nature portfolio

Peer Review File

A global analysis of dairy consumption and incident cardiovascular disease

Corresponding Author: Dr Jingjing Jiao

This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)
This is a prospective study of the association between dairy consumption and incidence of CVD, coronary heart disease and stroke among a large sample of individuals from the UK Biobank and the China Kadoorie Biobank (CKB). The authors also examined the association between different types of dairy products (cheese, milk, and yogurt) and the outcomes with data from the UK Biobank. The authors also performed a systemic review and an updated meta-analysis, including their findings, of dairy consumption and risk of CVD. In general, associations were found between dairy consumption and lower risk of CVD.

Main comments
Authors should explain in detail how many times diet was measured with a FFQ in the Chinese cohort. Using only a measure at the beginning of the follow-up seems too weak. It is also unclear why in that cohort, information on consumption of other sources of proteins in unavailable (line 341).
About the diet measurement in the UK Biobank, the authors need to explain that a very small % of the population in the study completed the 5 24h dietary records. Thus, how did the authors reached the total N used in the analyses? Did the considered any participant with at least one 24h dietary record? At least 2? This is a limitation of the study since it's unclear whether habitual diet has really been assessed. As in the Chinese cohort, the lack of measurements during the follow-up impeded calculate the cumulative exposure to dairy, this needs to be acknowledged.
Main results are not adjusted for total energy intake. The authors need to justify why, since this adjustment is necessary to understand the independent effect of food on health, independently of the amount of energy provided.

Minor
1. Lines 26-28. Please, verify the references. References 3 and 4, support the benefits of dairy consumption and CVD risk factors, whereas reference 5 supports the beneficial effect of a specific component of dairy. It is not clear whether the authors want to support the beneficial effects of dairy products or its nutritional content.
2. Reference 7 does not support the statement.
3. Lines 41-42. Please, provide a reference for this argument.
4. The authors include a significant number of results, considering all the supplementary figures and tables. It may be beneficial to consolidate this information into fewer tables, including clear estimates for the independent association of low-fat milk, yogurt, and cheese.
5. Null associations identified in the substitution analysis may warrant further discussion.
6. Significant interactions were found that are not further discussed. For instance, the association between dairy consumption and CVD in the CKB was only protective for men and those with hypertension. In the UK Biobank, the inverse associations of cheese consumption with CVD and with CHD are only found for those without diabetes. Only predefined differences across categories based on previous evidence need to be included. An explanation of the rationale behind needs to be added to the Methods section.
7. Lines 160-163. Although moderate milk consumption (>0 to 0.5 serving/d) was associated with a lower risk of hemorrhagic stroke (HR 0.43, 95% CI 0.21–0.87), this result should be interpreted with caution as the number of cases is very low (n=8).
8. Please, expand the discussion on the conflicting results for the association between dairy consumption and CVD in the CKB and the UKB. This is a main result that is briefly mentioned in the discussion.

Reviewer #2

(Remarks to the Author)
I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Nature Communications initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

Reviewer #3

(Remarks to the Author)
This manuscript describes a pooled analysis of UKB and CKB, assessing the asocition of dairy with CVD. They identified almost 100,000 CVD cases over 9-million person years of follow-up. They have also conducted a meta-analysis of other studies to add to the robustness of the findings. An extensive amount of supplementary material is provided that provides a full picture of methods and results. The findings were somewhat consistent between UKB and CKB except for higher CHD risk with regular dairy consumption in CKB. In the updated meta-analysis, dairy consumption was associated with lower CVD and stroke risk. This work is comprehensive and the manuscript is organized and well-written. The major missing piece is an assessment of the confidence in the body of evidence, using an approach such as that used by the WHO, and other groups, such as GRADE.

The noteworthy results are the updated analyses of UKB and CKB; and pooled with the previous cohort studies. The work will be of significance, but largely supports previous studies of the area, so will strengthen evidence.

1. The meta-analysis seems competently performed. One question about the categorization- you put together high-fat milk, high-fat yogurt with high-fat cheese, cream, or butter. Even high-fat milk and yogurt have substantially less fat than high-fat ice cream, cream, or butter. Coudl you justify why you've classified as you did.
2. In the meta-analysis of high-fat dairy, cheese was not included unless studies separately analyzed low-fat and high-fat cheese". Why? Isn't it more probable for all/most cheese consumption to be high-fat cheese?
3. The analyses in UKB and CKB were will performed.
4. What statistical approach to random-effects meta-analysis was used?
5. Why was soya milk (Supp. Table 21) included in this review- it is not a dairy product. Please justify why soy over other types of milk- and consider removing from the analysis.
5 Line 98: What were the results of interaction? Perhaps worth summarizing the sex-interaction in CKB
6. Line 110-112: This is a bit of an overstatement, implying that the addition of the 2 new studies resulted in a new conclusion- I would argue that it did not; the point estimate is the same with UKB and CKB, but the CI has narrowed, as expected with more studies.
7. Lines 112-115: The dose-response is interesting, but is there a "ceiling" effect? Over what range of doses was this dose-response valid? Please clarify this in the text- with the abundance of supplemental figures, this point could easily be missed.
8. Lines 120-122: Why the descriptive "especially cheese" is noted? The comparison between fermented dairy and cheese reveal practically identical point effects and CI- yes, cheese is 0.02-points lower, but I am not certain this difference is meaningful. Was there evidence of differential effect (e.g., subgroup differences?).
9. Lines 143-145. Conducting the fixed effect meta-analysis if there is no significant heterogeneity is ok, but did these analyses show any substantial difference from the RE models? And how did you define "significant heterogeneity"?
10. Lines 179-183. You cite other meta-analyses that have found protective associations with cheese and CVD. What degree of overlap was between the meta-analysis (updated) you performed; and the ones cited? If there is high overlap, it's not surprising. Please address this.
11. Line 197: good hypotheses for little (no) benefit of yogurt. Additionally, might consider yogurt as ultraprocessed food by the NOVA system- what data are there of the association of UPF and CVD?
12. Line 204-205: What is meant by "toxic""? This is a strong word, I think. The two studies cited are animal models; it's not clear how relevant these are for human levels of consumption of D-galactose. I would suggest citing stronger evidence in humans to make this statement.
13. What is the d-galactose content of cheese compared to milk? This would be useful to provide in light of the previous statement.
14. No attempt was made to assess the confidence in the findings, as is done in Cochrane reviews, and major guidelines organization (e.g., WHO). I would suggest an assessment of the exposure-outcomes associations using GRADE would help here. (https://macgrade.mcmaster.ca/grade-learning-hub/grade-for-systematic-reviews/)

Reviewer #4

(Remarks to the Author)
I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Nature Communications initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

Reviewer #2

(Remarks to the Author)
I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Nature Communications initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

Reviewer #3

(Remarks to the Author)
Thank you- for the most part you have addressed my suggestions thoroughly, and I hope you found them to improve the presentation of your work.

I would still like to see a more rigorous treatment of interaction. This should be done for any time you talk about subgroup differences -- the one below, for sex, is one example, but the principle should apply to all between-subgroup differences.

My original point #6 -- asked for the test of interaction. It's not adequate to say that two groups are different from each other simply because one group shows a "significant" effect and the other does not. What you need to do is the test for between-groups heterogeneity, or meta-regression to assess interaction between sex and dairy on CVD in CKB -- otherwise, this could simply be chance finding.

Reviewer #4

(Remarks to the Author)
I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Nature Communications initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

Version 2:

Reviewer comments:

Reviewer #3

(Remarks to the Author)
Thank you for your patience. I regret that it took me so long to re-assess this manuscript, and thank the authors for their understanding of our competing deadlines.

The investigation of the association between dairy foods and CVD, while not particularly novel itself, is important to continue to assess, as the food supply changes and dietary advice evolves. This manuscript does a good job of advancing the literature in this regard. The data analysis is sound, and interpretations and conclusions supported by the data. There is enough data provided to reproduce the findings.

Upon review, the authors have now treated the issue of interactions appropriately, which has satisfied my request regarding this deficiency. The quality of the manuscript is much improved as a result, and I am more confident in the observed interactions. No further revisions suggested by me.

Thank you for the opportunity to review this manuscript.

Reviewer #4

(Remarks to the Author)
I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Nature Communications initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

Response to Referees

Manuscript title: Dairy consumption and incident cardiovascular disease: a global analysis
Manuscript ID: NCOMMS-24-17291A

Dear editor,

Thank you for considering our manuscript. We sincerely appreciate the thoughtful suggestions provided by the reviewers and editors, which have significantly enhanced the quality of our work. We have made substantial revisions to address each comment and have provided a detailed and point-by-point response (with changes highlighted in yellow in the revised manuscript). We believe these revisions have greatly strengthened our manuscript. If there are any further requests or questions, please feel free to contact us. We look forward to your feedback.

Response to Reviewer #1:

This is a prospective study of the association between dairy consumption and incidence of CVD, coronary heart disease and stroke among a large sample of individuals from the UK Biobank and the China Kadoorie Biobank (CKB). The authors also examined the association between different types of dairy products (cheese, milk, and yogurt) and the outcomes with data from the UK Biobank. The authors also performed a systemic review and an updated meta-analysis, including their findings, of dairy consumption and risk of CVD. In general, associations were found between dairy consumption and lower risk of CVD.

Response: We appreciate your comprehensive summary of our study.

Main comments

1. **Authors should explain in detail how many times diet was measured with a FFQ in the Chinese cohort. Using only a measure at the beginning of the follow-up seems too weak. It is also unclear why in that cohort, information on consumption of other sources of proteins in unavailable (line 341).**

Response: Thank you for your insightful comments. Regarding the first question, the China Kadoorie Biobank (CKB) study administered a qualitative FFQ at baseline (2004–2008) and during the first resurvey (2008–2009). Subsequently, in the second resurvey (2013), a quantitative FFQ was introduced, which included three subtypes of dairy products: milk, yogurt, and other dairy products such as cheese and milk powder [1]. However, only 3.8% and 4.9% of participants attended the first and second resurveys, respectively. To maximize the sample size and statistical power for our analysis, we utilized data from the baseline dietary questionnaire in our main analysis, consistent with the approach taken in other studies[2]. We acknowledge that relying solely on baseline measurements may not fully capture long-term dietary changes during follow-up. Nevertheless, the adjusted Spearman coefficients for dairy product consumption frequency demonstrated a reproducibility of 0.4 when comparing the second and third survey FFQs with the baseline FFQ, suggesting that our exposure was relatively stable

and that baseline dairy consumption was suitable for analyzing its association with disease outcomes[1].

To better reflect long-term intake levels, we **have now calculated the long-term usual level of dairy consumption (g/day)** by incorporating data from three dietary surveys, following a previously published method[3], which allows us to control for regression dilution bias. The quantitative FFQ from the second resurvey provided more detailed dietary data, including daily portions of each food group and the consumption (both frequency and amount) of the three subtypes of dairy products. This allowed us to estimate the mean usual amount of consumption during the follow-up period for each food category at baseline[3]. We have now additionally analyzed the associations of long-term usual dairy intakes (per 50 g/d increment) with CVD, as presented in the **Supplementary Table 5**. These results were consistent with our main findings based on frequency data.

For the second question, since the CKB only collected the frequency of consumption for major food items rather than specific quantities at baseline, the amounts of other sources of proteins consumed (g/d) were not collected, so we could not conduct the substitution analysis. However, **we have now estimated the long-term usual dairy intakes for major food groups, including other sources of protein**, following the previously published method[3]. We have now additionally conducted the substitution analyses in the CKB and compared the results with those from the UKB. Notably, replacing every 50 g of dairy products with eggs was associated with higher risks of CVD, CHD, and stroke. Consuming dairy instead of fish or soybeans was associated with higher CHD incidence, whereas replacing meat or soybeans with dairy was associated with a lower risk of stroke (**Extended Data Fig. 2**). We have now added these results to the manuscript (**Extended Data Fig. 2**) and further discussed them.

Results, Page 4, lines 73 to 74:

Similar associations of CVD, CHD, and stroke were detected for the long-term usual dairy intakes (per 50 g/d increment) (**Supplementary Table 5**).

Results, Page 5, lines 105 to 110:

In hypothetical substitution analyses, no significant associations were found in UKB. In CKB, replacing 50 g/d of eggs with an equivalent amount of dairy products was associated with an 11% higher risk of CVD, a 13% higher risk of CHD, and a 9% higher risk of stroke. In addition, substituting dairy products for fish or soybeans was associated with a 4% increase in CHD risk, whereas replacing red meat or soybeans with dairy products was associated with a 2% or 3% reduction in stroke risk, respectively (**Extended Data Figure 2**).

Discussion, Page 11, lines 257 to 268:

The differing outcomes of substitution analyses between CKB and UKB may be attributed to differences in national dietary patterns and the metabolic profiles of their respective populations[63]. Research has indicated that egg consumption could confer health benefits in Asian populations[64]. A previous cohort study within the CKB cohort found that daily egg consumption (up to <1 egg/day) was associated with an 18% reduction in CVD mortality and a 26% lower risk of hemorrhagic stroke[65]. Our substitution model results aligned with these findings, suggesting that egg consumption may offer more significant cardioprotective benefits

than dairy products among the Chinese population. In contrast, the UKB substitution analysis showed a null association, indicating that the cardiometabolic impacts of other protein sources were comparable to those of dairy products in the UK. This is consistent with findings from a previous study in the US, which showed that replacing dairy products with other protein sources did not significantly affect CHD risk[66].

Dietary assessments, Pages 14, lines 343 to 346:
The adjusted Spearman coefficients of dairy consumption frequency were 0.4 for reproducibility and 0.5 for validity, comparing two FFQs conducted in the second and third surveys with the baseline FFQ, which implicated good performance of the FFQ [72].

Methods, Page 15, lines 347 to 350:
The long-term usual amount of consumption for each category of food consumption variable was estimated according to the previously published method using the data of two resurveys in the CKB[73]. The daily energy intake at baseline was also estimated[74].

Supplementary Table 5:
Hazard ratios (95% confidence intervals) for incident cardiovascular disease for each 50 g/day increase in usual dairy intake in the China Kadoorie Biobank

	HR (95% CI) for per 50 g/d	P value
CVD		
Model 1[a]	1.26(1.24–1.28)	<0.001
Model 2[b]	0.96(0.95–0.98)	<0.001
Model 3[c]	0.97(0.96–0.99)	0.006
Model 4[d]	1.01(0.99–1.03)	0.503
CHD		
Model 1[a]	1.45(1.42–1.48)	<0.001
Model 2[b]	1.03(1.01–1.06)	0.018
Model 3[c]	1.04(1.02–1.07)	0.002
Model 4[d]	1.07(1.04–1.10)	<0.001
Stroke		
Model 1[a]	1.15(1.13–1.17)	<0.001
Model 2[b]	0.91(0.89–0.94)	<0.001
Model 3[c]	0.93(0.90–0.95)	<0.001
Model 4[d]	0.96(0.94–0.99)	0.003
Haemorrhagic stroke		
Model 1[a]	0.58(0.55–0.61)	<0.001
Model 2[b]	0.75(0.70–0.80)	<0.001
Model 3[c]	0.78(0.73–0.83)	<0.001
Model 4[d]	0.84(0.78–0.89)	<0.001
Ischaemic stroke		
Model 1[a]	1.29(1.26–1.32)	<0.001
Model 2[b]	0.93(0.91–0.96)	<0.001
Model 3[c]	0.94(0.92–0.97)	<0.001

Model 4[d]	0.98(0.95–1.00)	0.063

[a]Model 1 was adjusted for age and sex.

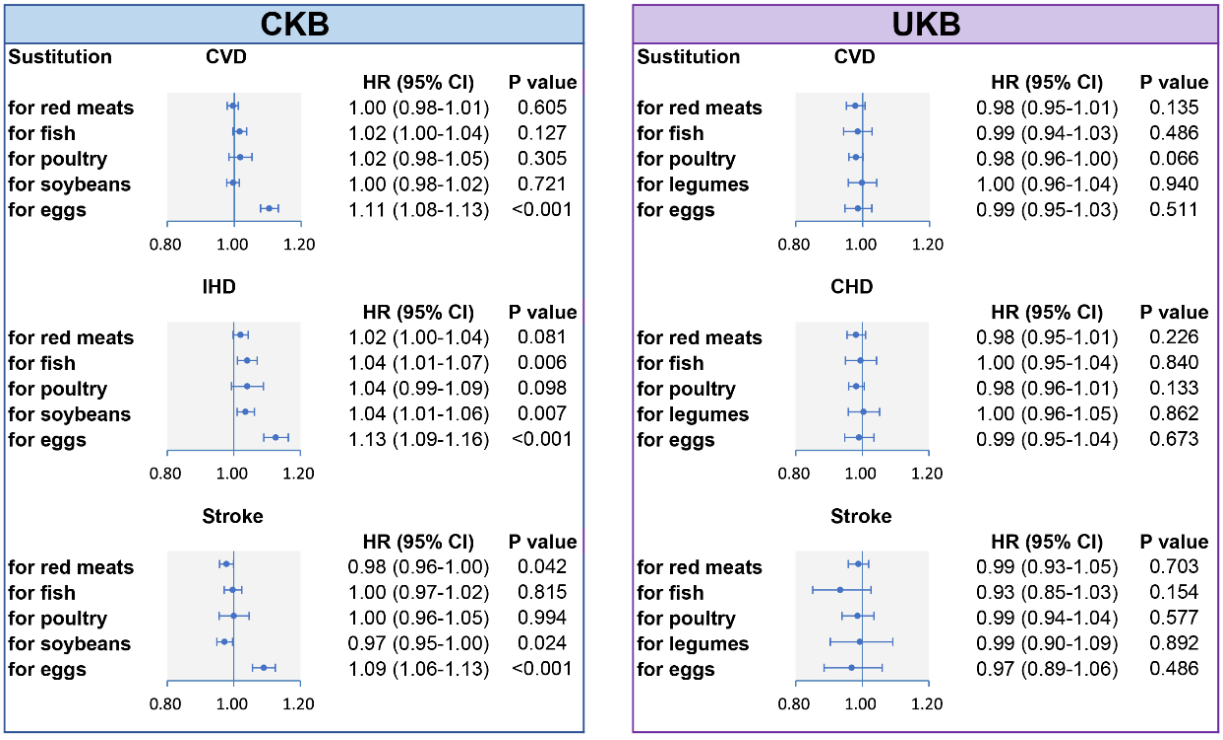
[b]Model 2 was further adjusted for study area (10 regions), survey season, education (no formal school, primary school, middle or high school, or college and above), income (in yuan/year; <5000, 5000-9999, 10 000–19 999, 20 000-34 999, or ≥35 000), physical activity (in MET-h/wk; quartiles), smoking (never/occasionally, former, or current smoker), alcohol drinking (never/occasionally, former, or current drinker), family history of CVD (yes or no), aspirin use (yes or no), vitamins use (yes or no), and minerals use (yes or no).

[c]Model 3 was further adjusted for body mass index (in kg/m^2; <18.5, 18.5-23.9, 24-27.9, or ≥28), history of hypertension (yes or no), and diabetes (yes or no).

[d]Model 4 was further adjusted for red meat, fish, poultry, eggs, fruits (never/rarely, monthly, 1–3 days/week, or regularly), and vegetables (daily or less than daily).

Extended Data Fig. 2:

Statistical model-based hazard ratios and 95% confidence intervals for incident cardiovascular disease, coronary heart diseases, stroke associated with replacement of one serving per day of other major protein sources with one serving per day of dairy products in China Kadoorie Biobank and UK Biobank.



2. **About the diet measurement in the UK Biobank, the authors need to explain that a very small % of the population in the study completed the 5 24h dietary records. Thus, how did the authors reached the total N used in the analyses? Did the considered any participant with at least one 24h dietary record? At least 2? This is a limitation of the study since it's unclear whether habitual diet has really been assessed. As in the Chinese cohort, the lack of measurements during the follow-up impeded calculate the cumulative exposure to dairy, this needs to be acknowledged.**

Response: We appreciate the reviewer's comment. In the analyses of UKB, the exposure included the frequency of cheese intake (n=418,895) and milk type (n=429,240) assessed by the touch-screen questionnaire (short FFQ), and dairy product intake assessed by the 24h dietary recalls (n=183,446). **To maximize the study sample size and statistical power in our study, we included participants with at least one 24-h dietary record (n=183,446) for assessing the dairy product intake in relation to CVD, which was valid as other studies did** [4-6]. Cumulative means of diary intakes were calculated using five 24-h dietary recalls. We admit that only a small proportion of participants (2.7%) completed the total five 24-h dietary records and 39.6% of participants only had one 24-h dietary record. Relying on one time dietary assessment at baseline may not capture dietary changes during follow-up, but this tends to dilute the observed associations because of the prospective design. **To better represent habitual diet, we have now only included individuals with at least two 24-h dietary records (n=110,739) in the sensitivity analysis. Results showed that the inverse association remained for dairy consumption with CVD risk** (**Supplementary Table 22**). We have now acknowledged and discussed these in the limitation.

For the CKB, we **have now calculated the long-term usual level of dairy consumption (g/day)** by incorporating data from dietary resurveys, following a previously published method[3], which allows us to control for regression dilution bias. We have now additionally analyzed the associations of long-term usual dairy intakes (per 50 g/d increment) with CVD, as presented in the **Supplementary Table 5**. These results were consistent with our main findings based on frequency data. We have now acknowledged and discussed these in the limitation.

Results, Page 5, lines 104 to 105:
Moreover, our results did not alter substantially in sensitivity analyses (**Supplementary Tables 21-24**).
Discussion, Page 13, lines 298 to 307:
Third, dairy consumption was assessed only once at baseline in the CKB study and only a small proportion of participants completed all five 24-hour dietary recalls in the UKB. As a result, dietary changes during the follow-up period could potentially weaken the observed associations. However, we estimated the long-term usual intake of dairy by incorporating data from dietary resurveys in the CKB and included participants with at least two 24-hour dietary recalls in UKB in sensitivity analyses, which yielded similar results. In addition, consistent findings were observed even with a shorter follow-up duration of 5 years, suggesting that the lack of repeated measurements is unlikely to have significantly impacted our findings. Nonetheless, further studies incorporating repeated measures of dairy intake are encouraged to validate these results.

Methods, Page 15, lines 358 to 365:
Five separate occasions of 24-hour dietary recalls were conducted during 2011-2012 to provide an average measure for individuals (repeated measurement per person). A total of 183,446 participants with at least one 24-hour dietary recall were included in the study. The number of 24-hour dietary records provided by these participants is detailed in **Supplementary Table 31**. The consistency between dietary touch-screen questionnaires and online 24-hour dietary assessments has been reported before [75]. The Spearman coefficients of cheese intake frequency

between baseline and resurveys during follow-up are higher than 0.5 (**Supplementary Table 32**).

Methods, Page 18, lines 425 to 427:

In UKB analysis, we further adjusted for salt added to food to see whether the main findings altered. Individuals with at least two 24-h dietary records were included to better represent their usual diet.

Supplementary Table 31:

Numbers of 24-h dietary records for participants included in analysis of UKB.

Number of 24-h dietary record	N (%)
1	72,707 (39.6)
2	42,018 (22.9)
3	37,081 (20.2)
4	26,638 (14.5)
5	5002 (2.7)

Supplementary Table 22:

Multivariable Hazard Ratios (95% CIs) of cardiovascular disease, coronary heart disease and stroke risk associated with total dairy consumption from sensitivity analyses in the UK Biobank.

	Frequency of Dairy Consumption			P trend
	≤0.5 serving/d	0.5–1.0 serving/d	> 1 serving/d	
Excluding participants with only one record of 24-h dietary recall				
CVD	1 [Reference]	0.93 (0.88–0.99)	0.94 (0.89–0.996)	0.037
CHD	1 [Reference]	0.94 (0.88–1.01)	0.95 (0.89–1.01)	0.107
Stroke	1 [Reference]	0.88 (0.77–1.00)	0.91 (0.81–1.04)	0.176

Supplementary Table 5:

Hazard ratios (95% confidence intervals) for incident cardiovascular disease for each 50 g/day increase in usual dairy intake in the China Kadoorie Biobank

	HR (95% CI) for per 50 g/d	P value
CVD		
Model 1[a]	1.26(1.24–1.28)	<0.001
Model 2[b]	0.96(0.95–0.98)	<0.001
Model 3[c]	0.97(0.96–0.99)	0.006
Model 4[d]	1.01(0.99–1.03)	0.503
CHD		
Model 1[a]	1.45(1.42–1.48)	<0.001
Model 2[b]	1.03(1.01–1.06)	0.018
Model 3[c]	1.04(1.02–1.07)	0.002
Model 4[d]	1.07(1.04–1.10)	<0.001
Stroke		
Model 1[a]	1.15(1.13–1.17)	<0.001

Model 2[b]	0.91(0.89–0.94)	<0.001
Model 3[c]	0.93(0.90–0.95)	<0.001
Model 4[d]	0.96(0.94–0.99)	0.003
Haemorrhagic stroke		
Model 1[a]	0.58(0.55–0.61)	<0.001
Model 2[b]	0.75(0.70–0.80)	<0.001
Model 3[c]	0.78(0.73–0.83)	<0.001
Model 4[d]	0.84(0.78–0.89)	<0.001
Ischaemic stroke		
Model 1[a]	1.29(1.26–1.32)	<0.001
Model 2[b]	0.93(0.91–0.96)	<0.001
Model 3[c]	0.94(0.92–0.97)	<0.001
Model 4[d]	0.98(0.95–1.00)	0.063

[a]Model 1 was adjusted for age and sex.

[b]Model 2 was further adjusted for study area (10 regions), survey season, education (no formal school, primary school, middle or high school, or college and above), income (in yuan/year; <5000, 5000-9999, 10 000–19 999, 20 000-34 999, or ≥35 000), physical activity (in MET-h/wk; quartiles), smoking (never/occasionally, former, or current smoker), alcohol drinking (never/occasionally, former, or current drinker), family history of CVD (yes or no), aspirin use (yes or no), vitamins use (yes or no) and minerals use (yes or no).

[c]Model 3 was further adjusted for body mass index (in kg/m^2; <18.5, 18.5-23.9, 24-27.9, or ≥28), history of hypertension (yes or no), and diabetes (yes or no).

[d]Model 4 was further adjusted for red meat, fish, poultry, eggs, fruits (never/rarely, monthly, 1–3 days/week, or regularly), and vegetables (daily or less than daily).

Supplementary Table 32:

The Spearman coefficients of cheese intake frequency between baseline and resurveys

	Baseline	**First repeat assessment (2012-2013)**	**Imaging visit (2014 and later)**
No. of participants	418,895	17,170	7,095
Baseline	1	0.56	0.52
First repeat assessment (2012-2013)		1	0.60
Imaging visit (2014 and later)			1

3. Main results are not adjusted for total energy intake. The authors need to justify why, since this adjustment is necessary to understand the independent effect of food on health, independently of the amount of energy provided.

Response: We appreciate this important question. Investigators of CKB collected daily amount intake of each food group at the second resurvey and we have now used the data to estimate

daily energy intake as other studies did[7-9]. We have now further adjusted the energy intake in the sensitivity analysis and the main findings were not materially changed in CKB and UKB.

Methods, Page 15, lines 349-350:
The daily energy intake at baseline was also estimated[74].

Methods, Page 17, lines 419 to 421:
Third, we further adjusted for total energy intake to assess whether the relationship of dairy consumption with CVD development was independent of the amount of energy provided.

Supplementary Table 1:
Baseline characteristics of participants by frequency of dairy consumption in the China Kadoorie Biobank.

Characteristics	Frequency of Dairy Consumption			
	Never/rarely	Monthly	1-3 d/wk	Regularly (≥4 d/wk)
Total energy intake (kcal/d)	1234.4 (338.6)	1383.0 (354.5)	1553.4 (358.7)	1757.0 (407.2)

Supplementary Table 2:
Baseline characteristics of participants by total dairy consumption from 24 h dietary recalls in UK Biobank.

Characteristics	Dairy Consumption			
	0 serving/d	0-0.5 serving/d	0.5-1.0 serving/d	> 1 serving/d
Total energy intake (kcal/d)	1971.1 (701.6)	2003.6 (564.9)	2095.9 (599.8)	2282.9 (683.7)

Supplementary Table 21:
Multivariable Hazard Ratios (95% CIs) of cardiovascular disease, coronary heart disease and stroke risk associated with dairy consumption from sensitivity analyses in the China Kadoorie Biobank.

	Frequency of Dairy Consumption				P trend
	Never/rarely	Monthly	1–3 d/wk	Regularly (≥4 d/wk)	
Further adjustment for energy intake					
CVD	1 [Reference]	1.03(1.00–1.05)	1.03(1.00–1.07)	1.01(0.98–1.03)	0.227
CHD	1 [Reference]	1.05(1.02–1.09)	1.07(1.03–1.12)	1.09(1.06–1.13)	<0.001
Stroke	1 [Reference]	1.01(0.98–1.04)	1.01(0.98–1.05)	0.95(0.91–0.98)	0.020

Supplementary Table 22:
Multivariable Hazard Ratios (95% CIs) of cardiovascular disease, coronary heart disease and stroke risk associated with total dairy consumption from sensitivity analyses in the UK Biobank.

	Frequency of Dairy Consumption				P trend
	0 serving/d	**≤0.5 serving/d**	**0.5–1.0 serving/d**	**> 1 serving/d**	
Further adjusting for energy intake					
CVD	1 [Reference]	0.96 (0.90–1.01)	0.93 (0.88–0.98)	0.94 (0.89–0.99)	0.013
CHD	1 [Reference]	0.96 (0.90–1.03)	0.94 (0.89–0.996)	0.94 (0.89–0.998)	0.039
Stroke	1 [Reference]	0.91 (0.80–1.03)	0.88 (0.79–0.99)	0.91 (0.81–1.02)	0.117

Minor

4. **Lines 26-28. Please, verify the references. References 3 and 4, support the benefits of dairy consumption and CVD risk factors, whereas reference 5 supports the beneficial effect of a specific component of dairy. It is not clear whether the authors want to support the beneficial effects of dairy products or its nutritional content.**

Response: We apologize for the confusion and have now revised these references. We have now cited relevant references for the specific component of dairy to emphasize the nutritional benefits of dairy products.

Introduction, Page 2, lines 25 to 27:

Dairy products contain various beneficial nutrients, including high biological value protein, milk fat globule phospholipids, and vitamins and minerals that could improve CVD risk factors [3-6]

5. **Reference 7 does not support the statement.**

Response: We apologize for this mistake and we have now replaced it with a more intuitive reference[10,11].

Introduction, Page 2, lines 27 to 28:

……and multiple anabolic hormones in dairy products might adversely affect the health benefit, such as IGF-1[8,9].

6. **Lines 41-42. Please, provide a reference for this argument.**

Response: Done. We have now provided references for the sentence[12-14].

Introduction, Page 2, lines 40 to 41:

Nonetheless, cheese is also a fermented food that can contain vitamin K2[26], high levels of milk fat globule membrane[27], as well as probiotics[28].

7. **The authors include a significant number of results, considering all the supplementary figures and tables. It may be beneficial to consolidate this information into fewer tables, including clear estimates for the independent association of low-fat milk, yogurt, and cheese.**

Response: We appreciate this comment. We have now added an assessment of the exposure-outcomes associations using GRADE which summarized the important findings of our meta-analyses[15].

Supplementary Table 30:

GRADE evidence profile for prospective cohort studies of dairy products and cardiovascular disease

Certainty assessment							№ of patients	Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		**Relative (95% CI)**	**Absolute (95% CI)**		
Total dairy-Cardiovascular disease incidence (follow-up: range 5.5 years to 30.0 years)											
26	Cohort studies	not serious	serious[a]	not serious	not serious	dose response gradient	136370/2322619 (5.9%)	**RR 0.963** (0.932 to 0.995)	**2 fewer per 1,000** (from 4 fewer to 1 fewer)	⨁⨁◯◯ Low	CRITICAL
Total dairy-Coronary heart disease incidence (follow-up: range 5.5 years to 30.0 years)											
19	Cohort studies	not serious	not serious[b]	not serious	not serious	dose response gradient	72466/1663988 (4.4%)	**RR 0.98** (0.93 to 1.02)	**1 fewer per 1,000** (from 3 fewer to 3 more)	⨁⨁⨁◯ Moderate	CRITICAL
Total dairy-Stroke incidence (follow-up: range 5.5 years to 26.0 years)											
14	Cohort studies	not serious	not serious[c]	not serious	not serious	dose response gradient	68106/1723800 (4.0%)	**RR 0.94** (0.90 to 0.98)	**2 fewer per 1,000** (from 4 fewer to 1 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Milk-Cardiovascular disease incidence (follow-up: range 5.5 years to 30.0 years)											
21	Cohort studies	not serious	not serious[d]	not serious	not serious	none	78140/1599231 (4.9%)	**RR 1.00** (0.97 to 1.04)	**0 fewer per 1,000** (from 1 fewer to 2 more)	⨁⨁◯◯ Low	CRITICAL
Milk-Coronary heart disease incidence (follow-up: range 5.5 years to 30.0 years)											

Certainty assessment							№ of patients	Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		**Relative (95% CI)**	**Absolute (95% CI)**		
15	Cohort studies	not serious	not serious	not serious	not serious	none	28421/937931 (3.0%)	**RR 1.03** (0.98 to 1.08)	**1 more per 1,000** (from 1 fewer to 2 more)	⨁⨁◯◯ Low	IMPORTANT
Milk-Stroke incidence (follow-up: range 5.5 years to 24.0 years)											
11	Cohort studies	not serious	not serious	not serious	not serious	none	29615/944409 (3.1%)	**RR 1.02** (0.96 to 1.08)	**1 more per 1,000** (from 1 fewer to 3 more)	⨁⨁◯◯ Low	IMPORTANT
Yogurt-Cardiovascular disease incidence (follow-up: range 5.5 years to 30.0 years)											
14	Cohort studies	not serious	serious[e]	not serious	not serious	none	42689/1322046 (3.2%)	**RR 0.99** (0.93 to 1.06)	**0 fewer per 1,000** (from 2 fewer to 2 more)	⨁◯◯◯ Very low	CRITICAL
Yogurt-Coronary heart disease incidence (follow-up: range 5.5 years to 30.0 years)											
9	Cohort studies	not serious	not serious[f]	not serious	not serious	none	21570/743767 (2.9%)	**RR 0.99** (0.91 to 1.08)	**0 fewer per 1,000** (from 3 fewer to 2 more)	⨁⨁◯◯ Low	IMPORTANT
Yogurt-Stroke incidence (follow-up: range 5.5 years to 15.0 years)											
5	Cohort studies	not serious	not serious[g]	not serious	not serious	none	14557/737371 (2.0%)	**RR 0.97** (0.88 to 1.07)	**1 fewer per 1,000** (from 2 fewer to 1 more)	⨁⨁◯◯ Low	IMPORTANT

Certainty assessment							№ of patients	Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Relative (95% CI)	Absolute (95% CI)		
Cheese-Cardiovascular disease incidence (follow-up: range 3.7 years to 30.0 years)											
20	Cohort studies	not serious	not serious	not serious	not serious	none	78508/1824374 (4.3%)	**RR 0.94** (0.91 to 0.97)	**3 fewer per 1,000** (from 4 fewer to 1 fewer)	⨁⨁◯◯ Low	CRITICAL
Cheese-Coronary heart disease incidence (follow-up: range 3.7 years to 30.0 years)											
14	Cohort studies	not serious	not serious	not serious	not serious	none	45680/1184988 (3.9%)	**RR 0.91** (0.87 to 0.96)	**3 fewer per 1,000** (from 5 fewer to 2 fewer)	⨁⨁◯◯ Low	CRITICAL
Cheese-Stroke incidence (follow-up: range 3.7 years to 15.0 years)											
10	Cohort studies	not serious	not serious	not serious	not serious	Possible publication bias [h]	28259/1251572 (2.3%)	**RR 0.94** (0.90 to 0.98)	**1 fewer per 1,000** (from 2 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL
Low-fat dairy-Cardiovascular disease incidence (follow-up: range 5.5 years to 30.0 years)											
20	Cohort studies	not serious	not serious	not serious	not serious	none	65789/1128406 (5.8%)	**RR 0.96** (0.92 to 0.99)	**2 fewer per 1,000** (from 5 fewer to 1 fewer)	⨁⨁◯◯ Low	CRITICAL
Low-fat dairy-Coronary heart disease incidence (follow-up: range 5.5 years to 30.0 years)											

Certainty assessment							№ of patients	Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Relative (95% CI)	Absolute (95% CI)		
13	Cohort studies	not serious	not serious	not serious	not serious	none	40133/737929 (5.4%)	**RR 0.97** (0.93 to 1.01)	**2 fewer per 1,000** (from 4 fewer to 1 more)	⨁⨁◯◯ Low	IMPORTANT
Low-fat dairy-Stroke incidence (follow-up: range 5.5 years to 26.0 years)											
9	Cohort studies	not serious	not serious[i]	not serious	not serious	none	21711/827027 (2.6%)	**RR 0.90** (0.84 to 0.98)	**3 fewer per 1,000** (from 4 fewer to 1 fewer)	⨁⨁◯◯ Low	CRITICAL
High-fat dairy-Cardiovascular disease incidence (follow-up: range 5.5 years to 30.0 years)											
21	Cohort studies	not serious	not serious	not serious	not serious	none	68040/1038281 (6.6%)	**RR 0.97** (0.93 to 1.01)	**2 fewer per 1,000** (from 5 fewer to 1 more)	⨁⨁◯◯ Low	CRITICAL
High-fat dairy-Coronary heart disease incidence (follow-up: range 5.5 years to 30.0 years)											
14	Cohort studies	not serious	not serious	not serious	not serious	Possible publication bias[j]	40697/743361 (5.5%)	**RR 0.96** (0.93 to 0.99)	**2 fewer per 1,000** (from 3 fewer to 1 more)	⨁⨁◯◯ Low	IMPORTANT
High-fat dairy-Stroke incidence (follow-up: range 5.5 years to 26.0 years)											
10	Cohort studies	not serious	not serious	not serious	not serious	none	21852/832459 (2.6%)	**RR 0.98** (0.92 to 1.04)	**1 fewer per 1,000** (from 2 fewer to 1 more)	⨁⨁◯◯ Low	IMPORTANT

Certainty assessment							№ of patients	Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Relative (95% CI)	Absolute (95% CI)		
Fermented dairy-Cardiovascular disease incidence (follow-up: range 3.7 years to 30.0 years)											
24	Cohort studies	not serious	not serious	not serious	not serious	none	76341/1729129 (4.4%)	**RR 0.96** (0.94 to 0.98)	**2 fewer per 1,000** (from 3 fewer to 1 fewer)	⨁⨁◯◯ Low	CRITICAL
Fermented dairy-Coronary heart disease incidence (follow-up: range 3.7 years to 30.0 years)											
16	Cohort studies	not serious	not serious	not serious	not serious	none	31828/1010125 (3.2%)	**RR 0.96** (0.93 to 0.99)	**1 fewer per 1,000** (from 2 fewer to 0 fewer)	⨁⨁◯◯ Low	CRITICAL
Fermented dairy-Stroke incidence (follow-up: range 3.7 years to 15.0 years)											
15	Cohort studies	not serious	not serious	not serious	not serious	none	37041/1182772 (3.1%)	**RR 0.95** (0.92 to 0.98)	**2 fewer per 1,000** (from 3 fewer to 1 fewer)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **RR:** risk ratio

a. Initial heterogeneity as measured by I^2=66.1%. One study (Ingegerd Johansson 2018) strongly influenced the pooled result. Removal of Ingegerd Johansson 2018 did not change the direction or significance of the pooled effect size (0.96 95% CI 0.92 to 0.99) however the heterogeneity remained high with an I^2 = 62.1%.

b. Initial heterogeneity as measured by I^2=70.5%. One study (results of CKB) strongly influenced the pooled result. Removal of Pan Zhuang 2023 (CKB) did not change the direction of the significance of the pooled result (0.966 95% CI 0.930 to 1.003) and the I^2 was reduced to 43.8%.

c. Initial heterogeneity as measured by I^2=61.8%. One study (Susanna C. Larsson 2009) strongly influenced the pooled result. Removal of Susanna C. Larsson 2009 did not change the direction of the significance of the pooled result (0.92 95% CI 0.89 to 0.96) and the I^2 was reduced to 44.6%.

d. Initial heterogeneity as measured by I^2=59.1%. One study (Ingegerd Johansson 2018) strongly influenced the pooled result. Removal of Ingegerd Johansson 2018 did not change the direction of the significance of the pooled result (0.99 95% CI 0.96 to 1.03) and the I^2 was reduced to 46.4%.

e. Initial heterogeneity as measured by I^2=64.8%. One study (Tammy Y.N. Tong 2020) strongly influenced the pooled result. Removal of Tammy Y.N. Tong 2020 did not change the direction or significance of the pooled effect size (1.01 95% CI 0.95 to 1.08) however the heterogeneity remained high with an I^2= 56.7%.

f. Initial heterogeneity as measured by I^2=60.7%. One study (Timothy J. Key 2019) strongly influenced the pooled result. Removal of Timothy J. Key 2019 did not change the direction of the significance of the pooled result (1.02 95% CI 0.93 to 1.11) and the I^2 was reduced to 39.7%.

g. Initial heterogeneity as measured by I^2=66.2%. One study (Susanna C. Larsson 2009) strongly influenced the pooled result. Removal of Susanna C. Larsson 2009 did not change the direction of the significance of the pooled result (0.929 95% CI 0.861 to 1.002) and the I^2 was reduced to 35.4%.

h. P value for Egger's test was 0.046.

i. Initial heterogeneity as measured by I^2=65.1%. One study (result of UKB) strongly influenced the pooled result. Removal of Pan Zhuang 2023 (UKB) did not change the direction of the significance of the pooled result (0.93 95%CI 0.87 to 0.99) and the I^2 was reduced to 32.7%.

j. P value for Egger's test was 0.036.

8. **Null associations identified in the substitution analysis may warrant further discussion.**

Response: We appreciate this comment. We have now further discussed the null association in the substitution analysis of UKB. Meanwhile, we have now also conducted the substitution analysis in CKB. Notably, replacing eggs with dairy products in equal amount was associated with higher risks of CVD, CHD, and stroke in CKB. We have now also discussed the differences in results of substitution analysis between CKB and UKB as follows.

Results, Page 5, lines 105 to 110:

In hypothetical substitution analyses, no significant associations were found in UKB. In CKB, replacing 50 g/d of eggs with an equivalent amount of dairy products was associated with an 11% higher risk of CVD, a 13% higher risk of CHD, and a 9% higher risk of stroke. Additionally, substituting dairy products for fish or soybeans was associated with a 4% increase in CHD risk, whereas replacing red meat or soybeans with dairy products was associated with a 2% or 3% reduction in stroke risk, respectively (**Extended Data Figure 2**).

Discussion, Page 11, lines 257 to 268:

The differing outcomes of substitution analyses between CKB and the UKB may be attributed to differences in national dietary patterns and the metabolic profiles of their respective populations[63]. Research has indicated that egg consumption could confer health benefits in Asian populations[64]. A previous cohort study within the CKB cohort found that daily egg consumption (up to <1 egg/day) was associated with an 18% reduction in CVD mortality and a 26% lower risk of hemorrhagic stroke[65]. Our substitution model results aligned with these findings, suggesting that egg consumption may offer more significant cardioprotective benefits than dairy products among the Chinese population. In contrast, the UKB substitution analysis showed a null association, indicating that the cardiometabolic impacts of other protein sources were comparable to those of dairy products in the UK. This is consistent with findings from a previous study in the US, which showed that replacing dairy products with other protein sources did not significantly affect CHD risk[66].

9. **Significant interactions were found that are not further discussed. For instance, the association between dairy consumption and CVD in the CKB was only protective for men and those with hypertension. In the UK Biobank, the inverse associations of cheese consumption with CVD and with CHD are only found for those without diabetes. Only predefined differences across categories based on previous evidence need to be included. An explanation of the rationale behind needs to be added to the Methods section.**

Response: We appreciate the reviewer's insightful suggestions. We have now incorporated a discussion of the significant interactions observed in our subgroup analyses, specifically focusing on sex, hypertension, and diabetes. These analyses were conducted to determine whether the documented associations varied by baseline

characteristics, which were identified as important covariates in previous studies included in our meta-analysis (**Supplementary Table 23**). In addition, we have expanded the Methods section to include an explanation of the rationale behind these subgroup analyses, emphasizing their relevance based on prior evidence.

Discussion, Page 11 to 12, lines 269 to 285:

The inverse association between total dairy intake and the risk of CVD and stroke was observed among individuals with hypertension but not among those without hypertension in the CKB study. Hypertension is a well-established risk factor for CVD, making those with high blood pressure more susceptible to cardiovascular damage[67]. As a result, the potential protective effects of dairy intake, such as improved blood pressure regulation, may have a more pronounced impact on reducing CVD and stroke risk in hypertensive individuals compared with those without hypertension. Interestingly, the significant inverse associations of dairy consumption with the risk of CVD and stroke were more evident among men than women in the CKB study. This disparity may be due to differences in how men and women metabolize nutrients, influenced by hormonal variations[68], which can affect the impact of dairy intake on stroke risk. In addition, men typically have higher baseline blood pressure levels, which might make them more responsive to the protective effects of dairy against stroke. Furthermore, the inverse association between cheese intake and CVD risk was significant only among participants without diabetes in UKB. This could be attributed to the altered lipid metabolism and insulin resistance commonly seen in individuals with diabetes[69], potentially diminishing the cardiovascular benefits of cheese. Further research is necessary to elucidate the significant interactions observed in our subgroup analyses.

Methods, Page 17, lines 411 to 415:

We further examined whether the documented associations varied by subgroups according to baseline characteristics which were important covariates based on previous studies (**Supplementary Table 26**), including age, sex, BMI, household income, smoking status, alcohol intake frequency, physical activity, diet quality, hypertension, diabetes, and family history of CVD.

10. **Lines 160-163. Although moderate milk consumption (>0 to 0.5 serving/d) was associated with a lower risk of hemorrhagic stroke (HR 0.43, 95% CI 0.21–0.87), this result should be interpreted with caution as the number of cases is very low (n=8).**

Response: Thank you for your suggestion and we have now deleted this description of UKB.

Discussion, Page 8, lines 172 to 174:

Congruously, we found that total dairy consumption (mainly fresh milk/liquid whole milk in China) [35,36] was related to lower hemorrhagic stroke risk in CKB.

11. Please, expand the discussion on the conflicting results for the association between dairy consumption and CVD in the CKB and the UKB. This is a main result that is briefly mentioned in the discussion.

Response: We appreciate this suggestion. Initially, we think the main reason causing the conflicting results between CKB and UKB could be the type of dairy product consumed. Nonetheless, we have now added further discussion about the conflicting results in CKB and UKB issue.

Discussion, Page 8, lines 184 to 196:

With regard to CHD, we found great heterogeneity between UKB and CKB studies, which was also shown in our further updated meta-analysis (I^2=68.6%). This heterogeneity could be attributed to several factors. First, the difference in dairy intake levels between the two cohorts is notable. The average intake of total dairy products in the UKB was more than four times higher than in the CKB[42]. It is plausible that the cardiometabolic benefits of dairy consumption may require a relatively high level of intake. Second, genetic differences between the populations may play a role. Chinese populations have a higher prevalence of lactose intolerance compared to European populations[43], which could influence the metabolic outcomes associated with dairy consumption and potentially contribute to the observed differences in CHD risk. Importantly, our further analyses suggest that the discrepancy between the studies may be largely attributable to the consumption of different subtypes of dairy products. Notably, cheese consumption ranked highest among dairy products in the UK, whereas liquid whole milk was the predominant dairy product in China[35,36].

Response to Reviewer #2

I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Nature Communications initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

Response: Thank you for your comment. We appreciate the initiative by Nature Communications to support training in peer review and recognize the contributions of Early Career Researchers.

Response to Reviewer #3

This manuscript describes a pooled analysis of UKB and CKB, assessing the association of dairy with CVD. They identified almost 100,000 CVD cases over 9-million person years of follow-up. They have also conducted a meta-analysis of other studies to add to the robustness of the findings. An extensive amount of supplementary material is provided that provides a full picture of methods and results. Findings were somewhat consistent between UKB and CKB except for higher CHD risk with regular dairy consumption in CKB. In the updated meta-

analysis, dairy consumption was associated with lower CVD and stroke risk. This work is comprehensive and the manuscript is organized and well-written. The major missing piece is an assessment of the confidence in the body of evidence, using an approach such as that used by the WHO, and other groups, such as GRADE.

The noteworthy results are the updated analyses of UKB and CKB; and pooled with the previous cohort studies. The work will be of significance, but largely supports previous studies of the area, so will strengthen evidence.

Response: We appreciate your comprehensive summary of our study.

1. **The meta-analysis seems competently performed. One question about the categorization- you put together high-fat milk, high-fat yogurt with high-fat cheese, cream, or butter. Even high-fat milk and yogurt have substantially less fat than high-fat ice cream, cream, or butter. Could you justify why you've classified as you did.**

Response: We appreciate these suggestions. The approach of grouping high-fat dairy products, such as high-fat milk, high-fat yogurt, high-fat cheese, cream, and butter, together in our analysis aligns with previous meta-analyses[16] and dietary guidelines that often evaluate the impact of saturated fats from these sources collectively on health outcomes. By grouping these products together, we aim to capture the overall impact of saturated fat from dairy on cardiometabolic outcomes, as is common practice in dietary research and systematic reviews[17,18]. This definition of high-fat dairy was also consistent with previous studies included in our meta-analysis[19-28].

Supplementary Method, Page 4 to 5:

High-fat dairy included high-fat milk, high-fat yogurt, high-fat cheese, and cream or butter, which was consistent with previous studies[3-5].

2. **In the meta-analysis of high-fat dairy, cheese was not included unless studies separately analyzed low-fat and high-fat cheese". Why? Isn't it more probable for all/most cheese consumption to be high-fat cheese?**

Response: Thank you for your insightful comment. We did not categorize all cheese as high-fat dairy because 17% of the total cheese intake in UKB data consisted of low-fat cheese varieties, including low-fat hard cheese, low-fat cheese spread, and cottage cheese (**Extended Data Fig. 1**). In addition, previous studies have also distinguished between low-fat and high-fat cheese, categorizing them accordingly in analyses of low-fat and high-fat dairy products[19,20,27,28]. In light of this, we have now separated cheese consumption in the UKB into low-fat and high-fat categories and have updated the meta-analysis results accordingly. The updated meta-analysis results showed that low-fat dairy was associated with lower risk of CVD and stroke (unchanged). High-fat dairy was not associated with total CVD but a lower risk of CHD, which could be mainly driven by high-fat cheese consumption (**Supplementary Tables 11-12**). The benefits of high-fat cheese could be explained by the content of calcium, conjugated linoleic acid, vitamin K_2, microorganisms or probiotics (see discussion).

Results, Page 4, lines 86 to 89:

Considering the fat content of cheese, a protective association with CVD and CHD was found for high-fat cheese (>0.5 serving/d) while low-fat cheese was negatively associated with stroke incidence, especially ischemic stroke **(Supplementary Table 11-12)**.

Results, Page 6, lines 137 to 141:

Consumption of high-fat dairy products (including high-fat milk, high-fat yogurt, high-fat cheese, and cream or butter) was not associated with CVD risk (RR: 0.97, 95% CI: 0.93–1.01, n=21 risk estimates) but inversely associated with CHD risk (RR: 0.96, 95% CI: 0.93–0.99, n=14 risk estimates) (**Figure 3 and Extended Data Fig. 10**).

Discussion, Page 10 to 11, lines 246 to 250:

Nonetheless, we observed an inverse but non-significant association between high-fat dairy consumption and CVD, characterized by slightly wider confidence intervals. In addition, a significant inverse relationship with CHD risk was identified, which may be driven by high-fat cheese consumption.

Supplementary Table 11:

Associations between low-fat cheese consumption from 24-h dietary recalls and cardiovascular disease risk in the UK Biobank.

	Frequency of Low-fat Cheese Consumption			***P* trend**
	0 serving/d	**≤0.5 serving/d**	**>0.5 serving/d**	
N	157,080	19,011	7355	
CVD				
No of cases (%)	10,457 (6.7)	1198 (6.3)	477 (6.5)	
Person-years	1,753,647.8	213,351.8	82,124.7	
Model 1*	1 [Reference]	0.95 (0.89–1.01)	1.01 (0.92–1.11)	0.416
Model 2†	1 [Reference]	0.96 (0.90–1.02)	0.97 (0.88–1.06)	0.170
Model 3‡	1 [Reference]	0.96 (0.90–1.02)	0.95 (0.87–1.05)	0.103
Model 4§	1 [Reference]	0.97 (0.91–1.03)	0.94 (0.86–1.04)	0.123
CHD				
No of cases (%)	8684 (5.5)	985 (5.2)	419 (5.7)	
Person-years	1,761,108.4	214,226.1	82,371.6	
Model 1*	1 [Reference]	0.94 (0.88–1.01)	1.08 (0.98–1.19)	0.850
Model 2†	1 [Reference]	0.96 (0.90–1.02)	1.03 (0.93–1.13)	0.735
Model 3‡	1 [Reference]	0.96 (0.89–1.02)	1.01 (0.92–1.12)	0.547
Model 4§	1 [Reference]	0.97 (0.91–1.03)	1.00 (0.91–1.11)	0.587
Stroke				
No of cases (%)	2127 (1.4)	253 (1.3)	76 (1.0)	
Person-years	1,796,977.7	218,245.0	84,219.5	
Model 1*	1 [Reference]	0.96 (0.84–1.10)	0.77 (0.61–0.97)	0.039
Model 2†	1 [Reference]	0.96 (0.84–1.10)	0.74 (0.59–0.93)	0.020

Model 3‡	1 [Reference]	0.96 (0.84–1.10)	0.73 (0.58–0.92)	0.016
Model 4§	1 [Reference]	0.98 (0.86–1.12)	0.73 (0.58–0.92)	0.021
Haemorrhagic stroke				
No of cases (%)	338 (0.2)	47 (0.3)	13 (0.2)	
Person-years	1,804,413.3	219,149.4	84,474.8	
Model 1*	1 [Reference]	1.11 (0.82–1.51)	0.82 (0.47–1.43)	0.891
Model 2†	1 [Reference]	1.11 (0.82–1.51)	0.80 (0.46–1.40)	0.836
Model 3‡	1 [Reference]	1.11 (0.82–1.50)	0.80 (0.46–1.39)	0.810
Model 4§	1 [Reference]	1.11 (0.82–1.52)	0.79 (0.45–1.38)	0.804
Ischaemic stroke				
No of cases (%)	1427 (0.9)	152 (0.8)	50 (0.7)	
Person-years	1,800,121.1	218,694.2	84,312.3	
Model 1*	1 [Reference]	0.86 (0.73–1.02)	0.76 (0.58–1.01)	0.013
Model 2†	1 [Reference]	0.87 (0.73–1.03)	0.73 (0.55–0.97)	0.007
Model 3‡	1 [Reference]	0.87 (0.73–1.02)	0.72 (0.54–0.96)	0.006
Model 4§	1 [Reference]	0.88 (0.75–1.04)	0.72 (0.54–0.95)	0.008

CI, confidence interval; HR, hazard ratio.

Other cheese including cheese spread, low-fat cheese spread, blue cheese, and other cheese.

*Model 1: results were adjusted for age and sex.

†Model 2: model 1 + centers, survey season, education, income, physical activity, smoking, alcohol drinking, family history of CVD, aspirin use, vitamins use and minerals use.

‡Model 3: model 2 + body mass index, history of hypertension, and diabetes.

§Model 4: model 3 + red meat, processed red meat, oily fish, non-oily fish, poultry, vegetables, fruits, eggs, and high-fat cheeses.

Supplementary Table 12:

Associations between high-fat cheese consumption from 24-h dietary recalls and cardiovascular disease risk in the UK Biobank

	Frequency of High-fat Cheese Consumption			***P* trend**
	0 serving/d	**≤0.5 serving/d**	**>0.5 serving/d**	
N	82,473	56,988	43,985	
CVD				
No of cases (%)	5880 (7.1)	3494 (6.1)	2758 (6.3)	
Person-years	915,769.2	640,634.6	492,720.6	
Model 1*	1 [Reference]	0.85 (0.81–0.88)	0.85 (0.81–0.88)	<0.001
Model 2†	1 [Reference]	0.91 (0.87–0.95)	0.90 (0.86–0.95)	<0.001
Model 3‡	1 [Reference]	0.92 (0.88–0.96)	0.92 (0.87–0.96)	<0.001
Model 4§	1 [Reference]	0.92 (0.89–0.96)	0.92 (0.88–0.96)	<0.001
CHD				
No of cases (%)	4910 (6.0)	2908 (5.1)	2270 (5.2)	
Person-years	919,860.6	643,088.0	494,757.3	
Model 1*	1 [Reference]	0.85 (0.81–0.89)	0.83 (0.79–0.88)	<0.001
Model 2†	1 [Reference]	0.91 (0.87–0.95)	0.89 (0.85–0.94)	<0.001
Model 3‡	1 [Reference]	0.93 (0.88–0.97)	0.91 (0.86–0.95)	<0.001

Model 4§	1 [Reference]	0.93 (0.89–0.98)	0.91 (0.87–0.96)	<0.001
Stroke				
No of cases (%)	1167 (1.4)	699 (1.2)	590 (1.3)	
Person-years	940,846.9	654,877.4	503,717.9	
Model 1*	1 [Reference]	0.85 (0.77–0.93)	0.93 (0.84–1.03)	0.044
Model 2†	1 [Reference]	0.90 (0.82–0.99)	0.98 (0.88–1.08)	0.408
Model 3‡	1 [Reference]	0.91 (0.82–1.00)	0.99 (0.89–1.09)	0.538
Model 4§	1 [Reference]	0.91 (0.82–1.00)	0.99 (0.89–1.09)	0.525
Haemorrhagic stroke				
No of cases (%)	185 (0.2)	122 (0.2)	91 (0.2)	
Person-years	944,921.3	657,306.0	505,810.3	
Model 1*	1 [Reference]	0.93 (0.74–1.17)	0.91 (0.71–1.17)	0.410
Model 2†	1 [Reference]	0.96 (0.76–1.20)	0.92 (0.72–1.19)	0.528
Model 3‡	1 [Reference]	0.97 (0.77–1.22)	0.93 (0.72–1.20)	0.591
Model 4§	1 [Reference]	0.96 (0.76–1.21)	0.93 (0.72–1.20)	0.573
Ischaemic stroke				
No of cases (%)	773 (0.9)	455 (0.8)	401 (0.9)	
Person-years	942,625.0	655,963.9	504,538.7	
Model 1*	1 [Reference]	0.83 (0.74–0.94)	0.95 (0.84–1.07)	0.169
Model 2†	1 [Reference]	0.89 (0.79–1.00)	1.01 (0.89–1.14)	0.802
Model 3‡	1 [Reference]	0.91 (0.81–1.02)	1.02 (0.90–1.16)	0.996
Model 4§	1 [Reference]	0.91 (0.81–1.03)	1.02 (0.90–1.15)	0.990

CI, confidence interval; HR, hazard ratio.

Other cheese including cheese spread, low-fat cheese spread, blue cheese, and other cheese.

*Model 1: results were adjusted for age and sex.

†Model 2: model 1 + centers, survey season, education, income, physical activity, smoking, alcohol drinking, family history of CVD, aspirin use, vitamins use and minerals use.

‡Model 3: model 2 + body mass index, history of hypertension, and diabetes.

§Model 4: model 3 + red meat, processed red meat, oily fish, non-oily fish, poultry, vegetables, fruits, eggs, and low-fat cheeses.

Figure 3:

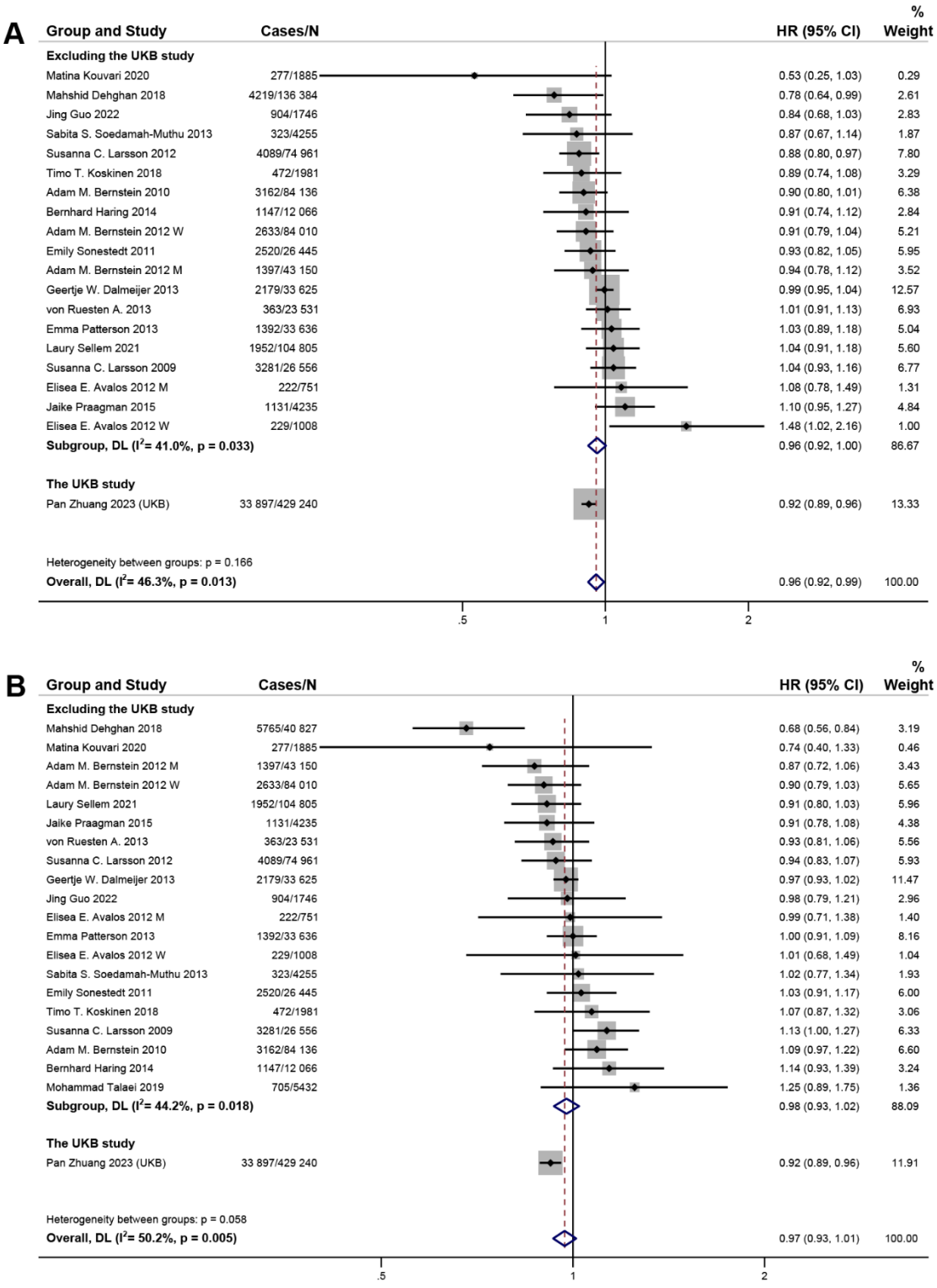
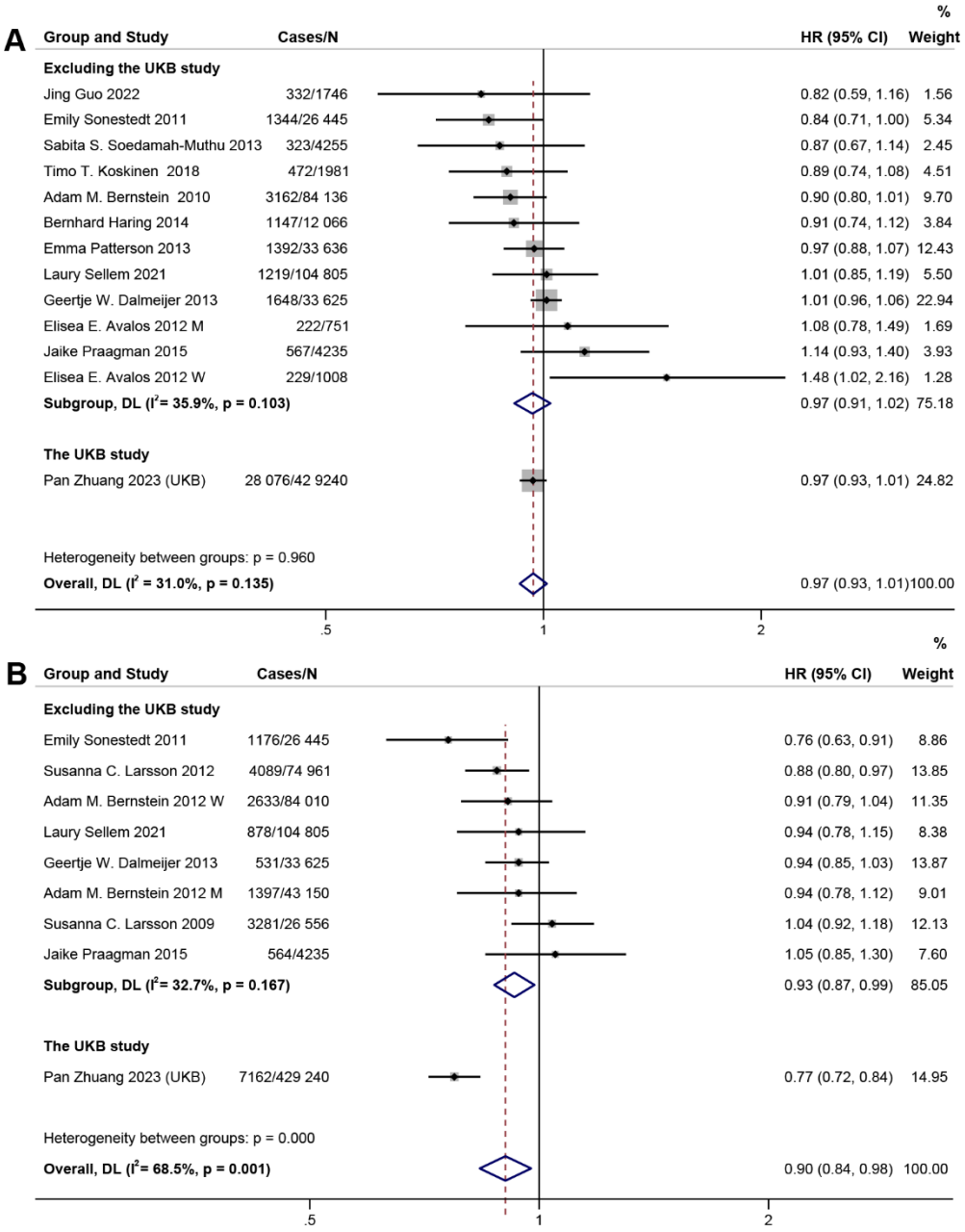


Fig. 3 Associations of low-fat and high-fat dairy consumption with cardiovascular disease risk for high compared with low category of intake using random effects meta-analysis

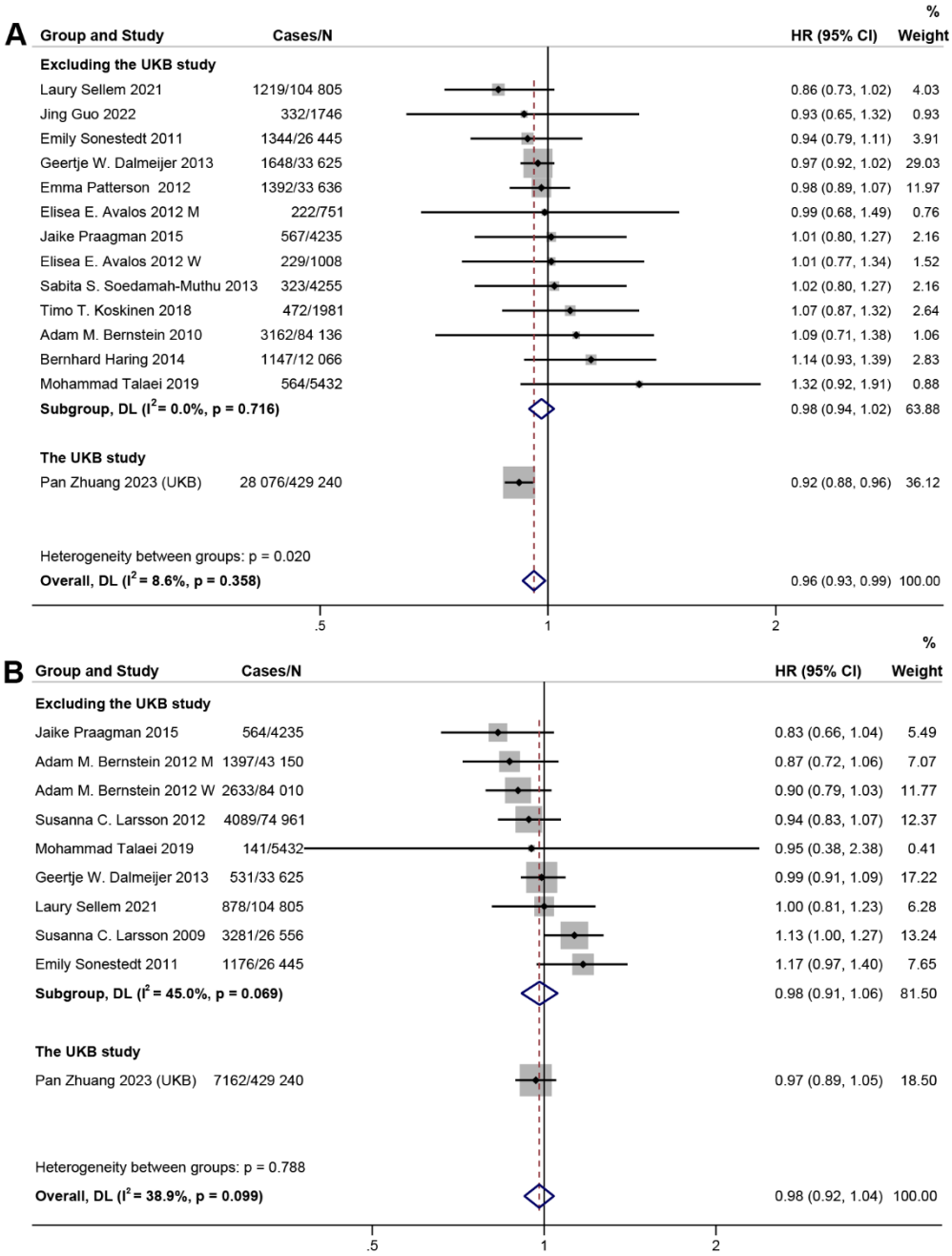
(A) Low-fat. (B) High-fat. Squares represent study-specific relative risk. Gray square areas are proportional to the individual study weight for the overall meta-analysis. Horizontal lines denote 95% CIs. I^2 refers to the proportion of heterogeneity among studies. *M* men; *W* women; *CKB* China Kadoorie Biobank; *UKB* UK Biobank.

Extended Fig. 9:



Extended Data Fig. 9 | Association of low-fat dairy consumption with coronary heart disease and stroke risk for high compared with low intake using random-effects meta-analysis.
(A) Coronary heart disease. (B) Stroke.

Extended Fig. 10:



Extended Data Fig. 10 | Association of high-fat dairy consumption with coronary heart disease and stroke risk for high compared with low intake using random-effects meta-analysis.
(A) Coronary heart disease. (B) Stroke.

Supplementary Method, Page 4 to 5:

Low-fat dairy included low-fat milk, low-fat yogurt, low-fat cheese and low-fat ice cream. High-fat dairy included high-fat milk, high-fat yogurt, high-fat cheese, and cream or butter, which was consistent with previous studies[3-5]. As the intake of low-fat cheese cannot be ignored in the UKB (**Extended Data Fig. 1**), we separately analyzed low-fat and high-fat cheese, categorizing them accordingly in analyses of low-fat and high-fat dairy products in meta-analysis.

3. The analyses in UKB and CKB were well performed.

Response: We appreciate your positive comments.

4. What statistical approach to random-effects meta-analysis was used?

Response: We thank this comment. We used the DerSimonian and Laird method for the random-effects meta-analysis by using "metan" package in STATA[29]. The DerSimonian and Laird method is one of the most commonly used approaches in random-effects meta-analyses. This method accounts for both within-study and between-study variability, allowing for the estimation of a summary effect size that reflects the distribution of true effect sizes across different studies. We have now indicated this accordingly.

Supplementary Methods, Page 5:

A random-effect model based on the DerSimonian and Laird method[6] was applied to calculate summary RRs and 95% CIs comparing the highest with the lowest category of intake.

5. Why was soya milk (Supp. Table 21) included in this review- it is not a dairy product. Please justify why soy over other types of milk- and consider removing from the analysis.

Response: We thank this thoughtful comment. Soy milk, a plant-based beverage made from soybeans, is commonly used as a dairy milk substitute for people who are lactose intolerant, vegan, or have dairy allergies. It was one of the available milk options in the touch screen questionnaire at baseline (Filed ID: 1418)[30]. We have now deleted it to avoid ambiguity.

Results, Page 5, lines 97 to 99:

Attentionally, the association of whole milk (HR: 0.93, 95% CI: 0.87–1.00) with CVD incidence was marginally inverse (**Supplementary Table 16**).

Methods, Page 15, line 355:

Soya milk was excluded from the analysis as it is made from soybeans.

6. Line 98: What were the results of interaction? Perhaps worth summarizing the sex-interaction in CKB

Response: We thank this comment. In our study, the inverse association of dairy consumption with CVD and stroke risk was only seen in men but not women in CKB. We have now further discussed it in the manuscript.

Results, Page 5, lines 101 to 104:

The inverse associations between dairy consumption and the risks of CVD and stroke were observed exclusively in men, not women, and in individuals with hypertension, but not in those without hypertension, in the CKB.

Discussion, Page 11 to 12, lines 269 to 280:

The inverse association between total dairy intake and the risk of CVD and stroke was observed among individuals with hypertension but not among those without hypertension in the CKB study. Hypertension is a well-established risk factor for CVD, making those with high blood pressure more susceptible to cardiovascular damage[67]. As a result, the potential protective effects of dairy intake, such as improved blood pressure regulation, may have a more pronounced impact on reducing CVD and stroke risk in hypertensive individuals compared with those without hypertension. Interestingly, the significant inverse associations of dairy consumption with CVD and stroke were more evident among men than women in the CKB study. This disparity may be due to differences in how men and women metabolize nutrients, influenced by hormonal variations[68], which can affect the impact of dairy intake on stroke risk. Additionally, men typically have higher baseline blood pressure levels, which might make them more responsive to the protective effects of dairy against stroke.

7. **Line 110-112: This is a bit of an overstatement, implying that the addition of the 2 new studies resulted in a new conclusion- I would argue that it did not; the point estimate is the same with UKB and CKB, but the CI has narrowed, as expected with more studies.**

Response: We thank this comment. Indeed, the addition of our two new studies narrowed the CI. We have now modified the description accordingly.

Results, Page 5 to 6, lines 118 to 122:

In the meta-analysis of previously published studies, a marginal inverse association was identified between total dairy intake and incident cardiovascular disease (CVD) (RR, 0.963; 95% CI, 0.926-1.001; n=24 risk estimates). When the results from the CKB and UKB studies were incorporated, the 95% CI of the summary RR narrowed to 0.963 (0.932-0.995) (**Figure 1**).

8. **Lines 112-115: The dose-response is interesting, but is there a "ceiling" effect? Over what range of doses was this dose-response valid? Please clarify this in the text- with the abundance of supplemental figures, this point could easily be missed.**

Response: Thank you for your insightful comments. In our study, we observed a dose-dependent inverse association between dairy intake and CVD risk across the range of doses analyzed. Notably, at the highest intake level of more than 7 servings per day, the estimated hazard ratio was lower than that at lower intake levels, with the 95% confidence interval remaining below 1 (**Extended Data Fig. 5**), indicating a sustained protective effect with no apparent 'ceiling' effect within this range. However, the possibility of a ceiling effect at higher doses cannot be excluded, and we acknowledge the need for future studies with a broader range of intake levels to further explore this relationship. We have now discussed this in the limitation.

Discussion, Page 13, lines 307 to 310:

Fourth, no apparent 'ceiling' effect was observed in our dose-response analysis, likely due to the limited number of studies with a broad range of dairy consumption. Additional studies encompassing a wider spectrum of intake levels are needed to fully explore this relationship.

9. **Lines 120-122: Why the descriptive "especially cheese" is noted? The comparison between fermented dairy and cheese reveal practically identical point effects and CI- yes, cheese is 0.02-points lower, but I am not certain this difference is meaningful. Was there evidence of differential effect (e.g., subgroup differences?).**

Response: We appreciate your observation. Fermented dairy products typically include yogurt and cheese[31]. In our meta-analyses, cheese consumption was significantly associated with a lower risk of cardiovascular disease (RR=0.94, 95% CI=0.91 to 0.97), whereas no significant association was observed for yogurt (RR=0.99, 95% CI=0.93 to 1.06). Therefore, we believe the inverse association between fermented dairy and cardiovascular disease risk is primarily driven by cheese consumption. We highlighted cheese within the fermented dairy category to underscore its role as the main contributor to the observed protective effect against cardiovascular disease.

10. **Lines 143-145. Conducting the fixed effect meta-analysis if there is no significant heterogeneity is ok, but did these analyses show any substantial difference from the RE models? And how did you define "significant heterogeneity"?**

Response: We thank this thoughtful comment. The **supplementary table 29** showed the results of fixed-effects model and there was no significant difference compared with random-effects models. The extent of heterogeneity was assessed by I^2 (range from 0%-100%) and Cochran's Q statistic test (significant at P<0.10)[32,33] like other studies did[34,35]. We have now added references in the supplementary methods.

Supplementary Method, Page 5:

The extent of heterogeneity was assessed by I^2 (ranging from 0% to 100%, >50% indicates heterogeneity among studies, >80% indicates severe heterogeneity among studies) and Cochran's Q statistic test (significant at P<0.10)[8,9].

11. **Lines 179-183. You cite other meta-analyses that have found protective associations with cheese and CVD. What degree of overlap was between the meta-analysis (updated) you performed; and the ones cited? If there is high overlap, it's not surprising. Please address this.**

Response: Thank you for your suggestion. We cited two previous meta-analyses on cheese intake and CVD risk in our discussion. One included 15 studies, and the other included 9 studies, with an overlap of 6 (40%) and 3 (33.3%) studies, respectively, with our meta-analysis[31,36]. This overlap is not substantial. In our study, the meta-analysis on cheese intake and cardiovascular disease risk included a total of 18 studies, including

the UK Biobank data. Importantly, 11 of these studies were not included in the previous meta-analyses, thus significantly expanding the evidence base. We have now clarified this point in the discussion.

Discussion, Page 9, lines 202 to 205:
Compared with these two meta-studies, our meta-analysis incorporated data from 11 additional studies, significantly increasing the sample size and further reinforcing the robustness of the protective association between cheese consumption and CVD risk.

12. **Line 197: good hypotheses for little (no) benefit of yogurt. Additionally, might consider yogurt as ultraprocessed food by the NOVA system- what data are there of the association of UPF and CVD?**

Response: Thank you for your positive feedback and thoughtful suggestion. Sweetened or flavored yogurts, which often contain added sugars, artificial flavors, and other additives, are indeed classified as ultra-processed foods, which have been associated with a higher risk of cardiovascular disease[37,38]. We have now incorporated this information into the discussion.

Discussion, Page 9, lines 220 to 221:
Sweetened or flavored yogurts are classified as ultra-processed foods, which have been linked to an increased risk of CVD[53,54].

13. **Line 204-205: What is meant by "toxic"? This is a strong word, I think. The two studies cited are animal models; it's not clear how relevant these are for human levels of consumption of D-galactose. I would suggest citing stronger evidence in humans to make this statement.**

Response: Thank you for your suggestion. We agree that the term "toxic" was too strong and may not accurately reflect the available evidence. The relationship between D-galactose consumption and cardiovascular disease in humans is not well-established. However, a feeding trial did find that galactose ingestion in a high-fat beverage exacerbated postprandial lipemia and increased plasma lactate concentrations compared with glucose in nonobese men[39]. Based on this, we have revised the wording to "might also adversely affect lipid metabolism " and have cited this human study to better support our statement.

Discussion, Page 10, lines 226 to 230:
In addition to the long even-chain SFAs elevating LDL cholesterol, a high D-galactose intake from non-fermented milk might also adversely affect lipid metabolism. A trial in nonobese men demonstrated that galactose ingestion within a high-fat beverage exacerbated postprandial lipemia and increased plasma lactate concentrations compared with glucose[56].

14. **What is the d-galactose content of cheese compared to milk? This would be useful to provide in light of the previous statement.**

Response: Thank you for your insightful suggestion. The galactose content in milk primarily results from the breakdown of lactose into glucose and galactose. A recent study indicates that milk typically contains around 1.34 to 2.52 grams of total galactose per 100 grams[40]. During cheese production, most of the lactose is either fermented by bacteria or removed with the whey, resulting in significantly lower galactose levels. For example, hard cheeses like Cheddar and Parmesan often contain less than 0.1 grams of galactose per 100 grams, while soft and fresh cheeses, such as cottage cheese and ricotta, may have slightly higher levels, though still generally lower than milk[41]. It is important to note that aged cheeses are typically allowed in a galactose-restricted diet, whereas other milk-based products are restricted[42]. We have now added the statement to point out that the d-galactose content of cheese is lower than milk.

Discussion, Page 10, lines 230 to 231:
Compared to cheese, milk generally contains higher concentrations of D-galactose[57,58].

15. **No attempt was made to assess the confidence in the findings, as is done in Cochrane reviews, and major guidelines organization (e.g., WHO). I would suggest an assessment of the exposure-outcomes associations using GRADE would help here. (https://macgrade.mcmaster.ca/grade-learning-hub/grade-for-systematic-reviews/)**

Response: We appreciate this excellent suggestion. In meta-analysis, GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) is a widely used framework for assessing the quality of evidence and strength of recommendations[15]. We have now performed this analysis and formed a table referring to two meta-analyses involving GRADE grading tables[35,43].

Supplementary Methods. Page 5:
We assessed the confidence of evidence using the GRADE approach, categorizing it into four levels: very low, low, moderate, and high[10-12]. All statistical analyses for the meta-analysis were conducted using Stata version 16.0 (StataCorp). Absolute risk values were calculated with GRADEpro software.

Results, Page 7, lines 155 to 157:
Results of the GRADE confidence in the estimates of associations are presented in **Supplementary Table 30** , indicating overall evidence of very low to moderate quality.

Supplementary Table 30:

GRADE evidence profile for prospective cohort studies of dairy products and cardiovascular disease

Certainty assessment							№ of patients	Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		**Relative (95% CI)**	**Absolute (95% CI)**		
Total dairy-Cardiovascular disease incidence (follow-up: range 5.5 years to 30.0 years)											
26	Cohort studies	not serious	serious[a]	not serious	not serious	dose response gradient	136370/2322619 (5.9%)	**RR 0.963** (0.932 to 0.995)	**2 fewer per 1,000** (from 4 fewer to 1 fewer)	⨁⨁◯◯ Low	CRITICAL
Total dairy-Coronary heart disease incidence (follow-up: range 5.5 years to 30.0 years)											
19	Cohort studies	not serious	not serious[b]	not serious	not serious	dose response gradient	72466/1663988 (4.4%)	**RR 0.98** (0.93 to 1.02)	**1 fewer per 1,000** (from 3 fewer to 3 more)	⨁⨁⨁◯ Moderate	CRITICAL
Total dairy-Stroke incidence (follow-up: range 5.5 years to 26.0 years)											
14	Cohort studies	not serious	not serious[c]	not serious	not serious	dose response gradient	68106/1723800 (4.0%)	**RR 0.94** (0.90 to 0.98)	**2 fewer per 1,000** (from 4 fewer to 1 fewer)	⨁⨁⨁◯ Moderate	CRITICAL
Milk-Cardiovascular disease incidence (follow-up: range 5.5 years to 30.0 years)											
21	Cohort studies	not serious	not serious[d]	not serious	not serious	none	78140/1599231 (4.9%)	**RR 1.00** (0.97 to 1.04)	**0 fewer per 1,000** (from 1 fewer to 2 more)	⨁⨁◯◯ Low	CRITICAL
Milk-Coronary heart disease incidence (follow-up: range 5.5 years to 30.0 years)											

Certainty assessment							№ of patients	Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		**Relative (95% CI)**	**Absolute (95% CI)**		
15	Cohort studies	not serious	not serious	not serious	not serious	none	28421/937931 (3.0%)	**RR 1.03** (0.98 to 1.08)	**1 more per 1,000** (from 1 fewer to 2 more)	⨁⨁◯◯ Low	IMPORTANT
Milk-Stroke incidence (follow-up: range 5.5 years to 24.0 years)											
11	Cohort studies	not serious	not serious	not serious	not serious	none	29615/944409 (3.1%)	**RR 1.02** (0.96 to 1.08)	**1 more per 1,000** (from 1 fewer to 3 more)	⨁⨁◯◯ Low	IMPORTANT
Yogurt-Cardiovascular disease incidence (follow-up: range 5.5 years to 30.0 years)											
14	Cohort studies	not serious	serious[e]	not serious	not serious	none	42689/1322046 (3.2%)	**RR 0.99** (0.93 to 1.06)	**0 fewer per 1,000** (from 2 fewer to 2 more)	⨁◯◯◯ Very low	CRITICAL
Yogurt-Coronary heart disease incidence (follow-up: range 5.5 years to 30.0 years)											
9	Cohort studies	not serious	not serious[f]	not serious	not serious	none	21570/743767 (2.9%)	**RR 0.99** (0.91 to 1.08)	**0 fewer per 1,000** (from 3 fewer to 2 more)	⨁⨁◯◯ Low	IMPORTANT
Yogurt-Stroke incidence (follow-up: range 5.5 years to 15.0 years)											
5	Cohort studies	not serious	not serious[g]	not serious	not serious	none	14557/737371 (2.0%)	**RR 0.97** (0.88 to 1.07)	**1 fewer per 1,000** (from 2 fewer to 1 more)	⨁⨁◯◯ Low	IMPORTANT

Certainty assessment							№ of patients	Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations		Relative (95% CI)	Absolute (95% CI)		
Cheese-Cardiovascular disease incidence (follow-up: range 3.7 years to 30.0 years)											
20	Cohort studies	not serious	not serious	not serious	not serious	none	78508/1824374 (4.3%)	**RR 0.94** (0.91 to 0.97)	**3 fewer per 1,000** (from 4 fewer to 1 fewer)	⨁⨁◯◯ Low	CRITICAL
Cheese-Coronary heart disease incidence (follow-up: range 3.7 years to 30.0 years)											
14	Cohort studies	not serious	not serious	not serious	not serious	none	45680/1184988 (3.9%)	**RR 0.91** (0.87 to 0.96)	**3 fewer per 1,000** (from 5 fewer to 2 fewer)	⨁⨁◯◯ Low	CRITICAL
Cheese-Stroke incidence (follow-up: range 3.7 years to 15.0 years)											
10	Cohort studies	not serious	not serious	not serious	not serious	Possible publication bias [h]	28259/1251572 (2.3%)	**RR 0.94** (0.90 to 0.98)	**1 fewer per 1,000** (from 2 fewer to 0 fewer)	⨁◯◯◯ Very low	CRITICAL
Low-fat dairy-Cardiovascular disease incidence (follow-up: range 5.5 years to 30.0 years)											
20	Cohort studies	not serious	not serious	not serious	not serious	none	65789/1128406 (5.8%)	**RR 0.96** (0.92 to 0.99)	**2 fewer per 1,000** (from 5 fewer to 1 fewer)	⨁⨁◯◯ Low	CRITICAL
Low-fat dairy-Coronary heart disease incidence (follow-up: range 5.5 years to 30.0 years)											

Certainty assessment							№ of patients	Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		**Relative (95% CI)**	**Absolute (95% CI)**		
13	Cohort studies	not serious	not serious	not serious	not serious	none	40133/737929 (5.4%)	**RR 0.97** (0.93 to 1.01)	**2 fewer per 1,000** (from 4 fewer to 1 more)	⨁⨁◯◯ Low	IMPORTANT
Low-fat dairy-Stroke incidence (follow-up: range 5.5 years to 26.0 years)											
9	Cohort studies	not serious	not serious[i]	not serious	not serious	none	21711/827027 (2.6%)	**RR 0.90** (0.84 to 0.98)	**3 fewer per 1,000** (from 4 fewer to 1 fewer)	⨁⨁◯◯ Low	CRITICAL
High-fat dairy-Cardiovascular disease incidence (follow-up: range 5.5 years to 30.0 years)											
21	Cohort studies	not serious	not serious	not serious	not serious	none	68040/1038281 (6.6%)	**RR 0.97** (0.93 to 1.01)	**2 fewer per 1,000** (from 5 fewer to 1 more)	⨁⨁◯◯ Low	CRITICAL
High-fat dairy-Coronary heart disease incidence (follow-up: range 5.5 years to 30.0 years)											
14	Cohort studies	not serious	not serious	not serious	not serious	Possible publication bias[j]	40697/743361 (5.5%)	**RR 0.96** (0.93 to 0.99)	**2 fewer per 1,000** (from 3 fewer to 1 more)	⨁⨁◯◯ Low	IMPORTANT
High-fat dairy-Stroke incidence (follow-up: range 5.5 years to 26.0 years)											
10	Cohort studies	not serious	not serious	not serious	not serious	none	21852/832459 (2.6%)	**RR 0.98** (0.92 to 1.04)	**1 fewer per 1,000** (from 2 fewer to 1 more)	⨁⨁◯◯ Low	IMPORTANT

Certainty assessment							№ of patients	Effect		Certainty	Importance
№ of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**		**Relative (95% CI)**	**Absolute (95% CI)**		
Fermented dairy-Cardiovascular disease incidence (follow-up: range 3.7 years to 30.0 years)											
24	Cohort studies	not serious	not serious	not serious	not serious	none	76341/1729129 (4.4%)	**RR 0.96** (0.94 to 0.98)	**2 fewer per 1,000** (from 3 fewer to 1 fewer)	⨁⨁◯◯ Low	CRITICAL
Fermented dairy-Coronary heart disease incidence (follow-up: range 3.7 years to 30.0 years)											
16	Cohort studies	not serious	not serious	not serious	not serious	none	31828/1010125 (3.2%)	**RR 0.96** (0.93 to 0.99)	**1 fewer per 1,000** (from 2 fewer to 0 fewer)	⨁⨁◯◯ Low	CRITICAL
Fermented dairy-Stroke incidence (follow-up: range 3.7 years to 15.0 years)											
15	Cohort studies	not serious	not serious	not serious	not serious	none	37041/1182772 (3.1%)	**RR 0.95** (0.92 to 0.98)	**2 fewer per 1,000** (from 3 fewer to 1 fewer)	⨁⨁◯◯ Low	CRITICAL

CI: confidence interval; **RR:** risk ratio

a. Initial heterogeneity as measured by I^2=66.1%. One study (Ingegerd Johansson 2018) strongly influenced the pooled result. Removal of Ingegerd Johansson 2018 did not change the direction or significance of the pooled effect size (0·96 95% CI 0·92 to 0·99) however the heterogeneity remained high with an I^2 = 62.1%.

b. Initial heterogeneity as measured by I^2=70.5%. One study (results of CKB) strongly influenced the pooled result. Removal of Pan Zhuang 2023 (CKB) did not change the direction of the significance of the pooled result (0·966 95% CI 0.930 to 1.003) and the I^2 was reduced to 43.8%.

c. Initial heterogeneity as measured by I^2=61.8%. One study (Susanna C. Larsson 2009) strongly influenced the pooled result. Removal of Susanna C. Larsson 2009 did not change the direction of the significance of the pooled result (0·92 95% CI 0.89 to 0.96) and the I^2 was reduced to 44.6%.

d. Initial heterogeneity as measured by I^2=59.1%. One study (Ingegerd Johansson 2018) strongly influenced the pooled result. Removal of Ingegerd Johansson 2018 did not change the direction of the significance of the pooled result (0·99 95% CI 0.96 to 1.03) and the I^2 was reduced to 46.4%.

e. Initial heterogeneity as measured by I^2=64.8%. One study (Tammy Y.N. Tong 2020) strongly influenced the pooled result. Removal of Tammy Y.N. Tong 2020 did not change the direction or significance of the pooled effect size (1.01 95%CI 0·95 to 1.08) however the heterogeneity remained high with an I^2= 56.7%.

f. Initial heterogeneity as measured by I^2=60.7%. One study (Timothy J. Key 2019) strongly influenced the pooled result. Removal of Timothy J. Key 2019 did not change the direction of the significance of the pooled result (1.02 95% CI 0.93 to 1.11) and the I^2 was reduced to 39.7%.

g. Initial heterogeneity as measured by I^2=66.2%. One study (Susanna C. Larsson 2009) strongly influenced the pooled result. Removal of Susanna C. Larsson 2009 did not change the direction of the significance of the pooled result (0·929 95% CI 0.861 to 1.002) and the I^2 was reduced to 35.4%.

h. P value for Egger's test was 0.046.

i. Initial heterogeneity as measured by I^2=65.1%. One study (result of UKB) strongly influenced the pooled result. Removal of Pan Zhuang 2023 (UKB) did not change the direction of the significance of the pooled result (0·93 95%CI 0.87 to 0.99) and the I^2 was reduced to 32.7%.

j. P value for Egger's test was 0.036.

Reviewer #4 (Remarks to the Author):

I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Nature Communications initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

Response: Thank you for your comment. We appreciate the initiative by Nature Communications to support training in peer review and recognize the contributions of Early Career Researchers.

References

1. Qin, C.*, et al.* The relative validity and reproducibility of food frequency questionnaires in the China Kadoorie Biobank study. *Nutrients* **14**, 794 (2022).
2. Zhuang, P.*, et al.* Preserved vegetable consumption and its association with mortality among 440,415 people in the China Kadoorie Biobank. *BMC Med* **21**, 135 (2023).
3. Kakkoura, M.G.*, et al.* Dairy consumption and risks of total and site-specific cancers in Chinese adults: an 11-year prospective study of 0.5 million people. *BMC Med* **20**, 134 (2022).
4. Chen, J.*, et al.* Intake of ultra-processed foods is associated with an increased risk of Crohn's disease: a cross-sectional and prospective analysis of 187 154 participants in the UK Biobank. *J Crohns Colitis* **17**, 535-552 (2023).
5. Ho, F.K.*, et al.* Associations of fat and carbohydrate intake with cardiovascular disease and mortality: prospective cohort study of UK Biobank participants. *BMJ* **368**, m688 (2020).
6. Zhang, Z.*, et al.* Sweetened beverages and incident heart failure. *Eur J Prev Cardiol* **30**, 1361-1370 (2023).
7. Song, S.*, et al.* Dietary factors and patterns in relation to risk of later-onset ulcerative colitis in Chinese: a prospective study of 0.5 million people. *Aliment Pharmacol Ther* **59**, 1425-1434 (2024).
8. Yu, W.*, et al.* Dietary patterns and risk of chronic obstructive pulmonary disease among Chinese adults: an 11-year prospective study. *Nutrients* **14**, 996 (2022).
9. Liu, Q.*, et al.* The prospective associations of lipid metabolism-related dietary patterns with the risk of diabetes in Chinese adults. *Nutrients* **14**, 980 (2022).
10. Um, C.Y., Prizment, A., Hong, C.P., Lazovich, D. & Bostick, R.M. Associations of calcium and dairy product intakes with all-cause, all-cancer, colorectal cancer and CHD mortality among older women in the Iowa Women's Health Study. *Br J Nutr* **121**, 1188-1200 (2019).
11. Romo Ventura, E.*, et al.* Association of dietary intake of milk and dairy products with blood concentrations of insulin-like growth factor 1 (IGF-1) in Bavarian adults. *Eur J Nutr* **59**, 1413-1420 (2020).
12. Mladěnka, P.*, et al.* Vitamin K - sources, physiological role, kinetics, deficiency, detection, therapeutic use, and toxicity. *Nutr Rev* **80**, 677-698 (2022).

13. Martini, M., Salari, F. & Altomonte, I. The macrostructure of milk lipids: the fat globules. *Crit Rev Food Sci Nutr* **56**, 1209-1221 (2016).
14. Companys, J., Pedret, A., Valls, R.M., Solà, R. & Pascual, V. Fermented dairy foods rich in probiotics and cardiometabolic risk factors: a narrative review from prospective cohort studies. *Crit Rev Food Sci Nutr* **61**, 1966-1975 (2021).
15. Balshem, H.*, et al.* GRADE guidelines: 3. rating the quality of evidence. *J Clin Epidemiol* **64**, 401-406 (2011).
16. Pokala, A.*, et al.* Whole milk dairy foods and cardiometabolic health: dairy fat and beyond. *Nutrition Research* **126**, 99-122 (2024).
17. Yuan, M., Singer, M.R., Pickering, R.T. & Moore, L.L. Saturated fat from dairy sources is associated with lower cardiometabolic risk in the Framingham Offspring study. *Am J Clin Nutr* **116**, 1682-1692 (2022).
18. Givens, D.I. Saturated fats, dairy foods and cardiovascular health: no longer a curious paradox? *Nutr Bull* **47**, 407-422 (2022).
19. Koskinen, T.T.*, et al.* Intake of fermented and non-fermented dairy products and risk of incident CHD: the Kuopio Ischaemic Heart Disease Risk Factor Study. *Br J Nutr* **120**, 1288-1297 (2018).
20. Dehghan, M.*, et al.* Association of dairy intake with cardiovascular disease and mortality in 21 countries from five continents (PURE): a prospective cohort study. *Lancet* **392**, 2288-2297 (2018).
21. Praagman, J.*, et al.* Dairy products and the risk of stroke and coronary heart disease: the Rotterdam Study. *Eur J Nutr* **54**, 981-990 (2015).
22. Soedamah-Muthu, S.S., Masset, G., Verberne, L., Geleijnse, J.M. & Brunner, E.J. Consumption of dairy products and associations with incident diabetes, CHD and mortality in the Whitehall II study. *Br J Nutr* **109**, 718-726 (2013).
23. Dalmeijer, G.W.*, et al.* Dairy intake and coronary heart disease or stroke--a population-based cohort study. *Int J Cardiol* **167**, 925-929 (2013).
24. Patterson, E., Larsson, S.C., Wolk, A. & Åkesson, A. Association between dairy food consumption and risk of myocardial infarction in women differs by type of dairy food. *J Nutr* **143**, 74-79 (2013).
25. von Ruesten, A., Feller, S., Bergmann, M.M. & Boeing, H. Diet and risk of chronic diseases: results from the first 8 years of follow-up in the EPIC-Potsdam study. *Eur J Clin Nutr* **67**, 412-419 (2013).
26. Larsson, S.C., Virtamo, J. & Wolk, A. Dairy consumption and risk of stroke in Swedish women and men. *Stroke* **43**, 1775-1780 (2012).
27. Bernstein, A.M.*, et al.* Dietary protein sources and the risk of stroke in men and women. *Stroke* **43**, 637-644 (2012).
28. Bernstein, A.M.*, et al.* Major dietary protein sources and risk of coronary heart disease in women. *Circulation* **122**, 876-883 (2010).
29. Jackson, D., White, I.R. & Thompson, S.G. Extending DerSimonian and Laird's methodology to perform multivariate random effects meta-analyses. *Stat Med* **29**, 1282-1297 (2010).
30. Zhou, J.*, et al.* Association of milk consumption with all-cause mortality and cardiovascular outcomes: a UK Biobank based large population cohort study. *J*

Transl Med **21**, 130 (2023).
31. Guo, J.*, et al.* Milk and dairy consumption and risk of cardiovascular diseases and all-cause mortality: dose-response meta-analysis of prospective cohort studies. *Eur J Epidemiol* **32**, 269-287 (2017).
32. Higgins, J.P., Thompson, S.G., Deeks, J.J. & Altman, D.G. Measuring inconsistency in meta-analyses. *BMJ* **327**, 557-560 (2003).
33. Hedges, L.V. & Olkin, I. Statistical methods for meta-analysis. (1987).
34. Wang, X.*, et al.* Fruit and vegetable consumption and mortality from all causes, cardiovascular disease, and cancer: systematic review and dose-response meta-analysis of prospective cohort studies. *BMJ* **349**, g4490 (2014).
35. de Souza, R.J.*, et al.* Intake of saturated and trans unsaturated fatty acids and risk of all cause mortality, cardiovascular disease, and type 2 diabetes: systematic review and meta-analysis of observational studies. *BMJ* **351**, h3978 (2015).
36. Chen, G.C.*, et al.* Cheese consumption and risk of cardiovascular disease: a meta-analysis of prospective studies. *Eur J Nutr* **56**, 2565-2575 (2017).
37. Srour, B.*, et al.* Ultra-processed food intake and risk of cardiovascular disease: prospective cohort study (NutriNet-Santé). *BMJ* **365**, l1451 (2019).
38. Fang, Z.*, et al.* Association of ultra-processed food consumption with all cause and cause specific mortality: population based cohort study. *BMJ* **385**, e078476 (2024).
39. Watkins, J.*, et al.* Galactose ingested with a high-fat beverage increases postprandial lipemia compared with glucose but not fructose ingestion in healthy men. *J Nutr* **150**, 1765-1772 (2020).
40. Ohlsson, J.A.*, et al.* Lactose, glucose and galactose content in milk, fermented milk and lactose-free milk products. *International Dairy Journal* **73**, 151-154 (2017).
41. Vitoria, I.*, et al.* Lactose and galactose content in Spanish cheeses: usefulness in the dietary treatment of patients with galactosaemia. *Nutrients* **15**, 594 (2023).
42. Bernstein, L.E. & van Calcar, S. The diet for galactosemia. in *Nutrition Management of Inherited Metabolic Diseases: Lessons from Metabolic University* (eds. Bernstein, L.E., Rohr, F. & Helm, J.R.) 285-293 (Springer International Publishing, Cham, 2015).
43. Reynolds, A.*, et al.* Carbohydrate quality and human health: a series of systematic reviews and meta-analyses. *Lancet* **393**, 434-445 (2019).

Response to Reviews

Dear editors and reviewers,

Thank you for considering our manuscript. We sincerely appreciate the thoughtful suggestions provided by the reviewers and editors, which have significantly enhanced the quality of our work. We have made revisions to address each comment and have provided a detailed and point-by-point response (with changes highlighted in yellow in the revised manuscript). We believe these revisions have greatly strengthened our manuscript.

The information of sex was accessed through the questionnaire in UKB (filed ID:31) and CKB included as a covariate in the statistical analyses. For UKB, the sex information is acquired from central registry at recruitment, but in some cases updated by the participant. Hence this field may contain a mixture of the sex the NHS had recorded for the participant and self-reported sex. Sex proportion was reported and subgroup analyses on sex were also conducted and results were reported regardless of positive or negative outcome. These have been indicated in the Reporting Summary file. If there are any further requests or questions, please feel free to contact me. We look forward to your feedback.

REVIEWER COMMENTS

Reviewer #1 (Remarks to the Author):
N/A

Reviewer #2 (Remarks to the Author):

I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Nature Communications initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.
Response: Thank you for your comment. We appreciate the initiative by Nature Communications to support training in peer review and recognize the contributions of Early Career Researchers.

Reviewer #3 (Remarks to the Author):

Thank you- for the most part you have addressed my suggestions thoroughly, and I hope you found them to improve the presentation of your work.
Response: We appreciate your insightful comments, which have greatly strengthened our manuscript.

I would still like to see a more rigorous treatment of interaction. This should be done for any time you talk about subgroup differences -- the one below, for sex, is one example, but the principle should apply to all between-subgroup differences.
Response: We appreciate your feedback regarding the need for a more rigorous treatment of interactions, particularly when discussing subgroup differences. We have conducted the interaction analysis to explore how dairy consumption interacts with various stratifying variables in relation to the risk of CVD. Specifically, we incorporated a cross-product term for the baseline stratifying variables with dairy in our model, which was a common method used in previous cohort studies[1-3] to assess subgroup differences. For sex, for example, we added the cross-product term (sex×dairy) in the Cox model. Then a likelihood ratio test was used to examine the significance of the interaction term. **This principle has been applied to all between-subgroup differences** (**Supplementary Tables 17 and 18**). However, we acknowledge that our initial submission did not adequately report the results of interaction tests. We have now reported the results of interaction in the revised manuscript.

My original point #6 -- asked for the test of interaction. It's not adequate to say that two groups are different from each other simply because one group shows a "significant" effect and the other does not. What you need to do is the test for between-groups heterogeneity, or meta-regression to assess interaction between sex and dairy on CVD in CKB -- otherwise, this could simply be chance finding.
Response: We appreciate your comment regarding the need for testing interaction. We have incorporated a cross-product term for the baseline stratifying variables with dairy in our model to assess the interaction between these variables and dairy consumption on CVD in CKB. A P-value for interaction < 0.05 indicates significant group differences, thereby reducing the likelihood of chance findings.

The results of these subgroup analyses are detailed in **Supplementary Tables 17 and 18**. Notably, we observed the inverse associations between dairy consumption and the risks of CVD and stroke were observed exclusively in men, not women (P-interaction<0.001), and in individuals with hypertension, but not in those without hypertension (P-interaction<0.001), in the CKB. Additionally, the inverse association of dairy consumption with CVD risk was significant in current smokers but not in non-smokers (P-interaction = 0.007) in UKB. We have now revised our manuscript to include a comprehensive description of these findings.

Thank you for highlighting the importance of this analysis, and we hope our revisions meet your expectations.

Results, Page 5, lines 101 to 106:
Notably, the inverse associations between dairy consumption and the risks of CVD and stroke were observed exclusively in men, not women (P-interaction<0.001), and in individuals with hypertension, but not in those without hypertension (P-interaction<0.001), in the CKB (**Supplementary Table 17**). The inverse association of dairy consumption and CVD risk was detected in current smokers but not in non-smokers (P-interaction=0.007) in UKB (**Supplementary Table 18**).

Supplementary Table 17. Associations of frequency of dairy consumption with cardiovascular disease, coronary heart disease, and stroke in subgroups in the China Kadoorie Biobank.

	Baseline age (years)				P for interaction
	Below median		Above median		
	HR (95% CI)	p value	HR (95% CI)	p value	
CVD	1.03 (0.97-1.10)	0.395	1.01 (0.98-1.04)	0.765	0.063
CHD	1.08 (1.00-1.17)	0.046	1.10 (1.06-1.14)	<0.001	0.328
Stroke	1.01 (0.93-1.10)	0.118	0.94 (0.90-0.97)	0.020	0.275

	Sex				P for interaction
	Men		Women		
	HR (95% CI)	p value	HR (95% CI)	p value	
CVD	0.95 (0.91-0.99)	0.015	1.03 (0.99-1.06)	0.169	<0.001
CHD	1.03 (0.97-1.09)	0.358	1.11 (1.06-1.16)	<0.001	<0.001
Stroke	0.90 (0.85-0.95)	<0.001	0.96 (0.91-1.00)	0.072	<0.001

	Baseline BMI (kg/m^2)				P for interaction
	<28		≥28		
	HR (95% CI)	p value	HR (95% CI)	p value	
CVD	0.99 (0.97-1.02)	0.704	1.00 (0.94-1.07)	0.966	0.129
CHD	1.08 (1.04-1.12)	<0.001	1.10 (1.01-1.19)	0.031	0.243
Stroke	0.94 (0.90-0.97)	<0.001	0.92 (0.84-1.01)	0.073	0.065

	Income				P for interaction
	<20,000 yuan/yr		≥20,000 yuan/yr		
	HR (95% CI)	p value	HR (95% CI)	p value	
CVD	1.02 (0.98-1.06)	0.279	0.96 (0.92-1.00)	0.050	0.586
CHD	1.13 (1.07-1.18)	<0.001	1.03 (0.97-1.08)	0.341	0.298
Stroke	0.94 (0.89-0.98)	0.009	0.92 (0.88-0.97)	0.003	0.719

	Current smoker				P for interaction
	No		Yes		
	HR (95% CI)	p value	HR (95% CI)	p value	
CVD	1.01 (0.98-1.04)	0.516	0.95 (0.90-1.00)	0.054	0.138
CHD	1.09 (1.05-1.13)	<0.001	1.04 (0.97-1.12)	0.258	0.643
Stroke	0.95 (0.91-0.99)	0.017	0.88 (0.82-0.95)	<0.001	0.171

	Alcohol drinker				P for interaction
	No		Yes		
	HR (95% CI)	p value	HR (95% CI)	p value	
CVD	1.02 (0.99-1.05)	0.266	0.92 (0.87-0.97)	0.003	0.012
CHD	1.11 (1.07-1.15)	<0.001	0.98 (0.90-1.05)	0.539	0.158

Stroke	0.95 (0.91-0.99)	0.010	0.88 (0.82-0.95)	<0.001	0.071

	Physical activity (MET-h/wk)				P for interaction
	Below median		Above median		
	HR (95% CI)	p value	HR (95% CI)	p value	
CVD	1.00 (0.97-1.03)	0.880	0.98 (0.93-1.04)	0.577	0.346
CHD	1.08 (1.04-1.12)	<0.001	1.09 (1.01-1.17)	0.022	0.372
Stroke	0.95 (0.91-0.99)	0.007	0.91 (0.84-0.98)	0.014	0.744

	Diet quality score				P for interaction
	Below median		Above median		
	HR (95% CI)	p value	HR (95% CI)	p value	
CVD	0.99 (0.95-1.04)	0.761	1.00 (0.97-1.04)	0.840	0.072
CHD	1.10 (1.03-1.17)	0.003	1.08 (1.03-1.12)	<0.001	0.115
Stroke	0.92 (0.86-0.97)	0.005	0.95 (0.91-1.00)	0.033	0.190

	Hypertension				P for interaction
	No		Yes		
	HR (95% CI)	p value	HR (95% CI)	p value	
CVD	1.05 (1.01-1.09)	0.016	0.95 (0.91-0.98)	0.005	<0.001
CHD	1.10 (1.04-1.16)	<0.001	1.06 (1.01-1.11)	0.022	<0.001
Stroke	1.00 (0.95-1.06)	0.882	0.88 (0.84-0.93)	<0.001	<0.001

	Diabetes				P for interaction
	No		Yes		
	HR (95% CI)	p value	HR (95% CI)	p value	
CVD	0.99 (0.97-1.02)	0.651	1.03 (0.94-1.11)	0.556	0.001
CHD	1.08 (1.04-1.12)	<0.001	1.09 (0.98-1.22)	0.105	0.033
Stroke	0.93 (0.90-0.97)	<0.001	0.98 (0.88-1.09)	0.650	0.002

	Family history of CVD				P for interaction
	No		Yes		
	HR (95% CI)	p value	HR (95% CI)	p value	
CVD	0.99 (0.96-1.02)	0.585	1.01 (0.96-1.06)	0.769	0.763
CHD	1.07 (1.02-1.11)	0.004	1.12 (1.05-1.19)	<0.001	0.011
Stroke	0.94 (0.90-0.98)	0.002	0.94 (0.88-1.00)	0.057	0.027

The multivariable model was adjusted for age, sex, centers, survey season, BMI, education, income, physical activity, smoking, alcohol drinking, history of hypertension, diabetes, family history of CVD, aspirin use, vitamins use, minerals use, and intake of red meat, processed red meat, oily fish, non-oily fish, poultry, vegetables, fruits, and eggs.

Supplementary Table 18. Associations of total dairy consumption with cardiovascular disease, coronary heart disease, and stroke in subgroups in the UK Biobank.

	Baseline age (years)				P for interaction
	Below median		Above median		
	HR (95% CI)	p value	HR (95% CI)	p value	
CVD	0.90 (0.82-0.99)	0.025	0.94 (0.85-1.000)	0.049	0.855
CHD	0.93 (0.84-1.03)	0.184	0.93 (0.87-0.999)	0.046	0.763
Stroke	0.72 (0.57-0.89)	0.003	0.98 (0.86-1.12)	0.774	0.943

	Sex				P for interaction
	Men		Women		
	HR (95% CI)	p value	HR (95% CI)	p value	
CVD	0.96 (0.88-1.05)	0.392	0.91 (0.86-0.97)	0.004	0.475
CHD	0.97 (0.88-1.07)	0.493	0.92 (0.86-0.99)	0.017	0.677
Stroke	0.94 (0.79-1.13)	0.517	0.86 (0.74-0.999)	0.048	0.498

	Baseline BMI (kg/m^2)				P for interaction
	<30		≥30		
	HR (95% CI)	p value	HR (95% CI)	p value	
CVD	0.95 (0.89-1.01)	0.089	0.88 (0.80-0.97)	0.007	0.277
CHD	0.94 (0.88-1.01)	0.091	0.91 (0.82-1.01)	0.062	0.712
Stroke	0.98 (0.86-1.12)	0.739	0.72 (0.57-0.89)	0.003	0.025

	Income				P for interaction
	<£31,000 /yr		≥£31,000 /yr		
	HR (95% CI)	p value	HR (95% CI)	p value	
CVD	0.90 (0.83-0.97)	0.006	0.97 (0.90-1.05)	0.471	0.353
CHD	0.90 (0.83-0.98)	0.012	0.99 (0.91-1.08)	0.758	0.108
Stroke	0.92 (0.78-1.09)	0.325	0.86 (0.73-1.03)	0.104	0.646

	Current smoker				P for interaction
	No		Yes		
	HR (95% CI)	p value	HR (95% CI)	p value	
CVD	0.95 (0.90-1.01)	0.073	0.76 (0.65-0.89)	<0.001	0.007
CHD	0.95(0.90-1.01)	0.108	0.80 (0.67-0.94)	0.009	0.051
Stroke	0.93 (0.83-1.05)	0.263	0.67 (0.48-0.94)	0.022	0.066

	Alcohol drinker				P for interaction
	No		Yes		
	HR (95% CI)	p value	HR (95% CI)	p value	
CVD	0.92 (0.82-1.04)	0.166	0.93 (0.88-0.99)	0.014	0.610
CHD	0.92 (0.81-1.04)	0.189	0.94 (0.88-0.999)	0.045	0.475
Stroke	0.83 (0.64-1.08)	0.160	0.92 (0.81-1.05)	0.199	0.669

	Physical activity (MET-h/wk)				P for interaction
	Below median		Above median		
	HR (95% CI)	p value	HR (95% CI)	p value	
CVD	0.97 (0.90-1.05)	0.431	0.89 (0.82-0.96)	0.003	0.411
CHD	0.98 (0.849-1.06)	0.563	0.89 (0.82-0.98)	0.012	0.967
Stroke	0.94 (0.78-1.12)	0.453	0.84 (0.71-1.003)	0.054	0.029

	Diet quality score				P for interaction
	Below median		Above median		
	HR (95% CI)	p value	HR (95% CI)	p value	
CVD	0.90 (0.84-0.97)	0.004	0.97 (0.90-1.05)	0.402	0.579
CHD	0.90 (0.83-0.97)	0.006	0.98 (0.90-1.07)	0.685	0.841
Stroke	0.90 (0.77-1.05)	0.180	0.93 (0.78-1.10)	0.379	0.650

	Hypertension				P for interaction
	No		Yes+G60:H61		
	HR (95% CI)	p value	HR (95% CI)	p value	
CVD	0.96 (0.87-1.06)	0.387	0.92 (0.86-0.97)	0.004	0.873
CHD	0.97 (0.86-1.08)	0.525	0.92 (0.86-0.98)	0.013	0.826
Stroke	0.95 (0.76-1.19)	0.642	0.88 (0.77-1.01)	0.066	0.817

	Diabetes				P for interaction
	No		Yes		
	HR (95% CI)	p value	HR (95% CI)	p value	
CVD	0.94 (0.89-0.995)	0.031	0.82 (0.70-0.97)	0.019	0.109
CHD	0.94 (0.89-1.002)	0.060	0.85 (0.71-1.01)	0.069	0.269
Stroke	0.93 (0.82-1.05)	0.236	0.71 (0.50-1.02)	0.062	0.068

	Family history of CVD				P for interaction
	No		Yes		
	HR (95% CI)	p value	HR (95% CI)	p value	
CVD	0.91 (0.84-0.996)	0.042	0.93 (0.88-0.995)	0.033	0.946
CHD	0.90 (0.82-0.99)	0.036	0.95 (0.89-1.02)	0.130	0.456
Stroke	0.98 (0.81-1.19)	0.839	0.86 (0.75-0.99)	0.035	0.108

The multivariable model was adjusted for age, sex, centers, survey season, BMI, education, income, physical activity, smoking, alcohol drinking, history of hypertension, diabetes, family history of CVD, aspirin use, vitamins use, minerals use, and intake of red meat, processed red meat, oily fish, non-oily fish, poultry, vegetables, fruits, and eggs.

Page 17, lines 418-420:

P interaction was calculated by adding a cross-product term for the baseline stratifying variable with dairy as an ordinal variable in the model.

Reviewer #4 (Remarks to the Author):

I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Nature Communications initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

Response: Thank you for your comment. We appreciate the initiative by Nature Communications to support training in peer review and recognize the contributions of Early Career Researchers.

References

1. Al-Shaar L, Satija A, Wang DD, et al. Red meat intake and risk of coronary heart disease among US men: prospective cohort study. BMJ. 2020;371:m4141.

2. Freedman ND, Park Y, Abnet CC, Hollenbeck AR, Sinha R. Association of coffee drinking with total and cause-specific mortality [published correction appears in N Engl J Med. 2012 Jul 19;367(3):285]. N Engl J Med. 2012;366(20):1891-1904.

3. Zhuang P, Zhang Y, He W, et al. Dietary Fats in Relation to Total and Cause-Specific Mortality in a Prospective Cohort of 521 120 Individuals With 16 Years of Follow-Up. Circ Res. 2019;124(5):757-768.

Dear editors and reviewers,
Thank you for accepting our manuscript. We have now made revisions to address the editorial requests and have provided a detailed and point-by-point response in Author Checklist (with changes highlighted in blue in the revised manuscript).

REVIEWER COMMENTS

Reviewer #3 (Remarks to the Author):

Thank you for your patience. I regret that it took me so long to re-assess this manuscript, and thank the authors for their understanding of our competing deadlines.
The investigation of the association between dairy foods and CVD, while not particularly novel itself, is important to continue to assess, as the food supply changes and dietary advice evolves. This manuscript does a good job of advancing the literature in this regard. The data analysis is sound, and interpretations and conclusions supported by the data. There is enough data provided to reproduce the findings.
Upon review, the authors have now treated the issue of interactions appropriately, which has satisfied my request regarding this deficiency. The quality of the manuscript is much improved as a result, and I am more confident in the observed interactions. No further revisions suggested by me.
Thank you for the opportunity to review this manuscript.

Response: We sincerely appreciate your thoughtful reassessment of our manuscript and your kind acknowledgment of the improvements made. We are glad to hear that the revisions addressing the interactions have satisfied your concerns and that the quality of the manuscript has met your expectations. Thank you for your valuable feedback and for taking the time to review our work. Your insights have significantly contributed to enhancing the clarity and rigor of our study, and we are grateful for the opportunity to have benefited from your expertise.

Reviewer #4 (Remarks to the Author):

I co-reviewed this manuscript with one of the reviewers who provided the listed reports. This is part of the Nature Communications initiative to facilitate training in peer review and to provide appropriate recognition for Early Career Researchers who co-review manuscripts.

Response: Thank you for your comment. We appreciate the initiative by Nature Communications to support training in peer review and recognize the contributions of Early Career Researchers.