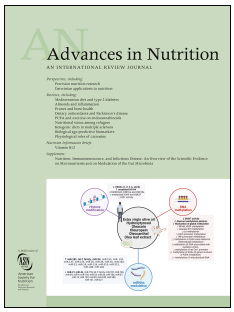
Journal Pre-proof



Long-term consumption of ten food groups and cardiovascular mortality: A systematic review and dose response meta-analysis of prospective cohort studies

Buna Bhandari, Zhixin Liu, Sophia Lin, Rona Macniven, Blessing Akombi-Inyang, John Hall, Xiaoqi Feng, Aletta E. Schutte, Xiaoyue Xu

PII: S2161-8313(22)01312-6

DOI: https://doi.org/10.1016/j.advnut.2022.10.010

Reference: ADVNUT 13

To appear in: *Advances in Nutrition*

Received Date: 14 July 2022

Revised Date: 27 September 2022

Accepted Date: 28 October 2022

Please cite this article as: B. Bhandari, Z. Liu, S. Lin, R. Macniven, B. Akombi-Inyang, J. Hall, X. Feng, A.E Schutte, X. Xu, Long-term consumption of ten food groups and cardiovascular mortality: A systematic review and dose response meta-analysis of prospective cohort studies, *Advances in Nutrition*, https://doi.org/10.1016/j.advnut.2022.10.010.

Long-term consumption of ten food groups and cardiovascular mortality: A systematic review and dose response meta-analysis of prospective cohort studies

Buna Bhandari,[1,2 3] Zhixin Liu,[4] Sophia Lin,[1] Rona Macniven,[1] Blessing Akombi-Inyang,[1] John Hall,[1,5] Xiaoqi Feng,[1] Aletta E Schutte[1,6], Xiaoyue Xu[1,6]

[1] School of Population Health, University of New South Wales, Sydney, Australia

[2]Central Department of Public Health, Tribhuvan University Institute of Medicine, Kathmandu, Nepal

[3]Department of Global Health and Population, Harvard T.H. Chan School of Public Health, Boston, USA

[4] Stat Central, University of New South Wales, Sydney, Australia

[5] Ministry of Health, New South Wales, Sydney, Australia

[6] The George Institute for Global Health, Sydney, Australia

Conflict of Interest and Funding Disclosure: No

Corresponding author

Name: Xiaoyue Xu

Mailing address: Room 210, Level 2, Samuels Building, University of New South Wales, Sydney, New South Wales, Australia. 2052. Telephone number: 61 401577818

E-mail address: luna.xu@unsw.edu.au

Running title: food groups and cardiovascular mortality

Sources of support: University of New South Wales (UNSW) School of Population Grant Building Support Scheme. XX is supported by a Post-doctoral Fellowship funded by the Heart Foundation of Australia (Award No. 102597), and Scientia Program at the UNSW, Australia.

Abbreviation used in the study

CVD, Cardiovascular disease; CI, Confidence interval; DASH, Dietary Approaches to Stop Hypertension; HRs, Hazard Ratios; IV, Inverse variance; MI, Myocardial infraction; ORs, Odds Ratios; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RR, Relative Risks

Abstract

A large body of evidence exist on diet and cardiovascular mortality, but limited studies have investigated the long-term intake of food groups, which may have cumulative effects on cardiovascular health in the long term. This review therefore evaluated the relationship between long-term consumption of ten food groups and cardiovascular mortality. We conducted a systematic search in Medline, Embase, Scopus, CINAHL and Web of Science up to January 2022. With a total 5,318 studies identified initially, 22 studies with a total of 70,273 participants with cardiovascular mortality were included. Summary Hazard Ratios (HR) and 95% CIs were estimated with the use of a random effects model. We found that a long-term high intake of whole grains (HR:0.87; 95% CI:0.80,0.95; P=0.001), fruits and vegetables (HR:0.72; 95% CI:0.61,0.85; P<0.0001) and nuts (HR: 0.73; 95% CI:0.66,0.81; P<0.00001) significantly reduced cardiovascular mortality. Each 10-gram increase in whole grain consumption per day was associated with a 4% reduction in the risk of cardiovascular mortality, whilst each 10-gram increase in red/processed meat consumption per day was associated with a 1.8% increase in the risk of cardiovascular mortality. Compared to the lowest intake category, red/processed meat consumption in the highest category was associated with an increased risk of cardiovascular mortality (HR:1.23; 95% CI:1.09,1.39; P=0.006). High intake of dairy products (HR:1.11; 95% CI:0.92,1.34; P=0.28) and legumes (HR:0.86; 95% CI:0.53,1.38; P=0.53) were not associated with cardiovascular mortality, but in the dose-response analysis each 10-gram increase in legume intake per week was associated with a 0.5% reduction in cardiovascular mortality. We conclude that the long-term high intake of whole grains, vegetables, fruits, nuts and low intake of red/processed meat are associated with reduced cardiovascular mortality. More data on the long-term effects of legumes on cardiovascular mortality are encouraged. This study was registered at PROSPERO as CRD42020214679.

Key words: Grains, Vegetables, Fruits, Meat, Legumes, Nuts, Cardiovascular mortality, Diet, Nutrition

Statement of Significance

This systematic review and meta-analysis with a dose-response analysis provides comprehensive information on long-term consumption of ten food groups and cardiovascular mortality. We conclude that the long-term high intake of whole grains, vegetables, fruits, nuts and low intake of red and processed meat are associated with reduced cardiovascular mortality.

Introduction

Cardiovascular disease (CVD) is the leading cause of death and disability globally (1). It accounted for 18.6 million preventable deaths in 2019 (2), which is one third (32%) of the total number of global deaths (1). The link between some risk factors and CVD have been well established, with a poor diet identified as a key risk factor (3). According to the Global Burden of Disease Study 2019, dietary risk was the second leading cause of cardiovascular mortality, responsible for more than 7.94 million cardiovascular deaths worldwide (2).

However, some important aspects of dietary risk have not been thoroughly investigated in previous studies. Firstly, limited studies have reviewed long-term dietary consumption (more than one-time point dietary measurements) in relation to cardiovascular mortality, with most studies commonly linking one-time point dietary consumption measurement to mortality. However, using one data point cannot determine long-term dietary habits and does not permit distinction between cause and effect (4). Secondly, previous reviews have often analysed either the effect of dietary patterns such as the Mediterranean diet, Dietary Approaches to

Stop Hypertension (DASH) diet, or individual food items in relation to cardiovascular mortality risk (5, 6). Although many national dietary guidelines used for population health promotion activities are based on food groups rather than food patterns (7, 8), there are limited collective evidence that have synthesised the risk of different food groups and cardiovascular mortality, particularly focusing on the effect of long-term consumption of different food groups and cardiovascular mortality. From a public health perspective, diet-disease relationships can be better understood through the study of specific food groups (9). Thirdly, although it is known that there are sex-specific food choice preferences for energy and nutrient intake, limited studies have reviewed sex-differences of dietary consumption in relation to cardiovascular mortality (10).

Therefore, we conducted a systematic review and meta-analysis with a dose-response analysis with robust inclusion criteria with restrictions to only analyse cohort studies that had repeated measures of dietary intake (at least two data collection points) throughout the study period. We analysed the relationship between the long-term consumption (>5 years) of main food groups defined a priori as whole grains, vegetables, fruits, nuts, legumes, eggs, poultry, dairy products, fish/seafood, red/processed meat, and cardiovascular mortality, stratified by sex (where possible).

Methods

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (11) (Supplementary File 1). This review is registered in the PROSPERO [CRD42020214679].

Search strategy

The search was conducted using the electronic databases MEDLINE, EMBASE, CINAHL, Scopus and Web of Science. The details of search terms used are provided in Supplementary methods. In addition, references from retrieved articles, including systematic reviews and meta-analyses, were manually checked for eligibility and inclusion. All searched studies were exported to Covidence software. Each abstract and title screening were performed by two of four independent reviewers (BB, XX, SL and RM) and full texts were reviewed by BB and XX. Any disagreements were resolved by consensus after discussion.

Study selection

Studies were included in the systematic review and meta-analysis if they 1) were prospective cohort studies; 2) were peer-reviewed and where the full text was available; 3) provided information about the association of food groups including whole grains, vegetables, fruits, nuts, legumes, eggs, poultry, dairy products, fish/seafood, red/processed meat. These ten food groups are the focus because they form the basis of most diet quality indexes or scores, as well as have been commonly reported in guidelines (7) and previous studies (9); 4) included participants aged ≥18 years; 5) considered cardiovascular mortality as an outcome; 6) measured the exposure of dietary consumption at more than one time point; 7) written in English; and 8) were published between January 2000 and January 2022. We excluded studies which measured the dietary consumption at only one timepoint or reported only all-cause mortality without specifying cardiovascular mortality.

Data extraction

During the screening process, duplicate records were first removed, followed by the screening of records based on titles and abstracts. In the final screening phase, full texts of articles were obtained and articles which met the inclusion criteria were retained. Two

independent reviewers (BB and XX) extracted the following information from the included studies: first author name, year of publication, country where study conducted, cohort study name, sample size, number of subjects, age at entry, sex, study duration (follow-up in years), outcomes, outcome assessment, assessment of food group, quantity of food consumed per day per individual, risk estimate [most adjusted measures; Hazard Ratios (HRs), Relative Risks (RRs), Odds Ratios (ORs) with their corresponding 95% confidence intervals (95%CIs)] and variables that were adjusted for.

If there were several risk estimates provided, HRs/RRs/ORs in the multivariable adjusted model were extracted for the meta-analysis. The most common adjusted factors were age, sex, current smoking status, BMI, alcohol intake and physical activity. If there were separate findings or risk estimates for male and female participants presented in a study, we extracted these included separately in the meta-analysis. The details of extracted articles are shown in the Supplementary Table 1-7.

Quality assessment

We used Newcastle-Ottawa quality Assessment Scale to assess studies quality given it commonly used to evaluate quality of cohort studies (12). We assessed study quality based on: how the studies ascertained exposure, how they assessed outcomes, whether follow-up time to mortality was adequate (>10 years in most of the included studies), and whether they included an unadjusted model and made any other relevant adjustments (e.g., age, sex, education, BMI, smoking and physical activity). A maximum of 9 points were given based on three scoring domains, including cohort selection (4 points), the comparability of the cohort design and analysis (2 points), and the adequacy of outcome measures (3 points). Detailed scoring criteria have been explained in the tool (12). A total score of more than 6 points was

considered good quality. The detailed scores have been calculated and shown in Supplementary Table 1-7. Two reviewers (BB and XX) assessed the risk of bias independently. Disagreements in score allocations were resolved by discussion and consensus.

Statistical analyses

A random effect model meta-analysis was performed to pool combined HRs/RRs/ORs of the association between each food group intake and cardiovascular mortality. The highest category of food intake was compared with the lowest category of food intake (reference group) with the use of the generic inverse-variance method. The actual amount of food intake was also converted into grams in dose-response analysis as described below. Statistical heterogeneity between the cohort was quantified with the use of the I^2 statistic; and $I^2 > 50\%$ indicated evidence of considerable heterogeneity. A funnel plot was used to explore the potential small-study effects such as publication bias. Due to the small number of studies (<10) included in each food group meta-analysis, an Egger test was not performed, as recommended by the Cochrane Handbook (13).

For the dose-response analysis, when food consumption was reported by intake range, the midpoint of the range was used. If the upper boundary of the highest category was not provided, it was assumed that the width of the category to be the same as the adjacent category. The two-stage random-effect model was used to examine the linear and non-linear dose-response relationship between food consumption and cardiovascular mortality. The Generalized least squares regression proposed by Greenland and Longnecker (14) and Orsini et al. (15) was initially used to estimate the trend of effect measure (HR); then non-linearity was examined based on restricted cubic splines with 3 knots (25, 50, and 75th percentiles).

The dose-response analysis could only be conducted on red/processed meat, whole grain, legumes, and dairy product groups. Nuts, eggs, and fruits and vegetables groups did not have sufficient studies for dose-response analysis.

All meta-analysis was performed with the use of Review Manager software (Revman, version 5.4; The Nordic Cochrane Centre, The Cochrane Collaboration) and dose-response analysis was performed in R software.

Results

Of the 5,687 records that were identified from the literature search, 226 full-text articles were assessed in detail because they reported cardiovascular mortality and different food groups in the title or abstract (Figure 1). After a full text review, a total of 22 studies were included for data extraction based on the review eligibility criteria. Among the included studies, three studies reported consumption of grains (16-18) (Supplementary Table 1), six studies for red/processed meat and eggs (19-24) (5 red meat, 1 egg) (Supplementary Table 2), four dairy product studies (25-28) (Supplementary Table 3), three nut consumption studies (29-31) (Supplementary Table 4), three legume studies (32-34) (Supplementary Table 5), two fruit (35, 36) and one vegetable study (37) (Supplementary Table 6). There were no studies for the food groups of fish/seafood and poultry based on our inclusion criteria of repeated measurements.

Figure 1 here

Characteristics of included studies

The characteristics of the included studies were shown in Supplementary Tables 1-6. Ten studies were conducted in the United States (17, 18, 20-22, 26, 28-31), three in Australia (27,

36, 37), three in Japan (16, 24, 32), two in Sweden (19, 25), one in United Kingdom (23), one in China (35), one in Spain (33) and one in Iran (34). The length of follow up ranged from 6 years to 34 years. Eighteen studies included both males and females (of these, only 38% reported sex-specific results), whereas 3 had only females and 1 had only male study participants. In terms of methods for the dietary data collection, of a total of 22 studies, 21 studies used a self-administered food frequency questionnaire (SFFQ), and 1 study (35) used an interviewer administered questionnaire. All included studies were of high quality having a score of 6 or above based on the Newcastle-Ottawa risk of bias assessment studies. Almost all the studies (21) reported the analysis was adjusted for potential confounders (Supplementary Tables 1-6).

Whole grains

Three studies (four groups) with a total of 9,610 cardiovascular mortality cases were included in the meta-analysis, comparing the highest intake to the lowest intake. Figure 2 shows an inverse association between cardiovascular mortality and whole grain intake was observed while comparing the extreme categories (Quintile 5 vs Quantile 1) with low heterogeneity among studies (Pooled HR: 0.87; 95% CI:0.80, 0.95; P=0.001; I^2=17%, P heterogeneity=0.31). However, one of the studies only included females with Type 2 diabetes mellitus (17), (Supplementary Table 1). There was no severe asymmetry observed from the visual inspection of the funnel plot (Supplementary Figure 1).

Figure 2 here

The dose-response analysis of the three included studies (four groups) showed that for each 10-gram per day increase in whole grain consumption, there is a 4% reduction in the risk of cardiovascular death (HR: 0.96; 95% CI: 0.95, 0.98) (Figure 3A) with a significant decrease

in the risk of cardiovascular death (p<0.0001) with higher grain intake. The non-linear trend was non-significant (p=0.23) (Supplementary Table 7).

Figure 3 here

Red and processed meat

Five studies (six groups) with a total of 15,651 cardiovascular mortality cases were included in the meta-analysis, comparing the highest intake to the lowest intake (Figure 4). A positive association was found between red and processed meat intake and cardiovascular mortality while comparing the highest and lowest categories (Quintile 5 vs Quantile 1) with a high heterogeneity among the studies (Pooled HR: 1.23; 95% CI: 1.09, 1.39; P=0.0006; I^2=80%, P-heterogeneity=0.0002) (Figure 4). There was no severe asymmetry observed from the visual inspection of the funnel plot (Supplementary Figure 2).

Figure 4 here

The dose-response analysis of four included studies (five groups) [excluded Zheng et al. (22) study due to not having category wise HR required for dose-response] showed for each 10-gram per day increase in red/processed meat consumption, there was a 1.8% increased risk in cardiovascular mortality (HR: 1.018; 95% CI: 1.014, 1.022) (Figure 3B) with a significant increase in the risk of cardiovascular mortality (p<0.0001) with higher meat intake. The non-linear trend was insignificant (p=0.06) (Supplementary Table 7).

Dairy products

Total four studies (eight groups) with a total of 29,990 cardiovascular mortality cases were included in the meta-analysis by comparing the highest to the lowest dairy product intake, with no significant association observed (Pooled HR: 1.11; 95% CI: 0.92,1.34; P=0.28;

229 I^2=93%, P-heterogeneity <0.00001) and very high between-study heterogeneity (Figure 5).
230 There was no severe asymmetry observed from the visual inspection of the funnel plot
231 (Supplementary Figure 3).
232 **Figure 5 here**
233
234 There was no significant association observed between dairy consumption and cardiovascular
235 death risk (p=0.13) in dose-response analysis of four studies (eight groups) as well (Figure 3
236 C). The non-linear trend is insignificant (p=0.11) (Supplementary Table 7).
237
238 **Nut**
239 Three studies (four groups) with a total of 8,700 cardiovascular mortality cases were included
240 in the meta-analysis, comparing the highest intake to the lowest nut intake. A strong inverse
241 association was observed (Pooled HR: 0.73; 95% CI:0.66 ,0.81; P <0.00001; I^2=0%, P-
242 heterogeneity=0.61), and zero heterogeneity among the included studies (Figure 6). There
243 was no severe asymmetry observed from the visual inspection of the funnel plot
244 (Supplementary Figure 4).
245 **Figure 6 here**
246
247 **Legume intake**
248 Three studies (four groups) with a total of 1086 cardiovascular mortality cases were included
249 in the meta-analysis, comparing the highest intake to the lowest legumes intake, with no
250 association observed (Pooled HR: 0.86; 95% CI: 0.53,0.1.38; P=0.53; I^2=76%, P-
251 heterogeneity=0.006), and high heterogeneity amongst the included studies (Figure 7). There
252 was no severe asymmetry observed from the visual inspection of the funnel plot
253 (Supplementary Figure 5).

Figure 7 here

However, higher legume consumption was associated with a significant decrease in the risk of cardiovascular death (p=0.02) in the dose-response analysis of three (four groups) included studies. The non-linear trend was non-significant (p=0.31). For each 10-gram per week increase in legume consumption, there is a 0.5% reduction in the risk of cardiovascular mortality (HR=0.995, 95% CI: 0.991, 0.999) (Figure 3D).

Fruits and vegetables

Three studies with a total of 6529 cardiovascular mortality cases were included in the highest intake quintile compared to the lowest intake quintile of fruits or vegetables meta-analysis. An inverse association (Pooled HR: 0.72; 95% CI:0.61 ,0.85; P < 0.0001; I^2=51%, P-heterogeneity=0.13) with low heterogeneity among the included studies was observed (Figure 8).

Figure 8 here

The meta-analysis showed that among the studies that examined fruit intake, the inverse association was greater (Pooled HR: 0.66; 95% CI: 0.61, 0.72; P< 0.00001; I^2=0%, P-heterogeneity=0.57) with zero heterogeneity among the studies (Supplementary figure 6). None of the studies had reported an effect for vegetables intake only. There was no severe asymmetry observed from the visual inspection of the funnel plot (Supplementary Figure 7).

Discussion

Our study analysed the results from prospective cohort studies that investigated the association between long-term intake of food groups and cardiovascular mortality. The findings indicate that the long-term consumption of fruits and vegetables, as well as whole

grains and nuts, reduced the risk of cardiovascular mortality, while long-term consumption of red/processed meat increased the risk of cardiovascular mortality in both meta- and dose-response analysis. Long-term consumption of dairy products had no effect on cardiovascular mortality in both meta- and dose-response analysis. Legume intake was not associated with cardiovascular mortality in the meta-analysis but had an inverse association with cardiovascular mortality in the dose-response analysis.

We found that each 10-gram increase in whole grains intake per day is associated with a 4% reduction in the risk of cardiovascular mortality. Compared to the lowest intake of whole grain intake, people with the highest whole grain intake had a 13% lower risk of cardiovascular mortality. Similarly, our results showed 27% lower risk of cardiovascular mortality in individuals with the highest nut intake compared to the lowest intake. Previous systematic reviews reported similar (18-19%) reductions of risk of cardiovascular mortality with a higher whole grain intake (38, 39). Evidence from 16 countries (40), as well as a meta-analysis of five studies (41), reported the protective effects of nut consumption and cardiovascular mortality which is consistent with our findings. In addition, our meta-analysis highlighted long-term higher fruit and vegetable intake to be associated with lower cardiovascular mortality by 28%, where a larger (36%) risk reduction was found with only higher fruit intake. These results are consistent with a review from 18 countries (42) that reported an inverse association between fruit and vegetable intake with cardiovascular mortality. A meta-analysis also reported a 4% risk reduction for cardiovascular mortality with each additional increase in serving of fruits and vegetables with no additional beneficial effects after consuming five servings of fruit and vegetables combined (43). However, an umbrella review showed no significant association with cardiovascular mortality with higher fruit and vegetable intake (3). These differences of risk might be due to methodological

variation, in particular the selection criteria of included studies in different reviews. By tracking long-term food groups consumption, our study findings emphasised the protective effects of food groups of whole grains, fruits and vegetables and nut intake on cardiovascular mortality.

Our study showed that each 10-gram increase in red/processed meat consumption per day is associated with an 1.8% increased risk of cardiovascular mortality, with individuals consuming the highest intakes having a 23% increased risk of cardiovascular mortality compared to those consuming the lowest amount. A previous meta-analysis by Abete I et al also reported harmful effects of red and processed meat intake on cardiovascular mortality where red meat intake increased cardiovascular mortality risk by 16% and processed meat increased it by 18% (44). Similarly, a review by Wang et al found an increased risk of cardiovascular mortality with processed meat intake among Asian and European populations (45). This harmful effect may be due to saturated and trans-fat contents in red and processed meat, which are associated with increased risk of hypercholesterolemia, endothelial dysfunction, insulin resistance and type 2 diabetes that contribute to cardiovascular mortality (46). Conversely, a meta-analysis conducted by Kim et al did not find an association between red meat consumption with stroke mortality (47). Further research is encouraged to confirm the effects of long-term red/processed meat consumption on stroke mortality.

Neither our meta nor dose-response analysis showed effects of dairy intake on the risk of cardiovascular mortality. In line with our findings, a previous systematic review also reported no effects of dairy intake with risk of coronary heart disease, regardless of the amount of dairy intake (48). However, another systematic review reported that total dairy consumption lowered the risk of cardiovascular mortality (pooled effect size: 0.93), while high fat milk

consumption (highest vs lowest intake) was associated with a higher risk of cardiovascular mortality (pooled effect size: 1.917) (49). The difference in findings could be explained through a single measurement of dairy intake in the included studies in previous reviews while our study considered long-term consumption of dairy intake.

We found no associations of legume intake with the risk of cardiovascular mortality in our meta-analysis, which is supported by a previous systematic review by Li et.al (50). However, in our dose-response analysis, we found each 10-gram increase in legume intake per week is associated with a negligible 0.5% reduction in the risk of cardiovascular mortality. This discrepancy between meta-analysis and dose-response analysis might be due to the exclusion of the Papandreou et.al (33) study as it had insufficient information to perform the dose-response analysis. The beneficial role of legumes in reducing cardiovascular mortality has been previously recognised as they contain high amounts of phytosterols that reduce serum total cholesterol and low-density lipoprotein cholesterol and increase the high-density lipoprotein cholesterol (51). High levels of dietary fibre in legumes also associated with lower cardiovascular risk due to its low-density lipoproteins cholesterol binding capability (52). Consumption of legumes also tends to replace red meat consumption which reduces saturated fat intake and further reducing cardiovascular risk (53).

Strengths and limitations of the study

To the best of our knowledge, this is the first comprehensive review to evaluate the long-term effects of food group intake and cardiovascular mortality by only including studies that had repeated measures of dietary intake. In addition, we have only included prospective cohort studies in our meta-analysis and performed dose-response analysis which provides robust information.

However, there is a need to interpret results with some caution. Firstly, all the included studies used self-reported measures to assess dietary intake which may potentially introduce measurement bias. However, compared to other simple self-reported dietary measurements (e.g, only answering yes/no for specific food consumption), all studies included in our analysis used detailed FFQs to measure dietary consumption which provided reasonable self-reported dietary data. Secondly, there were only few studies available based on our inclusion criteria, especially on nuts, fruits and vegetables which limits our dose-response analysis. Thirdly, although we attempted to explore sex-specific dietary habits related to cardiovascular mortality, there were very limited studies that allow us to do so. Fourthly, although it would be interesting to examine long-term dietary exposures and specific types of cardiovascular mortality (such as stoke, myocardial infarction), there are limited studies available that allow us to perform further analysis. Fifth, though an exploratory study on the interactions between food groups in relation to cardiovascular mortality could have been desirable, the included studies did not provide sufficient information to perform further analysis. Lastly, the specificity of dietary exposure, such as level of fat, and/or source (animal or plant derived) in dairy products were rarely mentioned in the included studies, which might lead to very high heterogeneity between studies.

In addition, there are some limitations due to nature of observational studies that need to be acknowledged: (1) causal association between CVD mortality and food intake cannot be determined from observational studies, (2) residual confounding in the original studies cannot be ruled out, and (3) the risk of making a type I error is increased due to conducting several statistical analyses without an alpha level adjustment.

Conclusion

Although a major proportion of studies evaluated dietary intake and cardiovascular mortality, studies used one data point for dietary analyses, and thus limited studies have reviewed long-term dietary habits in relation to cardiovascular mortality. We included 22 longitudinal studies which emphasised the benefit of long-term high consumption of whole grains and nuts, as well as fruit and vegetables, and harmful effects of long-term red/processed meat intake in relation to cardiovascular mortality. However, we were unable conclude on the effects of specific food groups such as fish and poultry on cardiovascular mortality, as there are limited studies that tracked long-term dietary habits. We also encourage more data on legume intake and cardiovascular mortality.

Acknowledgement

We gratefully acknowledge a UNSW academic librarian Ressie Davis for her contribution in finalizing the search terms and databases. We acknowledge funding from the UNSW School of Population Grant Building Support Scheme to support this work. XX is supported by a Post-doctoral Fellowship funded by the Heart Foundation of Australia (Award No. 102597), and Scientia Program at the UNSW, Australia.

Statement of authors' contributions to manuscript

All authors contributed to research design; BB and XX: protocol development and searches; BB, XX, RM, SL: screening; BB, XX: full text review and data extraction, risk of bias assessment, and synthesis; BB and ZL: meta- and dose-response analysis; BB and XX: wrote the first draft of the manuscript; All authors: reviewed and commented on versions of the manuscript and read and approved the final manuscript.

References

1. World Health Organisation. Cardiovascular diseases (CVDs) key facts World Health Organisation 2021 [updated 11 June 2021; cited 2021 27 June]. Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds).

2. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990–2019: Update From the GBD 2019 Study. Journal of the American College of Cardiology. 2020;76(25):2982-3021.

3. Chareonrungrueangchai K, Wongkawinwoot K, Anothaisintawee T, Reutrakul S. Dietary Factors and Risks of Cardiovascular Diseases: An Umbrella Review. Nutrients. 2020;12(4).

4. Huo Yung Kai S, Bongard V, Simon C, Ruidavets JB, Arveiler D, Dallongeville J, et al. Low-fat and high-fat dairy products are differently related to blood lipids and cardiovascular risk score. Eur J Prev Cardiol. 2014;21(12):1557-67.

5. Rodríguez-Monforte M, Flores-Mateo G, Sánchez E. Dietary patterns and CVD: a systematic review and meta-analysis of observational studies. British Journal of Nutrition. 2015;114(9):1341-59.

6. Soltani S, Arablou T, Jayedi A, Salehi-Abargouei A. Adherence to the dietary approaches to stop hypertension (DASH) diet in relation to all-cause and cause-specific mortality: a systematic review and dose-response meta-analysis of prospective cohort studies. Nutrition Journal. 2020;19(1):37.

7. Government of Australia. Eat for Health: Australian Dietary Guidelines Providing the Scientific Evidence for Healthier Australian Diets. . Commonwealth of Australia, National Health and Medical Research Council Canberra, Australia; 2013.

8. U.S. Department of Agriculture and U.S. Department of Health and Human Services. Dietary Guidelines for Americans, 2020-2025. 9th Edition. December 2020. Available at DietaryGuidelines.gov

9. Schwingshackl L, Schwedhelm C, Hoffmann G, Lampousi AM, Knüppel S, Iqbal K, et al. Food groups and risk of all-cause mortality: a systematic review and meta-analysis of prospective studies. Am J Clin Nutr. 2017;105(6):1462-73.

10. Shiferaw B, Verrill L, Booth H, Zansky SM, Norton DM, Crim S, et al. Sex-based differences in food consumption: Foodborne Diseases Active Surveillance Network (FoodNet) Population Survey, 2006-2007. Clin Infect Dis. 2012;54 Suppl 5:S453-7.

11. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Jama. 2000;283(15):2008-12.

12. Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. Newcastle-Ottawa quality assessment scale cohort studies. University of Ottawa. 2014.

13. Higgins JPT, Green S. Cochrane handbook for systematic reviews of interventions Version 5.1. 0. London, UK: The Cochrane Collaboration. 2011.

14. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol. 1992;135(11):1301-9.

15. Orsini N, Bellocco R, Greenland S. Generalized Least Squares for Trend Estimation of Summarized Dose–response Data. The Stata Journal. 2006;6(1):40-57.

16. Eshak ES, Iso H, Yamagishi K, Kokubo Y, Saito I, Yatsuya H, et al. Rice consumption is not associated with risk of cardiovascular disease morbidity or mortality in Japanese men and women: a large population-based, prospective cohort study. American Journal of Clinical Nutrition 2014;100(1):199-207.

17. He M, van Dam RM, Rimm E, Hu FB, Qi L. Whole grain, cereal fiber, bran, and germ intake and the risks of all-cause and CVD-specific mortality among women with type 2 diabetes. Circulation. 2010;121(20):2162.

18. Wu H, Flint AJ, Qi Q, van Dam RM, Sampson LA, Rimm EB, et al. Association between dietary whole grain intake and risk of mortality: two large prospective studies in US men and women. JAMA Intern Med. 2015;175(3):373-84.

19. Bellavia A, Stilling F, Wolk A. High red meat intake and all-cause cardiovascular and cancer mortality: is the risk modified by fruit and vegetable intake? Am J Clin Nutr. 2016;104(4):1137-43.

20. Pan A, Sun Q, Bernstein AM, Schulze MB, Manson JE, Stampfer MJ, et al. Red meat consumption and mortality: results from 2 prospective cohort studies. Archives of internal medicine. 2012;172(7):555-63.

21. McCullough ML, Gapstur SM, Shah R, Jacobs EJ, Campbell PT. Association between red and processed meat intake and mortality among colorectal cancer survivors. Journal of Clinical Oncology. 2013;31(22):2773.

22. Zheng Y, Li Y, Satija A, Pan A, Sotos-Prieto M, Rimm E, et al. Association of changes in red meat consumption with total and cause specific mortality among US women and men: two prospective cohort studies. BMJ Open 2019;365:l2110.

23. Appleby PN, Crowe FL, Bradbury KE, Travis RC, Key TJ. Mortality in vegetarians and comparable nonvegetarians in the United Kingdom. The American journal of clinical nutrition. 2016;103(1):218-30.

24. Nakamura Y, Okamura T, Tamaki S, Kadowaki T, Hayakawa T, Kita Y, et al. Egg consumption, serum cholesterol, and cause-specific and all-cause mortality: the National Integrated Project for Prospective Observation of Non-communicable Disease and Its Trends in the Aged, 1980 (NIPPON DATA80). The American journal of clinical nutrition. 2004;80(1):58-63.

25. Michaëlsson K, Wolk A, Langenskiöld S, Basu S, Lemming EW, Melhus H, et al. Milk intake and risk of mortality and fractures in women and men: cohort studies. Bmj. 2014;349.

26. Ding M, Li J, Qi L, Ellervik C, Zhang X, Manson JE, et al. Associations of dairy intake with risk of mortality in women and men: three prospective cohort studies. BMJ. 2019;367.

27. Bonthuis M, Hughes M, Ibiebele T, Green A, Van Der Pols JE. Dairy consumption and patterns of mortality of Australian adults. European journal of clinical nutrition. 2010;64(6):569-77.

28. Schmid D, Song M, Zhang X, Willett WC, Vaidya R, Giovannucci EL, et al. Yogurt consumption in relation to mortality from cardiovascular disease, cancer, and all causes: a prospective investigation in 2 cohorts of US women and men. The American journal of clinical nutrition. 2020;111(3):689-97.

29. Liu G, Guasch-Ferré M, Hu Y, Li Y, Hu FB, Rimm EB, et al. Nut consumption in relation to cardiovascular disease incidence and mortality among patients with diabetes mellitus. Circulation research. 2019;124(6):920-9.

30. Bao Y, Han J, Hu FB, Giovannucci EL, Stampfer MJ, Willett WC, et al. Association of nut consumption with total and cause-specific mortality. New England Journal of Medicine. 2013;369(21):2001-11.

31. Albert CM, Gaziano JM, Willett WC, Manson JE. Nut consumption and decreased risk of sudden cardiac death in the Physicians' Health Study. Archives of internal medicine. 2002;162(12):1382-7.

32. Kokubo Y, Iso H, Ishihara J, Okada K, Inoue M, Tsugane S. Association of dietary intake of soy, beans, and isoflavones with risk of cerebral and myocardial infarctions in

Japanese populations: the Japan Public Health Center-based (JPHC) study cohort I. Circulation. 2007;116(22):2553-62.

33. Papandreou C, Becerra-Tomás N, Bulló M, Martínez-González M, Corella D, Estruch R, et al. Legume consumption and risk of all-cause, cardiovascular, and cancer mortality in the PREDIMED study. Clinical nutrition (Edinburgh, Scotland). 2019;38(1):348-56.

34. Nouri F, Haghighatdoost F, Mohammadifard N, Mansourian M, Sadeghi M, Roohafza H, et al. The longitudinal association between soybean and non-soybean legumes intakes and risk of cardiovascular disease: Isfahan cohort study. British Food Journal. 2021;123(8):2864-79.

35. Du H, Li L, Bennett D, Yang L, Guo Y, Key TJ, et al. Fresh fruit consumption and all-cause and cause-specific mortality: findings from the China Kadoorie Biobank. International journal of epidemiology. 2017;46(5):1444-55.

36. Hodgson JM, Prince RL, Woodman RJ, Bondonno CP, Ivey KL, Bondonno N, et al. Apple intake is inversely associated with all-cause and disease-specific mortality in elderly women. British Journal of Nutrition. 2016;115(5):860-7.

37. Blekkenhorst LC, Bondonno CP, Lewis JR, Devine A, Zhu K, Lim WH, et al. Cruciferous and allium vegetable intakes are inversely associated with 15-year atherosclerotic vascular disease deaths in older adult women. Journal of the American Heart Association. 2017;6(10):e006558.

38. Chen GC, Tong X, Xu JY, Han SF, Wan ZX, Qin JB, et al. Whole-grain intake and total, cardiovascular, and cancer mortality: a systematic review and meta-analysis of prospective studies. Am J Clin Nutr. 2016;104(1):164-72.

39. Wei H, Gao Z, Liang R, Li Z, Hao H, Liu X. Whole-grain consumption and the risk of all-cause, CVD and cancer mortality: a meta-analysis of prospective cohort studies - CORRIGENDUM. Br J Nutr. 2016;116(5):952.

40. de Souza RJ, Dehghan M, Mente A, Bangdiwala SI, Ahmed SH, Alhabib KF, et al. Association of nut intake with risk factors, cardiovascular disease, and mortality in 16 countries from 5 continents: analysis from the Prospective Urban and Rural Epidemiology (PURE) study. The American Journal of Clinical Nutrition. 2020;112(1):208-19.

41. Mayhew AJ, de Souza RJ, Meyre D, Anand SS, Mente A. A systematic review and meta-analysis of nut consumption and incident risk of CVD and all-cause mortality. British Journal of Nutrition. 2016;115(2):212-25.

42. Miller V, Mente A, Dehghan M, Rangarajan S, Zhang X, Swaminathan S, et al. Fruit, vegetable, and legume intake, and cardiovascular disease and deaths in 18 countries (PURE): a prospective cohort study. Lancet. 2017;390(10107):2037-49.

43. Wang X, Ouyang Y, Liu J, Zhu M, Zhao G, Bao W, 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. 2014;349:g4490.

44. Abete I, Romaguera D, Vieira AR, Lopez de Munain A, Norat T. Association between total, processed, red and white meat consumption and all-cause, CVD and IHD mortality: a meta-analysis of cohort studies. Br J Nutr. 2014;112(5):762-75.

45. Wang X, Lin X, Ouyang YY, Liu J, Zhao G, Pan A, et al. Red and processed meat consumption and mortality: dose–response meta-analysis of prospective cohort studies. Public Health Nutr. 2016;19(5):893-905.

46. Bendinelli B, Palli D, Masala G, Sharp SJ, Schulze MB, Guevara M, et al. Association between dietary meat consumption and incident type 2 diabetes: the EPIC-InterAct study. Diabetologia. 2013;56(1):47-59.

47. Kim K, Hyeon J, Lee SA, Kwon SO, Lee H, Keum N, et al. Role of Total, Red, Processed, and White Meat Consumption in Stroke Incidence and Mortality: A Systematic

Review and Meta-Analysis of Prospective Cohort Studies. Journal of the American Heart Association. 2017;6(9).

48. Mullie P, Pizot C, Autier P. Daily milk consumption and all-cause mortality, coronary heart disease and stroke: a systematic review and meta-analysis of observational cohort studies. BMC Public Health. 2016;16(1):1236.

49. Naghshi S, Sadeghi O, Larijani B, Esmaillzadeh A. High vs. low-fat dairy and milk differently affects the risk of all-cause, CVD, and cancer death: A systematic review and dose-response meta-analysis of prospective cohort studies. Critical Reviews in Food Science and Nutrition. 2020:1-15.

50. Li H, Li J, Shen Y, Wang J, Zhou D. Legume consumption and all-cause and cardiovascular disease mortality. BioMed research international. 2017;2017.

51. Trinidad TP, Mallillin AC, Loyola AS, Sagum RS, Encabo RR. The potential health benefits of legumes as a good source of dietary fibre. British journal of nutrition. 2010;103(4):569-74.

52. Threapleton DE, Greenwood DC, Evans CEL, Cleghorn CL, Nykjaer C, Woodhead C, et al. Dietary fibre intake and risk of cardiovascular disease: systematic review and meta-analysis. BMJ (Clinical research ed). 2013;347:f6879-f.

53. Yu E, Malik VS, Hu FB. Cardiovascular Disease Prevention by Diet Modification: JACC Health Promotion Series. Journal of the American College of Cardiology. 2018;72(8):914-26.

Figures titles and legends

Figure 1: PRISMA flowchart of study selection[1]

[1] Preferred Reporting Items for Systematic Reviews and Meta-Analyses

Figure 2: Forest plot showing multivariate adjusted Hazard Ratio with 95% CIs for the highest versus the lowest whole grains consumption and cardiovascular mortality in adults.[1]

[1]95% CI, 95% confidence interval; calculated from random effect models; IV, Inverse variation; pooled estimates > 1 favour higher consumption and < 1 favours lower consumption; NHS, Nurses' Health Study; HPFS, Health Professional Health study

Figure 3: Linear dose-response relation between daily intakes of A. Whole grains B. Red/processed meat, C. Dairy Products D. Legumes and risk of cardiovascular mortality in adults[1]

***Solid lines represent linear trend, dashes represent confidence intervals, and dotted blue line represent cubine spline.*

Figure 4: Forest plot showing multivariate adjusted Hazard Ratio (HR) with 95% CIs for the highest versus the lowest red /processed meat consumption and cardiovascular mortality in adults.[1]

[1]95% CI, 95% confidence interval; calculated from random effect models; IV, Inverse variation; pooled estimates > 1 favour higher consumption and < 1 favours lower consumption; NHS, Nurses' Health Study; HPFS, Health Professional Health study

Figure 5: Forest plot showing multivariate adjusted Hazard Ratio (HR) with 95% CIs for the highest versus the lowest dairy consumption and cardiovascular mortality in adults.

[1]95% CI, 95% confidence interval; calculated from random effect models; IV, Inverse variation; pooled estimates > 1 favour higher consumption and < 1 favours lower consumption; NHS, Nurses' Health Study; HPFS, Health Professional Health study

Figure 6: Forest plot showing of multivariate adjusted Hazard Ratio (HR) with 95% CIs for the highest versus the lowest nut consumption and cardiovascular mortality for in adults.

[1]95% CI, 95% confidence interval; calculated from random effect models; IV, Inverse variation; pooled estimates > 1 favour higher consumption and < 1 favours lower consumption; NHS, Nurses' Health Study; HPFS, Health Professional Health study

Figure 7: Forest plot showing multivariate adjusted Hazard Ratio (HR) with 95% CIs for the highest versus the lowest legume consumption and cardiovascular mortality in adults.[1]

[1]95% CI, 95% confidence interval; calculated from random effect models; IV, Inverse variation; pooled estimates > 1 favour higher consumption and < 1 favours lower consumption

Figure 8: Forest plot showing multivariate adjusted Hazard Ratio (HR) with 95% CIs for the highest versus the lowest fruits/vegetables consumption and cardiovascular mortality in adults [1]

[1]95% CI, 95% confidence interval; calculated from random effect models; IV, Inverse variation; pooled estimates > 1 favour higher consumption and < 1 favours lower consumption

Figure 1

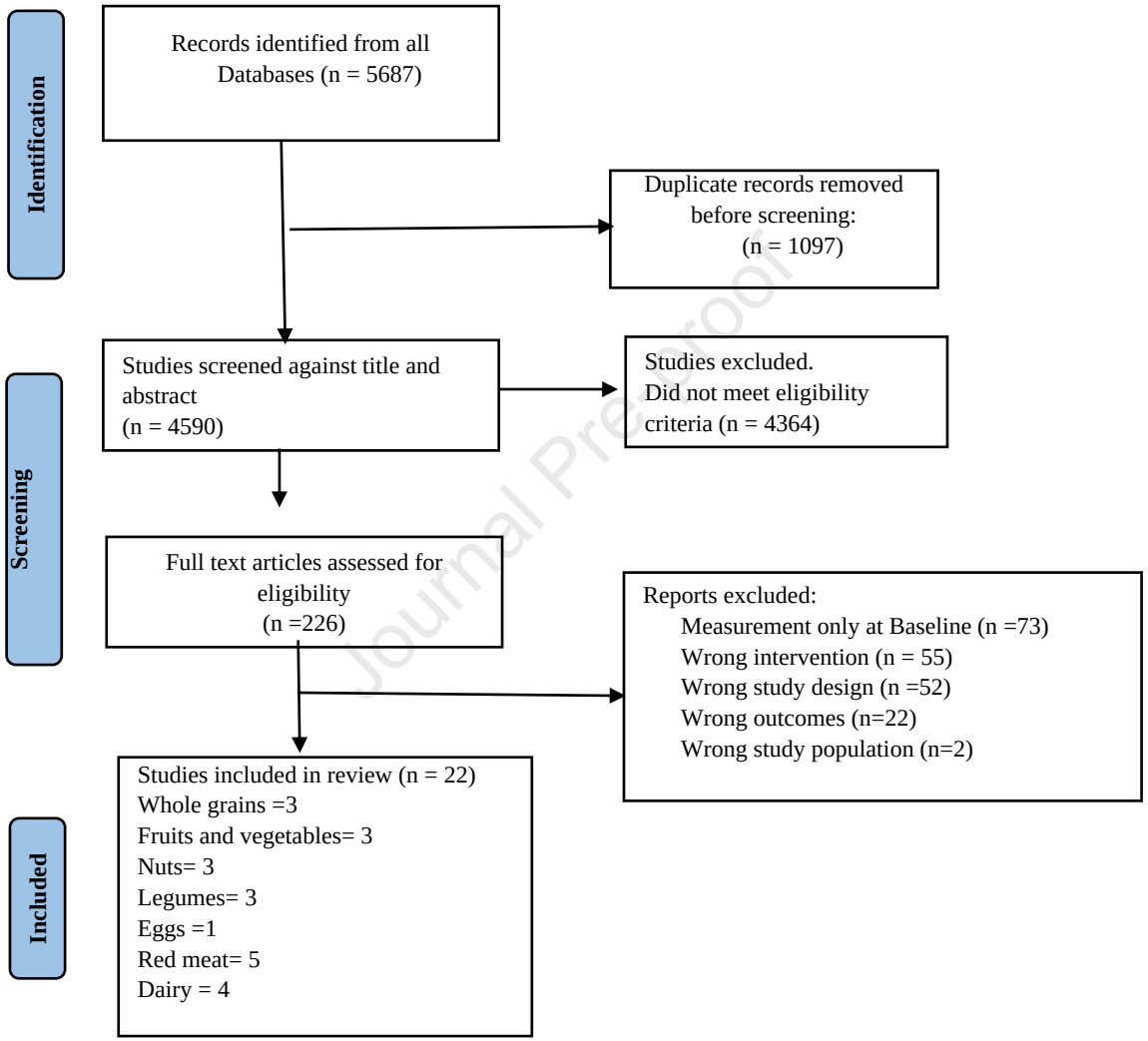


Figure 2

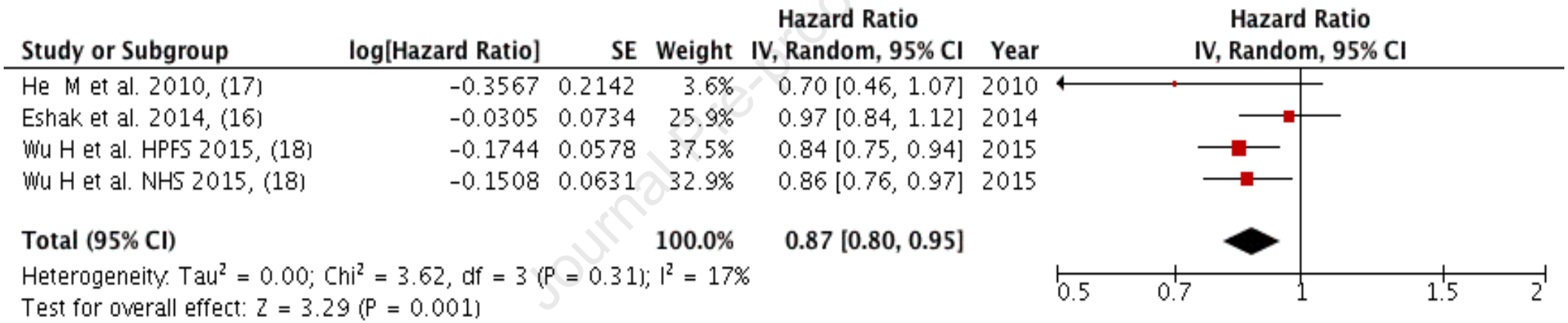


Figure 3

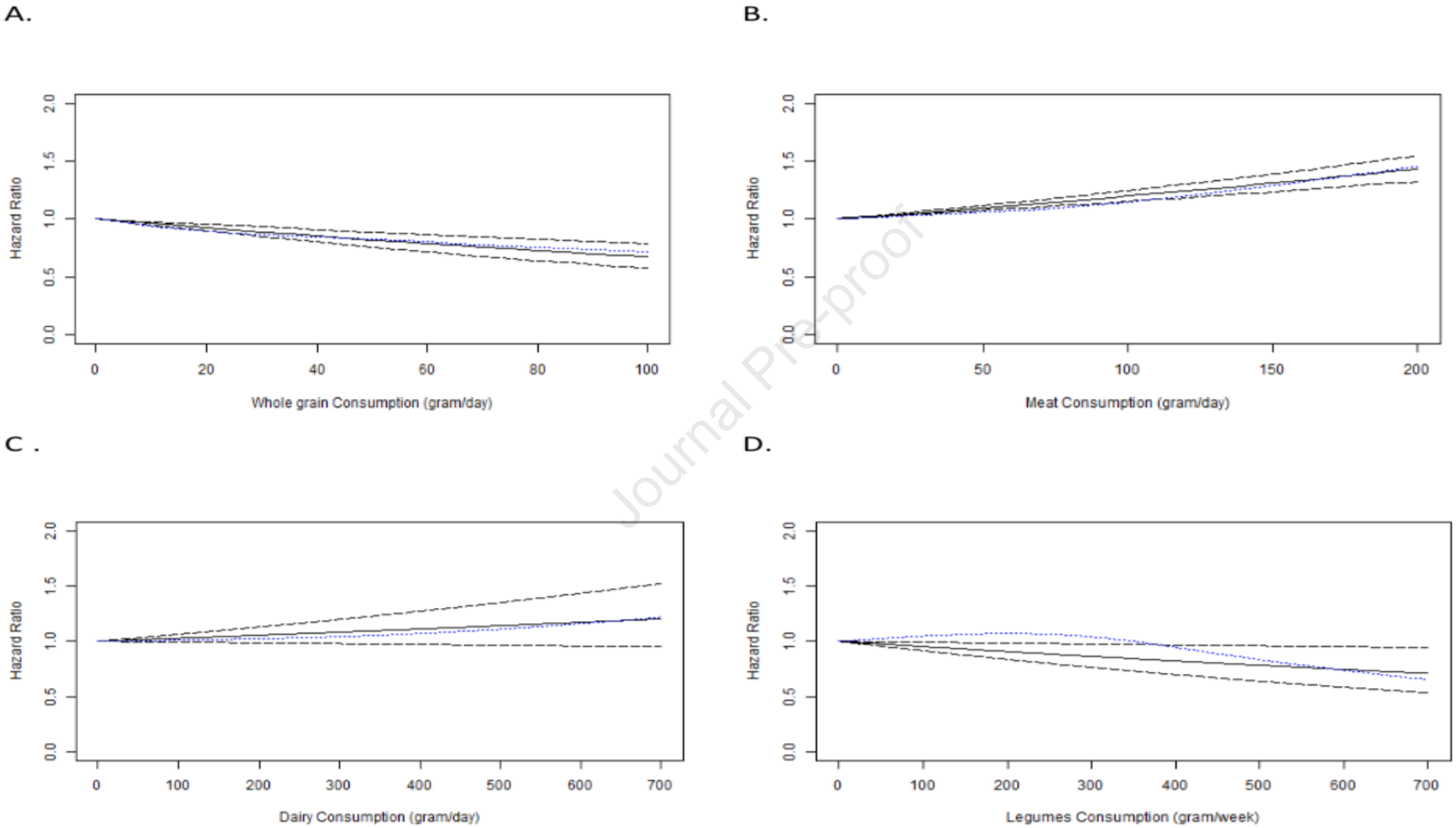


Figure 4

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI	Year
Pan A et al. HPFS 2012, (20)	0.3001	0.0644	18.6%	1.35 [1.19, 1.53]	2012
Pan A et al. NHS 2012, (20)	0.3716	0.0557	19.7%	1.45 [1.30, 1.62]	2012
McCullough et al. 2013, (21)	0.1655	0.2738	4.1%	1.18 [0.69, 2.02]	2013
Bellavia A et al. 2016, (19)	0.2546	0.0631	18.8%	1.29 [1.14, 1.46]	2016
Appleby PN et al. 2016, (23)	0.0198	0.0753	17.3%	1.02 [0.88, 1.18]	2016
Zheng Y et al. 2019, (22)	0.1044	0.0382	21.6%	1.11 [1.03, 1.20]	2019
Total (95% CI)			**100.0%**	**1.23 [1.09, 1.39]**	

Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 24.65$, df = 5 (P = 0.0002); $I^2 = 80\%$

Test for overall effect: Z = 3.45 (P = 0.0006)

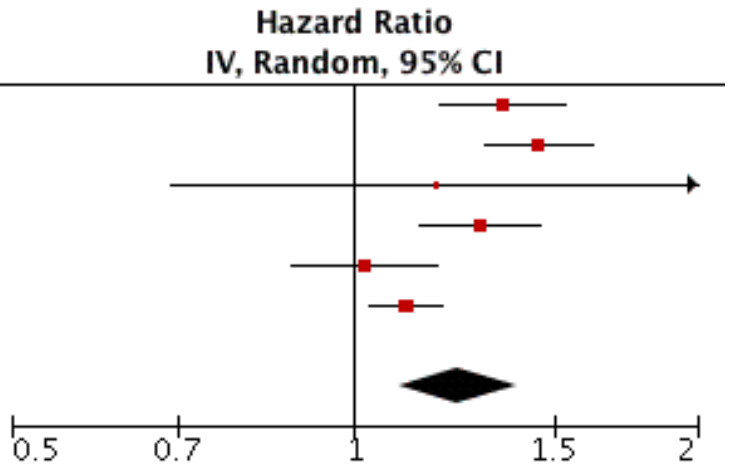


Figure 5

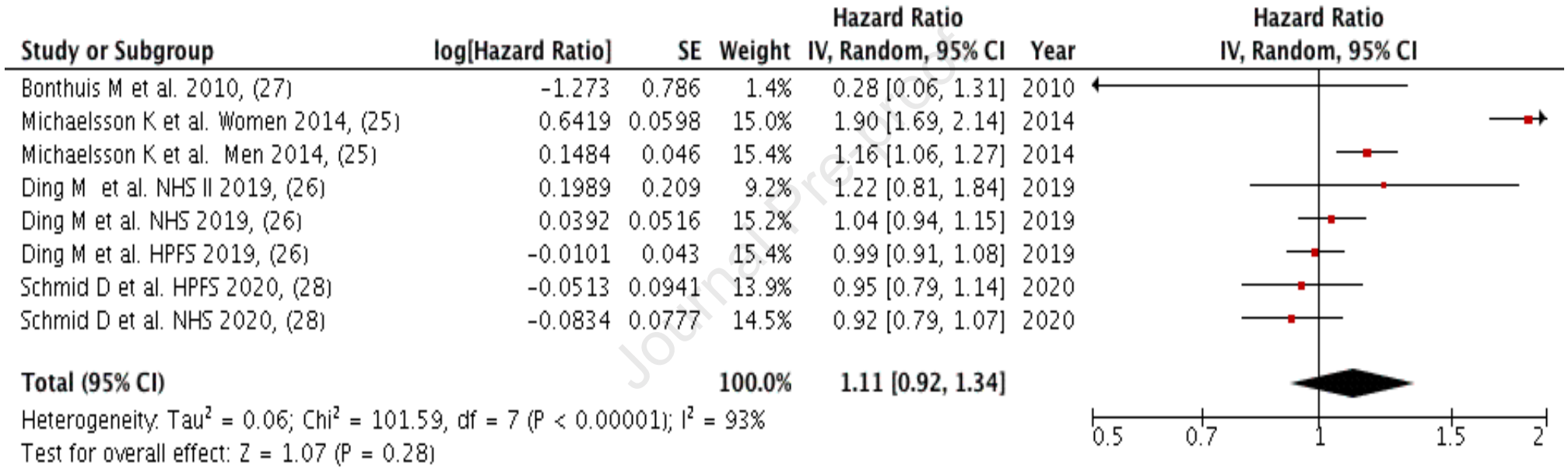

Study or Subgroup
log[Hazard Ratio]
SE
Weight
Hazard Ratio IV, Random, 95% CI
Year
Hazard Ratio IV, Random, 95% CI
Bonthuis M et al. 2010, (27) -1.273 0.786 1.4% 0.28 [0.06, 1.31] 2010
Michaelsson K et al. Women 2014, (25) 0.6419 0.0598 15.0% 1.90 [1.69, 2.14] 2014
Michaelsson K et al. Men 2014, (25) 0.1484 0.046 15.4% 1.16 [1.06, 1.27] 2014
Ding M et al. NHS II 2019, (26) 0.1989 0.209 9.2% 1.22 [0.81, 1.84] 2019
Ding M et al. NHS 2019, (26) 0.0392 0.0516 15.2% 1.04 [0.94, 1.15] 2019
Ding M et al. HPFS 2019, (26) -0.0101 0.043 15.4% 0.99 [0.91, 1.08] 2019
Schmid D et al. HPFS 2020, (28) -0.0513 0.0941 13.9% 0.95 [0.79, 1.14] 2020
Schmid D et al. NHS 2020, (28) -0.0834 0.0777 14.5% 0.92 [0.79, 1.07] 2020
Total (95% CI) 100.0% 1.11 [0.92, 1.34]
Heterogeneity: Tau² = 0.06; Chi² = 101.59, df = 7 (P < 0.00001); I² = 93%
Test for overall effect: Z = 1.07 (P = 0.28)
0.5
0.7
1
1.5
2

Figure 6

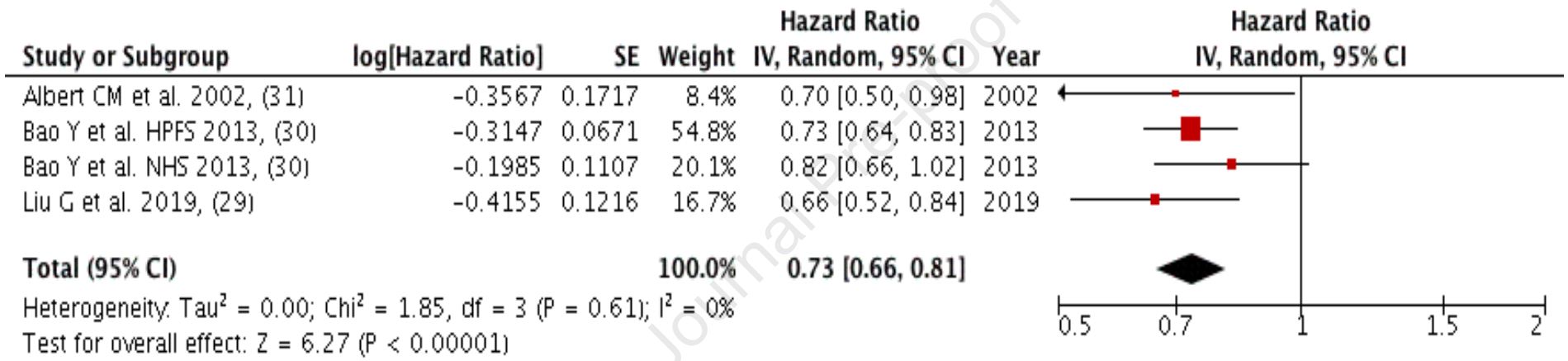


Figure 7

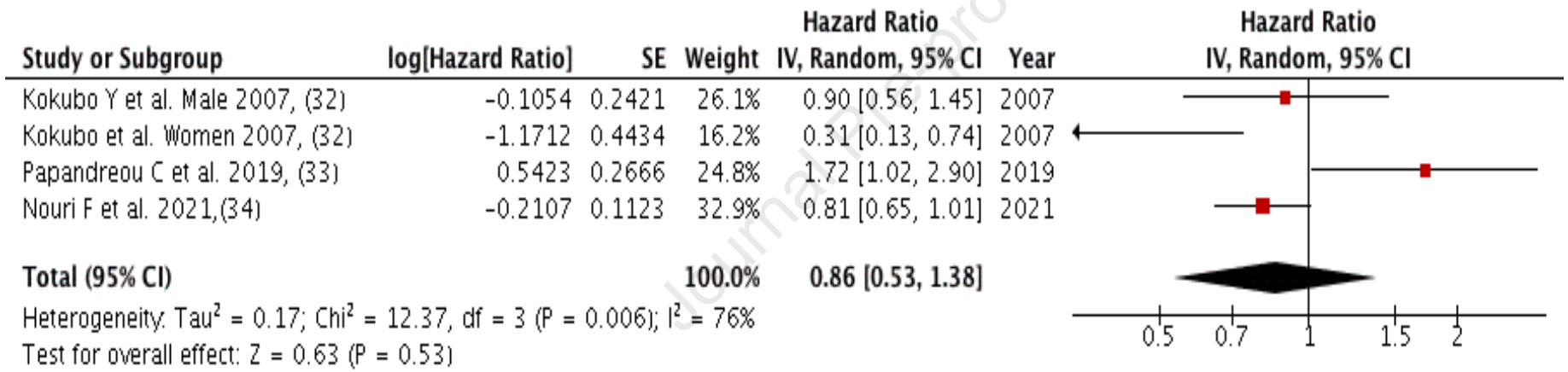

Study or Subgroup
log[Hazard Ratio]
SE
Weight
Hazard Ratio
IV, Random, 95% CI
Year
Hazard Ratio
IV, Random, 95% CI
Kokubo Y et al. Male 2007, (32) -0.1054 0.2421 26.1% 0.90 [0.56, 1.45] 2007
Kokubo et al. Women 2007, (32) -1.1712 0.4434 16.2% 0.31 [0.13, 0.74] 2007
Papandreou C et al. 2019, (33) 0.5423 0.2666 24.8% 1.72 [1.02, 2.90] 2019
Nouri F et al. 2021,(34) -0.2107 0.1123 32.9% 0.81 [0.65, 1.01] 2021
Total (95% CI) 100.0% 0.86 [0.53, 1.38]
Heterogeneity: Tau² = 0.17; Chi² = 12.37, df = 3 (P = 0.006); I² = 76%
Test for overall effect: Z = 0.63 (P = 0.53)
0.5
0.7
1
1.5
2

Figure 8