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Original article

Consumption of dairy product and its association with total and cause specific mortality – A population-based cohort study and meta-analysis

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SUMMARY

Background: The intake of dairy products has been thought to be associated with an increased risk of coronary heart diseases (CHD) and total mortality due to its relatively high content of saturated fat. However, reports on this association particularly among US adults are conflicting and controversial. Therefore, we used data from the 1999–2010 National Health and Nutrition Examination Surveys (NHANES) study to examine whether consumption of total dairy and dairy subgroups was associated with total and cause specific (CHD, cerebrovascular and cancer) mortality. Further we carried out a systematic review and meta-analysis of prospective studies to check for consistency with the NHANES findings.
Methods: In the NHANES cohort vital status through December 31, 2011 was ascertained. Cox proportional hazard regression models were used to relate baseline dairy intake with all-cause and cause-specific mortality. For the systematic review PubMed, SCOPUS, Web of Science and Google Scholar databases were searched (up to December 2017). The DerSimonian-Laird method and generic inverse variance methods were used for quantitative data synthesis.
Results: In the NHANES data set of 24,474 participants, 3520 deaths occurred during follow-up. In multivariate adjusted Cox models, total mortality risk was lower when comparing the top (Q4) with the lower (Q1) quartiles of total dairy (hazard ratio [HR] 0.98, 95% confidence interval [CI]: 0.95–0.99) and cheese (HR: 0.92, 95% CI: 0.87–0.97) consumption. Using a similar model, we have found a negative association between total dairy and milk consumption with risk of cerebrovascular mortality (HR: 0.96, 95% CI: 0.94–0.98, HR: 0.93, 95% CI: 0.91–0.96, respectively), while milk consumption was associated with increased CHD mortality (HR: 1.04, 95% CI: 1.02–1.06). The meta-analysis with 636,726 participants indicated a significant inverse association between fermented dairy products and total mortality (RR: 0.97, 95% CI: 0.96–0.99), while milk consumption was associated with higher CHD mortality (RR: 1.04, 95% CI: 1.01–1.05). These findings were robust in sensitivity analyses.

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Conclusions: Among American adults, higher total dairy consumption was associated with lower total and cerebrovascular mortality, while higher milk consumption was associated with higher risk of CHD. These findings do not support dogmatic public health advice to reduce total dairy fat consumption, although the association between milk consumption and CHD mortality requires further study.

1. Introduction

Because of a relatively high content of saturated fat, higher intake of dairy products has been hypothesized to result in an increased risk of cardiovascular diseases (CVD) and total mortality [1]. Available dietary recommendations suggest a diet limited in saturated fat and *trans* fat, and therefore advise consuming fat-free or low-fat dairy products [1]. They have been based on the positive linear relationship between dietary saturated fat, low density lipoprotein cholesterol (LDL-C) and CVD risk [2]. However, a recent meta-analysis combining data from 29 prospective cohort studies failed to detect an association between dairy products with either CVD or all-cause mortality [3]. In contrast, inverse associations between total fermented dairy with total and CVD mortality were reported [3]. Other authors noted that even though milk and dairy foods have been recommended in most dietary guidelines, the association of milk or dairy food consumption with CVD still remains controversial [4,5]. A dose-response meta-analysis of 17 prospective cohort studies showed no relation between intake of total dairy or milk and coronary heart disease (CHD) mortality [6]. The authors also showed that a higher intake of milk was associated with a non-significant 13% lower risk of fatal stroke [6]. In contrast, a large prospective study of Swedish adults reported that higher milk consumption (three or more glasses of milk a day compared with less than one) was associated with a doubling of mortality risk including CVD mortality in the cohort of women [7].

It is important to emphasize that consumption of dairy products in traditional diets vary essentially in different regions of the world [8]. Populations in tropical countries have not been traditional milk consumers, whereas North Americans have traditionally consumed far more milk and milk products as part of their diet [8]. It also needs to be noticed that different kinds of dairy products and different production processes vary in nutrient composition (such as minerals, protein and vitamins and content of fat) [9–11]; hence, they may have different effects on health [9–11]. The few studies among American populations have reported inconsistent results [9,12–17]; with regard to the link between total dairy intake and CVD, 2 out of 4 of the studies reported an increased risk [9,16] and the remaining demonstrated an inverse association [13,14]. Similar mixed results for the association between milk intake and all-cause mortality are evident [15–18]. What is more, the majority of studies were restricted to either including only men [14] or only women [9,13,17]. Finally, no study has investigated the association of yogurt intake with total and cause specific mortality among Americans [3,19].

Dairy products represent a heterogeneous food group of solid, semi-solid and liquid, fermented or non-fermented foods; each differing in nutrients such as fat and sodium [19]. Therefore, analysis needs to reflect specific dairy types. Taking all these factors together, the paucity of studies and conflicting findings we set up the present study to obtain more insight in specific dairy foods in relation to long-term risk of total and cause specific mortality based on a representative and large sample size of American adults in the 1999–2010 National Health and Nutrition Examination Surveys (NHANES) cohort study. We also conducted a comprehensive systematic review and meta-analysis to contextualize these data and examine the associations between dairy products with all-cause and cause specific mortality by using existing prospective cohort studies among American adults.

2. Methods

(a) NHANES data

2.1. Population

Dietary exposure was assessed in the US NHANES. The National Center for Health Statistics (NCHS) Research Ethics Review Board approved the protocol, and written informed consent was obtained from all subjects. The current study is based on analysis of data for NHANES survey cycles between 1999 and 2010 (no mortality results are available for data after 2010 in NHANES), restricted to participants aged ≥20 years. Details on NHANES Laboratory/Medical Technologists Procedures and Anthropometry Procedures have been described previously [20,21].

Dietary intake was assessed by means of 24 h recall obtained by a trained interviewer, with the use of a computer-assisted dietary interview system with standardized probes based on the US Department of Agriculture Automated Multiple-Pass Method (AMPM) [22,23]. Briefly, the type and quantity of all foods and beverages consumed in a single 24 h period before the dietary interview (from midnight to midnight) were collected with the use of AMPM. The AMPM is designed to enhance complete and accurate data collection while reducing respondent burden [23,24]. The United States Department of Agriculture (USDA) Food and Nutrient Database for Dietary Studies was used to determine the nutrient content of foods in 2005–2008 NHANES surveys. Servings, in cup equivalents, of total dairy, milk, cheese, and yogurt were determined using Food Patterns Equivalent Database for NHANES 2005–2010.

2.2. Endpoint definitions

The anonymized data of NHANES 1999–2010 participants were linked to longitudinal Medicare mortality data using the NHANES assigned sequence number. Mortality follow-up data were available from the date of survey participation until December 31st, 2011. We examined all-cause mortality, as well as mortality due to heart diseases (I00-I09, I11, I13, I20-I51), cancer (C00-C97), and cerebrovascular disease (I60-I69). CHD mortality was defined based on I11 and I20-I25 codes. Cause of death was determined using the 10th revision of the International Classification of Diseases (ICD-10).

2.3. Statistical analysis

Analyses were conducted according to the guidelines set by the Centers for Disease Control and Prevention for analysis of the NHANES dataset, accounting for the masked variance and using their suggested weighting methodology [25]. Continuous and categorical demographic variables were compared across quartiles of total dairy consumption using analysis of variance (ANOVA) and Chi-square tests, respectively. Multivariable Cox proportional hazards were applied to determine the hazard ratios (HRs) and 95% confidence intervals (95% CI) of mortality for each quartile of the total dairy, milk, yogurt, and cheese, with the lowest quartile (Q1) always used as reference. Schoenfeld's residuals were used to assess the proportional hazard assumption. Kaplan–Meier curves were used to compare the probability of total death across categories of total dairy consumption. To derive the HR and 95% CI we introduced three different models: *Model 1* was adjusted for age, sex, race, education, and marital status, poverty to income ratio, total energy intake, physical activity, smoking and alcohol consumption; *Model 2* included factors in Model 1 with additional adjustment for carbohydrates, saturated fat, protein and dietary fiber; *Model 3* included factors in Model 2 with additional adjustment for body mass index (BMI), hypertension and diabetes. A two-sided $p < 0.05$ was used to characterize significant results. Data analysis reflected the complex sampling structure of NHANES and was performed using SPSS with the complex sample model version 22.0 (IBM Corp, Armonk, NY).

(b) Systematic Review, Meta-Analysis

2.4. Literature search and study selection

This meta-analysis was designed, conducted and reported according to Meta-analysis Of Observational Studies in Epidemiology (MOOSE) guidelines [26] (MOOSE checklist is provided in Supplementary Table 1 & PRISMA checklist in the supplementary material). The primary exposure of interest was dairy product consumption while the primary outcome of interest was total and cause-specific mortality subsequent to dairy consumption.

Prospective cohort studies published up to 31st Dec. 2017 were searched using PubMed, Embase, and Scopus database; the query syntax of searching is shown in the supplemental methods (Supplementary Table 2). This was complemented by additional searches of the reference list of eligible articles, and email correspondences with authors for additional data where relevant.

After excluding duplicates and based on titles and abstracts, we excluded studies on animals, baseline age <18 years, or populations with prior CHD, diabetes, or any other chronic diseases. Eligible studies were selected by using predefined inclusion criteria of prospective cohort studies, healthy populations and original articles on the association of milk and dairy intake and all-cause and cause specific mortality (CHD, cerebrovascular and cancer). In addition, supplementary search of reference lists of previous reviews or meta-analyses was conducted. Of 34 eligible full articles, 13 articles met the inclusion criteria (12 based on the literature search and recent NHANES data) (Supplementary Fig. 1).

2.5. Study selection

Study selection started with the removal of duplicates; followed by screening of titles and abstracts by two reviewers (MM and MB). To avoid bias, the reviewers were blinded to the names, qualifications or the institutional affiliations of the study authors. The agreement between the reviewers was excellent (*Kappa* index: 0.89; $p < 0.001$). Disagreements were resolved at a meeting between reviewers prior to selected articles being retrieved (a flow chart is available in Supplementary Fig. 1).

We included studies if they met all the following criteria [1]: the topic of interest was dairy products intake [2]; the studies were population-based cohort studies and reported cancer, stroke or cardiovascular or all-cause mortality data [3]; relative risk (RR), hazard ratio (HR) or odds ratio (OR) estimates with 95% CI adjusted for multivariable factors were available or could be calculated [4]; original articles with full texts in English. Studies were excluded according to the following criteria [1]: reviews, letters, unpublished data or comments [2]; not population-based cohort studies [3]; RR, HR or OR estimates with 95% CI were not available or could not be calculated. In case of lack of some important data we contacted the investigators from given study in order to avoid excluding it due to insufficient data availability. Narrative reviews, comments, opinion pieces, methodological reports, editorials, letters or any other publications lacking primary data and/or explicit method descriptions, were also excluded. The Nurses' Health Study reported separate articles on low-fat and high-fat dairy [27] and other types of dairy [17], and both were included in the meta-analysis.

2.6. Data extraction and management

The full text of studies meeting inclusion criteria were retrieved and screened to determine eligibility by two reviewers. The study quality assessment was performed according to the Newcastle–Ottawa Scale (NOS, Supplementary Table 3) [28]. By evaluation of selection, comparability and outcome, the rating system scores studies from 0 (highest degree of bias) to 9 (lowest degree of bias). Additionally we investigated the funding sources of all of the eligible studies. Following assessment of methodological quality, the two reviewers' extracted data (MM & MB) using a purpose-designed data extraction form and independently summarized the most important results from each study. These summaries were compared and any differences of opinion resolved by discussion and consultation with a third reviewer (DPM). Any further calculations on study data considered necessary, was conducted by the first reviewer and checked by the second reviewer. Information extracted from each eligible study included the following items: Author, Year and References, Study name, %Men, Mean Age, Follow-Up Time (Years), No. of cases, No. of subjects, Dairy types, Dietary assessment, Outcome, Main confounders. RR, HR or OR estimates with 95% CI with regard to different types of dairy products and doses were recorded, respectively. Categorization of dairy types was primarily based on the categorization in the original studies (Supplementary Table 4).

2.7. Data synthesis and statistical analyses

Meta-analyses of each dairy type were performed if the number of studies was three or more. For studies that reported results from different multivariable-adjusted models, the model with the most confounding factors was extracted for the meta-analysis. The random-effect model was applied to calculate pooled RRs, 95% CI and p value for heterogeneity. RRs comparing the highest intake category with the lowest intake category were combined across studies to generate the summary associations. The extent of heterogeneity across studies was examined using the I^2 test [29–33] and I^2 >50% together with two-sided $p < 0.05$ indicated significant heterogeneity [29–33].

2.8. Publication bias

Potential publication bias was explored using visual inspection of Begg's funnel plot asymmetry, Begg's rank correlation and Egger's weighted regression tests. The Duval and Tweedie trim method was used to adjust the analysis for the effects of publication bias [32]. Meta-analysis was conducted using Comprehensive Meta-Analysis (CMA) V3 software (Biostat, NJ) [33].

3. Results

3.1. NHANES data

24,474 subjects were included in the final analysis, with a mean age of 47.6 years and comprising 48.6% men and 51.4% women. Demographic characteristics of participants are shown in Table 1. Subjects with higher intake of dairy were younger (Q1: 48.1 *vs* Q4: 43.2 years, $p < 0.001$). There were also more males in the highest quartiles of dairy consumption (male: 55.6% *vs* female: 44.4%, $p < 0.001$). The top quartile of dairy intake included fewer Mexican-American (18.0% *vs* 21.0%) and other Hispanics (7.6 *vs* 8.5%), while the Whites (non-Hispanic) were mainly in the top quartile (57.6 *vs* 34.5%). With regard to marital status, more widowed (9.0 *vs* 6.0%) and divorced (11.3 *vs* 9.0%) participants were in lowest quartile. The majority of subjects with "less than high school" level of education were in lowest quartile of dairy intake (36.0 *vs* 24.2%), while subjects with "more than high school" were mostly in highest quartile of dairy consumption (52.6 *vs* 39.3%).

During the follow-up period of mean 76.4 months, 3520 total deaths were recorded, including 827 cancer deaths, 709 cardiac deaths, and 228 cerebrovascular disease deaths. The distributions of total and cause specific mortality across quartiles of dairy consumption are shown in Table 1. Results from three multivariable Cox regression models for risk of death across quartiles of total dairy, milk, yogurt, and cheese are shown in Table 2.

In all three models subjects in top quartile (Q4) of total dairy consumption, had a lower risk of total mortality (model 1: HR = 0.92, 95% Cl: 0.90–0.94; model 2: HR = 0.95, 95% Cl: 0.93–0.97, and model 3: HR = 0.98, 95% Cl: 0.95–0.99; $p < 0.001$ for all, Table 2, Fig. 1). There was no significant association between CHD mortality and total dairy consumption in any models ($p \geq 0.256$ for trend). There was graded decrease in chance of cerebrovascular for all three models across the quartiles of total dairy consumption (for model 3: Q2: HR = 0.98, 95% Cl: 0.97–0.99, Q3: HR = 0.97, 95% Cl: 0.95–0.99, and Q4: HR: 0.96, 95% Cl: 0.94–0.98, $p < 0.001$ for trend). With regard to cancer mortality we found no link between total dairy consumption and risk of cancer mortality ($p \geq 0.243$ for trend).

There was graded increase in risk of total mortality across the quarters of milk intake (Q2: HR = 1.02, 95% Cl: 0.01–1.03), (Q3: HR = 1.03, 95% Cl: 1.01–1.05), (Q4: HR = 1.08, 95% Cl: 1.05–1.11; $p < 0.001$, Table 2) in model 1, however, this link disappeared after more adjustment (in models 2 & 3). Of note, there was graded increase in risk of CHD mortality for all three models (model 3 – Q4: HR = 1.04, 95% Cl 1.02–1.06), while there was ranked decrease in risk of for cerebrovascular mortality across the quartile of milk intake (all $p < 0.001$). There was also no association between milk consumption and risk of cancer mortality ($p > 0.392$, Table 2).

With regard to yogurt consumption, in model 1 there was significant graded reduction in risk between total, cancer, CHD and stroke mortality across the quartile of yogurt consumption (all $p < 0.001$, Table 2), however after more adjustment (models 2 & 3) no link persisted between yogurt intake and cause specific mortality ($p > 0.328$, Table 2), except for CHD mortality, however with no significant trend (model 3: Q2: HR = 1.01, 95% Cl: 0.99–1.02, Q3: HR = 1.02, 95% Cl: 0.98–1.04, and Q4: HR = 0.98, 95% Cl: 0.97–0.99, $p = 0.125$).

We have found a graded decrease in risk across the quartiles of cheese intake for total mortality and this link was robust even after adjustment (model 3: Q2 HR = 0.98, 95% Cl: 0.84–0.98, Q3: HR = 0.95, 95% Cl: 0.82–0.99, and Q4: HR = 0.92, 95% Cl: 0.87–0.94, $p < 0.001$, Table 2). No association was found between cheese intake and risk of CHD or cancer mortality ($p > 0.325$). There was significant reverse association (13%) between risk of cerebrovascular mortality across the quartiles of cheese intake in model 1 ($p < 0.001$), however this link disappeared after further adjustment (models 2 & 3, $p > 0.283$, Table 2).

3.2. Meta-analysis

Overviews of key characteristics of the 12 prospective cohort studies (based on literature search) and the results from this NHANES study above are shown in Table 3. A total of 636,726 participants, with 40,018 mortality cases were included in the analysis. A total of 8 studies presented single sex results, 4 studies involved men and 4 women. The duration of follow-up ranged from 6 to 28 years, with a mean follow-up of 14.7 years. Results of quality assessment are shown in the Supplemental Table 3, with 11 studies scoring ≥7.

Table 1
Characteristics of the study participants by quarters of total dairy consumption.

		Quartiles of total dairy consumption				*Trend P*
		Q1 (n = 6123)	Q2 (n = 6109)	Q3 (n = 6118)	Q4 (n = 6124)	
Total dairy intake (cup equivalent servings/day) Median (25th–75th)		0.25 (0.12–0.32)	0.79 (0.61–0.76)	1.57 (1.35–1.83)	3.08 (2.53–4.10)	
Age (years)		48.1 ± 0.1	49.2 ± 0.2	47.4 ± 0.1	43.2 ± 0.3	<0.001
Sex	Men (%)	48.5	44.9	45.6	55.6	<0.001
	Women (%)	51.5	55.1	54.4	44.4	
Race/Ethnicity	Mexican-American (%)	21.0	18.8	18.6	18.0	<0.001
	Other Hispanic (%)	8.5	7.9	9.3	7.6	
	White (non-Hispanic) (%)	34.5	46.2	50.4	57.6	
	Non-Hispanic Black (%)	29.8	23.1	17.3	13.3	
	Other (%)	6.1	3.9	4.5	3.5	
Marital Status	Married (%)	19.0	53.0	5.9	52.5	<0.001
	Widowed (%)	9.0	9.3	9.2	6.0	
	Divorced (%)	11.3	10.1	10.8	9.0	
	Never married (%)	19.4	17.3	18.7	20.5	
Education Status	Less than high school (%)	36.0	28.1	27.0	24.2	<0.001
	Completed high school (%)	24.6	24.2	23.5	23.2	
	More than high school (%)	39.3	47.5	49.2	52.6	
Mortality status	Total mortality [n (%)]	900 (25.5)	999 (28.3)	740 (20.9)	881 (25.0)	<0.001
	Cancer mortality [n (%)]	201 (24.3)	189 (22.8)	237 (28.6)	200 (24.1)	<0.001
	Heart disease mortality [n (%)]	140 (19.7)	153 (21.5)	240 (33.8)	176 (24.8)	<0.001
	Cerebrovascular disease mortality [n (%)]	53 (23.2)	51 (22.3)	68 (29.8)	56 (24.5)	<0.001

Groups across the quartiles compared by either chi-square or analysis of variance. Values expressed as mean standard deviation or %.

Table 2
Multivariable-adjusted HRs (95% CIs) for mortality across quarters of total dairy consumption and its sub-group.

		Quartiles of total dairy (mEq/d)				Quartiles milk[a,b]				Quartiles yogurt[a]				Quartiles cheese[a]			
		Q2 (n = 6109)	Q3 (n = 6118)	Q4 (n = 6124)	*P*	Q2 (n = 6275)	Q3 (n = 6277)	Q4 (n = 6279)	*P*	Q2 (n = 6275)	Q3 (n = 6277)	Q4 (n = 6279)	*P*	Q2 (n = 6275)	Q3 (n = 6277)	Q4 (n = 6279)	*P*
Total mortality	Model 1	0.98 (0.76–1.09)	0.96 (0.88–1.02)	0.92 (0.90–0.94)	<0.001	1.02 (0.01–1.03)	1.03 (1.01–1.05)	1.08 (1.05–1.11)	<0.001	0.86 (0.81–0.92)	0.79 (0.74–0.82)	0.76 (0.72–0.81)	<0.001	0.89 (0.79–0.94)	0.85 (0.74–0.95)	0.78 (0.70–0.86)	<0.001
	Model 2	0.99 (0.82–1.09)	1.00 (0.99–1.06)	0.95 (0.93–0.97)	<0.001	0.99 (0.95–1.04)	1.01 (0.99–1.03)	1.03 (0.98–1.06)	0.179	0.92 (0.87–0.94)	0.90 (0.84–0.96)	0.89 (0.83–0.94)	<0.001	0.92 (0.82–0.95)	0.90 (0.81–0.96)	0.88 (0.74–0.92)	<0.001
	Model 3	1.01 (0.98–1.03)	0.99 (0.95–1.09)	0.98 (0.95–0.99)	<0.001	1.00 (0.99–1.01)	1.00 (0.98–1.02)	0.99 (0.98–1.00)	0.182	0.99 (0.86–1.09)	1.01 (0.88–1.15)	0.93 (0.85–1.01)	0.523	0.98 (0.84–0.98)	0.95 (0.82–0.99)	0.92 (0.87–0.97)	<0.001
Cancer mortality	Model 1	0.88 (0.79–1.00)	1.06 (0.92–1.11)	0.94 (0.88–1.00)	0.243	1.00 (0.98–1.03)	0.99 (0.94–1.06)	1.02 (0.98–1.04)	0.392	0.86 (0.84–0.92)	0.86 (0.83–0.93)	0.82 (0.78–0.86)	<0.001	1.00 (0.98–1.02)	1.02 (0.95–1.06)	0.99 (0.98–1.01)	0.425
	Model 2	0.96 (0.94–0.98)	0.99 (0.97–1.03)	0.80 (0.61–1.00)	0.523	0.97 (0.95–1.04)	0.99 (0.94–1.09)	1.03 (0.98–1.07)	0.672	0.98 (0.93–1.02)	1.01 (0.99–1.02)	1.02 (0.99–1.04)	0.415	0.95 (0.86–1.12)	1.08 (0.82–1.23)	1.05 (0.88–1.09)	0.325
	Model 3	1.01 (0.88–1.15)	0.99 (0.98–1.00)	1.02 (0.94–1.10)	0.429	1.00 (0.99–1.02)	1.06 (0.92–1.11)	0.99 (0.96–1.03)	0.483	0.99 (0.96–1.02)	0.99 (0.97–1.03)	1.00 (0.99–1.01)	0.352	1.02 (0.98–1.04)	1.00 (0.99–1.01)	0.99 (0.98–1.02)	0.852
CHD mortality	Model 1	0.98 (0.76–1.23)	0.99 (0.95–1.04)	0.96 (0.96–1.02)	0.256	1.06 (1.02–1.11)	1.09 (0.06–1.19)	1.14 (1.09–1.24)	<0.001	0.98 (0.970.99)	0.96 (0.94–0.98)	0.88 (0.84–0.92)	<0.001	1.02 (0.97–1.04)	1.01 (0.99–1.02)	0.96 (0.92–1.08)	0.643
	Model 2	1.00 (0.99–1.02)	0.97 (0.86–1.12)	1.02 (0.85–1.18)	0.328	1.05 (1.02–1.08)	1.07 (1.03–1.12)	1.08 (1.06–1.14)	<0.001	1.00 (0.99–1.02)	0.99 (0.98–1.03)	0.94 (0.91–0.97)	0.765	0.86 (0.74–1.12)	0.98 (0.91–1.08)	1.02 (0.99–1.04)	0.763
	Model 3	0.98 (0.95–1.03)	1.03 (0.99–1.05)	0.99 (0.96–1.02)	0.439	1.02 (1.00–1.04)	1.03 (1.01–1.05)	1.04 (1.02–1.06)	<0.001	1.01 (0.99–1.02)	1.02 (0.98–1.04)	0.98 (0.97–0.99)	0.125	1.10 (0.91–1.19)	0.99 (0.86–1.09)	1.04 (0.88–1.11)	0.723
Cerebrovascular disease mortality	Model 1	0.92 (0.90–0.94)	0.90 (0.87–0.93)	0.90 (0.88–0.93)	<0.001	0.92 (0.87–0.94)	0.87 (0.82–0.92)	0.86 (0.81–0.92)	<0.001	0.96 (0.91–0.99)	0.95 (0.93–0.98)	0.94 (0.92–0.97)	<0.001	0.96 (0.88–0.99)	0.92 (0.78–0.96)	0.87 (0.74–0.62)	<0.001
	Model 2	0.94 (0.91–0.97)	0.92 (0.89–0.95)	0.91 (0.87–0.93)	<0.001	0.92 (0.88–0.94)	0.90 (0.88–0.92)	0.89 (0.87–0.91)	<0.001	0.99 (0.98–1.01)	1.02 (0.99–1.04)	0.99 (0.95–1.04)	0.423	1.01 (0.99–1.02)	1.00 (0.98–1.03)	0.99 (0.97–1.04)	0.342
	Model 3	0.98 (0.97–0.99)	0.97 (0.95–0.99)	0.96 (0.94–0.98)	<0.001	0.95 (0.93–0.97)	0.94 (0.92–0.97)	0.93 (0.91–0.96)	<0.001	1.00 (0.98–1.02)	0.99 (0.98–1.00)	1.02 (0.97–1.05)	0.328	1.01 (0.99–1.02)	0.99 (0.95–1.05)	1.03 (0.95–1.08)	0.283

Grey shade indicates significant values.
Model 1: Adjusted for age, sex, and race, education, and marital status, poverty to income ratio, total energy intake, physical activity, and smoking and alcohol consumption.
Model 2: Adjusted for age, sex, race, education, and marital status, poverty to income ratio, total energy intake, physical activity, smoking, alcohol consumption, carbohydrates, saturated fat, protein, and dietary fiber.
Model 3: Adjusted for age, sex, race, education, and marital status, poverty to income ratio, total energy intake, physical activity, smoking, alcohol consumption, carbohydrates, saturated fat, protein, dietary fiber, body mass index, hypertension and diabetes.
Q1: considered as reference.
[a] Cup equivalent servings: 1 cup of milk or yogurt, 1.5 oz natural cheese or 2 oz processed cheese. Values include milk and milk products used in food mixtures. Milk, unless otherwise specified, refers to whole, reduced-fat, low-fat, non-fat and acidophilus milk, buttermilk, and reconstituted dry milk.
[b] Cup equivalent servings for milk intake were as following: Q1- 0.10 (0.06–0.14), Q2- 0.15 (0.20–0.26), Q3- 0.75 (0.55–1.00), and Q4- 1.84 (1.48–2.40).

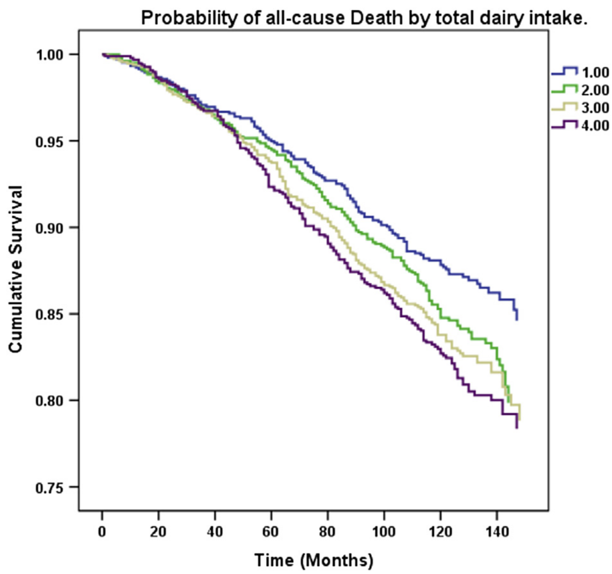

Fig. 1. Probability of all-cause death by total dairy intake.

3.3. Total dairy, low-fat dairy and high-fat dairy products

Total dairy consumption was not significantly associated with CHD mortality (RR: 1.01, 95% CI 0.98–1.03, $p = 0.586$, n = 5 studies, Fig. 2). There was minimal heterogeneity for CHD mortality and total dairy consumption (I^2: 10.2, $p = 0.846$). There was no association between either high fat dairy and low fat diary with CHD mortality (high fat = RR: 1.03, 95% CI 0.97–1.07, $p = 0.316$ (n = 4 studies, no heterogeneity, I^2: 9.36, $p = 0.893$) and low fat = RR: 0.97, 95% CI 0.93–1.01, $p = 0.190$, (n = 3 studies, no heterogeneity, I^2: 15.3, $p = 0.735$), Figs. 3 and 4). Moreover, we have found no link between total dairy intake with risk of cancer (RR: 1.00, 95% CI 0.93–1.07, $p = 0.989$, n = 6 studies, Fig. 5) with no sign of heterogeneity between studies – I^2: 17.4, $p = 0.349$.

3.4. Milk, cheese, yogurt, and total fermented dairy

There was no significant association between milk intake and total mortality (RR: 0.99, 95% CI 0.98–1.00, $p = 0.135$, n = 3 studies with no heterogeneity, I^2: 8.3, $p = 0.874$; Fig. 6), while there was a positive association between milk intake and CHD mortality (RR: 1.04, 1.02–1.06, $p < 0.001$, n = 3 studies, Fig. 7), with no sign of heterogeneity, I^2: 10.4, $p = 0.812$. Only one study evaluated the association of cheese and yogurt with outcomes, which therefore precluded a meta-analysis. However, we have run pooled meta-analysis on the impact of fermented dairy (cheese plus yogurt) on all-cause mortality and we noticed a significant and inverse association between fermented dairy consumption and risk of total mortality (RR: 0.98, 95% CI 0.96–0.99, $p = 0.023$, n = 3 studies, Fig. 8) with no sign of heterogeneity, I^2: 4.3, p = 0.941.

3.5. Sensitivity analysis

In leave-one-out sensitivity analyses, the pooled effect estimates remained similar for total dairy consumption and CHD mortality RR: 1.01, 95% CI 0.98–1.03 and for high fat dairy with CHD mortality RR: 1.03, 95% CI 0.97–1.07. This stability confirms that the significant difference between the studied groups is the overall effect of all included studies.

3.6. Publication bias

Visual inspection of funnel plot symmetry suggested no potential publication bias for the comparison of total dairy consumption and CHD mortality (Supplementary Fig. 2). Moreover, Egger's linear regression indicated absent publication bias (intercept = −0.45, 95% CI −6.91, 6.00, two-tailed $p = 0.837$); further Begg's rank correlation test (Kendall's Tau with continuity correction = 1.00, z = 0.244, two tailed $p = 0.806$) was not indicative for publication bias. After adjustment of effect size for potential publication bias using the 'trim and fill' correction, no potentially missing studies were imputed in funnel plot (RR = 1.01, 95% CI 0.98–1.03) (Supplementary Fig. 3). The 'fail-safe N' test showed that 123 studies would be needed to bring the weighted mean difference (WMD) down to a non-significant ($p > 0.05$) value.

4. Discussion

By applying both new analyses and meta-analysis results of current prospective studies in the US (for the homogeneity of comparison with NHANES participants) we present complementary information on the association of dairy consumption with total and cause-specific mortality. We have found that in an adjusted model, total dairy and cheese had beneficial association with total mortality, further both total dairy and milk consumption were associated with a lower risk of cerebrovascular mortality, while milk consumption associated with a higher risk of CHD mortality. For the first time we also presented separate data on yogurt, which was associated with a lower the risk of CHD, an association that attenuated after further adjustment. Our meta-analysis provided a better context of these results, as it showed a beneficial association of dairy products on total mortality risk. After pooling all the data from our original study and other published prospective studies together, we have found that milk consumption is associated with slightly higher risk (4%) of CHD mortality, whereas fermented dairy products were associated with lower total mortality.

We showed no associations between milk consumption and all-cause mortality, which is in agreement with other available studies [3,34,35]; however we also noticed a significant association of total dairy and total mortality (2–8% lower risks depending on the adjustment model). Larsson et al. [34] reported neutral associations of dairy and milk consumption with mortality or CHD mortality. Similar results were observed in the study by Mullie et al. [35]. In addition, the current study is in agreement with the systematic review by Drouin-Chartier et al. [36], which indicated no significant association between the consumption of total dairy and risk of CHD. In line with our results, the previous analyses also reported inverse associations between dairy product intake and stroke (RR 0.79; 95% CI: 0.68, 0.91) and all-cause mortality (RR 0.87; 95% CI: 0.77, 0.98) [37,38]. The previously reported inverse associations between milk intake and stroke (RR 0.79; 95% CI: 0.68, 0.91) [37,38], is in accordance with our study, however the level of risk reduction seems to be much less (7% for those with the highest milk consumption in fully adjusted model). Our findings did not also fully confirm the results of the meta-analysis by Hu et al., who reported a 9% lower risk for a high *vs* a low milk intake and the risk of stroke [39]. Our data suggest almost the same level of risk reduction for all milk consumers (Q2–Q4: 5–7%).

We have found a reverse link between total dairy and stroke mortality (in all models of adjustments), although a previous meta-analysis by de Goede et al. did not show such an association [19]. The reasons for the apparent association of total dairy intake with lower risk of stroke mortality remain unclear. Despite their fat content and composition, dairy products are rich in various minerals (e.g. calcium, potassium), protein and vitamins (e.g.

Table 3
Characteristics of 13 Prospective Cohort Studies on Dairy Consumption and mortality.

Author, year and References	Study	Men (%)	Mean Age (years)	Mean follow-up (years)	No. of cases	No. of subjects	Dairy types	Dietary assessment	Outcome	Main confounders
Kahn et al., 1984 [12]	California Seventh-Day Adventists	40	–	21	6180 deaths	27,530	Milk, Cheese	FFQ	All-cause mortality	Age, sex, smoking history, history of major chronic disease
Chow et al., 1992 [73]	Lutheran Brotherhood Insurance Society	100	–	20	219 lung cancer	17,633	Total dairy	FFQ	Lung cancer	Age, smoking status and industry/occupation
Hu et al., 1999 [9]	Nurses' Health Study	0	46.5	14	939 CHD	41,254	Total dairy, High-fat dairy, Low-fat dairy, Milk	FFQ	CHD (fatal and nonfatal)	Age, time period, BMI, smoking, menopausal status (including hormone replacement therapy), parental history of MI, vitamin E supplement, alcohol, history of hypertension, aspirin, physical activity, total energy intake
Bostick et al., 1999 [13]	Postmenopausal women, Iowa;	0	61.5	8	387 fatal IHD	34,486	Total dairy, High-fat dairy	FFQ	Fatal IHD	Age, total energy intake, body mass index, waist: ratio, history of diabetes mellitus, cigarette smoking status, postmenopausal estrogen use, alcohol intake, education, marital status, physical activity, dietary vitamin E and saturated fat intake
Iso et al., 1999 [17]	Nurses' Health Study	0	46	13.6	347 stroke	85,764	Milk Low-fat milk High-fat milk Yogurt Cheese	FFQ	Ischemic stroke	Age, smoking, time period, BMI, alcohol, menopausal status (including hormone replacement therapy), PA, multivitamin use, vitamin E supplementation, history of hypertension, DM, and hypercholesterolemia
Breslow et al., 2000 [74]	National Health Interview Survey	41	–	8.5	158 Lung cancer	20,004	Total dairy	FFQ	Lung cancer	Age, sex, smoking duration and packs per day smoked
Al-Delaimy et al., 2003 [14]	Health Professionals Follow-up Study	100	53	12	14,468 IHD (fatal and nonfatal)	39,800	Total dairy, High-fat dairy, Low-fat dairy, Milk	FFQ	IHD (fatal and nonfatal)	Age, time period, energy intake, history of diabetes, history of Hypercholesterolemia and hypertension, family history of MI, smoking history, aspirin, BMI, alcohol intake, physical activity, vitamin E, trans fatty acids, PUFA:SFA ratio, total protein intake, fiber, folate, n-3 fatty acids, and a-linolenic acid
Kelemen et al., 2005 [75]	Post-menopausal Iowa women	0		15	1676 cancer deaths	29,017	Total dairy	FFQ	All cancer	Age, total energy, carbohydrate, saturated fat, polyunsaturated fat, monounsaturated fat, trans-fat total fiber, dietary cholesterol, dietary methionine, alcohol, smoking, activity level, body mass index, history of hypertension, postmenopausal hormone use, multivitamin use, vitamin E supplement use, education and family history of cancer

(*continued on next page*)

Table 3 (*continued*)

Author, year and References	Study	Men (%)	Mean Age (years)	Mean follow-up (years)	No. of cases	No. of subjects	Dairy types	Dietary assessment	Outcome	Main confounders
Paganini-Hill et al., 2007 [15]	Leisure World Cohort Study	37	74	23	11,386 deaths	13,624	Milk	FFQ	All-cause mortality	Age, sex, smoking, exercise, BMI, alcohol, hypertension, angina, MI, stroke, diabetes, rheumatoid arthritis, cancer
Park et al., 2007 [76]	American Association of Retired Persons	100	–	6	305 prostate cancer	293,888	Whole milk	FFQ	Prostate cancer	Age, race, education, marital status, body mass index, vigorous physical activity, smoking, alcohol consumption, history of diabetes, family history of prostate cancer, screening for prostate cancer by use of prostate-specific antigen, intakes of tomatoes, red meat, fish, vitamin E, alphalinolenic acid and total energy
Song et al., 2013 [77]	Physicians' Health Study	100	–	28	2806 prostate cancer	21,660	Total dairy,	FFQ	Prostate cancer	Age, cigarette smoking, vigorous exercise, alcohol intake, race, body mass index, baseline diabetes status, red meat consumption, total energy intake from recorded food items, assignment in the original aspirin trial and assignment in the original β-carotene trial. In addition, the models for whole milk and skim/low-fat milk were mutually adjusted for each other
Haring et al., 2014 [16]	Atherosclerosis Risk in Communities Study	44.2	53.8	22	1147 CHD	12,066	Total dairy, High-fat dairy, Low-fat dairy	FFQ	CHD (fatal and nonfatal)	Age, sex, race, study centre, total energy intake, smoking, education, systolic blood pressure, use of antihypertensive medication, HDL cholesterol, total cholesterol, use of lipid lowering medication, body mass index, waist to-hip ratio, alcohol intake, sports-related physical activity, leisure-related physical activity, carbohydrate intake, fiber intake, and magnesium intake
Mazidi et al., 2018[a]	National Health and Nutrition Examination Survey	48.5	47.6	6.4	3520 deaths	24,474	Total dairy, Milk intake, Yogurt and Cheese intake	FFQ	All-cause, CHD, cerebrovascular, cancer mortality	Age, sex, race, education, and marital status, poverty to income ratio, total energy intake, physical activity, smoking, alcohol consumption, carbohydrates, saturated fat, protein, dietary fiber, body mass index, hypertension and diabetes.

Abbreviations: FFQ – food frequency questionnaire.
[a] Data of the NHANES analysis from the current paper.

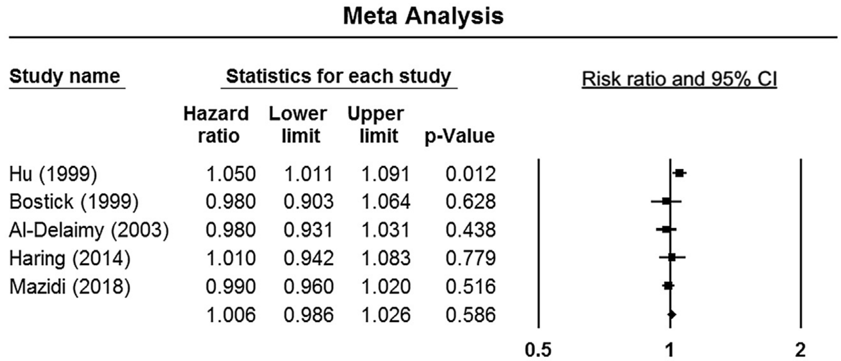

Fig. 2. Forest plot of total dairy consumption and risk of coronary heart disease mortality.

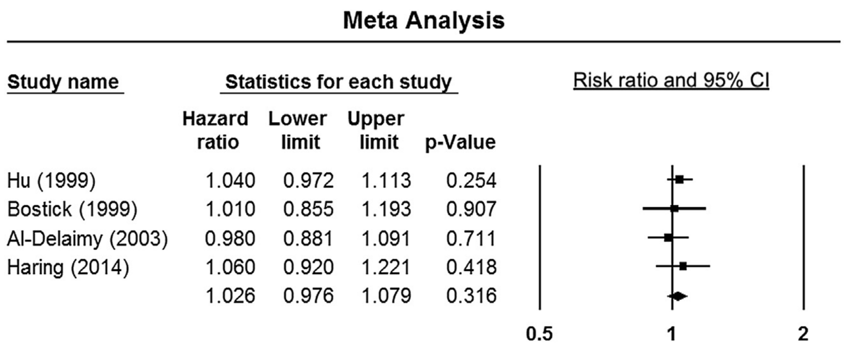

Fig. 3. Forest plot of high fat dairy consumption and risk of coronary heart disease mortality.

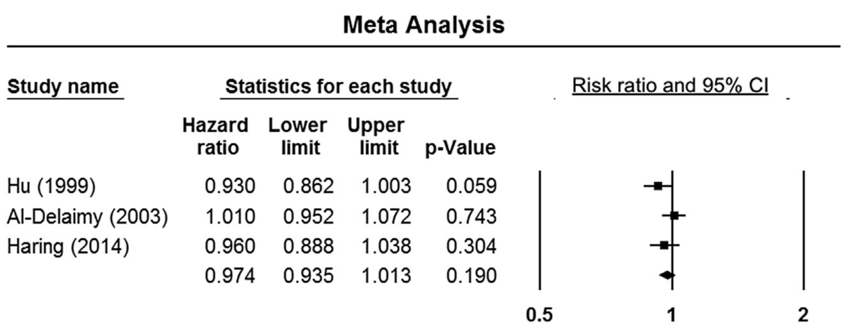

Fig. 4. Forest plot of low fat diary consumption and risk of coronary heart disease mortality.

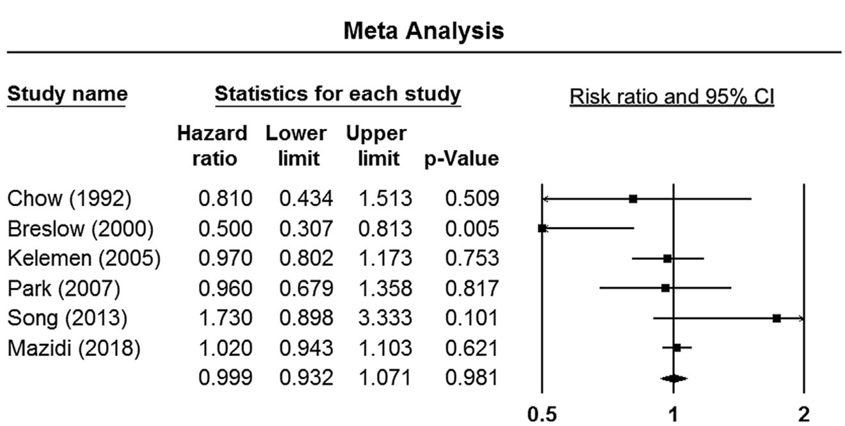

Fig. 5. Forest plot of total dairy consumption and risk of cancer mortality.

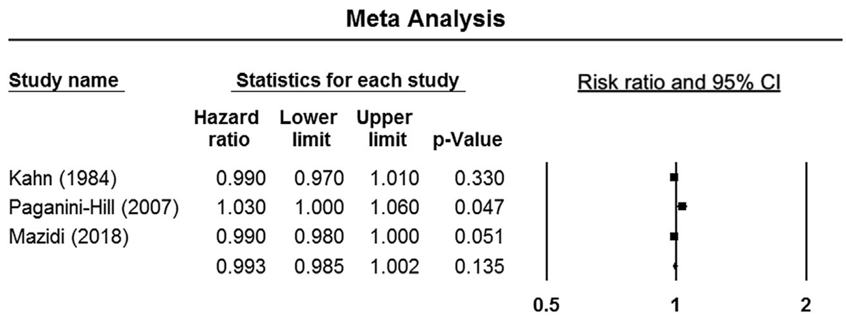

Fig. 6. Forest plot of milk consumption and risk of total mortality.

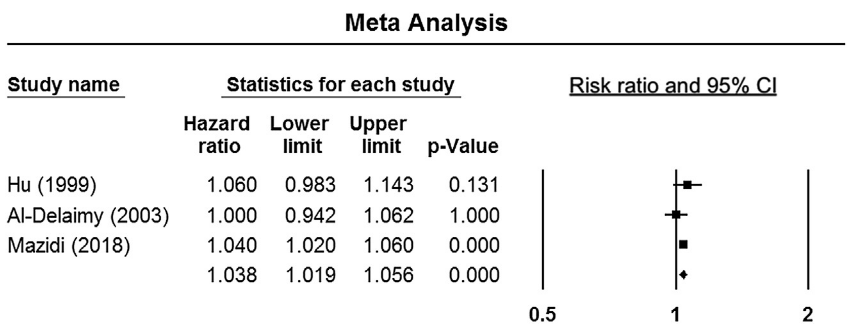

Fig. 7. Forest plot of milk consumption and risk of coronary heart disease mortality.

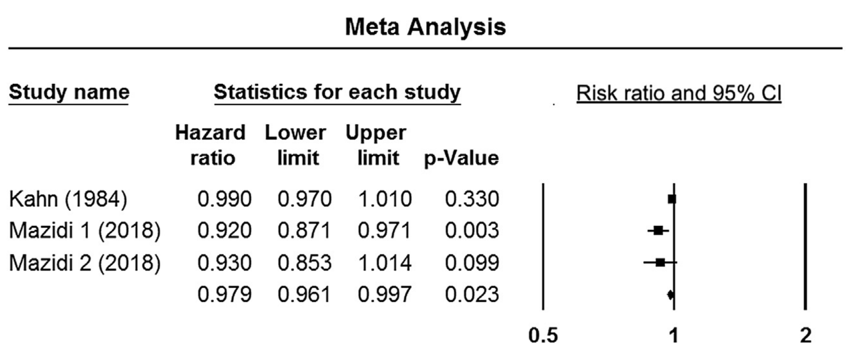

Fig. 8. Forest plot of fermented dairy consumption and risk of total mortality.

vitamin A and B12), and nutrients that have been suggested to be associated with lower stroke risk [3,40–44]. The available study also described dairy phosphorus as a major blood pressure-lowering mineral [45]. Other also indicated that subjects who had high-fat diets enriched with dairy minerals or calcium had significantly lower total cholesterol and LDL-C levels in comparison to those on a control diet [46,47]. A meta-analysis of 9 prospective cohort studies reported that milk was inversely associated with hypertension, a major risk factor for stroke [48]. Apart from butter, dairy products are an important source of calcium, which was inversely associated with stroke risk in a meta-analysis of 11 prospective cohort studies including populations with low-to-moderate calcium intakes [49]. The significant inverse association that we found for dairy intake in relation to stroke and all-cause mortality might have been also due to beneficial effects on blood pressure [50,51]. There is a number of available studies that clearly showed that the Dietary Approaches to Stop Hypertension (DASH) diet was associated with the significant reduction of systolic blood pressure, of which 50% could possibly be ascribed to intake of dairy products [52]. Interestingly, this effect has not been supported in randomized controlled trials (RCTs) that used consumption of low-fat dairy products as the intervention [53,54], which is in line with our results, which did not also show any significant association between either low or moderate diary intakes with total mortality.

We found no significant associations between high- and low-fat dairy and CHD mortality. This supports some results from previous meta-analyses, which also reported no association of high or low-fat dairy and CHD risk [6,55]. However US prospective cohort studies [56] showed a substantially lower risk of CHD when animal fats, including dairy fat, were replaced by unsaturated fats. Other meta-analyses [57,58] on this association included 12 prospective cohort studies, of which 8 were conducted before 1970, when only whole milk high in saturated fat was available, and the authors concluded that there was no clear evidence that dairy food consumption was related to a higher risk of CVD. Recently, UK National Health Service (NHS) has recommended low-fat milk and dairy products as healthy choices [56]. An analysis of the Nurses' Health Study investigators showed no association of high-fat dairy product intake with CHD [59].

Our analysis also showed total fermented dairy and cheese intake to be inversely associated with mortality risk, which is concordant with a recent study [3]. Our new analysis suggested that cheese consumption was inversely linked to total mortality. Similarly, the pooled analysis showed the same finding between fermented product including cheese and yogurt with total mortality. Alexander et al. [5] and Chen et al. [60] have also reported lower risk of CHD linked with higher intake of cheese. A systematic review and meta-analysis of 11 cohorts found cheese to be modestly and inversely associated with CHD risk [3]. After adjustment for wide range of confounders we failed to find a significant link between cheese or yoghurt intake with CHD or stroke mortality. The observed differences with other studies [61,62] might be due to the fact that only few covariates were adjusted in the investigated models in prior studies, as well as differences in the prevalence and stroke types between Asia and Western countries.

Unlike the result for cheese, yogurt intake was associated with a lower risk on all investigated outcomes; however for most of them (besides CHD mortality for those with the highest intake) such associated were significant only for the first model, attenuating to the null after further adjustment. We are the first that have evaluated the association of yogurt intake with total and cause specific mortality. A previous meta-analysis of RCTs suggested that yogurt is associated with lower risk of CVD [63]. Our results for yogurt intake and CVD may be due to the limited number of participants. Unfortunately, there was not a sufficient number of studies for a meta-analysis on this issue; however, by pooling fermented dairy (cheese plus yogurt), the meta-analysis showed a significant and inverse association with the risk of total mortality (RR 0.97, 95% CI 0.96–0.99). If this association represents a causal association, the mechanism of the beneficial association of fermented dairy products on reduced risk of mortality is uncertain. Evidence from RCTs suggests that, at least in part, this might be an effect of the food matrix reducing lipid absorption and short chain fatty acids (SCFA) produced by the bacteria in the large intestine [64,65]. SCFA are not only important for gut health and as signaling molecules, but might also enter the systemic circulation and directly affect metabolism or the function of peripheral tissues [65]. They contribute to improved glucose homeostasis and insulin sensitivity, which in turn can decrease oxidative stress and inflammation, which are triggers of stroke and mortality [65,66]. Moreover, omics-techniques have suggested that some of the beneficial effects of cheese can be accounted by microbial fermentation producing SCFA such as butyrate [65,67]. Cheese also contains a lot of sodium, which is directly linked to hypertension. A meta-analysis by Soedamah-Muthu et al. (2012), however, did not show a significant relation of cheese consumption to hypertension [48]. Thus, the mechanism of how dairy would protect against stroke is not clear yet.

In 2007 the World Cancer Research Fund (WCRF) team conducted several systematic reviews on the relation between dairy products and cancer [68]. The authors concluded that there was no significant link between dairy products and cancers of the lung, stomach and breast; however, higher consumption was suggested to increase the risk of prostate cancer [68]. In contrast, there was also suggestive evidence of an inverse association between milk intake and colon cancer [69]. We have found that after pooling all the data between US adults, there was no link between dairy intake and risk of cancer mortality, which is in accordance with other studies [70], unfortunately, because of relatively small sample size, we were not able to run sub-group analysis based on the type of cancer. All-cancer mortality represents a heterogeneous group of diseases, each with a different pathogenesis; this may have limited our ability to analyze these associations.

Our analyses have some strengths and limitations. NHANES is regarded as being reflective of the general USA population, and the use of the Centers for Medicare & Medicaid Services (CMS) provided quite complete follow-up for mortal events. As the data collection was performed on all days of the week throughout the year in NHANES, the potential for day-specific information bias is very low [71,72]. We have taken into account of the wide range of confounders in our analysis, which essentially decrease, but by no means exclude, the chance of residual confounding. Indeed, we recognize that since those with the lowest intakes of dairy products had lower educational status, and would likely be more overweight, then such individuals must be over-consuming other foods, which are more calorific and may increase risks of adverse outcomes. In our meta-analysis we observed very low level of heterogeneity, among others, because of using studies from the same county. As for comparisons, Hu et al. reported high heterogeneity for total dairy analyses in relation to stroke risk in Asian studies [39]. Finally, these results might have very important clinical relevance, especially in the time of low-protein and low-fat diets including such like vegan one, where all dairy products are forbidden. Based on our results it seems that the complete avoidance of dairy produces in our diet might be harmful for our health in the long-term perspective (especially over 3 years based on Kaplan-Maier survival curves). Taking into account the data on milk and slightly increased risk of CHD mortality it seems we should use only low-fat milk at moderate daily intake. However, having in mind the beneficial effect of milk intake on stroke mortality, the issue of daily milk intake and the possible mechanisms involved need to be still investigated and explained.

Despite the strengths of the NHANES, the findings from our study need to be considered in the context of some study limitations. One is associated with the use of recall from NHANES participants to assess dietary intake, and even with the application of AMPM this should be treated as methodological limitation of the study. Another one is associated with the types of dairy products investigated, as we analyzed them as a whole (taking into account available questionnaires there was no possibility to perform more detailed analysis) and in the consequence we cannot give the clear answer e.g. what kind of cheese or yoghurt is more or less healthy taking into account the obtained results. We were not also able to adjust the final results to all possible confounders, including osteoporosis diagnosis (where patients are advised to intake dairy products) or coffee intake (especially for those drinking white coffee). Due to the fact that NHANES population was restricted to individuals 20 + years of age our findings may not apply to the health effects of dairy product intake in early stages of life - in which intake particularly of milk is pretty high, and recommended by pediatricians. Moreover, because of the prospective design, the misclassification of exposure, which is unavoidable in dietary assessments, is most likely non-differential. It would have been better to analyze the risk of cancer and dairy intake with regard to different types of cancer, rather than total cancer mortality.

In conclusion, we have found that a greater intake of total dairy have beneficial associations with mortality (total and cerebrovascular) in US adults, although milk intake does seem to be associated with higher CHD mortality. These results shed light on the hitherto controversial facts about the dairy consumption. They might help policy makers to increase public awareness about the role of the diet, particularly dairy products. The present findings suggest that advice to limit dairy products should be interpreted with caution.

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Conflict of interest

All authors have nothing to declare in relation to the subject of this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2018.12.015.

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