

Food Groups and Risk of Hypertension: A Systematic Review and Dose-Response Meta-Analysis of Prospective Studies

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ABSTRACT

The aim of this systematic review and meta-analysis was to summarize the evidence on the relation of the intakes of 12 major food groups, including whole grains, refined grains, vegetables, fruits, nuts, legumes, eggs, dairy, fish, red meat, processed meat, and sugar-sweetened beverages (SSBs) with the risk of hypertension. PubMed, Scopus, and Web of Science were searched systematically until June 2017 for prospective studies having quantitatively investigated the above-mentioned foods. We conducted meta-analysis on the highest compared with the lowest intake categories and linear and nonlinear dose-response meta-analyses to analyze the association. Summary RRs and 95% CIs were estimated by using a random-effects model. Overall, 28 reports were included in the meta-analysis. An inverse association for the risk of hypertension was observed for 30 g whole grains/d (RR: 0.92; 95% CI: 0.87, 0.98), 100 g fruits/d (RR: 0.97; 95% CI: 0.96, 0.99), 28 g nuts/d (RR: 0.70; 95% CI: 0.45, 1.08), and 200 g dairy/d (RR: 0.95; 95% CI: 0.94, 0.97), whereas a positive association for 100 g red meat/d (RR: 1.14; 95% CI: 1.02, 1.28), 50 g processed meat/d (RR: 1.12; 95% CI: 1.00, 1.26), and 250 mL SSB/d (RR: 1.07; 95% CI: 1.04, 1.10) was seen in the linear dose-response meta-analysis. Indication for nonlinear relations of the intakes of whole grains, fruits, fish, and processed meats with the risk of hypertension was detected. In summary, this comprehensive dose-response meta-analysis of 28 reports identified optimal intakes of whole grains, fruits, nuts, legumes, dairy, red and processed meats, and SSBs related to the risk of hypertension. These findings need to be seen under the light of very-low to low quality of meta-evidence. However, the findings support the current dietary guidelines in the prevention of hypertension. *Adv Nutr* 2017;8:793–803.

Keywords: food groups, diet, meta-analysis, dose-response, hypertension

Introduction

Approximately 40% of people aged >25 y worldwide have hypertension, amounting to 1 billion in 2015, and the prevalence keeps rising sharply (1, 2). Additionally, hypertension is the most important risk factor for premature cardiovascular

disease and accounts globally for 50% of all ischemic heart diseases and stroke events (3).

Evidence indicates that dietary factors have an important impact on the primary and secondary prevention of hypertension (4). Nevertheless, in various countries, dietary recommendations for the prevention of hypertension are still vague. For instance, according to the 2016 Canadian Hypertension program, there is a moderate quality of evidence that a diet high in whole grains, fruits, vegetables, and low-fat dairy products is effective in the primary and secondary prevention of hypertension. However, the organization gives no recommendation regarding the specific quantities of these foods that should be consumed for the best preventive effect (5). In general, dietary guidelines to reduce the risk of hypertension in a primary prevention setting are mainly based on the results of the Dietary

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Supplemental Materials 1 and 2, Supplemental Tables 1–19, Supplemental Figures 1–24, and Supplemental References are available from the “Online Supporting Material” link in the online posting of the article and from the same link in the online table of contents at <http://advances.nutrition.org>.

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Abbreviations used: DASH, Dietary Approaches to Stop Hypertension Trial; RCT, randomized controlled trial; SSB, sugar-sweetened beverage.

Approaches to Stop Hypertension Trial (DASH) (diet rich in fruits, vegetables, and low-fat dairy products and low in sodium and total and saturated fats) (4, 6–11). DASH showed an important reduction in diastolic and systolic blood pressure by 3 and 5.5 mm Hg, respectively, compared with the control group, and reductions between 1.9 and 2.7 mm Hg compared with the fruit-and-vegetable group (7). Among hypertensive patients systolic and diastolic blood pressure reductions ranged between 11 and 5.5 mm Hg, and larger blood pressure–reduction effects were observed in black subjects compared with those of other ethnicities (7). Changes of potential confounders, such as SSC, body weight, and alcohol, were similarly distributed across the intervention groups.

Recently, we showed that the optimal consumption of risk-decreasing foods (whole grains, vegetables, fruits, and dairy) resulted in a 42% reduction of type 2 diabetes, and a high intake of risk-increasing foods [red and processed meats, sugar-sweetened beverages (SSBs), and eggs] resulted in a 200% increase compared with nonconsumption of the respective foods (12). Similar results could be observed regarding all-cause mortality (13).

Because of the high prevalence of hypertension and the preventive effects of dietary factors, the following question has yet to be answered: What is the trustworthiness of meta-evidence regarding the association of food groups in relation to the risk of hypertension?

Therefore, this meta-analysis was conducted with the aim of investigating the associations of 12 previously used food groups, including whole grains, refined grains, vegetables, fruits, nuts, legumes, eggs, dairy, fish, red meat, processed meat, and SSBs, with the risk of hypertension by evaluating the available evidence. Special focuses in our analyses were the strength and the shape (dose-specific) of the relation to identify an optimal intake of food groups for the lowest risk of hypertension. By applying the NutriGrade scoring system, we aimed to evaluate the food groups' trustworthiness of meta-evidence on their relation to hypertension risk.

Methods

The previously registered systematic review protocol was updated in PROSPERO (<https://www.crd.york.ac.uk/prospero/>, identifier CRD42016037069). Our strategy for the systematic review and meta-analysis was predefined in a published protocol (14) and has already been implemented for 2 recently published meta-analyses on all-cause mortality and type 2 diabetes, respectively (12, 13). This meta-analysis followed the guidelines for reporting proposed by the Meta-analyses Of Observational Studies in Epidemiology (15).

Search strategy

PubMed, Scopus, Web of Science, and Google Scholar, were searched until June 2017. The search was not restricted to calendar date or language. The full search strategy for PubMed is given in **Supplemental Material 1**.

Searches of reference lists from included prospective studies supplemented the electronic database searches. One author (LS) performed the literature search, while another author (HB) reviewed uncertain cases. Consensus was reached through discussion between both authors.

Study selection

We included studies with cohort, case-cohort, and nested case-control designs, as well as follow-ups of randomized controlled trials (RCTs).

Included studies investigated the association for ≥ 1 of the 12 food groups (whole grains or cereals, refined grains or cereals, vegetables, fruits, nuts, legumes, eggs, dairy products, fish, red meat, processed meat, and SSBs) on the risk of hypertension; the incidence of hypertension was defined as systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg for the first time in any follow-up checkup or when taking antihypertensive medication also for the first time in the follow-up visits in adults (those ≥ 18 y old).

Data extraction

Information extracted from the included studies included the name of first author, year of the publication, country, cohort name, number of participants, number of incident hypertension cases, baseline age, sex, length of follow-up, specification of outcome assessment, method of dietary assessment, quantity of food intake, multivariable effect estimate (RRs, HRs, or ORs including the corresponding CIs), and adjusted covariates. When the risk estimates for participants were reported only separately for men and women in a study, the RRs were combined by using a fixed-effect model.

Statistical analysis

To derive summary RRs and 95% CIs we applied a random-effects model (16) to investigate the associations of the categories of highest compared with lowest intake and the dose-response estimate for each of the 12 a priori–defined food groups with the risk of hypertension. Using an inverse variance method, we calculated the SE for the logarithm RR of each study. This was in turn considered the estimated variance of the logarithm RR (16). Meta-analysis was based on the assumption that all measures are RRs. For the dose-response analysis we applied the method described by Greenland and Longnecker (17) and Orsini et al. (18). The distribution of cases and person-years or noncases, as well as the RRs with the 95% CIs, was required for ≥ 3 quantitative exposure categories for the application of this method. If directly reported in a study, a linear dose-response trend with a 95% CI or SE was directly used in our analyses.

As previously described, if studies reported only the total number of cases or person-years and the exposure was defined in categories, the number of person-years or cases in each category was obtained from the total number of person-years or cases divided by the number of reported categories. We assigned the median or mean intake by quantile to the corresponding risk estimate. If studies reported intakes only as a range by quantile, the midpoint was calculated. In the case of an open-ended intake range, we assumed that the width was the same as the contiguous category. If the exposure was expressed per given unit of energy intake, we used the provided mean energy intake to rescale it.

The dose-response was expressed in the quantities as previously described (12–14). If studies reported exposure in serving size but did not specify the amount, recommended conversions were used (**Supplemental Table 1**).

Restricted cubic splines for each study with >3 quantiles of exposure were calculated to explore possible nonlinear associations. We used 3 fixed knots through the total range of the reported intake at 10%, 50%, and 90% and combined these using multivariate meta-analysis (19).

Moreover, the potential of foods to reduce the risk of hypertension was calculated by multiplying the RR by selecting an optimal consumption of risk-reducing foods (calculated by $1 - RR_{\text{reduced}}^*$) and risk-increasing foods noted as (calculated by $1 - \frac{1}{RR_{\text{increased}}^*}$). The optimal consumption of single food groups was defined as the serving category with the strongest association for hypertension risk.

Heterogeneity between studies was evaluated by using the Q test and the I^2 statistic. A value $>50\%$ for the I^2 statistic was regarded as potentially important statistical heterogeneity (20). If >5 studies were available for a food group in the linear dose-response analysis, subgroup analyses were performed to identify potential sources of heterogeneity by the following characteristics: sex, length of follow-up (mean or median ≥ 5 compared with <5 y), geographic location (by continent), number of cases (≥ 1000 compared with <1000), and validated or nonvalidated dietary assessment. Moreover, sensitivity analysis was carried out for a low risk of bias studies (>5 studies available).

As recommended by the Cochrane Handbook, if ≥ 10 studies were available (21), we explored potential small-study effects, such as publication

bias by using Egger's test and funnel plots (22). Stata version/SE 14.2 software (StataCorp) and Review Manager 5.3 (Nordic Cochrane Centre) were used to conduct statistical analyses.

Risk of bias assessment

The risk of bias of the included prospective studies was assessed by considering 4 categories (23): 1) exposure assessment [low risk of bias: validated, calibrated FFQ or 24-h recall, diet history, or diet records (multiple days)], 2) assessment of outcome (low risk of bias: accepted clinical criteria, record linkage (International Classification of Diseases codes), self-reported, and validated), 3) adequacy of follow-up length (low risk of bias: ≥ 5 y), and 4) adjusted basic model (low risk of bias, ≥ 2 factors: e.g., sex, education, and ethnicity; if only one sex included, then ≥ 1 factor) and outcome-relevant adjustments [low risk of bias, ≥ 3 factors: e.g., BMI (in kg/m²), smoking, energy intake, and physical activity].

As previously described, included reports were considered to be at low risk of bias if the rating did not correspond to high or unclear risk of bias in any of the 4 domains (13).

Quality of meta-evidence

Evidence-based dietary recommendations should be based on the completeness of the available evidence. However, many meta-analyses have not evaluated the quality of such evidence, which decreases our confidence in the observed effect.

To evaluate the trustworthiness (credibility) of meta-evidence for the association between 12 predefined food groups and the risk of hypertension we applied our recently developed NutriGrade scoring system (maximum of 10 points). NutriGrade should be applied to summarize the meta-evidence of diet-disease relations in meta-analyses, umbrella reviews, and meta-epidemiological studies (23).

Compared with the well-established Grading of Recommendations Assessment, Development and Evaluation approach, NutriGrade differs in the following aspects: it gives more weight to the evaluation of prospective observational study designs, because such design is important for the investigation of diet-disease relations; it assesses nutrition-specific aspects, such as dietary assessment methods and their validation, calibration of FFQs, or the assessment of diet associated biomarkers; and finally it also considers the conflict of interest and funding bias as a separate item.

This tool is based on the following 8 items for cohort studies: 1) risk of bias, study quality, study limitations (maximum 2 points); 2) precision (maximum 1 point); 3) heterogeneity (maximum 1 point); 4) directness (maximum 1 point); 5) publication bias (maximum 1 point); 6) funding bias (maximum 1 point); 7) effect size (maximum 2 points); and 8) dose-response (maximum 1 point) (23). To evaluate and interpret the meta-evidence, we recommend 4 categories based on this scoring system: high (≥ 8 points), moderate (6 to <8 points), low (4 to <6 points), and very low (0 to <4 points).

Results

Of the 6502 records that were identified by the literature search, 98 full text articles were assessed in detail because they reported on ≥ 1 of the targeted 12 foods groups and risk of hypertension (Figure 1, Supplemental Material 2).

Four prospective studies were included in the meta-analysis for consumption of whole grains (24–27), 3 studies for refined grains (25–27), 8 for vegetables (6 reports) (27–32), 7 for fruits (5 reports) (27, 28, 30–32), 4 for nuts (27, 33–35), 6 for legumes (4 reports) (27, 28, 34, 36), 1 for eggs (34), 9 for dairy products (27, 37–44), 8 for fish (6 reports) (27, 34, 38, 45–47), 7 for red meat (5 reports) (34, 38, 45, 48, 49), 5 for processed meat (3 reports) (45, 48, 49), and 5 for SSBs (3 reports) (27, 50, 51) (Supplemental Tables 2–13).

Whole grains

Four studies with 28,069 incident hypertension cases were included in the highest compared with the lowest intake category meta-analysis (overall intake range: 0–92 g/d). An inverse association between the risk of hypertension and whole-grain intake was observed (RR: 0.86; 95% CI: 0.79, 0.93; $I^2 = 72\%$; P -heterogeneity = 0.01) when comparing extreme categories (Supplemental Figure 1). An increase in whole-grain intake by 30 g/d was inversely associated with the risk of hypertension by 8% (RR: 0.92; 95% CI: 0.87, 0.98; $I^2 = 88\%$; P -heterogeneity < 0.0001 ; $n = 4$) (Supplemental Figure 2).

Furthermore, we detected that with an increase in the intake of whole grains, the risk of hypertension decreased by 15%. Despite a significant test for nonlinearity (P -nonlinearity < 0.01 ; $n = 4$ studies), an inverse relation was seen for an intake of whole grains as high as ~ 90 g/d (Figure 2).

Refined grains

Three studies with 18,842 incident hypertension cases were included in the highest compared with lowest intake category meta-analysis (range of intake: 0–122 g/d). Comparing categories of highest and lowest intake of refined grains, we observed no association with the risk of hypertension (RR: 0.95; 95% CI: 0.88, 1.03; $I^2 = 17\%$; P -heterogeneity = 0.30) (Supplemental Figure 3). Similarly, an increase in refined-grain intake by 30 g/d was not associated with the risk of hypertension (RR: 0.99; 95% CI: 0.96, 1.02; $I^2 = 37\%$; P -heterogeneity = 0.20; $n = 3$) (Supplemental Figure 4). No evidence of a nonlinear dose-response association was detected (P -nonlinearity = 0.11; $n = 3$ studies) (Figure 2).

Vegetables

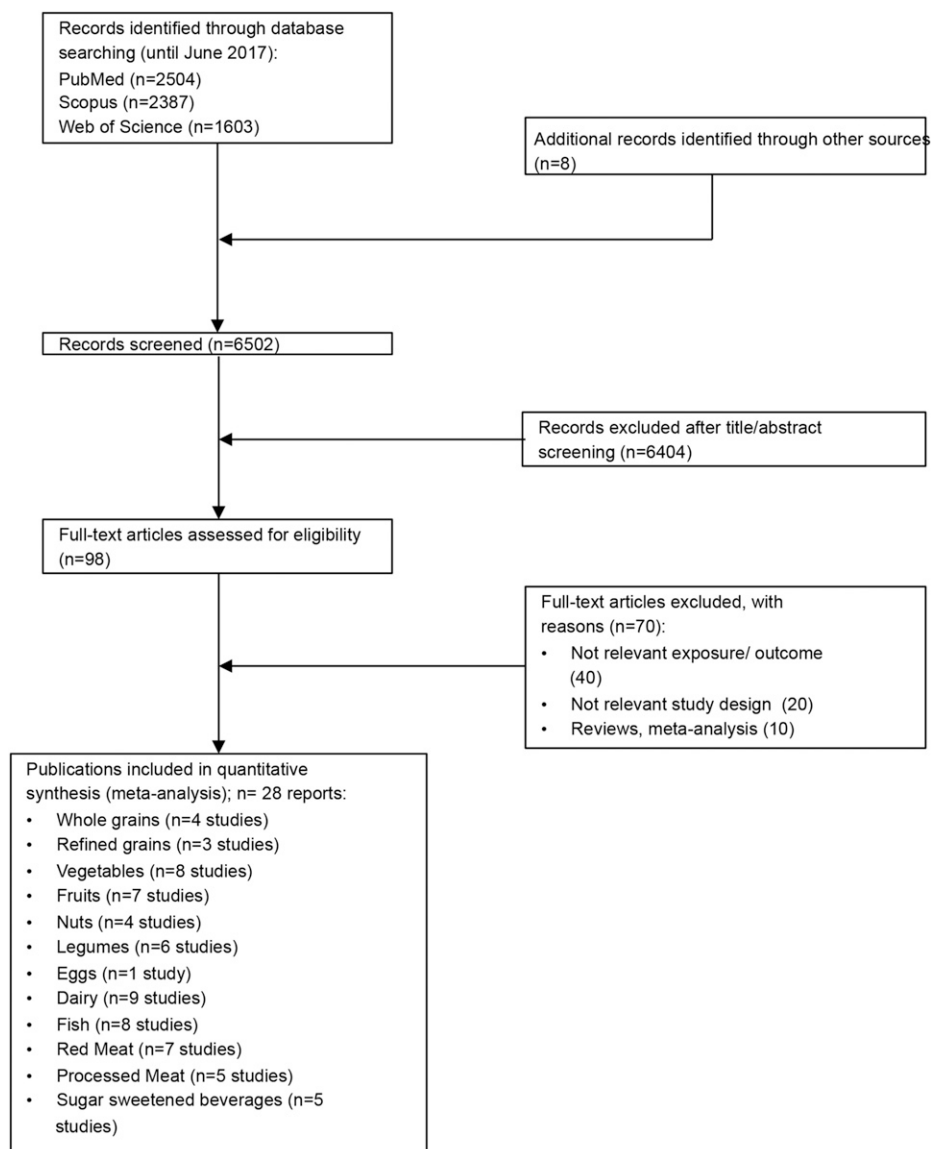
Eight studies including 94,772 incident hypertension cases were included in the meta-analysis comparing extreme intake categories (range of intake: 0–512 g/d). In this analysis we observed an inverse association between the risk of hypertension and vegetable intake (RR: 0.96; 95% CI: 0.91, 1.01; $I^2 = 0\%$; P -heterogeneity = 0.46) (Supplemental Figure 5) but not in the dose-response analysis (RR per 100 g/d: 1.00; 95% CI: 0.98, 1.01; $I^2 = 58\%$; P -heterogeneity = 0.03; $n = 7$) (Supplemental Figure 6).

The subgroup analyses showed an inverse association in studies conducted in Asia and Australia but not in Europe and America, in studies with a follow-up term < 5 y, and in studies with < 1000 cases (Supplemental Table 14). The stratified analyses showed evidence of heterogeneity between subgroups. There was no evidence of a nonlinear dose-response association (P -nonlinearity = 0.25; $n = 7$ studies) (Figure 2).

Fruits

Seven studies with 94,507 incident cases were included in the meta-analysis comparing extreme intake categories (range of intake: 0–360 g/d). In this analysis we observed an inverse association between the risk of hypertension and fruit intake (RR: 0.93; 95% CI: 0.87, 1.00; $I^2 = 55\%$; P -heterogeneity = 0.04) (Supplemental Figure 7). An

FIGURE 1 Flow diagram illustrating the identification and selection of studies.



increase in fruit intake by 100 g/d was inversely associated with the risk of hypertension (RR: 0.97; 95% CI: 0.96, 0.99; $I^2 = 64\%$; P -heterogeneity = 0.02; $n = 6$) (**Supplemental Figure 8**).

The heterogeneity persisted largely in stratified analyses (**Supplemental Table 15**). The subgroup analyses showed no inverse association in shorter-term studies, in European studies, and in studies with <1000 cases. Some evidence of heterogeneity was detected between subgroups in stratified analyses for country.

There was evidence of a nonlinear dose-response trend (P -nonlinearity = 0.06; $n = 6$ studies) with the strongest risk reduction at lower amounts of fruit intake. The risk of hypertension decreased by ~7% with increasing the intake of fruits ≤ 300 g/d (**Figure 2**).

Nuts

Four studies with 11,962 incident hypertension cases were included in the meta-analysis comparing extreme intake categories

(range of intake: 0–37 g/d). An inverse association between the risk of hypertension and nut intake observed (RR: 0.85; 95% CI: 0.78, 0.92; $I^2 = 0\%$; P -heterogeneity = 0.92) when comparing extreme categories (**Supplemental Figure 9**). An increase in nut intake by 28 g/d was inversely associated with the risk of hypertension (RR: 0.70; 95% CI: 0.45, 1.08; $I^2 = 69\%$; P -heterogeneity = 0.02; $n = 4$) (**Supplemental Figure 10**).

No evidence of a nonlinear dose-response association was observed (P -nonlinearity = 0.40; $n = 4$ studies). The risk of hypertension decreased by ~15% with increasing the intake of nuts ≤ 40 g/d (**Figure 2**).

Legumes

Six studies with 80,871 incident hypertension cases were included in the meta-analysis comparing extreme intake categories (range of intake: 0–71 g/d). In this analysis we observed an inverse association between the risk of hypertension and legume intake (RR: 0.92; 95% CI: 0.86, 0.98;

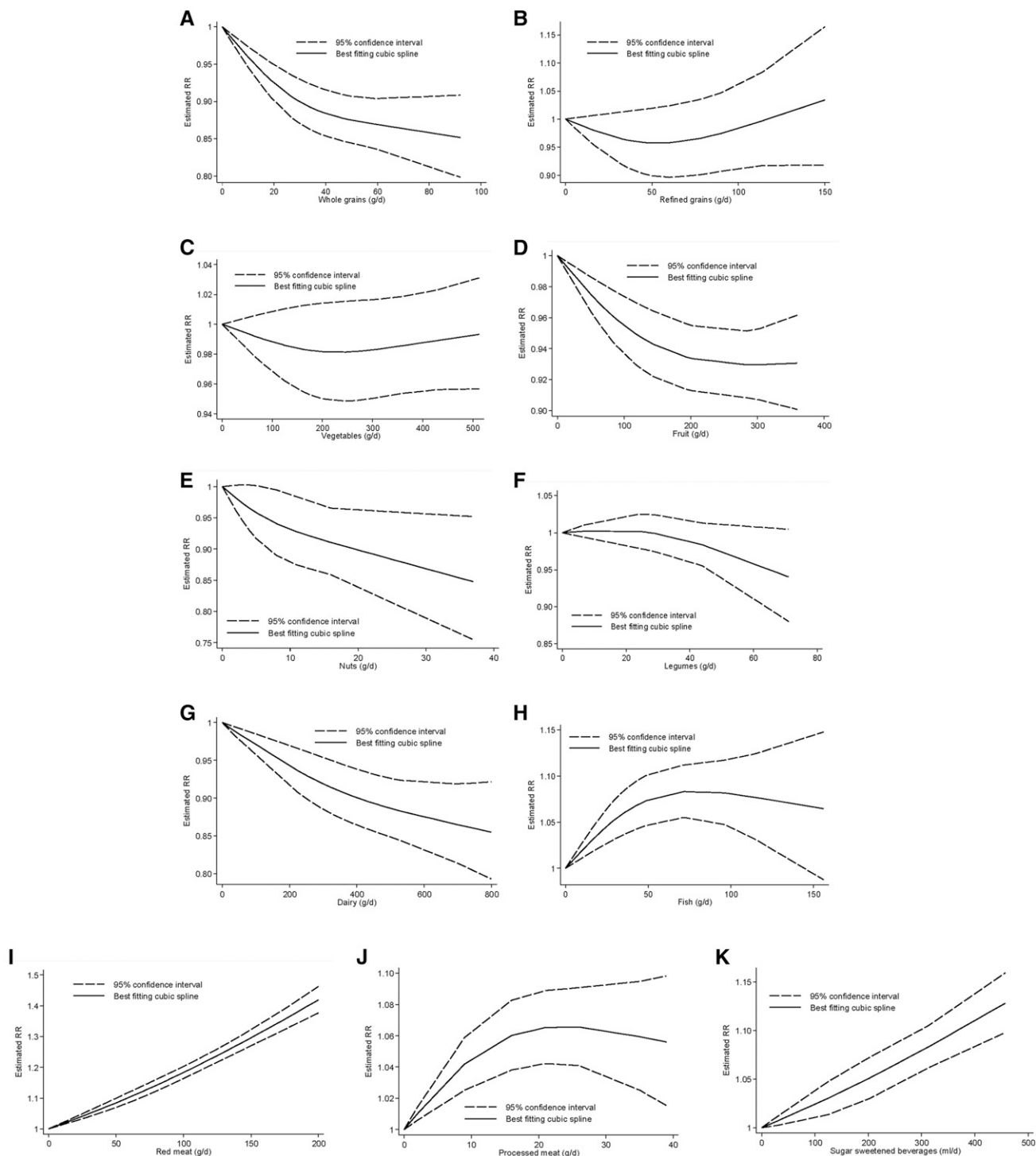


FIGURE 2 Nonlinear dose-response relation between daily intakes of whole grains (A) (P -nonlinearity < 0.01 ; $n = 4$ studies), refined grains (B) (P -nonlinearity = 0.11; $n = 3$ studies), vegetables (C) (P -nonlinearity = 0.25; $n = 7$ studies), fruits (D) (P -nonlinearity = 0.06; $n = 6$ studies), nuts (E) (P -nonlinearity = 0.40; $n = 4$ studies), legumes (F) (P -nonlinearity = 0.17; $n = 5$ studies), dairy (G) (P -nonlinearity = 0.22; $n = 8$ studies), fish (H) (P -nonlinearity < 0.01 ; $n = 7$ studies), red meat (I) (P -nonlinearity = 0.30; $n = 7$ studies), processed meat (J) (P -nonlinearity < 0.001 ; $n = 4$ studies), and sugar-sweetened beverages (K) (P -nonlinearity = 0.73; $n = 4$ studies) and the risk of hypertension.

$I^2 = 0\%$; P -heterogeneity = 0.49) (Supplemental Figure 11), but there was no association for each additional daily 50-g intake (RR: 0.98; 95% CI: 0.95, 1.01; $I^2 = 0\%$; P -heterogeneity = 0.43; $n = 5$) (Supplemental Figure 12).

No evidence of a nonlinear dose-response association was detected (P -nonlinearity = 0.17; $n = 5$ studies). The risk of hypertension decreased by $\sim 5\%$ with increasing the intake of legumes ≤ 70 g/d (Figure 2).

Eggs

One study with 144 incident hypertension cases was detected (range of intake: 0–23 g/d). This study showed an inverse association between the highest and lowest egg-intake category (RR: 0.54; 95% CI: 0.32, 0.91) (**Supplemental Figure 13**) and for each additional daily 50-g intake (RR: 0.25; 95% CI: 0.08, 0.74) (**Supplemental Figure 14**).

Dairy

Nine studies with 31,509 incident hypertension cases were included in the meta-analysis comparing extreme intake categories (range of intake: 0–800 g/d). An inverse association between the risk of hypertension and dairy intake was observed (RR: 0.89; 95% CI: 0.86, 0.93; $I^2 = 0\%$; P -heterogeneity = 0.65) when comparing extreme categories (**Supplemental Figure 15**). An increase in dairy intake by 200 g/d was inversely associated with the risk of hypertension by 5% (RR: 0.95; 95% CI: 0.94, 0.97; $I^2 = 0\%$; P -heterogeneity = 0.50; $n = 9$) (**Supplemental Figure 16**).

No significant differences were observed when comparing low- and high-fat dairy products. No inverse association was observed in studies with a shorter-term follow-up or in studies with nonvalidated dietary assessment (**Supplemental Table 16**). No evidence of a nonlinear dose-response association between dairy products and the risk of hypertension was detected (P -nonlinearity = 0.22; $n = 8$ studies). The risk of hypertension decreased by ~15% with increasing the intake of dairy \leq 800 g/d (**Figure 2**).

Fish

Eight studies with 83,612 incident hypertension cases were included in the meta-analysis comparing extreme intake categories (range of intake: 0–156 g/d). Comparing categories of highest and lowest intake of fish, we observed no association with the risk of hypertension (RR: 1.01; 95% CI: 0.92, 1.10; $I^2 = 57\%$; P -heterogeneity = 0.02) (**Supplemental Figure 17**). Similarly, an increase in fish intake by 100 g/d was not associated with the risk of hypertension (RR: 1.07; 95% CI: 0.98, 1.16; $I^2 = 74\%$; P -heterogeneity < 0.0001; $n = 7$) (**Supplemental Figure 18**).

None of the subgroup analyses showed an association between fish intake and the risk of hypertension (**Supplemental Table 17**). Evidence of a nonlinear dose-response association was observed (P -nonlinearity < 0.01; $n = 7$ studies). The risk increased by 8% with increasing the intake of fish \leq 100 g/d. No additional risk increasing association is apparent above this value (**Figure 2**).

Red meat

Seven studies with 97,745 incident hypertension cases were included in the meta-analysis comparing extreme intake categories (range of intake: 0–121 g/d). A positive association between the risk of hypertension and red meat intake was observed (RR: 1.15; 95% CI: 1.02, 1.28; $I^2 = 84\%$; P -heterogeneity < 0.001) when comparing extreme categories (**Supplemental Figure 19**). Each additional daily 100-g red-meat intake was

associated with a 14% increased risk of hypertension (RR: 1.14; 95% CI: 1.02, 1.28; $I^2 = 88\%$; P -heterogeneity < 0.001; $n = 7$) (**Supplemental Figure 20**). The observed heterogeneity persisted in the additional subgroup analyses. The positive associations were present in studies with a longer-term follow-up, studies including women and larger number of cases, and in studies conducted in the United States (**Supplemental Table 18**).

No evidence of a nonlinear dose-response association was detected (P -nonlinearity = 0.30; $n = 7$ studies). The risk increased by 40% with increasing the intake of red meat \leq 200 g/d (**Figure 2**).

Processed meat

Five studies with 97,441 incident hypertension cases were included in the meta-analysis comparing extreme intake categories (range of intake: 0–39 g/d). A positive association between the risk of hypertension and processed-meat intake was observed (RR: 1.12; 95% CI: 1.02, 1.23; $I^2 = 81\%$; P -heterogeneity < 0.001) when comparing extreme categories (**Supplemental Figure 21**), as well as for each additional daily 50-g processed-meat consumption (RR: 1.12; 95% CI: 1.00, 1.26; $I^2 = 82\%$; P -heterogeneity < 0.001; $n = 4$) (**Supplemental Figure 22**).

The test for nonlinearity showed a significant relation (P -nonlinearity < 0.001; $n = 4$ studies). The risk of hypertension increased by ~7% with increasing the intake of processed meat \leq 30 g/d. No additional risk-increasing association is apparent above this value (**Figure 2**).

SSBs

Five studies including 81,495 incident hypertension cases were included in the meta-analysis comparing extreme intake categories (range of intake: 0–457 mL/d). A positive association between the risk of hypertension and SSB intake was observed (RR: 1.12; 95% CI: 1.06, 1.18; $I^2 = 59\%$; P -heterogeneity = 0.04) when comparing extreme categories (**Supplemental Figure 23**), as well as for each additional daily 250-mL SSB consumption (RR: 1.07; 95% CI: 1.04, 1.10; $I^2 = 64\%$; P -heterogeneity = 0.04; $n = 4$) (**Supplemental Figure 24**). There was no evidence for a nonlinear relation (P -nonlinearity = 0.73; $n = 4$ studies); the risk of hypertension increased by ~13% with increasing the intake of SSB \leq 450 mL/d (**Figure 2**).

Summary across food groups

Table 1 shows the RR for hypertension from the nonlinear dose-response analysis of the 12 predefined food groups according to servings per day. Optimal consumption (lowest serving with significant results and no further substantial change in risk or no further data for higher amounts) of risk-decreasing foods (3 servings/d = 90 g whole grains/d, RR: 0.85; 2 servings/d = 160 g fruits/d, RR: 0.93; 1 serving/d = 28 g nuts/d, RR: 0.88; three-fourths serving/d = 75 g legumes/d, RR: 0.94; 4 servings/d = 800 g dairy/d, RR: 0.85) results in a 44% reduction of hypertension (calculated by $1 - RR_{\text{reduced}}^*$) when compared with nonconsumption of these foods.

TABLE 1 RRs from nonlinear dose-response analysis of 12 pre-defined food groups and risk of hypertension according to intakes of servings per day¹

Food group and daily serving size	Servings/d						
	0	1	2	3	4	5	6
Inverse association							
Whole grains (30 g)	1.00	0.90 (0.87, 0.93)	0.87 (0.84, 0.90)	0.85 (0.80, 0.91)	NA	NA	NA
Fruits (80 g)	1.00	0.96 (0.95, 0.98)	0.93 (0.91, 0.96)	0.93 (0.91, 0.95)	0.93 (0.91, 0.95)	0.93 (0.90, 0.96)	NA
Dairy (200 g)	1.00	0.94 (0.91, 0.97)	0.90 (0.86, 0.94)	0.87 (0.82, 0.92)	0.85 (0.79, 0.92)	NA	NA
Nuts (28 g)	1.00	0.88 (0.80, 0.96)	NA	NA	NA	NA	NA
Legumes (100 g)	1.00	0.94 (0.88, 1.00) ²	NA	NA	NA	NA	NA
Positive association							
Fish (100 g)	1.00	1.08 (1.05, 1.12)	NA	NA	NA	NA	NA
Red meat (85 g)	1.00	1.16 (1.14, 1.18)	1.35 (1.32, 1.38)	NA	NA	NA	NA
Processed meat (30 g)	1.00	1.07 (1.04, 1.09)	NA	NA	NA	NA	NA
SSB (250 mL)	1.00	1.06 (1.04, 1.08)	1.14 (1.11, 1.17)	NA	NA	NA	NA
No association							
Refined grains (30 g)	1.00	0.96 (0.92, 1.01)	0.96 (0.90, 1.02)	0.97 (0.91, 1.05)	1.00 (0.92, 1.08)	1.03 (0.92, 1.16)	NA
Vegetables (80 g)	1.00	0.99 (0.97, 1.01)	0.98 (0.95, 1.01)	0.98 (0.95, 1.02)	0.98 (0.95, 1.02)	0.99 (0.96, 1.02)	1.00 (0.96, 1.03)
Not applicable							
Eggs (55 g)	1.00	NA	NA	NA	NA	NA	NA

¹ Values are RRs (95% CIs). NA, not applicable; SSB, sugar-sweetened beverage.

² This value refers to a three-fourths serving (75 g).

Risk-increasing foods were red meat, processed meat, fish, and SSBs. Compared with nonconsumption, an intake of 2 servings red meat/d (170 g, RR: 1.35), 1 serving processed meat/d (35 g, RR: 1.07), 1 serving fish/d (100 g, RR: 1.08), and 2 servings SSBs/d (500 mL, RR: 1.14) was associated with a 78% increased risk ($RR_{\text{increased}}^*$). On the other hand, a risk reduction by $\sim 44\%$ would be achieved by not consuming these foods (calculated by $1 - \frac{1}{RR_{\text{increased}}}$).

Risk of bias and quality of meta-evidence

Because of the overall low number of included studies for each food group, it was not possible to conduct low-risk-of-bias sensitivity analysis for all food groups, except in the case of vegetable, fruit, dairy, fish, and red-meat intake (Supplemental Table 16). Findings including studies with a low risk of bias confirmed the results of the primary meta-analysis for these food groups. Overall, the quality of meta-evidence for the association between the 12 a priori defined food groups and the risk of hypertension was rated very low (refined grains, vegetables, legumes, and eggs) to low (whole grains, fruits, nuts, dairy, fish, red meat, processed meat, and SSBs) (Supplemental Table 19).

Discussion

This meta-analysis systematically evaluated the associations between 12 food groups (defined a priori) and the risk of hypertension by comparing extreme intake quantiles (highest compared with lowest) and by analyzing linear and nonlinear dose-responses.

In the linear dose-response meta-analysis an inverse association was present for whole grains, fruits, nuts, eggs, and dairy. On the other side, red meat, processed meat, and SSBs were associated with a higher risk of hypertension. We observed some evidence of nonlinearity between the intakes of whole grains, fruits, fish, and processed meat with the risk of hypertension. The trustworthiness of meta-

evidence was rated very-low to low by applying the Nutri-Grade scoring system, suggesting that further high-quality research would provide important evidence on the confidence for the association between the 12 food groups and the risk of hypertension.

To the best of our knowledge, there has not been another meta-analytical synthesis of any association of the food groups whole grains, refined grains, legumes, eggs, red meat, and processed meat with the risk of hypertension. For fruits, vegetables, dairy, fish, nuts, and SSBs, findings similar to ours have been shown in previous meta-analyses. These publications, like our results, reported an inverse association of hypertension with the consumption of nuts (52, 53), fruits (54, 55), and dairy (56, 57), a positive association with the consumption of SSBs (58–61), no association with fish (62), and conflicting associations for vegetable intake (54, 55). All these meta-analyses were based on a single food group (52–62), several publications combined different types of observational studies (prospective cohort studies, cross-sectional studies) (55, 62), and none of them differentiated between incident hypertension and the risk of elevated blood pressure (>130 mm Hg systolic blood pressure or >85 mm Hg diastolic blood pressure) (52–62). Moreover, most of these meta-analyses did not explore nonlinear dose-response relations and the trustworthiness of meta-evidence.

The observed inverse association between whole-grain intake and hypertension in the linear and nonlinear dose-response analysis is remarkably identical to results from meta-analyses that have linked whole-grain consumption with the reduced risk of weight gain, type 2 diabetes, cardiovascular diseases, cancer, and overall mortality (12, 13, 63, 64). Two RCTs have shown important reductions in blood pressure by comparing a whole-grain diet with a diet high in refined grains (65, 66). Antihypertensive effects of whole-grain intake are biologically plausible because of a lower risk of adiposity and the fact that $\sim 75\%$ of the incidence

of hypertension is related directly to obesity (67). Furthermore, whole-grain constituents, such as phytochemicals, and nutrients, such as magnesium, potassium, selenium, zinc, and fiber, have been shown to lower blood pressure (4, 68).

A recent umbrella review of 14 systematic reviews summarized the strength of the evidence for the association between the consumption of nuts and cardiovascular disease. Authors concluded that to clarify the mechanism behind the inverse association between the consumption of nuts and the risk of hypertension, more clinical and experimental studies are needed; meta-analyses of RCTs showed no effect of nut consumption on blood pressure in the normal range (69), despite the recently highly perceived findings from the PREDIMED (Prevención con Dieta Mediterránea) trial (70). Nuts are rich in MUFAs, PUFAs, magnesium, potassium, fiber, antioxidants, and vitamins that are linked to lower blood pressure (71–74).

Many meta-analyses have consistently found evidence of an inverse association between the intake of fruits and vegetables and the risk of weight gain, cardiovascular disease, cancer, type 2 diabetes, and all-cause mortality (12, 13, 75, 76). Moreover, a Cochrane review of 10 intervention trials including 1730 participants observed a reduction in blood pressure after fruit- and vegetable-based interventions (77). Although 2 servings fruits/d was associated with a 7% reduced risk of hypertension, no significant association was detected for vegetable consumption in general in our dose-response meta-analysis. One explanation could be the potential role of BMI as mediator for this association (67). Wang et al. (32) observed an elimination of the inverse associations after adjustment for BMI (potential overadjustment), suggesting that body-weight maintenance could be one important pathway through which vegetable consumption may contribute to blood pressure regulation (76). Further intervention studies are warranted to clarify the association of different types of vegetables and different cooking and processing methods with the risk of hypertension. In line with our findings, a clinical trial incorporating legumes as part of a low-glycemic index diet resulted in a significant blood pressure reduction in 121 participants (78).

The present meta-analysis shows a 13% lower risk of hypertension for 3 servings dairy/d. Several beneficial components of dairy products may contribute to the antihypertensive effect, including calcium and potassium (79), or lactotripeptides (80). Potential mechanistic evidence suggests that these peptides may inhibit the blood vessel-constrictive effect of angiotensin I-converting enzyme (81). Moreover, some evidence suggests that dairy products, especially fermented ones, are associated with a reduced risk of adiposity (82), one of the main causes of hypertension. Contradictory to our findings, a meta-analysis of the published clinical trials showed that a higher dairy intake has no significant effect on change in systolic blood pressure (83).

A detrimental effect of SSBs on hypertension is biologically plausible because of the convincing evidence that the consumption of SSBs is associated with weight gain and

obesity in adults (84). Moreover, previous dose-response meta-analyses have shown a moderate to high quality of meta-evidence for associations between SSBs and the increased risk of type 2 diabetes, coronary heart disease, stroke, heart failure, and all-cause mortality (12, 13). Our findings are supported by evidence from an RCT in which overweight participants consuming high quantities of SSBs (1 L/d for 6 mo) had significantly higher blood pressure values (85).

Red meat and processed meat were associated with an increase in risk of hypertension of 12–14% in the linear dose-response meta-analysis. The mechanism by which these types of meat increase hypertension risk seems to be complex and controversial. Some evidence indicates that Maillard reaction products in cooked meat, such as heterocyclic amines, advanced glycosylation end-products, and acrylamides, may induce hypertension because of inflammatory and oxidation pathways (86, 87). However, our findings regarding red meat and the risk of hypertension are only partly supported by RCT evidence. A recent meta-analysis of 24 RCTs did not find detrimental effects on blood pressure comparing ≥ 0.5 servings/d with < 0.5 serving of total red-meat intake (88). Additionally, in the Beef in an Optimal Lean Diet study, a moderate-protein DASH-like diet including lean beef, decreased systolic blood pressure in normotensive individuals (89).

In our study, fish consumption was associated with a slight increase in hypertension risk in the nonlinear dose-response analysis. No other association was observed in the high-compared with low-intake categories and dose-response meta-analysis. Because of these inconsistencies further research will provide important evidence.

Large clinical trials have shown that the DASH dietary pattern substantially lowers blood pressure among normotensive and hypertensive patients (6, 7). The DASH dietary pattern is based on several food groups, which are largely included in the present meta-analysis and comprise higher amounts of whole grains, fruits, vegetables, dairy products (mainly low-fat), and nuts, and lower intakes of red meat, processed meat, fats, oils, and SSBs (7). All the food groups recommended as part of the DASH dietary pattern (90) showed an inverse association with hypertension risk in the present meta-analysis via the linear and nonlinear dose-response analyses with the exception of vegetables. Moreover, food groups that should be avoided or consumed in lower amounts, such as red meat, processed meat, and SSBs, were consistently associated with hypertension risk.

With our operational definition, the optimal consumption of foods inversely associated with incident hypertension was associated with 44% lower risk, whereas avoidance of foods associated with higher risk was also associated with 44% lower incidence of hypertension.

Some strengths of the present meta-analysis are the large number of investigated food groups, the multiple types of meta-analyses performed (highest compared with lowest intake category, as well as linear and nonlinear dose-response), calculation of the optimal intake of combined food groups, the risk of bias assessment, and the assessment of the trustworthiness of the quality of the meta-evidence.

Some limitations should be considered when interpreting the results of the present meta-analytical synthesis. First, people with higher intakes of whole grains, fruits, vegetables, dairy, and nuts might have a different socioeconomic status or lifestyle than those with a lower intake, thus confounding by lifestyle factors should be considered a potential bias (28, 35, 44, 91). Second, because of the overall low number of included studies, subgroup and sensitivity analyses could be performed only for 5 (fruits, vegetables, dairy, fish, and red meat) of the 12 food groups. In line with this, it was also not possible to assess publication bias and small study effects. The results for several food groups should be cautiously interpreted because of the small number of studies, especially for whole grains, refined grains, nuts, and eggs (<5 prospective studies available).

In summary, this comprehensive meta-analysis of 28 studies identified the optimal intakes of whole grains, fruits, nuts, legumes, dairy, red meat, processed meat, and SSBs regarding the risk of hypertension. These findings need to be seen under the light of very-low to low credibility of meta-evidence. However, the findings support the current dietary recommendations in the primary prevention of hypertension.

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