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Impact of dietary patterns and the main food groups on mortality and recurrence in cancer survivors: a systematic review of current epidemiological literature

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ABSTRACT

Objective To determine whether there is an association between dietary patterns/indices and foods from the main food groups (highest vs lowest intakes) prior to or after cancer diagnosis and mortality and cancer recurrence in cancer survivors.

Participants Survivors of common cancers with a 10-year survival rate of ≥50%: bladder, bowel, breast, cervical, kidney, laryngeal, prostate, testicular, uterine cancer, malignant melanoma and (non-)Hodgkin's lymphoma.

Outcome measures Mortality (overall, cancer-specific, from other causes) and cancer recurrence.

Information sources PubMed, Embase and the Cochrane Library were searched from inception to April 2017. Additional studies were identified by searching reference lists. Two authors independently screened titles and abstracts, assessed study quality and extracted the data.

Results A total of 38 studies were included. The risk of bias was rated low for the included randomised controlled trials (RCTs) and moderate for the cohort studies. The quality of evidence was assessed with the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach and was rated moderate (RCTs), and (very)low (cohort studies). Reducing the amount of fat after diagnosis appears to decrease the risk of breast cancer recurrence. Adherence to a high-quality diet and prudent diet after diagnosis appears to decrease the risk of death from other causes (and overall mortality for high-quality diet) in breast cancer survivors. Adherence to a Western diet, before and after diagnosis, appears to increase the risk of overall mortality and death from other causes among breast cancer survivors. Evidence from studies among other cancer survivors was too limited or could not be identified.

Conclusion For many cancer survivors, there is little evidence to date to indicate that particular dietary behaviours influence outcomes with regard to recurrence and mortality. Notwithstanding, limited evidence suggests that a low-fat diet, a high-quality diet and a prudent diet are beneficial for breast cancer survivors, while a Western diet is detrimental for breast cancer survivors.

Strengths and limitations of this study

- ► Dietary patterns/indices and whole foods reflect the complexity of dietary intake and capture synergistic relationships between various dietary constituents.
- ► Most studies investigating dietary patterns/indices and foods before diagnosis do not consider potential modifications in dietary intake after cancer diagnosis.
- ► Cohort studies provide weaker empirical evidence than randomised controlled trials for examining relationships between dietary exposure and mortality and cancer recurrence.

INTRODUCTION

As cancer survival rates continue to improve, there is an increased need to identify modifiable lifestyle factors among cancer survivors in order to improve long-term health.

Adherence to a diet rich in fruit and vegetables could decrease the risk of several types of cancer and increase overall life expectancy.[1 2] The suggestion that epigenetic aberrations occurring in cancer could be altered by nutrients makes it plausible that dietary changes after successful cancer treatment could improve prognosis.[3 4]

Although cancer survivors are responsive to health promotion,[5 6] a recent study has indicated that survivors had poorer diets than individuals without cancer.[7] One possible explanation could be the difficulty for cancer survivors in adopting a healthier diet without clear evidence that it will improve their survival.[8] While guidelines have been well documented for the prevention of cancer, many uncertainties remain for nutrition after cancer treatment.[9] A systematic review, as part of the Continuous Update Project of the World Cancer Research Fund International, was published on diet, nutrition, physical activity and survival in breast cancer survivors.[10] The independent panel of scientists concluded that the evidence to date was

not strong enough to make specific recommendations for breast cancer survivors. A recent meta-analysis investigating the role of diet on overall mortality and recurrence among cancer survivors concluded that adherence to a Western diet is positively associated with overall mortality, and a high-quality diet/healthy dietary pattern is inversely associated with overall mortality among all cancer survivors.[11]

In the setting of survivors of cancers with a 10-year survival rate ≥50%, this systematic review provides a structured overview of randomised controlled trials (RCTs) and cohort studies addressing the relationship between adherence to dietary patterns/indices and intake of foods from the main food groups, prior to or after cancer diagnosis, and health outcomes including cancer recurrence, cancer-specific mortality, overall mortality and death from other causes than cancer. Given that these survivors have the potential for long-term survival, they may be most likely to benefit from dietary changes to prevent or delay cancer recurrence and improve survival. Notwithstanding, many of these survivors will die from other causes such as cardiovascular disease—even if the dietary exposures identified will not help the investigated outcomes, it could be desirable to follow a diet that could help reduce other conditions.

METHODS

Search strategy

From inception up to April 2017, PubMed, Embase and the Cochrane Library were searched to find English-language articles of original and published randomised trials and observational studies to answer the following research question: does adherence to/intake of dietary patterns/indices and foods (highest vs lowest adherence/intake) prior to or after cancer diagnosis increase or decrease the risk of mortality and cancer recurrence among cancer survivors of common cancers with a 10-year survival rate of ≥50%? This research question was developed using the PICO framework;P: patient, population, or problem; I: intervention, prognostic factor, or exposure; C: comparison or intervention; O: outcome (supporting data review protocol online supplementary file S1). Search strategies included search terms related to dietary patterns, dietary indices, diet quality, foods from the main food groups and outcomes of interest, including overall mortality, cancer-specific mortality, death from other causes and recurrence of cancer. Additionally, studies were identified by searching reference lists of relevant studies, literature reviews and meta-analyses. After the search was completed, articles were screened and selected independently based on the title and abstract by two of the authors (SJ and FvO). The data extraction was performed independently by the same authors (SJ and FvO) and any disagreements about study inclusion were resolved through consensus or a third party.

Inclusion and exclusion criteria

Eligibility criteria included adult survivors of cancer (no sex or age restriction) who were defined as individuals who had been diagnosed with a primary cancer, received cancer therapy and were in remission or had recovered completely from cancer. Considered cancer types were the commonly occurring cancers in the Western world with a 10-year net survival of at least 50% (based on cancer diagnoses of men and women during 2010–2011 in England and Wales).[12] These include in decreasing order of net survival: testicular cancer (98%), malignant melanoma (MM) (89%), prostate cancer (84%), Hodgkin's lymphoma (HL) (80%), breast cancer (78%), uterine cancer (77%), non-Hodgkin's lymphoma (NHL) (63%), cervical cancer (63%), laryngeal cancer (62%), bowel cancer (57% including both colon and rectal cancer), bladder cancer (50%) and kidney cancer (50%). In the statistical analyses, adjustments had to be made for at least age and disease stage at baseline and, where possible, for cancer treatment. Excluded papers did not state HRs or relative risks (RRs), nor 95% CIs; neither did they provide information on disease stage or tumour grade or therapy. Additionally, studies were excluded when outcomes were combined, such as mortality and cancer progression, mortality and diagnosed metastasis, or where prostate cancer recurrence was determined by a rising prostate specific antigen (PSA) level only.

Dietary exposure

Dietary patterns/indices that were considered were assessed by index-based methods and data-driven approaches, such as principal component analysis (factor analysis) and cluster analysis.[13] The following diet scores were considered: the Healthy Eating Index 2005 (HEI-2005),[14 15] the alternate Healthy Eating Index 2010 (AHEI),[16] the World Cancer Research Fund and the American Institute for Cancer Research (WCRF/AIRC) dietary guidelines adherence score[17] and the American Cancer Society (ACS) diet-specific recommendations for cancer prevention,[18] the recommended food score (RFS),[19] the Diet Quality Index-Revised (DQIR),[20] the Dietary Approaches to Stop Hypertension diet (DASH) diet,[21] the Healthy Nordic Food Index (HNFI)[22] and the alternate Mediterranean diet (aMed)[23 24]; empirical patterns reviewed included a low-fat diet, a prudent/healthy diet and a Western/unhealthy diet. The HEI-2005 was developed by the US Department of Agriculture and targets foods that could possibly reduce the risk of chronic diseases and include fruits, vegetables, fibre, soy, nuts, ratio white and red meat, alcohol, trans fat, saturated fat ratio and multivitamin use.[14] Five years later, the AHEI was introduced, which differs from the HEI-2005 by distinguishing quality within food groups and recognising health benefits of unsaturated oils.[25] The RFS includes the foods fruits, vegetables, whole grains, dairy and protein foods low in fat. Diet diversity and moderation was addressed by the DQIR and included fruits, vegetables, cholesterol, total fat, saturated fat, iron, calcium and fat/sugar moderation. The aMed is based on the original Mediterranean diet score and includes fruits, vegetables, legumes, nuts, whole grains, red and processed meat,

moderate alcohol and the ratio of monounsaturated and saturated fat.[26 27] In addition, whole foods of the main food groups (UK Eatwell Guide)[28] were considered. The composition of the investigated groups was as follows: (1) fruit and vegetables including citrus fruits, stone fruits, soft fruits, fleshy fruits, vine fruits, flower vegetables, leafy vegetables, stem vegetables, fruit vegetables, mushrooms, bulbs and roots; (2) grain foods including potatoes, bread, rice, pasta and cereal; (3) protein foods including unprocessed meat, red meat, poultry, fish, eggs, tofu, nuts, seeds, pulses, legumes and beans; (4) dairy and alternative products including yoghurt, milk and cheese; and (5) oils and spreads including vegetable oils and spreads. Although processed (red) meats are not included in the main food groups recommended by the UK Eatwell Guide, lean red meats (rich in protein, iron, zinc, selenium and B vitamins) can be part of a healthy diet. Therefore, studies that made no distinction between (lean) red meats and processed meats in their estimates were still included in this systematic review. Information on intake of food was obtained before or after cancer diagnosis with food records, food frequency questionnaires (FFQ) (self-administered or via an interview) or 24-hour recalls, and expressed in servings or (milli)grams per day/week/month. No restrictions were made for time of follow-up, and timing or frequency of dietary intake.

Mortality and cancer recurrence

Considered endpoints were overall mortality, cancer-specific mortality, death from other causes and cancer recurrence. The cause of death was confirmed via death certificates or the National Death Index in each of the studies. Cancer recurrence was defined as a new occurrence of cancer after a period of time during which the cancer could not be detected at the same or at a different site to the initial primary tumour. Cancer recurrence had to be confirmed by a biopsy, scan, medical record, cancer registry or treating physician.

Assessment risk of bias and level of quality

The Cochrane Collaboration risk of bias assessment tools were used for appraisal of RCTs[29] and cohort studies.[30] For RCTs, the RoB V.2.0 tool (a revised tool for risk of bias in randomised trials) was used to evaluate the risk of bias. Cohort studies were appraised with an adjusted version of the ROBINS-I tool.[29 30] Levels of quality were determined with the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) approach[31]; evidence from RCTs or multiple double-upgraded observational studies were considered as high quality, downgraded RCTs or upgraded observational studies were considered as moderate quality, double-downgraded RCTs or observational studies were considered as low quality, and triple-downgraded RCTs, downgraded observational studies or case series/case reports were considered as very low quality.[31] Factors reducing the quality of the evidence include limitations in study design, inconsistency between study results, indirectness of evidence, imprecision and publication bias. Factors increasing the quality of the evidence include a large magnitude of effect, correction for all plausible confounding that could reduce the demonstrated effect or increase the effect if no effect was observed, and presence of a dose–response gradient. For observational studies, this could intent controlling for key knows risk factors and confounders. GRADE separates the process of assessing the quality of evidence from making recommendations. To determine whether evidence for an association between dietary patterns/indices or foods and mortality or cancer recurrence among cancer survivors was conclusive, the risk of bias and levels of quality were considered.

RESULTS

The search resulted in 2883 citations after removal of duplicates. After screening the titles and abstracts, 95 full-text articles were assessed for eligibility—a total of 2 RCTs and 36 cohort studies were included in this systematic review. No studies could be identified for cervical, kidney, testicular, uterine cancer, HL or MM survivors. Dietary patterns/indices could be identified for bowel, breast, prostate cancer and NHL. Whole foods from the main food groups could be identified for bladder, bowel, breast, laryngeal, prostate cancer and NHL survivors.

The protocol used for this systematic review is available in the supporting data (online supplementary file S1). A detailed search strategy is provided in box and the search

Box Literature search for the PubMed database addressing the relationship between diet and mortality among bladder cancer survivors

("urinary bladder neoplasms"[Mesh] OR "urinary bladder neoplasm*" OR "bladder cancer*" OR "bladder tumor*" OR "bladder tumour*") AND ("mortalit*" OR "mortality"[Mesh] OR "death"[Mesh] OR "recurrence*" OR "recurrence"[Mesh] OR "surviv*" OR "survival"[Mesh] OR "disease-free survival"[Mesh] OR "survival analysis"[Mesh] OR "survival rate"[Mesh]) OR "proportional hazards models"[Mesh] OR "kaplan-meier" OR "cox" OR "survivors"[Mesh]) AND ("diet*" OR "diet"[Mesh] OR "dietary pattern*" OR "diet, Mediterranean"[Mesh] OR "diet, vegetarian"[Mesh] OR "diet, Western"[Mesh] OR "energy intake"[Mesh] OR "caloric restriction"[Mesh] OR "low calorie diet" OR "low fat diet" OR "dietary fat*" OR "dietary carbohydrate*" OR "dietary fiber OR "dietary protein*" OR "nutrition*" OR "food*" OR "fruit"[Mesh] OR "fruit*" OR "citrus fruit*" OR "vegetables"[Mesh] OR "vegetable*" OR "brassica" OR "cruciferous vegetable*" OR "meat"[Mesh] OR "red meat"[Mesh] OR "meat*" OR "beef" OR "pork" OR "lamb" OR "poultry" OR "chicken" OR "turkey" OR "duck" OR "fish products"[Mesh] OR "fish" OR "shellfish" OR "seafood" OR "dairy" OR "milk" OR "ghee" OR "cheese" OR "egg*" OR "nut*" OR "edible grain"[Mesh] OR "whole grains"[Mesh] OR "potato*" OR "bread" OR "cereal*" OR "rice*") NOT ("DNA-Binding Proteins"[Mesh] OR "Peptides"[Mesh] OR "Intercellular Signaling Peptides and Proteins"[Mesh] OR "Chromosomes, Human"[Mesh] OR "Immunohistochemistry"[Mesh] OR "In Situ Hybridization, Fluorescence"[Mesh]) AND ("humans"[MeSH Terms] AND English[lang]

Table 1 Number of studies investigating the association between prediagnosis dietary patterns/indices and mortality/cancer recurrence in different populations of cancer survivors

Cancer site/type	Diet quality indices					Prudent/healthy diet					Western diet/unhealthy diet				
	Studies (n)	CR	OM	CSM	DO	Studies (n)	CR	OM	CSM	DO	Studies (n)	CR	OM	CSM	DO
Bladder	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
Bowel	2	–	2	1	–	1	–	1	1	–	1	–	2	2	–
Breast	1	–	1	1	1	2	1	4	4	4	2	1	4	4	4
Cervix	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
HL	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
Kidney	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
Larynx	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
MM	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
NHL	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
Prostate	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
Testes	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
Uterus	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–

The number of studies does not correspond with the number of outcomes as some studies investigate multiple outcomes and several dietary patterns in the same population.
CR, cancer recurrence; CSM, cancer-specific mortality; DO, death from other causes than cancer; HL, Hodgkin's lymphoma; MM, malignant melanoma; NHL, non-Hodgkin's lymphoma; OM, overall mortality.

was adapted accordingly for the individual cancers and databases (online supplementary file S1). The review was written according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines.[32] A summary of the number of studies for prediagnosis dietary patterns/indices (table 1) and postdiagnosis dietary patterns/indices (table 2) and mortality and cancer recurrence is provided. Additionally, tables with the number of studies for prediagnosis food intake (table 3) and postdiagnosis food intake (table 4) and mortality and cancer recurrence are given. The study characteristics including the HRs/RRs with their corresponding 95% CI are provided in the supporting data (online supplementary file S2).

Templates of the RoB 2.0 and ROBINS-I tools can be found in the supporting data (online supplementary file S1). Results for the assessment of the risk of bias for each individual RCT (RoB 2.0) and cohort study (ROBINS-I)

Table 2 Number of studies investigating the association between postdiagnosis dietary patterns/indices and mortality/cancer recurrence in different populations of cancer survivors

Cancer site/type	Diet quality indices					Prudent diet/healthy diet					Western diet/unhealthy				
	Studies (n)	CR	OM	CSM	DO	Studies (n)	CR	OM	CSM	DO	Studies (n)	CR	OM	CSM	DO
Bladder	0	–	–	–	–	0	–	–	–	–	0		–	–	–
Bowel	2	–	5	3	–	2	1	2	1	–	2	1	2	1	–
Breast	7	1	11	9	8	2	1	2	2	2	2	1	2	2	2
Cervix	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
HL	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
Kidney	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
Larynx	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
MM	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
NHL	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
Prostate	1	–	1	1	–	1	–	1	1	–	1	–	1	1	–
Testes	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
Uterus	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–

The number of studies does not correspond with the number of outcomes as some studies investigate multiple outcomes and several dietary patterns in the same population.
CR, cancer recurrence; CSM, cancer-specific mortality; DO, death from other causes than cancer; HL, Hodgkin's lymphoma; MM, malignant melanoma; NHL, non-Hodgkin's lymphoma; OM, overall mortality.

Table 3 Number of studies investigating the association between prediagnosis foods and mortality/cancer recurrence in different populations of cancer survivors

Cancer site/type	Fruit and vegetables					Grain foods					Protein foods					Dairy and alternatives					Oils and spreads				
	Studies (n)	CR	OM	CSM	DO	Studies (n)	CR	OM	CSM	DO	Studies (n)	CR	OM	CSM	DO	Studies (n)	CR	OM	CSM	DO	Studies (n)	CR	OM	CSM	DO
Bladder	1	–	4	4	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
Bowel	0	–	–	–	–	1	–	5	–	–	3	1	6	6	2	2	–	6	6	–	0	–	–	–	–
Breast	5	–	7	5	1	1	–	1	1	–	3	–	6	3	1	1	–	1	1	–	0	–	–	–	–
Cervix	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
HL	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
Kidney	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
Larynx	1	–	3	–	–	1	–	3	–	–	1	–	4	–	–	1	–	2	–	–	1	–	2	–	–
MM	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
NHL	2	–	11	11	–	0	–	–	–	–	1	–	3	3	–	1	–	1	1	–	0	–	–	–	–
Prostate	0	–	–	–	–	0	–	–	–	–	1	–	–	1	–	0	–	–	–	–	0	–	–	–	–
Testes	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
Uterus	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–

The number of studies does not correspond with the number of outcomes as some studies investigate multiple outcomes and several food items in the same population.
CR, cancer recurrence; CSM, cancer-specific mortality; DO, death from other causes than cancer; HL, Hodgkin's lymphoma; MM, malignant melanoma; NHL, non-Hodgkin's lymphoma; OM, overall mortality.

Table 4 Number of studies investigating the association between postdiagnosis foods and mortality/cancer recurrence in different populations of cancer survivors

Cancer site/type	Fruit and vegetables					Grain foods					Protein foods					Dairy and alternatives					Oils and spreads				
	Studies (n)	CR	OM	CSM	DO	Studies (n)	CR	OM	CSM	DO	Studies (n)	CR	OM	CSM	DO	Studies (n)	CR	OM	CSM	DO	Studies (n)	CR	OM	CSM	DO
Bladder	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
Bowel	0	–	–	–	–	0	–	–	–	–	1	–	2	2	2	1	–	2	2	–	0	–	–	–	–
Breast	4	1	6	4	1	0	–	–	–	–	4	1	5	6	1	3	3	5	2	–	1	1	–	1	–
Cervix	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
HL	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
Kidney	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
Larynx	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
MM	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
NHL	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
Prostate	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	1	–	3	–	–	0	–	–	–	–
Testes	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–
Uterus	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–	0	–	–	–	–

The number of studies does not correspond with the number of outcomes as some studies investigate multiple outcomes and several food items in the same population.
CR, cancer recurrence; CSM, cancer-specific mortality; DO, death from other causes than cancer; HL, Hodgkin's lymphoma; MM, malignant melanoma; NHL, non-Hodgkin's lymphoma; OM, overall mortality.

will be provided on request. Briefly, the included RCTs investigating a low-fat diet and mortality among breast cancer survivors indicated a low risk of bias[33]; the included cohort studies all had a moderate risk of bias.[34]

An overview of the GRADE ratings with comments can be found in the supporting data (online supplementary file S3). As the risk of bias was rated 'low' and 'moderate', there was no reason to downgrade the quality of evidence on this matter. The quality level of the body of evidence of the studies was rated 'very low', 'low' and 'moderate' by two of the authors (SJ and FvO) when applying the grading system developed by the GRADE collaboration.[31] Briefly, the level of evidence for the association between a low-fat diet and bladder cancer recurrence and mortality was downgraded from 'high' to 'moderate' due to the presence of potential confounding factors in many studies. Evidence for associations between dietary factors and bladder cancer recurrence and mortality from cohort studies could not score higher than 'low' level of evidence and was downgraded to 'very low' if inconsistent, indirect or under suspicion of publication bias.

Bladder cancer

A total of one cohort study could be identified for bladder cancer survivors regarding fruit and vegetable consumption. The study of Tang *et al* investigated prediagnosis fruit and vegetable consumption with data from 239 male and female bladder cancer survivors from the Roswell Park Cancer Institute Tumor Registry.[35] After an average of 8-year follow-up, no associations were observed between overall mortality or bladder cancer-specific mortality when comparing survivors with the highest intakes of total fruit, total vegetables or other cruciferous vegetables (raw or cooked) with those in the lowest intake group. An association was, however, observed for broccoli intake (≥1 vs <1 serving per month) with overall mortality (broccoli raw HR=0.57; 95% CI 0.39 to 0.83, broccoli cooked HR=0.67; 95% CI 0.49 to 0.91) and bladder cancer-specific mortality (broccoli raw HR=0.43; 95% CI 0.25 to 0.74). The intake of other raw and cooked vegetables including cabbage, cauliflower, Brussels sprouts, kale, turnip, collard or mustard greens was not related with mortality.[35]

In summary, no conclusive evidence for an association between vegetable and fruit intake and mortality among bladder cancer survivors could be provided as evidence for each exposure and outcome was based on the results of one study only.

Bowel cancer

A total of 12 cohort studies could be identified for bowel cancer survivors. Three observational cohort studies could be identified investigating the role of a prediagnosis and postdiagnosis prudent diet on mortality in bowel cancer survivors. Results of the Cancer and Leukemia Group B study indicated no associations between a prudent diet after cancer diagnosis and decreased mortality.[36] However, there was a higher overall mortality among these survivors with the highest postdiagnosis intakes of a Western diet in comparison with those in the lowest category (HR=2.32; 95% CI 1.36 to 3.96).[36] When comparing participants in the Familial Bowel Cancer Registry with the highest and lowest intakes of a prudent diet before cancer diagnosis, no associations were found with mortality.[37] Besides a prudent diet, two other dietary patterns comparable with a Western diet were identified in this study: a high processed meat pattern and a high sugar pattern diet. No associations were reported for the pattern high in sugar and mortality when comparing the highest to the lowest intake group, whereas a high processed meat pattern was specifically related to increased colon cancer mortality (HR=2.13; 95% CI 1.03 to 4.43). This relationship between a processed meat pattern and bowel cancer survival was modified by sex.[37] In the Nurses' Health Study (NHS), no associations were observed between adherence to the AHEI, DASH or aMed score, a prudent diet or a Western diet after diagnosis and mortality in these bowel cancer survivors.[23] It should be noted, however, that even though there was 'no statistically significant' result for the role of a postdiagnosis Western diet in this study, the HR was >1 (HR=1.31; 95% CI 0.89 to 1.97) as observed in the earlier described study of Meyerhardt *et al* (HR=2.32; 95% CI 1.36 to 3.96).[36] Adherence to the HEI diet score was investigated in a large study including 5727 male and female survivors in the USA and indicated no association between prediagnosis adherence to the HEI-2005 score with overall mortality or cancer-specific mortality.[38] Recently, a German study examined adherence to the Modified Mediterranean Diet Score (MMDS) and the HNFI and found that postdiagnosis adherence to this MMDS was associated with a decreased risk of overall mortality among bowel cancer survivors (HR=0.48; 95% CI 0.32 to 0.74).[39] In the European Prospective Investigation into Cancer and Nutrition cohort, data from participants of 10 European countries were analysed on adherence to WCRF/AICR diet scores and intake of total dairy, milk, yoghurt, cheese, red meat and poultry.[39–42] Prediagnosis adherence to this high-quality diet score indicated a decreased risk of overall mortality among bowel cancer survivors (HR=0.79; 95% CI 0.65 to 0.98).[41] No evidence of an association with mortality was observed for foods from the main food groups, including fruits, vegetables, dairy or protein foods among these bowel cancer survivors.[42] The study by Yang *et al* indicated a protective association with milk consumption and overall mortality after a diagnosis of bowel cancer (RR=0.72; 95% CI 0.55 to 0.94).[43] Additionally, no association could be found for total dairy intake and mortality in this study.[43] Whole gains, another food group investigated in bowel cancer survivors, were not associated with overall mortality among 1119 Danish, Swedish and Norwegian bowel cancer survivors in the HELGA cohort.[44] Carr *et al* reported that red and processed meat consumption was not associated with a poorer survival among stage I–III bowel cancer survivors in a follow-up study of the Darmkrebs: Chancen der Verhutung durch Screening study.[45]

However, it should be noted that the authors investigated red and processed meat combined and they suggest that major changes in the consumption of red meat measured at 5-year follow-up could have influenced survival.[45] The study of McCullough *et al* indicated an association with mortality when comparing highest versus lowest prediagnosis and postdiagnosis red and processed meat consumption for overall mortality (RR=1.29; 95% CI 1.05 to 1.59) and death from other causes than bowel cancer (RR=1.39; 95% CI 1.00 to 1.92).[46] It should be noted that the authors combined the consumption of red and processed meat in these estimates, and that there were no associations found for 'fresh' meats and mortality.[46]

In summary, no conclusive evidence for an association between adherence to a high-quality diet, a prudent diet, a Western diet and the consumption of fruits, vegetables, meats or dairy and mortality in bowel cancer survivors could be provided as evidence for each exposure and outcome was based on the results of one study only or on inconsistent results.

Breast cancer

A total of 2 RCTs and 16 cohort studies could be identified for breast cancer survivors. Two dietary intervention trials among breast cancer survivors met the inclusion criteria.[47 48] The study of Chlebowski *et al* aimed to reduce postdiagnosis dietary fat intake to almost one-sixth of total energy intake while maintaining nutritional adequacy in women participating in the Women's Intervention Nutrition Study (trial registration number NCT00002564).[47] Breast cancer survivors in the intervention group were informed extensively on maintaining weight based on energy intake, while minimum dietary advice on nutrient intake was provided to breast cancer survivors in the control group. Women in the intervention group had a lower dietary fat intake compared with those in the control group, whereas no differences could be observed for a lower energy or higher dietary fibre intake. According to the authors of this study, there was no association with overall mortality between women adhering to a low-fat diet and women given minimum dietary advice (HR=0.89; 95% CI 0.65 to 1.21). However, for relapse events (including local, regional, distant or ipsilateral breast cancer recurrence or new contralateral breast cancer) the HR of an event in the intervention group compared with the control group was HR=0.76; 95% CI 0.60 to 0.98. This could indicate that a lifestyle intervention reducing dietary fat intake could improve relapse-free survival of breast cancer survivors.[47] In the Women's Healthy Eating and Living study (trial registration number NCT00003787), breast cancer survivors in the intervention group received telephone counselling with additional cooking classes and brochures to support adherence to a postdiagnosis diet high in fruit (three servings/day), high in vegetables (five servings/day and 16 oz of vegetable juice), high in fibre (30 g/day) and low in fat (15%–20% of energy intake from fat).[48] In the control group, breast cancer survivors received written advice to eat at least five portions of fruit and vegetables each day (five-a-day advice). Differences between the former and latter groups in mean consumption of vegetables (+65%), fruit (+25%), fibre (+30%) and energy from fat (−13%) were observed at 4 years. The authors of this trial reported that no associations were observed for overall survival when comparing women in the intervention group with those in the control group (HR=0.91; 95% CI 0.72 to 1.15).[48] Although the results for overall mortality in the trials were statistically non-significant, the HRs of both studies were <1 (HR=0.89; 95% CI 0.65 to 1.21[47] and HR=0.91; 95% CI 0.72 to 1.15[48]).

Postdiagnosis dietary indices were examined in the Health, Eating, Activity, and Lifestyle (HEAL) study,[49] Women's Health Initiative's Dietary Modification Trial and Observational Study (WHI),[50] NHS[24 51] and Cancer Prevention Study II Nutrition Cohort (CPS-II).[52] McCullough *et al* demonstrated that prediagnosis and postdiagnosis adherence to the ACS diet among breast cancer survivors in the CPS-II cohort was not association with breast cancer-specific mortality.[52] It should be noted, however, that an inverse association was observed for the continuous postdiagnosis diet scores and other causes of death (RR=0.88; 95% CI 0.79 to 0.99).[52] While no associations were found between prediagnosis and postdiagnosis fruit and vegetable intake and the intake of whole grains, detrimental associations were found with postdiagnosis red and processed meat consumption and overall mortality and death from other causes (respectively RR=0.64; 95% CI 0.49 to 0.84 and RR=0.57; 95% CI 0.39 to 0.82).[52] In the NHS, postdiagnosis dietary DQIR, RFS, aMed, AHEI and DASH scores were not associated with overall mortality or breast cancer-specific mortality.[24 51] Closer adherence to DASH and AHEI was, however, related to a lower risk of death from other causes than breast cancer (respectively RR=0.72; 95% CI 0.53 to 0.99 and RR=0.57; 95% CI 0.42 to 0.77).[51] George *et al* examined postdiagnosis adherence to the HEI-2005 scores and concluded that there was an association with a decreased risk of mortality (overall mortality HR=0.40; 95% CI 0.17 to 0.94 and breast cancer-specific mortality HR=0.12; 95% CI 0.02 to 0.99).[49] In the WHI cohort, results of postdiagnosis adherence to the HEI-2005 scores indicated that women who consumed better quality diets had a 26% lower risk of overall mortality (HR=0.74; 95% CI 0.55 to 0.99) and a 42% lower risk of death from non-breast cancer-related death (HR=0.58; 95% CI 0.38 to 0.87).[50] Even though the result for breast cancer-specific mortality and adherence to the HEI-2005 score in this study was statistically non-significant (HR=0.91; 95% CI 0.60 to 1.40), the HR is <1, as observed for women in the HEAL study regarding cancer-specific mortality.[49] Results of the NHS indicated that a postdiagnosis prudent diet was not associated with overall or breast cancer-specific mortality while death from other causes was associated with a prudent diet after diagnosis when comparing breast cancer survivors of the highest and lowest intake group (HR=0.54; 95% CI 0.31 to 0.95)[53]—adherence to a prudent diet before diagnosis

was not associated with mortality among breast cancer survivors in the NHS.[53] Both prediagnosis and postdiagnosis adherence to a Western diet was associated with death from other causes (respectively RR=1.95; 95% CI 1.06 to 3.60 and RR=2.31; 95% CI 1.23 to 4.32).[53] The study of Kwan *et al* concludes no associations between adherence to a prediagnosis or postdiagnosis Western diet and overall mortality, breast cancer-specific mortality or cancer recurrence.[54] The HR for a Western diet and death from other causes was, however, >1 (HR=2.15; 95% CI 0.97 to 4.77),[54] and therefore in agreement with the HR for a Western diet and death from other causes observed in the study of Kroenke *et al* (RR=2.09; 95% CI 1.30 to 3.36).[53] In the Life After Cancer Epidemiology (LACE) study, postdiagnosis adherence to a prudent diet in women with early-stage breast cancer resulted in a decreased risk of death from other causes (HR=0.35; 95% CI 0.17 to 0.73) and overall mortality (HR=0.57; 95% CI 0.36 to 0.90).[54] The study of Vrieling *et al* investigated associations between a 'healthy' and 'unhealthy' prediagnosis dietary pattern and mortality in German breast cancer survivors in the Mammary carcinoma Risk factor Investigation (MARIE) study.[55] The characteristics of the defined healthy diet are comparable with a prudent diet; nevertheless, no associations between the highest and lowest intake of this defined 'healthy' diet before cancer diagnosis and mortality in breast cancer survivors were observed. However, the results did indicate that a higher intake of an 'unhealthy' diet could increase the risk of death from other causes (HR=3.69; 95% CI 1.66 to 8.17) among breast cancer survivors compared with those with the lowest intake of this diet.[55]

The majority of studies investigating prediagnosis or postdiagnosis fruit and vegetable intake indicated no association with mortality in breast cancer survivors. However, one study found that, when comparing postmenopausal breast cancer survivors in the highest tertile to the lowest tertile group, prediagnosis total vegetable intake improved overall survival (HR=0.57; 95% CI 0.35 to 0.94)—no association was found for total fruit intake and mortality in this cohort of breast cancer survivors.[56] In addition, Dal Maso *et al* found an association with total fruit and vegetable consumption and overall mortality (HR=1.27; 95% CI 1.00 to 1.61) when comparing survivors of the lowest intake group to the highest intake group.[57] Results from the After Breast Cancer Pooling Project, combining data from four cohort studies, indicated no association between postdiagnosis intakes of cruciferous vegetables and survival among 11 390 breast cancer survivors.[58] Holmes *et al* reported an association between the highest postdiagnosis poultry consumption and mortality in women once diagnosed with breast cancer (HR=0.70; 95% CI 0.50 to 0.97).[59] No associations were found for fish or red meat consumption and mortality in this population. Additionally, a high dairy intake before diagnosis among female registered nurses who participated in the NHS was related to overall survival (HR=0.72; 95% CI 0.52 to 1.00).[59] Kroenke *et al* found that postdiagnosis dairy intake among women diagnosed with early-stage invasive breast cancer in the LACE study was associated with an increased overall mortality (HR=1.39; 95% CI 1.02 to 1.90).[60] More specifically, high-fat dairy was related to overall mortality and breast cancer-specific mortality in these women (respectively HR=1.64; 95% CI 1.24 to 2.17 and HR=1.49; 95% CI 1.00 to 2.24) while low-fat dairy was not.[60] Beasley *et al* examined both meat and dairy intake after diagnosis and found no association with survival in the Collaborative Woman's Longevity Study.[61] Prediagnosis intakes of neither bread, sunflower/pumpkin seeds nor sesame/flaxseeds reduced the risk of mortality in the MARIE study.[62] Finally, postdiagnosis butter/margarine/lard consumption did increase the risk of breast cancer recurrence in a follow-up study among 472 breast cancer survivors enrolled from the Memorial Sloan-Kettering Cancer Centre (RR=1.30; 95% CI 1.03 to 1.64).[63]

In summary, no conclusive evidence could be provided for an association between most foods of the main food groups, including fruits, vegetables, meat or dairy, and cancer recurrence or mortality—evidence for each exposure and outcome was based on the results of one study only or on inconsistent results. However, limited evidence appears to indicate that the reduction of dietary fat after breast cancer diagnosis could increase relapse-free survival among breast cancer survivors, adherence to the HEI-2005 score after diagnosis is associated with decreased overall mortality, adherence to the AHEI diet after diagnosis is associated with decreased death from other causes and that adherence to a prudent diet after diagnosis is associated with decreased death from other causes among breast cancer survivors. Adherence to a prediagnosis Western diet is associated with death from other causes while postdiagnosis adherence to a Western diet is associated with an increased risk of overall mortality in breast cancer survivors.

Laryngeal cancer

One cohort study could be identified for the association between several foods from the main food groups and mortality among laryngeal cancer survivors.[64] Crosignani *et al* examined dietary habits and survival in of 215 Italian male laryngeal cancer survivors on prediagnosis dietary habits and survival. The consumption of total vegetables (HR=0.57; 95% CI 0.35 to 0.94), beef/veal (HR=0.50; 95% CI 0.30 to 0.83) and bread (HR=0.54; 95% CI 0.32 to 0.90) were all associated with a decreased risk of overall mortality when comparing the highest versus the lowest intake group. No associations were found for poultry, fish, eggs, milk, cheese, pasta, potatoes, citrus fruits, other fruits, butter or olive oil. The authors speculate that the association between the highest beef/veal intakes and mortality could tentatively be interpreted as an indicator of a good nutritional status of those participants.[64]

In summary, no conclusive evidence for an association between fruits, vegetables, protein foods, grain foods, dairy or oils and spreads, and mortality among laryngeal cancer survivors could be provided, as evidence for each

exposure and outcome was based on the results of one study only.

Non-Hodgkin's lymphoma

A total of two cohort studies could be identified for NHL survivors regarding the intake of food items. One study indicated that prediagnosis intakes of total fruit and vegetables and vegetables only (highest vs lowest intake) were associated with decreased overall mortality (respectively HR=0.68; 95% CI 0.49 to 0.95 and HR=0.58; 95% CI 0.38 to 0.89) among female NHL survivors.[65] Additionally, the highest intakes of citrus fruits and green leafy vegetables compared with the lowest intakes were related to overall mortality among survivors with NHL (respectively HR=0.73; 95% CI 0.54 to 0.99 and HR=0.71; 95% CI 0.51 to 0.98). No associations were observed for total fruit intake, yellow vegetables, red vegetables or bean vegetables and mortality while subanalysis investigating fruit and vegetables separately for each NHL subtypes did; consumption of citrus fruits improved survival in diffuse large B-cell lymphoma survivors (overall mortality HR=0.40; 95% CI 0.22 to 0.72, cancer-specific mortality HR=0.36; 95% CI 0.16 to 0.80), and the highest consumption of green leafy vegetables favoured overall mortality in follicular lymphoma survivors (HR=0.27; 95% CI 0.10 to 0.76).[65] Although Leo *et al* found no association between prediagnosis intakes of fruit, vegetables, meat, fish or legumes, and mortality in 2339 NHL survivors,[66] dairy intake did appear to be associated with a higher overall mortality (HR=1.14; 95% CI 1.00 to 1.31), yet not with NHL-specific mortality (HR=1.16; 95% CI 0.98 to 1.37).[66]

In summary, no conclusive evidence for an association between intakes of fruit, vegetables, protein foods or dairy and mortality in NHL survivors could be provided as evidence for each exposure and outcome was based on the results of one study only or on inconsistent results.

Prostate cancer

For prostate cancer, four cohort studies could be identified. Adherence to a Western diet after prostate cancer diagnosis was associated with increased overall mortality (HR=1.67; 95% CI 1.16 to 2.42) and prostate cancer-specific mortality (HR=2.53; 95% CI 1.00 to 6.42) among non-metastatic prostate cancer survivors in the Physician's Health Study (PHS).[67] The derived Western dietary patterns appeared to be driven by the consumption of processed meat.[67] A prudent diet was investigated (showing overlapping characteristics with the Mediterranean diet examined in the Health Professionals Follow-up Study (HPFS)); adherence to a prudent diet after prostate cancer diagnosis was inversely associated with overall mortality (RR=0.64; 95% CI 0.44 to 0.93) and appeared to be driven by the use of oil and vinegar dressings.[67] The HPFS reported on a Mediterranean diet and mortality in prostate cancer survivors after diagnosis.[68] Kenfield *et al* demonstrated that postdiagnosis adherence to a Mediterranean diet was associated with decreased overall mortality (HR=0.78; 95% CI 0.67 to 0.90); no association was observed for prostate cancer-specific mortality and adherence to the Mediterranean diet.[68] A prediagnosis high fish consumption in men who were diagnosed with prostate cancer while participating in the PHS was related to prolonged survival (HR=0.52; 95% CI 0.30 to 0.91) according to Chavarro *et al*.[69] Another study of Yang *et al* investigated postdiagnosis dairy intake among prostate cancer survivors.[70] The consumption of total dairy was associated with increased overall mortality (HR=1.76; 95% CI 1.21 to 2.55). Both high-fat and low-fat dairy consumption contributed to this adverse association and overall mortality (respectively HR=1.22; 95% CI 1.08 to 1.38 and HR=1.17; 95% CI 1.05 to 1.29).[70]

In summary, no conclusive evidence for an association between a Mediterranean diet score, adherence to a prudent or Western diet, fish or dairy, and mortality in prostate cancer survivors could be provided as evidence for each exposure and outcome was based on the results of one study only.

DISCUSSION

This systematic review summarises current scientific literature regarding dietary patterns/indices and foods from the main food groups and health outcomes among different groups of cancer survivors. Limited evidence appears to indicate that the reduction of dietary fat after breast cancer diagnosis could increase relapse-free survival among breast cancer survivors, adherence to the HEI-2005 score after diagnosis is associated with decreased overall mortality, adherence to the AHEI diet after diagnosis is associated with decreased death from other causes and that adherence to a prudent diet after diagnosis is associated with decreased death from other causes among breast cancer survivors. Adherence to a prediagnosis Western diet is associated with death from other causes while postdiagnosis adherence to a Western diet is associated with an increased risk of overall mortality in breast cancer survivors. Although no conclusive evidence could be provided for other survivors than of breast cancer, the results of available studies investigating dietary patterns/indices and food in other cancer survivors were described in detail.

Dietary patterns/indices

It could be speculated that the lack of effect in the two identified RCTs investigating a low-fat diet in breast cancer survivors is a consequence of the relatively short follow-up period when using mortality as the primary outcome.[47 48] It did appear, however, that a reduction in dietary fat intake could increase relapse-free survival among these survivors.[47] Nevertheless, the true beneficial effect of dietary intake in this trial remains uncertain since increased exercise and weight loss during the intervention may also have advantaged these breast cancer survivors.[47] Adherence to a high-quality diet or a prudent diet and the increase in survival could be explained by the effects of fruit and vegetables on health in general.

This could also clarify the increase in mortality among survivors with adherence to a Western diet, as it is characterised by low intakes of vegetables and fruits. It remains difficult, however, to disentangle the beneficial effect of fruit and vegetables from other foods in the diet—it could even be speculated that not the consumption of fruit and vegetables in a high-quality and prudent diet decrease mortality, but eating less amounts of sugars, salt and saturated fats could explain the associations found with mortality and relapse-free survival.

Besides the evidence for a potential role of a low-fat diet in breast cancer recurrence, most studies showed an association with overall mortality and death from other causes; not with cancer-specific mortality or cancer recurrence. Even if the exposures identified cannot help these cancer outcomes, given the survivors of the investigated cancers have potential for long-term survival, it is desirable for them to follow a diet that could help reduce other conditions such as cardiovascular disease and increase overall life expectancy. The limited number of studies indicates that additional long-term prospective studies are urgently needed to improve the strength of evidence on the influence of dietary pattern/indices adherence on cancer survival.

Foods from the main food groups

The investigated healthy dietary patterns/indices are characterised by foods of the main food groups. Epidemiological research on fruit and vegetable intake and cancer risk increased rapidly over the last few decades and it has been suggested that people with high intakes of fruit and vegetables, compared with those with low intakes, have a reduced risk of developing cancer.[71] The wide variety of nutrients including vitamins, minerals, phytochemicals and fibre in fruit and vegetables could influence epigenetic processes and potentially via this way improve cancer outcomes.[72 73] However, the exact mechanisms of how diet can alter genetic and epigenetic changes in cancer cells have yet to be established. The majority of the identified studies found statistically non-significant results, based on a p value that indicates the degree to which the data conform to the pattern predicted by the test hypothesis and all the other assumptions used in the test. Nonetheless, the HRs<1 of two studies investigating prediagnosis fruit intake overall mortality,[62 56] although statistically non-significant results, could strengthen the evidence that adherence to a high-quality diet, characterised by high intakes of fruit and vegetables, could decrease overall mortality in breast cancer survivors. The consumption of fruits could, therefore, be encouraged in breast cancer survivors as they are an important part of a high-quality diet to increase overall life expectancy. Studies investigating the role of fruit after diagnosis in cancer survivors are urgently needed.

Study strengths and limitations

The strengths of this systematic review are the inclusion of dietary patterns/indices and whole foods, and the large total number of cancer survivors investigated. By examining the whole diet, the intake of nutrients in combination is considered which provides translatable real-life scenarios for clinical recommendations.

The limitations of this systematic review were the inclusion of only two RCTs, the few studies investigating postdiagnosis intake, the use of FFQs to collect dietary information from participants in most studies, and the considerable heterogeneity in study design and participant characteristics (tumour characteristics (stage/grade), treatment, age, time of follow-up, comorbidity, differences in countries and ethnicity). Due to potential bias, data from observational studies generally provide a lower strength of evidence than from RCTs, even if they were well conducted. Conducting RCTs to investigate dietary intake in cancer survivors with mortality as an outcome can be challenging for cancers with a relatively long survival necessitating adherence to a diet in the long term. The majority of studies included in this systematic review investigated foods before cancer diagnosis, with only a few studies in the postdiagnosis setting. Information on food intake after diagnosis is valuable for investigating the effect of dietary changes on health outcomes among cancer survivors—even though it is too late to amend lifestyle factors from before diagnosis, patients are more receptive to advice after diagnosis. Although the use of FFQs is an inexpensive approach to capture data from hundreds or thousands of individuals, it may not represent the usual foods or portion sizes chosen by participants, and intake data can be compromised when multiple foods are grouped with single listings. Developments in the screening, diagnosis and treatment of cancers differ greatly between countries and therefore could influence survival. Although most studies are adjusted for tumour stage, age and treatment, often no adjustments could be made for influential lifestyle factors including body mass index, physical activity and smoking. It remains a challenge to disentangle the impact of diet from other lifestyle factors, and this should always be taken into consideration when interpreting study results.

CONCLUSION

To conclude, the reduction of dietary fat after breast cancer diagnosis could increase relapse-free survival among breast cancer survivors, adherence to a high-quality diet may protect against overall mortality and death from other causes among breast cancer survivors, and adherence to a prudent diet may protect against death from other causes among breast cancer survivors. Adherence to a Western diet before diagnosis may be detrimental for breast cancer survivors concerning death from other causes while a Western diet after diagnosis may increase overall mortality among these survivors. Additional large and well-conducted studies, preferably RCTs, are needed to clarify whether dietary

patterns/indices and food intake could influence health outcomes in other cancer survivors.

Contributors SHJJ drafted the manuscript and worked on the conception, design and interpretation of data. SHJJ and FHMv0 selected articles, screened titles and abstracts, assessed study quality and extracted data. SHJJ, FHMv0, RTB and MPZ were involved in the interpretation and discussion of the results and critically revised the systematic review for important intellectual content. All authors approved the final version of the systematic review. SHJJ is the guarantor.

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