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BENEFICIAL MICROBES (2025) DOI:10.1163/18762891-BJA00106

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RESEARCH ARTICLE

Habitual consumption of fermented milk products containing *Lacticaseibacillus paracasei* strain Shirota and risk of anaemia in the elderly

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Received 8 August 2024 | Accepted 8 October 2025 | Published online 6 November 2025

Abstract

Anaemia in the elderly increases the risk of cardiovascular disease, cognitive decline, and death. Probiotics have recently been shown to be potentially effective in preventing the onset or improving the condition of anaemia. Here, we retrospectively investigated the relationship between fermented milk intake over the prior 10 years and the risk of developing anaemia during the same period. The participants were community-dwelling Japanese aged 65-94 years who had not developed anaemia in the 10 years prior to the time of the survey. They were divided into two groups based on their intake frequency (<3 or ≥3 days/week, n = 1,186 and n = 238, respectively) of fermented milk products containing *Lacticaseibacillus paracasei* strain Shirota (LcS products) for the prior 10 years. The incidence and risk of anaemia in the participants were analysed using chi-squared test and Cox proportional hazards regression analysis. The results indicated that incidence of anaemia over the 10-year interval was significantly lower in those who took LcS products ≥3 rather than <3 days/week (anaemia incidence: 0.8% vs 4.0%, $P = 0.016$). Furthermore, multivariable analysis using Cox proportional hazards regression to adjust for potential confounders also showed a significantly lower relative risk of developing anaemia in the group consuming LcS products ≥3 days/week (hazard ratio 0.219; 95% confidence interval 0.053-0.902; $P = 0.035$). These findings suggest that habitual consumption of LcS products on ≥3 days/week by individuals 65 years or older may reduce their risk of developing anaemia.

Keywords

probiotics – aging – anaemic – Nakanojo Study

1 Introduction

The incidence of anaemia increases with age 65 years and older; the incidence in this population has been reported to be approximately 17% (Gaskell *et al.*, 2008). Anaemia in the elderly increases the risk of cardiovascular disease (Culleton *et al.*, 2006), decreased quality of life (Den Elzen *et al.*, 2009), cognitive decline (Hong *et al.*, 2013; Lucca *et al.*, 2008), and even mortality (Zakai *et al.*, 2005). The population is rapidly aging worldwide, including in developing regions (Raftery and Sevcikova, 2023), and prevention of anaemia should be addressed to extend both life expectancy and healthy life expectancy in the elderly.

Iron deficiency anaemia, inflammatory anaemia, and renal anaemia are common anaemias that can develop in the elderly (Stauder *et al.*, 2018). Although contributing factors vary, the prevention and treatment

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of anaemia generally involves dietary guidance regarding iron and folic acid intake or treatment of various chronic diseases (Wicinski *et al.*, 2020). In addition, recent studies have shown that probiotics may be effective in preventing or improving the onset of iron deficiency anaemia. For example, *Lactiplantibacillus plantarum* 299v (Vonderheid *et al.*, 2019) and *Lactococcus lactis* subsp. *cremoris* H61 (Takaragawa *et al.*, 2022) have been reported to promote iron absorption and may inhibit the development or improve the severity of iron deficiency anaemia. However, these studies were performed mainly in younger populations, and the anaemia-preventive effect of probiotics in the elderly has not yet been sufficiently investigated.

Since 2000, we have been conducting an epidemiological study in the community of Nakanojo Town, Gunma Prefecture, Japan (the Nakanojo Study) (Aoyagi *et al.*, 2017, 2019; Aoyagi and Shephard, 2009, 2010, 2011, 2013) to investigate the relationship between health status and lifestyle habits in people aged 65 years and older. In this study, the frequency of consumption of fermented milk products containing *Lacticaseibacillus paracasei* strain Shirota (LcS products) has been investigated through interviews of participants with nutritionists. LcS is widely consumed around the world as a probiotic strain, showing various beneficial effects on human health, including regulation of intestinal motility (Matsumoto *et al.*, 2006; Nagata *et al.*, 2011, 2016), protection against infection (Gleeson *et al.*, 2011; Kushiro *et al.*, 2019; Nagata *et al.*, 2011; Shida *et al.*, 2017), and immunoregulation (Nagao *et al.*, 2000; Tamura *et al.*, 2007). Some case-control studies have shown that intake of LcS also lowers the risks of bladder (Ohashi *et al.*, 2002) and breast cancers (Toi *et al.*, 2013). Our epidemiological study has previously shown that elderly people who habitually consume LcS products have a lower risk of developing hypertension (Aoyagi *et al.*, 2017) and a lower risk of low frequency of bowel movements (Aoyagi *et al.*, 2019), but the potential benefits of LcS products in preventing or treating anaemia have not been clarified. In this epidemiological study, we investigated the relationship between the intake of lactobacilli and the risk of developing anaemia in the elderly through a retrospective analysis.

2 Materials and methods

Participants

The participants were community-dwelling Japanese volunteers aged 65 years or older who were recruited to the Nakanojo Study (Aoyagi and Shephard, 2009, 2010, 2011, 2013). Inclusion criteria included a willingness to participate, attendance at an annual medical examination, functional independence, and the absence of chronic or progressive conditions that could limit physical activity or have a major effect on the individual's perceived quality of life (e.g. Parkinson's disease, Alzheimer's disease, multiple sclerosis, amyotrophic lateral sclerosis, and dementia) (Aoyagi and Shephard, 2009, 2010, 2011, 2013). In addition, the study excluded participants with anaemia more than 10 years before the time of the survey; those who could not state their age at onset of anaemia; those who were unable to recall the frequency of LcS product intake; or those who had no associated data on smoking, alcohol consumption, or nutrition. Participants provided written informed consent to participate in the study as approved by the Ethics Review Committee of the Tokyo Metropolitan Institute of Gerontology, after the protocol, stresses, and possible risks had been fully explained to them. In the present study, 1,424 participants (683 men, 741 women) aged 65–94 years were selected.

Medical history

Participants were interviewed by a public health nurse or certified nutritionist to determine whether they had been diagnosed with anaemia in accordance with the following criteria: overall physician judgment based on haemoglobin levels below World Health Organization (WHO)-defined reference values (<130 g/l for men, <120 g/l for women) and/or non-specific anaemia symptoms (e.g. fatigue, shortness of breath, pallor, headache). The age at diagnosis was also noted.

Frequency of intake of LcS products

The intake frequency of LcS products was estimated by a certified nutritionist in an interview using pictures of a series of LcS products, including 'Yakult', 'Joie', 'Soful', and 'Pretio' (Yakult Honsha, Tokyo, Japan), each of which contains 0.9-100 × 10^9 live LcS per bottle. Participants were asked how many days/week products of this type were consumed over the prior 10-year period. The frequency of intake of general fermented milk products (hereinafter referred to as 'overall fermented milk products'), such as yoghurt (and including the above LcS products), was also estimated by the same procedure. The distribution of the intake frequency of LcS products and overall fermented milk products for our population is summarized in Table 1. Participants were classed as consuming a bottle of the product 2 days/week or less (designated as the '<3 days/week' group) or 3 days/week

TABLE 1 Frequency of consumption of fermented milk products containing *Lacticaseibacillus paracasei* strain Shirota (LcS) and overall fermented milk products in a sample of 1,424 elderly Japanese individuals

	Intake frequency (days/week)							
	0	1	2	3	4	5	6	7
LcS products	964	149	73	69	16	15	4	134
Overall fermented milk products	436	213	163	160	61	37	10	344

or more (designated as the '≥3 days/week' group), as categorized in the Framingham Heart Study (Wang *et al.*, 2015).

Nutrient intake

The nutritional status of the participants was evaluated by nutritionists over a 1-week period using Version 3.5 of the Food Frequency Questionnaire Based on Food Groups (Kenpakusha, Tokyo, Japan) (Takahashi *et al.*, 2001), which is a 20-item questionnaire regarding the consumption of items from 29 food groups and 10 methods of food preparation. On the basis of responses to this questionnaire, the daily consumption of energy, nutrients, and food groups was estimated for the 1-2 month period prior to the start of the study. The estimated nutrients included protein, lipid, carbohydrate, dietary fibre, saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids, cholesterol, sodium, calcium, and iron.

Physical activity patterns and physical health

The average number of steps taken per day was obtained by tracking steps 24 h/day over a 1-month period with a uniaxial acceleration sensor (Lifecorder; Suzuken, Nagoya, Japan), as described previously (Aoyagi and Shephard, 2013). Preferred and maximum walking speeds were determined over a 5-m distance using a stopwatch (SVAE101; Seiko, Tokyo, Japan), as described previously (Aoyagi *et al.*, 2004). Each participant completed two trials for both comfortable and maximum walking speeds; the averaged and the higher velocities were both recorded. Peak handgrip force was assessed for the dominant hand using a Smedley dynamometer (ES-100; Evernew, Tokyo, Japan). Two trials were performed, and the larger of the two readings was recorded. Quantitative ultrasound measurements of the osteosonic index for the calcaneus were made by using an Achilles ultrasonic bone densitometer (AOS-100; Aloka, Musashino, Japan), as described previously (Shephard *et al.*, 2017).

Anthropometric characteristics and blood profiles

The physical characteristics of each participant (including age, height, body mass, body mass index, abdominal circumference, body fat ratio, fat mass, fat-free mass, and muscle mass) were determined by standard anthropometric techniques (Shephard *et al.*, 2013). The biochemical profiles of each participant (red blood cells, haemoglobin, haematocrit, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, glycosylated haemoglobin A1c, fasting blood sugar, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, γ-glutamyl transpeptidase, albumin, creatinine, uric acid concentrations, and estimated glomerular filtration rate) were measured by standard methods (Health Sciences Research Institute Inc., Yokohama, Japan).

Statistical analyses

R software Version 4.1.3 (https://cran.r-project.org/) (Ihaka and Gentleman, 1996) was used throughout. Participants were divided into two groups based on the intake frequency of LcS products or overall fermented milk products (<3 and ≥3 days/week). Analysis of covariance was used to assess independent differences between these two groups with respect to anthropometric, physical activity, physical fitness, calcaneal, nutritional, and blood variables after controlling data for age and/or sex. Chi-squared tests were used to assess differences in the male/female ratio, alcohol consumption, smoking, and the incidence of anaemia between the two groups. Kaplan–Meier plots were used to examine changes in the proportion of participants within each group who remained free of anaemia over the 10-year study, and log-rank tests were used to analyse the significance of differences between the two curves. Subgroup analyses for males or females were also performed using the chi-squared test and log-rank test. Cox proportional hazards regression analyses were used to assess independent relationships between intake of LcS products or overall fermented milk products and the estimated risk of anaemia over the 10 years, after controlling for age, sex, body mass index, smoking status, and alcohol consumption (Model 1). In addition, to adjust for differences in the intake of various nutrients between the groups, further analyses were conducted by adding iron (Model 2), protein (Model 3), cholesterol (Model 4), and calcium (Model 5) to the confounding factors in Model 1. Statistical significance was set at the 0.05 threshold.

3 Results

Participant characteristics

Among the 1,424 Japanese participants aged 65 years or over (mean [±SD] age 73.2 ± 6.4 years), 1,186 and 238 participants consumed LcS products <3 and ≥3 days/week, respectively, and 812 and 612 participants consumed overall fermented milk products <3 and ≥3 days/week, respectively (Table 1). Compared with those who took LcS products <3 days/week, the ≥3 days/week group was older, had a higher percentage of females, and had a lower percentage of habitual alcohol drinkers (Table 2). Daily intake of protein, cholesterol, calcium, iron, and vitamin B_{12} was also significantly higher in the ≥3 days/week group than in the <3 days/week group (Table 2). There were no differences between groups in blood biochemistry data, including blood anaemia indices (red blood cell count, haemoglobin, haematocrit).

Similar results were observed in the separate analysis for overall fermented milk product and LcS product intake (Supplementary Table S1).

Relationship between intake of fermented milk products and incidence of anaemia

Over the prior 10 years, 49 participants (28 of 683 males [4.1%] and 21 of 741 females [2.8%]) developed anaemia, with no significant sex differences in incidence. Hence, a sex-integrated analysis was performed as the main result for this study.

The number of participants who developed anaemia in the prior 10 years showed significant group differences (P = 0.016) in the chi-squared test for LcS product intake, with 2 of 238 participants (0.8%) in the ≥3 days/week group and 47 of 1,186 participants (4.0%) in the <3 days/week group. In contrast, there was no significant group difference (P = 0.075) between the groups consuming overall fermented milk products ≥3 and <3 days/week (15 of 612 participants [2.5%] vs 34 of 812 participants [4.2%], respectively).

Males in the group consuming LcS products ≥3 days/week showed a significantly lower incidence of anaemia over the prior 10 years (0 of 90 participants [0%]) than those in the <3 days/week group (28 of 593 participants [4.7%]; P = 0.035) in the chi-squared test. Females in the group consuming LcS products ≥3 days/week (2 of 148 participants [1.4%]) also showed a lower incidence of anaemia over the prior 10 years than those in the <3 days per week group (19 of 593 participants [3.2%]), although the difference was not significant in the chi-squared test (P = 0.224). No difference was found in the incidence of anaemia between the groups consuming overall fermented milk products at different frequencies for either males or females (P = 0.314 and P = 0.215, respectively).

Comparison of anaemia risk

Kaplan-Meier curves showed a significant difference in the rates of individuals without an anaemia diagnosis over 10 years between the groups consuming LcS products <3 and ≥3 days/week (P = 0.017; Figure 1A). In contrast, for overall fermented milk product intake, there were no significant differences in the rates of individuals without an anaemia diagnosis between the <3 and ≥3 days/week groups (P = 0.076; Figure 1B). Very similar results were observed for both sexes for both LcS product intake and overall fermented milk product intake (Supplementary Figure S1), as well as for the comparison of the incidence of anaemia by the chi-squared test.

In terms of LcS product intake, a multivariable-adjusted Cox proportional hazards model showed a statistically significant intergroup difference in the incidence of anaemia over the 10-year interval (Table 3), with a substantial advantage to the ≥3 days/week group (hazard ratio [HR] 0.219; 95% confidence interval [CI] 0.053-0.902) relative to the <3 days/week group (P = 0.035). The corresponding comparison for overall fermented milk products was not statistically significant (P = 0.086; HR 0.583; 95% CI 0.315-1.080). In addition, the analyses controlling for confounding factors such as iron and protein intake, which showed significant differences between the groups consuming LcS products <3 and ≥3 days/week group, also indicated that the group consuming LcS products ≥3 days/week was at significantly lower risk of developing anaemia (Table 4, Models 2–5). For the subgroup analyses by sex, Cox proportional hazards regression analysis was not possible because there were no males in the ≥3 days/week LcS product intake group who had developed anaemia in the prior 10 years.

TABLE 2 Characteristics of participants consuming LcS products for <3 or ≥3 days per week

	<3 days/week		≥3 days/week		*P*-value for
	n	Value[1]	n	Value[1]	difference[2]
Anthropometric characteristics					
Age (years)	1,186	73.0 ± 6.3	238	74.3 ± 6.7	0.006
Sex (male/female, %)	1,186	50.0 / 50.0	238	37.8 / 62.2	0.001
Smoking status (smoker/non-smoker, %)	1,186	8.3 / 91.7	238	6.7 / 93.3	0.401
Alcohol intake (alcohol consumer/non-alcohol consumer, %)	1,186	42.2 / 57.8	238	34.9 / 65.1	0.037
Height (m)	1,186	1.57 ± 0.09	238	1.55 ± 0.08	0.387
Body mass (kg)	1,186	57.5 ± 10.5	238	55.7 ± 9.6	0.830
Body mass index (kg/m^2)	1,186	23.3 ± 3.1	238	23.1 ± 3.1	0.943
Body fat ratio (%)	774	25.7 ± 8.2	157	27.3 ± 8.0	0.348
Fat mass (kg)	774	14.5 ± 5.7	157	15.0 ± 5.5	0.491
Fat-free mass (kg)	774	41.4 ± 8.0	157	39.6 ± 7.1	0.944
Muscle mass (kg)	774	39.2 ± 7.6	157	37.5 ± 6.8	0.926
Blood pressures, physical activity, and physical health					
Systolic blood pressure (mmHg)	1,102	131 ± 17	210	129 ± 17	0.135
Diastolic blood pressure (mmHg)	1,102	76.7 ± 10.3	210	75.1 ± 9.6	0.236
Step count (steps/day)	444	7,295 ± 3,390	98	6,622 ± 2,560	0.190
Preferred walking speed (m/s)	756	1.35 ± 0.22	158	1.32 ± 0.23	0.510
Maximum walking speed (m/s)	751	2.02 ± 0.40	155	1.95 ± 0.37	0.479
Peak handgrip force (N)	767	278 ± 92	159	255 ± 81	0.534
Osteosonic index	780	2.36 ± 0.34	159	2.28 ± 0.32	0.365
Nutrient intake					
Energy (kcal/day)	1,186	1,960 ± 536	238	2,017 ± 491	0.103
Protein (g/day)	1,186	70.7 ± 22.5	238	74.7 ± 23.2	0.035
Lipid (g/day)	1,186	64.2 ± 23.5	238	67.3 ± 24.2	0.143
Carbohydrate (g/day)	1,186	259 ± 70	238	265 ± 63	0.197
Dietary fibre (g/day)	1,186	15.6 ± 5.2	238	16.1 ± 4.6	0.442
Saturated fatty acid (g/day)	1,186	19.6 ± 7.8	238	20.6 ± 7.9	0.148
Monounsaturated fatty acid (g/day)	1,186	21.5 ± 8.3	238	22.2 ± 8.8	0.339
Polyunsaturated fatty acid (g/day)	1,186	13.7 ± 5.0	238	13.9 ± 4.6	0.875
Cholesterol (mg/day)	1,186	323 ± 128	238	347 ± 118	0.039
Sodium (mg/day)	1,186	4,109 ± 1,618	238	4,294 ± 1,462	0.218
Calcium (mg/day)	1,186	681 ± 249	238	731 ± 245	0.029
Iron (mg/day)	1,186	8.51 ± 2.98	238	9.10 ± 3.21	0.028
Vitamin B_{12} (µg/day)	1,186	7.55 ± 3.85	238	8.27 ± 4.05	0.039
Folic acid (µg/day)	1,186	331 ± 121	238	340 ± 111	0.525
Blood profile					
Red blood cells (/µl)	802	447 ± 43	144	446 ± 42.	0.289
Haemoglobin (g/l)	802	138 ± 13	144	137 ± 14	0.252
Haematocrit (%)	802	43.4 ± 3.9	144	43.2 ± 4.1	0.331
Triglyceride (mmol/l)	1,045	1.52 ± 0.94	200	1.53 ± 0.98	0.742
High-density lipoprotein cholesterol (mmol/l)	1,045	1.58 ± 0.44	200	1.60 ± 0.40	0.916
Low-density lipoprotein cholesterol (mmol/l)	1,045	3.05 ± 0.77	200	3.10 ± 0.71	0.843
Glycosylated haemoglobin A1c (%)	1,045	5.7 ± 0.6	200	5.7 ± 0.5	0.319
Glutamic oxaloacetic transaminase (IU/l)	1,045	23.8 ± 8.2	200	23.8 ± 6.3	0.791
Glutamic pyruvic transaminase (IU/l)	1,045	19.9 ± 8.5	200	19.3 ± 7.8	0.966
γ-Glutamyl transpeptidase (IU/l)	1,045	31.0 ± 43.1	200	26.4 ± 19.2	0.394

TABLE 2 (Continued)

	<3 days/week				≥3 days/week				P-value for
	n	Value[1]			n	Value[1]			difference[2]
Albumin (g/l)	1,045	43.5	±	2.8	200	43.5	±	2.5	0.878
Creatinine (μmol/l)	1,045	74.2	±	32.1	200	71.9	±	18.1	0.907
Uric acid (μmol/l)	1,043	306	±	74	200	303	±	72	0.398
Estimated glomerular filtration rate (ml/min/1.73 m^2)	1,045	63.8	±	13.0	200	62.4	±	12.5	0.292

1 Unless indicated otherwise, data are presented as the mean ± standard deviation.
2 Intergroup differences in the male/female ratio, smoking status, and alcohol intake were assessed by chi-squared tests; intergroup differences in other parameters were evaluated by analysis of covariance after adjusting the data on age for sex and the other data for age and sex.

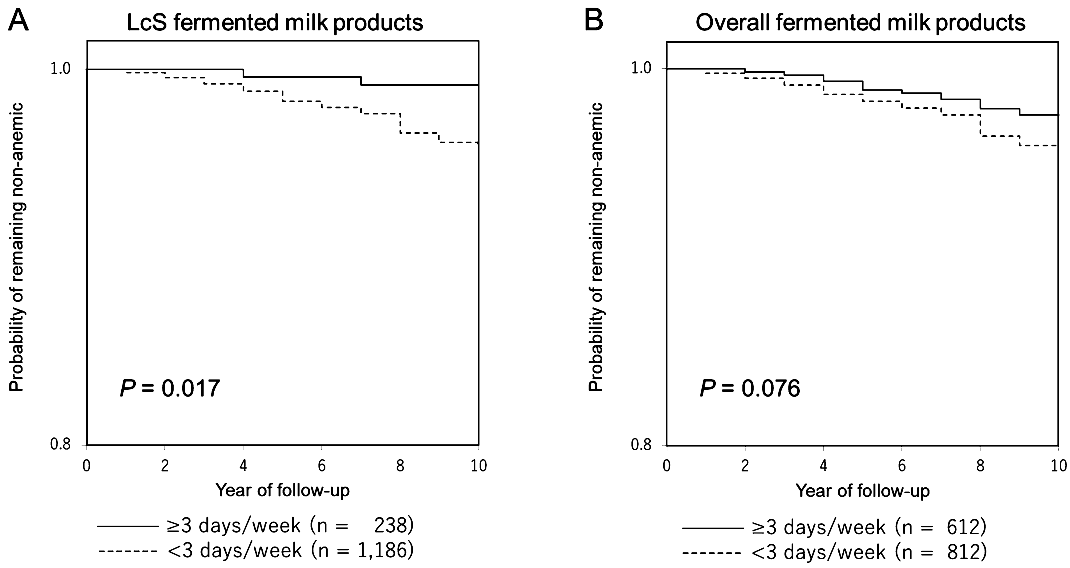

FIGURE 1 Kaplan-Meier curves showing the rates of participants without anaemia for the prior 10 years. Log-rank test comparing the rate of participants without anaemia in the groups consuming (A) LcS products or (B) overall fermented milk products ≥3 days/week (solid line) and <3 days/week (dashed line).

4 Discussion

This retrospective epidemiological study showed that the risk of developing anaemia over the prior 10 years was significantly lower ($P = 0.035$; Table 3) in a group consuming LcS products at least 3 days/week than in a group consuming these products <3 days/week. In contrast, more frequent consumption of overall fermented milk products was not clearly related to the risk of developing anaemia ($P = 0.086$; Table 3). These results remained unchanged after adjusting for iron intake, which has a strong influence on the development of anaemia, and after adjusting the intake of other nutrients such as protein and cholesterol, which differed between the groups, suggesting that the effect of LcS products on anaemia was independent from the intake of nutrients such as iron.

The intake of LcS products could suppress the onset of anaemia through several mechanisms, for example by ameliorating iron deficiency, one of the most common causes of nutritional deficiency anaemia (Bergqvist *et al.*, 2006; Camaschella, 2019; Jimenez *et al.*, 2015), which is, in turn, one of the most frequent forms of anaemia. Large amounts of iron are used in the erythropoietic system for haemoglobin synthesis, and a lack of available iron for haematopoiesis leads to anaemia. One effective way to improve iron deficiency is to increase the rate of iron absorption in the body, and lactic acid has been reported to promote iron absorption (Bergqvist *et al.*, 2006; Proulx and Reddy, 2007). Previous studies have shown that lactic acid weakly binds to iron, which maintains iron solubility in the intestinal tract (Scheers *et al.*, 2016). Moreover, more iron is absorbed when lactic acid and iron are co-added to Caco-2 human epithelial cells than when iron alone is added (Bergqvist *et*

TABLE 3 Risk of developing anaemia over the 10-year study in groups consuming LcS products and overall fermented milk products for <3 or ≥3 days per week[1]

	Intake frequency	n	Hazard ratio	95% confidence interval	*P*-value for difference
LcS products	<3 days/week	1,186	1	–	–
	≥3 days/week	238	0.219	0.053-0.902	0.035
Overall fermented milk products	<3 days/week	812	1	–	–
	≥3 days/week	612	0.583	0.315-1.080	0.086

1 Intergroup differences in the relative risk of developing anaemia were assessed by Cox proportional hazards regression analyses adjusted for age, sex, body mass index, smoking status, and alcohol intake.

TABLE 4 Analyses of the intake of various nutrients considering the risk of developing anaemia over a 10-year period among groups consuming LcS products for <3 or ≥3 days per week [1]

	Intake frequency	n	Hazard ratio	95% confidence interval	*P*-value for difference
Model 1	<3 days/week	1,186	1	–	–
	≥3 days/week	238	0.219	0.053-0.902	0.035
Model 2	<3 days/week	1,186	1	–	–
	≥3 days/week	238	0.219	0.053-0.906	0.036
Model 3	<3 days/week	1,186	1	–	–
	≥3 days/week	238	0.217	0.053-0.897	0.035
Model 4	<3 days/week	1,186	1	–	–
	≥3 days/week	238	0.218	0.053-0.902	0.035
Model 5	<3 days/week	1,186	1	–	–
	≥3 days/week	238	0.219	0.053-0.903	0.036
Model 6	<3 days/week	1,186	1	–	–
	≥3 days/week	238	0.218	0.053-0.901	0.035

1 Intergroup differences in the relative risk were assessed by Cox proportional hazards regression analyses adjusted for the following confounding factors: Model 1: age, sex, body mass index, smoking status, and alcohol intake; Model 2: age, sex, body mass index, smoking status, alcohol intake, and iron intake; Model 3: age, sex, body mass index, smoking status, alcohol intake, and protein intake; Model 4: age, sex, body mass index, smoking status, alcohol intake, and cholesterol intake; Model 5: age, sex, body mass index, smoking status, alcohol intake, and calcium intake; Model 6: age, sex, body mass index, smoking status, alcohol intake, and vitamin B_{12} intake.

al., 2006). LcS produces lactic acid in De Man-Rogosa-Sharpe (MRS) medium, anaerobic International *Lactobacillus* Sub-committee (ILS) medium, and milk-based culture medium (Makras *et al.*, 2006; Ogawa *et al.*, 2001; Zalán *et al.*, 2010). Because LcS is resistant to gastric and bile acids, which allows it to reach the intestinal tract alive and produce lactic acid (Cook *et al.*, 2023; Koebnick *et al.*, 2003; Takada *et al.*, 2020), it may have enhanced the absorption of iron and prevented anaemia in our study population.

A second possibility is that LcS may have inhibited the anaemia of inflammation. Under chronic inflammation, anaemia develops due to factors such as decreased blood cell lifespan, decreased erythropoiesis in the bone marrow, and inhibition of iron absorption and recycling by hepcidin induced by the proinflammatory cytokine interleukin-6 (Di Paola *et al.*, 2022; Weiss *et al.*, 2019). LcS is known for its unique cell wall polysaccharide, which exhibits anti-inflammatory properties through its anti-IL-6 activity (Matsumoto *et al.*, 2005), and continuous intake of LcS may inhibit the development and exacerbation of chronic inflammation (Okubo *et al.*, 2013). LcS has also been shown to enhance adhesion between epithelial cells of the gastrointestinal tract and inhibits the transfer of intestinal bacteria that cause chronic inflammation into the bloodstream (Sato *et al.*, 2017). Moreover, intake of LcS reduces interleukin-6 production in the blood of patients with chronic inflammation-related diseases, such as allergic rhinitis and depression (Ivory *et al.*, 2008; Zhang *et al.*, 2021).

These results suggest that the suppression of chronic inflammation by LcS could contribute to the reduced risk of developing anaemia in habitual consumers of LcS products.

Development of gastrointestinal and other cancers induces anaemia, suggesting a third possibility: that the reduction of anaemia risk by LcS may have been mediated by the inhibitory effect of LcS on cancer development. Cancer patients are known to develop anaemia due to iron deficiency caused by bleeding, decreased blood cell production capacity due to anticancer drugs, and the development of chronic inflammation (Groopman and Itri, 1999; Merchant and Roy, 2012). LcS has shown inhibitory effects against colon cancer, bladder cancer, and breast cancer (Aso *et al.*, 1995; Ishikawa *et al.*, 2005; Ohashi *et al.*, 2002). Although the mechanism by which LcS prevents carcinogenesis has not yet been fully elucidated, the production of toxic substances associated with inhibiting the growth of pathogenic intestinal bacteria (De Preter *et al.*, 2004; Hayatsu and Hayatsu, 1993; Tohyama *et al.*, 1981) and the enhancement of natural killer cells, which inhibit the proliferation of cancer cells (Nagao *et al.*, 2000), may be involved. Although this study could not clarify whether LcS intake reduces the risk of carcinogenesis due to the small number of participants with cancers, the inhibitory effect of LcS on carcinogenesis may consequently lead to the inhibition of the onset of anaemia. Although the relationship between the consumption of overall fermented milk products and the risk of developing anaemia is not clearly defined, differences in the viability of each lactic acid bacterial strain and in their inhibition of chronic inflammation and carcinogenesis may lead to differences in the risk of developing anaemia. It is challenging to indicate that these hypotheses are specific to LcS; however, significant differences were specifically observed with LcS intake ($P = 0.035$), whereas the consumption of overall fermented milk products demonstrated only marginal significance ($P = 0.086$), suggesting that LcS may have a substantial effect compared with other probiotics.

One of the limitations of this study is that it is not possible to discuss the causal relationship between LcS product consumption and the development of anaemia because this was a retrospective epidemiological study. In addition, we have done a sex-specific analysis because the prevalence of anaemia is known to be higher in males than in females among those aged ≥65 years (Bach *et al.*, 2014). However, it was impossible to perform a multivariable analysis due to the low incidence rate of anaemia among the analysed population and the 0% incidence of anaemia among males who consumed LcS products at least 3 days/week. In the female subgroup, the incidence of anaemia was lower in the group consuming LcS products ≥3 days/week, but this difference was not significant. Furthermore, this study did not collect the names of the products consumed, which limits the analysis based on individual product components, such as iron-fortified products. However, because iron-fortified fermented milk and LcS products represent a minor segment of the market, we believe that their effect on our results is likely to be insignificant. Further investigation is needed to determine whether there are sex differences in the relationship between LcS and the development of anaemia.

In conclusion, this retrospective epidemiological study showed that habitual consumption of LcS products on 3 or more days per week may reduce the risk of developing anaemia in the elderly. Anaemia in the elderly is associated with a decline in quality of life and cognitive function, as well as an increased risk of mortality. Our study revealed the potential contribution of habitual intake of a probiotic, such as LcS, to the health of the elderly, although this will need to be substantiated with further research.

Supplementary materials

Data is available on https://doi.org/10.1163/18762891-bja00106 under Supplementary Materials.

Table S1. Characteristics of participants consuming overall fermented milk products <3 or ≥3 days/week over 10 years.

Figure S1. Kaplan–Meier curves showing the rates of participants without anaemia for the prior 10 years.

Acknowledgements

We gratefully acknowledge the expert technical assistance of the research and nursing staff of the Tokyo Metropolitan Institute of Gerontology, the Yakult Central Institute, the University of Tokyo, and the Nakanojo Public Health Center. We thank the subjects whose conscientious participation made the Nakanojo Study possible. This study was supported by grants [Grant-in-Aid for Encouragement of Young Scientists: 12770037 and Grant-in-Aid for Scientific Research (C): 15500503, (C): 17500493, (B): 19300235, and (B): 23300259] from the Japan Society for the Promotion of Science and grants from the Yakult Honsha Co., Ltd. and the Tokyo Metropolitan Institute of Gerontology.

Authors' contribution

YA and TS designed the research. TS, RA, KS, SP, SM and HM conducted the research. YA analysed the data. YA and TS drafted the paper. YA has primary responsibility for the final content. All authors critically revised the manuscript for important intellectual content and read and approved the final manuscript.

Conflict of interest

The authors declare that they have no conflict of interest.

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