Dairy Consumption and Body Mass Index Among Adults: Mendelian Randomization Analysis of 184,802 Individuals from 25 Studies

Mendelian Randomization of Dairy Consumption Working Group

BACKGROUND: Associations between dairy intake and body mass index (BMI) have been inconsistently observed in epidemiological studies, and the causal relationship remains ill defined.

METHODS: We performed Mendelian randomization (MR) analysis using an established dairy intake-associated genetic polymorphism located upstream of the lactase gene \( LCT \) (rs4988235) as an instrumental variable (IV). Linear regression models were fitted to analyze associations between (a) dairy intake and BMI, (b) rs4988235 and dairy intake, and (c) rs4988235 and BMI in each study. The causal effect of dairy intake on BMI was quantified by IV estimators among 184,802 participants from 25 studies.

RESULTS: Higher dairy intake was associated with higher BMI \((\beta = 0.03 \text{ kg/m}^2\text{ per serving/day}; 95\% \text{ CI}, 0.00–0.06; P = 0.04)\), whereas the \( LCT \) genotype with 1 or 2 T allele was significantly associated with 0.20 (95% CI, 0.14–0.25) serving/day higher dairy intake \((P = 3.15 \times 10^{-8})\) and 0.12 (95% CI, 0.06–0.17) kg/m\(^2\) higher BMI \((P = 2.11 \times 10^{-8})\). MR analysis showed that the genetically determined higher dairy intake was significantly associated with higher BMI \((\beta = 0.60 \text{ kg/m}^2\text{ per serving/day}; 95\% \text{ CI}, 0.27–0.92; P = 3.0 \times 10^{-9})\).

CONCLUSIONS: The present study provides strong evidence to support a causal effect of higher dairy intake on increased BMI among adults.

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Methods

STUDY DESIGN
The study design consisted of 2 steps. First, using cross-sectional and prospective cohort studies, we tested the

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dairy intake-associated \textit{LCT-13910 C/T}, rs4988235 for association with dairy intake and body mass index (BMI). Second, the causal effect of dairy intake on BMI was quantified with instrumental variable (IV) estimators among 184,802 participants from 25 studies.

\textbf{STUDY PARTICIPANTS}

The study was conducted within the Mendelian Randomization of Dietary Consumption Working Group, represented here by 25 cohort studies and up to 184,802 participants (see Table 1 in the Data Supplement that accompanies the online version of this article at http://www.clinchem.org/content/vol64/issue1). Descriptions of each participating study are shown in Table 2 of the online Data Supplement. Participants from all participating studies provided written informed consent, and ethical approval was granted by local institutional review boards (see Table 3 in the online Data Supplement). Intake of dairy products was collected by self-reported questionnaires in each study; detailed information on cohort-specific data collection methods is provided in Table 4 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 outcome is follow-up BMI or baseline BMI, calculated as weight in kilograms divided by the square of height in meters. Height and body weight were directly measured in some studies and self-reported in others. Detailed information on the outcome measure for each study is reported in Table 5 of the online Data Supplement.

\textbf{SINGLE-NUCLEOTIDE POLYMORPHISM SELECTION AND GENOTYPE PROPERTIES}

The \textit{LCT-13910 C/T} polymorphism (rs4988235), located upstream from the \textit{LCT} gene, affects the transcription of the lactase enzyme and is associated with lactase persistence and thereby with the ability to digest lactose, the primary source of carbohydrates in milk (11). Lactase persistence is a dominantly inherited genetic trait. The TT and TC genotypes are associated with lactase persistence, and the CC genotype is associated with nonpersistence. In the present study, we chose the widely confirmed and extensively studied variant rs4988235 as the IV for dairy intake (12–14). Twenty 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 CEU (European) reference panel-imputed genetic information from genome-wide association studies (http://hapmap.ncbi.nlm.nih.gov/downloads/genotypes/2008-10_phaseII/) for rs4988235 or \((b)\) genotype information from a predefined list of proxies 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 \textit{LCT-13910 C/T} are listed in Tables 1 and 6 of the online Data Supplement.

\textbf{STATISTICAL ANALYSIS}

A standard analysis protocol was applied to each individual study to produce comparable results. As lactase persistence is a dominantly inherited genetic trait, we examined the genetic association primarily under a dominant model (CC vs CT + TT). We also applied an additive and recessive model (CC + CT vs TT) to examine the genetic association of \textit{LCT-13910 C/T} with dairy intake and BMI. Linear regression was used to test the association of dairy intake with BMI 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 association of \textit{LCT-13910 C/T} with dairy intake or BMI after adjustment for age, sex, ethnicity, region, and total energy. Table 5 in the online Data Supplement shows the BMI outcome information.

\textbf{METAANALYSIS AND BETWEEN-STUDY HETEROGENEITY}

Metaanalyses were conducted using individual participant data in each study and then pooled \(\beta\) coefficients across studies using random-effects or fixed-effects metaanalysis. Metaanalyses were conducted in Stata version 13.0 (StataCorp, www.stata.com). All \(P\) values reported were 2-sided. We assessed between-study heterogeneity via Cochrane’s \(Q\) and \(I^2\) statistics (15–17). For the proposed cutoff of \(I^2 > 0.25\), we found nonnegligible heterogeneity between studies, in particular among the dairy–BMI associations, but also for the association between \textit{LCT-13910 C/T} and dairy intake (\(I^2 = 0.55\). As a consequence, we used random-effects metaanalysis throughout. Furthermore, metaregression was used to investigate the extent to which statistical heterogeneity between results of studies could be related to 1 or more characteristics of the studies.

\textbf{SE AND INFERENCE FOR THE IV ESTIMATOR}

After metaanalysis, we used the IV estimator to quantify the strength of the causal association of dairy intake and BMI (18). The IV estimator was calculated as the \(\beta\) of the regression coefficients for \textit{LCT-13910 C/T} and dairy intake (\(I^2 = 0.55\)). As a consequence, we used random-effects metaanalysis throughout. Furthermore, metaregression was used to investigate the extent to which statistical heterogeneity between results of studies could be related to 1 or more characteristics of the studies.

\textbf{BASELINE CHARACTERISTICS OF PARTICIPATING STUDIES}

Baseline characteristics of the 184,802 participants from 25 studies are shown in Table 1 here and in Table 1 of the
DAIRY INTAKE AND BMI

Random-effects metaanalysis was used to pool the association between dairy intake and BMI in the 176100 participants from 24 studies. We observed that high dairy intake was significantly associated with higher BMI ($\beta = 0.03$ kg/m$^2$ per serving/day; 95% CI, 0.00–0.06; $P = 0.04$). The $\beta$ coefficient estimates of effect sizes for the association between dairy intake and BMI ranged from $-0.18$ to $0.20$ kg/m$^2$ per serving/day of dairy intake, yielding an $I^2$ for heterogeneity between studies of 79.7% (Fig. 1). Metaregression analysis showed that age significantly influenced the association of dairy consumption with BMI ($P = 0.02$). Stratified analysis by age showed that dairy consumption was significantly associated with higher BMI among participants $\geq 50$ years ($\beta = 0.05$ kg/m$^2$ per serving/day; 95% CI, 0.02–0.07) but tended to be associated with lower BMI among participants $<50$ years ($\beta = -0.04$ kg/m$^2$ per serving/day; 95% CI, $-0.11$ to $-0.03$).

GENETIC ASSOCIATION OF LCT-13910 C/T WITH DAIRY INTAKE AND BMI

Random-effects metaanalysis, with a dominant model, was used to pool the genetic association of the LCT-
13910 C/T with dairy intake in the 176100 participants from 24 studies ($I^2 = 83.0\%$). We found that the LCT-13910 C/T CT genotype was significantly associated with 0.20 more dairy servings per day ($0.20$ serving/day; 95% CI, 0.14–0.25; $P = 3.15 \times 10^{-12}$).

We also pooled the genetic association with BMI in the 184802 participants from 25 studies using fixed-effects metaanalysis ($I^2 = 14.4\%; P = 0.258$) and found that the LCT-13910 C/T CT genotype was significantly associated with 0.12 higher BMI unit ($kg/m^2$) ($0.12$; 95% CI, 0.06–0.17; $P = 2.11 \times 10^{-5}$) (Fig. 2).

In sensitivity analyses, we found similarly significant genetic associations of LCT-13910 C/T with dairy intake ($0.09$ serving/day; 95% CI, 0.06–0.12; $P = 4.24 \times 10^{-9}$), and genetic association with BMI ($0.09$ serving/day; 95% CI, 0.04–0.14; $P = 0.0003$) under the additive model (see Fig. 1 in the online Data Supplement). Significant genetic associations were also observed under the recessive model (see Table 7 in the online Data Supplement).

IV ESTIMATED CAUSALITY BETWEEN DAIRY INTAKE AND BMI
After we pooled estimated effect sizes from each study using metaanalysis, we used the IV estimators to quantify the strength of the causal association of dairy intake and BMI, with the LCT-13910 C/T used as an IV. The MR estimate was computed from the ratio of the coefficient of the association between the LCT-13910 C/T and BMI 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. Fig. 3 presents the observational association of dairy intake with BMI, as well as the IV estimated causal effect of dairy intake on BMI. The pooled results show that genetically higher dairy intake was significantly associated with higher BMI ($0.60$ kg/m$^2$ per 1 serving/day; 95% CI, 0.27–0.92; $P = 3.0 \times 10^{-4}$) under the dominant model. We also found evidence of significant causal association between dairy intake and BMI under the additive model ($1.00$ kg/m$^2$; 95% CI, 0.30–1.69; $P = 4.0 \times 10^{-3}$) and the recessive model ($1.59$ kg/m$^2$; 95% CI, 0.28–2.91; $P = 0.009$) (see Fig. 1 and Table 7 in the online Data Supple-
Dairy Intake and BMI

We did not observe significant differences in observational results or IV estimated results ($P = 0.63$).

We further conducted stratified analyses of genetic association with dairy intake and BMI and estimated causality by age, BMI, follow-up years, sample size, study design, and ethnic group. Table 2 presents the genetic associations and the IV estimate for the association of dairy intake with BMI from overall and subgroup analyses. Genetic associations of the LCT-13910 C/T with BMI and a causal effect of dairy intake on BMI were observed only among those of European ancestry and in studies with mean age $\geq 50$ years, BMI $\geq 25$ kg/m$^2$, follow-up time $\geq 5$ years, and sample size $\geq 1000$.

Discussion

In thus far the largest MR analysis study, including 184802 adults from 25 cohorts, our results support a
causal relation between higher dairy intake and increased BMI in the absence of caloric restriction.

A number of recent prospective cohort studies exploring the association between intake of dairy foods and weight status have generated inconsistent results (12, 20 – 22). Evidence from a systematic review showed that much confusion remains about this relationship (2). Possible reasons for such apparent inconsistencies in findings include varying sample sizes, residual and unmeasured confounding, and reverse causality because of changes in outcome and factors over time. In addition, a metaanalysis of RCTs showed that ad libitum dairy interventions in long-term trials might increase body weight (5). However, several RCTs with energy restriction reported opposing effects (5). Differences in dose of dairy, foods included as diary, mode of administration, duration of intervention, energy restriction, or baseline differences in dairy intake or body weight between the trials may be prone to bias, undermining their validity. Furthermore, the types of dairy products may also partly account for this apparent discrepancy. A limited number of studies have examined the impact of type of dairy product on body composition. In one metaanalysis study, both whole fat and low fat dairy food intervention significantly increased body weight (4). In addition, fermented milk products such as yogurt have shown beneficial effects in the control of body weight (23), whereas cheese intake has exhibited a positive association with obesity (24). Taken together, previous evidence makes definitive conclusions on the relation between dairy consumption and adiposity difficult.

Recently, genetic analysis has become widely used to infer causality of environmental factors on human disease (7). The MR analysis is a method that uses genetic variants that are robustly associated with such modifiable factors to generate more reliable evidence regarding which interventions should produce health benefits (25). The MR analysis is not prone to confounding or reverse

### Table 2. Stratified analyses of estimated causality between dairy intake and BMI in dominant model.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Dairy (outcome), serving/day</th>
<th>Studies SNP (IV)</th>
<th>BMI (outcome), kg/m²</th>
<th>Studies SNP (IV)</th>
<th>Estimated causality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>β (95% CI)</td>
<td>P value</td>
<td>No.</td>
<td>β (95% CI)</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50</td>
<td>19</td>
<td>0.19 (0.12–0.26)</td>
<td>&lt;0.001</td>
<td>19</td>
<td>0.12 (0.05–0.19)</td>
</tr>
<tr>
<td>&lt;50</td>
<td>5</td>
<td>0.35 (0.17–0.53)</td>
<td>&lt;0.001</td>
<td>6</td>
<td>0.06 (–0.13 to 0.24)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥25</td>
<td>19</td>
<td>0.20 (0.14–0.27)</td>
<td>&lt;0.001</td>
<td>19</td>
<td>0.11 (0.06–0.17)</td>
</tr>
<tr>
<td>&lt;25</td>
<td>5</td>
<td>0.21 (0.15–0.27)</td>
<td>&lt;0.001</td>
<td>6</td>
<td>0.15 (–0.17 to 0.47)</td>
</tr>
<tr>
<td>Follow-up, years</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≥5</td>
<td>13</td>
<td>0.20 (0.13–0.27)</td>
<td>&lt;0.001</td>
<td>14</td>
<td>0.11 (0.03–0.19)</td>
</tr>
<tr>
<td>&lt;5</td>
<td>11</td>
<td>0.24 (0.13–0.36)</td>
<td>&lt;0.001</td>
<td>11</td>
<td>0.13 (–0.01 to 0.26)</td>
</tr>
<tr>
<td>Sample size</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>≥1000</td>
<td>20</td>
<td>0.23 (0.17–0.29)</td>
<td>&lt;0.001</td>
<td>21</td>
<td>0.12 (0.05–0.18)</td>
</tr>
<tr>
<td>&lt;1000</td>
<td>4</td>
<td>0.21 (0.15–0.27)</td>
<td>&lt;0.001</td>
<td>4</td>
<td>0.04 (–0.35 to 0.43)</td>
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<tr>
<td>Ethnic group</td>
<td></td>
<td></td>
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<tr>
<td>European</td>
<td>19</td>
<td>0.21 (0.15–0.28)</td>
<td>&lt;0.001</td>
<td>20</td>
<td>0.13 (0.08–0.18)</td>
</tr>
<tr>
<td>Non-European</td>
<td>5</td>
<td>0.22 (0.04–0.41)</td>
<td>&lt;0.001</td>
<td>5</td>
<td>–0.18 (–0.42 to 0.07)</td>
</tr>
<tr>
<td>Study design</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cohort</td>
<td>19</td>
<td>0.20 (0.17–0.22)</td>
<td>&lt;0.001</td>
<td>20</td>
<td>0.12 (0.06–0.17)</td>
</tr>
<tr>
<td>Cross-sectional</td>
<td>5</td>
<td>0.1 (0.13–0.19)</td>
<td>&lt;0.001</td>
<td>5</td>
<td>0.11 (–0.01 to 0.22)</td>
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<tr>
<td>HWE</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤0.05</td>
<td>20</td>
<td>0.23 (0.16–0.28)</td>
<td>&lt;0.001</td>
<td>21</td>
<td>0.12 (0.07–0.19)</td>
</tr>
<tr>
<td>&gt;0.05</td>
<td>4</td>
<td>0.21 (0.16–0.28)</td>
<td>&lt;0.001</td>
<td>4</td>
<td>0.05 (–0.34 to 0.45)</td>
</tr>
</tbody>
</table>

SNP, single-nucleotide polymorphism; HWE, Hardy-Weinberg equilibrium. Linear regression was used to test the association of MCM6 variant rs4988235 with dairy intake or BMI 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 metaanalysis because of the heterogeneity between studies (I² > 50%; P < 0.001).

We used the IV estimators to quantify the strength of the causal association of dairy intake and BMI in each study. The IV estimator that is identical to that derived by the widely used 2-stage least-squares method will be calculated as the β of the regression coefficients MCM6 rs4988235-BMI and MCM6 rs4988235-dairy.
causation. It is well known that alleles that are randomly assigned at meiosis are independent of nongenetic confounding and are unmodified by health conditions. Therefore, MR is analogous to an RCT and can be used to support the hypothesis that the association of dairy intake with BMI is causal. Recently, a genetic analysis from the 1982 Pelotas (Brazil) Birth Cohort (26) did not support a causal relationship between high dairy intake and increased BMI. However, this study was limited by small sample size (n = 2808) and low power to derive valid conclusions. In our well-powered study, we individually analyzed 184,802 individuals from 25 cohorts and provide strong evidence that high dairy intake was causally associated with higher BMI. Results from our MR and multivariable analyses were highly consistent, both confirming higher BMI in those eating more dairy products.

The potential mechanisms underlying the impact of dairy intake on the regulation of body weight have not been clearly elucidated. The most postulated mechanism is that the hormone estrone found in dairy products may promote increases in body weight (20, 27). In addition, intake of dairy foods is associated with higher plasma insulin-like growth factor I, which may contribute to weight gain (28). Furthermore, previous studies suggested that extra dairy intake in ad libitum dietary interventions may lead to increased energy intake, which may result in weight gain, offsetting the otherwise potential protective effect of the dairy intervention (5). In contrast, in most energy-restricted trials, energy intakes were better controlled. Thus, the potential benefits of dairy on body weight could be interpreted as the effect of the substitution of dairy products for certain other foods (5). Therefore, total energy intake needs to be considered when assessing the role of dairy intake in weight control (3–6). In addition, metaanalysis of RCT’s showed that dairy consumption increased lean (muscle) mass and decreased body fat (3). Increased protein intake from dairy products may promote maintenance of lean mass (6). Thus, in the present study, it is possible that the higher BMI related to high dairy intake could be mainly because of increased lean muscle mass. Future research is needed to further illustrate potential mechanisms of dairy products on body weight and composition in the context of energy restriction.

Our study has several strengths. First, to the best of our knowledge, this is thus far the largest MR analysis on the causality of high dairy intake on BMI. The large sample size allowed us to assess the consistency of associations across multiple studies and to gain sufficient power for conclusive estimation of causal effect. Second, the MR design used in our genetic analyses should have largely prevented potentially distorting influences. Third, the lactose-tolerance variant is a well-established genetic marker for dairy intake, with solid biological basis and, therefore, a valid IV for dairy intake (10, 13). Lastly, most of the studies included were homogeneous, and we performed analysis individually in each study. Therefore, the effect of population stratification on the instrumental results should be minimal.

Potential limitations with the MR approach include the possibility of pleiotropy and population stratification. Pleiotropy refers to a situation in which a gene affects ≥2 apparently unrelated phenotypic traits; we could not exclude the possibility of pleiotropic effects of the *LCT* genotype. However, to our knowledge, no pleiotropic effect has been reported. Furthermore, the associations of rs4988235 with lactase persistence and milk intake vary across populations. We adjusted for only geographical region and ethnicity in the statistical models. Hence, bias from population stratification is deemed likely (29). Finally, although many important covariates were adjusted in our models, some residual and unmeasured confounding might remain.

**Conclusions**

In summary, the present study suggests a causal effect of higher dairy intake on increased BMI; our results also emphasize that total energy intake needs to be considered when assessing the role of dairy intake in weight control.

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