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Milk intake is not associated with low risk of diabetes or overweight-obesity: a Mendelian randomization study in 97,811 Danish individuals[1–3]

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ABSTRACT

Background: High dairy/milk intake has been associated with a low risk of type 2 diabetes observationally, but whether this represents a causal association is unknown.

Objective: We tested the hypothesis that high milk intake is associated with a low risk of type 2 diabetes and of overweight-obesity, observationally and genetically.

Design: In 97,811 individuals from the Danish general population, we examined the risk of incident type 2 diabetes and of overweight-obesity by milk intake observationally and by *LCT-13910 C/T* genotype [polymorphism (rs4988235) upstream from the lactase (*LCT*) gene], where *TT* and *TC* genotypes are associated with lactase persistence and *CC* with nonpersistence.

Results: Observationally for any compared with no milk intake, the HR for type 2 diabetes was 1.10 (95% CI: 0.98, 1.24; $P = 0.11$), whereas the OR for overweight-obesity was 1.06 (1.02, 1.09; $P = 0.002$). Median milk intake was 5 glasses/wk (IQR: 0–10) for lactase *TT/TC* persistence and 3 (0–7) for *CC* nonpersistence. Genetically for lactase *TT/TC* persistence compared with *CC* nonpersistence, the OR was 0.96 (0.86, 1.08; $P = 0.50$) for type 2 diabetes and 1.06 (1.00, 1.12; $P = 0.04$) for overweight-obesity. In a stratified analysis for type 2 diabetes, corresponding values in those with and without milk intake were 0.88 (0.76, 1.03; $P = 0.11$) and 1.35 (1.07, 1.70; $P = 0.01$) (P-interaction: 0.002), whereas no gene-milk interaction on overweight-obesity was found. For a 1-glass/wk higher milk intake, the genetic risk ratio for type 2 diabetes was 0.99 (0.93, 1.06), and the corresponding observational risk was 1.01 (1.00, 1.01). For overweight-obesity, the corresponding values were 1.01 (1.00, 1.02) genetically and 1.00 (1.00, 1.01) observationally.

Conclusions: High milk intake is not associated with a low risk of type 2 diabetes or overweight-obesity, observationally or genetically via lactase persistence. The higher risk of type 2 diabetes in lactase-persistent individuals without milk intake likely is explained by collider stratification bias. *Am J Clin Nutr* doi: 10.3945/ajcn.114.105049.

Keywords: diabetes, lactase persistence, Mendelian randomization, milk, overweight, body mass index

INTRODUCTION

High dairy/milk intake has been associated with a low risk of diabetes in meta-analyses of observational studies (1–6), but it is unclear whether this association is causal. Because no adequately powered long-term, large-scale, randomized trial has addressed this question, an alternative approach is to use the Mendelian randomization design to indirectly infer causality.

The *LCT-13910 C/T* polymorphism, located upstream from the lactase (LCT) gene, (rs4988235) affects the transcription of the lactase enzyme and is associated with lactase persistence and thereby with the ability to digest milk (7). In lactase-nonpersistent individuals (<10% of Danes), milk intake may cause symptoms of lactose intolerance, and milk intake may therefore be reduced or even avoided. Individuals with the genotype *TT/TC* are genetically lactase persistent throughout their adult lives and can digest and tolerate more milk than can participants with the lactase-nonpersistent genotype *CC*. The Mendelian randomization

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[3] Supplemental Methods, Supplemental Tables 1–10, and Supplemental Figures 1 and 2 are available from the "Supplemental data" link in the online posting of the article and from the same link in the online table of contents at http://ajcn.nutrition.org.

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design enables us to use this genetic variant as a proxy for the long-term differences in milk intake, thereby largely avoiding confounding and reverse causation (8).

We tested the hypothesis that high milk intake is associated with a low risk of type 2 diabetes and of overweight-obesity, observationally and genetically, via lactase persistence. For this purpose we included 97,811 white individuals of Danish descent from 3 studies of the general population. First, we analyzed the observational association between milk intake and risk of type 2 diabetes and of overweight-obesity. Second, we confirmed the association between the *LCT-13910 C/T* genotype and milk intake. Third, we investigated the association between the *LCT-13910 C/T* genotype and risk of type 2 diabetes and of overweight-obesity. Finally, we compared the genetic risk ratios obtained by instrumental variable analysis with observational HRs for a 1-glass/wk higher milk intake on risk of type 2 diabetes and of overweight-obesity.

Denmark is well suited for this study because the production of milk and other dairy products is high, and these food items often are included in the Danish diet. In addition, we have a long tradition for diagnosis and treatment of people with diabetes.

METHODS

The studies were approved by institutional review boards and by Danish ethical committees. Written informed consent was obtained from all participants, and the investigation conforms with the principles of the Declaration of Helsinki.

Study populations

We included white individuals aged 20–100 y and of Danish descent who participated in 1 of 3 studies of the Danish general population: the Copenhagen City Heart Study (9) 1991–1994 examination (CCHS[10]; n = 8,731), the Copenhagen General Population Study (9, 10) (CGPS; n = 74,247), and the Danish General Suburban Population Study (11) (GESUS; n = 14,833). A person of Danish descent was defined as an individual with Danish citizenship who was born in Denmark and whose parents likewise both were Danish citizens born in Denmark. Potential overlap between study participants from CCHS, CGPS and GESUS was estimated to be ~0.1% based on data from Statistics Denmark (see **Supplemental Methods**).

Intake of milk and other dairy products

Information on milk and dairy product intake was self-reported in questionnaires from the CGPS and GESUS but was unfortunately not available in the CCHS. Milk was reported in glasses per week for whole milk (3.5% fat), semi-skim milk (0.5–1.5% fat), and skim milk (0.1–0.3% fat). Information on cheese consumption (no/yes) was available from both the CGPS and GESUS, whereas consumption of any fermented milk products (such as yogurt) in measures of 0.5 L/wk was available from GESUS only. Milk intake in the CGPS was divided into approximate quintiles: quintile 1 (0 glasses of milk/wk), quintile 2 (1–3 glasses/wk), quintile 3 (4–7 glasses/wk), quintile 4 (8–10 glasses/wk), and quintile 5 (≥11 glasses/wk). We also constructed variables comparing any milk and types of milk [high-fat (0.5–3.5%) and fat-free (0.1–0.3%)] with no milk intake.

Other covariates

Physical activity at work was categorized as mainly sitting, sitting/standing/walking, walking and some lifting, heavy bodywork, and not part of the workforce. Physical activity in leisure time was categorized as mainly passive, light activity 2–4 h/wk, light/moderate activity >4 h/wk, and very active >4 h/wk. Information on self-reported alcohol intake was categorized as ≤7, 8–14, and >14 drinks/wk for women and ≤14, 15–21, and >21 drinks/wk for men; 1 drink is equivalent to ~12 g alcohol. Self-reported smoking status was categorized as never-smokers, previous smokers, and current smokers. Information on education, i.e., level of education obtained since the individual finished the mandatory 7–9 y of lower and middle school education, was categorized as none (including students), practical, short (<3 y), middle (3–4 y), or long (≥5 y). Self-reported family history of diabetes (no/yes/unknown) included information on diabetes in parents and/or siblings (information on siblings not available in GESUS). Fruit intake, vegetable intake, and fish intake were categorized as no intake, ≤4 times/wk, 5–7 times/wk, or >7 times/wk; intake of fast food was categorized as no intake, once per week, or twice or more per week; and intake of soda drinks was categorized as no intake, <7 bottles/wk, or ≥7 bottles/wk (1 bottle = 0.5 L). Use of lipid-lowering therapy (no/yes) was self-reported. Hypertension (no/yes), available from the national Danish Patient Registry, was combined with self-reported use of blood pressure–lowering medication. BMI was calculated as measured weight (kg) divided by measured height (m) squared and categorized as <18.5, 18.5–24.9, 25–29.9, and ≥30. Nonfasting total cholesterol, HDL cholesterol, triglycerides, and blood glucose (all in mmol/L) were measured by using standard hospital assays. LDL cholesterol was calculated by using the Friedewald equation for participants with triglycerides ≤4.0 mmol/L but was measured directly for all other participants. Systolic and diastolic blood pressures (mm Hg) were measured.

Diabetes and overweight-obesity

Information on diabetes and diabetes-related deaths was from the national Danish Patient Registry (International Classification of Diseases code 8: 249–250; International Classification of Diseases code 10: E10, E11, E13, and E14) and the national Danish Causes of Death Registry. Registry information was combined with self-reported information on diabetes, use of insulin, use of other diabetes medication, and measured nonfasting glucose >11 mmol/L indicating diabetes. We focused on type 2 diabetes because the onset of type 1 diabetes usually occurs before downregulation of the lactase enzyme. Overweight-obesity was defined as BMI (in kg/m^2) ≥25.

Genotyping

In the CGPS and CCHS, genotyping for the *LCT-13910 C/T* (rs4988235) polymorphism (7) was performed by using the TaqMan assay (call rates 99.9% after reruns) (Applied Biosystems; details available from authors). In GESUS, genotyping was performed by using KASPar allelic discrimination (LGC Genomics; call rate of 99.3%) (Supplemental Methods). The

[10] Abbreviations used: CCHS, the Copenhagen City Heart Study; CGPS, the Copenhagen General Population Study; GESUS, Danish General Suburban Population Study.

LCT-13910 C/T genotype was categorized as *CC*, *TC*, and *TT* (codominant model) or as *CC* and *TC+TT* (dominant model), because both individuals with *TC* and *TT* are lactase persistent. Genotypes were in Hardy-Weinberg equilibrium in GESUS, but not in the CGPS and CCHS (**Supplemental Table 1**).

Statistical analyses

Statistical analyses were performed by using STATA 12 (StataCorp.). Using the *impute* command (single conditional mean imputation), missing information on the following covariates from the CGPS, CCHS, and GESUS combined ($n = 97{,}811$) were imputed based on sex, age, and population to obtain a balanced data set: physical activity in leisure time (1.2%), smoking status (0.3%), education (0.6%), height (0.1%), BMI (0.2%), total cholesterol (0.06%), LDL cholesterol (0.9%), HDL cholesterol (0.07%), triglycerides (0.09%), systolic blood pressure (0.05%), and diastolic blood pressure (0.05%).

Pearson's chi-square test was used for categorical variables, and the Mann-Whitney *U* or Kruskal-Wallis test was used for continuous variables when population characteristics were examined by genotype (to confirm the independence of the genetic variant), milk intake, and disease status. Bonferroni correction was used to account for multiple comparisons.

First, an observational analysis of milk intake and risk of incident type 2 diabetes was performed by Cox regression, with age as the underlying time scale (referred to as age-adjusted), using a sex- and age-adjusted model and a multivariable-adjusted model including sex, age, physical activity in leisure time and at work, smoking, alcohol intake, education, family history of diabetes, fruit intake, vegetable intake, fish intake, intake of fast food, and intake of soda drinks (model A). These covariates were chosen because they may each be associated with milk intake and/or diabetes. A model including lipid-lowering therapy, hypertension, and BMI was also constructed (model B); however, these variables might be on the pathway from milk intake to diabetes. We tested for interactions using the likelihood-ratio test, and Schoenfeld residuals were used to test proportional hazards assumption. Because overweight-obesity is associated with the development of type 2 diabetes, we examined the association of milk intake with overweight-obesity using logistic regression (cross-sectional data) with adjustment for sex, age, and the covariates in model A.

Second, we compared differences in milk intake according to the *LCT-13910 C/T* genotypes in the CGPS and GESUS (*TT* or *TC* vs. *CC*, and *TT/TC* vs. *CC*). To compare our results with those from other European populations, we searched PubMed for European studies reporting the frequency of the *LCT-13910 C/T* variant and milk intake: ([milk (MeSH terms) OR milk OR dairy OR yogurt OR ice cream OR cheese] AND [lactase OR LCT-13910 OR rs4988235]) AND ["Europe" (MeSH) OR Europe OR European] OR ([milk (MeSH terms) OR milk OR dairy] AND [*LCT-13910* OR rs4988235]). Information on mean milk intake (g/d) and genotype frequency was collected. Studies reporting milk in other units (dL or glasses/wk) were recalculated to g/d, assuming that 1 glass of milk contains 2.5 dL and that 1 dL weighs 100 g.

Third, we investigated the association between the genetic variant and risk of type 2 diabetes and overweight-obesity using unadjusted logistic regression analysis in 97,811 participants from the CCHS, CGPS, and GESUS combined. Analyses were also performed with adjustment for sex, age, height, and population. Data from genome-wide association studies were not available to adjust for potential population admixture using principal component data, so we used height adjustment instead. The gene-environment interaction between the *LCT-13910* and milk intake was investigated for both type 2 diabetes and overweight-obesity, and results stratified by milk intake (no/yes) were presented for interactions with $P < 0.05$. Because collider stratification bias could be introduced when the gene-diabetes analysis was stratified by milk intake, it was partly investigated by stratifying the association between the *LCT-13910* and population characteristics by milk intake (no/yes).

Finally, we performed an instrumental variable analysis using the multiplicative generalized methods of moments estimator in participants from the CGPS and GESUS combined to obtain risk estimates of genetically higher milk intake on risk of type 2 diabetes and overweight-obesity. *F* statistics and R^2 values were obtained by ordinary least-squares regression analysis. *F* statistics indicate the strength of the genotype as an instrument for milk intake, where $F > 10$ implies sufficient statistical strength (8). R^2 indicates the variation in milk intake explained by the genotype. Sensitivity analyses in the 2 separate populations were performed as were analyses using 2 additional types of instrumental variables: the extreme genotype score (12) and 2-stage least squares with logistic regression analysis as second stage (13). The extreme genotype score was obtained by dividing the β value (from a logistic-regression analysis of genotype on diabetes/overweight-obesity adjusted for sex and age) with the mean difference in milk intake between genotypes *TT/TC* and *CC* and subsequent exponentiation of this value to obtain the genetic ORs and 95% CIs were obtained by using the Fiellers method (14). Genetic estimates were compared with observational HRs obtained from Cox regression (for diabetes) and ORs from logistic regression (for overweight-obesity) by using multivariable-adjusted model A with milk intake on a continuous scale (glasses/wk).

We performed power calculations using PASS12 (NCSS Software) (Supplemental Methods) (15). With the assumption of 2-sided $P = 0.05$ (α), we had 80% power to detect an OR ≤ 0.84 and ≥ 1.18 for type 2 diabetes when comparing genotype *TT/TC* with *CC* (**Supplemental Figure 1**). Likewise, we had 80% power to detect an HR ≤ 0.84 and ≥ 1.18 for type 2 diabetes when comparing any milk intake with no milk intake (**Supplemental Figure 2**).

RESULTS

We found a difference of 1 cm in height between *TT/TC* and *CC* (**Table 1**) and a minor influence on HDL-cholesterol concentrations, which could be a potential mediator. No other population characteristics were associated with the genotype overall (Table 1); however, several characteristics were distributed differently by genotype in those with and without milk intake, e.g., sex and intake of fruit and vegetables (**Supplemental Tables 2** and **3**), likely explained by collider stratification bias. In contrast with genotype, milk intake and diabetes were associated with all potential confounders (**Supplemental Tables 4** and **5**) (*P* values for genotype, milk intake, and diabetes are compared in Table 1).

TABLE 1
Population characteristics by *LCT-13910 C/T* genetic variant in 97,811 participants from the Copenhagen General Population Study, the Copenhagen City Heart Study, and the Danish General Suburban Population Study combined[1]

	Genotype[2]						*P* value[3]		
	CC		*TC*		*TT*				
Characteristics	*n*	Value	*n*	Value	*n*	Value	Genotype	Milk intake[4]	Diabetes[5]
All, %	5790	5.9	34,984	35.8	57,037	58.3			
Sex, %									
Women	3217	55.6	19,375	55.4	31,385	55.0	0.48	4×10^{-95}	
Men	2573	44.4	15,609	44.6	25,652	45.0			6×10^{-6}
Age, y	5790	57 (47–66)[6]	34,984	57 (47–67)	57,037	57 (47–67)	0.63	1×10^{-300}	1×10^{-300}
Physical activity at work, %									
Mainly sitting	1559	26.9	9249	26.4	15,330	26.9	0.47	2×10^{-140}	
Sitting/standing/walking	1545	26.7	9186	26.3	14,862	26.1			2 × 10–7
Walking, some lifting	937	16.2	5814	16.6	9,334	16.4			3×10^{-3}
Heavy bodywork	188	3.3	1056	3.0	1836	3.2			2×10^{-5}
Not in workforce	1561	27.0	9679	27.7	15,675	27.5			1×10^{-176}
Physical activity in leisure time, %									
Mainly passive	388	6.7	2373	6.8	4070	7.1	0.08	2×10^{-51}	
Light activity, 2–4 h/wk	2707	46.8	16,026	45.8	26,179	45.9			2×10^{-34}
Light/moderate activity, >4 h/wk	2393	41.3	14,537	41.6	23,625	41.4			2×10^{-104}
Very active, >4 h/wk	302	5.2	2048	5.9	3163	5.6			5×10^{-47}
Alcohol intake (standard drinks),[7] %									
Women ≤7, men ≤14	3705	64.0	22,244	63.6	36,099	63.3	0.38	2×10^{-177}	
Women 8–14, men 15–21	1162	20.1	7046	20.1	11,417	20.0			8×10^{-20}
Women >14, men >21	923	15.9	5694	16.3	9521	16.7			4×10^{-1}
Smoking, %									
Never smoker	2273	39.3	13,722	39.2	22,303	39.1	0.58	4×10^{-64}	
Former smoker	2287	39.5	13,544	38.7	22,103	38.8			2×10^{-40}
Current smoker	1230	21.2	7718	22.1	12,631	22.2			3×10^{-31}
Education,[8] %									
None/student	749	12.9	4,338	12.4	7177	12.6	0.25	3×10^{-57}	
Practical	2055	35.5	12,848	36.7	21,081	37.0			8×10^{-23}
Short, <3 y	711	12.3	4215	12.1	6858	12.0			1×10^{-27}
Middle, 3–4 y	1377	23.8	8330	23.8	13,619	23.9			5×10^{-94}
Long, ≥5 y	898	15.5	5253	15.0	8302	14.6			3×10^{-89}
Family history of diabetes, %									
No	3955	75.5	24,153	75.6	39,440	76.0	0.41	2×10^{-13}	
Yes	976	18.6	6049	18.9	9646	18.6			3×10^{-261}
Unknown	310	5.9	1736	5.4	2815	5.4			1×10^{-125}
Fruit,[9] %									
No intake	202	3.9	1276	4.0	2178	4.2	0.08	5×10^{-77}	
≤4 times/wk	1171	22.3	7437	23.3	12,144	23.4			0.02
5–7 times/wk	1702	32.5	10,465	32.8	17,153	33.1			0.03
>7 times/wk	2166	41.3	12,760	40.0	20,426	39.4			3×10^{-4}
Vegetables, %[9]									
No intake	220	4.2	1337	4.2	2165	4.2	0.01[10]	4×10^{-50}	
≤4 times/wk	1294	24.7	8098	25.4	13,470	26.0			0.01
5–7 times/wk	1949	37.2	12,157	38.1	19,915	38.4			7×10^{-11}
>7 times/wk	1778	33.9	10,346	32.4	16,351	31.5			3×10^{-20}
Fish,[9] %									
No intake	690	13.2	4170	13.1	7192	13.9	0.04[10]	3×10^{-38}	
≤4 times/wk	2995	57.2	18,088	56.6	29,270	56.4			7×10^{-4}
5–7 times/wk	990	18.9	6253	19.6	9932	19.1			0.92
>7 times/wk	566	10.8	3427	10.7	5507	10.6			2×10^{-8}
Fast food,[9] %									
No intake	4255	81.2	25,955	81.3	42,076	81.1	0.78	6×10^{-63}	
Once per week	860	16.4	5286	16.6	8641	16.7			3×10^{-23}
Twice or more per week	126	2.4	697	2.2	1184	2.3			0.08
Soda drinks,[9] %									
No intake	3174	60.6	19,593	61.4	31,435	60.6	0.14	2×10^{-103}	
<7 0.5 L bottles/wk	1713	32.7	10,360	32.4	17,105	33.0			0.42

(Continued)

TABLE 1 (*Continued*)

	Genotype[2]						*P* value[3]		
	CC		*TC*		*TT*				
Characteristics	*n*	Value	*n*	Value	*n*	Value	Genotype	Milk intake[4]	Diabetes[5]
≥7 0.5 L bottles/wk	354	6.8	1985	6.2	3361	6.5			5×10^{-35}
Lipid-lowering therapy, %									
No	5126	88.5	31,208	89.2	51,114	89.6	0.01[10]	6×10^{-29}	
Yes	664	11.5	3776	10.8	5923	10.4			1×10^{-300}
Hypertension, %									
No	4356	75.2	26,381	75.4	42,953	75.3	0.92	9×10^{-82}	
Yes	1434	24.8	8603	24.6	14,084	24.7			1×10^{-300}
Height, m	5790	1.70 (1.64–1.77)	34,984	1.70 (1.64–1.78)	57,037	1.71 (1.64–1.78)	9×10^{-4}	3×10^{-137}	2×10^{-13}
BMI, kg/m^2	5790	25.5 (23.1–28.3)	34,984	25.6 (23.2–28.5)	57,037	25.7 (23.2–28.6)	0.02[10]	4×10^{-5}	1×10^{-300}
BMI group, %									
<18.5 kg/m^2	65	1.1	329	0.9	548	1.0	0.31	3×10^{-6}	
18.5–24.9 kg/m^2	2524	43.6	14,805	42.3	24,190	42.4			0.50
25–29.9 kg/m^2	2276	39.3	14,018	40.1	22,688	39.8			1×10^{-4}
≥30 kg/m^2	925	16.0	5832	16.7	9611	16.9			5×10^{-18}
Total cholesterol, mmol/L	5790	5.6 (4.9–6.4)	34,984	5.6 (4.9–6.3)	57,037	5.6 (4.9–6.3)	0.02[10]	1×10^{-84}	6×10^{-152}
LDL cholesterol, mmol/L	5790	3.2 (2.6–3.9)	34,984	3.2 (2.6–3.9)	57,037	3.2 (2.6–3.9)	0.47	2×10^{-17}	4×10^{-232}
HDL cholesterol, mmol/L	5790	1.6 (1.3–1.9)	34,984	1.6 (1.2–1.9)	57,037	1.5 (1.2–1.9)	6×10^{-5}	1×10^{-158}	5×10^{-229}
Triglycerides, mmol/L	5790	1.4 (1.0–2.1)	34,984	1.4 (1.0–2.1)	57,037	1.4 (1.0–2.1)	0.72	5×10^{-16}	3×10^{-289}
Systolic blood pressure, mm Hg	5790	137 (124–151)	34,984	138 (124–152)	57,037	138 (124–152)	0.11	2×10^{-85}	1×10^{-141}
Diastolic blood pressure, mm Hg	5790	81 (74–90)	34,984	81 (75–90)	57,037	82 (75–90)	0.04[10]	3×10^{-24}	4×10^{-7}

[1]Missing values in the total population (n = 97,811): physical activity in leisure time (1.2%), smoking status (0.3%), education (0.6%), BMI (0.2%), total cholesterol (0.06%), LDL cholesterol (0.9%), HDL cholesterol (0.07%), triglycerides (0.09%), systolic blood pressure (0.05%), diastolic blood pressure (0.05%), and height (0.1%). Missing values were imputed based on sex, age, and population.

[2]*LCT-13910 C/T* genotypes: *CC* (lactase nonpersistent), *TC* (lactase persistent), and *TT* (lactase persistent).

[3]*P* values were derived from a chi-square, Kruskal-Wallis, or Mann Whitney *U* test.

[4]From Supplemental Table 4: *P* values of population characteristics by milk intake in quintiles (glasses/wk).

[5]From Supplemental Table 5: *P* values from logistic regression of population characteristics on diabetes status (yes/no).

[6]Median; IQR in parentheses (all such values).

[7]A "standard drink" in Denmark is defined as 1 glass of wine (12.5 cL), 1 bottle of beer (33 cL), 1 glass of liqueur (12.5 cL), or 1 shot glass of spirits (4 cL) and contains ∼12 g alcohol.

[8]The education variable indicates the level of education obtained since the individual left the mandatory 7–9 y of lower and middle-school education. The education category "none/student" includes active students, ie, those who have not yet finished an education.

[9]Data not available for the Copenhagen City Heart Study.

[10]$P > 0.05$ after correction for multiple comparisons by using the Bonferroni method (correction for 24 parallel tests: $P = 0.05/24 = 0.002$).

Milk intake and risk of type 2 diabetes and overweight-obesity: observational estimates

No consistent observational associations with risk of type 2 diabetes were found between people drinking milk (divided in quintiles, any intake, or milk type) compared with people drinking no milk (**Figure 1**). Median follow-up time (IQR) was 5.5 (3.7–7.3) y with a total of 1355 events. However, individuals drinking 1–3 glasses/wk, ≥11 glasses/wk, and fat free milk all had higher HRs for type 2 diabetes. When lipid-lowering therapy, hypertension, and BMI were included in the model, the results were similar (**Supplemental Table 6**). Risk estimates for overweight-obesity were similar to those for type 2 diabetes, but with narrower 95% CIs (Figure 1 and **Supplemental Table 7**).

Genotype and milk intake

Median milk intake was 5 glasses/wk (IQR: 0–10) for lactase *TT/TC*–persistent individuals and 3 (0–7) for lactase *CC*–nonpersistent individuals (**Figure 2** and **Supplemental Table 8**). When people with known cardiovascular disease, diabetes, or use of lipid-lowering therapy were included, the results were similar. We found no difference in intake of cheese or fermented milk among the *LCT-13910 C/T* genotypes (data not shown).

Genotype and risk of type 2 diabetes and overweight-obesity

Genetically for lactase *TT/TC*–persistent individuals compared with lactase *CC*–nonpersistent individuals, the sex-, age-, and population-adjusted OR was 0.96 (0.86, 1.08; $P = 0.50$) for type 2 diabetes and 1.06 (1.00, 1.12; $P = 0.04$) for overweight-obesity (**Table 2**, **Table 3**, and **Supplemental Table 9**). In stratified analysis for type 2 diabetes, the corresponding values in those with and without milk intake were 0.88 (0.76, 1.03; $P = 0.11$) and 1.35 (1.07, 1.70; $P = 0.01$) (P-interaction = 0.002; Table 2), whereas no gene-milk interaction on overweight-obesity was found (Table 3).

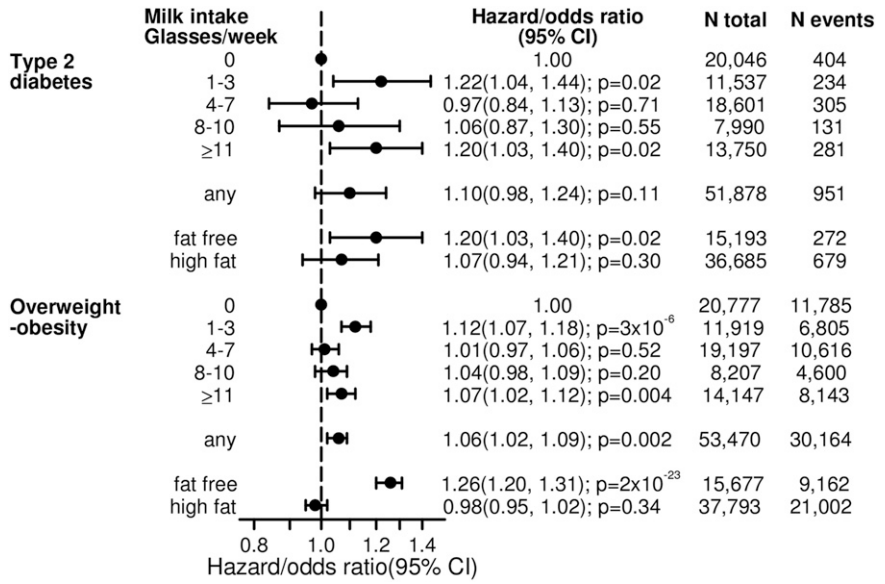


FIGURE 1 Risk of type 2 diabetes and overweight-obesity by milk intake. HRs and 95% CIs for type 2 diabetes and ORs (95% CIs) for overweight-obesity by milk intake (quintile, any, and type) in 71,775 participants from the Copenhagen General Population Study. Adjusted for sex, age, physical activity, smoking, alcohol intake, education, family history of diabetes, and intakes of fruit, vegetables, fish, fast food, and soda drinks. High fat: whole milk (3.5% fat) and semiskim milk (0.5–1.5% fat) combined. Fat free: skim milk (0.1–0.3% fat).

Milk intake and risk of diabetes and overweight-obesity: genetic vs. observational estimates

For a 1-glass/wk higher milk intake, the genetic risk ratio for type 2 diabetes was 0.99 (0.93, 1.06) with a corresponding observational risk of 1.01 (1.00, 1.01) (**Figure 3**). For overweight-obesity, the corresponding values were 1.01 (1.00, 1.02) genetically and 1.00 (1.00, 1.01) observationally. Sensitivity analyses for type 2 diabetes and overweight-obesity showed similar results when other methods of instrumental variable analysis were used (**Supplemental Table 10**).

DISCUSSION

In 97,811 individuals from the Danish general population, high milk intake was not associated with a low risk of type 2 diabetes or overweight-obesity, observationally or genetically via lactase persistence. The higher risk of type 2 diabetes in lactase-persistent individuals without milk intake likely is explained by collider stratification bias.

Research in context

At first sight, the lack of association in our observational analysis of type 2 diabetes seems to contrast with results from several meta-analysis of prospective cohort studies, which indicated that high compared with low intake of dairy/milk products was associated with a low risk of type 2 diabetes (1–6). However, many of the studies combined in the meta-analyses included different types of dairy/calcium intake as the exposure, as opposed to an investigation of the effect of milk alone as done in the current study. Thus, when the former analyses were restricted to milk intake (2–4), most studies found no association and only one found a reduced risk of diabetes for low-fat compared with high-fat milk (4). Differences in study design along with geographic heterogeneity among the populations included in the meta-analyses also made the studies difficult to compare and may explain why our observational results differ from the overall conclusion in the meta-analyses. The inconsistent association between milk intake and risk of diabetes in our observational study could also be a result of reverse causation and/or residual confounding. However, reverse causation and residual confounding from lifestyle factors should be largely avoided in the genetic analysis. Indeed, the lack of association in our overall genetic analysis on risk of type 2 diabetes supports the idea of a rather neutral effect of high milk intake, as does our genetic results on risk of overweight-obesity.

No difference in intake of fermented milk or cheese consumption was observed between the genotypes in the individuals in

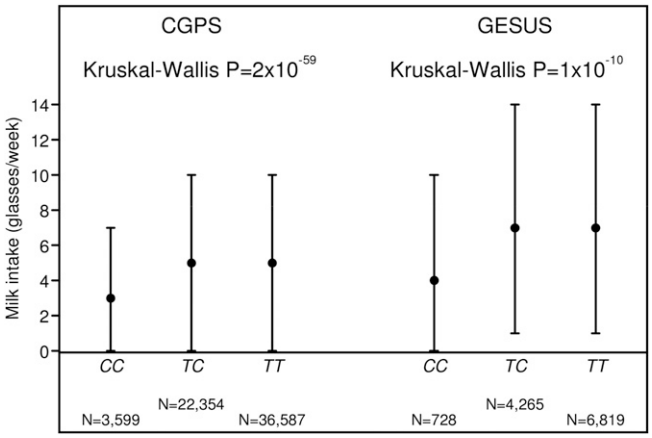


FIGURE 2 Median milk intake by *LCT-13910 C/T* lactase persistent/nonpersistent genotypes. Median milk intake and IQR by *LCT-13910* C/T genotype in participants from the CGPS (n = 62,540) and the GESUS (n = 11,812). Participants with ischemic heart disease, with ischemic cerebrovascular disease, with diabetes mellitus and using lipid-lowering therapy were excluded. *CC,* lactase nonpersistent; *TT/TC,* lactase persistent. CGPS, Copenhagen General Population Study; GESUS, Danish General Suburban Population Study.

TABLE 2
Diabetes by *LCT-13910 C/T* genetic variant

	Median milk intake (IQR), glasses/wk	Total, *n*	Events, *n*	Unadjusted		Adjusted for sex, age, and population		Adjusted for sex, age, population, and height	
				OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Type 2 diabetes[1]									
Lactase genotype									
CC (nonpersistence)	3 (0–7)	5790	327	1		1		1	
TC (persistence)	5 (0–10)	34,984	1872	0.94 (0.84, 1.07)	0.36	0.94 (0.83, 1.06)	0.33	0.97 (0.86, 1.09)	0.56
TT (persistence)	5 (0–10)	57,037	3134	0.97 (0.86, 1.09)	0.63	0.97 (0.86, 1.09)	0.57	0.98 (0.87, 1.10)	0.67
TC/TT (persistence)	5 (0–10)	92,021	5006	0.96 (0.86, 1.08)	0.50	0.96 (0.85, 1.08)	0.46	0.97 (0.87, 1.09)	0.62
LCT gene (codominant model) × milk (no/yes) interaction test[2,3]					0.01		0.004		0.005
LCT gene (dominant model) × milk (no/yes) interaction test[2,3]					0.002		0.001		0.002
Type 2 diabetes among no-milk drinkers[3]									
Lactase genotype									
CC (nonpersistence)	0 (0–0)	1909	80	1		1		1	
TC (persistence)	0 (0–0)	8797	474	1.30 (1.02, 1.66)	0.03	1.30 (1.02, 1.66)	0.03	1.31 (1.02, 1.67)	0.03
TT (persistence)	0 (0–0)	13,814	789	1.38 (1.09, 1.75)	0.01	1.38 (1.09, 1.75)	0.01	1.39 (1.10, 1.76)	0.01
TC/TT (persistence)	0 (0–0)	22,611	1263	1.35 (1.07, 1.70)	0.01	1.35 (1.07, 1.71)	0.01	1.36 (1.08, 1.71)	0.01
Type 2 diabetes among milk drinkers[3]									
Lactase genotype									
CC (nonpersistence)	7 (3–10)	3332	178	1		1		1	
TC (persistence)	7 (4–13)	23,141	1094	0.88 (0.75, 1.03)	0.12	0.85 (0.72, 1.01)	0.06	0.86 (0.73, 1.01)	0.07
TT (persistence)	7 (4–14)	38,087	1810	0.88 (0.75, 1.04)	0.13	0.86 (0.73, 1.01)	0.06	0.86 (0.74, 1.02)	0.08
TC/TT (persistence)	7 (4–14)	61,228	2904	0.88 (0.76, 1.03)	0.11	0.86 (0.73, 1.00)	0.05	0.86 (0.74, 1.01)	0.07

[1]Data are from the CGPS, the CCHS, and the GESUS combined. CCHS, Copenhagen City Heart Study; CGPS, Copenhagen General Population Study; GESUS, Danish General Suburban Population Study.

[2]Test of interaction by likelihood ratio. Unadjusted; adjusted for sex, age, and population; and adjusted for sex, age, population, and height, including milk (no/yes) as a covariate tested against a model with LCT genotype × milk interaction term included. The LCT gene was included as a codominant variable (*TT* and *TC* vs. *CC*) and as a dominant variable (*TT*/*TC* vs. *CC*).

[3]Data on milk intake were not available from the CCHS. Data include people from CGPS and GESUS only.

our study, which was expected because these products are generally better tolerated, partly because they have a lower content of lactose. Results from a dose-response meta-analysis of dairy product intakes and risk of type 2 diabetes suggested an inverse association between total dairy product intake from low amounts (≤300–400 g/d) and risk of type 2 diabetes, but no further reduction in risk was observed when even higher amounts of dairy products were examined. In addition, no association was found when only milk intake was considered (2). This may explain the lack of association in our study, because the Danish population in general has a high intake of milk and dairy products. Perhaps the Danish people have simply reached the threshold for dairy intake in terms of effect on risk of disease, which makes it difficult to detect any differences by genotype. Also in support of a neutral effect of milk intake are the results from a meta-analysis of randomized controlled trails, which found no effect of increased milk/dairy intake compared with usual diet on fasting glucose concentrations and HOMA-insulin resistance (16).

A French and a Finnish study have also used the genetic variant *LCT-13910 C/T* in an attempt to indirectly assess causality between milk intake and diabetes. Their results are in line with our overall finding of no consistent association between lactase-persistence genotypes and risk of type 2 diabetes (17, 18). The French study found no effect on type 2 diabetes, impaired fasting glucose, or the metabolic syndrome when using a codominant (*CC* vs. *TC* vs. *TT*) or dominant model (*CC* vs. *TC/TT*), but did find that the *C* allele was associated with impaired fasting glucose and/or type 2 diabetes (17). Results from other studies with overlapping endpoints also exist, and, whereas the association between the lactase *TC/TT*–persistent genotypes and overweight-obesity have been found in most (19, 20) (including ours), but not all (18) studies—along with a higher frequency of the metabolic syndrome (21)—there is no difference in concentrations of fasting glucose among genotypes (17). However, all previous studies were limited in the number of participants and did not obtain genetic risk estimates by applying instrumental variable analysis, and one failed to confirm the necessary association between milk intake and the *LCT-13910 C/T* genetic variant (19).

Strengths and limitations

Our study included 97,811 individuals, which made this the largest Mendelian randomization study of milk intake and risk of diabetes and overweight-obesity to date. We estimated that there may be a slight overlap in participants between our 3 general population studies; however, exclusion of the roughly 0.1% overlapping participants was not expected to have any major influence on our results.

Whereas the results from our observational analyses may have been influenced by residual confounding and reverse causation,

TABLE 3
Overweight-obesity by *LCT-13910 C/T* genetic variant

	Median milk intake (IQR), glasses/wk	Total, *n*	Events, *n*	Unadjusted		Adjusted for sex, age, and population		Adjusted for sex, age, population, and height	
				OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Overweight-obesity[1]									
Lactase genotype									
CC (nonpersistence)	3 (0–7)	5790	3201	1		1		1	
TC (persistence)	5 (0–10)	34,984	19,850	1.06 (1.00, 1.12)	0.04	1.06 (1.00, 1.12)	0.06	1.06 (1.00, 1.13)	0.04
TT (persistence)	5 (0–10)	57,037	32,299	1.06 (1.00, 1.12)	0.05	1.05 (0.99, 1.11)	0.08	1.06 (1.00, 1.12)	0.04
TC/TT (persistence)	5 (0–10)	92,021	52,149	1.06 (1.00, 1.12)	0.04	1.05 (1.00, 1.11)	0.07	1.06 (1.00, 1.12)	0.04
LCT gene (*TT; TC; CC*) × milk (no/yes) interaction test[2,3]					0.73		0.98		0.98
LCT gene (*TT/TC; CC*) × milk (no/ yes) interaction test[2,3]					0.48		0.95		0.98

[1]Overweight-obesity was defined as a BMI (kg/m^2) ≥25 vs. <25. Data are from the CGPS, the CCHS, and the GESUS combined. CCHS, Copenhagen City Heart Study; CGPS, Copenhagen General Population Study; GESUS, Danish General Suburban Population Study.

[2]Test of interaction by likelihood ratio test. Test of model (unadjusted; adjusted for sex, age, and population; adjusted for sex, age, population, and height), including milk (no/yes) as a covariate against a model with LCT-genotype × milk interaction term included.

[3]Data included people from CGPS and GESUS only, because data on milk intake were not available from the CCHS.

the Mendelian randomization design used in our genetic analyses should have largely prevented such potentially distorting influences because of the random assortment of alleles before gamete formation. However, some potential sources of bias include pleiotropy and population stratification. Pleiotropy refers to a situation in which a gene affects ≥2 apparently unrelated phenotypic traits; however, to our knowledge, no pleiotropic effect of the *LCT-13910 C/T* genetic variant has been detected. To limit the influence of population stratification bias, we strived to obtain a study population of homogenous ancestry by including only white participants of Danish descent. In addition, we included height in the model to adjust for a hidden population substructure, because genome-wide data were not available. Importantly however, the difference in height between genotypes was small, and the adjustment for height gave similar results.

The strength of the association between the *LCT-13910 C/T* genetic variant and milk intake is dependent on how rare the minor allele is and on cultural practices for dairy farming and traditions for including milk and dairy products in the diet. A PubMed search resulted in 123 hits, from which we retrieved information on milk intake and genotype frequency from 5 studies of different European populations for comparison with our own data (**Figure 4**). The mean milk intake was higher in lactase *TT/TC*–persistent individuals than in lactase *CC*–nonpersistent individuals from Finland (22), Sweden (23), Denmark (current study), Estonia (24), Spain (19), and Italy (25). The highest milk intake was in Finland and Sweden, where the difference in milk intake between lactase *TT/TC*–persistent individuals and lactase *CC*–nonpersistent individuals was largest. Milk intake differed only slightly by genotype, e.g., in Italy (25), where a much larger part of the population is lactase *CC* nonpersistent compared with the population in northern countries. There is a north-south gradient of lactase persistence in Europe, with prevalences ranging from 80% in northern Europe to 5–10% in southern Europe (26, 27). Also, there seems to be a similar gradient in milk intake because individuals from northern Europe (22, 23) report higher milk intakes than do individuals from southern Europe (25), and milk intake in northern Europe seems to be consistently higher in lactase-persistent individuals than in lactase-nonpersistent individuals. Lactase nonpersistence is of low prevalence in Denmark (6%); thus, because milk drinking is the norm in Denmark, this cultural practice may have a strong influence on milk consumption among Danish individuals, even among lactase-nonpersistent individuals. Furthermore, evidence suggests that individuals with lactose malabsorption or lactose intolerance may tolerate a limited amount of milk without experiencing major symptoms of lactose intolerance (28). These factors may explain the relatively small difference of a median of 2 glasses/wk in milk consumption between the lactase *TC/TT*–persistent and lactase *CC*–nonpersistent individuals in our study. The difference in milk intake was statistically significant (likely because of the large

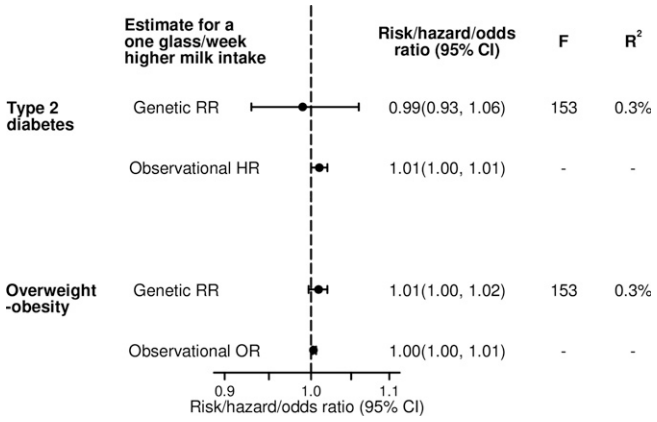
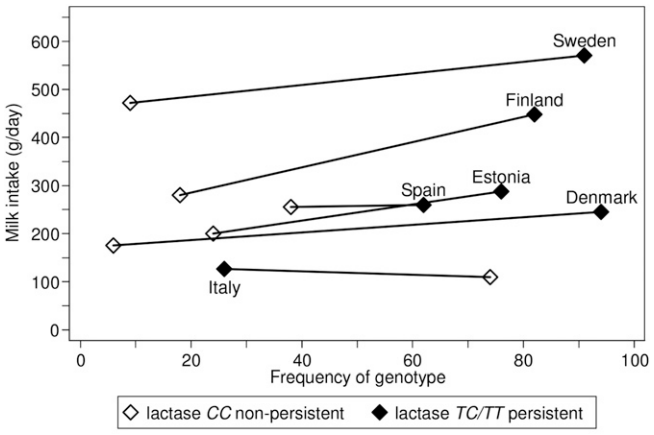


FIGURE 3 Observational and genetic risk of type 2 diabetes and overweight-obesity for a 1 glass/wk higher milk intake. Data from the Copenhagen General Population Study and the Danish General Suburban Population Study combined. Unadjusted genetic RRs (95% CIs) were estimated by multiplicative generalized methods of moments. *F* statistics indicate the statistical strength of the genotype as instrument for milk intake, whereas R^2 (%) indicates variation in milk intake explained by genotype; obtained by ordinary least-squares regression analysis. Observational HRs (95% CIs) for type 2 diabetes and ORs (95% CIs) for overweight-obesity adjusted for sex, age, physical activity in leisure time and at work, smoking, alcohol intake, education, family history of diabetes, fruit intake, vegetables intake, fish intake, intake of fast food, and intake of soda drinks.



Higher milk intake in lactase *TC/TT* persistence vs. *CC* non-persistence

	Absolute difference in milk intake (g/day)	Relative difference in percent
Finland(22)	168	37
Sweden(23)	99	17
Denmark(present study)	70	29
Estonia(24)	88	30
Spain(19)	5	2
Italy(25)	17	13

FIGURE 4 *LCT-13910 C/T* genotype frequency and milk intake in European countries. European studies reporting the frequency of the *LCT-13910 C/T* genotypes and milk intake (mean or median). Danish estimates are from the current study. For studies reporting milk intake in units other than g/d, milk intake was recalculated assuming that 1 glass of milk contains 2.5 dL and that 1 dL weighs 100 g. Difference in milk intake between the lactase *TC/TT* persistent and *CC* nonpersistent individuals (absolute and in percentage) is given for each country. *CC,* lactase nonpersistent; *TT/TC,* lactase persistent.

number in our study) and should be strong enough to ensure the function of the genotype as a sufficient instrument for long-term difference in milk intake, according to the large F value of 153 in the instrumental variable analysis. However, the relatively small difference in milk intake between the genotypes in combination with the low frequency of the *CC* genotype in Denmark will likely affect our statistical power to detect a difference in risk of diabetes and overweight-obesity.

Stratifying the gene-diabetes analysis for milk intake may have introduced collider stratification bias. Indeed, it is disturbing that several characteristics were distributed differently by genotype in those with and without milk intake, e.g., sex and intake of fruit and vegetables. We believe that these findings point toward collider stratification bias, which could possibly explain why, among individuals without milk intake, we observed that lactase *TC/TT*–persistent individuals had a higher risk of type 2 diabetes than did lactase *CC*–nonpersistent individuals, with a trend toward the opposite direction among individuals with milk intake. Supporting this interpretation, it seems very difficult to understand how a genotype having an effect on milk intake should influence the risk of diabetes mainly in those without milk intake. In other words, these findings from the analysis stratified by milk intake do not seem to be biologically meaningful.

The *LCT-13910 C/T* polymorphism was in slight Hardy-Weinberg disequilibrium in the CCHS and CGPS, but not in GESUS, and additional analyses were performed to rule out genotyping errors as an explanation for the disequilibrium. Therefore, it is possible that the *LCT-1310 C/T* genotype is still adjusting in populations, which may account for the slight disequilibrium (29).

Information on type 2 diabetes was obtained by linkage to Danish registries, i.e., to the national Danish Patient Registry (30), the national Danish Civil Registration System (31), and the national Danish Causes of Death Registry (32). These registries provide unique possibilities for large-scale population studies and research in general; however, the Danish Patient Registry is foremost an administrative registry and thus has some limitations concerning its use in research. It contains information on all hospital contact since 1977 and is updated monthly, but it does not include diagnoses made by general practitioners. To compensate for this limitation, we combined the registry diagnosis with self-reported information on diabetes and use of insulin and other antidiabetic medication and with measured baseline concentrations of nonfasting glucose to better identify individuals with diabetes.

Interpretation

High milk intake was not associated with a low risk of type 2 diabetes or overweight-obesity, observationally or genetically via lactase persistence. The higher risk of type 2 diabetes observed in lactase-persistent individuals without milk intake likely is explained by collider stratification bias.

The authors' responsibilities were as follows—BGN and CE: conceived and designed the research, acquired the data, and handled the supervision; HKMB: performed the literature search, prepared the data, performed the statistical analysis, and drafted the manuscript; and HKMB, BGN, and CE: critically revised the manuscript and contributed intellectually to its development. All authors provided final approval of the manuscript, had full access to all of the data in the study, took responsibility for the integrity of the data and the accuracy of the data in the analysis, and affirmed that the article is an honest, accurate, and transparent account of the study being reported and that no important aspects of the study have been omitted. HKBM reported grants from the Danish Dairy Research Foundation during the conduct of the study. BGN and CE reported no conflicts of interest. None of the funding sources were involved in the study design, conduct of the study, or collection, management, analysis, or interpretation of the data or in the preparation or review of the manuscript and had no right to approve or disapprove of the submitted manuscript. All authors completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author).

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