food & nutrition research

ORIGINAL ARTICLE

Causal link between milk consumption and obesity? A 10-year longitudinal study and a Mendelian randomization study

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Popular scientific summary

Randomized controlled clinical trials in western countries have demonstrated efficacy of dairy supplementation on fat mass reduction and lean mass increase. It is crucial to know whether milk is causally beneficial to Asians, since lactose intolerance is a key factor preventing people to drink milk in Asians. In this study, we found inverse association between milk consumption and body mass index (BMI) increment and between genetic propensity on lactose tolerance and BMI. These findings support current food guide to include dairy group as one of the six food groups.

Abstract

***Background*:** Obesity control and prevention remains challenging. Randomized controlled trials in western countries have demonstrated efficacy of dairy supplementation on fat mass reduction and lean mass increase, when combined with energy restriction protocols. However, there is scanty information on this issue among the East Asian population.

***Objective*:** The aim of this study is to investigate the association between milk consumption and weight status in Asian.

***Design*:** Firs*t*, we studied the association between milk intake and body mass index (BMI) changes in a 10-year longitudinal study of Cardiovascular Disease Risk Factor Two-township Study (CVDFACTS) with 1,644 adults. Second, taking advantage of the genetic and phenotype data of 10,000 participants collected by Taiwan Biobank (TWB), we carried out a Mendelian randomization (MR) study to investigate the causal relationship between milk intake and BMI. A lactase persistence genetic marker (rs4954490) was used as the instrumental variable.

***Results*:** We found in the longitudinal study that higher baseline milk consumption level was associated with lower odds of increasing BMI or maintaining overweight/obesity status. In the MR study, we found that G allele of the rs4954490, a surrogate of greater milk intake, was associated with lower odds of being obese (BMI > 27 kg/m^2); the odds ratio (OR) for the GG versus AA is 0.85 (P = 0.037), and the OR for the GA versus AA is 0.84 (P = 0.032).

***Conclusions*:** These findings support current food guide in Asian countries to include dairy group as one of the six food groups for nutrition recommendation.

Keywords: *milk*; *dairy*; *body mass index*; *longitudinal study*; *CVDFACTS*; *Mendelian randomization*; *Taiwan Biobank*

To access the supplementary material, please visit the article landing page

Received: 22 December 2020; Revised: 7 August 2021; Accepted: 9 August 2021; Published: 16 September 2021

Obesity is a chronic condition of positive energy balance, which leads to long-term excessive body fat accumulation. However, it has been gradually recognized that high energy input from overeating and low energy output from insufficient physical activity are not the only cause of obesity. Not all people exposed to the same risk factors become obese, which suggests the existence of complex underlying genetic and metabolic mechanisms operating to affect energy metabolism efficiency, social interactions, and eating behaviors at the individual level (1, 2).

 Citation: Food & Nutrition Research 2021, **65**: 6300 - http://dx.doi.org/10.29219/fnr.v65.6300

Higher metabolic disease susceptibility has been well-documented in both South and East Asians despite relatively lower body mass index (BMI) compared to Caucasians (3–5). For example, the prevalence rate of type 2 diabetes (T2D) and gout in Taiwan is 10% (6) and 8.21% (7), respectively, while the prevalence rate of T2D and gout is 6.2% (6) and 1.4% (3) in the UK, respectively. Comparing people with the same BMI values, the prevalence rate of hypertension, T2D, and hyperuricemia was higher for Taiwanese than for US Caucasians (4). It is essential to find non-pharmacological measures to modify this risk. Meta-analysis of cross sectional studies (5) and randomized controlled clinical trials (RCTs) (8) have shown an inverse relationship between dairy intake and obesity, including central obesity, although controversial findings were observed in a limited number of prospective studies and Mendelian randomization (MR) studies (9–11).

Dietary recommendations in most Asian countries include dairy as one of the six food groups due to its high nutritional density, inclusive of protein, B-vitamins, and several beneficial minerals, such as magnesium, potassium, and calcium for cardiac and metabolic protections (12–14). However, lactose intolerance is a key factor preventing people to drink milk in Asians (15). According to a large-scale meta-analysis, the standardized regional prevalence rate of lactose intolerance was 64% in east and south Asia, 42% in northern America, and 28% in northern, southern, and western Europe (16). It is crucial to know whether milk or dairy food is causally beneficial to Asians, using the best available methodology. If its health benefits of dairies are confirmed, public health measures may be designed to overcome the hurdles.

The MR study, a nature-made clinical trial, has been widely used to infer the causal relationship between exposure and outcome. The underlying presumption of MR includes that genetic variants (single nucleotide polymorphisms, SNPs) are in principle randomly assigned by the meiosis process, and such genetic variations are not associated with behavioral and socioeconomic factors that may influence the phenotype (milk intake) (17). Therefore, the degree of genetic propensity may be used as an instrumental variable (IV) representing varied levels of milk intake after birth to confirm the causal relationship between the milk intake and obesity.

In this study, we used two methods to investigate the causal relationship between milk intake and BMI. First, we conduct a 10-year longitudinal study that used data from cycle 2 (1991–1993) and cycle 5 (1999–2002) of the Cardio-Vascular Disease risk Factors Two-township study (CVDFACTS) (18) to investigate the association between the baseline milk intake and BMI change status. Second, an MR study was further conducted using the data of SNPs from the Taiwan Biobank (TWB) to validate the causal relationship between milk intake and BMI.

Methods and materials

We used two studies to investigate the association between milk intake and BMI: a longitudinal study and an MR study. The studies have been approved by Academia Sinica ethical committees (permit number: AS-IRB-BM-07021 for CVDFACTS and AS-IRB02-104160 for TWB). A written informed consent was obtained from each participant.

Longitudinal study

A longitudinal study was conducted, which used data from CVDFACTS to investigate the association between the milk intake status and BMI change between baseline (1991–1993) and follow-up examination (1999–2002). The average follow-up time was 9.5 ± 0.7 years. CVDFACTS is a community-based follow-up study focusing on cardiovascular diseases (CVD) and their risk factors evolution in Taiwan since 1989. Five villages, each with more than 1,000 people and a population density greater than 200 persons per km^2, were randomly selected from Chu-Dong (northwest Taiwan) and Pu-Tzu (southwest Taiwan). Data regarding lifestyle, risk factors, medications, medical history, and urine and blood chemistry were collected. All subjects were asked to fast overnight (more than 8 h) before blood specimen collection. Weight, height, and waist circumference were measured with standard procedures. BMI was calculated as weight (kg)/height^2 (m^2). Blood pressure was measured three times, consecutively, after sitting for 5 min, and the mean of the last two readings was used for analysis. Questionnaire responses regarding demographic data (birth date and sex), lifestyle (smoking, alcohol consumption, and physical activity), and self-reported health conditions (disease status and drug using record) were also collected (19). Baseline information collection and repeated examinations were carried out in five cycles (1989–1991, 1991–1993, 1993–1997, 1997–1999, and 1999–2002).

A validated food frequency questionnaire (FFQ) was used in cycle 2 to assess dietary intake in the previous year. This included the frequencies and amounts of the milk along with 85 other food items and nutrients consumed. The FFQ had two parts. The first part is a semi-quantitative FFQ with a fixed format. Three-dimension food models were used for probing portion sizes, and the frequency of consumption was recorded with 10 frequency responses (≤6 times/year, 1–3 times/month, 1 time/week, 2–4 times/week, 5–6 times/week, 1 time/day, 2 times/day, 3 times/day, 4–5 times/day, and ≥6 times/day). The second part involves open-ended questions on the kinds and the frequency of major staple foods consumed in three meals and as snacks. Type of oils/fats used in cooking at home and whether sugars were added to the drink or foods were also asked. The food-composition database used to calculate nutrient values is based primarily on Taiwan Food Composition

Citation: Food & Nutrition Research 2021, **65**: 6300 - http://dx.doi.org/10.29219/fnr.v65.6300

Database (20). The validity of this FFQ has been published previously (21). More details about sampling and data collection have been described previously (19).

The data from cycle 2 (1991–1993) and cycle 5 (1999–2002) of CVDFACTS study were used to analyze the association of milk intake with BMI change. The total weight of milk consumed daily was the sum of whole milk (3.0–3.8% fat), low-fat milk (0.5–1.5% fat), skimmed milk (<0.5% fat), and half of the flavored milk. Nutrient intake levels were calculated by multiplying the amount of food eaten daily, frequency, and nutrient concentrations. Calorie intake level was calculated by summing the calories from food and alcohol consumed. All nutrients were calorie-adjusted by residual method (22).

The BMI change status from cycle 2 to cycle 5 was used as outcome. The BMI cut-off points were defined according to the Ministry of Health and Welfare in Taiwan. Overweight and obesity categories are defined as BMI ≥ 24 and 27 kg/m^2, respectively (23). Participants were then classified into four groups according to the BMI change between cycle 2 and cycle 5: (1) stable low (healthy in both cycles): BMI < 24 kg/m^2 in cycle 2 and cycle 5; (2) stable high (overweight in both cycles): BMI ≥ 24 kg/m^2 in cycle 2 and cycle 5; (3) increasing (switch from healthy weight to overweight): BMI < 24 kg/m^2 in cycle 2 and ≥24 kg/m^2 in cycle 5; and (4) decreasing (switch from overweight to normal weight): BMI ≥ 24 kg/m^2 in cycle 2 and <24 kg/m^2 in cycle 5. Participants were excluded if FFQ had missing data (n = 2,830), had a total energy intake less than 500 kcal/day or greater than 5,000 kcal/day (n = 139), or were lost to follow-up (n = 1,440). We further removed participants who had cancer or diabetes at baseline, which may deviate the follow-up BMI from natural course. In the end, there were 1,644 eligible participants for data analysis in this study. The detailed participant flow chart is shown in the Supplementary Fig. 1.

Sex-stratified polytomous logistic regression models were used to evaluate the independent effect of milk intake levels on BMI change status controlling for other confounding factors. The confounders adjusted were age, education level, smoking, drinking, physical activity, total calorie intake, total carbohydrate intake, total protein intake, total fat intake, and total fiber intake. Also, to make sure the effect was not due to other foods, we used partial Pearson's correlation, adjusting age, sex, and total calorie, to select the milk-correlated foods among the 85 food items that were collected using the FFQ in CVDFACTS. A total of 21 milk-correlated items were further adjusted in the polytomous regression models (Supplementary Table 1). Milk intake was also treated as continuous outcome (g/day) and categorical outcome ('high' and 'low' according the average of milk intake in man and in women), respectively. All statistical analyses were performed using SAS 9.4.

Mendelian randomization study

An MR approach to investigate the causal relationship between milk intake and obesity was employed. The genetic and exposure information of 10,000 participants (5,000 men and 5,000 women) from the Taiwan Han-Chinese Biobank (TWB) (24) were used. Details on the TWB can be found on its official website (25).

Table 1. Sample characteristics of the 10-year follow-up study on CVDFACTS cohort

BMI trends from baseline	Stable low[a] (N = 718)		Decreasing[b] (N = 59)		Increasing[c] (N = 239)		Stable high[d] (N = 628)		P
	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%	Mean/N	SD/%	
Milk intake (g/day)	87.3	118.8	63.7	131.2	69.0	105.3	53.7	92.7	<0.0001
Sex (n, %)									0.6
Male	353	41.48%	50	46.73%	123	44.73%	344	42.36%	–
Age (year)	45.4	14.1	55.4	11.3	43.9	13.6	50.0	11.2	<0.0001
Smoking (total no. of cigarette)	27,834.7	76,370.6	37,373.3	86,104.5	23,738.3	68,485.9	30,355.3	80,443.0	0.4
Alcohol (total amount, kg)	8.3	104.5	4.8	20.7	5.6	38.8	18.5	117.6	0.11
Physical activity (min/month)	974.9	2,292.9	1,033.9	2,037.3	1,012.8	2,366.4	1,387.8	3,035.8	0.009
Calorie intake (kcal/day)	2,056.0	677.3	2,040.7	743.8	2,077.2	694.9	2,148.5	761.9	0.051
Protein intake (g/day)	70.9	14.8	70.7	19.9	72.0	15.1	71.1	15.8	0.76
Fat intake (g/day)	65.0	19.9	61.6	19.6	67.5	19.5	66.0	20.6	0.05
Carbohydrate intake (g/day)	292.3	48.3	300.5	51.7	285.6	48.1	292.8	50.2	0.045
Fiber intake (g/day)	8.3	4.5	7.6	3.5	8.6	4.8	8.8	5.2	0.016
Education level (n, %)									<0.0001
Elementary school	308	36.19%	66	61.68%	110	40%	417	51.35%	–
High school	384	45.12%	29	27.10%	116	42.18%	315	38.79%	–
University or above	159	18.68%	12	11.21%	49	17.82%	80	9.85%	–

[a]Healthy in both cycles; [b]Switch from overweight to normal weight; [c]Switch from healthy weight to overweight; [d]Overweight in both cycles.

Instrumental variable

The *MCM6*-rs4988235 SNP (*LCT*-13910 C/T) at intron 13 is often used to study lactase persistence and milk intake. Nonetheless, this SNP is not polymorphic in Asian population (26). Another nearby SNP, *MCM6*-rs3754686, approximately 5,370 base pairs downstream from rs4988235, occurs more frequently in the global regions and represents alternatives in diverse cohorts (27). Thus, we used the rs3754686 as the IV in our MR study. However, this SNP was not included on the TWB array. Thus, we used a web tool LDlink (28) to select a proxy SNP, rs4954490 (D' = 1, R^2 = 0.98), based on the Chinese population information in the 1,000 genomes project.

Analysis of variance (ANOVA) and Chi-square (χ^2) analysis were used to compare continuous and categorical descriptive variables by genotypes (GG, GA, and AA), respectively. BMI was classified into two groups according to the cutoff points for overweight (BMI ≥ 24 kg/m^2 vs. BMI < 24 kg/m^2) and obesity (BMI ≥ 27 kg/m^2 vs. BMI < 27 kg/m^2). Logistic regression models were used to evaluate the associations between BMI groups and genotype of SNP-rs4954490 (GG, GA, and AA). All statistical analyses were performed using SAS 9.4.

Results

Longitudinal study on dairy consumption and BMI status changes

Table 1 shows the baseline characteristics of the participants of the four BMI status change groups from CVD-FACTS. According to the univariate (global ANOVA) test, the amount of milk consumption was significantly different among the four groups. The group 'stable low' (normal in both cycles) has the highest daily milk intake (mean = 87.3 g/day), whereas the stable high group (overweight in both cycles) has the lowest daily milk intake (mean = 53.7 g/day). The age (P < 0.0001), physical activity (P = 0.009), education level (P < 0.0001), calorie-adjusted total carbohydrate intake (P = 0.045), and adjusted total fiber intake (P = 0.016) are also significantly different among the four BMI change groups. The age of the increasing group (switching from normal weight to overweight) was the youngest group (43.9 years), and the decreasing group (switching from overweight to normal weight) is the oldest group (55.4 years). For the physical activity, 'stable high' group had the most physical activity time (1387.8 min/month), and the 'stable low' group has the least activity time (974.7 min/month). For carbohydrate intake, the 'decreasing' group consumed the most carbohydrates (300.5 g/day), compared with the other three groups. For the daily fiber intake, 'decreasing' group had the least amount of fiber intake (7.6 g/day), and the other three groups had similar amounts. In addition, the 'stable high' group had the lowest percentage of high education (university or above) among participants, compared with the other three groups. These differences should be taken into account in the subsequent analysis.

Table 2 provides the polytomous logistic regression results. The amount of milk consumption was treated as either a continuous (glass/day) or a categorical (high consumption vs. low consumption) variable. Sex-stratified analyses were

Table 2. The odds ratios associating milk intake amount and status with BMI change status

		BMI change status (cut-point = 24)			
		Stable low[a]	Decreasing[b]	Increasing[c]	Stable high[d]
Milk intak (Cup*/day)	**Male**	*N* = 282	*N* = 26	*N* = 106	*N* = 264v
	OR (95% CI)	1 (ref.)	–	0.78 (0.43–1.39)	0.35 (0.20–0.62)
	P	–	–	0.39	0.00028
	Female	*N* = 436	*N* = 33	*N* = 133	*N* = 364
	OR (95% CI)	1 (ref.)	–	0.80 (0.45–1.40)	0.58 (0.38–0.89)
	P	–	–	0.43	0.013
		Stable low	Decreasing	Increasing	Stable high
Milk intake (High vs. low)[$]	**Male**	*N* = 282	*N* = 26	*N* = 106	*N* = 264
	OR (95% CI)	1 (ref.)	–	0.61 (0.35–1.09)	0.41 (0.26–0.65)
	P	–	–	0.09	0.00013
	Female	*N* = 436	*N* = 33	*N* = 133	*N* = 364
	OR (95% CI)	1 (ref.)	–	0.74 (0.43–1.28)	0.63 (0.41–0.94)
	P	–	–	0.28	0.024

Note: Sex-stratified polytomous logistic regression models were used to evaluate the independent effect of milk intake levels on BMI change status controlling for other confounding factors. The confounders adjusted were age, education level, smoking, drinking, physical activity, total calorie intake, total carbohydrate intake, total protein intake, total fat intake, total fiber intake, and 21 milk-correlated foods intake.

*: 1 cup = 240 g. $: The milk intake was classified as high and low according the average of milk intake in men and women, respectively.

[a]Healthy in both cycles; [b]Switch from overweight to normal weight; [c]Switch from healthy weight to overweight; [d]Overweight in both cycles.

Citation: Food & Nutrition Research 2021, **65**: 6300 - http://dx.doi.org/10.29219/fnr.v65.6300

performed with the adjustment of age, education, smoking, drinking, physical activity, total calorie intake, and total carbohydrate intake, total protein intake, total fat intake, and total fiber intake. The food items that were highly correlated with the milk intake were also adjusted in the polytomous regression model (Supplementary Table 1 shows the results of partial Pearson's correlation).

When milk intake (glass/day) was considered as a continuous variable, the higher the milk intake, the lower the odds of being in the stable high group (overweight remained as overweight) versus that in the stable low group in either males (P = 0.00028, odds ratio [OR] = 0.35, confidence interval [CI] = 0.2–0.62) or in females (P = 0.013, OR = 0.58, CI = 0.38–0.89 in the female). Participants with higher milk consumption had a lower risk of being in the stable high group in both males (P = 0.00013, OR = 0.41, CI = 0.26–0.65) and females (P = 0.024, OR = 0.63, CI = 0.41–0.93). The odds of being in the increasing group (from normal weight to overweight) is lower than those in the stable low group. However, this difference was not significant. As the sample size in the BMI decreasing group is very small, the results were not shown.

Mendelian randomization study

The SNP-r4954490 of the TWB array was selected as the designated IV in this MR study, since it is in linkage disequilibrium (LD, D' = 0.96 and R^2 = 0.87) with the rs3754686, a known lactase persistence marker on *MCM6* gene (27).

Characteristics of the three genotypes (GG, GA, and AA) of rs4954490 are provided in Table 3. The MR study is used to mimic a RCTs. As expected, no significant differences were observed across the three genotype groups with respect to age, sex, education level, smoking status, drinking status, exercise habit, marital status, and residential location. Table 4 presents the results of the MR study, that is, the overweight/obesity status by the genotypes of rs4954490. In model 2 (with age and sex adjustments), the risk of overweight (BMI ≥ 24) was significantly lower in the GG genotype group (lactase persistent group) than those of the AA genotype (P = 0.015, OR = 0.85, CI = 0.74–0.97). A similar trend was also observed in the GA versus AA, but was not statistically significant (P = 0.17, OR = 0.91, CI = 0.8–1.04).

The same phenomenon was observed for obesity status (BMI ≥ 27) (GG vs. AA: P = 0.037, OR = 0.85, CI = 0.72–0.99; GA vs. AA: P = 0.032, OR = 0.84, CI = 0.72–0.99).

Discussion

In this study, we used two approaches to study the causal relations between milk consumption and obesity, a 10-year longitudinal study and an MR study, and conclude that increasing milk intake is protective against obesity development in the Taiwanese population where average milk intake is only half a glass of milk per day (15).

In northern European populations, lactase persistence is largely determined by the genotypes of the *MCM6* gene that is adjacent to the *LCT* gene and influences differential transcriptional activation of the *LCT* promoter. The *MCM6*-rs4988235 SNP (*LCT*-13910 C/T) at intron 13 is often used to study lactase persistence and milk intake. However, this SNP is not polymorphic in Asian population (13). Another nearby SNP, *MCM6*-rs3754686, approximately 5,370 base pairs downstream from rs4988235, occurs more frequently in the global regions (11). Thus, we used the rs3754686 as the IV in our MR study.

There are relatively few cohort studies investigating this issue. A recent meta-analysis compiled findings from cross-sectional studies and suggested an inverse association between milk and dairy intake and weight status (5). Meanwhile, a Swedish study on a male cohort with a 12-year follow-up showed that with higher dairy intake, there is a lower risk of central obesity (29). In addition, a few prospective studies showed the opposite or no association (9–11). A meta-analysis analyzing 14 RCTs has shown that the inclusion of dairy products along with energy-restrictive weight loss diets significantly affected weight, body fat mass, lean mass, and waist circumference, compared with those in the usual weight loss diets (8). Despite the beneficial effects found from RCT studies, a few recent MR studies in northern European countries (30, 31) found no association between milk intake and BMI. Another large-scale MR meta-analysis study that analyzed the causal effect of dairy intake among 184,802 participants from 25 studies (23 on European ancestry, one on African ancestry, and one on Puerto Rican) suggested a causal effect of higher dairy intake on increased BMI. The contrasting results between Asian and European may be resulted from large differences in milk intake across regions. According to the data collected by the food and agriculture organization (FAO) (http://www.fao.org/faostat/en/#data/CL) in 2013 (Supplementary Fig. 2), the consumption of milk in Asian countries is far less than the world average (112.85 kg/capita/year). In Taiwan, only 41.72 kg was consumed per person in 2013, while 430.76 kg was consumed in Finland. We postulate that dairy foods–BMI relationship may be curvy linear, which may exert beneficial effects in the low-consumption regions while demonstrating harmful effects in the high-consumption regions (32). Further studies are needed to understand the interaction among the genetics, environmental factors (e.g. lifestyle and dietary pattern), and obesity.

Although the potential mechanisms by which milk products may have a beneficial effect on body weight and composition have not been fully elucidated, previous studies have determined that some components in milk, such as calcium (33, 34), vitamin D (35), dairy protein and

Table 3. Characteristics of the participants by genotypes, Taiwan Biobank

	rs4954490						
	GG (*N* = 4,224)		GA (*N* = 4,594)		AA (*N* = 1,170)		*P*
Age (mean, SD)	48.83	11.2	48.79	11.0	49.03	11.1	0.81
Sex (*N*, %)							0.47
M	2,141	50.7%	2,279	49.6%	574	50.9%	
F	2,083	49.3%	2,315	50.4%	596	50.9%	
Education (*N*, %)							0.72
Elementary school	312	7.4%	310	6.8%	87	7.5%	
Junior high/senior high	1,721	40.8%	1,907	41.5%	488	41.8%	
BS/MS/PhD	2,190	51.9%	2,374	51.7%	593	50.8%	
Smoking (*N*, %)							0.25
Yes	418	11.4%	537	11.7%	140	12.0%	
Few	358	8.5%	401	8.7%	79	6.8%	
No	2,862	67.8%	3,142	68.4%	818	69.9%	
Quit	523	12.4%	514	11.2%	133	11.4%	
Drinking (*N*, %)							0.42
Yes	335	7.9%	379	8.3%	82	7.0%	
No	3,748	88.7%	4,078	88.8%	1,044	89.2%	
Quit	141	3.3%	137	3.0%	44	3.8%	
Regular exercise (*N*, %)							0.57
No	2,459	58.2%	2,724	59.3%	692	59.2%	
Yes	1,765	41.8%	1,870	40.7%	478	40.9%	
Marriage (*N*, %)							0.49
Single	500	11.9%	504	11.0%	146	12.5%	
Married	3,315	78.5%	3,617	78.8%	907	77.5%	
Divorce/widowed	406	9.6%	468	10.2%	117	10.0%	
Place (*N*, %)							0.38
East	1	0.0%	4	0.1%	0	0.0%	
Middle	1,038	24.6%	1,221	26.6%	291	24.9%	
North	1,263	29.9%	1,373	29.9%	351	30.0%	
South	1,921	45.5%	1,995	43.4%	528	45.1%	
Island	1	0.0%	1	0.0%	0	0.0%	

Note: ANOVA and χ^2 analysis were used to compare continuous and categorical descriptive variables by genotype (GG, GA, and AA), respectively. G allele is the lactase persistent allele.

bioactive peptides (36), medium-chain fatty acids (33), conjugated linoleic acid (33, 37), and lactose (33, 38), are beneficial to energy metabolism and weight control.

Dietary calcium may influence body composition through multiple mechanisms, such as decreasing fatty acid absorption, increasing lipid metabolism in adipocyte, promoting energy expenditure, and facilitating appetite control (33, 34, 39). However, a 12-week multicenter RCT study (n = 106), which compared the effects among low calcium (~600 mg/day), high calcium (~1,400 mg/day), and high dairy (three dairy servings and diet totaling ~1,400 mg/day) diets, has demonstrated that increasing the intake of dairy foods while restricting dietary energy for weight loss resulted in augmentation of weight and fat loss in overweight and obese subjects. Additionally, they also found that even though the calcium dosage is the same, the weight loss effect in the milk-intake group is greater than the calcium group (40). Thus, constituents such as protein or vitamin D may play a role. Adequate vitamin D status may enhance fat oxidation and the thermic effect of meals (35).

Additionally, milk is an excellent source of protein, which induces satiety by stimulating the secretion of gastrointestinal hormones. Bioactive peptides can stimulate the secretion of insulin, which also suppresses appetite. This may directly affect food intake and indirectly affect body weight (36). Some studies also found that lactose may help to reduce caloric intake and acute appetite and help weigh control (33, 38). Milk products are also a source of medium-chain fatty acids. Some animal and human

Citation: Food & Nutrition Research 2021, **65**: 6300 - http://dx.doi.org/10.29219/fnr.v65.6300

Table 4. Results of Mendelian randomization study: odds ratios associating genotypes and overweight or obesity status

BMI	Models	OR	95%	CI	*P*
BMI < 24 vs. BMI ≥ 24	**Model 1**				
	GG vs. AA	0.87	0.76	0.99	***0.03****
	GA vs. AA	0.92	0.81	1.04	0.19
	Model 2				
	GG vs. AA	0.85	0.74	0.97	***0.015****
	GA vs. AA	0.91	0.8	1.04	0.172
BMI < 27 vs. BMI ≥ 27	**Model 1**				
	GG vs. AA	0.86	0.73	1	0.053
	GA vs. AA	0.85	0.73	0.99	***0.038****
	Model 2				
	GG vs. AA	0.85	0.72	0.99	***0.037****
	GA vs. AA	0.84	0.72	0.99	***0.032****

Note: G allele is the lactase persistent allele.
Model 1: crude model; Model 2: model with the age and sex adjustments.
*P < 0.05; N: <24 = 5,070, >24 = 4,912; <27 = 7,993, >27 = 1,995.
*The *p*-values <0.05 are shown in bold italics.

studies have shown that a diet high in medium-chain fatty acids can reduce body fat (33). However, there is a lack of well-designed large-scale intervention studies to confirm the impact of these constituents of milk (33).

In our 10-year follow-up study, the milk intake data were only collected at baseline. The habit may change during follow-up that may result in some degree of non-differential misclassification. But even so, we still observed a significant association between milk intake and BMI status change. In addition, according to the literature, the proportion of variation in the exposure variable (milk intake) explained by the IV SNP ranges from 0.7 to 1.5% (27). Although the genetic effect is relatively small, the sample size used in this study (n = 10,000) was adequately powered (power >80% and alpha 5%) to detect the association according to the statistical power calculator for MR study developed by Brion et al. (41); thus, our MR study supports a causal link between modest increase in milk consumption and lower BMI.

In conclusion, both of our 10-year longitudinal study and the MR study have demonstrated inverse associations between milk consumption and BMI in Chinese population. These findings support current dietary guidelines in Asian countries to include dairy group as one of the six food groups for nutrition guidance. However, the precise mechanism as to how milk consumption plays a role in weight control remains unclear. Further investigations are needed to elucidate how and under what circumstances dairy foods have an influence on obesity control.

Acknowledgments

Data analyzed in this article were collected by the research project 'CardioVascular Disease risk FACtors Two-township Study (CVDFACTS)' and 'Taiwan Biobank'. The assistance provided by the institute and all of those who have contributed to the formation and data collection of the CVDFACTS and Taiwan Biobank are greatly appreciated. The views expressed herein are solely those of the authors.

Conflict of interest and funding

The authors declare that they have no competing interests. The authors received no financial support for the research, authorship, and publication of this article.

Authors' contributions

KMC and WHP conceived and coordinated the investigation. KMC wrote the manuscript and was responsible for the preparation of data and statistical analysis. WHP undertook revisions and contributed intellectually to the development of this paper.

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Citation: Food & Nutrition Research 2021, **65**: 6300 - http://dx.doi.org/10.29219/fnr.v65.6300