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Prevention of Age-Related-Increases in the Risks of Incident Functional Disability and Dementia by Home-Delivered Functional Dairy Product Consumption in Japanese Older Adults

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Summary Dairy products formulated with bioactives are widely distributed in Japan, but it remains to be clear whether a regular consumption of these products would help reduce the risks of incidental functional disability and dementia in older adults. This study aimed to investigate Japanese subjects aged ≥65 y (n=629) that routinely consumed three functional dairy products, a calcium-enriched milk supplemented with *Bifidobacterium longum* BB536, a yogurt supplemented with lactoferrin, *B. longum* BB536 and heat-killed *Lacticaseibacillus paracasei* MCC1849, and a drinkable yogurt supplemented with lactoferrin, *B. longum* BB536 and heat-killed *L. paracasei* MCC1849, through a home delivery service. Intake frequency and intake duration of these functional dairy products were compared with the risk scores of incident functional disability and dementia, developed by the Japan Gerontological Evaluation Study. In the participants aged <75 y, the incident functional disability risk was significantly maintained or decreased in the participants with the long intake duration level compared with the short intake duration level (OR, 95% CI: 0.48, 0.25–0.93). In the participants aged ≥75 y, the dementia risk was significantly maintained or decreased in the participants with the high intake frequency level compared with the low intake frequency level (OR, 95% CI: 0.46, 0.22–0.95). A high intake frequency or long term duration of these functional dairy products may be effective in preventing an aging-related increase in the risks of incident functional disability and dementia in older adults, but this warrants further investigation using different products containing different bioactives.

Key Words bioactives, calcium, dementia, home-delivered functional dairy products, incident functional disability, milk protein, preserving physical function, motivation of going out, social participation

A demographic shift to older societies proceeds worldwide (*1*). Incident functional disability has been prevailing among older adults, and dementia is one of the main causes of incident functional disability (*2*). Hence, the risks of incident functional disability as well as dementia need to be addressed to secure the healthier longevity. Modifiable factors for reducing these risks include exercise, smoking and alcohol drinking, social participation, and diet (*3*). Many epidemiological studies have demonstrated that dairy consumption has beneficial impacts on the physical and cognitive functions of community-dwelling older adults. Specifically, according to the Hisayama study, one of the oldest cohort studies of community-dwelling older adults on a large scale in Japan, higher dairy intake was associated with a lower risk of functional disability and its progression, and the association was considered to be mediated via an increase in protein intake (*4*). The Hisayama study also showed that higher dairy intake reduced the risk of dementia, especially of the Alzheimer's disease; calcium and magnesium that are abundant in milk and dairy products would partly be responsible for this (*5*, *6*). On the other hand, some of the dairy products are formulated with the addition of bioactives such as prebiotics, probiotics, and bioactive proteins, and these kinds of products are occasionally labeled with health claims under the legal regulation (*7*). However, it has not been fully proven to what extents these "functional" dairy products would be effective in reducing the incident functional disability risk and the dementia risk in older adults. Especially, long-term intervention studies can hardly be feasible that follow up the onset of incident functional disability and dementia.

Home delivery service is one of the popular means of distribution for milk and dairy products, and the consumers normally take these products in a constant manner for a long period of time. Hence, it was considered that the follow-up of older people who subscribe

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functional dairy products through home delivery service may help understand the efficacy of these products in reducing the risks of incident functional disability and dementia. We previously conducted a cross-sectional observation study on older adults consuming at least one of the three home-delivered functional dairy products, i.e., a calcium-enriched milk supplemented with *Bifidobacterium longum* BB536, a yogurt supplemented with lactoferrin, *B. longum* BB536 and heat-killed *Lacticaseibacillus paracasei* MCC1849, and a drinkable yogurt supplemented with lactoferrin, *B. longum* BB536 and heat-killed *L. paracasei* MCC1849 (*3*). *B. longum* BB536 is a well-established probiotic effective in improving gastrointestinal condition (*8*). It is also one of the probiotic strains that produce indole-3-lactic acid, a tryptophan-derived metabolite potentially contributing to brain health through the gut-brain axis (*9*); this metabolite has been reported to serve as a ligands of the aryl hydrocarbon receptor and substantially promoted a nerve growth factor-induced neurite outgrowth in the PC12 line of rat adrenal pheochromocytoma cells (*10*). Lactoferrin is a milk glycoprotein, and is known to exert immunomodulatory effects and alleviate systemic and respiratory symptoms in healthy adults (*11*). The heat-killed *L. paracasei* MCC1849 is a post-biotic, and is known to exert various immunemodulations such as enhancing responsiveness of acquired immunity to influenza vaccination in people aged ≥85 y, and suppressing common cold symptoms in heathy adults (*12–14*). In the previous cross-sectional analysis of ours, it was found that the dementia risk was reduced in subjects aged ≥75 y consuming dairy products including these functional dairy products twice/d or more, compared with those having dairy products less than once/d and not using any of these functional dairy products (*3*). Potential of these functional dairy products in reducing the dementia risk was thus suggested, but further studies including longitudinal analyses were warranted to substantiate this.

We hypothesized that a regular consumption of functional dairy products would be effective in reducing the risks of incident functional disability and dementia in older population. We aimed to conduct a longitudinal analysis on older adults that routinely consumed the above-mentioned three functional dairy products through a home delivery service, and compare the relationship between the intake frequency/duration and the risks of incident functional disability and dementia.

MATERIALS AND METHODS

Participants and study design. The baseline survey was conducted in 2019 as described previously (*3*). Briefly, a total of 7,000 self-administered questionnaires were sent to older adults aged ≥65 y, who lived in Aichi prefecture, Japan, and subscribed at least one of the following functional dairy products; 1) a calcium-enriched milk supplemented with *B. longum* BB536 (Morinaga Milk Industry, Tokyo, Japan), 2) a yogurt supplemented with lactoferrin, *B. longum* BB536 and heat-killed *L. paracasei* MCC1849 (Morinaga Milk Industry), and 3) a drinkable yogurt supplemented with lactoferrin, *B. longum* BB536 and heat-killed *L. paracasei* MCC1849 (Morinaga Milk Industry). The choice of these products and their delivery frequencies were made by each participant freely. These three products were termed hereafter the MILK, the YOGURT, and the D-YOGURT, respectively, and the nutrition facts are presented in Table 1. A total of 1,536 subjects responded, and 1,230 respondents were eligible for age and residential areas, and provided written informed consents. The follow-up survey was conducted in 2022, namely 3 y after the baseline survey. The self-administered questionnaires were sent to 897 subjects, who were included in the baseline survey and kept subscribing the above functional dairy products as of the date. While 727 subjects responded, 2 subjects were excluded as they were found to be erroneously included despite the baseline age <65 y, 41 excluded as they answered mismatched sex in the two surveys, 45 excluded as they answered dependence of activity of daily living (ADL) or missed answering ADL dependence/independence in the baseline survey, and 10 excluded as they had insufficient information for calculating body mass index (BMI). The remaining 629 respondents were included in the analysis (Fig. 1). This longitudinal study was conducted in accordance with the principles of the Declaration of Helsinki and with the approval of ethics committees of Japan Conference of Clinical Research (protocol No. LB-0001, approved on August 30, 2019).

Table 1. Nutrition facts of functional dairy products (per serving).

	MILK (180 mL)	YOGURT (100 g)	D-YOGURT (100 g)
Nutrients			
Energy	113 kcal	93 kcal	62 kcal
Protein	8.8 g	3.5 g	3.1 g
Fat	3.8 g	3.6 g	1.0 g
Carbohydrate	10.9 g	11.6 g	10.1 g
Sodium	132 mg	0.11 g	0.11 g
Calcium	413 mg	114 mg	103 mg
Iron	1.0 mg	Not indicated	Not indicated
Bioactives			
BB536	≥2.0 billion cfu	Not indicated	Not indicated
Lactoferrin	—	100 mg	100 mg
MCC1849	—	Not indicated	Not indicated

MILK, the calcium-enriched milk supplemented with *Bifidobacterium longum* BB536; YOGURT, the yogurt supplemented with lactoferrin, *B. longum* BB536 and heat-killed *Lacticaseibacillus paracasei* MCC1849; and D-YOGURT, the drinkable yogurt supplemented with lactoferrin, *B. longum* BB536 and heat-killed *L. paracasei* MCC1849.

Dependent variables. The Japan Gerontological Evaluation Study (JAGES) developed a risk assessment scale predicting incident functional disability (*15*), and a risk score for long-term care eligibility certification with dementia onset (*16*). Both of these were able to be cal-

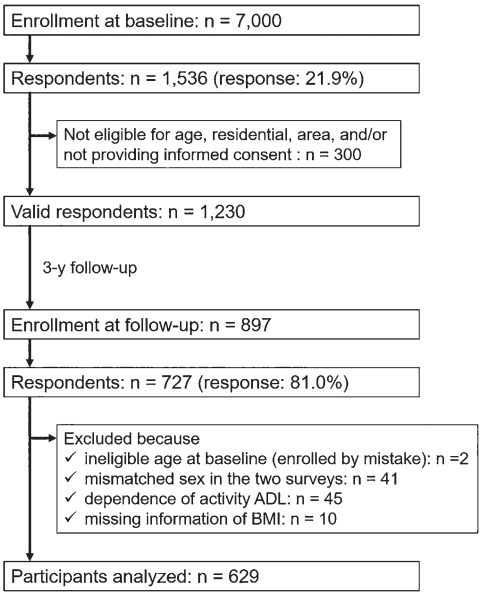

Fig. 1. Flowchart of selecting participants for longitudinal analysis. In the baseline survey, a total of 7,000 self-administered questionnaires were sent to older adults aged ≥65 y, who lived in Aichi prefecture, Japan, and subscribed at least one of the following functional dairy products; the MILK, the YOGURT, and the D-YOGURT. A total of 1,536 subjects responded, and 1,230 respondents were eligible for age and residential areas, and provided written informed consents. After 3 y, the follow-up survey was conducted by sending the self-administered questionnaires to 897 subjects, who were included in the baseline survey and kept subscribing the above functional dairy products as of the date. Among the 727 subjects responded, 629 respondents were included in the analysis. MILK, the calcium-enriched milk supplemented with *Bifidobacterium longum* BB536; YOGURT, the yogurt supplemented with lactoferrin, *B. longum* BB536 and heat-killed *Lacticaseibacillus paracasei* MCC1849; and D-YOGURT, the drinkable yogurt supplemented with lactoferrin, *B. longum* BB536 and heat-killed *L. paracasei* MCC1849.

culated from the self-administered questionnaire in the present study, and they were designated here as the "incident functional disability risk score" and the "dementia risk score," respectively. It is noted that the incident functional disability risk score is calculated from sex, age, and the 10 survey items regarding exercise capacity, nutritional status, and going out frequency; the contribution of age to this score is considerably large, as the 3-y score change ranges from 1 to 4 points depending on the baseline age. Hence, in the present study, the "age-corrected" incident functional disability risk score was employed for the follow-up survey, by assigning the baseline age for calculation as done previously (*17*).

Each risk score change, from the baseline survey to the follow-up survey, was obtained, which was dichotomized into two risk levels of "increased (delta score >0)" and "maintained or decreased (delta score ≤0)." They were used as binary dependent variables, and termed the incident functional disability risk, and the dementia risk, respectively.

Independent variables. Intake "frequency" and "duration" of home delivery functional dairy products at the baseline were used as independent variables.

The intake frequency of each functional dairy product was surveyed in the self-administered questionnaire with the following six choices: "almost every day (i.e., almost 7 servings/wk)," "4–5 servings/wk," "2–3 servings/wk," "1 serving/wk," "scarcely not," and "never." Missing data of intake frequency were treated as "never." After these 6 frequency choices were weighed as the frequency of 6.5, 4.5, 2.5, 1, 0.5, and 0 serving(s)/wk, respectively, serving frequencies of the three functional dairy products were summed up for each participant on one hand; the summed intake frequency was then used as an ordinal independent variable with the three levels: "high frequency (≥8 servings/wk)," "medium frequency (6–7 servings/wk)," and "low frequency (≤5 servings/wk)." On the other hand, the intake frequency of each product for each participant was also employed as another ordinal variable with the levels: "high frequency (≥7 servings/wk)," "low & medium frequency (0.5–6.5 servings/wk)," and "zero frequency (0 serving/wk)."

The intake duration of each functional dairy product was surveyed in the self-administered questionnaire with the following four choices: "3 y or more," "2 y or more but less than 3 y," "1 y or more but less than 2 y," and "less than 1 y." Missing data of intake duration were treated as "less than 1 y." The choice of the longest duration among the three products was assigned for each participant on one hand; the assigned intake duration was then used as an ordinal independent variable with the three levels: "long duration (≥3 y)," "middle duration (2–3 y)," and "short duration (<2 y)," as the number of participants of "1 y or more but less than 2 y," and "less than 1 y" were limited (n=56 and 49, respectively). On the other hand, the intake duration of each product for each participant was also employed as another ordinal variable with the three levels: "long duration (≥3 y)," "middle duration (2–3 y)," and "short duration (<2 y)."

Covariates. Following variables in the baseline survey were used as covariates. Initially, variables that would be potential confounding factors associated with the risks of incident functional disability and/or dementia were included as in our previous report (*3*): sex (categorical: male or female), age (continuous), household composition (categorical: living alone or living with others), education attainment (ordinal: ≤9 y, 10–12 y, or ≥13 y), economical status (ordinal: poor, fair, or good), current employment (categorical: unemployed or employed), comorbidities of hypertension, stroke or diabetes mellitus (categorical: yes or no), current smoking (categorical: yes or no), current alcohol consumption (categorical: yes or no), mealtime environment (categorical: eating alone or eating with others), monthly social participation (categorical: once or more, or less than once), daily walking time (categorical: 1 h or more, or less than 1 h), and daily intake frequency of

Table 2. Characteristics of the total participants in baseline survey.

Total participants (n=629)		n (%)
Age (y)		74.3±6.2[1]
	<75 y	345 (54.8%)
	≥75 y	284 (45.2%)
Sex	Male	205 (32.6%)
	Female	424 (67.4%)
Household composition	Livimg alone	549 (87.3%)
	Living with others	80 (12.7%)
Education attainment	≤9 y	91 (14.9%)
	10–12 y	304 (48.3%)
	≥13 y	231 (36.7%)
Economical status	Poor	45 (7.2%)
	Fair	386 (61.4%)
	Good	198 (31.5%)
Comorbidity (Yes)	Stroke	13 (2.1%)
	Hypertension	259 (41.2%)
	Cardiovascular diseases	51 (8.1%)
	Diabetes mellitus	70 (11.1%)
Alcohol consumption	Yes	215 (34.2%)
	No	414 (65.8%)
Smoking	Yes	33 (5.2%)
	No	596 (94.8%)
Social participation	<1/mo	169 (26.9%)
	≥1/mo	460 (73.1%)
Walking time	<1 h/d	75 (11.9%)
	≥1 h/d	554 (88.1%)
Eating status	Eating alone	153 (24.3%)
	Eating with others	476 (75.7%)
Milk and dairy product consumption[2]	≤1/d	352 (56.0%)
	2/d	173 (27.5%)
	≥3/d	104 (16.5%)
Other consumption	Meat (≥1/d)	573 (91.1%)
	Fish (≥1/d)	577 (91.7%)
	Egg (≥1/d)	585 (93.0%)
	Soy (≥1/d)	550 (87.4%)

[1] Means±SDs.
[2] Including three functional dairy products surveyed in the present study.

Table 3. Distribution of functional dairy product consumption according to intake frequency.[1]

	Low	Medium	High
Total (n=629)		n (%)	
Baseline	252 (40.1%)	240 (38.2%)	137 (21.8%)
Follow-up	252 (40.1%)	220 (35.0%)	157 (25.0%)
<75 y (n=345)		n (%)	
Baseline	157 (45.5%)	142 (41.2%)	46 (13.3%)
Follow-up	165 (47.8%)	126 (36.5%)	54 (15.7%)
≥75 y (n=284)		n (%)	
Baseline	95 (33.5%)	98 (34.5%)	91 (32.0%)
Follow-up	87 (30.6%)	94 (33.1%)	103 (36.3%)

[1] Consumption of three functional dairy products surveyed in the present study were presented according to intake frequency levels. No significant difference was seen in the distributions between the baseline and follow-up surveys in all the participants as well as both of the two age groups using the Bowker test (p=0.22–0.57).
Low, low intake frequency (≤5 servings/wk); Medium, medium intake frequency (6–7 servings/wk); and High, high intake frequency (≥8 servings/wk).

Table 4. Distribution of functional dairy product consumption according to intake duration.[1]

	Short	Middle	Long
Total (n=629)		n (%)	
Baseline	105 (16.7%)	96 (15.3%)	428 (68.0%)
Follow-up***	95 (15.1%)	41 (6.5%)	493 (78.4%)
<75 y (n=345)		n (%)	
Baseline	66 (19.1%)	65 (18.8%)	214 (62.0%)
Follow-up***	52 (15.1%)	24 (7.0%)	269 (78.0%)
≥75 y (n=284)		n (%)	
Baseline	39 (13.7%)	31 (10.9%)	214 (75.3%)
Follow-up#	43 (15.1%)	17 (6.0%)	224 (78.9%)

[1] Consumption of three functional dairy products surveyed in the present study were presented according to intake duration levels. Distributions were compared between the baseline and follow-up surveys using the Bowker test in all the participants as well as both of the two age groups. # p<0.05 and *** p<0.0001.
Short, short intake duration (<2 y); Middle, middle intake duration (2–3 y); and Long, long intake duration (≥3 y).

meat, fish, egg, or soybean (categorical: once/d or more, or less than once/d). Daily intake frequency of milk and dairy product (including functional dairy product intakes) was also employed as an ordinal covariate with the three levels: "less than once," "1–2 times," or "3 times or more." Finally, the baseline level of each risk score was set as a continuous covariate for the corresponding dependent variable.

Statistical analyses. All data were analyzed using JMP software (version 14.0.0; SAS Institute, Cary, NC). Multiple imputation was made for missing data, except for the variables described above, by performing multivariate singular value decomposition imputation in the software. The risk scores in the baseline survey and the follow-up survey were compared by using the Wilcoxon signed-rank test. The intake frequencies or durations of functional dairy products, in the baseline and follow-up surveys, were compared by using the Bowker test. Multiple logistic regression analyses were performed for the association between the incident functional disability risk or the dementia risk as a dependent variable, and both intake frequency and intake duration of the functional dairy products as two independent variables, which was adjusted for the above-mentioned covariates. Significance was demonstrated at p<0.05.

RESULTS

Characteristics of participants at baseline

Baseline characteristics of the participants are sum-

Table 5. Risk scores of incident functional disability and dementia.[1]

	Baseline	Follow-up
Incident functional disability risk score		
Total (n=629)	13.5±8.7	14.5±9.3[2,***]
<75 y (n=345)	7.0±4.7	7.6±4.8[2,*]
≥75 y (n=284)	21.4±5.4	22.7±6.0[2,***]
Dementia risk score		
Total (n=629)	3.1±2.1	3.8±2.2***
<75 y (n=345)	1.6±1.3	2.5±1.8***
≥75 y (n=284)	5.0±1.2	5.4±1.6***

[1] Data are expressed as means±SDs. Scores of the baseline and follow-up surveys were compared by the Wilcoxon signed-rank test. * p<0.01 and *** p<0.0001.
[2] The age-corrected incident functional disability risk score was employed as reported previously (*17*).

marized in Table 2. Briefly, the mean±SD age was 74.3±6.2 y, and participants aged ≥75 y comprised 45.2% (n=284) of the total participants. The number of males and females were 205 and 424, respectively (32.6% and 67.4%, respectively). More than 50% of the total participants consumed milk and dairy products (including the three functional dairy products) once/d or less. Approximately 90% of the total participants consumed meat, fish, egg, or soy once/d or more.

Intake frequency and intake duration of functional dairy products

The intake frequencies of the three functional dairy products were compared between the baseline survey and the follow-up survey in all the participants, the participants aged <75 y, and the participants aged ≥75 y (Table 3). No significant differences in intake frequency were seen between the two surveys in all the participants as well as both of the two age groups (p=0.22–0.57). The intake durations of these functional dairy products were also compared (Table 4), and the intake duration was found to change significantly from the baseline survey to the follow-up survey in all of the three groups (p<0.0001–0.05).

Consumption of the three functional dairy products, expressed as the percentage of each product to all the three products in each intake frequency level, is shown in Fig. S1 (Supplemental Online Material). The number and ratio of participants consuming each functional dairy product in each intake duration level is shown in Table S1 (Supplemental Online Material).

Incident functional disability risk score and dementia risk score

The incident functional disability risk score and the dementia risk score were calculated from the self-administered questionnaire, and the means±SD are present for all the participants, the participants aged <75 y, and the participants aged ≥75 y (Table 5). Both incident functional disability risk score and dementia risk score increased significantly from the baseline survey to the follow-up survey in all the participants as well as both of the age groups (p<0.0001–0.01).

Table 6. Association between intake frequency/duration of functional dairy products and risks of incident functional disability and dementia.[1]

	Incident functional disability risk score	Dementia risk score
Intake frequency	OR (95% CI)	
Total		
Low (n=252)	Ref.	Ref.
Medium (n=240)	0.96 (0.66–1.42)	0.83 (0.56–1.23)
High (n=137)	1.25 (0.78–2.02)	0.72 (0.44–1.18)
<75 y		
Low (n=157)	Ref.	Ref.
Medium (n=142)	1.38 (0.82–2.31)	0.81 (0.45–1.46)
High (n=46)	1.48 (0.69–3.18)	1.13 (0.47–2.71)
≥75 y		
Low (n=95)	Ref.	Ref.
Medium (n=98)	**0.52 (0.27–0.98)**	0.69 (0.35–1.36)
High (n=91)	0.82 (0.41–1.65)	**0.46 (0.22–0.95)**
Intake duration	OR (95% CI)	
Total		
Short (n=105)	Ref.	Ref.
Middle (n=96)	1.02 (0.56–1.85)	0.90 (0.48–1.67)
Long (n=428)	0.72 (0.45–1.17)	0.88 (0.54–1.45)
<75 y		
Short (n=66)	Ref.	Ref.
Middle (n=65)	0.76 (0.35–1.66)	1.19 (0.47–2.96)
Long (n=214)	**0.48 (0.25–0.93)**	0.95 (0.44–2.04)
≥75 y		
Short (n=39)	Ref.	Ref.
Middle (n=31)	1.68 (0.59–4.78)	0.76 (0.25–2.33)
Long (n=214)	1.29 (0.59–2.84)	0.88 (0.39–2.01)

[1] The risks of incident functional disability and dementia were compared with consumption of three functional dairy products surveyed in the present study. Multiple logistic regression analyses were performed for intake frequency and duration (independent variables) and each score change from the baseline survey to follow-up survey (dependent variable; dichotomized into two levels of "increased (delta score >0)" and "maintained or decreased (delta score ≤0)"), adjusting for sex, age, household composition, education attainment, economical status, hypertension, stroke, and diabetes mellitus, smoking, alcohol consumption, mealtime environment, social participation, walking time, intake frequency of meat, fish, egg, soybean, and milk/dairy products, and baseline level of each risk score. p<0.05 (shown in bold).
Low, low intake frequency (≤5 servings/wk); Medium, medium intake frequency (6–7 servings/wk); High, high intake frequency (≥8 servings/wk); Short, short intake duration (<2 y); Middle, middle intake duration (2–3 y); and Long, long intake duration (≥3 y).

Incident functional disability risk and dementia risk in negative association with intake frequency and intake duration of functional dairy products

The risks of incident functional disability and dementia were compared with intake frequency of the three functional dairy products in all the participants, the participants aged <75 y, and the participants aged ≥75 y (Table 6). The incident functional disability risk

was significantly maintained or decreased in the participants aged ≥75 y with the medium intake frequency level compared with the low intake frequency level (OR, 95% CI: 0.52, 0.27–0.98). The dementia risk was significantly maintained or decreased in the participants aged ≥75 y with the high intake frequency level compared with the low intake frequency level (OR, 95% CI: 0.46, 0.22–0.95). These risks were also compared with intake frequency each of these products (Table S2, Supplemental Online Material). It was found that the dementia risk was significantly maintained or decreased in all the participants with the high MILK intake frequency level compared with the zero MILK intake frequency level (OR, 95% CI: 0.29, 0.11–0.81), in the participants aged <75 y with the medium and high MILK intake frequency levels compared with the zero MILK intake frequency level (OR, 95% CI: 0.08, 0.01–0.76, and 0.01, 0.01–0.78, respectively), and in the participants aged ≥75 y with the high MILK intake frequency level compared with the zero MILK intake frequency level (OR, 95% CI: 0.19, 0.05–0.76).

The risks of incident functional disability and dementia were also compared with intake duration of the three functional dairy products (Table 6). The incident functional disability risk was significantly maintained or decreased in the participants aged <75 y with the long intake duration level compared with the short intake duration level (OR, 95% CI: 0.48, 0.25–0.93). These risks were also compared with intake duration each of these products (Table S2). It was found that the incident functional disability risk was significantly maintained or decreased in the participants aged <75 y with the middle and long MILK intake duration level compared with the short MILK intake duration level (OR, 95% CI: 0.14, 0.02–0.83, and 0.02, 0.02–0.68, respectively). It was also observed that the dementia risk was increased in the participants aged <75 y with the long MILK intake duration level compared with the short MILK intake duration level (OR, 95% CI: 11.0, 1.1–105.9).

DISCUSSION

This longitudinal study surveyed older adults aged ≥65 y who kept subscribing the three functional dairy products for 3 y. Prevention of age-related increases in these risks were observed in an intake frequency-dependent or an intake duration-dependent manner; an age-related increase in the incident functional disability risk was prevented in subjects aged <75 y with the long intake duration level compared with the short intake duration level; and an age-related increase in the dementia risk was significantly prevented in subjects aged ≥75 y with the high intake frequency level compared with the low intake frequency level.

The study participants consisted of more female (67.4%), and about the half the participants were ≥75 y at the baseline (45.2%) (Table 2). Despite the fact that this study selected subjects subscribing at least one of the above three functional dairy product through a home delivery service, more than half of the participants answered that they consumed only one serving/d or less of milk and dairy products, indicating that these functional dairy products comprised the large part of total milk and dairy product consumptions in these participants. During the 3-y survey period, the participants did not change the type and amount of the functional dairy product consumption significantly, and kept consuming them for a significant period of time (Tables 3 and 4).

The incident functional disability risk was significantly maintained or decreased in the participants aged <75 y with the long intake duration level compared with the short intake duration level of these three functional dairy products, after being adjusted for the above-mentioned confounding factors (Table 6), which was compatible with the observation that a maintenance or increase in this risk was also observed in the participants aged <75 y with the long MILK intake duration levels compared with the short MILK intake duration level (Table S2). More than half of the participants with the long intake duration level consumed the MILK in the baseline survey, and nearly half of the participants kept consuming the MILK in the follow-up survey (Table S1). When scrutinizing the answers to the questionnaire items for the age-corrected incident functional disability score, physical function would be preserved in the long intake duration level compared with the short intake duration level, as suggested by the ratios of participants who had increases in the incident functional disability risk score due to answering "No" to "Do you normally climb stairs without using handrail or wall for support?" and "No" to "Do you normally walk continuously for 15 min?" (data not shown). Collectively, the long-term intake of the MILK would contribute to sustaining physical function, leading to prevention of an age-related increase in the incident functional disability risk in subjects aged <75 y. Furthermore, the MILK was rich in milk protein and calcium (Table 1), and these enriched nutrients may be responsible for prevention of an age-related increase in the incident functional disability risk, as has been shown for milk and dairy products (*4*). Besides, this association was significant only in the participants aged <75 y, and can be interpreted as being that long-term continuous consumption of the MILK at the early stage of aging may repel aging-related declines in energy intake and body weight (*18*), thereby maintaining or decreasing the incident functional disability risk.

The dementia risk was significantly maintained or decreased in participants aged ≥75 y with the high intake frequency level compared with those with the low intake frequency level, after being adjusted for confounding factors including comorbidities, socioeconomic status, and dietary habits (*3*), which was supportive of the observation that a maintenance or increase in this risk was also observed not only in the participants aged ≥75 y with the high MILK intake frequency level compared with the zero MILK intake frequency level, but also in all the participants with the high MILK intake frequency level compared with the

zero MILK intake frequency level (Table S2). The MILK was the most consumed product for participants with all the intake frequency levels (Fig. S1c and f), and the difference of the intake frequency levels could translate primarily to the difference in the MILK consumption. When scrutinizing answers to the questionnaire items for the dementia risk score, the motivation of going out and social participation would be sustained in the high intake frequency level compared with the low intake frequency level, as suggested by the ratios of participants who had increases in the dementia risk score due to answering "No" to "Can you go out by bus or train by yourself?" and answering "Never" to "How often do you participate in the sports groups or clubs?" (data not shown). Collectively, the high intake frequency of the MILK would lead to the motivation of going out and social participation in subjects aged ≥75 y. Of note, sufficient calcium intake is known to be vascular-protective and associated with the reduction in the risk of dementia (5), and calcium rich in the MILK could be responsible for prevention of an age-related increase in the dementia risk. Besides, the MILK was formulated with ≥2 billions cfu/serving of *B. longum* BB536, which is one of the probiotics that produces an indole-3-lactic acid, a metabolite potentially contributing to brain health (*9*). However, the association between this probiotic strain and brain health has not been elucidated to date in humans, and effects of probiotics on human brain health has normally been confirmed when they are taken in higher doses (5–20 billion cfu/d) (*19–21*). Still, the association between the intake frequency of these functional dairy products and the dementia risk might reflect the fact that higher doses are important for probiotic strains to exert a brain health-promoting effect. Finally, a decrease in the dementia risk was more evident in the participants aged ≥75 y in the present study. This may be related to the fact that the age group 75–79 comprised the largest proportion of total dementia onset in Asian population aged ≥60 y, which is followed by the age group 80–84 y (*22*). Namely, subjects aged ≥75 y are highly susceptible to dementia, and the effect of dietary factors on dementia might be easier to be manifested in this age group.

One of the largest limitations was missing of the appropriate control group, i.e., subjects with no use of functional dairy products. Instead, this study compared the subjects with different intake frequency/duration levels of the three functional dairy products. Prevention of age-related increases in these risks were observed in an intake frequency-dependent or an intake duration-dependent manner, thus considerably supporting the usefulness of these functional dairy products in suppressing these risks. Still, additional studies are necessary to substantiate the certainty of this notion by including the control group. Another large limitation was that this study examined only three kinds of functional dairy products, and a more variety of commercial functional dairy products with different bioactives shall be investigated to gain more insights into the role of functional dairy products in the health of older adults.

In conclusion, age-related increased risks of incident functional disability and dementia can be prevented in older adults by regularly consuming three functional dairy products surveyed in the present study, as we hypothesized. Prevention of an age-related increase in the incident functional disability risk is more likely to be manifested in subjects aged <75 y, and prevention of an age-related increase in the dementia risk is more likely to become evident in subjects aged ≥75 y. Nutrients such as milk protein and calcium, and a probiotic might be responsible for these effects, but further investigations are necessary using different functional dairy products with different bioactives to consolidate the effectiveness of functional dairy products in geriatric health.

Authorship

A.M.T., M.T., and K.K. conceived the study; A.M.T., M.Y., and K.K. designed the study; Y.W. and A.M.T. conducted experiments and analyzed the data; Y.W. interpreted the data and wrote the manuscript; and Y.W. had primary responsibility for the final content. All authors have read and agreed to the manuscript.

Disclosure of state of COI

Y.W., A.M.T., and M.T. are the employees of Morinaga Milk Industry Co., Ltd. M.Y. and K.K. declare no conflicts of interest.

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Supporting Information

Supplemental online material is available on J-STAGE.

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