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Dairy Intake and Body Composition and Cardiometabolic Traits among Adults: Mendelian Randomization Analysis of 182041 Individuals from 18 Studies

Mendelian Randomization of Dairy Consumption Working Group

BACKGROUND: Associations between dairy intake and body composition and cardiometabolic traits have been inconsistently observed in epidemiological studies, and the causal relationship remains ill-defined.

METHODS: We performed Mendelian randomization analysis using an established genetic variant located upstream of the lactase gene (*LCT*-13910 C/T, rs4988235) associated with dairy intake as an instrumental variable (IV). The causal effects of dairy intake on body composition and cardiometabolic traits (lipids, glycemic traits, and inflammatory factors) were quantified by IV estimators among 182041 participants from 18 studies.

RESULTS: Each 1 serving/day higher dairy intake was associated with higher lean mass [β (SE) = 0.117 kg (0.035); $P = 0.001$], higher hemoglobin A_{1c} [0.009% (0.002); $P < 0.001$], lower LDL [−0.014 mmol/L (0.006); $P = 0.013$], total cholesterol (TC) [−0.012 mmol/L (0.005); $P = 0.023$], and non-HDL [−0.012 mmol/L (0.005); $P = 0.028$]. The *LCT*-13910 C/T CT + TT genotype was associated with 0.214 more dairy servings/day (SE = 0.047; $P < 0.001$), 0.284 cm higher waist circumference (SE = 0.118; $P = 0.017$), 0.112 kg higher lean mass (SE = 0.027; $P = 3.8 \times 10^{-5}$), 0.032 mmol/L lower LDL (SE = 0.009; $P = 0.001$), and 0.032 mmol/L lower TC (SE = 0.010; $P = 0.001$). Genetically higher dairy intake was associated with increased lean mass [0.523 kg per serving/day (0.170); $P = 0.002$] after correction for multiple testing (0.05/18). However, we find that genetically higher dairy intake was not associated with lipids and glycemic traits.

CONCLUSIONS: The present study provides evidence to support a potential causal effect of higher dairy intake on increased lean mass among adults. Our findings suggest that the observational associations of dairy intake with lipids and glycemic traits may be the result of confounding.

Observational studies, in which reverse causation, residual confounding, and limited generalizability are often nonnegligible *(1)*, reported an association of dairy consumption with body composition *(2, 3)*. Meta-analyses of both observational studies *(4)* and randomized controlled trials (RCTs)[61] *(5–7)* demonstrated that high dairy intake in the absence of energy restriction increased body weight. However, meta-analysis of randomized studies showed that there were no changes in cardiometabolic risk factors such as fasting glucose, insulin resistance, lipids, or C-reactive protein (CRP) *(8)*. In contrast, another meta-analysis of controlled short-term intervention studies showed that a fermented yogurt product was associated with a 4% decrease in total cholesterol (TC) and a 5% decrease in LDL cholesterol *(9)*. Therefore, results for cardiometabolic traits are still inconclusive. Mendelian randomization (MR) analysis *(10–13)*, which is analogous to an RCT, when randomization to genotype takes place at conception *(14)*, has been widely used to assess potential causal associations of lifetime variations of modifiable factors with diseases *(10, 15–20)*.

Previous large-scale MR analyses, adopting a well-established genetic marker (*LCT*-13910 C/T, rs4988235) as an instrumental variable (IV) for dairy intake, demonstrated that genetically predicted high dairy intake is associated with higher body mass index (BMI) *(18)* but not causally related to hypertension *(10)*, diabetes *(11)*, and cardiovascular diseases *(12, 13)*. However, whether dairy intake is causally associated with body

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[61] Nonstandard abbreviations: RCT, randomized controlled trial; CRP, C-reactive protein; TC, total cholesterol; MR, Mendelian randomization; IV, instrumental variable; BMI, body mass index; TG, triglyceride; apoB, apolipoprotein B; HbA_{1c}, hemoglobin A_{1c}; hs, high sensitivity.

composition and other important cardiometabolic traits is largely unknown.

Therefore, in the current study, we performed MR analysis among 182041 adult participants from 18 cohorts using an established dairy intake-associated genetic variant located near the lactase gene *LCT*[62] to examine the causal association of habitual dairy intake with body composition and cardiometabolic traits such as lipids, glycemic traits, and inflammatory factors in general populations.

Materials and Methods

STUDY PARTICIPANTS

The study was conducted within the Mendelian Randomization of Dairy Consumption Working Group, represented here by 18 cohort studies including 182041 individuals in total. Detailed descriptions of each study are presented in Table 1 of the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol65/issue6. Participants from each study provided written informed consent, and local institutional review boards (see Table 2 in the online Data Supplement) granted ethical approval.

DAIRY INTAKE ASSESSMENT AND OUTCOMES

Information on intake of dairy products was collected by self-reported questionnaire in each study; detailed information on cohort-specific data collection methods is provided in Table 3 of the online Data Supplement. Total dairy products included skim/low fat milk, whole milk, ice cream, yogurt, cottage/ricotta cheese, cream cheese, other cheese, and cream. The primary outcomes are body composition (body fat percentage, waist circumference, waist to hip ratio, lean mass, and fat mass), cardiometabolic traits [lipids: HDL cholesterol, LDL cholesterol, TC, total triglyceride (TG), non-HDL cholesterol, and apolipoprotein B (apoB)], glycemic traits [fasting glucose, hemoglobin A_{1c} (HbA_{1c}), fasting insulin, insulin resistance, and insulin sensitivity], and inflammatory factors [regular CRP and high-sensitivity CRP (hsCRP)] at baseline or during follow-up. Detailed information on the outcome measure for each study is reported in Table 4 of the online Data Supplement.

SINGLE-NUCLEOTIDE POLYMORPHISM SELECTION AND GENOTYPING METHODS

In the present study, we chose the widely confirmed and extensively studied variant *LCT*-13910 C/T, rs4988235 as the IV for dairy intake *(11, 12, 21)*. The variant rs4988235, located upstream from the *LCT* gene, is associated with lactase persistence and thereby with the ability to digest lactose, the primary source of carbohydrates in milk *(22)*. The TT and TC genotypes are associated with lactase persistence, and CC is associated with nonpersistence. Therefore, lactase persistence is a dominantly inherited genetic trait. Most studies used direct genotype information on rs4988235 from previously genotyped array data. Whenever rs4988235 was not genotyped directly, we used either (*a*) the HapMap II reference panel-imputed genetic information for rs4988235 or (*b*) genotype information of proxy that are in high linkage disequilibrium with rs4988235 (n = 5; $r^2 > 0.9$). Genotyping platforms, genotype frequencies, Hardy–Weinberg equilibrium *P* values, and call rates (median of 98.8%) for *LCT*-13910 C/T are listed in Table 5 of the online Data Supplement.

STATISTICAL ANALYSIS

Our study tested the (*a*) observational associations of dairy intake with body composition, lipids, glycemic traits, and inflammatory factors; (*b*) genetic associations of the *LCT*-13910 C/T, rs4988235 with dairy intake and cardiometabolic traits under a dominant model (CC vs CT + TT); and (*c*) causal effect of dairy intake on outcomes by using the IV estimator.

A standard analysis protocol was applied to each individual study to produce comparable results. Linear regression was used to test the observational associations of dairy intake with cardiometabolic traits after adjustment for age, sex, ethnicity, region, years of follow-up, and other baseline covariates (smoking status, physical activity, total energy intake, and alcohol intake), as available. Linear regression was used to test the genetic associations of *LCT*-13910 C/T with dairy intake and cardiometabolic traits, respectively, after adjustment for age, sex, ethnicity, region, and total energy.

META-ANALYSIS AND BETWEEN-STUDY HETEROGENEITY

Meta-analyses were conducted using individual participant data in each study and then pooled β coefficients across studies using random-effects or fixed-effects meta-analysis. We assessed between-study heterogeneity via Cochrane's *Q* and I^2 statistics *(23–25)*. We used random-effects meta-analysis if $I^2 > 0.25$; otherwise, fixed-effects models were used *(26)*.

SE AND INFERENCE FOR THE IV ESTIMATOR

After meta-analysis, we used the IV estimators to quantify the strength of the causal association of dairy intake with cardiometabolic traits (Fig. 1) *(27)*. The IV estimator, which is identical to that derived by the widely used 2-stage least-squares method *(28)*, was calculated as the β of the regression coefficients *MCM6* variant 4988235-outcome and *MCM6* variant 4988235-dairy:

[62] Human Genes: *LCT*, lactase; *MCM6*, minichromosome maintenance complex component 6.

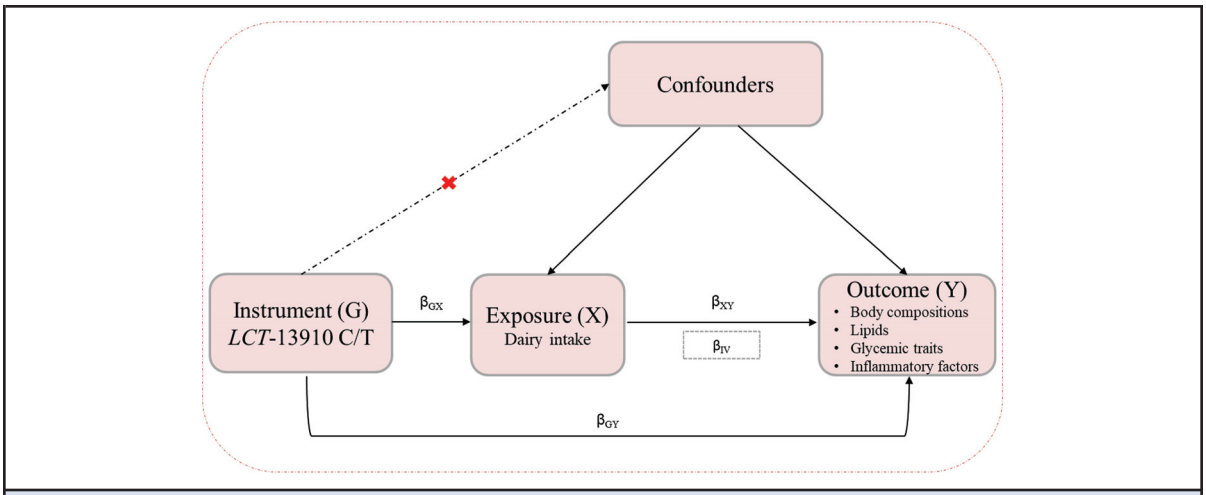

Fig. 1. A schematic description of a Mendelian randomization analysis.

MR can be used to test the hypothesis that exposure (dairy intake) causes outcomes (cardiometabolic traits). Three assumptions of MR: (*a*) genetic variants must be associated with dairy intake; (*b*) genetic variants must not be associated with confounders; and (*c*) genetic variants must influence cardiometabolic traits only through dairy intake, not through other pathways. The IV estimator was used to quantify the strength of the causal association of dairy intake with cardiometabolic traits using *LCT*-13910 C/T as an IV.

$$\beta_{IV} = \frac{\beta_{SNP\_Outcome}}{\beta_{SNP\_Dairy}} \quad (1)$$

$$se_{IV} = abs(\beta_{IV}) \sqrt{\left(\frac{se_{SNP\_Dairy}}{\beta_{SNP\_Dairy}}\right)^2 + \left(\frac{se_{SNP\_Outcome}}{\beta_{SNP\_Outcome}}\right)^2} \quad (2)$$

Furthermore, to explore potential sources of heterogeneity, we conducted subgroup analysis using age of participants (<50 years and ≥50 years), follow-up years (<5 years and ≥5 years), region or country (Europe and non-Europe), study design (cohort and cross-sectional), and CC genotype frequency (≤10% and >10%) as putative categorical moderators. The Bonferroni correction was conducted for multiple comparisons ($P = 0.05/18 = 0.003$). Statistical analyses were conducted using Stata 14.0 software. All *P* values reported were 2-sided.

Results

BASELINE CHARACTERISTICS OF PARTICIPATING STUDIES

Baseline characteristics of the 182041 participants from 18 studies are shown in Table 1 here and Tables 6–8 of the online Data Supplement. A description of each study and additional characteristics of participants are presented in Tables 1 and 6 of the online Data Supplement. A total of 17 studies provided data for *LCT*-13910 C/T, and 1 study (ARIC-AA) provided results for the proxy single-nucleotide polymorphism rs1446585 (defined on the basis of $r^2 \geq 0.90$ with rs4988235 in individuals). The χ^2 tests showed that the CCHS, CGPS, and FamHS studies did not achieve Hardy–Weinberg equilibrium (see Table 5 in the online Data Supplement).

OBSERVATIONAL ASSOCIATIONS OF DAIRY INTAKE WITH CARDIOMETABOLIC TRAITS

Our meta-analysis showed that high dairy intake was significantly associated with higher lean mass ($\beta = 0.117$ kg per serving/day; SE = 0.035; $P = 0.001$), higher HbA_{1c} ($\beta = 0.009\%$ per serving/day; SE = 0.002; $P < 0.001$), lower LDL ($\beta = -0.014$ mmol/L per serving/day; SE = 0.006; $P = 0.013$), lower TC ($\beta = -0.012$ mmol/L per serving/day; SE = 0.005; $P = 0.023$), and lower non-HDL ($\beta = -0.012$ mmol/L per serving/day; SE = 0.005; $P = 0.028$) (Fig. 2).

GENETIC ASSOCIATION OF THE LCT-13910 C/T WITH DAIRY INTAKE AND CARDIOMETABOLIC TRAITS

In a dominant model, we found that the *LCT*-13910 C/T CT + TT genotype was significantly associated with 0.214 more dairy servings/day ($\beta = 0.214$ serving/day; SE = 0.047; $P = 6.8 \times 10^{-6}$). We pooled the genetic association with cardiometabolic traits from 18 studies using fixed- or random-effects meta-analysis and found that the *LCT*-13910 C/T CT + TT genotype was significantly associated with 0.284 cm higher waist circumference ($\beta = 0.284$; SE = 0.118; $P = 0.017$), 0.112 kg higher lean mass ($\beta = 0.112$; SE = 0.027; $P = 3.8 \times 10^{-5}$), 0.032 mmol/L lower LDL ($\beta = -0.032$ mmol/L per serving/day; SE = 0.009;

Table 1. Baseline characteristics of participating studies.[a]

Study name[b]	Study design	Number of participants, n	Follow-up, years	Age, years	Total dairy intake, serving/day	Country	Male, n (%)	BMI, kg/m^2	rs4988235, n (%)		
									CC	CT	TT
ARIC-AA[c]	Cohort	2178	2.8	53.5 (5.7)	1.18 (1.16)	US	793 (36.4)	29.74 (6.01)	1694 (77.78)	450 (20.66)	34 (1.56)
ARIC-EA[d]	Cohort	8170	2.9	54.2 (5.6)	1.82 (1.37)	US	3882 (47.5)	26.95 (4.78)	1020 (12.48)	3392 (41.52)	3758 (46.00)
CCHS	Cohort	8721	0	58.0 (15.1)	NA[e]	Denmark	3911 (44.8)	25.6 (4.32)	548 (6.28)	3041 (34.87)	5132 (58.85)
CGPS	Cohort	74243	0	57.0 (13.3)	1.69 (1.21)	Denmark	33134 (44.6)	26.20 (4.30)	4348 (5.86)	26571 (35.79)	43324 (58.35)
CHS	Cohort	1863	4.9	70.9 (4.2)	1.38 (0.70)	US	704 (37.8)	26.43 (4.25)	68 (3.65)	804 (43.16)	991 (53.19)
DCH	Cohort	8026	NA		2.50 (1.46)	Denmark	3919 (48.8)	26.84 (4.44)	460 (5.73)	2674 (33.32)	4892 (60.95)
DILGOM	Cohort	1227	7	52.6 (13.1)	5.83 (3.05)	Finland	528 (43.0)	26.41 (4.65)	196 (16.0)	332 (84)	
FamHS	Cohort	2131	7.9	50.5 (13.0)	2.05 (1.47)	US	961 (45.1)	27.57 (5.30)	250 (11.73)	893 (41.91)	988 (46.36)
GESUS	Cohort	20459	0	55.8 (13.6)	2.37 (1.53)	Denmark	9334 (45.6)	26.72 (4.66)	1212 (5.92)	7379 (36.07)	11868 (58.01)
H2000	Cohort	3445	10.9	49.0 (11.8)	6.06 (2.98)	Finland	1551 (45.0)	26.64 (4.45)	608 (17.65)	1667 (48.39)	1170 (33.96)
HPFS	Cohort	6914	24	54.8	2.04	US	NA	25.32	841 (15.13)	2509 (45.14)	2208 (39.73)
MESA	Cohort	4455	10	60.4 (9.5)	1.87 (1.72)	US	2110 (47.3)	28.44 (5.66)	2404 (53.96)	1275 (28.62)	776 (17.42)
NHS	Cohort	11287	26	52.7 (6.5)	2.05 (1.34)	US	NA	NA	1227 (16.23)	3600 (47.61)	2735 (36.17)
PREDIMED-Valencia	Cohort	940	1–2[f]	67.0	1.86 (1.14)	Spain	338 (36.0)	30.11 (4.22)	357 (38)	430 (45.7)	153 (16.3)
RAINE	Cohort	527	2.3	19.9 (0.3)	1.760 (0.956)	Australia	270 (51.2)	24.29 (4.842)	255 (48.39)	202 (38.33)	70 (13.28)
THISEAS	Case–control	2565	NA	59.1 (0.3)	0.83 (0.03)	Greece	59	28.15 (0.10)	78	20	1.4
WGHS	Cohort	23294	NA	54.7 (7.1)	1.98 (1.36)	US	NA	25.91 (4.96)	2839 (12.19)	9819 (42.15)	10636 (45.66)
YFS	Cohort	1596	4	37.7 (5.0)	4.20 (2.49)	Finland	714 (44.7)	25.79 (4.57)	243 (15.2)	798 (50.0)	555 (34.8)

[a] Mean (SD) for continuous variables, and n (%) for categorical variables.
[b] Study abbreviation definitions and study descriptions are provided in Table 1 of the online Data Supplement.
[c] ARIC-AA, African Ancestry.
[d] ARIC-EA, European Ancestry.
[e] NA, not applicable.
[f] 2 years for anthropometrics and 1 year for lipids and glycemic traits.

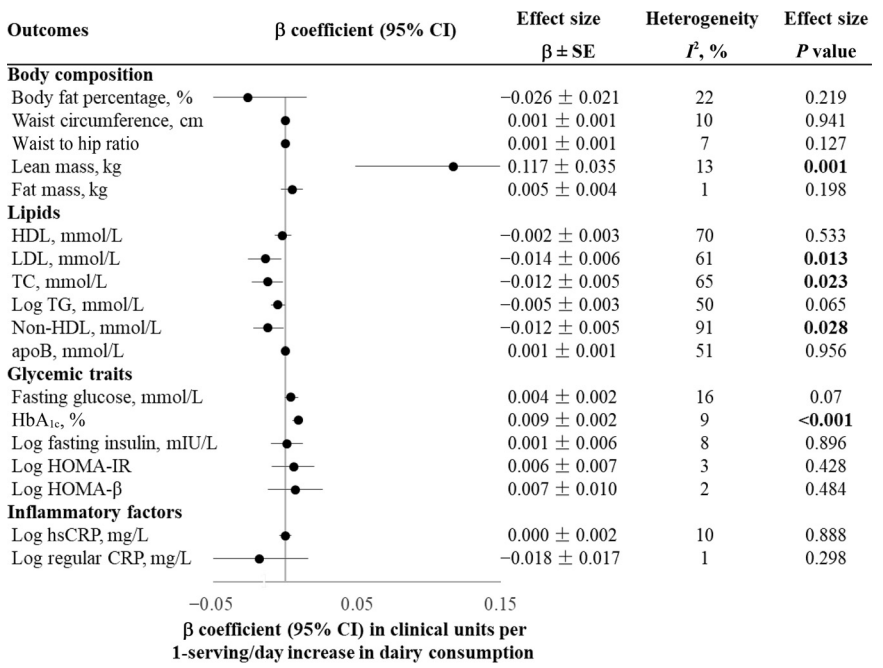

Fig. 2. Association between dairy intake and cardiometabolic traits among 182041 participants from 18 studies.

Linear regression was used to test the association of dairy intake (serving/day) with cardiometabolic traits after adjustment of sex, ethnicity, region, years of follow-up, and other baseline covariates if available (age, smoking status, physical activity, total energy intake, and alcohol intake) in each study. We pooled β coefficients across studies using random-effects ($I^2 \geq 25\%$) or fixed-effects ($I^2 < 25\%$) meta-analyses based on the heterogeneity between studies.

$P = 0.001$), and 0.032 mmol/L lower TC ($\beta = -0.032$ mmol/L per serving/day; SE = 0.010; $P = 0.001$) (Fig. 3).

IV ESTIMATED CAUSALITY BETWEEN DAIRY INTAKE AND CARDIOMETABOLIC TRAITS

Fig. 3 presents the genetic association with cardiometabolic traits and the IV estimated causal effects of dairy intake on cardiometabolic traits. Genetically determined higher dairy intake was associated with increased waist circumference ($\beta = 1.327$ cm per serving/day; SE = 0.623; $P = 0.020$), increased lean mass ($\beta = 0.523$ kg per serving/day; SE = 0.170; $P = 0.002$), decreased LDL ($\beta = -0.150$ mmol/L per serving/day; SE = 0.053; $P = 0.005$), and decreased TC ($\beta = -0.150$ mmol/L per serving/day; SE = 0.057; $P = 0.008$). After correction for multiple testing, MR association of dairy intake with lean mass remained significant at $P = 0.002$ (0.05/18) (Fig. 3).

We further conducted stratified analyses of estimated causality by age, follow-up years, study design, ethnic group, and CC genotype frequency (Table 2). We observed significant MR associations of genetically determined higher dairy intake only on LDL and TC in studies with a patient mean age of ≥50 years and studies with follow-up time <5 years.

Discussion

In thus far the largest MR analysis study, including 182041 adults from 18 cohorts, our results support a causal relationship between higher dairy intake and increased lean mass. In addition, our findings imply that the observational associations of dairy intake with lipids and glycemic traits could be the result of confounding.

In our well-powered study, we individually analyzed 182041 individuals and provided strong evidence that high dairy intake was causally associated with higher lean mass. Results from our observational analyses and our MR analyses were highly consistent, both suggesting higher lean mass in those with high intake of dairy products. In line with our findings, a previous meta-analysis of RCTs showed that dairy consumption increased lean mass *(5)*. Several mechanisms might be responsible for the impact of dairy intake on the regulation of lean mass. First, increased protein intake from dairy products may promote maintenance of lean mass *(7)*. Second, the hormone estrone found in dairy products may promote increases in body weight *(18, 29, 30)*. Third, higher intake of dairy foods is associated with higher plasma insulin-like growth factor 1, which may contribute to weight gain *(18, 31)*. However, future research is needed to further

Outcomes	Genetic associations			IV estimated causality		
	β ± SE	*P* value	I^2, %	β ± SE	β coefficient (95% CI)	*P* value
Body composition						
Body fat percentage, %	0.183 ± 0.120	0.130	49	0.855 ± 0.592		0.149
Waist circumference, cm	0.284 ± 0.118	**0.017**	58	1.327 ± 0.623		**0.020**
Waist to hip ratio	0.001 ± 0.001	0.656	15	0.001 ± 0.004		0.904
Lean mass, kg	0.112 ± 0.027	$\mathbf{3.8 \times 10^{-5}}$	65	0.523 ± 0.170		**0.002**
Fat mass, kg	0.196 ± 0.204	0.337	65	0.916 ± 0.974		0.353
Lipids						
HDL, mmol/L	−0.005 ± 0.004	0.228	1	−0.023 ± 0.020		0.237
LDL, mmol/L	−0.032 ± 0.009	**0.001**	0	−0.150 ± 0.053		**0.005**
TC, mmol/L	−0.032 ± 0.010	**0.001**	25	−0.150 ± 0.057		**0.008**
Log TG, mmol/L	0.006 ± 0.005	0.180	0	0.028 ± 0.022		0.209
Non-HDL, mmol/L	−0.004 ± 0.011	0.704	0	−0.019 ± 0.050		0.722
apoB, mmol/L	0.009 ± 0.019	0.623	0	0.042 ± 0.087		0.642
Glycemic traits						
Fasting glucose, mmol/L	−0.014 ± 0.021	0.505	47	−0.065 ± 0.098		0.516
HbA_{1c}, %	0.001 ± 0.009	0.944	7	0.005 ± 0.044		0.922
Log fasting insulin, mIU/L	−0.009 ± 0.015	0.534	0	−0.042 ± 0.071		0.563
Log HOMA-IR	−0.007 ± 0.019	0.724	0	−0.033 ± 0.087		0.720
Log HOMA-β	0.003 ± 0.025	0.906	29	0.014 ± 0.116		0.912
Inflammatory factors						
Log hsCRP, mg/L	0.003 ± 0.01	0.768	0	0.014 ± 0.048		0.781
Log regular CRP, mg/L	0.106 ± 0.085	0.213	79	0.495 ± 0.411		0.230
Dairy intake, serving/day	0.214 ± 0.047	$\mathbf{6.8 \times 10^{-6}}$	97			

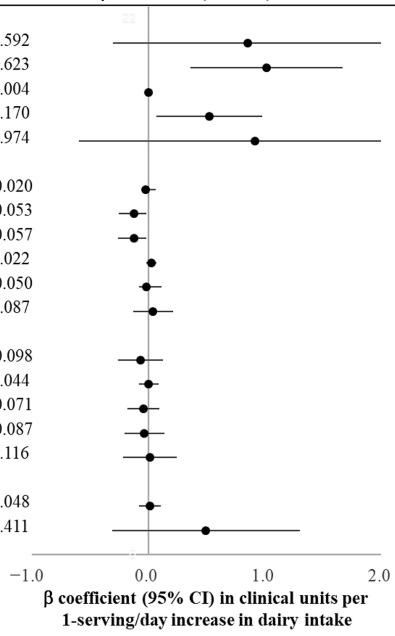

Fig. 3. Genetic association and estimated causality between dairy intake and cardiometabolic traits.

The *LCT*-13910 C/T located in upstream of the lactase (*LCT*) gene was selected as an instrumental variable. The MR estimate was computed from the ratio of the coefficient of the association between the *LCT*-13910 C/T and cardiometabolic traits to that of the association between the *LCT*-13910 C/T and dairy intake. This IV estimate reflects the potential causal effect of dairy intake on BMI. We pooled β coefficients across studies using random-effects ($I^2 \geq 25\%$) or fixed-effects ($I^2 < 25\%$) meta-analyses based on the heterogeneity between studies.

illustrate the precise mechanisms of dairy products on body composition in the context of energy restriction.

By using the *LCT*-13910 C/T as an instrument for dairy intake, our MR results indicated that higher dairy intake is marginally associated with decreased circulating concentrations of TC and LDL. In contrast, observational evidence from Mediterranean, Danish, and American populations suggested that milk intake was not associated with lipids *(12, 13)*. However, our meta-analysis of observational studies showed that high dairy intake was significantly associated with lower LDL and TC. Such observations are supported by previous meta-analysis of controlled short-term intervention studies using a probiotic milk product, in which the fermented yogurt product was associated with a 4% decrease in TC and a 5% decrease in LDL cholesterol *(9)*. Thus, it is possible that intake of probiotic milk products, fermented yogurt especially, drives the beneficial effect of intake of dairy products on lipid levels. It is worth noting that using the *LCT*-13910 C/T as an IV of dairy intake in general, rather than milk intake specifically, complicates the interpretation of our results. Previous studies indicate that the association between this genetic variant and dairy intake is specific to milk *(1)*, possibly because of probiotics in some nonmilk dairy products (such as yogurt and fermented milk) that may facilitate the digestion of lactose and/or differences in lactose concentration. In the current study, the use of total dairy products including skim/low fat milk, whole milk, ice cream, yogurt, cottage/ricotta cheese, cream cheese, other cheese, and cream may largely attenuate our findings. Future study on the causal relationship between dairy-specific product and lipids is needed.

We did not find a causal association between dairy intake and glycemic traits such as fasting glucose, insulin, insulin sensitivity, and insulin resistance. Likewise, previous MR analyses demonstrated genetically high milk intake also did not influence plasma concentrations of glucose *(12, 13)*. Our findings were also supported by a 3-week randomized crossover study indicating that both whole milk and skim milk did not affect fasting glucose or insulin in healthy adults *(32)*. Our MR results may potentially explain the nonsignificant causal effect of high milk intake on risk of type 2 diabetes *(11)*. However, previous MR analysis observed a significant sex difference in genetic association with fasting glucose *(13)*,

Table 2. Stratified analysis on causal estimates of dairy consumption (serving/day) with cardiometabolic traits.[a]

	Age, years		Follow-up, years		Region or country		Study design		CC genotype frequency	
Outcomes	≥50	<50	≥5	<5	Europe	non-Europe	Cross-sectional	Cohort	≤10%	>10%
Body composition										
Body fat percentage, %	0.75 (−0.54, 2.04)	0.58 (−2.10, 3.26)	1.60 (−2.19, 5.39)	0.55 (−0.41, 1.50)	1.27 (−1.43, 3.97)	0.73 (−0.54, 1.99)	0.81 (−0.70, 2.32)	0.95 (−1.50, 3.39)	0.77 (−0.76, 2.30)	1.00 (−0.89, 2.90)
Waist circumference, cm	1.50 (−0.16, 3.16)	1.21 (−2.05, 4.46)	1.26 (−1.65, 4.17)	1.53 (0.13, 2.93)	2.23 (−0.45, 4.91)	0.90 (−0.55, 2.34)	1.45 (−0.35, 3.26)	1.37 (0.25, 2.49)	1.62 (−0.11, 3.35)	1.07 (−0.05, 2.19)
Waist to hip ratio	0.00 (−0.01, 0.01)	0.02 (−0.03, 0.08)	0.00 (−0.04, 0.04)	0.00 (−0.01, 0.01)	0.01 (−0.01, 0.03)	0.00 (−0.01, 0.01)	0.01 (−0.01, 0.03)	0.00 (−0.01, 0.01)	0.01 (−0.01, 0.03)	0.00 (−0.01, 0.00)
Lean mass, kg	0.66 (−2.10, 3.42)	0.01 (−1.40, 1.41)	−0.81 (−3.28, 1.65)	1.33 (−1.27, 3.93)	4.33 (0.32, 8.34)	−0.18 (−1.33, 0.97)	0.78 (−3.24, 4.81)	0.10 (−1.30, 1.50)	0.74 (−3.06, 4.54)	0.10 (−1.27, 1.46)
Fat mass, kg	0.40 (−2.89, 3.68)	0.88 (−1.86, 3.63)	−0.12 (−8.38, 8.13)	0.85 (−0.89, 2.59)	3.20 (−1.15, 7.54)	0.54 (−1.37, 2.45)	0.95 (−1.98, 3.88)	0.85 (−2.52, 4.21)	1.04 (−1.89, 3.96)	0.67 (−2.08, 3.41)
Lipids										
HDL, mmol/L	−0.02 (−0.07, 0.02)	−0.04 (−0.16, 0.07)	0.01 (−0.07, 0.10)	−0.05 (−0.10, −0.01)	0.01 (−0.09, 0.10)	−0.05 (−0.10, 0.00)	0.01 (−0.05, 0.06)	−0.05 (−0.11, 0.00)	0.00 (−0.05, 0.05)	−0.05 (−0.09, 0.00)
LDL, mmol/L	−0.16 (−0.31, −0.02)	0.03 (−0.15, 0.21)	−0.06 (−0.23, 0.10)	−0.17 (−0.32, −0.03)	−0.18 (−0.39, 0.03)	−0.08 (−0.21, 0.06)	−0.13 (−0.28, 0.02)	−0.14 (−0.31, 0.04)	−0.12 (−0.26, 0.02)	−0.13 (−0.30, 0.04)
TC, mmol/L	−0.18 (−0.32, −0.03)	0.08 (−0.14, 0.30)	0.01 (−0.17, 0.20)	−0.18 (−0.34, −0.02)	−0.11 (−0.30, 0.09)	−0.12 (−0.29, 0.04)	−0.09 (−0.23, 0.06)	−0.23 (−0.47, 0.00)	−0.08 (−0.22, 0.06)	−0.22 (−0.44, 0.00)
Log TG, mmol/L	0.03 (−0.02, 0.08)	0.05 (−0.09, 0.18)	0.01 (−0.09, 0.11)	0.03 (−0.01, 0.08)	0.06 (−0.02, 0.15)	0.00 (−0.05, 0.05)	0.05 (−0.03, 0.13)	0.02 (−0.03, 0.06)	0.06 (−0.01, 0.12)	0.00 (−0.05, 0.05)
Non-HDL, mmol/L	−0.04 (−0.15, 0.08)	0.09 (−0.18, 0.36)	0.08 (−0.12, 0.29)	−0.06 (−0.17, 0.06)	−0.05 (−0.25, 0.15)	−0.01 (−0.11, 0.10)	−0.02 (−0.18, 0.15)	−0.02 (−0.14, 0.09)	−0.01 (−0.17, 0.15)	−0.02 (−0.13, 0.09)
apoB, mmol/L	−0.01 (−0.61, 0.60)	0.13 (−0.26, 0.52)	0.02 (−0.17, 0.21)	0.09 (−1.20, 1.39)	0.30 (−5.88, 6.49)	0.06 (−0.21, 0.33)	0.05 (−0.14, 0.25)	−1.80 (−7.18, 3.57)	0.05 (−0.14, 0.24)	−5.37 (−12.82, 2.09)
Glycemic traits										
Fasting glucose, mmol/L	−0.12 (−0.41, 0.17)	0.02 (−0.14, 0.18)	−0.37 (−1.10, 0.37)	0.01 (−0.18, 0.20)	0.01 (−0.42, 0.43)	−0.08 (−0.29, 0.12)	−0.12 (−0.40, 0.15)	−0.02 (−0.40, 0.37)	−0.09 (−0.33, 0.16)	−0.09 (−0.47, 0.30)
HbA_{1c}, %	−0.01 (−0.09, 0.08)	0.16 (−0.27, 0.59)	−0.12 (−0.41, 0.17)	0.02 (−0.08, 0.12)	−0.07 (−0.19, 0.06)	0.09 (−0.03, 0.21)	−0.10 (−0.33, 0.14)	0.02 (−0.06, 0.10)	−0.05 (−0.16, 0.06)	0.07 (−0.03, 0.18)
Log fasting insulin, mIU/L	−0.10 (−0.27, 0.08)	0.08 (−0.16, 0.31)	−0.20 (−0.51, 0.11)	0.01 (−0.15, 0.17)	−0.04 (−0.24, 0.16)	−0.05 (−0.28, 0.19)	−0.05 (−0.21, 0.11)	NA	−0.06 (−0.22, 0.10)	0.07 (−0.43, 0.57)
Log HOMA-IR[b]	−0.07 (−0.30, 0.16)	0.02 (−0.16, 0.20)	−0.03 (−0.21, 0.15)	NA	0.01 (−0.26, 0.28)	−0.07 (−0.30, 0.16)	−0.04 (−0.23, 0.16)	NA	−0.03 (−0.22, 0.16)	−0.05 (−0.66, 0.55)
Log HOMA-β	−0.05 (−0.44, 0.34)	0.07 (−0.18, 0.33)	0.01 (−0.22, 0.25)	NA	0.06 (−0.18, 0.31)	−0.05 (−0.44, 0.35)	0.02 (−0.25, 0.28)	NA	−0.03 (−0.30, 0.24)	0.26 (−0.23, 0.75)
Inflammatory factors										
Log hsCRP, mg/L	0.03 (−0.08, 0.13)	−0.02 (−0.36, 0.32)	−0.08 (−0.31, 0.14)	0.08 (−0.08, 0.25)	0.13 (−0.08, 0.35)	−0.03 (−0.12, 0.07)	−0.06 (−0.30, 0.17)	0.08 (−0.09, 0.24)	0.06 (−0.15, 0.27)	−0.02 (−0.11, 0.08)
Log regular CRP, mg/L	0.03 (−0.24, 0.30)	1.45 (−1.66, 4.56)	0.11 (−0.63, 0.84)	0.74 (−0.53, 2.00)	0.57 (−0.41, 1.55)	NA	0.93 (−0.68, 2.54)	0.01 (−0.23, 0.25)	0.88 (−0.64, 2.39)	0.01 (−0.22, 0.24)

[a] >β coefficients (95% CI) represent the changes in cardiometabolic traits per 1 serving/day increase in genetically predicted dairy intake; linear regression was used to test the association of *MCM6* variant rs4988235 with dairy intake or cardiometabolic traits after adjustment of age, sex, ethnicity, region, total energy, and principal component for population stratification, as appropriate; We pooled β coefficients across studies using random-effect ($I^2 \geq 25\%$) or fixed-effect ($I^2 < 25\%$) meta-analyses based on the heterogeneity between studies. We used the IV estimators to quantify the strength of the causal association of dairy intake and cardiometabolic traits in each study. The IV estimator, which is identical to that derived by the widely used 2-stage least-squares method, was calculated as the β of the regression coefficients *MCM6* rs4988235-outcomes and *MCM6* rs4988235-dairy.

[b] HOMA: homeostatic model assessment, IR: insulin resistance, NA: not applicable.

in which the T allele was significantly associated with lower fasting glucose in women but not in men. The association in women in which the T allele was associated with higher milk intake is inversely associated with fasting glucose *(13)*. Further RCTs or MR investigations are needed to explore whether there is a true sex difference in genetic association of *LCT*-13910 C/T, rs4988235 with fasting glucose and whether milk intake may modulate such genetic association.

Several strengths of the current study merit consideration. First, in the present consortium-based effort involving 18 studies, we used a standardized analysis plan, which is less likely to be affected by publication bias than meta-analyses based on published reports. The large sample size allowed us to assess the consistency of associations across several studies and to gain sufficient power for conclusive estimation of causal effect. Second, the lactase-persistent variant is a well-established genetic marker for dairy intake, with solid biological basis and, therefore, a valid IV for dairy intake *(10–12, 18)*. The instrument for carrying out this MR study has largely prevented potentially distorting influences. Our findings are of great benefit for future decision-making upon the development of novel behavioral interventions.

Furthermore, our MR results for lipids showed a suggestive causal effect of dairy consumption on improving lipids. This finding was supported by the results of a previous multicenter, randomized double-blind study among hypercholesterolemic patients demonstrating that consumption of dairy product favorably changed the lipid profile by reducing TC and LDL cholesterol *(33)*.

Despite the convincing concept of MR analysis, several limitations have to be considered while interpreting our results. First, the MR study added to established study designs such as RCT without the ability to fully replace them. Second, we could not exclude the possibility of pleiotropic effects of the *LCT* genotype (a gene affects ≥2 apparently unrelated phenotypic traits). However, to our knowledge, no pleiotropic effect has been reported previously. This genetic variant is specific to milk, or at least has a stronger association with milk *(1)*; therefore, the use of total dairy products may largely attenuate our findings. Furthermore, the associations of *LCT* genotype with lactase persistence and milk intake vary across populations. Although the *LCT*-13910 C/T is highly associated with lactase persistence and dairy intake in northern European populations, its association with dairy intake is not universal *(34)*. Other single-nucleotide polymorphisms, including *MCM6* rs3754686 at intron 15, occur more frequently in some global regions *(35)* and, therefore, represent plausible alternatives in diverse cohorts. Hence, bias from population stratification is deemed likely. Finally, differences in definition of total dairy products between studies might lead to the heterogeneity observed in some analyses and dilute the association.

In summary, the present study suggests a causal effect of higher dairy intake on increased lean mass. Our findings also suggest that the observational associations of dairy intake with lipids and glycemic traits could be the result of confounding. Our results emphasize that high intake of dairy may promote the maintenance of lean mass.

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References

1. Hartwig FP, Davey Smith G. Lactase persistence and body mass index: the contribution of Mendelian randomization. Clin Chem 2018;64:4–6.
2. Wang H, Troy LM, Rogers GT, Fox CS, McKeown NM, Meigs JB, et al. Longitudinal association between dairy consumption and changes of body weight and waist circumference: the Framingham Heart Study. Int J Obes (Lond) 2014;38:299–305.
3. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med 2011;364:2392–404.
4. Louie JC, Flood VM, Hector DJ, Rangan AM, Gill TP. Dairy consumption and overweight and obesity: a systematic review of prospective cohort studies. Obes Rev 2011;12:e582–92.
5. Abargouei AS, Janghorbani M, Salehi-Marzijarani M, Esmaillzadeh A. Effect of dairy consumption on weight and body composition in adults: a systematic review and meta-analysis of randomized controlled clinical trials. Int J Obes (Lond) 2012;36:1485–93.
6. Chen M, Pan A, Malik VS, Hu FB. Effects of dairy intake on body weight and fat: a meta-analysis of randomized controlled trials. Am J Clin Nutr 2012;96:735–47.
7. Booth AO, Huggins CE, Wattanapenpaiboon N, Nowson CA. Effect of increasing dietary calcium through supplements and dairy food on body weight and body composition: a meta-analysis of randomised controlled trials. Br J Nutr 2015;114:1013–25.
8. Benatar JR, Sidhu K, Stewart RA. Effects of high and low fat dairy food on cardio-metabolic risk factors: a meta-analysis of randomized studies. PLoS One 2013;8:e76480.
9. Agerholm-Larsen L, Bell ML, Grunwald GK, Astrup A. The effect of a probiotic milk product on plasma cholesterol: a meta-analysis of short-term intervention studies. Eur J Clin Nutr 2000;54:856–60.
10. Ding M, Huang T, Bergholdt HKM, Nordestgaard BG, Ellervik C, Qi L, et al. Dairy consumption, systolic blood pressure, and risk of hypertension: Mendelian randomization study. BMJ 2017;356:j1000.
11. Bergholdt HK, Nordestgaard BG, Ellervik C. Milk intake is not associated with low risk of diabetes or overweight-obesity: a Mendelian randomization study in 97,811 Danish individuals. Am J Clin Nutr 2015;102:487–96.
12. Bergholdt HK, Nordestgaard BG, Varbo A, Ellervik C. Milk intake is not associated with ischaemic heart disease in observational or Mendelian randomization analyses in 98,529 Danish adults. Int J Epidemiol 2015;44:587–603.
13. Smith CE, Coltell O, Sorli JV, Estruch R, Martinez-

Gonzalez MA, Salas-Salvado J, et al. Associations of the MCM6-rs3754686 proxy for milk intake in Mediterranean and American populations with cardiovascular biomarkers, disease and mortality: Mendelian randomization. Sci Rep 2016;6:33188.
14. Lawlor DA, Harbord RM, Sterne JA, Timpson N, Davey Smith G. Mendelian randomization: using genes as instruments for making causal inferences in epidemiology. Stat Med 2008;27:1133–63.
15. Nelson CP, Hamby SE, Saleheen D, Hopewell JC, Zeng L, Assimes TL, et al. Genetically determined height and coronary artery disease. N Engl J Med 2015;372:1608–18.
16. Geng T, Smith CE, Li C, Huang T. Childhood BMI and adult type 2 diabetes, coronary artery diseases, chronic kidney disease, and cardiometabolic traits: a Mendelian randomization analysis. Diabetes Care 2018;41:1089–96.
17. Ding R, Huang T, Han J. Diet/lifestyle and risk of diabetes and glycemic traits: a Mendelian randomization study. Lipids Health Dis 2018;17:18.
18. Huang T, Ding M, Bergholdt HKM, Wang TG, Heianza Y, Sun DJ, et al. Dairy consumption and body mass index among adults: Mendelian randomization analysis of 184802 individuals from 25 studies. Clin Chem 2018; 64:183–91.
19. Wang TG, Huang T, Li YP, Zheng Y, Manson JE, Hu FB, et al. Low birthweight and risk of type 2 diabetes: a Mendelian randomisation study. Diabetologia 2016;59:1920–7.
20. Huang T, Ren JJ, Huang JY, Li D. Association of homocysteine with type 2 diabetes: a meta-analysis implementing Mendelian randomization approach. BMC Genomics 2013;14.
21. Travis RC, Appleby PN, Siddiq A, Allen NE, Kaaks R, Canzian F, et al. Genetic variation in the lactase gene, dairy product intake and risk for prostate cancer in the European prospective investigation into cancer and nutrition. Int J Cancer 2013;132:1901–10.
22. Enattah NS, Sahi T, Savilahti E, Terwilliger JD, Peltonen L, Jarvela I. Identification of a variant associated with adult-type hypolactasia. Nat Genet 2002; 30:233–7.
23. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327: 557–60.
24. Ioannidis JP, Patsopoulos NA, Evangelou E. Uncertainty in heterogeneity estimates in meta-analyses. BMJ 2007;335:914–6.
25. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.
26. Borenstein M, Hedges LV, Higgins JP, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods 2010;1: 97–111.
27. Wald A. The fitting of straight lines if both variables are subject to error. Ann Math Stat 1940;11:284–300.
28. Palmer TM, Sterne JA, Harbord RM, Lawlor DA, Sheehan NA, Meng S, et al. Instrumental variable estimation of causal risk ratios and causal odds ratios in Mendelian randomization analyses. Am J Epidemiol 2011;173: 1392–403.
29. Berkey CS, Rockett HR, Willett WC, Colditz GA. Milk, dairy fat, dietary calcium, and weight gain: a longitudinal study of adolescents. Archiv Pediatr Adolesc Med 2005;159:543–50.
30. Remesar X, Tang V, Ferrer E, Torregrosa C, Virgili J, Masanes RM, et al. Estrone in food: a factor influencing the development of obesity? Eur J Nutr 1999;38:247–53.
31. Ma J, Giovannucci E, Pollak M, Chan JM, Gaziano JM, Willett W, et al. Milk intake, circulating levels of insulin-like growth factor-I, and risk of colorectal cancer in men. J Nat Cancer Inst 2001;93:1330–6.
32. Engel S, Elhauge M, Tholstrup T. Effect of whole milk compared with skimmed milk on fasting blood lipids in healthy adults: a 3-week randomized crossover study. Eur J Clin Nutr 2018;72:249–54.
33. Mannarino E, Pirro M, Cortese C, Lupattelli G, Siepi D, Mezzetti A, et al. Effects of a phytosterol-enriched dairy product on lipids, sterols and 8-isoprostane in hypercholesterolemic patients: a multicenter Italian study. Nutr Metab Cardiovasc Dis 2009;19:84–90.
34. Mulcare CA, Weale ME, Jones AL, Connell B, Zeitlyn D, Tarekegn A, et al. The T allele of a single-nucleotide polymorphism 13.9 kb upstream of the lactase gene (LCT) (C-13.9kbT) does not predict or cause the lactase-persistence phenotype in Africans. Am J Human Genet 2004;74:1102–10.
35. Enattah NS, Trudeau A, Pimenoff V, Maiuri L, Auricchio S, Greco L, et al. Evidence of still-ongoing convergence evolution of the lactase persistence T-13910 alleles in humans. Am J Human Genet 2007;81:615–25.