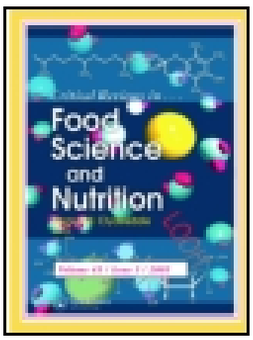

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Food groups and risk of coronary heart disease, stroke and heart failure: a systematic review and dose-response meta-analysis of prospective studies

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First author's surname: Bechthold

Short Title: Food groups and CVD

Abstract

Background: Despite growing evidence for food-based dietary patterns' potential to reduce cardiovascular disease risk, knowledge about the amounts of food associated with the greatest change in risk of specific cardiovascular outcomes and about the quality of meta-evidence is limited.Therefore, the aim of this meta-analysis was to synthesize the knowledge about the relation between intake of 12 major food groups (whole grains, refined grains, vegetables, fruit, nuts, legumes, eggs, dairy, fish, red meat, processed meat, and sugar-sweetened beverages [SSB]) and the risk of coronary heart disease (CHD), stroke and heart failure (HF).

Methods: We conducted a systematic search in PubMed and Embase up to March 2017 for prospective studies. Summary risk ratios (RRs) and 95% confidence intervals (95% CI) were estimated using a random effects model for highest versus lowest intake categories, as well as for linear and non-linear relationships.

Results: Overall, 123 reports were included in the meta-analyses. An inverse association was present for whole grains (RR_{CHD}: 0.95 (95% CI: 0.92-0.98), RR_{HF}: 0.96 (0.95-0.97)), vegetables

and fruits (RR_{CHD}: 0.97 (0.96-0.99), and 0.94 (0.90-0.97); RR_{stroke}: 0.92 (0.86-0.98), and 0.90 (0.84-0.97)), nuts (RR_{CHD}: 0.67 (0.43-1.05)), and fish consumption (RR_{CHD}: 0.88 (0.79-0.99), RR_{stroke}: 0.86 (0.75-0.99), and RR_{HF}: 0.80 (0.67-0.95)), while a positive association was present for egg (RR_{HF}: 1.16 (1.03-1.31)), red meat (RR_{CHD}: 1.15 (1.08-1.23), RR_{stroke}: 1.12 (1.06-1.17), RR_{HF}: 1.08 (1.02-1.14)), processed meat (RR_{CHD}: 1.27 (1.09-1.49), RRstroke: 1.17 (1.02-1.34), RR_{HF}: 1.12 (1.05-1.19)), and SSB consumption (RR_{CHD}: 1.17 (1.11-1.23), RR_{stroke}: 1.07 (1.02-1.12), RR_{HF}: 1.08 (1.05-1.12)) in the linear dose-response meta-analysis. There were clear indications for non-linear dose-response relationships between whole grains, fruit, nuts, dairy, and red meat and CHD.

Conclusion: An optimal intake of whole grains, vegetables, fruit, nuts, legumes, dairy, fish, red and processed meat, eggs and SSB showed an important lower risk of CVD.

Keywords: food, diet, meta-analysis, dose-response, cardiovascular, coronary heart disease, stroke, heart failure

Background

The global challenges of cardiovascular diseases (CVD) present an enormous health burden (Fuster and Kelly, 2010). In 2015, CVD were among the leading causes of disease burden worldwide (Kassebaum et al., 2016). Lifestyle, especially unhealthy dietary patterns, represents a major trigger in the development of CVD and its associated risk factors (e.g., hypercholesterolemia, hypertension, and type 2 diabetes mellitus) (Moran et al., 2014; Scarborough et al., 2011; Verschuren et al., 1995). On the other hand, healthy food and an overall balanced dietary pattern may exert beneficial effects on cardiovascular health.

On the basis of the current evidence, food-based priorities to reduce CVD risk are to increase consumption of whole grains, fruits, vegetables, legumes, nuts and seeds, and fish, to keep a moderate dairy and vegetable oil intake, and to avoid/reduce consumption of refined grains, sugar-sweetened beverages (SSBs), and red and processed (sodium-preserved) meats (Anand et al., 2015; Moran et al., 2014; Mozaffarian, 2016). Thus, the United States Dietary Guidelines (healthy American diet, the Mediterranean diet and the vegetarian diet) (USDA., 2015) and scientific societies (Anderson et al., 2013; Eckel et al., 2014; Perk et al., 2012), for example, recommend dietary patterns that combine these food-based recommendations regarding prevention of chronic diseases.

There is growing evidence and consensus for such food-based dietary patterns as the best means to reduce CVD, obesity, weight gain, and diabetes mellitus (Mozaffarian, 2016). The approach to primarily consider diet at the level of consumption of food groups instead of nutrients and other dietary compounds is directly linked to the concept of food-based dietary guidelines that should

be formulated for each country depending on the current dietary practice and the level of intake (Efsa Panel on Dietetic Products and Allergies, 2010). Evidence for relationships between food consumption and disease risk from meta-analyses is a key component in this process and independent from the country-specific situation.

Even though evidence about the association of CVD risk with some foods and food groups has been reviewed and summarized (Eckel et al., 2014; Kromhout et al., 2016; Nordic Council of Ministers, 2014; USDA., 2015), a remaining question is which amounts of foods or food groups are associated with the greatest change in risk of CVD (referred to hereinafter as optimal intakes), differentiated according to the separate CVD outcomes coronary heart disease (CHD), stroke, and heart failure (HF). As previously shown, selecting specific optimal intakes among the selected food groups can lead to a considerable change in risk of premature death (Schwingshackl et al., 2017c) and morbidity e.g. type 2 diabetes (Schwingshackl et al., 2017a), and hypertension (Schwingshackl et al., 2017). Furthermore, trustworthiness of meta-evidence is very rarely performed in previous meta-analyses (Mozaffarian, 2016). Consequently, one of the most important questions that remain to be answered is which food groups show high quality meta-evidence of protective or detrimental associations with risk of CHD, stroke, and HF using a comprehensive approach.

To address these issues, we conducted a systematic review and meta-analysis of prospective studies to summarize findings of the associations between 12 a priori defined food groups, including whole grains, refined grains, vegetables, fruit, nuts, legumes, eggs, dairy, fish, red meat, processed meat, and SSB with risk of CHD, stroke, and HF. The focus is based on these 12

food groups since most diet quality indices/scores were based on these (Schwingshackl and Hoffmann, 2015a, b; Schwingshackl et al., 2015), as previously reported (Schwingshackl et al., 2016a). The relation between the selected food groups and the mentioned CVD outcomes were calculated separately given their distinct pathogenically and thus different risk associations between exposure factors and individual endpoints could exist and have to be identified (instead of adding further evidence for aggregated CVD). Special attention was given to strength and dose-specific shape of the relationship for finding an optimal intake for lowest risk by high versus low and linear as well as non-linear dose-response meta-analyses. Finally, using the NutriGrade scoring system, we aimed to evaluate food groups' quality of meta-evidence on their protective or detrimental associations with risk of CHD, stroke, and HF, respectively.

Materials and Methods

The review was registered in PROSPERO International Prospective Register of Systematic Reviews (www.crd.york.ac.uk/prospero/index.asp, identifier CRD42016037069). Our strategy for the systematic review and meta-analysis was pre-defined in a published protocol (Schwingshackl et al., 2016a) and has already been implemented for two recently published meta-analyses on all-cause mortality and type 2 diabetes, respectively (Schwingshackl et al., 2017a; Schwingshackl et al., 2017c). This systematic review was planned and conducted according to the standards of the Meta-analysis of Observational Studies in Epidemiology (Stroup et al., 2000).

Search strategy

Literature search was performed using the electronic databases PubMed (until March 2017) and Embase (until March 2017), with no restriction to language and calendar date using the search terms described in Supplementary Appendix S1.

Additionally, the reference lists from the retrieved articles were checked to identify further relevant studies. Published systematic reviews and meta-analyses were also used as a data source. Literature search was conducted by two authors (AB, LS), with disagreement resolved by consensus of another reviewer (HB).

Study selection

Studies were included in the meta-analysis if they met all of the following criteria: (1) prospective design (cohort studies, case-cohort studies, nested case-control studies, follow-up studies of RCTs); (2) information about the association for at least one of the following 12 food

groups: whole grains/cereals, refined grains/cereals, vegetables, fruits, nuts, legumes, eggs, dairy products, fish, red meat, processed meat, SSB; (3) Participants aged ≥18 years; and (4) considering CHD including myocardial infarction and other coronary artery diseases (like angina); stroke (haemorrhagic, ischemic); and HF as outcomes. Exclusion criteria were (1) studies including populations suffering from chronic disease; (2) studies reporting only fatal outcomes, since mortality was included in a previous meta-analysis (Schwingshackl et al., 2017c); (3) studies aggregating outcomes as total CVD, and not reporting on CHD, stroke or HF separately; (4) when a study appeared to have been published in duplicate, the version containing the longest follow-up was selected.

Data extraction

Two authors (AB, LS) extracted the following characteristics: the first author's last name, year of publication, study origin, cohort name, sample size, number of cases, age at entry, sex, study length (follow-up in years), outcome, outcome assessment, assessment of food group, quantity of food, risk estimate (most adjusted measures) (hazard ratios (HR), risk ratios (RR), or odds ratios (OR) with their corresponding 95% confidence intervals (CIs)), and adjustment factors.

When a study provided several risk estimates, the multivariable model was chosen. When only separate risk estimates for male and female participants were available in a study, we combined the RRs using a fixed effect model before inclusion in the meta-analysis.

Risk of bias assessment

To assess the risk of bias of the prospective studies, we assessed ascertainment of exposure (low risk of bias: validated, calibrated FFQ or 24-h recall, diet history, or diet records (multiple days)),

assessment of outcome (low risk of bias: record linkage (ICD codes), accepted clinical criteria, self-reported and validated), duration of follow-up (<10 versus ≥10 years), and whether basic model was adjusted and outcome relevant adjustments (age, sex, education, body mass index, smoking, physical activity, energy intake) were made (Schwingshackl et al., 2016c). Studies were classified as being at low risk of bias in general only if none of the domains established a high /unclear risk of bias.

Statistical analysis

For high versus low and dose-response meta-analyses, a random effects model was used to calculate summary RRs/HRs/ORs and 95% CIs summarizing associations between the food groups (whole grains/cereals, refined grains/cereals, vegetables, fruit, nuts, legumes, eggs, dairy products, fish, red meat, processed meat, SSB), and risk of CHD, stroke, and HF (DerSimonian and Laird, 1986), which incorporated both within and between study variability. Meta-analysis was based on the assumption that all measures are RRs. To evaluate the weighting of each study, the standard error for the log-transformed RR of each study was calculated and regarded as the estimated variance of the log-transformed RR, using an inverse variance method (DerSimonian and Laird, 1986).

The method described by Greenland and Longnecker (Greenland and Longnecker, 1992) was applied for the dose-response analysis and computed study-specific slopes (linear trends) and corresponding 95% CIs from the natural logs of the RRs and CIs across intake categories of the 12 food groups. The method requires that the distribution of cases, person-years or non-cases, and the RRs with the 95% CI for at least three quantitative exposure categories are known.

When studies reported only the total number of cases or total person-years and the exposure was defined in quantiles, the distribution of cases or person-years was calculated by dividing the total number by the number of quantiles, thus assuming an equal distribution across exposure quantiles. Whenever reported, the mean or median intake by category was assigned to the corresponding RR. The midpoint was calculated for studies that only reported a range of intake by category. When the intake range was open-ended, we assumed that its width was the same as the adjacent category. For studies presenting the exposure per given unit of energy intake, we rescaled it using the mean energy intake provided.

Where studies had already reported a linear dose-response trend, with CI or standard error, this was used directly.

The units of exposure were defined as follows: whole grains/cereals (30g/d), refined grains/cereals (30g/d), vegetables (100g/d), fruits (100g/d), nuts (28g/d), legumes (50g/d), eggs (50g/d), dairy products (200g/d), fish (100g/d), red meat (100g/d), processed meat (50g/d), and sugar sweetened beverages (250ml/d). For studies that reported intake only as serving size (and did not specify the quantitative amount), we used recommended conversions (WCRF, 2017) (Supplemental Table 1).

To examine possible non-linear associations, we calculated restricted cubic splines for each study with more than three categories of exposure, using three fixed knots at 10%, 50%, and 90% through the total distribution of the reported intake, and combined them using multivariable meta-analysis (Durrleman and Simon, 1989) (if at least 2 studies with at least three quantitative exposure levels were known for one of the 12 food groups with the corresponding outcome).

Moreover, the risk reduction potential of foods was calculated by multiplying the RR by selecting an optimal consumption of risk-reducing foods (calculated by $1 - \mathrm{RR}^{*}_{\mathrm{reduced}}$), and risk-increasing foods noted as $\left(\text{calculated by } 1 - \frac{1}{\mathrm{RR}^{*}_{\mathrm{increased}}}\right)$. The optimal consumption was defined as the serving category of a single food group with the strongest association for CHD, stroke, and HF risk, respectively.

To explore heterogeneity between studies, we used Cochran's Q test and calculated the I^2 statistic (with a value of $I^2 > 50\%$ considered to represent potentially important statistical heterogeneity) (Higgins and Thompson, 2002). In addition, to identify potential sources of heterogeneity, we stratified the meta-analysis by subgroups. If more than five studies were available for a food group in the highest vs. lowest category meta-analysis or in the linear dose-response analysis, subgroup analyses were performed by the following characteristics: sex, length of follow-up (mean or median ≥10 years vs. <10 years), geographic location (Europe, America, Asia and Australia), number of cases (≥1,000 vs. <1,000), and dietary assessment (validated vs. non-validated). Furthermore, we performed sensitivity analyses for low risk of bias studies, excluding nested case-control studies and studies based on ORs.

Potential small-study effects, such as publication bias, were explored using Egger´s test and funnel plots (Egger et al., 1997), if at least 10 studies were available (Higgins and Green, 2011).

Review Manager 5.3 (Nordic Cochrane Center, Copenhagen), and Stata version 14 software (StataCorp, College Station, TX) were used for the statistical analyses.

Quality of meta-evidence

Quality of evidence of the meta-analyses (i.e., meta-evidence) was defined as the confidence in the estimate. To evaluate the meta-evidence for the association between the 12 pre-defined food groups and CHD, stroke, and HF risk, we applied the NutriGrade scoring system (max 10 points) which comprises the following items: (i) risk of bias/study quality/study limitations (max. 2 points), (ii) precision (max. 1 point), (iii) heterogeneity (max. 1 point), (iv) directness (max. 1 point), (v) publication bias (max. 1 point), (vi) funding bias (max. 1 point) , (vii) effect size (max. 2 points), and (viii) dose-response (max. 1 point) (Schwingshackl et al., 2016c). Based on this scoring system we defined four meta-evidence levels: high (≥8 points), moderate (6-<8 points), low (4-<6 points), and very low (0-<4 points).

Results

Out of the 16623 records which were identified by the systematic literature search, 261 full text articles were assessed in detail as they reported on at least one of the 12 food groups and CVD outcomes in the title/abstract (Figure 1; Supplemental Appendix 2).

Sixteen prospective studies were included in the meta-analysis for consumption of whole grains (16 reports) (Del Gobbo et al., 2015; Djousse and Gaziano, 2007; Hansen et al., 2017; Helnaes et al., 2016; Jensen et al., 2004; Liu et al., 2000b; Liu et al., 1999; Mizrahi et al., 2009; Muraki et al., 2015; Neelakantan et al., 2016; Nettleton et al., 2008; Rautiainen et al., 2012; Sonestedt et al., 2015; Steffen et al., 2003; Tektonidis et al., 2015, 2016) (Supplemental Table 2), 9 studies for refined grains (8 reports) (Djousse and Gaziano, 2007; Eshak et al., 2014; Liu et al., 2000b; Mizrahi et al., 2009; Muraki et al., 2015; Sonestedt et al., 2015; Steffen et al., 2003; Yu et al., 2013) (Supplemental Table 3), 35 for vegetables (32 reports) (Belin et al., 2011a; Bendinelli et al., 2011; Bhupathiraju et al., 2013; Buckland et al., 2009; Dauchet et al., 2004; Del Gobbo et al., 2015; Dilis et al., 2012; Gillman et al., 1995; Hansen et al., 2017; Hansen et al., 2010; Hirvonen et al., 2001; Johnsen et al., 2003; Joshipura et al., 1999; Keli et al., 1996; Kobylecki et al., 2015; Larsson et al., 2009b; Larsson et al., 2013; Lin et al., 2013; Liu et al., 2001; Liu et al., 2000a; Martinez-Gonzalez et al., 2011; Misirli et al., 2012; Mizrahi et al., 2009; Neelakantan et al., 2016; Oude Griep et al., 2012; Rautiainen et al., 2015; Sonestedt et al., 2015; Tognon et al., 2014; Wurtz et al., 2016; Yokoyama et al., 2000; Yu et al., 2014; Zhang et al., 2011) (Supplemental Table 4), 32 for fruit (30 reports) (Belin et al., 2011a; Bendinelli et al., 2011; Bhupathiraju et al., 2013; Buckland et al., 2009; Dauchet et al., 2004; Del Gobbo et al., 2015; Du et al., 2016; Fraser et al., 1992; Gillman et al., 1995; Hansen et al., 2017; Hansen et al., 2010;

Hirvonen et al., 2001; Johnsen et al., 2003; Joshipura et al., 1999; Keli et al., 1996; Kobylecki et al., 2015; Larsson et al., 2009b; Larsson et al., 2013; Lin et al., 2013; Liu et al., 2000a; Mizrahi et al., 2009; Neelakantan et al., 2016; Oude Griep et al., 2012; Rautiainen et al., 2015; Sonestedt et al., 2015; Tognon et al., 2014; Yamada et al., 2011; Yokoyama et al., 2000; Yu et al., 2014; Zhang et al., 2011) (Supplemental Table 5), 13 for nuts (12 reports) (Albert et al., 2002; Bernstein et al., 2012b; Bernstein et al., 2010; Del Gobbo et al., 2015; di Giuseppe et al., 2015; Djousse et al., 2010; Djousse et al., 2008; Fraser et al., 1992; Haring et al., 2014; Haring et al., 2015; Nettleton et al., 2008; Yaemsiri et al., 2012) (Supplemental Table 6), 15 for legumes (13 reports) (Bazzano et al., 2001; Bernstein et al., 2012b; Bernstein et al., 2010; Buckland et al., 2009; Dilis et al., 2012; Fraser et al., 1992; Haring et al., 2014; Haring et al., 2015; Kokubo et al., 2007; Martinez-Gonzalez et al., 2011; Misirli et al., 2012; Mizrahi et al., 2009; Yu et al., 2014) (Supplemental Table 7), 17 for eggs (16 reports) (Bernstein et al., 2012b; Bernstein et al., 2010; Burke et al., 2007; Dilis et al., 2012; Djousse and Gaziano, 2008a, b; Goldberg et al., 2014; Haring et al., 2014; Haring et al., 2015; Hu et al., 1999; Larsson et al., 2015; Misirli et al., 2012; Nettleton et al., 2008; Qureshi et al., 2007; Virtanen et al., 2016; Yaemsiri et al., 2012) (Supplemental Table 8), 24 for dairy products (24 reports) (Avalos et al., 2013; Bergholdt et al., 2015; Bernstein et al., 2012b; Bernstein et al., 2010; Buckland et al., 2009; Dalmeijer et al., 2013; Dilis et al., 2012; Elwood et al., 2004; Fraser et al., 1992; Haring et al., 2014; Haring et al., 2015; Larsson et al., 2009a; Larsson et al., 2012; Lin et al., 2013; Martinez-Gonzalez et al., 2011; Misirli et al., 2012; Nettleton et al., 2008; Patterson et al., 2013; Praagman et al., 2015; Soedamah-Muthu et al., 2013; Sonestedt et al., 2011; Tektonidis et al., 2015, 2016; Yaemsiri et al., 2012) (Supplemental Table 9), 47 for fish (47 reports) (Albert et al., 1998; Amiano et al.,

2016a; Ascherio et al., 1995; Atkinson et al., 2011; Belin et al., 2011b; Bernstein et al., 2012b; Bernstein et al., 2010; Bjerregaard et al., 2010; Buckland et al., 2009; de Goede et al., 2010; de Goede et al., 2012; Del Gobbo et al., 2015; Dijkstra et al., 2009; Dilis et al., 2012; Fraser et al., 1992; Gammelmark et al., 2016; Gillum et al., 2000; Gillum et al., 1996; Hansen et al., 2017; Haring et al., 2014; Haring et al., 2015; Holmberg et al., 2009; Iso et al., 2006; Keli et al., 1994; Kuhn et al., 2013; Larsson et al., 2011a; Levitan et al., 2009, 2010; Martinez-Gonzalez et al., 2011; Misirli et al., 2012; Montonen et al., 2009; Morris et al., 1995; Mozaffarian et al., 2005a; Mozaffarian et al., 2003; Mozaffarian et al., 2005b; Myint et al., 2006; Nahab et al., 2016; Nettleton et al., 2008; Orencia et al., 1996; Osler et al., 2003; Salonen et al., 1995; Tektonidis et al., 2015; Tognon et al., 2014; Wennberg et al., 2011; Wennberg et al., 2007; Wilk et al., 2012; Wurtz et al., 2016) (Supplemental Table 10), 15 for red meat (Amiano et al., 2016b; Ashaye et al., 2011; Bernstein et al., 2012b; Bernstein et al., 2010; Del Gobbo et al., 2015; Fraser et al., 1992; Haring et al., 2014; Haring et al., 2015; Kaluza et al., 2014, 2015; Larsson et al., 2011b, c; Nettleton et al., 2008; Wurtz et al., 2016; Yaemsiri et al., 2012) (Supplemental Table 11), 14 for processed meat (13 reports) (Amiano et al., 2016b; Ascherio et al., 1994; Bernstein et al., 2012b; Bernstein et al., 2010; Burke et al., 2007; Del Gobbo et al., 2015; Haring et al., 2014; Haring et al., 2015; Kaluza et al., 2014, 2015; Larsson et al., 2011b, c; Wurtz et al., 2016) (Supplemental Table 12), and 11 for SSB (9 reports) (Bernstein et al., 2012a; de Koning et al., 2012; Del Gobbo et al., 2015; Eshak et al., 2012; Fung et al., 2009; Gardener et al., 2012; Larsson et al., 2014; Rahman et al., 2015; Sonestedt et al., 2015) (Supplemental Table 13).

Whole grains

For whole grains, 7 studies with 6,834 cases were included in the high vs. low intake meta-

analysis (overall intake range: 0−220 g/d) for CHD, 7 studies with 11,114 cases (overall intake range: 0−670 g/d) for stroke and 5 studies with 6,455 cases (overall intake range: 0−280 g/d) for HF.

Comparing the highest to the lowest categories of whole grain intake, an inverse associations with risk of CHD (RR: 0.85; 95% CI 0.81 to 0.90, I^2=0%, $p_{heterogeneity}$=0.72), stroke (RR: 0.91; 95% CI 0.82 to 1.02, I^2=53%, $p_{heterogeneity}$=0.05), and HF (RR: 0.91; 95% CI 0.85 to 0.97, I^2=35%, $p_{heterogeneity}$=0.19) were observed (Supplemental Figure 1).

Each additional daily 30 g of whole grains were inversely associated with risk of CHD (RR: 0.95; 95% CI 0.92 to 0.98, I^2=46%, $p_{heterogeneity}$=0.11, n=5) and HF (RR: 0.96; 95% CI 0.95 to 0.97, I^2=0%, $p_{heterogeneity}$=0.36, n=2), but not with risk of stroke (RR: 0.99; 95% CI 0.95 to 1.03, I^2=65%, $p_{heterogeneity}$=0.04, n=4) (Supplemental Figure 2).

Heterogeneity observed in the high vs. low whole grain intake meta-analysis for stroke persisted in stratified analyses (Supplemental Table 14a-b) and, where detectable, no evidence of heterogeneity for subgroup-differences was observed.

There was evidence of a non-linear dose-response association ($p_{non\text{-}linearity}$<0.001, n=5 studies) for CHD, but not for stroke ($p_{non\text{-}linearity}$=0.77, n=3 studies). The risk of CHD decreased by 17% with increasing intake of whole grains up to ~100 g/d. No benefit for increasing intake was apparent above this intake (Figure 2). No association was observed for whole grain intake and risk of stroke in the non-linear dose-response analysis (Figure 3).

Refined grains

Five studies with 3,286 cases were included in the high vs. low intake meta-analysis (overall

intake range: 15−540 g/d) for CHD, 6 studies with 11,434 cases (overall intake range: 15−540 g/d) for stroke, and 1 study with 1018 cases (overall intake range: 0−40 g/d) for HF.

Comparing the highest to the lowest categories of intake, a trend for a positive association between risk of CHD (RR: 1.11; 95% CI 0.99 to 1.25, I^2=0%, $p_{heterogeneity}$=0.52) and refined grain intake was observed, whereas no association was detected for stroke (RR: 1.02; 95% CI 0.94 to 1.11, I^2=2%, $p_{heterogeneity}$=0.41), or HF (RR: 0.83; 95% CI 0.58 to 1.19) (Supplemental Figure 3).

No association was observed for each additional daily 30 g of refined grains and risk of CHD (RR: 1.01; 95% CI 0.99 to 1.04, I^2=0%, $p_{heterogeneity}$=0.51, n=4), stroke (RR: 1.00; 95% CI 0.98 to 1.01, I^2=0%, $p_{heterogeneity}$=0.51, n=4), or HF (RR: 0.86; 95% CI 0.68 to 1.09, n=1) (Supplemental Figure 4).

No evidence of heterogeneity was detected between subgroups in stratified analyses (high vs. low meta-analysis) on refined grains and stroke (Supplemental Table 15).

There was no evidence of a non-linear dose-response association between refined grains and CHD ($p_{non\text{-}linearity}$=0.25, n=4 studies), or stroke ($p_{non\text{-}linearity}$=0.42, n=4 studies) (Figure 2 and 3).

Vegetables

Nineteen studies with 19,402 cases were included in the high vs. low intake meta-analysis for vegetables and CHD (overall intake range: 0−1300 g/d), 16 studies with 12,442 cases for stroke (overall intake range: 0−500 g/d), and 3 studies with 6,267 cases for HF (overall intake range: 100−460 g/d).

Comparing the highest to the lowest categories of vegetable intake, an inverse association was observed for risk of CHD (RR: 0.92; 95% CI 0.87 to 0.98, I^2=42%, $p_{heterogeneity}$=0.03) and stroke

(RR: 0.87; 95% CI 0.82 to 0.93, I^2=38%, $p_{heterogeneity}$=0.06), while no association was observed for risk of HF (RR: 0.99; 95% CI 0.82 to 1.18, I^2=80%, $p_{heterogeneity}$=0.007) (Supplemental Figure 5).

Each additional daily 100 g of vegetables were inversely associated with risk of CHD (RR: 0.97; 95% CI 0.96 to 0.99, I^2=12%, $p_{heterogeneity}$=0.32, n=14), stroke (RR: 0.92; 95% CI 0.86 to 0.98, I^2=79%, $p_{heterogeneity}$<0.001, n=10), and HF (RR: 0.96; 95% CI 0.94 to 0.98, n=1) (Supplemental Figure 6).

No evidence of heterogeneity was detected between subgroups in stratified analyses (high vs. low meta-analysis) on vegetables and CHD and stroke (Supplemental Table 16a-b). In stratified analyses (dose-response meta-analysis) the inverse association between vegetable intake and CHD risk was no longer significant in men, in studies conducted in Europe, Asia and Australia, in smaller studies (<1,000 cases), and studies using non-validated dietary assessment methods, possibly due to limited number of studies (Supplemental Table 16c). The heterogeneity of studies included in dose-response analysis on vegetable intake and stroke persisted in additional analyses stratified by subgroups (Supplemental Table 16d). Evidence for an inverse association was observed in men (no studies in women only), in long-term and European, Asian and Australian studies. No evidence of heterogeneity was detected between subgroups in stratified analyses.

There was evidence for small study effects in the high vs. low (p=0.03), but not in the dose-response analysis for CHD. No evidence for small study effects was observed for stroke. Visual inspection of the funnel plots (dose-response analysis) suggested little asymmetry for CHD (Supplemental Figure 25), but not for stroke (Supplemental Figure 26).

There was no evidence of a non-linear dose-response association for CHD ($p_{non\text{-}linearity}$=0.19, n=13 studies), but there was for stroke ($p_{non\text{-}linearity}$=0.03, n=8 studies). The risk of CHD and stroke decreased by approximately 12% with increasing intake of vegetables up to ~400 g/d. Additional benefit for increasing intake is apparent above this value for CHD but not for stroke (Figure 2 and 3).

Fruit

Seventeen studies with 17,827 cases were included in the high vs. low intake meta-analysis for fruit and CHD (overall intake range: 0−1820 g/d), 17 studies with 30,523 cases for stroke (overall intake range: 0−595 g/d), and 3 studies with 6,267 cases for HF (overall intake range: 50−300 g/d) for HF.

Comparing the highest to the lowest categories of fruit intake, an inverse association was observed for risk of CHD (RR: 0.89; 95% CI 0.84 to 0.93, I^2=10%, $p_{heterogeneity}$=0.34), stroke (RR: 0.83; 95% CI 0.77 to 0.89, I^2=40%, $p_{heterogeneity}$=0.05), and risk of HF (RR: 0.95; 95% CI 0.88 to 1.02, I^2=0%, $p_{heterogeneity}$=0.73) (Supplemental Figure 7).

Each additional daily 100 g of fruit were inversely associated with risk of CHD (RR: 0.94; 95% CI 0.90 to 0.97, I^2=71%, $p_{heterogeneity}$<0.001, n=13) and stroke (RR: 0.90; 95% CI 0.84 to 0.97, I^2=86%, $p_{heterogeneity}$<0.001, n=10), but not with risk of HF (RR: 0.98; 95% CI 0.94 to 1.01, n=1) (Supplemental Figure 8).

No evidence of heterogeneity was detected between subgroups in stratified analyses (high vs. low meta-analysis) on fruit and CHD (Supplemental Table 17a), whereas some evidence of heterogeneity was observed for stroke (follow-up and geographic location) (Supplemental Table

17b). In analyses stratified by subgroups (dose-response meta-analysis), the inverse association between fruit intake and CHD risk was not observed in studies including only women, in European, Asian and Australian studies, in studies with <1,000 cases, and studies using non-validated dietary assessment (Supplemental Table 17c). These subgroup-differences were not statistically significant, with one exception; after stratification by included number of cases, heterogeneity was observed (borderline significant p=0.05), showing an inverse association between fruit intake and risk of CHD only for studies including ≥1,000 cases. Referring to stroke, we observed evidence of heterogeneity in subgroups stratified for geographical location, showing greatest risk reduction for studies conducted in Asia and Australia (Supplemental Table 17d).

There was evidence for small study effects, in the high vs. low (p=0.08) analysis for stroke, and in the dose-response analysis for CHD (p=0.04). Visual inspection of the funnel plots (dose-response analysis) suggested little symmetry (Supplemental Figure 27 and 28).

There was evidence of a non-linear dose-response association for CHD ($p_{non\text{-}linearity}$<0.001, n=12 studies), but not for stroke ($p_{non\text{-}linearity}$=0.54, n=8 studies). The risk of CHD and stroke decreased by approximately 15% and 20% with increasing intake of fruit up to ~200 g/d, respectively. No benefit for increasing intake was apparent above this value (Figure 2 and 3).

Nuts

Four studies with 5,480 cases were included in the high vs. low intake meta-analysis for nuts and CHD (overall intake range: 0−28 g/d), 6 studies with 7,490 cases for stroke (overall intake range: 0−38 g/d) and 3 studies with 3,613 cases for HF (overall intake range: 0−30 g/d).

Comparing the highest to the lowest categories of nut intake revealed a trend for an inverse association between nut intake and risk of CHD (RR: 0.80; 95% CI 0.62 to 1.03, I^2=79%, $p_{heterogeneity}$=0.002), which was not present in the case of stroke (RR: 0.94; 95% CI 0.85 to 1.05, I^2=18%, $p_{heterogeneity}$=0.30) and HF (RR: 0.99; 95% CI 0.86 to 1.15, I^2=57%, $p_{heterogeneity}$=0.10) (Supplemental Figure 9).

An inverse association was observed for each additional daily 28 g of nuts and risk of CHD (RR: 0.67; 95% CI 0.43 to 1.05, I^2=85%, $p_{heterogeneity}$=0.001, n=4), but not for stroke (RR: 0.99; 95% CI 0.84 to 1.17, I^2=45%, $p_{heterogeneity}$=0.11, n=6) or HF (RR: 1.09; 95% CI 0.97 to 1.22, I^2=0%, $p_{heterogeneity}$=0.79, n=2) (Supplemental Figure 10).

No important evidence of heterogeneity was detected between subgroups in stratified analyses on nuts consumption and risk of stroke in the categorical and dos-response meta-analysis (Supplemental Table 18a-b).

There was evidence of a non-linear dose-response association for CHD ($p_{non-linearity}$<0.001, n=4 studies) and stroke ($p_{non-linearity}$=0.05, n=5 studies). The risk of CHD decreased by approximately 21% with increasing intake of nuts up to ~10-15 g/d. No benefit for increasing intake was apparent above this value (Figure 2). No association was observed for nut intake and risk of stroke in the non-linear dose-response analysis (Figure 3).

Legumes

For legumes, 10 studies with 8,228 cases were included in the high vs. low intake meta-analysis for CHD (overall intake range: 0−230 g/d) and 6 studies with 6,333 cases for stroke (overall intake range: 0−60 g/d). No study was available on HF.

Comparing the highest to the lowest categories of legume intake, an inverse association between legume intake and risk of CHD (RR: 0.91; 95% CI 0.84 to 0.99, I^2=33%, $p_{heterogeneity}$=0.14), but not with risk of stroke (RR: 0.98; 95% CI 0.88 to 1.10, I^2=56%, $p_{heterogeneity}$=0.04) was observed (Supplemental Figure 11).

A small inverse association was observed for each additional daily intake of 50 g of legumes and risk of CHD (RR: 0.96; 95% CI 0.92 to 1.01, I^2=39%, $p_{heterogeneity}$=0.12, n=8), but not for stroke (RR: 1.00; 95% CI 0.88 to 1.13, I^2=62%, $p_{heterogeneity}$=0.02, n=6) (Supplemental Figure 12).

No association was observed in any of the stratified analyses, neither for CHD nor for stroke (Supplemental Table 19a-d).

No evidence for small study effects was observed in the high vs. low intake analysis of legumes and risk of CHD. Some evidence of a non-linear dose-response association was observed for CHD ($p_{non\text{-}linearity}$=0.07, n=8 studies), but not for stroke ($p_{non\text{-}linearity}$=0.08, n=5 studies). The risk of CHD decreased by approximately 10% with increasing intake of legumes up to ~100 g/d (Figure 2). No benefit for increasing intake was apparent above this value (Figure 2). No association was observed for legume intake and risk of stroke in the non-linear dose-response analysis (Figure 3).

Eggs

For eggs, 11 studies with 14,370 cases were included in the high vs. low intake meta-analysis (overall intake range: 0−75 g/d) for CHD, 10 studies with 12,735 cases (overall intake range: 0−75 g/d) for stroke and 4 studies with 5,059 cases (overall intake range: 0−140 g/d) for HF.

Comparing the highest to the lowest categories of egg intake, no association between egg intake and risk of CHD (RR: 0.99; 95% CI 0.94 to 1.05, I^2=0%, $p_{heterogeneity}$=0.49) or risk of stroke (RR:

0.99; 95% CI 0.93 to 1.05, I^2=3%, $p_{heterogeneity}$=0.41) was observed. A positive association between egg intake and risk of HF (RR: 1.25; 95% CI 1.12 to 1.39, I^2=0%, $p_{heterogeneity}$=0.46) was detected (Supplemental Figure 13).

In the dose-response meta-analysis, there was no association between each increment of 50 g of daily egg intake and risk of CHD (RR: 1.00; 95% CI 0.95 to 1.06, I^2=0%, $p_{heterogeneity}$=0.93, n=9) or stroke (RR: 0.99; 95% CI 0.93 to 1.05, I^2=0%, $p_{heterogeneity}$=0.44, n=10) but with risk of HF (RR: 1.16; 95% CI 1.03 to 1.31, I^2=55%, $p_{heterogeneity}$=0.08, n=4) (Supplemental Figure 14).

No association was observed in any of the stratified analyses, neither for eggs and CHD nor for eggs and stroke (Supplemental Table 20a-d).

No evidence for small study effects was observed in the high vs. low intake meta-analysis for eggs and CHD, as was also the case for stroke both in the high vs. low and dose-response analysis. Visual inspection of the funnel plots (dose-response analysis) suggests moderate asymmetry (Supplemental Figure 29).

There was no evidence of a non-linear dose-response association for CHD ($p_{non\text{-}linearity}$=0.81, n=9 studies), and stroke ($p_{non\text{-}linearity}$=0.39, n=9 studies) (Figure 2 and 3), but there was for HF ($p_{non\text{-}linearity}$=0.04, n=3 studies). The risk of HF increased by approximately 50% with increasing intake of egg up to ~100 g/d (Supplemental Figure 34). No association was observed for egg intake and risk of CHD and stroke in the non-linear dose-response analysis.

Dairy

Thirteen studies with 15,790 cases were included in the high vs. low intake meta-analysis for dairy and CHD (overall intake range: 0−3000 g/d), 12 studies with 16,887 cases for stroke

(overall intake range: 0−1860 g/d), and 3 studies with 4,057 cases for HF (overall intake range: 0−1390 g/d).

Comparing the highest to the lowest categories of dairy intake, no associations between dairy intake and risk of CHD (RR: 0.99; 95% CI 0.92 to 1.07, I^2=59%, $p_{heterogeneity}$=0.004), stroke (RR: 0.96; 95% CI 0.90 to 1.01, I^2=43%, $p_{heterogeneity}$=0.05), or HF (RR: 1.00; 95% CI 0.90 to 1.10, I^2=67%, $p_{heterogeneity}$=0.05) were observed (Supplemental Figure 15).

Each additional daily 200 g of dairy were not associated with risk of CHD (RR: 0.99; 95% CI 0.96 to 1.02, I^2=55%, $p_{heterogeneity}$=0.02, n=10) or stroke (RR: 0.98; 95% CI 0.96 to 1.00, I^2=50%, $p_{heterogeneity}$=0.03, n=11), but were positively associated with risk of HF (RR: 1.08; 95% CI 1.01 to 1.15, n=1) (Supplemental Figure 16).

No association between dairy intake and risk of CHD was observed in any of the stratified analyses (Supplemental Table 21a and c). Referring to stroke, we observed heterogeneity in subgroups stratified for sex (dose-response) and geographical location, showing an inverse association in women and in American studies only (Supplemental Table 21b and d).

Comparing low-fat and high-fat dairy products, no significant differences could be observed for CHD and stroke.

There was no evidence of small study effects in the high vs. low and dose-response meta-analysis for dairy and CHD, and for dairy and stroke. Visual inspection of the funnel plots (dose-response analysis) suggests moderate symmetry (Supplemental Figure 30 and 31).

There was evidence of a non-linear dose-response association between dairy products and CHD ($p_{non\text{-}linearity}$<0.01, n=9 studies), but not for stroke ($p_{non\text{-}linearity}$=0.71, n=8 studies). The risk of

stroke decreased by approximately 5% with increasing intake of dairy intake up to ~500 g/d (Figure 3), whereas no association was observed for CHD (Figure 2).

Fish

For fish, 22 studies with 16,732 cases were included in the high vs. low intake meta-analysis (overall intake range: 0−320 g/d) for CHD, 20 studies with 14,360 cases (overall intake range: 0−130 g/d) for stroke, and 8 studies with 7,945 cases (overall intake range: 0−80 g/d) for HF. Comparing the highest to the lowest categories, a small inverse association between fish intake and risk of CHD (RR: 0.94; 95% CI 0.88 to 1.02, I^2=52%, $p_{heterogeneity}$=0.003) or stroke (RR: 0.95; 95% CI 0.89 to 1.01, I^2=37%, $p_{heterogeneity}$=0.05), and a stronger inverse association between fish intake and risk of HF (RR: 0.89; 95% CI 0.80 to 0.99, I^2=18%, $p_{heterogeneity}$=0.29) was observed (Supplemental Figure 17).

Each additional daily 100 g of fish were inversely associated with risk of CHD (RR: 0.88; 95% CI 0.79 to 0.99, I^2=40%, $p_{heterogeneity}$=0.06, n=15), stroke (RR: 0.86; 95% CI 0.75 to 0.99, I^2=25%, $p_{heterogeneity}$=0.18, n=15), and HF (RR: 0.80; 95% CI 0.67 to 0.95, I^2=20%, $p_{heterogeneity}$=0.28, n=7) (Supplemental Figure 18).

No important evidence of heterogeneity was detected between subgroups in stratified analyses (high vs. low meta-analysis) on fish consumption and risk of CHD and stroke (Supplemental Table 22a-b). We observed heterogeneity in subgroups (dose-response meta-analysis) stratified for sex, showing an inverse association between fish intake and CHD solely in the study including women only (Supplemental Table 22c). Referring to stroke (dose-response meta-analysis), there was an inverse association observed in studies including women only, long-term

studies and studies using validated dietary assessment (Supplemental Table 22d). These subgroup-differences were not statistically significant.

There was no evidence of small study effects in the high vs. low analysis for CHD or in the dose-response meta-analysis for CHD and stroke, but there was in the high vs. low analysis for stroke (p=0.07). Visual inspection of the funnel plots (dose-response analysis) suggests little symmetry (Supplemental Figure 32 and 33).

There was no evidence of a non-linear dose-response association between fish intake and CHD ($p_{non\text{-}linearity}$=0.10, n=15 studies), stroke ($p_{non\text{-}linearity}$=0.37, n=15 studies), or HF ($p_{non\text{-}linearity}$=0.14, n=6 studies). The risk of CHD decreased by approximately 15% with increasing intake of fish up to ~250 g/d (Figure 2), whereas the risk of stroke and HF decreased by approximately 10 and 20% with increasing intake of fish up to ~80-100 g/d, respectively (Figure 3 and Supplemental Figure 35).

Red meat

For red meat, 3 studies with 6,659 cases were included in the high vs. low intake meta-analysis (overall intake range: 9−205 g/d) for CHD, 7 studies with 10,541 cases (overall intake range: 6−195 g/d) for stroke, and 5 studies with 9,229 cases (overall intake range: 0−175 g/d) for HF.

Comparing the highest to the lowest categories, a positive association between red meat intake and risk of CHD (RR: 1.16; 95% CI 1.08 to 1.24, I^2=0%, $p_{heterogeneity}$=0.89), stroke (RR: 1.16; 95% CI 1.08 to 1.25, I^2=0%, $p_{heterogeneity}$=0.69), and HF (RR: 1.12; 95% CI 1.04 to 1.21, I^2=26%, $p_{heterogeneity}$=0.25) was observed (Supplemental Figure 19).

In the dose-response meta-analysis, each additional daily 100 g of red meat were positively

associated with risk of CHD (RR: 1.15; 95% CI 1.08 to 1.23, I^2=0%, $p_{heterogeneity}$=0.68, n=3), stroke (RR: 1.12; 95% CI 1.06 to 1.17, I^2=0%, $p_{heterogeneity}$=0.50, n=7), and HF (RR: 1.08; 95% CI 1.02 to 1.14, I^2=4%, $p_{heterogeneity}$=0.37, n=4) (Supplemental Figure 20).

No evidence of heterogeneity was detected between subgroups in stratified analyses on red meat and stroke. The observed positive association between red meat intake and stroke risk was not seen in studies including both women and men, short-term studies, European studies and studies including <1,000 stroke cases (Supplemental Table 23a-b).

There was evidence of a non-linear dose-response association between red meat and CHD ($p_{non-linearity}$<0.01, n=2 studies), and HF ($p_{non-linearity}$=0.02, n=3 studies), but not for stroke ($p_{non-linearity}$=0.91, n=6 studies). The risk of CHD, stroke, and HF increased by approximately 10-20% with increasing intake of red meat up to ~100 g/d (Figure 2, 3, and Supplemental Figure 36).

Processed meat

For processed meat, 5 studies with 7,038 cases were included in the high vs. low intake meta-analysis (overall intake range: 0−150 g/d) for CHD, 6 studies with 9,492 cases (overall intake range: 0−85 g/d) for stroke, and 3 studies with 7,077 cases (overall intake range: 12−90 g/d) for HF.

Comparing the highest to the lowest categories, a positive association between processed meat intake and risk of CHD (RR: 1.15; 95% CI 0.99 to 1.33, I^2=44%, $p_{heterogeneity}$=0.13), stroke (RR: 1.16; 95% CI 1.07 to 1.26, I^2=12%, $p_{heterogeneity}$=0.34) and HF (RR: 1.27; 95% CI 1.14 to 1.41, I^2=0%, $p_{heterogeneity}$=0.87) was observed (Supplemental Figure 21).

Each additional daily 50 g of processed meat were positively associated with risk of CHD (RR:

1.27; 95% CI 1.09 to 1.49, I^2=0%, $p_{heterogeneity}$=0.51, n=3), stroke (RR: 1.17; 95% CI 1.02 to 1.34, I^2=56%, $p_{heterogeneity}$=0.05, n=6), and HF (RR: 1.12; 95% CI 1.05 to 1.19, I^2=0%, $p_{heterogeneity}$=0.62, n=2) (Supplemental Figure 22).

Referring to stroke, there was evidence of heterogeneity in subgroups stratified for geographical location, showing a stronger association in studies conducted in America compared to studies conducted in Europe ($p_{heterogeneity}$=0.02; Supplemental Table 24a-b).

There was no evidence of a non-linear dose-response association between processed meat and CHD ($p_{non-linearity}$=0.41, n=2 studies), stroke ($p_{non-linearity}$=0.65, n=6 studies), or HF ($p_{non-linearity}$=0.62, n=2 studies). The risk of stroke increased by approximately 15% (Figure 3), and the risk of HF by 25% with increasing intake of processed meat up to ~70 g/d (Figure 3, and Supplemental Figure 37). No associations were observed for processed meat and CHD (Figure 2).

Sugar-sweetened beverages

Five studies with 8,740 cases were included in the high vs. low intake meta-analysis for SSB and CHD (overall intake range: 0−650 g/d), 7 studies with 11,187 cases for stroke (overall intake range: 0−2500 g/d), and 2 studies with 8,603 cases for HF (overall intake range: 0−625 g/d).

Comparing the highest to the lowest categories, a positive association between SSB intake and risk of CHD (RR: 1.10; 95% CI 1.01 to 1.20, I^2=50%, $p_{heterogeneity}$=0.09) and stroke (RR: 1.09; 95% CI 1.01 to 1.18, I^2=0%, $p_{heterogeneity}$=0.43), but no association with HF risk (RR: 1.11; 95% CI 0.88 to 1.39, I^2=81%, $p_{heterogeneity}$=0.02) were observed (Supplemental Figure 23).

Each additional daily 250 ml of SSB were positively associated with risk of CHD (RR: 1.17;

95% CI 1.11 to 1.23, I^2=0%, $p_{heterogeneity}$=0.66, n=4), stroke (RR: 1.07; 95% CI 1.02 to 1.12, I^2=0%, $p_{heterogeneity}$=0.59, n=6), and HF (RR: 1.08; 95% CI 1.05 to 1.12, n=1) (Supplemental Figure 24).

Referring to stroke, the positive association with SSB intake was no longer statistically significant in studies including women or both women and men, in an Asian and Australian study and in a study including <1,000 stroke cases. However, no evidence for subgroup-differences was observed (Supplemental Table 25a-b).

There was no evidence of a non-linear dose-response association between SSB and CHD ($p_{non-linearity}$=0.83, n=4 studies), or stroke ($p_{non-linearity}$=0.83, n=6 studies). The risk of CHD increased by approximately 35%, and the risk of stroke by 16% with increasing intake of SSB up to ~500 ml/d (Figure 2 and 3).

Summary across food groups

Table 1 and 2 show the risk ratios for CHD and stroke from the non-linear dose-response analyses of the 12-pre-definded food groups according to servings/day. Optimal consumption (lowest serving with significant results and no further substantial change in CHD risk or no further data for higher amounts) of risk-decreasing foods would result in a 65% reduction in CHD, and a 40% reduction in stroke risk (calculated by $1 - RR^{*}_{reduced}$) compared to non-consumption of these foods.

Furthermore, Table 1 shows that increasing the daily consumption of foods with an inverse relation to risk beyond 3 servings/d of whole grains (90 g/d), and 3 servings/d of fruits (~250 g/d), and 1 serving/d (~100 g/d) of legumes would not further reduce the risk of CHD.

We could further calculate that a consumption of risk-increasing food of 2 servings/d of red meat (170 g, RR=1.20), 2 servings/d of processed meat (60g, RR=1.16) and 2 servings/d of SSB (500 ml, RR=1.16), was associated with a 60% increased risk of stroke (i.e., $\mathrm{RR}^{*}_{\mathrm{increased}} = 1.60$) compared to non-consumption. Not consuming these foods would reduce the risk of stroke of about 38% (calculated by $1 - \frac{1}{\mathrm{RR}^{*}_{\mathrm{increased}}}$).

Risk of bias and sensitivity analysis

The results varied little when including only studies with a low risk of bias (Supplemental Table 26). In the sensitivity analysis for linear dose-response meta-analysis, findings including studies with low risk of bias suggested a weaker inverse association for intake of fruit and a stronger inverse association for whole grain intake regarding risk of CHD. The inverse association between fish intake and CHD was not longer significant in the linear dose-response meta-analysis including studies with low risk of bias. For risk of stroke, stronger inverse associations were also observed for intake of fruit and fish.

In the sensitivity analyses excluding the three identified nested-case control studies (Neelakantan et al., 2016; Wennberg et al., 2011; Wennberg et al., 2007), and studies reporting Odds ratios (Holmberg et al., 2009; Wennberg et al., 2011; Wennberg et al., 2007) no changes in the results of the main analysis were detected.

Quality of meta-evidence

We rated the quality of meta-evidence for the 12 food groups regarding risk of CHD, stroke and HF. The NutriGrade meta-evidence grading regarding CHD was rated “low” for refined grains, and eggs and “moderate” for the 10 other food groups. The NutriGrade meta-evidence grading regarding stroke was rated “low” for whole grains, refined grains, nuts and legumes and “moderate” for the eight other food groups. Regarding HF, the NutriGrade meta-evidence grading was rated “very low” for refined grains and “low” for whole grains, vegetables, fruit, nuts, dairy, and SSB and “moderate” for eggs, fish, red meat, and processed meat (Supplemental Table 27a-c).

Discussion

The associations between 12 a priori defined food groups and risk of CHD, stroke, and HF were systematically assessed in this meta-analysis through comparison of the highest to the lowest categories and dose-response analyses both for linear and non-linear relationships. In the linear dose-response meta-analysis, an inverse association for was present for whole grain (CHD, HF), vegetables (CHD, stroke, HF), fruit (CHD, stroke), nuts (CHD), legumes (CHD), and fish (CHD, stroke, HF) consumption, while a positive association was present for egg (HF), dairy (HF), red meat (CHD, stroke, HF), processed meat (CHD, stroke, HF), and SSB (CHD, stroke, HF) consumption. There was clear indication for non-linearity between intake of whole grain, fruit, nuts, dairy, red meat and risk of CHD, and intake of vegetables and risk of stroke. The NutriGrade tool for evaluating the meta-evidence suggested a moderate confidence in the effect estimate for eggs, dairy, fish, red meat, and processed meat with respect to all three outcomes simultaneously; the confidence in the effect estimate for the other relationships was lower. The maximum moderate quality of evidence implies that further research could or will add evidence on the confidence and may change the effect estimate.

Our findings are in line with previous meta-analyses conducted mostly on single food groups and not synoptically for 12 food groups and often not separately for individual CVD outcomes. Moreover, this is to our knowledge, the first meta-analysis that investigated the association between whole grain intake and HF, showing an inverse association. The observed inverse association between whole grain intake and risk of CHD is consistent with results from

previous meta-analyses on CHD (Anderson et al., 2000; Aune et al., 2016b; Mellen et al., 2008; Mente et al., 2009; Tang et al., 2015). The essential nutrients along with the phytonutrients and fibre present in whole grains may synergistically contribute to their beneficial effects. A number of mechanisms have been suggested for the risk reduction associated with whole grains; for example, reduction of LDL-cholesterol concentrations through soluble fiber; the antioxidant and anti-inflammatory properties, possibly due to the presence of polyphenols and other phytonutrients; modulation of blood glucose and insulin responses, improving vascular function and blood pressure, and weight control (Jonnalagadda et al., 2011).

For vegetables and fruit, our results are similar to previous meta-analyses that revealed an inverse association between intake and CHD (Gan et al., 2015; Mente et al., 2009) (Dauchet et al., 2006; He et al., 2007), and stroke risk (Aune et al., 2017; He et al., 2006; Hu et al., 2014). While we detected no further risk reduction beyond intake of 250g fruit per day, another current meta-analysis showed reductions in risk up to 800g per day. This difference could be explained by the greater number of studies (due to inclusion of studies on cause-specific mortality and overall CVD) included by Aune et al. (Aune et al., 2017). Vegetables and fruit, like the nutrients and phytochemicals therein, influence not only inflammatory processes, but also cellular redox processes as well as endothelial and metabolic processes; it is assumed that these mechanisms are primarily responsible for the risk-reducing association between vegetable and fruit consumption and risk of cardiovascular and other diseases (Boeing et al., 2012).

We observed a trend for a strong inverse association between nut consumption and risk of CHD. In line with this, previous analyses found that higher nut consumption is associated with reduced CHD risk (Afshin et al., 2014; Aune et al., 2016a; Kelly and Sabate, 2006; Ma et al.,

2014; Mayhew et al., 2016; Mente et al., 2009; Weng et al., 2016). An umbrella review found an inverse association of nut intake and risk of CVD, hypertension, and lower levels of total cholesterol and LDL-cholesterol. Plausible mechanisms how the consumption of nuts can affect cardiovascular risk are through their content of unsaturated fatty acids, protein, fiber, vitamin E, potassium, magnesium, and phytochemicals (Schwingshackl et al., 2017b).

Despite the absence of a linear association between legumes and investigated outcomes, the non-linear analysis showed a 10% reduction in CHD risk when consuming up to 100 g/d. Results from previous analyses provide moderate evidence for a benefit on CHD (Afshin et al., 2014; Lou et al., 2016; Marventano et al., 2017; Yan et al., 2017). Legumes are good sources of fiber, protein, and some bioactive compounds such as phytosterols. These components have shown inverse associations with total cholesterol, triacylglycerol and LDL-cholesterol concentrations, and a positive association with HDL-cholesterol concentrations in pooled analyses of intervention trials (Anderson and Bush, 2011). Other bioactive compounds in legumes are protein-derived bioactive peptides that have been found to have blood pressure- and cholesterol-lowering effects, as well as antithrombotic and antioxidant activities in in vitro studies (Malaguti et al., 2014).

We observed a positive association between egg consumption and HF risk, as is the case in another current analysis based on the same 4 cohort studies, but not performing dose-response analysis (Khawaja et al., 2017). Eggs are a major source of dietary choline and consumption results in increased exposure to trimethylamine-*N*-oxide, a metabolite linked to atherosclerosis (Miller et al., 2014; Senthong et al., 2016). At the same time, egg yolks are a source of bioavailable xanthophyll carotenoids with anti-inflammatory, anti-oxidative and anti-

atherosclerotic effects that may possibly promote cardiovascular health (Clayton et al., 2017). Because definite mechanisms of possible effects of eggs and observed relationships are not clear and vary regarding individual outcomes, respectively, the association between egg consumption and HF should be interpreted with caution.

Authors of a previous meta-analysis suggested an inverse association between dairy products consumption and risks of CHD and stroke, but demanded additional data to more comprehensively examine potential dose-response patterns (Alexander et al., 2016). In linear dose-response analysis we observed an 8% increased HF risk by each additional daily 200 g of dairy. Despite the absence of a linear association between dairy intake and stroke, the non-linear analysis showed a 5% reduction in stroke risk when consuming up to 500 g/d. A recent meta-analysis observed no association between dairy intake and CHD incidence, too (Gholami et al., 2017). Dairy products are a rich source of minerals, such as calcium, vitamins and protein; all of these nutrients may have a beneficial effect on cardiovascular health. Otherwise, dairy products contain saturated fatty acids, and the potential role of saturated fatty acids and cardiovascular health is controversial (Mozaffarian, 2016). Furthermore, there is some evidence that dairy products, especially those that are fermented, are associated with reduced risk of adiposity (Schwingshackl et al., 2016b). Due to inconclusive findings, recommendations on dairy consumption relating to cardiovascular health can-not be given yet.

Our analysis confirmed the well-established risk-decreasing potential of fish on CHD (Leung Yinko et al., 2014; Mente et al., 2009; Whelton et al., 2004), on stroke (Bouzan et al., 2005; Chowdhury et al., 2012; He et al., 2004; Larsson and Orsini, 2011; Xun et al., 2012), and on HF (Djousse et al., 2012; Li et al., 2013). The non-linear analyses showed that CHD risk was

reduced by 15% with increasing fish consumption up to 250 g/d and a 10 and 20 % reduction in risk of stroke and HF, respectively, with up to 80-100 g/d. This association is biologically plausible through effects of long chain n-3 poly-unsaturated fatty acids, which are abundant in fatty fish and have been associated with anti-atherosclerotic and anti-thrombotic effects (Chapkin et al., 2007; Saravanan et al., 2010). In observational studies, very-long chain n-3 poly-unsaturated fatty acids can be used as valid markers for habitual fish intake (Amiano et al., 2001). With this in mind, a large meta-analysis of observational studies showed that circulating long-chain n-3 poly-unsaturated fatty acids were associated with lower risk of coronary disease (Chowdhury et al., 2014). Although, the risk-decreasing potential of fish is well established and confirmed by the results of our meta-analysis, the unavoidable presence of environmental contaminants (Domingo, 2016) and aspects of sustainability should be also taken into account, if larger amounts were consumed.

We observed positive associations between red meat intake and CHD, stroke, and HF risk. Consuming red meat up to 150 g/d is associated with a 10-20% increased risk in non-linear dose-response analyses. Furthermore, we observed positive associations between processed meat intake and stroke, and HF risk. The non-linear analyses showed a 15% and 25% increased risk of stroke and HF, respectively, consuming processed meat up to 70 g/d. A positive association has been previously reported between consumption of red and especially processed meat and CHD and stroke risk, but, to our knowledge, it has not been reported on HF risk (Chen et al., 2013; Kaluza et al., 2012; Mente et al., 2009; Micha et al., 2012; Micha et al., 2010; Yang et al., 2016). Unfavorable associations with food groups such as red and processed meat might be based upon

pro-inflammatory or pro-oxidative compounds, triggered by nitrosamines, iron, or saturated fatty acids (Mozaffarian, 2016).

There is evidence that SSB intake is related to vascular risk factors, whereas associations with CVD were less consistent (Keller et al., 2015) and possibly a consequence of SSB consumption being a surrogate for adverse health behaviours (Narain et al., 2016). Our meta-analyses add moderate evidence for a risk-increasing association between SSB intake and CHD and stroke. The non-linear analyses show a 35% increased risk of CHD and a 16% increased risk of stroke by consuming up to 500 ml/d. The risk-increasing association observed for SSB may be partly attributed to impairments of the otherwise working regulation of hunger and satiety (DiMeglio and Mattes, 2000). Evidence of a positive association between SSB consumption and weight gain and obesity in adults is strong (Malik et al., 2013); obesity is an important risk factor for CVD.

The results of the present meta-analysis add further scientific evidence supporting the inclusion of some food groups into food-based dietary guidelines aimed at CVD prevention. Optimal consumption of whole grains, vegetables, fruit, nuts, legumes, dairy, and fish was associated with a 65% reduced risk of CHD and optimal consumption of vegetables, fruit, dairy, and fish was associated with a 40 % stroke reduction. Reducing the consumption of the risk-increasing food groups red meat, processed meat, SSB, eggs and dairy in relation to HF is preventive, too.

Our results support current food-based dietary guidelines that promote the consumption of a dietary pattern that emphasizes intake of vegetables, fruit, and whole grains and includes,

among other foods, legumes, nuts and fish, while it limits intake of red meat and processed meat and SSB as a "heart healthy" diet (Eckel et al., 2014; Perk et al., 2012; USDA., 2015). Our results however do not support the recommendation to include low-fat dairy products. To obtain a complete picture it seems useful to extend the type of food groups to be considered.

Strengths and limitations

Among the strengths of the present meta-analysis are the a priori published systematic review protocol (Schwingshackl et al., 2016a), the comprehensive literature search, the large number of included prospective studies, cases, and food groups. Furthermore, we performed different types of analyses (high vs. low, linear and non-linear dose-response meta-analyses, subgroup and sensitivity analyses), which allowed us to detect associations where the relation was non-linear and find an optimal consumption with the lowest risk of all-cause mortality. Finally, it is a strength of this study that the quality of meta-evidence for each food group was assessed with the NutriGrade scoring system.

A limitation of this systematic review is that for some of the included studies, only baseline food intake could be used (assuming a stable consumption over time). Furthermore, there was substantial heterogeneity with respect to the analyzed population size, follow-up length, baseline age, and food consumption. We conducted subgroup analyses for sex, length of follow-up, geographic location, number of cases, and dietary assessment methods to explore high degrees of statistical heterogeneity. Overall, for most food groups high levels of statistical heterogeneity persisted in subgroup analyses. People with a high intake of whole grains, vegetables, fruit, nuts, legumes or fish might have different lifestyles, or socioeconomic status

compared to those with lower intakes, representing important confounders (Darmon and Drewnowski, 2008). However, in sensitivity analyses including only studies with a low risk of bias (adjusted for important lifestyle factors: smoking, physical activity, body mass index), the results of the primary analysis were confirmed. For most food groups in association with HF, a very limited amount of studies was found. Therefore, some of these results should be interpreted with caution. Finally, another major limitation explaining differences between results of our and other meta-analyses on specific food groups could be that we did not include prospective studies on overall CVD and on outcome-specific mortality.

Conclusion

An optimal intake of whole grains, vegetables, fruit, nuts, legumes, dairy, fish, red and processed meat, eggs and SSB showed an important lower risk of CHD, stroke and HF. Even though quality of meta-evidence according to NutriGrade is moderate, the results of this comprehensive meta-analysis may serve as key component in deriving food-based dietary guidelines for prevention of CVD.

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NM, SDH drafted this paper. All authors provided critical revisions of the meta-analysis and approved submission of the final manuscript.

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Food group	Risk Ratio (RR), 95% CI						
Inverse association							
Servings per day	0	1	2	3	4	5	6
Whole grains (1 serving = 30g/d)	1.00	0.91 (0.88, 0.95)	0.86 (0.80, 0.92)	0.83 (0.78, 0.90)	0.83 (0.77, 0.89)	0.83 (0.77, 0.90)	0.83 (0.77, 0.91)
Vegetables (1 serving = 80g/d)	1.00	0.96 (0.94, 0.98)	0.92 (0.89, 0.96)	0.90 (0.86, 0.94)	0.88 (0.84, 0.93)	0.88 (0.83, 0.92)	0.87 (0.82, 0.92)
Fruit (1 serving = 80g/d)	1.00	0.89 (0.86, 0.93)	0.84 (0.80, 0.89)	0.83 (0.79, 0.89)	0.83 (0.79, 0.89)	0.86 (0.75, 0.96)	NA
Nuts (1 serving = 28g/d)	1.00	0.84 (0.73, 0.97)	NA	NA	NA	NA	NA
Legumes (1 serving = 100g/d)	1.00	0.89 (0.81, 0.97)	0.90 (0.81, 1.01)	NA	NA	NA	NA
Dairy (1 serving = 200g/d)	1.00	0.96 (0.92, 0.99)	0.96 (0.92, 1.01)	1.02 (0.96, 1.07)	NA	NA	NA
Fish (1 serving = 100g/d)	1.00	0.91 (0.86, 0.96)	0.87 (0.78, 0.97)	0.83 (0.70, 0.98)	NA	NA	NA
Positive association							
SSB (1 serving= 250ml/d)	1.00	1.15 (1.07, 1.23)	1.36 (1.19, 1.57)	NA	NA	NA	NA
No association							
Refined grains (1 serving = 30g/d)	1.00	0.99 (0.94, 1.04)	0.99 (0.90, 1.08)	0.99 (0.88, 1.12)	1.01 (0.88, 1.17)	1.04 (0.90, 1.20)	1.10 (0.94, 1.27)
Eggs (1 serving = 55g/d)	1.00	1.02 (0.96, 1.09)	NA	NA	NA	NA	NA

Red meat (1 serving = 85g/d)	1.00	1.09 (0.98, 1.20)	NA	NA	NA	NA	NA
Processed meat (1 serving = 30g/d)	1.00	1.11 (0.94, 1.31)	NA	NA	NA	NA	NA

Table 1: Relative risks from non-linear dose-response analysis of 12 pre-defined food groups and risk of coronary heart disease according to intakes of servings/day. NA, not applicable

Food group	Risk Ratio (RR), 95% CI						
Inverse association							
Servings per day	0	1	2	3	4	5	6
Vegetables (1 serving = 80g/d)	1.00	0.93 (0.90, 0.97)	0.90 (0.84, 0.95)	0.90 (0.84, 0.95)	0.91 (0.85, 0.97)	0.92 (0.84, 1.01)	NA
Fruit (1 serving = 80g/d)	1.00	0.86 (0.83, 0.89)	0.80 (0.77, 0.85)	0.80 (0.74, 0.86)	0.80 (0.72, 0.88)	0.81 (0.68, 0.96)	NA
Dairy (1 serving = 200g/d)	1.00	0.98 (0.95, 1.00)	0.96 (0.92, 1.00)	0.95 (0.91, 1.00)	0.95 (0.91, 1.00)	0.96 (0.91, 1.01)	NA
Fish (1 serving = 100g/d)	1.00	0.89 (0.79, 1.00)	NA	NA	NA	NA	NA
Positive association							
Red meat (1 serving = 85g/d)	1.00	1.10 (1.03, 1.16)	1.20 (1.10, 1.31)	NA	NA	NA	NA
Processed meat (1 serving = 30g/d)	1.00	1.13 (1.06, 1.21)	1.16 (1.04, 1.28)	NA	NA	NA	NA
SSB (1 serving = 250ml/d)	1.00	1.07 (1.01, 1.13)	1.16 (1.06, 1.26)	NA	NA	NA	NA
No association							
Whole grains (1 serving = 30g/d)	1.00	0.97 (0.90, 1.03)	0.95 (0.87, 1.04)	0.93 (0.80, 1.07)	0.92 (0.79, 1.08)	0.92 (0.78, 1.09)	0.93 (0.79, 1.10)
Refined grains (1 serving = 30g/d)	1.00	1.00 (0.98, 1.02)	0.99 (0.95, 1.04)	0.99 (0.93, 1.05)	0.99 (0.92, 1.06)	0.98 (0.92, 1.06)	0.98 (0.91, 1.06)
Nuts (1 serving = 28g/d)	1.00	1.07 (0.93, 1.22)	NA	NA	NA	NA	NA
Legumes	1.00	0.98	NA	NA	NA	NA	NA

(1 serving = 100g/d)		(0.86, 1.11)					
Eggs (1 serving = 55g/d)	1.00	0.99 (0.92, 1.06)	NA	NA	NA	NA	NA

Table 2: Relative risks from non-linear dose-response analysis of 12 pre-defined food groups and risk of stroke according to intakes of servings/day. NA, not applicable

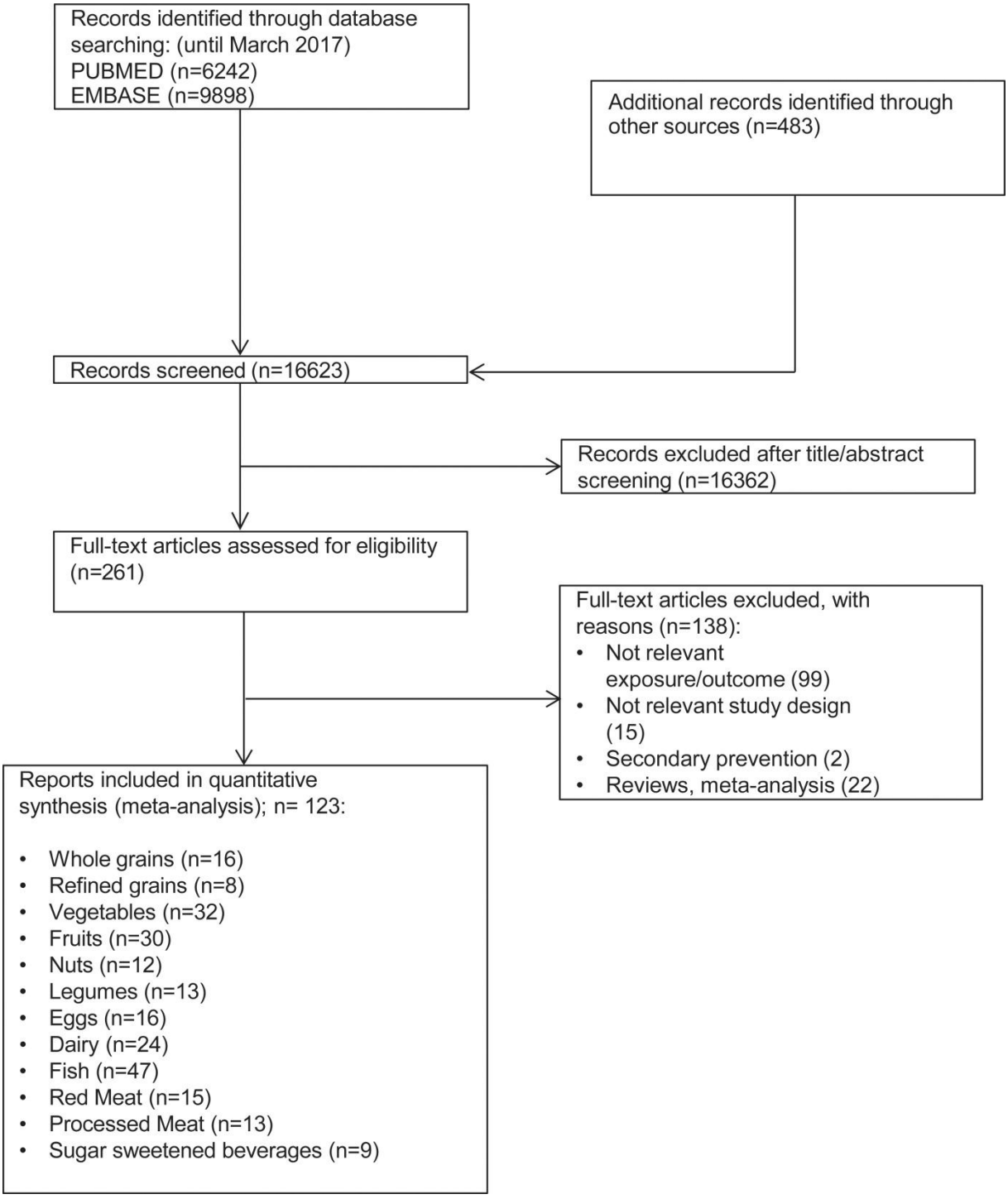

Figure 1: Flow chart of study selection

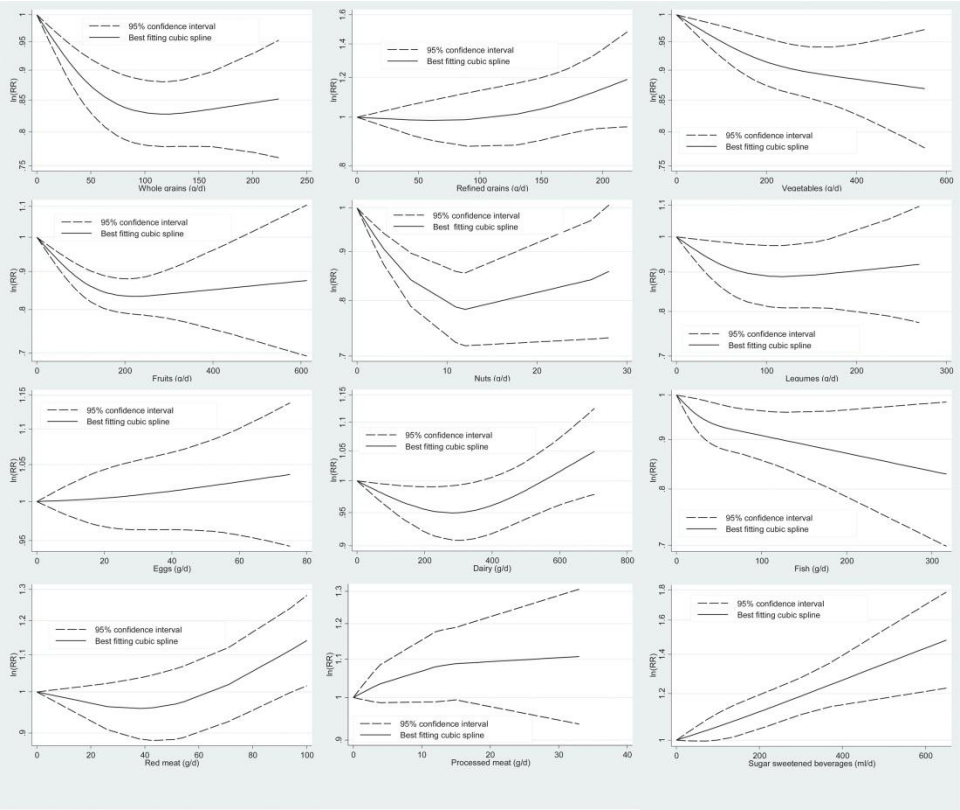

Figure 2: Non-linear dose-response relationship between daily intakes whole grains (p for non-linearity <0.001; n=5 studies), refined grains (p for non-linearity =0.25; n=4 studies), vegetables (p for non-linearity =0.19; n=13 studies), fruits (p for non-linearity <0.001; n=12 studies), nuts (p for non-linearity <0.001; n=4 studies), legumes (p for non-linearity =0.07; n=8 studies), eggs (p for non-linearity =0.81; n=9 studies), dairy (p for non-linearity <0.01; n=9 studies), fish (p for non-linearity =0.10; n=15 studies), red meat (p for non-linearity <0.01; n=2 studies), processed meat (p for non-linearity =0.41; n=2 studies), and sugar sweetened beverages (p for non-linearity =0.83; n=4 studies) and risk of coronary heart disease.

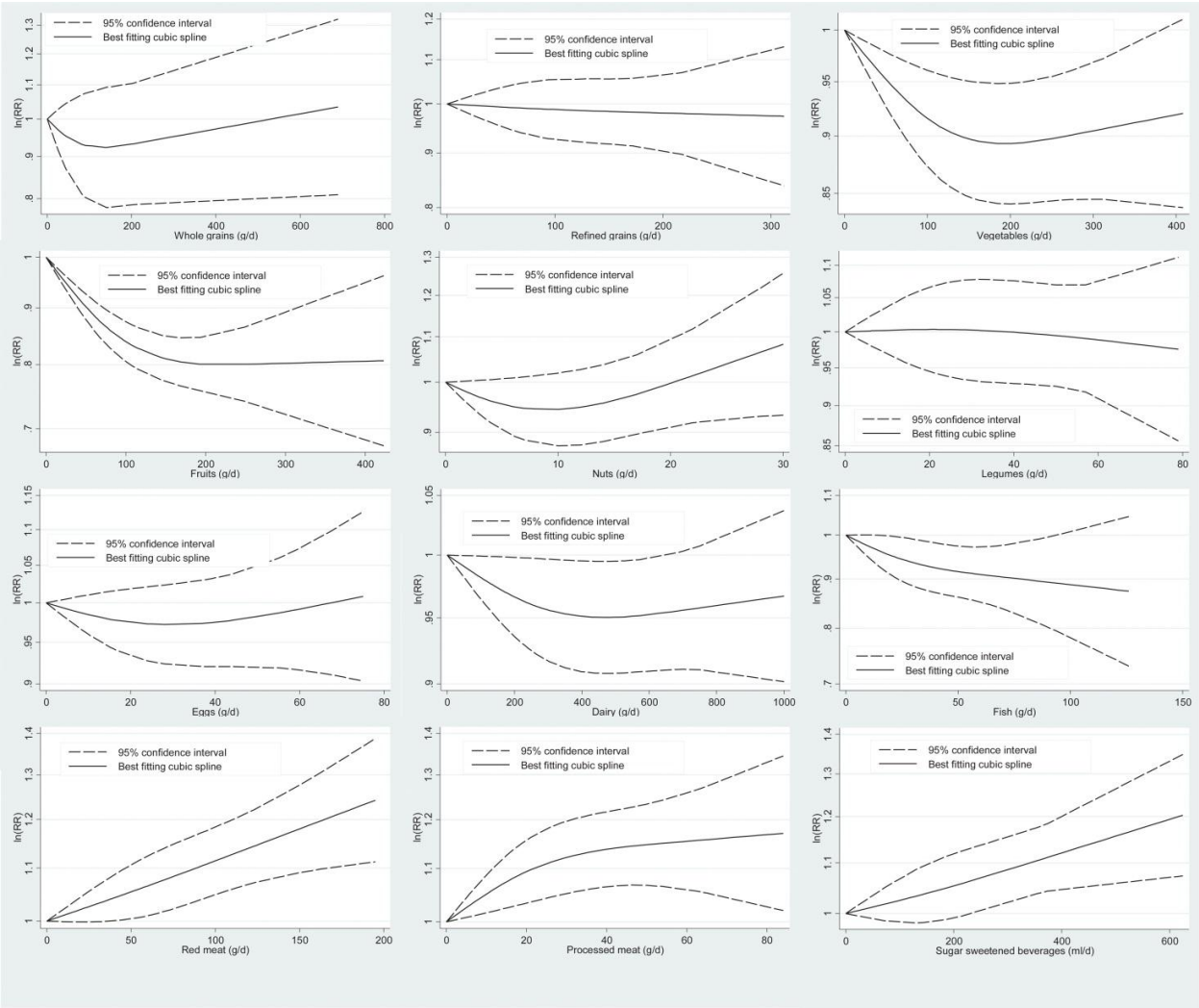

Figure 3: Non-linear dose-response relationship between daily intakes whole grains (p for non-linearity =0.77; n=3 studies), refined grains (p for non-linearity =0.42; n=4 studies), vegetables (p for non-linearity =0.03; n=8 studies), fruits (p for non-linearity =0.54; n=8 studies), nuts (p for non-linearity =0.05; n=5 studies), legumes (p for non-linearity =0.08; n=5 studies), eggs (p for non-linearity =0.39; n=9 studies), dairy (p for non-linearity =0.71; n=8 studies), fish (p for non-linearity =0.37; n=15 studies), red meat (p for non-linearity =0.91; n=6 studies), processed meat

(p for non-linearity =0.65; n=6 studies), and sugar sweetened beverages (p for non-linearity =0.83; n=6 studies) and risk of stroke.

