Association of dairy intake with cardiovascular disease and mortality in 21 countries from five continents (PURE): a prospective cohort study

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Summary

Background Dietary guidelines recommend minimising consumption of whole-fat dairy products, as they are a source of saturated fats and presumed to adversely affect blood lipids and increase cardiovascular disease and mortality. Evidence for this contention is sparse and few data for the effects of dairy consumption on health are available from low-income and middle-income countries. Therefore, we aimed to assess the associations between total dairy and specific types of dairy products with mortality and major cardiovascular disease.

Methods The Prospective Urban Rural Epidemiology (PURE) study is a large multinational cohort study of individuals aged 35–70 years enrolled from 21 countries in five continents. Dietary intakes of dairy products for 136 384 individuals were recorded using country-specific validated food frequency questionnaires. Dairy products comprised milk, yoghurt, and cheese. We further grouped these foods into whole-fat and low-fat dairy. The primary outcome was the composite of mortality or major cardiovascular events (defined as death from cardiovascular causes, non-fatal myocardial infarction, stroke, or heart failure). Hazard ratios (HRs) were calculated using multivariable Cox frailty models with random intercepts to account for clustering of participants by centre.

Findings Between Jan 1, 2003, and July 14, 2018, we recorded 10 567 composite events (deaths [n=6796] or major cardiovascular events [n=5855]) during the 9·1 years of follow-up. Higher intake of total dairy (>2 servings per day compared with no intake) was associated with a lower risk of the composite outcome (HR 0·84, 95% CI 0·75–0·94; p_{trend}=0·0004), total mortality (0·83, 0·72–0·96; p_{trend}=0·0052), non-cardiovascular mortality (0·86, 0·72–1·02; p_{trend}=0·046), cardiovascular mortality (0·77, 0·58–1·01; p_{trend}=0·029), major cardiovascular disease (0·78, 0·67–0·90; p_{trend}=0·0001), and stroke (0·66, 0·53–0·82; p_{trend}=0·0003). No significant association with myocardial infarction was observed (HR 0·89, 95% CI 0·71–1·11; p_{trend}=0·163). Higher intake (>1 serving *vs* no intake) of milk (HR 0·90, 95% CI 0·82–0·99; p_{trend}=0·0529) and yogurt (0·86, 0·75–0·99; p_{trend}=0·0051) was associated with lower risk of the composite outcome, whereas cheese intake was not significantly associated with the composite outcome (0·88, 0·76–1·02; p_{trend}=0·1399). Butter intake was low and was not significantly associated with clinical outcomes (HR 1·09, 95% CI 0·90–1·33; p_{trend}=0·4113).

Interpretation Dairy consumption was associated with lower risk of mortality and major cardiovascular disease events in a diverse multinational cohort.

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Introduction

Cardiovascular disease is the leading cause of mortality worldwide,[1] with 80% of the burden in low-income and middle-income countries. Dairy products are a major source of saturated fats, which have been presumed to adversely affect blood lipids and increase cardiovascular disease and mortality. Using this framework, dietary guidelines recommend minimising consumption of whole-fat dairy products for cardiovascular disease prevention in populations.[2] However, dairy products and dairy fat also contain potentially beneficial compounds—including specific aminoacids, medium-chain and odd-chain saturated fats, milk fat globule phospholipids, unsaturated and branched-chain fats, natural trans fats, vitamin K1 and K2, and calcium—and can contain probiotics, many of which might also affect health outcomes.[3] Therefore, the net effect of dairy intake on health outcomes might not be reliably informed solely

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Research in context

Evidence before this study

Dietary guidelines recommend restricting the consumption of whole-fat dairy products based on concerns about an adverse effect on blood lipids. We systematically searched PubMed for relevant articles on dairy consumption published between Jan 1, 1970, and April 1, 2018, restricted to the English language using the search terms "total dairy", "milk", "yoghurt", "yogurt", "cheese", "cream", "butter", "low fat dairy", "whole fat dairy", "high fat dairy", "mortality", and "cardiovascular disease". Studies that evaluated association of dairy or dairy products and mortality and cardiovascular disease were considered. Most data are from Europe and North America and have yielded conflicting results, perhaps because of their relatively small sizes and few events.

Added value of this study

We studied 136 384 individuals from 21 countries in whom 10 567 events were recorded. Consistent with the meta-analysis of observational studies and randomised trials, but in contrast to current dietary guidelines, we found that greater dairy consumption was associated with lower risk of mortality and cardiovascular disease.

Implications of all the available evidence

In the context of all other related studies, findings from the Prospective Urban Rural Epidemiology (PURE) study indicate that consumption of dairy products should not be discouraged and perhaps even be encouraged in low-income and middle-income countries where dairy consumption is low.

from its effect on a single risk marker (ie, LDL cholesterol) or fatty acids.

Dairy products are a diverse food group, some are non-fermented (eg, milk) and others are fermented (eg, yoghurt and cheese), and these different foods could have varying effect on cardiovascular diseases and mortality. For example, a meta-analysis of cohort studies suggested a lower risk of hypertension with increasing milk consumption,[4] with a neutral effect on cardiovascular disease.[5] Mendelian randomisation studies did not show that dairy may be associated with hypertension, although a reduction in blood pressure was associated with dairy intake in the Dietary Approaches to Stop Hypertension (DASH) trial.[5,6] Meta-analysis of 20 randomised trials showed a non-significant increase in LDL cholesterol with either higher intake of whole-fat dairy or low-fat dairy.[7] Another meta-analysis of small randomised trials showed that compared with tofu or fat-modified cheeses, cheese consumption increased LDL cholesterol concentration by a modest amount.[8] Butter is also weakly associated with total mortality but is not associated with cardiovascular disease.[9] However, other cohort studies have reported inconsistent results.[10] Furthermore, most studies have been done in North America and Europe, where dairy consumption and saturated fatty acids intake are much higher than in other regions of the world (eg, China, India, and Africa). In North America and Europe, coronary heart disease is more common than strokes, whereas strokes are more common than coronary heart disease in other regions such as east Asia and Africa. Therefore, data from all world regions are essential to making global policy recommendations.

The Prospective Urban Rural Epidemiology (PURE) study provides a unique opportunity to study the associations of dairy intake and types of dairy products with cardiovascular disease events and mortality in diverse settings. Our aim was to assess the associations between total dairy and specific types of dairy products with mortality and major cardiovascular disease.

Methods

Study design and participants

The design and methods of the PURE study have been described previously.[11,12] Briefly, the first and second phases of PURE included 136 384 individuals aged 35–70 years who had complete information about their diet. Participants came from 21 countries (Argentina, Bangladesh, Brazil, Canada, Chile, China, Colombia, India, Iran, Malaysia, occupied Palestinian territory, Pakistan, Philippines, Poland, South Africa, Saudi Arabia, Sweden, Tanzania, Turkey, United Arab Emirates, and Zimbabwe) and had completed at least one follow-up visit. The sampling and recruitment strategy used in PURE has been published previously[13] and is also described in the appendix (p 6). Data were collected at the community, household, and individual levels with standardised questionnaires. Standard case-report forms were used to record data for major cardiovascular events and mortality (classified by cause) during follow-up, which were adjudicated centrally in each country by trained physicians using common definitions (appendix pp 9–18) and supporting documents. For the current analysis, we included all outcome events until July 14, 2018. The study was coordinated by the Population Health Research Institute, Hamilton Health Sciences and McMaster University, Hamilton, ON, Canada.

Procedures

Each participant's habitual food intake was recorded using country-specific (region-specific in India) validated food frequency questionnaires (FFQs) at baseline. For countries where a validated FFQ was not available, we developed and validated FFQs using a standard method (appendix pp 19, 20). Participants were asked how often they had consumed specific foods or drinks on average in the past year, and a list of these food items was given. For almost all countries, FFQs had the same format and frequencies of consumption recorded, and these varied from never to more than six times per day. Standard serving sizes (such as a glass of milk, a cup of yoghurt, or a slice of cheese) were assigned to each food item. Because some participants might eat both whole-fat and low-fat dairy, separate questions were assigned for each type. To compute the daily food and nutrient intakes, the reported frequency of consumption for each food item was converted to daily intake and then was multiplied by the serving size. To convert food into nutrients, country-specific nutrient databases were constructed with information about 43 macronutrients and micronutrients. The nutrient databases are primarily based on the US Department of Agriculture food composition database (release 18 and 21), modified with reference to local food composition tables, and supplemented with recipes of local mixed dishes. However, for Canada, China, India, Malaysia, South Africa, Sweden, and Turkey, we used the nutrient databases that were used for validation of the FFQs.[14]

Dairy comprised milk, yoghurt, various types of cheese, yoghurt drink, and mixed dishes prepared with dairy. Mixed dishes prepared with dairy were disaggregated into their constituents and a proportional weight was assigned to each component. Then each component was included in the related dairy group. We further grouped these foods into whole-fat dairy (whole milk, whole-fat yoghurt, whole-fat cheese, whole-fat yoghurt drinks, and mixed dishes prepared with whole-fat dairy products) and low-fat dairy (low-fat milk, skimmed milk, low-fat yoghurt, low-fat cheese, and low-fat yoghurt drink). To make the unit of consumption consistent between countries, we used daily standard serving intake for each dairy product. Butter and cream were not included in the total dairy and whole-fat dairy groups. Butter intakes were not recorded as an item on the FFQ in China, Malaysia, Pakistan, and Sweden; therefore, the association between butter and outcomes was assessed only in those countries where butter intake was recorded.

Outcomes

The primary outcome was the composite of mortality or major cardiovascular events (defined as death from cardiovascular causes, non-fatal myocardial infarction, stroke, or heart failure). Other outcomes were total mortality and major cardiovascular disease (fatal and non-fatal myocardial infarction, fatal and non-fatal strokes, heart failure, and cardiovascular mortality). Details of definition of events and the process of adjudication have been published previously.[15]

Statistical analysis

Continuous variables were expressed as means (SD) and categorical variables as percentages. Education was categorised as none or primary school (first 6 years of age), secondary school (7–11 years of age), and college, trade school, or university (>11 years of age). Smoking status was categorised as never, former, or current. Physical activity was assessed using the International Physical Activity Questionnaire.[15] Physical activity was categorised based on the metabolic equivalent of task (MET) per min per week into low (<600 MET min per week), moderate (600–3000 MET min per week), and high (>3000 MET min per week) activity.[15] We categorised countries into seven geographical regions based on similarities in their patterns of food consumption. These regions were China, south Asia, Europe and North America, South America, the Middle East, southeast Asia, and Africa.

For the overall analysis of total dairy, participants were grouped into zero, less than one serving per day, one to two servings per day, and more than two servings per day of intake, and the lowest intake group was used as the reference group. Categories for milk, yoghurt, cheese, and butter consumption were zero, less than half a serving per day, half to one serving per day, and more than one serving per day. We used standard serving size for each dairy product—eg, a glass of milk and a cup of yoghurt was 244 g, one slice of cheese was 15 g, and a teaspoon of butter was 5 g. For analysis of saturated fats (g per day) and protein (g per day) from dairy sources, participants were categorised by quartiles of daily intake.

We calculated hazard ratios (HRs) using multivariable Cox frailty model with random intercepts to account for centre clustering, which also automatically adjusts for both region and country. Estimates of HRs and 95% CIs are presented for categories of total dairy and dairy products. All models were adjusted for age, sex, education, urban or rural location, smoking status, physical activity, history of diabetes, family history of cardiovascular disease, family history of cancer, quintiles of fruit and vegetable (g per day), red meat (g per day), starchy foods (g per day) consumptions, and total energy intake. Because of very low intake of processed meat and soft drink in low-income and middle-income countries (except Argentina), we did not include them as covariates in the models. Because the effect of dairy on outcome might be mediated through obesity, we did not include body-mass index (BMI) and waist-to-hip ratio in the primary multivariable models. For analyses of saturated fats and protein from dairy sources versus clinical outcomes, the saturated fatty acid models were adjusted for protein intake and vice versa. The proportional hazards assumption was evaluated by visual inspection of log–log plots.

Because the amount and types of dairy foods differ across world regions (eg, intake of dairy is relatively high in Europe and North America, South America, and the Middle East, and low in China, south Asia, southeast Asia, and Africa), we did an exploratory subgroup analysis to examine whether the associations of dairy intake with outcomes were similar in each region. We examined associations within each geographical region except southeast Asia and Africa because of low dairy consumption and few number of events. To minimise the potential for reverse causality, we excluded those with known cardiovascular disease from this analysis.

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See Online for appendix

	Overall (n=136 384)	Europe and North America (n=14 169)	South America (n=21 652)	Africa (n=5797)	Middle East (n=12 881)	South Asia (n=29 265)	Southeast Asia (n=11 032)	China (n=41 588)
Age (years)	50·1 (9·9)	52·7 (9·1)	50·9 (9·6)	49·8 (10·5)	48·0 (9·1)	48·1 (10·2)	51·5 (9·8)	50·5 (9·8)
Men	56 932 (41·7%)	6259 (44·2%)	8334 (38·5%)	1766 (30·5%)	5877 (45·6%)	12 757 (43·6%)	4543 (41·2%)	17 396 (41·8%)
Urban	72 169 (52·9%)	10 010 (70·6%)	12 244 (56·5%)	2857 (49·3%)	7705 (59·8%)	14 113 (48·2%)	5377 (48·7%)	19 863 (47·8%)
Current smoker	28 379 (20·8%)	2144 (15·1%)	4533 (20·9%)	1384 (23·9%)	2367 (18·4%)	6721 (23·0%)	1722 (15·6%)	9508 (22·9%)
Energy intake (kcal)	2150 (818)	2265 (825)	2213 (798)	2029 (947)	2336 (845)	2109 (828)	2501 (1018)	1977 (668)
Dairy intake (g per day)								
Total dairy	175·2 (224·6)	368·4 (282·5)	264·5 (292·5)	90·5 (111·0)	299·7 (213·3)	147·2 (189·1)	36·7 (75·4)	101·7 (139·2)
Whole-fat dairy	123·3 (177·2)	133·0 (142·5)	191·2 (262·2)	85·6 (106·6)	177·2 (172·7)	138·7 (185·2)	35·9 (74·3)	90·9 (135·0)
Low-fat dairy*	47·2 (133·7)	235·4 (251·9)	73·3 (165·1)	4·9 (21·0)	78·8 (126·2)	5·6 (33·7)	0·80 (6·5)	10·9 (46·7)
Milk	102·0 (165·2)	231·1(242·7)	192·1 (248·3)	86·8 (109·6)	74·7 (105·1)	51·5 (95·6)	35·1 (75·0)	79·8 (115·6)
Yoghurt	59·5 (117·6)	94·1 (124·8)	48·2 (99·8)	2·8 (11·8)	184·8 (175·8)	89·2 (139·0)	0·12 (3·3)	21·0 (58·4)
Cheese	9·7 (23·0)	34·5 (35·2)	16·6 (23·8)	0·7 (3·8)	31·7 (37·3)	1·3 (7·1)	1·3 (4·2)	1·1 (7·1)
Butter†	2·2 (7·5)	3·5 (7·9)	2·4 (8·6)	0·3 (1·6)	2·7 (5·3)	1·5 (7·4)	0·6 (0·95)	NR
Nutrient from dairy sources								
Saturated fatty acids (g per day)	3·8 (5·01)	8·0 (6·1)	6·3 (6·1)	1·84 (2·28)	8·7 (5·1)	2·0 (3·1)	1·7 (2·5)	2·0 (3·05)
Protein (g per day)	7·4 (10·1)	19·3 (13·3)	11·1 (10·7)	3·4 (4·4)	15·4 (11·1)	3·2 (6·1)	2·6 (5·4)	3·1 (4·61)

Data are mean (SD) or n (%). Means are adjusted for age, sex, education, urban or rural location, smoking status, history of diabetes, and intake of fruit, vegetable, red meat, starchy foods, and energy; centre was also included as a random effect. NR=not recorded. *Low-fat dairy was not recorded in two centres in India (Trivandrum and Jaipur), Malaysia, and South Africa. †Butter intake was not recorded in China, Malaysia, the occupied Palestinian territory, and Sweden.

Table 1: **Characteristics of the study participants at enrolment by regions**

	Events				HR (95% CI)				p_{trend}
	0 (n=28 674)	<1 serving per day (n=55 651)	1–2 servings per day (n=24 423)	>2 servings per day (n=27 636)	0	<1 serving per day	1–2 servings per day	HR (95% CI)	
Median intake (serving per day)	0 (0–0)	0·4 (0·16–0·83)	1·4 (1·17–1·72)	3·2 (2·52–4·71)	..	..	..	..	..
Composite outcome	2501 (8·7%)	4871 (8·8%)	1602 (6·6%)	1593 (5·8%)	1 (ref)	1·03 (0·96–1·11)	0·87 (0·78–0·96)	0·84 (0·75–0·94)	0·0004
Total mortality	1612 (5·6%)	3233 (5·8%)	1020 (4·2%)	931 (3·4%)	1 (ref)	0·99 (0·90–1·08)	0·85 (0·75–0·97)	0·83 (0·72–0·96)	0·0052
Non-cardiovascular mortality	1147 (4·0%)	2248 (4·0%)	723 (3·0%)	678 (2·5%)	1 (ref)	1·01 (0·90–1·13)	0·89 (0·76–1·04)	0·86 (0·72–1·02)	0·046
Cardiovascular mortality	465 (1·6%)	985 (1·8%)	297 (1·2%)	253 (0·9%)	1 (ref)	0·96 (0·81–1·13)	0·78 (0·61–0·99)	0·77 (0·58–1·01)	0·029
Major cardiovascular disease	1398 (4·9%)	2620 (4·7%)	878 (3·6%)	959 (3·5%)	1 (ref)	1·01 (0·93–1·10)	0·80 (0·70–0·92)	0·78 (0·67–0·90)	0·0001
Myocardial infarction	467 (1·6%)	1153 (2·1%)	457 (1·9%)	517 (1·9%)	1 (ref)	1·01 (0·87–1·18)	0·86 (0·70–1·05)	0·89 (0·71–1·11)	0·163
Stroke	822 (2·9%)	1224 (2·2%)	346 (1·4%)	326 (1·2%)	1 (ref)	1·01 (0·90–1·13)	0·78 (0·65–0·94)	0·66 (0·53–0·82)	0·0003
Heart failure	97 (0·3%)	212 (0·4%)	77 (0·3%)	130 (0·5%)	1 (ref)	0·96 (0·72–1·28)	0·82 (0·56–1·19)	1·06 (0·71–1·57)	0·90

Data are median (IQR) or n (%), unless otherwise stated. Models are adjusted for age, sex, education, urban or rural location, smoking status, physical activity, history of diabetes, family history of cardiovascular disease, family history of cancer, and quintiles of fruit, vegetable, red meat, starchy foods intake, and energy; centre was also included as a random effect. The appendix (p 24) shows the analysis by whole-fat and low-fat dairy. HR=hazard ratio. ref=reference.

Table 2: **Associations between consumption of total dairy and clinical outcomes (n=136 384)**

In sensitivity analyses, we further excluded cardiovascular disease events and deaths occurring in the first 24 months of follow-up. To assess the association between whole-fat and low-fat dairy intake with outcomes, participants were stratified based on the predominant type of dairy intake and four mutually exclusive groups were created. In our FFQs, the frequency of consumption as never or less than once per month was used as an indicator for food items never or rarely consumed. Therefore, whole-fat dairy intake was defined as an intake of whole-fat dairy of one serving or more per month and an intake of low-fat dairy of less than one serving per month. Intake of more than one serving of low-fat dairy per month and less than one serving of whole-fat dairy per month was defined as low-fat dairy intake. However, our study was underpowered to detect an association separately in this subgroup owing to a low number of participants in this particular group. Both low-fat and whole-fat dairy intakes were defined as intake of at least one serving of whole-fat dairy and one serving of low-fat dairy per month. Individuals whose intake of dairy was reported to be fewer than once per month or never were considered as having no intake. In each group, the lowest intake was used as the reference group. Statistical

	Events				HR (95% CI)				p_{trend}
	0	<0·5 servings per day	0·5–1 serving per day	>1 serving per day	0	<0·5 servings per day	0·5–1 serving per day	>1 serving per day	
Milk*									
Median intake (serving per day)	0 (0–0)	0·1 (0·07–0·42)	1·0 (0·81–0·98)	2·0 (1·12–2·97)	..	..	..	..	..
Composite outcome	4464 (8·7%)	2985 (7·6%)	1770 (7·2%)	1217 (6·2%)	1 (ref)	1·00 (0·93–1·07)	0·98 (0·91–1·05)	0·90 (0·82–0·99)	0·0529
Total mortality	3274 (6·4%)	2167 (5·5%)	1098 (4·4%)	834 (4·2%)	1 (ref)	1·00 (0·91–1·08)	1·00 (0·90–1·10)	0·89 (0·79–1·00)	0·106
Major cardiovascular disease	2438 (4·8%)	1571 (4·0%)	1098 (4·4%)	658 (3·3%)	1 (ref)	0·96 (0·88–1·04)	0·93 (0·85–1·02)	0·82 (0·72–0·93)	0·0027
Yoghurt†									
Median intake (serving per day)	0 (0–0)	0·1 (0·07–0·33)	0·8 (0·64–0·98)	1·5 (1·19–1·96)	..	..	..	..	..
Composite outcome	5061 (8·4%)	3091 (7·8%)	907 (6·4%)	652 (6·5%)	1 (ref)	0·95 (0·89–1·02)	0·87 (0·78–0·97)	0·86 (0·75–0·99)	0·0051
Total mortality	3411 (5·7%)	2296 (5·8%)	611 (4·3%)	444 (4·4%)	1 (ref)	0·98 (0·89–1·07)	0·92 (0·80–1·05)	0·83 (0·69–0·99)	0·0404
Major cardiovascular disease	2913 (4·9%)	1606 (4·1%)	535 (3·7%)	381 (3·8%)	1 (ref)	0·93 (0·85–1·02)	0·83 (0·72–0·94)	0·90 (0·75–1·07)	0·0162
Cheese‡									
Median intake (serving per day)	0 (0–0)	0 2 (0 09–0 35)	0·8 (0·59–0·85)	1·7 (1·21–2·60)	1 (ref)	..	..	..	..
Composite outcome	4815 (8·0%)	1409 (5·7%)	539 (4·9%)	809 (5·6%)	1 (ref)	0·90 (0·80–1·02)	0·87 (0·74–1·01)	0·88 (0·76–1·02)	0·1399
Total mortality	3103 (5·2%)	944 (3·8%)	342 (3·1%)	466 (3·2%)	1 (ref)	0·89 (0·77–1·04)	0·88 (0·73–1·06)	0·87 (0·72–1·05)	0·2383
Major cardiovascular disease	2974 (5·0%)	822 (3·3%)	313 (2·9%)	514 (3·6%)	1 (ref)	0·90 (0·77–1·06)	0·85 (0·70–1·03)	0·92 (0·77–1·11)	0·5024
Butter§									
Median intake (serving per day)	0 (0–0)	0·07 (0·01–0·14)	0·8 (0·71–0·80)	1·0 (1·00–2·50)	..	..	..	..	..
Composite outcome	4477 (8·9%)	1126 (6·1%)	87 (6·3%)	149 (6·8%)	1 (ref)	1·01 (0·91–1·11)	1·06 (0·81–1·38)	1·09 (0·90–1·33)	0·4113
Total mortality	3578 (7·1%)	743 (4·1%)	62 (4·5%)	100 (4·6%)	1 (ref)	0·99 (0·88–1·12)	1·17 (0·84–1·62)	1·02 (0·80–1·29)	0·7747
Major cardiovascular disease	2084 (4·1%)	672 (3·7%)	49 (3·5%)	89 (4·1%)	1 (ref)	1·00 (0·88–1·13)	0·92 (0·65–1·31)	1·19 (0·92–1·53)	0·4099

Data are median (IQR) or n (%), unless otherwise stated. Models are adjusted for age, sex, education, urban or rural location, smoking status, physical activity, history of diabetes, family history of cardiovascular disease, family history of cancer, and quintiles of fruit, vegetable, red meat, starchy foods intake, and energy; centre was also included as a random effect. HR=hazard ratio. ref=reference. *One serving is equivalent to a glass of milk (244 g); n=51 120 for 0 servings, n=39 349 for <0·5 servings per day, n=24 746 for 0·5–1 serving per day, and n=19 697 for >1 serving per day. †One serving is equivalent to a cup of yoghurt (244 g); n=59 961 for 0 servings, n=39 564 for <0·5 servings per day; n=14 277 for 0·5–1 serving per day, and n=10 028 for >1 serving per day. ‡One serving is equivalent to one slice of cheese (15 g); n=59 895 for 0 servings, n=24 843 for <0·5 servings per day, n=10 896 for 0·5–1 serving per day, n=14 342 for >1 serving per day. §One serving is equivalent to a teaspoon of butter (5 g); n=50 274 for 0 servings, n=18 327 for <0·5 servings per day, n=1381 for 0·5–1 serving per day, n=2193 for >1 serving per day. Butter intake was not recorded in China, Malaysia, the occupied Palestinian territory, and Sweden.

Table 3: **Associations between different types of dairy and clinical outcomes (n=136 384)**

analyses were done with SAS (version 9.4) of the SAS System for SunOS (SAS Institute, Cary, NC, USA).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author (MD), coauthors (AM and SR), and a senior author (SY) had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between Jan 1, 2003, and July 14, 2018, a total of 153 220 participants completed the FFQ, of which 147 813 (96·5%) participants had plausible energy intakes (500–5000 kcal per day) and had their age and sex recorded. We excluded 11 429 (7·7%) of 147 813 participants with a history of cardiovascular disease at baseline. The remaining 136 384 (92·3%) individuals are included in this study. During the median follow-up of 9·1 years (IQR 6·4–9·9), we recorded 10 567 (7·7%) individuals who either died (n=6796) or had major cardiovascular events (n=5855; 4796 non-cardiovascular deaths, 2000 cardiovascular deaths, 2594 myocardial infarction, 2718 stroke, and 516 heart failure).

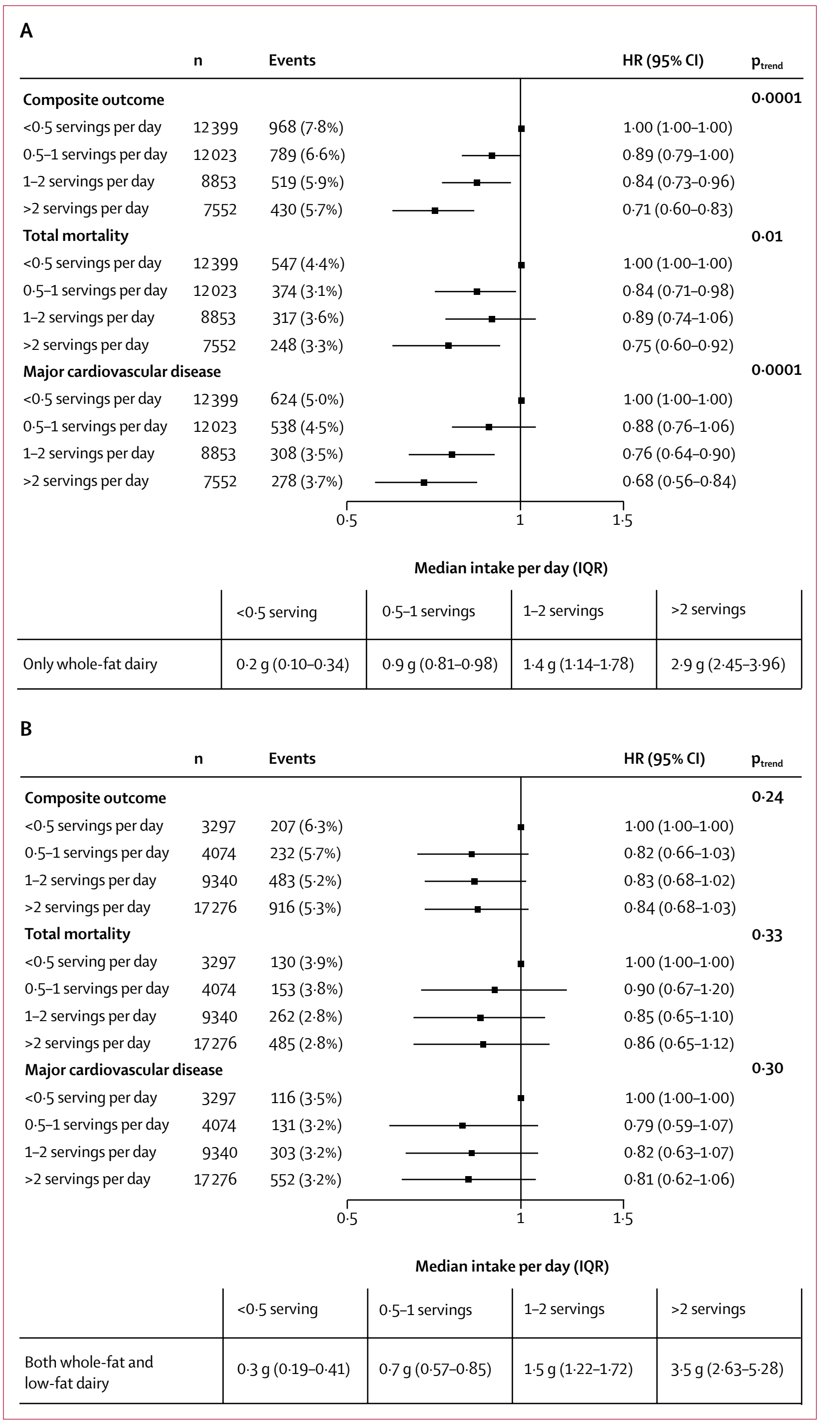
Total dairy intake was higher in Europe and North America, the Middle East, and South America than in other regions (table 1). The highest yoghurt intake was in the Middle East, Europe and North America, and south Asia. Intake of cheese was highest in Europe and North America and the Middle East. The highest amount of butter was consumed in South America, Europe and North America, and the Middle East but the mean level of intake in all these countries was modest.

Tables 2 and 3 show the association between intake of total dairy and types of dairy products with risk of various clinical outcomes. Higher intake of total dairy (>2 servings per day) versus zero intake was associated with lower risk of the composite outcome (HR 0·84, 95% CI 0·75–0·94; p_{trend}=0·0004), total mortality (0·83, 0·72–0·96; p_{trend}=0·0052), non-cardiovascular mortality (0·86, 0·72–1·02; p_{trend}=0·046), cardiovascular mortality (0·77, 0·58–1·01; p_{trend}=0·029), major cardiovascular disease (0·78, 0·67–0·90; p_{trend}=0·0001), and stroke (0·66, 0·53–0·82; p_{trend}=0·0003; table 2). Similar associations were observed for whole-fat and low-fat dairy (appendix p 24). No significant association was observed for myocardial infarction (HR 0·89, 95% CI 0·71–1·11; p_{trend}=0·163; table 2).

Higher intake of milk (>1 serving per day) versus zero intake was significantly associated with a lower risk of composite outcome (HR 0·90, 95% CI 0·82–0·99; p_{trend}=0·0529) and major cardiovascular disease (0·82, 95% CI 0·72–0·93; p_{trend}=0·0027; table 3). Compared with zero intake, higher yoghurt intake (>1 serving per day) was associated with lower risks of the composite outcome (HR 0·86, 95% CI 0·75–0·99; p_{trend}=0·0051), total mortality (0·83, 0·69–0·99; p_{trend}=0·0404), and major cardiovascular disease (0·90, 0·75–1·07; p_{trend}=0·0162). High cheese consumption (>1 serving per day) versus zero intake was associated with a lower risk of the composite outcome, total mortality, and major cardiovascular disease, but these associations were not significant (table 3). Higher intake of butter (>1 serving per day) versus zero intake was associated with non-significantly higher risk of composite outcome (HR 1·09, 95% CI 0·90–1·33; p_{trend}=0·4113) and major cardiovascular disease (1·19, 0·92–1·53; p_{trend}=0·4099). Results were unchanged after further adjustment for alcohol intake and number of cigarettes per day (appendix pp 26–28).

Among those who consumed only whole-fat dairy, higher intake of total dairy was associated with lower risk of the composite outcome (comparing >2 servings per day with <0·5 servings per day, HR 0·71 [95% CI 0·60–0·83]; p_{trend}=0·0001), total mortality (0·75 [0·60–0·92]; p_{trend}=0·015), and major cardiovascular disease (0·68 [0·56–0·84]; p_{trend}=0·0001; figure 1A). A similar, inverse association between total dairy consumption and health outcomes was observed in those who consumed both whole-fat and low-fat dairy products for the composite outcome (comparing >2 servings per day with <0·5 servings per day, HR 0·84 [95% CI 0·68–1·03]; p_{trend}=0·24), total mortality (0·86 [0·65–1·12]; p_{trend}=0·33), and major cardiovascular disease (0·81 [0·62–1·06]; p_{trend}=0·30; figure 1B). Higher intake of saturated fatty acids from dairy sources was not significantly associated with the composite outcome (HR 0·95, 95% CI 0·80–1·12; p_{trend}=0·60), total mortality (0·87, 0·70–1·08; p_{trend}=0·26), or major cardiovascular disease (0·94, 0·75–1·17; p_{trend}=0·39; figure 2A). A similar trend was observed for higher protein intake from dairy sources and risk of all outcomes (figure 2B).

The results were consistent in regions with low dairy or high dairy intake. Higher dairy intake was associated with a lower risk of composite outcome with a larger



A

	n	Events	HR (95% CI)	p_{trend}
Composite outcome				0·0001
<0·5 servings per day	12 399	968 (7·8%)	1·00 (1·00–1·00)	
0·5–1 servings per day	12 023	789 (6·6%)	0·89 (0·79–1·00)	
1–2 servings per day	8853	519 (5·9%)	0·84 (0·73–0·96)	
>2 servings per day	7552	430 (5·7%)	0·71 (0·60–0·83)	
Total mortality				0·01
<0·5 servings per day	12 399	547 (4·4%)	1·00 (1·00–1·00)	
0·5–1 servings per day	12 023	374 (3·1%)	0·84 (0·71–0·98)	
1–2 servings per day	8853	317 (3·6%)	0·89 (0·74–1·06)	
>2 servings per day	7552	248 (3·3%)	0·75 (0·60–0·92)	
Major cardiovascular disease				0·0001
<0·5 servings per day	12 399	624 (5·0%)	1·00 (1·00–1·00)	
0·5–1 servings per day	12 023	538 (4·5%)	0·88 (0·76–1·06)	
1–2 servings per day	8853	308 (3·5%)	0·76 (0·64–0·90)	
>2 servings per day	7552	278 (3·7%)	0·68 (0·56–0·84)	

Median intake per day (IQR)

	<0·5 serving	0·5–1 servings	1–2 servings	>2 servings
Only whole-fat dairy	0·2 g (0·10–0·34)	0·9 g (0·81–0·98)	1·4 g (1·14–1·78)	2·9 g (2·45–3·96)

B

	n	Events	HR (95% CI)	p_{trend}
Composite outcome				0·24
<0·5 servings per day	3297	207 (6·3%)	1·00 (1·00–1·00)	
0·5–1 servings per day	4074	232 (5·7%)	0·82 (0·66–1·03)	
1–2 servings per day	9340	483 (5·2%)	0·83 (0·68–1·02)	
>2 servings per day	17 276	916 (5·3%)	0·84 (0·68–1·03)	
Total mortality				0·33
<0·5 serving per day	3297	130 (3·9%)	1·00 (1·00–1·00)	
0·5–1 servings per day	4074	153 (3·8%)	0·90 (0·67–1·20)	
1–2 servings per day	9340	262 (2·8%)	0·85 (0·65–1·10)	
>2 servings per day	17 276	485 (2·8%)	0·86 (0·65–1·12)	
Major cardiovascular disease				0·30
<0·5 serving per day	3297	116 (3·5%)	1·00 (1·00–1·00)	
0·5–1 servings per day	4074	131 (3·2%)	0·79 (0·59–1·07)	
1–2 servings per day	9340	303 (3·2%)	0·82 (0·63–1·07)	
>2 servings per day	17 276	552 (3·2%)	0·81 (0·62–1·06)	

Median intake per day (IQR)

	<0·5 serving	0·5–1 servings	1–2 servings	>2 servings
Both whole-fat and low-fat dairy	0·3 g (0·19–0·41)	0·7 g (0·57–0·85)	1·5 g (1·22–1·72)	3·5 g (2·63–5·28)

Figure 1: **Association between total dairy intake and risk of clinical outcomes**
(A) Consumption of only whole-fat dairy (n=40 827). (B) Consumption of both whole-fat and low-fat dairy (n=33 987). Full models are adjusted for age, sex, education, urban or rural location, smoking status, physical activity, history of diabetes, family history of cardiovascular disease, family history of cancer, and quintiles of fruit, vegetable, red meat, starchy foods intake, and energy; centre was also included as a random effect. Further analyses of whole-fat and low-fat dairy intake are provided in the appendix (p 24). HR=hazard ratio.

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protective effect in regions with higher dairy consumption (p_{trend}=0·01; figure 3). Also, these associations were directionally similar across different regions (appendix p 30).

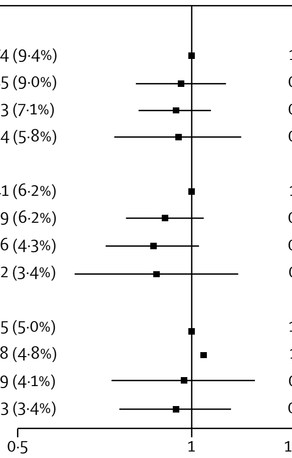
In the sensitivity analysis, adjustments for waist-to-hip-ratio or BMI separately in the multivariable models did not substantially change the findings (appendix p 23). Exclusion of those who had a cardiovascular disease event or death in the first 24 months of follow-up did not alter the results (appendix p 23).

Discussion

In this large, multinational, prospective cohort study involving participants from 21 countries in 5 continents, we found inverse associations between total dairy consumption and mortality or major cardiovascular disease events. The risk of stroke was markedly lower with higher consumption of dairy. No association was found between higher dairy consumption and myocardial infarction. Overall, butter intake was low and was not significantly associated with increased risk of cardiovascular disease or mortality. Our findings support that consumption of dairy products might be beneficial for mortality and cardiovascular disease, especially in low-income and middle-income countries where dairy consumption is much lower than North America and Europe.

Current dietary guidelines recommend the consumption of two to four servings of fat-free or low-fat dairy. A focus on low-fat is predominantly based on the presumed harms of a single macronutrient category (saturated fatty acids) on a single cardiovascular risk marker (LDL cholesterol), and concerns about higher calories in higher fat foods. Dairy products are a diverse food group that include fermented and cultured products with many different nutrients,[3] and their impact on health outcomes cannot be characterised fully by the presumed effect of one nutrient on a single biomarker. Even saturated fats are a diverse group[16,17] and their effects might vary depending on the content of a specific saturated fatty acid in various foods. Dairy fatty acids contain medium-chain and branched-chain fatty acids, and their effect on health might differ[16,17] from saturated fat in meat and processed meats (mainly long-chain fatty acids). The potential benefits of increased dairy consumption might be particularly marked in countries where strokes are relatively more common, such as China or Africa. Moreover, these countries have low consumption of dairy and high risk of hypertension, both of which might be reduced by increasing dairy consumption. Our study (unpublished data) and others have shown a lower blood pressure with higher consumption of dairy[18] and this effect might explain the lower risks of strokes that we have observed. Furthermore, there was no impact on LDL cholesterol but a lower triglyceride blood concentration with higher dairy consumption, and this finding might explain the non-significant and lower risk of myocardial infarction observed in this study.

Previous meta-analyses of cohort studies have reported about a 10% lower risk of cardiovascular disease and a 13% lower risk of stroke with higher dairy consumption.[19,20] This finding is consistent with our observations, and no



A

	n	Events	HR (95% CI)	p_{trend}
Composite outcome				**0·60**
Q1	32 677	3074 (9·4%)	1·00 (1·00–1·00)	
Q2 vs Q1	32 678	2945 (9·0%)	0·96 (0·85–1·08)	
Q3 vs Q1	32 672	2333 (7·1%)	0·94 (0·81–1·08)	
Q4 vs Q1	32 674	1884 (5·8%)	0·95 (0·80–1·12)	
Total mortality				**0·26**
Q1	32 677	2041 (6·2%)	1·00 (1·00–1·00)	
Q2 vs Q1	32 678	2019 (6·2%)	0·90 (0·77–1·05)	
Q3 vs Q1	32 672	1406 (4·3%)	0·86 (0·71–1·03)	
Q4 vs Q1	32 674	1102 (3·4%)	0·87 (0·70–1·08)	
Major cardiovascular disease				**0·39**
Q1	32 677	1625 (5·0%)	1·00 (1·00–1·00)	
Q2 vs Q1	32 678	1578 (4·8%)	1·05 (0·89–1·23)	
Q3 vs Q1	32 672	1339 (4·1%)	0·97 (0·80–1·17)	
Q4 vs Q1	32 674	1123 (3·4%)	0·94 (0·75–1·17)	

Median intake per day (IQR)

	Q1	Q2	Q3	Q4
Saturated fat	0·01 g (0·01–0·02)	0·97 g (0·54–1·5)	3·9 g (2·9–4·3)	8·9 g (7·0–12·4)

B

	n	Events	HR (95% CI)	p_{trend}
Composite outcome				**0·12**
Q1	33 235	3224 (9·7%)	1·00 (1·00–1·00)	
Q2 vs Q1	33 231	2842 (8·6%)	1·14 (1·02–1·27)	
Q3 vs Q1	33 233	2141 (6·4%)	0·97 (0·84–1·12)	
Q4 vs Q1	33 233	1853 (5·5%)	0·90 (0·76–1·07)	
Total mortality				**0·15**
Q1	33 235	2204 (6·6%)	1·00 (1·00–1·00)	
Q2 vs Q1	33 231	1883 (5·6%)	1·10 (0·96–1·27)	
Q3 vs Q1	33 233	1265 (3·8%)	0·98 (0·81–1·19)	
Q4 vs Q1	33 233	1049 (3·2%)	0·87 (0·70–1·09)	
Major cardiovascular disease				**0·14**
Q1	33 235	1677 (5·0%)	1·00 (1·00–1·00)	
Q2 vs Q1	33 231	1568 (4·7%)	1·04 (0·90–1·21)	
Q3 vs Q1	33 233	1322 (4·0%)	0·90 (0·74–1·09)	
Q4 vs Q1	33 233	1132 (3·4%)	0·86 (0·68–1·08)	

Median intake per day (IQR)

	Q1	Q2	Q3	Q4
Protein	0·01 g (0·01–0·02)	1·12 g (0·46–2·05)	7·2 g (5·6–8·4)	20·0 g (14·3–28·9)

Figure 2: **Associations between saturated fats and protein (g per day) from dairy sources with clinical outcomes**
(A) Consumption of saturated fatty acids from dairy sources; data from the occupied Palestinian territory, Philippines, and Saudi Arabia were not included in the analysis of saturated fatty acids. (B) Consumption of protein from dairy sources; data from South Africa were not included in the analysis of protein. Full models are adjusted for age, sex, education, urban or rural location, smoking status, physical activity, history of diabetes, family history of cardiovascular disease, family history of cancer, and energy; centre was also included as a random effect. The saturated fatty acid analysis models are adjusted for protein intake (g per day) and vice versa. HR=hazard ratio. Q1–Q4=quintiles 1–4.

	n	Events	HR (95% CI)	p_{trend}
Low dairy intake regions (China, south Asia, southeast Asia, Africa)				0·06
0	27589	2430 (8·8%)	1·00 (1·00–1·00)	
<1 serving per day	44496	4227 (9·5%)	1·05 (0·98–1·13)	
1–2 servings per day	11196	930 (8·3%)	0·88 (0·77–1·00)	
>2 servings per day	4401	385 (8·7%)	0·80 (0·66–0·97)	
High dairy intake regions (Europe and North America, South America, the Middle East)				0·01
0	1096	71 (6·5%)	1·00 (1·00–1·00)	
<1 serving per day	11148	644 (5·8%)	0·94 (0·71–1·24)	
1–2 servings per day	13223	672 (5·1%)	0·84 (0·63–1·11)	
>2 servings per day	23235	1208 (5·2%)	0·80 (0·60–1·06)	

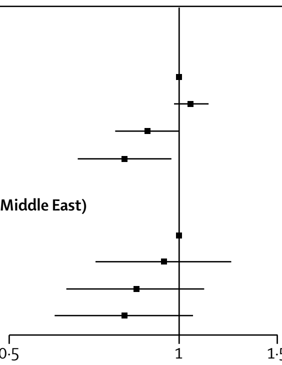


***Figure 3:* Association between total dairy intake with risk of the composite outcome and cardiovascular disease in low and high dairy intake regions**
n=87 682 for low dairy intake regions, and n=48 702 for high dairy intake regions. Full models are adjusted for age, sex, education, urban or rural location, smoking status, physical activity, history of diabetes, family history of cardiovascular disease, family history of cancer, and quintiles of fruit, vegetable, red meat, starchy foods intake, and energy; centre was also included as a random effect. HR=hazard ratio.

long-term study has indicated higher cardiovascular disease or mortality from dairy consumption in low-income and middle-income countries. However, in a prospective cohort study of 103 256 people in Sweden, consumption of two or more servings of milk per day was associated with a 32% higher risk of mortality. It is noteworthy that in Sweden intake of dairy is markedly higher than in PURE and is the third highest in the world.[21] A meta-analysis of cohort studies reported higher risk of prostate cancer with higher intake of dairy (relative risk 1·07, 95% CI 1·02–1·12).[22] However, several studies did not find associations between dairy intake and total mortality or different types of cancer.[23] Our findings are robust and more widely applicable because our large study recorded more than 10 000 deaths or major cardiovascular events across a broad range of dairy consumption (IQR 0–99·0 g per day) in a variety of different settings and cultures with varying dietary patterns. Also, adjustments for confounders, for consumption of other food groups, and analyses to exclude reverse causality (by excluding those with previous cardiovascular disease or those who died or had an event in the first 2 years) did not alter our results. However, our findings require confirmation from randomised trials evaluating the effects of increasing dairy consumption on blood pressure, blood glucose concentrations, and clinical outcomes.

For **Food and Agriculture Organization statistics about Sweden** see http://faostat3.fao.org/

Our observation that yoghurt consumption was inversely associated with risks of mortality and cardiovascular disease events is consistent with two large cohort studies, showing an approximately 10% lower risk of mortality and cardiovascular disease with high yoghurt intake.[19,24] Butter consumption was associated with an increased risk of cardiovascular disease, but the results were not significant. This finding is consistent with a meta-analysis of 636 151 individuals from 15 countries, showing that high consumption of butter (up to 14 g per day) was weakly associated with increased mortality but not associated with increased risk of cardiovascular disease.[9] Higher intake of saturated fatty acids from dairy was reported to be associated with lower risk of total mortality and cardiovascular events in the Multi-Ethnic Study of Atherosclerosis,[25] which reported a 21% lower risk of cardiovascular disease for every 5 g per day increase in saturated fatty acid intake from dairy sources, and a cohort study of 70-year-old Swedes,[26] which observed a lower risk of mortality in those consuming higher amounts of fat from cheese. In a recent analysis from the Cardiovascular Health Study,[27] serial blood biomarkers of fatty acids found in dairy fat were not significantly associated with total mortality but were associated with a higher risk of non-cardiovascular disease mortality (extreme-quintile HR 1·27, 95% CI 1·07–1·52), but also with lower cardiovascular disease mortality (0·77, 0·61–0·98), especially for stroke mortality (0·58, 0·35–0·97).

Why might greater consumption of dairy reduce cardiovascular disease and mortality? A range of potential compounds and related mechanisms in dairy foods might improve health.[3] In mechanistic studies, diverse characteristics of dairy products influence various pathways such as angiotensin-converting enzymes,[28] osteocalcin,[29] gut microbiome interactions[3] such as intestinal integrity, and endotoxaemia.[30] Processes such as fermentation and homogenisation might also influence health effects.[3] The complexity of these pathways and accompanying biological responses highlights the need to study direct associations of foods in large prospective cohorts and trials, rather than relying on assumptions based on isolated ingredients in such foods.

To our knowledge, PURE is the first large multinational cohort study to examine the association of dairy products with mortality and cardiovascular events. We used standardised methods to measure diet using country-specific validated FFQs. Also, standardised methods were used to record events and supporting documents were available in 90% of cases permitting central adjudication of events. Nonetheless, our study has potential limitations. Multiple weighed food records might be more accurate for measuring individual's diets, but require extensive participant training, motivation, awareness of food intake, literacy, and repeated measures over a year; each of which reduces practicality for large long-term, socioeconomically diverse studies. Despite using country-specific validated FFQs, some measurement error is inevitable, which in a prospective analysis would most often attenuate findings toward the null. FFQs are not optimal for measuring an individual's absolute intake, but rather useful in categorising individuals on the basis of relative intakes (ie, into groups with high, intermediate, or low consumption of specific foods or nutrients) and so our findings should be considered as comparisons of higher versus lower dairy consumption. As with any observational study, residual confounding is a possibility;

however, we adjusted for established and potential risk factors of mortality and cardiovascular disease as well as for other dietary variables. Furthermore, the consistency of results across regions with markedly different lifestyles makes it less likely that confounders, which are likely to vary in different regions, explain our observations. We only measured diet comprehensively at baseline, and changes in diet during the follow-up might have occurred and would be expected to weaken the observed associations. However, we found that the association between milk intake, recorded at 3 years of follow-up, and cardiovascular disease was similar to the analyses using the baseline information (appendix p 25), indicating that repeat dietary measures are unlikely to alter our findings. Because of low literacy in some areas, the comprehensive FFQs at baseline administered by interviewing participants took between 40–45 min. For a large multinational study, such as the PURE study, feasibility and scarce resources are important practical considerations. Therefore, during the follow-up, individual's dietary intake was measured using short FFQs, which included milk consumption. Intake of low-fat dairy products was not specifically recorded in Malaysia, South Africa, and at two centres in India, because low-fat dairy products were not frequently consumed or were not available based on the reports of our investigators. Exclusion of the data from these centres did not alter our findings. Finally, the relatively modest number of events in Africa and south east Asia precluded separate analysis in these geographic regions. However, we grouped the regions by those with high or low dairy intake and observed consistent associations with clinical outcomes in region with either low or high dairy intakes. With further follow up and expansion of the PURE population to 200 000 people, future analyses will have adequate statistical power to examine the effects of diet within each region.

In conclusion, we observed that higher dairy consumption was associated with lower risks of mortality and cardiovascular disease, particularly stroke. Our study suggests that consumption of dairy products should not be discouraged and perhaps should even be encouraged in low-income and middle-income countries where dairy consumption is low.

Contributors

MD wrote the analysis plan, and the first and final draft of the paper with input from AM, SSA, and SY. AM and SSA provided input on the data analysis, all the drafts, and the final paper. SY designed and supervised the conduct of the PURE study, supervised the data analysis, interpreted the data, and reviewed and commented on all drafts and the final paper. PS did the statistical analysis and reviewed and commented on all drafts and the final paper. DM reviewed and commented on the data analysis, all drafts, and the final paper. SR coordinated the worldwide study, and reviewed and commented on all drafts and the final paper. All other authors coordinated the study in their respective countries and commented on all the drafts and the final paper.

Declaration of interests

We declare no competing interests.

Data sharing

No additional data are available for this Article.

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