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REVIEW

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Dietary or supplemental intake of antioxidants and the risk of mortality in older people: A systematic review

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Abstract

Purpose: Antioxidants have a protective role in the prevention of cancer, cardiovascular disease and all-cause mortality. The association between dietary or supplemental intake of various antioxidants and all-cause mortality or cause-specific mortality among older populations is inconclusive. This systematic review aimed to systematically evaluate whether higher dietary or supplemental intake of antioxidants can lower the risk of all-cause mortality or cause-specific mortality in the older population.

Methods: Five electronic databases were searched to identify studies that evaluated the effects of dietary or supplemental intake of antioxidants on cause-specific or all-cause mortality in the older population aged ≥65 years. The overall quality of the evidence was assessed using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system. Twenty-two longitudinal, prospective observational studies and randomised controlled trial (RCT) studies involving 1 090 844 cases of cause-specific and all-cause mortality were included. The overall quality of studies was high with a low risk of bias.

Result: Of the 22 studies, 16 were observational studies and 6 were RCTs. The overall quality of evidence for observational studies and RCTs were rated down as low (due to very serious risk of bias and indirectness) and moderate (due to unable to rule out publication bias), respectively. Nine studies showed significant decreases, four found significant increases and nine reported no association between antioxidant intake and risk of mortality.

Conclusion: There was inconclusive evidence on the associations between dietary or supplemental intake of antioxidants and mortality in the older population. More clinical trials are required to confirm the associations.

KEYWORDS

antioxidant, mortality, older adults, systematic review, vitamin

1 | INTRODUCTION

Existing evidence suggests that oxidative stress is an independent factor in the aetiology and pathophysiology of many chronic diseases, such as cancer,

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cardiovascular disease and respiratory infection, which in turn leads to early mortality.[1,2] Recent research has shown that factors such as excessive reactive oxygen species (ROS), mitochondrial dysfunction and impairment of the antioxidant system, individually or together, can intensify oxidative stress.[3-5] The production of ROS can also be exacerbated by ageing as well as acute or chronic health conditions.[6] Antioxidants can mitigate the detrimental effects of oxygenated and nitrogenous free radical activity and allow the normal physiological function of the organism.[6] Epidemiological studies have indicated beneficial effects of individual antioxidant nutrients (ie, vitamin C, vitamin E, carotenoids and selenium) in the prevention of cancer by inhibiting the formation of carcinogens, preventing DNA damage from oxidative stress and improving immune function.[7-10] Antioxidant nutrients have also been shown to reduce cardiovascular disease mortality and all-cause mortality.[7,11-17] A recent systematic review and meta-analysis[17] found that higher dietary intake of antioxidants may reduce the risk of all-cause mortality in the general population aged 18 years and over. In contrast, other systematic reviews have shown that antioxidant supplements may increase the risk of mortality or that there are no associations with mortality among the general population.[18,19] To date, however, no definitive systematic review has summarised findings on the efficacy of dietary or supplemental antioxidant intake in reducing mortality among older people. Therefore, the aim of this review was to systematically evaluate whether higher dietary or supplemental intake of antioxidants can lower the risk of all-cause mortality or cause-specific mortality in the older population.

2 | METHODS

This systematic review was registered at the PROSPERO International Prospective Register of Systematic Reviews (registration number: 42017056800). The review was reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[20,21]

Five databases—MEDLINE (Ovid interface), PreMedline, PubMed, Web of Science (Web of Knowledge portal) and Cochrane CENTRAL—were used to extract relevant literature published between the inception of each database and December 2018. The search strategy combined three groups of keywords (older people, antioxidants and mortality) as follows.

Older people OR Elderly OR, Older OR, Aged OR, People OR, Persons OR, Population AND Mortality OR mortality AND Antioxidant OR Antioxidants OR, Vitamin A OR, Carotenoid OR, Carotenoids OR, beta carotene OR, β-carotene OR Vitamin C OR, Ascorbic acid OR, Vitamin E OR, Tocopherols OR, alpha-Tocopherol OR, α Tocopherol OR, beta-Tocopherols OR, β Tocopherols OR, Selenium.

The complete search results for the MEDLINE electronic database are presented in Table S1.

Inclusion and exclusion criteria were described based on the PICOS framework, as shown in Table 1. Study designs included in the present systematic review were

TABLE 1 PICOS criteria for inclusion and exclusion of studies

Criteria	Inclusion criteria	Exclusion criteria
Population	• Aged 65 years and above • Male and female	• Male and females aged below 65 years
Intervention/exposure	• Dietary or supplemental intakes of any of the following antioxidants: vitamin C, vitamin E, vitamin A, retinol, carotenoids, selenium, flavonoids, polyphenol and total antioxidant capacity	• Dietary or supplemental intakes of antioxidants not indicated • Investigation of antioxidant rich fruits and vegetables.
Outcome	• Specific and all-cause mortality	• Studies that used antioxidants only as a predictor of treatment outcomes
Study design	• Randomised controlled trials • Case–control study • Prospective cohort studies • Longitudinal	• Review articles • Cross-sectional study • Case studies • Surveys • Abstracts • Conference papers • Unpublished studies • Literature reviews

prospective studies, longitudinal studies, randomised controlled trials (RCTs) and cohort studies. Studies were included that assessed and reported baseline dietary or supplemental intake of any of the following antioxidants: vitamin C, vitamin E, vitamin A, total and/or individual carotenoids, retinol, selenium, flavonoids, polyphenols and antioxidant capacity. Only original research studies were included. Review articles, reports, case studies, cross-sectional studies, surveys, abstracts and conference papers were excluded. To be eligible, studies had to assess the effects of antioxidants (dietary or supplemental) on all-cause and/or cause-specific mortality in the population aged 65 years and over, or mean age 65 years and over.

Studies with the following characteristics were excluded: population average age below 65 years; patients with specific chronic diseases (ie, diabetes, hyperlipidemia, chronic renal insufficiency, liver cirrhosis, chronic obstructive pulmonary disease, immunodeficiency disorder, chronic alcoholism); institutionalised older people; diseases not related to mortality (eg, cognitive deterioration, hypertension, arthritis, impaired mobility, eye disease); studies that only assessed the association between serum antioxidants and mortality; cross-sectional and case-control studies (cannot predict causation of the exposure for the outcome); unpublished studies; literature reviews; letters; comments; short communication; animal studies; studies that analysed antioxidants only as a predictor of treatment outcomes; studies reported in languages other than English; and any studies without accessible full-text.

Titles and abstracts of the articles were independently screened by two authors (AD and MSHH). Duplicate studies were removed. The full texts of potential articles were independently reviewed and screened by the same authors based on the eligibility criteria. Any uncertainties over the inclusion of specific studies were discussed with the third and fourth authors (VH and AR). The following data were included: study details (type, authors, year and country of publication, gender, study population, study duration and follow-up periods, intervention details and theoretical framework); participant information (sample size, socio-demographics, cause of mortality, recruitment method, attrition); and dietary measures (dietary assessment, antioxidant components, time points measured, statistical analysis, key results). Authors of eligible studies were contacted in cases where the full text was unavailable.

In addition, the bibliographies of the included articles were screened for further relevant articles. A detailed overview of study selection is shown in Figure 1.

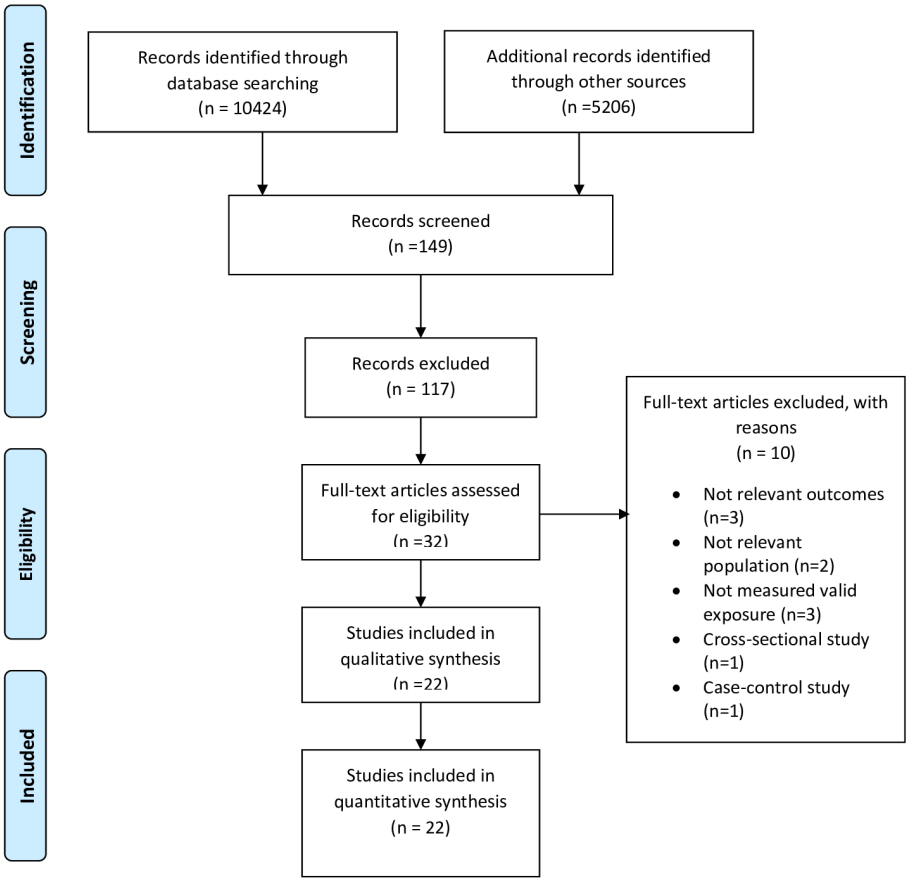

FIGURE 1 PRISMA diagram: flowchart of studies included in the systematic review

The Evidence Analysis Manual developed by the American Dietetic Association (ADA) was used to assess the quality of the journal articles that met the criteria for the second screening stage.[22] Two authors completed the quality assessment. The first author (AD) independently assessed the quality of all included articles and the second author (MH) independently assessed the quality of 20% of the included articles, with excellent agreement between the two assessors, indicating reliable quality assessment.

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system was used to assess the overall quality of the evidence within studies.[23] Two different GRADE assessments were conducted, one for observational studies and one for RCTs. Five criteria were assessed for each outcome to rate the quality of evidence: risk of bias, inconsistency, indirectness, imprecision and publication bias.[23]

3 | RESULTS

A total of 10 424 abstracts were extracted from the first screening of the five databases. After 5218 duplicates were removed, 149 articles were considered for full-text review based on their titles and abstracts. After the full-text screening, 22 articles were included for quality assessment and data extraction (see Figure 1).

The characteristics of the selected studies are presented in Table 2. All studies were published between 1980 and 2018. Of 22 studies, six were RCTs,[24-29] and the remaining 16 were longitudinal or prospective studies.[10,30-44] The studies were conducted in various countries including United States (n = 11), United Kingdom (n = 3), Netherlands (n = 2), Spain (n = 2), Italy (n = 1), Norway (n = 1), Canada (n = 1) and Poland (n = 1). Study periods and follow-up time frames ranged from 3.5 to 32 years. All studies recruited their participants from the community, and the minimum age of the participants was 65 years. Four studies recruited men only,[31,33,39,44] one assessed women only,[30] and the remaining 18 recruited both men and women.[10,24-29,32,34-38,40-43]

Dietary intake measures varied between studies (Table 3). The majority used a food frequency questionnaire (n = 8) to assess dietary intake,[10,24,26,30,31,38-40] while three studies used the diet history method[33,41,44] and three used a food diary.[34-36] Studies that assessed supplemental antioxidants used self-reported questionnaires asking about the brand, formulation and frequency of use.[32,41-43] Other RCT studies[25,27-29] used supplements with a specific dose and duration (see Table 4).

A summary of the study outcomes is presented in Tables 3 and 4. All-cause mortality was reported in 11 studies,[10,24,26,27,34,35,38,40-43] cancer-specific mortality in nine studies,[28,30-32,34,35,37,39,43] CVD-specific mortality in eight studies[25,26,29,32-35,45] coronary heart disease (CHD)-specific mortality in four studies[29,43-45] and one study[34] reported respiratory-specific mortality. Potential confounding factors for most studies included baseline demographic characteristics, smoking status, alcohol intake, physical activity, medical history and use of medications (Tables 3 and 4).

Of the 22 studies included in the review, 13 assessed the association between vitamin E and mortality[10,26,27,29,30,32-35,37,38,41,42] (see Tables 3 and 4). Of these, three showed an inverse association between vitamin E and mortality.[30,34,35] One prospective study showed an inverse association between dietary intake of vitamin E and cancer mortality[34] and another longitudinal study found vitamin E supplementation in combination with multivitamins reduced the risk of mortality among cancer survivors with higher dietary vitamin E intake.[30] Additionally, a longitudinal study observed a trend for an inverse association between vitamin E intake and mortality from heart disease.[35] The majority of studies (n = 9) that examined the effectiveness of vitamin E found no association between vitamin E and mortality.[10,26,27,29,33,37,38,41] However, one longitudinal study reported that mortality rate increased over 6-year follow-up among participants who used vitamin E supplements of 1000 IU/day or more,[32] and a prospective study observed that vitamin E supplementation increased mortality among people who had a history of myocardial infarction, stroke, coronary bypass graft surgery or severe cardiovascular disease, as well those taking nitrates, warfarin or diuretics.[42]

Eleven out of the 22 studies evaluated the association between dietary or supplemental intake of vitamin C and mortality[10,26,30,32-38,41] (Tables 3 and 4). Of these, two studies observed an inverse association between vitamin C intake and mortality.[35,36] One cohort study reported an inverse association between dietary vitamin C and mortality from a stroke but not CHD,[36] while the other prospective study showed an inverse association between the increasing quintile of dietary intake of vitamin C and mortality from heart disease and overall mortality.[35] Eight studies indicated no association between vitamin C intake and mortality.[10,26,30,32-34,37,38,41]

Of the 22 studies, 11 assessed the association between vitamin A intake (carotenoids, retinol and lycopene) and mortality[10,26,28,30-35,38,41] (Tables 3 and 4). Of these, two longitudinal/prospective studies showed an inverse association between carotenoids and mortality,[33,35] one for cardiovascular disease[33] and one for overall mortality.[35] In contrast, nine studies

TABLE 2 Characteristics of selected studies (n = 22)

References	Year	Country	Age, mean/ age range (years)	Gender	Sample size	Type of study	Duration (years)
Alehagen[25]	2015	Norway	78	Men and women	221	Prospective randomised double-blind placebo-controlled trial	10
Bates[34]	2010	UK	75	Men and women	1054	Prospective	14
Brzozowska[41]	2008	Poland	73	Men and women	1900	Longitudinal	10
Buijsse[33]	2008	Netherlands	71	Men	5744	Prospective cohort	15
Enstrom[32]	1982	USA	74	Men and women	479	Longitudinal	6
Fletcher[26]	2003	UK	78	Men and women	1214	Randomised trial	4.4
Gale[36]	1995	UK	≥65	Men and women	730	Cohort	20
GISSI-Prevenzione investigators[27]	1999	Italy	≥65	Men and women	11 324	Randomised control trial	3.5
Hayden[42]	2007	USA	73	Men and women	4416	Prospective cohort	7
Henriquez-Sanchez [38]	2016	Spain	66	Men and women	7447	Randomised, multi-center, parallel group, single-blinded dietary intervention trial, however, data were analysed as an observational cohort	7
Hertog et al.[44]	1997	Netherlands	71	Men	804	Longitudinal	10
Inoue-Choi [30]	2014	USA	78	Women	2118	Longitudinal	6
Jacobs[37]	2001	USA	≥65	Men and women	1 000 000	Prospective	16
Kenfield[39]	2015	USA	68	Men	4459	Prospective cohort	22
Losonczy[43]	1996	USA	75	Men and women	11 178	Longitudinal	9
Mayne[28]	2001	USA	67	Men and women	264	Randomised, placebo-controlled, double-blinded clinical trial	5
Paganini-Hill[10]	2014	USA	74	Men and women	13 978	Prospective study	32
Sahyoun.[35]	1996	USA	72	Men and women	725	Longitudinal	9-12
Semba[40]	2014	USA	73	Men and women	783	Longitudinal	9
Tresserra-Rimbau[24]	2014	Spain	67	Men and women	7447	Randomised, multicenter, controlled trial	5
Wang[31]	2016	USA	72	Men	5018	Prospective	20
Yusuf[29]	2000	Canada	66	Men and women	9541	Double-blind, randomised trial	5

reported no association between dietary or supplemental intake of vitamin A and mortality.[10,26,28,30-32,34,38,41]

Four studies assessed the association between supplemental intake of selenium and mortality[25,30,38,39] (Table 4). Of these, one prospective randomised double-blind placebo-controlled trial studies showed an inverse association between selenium supplementation and cardiovascular mortality.[25] Two prospective studies indicated no association between the use of selenium supplements and mortality,[30,38] whereas one longitudinal study observed an increased risk of prostate cancer mortality with selenium supplementations.[39]

Three studies evaluated the association between polyphenols (flavonoids, resveratrol) and mortality[24,40,44] (Table 3). One longitudinal study found an inverse association between dietary polyphenol intake (flavonoid) and coronary heart disease and all-cause mortality.[44] In addition, a randomised, multicenter, controlled trial indicated a higher intake of dietary polyphenols (particularly stilbenes and lignans) significantly reduced the risk of all-

TABLE 3 Study outcomes (observational studies); (n = 16)

References	Dietary assessment	Antioxidant component	Outcome	Statistical methods	Confounders adjusted for	Result, multivariate adjusted models
Bates et al.[34]	4 days weighed dietary record	Vitamin C (dietary) Vitamin A (dietary retinol) Total carotenoid (dietary) Vitamin E (dietary) Zinc (dietary)	All-cause, vascular, cancer and respiratory disease mortality	Cox proportional hazards regression model.	BMI, systolic blood pressure, current smoking habits, number of prescribed medicines, self-reported health score, physical activity score and receipt (or not) of certain state benefits (as an index of poverty)	Dietary vitamin E and Cancer mortality HR:0.16 (95% CI 0.04-0.65)
Brzozowska et al.[41]	Modified diet history method used for dietary intake Information about vitamins/minerals supplement and daily doses data were collected using standard interview questions	Vitamin C (supplement) Vitamin A (supplement) Vitamin E (supplement)	All-cause mortality	Cox proportional hazards regression models.	Age (continuous), sex, years of education (continuous), physical activity, BMI, chronic diseases, modified Mediterranean diet score (MDS), alcohol use and the place of living.	Vitamin C supplementation among smokers HR: 1.55 (95%CI 0.97-2.46)
Buijsse et al.[33]	Diet history method was used to measure dietary intake Use of supplement data was collected using a questionnaire. Dosage of supplements was not collected.	Total carotene (dietary), vitamin C (dietary +supplements), vitamin E (dietary +supplements),	Cardiovascular mortality	Cox proportional hazards regression model.	Age (continuous), (continuous), smoking habit, alcohol consumption, socioeconomic status, BMI (continuous), physical activity (continuous), use of multivitamin supplements, vitamin C supplements, use of aspirin, antihypertensive drugs, anticoagulants, intake of energy, fibre, β-carotene, vitamin C, α-tocopherol, folate, saturated fatty acids, trans fatty acids, polyunsaturated fatty acids.	Dietary α-Carotene RR:0.81 (95% CI 0.66-0.99) Dietary β-Carotene RR: 0.80 (95% CI 0.66-0.97)
Enstrom et al.[32]	Self-reported questionnaire	Vitamin E (supplements), vitamin C (supplements), vitamin A (supplements)	Cardiovascular mortality, cancer mortality and all-cause mortality	Chi-square test	Not reported	Vitamin E supplement ≥1000 IU/day RR: 2.97
Gale et al.[36]	Food diary	Vitamin C (dietary)	Coronary heart disease mortality, mortality from ischemic stroke	Cox proportional hazards regression model.	Age, sex, height, weight, blood pressure, smoking habits and use of Medication.	Vitamin C > 44.9 mg/day and mortality from stroke RR: 0.5 (95% CI 0.3-0.8)

(Continues)

TABLE 3 (Continued)

References	Dietary assessment	Antioxidant component	Outcome	Statistical methods	Confounders adjusted for	Result, multivariate adjusted models
Hayden et al.[42]	Interviewed about use of nutritional supplements and it was verified by visual inspection of medicine cabinet contents	Vitamin E (supplements)	Mortality from stroke, myocardial infarction, coronary artery bypass graft surgery and cardiovascular disease	Cox proportional hazards methods.	Age, sex, and self- or proxy-reported history of diabetes, stroke, CABG, and myocardial infarction	Participants who had history of the following health issues Stroke HR: 3.64 (95% CI, 1.73-7.68) Coronary bypass graft surgery HR: 4.40 (95% CI, 2.83-6.83) Myocardial infarction HR: 1.95 (95% CI, 1.29-2.95) Participants who used following medication Nitrates HR: 3.95 (95% CI, 2.04-7.65) Warfarin HR: 3.71 (95% CI, 2.22-6.21), Diuretics HR: 1.83 (95% CI, 1.35-2.49)
Henriquez-Sanchez et al.[38]	Dietary antioxidant intake was measured using FFQ Dietary total antioxidant capacity was estimated using published databases that provided the antioxidant capacity measured in foods by assays ferric-reducing antioxidant power (FRAP).	Vitamin C (dietary), vitamin E (dietary), total carotene (dietary), selenium (dietary) and zinc (dietary)	All-cause mortality	Cox regression models.	Age, sex, education, marital status, BMI, smoking habit, alcohol consumption (continuous), recruitment center, intervention group, glycemic index and medical history of hypertension, diabetes, dyslipidemia and cancer, total energy intake (continuous), energy-adjusted intake of saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids.	No significant associations between antioxidants and mortality (Data not reported).
Hertog et al.[44]	Diet history	Flavonoid (dietary)	Coronary heart disease mortality and all-cause mortality	Cox proportional hazards methods.	Age, BMI, smoking, serum total and HDL cholesterol, blood pressure, physical activity, coffee consumption, and intake of energy, vitamin C, vitamin E, β-carotene, and dietary fibre.	Flavonoid >29.9 mg/day and mortality from CHD RR: 0·47 (95% CI 0·27-0·82)

(Continues)

TABLE 3 (Continued)

References	Dietary assessment	Antioxidant component	Outcome	Statistical methods	Confounders adjusted for	Result, multivariate adjusted models
Inoue-Choi et al.[30]	Dietary intake was assessed using the Harvard FFQ. Dietary supplement use (multivitamin and 18 non-multivitamin supplements) was assessed using FFQ.	Vitamin A (supplement), β–carotene (supplement), vitamin C (supplement),vitamin E (supplement), selenium (supplement) and zinc (supplement) Multivitamin supplement	All-cause mortality among cancer survivors	Cox proportional hazards regression	Age, energy, BMI, education, physical activity level, current smoking, total comorbidity count, perceived general health, history of diabetes, history of hypertension, type and stage of cancer, surgery, chemotherapy as a first course of therapy, number of cancers, current cancer treatment, years since cancer diagnosis and diet quality score.	Vitamin E supplement ≥ 11.25 IU/day + multivitamin and all-cause mortality among cancer survivors HR:0.61(95% CI, 0.39-0.94)
Jacobs et al.[37]	Frequency of current use of vitamin supplements (no. of times in the month, no. of years use) No information was collected on doses and brand	Vitamin C, vitamin E and multivitamin	Colorectal cancer mortality	Cox proportional hazards models	Age, sex, race, education, smoking, consumption of vegetables, citrus fruits/juices and high-fibre grains, and use of aspirin	No significant associations between antioxidants and mortality (data not reported).
Kenfield et al.[39]	FFQ was used to assess brand and dosage of vitamin supplements	Selenium (supplement)	Prostate cancer mortality, cardiovascular mortality and all-cause mortality	Cox proportional hazards regression	Age, clinical variables stages, Gleason score, primary treatment, BMI, vigorous physical activity, smoking, vitamin E, vitamin C, calcium, and zinc supplement use in dosage categories, multivitamin use and selenium supplement use before diagnosis.	Selenium supplementation ≥140 μg/day and prostate cancer mortality HR: 2.60 (95% CI 1.44-4.70)
Losonczy et al.[43]	Interviewed about use of nutritional supplements	Vitamin E (supplement) and vitamin C (supplement)	All-cause, coronary heart disease, cancer mortality and other mortality	Cox proportional hazards methods.	Age, sex, BMI, education, race, alcohol consumption, smoking history, aspirin use and history of coronary disease, stroke, diabetes, cancer, and hypertension.	Vitamin E + C supplements All-cause mortality RR:0.63 (95% CI 0.46-0.86) Coronary heart disease RR: 0.52 (95% CI 0.28-0.97)
Paganini-Hill et al.[10]	FFQ was used to assess dietary intake Information on the brand, formulation and frequency of	Vitamin A (diet, supplement), Vitamin C (diet, supplement), and vitamin E (diet, supplement)	All-cause mortality	Cox regression analysis	Age, smoking, body mass index, exercise, alcohol intake, caffeine consumption, and histories of hypertension, angina, heart	No significant associations between antioxidants and mortality (Data not reported)

(Continues)

TABLE 3 (Continued)

References	Dietary assessment	Antioxidant component	Outcome	Statistical methods	Confounders adjusted for	Result, multivariate adjusted models
	supplements use was collected using questionnaire				attack, stroke, diabetes, rheumatoid arthritis, and cancer	
Sahyoun et al.[35]	3 day food record was used to assess dietary and vitamin supplements	Vitamin C (diet, supplement), vitamin E (diet, supplement), carotenoid (diet) and multivitamin (supplement)	Overall, heart disease, cancer and other cause mortality	Cox proportional hazards regression model.	Age, sex, serum cholesterol, disease status, and disabilities affecting shopping.	Highest quintile of vitamin C Overall mortality RR:0.55 (95% Cl 0.34-0.88) Mortality from heart disease RR:0.38 (95% CI 0.19-0.75) Highest quintile of carotenoid and other-cause mortality RR:0.38 (95% CI 0.14-2.76) Highest quintile of vitamin E and CVD mortality RR:0.75 (95% CI 0.41-1.39)
Semba et al.[40]	Daily alcohol and resveratrol intakes were determined using the European Prospective Investigation into Cancer and Nutrition (EPIC) FFQ	Resveratrol (diet)	All-cause mortality	Cox proportional hazards models.	Age, sex, education, BMI, physical activity, total cholesterol, HDL cholesterol, Mini-mental State examination (MMSE) score, mean arterial BP, and chronic diseases	No significant associations between resveratrol and mortality (data not reported)
Wang et al.[31]	FFQ	Lycopene (diet)	Prostate cancer	Cox proportional hazards regression	Age, BMI, smoking status, diagnosis year, treatment, current multivitamin use in pre-diagnosis models and multivitamin or any lycopene supplement use in post-diagnosis models	No significant associations between lycopene and mortality (data not reported)

Abbreviations: CVD, cardiovascular disease; CHD, coronary heart disease; FFQ, Food Frequency Questionnaire; MI, myocardial infarction.

TABLE 4 Study outcomes (randomised controlled trial studies); (n = 6)

References	Supplement, dose and duration	Cause of mortality	Statistical Methods	Confounders	Result
Alehagen et al.[25]	200 mg/day Selenium and 200 mg/day coenzyme Q10 for 4 years Or similar placebo	Cardiovascular mortality	Cox proportional hazard regression.	Age, smoking, hypertension, diabetes, ischemic heart disease, Hb < 120 g/L, ejection function<40% and NT-proBNP	Cardiovascular mortality HR: 0.51; 95%CI 0.36-0.74
Fletcher et al.[26]	UK EPIC study (European Prospective Investigation into Cancer and Nutrition) FFQ for dietary intake (vitamin C, E, β-carotene and retinol) data. Information on supplement and type was collected using questionnaire but the data could not include in the daily intake due to insufficient data on doses	Cardiovascular and all-cause mortality	Cox proportional hazard regression.	Age, sex, BMI, cholesterol, systolic blood pressure, smoking, alcohol, diabetes, history of CVD or cancer, physical activity, housing tenure, and supplement use.	No significant associations between antioxidants and mortality (data not reported).
GISSI-Prevenzione investigators[27]	Daily supplementation with n-3 PUFA +300 mg vitamin E vs n-3 PUFA only vs 300 mg vitamin E vs control (nil supplements) for 3.5 years	All-cause mortality, and cardiovascular mortality	Cox proportional hazard regression	Not reported	No significant associations between vitamin E and mortality (Data not reported).
Mayne et al.[28]	50 mg/day β-Carotene or placebo capsule for 7.5 years	Second head and neck cancer, lunch cancer and total mortality	Cox proportional hazards models.	Several indices of tobacco exposure, plasma b-carotene levels at baseline, gender, and age.	No significant associations between β-carotene and mortality (Data not reported).
Tresserra-Rimbau et al.[24]	Mediterranean diet supplemented with extra virgin olive oil (1 L/week) or 30 g/day of mixed nuts (15 g walnuts, 7.5 g hazelnuts and 7.5 g almonds) or control low-fat diet for 5 year. (Measure: FFQ for polyphenol intake; National Death Index and death certificates for mortality)	All-cause mortality in high cardiovascular risk	Cox proportional hazard regressions.	Age, sex, smoking status, BMI, baseline diabetes, alcohol consumption, total energy intake (continuous variable), physical activity (continuous variable), family history of CVD and/or cancer, aspirin use, antihypertensive drug use, use of cardiovascular medication, use of oral hypoglycemic agents, insulin and other medication. In addition adjusted by intake of protein, saturated fatty acids, polyunsaturated fatty acids, monounsaturated fatty acids and cholesterol	Stilbenes HR: 0.48 (95% CI 0.25-0.91) Lignans HR: 0.60 (95% CI 0.37-0.97)

(Continues)

TABLE 4 (Continued)

References	Supplement, dose and duration	Cause of mortality	Statistical Methods	Confounders	Result
Yusuf et al.[29]	Daily supplement of 400 IU of vitamin E from natural sources or matching placebo + an angiotensin-converting–enzyme inhibitor (ramipril) or matching placebo for 4.5 year	Cardiovascular mortality, mortality from myocardial infarctions, stroke or any cause	Not reported	Not reported	No significant associations between vitamin E and mortality (data not reported)

Abbreviations: CVD, cardiovascular disease; FFQ, Food Frequency Questionnaire; MI, myocardial infarction.

cause mortality,[24] whereas a longitudinal study reported no association between polyphenol intake (resveratrol) and all-cause mortality.[40]

Three longitudinal studies evaluated the association between zinc and mortality. None of these studies found an association between zinc and mortality[30,34,38] (Table 3).

One study reported data on the total antioxidant capacity (considered a useful tool in antioxidant intake assessment) of the diet and mortality[38] (Table 3). This randomised, multicenter, parallel-group, single-blinded dietary intervention trial found no significant association.

One longitudinal study reported that a combination of vitamin E and C supplementation reduced the risk of mortality from coronary heart disease[43] (Table 3).

The quality of assessment showed that of the 22 studies included as body of evidence, 16 were observational and 6 were RCTs. Of the 16 observational studies, 12 were considered to have a "positive" score or low risk of bias[30,31,33-35,37-40,42-44] and 4 had a "neutral" score or moderate risk of bias.[10,32,36,41] Similarly, of the six RCTs, five studies were rated as a "positive" score or low risk of bias[24,26-29] and one study was rated as a "neutral" score or moderate risk of bias[25] (see Table 5).

A summary of the overall quality of evidence assessment for the effect of dietary or supplemental intake of antioxidants on the outcome measures for observational studies and RCTs are shown in Table S2 and S3.

Of the 22 studies included in the quality analysis, 16 were observational studies and 6 were RCTs. Of the 16 observational studies, the majority of the studies were rated as low risk of bias (n = 12). One study did not describe the appropriate eligible criteria.[32] The study outcome remains unclear for two studies.[10,32] Since these studies were observational, none included blinding, randomisation, allocation and concealment. Therefore, we rated down by two levels for risk of bias, as all the studies were considered to be at high risk of bias.

Of the six RCTs, five studies blinded participants[24,26-29] and one did not blind participants to intervention.[25] All studies reported concealment methods except one,[25] the same study was also unclear about the outcome events. We did not downgrade for serious risk of bias, as all the studies were RCTs and the majority of studies included randomisation, blinding, allocation and concealment.

Of the 16 observational studies, eight studies reported all-cause mortality,[10,34,35,38,40-43] cancer-specific mortality in eight studies,[30-32,34,35,37,39,43] CVD-specific mortality in five studies,[32-35,45] three studies reported coronary heart disease (CHD)-specific mortality[43-45] and one study

TABLE 5 Risk of bias using the ADA tool (n = 22)

References	1 Research question	2 Selection of units	3 Comparability of units	4 Withdrawals	5 Blinding	6 Intervention and intervening factors	7 Outcomes	8 Statistics	9 Conclusions	10 Funding	Overall Risk of bias
Alehagen[25]	Yes	No	Yes	Yes	No	Yes	No	Yes	Yes	Yes	Neutral/moderate risk
Bates[34]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Unclear	Yes	Positive/low risk
Brzozowska[41]	Yes	Yes	Yes	Yes	No	No	Yes	Yes	Unclear	Yes	Neutral/moderate risk
Buijsse[33]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Positive/low risk
Enstrom[32]	Yes	No	Yes	Yes	Yes	Unclear	No	No	Yes	Yes	Neutral/moderate risk
Fletcher[26]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Positive/low risk
Gale[36]	Yes	Yes	Yes	No	Yes	Unclear	Yes	Yes	Yes	Yes	Neutral/moderate risk
GISSI-Prevenzione investigators[27]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Positive/low risk
Hayden[42]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Positive/low risk
Henriquez-Sanchez[38]	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Positive/low risk
Hertog[44]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Positive/low risk
Inoue-Choi[30]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Positive/low risk
Jacobs[37]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Positive/low risk
Kenfield[39]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Positive/low risk
Losonczy[43]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Positive/low risk
Mayne[28]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Positive/low risk
Paganini-Hill[10]	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Neutral/moderate risk
Sahyoun[35]	Yes	Yes	Yes	Unclear	Yes	Yes	Yes	Yes	Yes	Yes	Positive/low risk
Semba[40]	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Positive/low risk
Tresserra-Rimbau[24]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Positive/low risk
Wang.[31]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Positive/low risk
Yusuf[29]	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Positive/low risk

reported respiratory-specific mortality.[34] The duration of follow-up time between studies ranged from 6 to 32 years. The exposure variables also varied across studies as each study examined different antioxidants and dietary measures. We could not compare directly all the 16 studies with each other due to inconsistencies among the outcome measures, duration of follow-up, types of dietary or supplemental antioxidants examined.

Of the six RCTs, two studies reported a significant reduction of hazard ratios[24,25] and the remaining four studies failed to show statistically significant results.[26-29] Hence, we did not downgrade the quality of evidence for inconsistency since the majority of studies reported non-significant results.

All the 16 selected observational studies were comparable by population as they included a community-dwelling older population aged ≥65 years. However, there were variations in the gender, exposure and outcome measurements that affect the applicability of the results. Of the 16 observational studies, the majority of studies evaluated older men and women (n = 11), four studies exclusively evaluated older men[31,33,39,44] and one study exclusively evaluated older women.[30] The majority of studies (n = 10) included in the present review assessed all-cause mortality as well as cancer and cardiovascular mortality[10,32,34,35,38,40-44]; two studies assessed cardiovascular mortality[33,45] and four studies evaluated cancer mortality.[30,31,37,39] Furthermore, the dietary measures included across the selected studies varied widely. We downgraded by one level for indirectness, as participants, exposure and outcome measures across studies were not comparable.

On the other hand, six RCTs evaluated older men and women[24-29] and the majority of them assessed all-cause mortality as well as cancer and cardiovascular mortality[24-27,29]; only one study assessed cancer mortality.[28] As the majority of observational studies and RCTs assessed older men and women, all-cause and cause-specific mortality, there is sufficient evidence to answer the aim of the systematic review; no deduction was made for directness.

The total number of participants included in observational studies was large (n = 1 060 833), however, the overall treatment effect was not possible to calculate. The majority of studies did not have wide confidence intervals; only two observational studies have wide confidence intervals.[39,42] Therefore, studies were not directly comparable.

The total number of participants included across 6 RCTs was large (n = 30 011), which is considered sufficient. Two studies reported significant confidence intervals, which were not broad confidence intervals and the remaining five studies reported non-significant results. The majority of RCTs included in this systematic review have enough information to calculate a precise effect estimate; no deduction was made for imprecision.

A comprehensive search strategy was implemented to ensure that all available literature was captured. This involved a comprehensive search of five major electronic databases, searches of the reference lists of the eligible studies and of the grey literature, and contact with authors to obtain further information. In addition, we may have missed unpublished studies, those with negative or insignificant findings, studies not published in English or those without accessible full-text. It was not possible to conduct a funnel plot as there was no summary estimate of the overall effect, however, hazard ratios and odds ratios were examined in each of the selected studies. Although this systematic review presents both significant and insignificant outcomes, we cannot rule out publication bias.

Taken together, the overall quality of evidence for 16 observational studies was therefore rated as low due to downgrading for a very serious risk of bias and serious indirectness. Additionally, we could not rule out publication bias. Furthermore, the overall quality of evidence for six RCTs was rated as moderate, since we could not rule out publication bias.

4 | DISCUSSION

The objective of this systematic review was to evaluate the associations between dietary or supplemental intake of antioxidants and risks of cause-specific and all-cause mortality among community-dwelling older adults. Inconsistent findings regarding associations between dietary or supplemental intake of antioxidants and risks of cause-specific and all-cause mortality in this population were noted.

The screening stages resulted in 22 studies, which comprised 16 observational studies and six RCTs. While statistically significant and non-significant data were obtained from 16 observational studies and six RCTs, measures of exposure (dietary/supplemental intake measure), exposure variables (antioxidants intake), outcome and duration of follow-up varied widely; hence, studies were not directly comparable. Therefore, the overall quality of evidence for observational studies and RCTs was rated as low and moderate, respectively.

Of 22 studies, 7 studies with a positive or low risk of bias[24,30,33-35,43,44] and 2 with a neutral or moderate risk of bias showed an inverse association,[25,36] 2 studies showed an increase[32,39] and the remaining 10 studies showed no associations between dietary or supplemental intake of antioxidants and risk of cause-specific and all-cause mortality.[10,26-29,31,37,38,40,41] In addition, one study indicated

that 1000 IU/day vitamin E supplementation increased the risk of mortality for older people who had a history of stroke, coronary bypass graft surgery or myocardial infarction or those who used nitrates, warfarin or diuretics.[42] Therefore, studies varied widely with respect to the association between antioxidant intake and mortality. On the other hand, findings from some studies suggested a protective effect of intakes of vitamin E and polyphenols on cancer, heart disease and all-cause mortality.[24,30,34,35,44] It could be hypothesised that vitamin E protects membranes against oxidative injury, thereby enhancing immune function.[46,47] Similarly, it is possible that polyphenols reduce inflammation through their antioxidant properties or by obstructing proinflammatory cytokines or endotoxin-mediated kinases and transcription factors involved in metabolic disease.[48] Polyphenol-rich foods such as fruits, vegetables, nuts, herbs, spices, olive oil and red wine are also considered as key components of the Mediterranean diet.[49] Several studies have suggested that a Mediterranean dietary pattern is associated with decreased risk of all-cause and cause-specific mortality.[50-53] It seems that the high polyphenols content of the Mediterranean diet may be inversely associated with mortality in older individuals by reducing inflammation, oxidative stress and biochemical process which are associated with CVD and cancer.[54] Therefore, it is required to promote awareness of the traditional Mediterranean diet to improve overall diet quality and distribution of antioxidants with a dietary pattern-based approach among the older population. Since the overall evidence was inconsistent, we could not draw a firm conclusion on the associations between dietary or supplemental intake of antioxidants and mortality in the community-dwelling older population.

In contrast to our study, findings from a recent systematic review and meta-analysis[17] indicated that dietary intake of total carotenoids, total antioxidant capacity, selenium, α-carotene, β-carotene and vitamin C may reduce the risk of all-cause mortality in the general population.[17] In a previous Cochrane systematic review and meta-analysis, Bjelakovic et al.[19] suggested that β-carotene, vitamin A and vitamin E individually or together with other antioxidant supplements significantly increased the risk of mortality in middle-aged adults (mean age 63 years). In contrast, this study showed no beneficial association of vitamin C or selenium with the risk of mortality.[19] Our study differs from both these systematic reviews and meta-analyses by including all of the following: dietary and supplemental intake of antioxidants; studies that assessed cause-specific and all-cause mortality; and longitudinal, prospective and randomised clinical trial studies.

Inconsistent results across the studies could be due to the high level of differences in study design (RCT, longitudinal or prospective and duration of follow-up), country of origin, age range of participants (65-78 years), dietary measures, type of antioxidant intake, outcome measures and potential confounding variables for adjustment. Several confounding variables potentially influence both antioxidant intake and mortality. For instance, a history of cardiovascular disease or cancer and smoking habits are powerful confounders between antioxidant intake and increased risk of mortality,[39,41,42] hence the direction of causality (ie, antioxidant intake to mortality) cannot be assumed, particularly in observational designs. If confounding factors are associated with both antioxidant intake and mortality, this may bias study results.

It should be noted that self-reported dietary data tend to provide low accuracy and recall in older populations, which may contribute to inaccurate dietary assessment.[55] As the majority of the included studies used diet history, food frequency questionnaires, food diaries and 24-hour recall, these may have introduced recall bias on habitual intake, recall errors and under- or over-estimation of daily nutrient intakes. Additionally, information on the consumption of antioxidant supplements was not consistently provided across all included studies, which may have contributed to the variation in reported associations. In particular, most of the included studies lacked details about doses, brands, formulation of supplements, duration of treatment and route of administration (ie, intervention or placebo or non-intervention).

Finally, differences in adjustment for confounding factors may have contributed to the inconsistent findings. For instance, two important confounding factors—energy and nutrient intake and supplement use—were adjusted for in only seven studies.[24,26,31,33,38,39,44] Two studies adjusted for caffeine consumption[10,44] and one study adjusted for fruit and vegetable intake.[37] Some studies adjusted for an extensive range of confounding factors.[24,30,33,38] However, it remains unclear whether there are any interactions of a history of chronic disease, use of medications, antioxidant intake and mortality. Additionally, long-term oxidant exposure, for instance from smoking, alcohol consumption or exercise, may increase oxidative stress and subsequent mortality, which is an important consideration. However, the findings from studies that adjusted for limited confounders did not show any differences from those that adjusted for an extensive range of confounding factors.

The present systematic review has several strengths. It was conducted according to the PRISMA guidelines.[20] As such, it involved a systematic search of five databases with large sample sizes and sample diversity across nine countries, thus enabling an analysis of the associations between antioxidant intake and all-cause or cause-

specific mortality in different older populations throughout the world. The present review had clearly defined inclusion and exclusion criteria, and two authors were involved in screening, data extraction and quality assessment of publications using the ADA tool. The study quality was assessed by two authors. Additionally, most of the included studies were prospective or longitudinal in design, with long-term follow-up. Finally, the majority of studies in this systematic review investigated both male and female participants.

Some limitations should be acknowledged. The review did not include unpublished literature. Only 6 studies were RCTs, the gold standard for testing the effectiveness of interventions. The majority of studies used food frequency questionnaires that may overestimate the intake of fruits, vegetables (ie, water-soluble antioxidants) and underestimate the intake of fat-soluble antioxidants.[56] Self-reported questionnaires on the use of antioxidant supplements generally underreport intake due to the lack of information on dose, brand and formulation.[19] This may underestimate the beneficial effects of antioxidant supplements on mortality. Furthermore, it was unknown whether diet and lifestyle habits changed over time or even within the course of a study. Finally, the heterogeneity of the studies (ie, baseline age, geographic location, study quality, follow-up duration, dietary assessment method and adjustment for main confounders) prevented the synthesis of a meta-analysis.

5 | CONCLUSION

In this systematic review, we found inconclusive results on the associations between dietary or supplemental intake of antioxidants and the risk of mortality among older people. Nonetheless, 11 out of 22 studies indicated positive effects of vitamin E and polyphenols on cancer, heart disease and all-cause mortality. Overall, this systematic review yielded insufficient evidence that the consumption of antioxidant nutrients can lower the risk of all-cause mortality or cause-specific mortality in the older population. Most importantly, there is inconclusive evidence that the use of antioxidant supplements reduces the risk of mortality among the older population. It seems that intakes of antioxidant supplements may increase the risk of mortality in smokers and individuals with a pre-existing chronic health condition such as CVD. Furthermore, long-term use of selenium supplements may increase the risk of mortality. Perhaps use of multiple antioxidant supplements instead of single antioxidant supplement usage may reduce the risk of mortality. With respect to the dosage, it was not possible to determine the effect of the dose of antioxidant supplements on mortality due to the variations in the duration of supplementation use of single or combinations of antioxidant supplements. Optimising dietary antioxidant intake may be important for reducing the risk of chronic diseases. Further clinical trials are needed to investigate the efficacy and effectiveness of intakes of the Mediterranean diet and antioxidant supplementation among the older population.

CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

A.D. and V.H. conceptualised the systematic review. A.D. and M.H. contributed to the literature search, data extraction and quality assessment. A.D. drafted the manuscript. All authors reviewed and approved the final draft for submission. None of the authors has any conflict of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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