, an intervention study should be performed to clarify whether low-fat dairy has a beneficial effect on serum adiponectin levels among healthy, non-obese individuals.

Dairy products are the richest source of calcium [24], and dietary calcium has a potential role in the regulation of oxidative and inflammatory stress (which stress is related to adipose tissue dysfunction [25–27]) in adipose tissue [28, 29], and dietary calcium might therefore be an important factor. In this study, low-fat dairy was strongly related with the high dietary calcium consumption. Furthermore, previous studies indicated that dairy products contain, in addition to calcium, bioactive compounds that may suppress oxidative and inflammatory stress [2]. Additionally, a previous study also indicated that skim milk largely increased the gene expression of adiponectin in adipose tissue as compared to dietary calcium, and only skim milk increased the concentration of plasma adiponectin in mice [23]. Thus, these data prove the hypothesis that a combination effect of nutrients (calcium and other bioactive compounds) present in low-fat dairy underlies the relationship between low-fat dairy and adiponectin. Although whole-/high-fat dairy is also strongly related with the high dietary calcium consumption, we did not observe any significant relationship between whole-/high-fat dairy and adiponectin. Similar to our results, several previous cohort studies have also suggested that low-fat dairy consumption, but not whole-fat dairy, was significantly related with type 2 diabetes [3, 4], hypertension [30], and metabolic syndrome. The reason is unclear; however, saturated fat present in whole-/high-fat dairy may mitigate the potential benefits of dairy products, accounting for this result. For example, the high fat content of whole-fat dairy might inhibit calcium absorption [31], thereby reducing the bioactivity of calcium. Interestingly, the consumption of low-fat dairy is also related to high SFA consumption in this study. This result suggests that high fat present in dairy products, but not from other foods, might inhibit the absorption of calcium also present in dairy. Further study is needed to confirm this finding.

The present study has two limitations. First, because this is an observational study, we could not conclude whether low-fat dairy increased adiponectin concentration. Second, since other dairy products, such as sour milk, cheese, and butter have not been assessed, we cannot analyze the relationships between these dairy products and adiponectin. However, because the consumption of these dairy products is very low in Japan [32], we believe that not directly accounting for them in our analyses had little effect on our findings. Finally, a recent review shows that adiponectin was intricately related to insulin action in humans [33]. However, we could not evaluate the relationship of low-fat dairy or adiponectin with plasma insulin values due to lack of information. More in-depth study is needed to explore this issue further.

In the present study, higher consumption of low-fat dairy, but not of whole-/high-fat dairy, was significantly related with higher adiponectin and increased adiponectin during one-year follow-up. These results suggest that the consumption of low-fat dairy may have a beneficial effect on serum adiponectin levels. Further study is needed to confirm these findings.

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Conflict of interest All the authors have no conflicts of interest exists to disclose.

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