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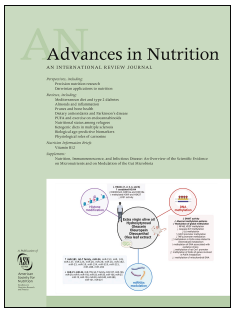

Dairy intake and risk of cognitive decline and dementia: A systematic review and dose-response meta-analysis of prospective studies

Fanny Villoz, Tommaso Filippini, Natalia Ortega, Doris Kopp-Heim, Trudy Voortman, Manuel R. Blum, Cinzia Del Giovane, Marco Vinceti, Nicolas Rodondi, Patricia O. Chocano-Bedoya

PII: S2161-8313(23)01447-3

DOI: https://doi.org/10.1016/j.advnut.2023.100160

Reference: ADVNUT 100160

To appear in: *Advances in Nutrition*

Received Date: 12 April 2023

Revised Date: 20 November 2023

Accepted Date: 27 November 2023

Please cite this article as: F. Villoz, T. Filippini, N. Ortega, D. Kopp-Heim, T. Voortman, M.R. Blum, C. Del Giovane, M. Vinceti, N. Rodondi, P.O. Chocano-Bedoya, Dairy intake and risk of cognitive decline and dementia: A systematic review and dose-response meta-analysis of prospective studies, *Advances in Nutrition*, https://doi.org/10.1016/j.advnut.2023.100160.

Title: Dairy intake and risk of cognitive decline and dementia: A systematic review and dose-response meta-analysis of prospective studies

Authors: Fanny Villoz[1,2*], Tommaso Filippini[3,4*], Natalia Ortega[1,5], Doris Kopp-Heim[6], Trudy Voortman[7], Manuel R. Blum[1,2], Cinzia Del Giovane[1,5], Marco Vinceti[3,8], Nicolas Rodondi[1,2], Patricia O. Chocano-Bedoya[1,5]

*Shared first authorship

Affiliations:

[1]Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland

[2]Department of General Internal Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland

[3]Section of Public Health, Department of Biomedical, Metabolic and Neural Sciences. University of Modena and Reggio Emilia, Italy

[4]School of Public Health, University of California Berkeley, Berkeley, CA, USA

[5]Population Health Lab, University of Fribourg, Fribourg, Switzerland

[6]Public Health & Primary Care Library, University Library of Bern, University of Bern, Bern, Switzerland

[7]Department of Epidemiology, Erasmus MC University Medical Center, Rotterdam, the Netherlands

[8]Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA

Corresponding Author: Patricia O. Chocano-Bedoya, Mittelstrasse 43. Bern, Switzerland. Tel: +41 31 684 58 69. Email: patricia.chocano@biham.unibe.ch

Funding:

This systematic review and meta-analysis is funded by the SNF-project grant 204967 "Prospective international study of dairy and inflammation on cognitive decline" (PI: PC-B), which also funds NO. TF and MV were supported by the grant "Dipartimenti di Eccellenza 2018–2022" to the Department of Biomedical, Metabolic and Neural Sciences, University of Modena and Reggio Emilia from the Italian Ministry of University and Research. TF is supported by grants PRIN 2022 (no. 2022MHMRPR) and PRIN 2022 PNRR (no. P20229KSXB) from the Italian Ministry of University, and by grant FAR2023 from University of Modena and Reggio Emilia.

Abbreviations

BMI, body mass index

CI, confidence interval

FFQ, food frequency questionnaire

ICD, International Classification of Diseases

IQR, interquartile range

MCI, mild cognitive impairment

MMSE, Mini-Mental State Examination

OR, odds ratio

RCT, randomized controlled trial

RR, risk ratio

Abstract

Background: Dairy intake may influence cognition through several molecular pathways. However, epidemiologic studies yield inconsistent results, and no dose-response meta-analysis has been conducted yet.

Objective: We performed a systematic review with dose-response meta-analysis about the association between dairy intake and cognitive decline or incidence of dementia.

Methods: We investigated prospective studies with a follow-up ≥6 months on cognitive decline or dementia incidence in adults without known chronic conditions through a systematic search of Embase, Medline, Cochrane Library, Web of Science and Google Scholar from inception to July 11, 2023. We evaluated dose-response association using a random-effects model.

Results: We identified 15 eligible cohort studies, with over 300,000 participants and a median follow-up of 11.4 years. We observed a negative non-linear association with cognitive decline/dementia incidence and dairy intake as assessed through quantity of consumption, with the nadir at approximately 150 g/day (RR=0.88, 95% CI 0.78-0.99). Conversely, we found an almost linear negative association when we considered frequency of consumption (RR for linear trend 0.84, 95% CI 0.77-0.92 for 1 time/day increase of dairy products). Stratified analysis by dairy products showed different shape of the association with linear inverse relationship for milk intake, while possibly non-linear for cheese. The inverse association was limited to Asian populations characterized by generally lower intake of dairy products, compared with the null association reported by European studies.

Conclusion: Our study suggests a non-linear inverse association between dairy intake and cognitive decline or dementia, also depending on dairy types and population characteristics, although the heterogeneity was still high in overall and several subgroup analyses. Additional studies should be performed on this topic, also including a wider range of intake and types of dairy products, to confirm a potential preventing role of dairy intake on cognitive decline and identify ideal intake doses.

Keywords: dairy products; dementia; dose-response meta-analysis; cohort studies; cognitive decline

PROSPERO's registry number CRD42020192395

Statement of Significance

This systematic review and meta-analysis identified 15 prospective observational studies evaluating the role of dairy on cognitive function. Our results suggest that dairy might be associated with lower risk of cognitive decline or dementia, but that the relation seems non-linear with also differences by sex, age, region of origin, level of intake and type of dairy products.

Introduction

Cognitive decline ranges from the minimal decline that is associated with normal ageing, to dementia. In between these two extremities, Mild Cognitive Impairment (MCI) corresponds to an intermediate stage (1). With an overall prevalence of MCI worldwide assessed at 15.6 % in 2022 and an estimate of 57.4 million cases of dementia worldwide in 2019 (2), cognitive decline represents a major health issue. Moreover, this burden will be of even greater concern in the future with a projection of 152.8 million cases of dementia in 2050 (3). While no effective treatment is available to counteract dementia progression (4), up to 40% of dementias could be prevented or delayed if addressing modifiable risk factors (5).

Growing evidence from *in vitro* or in animal models and from individual epidemiologic studies in healthy adults highlights cues of association between nutrition and cognitive function through several mechanisms, including inflammation, oxidative stress and control of other risk factors (6). Dairy products may have anti-inflammatory and neuroprotective properties (7-9). In addition, dairy products might lower the risk of cardiovascular and metabolic disease (10, 11) which are known risk factors for cognitive impairment and dementia (12). Nevertheless, on a meta-analytical level, the association between dairy intake and cognitive function could not be robustly illustrated yet. Previous systematic reviews and meta-analyses have led to conflicting trends (13, 14). On the one hand, the meta-analysis by Wu et al. 2016 (14), including 3 cross-sectional and 4 cohort studies, found that high milk consumption was associated with decreased risk of cognitive disorders (OR=0.72, 95% CI 0.56-0.93). However, this result was treated with caution in the perspective of many limitations of the study which were principally the large heterogeneity (I^2=64%) due to type of outcome and characteristics of participants. As a matter of fact, the authors reported stronger negative association with no heterogeneity (I^2=0%) in subjects with Alzheimer's disease compared to cognitive impairment/decline and overall dementia, and in Asian and African populations compared to Caucasian. On the other hand, the more recent systematic review and meta-analysis by Lee et al. (2018) (13) identified one

randomized controlled trial (RCT) and seven observational cohort studies. Due to limited reported data, the meta-analysis was conducted only among three observational cohort studies. While the authors reported no association between dairy intake and cognitive decline, their results were in opposite direction to those of Wu et al. (14) with higher risk of cognitive decline with higher dairy intake (RR=1.21, 95% CI: 0.81-1.82, for the highest vs. the lowest intake, I^2=64%).

Since additional prospective studies on dairy and cognition have been recently published (15-19), and no dose-response meta-analysis is available, we decided to carry out a new meta-analysis. We decided also to take into account the all dairy foods as one food group and whenever possible subgroups of dairy products, dose-response relationship, geographical differences and length of follow-up, which could have led to high heterogeneity in previous meta-analysis.

The objective of this systematic review and meta-analysis is to summarize the literature on the association between dairy and cognitive decline or incident dementia and to explore the shape of the association using whenever possible dose-response non-linear modeling.

Methods

The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number CRD42020192395 and adheres to the preferred reporting items for systematic reviews and meta-analyses (PRISMA) (20).

Literature search

We conducted a comprehensive literature search in cooperation with an experienced medical information specialist in Embase.com (Elsevier), Medline (Ovid), Cochrane Central Register of Controlled Trials (Wiley), Cochrane Database of Systematic Reviews (Wiley), Web of Science Core Collection (Clarivate) and Google Scholar, from inception up to July 11, 2023 (last date searched) to identify all prospective observational studies and RCTs that reported data on usual dairy intake at

baseline, with prospective follow-up data on cognitive decline or incidence dementia among adults. The search strategy combined terms related to dairy intake (among others dairy products, milk, yogurt, butter, cheese, cream, whey, casein, lactalbumin) and cognitive decline (dementia, memory disorder, cognitive defect, Alzheimer, neuro-degenerative disease). No date or language limits were applied. The full search strategies in all databases are provided in **Supplementary Material SM1**. In addition, we reviewed reference lists of included studies to retrieve additional relevant articles. We removed duplicate records using Deduklick, a fully automated deduplication algorithm (21). The results of the searches were uploaded into Rayyan (22) for title/abstract screening and full-text evaluation.

Study selection and data extraction

Two reviewers (FV and TF) independently screened the titles and abstracts of the retrieved studies to exclude articles that did not meet the eligibility criteria. Then, they retrieved full texts of the potentially eligible studies and again assessed their eligibility independently. We included studies only in English and in peer reviewed journals. We excluded studies which recruited only subjects with chronic conditions (e.g. diabetes, hypertension, metabolic syndrome, dyslipidemia, etc.), cross-sectional studies and studies with a follow-up less than 6 months. For RCTs we additionally required that studies have a non-dairy or low-dairy control group (i.e., not only comparing different dairy products). We also excluded studies that used non-bovine or human milk interventions. We recorded reasons for exclusion in the full-text screening (**Supplementary Material SM2**). Any disagreement between the authors regarding the eligibility of a study was resolved through discussion with a third reviewer (PC). We illustrated the selection process in a PRISMA flow diagram.

Two reviewers (FV and TF) independently extracted multiple fields based on the following categories: general study information (authors, journal, year of publication, title), study design (country of origin, setting, sample size, follow-up time), participant characteristics (age, sex, body weight, body mass index-BMI), exposure (dietary assessment, type of dairy), outcome assessment method (cognitive

decline or incident dementia), outcome data (effect estimates with measures of variation and covariates). When a study reported stratified analysis only divided by characteristics of study population (e.g., APOE status) or type of outcome (e.g., AD and non-AD diagnosis), we combined their results using a fixed-effects model and then included them into the analysis comparing the highest-versus-lowest exposure (e.g. forest-plots). Conversely, when including study results in the dose-response analysis, we had to considered them as strata-specific study results. From observational studies, we extracted the outcome data from the most adjusted multivariable models. We extracted relative risk (RR) or hazard ratio (HR) along with 95% confidence intervals (CI) for dichotomous outcomes, and mean differences and standard deviation/standard error for continuous outcomes. Finally, we asked the authors of four studies (23-26) to give us further information of median dose or ranges in each category or to clarify the definition of serving size. However, we did not receive additional information.

Data synthesis and analysis

We performed pairwise meta-analyses for all exposure and outcomes using a restricted maximum likelihood random-effects model (27). We planned to analyze observational studies separately from RCTs. For dichotomous outcomes (cognitive decline or dementia), we computed the summary RR. Results are presented for the combined outcome (i.e., cognitive decline or dementia incidence) and we performed stratified analysis whenever possible (see below subgroup analyses). We have focused our description and interpretation of the results on the assessment of the size of point estimates and their measures of statistical precision (CIs) without p-value fixed cutpoints (28-30).

We assessed potential non-linear relationship through estimation of dose-response relationship between dairy intake (measured as amount in g/day or frequency in times/day) and cognition. For each category of exposure, we assigned the mean or median intake along with the RR and the confidence interval, the number of cases and of person years. When means or the median were not available, we used the

midpoint of each category of intake. For open-ended categories, we used a value 20% lower or higher than the boundary values as performed in other fields (31-33). For one study (15) reporting mean dairy intake in g/1000 kcal/day for each category, we used the mean kcal of the same category to calculate the value in g/day. We used a restricted cubic spline function with three knots at fixed cut-points (10th, 50th and 90th percentiles) using a restricted maximum likelihood random-effects model (34), assessing also the presence of a linear trend (35). We also presented the results as RR and relative 95% CIs comparing the highest versus the lowest exposure category in forest plots.

Subgroup and sensitivity analyses

Whenever possible, we conducted subgroup analysis by type of dairy product, mean age (<65 vs. ≥65 years), sex, region of origin (Asia, Europe and Oceania), length of follow-up (<10 vs. ≥10 years), and excluding studies at high risk of bias to reveal potential sources of heterogeneity. In addition, we performed a meta-regression analysis using cognitive function (cognitive decline or dementia incidence) as dependent variable and the length of follow-up as independent variable in an adjusted model for potential confounders.

We tested heterogeneity among studies using the I^2 test and by visual inspection of the forest plots. We interpreted I^2 values of ≤25%, between 25% and 50%, and above 50% as 'low', 'moderate' and 'high' heterogeneity between studies, respectively. We also computed the τ^2 to assess the between-study variance and reported the 95% prediction intervals to evaluate the variation of the effect size of a future new study. In the non-linear analysis, we also assessed the variation across individual study results showing the study-specific trends using predicted curves (36). We used Stata version 18.0 (StataCorp., College Station, TX, 2023) for all statistical analyses, specifically the 'meta', 'mkspline', and 'drmeta' routines.

158

159 ***Quality assessment***

160 We assessed the quality and risk of bias of the included studies with the Nutrition Quality Evaluation
161 Strengthening Tools (NUQUEST), specially developed for dietary methods assessment (37). We used
162 the version for cohort studies that consists of four domains related to selection of the cohort,
163 comparability, ascertainment of the outcomes and nutrition specific. The overall rating is expressed as
164 poor (most criteria are not met, leading to a high risk of bias), neutral (most criteria are met and are of
165 little or no concern) and good (almost all criteria are met, leading to a low risk of bias). Study quality
166 was evaluated by two reviewers (FV and NO) and discrepancies in each domain were resolved with the
167 help of a third author (TF) in case of disagreements. We used the Egger's test and funnel plot to
168 visually assess indication of publication bias (38).

169

170 **Results**

171 The systematic search identified 3663 records (**Figure 1**) and one additional paper was retrieved
172 through reference list scanning. After removing duplicates, we screened 2299 records of which 2253
173 were excluded based on title and abstract screening. We retrieved 46 full-text articles for evaluation.
174 We excluded 31 articles based on the eligibility criteria: population with chronic conditions (n=3), not
175 evaluating milk or dairy (n=12), follow-up duration less than 6 months (n=6), cognitive decline or
176 dementia not the outcome of interest (n=1), no results available (n=1), not in English language (n=1),
177 cross-sectional studies (n=5), not peer-reviewed (n=1), and same cohort as another included study
178 (n=1).
179 We included the remaining 15 studies, all with prospective cohort design and including a total of
180 312,580 participants (**Table 1**). Participants mean age ranged from 53 (17) to 91 years (16) at baseline.
181 In the study by Yamada et al. (26) in the Adult Health Follow-Up study participants were 30 years and
182 older (26). Seven studies were from Europe (16, 18, 25, 39-42), six studies from Asia (15, 17, 19, 24,

26, 43), one from Australia (23), and one from the USA (44). Participants were followed for a minimum of 4.8 years (23) to a maximum of 30 years (26) with a median follow-up of 11.4 years. Among the selected studies, five studies included the outcome of dementia incidence using ICD 8-10 or DSM-IIIR/DSM-IV criteria (16, 18, 26, 39, 43) and ten studies evaluated cognitive function (15, 17, 19, 23-25, 40-42, 44). Most studies evaluated cognitive function with the MMSE (16, 17, 19, 23-25, 41) while others used other neuropsychological tests (40-42, 44). Six studies used food frequency questionnaires (15-17, 25, 39, 41, 43, 44) including between 26 (16) to 188 (35) food items. Other studies used dietary records (18, 24, 40), dietary history (42) or other questionnaires (19, 23, 26). While two studies only evaluated milk intake (high fat (23) or total (44)) and one cheese intake (39), most studies evaluated total dairy intake (15-19, 24, 25, 40-42, 45). The selection of covariates for adjustment was diverse, most studies adjusted their results for age, sex, education, physical activity, BMI, and previous comorbidities. Almost all studies adjusted their results for total calorie intake, except those without a full dietary assessment (16, 19, 23, 26). Moreover, some studies adjusted their outcomes for additional nutritional factors, for example fruit/vegetable intakes (15, 17, 18, 39) or 'healthy' dietary patterns (17, 40, 43), among others.

The assessment with the NUQUEST revealed that out of 15 studies, there were one poor, 10 neutral (67%) and 4 good studies. Even if none of the studies assessed if the exposure difference was maintained over the study period, 14 out of 15 were rated as good in the nutrition domain. The main risk of bias came from the comparability domain because few of them reported the baseline differences between those lost to follow-up and the included participants, compared how many participants were lost to follow-up in each exposure group or performed repeated measurements of the nutritional aspect under study. The detailed results are available in **Supplementary Table S1**.

The dose-response analyses (**Figure 2**) included ten studies that had sufficient information on consumption of dairy products by increasing quantity (15, 17, 18, 41-43) or by increasing frequency (16, 17, 19, 26, 39) in relation to cognitive decline or dementia. When assessing quantity of

consumption, we observed a non-linear association, with an initial decline in risk until 150 g/day (RR=0.88, 95% CI 0.78-0.99), after which a slight change in direction was observed. We found an almost linear negative association when we considered frequency of consumption (RR for linear trend 0.84, 95% CI 0.77-0.92 for 1 time/day increase of dairy products).

The results of the combined outcome (i.e., dementia or cognitive decline) showed that the highest intake of dairy products compared to the lowest intake has no association with cognitive decline or dementia with RR=0.94 (95% CI=0.82-1.07) with high heterogeneity (I^2=69.2%) and between-study variance (τ^2=0.03) as showed by the wide prediction intervals (95% CI 0.61-1.45) (**Supplementary Figure S1**). For the outcome cognitive decline, we were able to combine seven of the nine studies (17, 19, 23-25, 41, 42): we observed no associations of the highest vs. the lowest dairy intake on cognitive decline (RR=1.01, 95% CI=0.86-1.20) with high heterogeneity (I^2=73.5%) and between-study variance (τ^2=0.03) and wide prediction intervals (95% CI 0.60-1.72). Only two studies reported continuous results for cognitive function (40, 44) and total dairy intake using linear regression analysis, thus a meta-analysis with risk estimates was not possible. For the outcome of incident dementia, we identified six studies (15, 16, 18, 26, 39, 43). We observed a decreased risk of dementia with the highest intake of dairy vs. the lowest intake (RR=0.83, 95% CI 0.67-1.03) although characterized by high heterogeneity (I^2=63.0%) and between-study variance (τ^2=0.04) leading to wide prediction intervals (95% CI 0.44-1.59) (**Supplementary Figure S1**).

In subgroup analyses, we observed that part of the heterogeneity could be explained by sex as studies carried out in both males and females reported inverse association (RR=0.85, 95% CI 0.78-0.93) also characterized by negligible heterogeneity (I^2=2.6%, τ^2=0.00), while the studies reporting sex-specific results showed very heterogeneous and imprecise positive (in males) or null (in females) associations (**Supplementary Figure S2**). The dose-response meta-analysis restricted to such studies carried out in both sexes (15, 17, 41, 43) showed non-linear association although imprecise to due lower number of studies, with nadir at 100-150 g/day (**Supplementary Figure S3**).

Stratified analysis by age at recruitment of study participants showed lower risk in studies considering younger subjects (<65 years: RR=0.88, 95% CI 0.76-1.01) also characterized by limited heterogeneity (I^2=24.3%, τ^2=0.01) compared to studies recruiting older subjects ≥65 years (RR=0.95, 95% CI 0.75-1.21, I^2=77.4%, τ^2=0.08) (**Supplementary Figure S4**).

In the subgroup analyses by region of origin (**Figure 4**), there was a reduced risk of cognitive decline or dementia with the highest dairy intake compared with the lowest dairy intake in the studies from Asia (RR=0.83, 95% CI 0.75-0.92, I^2=0.0% and τ^2=0.00) (15, 17, 19, 24, 26, 43). Conversely, we found no association between dairy and cognitive decline or incident dementia among studies from Europe (RR=1.01, 95% CI 0.86-1.19, I^2=41.6% and τ^2=0.02) (16, 18, 25, 39, 41, 42) and higher risk with the highest intake compared with the lowest dairy intake in one single study from Oceania (RR=1.75, 95% CI 1.17-2.62).

In the analysis investigating different types of dairy products (**Supplementary Figure S5**), we found an inverse association with cognitive decline or dementia when all dairy types are considered (RR=0.89, 95% CI 0.83-0.95, I^2=0.33% and τ^2=0.00). Conversely, the association with specific dairy products was very heterogenous and inconsistent as it was reported in a lower number of studies, with the exception of milk and cheese intake alone, investigated in five and four studies, respectively, and reporting both null associations. The dose-response meta-analysis by dairy type (**Figure 3**) was feasible for these latter subgroups. The analysis showed a null association with milk consumption up to 0.3 times/day, while negative association emerged for high intakes. Conversely, the association seemed to be non-linear for cheese consumption, with lower risk at 0.3 times/day and null/positive association at higher intakes.

The sensitivity analysis excluding the one study judged at possible high risk of bias (23) suggests a stronger negative association between dairy intake for cognitive decline or dementia outcome (overall RR=0.90, 95% CI 0.82-1.00) with decreased heterogeneity (I^2=44.7%) and lower study variance (τ^2=0.01) despite the still wide prediction intervals (95% CI 0.69-1.18) (**Supplementary Figure S6**). In

addition, the association became slightly negative also for cognitive decline (0.94, 95% CI 0.83-1.07). Conversely, the dose-response meta-analysis did not change as the one study at high risk of bias was excluded already not reporting exposure doses of dairy intake.

Stratified analysis by duration of follow-up (<10 years and ≥10 years) showed little influence in the overall estimate (**Supplementary Figure S7**). Similarly, the meta-regression analysis for increasing years of length of follow-up adjusting for potential cofounders based on previous stratified analyses (i.e. sex, age category at recruitment, and region of origin) showed almost negligible association with risk of cognitive decline or dementia incidence (beta regression coefficient= –0.005, 95% CI –0.023 to 0.014) (**Supplementary Figure S8**).

Assessment of small-study bias showed low effects, with symmetry of funnel plot and low effect-based Egger's test (slope=–0.17, 95% CI –2.78 to 2.44) (**Supplementary Figure S9**). Assessment of study-specific curves showed higher variation in studies using quantity compared to frequency of consumption of dairy intake (**Supplementary Figure S10**) when considering overall dairy products. Conversely, stratified analysis by dairy types showed high variation in both studies measuring milk and cheese intake using frequency of consumption (**Supplementary Figure S11**).

Discussion

This systematic review and meta-analysis identified 15 prospective observational studies involving more than 300,000 participants. Results suggest that dairy might be associated with lower risk of cognitive decline or dementia, but that there may be differences by sex, age, region of origin, level of intake and type of dairy products. To our knowledge, we are the first study to evaluate dose-response relationships in a meta-analysis of dairy and cognition, suggesting a non-linear relation with lower risk at approximately 150 g/day of overall dairy intake. Our subgroup analyses suggest that this could mainly be explained by differences in level of intake and type of dairy products. As a matter of that, intake of dairy products greatly varies across the included studies, mainly depending on region of

origin. Considering only studies in Asia, the highest dairy intake was associated with much reduced risk of cognitive decline or dementia and low heterogeneity compared with European studies. Among European studies, there was no association between dairy intake and cognitive decline or dementia. In contrast, the single study conducted in Oceania reported a higher risk of cognitive decline with the highest dairy intake compared to the lowest, although such study was deemed at high risk of bias thus limiting the reliability of such results. Similar results were reported in the 2016 meta-analysis by Wu et al. (14), where in the stratified analysis by race, studies conducted among Asians had a 43% lower risk of cognitive disorders with higher dairy intakes, while for those conducted in Caucasians there was no association. Divergent results between Asian and European countries have been also reported for stroke (46). The amount and types of dairy consumption between regions were considerably higher in studies carried out in European countries, between 170-711 g/day on average, than studies in Asian countries where total dairy intake ranged between 29-165 g/day on average. Despite the "Westernization" of Asian diets, populations in Asian countries on average still consume lower quantities of dairy products (47). Also, in Asian countries recommendations of dairy intake range between 1-4 servings per day, whereas in Europe they are slightly higher at 2-4 servings per day (48) and milk is consumed more frequently than other dairy products (46, 49).

Dairy is a heterogeneous food group including fermented or non-fermented foods and differing in nutrients such as fat and sodium. Stratified analysis by dairy type suggested an inverse linear relation when milk intake was considered only, while the shape of the association seemed to be non-linear for cheese intake. In the study by Kesse-Guyot et al. (40), total dairy intake was not associated with any of the cognitive outcomes, milk intake was associated with worse verbal memory and yogurt and cheese were associated with better verbal memory in some models. In particular, the study reported a detrimental of dairy products effects on working memory performance at intakes higher than recommended, possible supporting the U-shape association we noted in the dose-response meta-analysis. Unfortunately, we were not able to perform additional analyses for other dairy types due to

limited number of studies. It is noteworthy that the two studies investigating the relation between dairy desserts, a detrimental association was found with 30% higher odds of cognitive decline (42) and lower scores for both working and verbal memory (40). It should be noted that guidelines for dairy intake rarely include dairy desserts, being generally included in sweets products as they may contain high amount of sugar (50, 51). Overall, these results suggest that the different types of dairy can have opposite effects on cognition. Dairy is also an heterogeneous food group regarding the fat content. We were not able to stratify results by amount of fat in dairy products (full-fat vs. low-fat products). Two previous studies suggested that the fat content of milk might be associated with worse cognition (23, 42). In line with the results by Vercambre et al. (France) (42), where dairy desserts and ice-cream were associated with worse cognition, in the study by Almeida et al. (Australia) (23) higher intakes of "full-cream dairy" were associated with worse mental health outcomes. The study by Petruvski-Ivleva et al. (USA) (44) reported that higher total milk intake was associated with greater cognitive decline, and while they did not report stratified results, up to 75% of participants reported skim/low-fat milk intake, in contrast to the two previous studies. Therefore, the role of high-fat vs. low-fat dairy is still controversial and should be further evaluated.

Dairy products are rich in proteins, minerals, vitamins and essential amino acids that have been directly or indirectly associated with cognitive function (52, 53). Previous studies have shown beneficial effects of some dairy products, in particular fermented products, on cardiovascular disease or diabetes (10, 54-56), which could be mediators of the associations of dairy intake and cognitive decline (57). Fermented dairy products have anti-inflammatory components that can affect the risk of dementia (7, 9, 58, 59). Yet, the high content of fat in some dairy products can affect cognition negatively through hyperinsulinemia, endothelial damage, oxidative stress and inflammation (53, 60, 61). In a study about fat intake at midlife and cognitive decline that did not qualify for our review (as it reported only fat intake from foods, but not food intakes), high saturated fat intake from milk products and spreads was associated with poorer cognitive outcomes and the results did not change after adjusting for several

cardiovascular risk factors and diseases (61). In addition, calcium content may greatly vary among different types of dairy products with possible effects on oxidative stress as a positive association between both consumption of dairy products and calcium intake have been associated with higher glutathione peroxidase in the brain, suggesting possible protective mechanisms of the such negative association (62).

Concomitantly, lower intake of dairy products could be associated with a specific dietary pattern, rich in plant-based foods and low in saturated fats, which have been shown to positively modulate inflammatory and immune response and to decrease the risk of neurocognitive impairments and eventually the onset of dementia (63). For instance, higher adherence to the Mediterranean diet was associated to a positive effect in cognitive decline (64). The Japanese-style diet has been associated with lower risk of CVD, stroke, or heart disease mortality (65). However, according to the 2016 Japanese National Health and Nutrition Survey, consumers of a non-dairy diet were less likely to meet dietary requirements, whereas dairy consumers were more likely to exceed the recommendations for saturated fat (66). In fact, studies that took into account other food groups or dietary patterns that could affect the relationship between dairy consumption and cognitive function found no associations (17, 18, 39, 40, 43, 44).

In our search, we did not identify any RCT evaluating the effect of dairy on cognition, probably due to our strict inclusion criteria regarding dairy and cognitive assessments, as well as duration of the intervention longer than 6 months. Given that we present only results from observational studies, the interpretation of the results regarding cause and effect between dairy and cognition should be done carefully. Most of the studies adjusted for sex, age at recruitment, physical activity, smoking status, BMI, educational level and past major cardiovascular events (stroke, coronary heart disease, myocardial infarction) or related risk factors (hypertension, dyslipidemia). Some of them missed to adjust for total calories intake (17, 19, 26), depression or psychological distress (17, 24, 25, 41, 42) and cancer (15-17, 24, 41, 45). However, we cannot discard that the observed association is affected by

residual confounding. In addition, dietary assessments were heterogeneous regarding the type of questionnaires used, definitions of dairy intake, and recall timeline. In addition, each study defined the outcome for cognition differently which may be the main challenge when interpreting the results of our review. Many studies used nonspecific global screening tools, many of which could have demographic biases if they have not suitably validated in representative populations.

Regarding the optimal intake of dairy that can be associated with greater cognitive health, our dose-response analysis for the continuous intake of dairy products suggests a non-linear association with nadir at 150 g/day of dairy intake. For example, this would be equivalent to consuming 1 yogurt or 1 glass of milk per day, corresponding to 125-200 g/4.4-7 oz of yogurt or 200-250 mL/6.8-8.5 oz of milk per day according to Food-Based Dietary Guidelines in Europe (67). This is in line with the mean dairy intakes in Japan among milk consumers (approximately 160 g) (66), but lower that average intakes in Europe, where 91.6% consume 2 or more dairy servings per week in older adults (68). However, these results should be interpreted with caution. The included studies used a variety of categories of milk intake ("times per week", "times per day", "g/d", "serving/d, "high/low intake", "tertiles", etc.). Many studies did not report exact doses for "servings" and "time", therefore only a limited set of studies could be included in this analysis.

Because most studies reported only one measurement of diet, this might not reflect long-term consumption patterns. The lack of multiple dietary assessment hampered the evaluation of possible changes of time of dairy intake. Even though some studies suggest that the recall of past dairy intake may be more reliable due to stable consumption (69, 70), more recent prospective studies assessing dairy product consumption over the life course are needed to evaluate dairy consumption changes. By including prospective studies of long duration, we aimed to include subjects whose diet was monitored long before cognition was assessed. However, we cannot discard differential measurement error due to recall bias, as early symptomatology of cognitive decline could have affected the way people report their diet or their dietary choices (71). Deteriorating cognition could also impact food selection or

dietary behaviors. However, most of the studies have a low prevalence of cognitive impaired subjects (17, 26, 40) or excluded them in the analysis (18, 19, 24, 25, 41, 43) and for most studies there were many years between dietary and cognitive assessments in many studies. In our review, the stratified analysis by duration of follow-up showed only a slight reduction of risk of cognitive decline with the highest dairy intake in studies of more than 10 year of follow-up that was also consistent the meta-regression analysis suggesting a slightly negative association with increasing follow-up duration. In the future, biomarkers of dairy intake could help prevent recall errors as well as multiple assessment of dietary habits (72).

In this review, our focus was specifically on studies conducted relatively healthy populations and for primary prevention of cognitive decline. Consequently, we deliberately excluded studies involving only patients with conditions such as diabetes, hypertension, and other chronic diseases. The association between hypertension (73), diabetes (74) or metabolic syndrome (75) and dementia has been extensively studied and these conditions are considered to be modifiable risk factors for dementia in contemporary guidelines (5). Healthcare professionals are actively encouraging patients to modify their lifestyles as part of their clinical management (76). In the context of cognitive decline and dementia, dietary modifications among these patients are actually for secondary rather than primary prevention. Therefore, dietary recommendations to prevent dementia among patients with chronic diseases at high risk for dementia might be different than the recommendations to the general population. Considering that studies conducted among patients usually recruit from hospitals, it's essential to acknowledge that hospitalization can impact dietary recall and potentially influence recent dietary habits. Thus, dietary questionnaires collected during or close to a hospital stay may not accurately represent an individual's typical long-term dietary exposure. Most importantly, dietary modifications to prevent further consequences of other chronic conditions might lead to reverse causation.

As prevalence of the chronic disease is very high in Western populations such as the US one, being in the order of >10% for diabetes, nearly 50% for hypertension, and 40% for metabolic syndrome (77), the

results and the findings of our meta-analysis would not be automatically and directly applicable to a substantial part of the population, limiting the generalizability of our results. Future studies should evaluate in detail the role of dairy intake on cognition among people with comorbidities such as diabetes and other populations at high risk of dementia.

As strengths of our study, we included only prospective studies and planned several subgroup analyses to address the heterogeneous results of the previous literature. However, we acknowledged that some amount of heterogeneity was still present in stratified analyses, probably linked to the different types of dairy products or to the modality of outcome assessment characterized by high variation across studies and countries. Compared to previous meta-analyses of prospective observational studies on dairy intake and cognitive decline, we additionally included 5 recent studies and 2 older studies that were not included in the two previous meta-analyses (13, 14), with the opportunity to implement several stratified analyses showing the effect modification of sex, region of origin, and especially types of dairy products. Nonetheless, the number of studies in some of them was still limited, with consequent high heterogeneity. In addition, restricting our analysis to individuals without (known) chronic diseases would have limited the external validity of our findings, but may have increased the internal validity by avoiding the risk of reverse causation linked to dietary advice in diseased participants, thus reducing the risk of bias in exposure assessment.

Our exclusion criteria allow us to focus on the long-term effects of usual dairy intake and prevent potential recall bias. However, this led to not including RCTs as they were of too short duration. In addition, due to the small number of studies reporting continuous effects and stratified analyses by type of dairy, we could not conduct relevant stratified analyses.

In conclusion, the results from our systematic review and meta-analysis suggest a potential negative association of dairy intake on dementia, with regional differences. Future studies should evaluate the role of specific types of dairy products on cognition, focusing on potential differences on dairy types, intake levels and population characteristics.

Acknowledgements

Statement of authors' contributions to manuscript: PC designed the study with feedback from NR, MV and CDG. DK prepared the literature search. FV and TF conducted the systematic review and selection of the articles, with feedback from PC. FV and NO performed the risk of bias assessment with feedback from TF. TF conducted all statistical analyses. FV, TF and PC interpreted the results with feedback from all authors and wrote the first draft of the manuscript. PC had primary responsibility for final content. All authors have read and approved the final manuscript.

Data availability: Data described in the manuscript, code book, and analytic code will be made available upon request pending application and approval of the corresponding author.

Competing interests: None declared.

Amendments: None declared.

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Figure legends

Figure 1. PRISMA flow diagram summarizing literature search, study identification and selection.

Figure 2. Dose-response analysis according: quantity of consumption of dairy products in g/day (A): six studies: Lu 2023 (Asia), Ozawa 2014 (Asia), Talaei 2020 (Asia), Tanaka 2018 (Europe), Vercambre 2009 (Europe) and Ylilauri 2022 (Europe); frequency of consumption of dairy products in times/day (B): five studies: Dobreva 2022 (Europe), Nicoli 2021 (Europe), Talaei 2020 (Asia), Yamada 2003 (Asia), Zhang 2021 (Asia). Spline curve (solid black line) with 95% confidence limits (grey area). RR: relative risk.

Figure 3. Dose-response analysis according frequency of consumption of dairy products in times/day divided by type of dairy product: milk reported in three studies: Lu 2023, Talaei 2020, and Yamada 2003 (A); and cheese reported in two studies: Dobreva 2022 and Lu 2023 (B). Spline curve (solid black line) with 95% confidence limits (grey area). RR: relative risk.

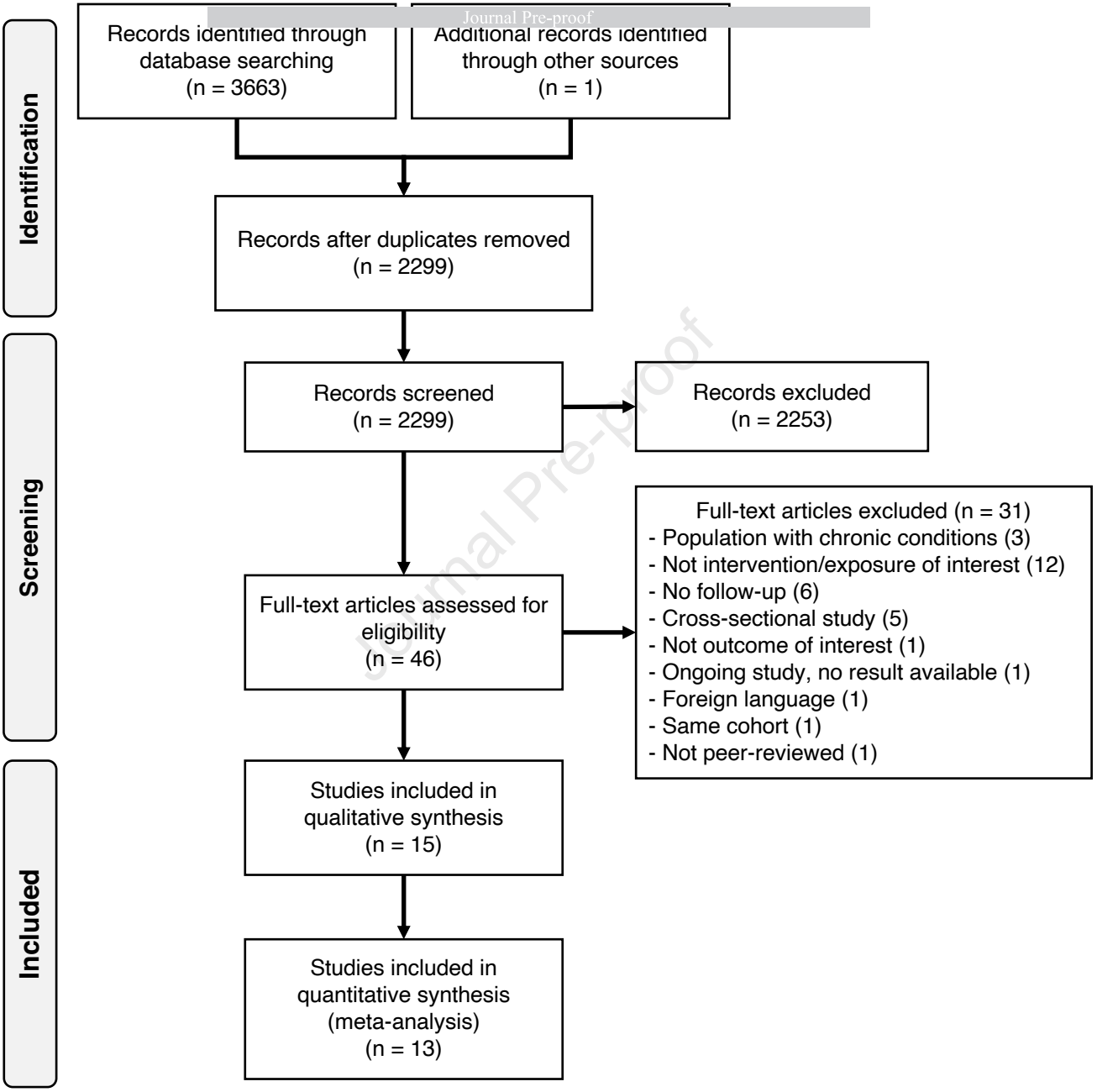
Figure 4. Forest plot showing the highest versus lowest exposure meta-analysis of dairy intake and cognition divided by region. RR: relative risk; CI: confidence interval. The area of each gray square is proportional to the inverse of the variance of the estimated log RR (i.e. weight in %) and the horizontal line the 95% CI of each individual study. Vertical axis of the gray diamonds represents the point estimate of the overall RR and the vertical axis its 95% CI, while horizontal line represents the 95% prediction interval intervals (CIs). The solid vertical line represents RR=1.

Table 1. Summary of studies included in the meta-analysis.

Author, year, cohort name, country	Follow-up (years)	Male (%)	Baseline age (years)	Number of participants	Exposure (Method of Assessment)	Dairy products dose (g/day)	Outcome (Method of Assessment)	Adjustments
Almeida 2006 (23), NR, Australia	4.8	100	77.5	601	Consumed full-cream milk (Self-reported questionnaire)	-	Cognitive function (MMSE, GDS-15)	age, history of diabetes, consumption of full-cream milk, high school or university education, and vigorous physical activity
Dobreva 2022 (39), UK Biobank, UK	11.4	46.7	62	249,511	Cheese intake (FFQ)	-	All-cause Dementia (ICD 9 and 10)	sociodemographic (age, sex, Townsend deprivation score, age left education, household income), life- style (physical activity, smoking status, weekly alcohol units), mental health factors (loneliness, depression) and physical health factors (BMI, cholesterol, diabetes, hypertension, cardiovascular events, major dietary changes) and all other food categories
Kesse-Guyot 2016 (40), the SU.VI.Max 2 observational follow-up study, France	13	52	53.7	3,076	Total dairy products (24-h dietary records)	-	Cognitive function (RI-48 test, verbal fluency tasks, digit span tests, and TMT)	age, sex, education and follow-up time between baseline and cognitive evaluation, occupational status, intervention group during the trial phase, smoking status, physical activity, alcohol consumption, depressive symptoms, baseline memory troubles, body mass index, energy intake, number of 24h dietary records and history of diabetes, hypertension and CVD, western and healthy dietary pattern score
Lu 2023 (15), The Ohsaki Cohort 2006 study, Japan	5.7	44.5	73.5	11,636	Total dairy intake (FFQ), milk, yogurt and cheese intake	Mean (SD) 116.8 (81.4) g/1000 kcal per day	Incidence of dementia (LTCI system based on Dementia Scale)	sex, age, education level, BMI, smoking status, alcohol drinking status, time spent walking, psychological distress, history of diseases, energy intake, energy-adjusted vegetable and fruit intake, and energy-adjusted fish intake
Nicoli 2021 (16), the Monzino 80-plus study, Italy	12	31	91.1	512	Milk and cheese intake (FFQ)	-	Incidence of dementia (DSM-IV)	age, sex, education, total energy intake, smoke, alcohol, physical activity, chronic obstructive pulmonary disease, lifetime depression, previous stroke, previous transient ischemic attack, and place of residence
Otsuka 2014 (24), National Institute for Longevity Sciences – Longitudinal Study of Aging, Japan	Men: 8.0 Women: 8.2	51.6	Men: 67.7; Women: 68.0	Men: 1,137; Women 1,065	Milk and dairy products (3-day dietary record)	Mean (SD) 164.77 (129.3)	Cognitive function (MMSE)	age, follow-up time, MMSE score at baseline, education, body mass index, household annual income, current smoking status, energy intake, and history of heart disease, hypertension, hyperlipidemia, and diabetes
Ozawa 2014 (43), The Hisayama Study, Japan	17	42.3	69.4	1,081	Milk and dairy consumption (FFQ)	Median (IQR) 97 (45-197)	All-cause Dementia, AD, VaD (DSM-III)	age, sex, low education, history of stroke hypertension, diabetes mellitus, total cholesterol, body mass index, smoking habits, regular exercise and energy, vegetable, fruit, fish, and meat intake
Petruski-Ivleva 2017 (44), The Atherosclerosis Risk in Communities (ARIC) cohort, USA	20	44	57.5	13,752	Milk intake (FFQ)	Categorical	Cognitive function (DWRT, DSST, WFT)	age, sex, race-center, education level, APOE4, BMI, smoking, alcohol intake, diabetes, physical activity, total energy intake, diet quality
Talaei 2020 (17), Singapore Chinese Health Study, Singapore	23	40.8	53	16,948	Dairy products (FFQ)	Median (IQR) (28.7 11.0-83.7)	Cognitive impairment (MMSE)	age, sex, dialect, year of interview, educational level, marriage status, body mass index, physical activity, smoking status, alcohol use, baseline history of self-reported hypertension, diabetes, heart attack, and stroke, history of cancer, sleep status,

								total energy intake, soy, red meat, poultry, fish, vegetables, fruits, tea, coffee, and soda, vegetable-fruit-soy dietary pattern
Tanaka 2008 (41), InCHIANTI study, Italy	Mean 10.1; max 18.2	43.5	75.4	832	Dairy products (FFQ)	Mean (SD) 170.3 (141.7)	Cognitive function (MMSE and additional neuropsychological tests)	age, sex, study site, chronic diseases, years of education, total energy intake, physical activity, BMI, ApoE4 carrier status, CRP, IL-6, plasma omega-3, plasma omega-6, plasma beta-carotene, and plasma alpha-tocopherol
Trichopoulou 2015 (25),European Prospective Investigation into Cancer and Nutrition-Greece (EPIC-Greece), Greece	Median 6.8; range 5.1-8.2	35.9	74	401	Dairy products (FFQ)	Median (IQR) 205 (130-333)	Cognitive decline (MMSE)	sex, age, years of education, BMI, physical activity, smoking, diabetes, hypertension, cohabiting, and total energy intake
Vercambre 2009 (42), E3N (Etude Epidémiologique auprès de femmes la Mutuelle Générale de l'Education Nationale) subcohort, France	13	0	65.5	4,809	French dietary history questionnaire	Mean (SD) 283.6 (231.1)	Cognitive decline (DECO)	age at cognitive assessment, education level, BMI, physical activity, energy intake, smoking status, use of supplements, use of postmenopausal hormones, depression, cancer, CHD, stroke, diabetes, hypertension, hypercholesterolemia
Yamada 2003 (26), Adult Health Study follow-up study, Japan	25	26.8	>30	1,774	Milk intake (dietary questionnaire)	Categorical	AD, VaD (DSM-IIIR and DSM-IV)	age, sex, education, and 10mmHg systolic blood pressure increase
Ylilauri 2022 (18), Kuopio Ischemic Heart Disease Risk Factor Study, Finland	21.9	100	53	2,416	Dairy products (4-days dietary records)	Mean (SD) [median] 711 (360) [688] 27% fermented	Any dementia, AD (ICD 8, 9 and 10)	age, baseline examination year, energy intake, education years, pack-years of smoking, body mass index, diabetes, leisure-time physical activity, history of coronary heart disease, use of lipid-lowering medication, intakes of alcohol, fiber, sum of fruits, berries and vegetables and dietary fat quality (ratio of polyunsaturated fatty acids plus monounsaturated fatty acids to saturated fatty acids plus trans fatty acids)
Zhang 2021 (19), Chinese Longitudinal Healthy Longevity Survey, China	6	50.7	77.8	3,029	Dairy intake (frequency dietary questionnaire)	-	Cognitive decline (MMSE)	sex, age, education, occupation before retirement, marital status, smoking, alcohol drinking, physical exercise, body mass index, hypertension, diabetes, heart disease, and cerebrovascular disease

AD: Alzheimer Dementia; ApoE4: Apolipoprotein E4; BMI: Body Mass Index; CHD: Chronic Heart Failure; CRP: C Reactive Protein; CVD: Cardiovascular Disease; DECO: Détérioration cognitive observée; Dementia Scale: Degree of Independence in Daily Living for Elderly with Dementia; DSM: Diagnostic and Statistical Manual; DSST: Digit symbol substitution test; DWRT: Delayed Word Recall Test; FFQ Frequency Food Questionnaire; GDS Geriatric Depression Scale; ICD International Classification of Disease; IL: Interleukin; IQR: Interquartile Range; LTCI: Long-term care insurance; MMSE: Mini Mental State Examination; NR :not reported; RI-48 test: Rappel Indicé; SD: Standard Deviation; TMT: Trail Making Test; UK: United Kingdom; USA: United States of America; VaD: Vascular dementia; WFT: Word Fluency Test



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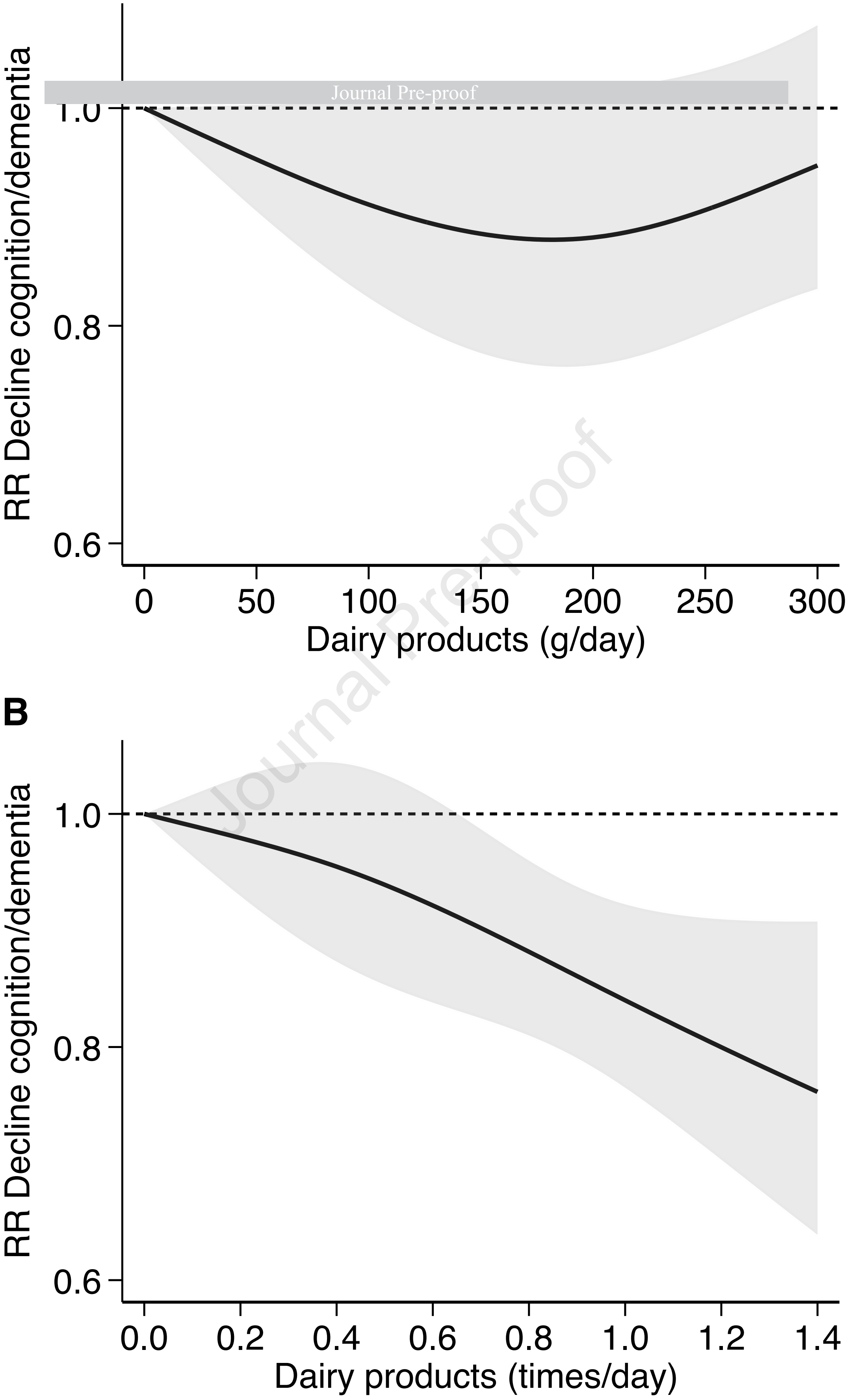

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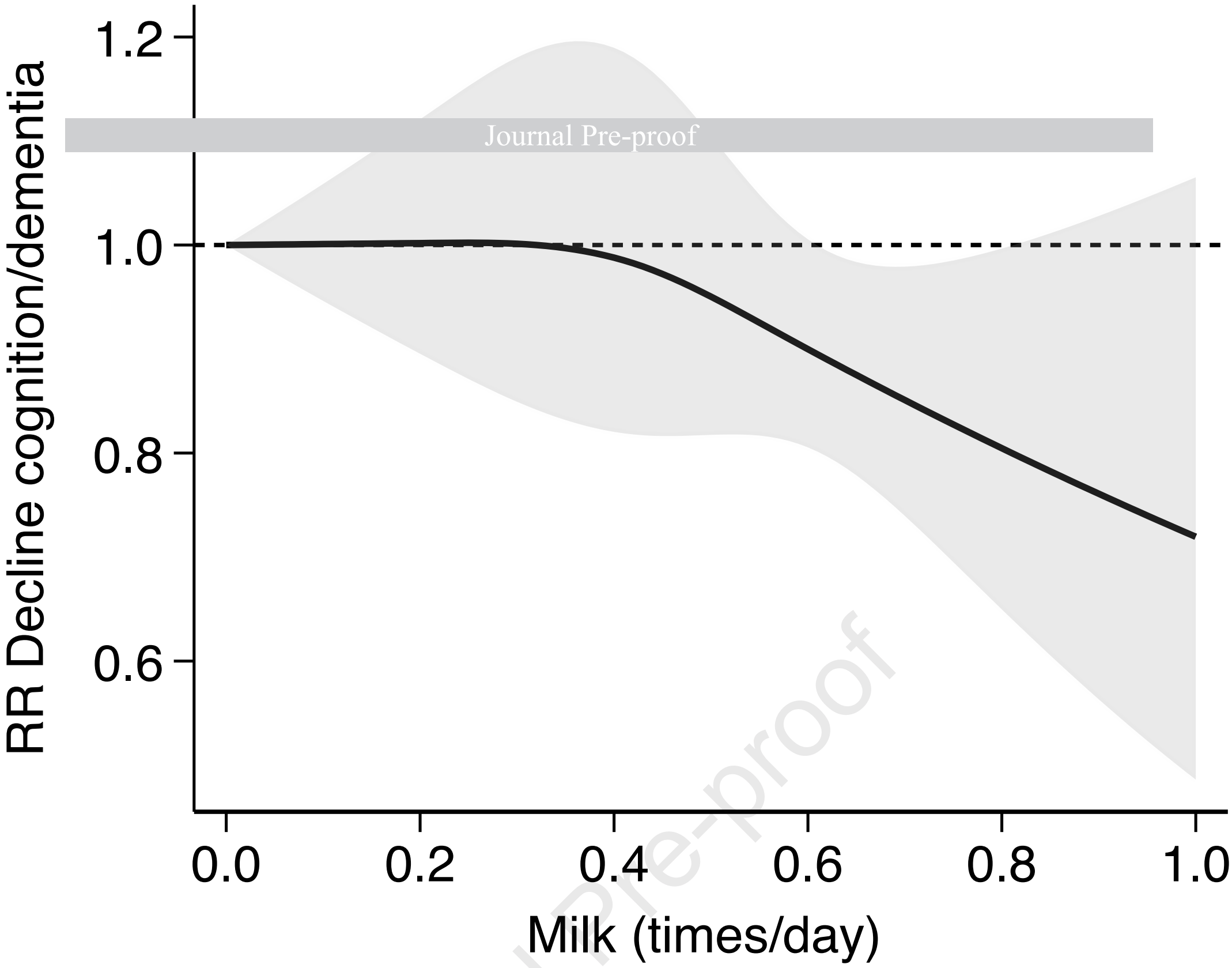

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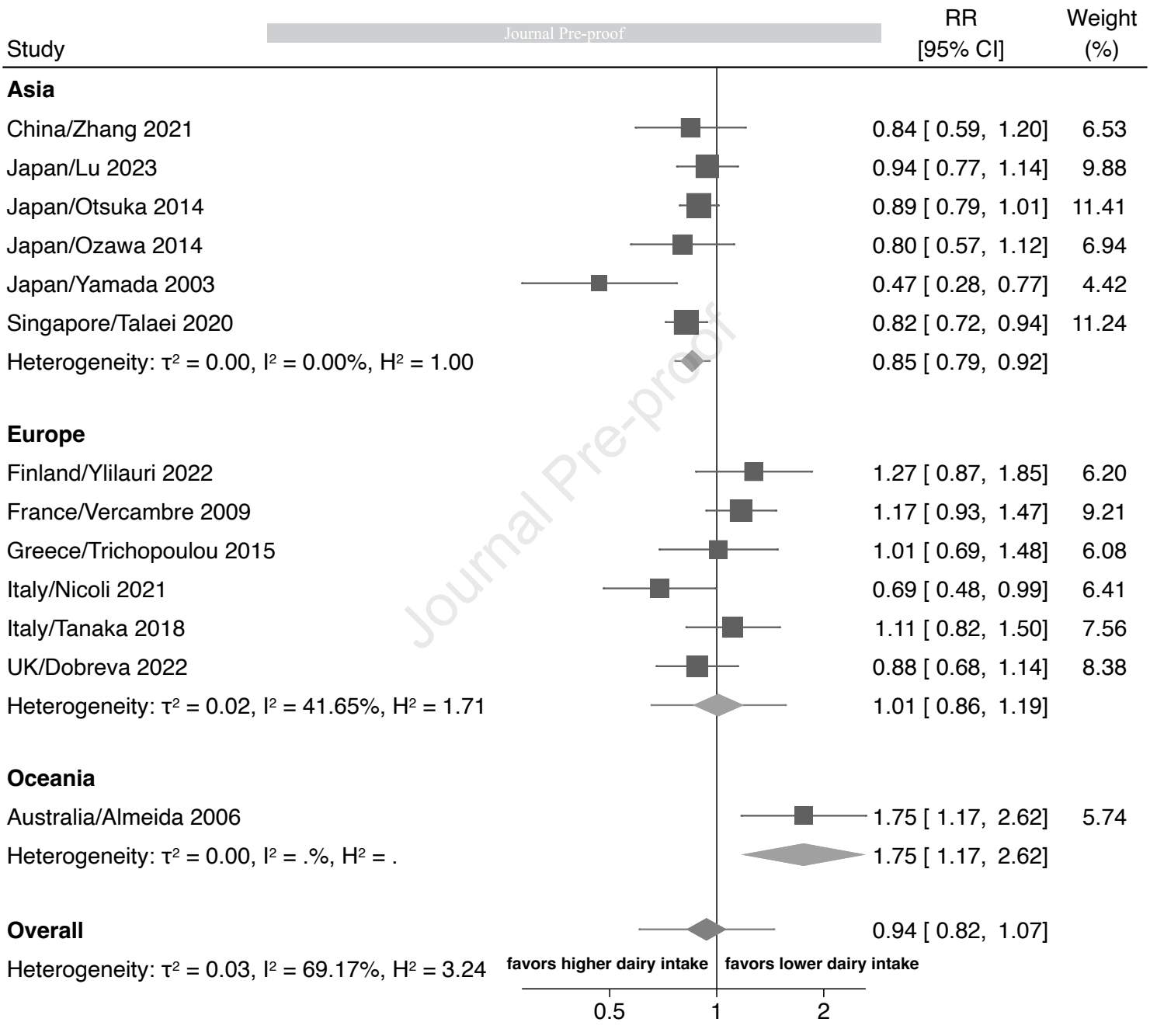

Declaration of interests

☐ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Natalia Ortega reports financial support was provided by Swiss National Science Foundation. Marco Vinceti and Tommaso Filippini reports financial support was provided by Italian Ministry of University and Research. Trudy Voortman reports a relationship with National Dairy Council that includes: funding grants. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.