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Dairy product consumption is associated with pre-diabetes and newly diagnosed type 2 diabetes in the Lifelines Cohort Study

Elske M. Brouwer-Brolsma[1]*, Diewertje Sluik[1], Cecile M. Singh-Povel[2] and Edith J. M. Feskens[1]

[1]*Division of Human Nutrition, Wageningen University, 6700 AA Wageningen, The Netherlands*
[2]*FrieslandCampina, 3800 BN Amersfoort, The Netherlands*

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Abstract

Previous studies show associations between dairy product consumption and type 2 diabetes, but only a few studies conducted detailed analyses for a variety of dairy subgroups. Therefore, we examined cross-sectional associations of a broad variety of dairy subgroups with pre-diabetes and newly diagnosed type 2 diabetes (ND-T2DM) among Dutch adults. In total, 112 086 adults without diabetes completed a semi-quantitative FFQ and donated blood. Pre-diabetes was defined as fasting plasma glucose (FPG) between 5·6 and 6·9 mmol/l or HbA1c% of 5·7–6·4 %. ND-T2DM was defined as FPG ≥7·0 mmol/l or HbA1c ≥6·5 %. Logistic regression analyses were conducted by 100 g or serving increase and dairy tertiles ($T1^{ref}$), while adjusting for demographic, lifestyle and dietary covariates. Median dairy product intake was 324 (interquartile range 227) g/d; 25 549 (23 %) participants had pre-diabetes; and 1305 (1 %) had ND-T2DM. After full adjustment, inverse associations were observed of skimmed dairy ($OR^{100\,g}$ 0·98; 95 % CI 0·97, 1·00), fermented dairy ($OR^{100\,g}$ 0·98; 95 % CI 0·97, 0·99) and buttermilk ($OR^{150\,g}$ 0·97; 95 % CI 0·94, 1·00) with pre-diabetes. Positive associations were observed for full-fat dairy ($OR^{100\,g}$ 1·003; 95 % CI 1·01, 1·06), non-fermented dairy products ($OR^{100\,g}$ 1·01; 95 % CI 1·00, 1·02) and custard ($OR^{serving/150\,g}$ 1·13; 95 % CI 1·03, 1·24) with pre-diabetes. Moreover, full-fat dairy products (OR^{T3} 1·16; 95 % CI 0·99, 1·35), non-fermented dairy products ($OR^{100\,g}$ 1·05; 95 % CI 1·01, 1·09) and milk ($OR^{serving/150\,g}$ 1·08; 95 % CI 1·02, 1·15) were positively associated with ND-T2DM. In conclusion, our data showed inverse associations of skimmed and fermented dairy products with pre-diabetes. Positive associations were observed for full-fat and non-fermented dairy products with pre-diabetes and ND-T2DM.

Key words: **Diabetes: Glucose: Dairy products: Fermentation: Cohorts**

The number of people with one or more chronic diseases, including type 2 diabetes (T2DM), is rising and lifestyle factors seem to play an important role in this development. Scientific literature suggests that dairy product intake may affect glucose tolerance and hence the development of T2DM.

Mechanistically, beneficial effects of dairy product consumption in the prevention of glucose intolerance and T2DM may be explained by the presence of calcium and protein and their favourable influence on energy balance and body weight maintenance[(1)]. Beneficial links have also been observed between whey protein and the regulation of particular satiety-related hormones, lipid metabolism and insulin secretion[(2,3)]. In addition, possible metabolic effects of dairy products have been proposed for Mg (e.g. by promoting insulin sensitivity)[(4)], conjugated linoleic acid (e.g. body weight regulation)[(5)] and lactic acid bacteria present in fermented products (e.g. gut microbiota and satiety)[(6–8)]. Conversely, unfavourable metabolic effects may occur following the consumption of dairy products with a relatively high energy density, such as full-fat dairy products, for instance via raising blood LDL-cholesterol concentrations[(9)]. Moreover, given the suggested impact of sugar-sweetened beverages on the development of T2DM[(10)], also adverse effects may result from the consumption of sugar-sweetened dairy products. Given these potential favourable, as well as less favourable, pathways of various dairy product nutrients, it is challenging to value the actual health impact of dairy product consumption as a whole; the different nutrients may strengthen but also weaken each other's effects.

As a result, several observational studies[(7,11–28)] and meta-analyses[(29)] investigated associations between dairy product intake and incident T2DM. Chen *et al.*[(11)] conducted a meta-analysis of prospective cohort studies and concluded that there is no convincing evidence for an association between total dairy product consumption and incidence of T2DM (*n* 14, relative risk (RR) per one serving of dairy products: 0·98; 95 % CI 0·96, 1·01)[(11)]. In contrast, a meta-analysis by Aune *et al.*[(30)] did suggest a link between total dairy product intake and incident T2DM (*n* 12, RR/400 g 0·93; 95 % CI 0·87, 0·99). Despite the null

Abbreviations: FPG, fasting plasma glucose; ND-T2DM, newly diagnosed type 2 diabetes; T2DM, type 2 diabetes.

* **Corresponding author:** E. M. Brouwer-Brolsma, fax +31 317 484987, email elske.brouwer-brolsma@wur.nl

findings for total dairy product resulting from the meta-analysis by Chen *et al*., subgroup analyses did show a significant inverse association between yoghurt consumption and T2DM[11]. This illustrates that analyses of specific dairy product subgroups, rather than total dairy products, may improve the understanding of potential effects of the dairy product matrix. Hence, the research field is now evolving to more detailed analyses including different dairy product subgroups as for instance shown by the recent meta-analysis of Gijsbers *et al*.[31] and systematic review of meta-analyses by Drouin-Chartier *et al*.[29]. This last mentioned research group concluded their work by stating that current epidemiologic evidence largely points towards neutral or beneficial associations between dairy product intake and incident T2DM, but that recommendations to consume low-fat dairy products instead of full-fat products are currently insufficiently supported[29].

As original studies with analyses on the dairy product subgroup level are still scarce[31], we explored associations of dairy product intake with pre-diabetes and newly diagnosed T2DM (ND-T2DM) prevalence – defined using the aetiological markers fasting plasma glucose (FPG) and HbA1c% – in a uniquely large population of Dutch adults by subdividing total dairy product intake into a broad variety of dairy product subclasses, including skimmed dairy products, semi-skimmed dairy products, full-fat dairy products, non-fermented dairy products, fermented dairy products, total milk, skimmed milk, semi-skimmed milk, full-fat milk, total yogurt, skimmed yogurt, full-fat yogurt, buttermilk, curd cheese/quark, custard, flavoured yogurt drinks, total cheese, low-fat cheese and regular-fat cheese. We also studied potential effect modification of dairy product intake with age, sex and BMI, and mediation effects by markers of lipid metabolism.

Methods

Participants

This cross-sectional study was performed using data of the Lifelines Cohort Study. Lifelines is a multi-disciplinary prospective population-based cohort study examining in a unique three-generation design the health and health-related behaviours of 167 729 persons living in the North of the Netherlands. It uses a broad range of investigative procedures in assessing the biomedical, socio-demographic, behavioural, physical and psychological factors that contribute to the health and disease of the general population, with a special focus on multi-morbidity and complex genetics[32]. Between 2006 and 2013, inhabitants of the three Northern provinces of The Netherlands (Friesland, Groningen and Drenthe) and their families were invited for participation in the study, with the goal to create a three-generation design. The first group of participants, aged 25–50 years old, was recruited through their general practitioner. Exclusion criteria included having a severe psychiatric or physical illness, limited life expectancy (<5 years) and insufficient knowledge of the Dutch language to complete a Dutch questionnaire. When a participant was considered to be eligible to the study, he or she received a baseline questionnaire and was invited to the Lifelines research site for a comprehensive health assessment. During the visit at the research centre, participants were also asked to indicate whether family members would be willing to participate in the study; in case of a positive response, family members were invited as well. In addition to this recruitment strategy, inhabitants of the northern part of The Netherlands could also register themselves via the Lifelines website. A more detailed description of the Lifelines study can be found in the article on the cohort description[32]. All participants gave written informed consent. The Lifelines study is conducted according to the principles of the Declaration of Helsinki and in accordance with the research code of the University Medical Centre Groningen. The Lifelines study is approved by the medical ethical committee of the UMCG, the Netherlands.

Population for analyses

In total, 144 095 out of 167 729 participants completed a baseline FFQ. Participants with unreliable dietary data (*n* 29 413) – that is men with energy intakes <3347 kJ or > 17 573 kJ and women with energy intakes <2092 kJ or > 14 644 kJ – and/or FFQ judged as unreliable by the research dieticians, for example owing to nutrient or food group reports below the possible under or upper limit, or reporting to have diabetes (*n* 2596) were excluded from the analyses. Finally, 112 086 participants were included in our analyses.

Dietary assessment

Dietary intake was assessed by the 'flower FFQ', which has been developed as an alternative for the regular – often time-consuming – FFQ. The name 'flower FFQ' has been derived from its design, consisting of one main questionnaire on energy and macronutrient intake (heart), and four complementary food questionnaires (petals) on micronutrients and eating behaviour, with overlapping questions to provide information on covariance. For the current analyses, only data of the flower heart were available, which comprised 110 food items, including all major food groups such as dairy products (further specified in Table 1), bread, pasta, rice, potatoes, fruit, vegetables, legumes, meat, fish, coffee, tea and soda/juice. Portion sizes were estimated using natural portions and commonly used household measures[33]. FFQ data were converted into total intakes of energy and nutrients by means of the Dutch Food Composition table 2011 (NEVO)[34]. A more detailed description of the Flower FFQ can be found elsewhere[35]. Before entering the dietary variables in the statistical models, they were all adjusted for energy intake by means of the residual method[36]. The questionnaire also included an item about whether or not participants were on a weight loss diet at the time of the dietary assessment. Currently, researchers are working on the validation of the 'flower FFQ'.

Markers of glucose homoeostasis

Fasting blood samples were collected at baseline, processed on the day of collection and either directly analysed or stored at −80°C in a fully automated storage facility. FPG was determined in venous plasma by means of the Roche glucose assay (hexokinase/glucose-6-phosphate dehydrogenase enzymatic

Table 1. Dairy product group classification

Dairy product groups	Included dairy products*
Total dairy products	All dairy products, except butter
Skimmed dairy products	All types of skimmed milk (0·1 g fat, 4 %) and yogurt (0·2 g fat, 27 %), buttermilk (0·2 g fat, 24 %) and flavoured yogurt drinks (0·2 g fat, 45 %)
Semi-skimmed dairy products	All types of semi-skimmed milk (1·5 g fat, 74 %) and low-fat cheese (15 g fat, 26 %)
Full-fat dairy products	All types of full-fat milk (3·5 g fat, 23 %) and yogurt (2·9 g fat, 7 %), regular-fat cheese (≥24 g fat, 43 %), cream (35 g fat, 3 %), milk-based ice cream (12 g fat, 12 %), chocolate milk (1·9 g fat, 12 %)
Fermented dairy products	All types of yogurt (22 %), curd cheese/quark (10 %), buttermilk (15 %), cheese (34 %) and flavoured yogurt drinks (19 %)
Non-fermented dairy products	All types of milk (73 %), custard (9 %), porridge (3 %), milk-based ice cream (11 %) and cream (4 %).
Milk	All types of milk, including plain milk (63 %), coffee milk (25 %) and chocolate milk (12 %).
Skimmed milk	All types of skimmed milk (0·1 g fat)
Semi-skimmed milk	All types of semi-skimmed milk (1·5 g fat)
Full-fat milk	All types of full-fat milk (3·5 g fat)
Yogurt	All types of yogurt
Skimmed yogurt	All types of skimmed yogurt (0·2 g fat)
Full-fat yogurt	All types of full-fat yogurt (2·9 g fat)
Buttermilk	All types of buttermilk
Curd cheese/quark	All types of curd cheese/quark
Flavoured yogurt drinks	All types of flavoured yogurt drinks
Custard	All types of custard
Cheese	All types of cheese, including Dutch cheeses (soft and hard cheeses) (68 %) and other cheeses (i.e. cream cheese, foreign cheeses, cheese snack) (32 %)
Low-fat cheese	All types of low-fat cheese (15 g fat)
Regular-fat cheese	All types of regular-fat cheese (≥24 g fat)
Dutch cheese	All types of Dutch (yellow) cheeses

* The first number following the dairy product in the second column indicates the fat quantity (g) per 100 g; the percentage (%) refers to the contribution of that specific dairy product to that category.

reactions) and the Modular P analyser (Roche Diagnostics). HbA1c was determined in whole blood (EDTA-anticoagulated) by means of turbidimetric inhibition immunoassay on a Cobas Integra 800 CTS analyser (Roche Diagnostics Netherland BV), which has been shown to have a coefficient of variation of 2·1 % for a mean HbA1c of 5·5 %, and 1·9 % for a mean HbA1c of 10·6 %[37]. Subsequently, pre-diabetes was defined as having a FPG between 5·6 and 6·9 mmol/l or an HbA1c of 5·7–6·4 %[38]. ND-T2DM was defined as having a FPG ≥7·0 mmol/L or HbA1c ≥6·5 %[38].

Non-dietary covariates

Baseline data on demographic factors, education level (primary, secondary, higher or other education), current and past active smoking behaviour, physical activity (SQUASH)[39], ethanol consumption (none, 1–9, 10–19, ≥20 g/d), history and prevalence of diseases (i.e. hypertension and hypercholesterolaemia) and family history of diseases were collected by means of questionnaires. Weight was measured to the nearest 0·1 kg, without shoes and heavy clothing, using a calibrated SECA 761 scale. Height was measured to the nearest 0·1 cm, without shoes, using a calibrated SECA222 stadiometer. BMI was calculated as weight/height squared (kg/m^2). Waist circumference was measured twice, to the nearest 0·1 cm, midway between the lowest rib and the top of the iliac crest at the end of gentle expiration, using SECA 200 measuring tape. The mean of the two measurements was used in the analyses[40]. Total cholesterol (TC) and HDL-C were assessed in serum using an enzymatic colorimetric method. LDL-C was determined in serum with a colorimetric method. Serum TAG concentrations were measured with a colorimetric UV method. All these cholesterol measurements were done on a Roche Modular P chemistry analyser (Roche)[41].

Statistical analyses

Participant characteristics are reported as mean values and standard deviations, numbers and percentages. Medians and interquartile ranges (IQR) were used to report skewed variables. Differences over tertiles of total dairy product intake were tested by means of χ^2 tests in case of categorical variables, one-way ANOVA in case of normally distributed continuous variables and Kruskal–Wallis test in case of skewed continuous variables. Logistic regression analysis was conducted to calculate OR for pre-diabetes and ND-T2DM per dairy product intake tertile, using the lowest tertile as the reference group. OR per 100 g/d or serving increase in dairy product intake were calculated as well. Models were adjusted for age (years), sex (model 1), model 1 + alcohol (0, 1–9, 10–19, ≥20 g/d), smoking (never, former, current), education (primary, secondary, higher, other), physical activity (number of days/week of at least moderate intensity physical activity) (model 2), model 2 + total energy intake (kJ/d), intake of energy adjusted bread, pasta, rice, potato, fruit, vegetables, legumes, meat, fish, coffee, tea, soda/juice, other dairy product groups (g/d) (model 3), model 3 + BMI (kg/m^2) and waist circumference (cm) (model 4). Potential mediation by markers of lipid metabolism was examined by adding TC, HDL-cC, LDL-C and TAG to model 4 (model 5). The $P_{\text{for trend}}$ across medians of dairy product intake tertiles was calculated to study potential dose–response associations of dairy product intake with prevalent pre-diabetes and ND-T2DM. Possible interactions between dairy product intake and age, sex and BMI in association with FPG and HbA1c were tested through the inclusion of a cross-product term

British Journal of Nutrition

in linear models and visualised through stratified analyses. A two-sided P value $\leq 0{\cdot}05$ was considered to be statistically significant for all analyses. Analyses were performed using the statistical package SPSS, version 22 (IBM SPSS Inc.).

Results

The characteristics of the population are described in Table 2. Comparison of the top and bottom tertile of total dairy product intake shows that participants in the top tertile were more likely to be older, women, former smokers, overweight, to be diagnosed with hypertension and hypercholesterolaemia and to have a higher intake of fruits. Analyses on the key variables in this study showed that 25 549 (23 %) participants had pre-diabetes and 1305 (1 %) had ND-T2DM. Median dairy product intake of the total population was 324 (IQR 227) g/d. Participants consumed more semi-skimmed dairy products than skimmed or full-fat products, and higher quantities of non-fermented dairy products than fermented dairy products. On the product level, milk was the largest contributor to the total sum of dairy products – that is 98 (IQR 170) g/d.

Table 2. Baseline characteristics according to tertiles (T) of total dairy product intake of 112 086 participants without self-reported diabetes
(Mean values and standard deviations; medians and interquartile ranges (IQR); numbers and percentages)

				Tertiles of total dairy product intake						
		Total		T1 (*n* 34 716)		T2 (*n* 39 063)		T3 (*n* 38 307)		
	n	Median	IQR	Median	IQR	Median	IQR	Median	IQR	*P**
Range in total dairy product intake (g/d)	11 2086	324	227	< 245		245–394		≥ 395		
Age (years)	11 2086									<0·0001
Mean		45		42		45		46		
SD		13		12		13		13		
Men	11 2086									<0·0001
n		46 063		16 979		14 955		14 129		
%		41		49		38		37		
Smoking	11 1828									<0·0001
Never										
n		35 672		10 579		12 771		12 322		
%		32		30		33		32		
Former										
n		52 974		14 782		18 558		19 634		
%		47		43		47		51		
Current										
n		23 182		9257		7652		6273		
%		21		27		20		16		
BMI (kg/m^2)	11 2065									<0·0001
Mean		25·6		25·5		25·6		25·8		
SD		4·0		4·1		3·9		4·0		
Education	11 1649									<0·0001
Primary										
n		2405		735		840		830		
%		2		2		2		2		
Secondary										
n		63 023		19 075		21 790		22 158		
%		56		55		56		58		
Higher										
n		44 150		14 236		15 572		14 342		
%		40		41		40		38		
Other										
n		2071		560		703		808		
%		2		2		2		2		
Moderate-intensity physical activity (d/week)	10 4152	5	6	5	6	5	7	5	7	<0·0001
Hypertension	11 1926									<0·0001
n		22 868		6263		8194		8411		
%		20		18		21		22		
Hypercholesterolaemia	111 924									<0·0001
n		13 682		3873		4912		4897		
%		12		11		13		13		
Alcohol intake	112 086									<0·0001
0 g/d										
n		2448		731		735		982		
%		2		2		2		3		
1–9 g/d										
n		79 231		21 879		28 170		29 182		
%		71		63		72		76		
10–19 g/d										
n		21 834		7945		7672		6217		
%		19		23		20		16		

Table 2. *Continued*

		Total		Tertiles of total dairy product intake						
				T1 (*n* 34 716)		T2 (*n* 39 063)		T3 (*n* 38 307)		
	n	Median	IQR	Median	IQR	Median	IQR	Median	IQR	*P**
≥ 20 g/d										
n		8573		4161		2486		1926		
%		8		12		6		5		
Pre-diabetes	110 781									<0·0001
n		25 549		7167		9041		9341		
%		23		21		23		25		
Newly diagnosed type 2 diabetes	112 086									<0·0001
n		1305		364		444		497		
%		1		1		1		1		
Fasting plasma glucose (mmol/l)	109 343	4·93	0·61	4·9	0·59	4·9	0·62	4·9	0·62	0·75
HbA1c, % (mmol/mol)	110 877	37		36		37		37		0·004
Mean		5·52		5·49		5·52		5·54		
SD		0·36		0·35		0·36		0·37		
Creatinine (μmol/l)	111 550									<0·0001
Mean		73·4		74·1		73·2		72·9		
SD		13·2		13·2		13·3		13·0		
Total cholesterol (mmol/l)	111 549									0·01
Mean		5·10		5·07		5·11		5·11		
SD		0·40		1·01		1·01		0·99		
LDL-cholesterol	111 541									<0·0001
Mean		3·24		3·22		3·24		3·25		
SD		0·92		0·93		0·92		0·90		
HDL-cholesterol (mmol/l)	111 549									0·07
Mean		1·51		1·48		1·52		1·52		
SD		0·40		0·39		0·40		0·40		
TAG (mmol/l)	111 549	0·96	0·66	0·97	0·69	0·95	0·65	0·95	0·64	<0·0001
Energy intake (kJ/d)	112 086									<0·0001
Mean		8985		9276		8655		9057		
SD		2304		2432		2151		2293		
Total fat (En%)	112 086									<0·0001
Mean		36		36		36		35		
SD		5		5		5		5		
Protein (En%)	112 086									<0·0001
Mean		15		14		15		16		
SD		2		2		2		2		
Carbohydrates (En%)	112 086									<0·0001
Mean		45		45		45		45		
SD		5		6		5		5		
Skimmed dairy products (g/d)	112 086	54	129	16	48	63	112	129	200	<0·0001
Semi-skimmed dairy products (g/d)	112 086	50	125	21	44	59	103	146	240	<0·0001
Full-fat dairy products (g/d)	112 086	59	58	49	46	63	57	67	74	<0·0001
Fermented dairy products (g/d)	112 086	121	139	69	70	134	111	202	204	<0·0001
Non-fermented dairy products (g/d)	112 086	126	168	59	71	137	115	263	210	<0·0001
Total milk (g/d)	112 086	103	160	43	63	112	112	237	207	<0·0001
Total yogurt (g/d)	112 086	17	54	0	27	23	56	34	70	<0·0001
Buttermilk (g/d)	112 086	1	35	1	2	1	34	2	119	<0·0001
Curd cheese (g/d)	112 086	1	23	1	13	1	24	1	28	<0·0001
Custard (g/d)	112 086	3	14	2	9	4	16	4	21	<0·0001
Flavoured yogurt drinks (g/d)	112 086	8	33	5	17	9	40	9	65	<0·0001
Total cheese (g/d)	112 086	26	28	23	27	27	27	27	29	<0·0001
Fruits (g/d)	112 086	111	174	87	177	111	172	149	147	<0·0001
Vegetables (g/d)	112 086	107	74	103	78	108	53	108	74	<0·0001
Legumes (g/d)	112 086	13	27	13	28	14	25	14	26	<0·0001
Bread (g/d)	112 086	142	62	147	70	143	57	136	58	<0·0001
Meat (g/d)	112 086	80	42	81	45	81	41	78	42	<0·0001
Pasta (g/d)	112 086	21	19	21	22	21	19	19	17	<0·0001
Rice (g/d)	112 086	17	19	18	23	17	18	16	18	<0·0001
Potatoes (g/d)	112 086	90	61	87	66	92	59	90	59	<0·0001
Fish (g/d)	112 086	10	12	10	13	10	12	10	12	0·02
Coffee (g/d)	112 086	421	358	396	419	428	343	435	336	<0·0001
Tea (g/d)	112 086	198	304	178	311	201	296	205	303	<0·0001
Soda/fruit juice (g/d)	112 086	101	161	119	202	102	147	89	139	<0·0001
Current weight loss die	111 419									<0·0001
n		4950		1132		1804		2014		
%		4		3		5		5		

* Differences across quintiles are investigated using ANOVA in case of normally distributed continuous variables, Kruskal–Wallis test in case of skewed continuous variables and χ^2 tests in case of categorical variables.

Pre-diabetes

After full adjustment (model 4), significant inverse associations were observed of skimmed (OR per 100 g ($OR^{100\,g}$) 0·98; 95 % CI 0·97, 1·00; $P=0·02$ and OR of the third tertile (OR^{T3}) 0·95; 95 % CI 0·92, 0·99; $P=0·02$) and fermented dairy product intake ($OR^{100\,g}$ 0·98; 95 % CI 0·97, 0·99; $P=0·004$ and OR^{T3} 0·94; 95 % CI 0·90, 0·98; $P=0·004$) with pre-diabetes, showing a 2 % lower odds of pre-diabetes with each 100-g increase in dairy product intake for both dairy product subclasses. Positive associations were observed for full-fat ($OR^{100\,g}$ 1·03; 95 % CI 1·01, 1·06; $P=0·004$ and OR^{T3} 1·10; 95 % CI 1·06, 1·15; $P<0·0001$) and non-fermented dairy products ($OR^{100\,g}$ 1·01; 95 % CI 1·00, 1·02; $P=0·30$ and OR^{T3} 1·05; 95 % CI 1·00, 1·09 $P=0·03$) with pre-diabetes. On the product level, a significant inverse association was observed between buttermilk ($OR^{serving/150\,g}$ 0·97; 95 % CI 0·94, 1·00; $P=0·04$ and OR^{T3} 0·99; 95 % CI 0·95, 1·04; $P=0·68$) and pre-diabetes, whereas a positive association was observed for custard with pre-diabetes ($OR^{serving/150\,g}$ 1·13; 95 % CI 1·03, 1·24; $P=0·01$ and OR^{T3} 1·05; 95 % CI 1·01, 1·10; $P=0·02$) (Table 3). No associations were observed for the intake of total dairy products, semi-skimmed dairy products, milk, yogurt, curd cheese, yogurt drinks or cheese with pre-diabetes. However, more specific analyses for milk, yogurt and cheese that were further subdivided based on fat content did show positive associations for full-fat milk ($OR^{serving/150\,g}$ 1·03; 95 % CI 0·99, 1·08; $P=0·19$ and OR^{T3} 1·07; 95 % CI 1·02, 1·11; $P=0·002$) and full-fat yogurt ($OR^{serving/150\,g}$ 1·09; 95 % CI 0·99, 1·19; $P=0·08$ and OR^{T3} 1·07; 95 % CI 1·02, 1·12; $P=0·007$), whereas an inverse association was observed for low-fat cheese ($OR^{serving/20\,g}$ 0·97; 95 % CI 0·95, 0·99; $P=0·004$ and OR^{T3} 0·96; 95 % CI 0·92, 1·00; $P=0·08$) (Table 4). Including markers of lipid metabolism (model 5) – that is potential intermediates – did not affect the associations between dairy product intake and pre-diabetes (data not shown).

Newly diagnosed type 2 diabetes

Exploration of the associations between dairy product intake and ND-T2DM showed significant positive associations between full-fat ($OR^{100\,g}$ 1·04; 95 % CI 0·96, 1·13; $P=0·29$; OR^{T2} 1·18; 95 % CI 1·01, 1·37; $P=0·03$ and OR^{T3} 1·16; 95 % CI 0·99, 1·35; $P=0·07$) and non-fermented dairy product ($OR^{100\,g}$ 1·05; 95 % CI 1·01, 1·09; $P=0·01$ and OR^{T3} 1·10; 95 % CI 0·95, 1·27; $P=0·21$) with ND-T2DM (Table 5). On the product level, a significant positive association was observed between milk and ND-T2DM ($OR^{serving/150\,g}$ 1·08; 95 % CI 1·02, 1·15; $P=0·006$ and OR^{T3} 1·10; 95 % CI 0·95, 1·27; $P=0·19$), which was predominantly driven by skimmed milk consumption ($OR^{serving/150\,g}$ 1·21; 95 % CI 1·04, 1·41; $P=0·01$ and OR^{T3} 1·17; 95 % CI 0·94, 1·47; $P=0·16$). No associations were observed for the consumption of total, skimmed, semi-skimmed and fermented dairy product, yogurt, buttermilk, curd cheese, custard, flavoured yogurt drinks and cheese with ND-T2DM. Including markers of lipid metabolism (model 5) did not influence the associations between dairy product intake and – ND-T2DM (data not shown).

Moreover, although our analyses showed several significant interactions between dairy product intake and age, sex and/or BMI in relation to FPG and HbA1c, no consistent patterns could be identified for these three elements (online Supplementary Table S1).

Discussion

Our analyses of dairy product intake with pre-diabetes and ND-T2DM among Dutch adults in the Lifelines Cohort Study showed inverse associations of skimmed dairy products, fermented dairy products, buttermilk and low-fat cheese with pre-diabetes. Positive associations were observed for full-fat dairy products, non-fermented dairy products, custard, full-fat milk and full-fat yogurt with pre-diabetes. The observed associations for dairy product intake and ND-T2DM were less convincing, but did show positive associations for full-fat dairy products, non-fermented dairy products, total milk and skimmed milk. Our analyses did not point towards effect modification by age, sex and BMI, or mediation through markers of lipid metabolism.

When comparing our data on skimmed, semi-skimmed and full-fat dairy products with other prospective studies and meta-analyses, our findings on pre-diabetes are partly in line with data of the Black Women's Health Study and the Women's Health Study[17,23]. These two studies also showed an inverse association between low-fat dairy products and T2DM incidence[17,23]. However, no such association was observed for high-fat dairy products[17,23]. Moreover, no difference between low-fat and high-fat products in association with incident T2DM was observed in several other prospective studies[11,18,21,22]. Yet, a meta-analysis of thirteen studies showed a 4 % lower risk of incident T2DM per 200 g/d low-fat dairy product intake (RR 0·96; 95 % CI 0·92, 1·00), whereas no significant association was observed for high-fat dairy product intake (RR 0·98; 95 % CI 0·93, 1·04)[31]. This meta-analysis also showed a 12 % lower risk of incident T2DM for an intake of 40 g of fermented dairy products per day (n 5)[31]. Although we did not observe an association between fermented dairy product intake and ND-T2DM, we did observe a 6 % lower odds of having pre-diabetes for participants in the highest fermented dairy products intake tertile. To note, as there was quite some overlap between the consumed products in the fermented dairy products and skimmed dairy product groups in our study, the inverse associations of skimmed and fermented dairy products with pre-diabetes may partly be explained by the consumption of the same products.

As potential dairy product effects may be related to particular product-specific nutrients, we hypothesised that more detailed analyses on the product level could provide more insight in the potential link between dairy product intake and T2DM. For instance, milk and yogurt are important sources of whey protein, which have been associated with lower postprandial glucose concentrations in patients with T2DM risk[42]. Moreover, both whey and casein have been shown to decrease food intake, body weight and body fat, and beneficially affect glucose tolerance and gut hormones in diet-induced obese rats[43]. Beneficial associations as previously observed for fermented products and T2DM risk[6,7] may be related to potential effects on gut microbiota and satiety[8]. In addition, ruminant trans-fatty acids have been associated with beneficial effects on glucose homoeostasis as well, where the suggested pathways include

British Journal of Nutrition

Table 3. Associations between dairy product consumption and pre-diabetes (fasting plasma glucose (FPG) 5·6–6·9 mmol/l or HbA1c 5·7–6·4 %) in Lifelines (*n* 110 781)
(Odds ratios and 95 % confidence intervals)

	Continuous		Tertiles of dairy product intake					
				T2		T3		
	OR	95 % CI	T1	OR	95 % CI	OR	95 % CI	$P_{for\ trend}$
Total dairy products	100 g							
Median	324		173	318		500		
Total *n*/cases	110 781/25 549		34 352/7167	38 619/9041		37 810/9341		
Crude model	1·05	1·04, 1·05	1·0	1·16	1·12, 1·20	1·25	1·20, 1·29	<0·0001
Model 1*	1·00	0·99, 1·01	1·0	0·96	0·92, 0·99	0·98	0·94, 1·02	0·40
Model 2†	1·00	0·99, 1·01	1·0	0·96	0·92, 1·00	0·99	0·95, 1·03	0·80
Model 3‡	1·00	0·99, 1·01	1·0	0·97	0·94, 1·01	0·98	0·94, 1·03	0·52
Model 4§	0·99	0·99, 1·00	1·0	0·97	0·93, 1·01	0·97	0·93, 1·01	0·13
Skimmed dairy products	100 g							
Median	54		3	53		172		
Total *n*/cases	110 781/25 549		36 532/8544	36 712/7995		37 537/9010		
Crude model	1·03	1·02, 1·05	1·0	0·91	0·88, 0·94	1·04	1·00, 1·07	<0·0001
Model 1*	0·97	0·96, 0·98	1·0	1·00	0·96, 1·03	0·92	0·89, 0·96	<0·0001
Model 2†	0·98	0·97, 1·00	1·0	1·01	0·97, 1·05	0·96	0·92, 0·99	0·009
Model 3‡	0·99	0·98, 1·00	1·0	1·01	0·98, 1·05	0·97	0·93, 1·01	0·07
Model 4§	0·98	0·97, 1·00	1·0	0·99	0·95, 1·03	0·95	0·92, 0·99	0·02
Semi-skimmed dairy products	100 g							
Median	50		5	49		187		
Total *n*/cases	110 781/25 549		36 700/8518	36 540/8344		37 541/8687		
Crude model	1·00	0·99, 1·01	1·0	0·98	0·95, 1·01	1·00	0·96, 1·03	0·88
Model 1*	1·02	1·00, 1·03	1·0	0·94	0·91, 0·98	1·00	0·97, 1·04	0·24
Model 2†	1·02	1·01, 1·03	1·0	0·94	0·91, 0·98	1·01	0·97, 1·05	0·20
Model 3‡	1·02	1·00, 1·03	1·0	1·00	0·96, 1·04	1·03	0·99, 1·07	0·16
Model 4§	1·00	0·99, 1·02	1·0	0·98	0·94, 1·02	0·99	0·95, 1·03	0·68
Full-fat dairy products	100 g							
Median	59		26	59		114		
Total *n*/cases	110 781/25 549		36 656/7306	36 558/8445		37 567/9798		
Crude model	1·15	1·13, 1·17	1·0	1·21	1·17, 1·25	1·42	1·37, 1·47	<0·0001
Model 1*	1·05	1·03, 1·08	1·0	1·02	0·98, 1·06	1·11	1·07, 1·15	<0·0001
Model 2†	1·03	1·01, 1·05	1·0	1·02	0·98, 1·06	1·07	1·02, 1·11	0·001
Model 3‡	1·02	0·99, 1·04	1·0	1·05	1·01, 1·09	1·07	1·02, 1·11	0·005
Model 4§	1·03	1·01, 1·06	1·0	1·06	1·02, 1·11	1·10	1·06, 1·15	<0·0001
Fermented dairy products	100 g							
Median	121		45	120		247		
Total *n*/cases	110 781/25 549		36 611/8049	36 609/8264		37 561/9236		
Crude model	1·05	1·04, 1·07	1·0	1·04	1·00, 1·07	1·16	1·12, 1·20	<0·0001
Model 1*	0·97	0·96, 0·98	1·0	0·95	0·91, 0·98	0·90	0·87, 0·94	<0·0001
Model 2†	0·98	0·97, 0·99	1·0	0·97	0·93, 1·01	0·94	0·90, 0·98	0·002
Model 3‡	0·98	0·97, 1·00	1·0	0·98	0·94, 1·02	0·95	0·91, 0·98	0·006
Model 4§	0·98	0·97, 0·99	1·0	0·97	0·93, 1·01	0·94	0·90, 0·98	0·004
Non-fermented dairy products	100 g							
Median	126		40	125		284		
Total *n*/cases	110 781/25 549		36 678/7992	36 602/8504		37 501/9053		
Crude model	1·03	1·02, 1·04	1·0	1·09	1·05, 1·13	1·14	1·10, 1·18	<0·0001
Model 1*	1·03	1·02, 1·04	1·0	1·05	1·01, 1·09	1·11	1·07, 1·15	<0·0001
Model 2†	1·02	1·01, 1·03	1·0	1·03	0·99, 1·07	1·08	1·04, 1·12	<0·0001
Model 3‡	1·01	1·00, 1·03	1·0	1·05	1·01, 1·09	1·07	1·03, 1·11	0·002
Model 4§	1·01	1·00, 1·02	1·0	1·04	1·00, 1·08	1·05	1·00, 1·09	0·05
Milk	Serving (150 g)							
Median	103		25	101		261		
Total *n*/cases	110 781/25 549		36 676/8192	36 610/8489		37 495/8868		
Crude model	1·02	1·01, 1·04	1·0	1·05	1·01, 1·09	1·08	1·04, 1·12	<0·0001
Model 1*	1·03	1·02, 1·05	1·0	1·04	1·00, 1·08	1·07	1·04, 1·11	<0·0001
Model 2†	1·02	1·01, 1·04	1·0	1·02	0·98, 1·06	1·05	1·01, 1·09	0·02
Model 3‡	1·02	1·00, 1·03	1·0	1·04	1·00, 1·08	1·04	1·00, 1·08	0·08
Model 4§	1·00	0·98, 1·02	1·0	1·03	0·99, 1·08	1·01	0·97, 1·06	0·76
Yogurt	Serving (150 g)							
Median	34		0	23		69		
Total *n*/cases	110 781/25 549		45 770/10 587	27 357/5896		37 654/9066		
Crude model	1·10	1·05, 1·15	1·0	0·91	0·88, 0·95	1·05	1·02, 1·09	<0·0001
Model 1*	0·90	0·86, 0·95	1·0	1·01	0·97, 1·05	0·95	0·92, 0·99	0·003
Model 2†	0·94	0·89, 0·99	1·0	1·03	0·99, 1·07	0·98	0·95, 1·02	0·21
Model 3‡	0·96	0·91, 1·01	1·0	1·02	0·98, 1·07	0·99	0·95, 1·02	0·38
Model 4§	0·98	0·93, 1·03	1·0	1·00	0·96, 1·04	0·99	0·96, 1·03	0·76

Table 3. *Continued*

	Continuous		Tertiles of dairy product intake					
				T2		T3		
	OR	95 % CI	T1	OR	95 % CI	OR	95 % CI	$P_{for\ trend}$
Buttermilk	Serving (150 g)							
Median	1		0	1		71		
Total *n*/cases	110 781/25 549		36 833/7988	36 483/7866		37 465/9695		
Crude model	1·20	1·16, 1·23	1·0	0·99	0·96, 1·03	1·26	1·22, 1·30	<0·0001
Model 1*	0·94	0·91, 0·96	1·0	0·87	0·83, 0·90	0·89	0·85, 0·92	0·005
Model 2†	0·96	0·93, 0·99	1·0	0·86	0·82, 0·90	0·91	0·87, 0·95	0·39
Model 3‡	0·97	0·94, 1·00	1·0	0·99	0·94, 1·04	1·00	0·96, 1·04	0·80
Model 4§	0·97	0·94, 1·00	1·0	0·99	0·94, 1·04	0·99	0·95, 1·04	0·83
Curd cheese	Serving (150 g)							
Median	1		0	1		29		
Total *n*/cases	110 781/25 549		36 598/8657	36 406/8115		37 777/8777		
Crude model	1·00	0·93, 1·09	1·0	0·93	0·89, 0·96	0·98	0·94, 1·01	0·40
Model 1*	0·89	0·81, 0·97	1·0	0·89	0·85, 0·92	0·92	0·89, 0·96	0·16
Model 2†	0·92	0·84, 1·00	1·0	0·88	0·84, 0·91	0·93	0·89, 0·96	0·43
Model 3‡	0·93	0·85, 1·02	1·0	0·97	0·93, 1·02	0·97	0·93, 1·01	0·39
Model 4§	0·94	0·86, 1·04	1·0	0·97	0·93, 1·01	0·97	0·94, 1·02	0·52
Custard	Serving (150 g)							
Median	3		0	3		26		
Total *n*/cases	110 781/25 549		36 649/8214	36 379/8311		37 753/9024		
Crude model	1·38	1·28, 1·49	1·0	1·03	0·99, 1·06	1·09	1·05, 1·13	<0·0001
Model 1*	1·13	1·03, 1·22	1·0	0·90	0·87, 0·94	0·98	0·95, 1·02	0·14
Model 2†	1·08	0·99, 1·18	1·0	0·90	0·86, 0·94	0·96	0·92, 1·00	0·85
Model 3‡	1·05	0·96, 1·15	1·0	1·01	0·96, 1·06	1·01	0·97, 1·05	0·84
Model 4§	1·13	1·03, 1·24	1·0	1·01	0·97, 1·06	1·05	1·01, 1·10	0·008
Flavoured yogurt drinks	Serving (150 g)							
Median	8		0	7		63		
Total *n*/cases	110 781/25 549		36 441/9357	36 367/8670		37 973/7522		
Crude model	0·85	0·82, 0·87	1·0	0·91	0·88, 0·94	0·72	0·69, 0·74	<0·0001
Model 1*	1·01	0·97, 1·04	1·0	0·90	0·87, 0·94	0·97	0·93, 1·00	0·73
Model 2†	1·00	0·96, 1·03	1·0	0·90	0·86, 0·93	0·95	0·91, 0·99	0·72
Model 3‡	0·99	0·95, 1·02	1·0	0·99	0·94, 1·03	0·99	0·95, 1·03	0·78
Model 4§	0·97	0·93, 1·00	1·0	0·98	0·49, 1·03	0·96	0·93, 1·01	0·10
Total cheese	Serving (20 g)							
Median	26		10	26		50		
Total *n*/cases	110 781/25 549		36 820/7189	36 544/8418		37 417/9942		
Crude model	1·12	1·11, 1·13	1·0	1·23	1·19, 1·28	1·49	1·44, 1·54	<0·0001
Model 1*	1·00	0·99, 1·01	1·0	0·96	0·93, 1·00	0·98	0·95, 1·02	0·63
Model 2†	1·01	1·00, 1·02	1·0	0·98	0·94, 1·02	1·01	0·97, 1·05	0·59
Model 3‡	1·01	0·99, 1·02	1·0	1·02	0·98, 1·06	1·02	0·98, 1·06	0·34
Model 4§	1·00	0·99, 1·01	1·0	1·00	0·96, 1·04	1·00	0·96, 1·05	0·88
Dutch cheese	Serving (20 g)							
Median	18		5	18		39		
Total *n*/cases	110 781/25 549		36 871/7153	36 534/8505		37 376/9891		
Crude model	1·14	1·13, 1·16	1·0	1·26	1·22, 1·31	1·50	1·44, 1·55	<0·0001
Model 1*	1·00	0·99, 1·02	1·0	0·97	0·93, 1·01	0·98	0·94, 1·02	0·39
Model 2†	1·00	0·98, 1·01	1·0	0·98	0·94, 1·02	0·97	0·93, 1·01	0·16
Model 3‡	0·99	0·98, 1·01	1·0	1·01	0·97, 1·06	0·98	0·94, 1·02	0·20
Model 4§	0·99	0·98, 1·01	1·0	1·00	0·96, 1·05	0·97	0·93, 1·01	0·11

T, tertile.
* Model 1 was adjusted for age (years, continuous) and sex (men/women).
† Model 2 was adjusted for age (years, continuous), sex (men/women), alcohol (categorical), smoking (categorical), education (categorical) and physical activity (moderate intensity exercise, d/week).
‡ Model 3 was adjusted for age (years, continuous), sex (men/women), alcohol (categorical), smoking (categorical), education (categorical), physical activity (moderate intensity exercise, d/week), total energy intake (kJ/d, continuous) and the intake of energy-adjusted bread, pasta, rice, potato, fruit, vegetables, legumes, meat, fish, coffee, tea, soda/fruit juice and other dairy product groups (g/d, continuous).
§ Model 4 was adjusted for age (years, continuous), sex (men/women), alcohol (categorical), smoking (categorical), education (categorical), physical activity (moderate intensity exercise, d/week), total energy intake (kJ/d, continuous), the intake of energy-adjusted bread, pasta, rice, potato, fruit, vegetables, legumes, meat, fish, coffee, tea, soda/fruit juice, other dairy product groups (g/d, continuous), BMI (kg/m^2, continuous) and waist circumference (cm, continuous).

modulation of the hepatic fat content, expression of PPAR-γ and PPAR-α, and inflammatory state[44].

Our analyses on the product level showed an inverse association for buttermilk with pre-diabetes and a positive association for custard intake and pre-diabetes; no associations were observed for milk, yogurt, curd cheese, flavoured yogurt drinks or cheese intake. Milk consumption, particularly skimmed milk, was positively associated with ND-T2DM, whereas

Table 4. Associations of milk, yogurt and cheese classified on the basis of fat content with pre-diabetes (PD) (fasting plasma glucose (FPG) 5·6–6·9 mmol/l or HbA1c 5·7–6·4 %) (*n* 110 781) and newly diagnosed type 2 diabetes (ND-T2DM) (FPG ≥ 7·0 mmol/l) (*n* 112 086) in Lifelines*
(Odds ratios and 95 % confidence intervals)

	Continuous		Tertiles of dairy product intake					
				T2		T3		
	OR	95 % CI	T1	OR	95 % CI	OR	95 % CI	$P_{for\ trend}$
Skimmed milk	Serving (150 g)							
Median	1		0·74	0·95		1·30		
Total *n*/PD	110 781/25 549		36 394/8356	36 566/8474		37 821/8719		
Fully adjusted OR	1·00	0·95, 1·06	1·0	1·04	0·99, 1·09	1·06	0·99, 1·13	0·12
Total *n*/ND-T2DM	112 086/1305		36 812/418	37 005/439		38 269/448		
Fully adjusted OR	1·21	1·04, 1·41	1·0	1·06	0·89, 1·25	1·17	0·94, 1·47	0·15
Semi-skimmed milk	Serving (150 g)							
Median	39		1	38		177		
Total *n*/PD	110 781/25 549		36 560/8678	36 639/8262		37 582/8609		
Fully adjusted OR	1·00	0·98, 1·02	1·0	1·00	0·96, 1·05	0·99	0·95, 1·03	0·58
Total *n*/ND-T2DM	112 086/1305		37 015/455	37 025/386		38 046/464		
Fully adjusted OR	1·05	0·98, 1·13	1·0	0·90	0·78, 1·05	0·99	0·86, 1·14	0·75
Full-fat milk	Serving (150 g)							
Median	10		0	10		39		
Total *n*/PD	110 781/25 549		36 735/7680	36 568/7926		37 478/9943		
Fully adjusted OR	1·03	0·99, 1·08	1·0	1·00	0·95, 1·04	1·07	1·02, 1·11	<0·0001
Total *n*/ND-T2DM	112 086/1305		37 142/407	36 979/411		37 965/487		
Fully adjusted OR	0·98	0·82, 1·17	1·0	1·02	0·87, 1·20	0·98	0·84, 1·14	0·69
Skimmed yogurt	Serving (150 g)							
Median	2		0	2		54		
Total *n*/PD	110 781/25 549		36 406/8604	36 767/8197		37 608/8748		
Fully adjusted OR	0·95	0·90, 1·00	1·0	1·00	0·95, 1·05	0·97	0·93, 1·01	0·10
Total *n*/ND-T2DM	112 086/1305		36 858/452	37 194/427		38 034/426		
Fully adjusted OR	1·06	0·86, 1·30	1·0	1·04	0·89, 1·23	0·99	0·86, 1·15	0·68
Full-fat yogurt	Serving (150 g)							
Median	2		0	2		14		
Total *n*/PD	110 781/25 549		36 681/8240	36 390/8390		37 710/8919		
Fully adjusted OR	1·09	0·99, 1·19	1·0	1·04	0·99, 1·09	1·07	1·02, 1·12	0·02
Total *n*/ND-T2DM	112 086/1305		37 113/432	36 838/448		38 135/425		
Fully adjusted OR	0·89	0·61, 1·30	1·0	0·95	0·80, 1·14	1·03	0·86, 1·23	0·40
Low-fat cheese	Serving (20 g)							
Median	1		0·70	1·22		14·93		
Total *n*/PD	110 781/25 549		36 848/8400	36 700/7907		37 233/9242		
Fully adjusted OR	0·97	0·95, 0·99	1·0	1·00	0·96, 1·05	0·96	0·92, 1·00	0·02
Total *n*/ND-T2DM	112 086/1305		37 276/428	37 061/361		37 749/516		
Fully adjusted OR	1·03	0·96, 1·11	1·0	0·85	0·71, 1·01	1·03	0·88, 1·19	0·08
Regular-fat cheese	Serving (20 g)							
Median	11		2	11		31		
Total *n*/PD	110 781/25 549		36 523/7957	36 576/7915		37 682/9677		
Fully adjusted OR	1·01	0·99, 1·03	1·0	1·00	0·96, 1·04	1·01	0·97, 1·05	0·48
Total *n*/ND-T2DM	112 086/1305		36 930/407	36 965/389		38 191/509		
Fully adjusted OR	1·01	0·95, 1·07	1·0	1·00	0·86, 1·17	1·05	0·91, 1·21	0·44

T, tertile.
* The fully adjusted OR was adjusted for age (years, continuous), sex (men/women), alcohol (categorical), smoking (categorical), education (categorical), physical activity (moderate intensity exercise, d/week), total energy intake (kJ/d, continuous), the intake of energy-adjusted bread, pasta, rice, potato, fruit, vegetables, legumes, meat, fish, coffee, tea, soda/fruit juice, other dairy product groups (g/d, continuous), BMI (kg/m^2, continuous) and waist circumference (cm, continuous).

none of the other dairy products were associated with ND-T2DM. Evaluation of the literature with respect to the different dairy product groups shows that our null findings for milk in relation to pre-diabetes are in line with several other observational studies[7,12,15,21,22,24], but in contrast to two observational studies in Asian populations, with relatively low milk intakes, showing inverse associations[25,27]. None of the other studies observed a positive association between milk consumption and T2DM. Moreover, a recent meta-analysis including 11 studies did not show a significant link between milk intake and T2DM risk either (RR 0·97 per 200 g/d; 95 % CI 0·93, 1·02; $P = 0·25$)[31]. Although we observed significant associations of higher fermented dairy product and buttermilk intakes and a lower odds of pre-diabetes, we did not observe associations between yogurt, curd cheese or flavoured yogurt drinks and T2DM or pre-diabetes. However, full-fat yogurt was positively associated with pre-diabetes. Other cohort studies that investigated associations between the intake of yogurt and T2DM showed varying results, ranging from no association[11,14,21,22], borderline non-significant inverse associations[7,11,15] to significant inverse associations[11,17,19]. In contrast to our findings, meta-analysis of eleven studies does suggest a significant inverse association between yogurt intake and risk of T2DM (RR for 80 g/d: 0·86 compared with 0 g/d; 95 % CI 0·83, 0·90;

British Journal of Nutrition

Table 5. Associations between dairy product consumption and newly diagnosed type 2 diabetes (fasting plasma glucose (FPG) ≥ 7·0 mmol/l) in Lifelines (*n* 112 086)
(Odds ratios and 95 % confidence intervals)

	Continuous		Tertiles of dairy product intake					
			T1	T2		T3		
	OR	95 % CI		OR	95 % CI	OR	95 % CI	$P_{for\ trend}$
Total dairy products	100 g							
Median	324		173	318		500		
Total *n*/cases	112 086/1305		34 716/364	39 063/444		38 307/497		
Crude model	1·05	1·02, 1·08	1·0	1·09	0·94, 1·25	1·24	1·08, 1·42	0·002
Model 1*	1·01	0·98, 1·04	1·0	0·90	0·78, 1·04	0·99	0·86, 1·13	0·92
Model 2†	1·02	0·99, 1·05	1·0	0·91	0·79, 1·06	1·03	0·89, 1·19	0·53
Model 3‡	1·03	1·00, 1·07	1·0	0·96	0·83, 1·12	1·11	0·95, 1·29	0·12
Model 4§	1·03	1·00, 1·06	1·0	0·98	0·84, 1·14	1·10	0·94, 1·28	0·16
Skimmed dairy products	100 g							
Median	54		3	53		172		
Total *n*/cases	112 086/1305		36 977/445	37 107/395		38 002/465		
Crude model	1·03	0·98, 1·08	1·0	0·88	0·77, 1·01	1·02	0·89, 1·16	0·44
Model 1*	0·98	0·93, 1·03	1·0	1·01	0·88, 1·15	0·94	0·82, 1·07	0·30
Model 2†	1·00	0·96, 1·06	1·0	1·03	0·89, 1·18	1··00	0·87, 1·15	0·93
Model 3‡	1·03	0·98, 1·09	1·0	1·06	0·92, 1·23	1·08	0·94, 1·24	0·35
Model 4§	1·03	0·98, 1·09	1·0	1·02	0·88, 1·18	1·08	0·93, 1·24	0·30
Semi-skimmed dairy products	100 g							
Median	50		5	49		187		
Total *n*/cases	112 086/1305		37 126/426	36 951/411		38 009/468		
Crude model	1·05	1·01, 1·09	1·0	0·97	0·85, 1·11	1·07	0·94, 1·23	0·18
Model 1*	1·06	1·02, 1·11	1·0	0·98	0·85, 1·13	1·08	0·94, 1·23	0·17
Model 2†	1·05	1·01, 1·10	1·0	0·99	0·86, 1·15	1·07	0·93, 1·23	0·30
Model 3‡	1·06	1·02, 1·11	1·0	1·03	0·88, 1·19	1·11	0·96, 1·28	0·15
Model 4§	1·04	0·99, 1·09	1·0	1·01	0·87, 1·17	1·05	0·90, 1·21	0·52
Full-fat dairy products	100 g							
Median	59		26	59		114		
Total *n*/cases	112 086/1305		37 005/349	37 016/458		38 065/498		
Crude model	1·11	1·05, 1·19	1·0	1·32	1·14, 1·51	1·39	1·21, 1·60	<0·0001
Model 1*	1·02	0·95, 1·10	1·0	1·15	1·00, 1·33	1·11	0·96, 1·27	0·29
Model 2†	1·00	0·93, 1·08	1·0	1·14	0·98, 1·32	1·07	0·92, 1·23	0·63
Model 3‡	1·02	0·95, 1·11	1·0	1·17	1·01, 1·36	1·12	0·97, 1·31	0·27
Model 4§	1·04	0·96, 1·13	1·0	1·18	1·01, 1·37	1·16	0·99, 1·35	0·13
Fermented dairy products	100 g							
Median	121		45	120		247		
Total *n*/cases	112 086/1305		37 061/450	37 010/401		38 015/454		
Crude model	1·02	0·97, 1·06	1·0	0·89	0·78, 1·02	0·98	0·86, 1·12	0·98
Model 1*	0·95	0·91, 1·00	1·0	0·85	0·74, 0·97	0·82	0·71, 0·93	0·006
Model 2†	0·98	0·94, 1·03	1·0	0·87	0·76, 1·01	0·89	0·77, 1·02	0·14
Model 3‡	1·01	0·97, 1·06	1·0	0·92	0·80, 1·07	0·97	0·84, 1·13	0·85
Model 4§	1·02	0·97, 1·07	1·0	0·93	0·81, 1·08	1·00	0·86, 1·15	0·92
Non-fermented dairy products	100 g							
Median	126		40	125		284		
Total *n*/cases	112 086/1305		37 074/396	37 012/410		38 000/499		
Crude model	1·07	1·03, 1·10	1·0	1·04	0·90, 1·19	1·23	1·08, 1·41	0·001
Model 1*	1·06	1·02, 1·10	1·0	1·00	0·87, 1·15	1·16	1·01, 1·32	0·02
Model 2†	1·05	1·02, 1·09	1·0	0·96	0·83, 1·11	1·10	0·96, 1·27	0·10
Model 3‡	1·06	1·02, 1·10	1·0	0·98	0·85, 1·14	1·14	0·98, 1·31	0·05
Model 4§	1·05	1·01, 1·09	1·0	0·97	0·84, 1·13	1·10	0·95, 1·27	0·13
Milk	Serving (150 g)							
Median	103		25	101		261		
Total *n*/cases	112 086/1305		37 084/408	37 011/401		37 991/496		
Crude model	1·10	1·04, 1·15	1·0	0·99	0·86, 1·13	1·19	1·04, 1·36	0·003
Model 1*	1·10	1·05, 1·16	1·0	0·98	0·86, 1·13	1·16	1·02, 1·33	0·01
Model 2†	1·09	1·03, 1·15	1·0	0·95	0·82, 1·09	1·11	0·97, 1·27	0·07
Model 3‡	1·11	1·05, 1·18	1·0	0·97	0·84, 1·13	1·15	1·00, 1·33	0·02
Model 4§	1·08	1·02, 1·15	1·0	0·97	0·84, 1·13	1·10	0·95, 1·27	0·11
Yogurt	Serving (150 g)							
Median	17		0	23		69		
Total *n*/cases	112 086/1305		46 351/581	27 667/310		38 068/414		
Crude model	0·92	0·77, 1·11	1·0	0·89	0·78, 1·03	0·87	0·76, 0·98	0·03
Model 1*	0·80	0·66, 0·96	1·0	1·04	0·90, 1·20	0·82	0·72, 0·94	0·002
Model 2†	0·86	0·71, 1·04	1·0	1·07	0·92, 1·24	0·88	0·77, 1·00	0·04
Model 3‡	0·94	0·78, 1·14	1·0	1·06	0·92, 1·23	0·93	0·81, 1·06	0·22
Model 4§	1·02	0·84, 1·23	1·0	1·02	0·88, 1·18	0·97	0·84, 1·11	0·59

Table 5. *Continued*

	Continuous		Tertiles of dairy product intake					
			T1	T2		T3		
	OR	95 % CI		OR	95 % CI	OR	95 % CI	$P_{for\ trend}$
Buttermilk	Serving (150 g)							
Median	1		0	1		71		
Total *n*/cases	112 086/1305		37 244/411	36 896/413		37 946/481		
Crude model	1·11	1·00, 1·22	1·0	1·02	0·88, 1·16	1·15	1·01, 1·31	0·02
Model 1*	0·89	0·80, 0·99	1·0	0·96	0·83, 1·11	0·88	0·76, 1·01	0·07
Model 2†	0·95	0·85, 1·06	1·0	0·97	0·83, 1·13	0·95	0·82, 1·10	0·61
Model 3‡	1·01	0·90, 1·13	1·0	0·99	0·82, 1·19	1·03	0·88, 1·20	0·58
Model 4§	1·02	0·91, 1·14	1·0	1·00	0·83, 1·21	1·03	0·88, 1·21	0·67
Curd cheese	Serving (150 g)							
Median	1		0	1		29		
Total *n*/cases	112 086/1305		37 048/450	36 864/458		38 174/397		
Crude model	0·70	0·49, 1·00	1·0	1·02	0·90, 1·17	0·86	0·75, 0·98	0·006
Model 1*	0·70	0·49, 1·00	1·0	1·08	0·94, 1·24	0·89	0·78, 1·03	0·01
Model 2†	0·83	0·58, 1·18	1·0	1·10	0·95, 1·27	0·98	0·84, 1·13	0·28
Model 3‡	0·90	0·63, 1·29	1·0	1·11	0·95, 1·31	1·01	0·87, 1·18	0·55
Model 4§	0·95	0·66, 1·36	1·0	1·11	0·95, 1·31	1·04	0·89, 1·21	0·80
Custard	Serving (150 g)							
Median	3		0	3		26		
Total *n*/cases	112 086/1305		37 076/427	36 813/434		38 197/444		
Crude model	1·05	0·76, 1·44	1·0	1·02	0·90, 1·17	1·01	0·88, 1·15	0·99
Model 1*	0·79	0·67, 1·09	1·0	0·97	0·84, 1·12	0·95	0·83, 1·09	0·50
Model 2†	0·78	0·55, 1·09	1·0	0·98	0·85, 1·14	0·95	0·82, 1·09	0·47
Model 3‡	0·78	0·55, 1·10	1·0	0·99	0·83, 1·17	0·95	0·82, 1·10	0·45
Model 4§	0·93	0·66, 1·30	1·0	1·01	0·85, 1·20	1·06	0·91, 1·24	0·40
Flavoured yogurt drinks	Serving (150 g)							
Median	8		0	7		63		
Total *n*/cases	112 086/1305		36 933/492	36 809/442		38 344/371		
Crude model	0·88	0·77, 1·01	1·0	0·90	0·79, 1·02	0·72	0·63, 0·83	<0·0001
Model 1*	1·07	0·95, 1·20	1·0	0·97	0·85, 1·11	1·05	0·91, 1·21	0·33
Model 2†	1·05	0·93, 1·19	1·0	0·98	0·85, 1·13	1·03	0·89, 1·20	0·54
Model 3‡	1·05	0·93, 1·20	1·0	0·99	0·84, 1·16	1·04	0·89, 1·21	0·53
Model 4§	1·02	0·90, 1·16	1·0	1·01	0·86, 1·19	1·02	0·88, 1·19	0·80
Total cheese	Serving (20 g)							
Median	26		10	26		50		
Total *n*/cases	112 086/1305		37 170/350	36 968/424		37 948/531		
Crude model	1·12	1·08, 1·16	1·0	1·22	1·06, 1·41	1·49	1·30, 1·71	<0·0001
Model 1*	1·02	0·97, 1·06	1·0	0·98	0·85, 1·14	1·01	0·88, 1·17	0·77
Model 2†	1·02	0·98, 1·07	1·0	1·03	0·88, 1·19	1·08	0·93, 1·25	0·28
Model 3‡	1·04	1·00, 1·09	1·0	1·08	0·93, 1·26	1·15	0·99, 1·34	0·07
Model 4§	1·03	0·99, 1·08	1·0	1·04	0·89, 1·22	1·10	0·95, 1·28	0·21
Dutch cheese	Serving (20 g)							
Median	18		5	18		39		
Total *n*/cases	112 086/1305		37 192/321	37 000/466		37 894/518		
Crude model	1·15	1·10, 1·20	1·0	1·47	1·27, 1·69	1·59	1·38, 1·83	<0·0001
Model 1*	1·02	0·97, 1·07	1·0	1·15	1·00, 1·34	1·05	0·91, 1·22	0·87
Model 2†	1·01	0·96, 1·06	1·0	1·20	1·03, 1·39	1·07	0·92, 1·25	0·81
Model 3‡	1·02	0·97, 1·08	1·0	1·26	1·08, 1·47	1·14	0·98, 1·33	0·35
Model 4§	1·02	0·97, 1·07	1·0	1·23	1·06, 1·44	1·11	0·95, 1·30	0·49

T, tertile.
* Model 1 was adjusted for age (years, continuous) and sex (men/women).
† Model 2 was adjusted for age (years, continuous), sex (men/women), alcohol (categorical), smoking (categorical), education (categorical) and physical activity (moderate intensity exercise, d/week).
‡ Model 3 was adjusted for age (years, continuous), sex (men/women), alcohol (categorical), smoking (categorical), education (categorical), physical activity (moderate intensity exercise, d/week), total energy intake (kJ/d, continuous) and the intake of energy-adjusted bread, pasta, rice, potato, fruit, vegetables, legumes, meat, fish, coffee, tea, soda/fruit juice and other dairy product groups (g/d, continuous).
§ Model 4 was adjusted for age (years, continuous), sex (men/women), alcohol (categorical), smoking (categorical), education (categorical), physical activity (moderate intensity exercise, d/week), total energy intake (kJ/d, continuous), the intake of energy-adjusted bread, pasta, rice, potato, fruit, vegetables, legumes, meat, fish, coffee, tea, soda/fruit juice, other dairy product groups (g/d, continuous), BMI (kg/m^2, continuous) and waist circumference (cm, continuous).

$P < 0·0001$)[31]. Finally, in line with our findings on total cheese intake, most other studies exploring the association between cheese intake and the development of T2DM, although not all[7,11], do not point towards an association[11,14,15,21,22,24]. In line, a recent meta-analyses by Gijsbers and colleagues (2016) did not detect a significant relationship for this dairy product and incident T2DM (*n* 12, RR 1·00 per 10 g/d)[31]. However, our analyses did show a significant inverse association for low-fat cheese and pre-diabetes. Conversely, our data did not indicate that the association between Dutch cheese and glucose homoeostasis is any different from the impact of total cheese.

It may be noted that, in contrast to the suggested favourable effect of trans-ruminant fatty acids on glucose homoeostasis[44], our data showed positive associations for full-fat dairy products as a whole, as well as various full-fat dairy products. We do not have a clear-cut explanation for the positive associations as observed in our study other than that full-fat dairy products have a higher energy content and hence may contribute to weight gain and as such glucose intolerance. On the contrary, adding BMI did not change the associations, which does not support this speculation on energy content. In addition, the positive association for full-fat dairy products with pre-diabetes in this population was predominantly driven by the subgroups with the lowest fat content within this full-fat dairy product subclass – that is full-fat milk (3·5 g fat) (fully adjusted OR per serving (150 g): 1·03, 95 % CI 0·99, 1·08), full-fat yogurt (2·9 g fat) (fully adjusted OR per serving (150 g) 1·09; 95 % CI 0·99, 1·19) and milk-based ice cream (12 g fat) (fully adjusted OR per serving (75 g) 1·31; 95 % CI 1·16, 1·48), whereas associations for the three food groups with the highest fat content within this full-fat dairy product subclass – that is cream (35 g fat) (fully adjusted OR per serving (30 g) 1·17; 95 % CI 0·94, 1·44), regular-fat cheese (≥24 g fat) (fully adjusted OR per serving (20 g) 1·01; 95 % CI 0·99, 1·03) and chocolate milk (1·9 g fat) (fully adjusted OR per serving (150 g) 0·98; 95 % CI 0·91, 1·06) – with pre-diabetes were less pronounced or even absent. These findings stress the confusing aspect of dairy food categorisation based on 'fat content' in association with diabetes-related outcomes and call for future studies investigating the impact of dairy products in even more detail (i.e. individual dairy products).

In addition to above summarised studies, our findings display important resemblances with the recently published cross-sectional (Dutch) Maastricht Study with data of 2391 participants[45], which also showed significant inverse associations of skimmed dairy products (OR^{T3} 0·73; 95 % CI 0·55, 0·96) and fermented dairy products (OR^{T3} 0·74; 95 % CI 0·54, 0·99) with impaired glucose metabolism, whereas no associations for skimmed dairy products and fermented dairy products were observed for ND-T2DM. Moreover, in line with our findings, the Maastricht study also showed a positive association between full-fat dairy product (OR^{T3} 2·01; 95 % CI 1·16, 3·47) consumption and ND-T2DM. In contrast to the Maastricht Study, we did not observe a significant inverse association between total dairy product consumption and ND-T2DM. Even with the important resemblances, it needs to be noted that the associations observed in the Maastricht Study are substantially stronger than the associations observed in the Lifelines population. Although we do not have a straightforward explanation for this difference, the cut-offs for the lowest tertiles in the Maastricht Study are markedly lower than the cut-offs in our study, which may partly explain the difference in strength of the associations. Another explanation may be that the Maastricht Study was conducted among adults between 40 and 75 years of age, while we included men and women aged 18 years and over. As suggested by the meta-analysis of Gijsbers *et al.*[31], associations between dairy product intake and glucose homoeostasis tend to be stronger in older populations. Then again, we did not observe consistent interactions between markers of glucose homoeostasis and age. Moreover, dairy product intake was not associated with any dairy product subclass in older Dutch adults aged ≥55 years participating in the Rotterdam study[28]. Finally, we do not have a direct explanation for the different findings for pre-diabetes and ND-T2DM as shown in these two studies. It may be postulated that the null associations for ND-T2DM are related to the low number of ND-T2DM cases and hence reflect a power issue. This idea is strengthened by the fact that Lifelines data do show significant associations for non-fermented dairy products (5 % higher odds of ND-T2DM per 100 g) and milk (8 % higher odds of ND-T2DM per serving/150 g) with ND-T2DM when analysed continuously.

A limitation of this study is that we only had cross-sectional data. Therefore, it may be that it was not dairy product consumption that affected glucose homoeostasis, but that people with impaired glucose homoeostasis made other decisions regarding their dietary behaviours and hence their dairy product intake. However, as we had the possibility to study pre-diabetes and ND-T2DM defined based on aetiologic markers rather than self-report, where all self-reported diabetics were excluded to prevent the introduction of reverse causation, we feel that we successfully prevented the introduction of reverse causation. Specifically, analyses on dairy product intake and self-report T2DM within this study showed clear patterns of reverse causation, including a positive association between semi-skimmed dairy products and self-reported T2DM and inverse associations of full-fat dairy products and custard with self-reported T2DM (data not shown), whereas our analyses using the aetiologic markers to define pre-diabetes/T2DM did not. Important advantages of the current analyses include the detailed inquiry of dairy product intake (i.e. ranging from the intake of skimmed dairy products to full-fat dairy products, non-fermented to fermented dairy products and milk to flavoured yogurt drinks), the relatively large range in dairy product intake, its huge sample size ($n \geq 100\,000$) and the possibility to conduct well-powered stratified analyses for age (<50, 50–65 and ≥65 years), sex and BMI (<25, 25–30, ≥30 kg/m^2). Moreover, the dairy product intake in this population was very comparable to the dairy product intake as estimated in the most recent Dutch Food Consumption Survey (i.e. 355 g/d)[46], suggesting that the Lifelines population is a representative sample with respect to Dutch dairy product intakes. Finally, we had the possibility to include many potential covariates, including all other major food groups, while retaining sufficient power.

In conclusion, these detailed cross-sectional data on dairy products intake within the Lifelines Cohort Study showed inverse associations of skimmed dairy products, fermented dairy products and buttermilk with pre-diabetes. Moreover, positive associations were observed for full-fat dairy products, non-fermented dairy products and custard, and pre-diabetes. Finally, full-fat dairy products, non-fermented dairy products and milk were positively associated with ND-T2DM. On the basis of our results, it may be speculated that the aspect of fermentation is important to determine whether dairy products is beneficial for diabetes prevention or increases the risk. Future prospective analyses, focusing on a wide range of dairy products, within Lifelines, as well as other mega-cohorts, are wanted to verify the findings of the current study.

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The authors declare that there are no conflicts of interest.

Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114517003762

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