IJC
International Journal of Cancer

Food groups and risk of colorectal cancer

Lukas Schwingshackl[1], Carolina Schwedhelm[1], Georg Hoffmann[2], Sven Knüppel[1], Anne Laure Preterre[1], Khalid Iqbal[1], Angela Bechthold[3], Stefaan De Henauw[4], Nathalie Michels[4], Brecht Devleesschauwer[5], Heiner Boeing[1] and Sabrina Schlesinger[6]

[1] Department of Epidemiology, German Institute of Human Nutrition Potsdam-Rehbruecke (DIfE), Arthur-Scheunert-Allee 114-116, Nuthetal 14558, Germany
[2] Department of Nutritional Sciences, University of Vienna, Althanstraße 14, UZA II, Vienna 1090, Austria
[3] German Nutrition Society, Godesberger Allee 18, Bonn 53175, Germany
[4] Department of Public Health, Ghent University, Gent 9000, Belgium
[5] Department of Public Health and Surveillance, Scientific Institute of Public Health (WIV-ISP), Rue Juliette Wytsmanstraat 14, Brussels 1050, Belgium
[6] Institute for Biometry and Epidemiology, German Diabetes Center, Leibniz Institute for Diabetes Research at the Heinrich-Heine-University Düsseldorf, Düsseldorf D-40225, Germany

The aim of this systematic review and meta-analysis was to summarize the evidence on the relationship between intake of 12 major food groups, including whole grains, refined grains, vegetables, fruit, nuts, legumes, eggs, dairy, fish, red meat, processed meat and sugar-sweetened beverages with risk of colorectal cancer (CRC). We conducted a systematic search in PubMed and Embase for prospective studies investigating the association between these 12 food groups and risk of CRC until April 2017. Summary risk ratios (RRs) and 95% confidence intervals (95% CI) were estimated using a random effects model for high *vs*. low intake categories, as well as for linear and nonlinear relationships. An inverse association was observed for whole grains ($RR_{30g/d}$: 0.95, 95% CI 0.93, 0.97; $n = 9$ studies), vegetables ($RR_{100g/d}$: 0.97, 95% CI 0.96, 0.98; $n = 15$), fruit ($RR_{100g/d}$: 0.97, 95% CI 0.95, 0.99; $n = 16$) and dairy ($RR_{200g/d}$: 0.93, 95% CI 0.91, 0.94; $n = 15$), while a positive association for red meat ($RR_{100g/d}$: 1.12, 95% CI 1.06, 1.19; $n = 21$) and processed meat ($RR_{50g/d}$: 1.17, 95% CI 1.10, 1.23; $n = 16$), was seen in the linear dose-response meta-analysis. Some evidence for nonlinear relationships was observed between vegetables, fruit and dairy and risk of colorectal cancer. Findings of this meta-analysis showed that a diet characterized by high intake of whole grains, vegetables, fruit and dairy products and low amounts of red meat and processed meat was associated with lower risk of CRC.

Cancer Epidemiology

Introduction

Worldwide, colorectal cancer (CRC) is the second most common cancer in women and the third most common cancer in men. In 2012, around 694,000 men and women died because of CRC.[1] The etiology is multifactorial, and it has been demonstrated that lifestyle factors, including diet, are associated with risk of CRC, and thus a healthy diet may play a key role for prevention. A recent systematic review and meta-analysis summarized evidence on dietary factors and risk of CRC and indicated that higher intake of red and processed meat was associated with increased risk of CRC, while higher intake of whole grains, dairy products, vegetable and fish showed inverse associations with risk.[2] Previous meta-analyses pointed out that dietary patterns were also related to risk of CRC, and mortality among CRC survivors.[3,4] A "healthy" dietary pattern, characterized by high intake of vegetables, fruit, whole grains, olive oil, fish, soy, poultry and low-fat dairy was associated with decreased risk of CRC, whereas a "western" diet, characterized by high consumption of red and/or processed meat, refined grains, sweets, high-fat dairy products, butter, potatoes and high-fat gravy and low intake of fruit and vegetables was related to increased risk of CRC.[3] Although evidence on single dietary factors and dietary patterns in relation to risk of CRC has been summarized, it remains unclear what the optimal intakes of foods or food groups are that might be associated with strongest change in risk of CRC. As previously shown, selecting specific optimal intakes among 12 *a priori* defined food groups including whole grains, refined grains, vegetables, fruit, nuts, legumes, eggs, dairy, fish, red meat, processed meat and sugar-sweetened beverages (SSB),[5] can lead to a considerable change in risk of premature death, cardiovascular disease,

Key words: food groups, diet, meta-analysis, dose-response, colorectal cancer

Abbreviations: BMI: body mass index; CI: confidence interval; CRC: colorectal cancer; HR: hazard ratio; RR: risk ratio; SSB: sugar sweetened beverages

Additional Supporting Information may be found in the online version of this article.

Conflict of interest: No conflict of interest to declare.

Grant information: No funding to declare

DOI: 10.1002/ijc.31198

History: Received 4 Sep 2017; Accepted 21 Nov 2017; Online 6 Dec 2017

Correspondence to: Lukas Schwingshackl, Arthur-Scheunert-Allee 114-116, Nuthetal 14558, Germany, E-mail: lukas.schwingshackl@dife.de; T: +49 033200882712

What's new?

Diet is known to affect risk of colorectal cancer (CRC), but what are the optimal intakes of foods remain unclear. In this systematic review and meta-analysis, the authors investigated the association between 12 *a priori*-defined food groups and risk of CRC. Optimal consumption of risk-decreasing foods (6 servings/day of whole grains, vegetables and dairy, and 3 servings/day of fruits) results in a 56% risk reduction. Consumption of risk-increasing foods of 2 servings/day of red meat, and 4 servings/day of processed meat associated with a 1.8-fold increased risk. A plant-based diet can thus lead to an important risk reduction of CRC.

type 2 diabetes and hypertension.[6–9] By analogy, it is of great importance to account for quality of meta-evidence to make a conclusion about the relationship between dietary factors and CRC prevention.

Thus, our aim was to conduct a systematic review on the 12 food groups (whole grains, refined grains, vegetables, fruit, nuts, legumes, eggs, dairy, fish, red meat, processed meat, SSB) and risk of CRC. Specifically, we conducted high *vs*. low, linear and nonlinear dose-response meta-analyses to quantify the strengths of the associations between food groups and risk of CRC, to explore the shape of the relationship, and to provide cut-off values for optimal food intakes regarding a low CRC risk. Finally, we investigated the quality of meta-evidence using the established approach of the NutriGrade scoring system.

Methods

The meta-analysis was registered in PROSPERO International Prospective Register of Systematic Reviews (www.crd.york.ac.uk/prospero/index.asp, identifier CRD42016037069). This systematic review was planned and conducted according to the standards of the Meta-Analysis of Observational Studies in Epidemiology.[10]

Study selection

Inclusion criteria were as follows: (1) cohort studies, case–cohort studies, follow-up of RCTs and nested case–control studies (case–control study nested in a prospective study); (2) information about the association for at least one of the following 12 food groups: whole grains/cereals, refined grains/cereals, vegetables, fruit, nuts, legumes, eggs, dairy products, fish, red meat, processed meat and SSB (the focus is based on these 12 food groups since most diet quality indices/score were based on these,[11–13] as previously reported[5]); (3) participants aged ≥18 years and (4) considering CRC, colon or rectal cancer as outcome.

Search strategy

PubMed and Embase were searched for prospective studies until April 2017 based on the above defined inclusion criteria, with no restriction to language and calendar date using the search terms listed in the Supplemental Material 1.

To identify further relevant studies, the reference lists from the retrieved articles, systematic reviews and meta-analyses were checked. Two authors (LS, ALP) conducted the literature search, with disagreement resolved by consensus of another reviewer (HB).

Data extraction

Two reviewers extracted the following information: name of first author, year of publication, study origin (country), cohort name, age at entry, sex, sample size, total cases, dietary assessment, outcome, outcome assessment, type and specification of food group, adjustment factors, study length (follow-up in years), outcome, quantity of food, risk estimate (most adjusted measures) (risk ratios (RR), hazard ratios or odds ratios (OR) with their corresponding 95% confidence intervals (CIs)).

When a study provided several risk estimates, the multivariable adjusted model was chosen. For studies that reported estimates stratified by sex, or cancer site (colon and rectal), we used a fixed effect model to combine the estimates for the primary analysis (CRC).

Risk of bias assessment

We assessed ascertainment of exposure, assessment of outcome, adequacy of follow-up (≥10 years) and adjustment factors (age, sex education, body mass index, smoking, physical activity, energy intake) to evaluate the risk of bias of the prospective studies.[14] Studies were classified as being at low risk of bias in general only if none of the domains established a high or unclear risk of bias.

Statistical analysis

To calculate summary RRs and 95% CIs for the associations between CRC and the highest *vs*. the lowest intake categories a random effects model was used for each of 12 food groups. In addition, the meta-analyses,[15] incorporated both within and between study variability. 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, to evaluate the weighting of each study.[15]

The method described by Greenland and Longnecker[16,17] was applied for the dose-response analysis and computed study-specific slopes (linear trends) and 95% CIs from the natural logs of the RRs and CIs across intake categories of the 12 food groups. For this method, distribution of cases

and person-years or non-cases and the RRs with the 95% CI for at least three quantitative exposure categories is required.

The Q test and the I^2 statistic (with a value of I^2 >50% considered to represent potentially important statistical heterogeneity[18]) was used to explore heterogeneity between studies.

If at least 10 studies were available, we explored potential small-study effects such as publication bias by using Egger's test and funnel plots.[19] Stata version/SE 14.2 software (StataCorp, College Station, TX) and Review Manager 5.3 (Nordic Cochrane Centre, Copenhagen, Denmark) were used to conduct statistical analyses.

Quality of meta-evidence

The NutriGrade scoring system was applied to evaluate the trustworthiness of meta-evidence for the association between 12 pre-defined food groups and risk of CRC (max 10 points).[14] Please review Supplemental Material 2 for detailed description of statistical analysis, risk of bias- and quality of meta-evidence assessment.

Results

Out of the 6,365 records which were identified by the literature search, 129 full text articles were assessed in detail as they reported on at least one of the twelve foods groups and CRC, colon or rectal cancer in the title/abstract (Fig. 1, Supplemental Material 3).

Eleven prospective studies (11 reports) were included in the meta-analyses for consumption of whole grains (Supplemental References 48–58), 3 studies (3 reports) for refined grains (Supplemental References 51, 54, 58), 23 studies for vegetables (25 reports) (Supplemental References 49, 52–54, 56, 57, 59–77), 21 studies for fruits (24 reports) (Supplemental References 49, 52–54, 56–70, 72–76), 7 studies for nuts (7 reports) (Supplemental References 49, 65, 71, 78–81), 14 studies for legumes (14 reports) (Supplemental References 59, 60, 65, 66, 68, 71, 72, 75, 76, 81–85), 5 studies for egg consumption (4 reports) (Supplemental References 54, 86–88), 20 studies for dairy products (21 reports) (Supplemental References 49, 52–54, 58, 59, 62, 71, 87, 89–100), 25 studies for fish (25 reports) (Supplemental References 7, 53, 54, 59, 62, 83, 91, 101–118), 28 studies for red meat (28 reports) (Supplemental References 7, 53, 59, 60, 62, 71, 86, 87, 99, 101, 102, 105, 107, 111, 113, 116, 119–130), 22 studies for processed meat (23 reports) (Supplemental References 7, 53, 60, 62, 91, 101, 102, 105, 107, 109, 111, 113, 116, 120, 122, 123, 125–131) and 3 studies for SSB (2 reports) (Supplemental References 49, 132) (Supplemental Tables S2–S13, Supplemental Material 4).

Whole grains

Ten studies with 9,223 CRC cases were included in the high *vs.* low intake meta-analysis (overall intake range: 0–374 g/d). Comparing extreme categories, an inverse association between risk of CRC and whole grain intake was observed (RR: 0.88; 95% CI 0.83, 0.94, $I^2 = 35\%$, $p_{\text{heterogeneity}} = 0.13$) (Supplemental Fig. S1). Each additional daily 30 g of whole grains was inversely associated with CRC risk (RR: 0.95; 95% CI 0.93, 0.97, $I^2 = 58\%$, $p_{\text{heterogeneity}} = 0.02$, $n = 9$) (Supplemental Fig. S2). The inverse association was confirmed in additional analyses stratified by sex (no association for men), follow-up length, geographic location, number of cases, dietary assessment method (Supplemental Table S14) and comparing colon and rectal cancer (Supplemental Figs. S3 and S4). These subgroup-differences were not statistically significant, with the exception for geographic location, showing a stronger inverse association for studies conducted in North America.

There was significant evidence for small study effects in the high *vs.* low meta-analysis ($p = 0.07$). Furthermore, there was no evidence of a nonlinear dose-response association ($p_{\text{nonlinearity}}$ $p = 0.16$, $n = 7$ studies). The risk of CRC decreased by 20% with increasing intake of whole grains up to ~120 g/d (Fig. 2).

Refined grains

Two studies with 900 CRC cases were included in the high *vs.* low intake meta-analysis (overall intake range: 15–585 g/d). No association was observed for the highest *vs.* lowest refined grain intake category (RR: 1.46; 95% CI 0.80, 2.67, $I^2 = 71\%$, $p_{\text{heterogeneity}} = 0.06$) (Supplemental Fig. S5). No studies were available to conduct linear dose-response meta-analysis, and nonlinear dose-response analyses. In a subgroup analysis a positive association was observed for colon cancer (high *vs.* low: RR: 1.27; 95% CI 1.02, 1.57, $I^2 = 0\%$, $p_{\text{heterogeneity}} = 0.89$) (Supplemental Fig. S6).

Vegetables

Twenty studies with 20,490 CRC cases were included in the high *vs.* low intake meta-analysis (overall intake range: 0–972 g/d). A small inverse association was observed for the high *vs.* low (RR: 0.96; 95% CI 0.92, 1.00, $I^2 = 17\%$, $p_{\text{heterogeneity}} = 0.24$) (Supplemental Fig. S7) and for the dose-response meta-analysis (RR per 100 g/d: 0.97; 95% CI 0.96, 0.98, $I^2 = 0\%$, $p_{\text{heterogeneity}} = 0.64$, $n = 15$) (Supplemental Fig. S8).

The small inverse association persisted largely in additional analyses stratified by sex, follow-up length, geographic location, number of cases and dietary assessment (Supplemental Table S16). No important evidence of heterogeneity was detected between subgroups in stratified analyses. In additional subgroup analyses, the inverse association was observed only for colon, but not for rectal cancer (Supplemental Figs. S9 and S10).

There was no significant evidence for small study effects, both in the high *vs.* low ($p = 0.22$) and dose-response analysis ($p = 0.89$). Visual inspection of the funnel plot (dose-response analysis) suggests moderate symmetry (Supplemental Fig. S11). There was evidence of a nonlinear dose-response association ($p_{\text{nonlinearity}}$=0.01, $n = 14$ studies): risk

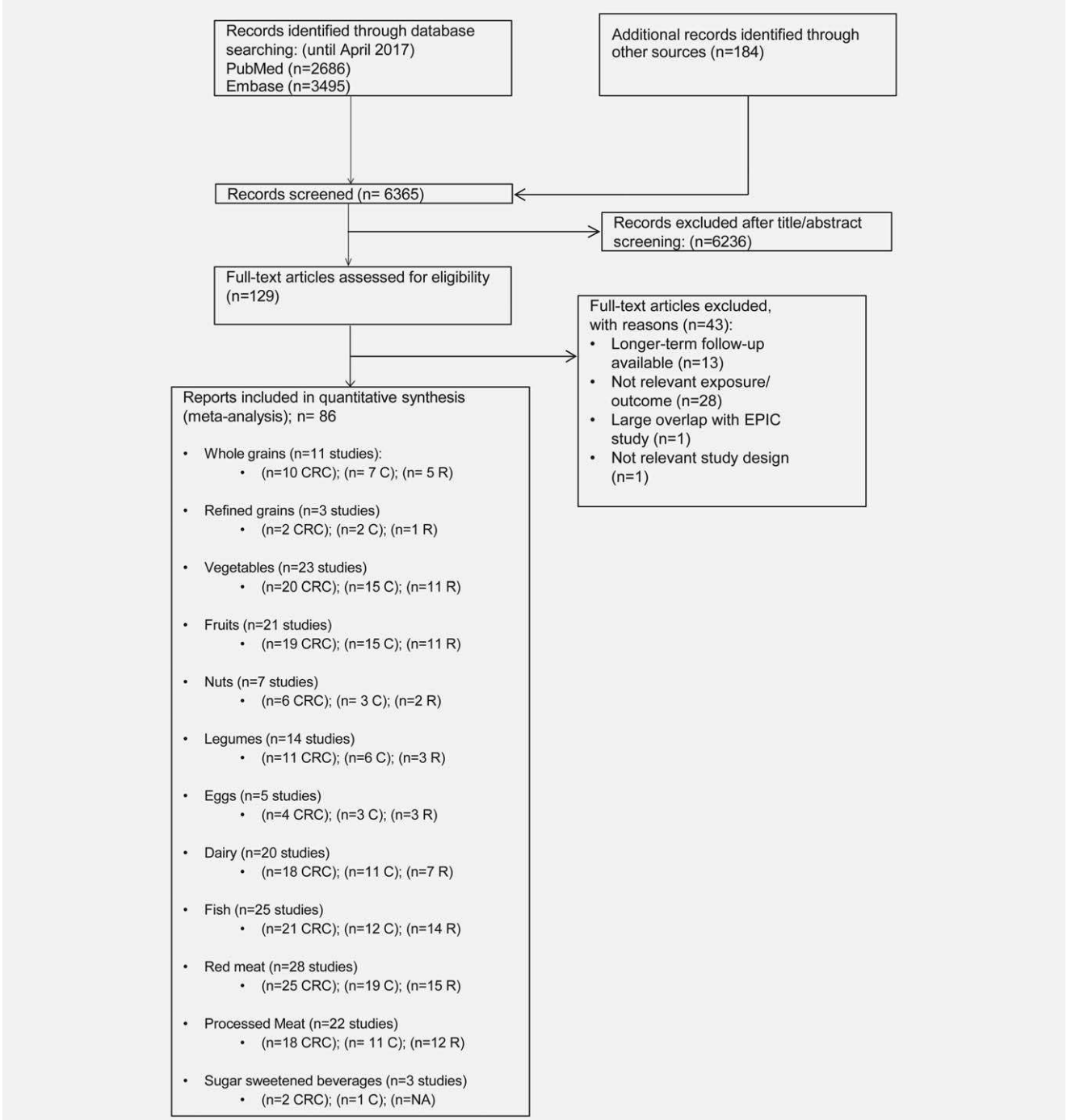

Figure 1. Flow chart of study selection. CRC, colorectal cancer; C, colon; R, rectum.

reduction of CRC was observed across the whole range of vegetable intake, with the strongest risk reduction (by 7%) up to ~200 g/d (Fig. 2).

Fruit

Nineteen studies with 20,148 CRC cases were included in the high *vs.* low intake meta-analysis (overall intake range: 4–1,384 g/d) resulting in an inverse association (RR: 0.93; 95% CI 0.88, 0.98, $I^2 = 49\%$, $p_{\text{heterogeneity}} < 0.01$) (Supplemental Fig. S12). Each additional daily 100 g of fruits was inversely associated with CRC (RR: 0.97; 95% CI 0.95, 0.99, $I^2 = 61\%$, $p_{\text{heterogeneity}} < 0.001$, $n = 16$) (Supplemental Fig. S13).

The inverse association was not observed in Asian and Australian studies, and studies including only women (Supplemental Table S17). However, no evidence of heterogeneity was detected between subgroups in stratified analyses. In

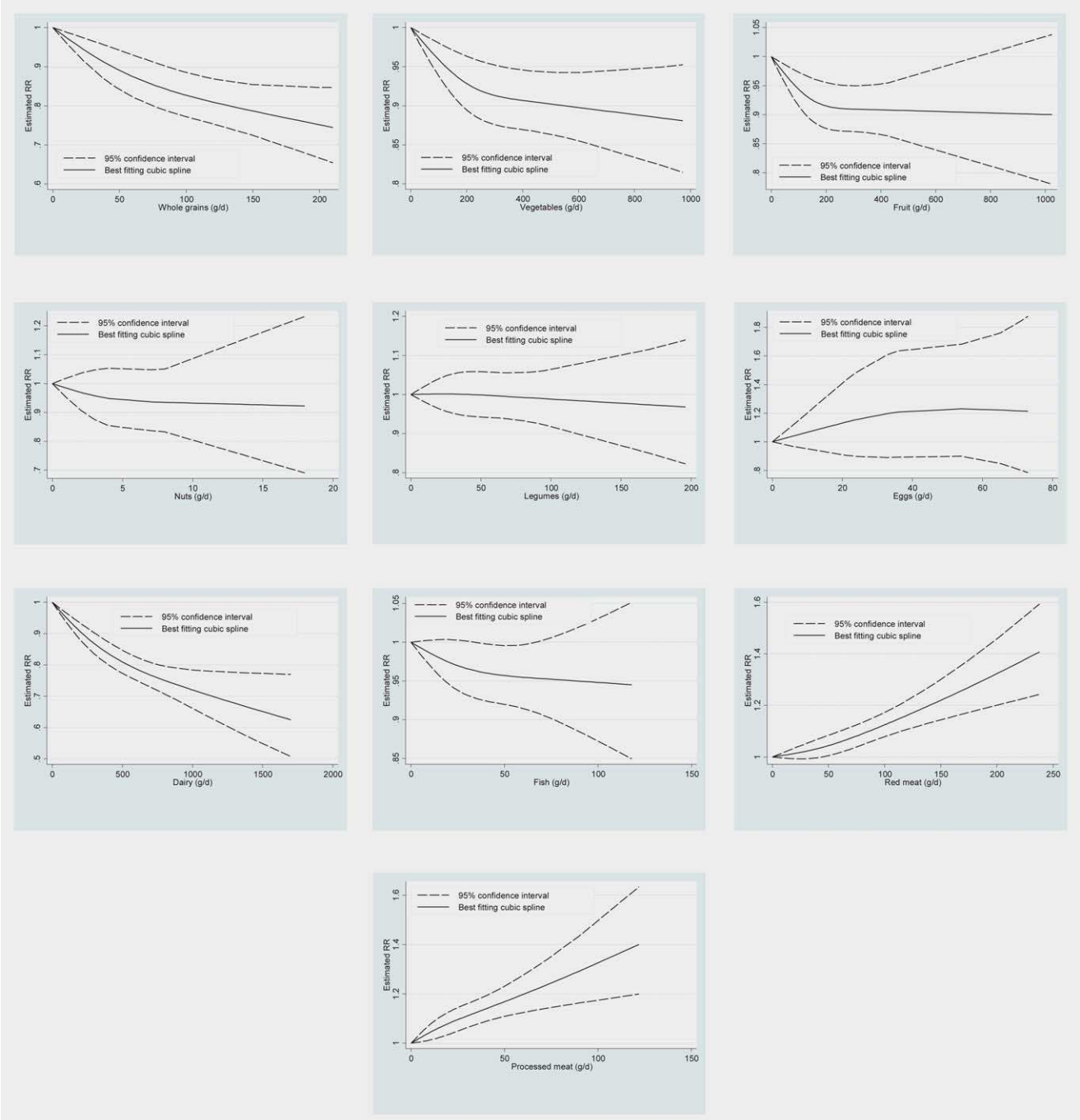

Figure 2. Nonlinear dose-response relationship between daily intakes of whole grains ($p = 0.16$), vegetables ($p = 0.01$), fruits ($p = 0.01$), nuts ($p = 0.58$), legumes ($p = 0.84$), eggs ($p = 0.55$), dairy ($p = 0.06$), fish ($p = 0.38$), red meat ($p = 0.25$) and processed meat ($p = 0.40$) and risk of colorectal cancer. [Color figure can be viewed at wileyonlinelibrary.com]

additional subgroup analyses, the inverse association was observed for colon and for rectal cancer (Supplemental Figs. S14 and S15).

There was no significant evidence for small study effects, in the high *vs.* low ($p = 0.14$) and dose-response analyses ($p = 0.22$). Visual inspection of the funnel plots (dose-response analysis) suggests moderate symmetry (Supplemental Fig. S16). There was indication of a nonlinear dose-response association ($p_{\text{nonlinearity}}=0.01$, $n = 14$ studies), with strongest risk reduction of CRC (by approximately 8%) with increasing fruit intake up to ~200 g/d. Little additional benefit for increasing intake is apparent above this value (Fig. 2).

Nuts

Six studies with 7,283 CRC cases were included in the high *vs.* low intake meta-analysis (overall intake range: 0–22 g/d).

No association was observed for the highest *vs*. lowest nut intake category (RR: 0.96; 95% CI 0.90, 1.02, $I^2 = 4\%$, $p_{heterogeneity} = 0.39$) (Supplemental Fig. S17), or for each additional daily 28 g (RR: 0.96; 95% CI 0.76, 1.21, $I^2 = 25\%$, $p_{heterogeneity} = 0.26$, $n = 4$) (Supplemental Fig. S18). In an additional subgroup analysis, we observed an inverse association for colon, but not for rectal cancer (Supplemental Figs. S19 and S20).

There was no association in any of the additional stratified analyses (Supplemental Table S18). There was no evidence of a nonlinear dose-response association ($p_{nonlinearity}$=0.58, $n = 3$ studies) (Fig. 2).

Legumes

Eleven studies with 12,508 CRC cases were included in the high *vs*. low intake meta-analysis (overall intake range: 0–173 g/d). No inverse association was observed for the highest *vs*. lowest legume intake category (RR: 0.99; 95% CI 0.92, 1.06, $I^2 = 23\%$, $p_{heterogeneity} = 0.23$) (Supplemental Fig. S21), or for each additional daily 50 g (RR: 1.00; 95% CI 0.92, 1.08, $I^2 = 50\%$, $p_{heterogeneity} = 0.04$, $n = 10$) (Supplemental Fig. S22).

There was no association in any of the additional stratified analyses (Supplemental Table S19, Supplemental Figs. S23 and S24). No evidence for small study effects was detected in the high *vs*. low analysis ($p = 0.18$) and dose-response analysis ($p = 0.59$) (Supplemental Fig. S25). No evidence of a nonlinear dose-response association was observed ($p_{nonlinearity}$= 0.84, $n = 9$ studies) (Fig. 2).

Eggs

Four studies with 598 CRC cases were included in the highest compared to the lowest intake category analysis (overall intake range: 0–73 g/d). A positive association was observed for the highest *vs*. lowest egg intake category (RR: 1.35; 95% CI 1.11, 1.66, $I^2 = 0\%$, $p_{heterogeneity} = 0.97$) (Supplemental Fig. S26), but the finding for each additional daily 50 g egg intake was not statistically significant (RR: 1.18; 95% CI 0.89, 1.56, $I^2 = 0\%$, $p_{heterogeneity} = 0.96$, $n = 3$) (Supplemental Fig. S27).

There was no association in any of the additional stratified analyses (Supplemental Table S20, Supplemental Figs. S28 and S29). There was no evidence of a nonlinear dose-response association ($p_{nonlinearity} = 0.55$, $n = 3$ studies) (Fig. 2).

Dairy

Eighteen studies with 16,910 CRC cases were included in the highest compared to the lowest intake category meta-analysis (overall intake range: 0–1,700 g/d). A strong inverse association was observed (RR: 0.83; 95% CI 0.76, 0.89, $I^2 = 61\%$, $p_{heterogeneity} < 0.001$) (Supplemental Fig. S30) for the high *vs*. low, and for each additional daily 200 g of dairy products (RR: 0.93; 95% CI 0.91, 0.94, $I^2 = 0\%$, $p_{heterogeneity} = 0.64$, $n = 15$) (Supplemental Fig. S31).

The observed inverse association persisted largely in additional analyses stratified by sex, length of follow-up, geographic location and number of cases. The inverse associations were not observed in studies conducted in Asia and Australia, and also not in studies applying non-validated dietary assessment methods. No significant heterogeneity was observed between the subgroups. Both low and high-fat dairy products showed an inverse association for CRC risk (Supplemental Table S21). In additional subgroup analyses, we observed a stronger inverse association for colon compared to rectal cancer (Supplemental Figs. S32 and S33).

There was no evidence for small study effects in the in the high *vs*. low analysis ($p = 0.17$) and dose-response meta-analysis ($p = 0.66$). Visual inspection of the funnel plots (dose-response analysis) suggests moderate symmetry (Supplemental Fig. S34). There was some indication of a nonlinear dose-response association between dairy products and risk of CRC ($p_{nonlinearity}$=0.06, $n = 13$ studies). The risk of CRC decreased by approximately 17% with increasing intake of dairy up to ~400 g/d. Additional benefit for increasing intake is apparent above this value (Fig. 2).

Fish

Twenty-one studies with 19,996 CRC cases were included in the highest compared to the lowest intake category meta-analysis (overall intake range: 0–280 g/d). A trend for an inverse association was observed for the highest *vs*. lowest fish intake category (RR: 0.96; 95% CI 0.90, 1.01, $I^2 = 20\%$, $p_{heterogeneity} = 0.21$) (Supplemental Fig. S35), and for each additional daily 100 g (RR: 0.93; 95% CI 0.85, 1.01, $I^2 = 12\%$, $p_{heterogeneity} = 0.32$, $n = 16$) (Supplemental Fig. S36).

We observed significant heterogeneity in subgroups stratified for gender, showing an inverse association for men, but not for women (Supplemental Table S22). Moreover, an inverse association was observed for studies conducted in Europe, for long-term studies, and studies with ≥1,000 cases. In additional subgroup analyses, the test for subgroup difference comparing colon and rectal cancer was not significant (Supplemental Figs. S37 and S38).

No evidence for small study effects was observed in the high *vs*. low ($p = 0.90$) and dose-response meta-analysis ($p = 0.91$). Visual inspection of the funnel plot suggests moderate symmetry (Supplemental Fig. S39). There was no evidence of a nonlinear dose-response association ($p_{nonlinearity}$ $p = 0.38$, $n = 15$ studies) (Fig. 2).

Red meat

Twenty-five studies with 22,286 CRC cases were included in the high *vs*. low intake meta-analysis (overall intake range: 0–203 g/d). A positive association was observed in the high *vs*. low intake meta-analysis (RR: 1.12; 95% CI 1.06, 1.18, $I^2 = 31\%$, $p_{heterogeneity} = 0.08$) (Supplemental Fig. S40). Each additional daily 100 g of red meat was positively associated with risk of CRC (RR: 1.12; 95% CI 1.06, 1.19, $I^2 = 27\%$, $p_{heterogeneity} = 0.13$, $n = 21$) (Supplemental Fig. S41).

The observed positive associations persisted in additional analyses stratified by follow-up length, geographic location, and number of cases, dietary assessment method, and colon and rectal cancer. Stronger associations were observed for studies conducted in Asia and Australia, compared to Europe and North America (Supplemental Table S23, Supplemental Figs. S42 and S43).

There was no evidence of small study effects in the in high *vs*. low intake ($p = 0.20$) or in the dose-response meta-analysis ($p = 0.62$). Visual inspections of the funnel plots suggest symmetry (Supplemental Fig. S44). There was no evidence of a nonlinear dose-response association ($p_{\text{nonlinearity}} = 0.25$, $n = 20$ studies). The risk of CRC increased by approximately 20% with increasing intake of red meat up to ~150 g/d (Fig. 2).

Processed meat

Eighteen studies with 20,283 CRC cases were included in the high *vs*. low intake meta-analysis (overall intake range: 0–122 g/d). A positive association was observed in the high *vs*. low intake meta-analysis (RR: 1.14; 95% CI 1.06, 1.21, $I^2 = 22\%$, $p_{\text{heterogeneity}} = 0.20$) (Supplemental Fig. S45). Each additional daily 50 g of processed meat was associated with an increased risk of CRC (RR: 1.17; 95% CI 1.10, 1.23, $I^2 = 6\%$, $p_{\text{heterogeneity}} = 0.39$, $n = 16$) (Supplemental Fig. S46).

The observed positive associations persisted in additional analyses stratified by sex, follow-up length, geographic location, and number of cases, dietary assessment, and colon and rectal cancer (Supplemental Table S24, Supplemental Figs. S47 and S48). Stratified by sex, only studies conducted in women maintained the observed positive association.

There was no evidence of small study effects in the in high *vs*. low intake ($p = 0.78$) and dose-response meta-analysis ($p = 0.66$). Visual inspections of the funnel plot suggest moderate symmetry (Supplemental Fig. S49). There was no evidence of a nonlinear dose-response association ($p_{\text{nonlinearity}} = 0.40$, $n = 16$ studies). The risk of CRC increased by approximately 20% with increasing intake of processed meat up to ~60 g/d (Fig. 2).

Sugar sweetened beverages

Two studies with 2,464 CRC cases were included in the high *vs*. low intake meta-analysis (overall intake range: not reported). No association between CRC and SSB was observed in the linear dose-response meta-analysis (equal to high *vs*. low intake meta-analysis) (RR: 1.09; 95% CI 0.97, 1.22, $I^2 = 46\%$, $p_{\text{heterogeneity}} = 0.18$, $n = 2$) (Supplemental Fig. S50). No studies were available to conduct nonlinear dose-response analysis.

Summary across food groups

Table 1 shows the RR for CRC from nonlinear dose-response analysis of the 12 predefined food groups according to servings/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 (6 servings/d of whole grains, RR = 0.77; 6 servings/d of vegetables, RR = 0.90; 3 servings/d of fruit, RR = 0.91; 6 servings/d of dairy, RR = 0.70) results in a 56% reduction compared to non-consumption of these foods. The combined amounts of these food groups are quite high, and mark only the theoretical "optimal" consumption for all four food groups. The highest reduction in risk of CRC in terms of servings could be observed for dairy; 1,200 g/d (6 servings/d) was associated with a 30% reduction in risk compared to non-consumption of this food group. We could further calculate that a consumption of risk-increasing foods of 2 servings/d of red meat (170 g, RR = 1.27), and 4 servings/d of processed meat (120 g, RR = 1.40), is associated with a 1.8-fold increased risk ($RR^*_{\text{increased}}$) compared to non-consumption. Not consuming these foods would reduce the risk of CRC by about 44%.

Risk of bias

The results varied little by methodological assumption, including only studies with a low risk of bias (Supplemental Tables S14–S25). Findings including studies with low risk of bias suggest no inverse association between fruit ($n = 5$) and risk of CRC in the linear dose-response meta-analysis, but a stronger inverse association for each additional 100 g/d of fish. However, including only lower risk of bias studies showed a smaller but persistent positive association between red and processed meat and risk of CRC.

Quality of meta-evidence

We rated the quality of meta-evidence for the 12 food groups. Our confidence in the linear dose-response effect estimates was rated according to the NutriGrade recommendation as "very low" for nuts and eggs, "low" for legumes and SSB, and "moderate" for whole grains, vegetables, fruits, dairy, fish, red meat and processed meat (Supplemental Table S26).

Discussion

In this systematic review and meta-analysis we investigated the association between 12 *a priori* defined food groups (whole grains, refined grains, vegetables, fruit, nuts, legumes, eggs, dairy, fish, red meat, processed meat, SSB) and risk of CRC, conducting high *vs*. low, linear and nonlinear dose-response meta-analyses. We identified a reduced risk of CRC with high intake of whole grains, vegetables, fruit and dairy, while increased intake of red meat and processed meat was associated with higher risk of CRC. A positive association between egg consumption and risk of CRC was observed in high *vs*. low, but not in dose-response meta-analysis, and for the intake of nuts, a decreased risk was observed for colon cancer only. No statistically significant associations were observed for refined grains, legumes, fish and SSB regarding risk of CRC. Evaluating the meta-evidence by the NutriGrade tool, we observed moderate confidence in the effect estimates for CRC and whole grains, vegetables, fruit, dairy, fish, red

Table 1. Relative risks from nonlinear dose-response analysis of 12 pre-defined food groups and colorectal cancer risk according to intakes of servings/day

Food group	Risk ratio (RR), 95% CI						
Inverse association							
Servings per day	0	1	2	3	4	5	6
Whole grains ($n = 7$ studies) (1 serving = 30 g/d)	1.00	0.91 (0.89–0.96)	0.88 (0.82–0.93)	0.84 (0.78–0.90)	0.81 (0.75–0.87)	0.79 (0.73–0.85)	0.77 (0.70–0.85)
Vegetables ($n = 14$ studies) (1 serving = 80 g/d)	1.00	0.97 (0.95–0.98)	0.94 (0.91–0.97)	0.92 (0.88–0.96)	0.91 (0.87–0.95)	0.91 (0.87–0.95)	0.90 (0.86–0.94)
Fruit ($n = 14$ studies) (1 serving = 80 g/d)	1.00	0.96 (0.94–0.98)	0.92 (0.89–0.96)	0.91 (0.87–0.95)	0.91 (0.87–0.95)	0.91 (0.86–0.95)	0.91 (0.86–0.95)
Dairy ($n = 13$ studies) (1 serving = 200 g/d)	1.00	0.91 (0.88–0.93)	0.83 (0.80–0.87)	0.79 (0.75–0.83)	0.75 (0.70–0.79)	0.72 (0.66–0.78)	0.70 (0.63–0.78)
Positive association							
Red meat ($n = 20$ studies) (1 serving = 85 g/d)	1.00	1.10 (1.06–1.15)	1.27 (1.17–1.37)	NA	NA	NA	NA
Processed meat ($n = 16$ studies) (1 serving = 30 g/d)	1.00	1.11 (1.06–1.16)	1.20 (1.12–1.28)	1.29 (1.16–1.43)	1.40 (1.20–1.63)	NA	NA
No association							
Nuts ($n = 3$ studies) (1 serving = 28 g/d)	1.00	0.92 (0.69–1.23)[1]	NA	NA	NA	NA	NA
Legumes ($n = 9$ studies) (1 serving = 100 g/d)	1.00	0.99 (0.92–1.06)	0.97 (0.82–1.14)	NA	NA	NA	NA
Fish ($n = 15$ studies) (1 serving = 100 g/d)	1.00	0.95 (0.87–1.03)	NA	NA	NA	NA	NA
Eggs ($n = 3$ studies) (1 serving = 55 g/d)	1.00	1.23 (0.90–1.68)	NA	NA	NA	NA	NA
Not applicable							
Refined grains ($n = 0$ studies) (1 serving = 30 g/d)	1.00	NA	NA	NA	NA	NA	NA
SSB ($n = 0$ studies) (1 serving = 250 ml/d)	1.00	NA	NA	NA	NA	NA	NA

Abbreviation: NA, not applicable (no data/studies available to calculate nonlinear relations).
[1]This value refers to a two-thirds serving (18 g).

meat and processed meat, low confidence for legumes and SSB, and very low confidence for nuts and eggs.

These findings are in line with previous reports. A recent meta-analysis from the WCRF-AICR CUP summarized evidence for the association between food groups and risk of CRC and indicated that high intake of whole grains, dairy, vegetables and fish was associated with decreased risk of CRC, and high intake of red and processed meat was related to increased risk.[2] Compared to the WCRF-AICR CUP (literature search through May 2015) we were able to identify additional studies which have been published after that date ($n = 3$ for whole grains; $n = 4$ for vegetables, $n = 3$ fruits, $n = 5$ for dairy products, $n = 6$ for legumes, $n = 5$ for fish and $n = 6$ for red and processed meat). We meta-analyzed the association between refined grains, nuts, eggs and SSB with colorectal cancer risk, which was not been reported by

the WCRF-AICR CUP, and we rated the credibility of meta-evidence for these 12 food groups. Moreover, we calculated the combined risk reduction potential for optimal intake values of risk-reducing or risk-increasing foods in our meta-analysis.

In this previous meta-analysis, there was no statistically significant association between fruit intake and risk of CRC (based on 13 studies). In our dose-response analysis, we included 16 studies on fruit intake and CRC and identified an inverse association. Although the association was not very strong, these findings add to the current knowledge that a high intake of fruit might contribute to prevention of CRC. As regards fish consumption, the previous meta-analysis has shown an inverse relationship between fish intake and risk of CRC, which was however mostly driven by one study.[2,20] In our report, more studies were included and we did not observe a statistically significant association between fish intake and risk of CRC.

The findings on egg consumption and risk of CRC were not clear in our analysis. While we observed a positive significant association in the high *vs*. low meta-analysis, results were not significant in the dose-response analysis. However, the analysis was based on a small number of studies (4 studies in the high *vs*. low and 3 studies in the dose-response analysis) and the confidence of meta-evidence was very low. Thus, the findings should be interpreted with caution. Moreover, we identified nonlinear relationships between intake of vegetables, and fruit with risk of CRC. Risk reduction was observed among the whole range of these food groups, however the strongest associations were detected for intake of vegetables as well as for fruit up to approximately 200 g per day.

Our findings were robust across subgroups, with few exceptions. There was indication that the associations for intake of vegetables and dairy products were stronger for colon than for rectal cancer. In addition, for colon cancer, intake of nuts was related to reduced risk, while a positive association was observed for refined grains. However, findings on refined grains and nut intake with colon cancer should be interpreted carefully because both meta-analyses were based on few studies (3 studies for nut intake and 2 studies for intake of refined grains), and quality of meta-evidence was very low for nut intake and not possible to assess for consumption of refined grains (since no studies were available for the dose-response meta-analysis). In this context, previous studies have shown that also other lifestyle or lifestyle related factors, including physical activity, smoking, weight gain and obesity, were stronger related to colon than to rectal cancer indicating that lifestyle factors play an important role, particularly in the etiology of colon cancer.[21–24]

Moreover, it is evident that analyses of single nutrients, foods or food groups does do not account for the complexity and the potential interaction between different components regarding the whole range of the diet-diseases association.[25] Meta-analyses, investigating the relationship between dietary patterns and risk of CRC, reported that a "healthy" diet characterized by high intake of fruit, vegetables, whole grains, olive oil, fish, soy, poultry and low-fat dairy was associated with a 20–25% decreased risk of CRC, while the "Western" dietary pattern, characterized by high intake of red and processed meat was associated with a 20–40% increased risk of CRC[25,26] with stronger associations for colon cancer compared to rectal cancer.[26]

The mechanisms relating diet with CRC are complex and still poorly understood. A diet with high intake of whole grains, fruit and vegetable is accompanied by intake of lower-energy-density foods and lower intake of foods with high glycemic index, glycemic load and fat, which has been shown to be related to decreased risk of obesity[27,28] and diabetes[29] – both identified risk factors for CRC.[30]

Nonetheless, studies that controlled for obesity and diabetes reported that associations persisted in adjusted analyses. Further possible explanations for the reduced risk of CRC and intake of these food groups might be driven by the high content of fiber, including also resistant starch, oligosaccharides, and lignins, which are related to increased stool mass, decreasing colonic transit time, prebiotic effects such as action of bacterial enzymes, and fecal bile acid concentration, and are suggested to play a role in colorectal carcinogenesis.[31,32] Moreover, whole grains, fruits and vegetables are a source of minerals (e.g., magnesium), and particularly fruit contains a wide range of antioxidant vitamins, flavonoids and carotenoids, and studies suggested a potential protective role against CRC.[33]

The mechanism by which dairy products decrease the risk of CRC might be complex. Dairy products include various foods with different contents of carbohydrates, protein, fatty acids, calcium, conjugated linoleic acid (CLA). Furthermore, intakes and composition vary also between region and countries.[34,35] One hypothesis for protective effects in CRC risk, might be the main factor responsible for this association. A systematic review and meta-analysis on calcium intake and risk of CRC showed that both dietary and supplementary calcium intake were related to decreased risk of CRC.[36] Studies in animals and in humans have shown that calcium is involved in the regulation of cell proliferation, differentiation and apoptosis in colonic cells.[37] Calcium and vitamin D were shown to stimulate the calcium sensing receptor promoter activity in colonic cells. In the case of calcium, this was associated with a subsequent inhibition of transcription factor-4 as well as an increased expression of E-cadherin. These changes may promote differentiation and chemo-preventive effects.[38] In addition, dairy products contain other beneficial components, such, butyric acid and CLA, lactic acid bacteria from fermented products, lactoferrin and folate, which have been suggested to inhibit colon carcinogenesis.[39] Lactoferrin is a Fe-binding antimicrobial protein which was shown to reduce inflammatory-related transformations and increase colorectal cancer mucosal immunity in animal studies.[40]

Experimental studies in mice have shown that CLA, a component of dietary fat, may inhibit colonic tumorigenesis in part through a PPARγ-dependent mechanism, thereby suppressing inflammation and epithelial erosion, and stimulating the immune response in the gut mucosa.[41] In colon cancer cell lines, an anti-proliferative effect was recently also observed for Lactobacillus bacteria isolated form dairy products.[42]

Red and processed meat contains heme iron and multiple carcinogenic chemicals, for example polycyclic aromatic hydrocarbons, N-nitroso compounds, and heterocyclic aromatic amines.[43,44] The amount of these chemicals in meat products depends on processing and preparation and these compounds are suspected to be involved in colorectal carcinogenesis. Besides the fact that mutagens link the association between red or processed red meat and risk of CRC, recent research indicated that the intestinal microbiota (e.g., *Bacteroides*) might be relevant for colorectal carcinogenesis. However, more studies are needed that investigate interactions and potential mechanisms between dietary factors and gut microbiota regarding CRC risk.[45,46]

Our systematic review has several strengths, and also limitations. The first limitation is that dietary behavior is often associated with other factors related to risk of CRC, such as physical activity, smoking, alcohol intake and obesity, and it might be possible that these factors affect our observations. Although most of the studies adjusted for these factors, residual confounding cannot be ruled out. Second, in our meta-analyses, we identified weak to moderate heterogeneity between studies, and methodological aspects were not identified as a source for heterogeneity. However, after stratification for cancer site, heterogeneity between studies was low for colon cancer, but persisted for rectal cancer. Third, the meta-analyses on nuts, and on eggs were based on a small number of studies and meta-evidence was low to very low, and thus findings for these food groups should be interpreted with caution.

Among the strengths is the *a priori* published protocol, which describes the methods in detail.[5] In addition, we performed a comprehensive literature search, and included a large number of studies and cases. To preclude recall and selection bias we only included prospective studies. Moreover, we conducted different types of analyses, including high *vs*. low intake meta-analysis, linear and nonlinear dose-response meta-analysis and investigated associations in different subgroups and sensitivity analyses. For food groups showing a nonlinear association with CRC, we described optimal intake values with the lowest risk. Finally, we assessed the meta-evidence of each meta-analysis using the NutriGrade scoring system.

In conclusion, findings of this meta-analysis showed that a diet characterized by high intake of whole grains, vegetables, fruit and dairy products and low amounts of red meat and processed meat was associated with lower risk of CRC.

Thus, a plant-based diet as a modifiable lifestyle factor should be promoted regarding CRC prevention.

References

1. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015;136:E359–E86.
2. Vieira AR, Abar L, Chan DSM, et al. Foods and beverages and colorectal cancer risk: a systematic review and meta-analysis of cohort studies, an update of the evidence of the WCRF-AICR Continuous Update Project. *Ann Oncol* 2017;28:1788–802.
3. Feng YL, Shu L, Zheng PF, et al. Dietary patterns and colorectal cancer risk: a meta-analysis. *Eur J Cancer Prev* 2017;26:201–11.
4. Schwedhelm C, Boeing H, Hoffmann G, et al. Effect of diet on mortality and cancer recurrence among cancer survivors: a systematic review and meta-analysis of cohort studies. *Nutr Rev* 2016; 74:737–48.
5. Schwingshackl L, Chaimani A, Bechthold A, et al. Food groups and risk of chronic disease: a protocol for a systematic review and network meta-analysis of cohort studies. *Syst Rev* 2016;5:125.
6. Schwingshackl L, Hoffmann G, Lampousi AM, et al. Food groups and risk of type 2 diabetes mellitus: a systematic review and meta-analysis of prospective studies. *Eur J Epidemiol* 2017;32:363–75.
7. Schwingshackl L, Schwedhelm C, Hoffmann G, et al. Food groups and risk of all-cause mortality: a systematic review and meta-analysis of prospective studies. *Am J Clin Nutr* 2017;105:1462–73.
8. Bechthold A, Boeing H, Schwedhelm C, et al. Food groups and risk of coronary heart disease, stroke and heart failure: a systematic review and dose-response meta-analysis of prospective studies. *Crit Rev Food Sci Nutr* 2017. epub ahead of print
9. Schwingshackl L, Schwedhelm C, Hoffmann G, et al. Food groups and risk of hypertension: a systematic review and dose-response meta-analysis of prospective studies. *Adv Nutr* 2017;8:793–803.
10. Stroup DF, Berlin JA, Morton SC, et al. Meta-Analysis of Observational Studies in Epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. *JAMA* 2000;283:2008–12.
11. Schwingshackl L, Hoffmann G. Adherence to Mediterranean diet and risk of cancer: an updated systematic review and meta-analysis of observational studies. *Cancer Med* 2015;4:1933–47.
12. Schwingshackl L, Hoffmann G. Adherence to Mediterranean diet and risk of cancer: a systematic review and meta-analysis of observational studies. *Int J Cancer* 2014;135:1884–97.
13. Schwingshackl L, Bogensberger B, Hoffmann G. Diet quality as assessed by the healthy eating index, alternate healthy eating index, dietary approaches to stop hypertension score, and health outcomes: an updated systematic review and meta-analysis of cohort studies. *J Acad Nutr Diet* 2017. epub ahead of print
14. Schwingshackl L, Knüppel S, Schwedhelm C, et al. Perspective: NutriGrade: a scoring system to assess and judge the meta-evidence of randomized controlled trials and cohort studies in nutrition research. *Adv Nutr* 2016;7:994–1004.
15. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986;7:177–88.
16. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol* 1992;135:1301–9.
17. Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose-response data. *Stata J* 2006;6:40–57.
18. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002;21:1539–58.
19. Egger M, Smith GD, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629–34.
20. Bamia C, Lagiou P, Buckland G, et al. Mediterranean diet and colorectal cancer risk: results from a European cohort. *Eur J Epidemiol* 2013;28:317–28.
21. Aleksandrova K, Pischon T, Buijsse B, et al. Adult weight change and risk of colorectal cancer in the European Prospective Investigation into Cancer and Nutrition. *Eur J Cancer* 2013;49: 3526–36.
22. Pischon T, Lahmann PH, Boeing H, et al. Body size and risk of colon and rectal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). *J Natl Cancer Inst* 2006;98: 920–31.

23. Leufkens AM, Van Duijnhoven FJ, Siersema PD, et al. Cigarette smoking and colorectal cancer risk in the European Prospective Investigation into Cancer and Nutrition study. *Clin Gastroenterol Hepatol* 2011;9:137–44.
24. Robsahm TE, Aagnes B, Hjartaker A, et al. Body mass index, physical activity, and colorectal cancer by anatomical subsites: a systematic review and meta-analysis of cohort studies. *Eur J Cancer Prev* 2013;22:492–505.
25. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. *Curr Opin Lipidol* 2002;13:3–9.
26. Magalhaes B, Peleteiro B, Lunet N. Dietary patterns and colorectal cancer: systematic review and meta-analysis. *Eur J Cancer Prev* 2012;21:15–23.
27. Brand-Miller JC, Holt SH, Pawlak DB, et al. Glycemic index and obesity. *Am J Clin Nutr* 2002;76: 281s–5s.
28. Bray GA, Popkin BM. Dietary fat intake does affect obesity! *Am J Clin Nutr* 1998;68:1157–73.
29. Medina-Remon A, Kirwan R, Lamuela-Raventos RM, et al. Dietary patterns and the risk of obesity, type 2 diabetes mellitus, cardiovascular diseases, asthma, and neurodegenerative diseases. *Crit Rev Food Sci Nutr* 2016;1–35. epub ahead of print
30. Kyrgiou M, Kalliala I, Markozannes G, et al. Adiposity and cancer at major anatomical sites: umbrella review of the literature. *BMJ* 2017;356:j477.
31. Kaubisch S, Lum BL, Reese J, et al. Stage T1 bladder cancer: grade is the primary determinant for risk of muscle invasion. *J Urol* 1991;146:28–31.
32. McPherson-Kay R. Fiber, stool bulk, and bile acid output: implications for colon cancer risk. *Prev Med* 1987;16:540–4.
33. Leenders M, Leufkens AM, Siersema PD, et al. Plasma and dietary carotenoids and vitamins A, C and E and risk of colon and rectal cancer in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 2014;135:2930–9.
34. Milk and Dairy Products. In: Food chemistry. Springer, Berlin, Heidelberg, 2009.
35. European Food Safety Authority. The EFSA Comprehensive European Food Consumption and Composition Database (https://www.efsa.europa.eu/en/science/data: accessed 12.10.2017), 2015.
36. Keum N, Aune D, Greenwood DC, et al. Calcium intake and colorectal cancer risk: dose-response meta-analysis of prospective observational studies. *Int J Cancer* 2014;135:1940–8.
37. Lamprecht SA, Lipkin M. Cellular mechanisms of calcium and vitamin D in the inhibition of colorectal carcinogenesis. *Ann N Y Acad Sci* 2001; 952:73–87.
38. Chakrabarty S, Wang H, Canaff L, et al. Calcium sensing receptor in human colon carcinoma: interaction with Ca(2+) and 1,25-dihydroxyvitamin D(3). *Cancer Res* 2005;65:493–8.
39. Norat T, Riboli E. Dairy products and colorectal cancer. A review of possible mechanisms and epidemiological evidence. *Eur J Clin Nutr* 2003;57:1–17.
40. Ye Q, Zheng Y, Fan S, et al. Lactoferrin deficiency promotes colitis-associated colorectal dysplasia in mice. *PLoS One* 2014;9:e103298
41. Evans NP, Misyak SA, Schmelz EM, et al. Conjugated linoleic acid ameliorates inflammation-induced colorectal cancer in mice through activation of PPARgamma. *J Nutr* 2010;140:515–21.
42. Faghfoori Z, Pourghassem Gargari B, Saber A, et al. Prophylactic effects of secretion metabolites of dairy lactobacilli through downregulation of ErbB-2 and ErbB-3 genes on colon cancer cells. *Eur J Cancer Prev* 2017. epub ahead of print
43. Norat T, Riboli E. Meat consumption and colorectal cancer: a review of epidemiologic evidence. *Nutr Rev* 2001;59:37–47.
44. Cross AJ, Pollock JR, Bingham SA. Haem, not protein or inorganic iron, is responsible for endogenous intestinal N-nitrosation arising from red meat. *Cancer Res* 2003;63:2358–60.
45. Yu YN, Fang JY. Gut microbiota and colorectal cancer. *Gastrointest Tumors* 2015;2:26–32.
46. Tuan J, Chen YX. Dietary and lifestyle factors associated with colorectal cancer risk and interactions with microbiota: fiber, red or processed meat and alcoholic drinks. *Gastrointest Tumors* 2016;3:17–24.