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REVIEW

Dietary total antioxidant capacity and mortality from all causes, cardiovascular disease and cancer: a systematic review and dose–response meta-analysis of prospective cohort studies

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Abstract

Purpose No conclusive information is available about the association between dietary total antioxidant capacity (DTAC) and risk of mortality. Current meta-analysis of prospective cohort studies was done to summarize available findings on the association between DTAC and risk of death from all-cause, cancer and cardiovascular diseases (CVDs).

Methods Online databases were searched to detect relevant publications up to January 2018, using relevant keywords. To pool data, either fixed-effects or random-effects model was used. Furthermore, linear and non-linear dose–response analyses were also done.

Results In total, five prospective studies were included in the current systematic review and meta-analysis. In a follow-up period of 4.3–16.5 years, there were 38,449 deaths from all-cause, 4470 from cancer and 2841 from CVDs among 226,297 individuals. A significant inverse association was found between DTAC and all-cause mortality (combined effect size: 0.62, 95% CI 0.60–0.64). Such finding was also seen for cancer (combined effect size: 0.81, 95% CI 0.75–0.88) and CVD (combined effect size: 0.71, 95% CI 0.63–0.82) mortality. Findings from linear dose–response meta-analysis revealed that a 5 mmol/day increment in DTAC based on ferric reducing antioxidant power (FRAP) and oxygen radical absorbance capacity (ORAC) was associated with 7% and 15% lower risk of all-cause mortality, respectively. Based on findings from non-linear dose–response meta-analysis, a significant reduction in risk of all-cause mortality was seen when increasing FRAP from 2 to 12 mmol/day (P-nonlinearity = 0.002) and ORAC from 5 to 11 mmol/day (P-nonlinearity < 0.001).

Conclusions Adherence to diet with high total antioxidant capacity was associated with decreased risk of death from all-cause, cancer and CVDs.

Keywords Antioxidants · Mortality · Meta-analysis · Dose–response · Cancer · Cardiovascular

Abbreviations

DTAC	Dietary total antioxidant capacity
FRAP	Ferric reducing antioxidant power
TRAP	Total radical trapping antioxidant parameter
TEAC	Trolox equivalence antioxidant capacity

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ORAC	Oxygen radical absorbance capacity
OR	Odds ratio
RR	Relative risk
HR	Hazard ratio
FFQ	Food frequency questionnaire
CVD	Cardiovascular disease

Introduction

It is now well accepted that increased oxidative stress has been implicated as a key etiology in development and progression of various chronic diseases such as obesity, diabetes, cardiovascular diseases (CVDs) and some cancers [1–3]. Dietary intakes of antioxidants might have protective effects against oxidative stress [4, 5]. Increasing evidences from both experimental and clinical studies have suggested that high consumption of antioxidant-rich foods such as fruits and vegetables decreases risk of death through a reduction in markers of oxidative stress [6–13]. However, fruits and vegetables are not the only source of antioxidants in a diet. Chocolate, coffee, tea, wine, beer, fresh herbs and apices are other antioxidant-rich food items which are involved in total antioxidant capacity of diet [14, 15].

Previous studies have mainly focused on intake of a single antioxidant or a group of antioxidants in relation to risk of mortality and presented inconsistent findings [16–18]. One reason for this discrepancy is that earlier studies might fail to measure dietary antioxidants intake accurately due to measurement errors or failure to capture the entire antioxidant capacity of diet [6]. Furthermore, potential interaction between the different antioxidants is another reason for this discrepancy. Considering the diversity in the sources of antioxidants and potential interactions between the various individual antioxidants, dietary total antioxidant capacity (DTAC) has been introduced as a cumulative tool for measuring the overall effects of antioxidants present in mixed foods by taking into account the synergic and redox interactions between the different antioxidant substances from all sources [19]. This index considers known antioxidants as well as those that have not been well characterized, such as flavonoids [19]. However, some researchers reported a weak correlation between DTAC and plasma TAC as an important limitation of this index [19–21]. On the other hand, DTAC is an in vitro parameter, which does not consider the antioxidants' bioavailability, in vivo stability, storage and reactivity in tissues [19, 20, 22]. However, some researchers had opposite opinion and reported that DTAC or dietary antioxidants could enhance the plasma levels of antioxidants [23–28]. Furthermore, similar findings obtained for DTAC, plasma TAC and individual antioxidants in relation to chronic diseases are another reason for validity of DTAC and its correlation with plasma TAC [29, 30].

Several studies have evaluated the association between DTAC and risk of mortality [6–10]; however, their findings are conflicting. We are aware of no meta-analysis that summarized available findings in this regard. Thus, we aimed to systematically review the present evidences on the association between DTAC and risk of death from all-cause, CVDs, and cancer, and to summarize the available findings in a meta-analysis.

Materials and methods

Study protocol

Current systematic review and meta-analysis were designed, conducted and reported in adherence to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [31].

Search strategy

We performed a literature search using the online databases of PubMed, ISI, Web of Science, Scopus, ProQuest, Science Direct and Embase for relevant publications up to January 2018. The following medical subject headings (MeSH) and non-MeSH keywords were used in our search strategy: "Trolox equivalence antioxidant capacity" OR "Oxygen radical absorbance capacity" OR "vitamin C equivalent" OR "total radical trapping antioxidant potential" OR "total antioxidant capacity" OR "dietary TAC" OR "dietary total antioxidant capacity" OR "Non-enzymatic antioxidant capacity" OR "Ferric reducing antioxidant power" OR DTAC AND "Mortality" OR "Death" OR "Fatal Outcome" OR "Survival" OR Mortality OR "Death" OR "Fatal Outcome" OR "Survival". Literature search was done by two independent investigators (MP and JAS). We also searched the reference lists of the relevant publications to identify studies that might have been missed. No restriction was applied on time of publication and language. In the search strategy, unpublished studies as well as duplicate citations were excluded. To facilitate the screening process of papers from databases, all literature searches were downloaded into an EndNote library (version X7, for Windows, Thomson Reuters, Philadelphia, PA, USA).

Inclusion criteria

In our meta-analysis, eligible publications were included if they met the following criteria: (1) all studies assessing the association between dietary total antioxidant capacity (DTAC) as an exposure and mortality risk from all causes, CVDs, cancer and inflammatory diseases as the major outcomes of interest; (2) studies that were of prospective design; (3) those that reported odds ratios (ORs) or relative risks (RRs) or hazard ratios (HRs) along with 95% confidence intervals (CIs) for the relationship between DTAC and mortality risk; and (4) studies that measured DTAC by use of following methods: Ferric reducing antioxidant power (FRAP), total radical trapping antioxidant potential (TRAP), trolox equivalence antioxidant capacity (TEAC) oxygen radical absorbance capacity (ORAC) and vitamin C equivalent (VCE). In case of multiple published reports on the same dataset, we selected the most recent study; otherwise, the one with the most number of cases was selected.

Data extraction

Data extraction from each eligible study was independently done by two reviewers (MP and JAS), and any disagreements were reconciled by discussion. The presence of participants across categories of DTAC at study baseline was the main exposure variable. Furthermore, the key outcome variable was incidence of mortality from all causes, CVD and cancer during follow-up. Any reported ORs or HRS or RRs estimates with corresponding 95% CIs for the highest vs. lowest categories of DTAC were extracted from eligible studies. In one study, effect sizes for mortality across categories of DTAC were not reported, which we calculated in accordance with provided data and included in the meta-analysis [8]. Furthermore, some studies had reported risk estimates for mortality based on one unit increase in DTAC [9, 10]. Mentioned effect sizes were also extracted. Information was recorded from each study as follows: first author, year of publication, country of origin, age range at study baseline, gender, sample size, number of participants who were died, duration of follow-up, person-year, methods used for assessing dietary total antioxidant capacity, outcome type and statistical adjustment for confounding variables. If a study had presented gender-stratified effect sizes, we considered it as two separate studies.

Excluded studies

In this meta-analysis, we excluded letters, comments, short communication, reviews, meta-analyses, ecological studies and animal studies. In our initial search, we found 370 articles. On the basis of title and abstract, 354 papers were excluded. Out of remaining 16 articles, 10 were excluded because of the following reasons: (1) studies that examined the association between serum levels of antioxidants and mortality risk ($n=4$) [32–35]; (2) publication that assessed the relationship between an individual antioxidant intake and mortality risk ($n=1$) [36]; and (3) those that evaluated the association between DTAC and chronic diseases without considering mortality ($n=5$) [37–41]. Out of remaining 6 papers, one did not separate risk of heart failure from risk of death due to CVD and, therefore, was excluded [42]. Finally, we included 5 prospective studies in the current systematic review and meta-analysis [6–10] (Fig. 1).

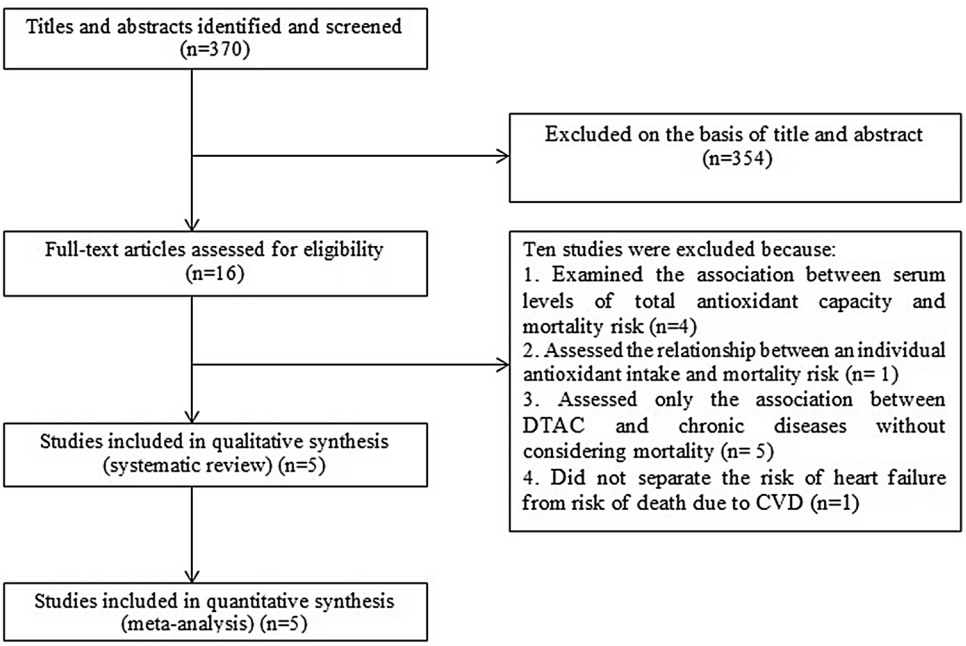

Fig. 1 Flow diagram of study selection

Assessment of study quality

We used a form of the Newcastle Ottawa Scale (NOS), designed for non-randomized studies, to evaluate quality of chosen studies [43]. Based on this scale, a maximum of nine points can be awarded to each prospective study: four for selection, two for comparability, and three for assessment of outcomes (nine represented the highest quality). Any contradictions were figured out by discussion. In the present study, papers with the NOS score of ≥ 5 were considered as high quality publications.

Statistical analysis

We used RRs, ORs and HRs (and their 95% confidence intervals) reported for the association between DTAC and mortality, to calculate log RRs and their standard errors (SEs). Then, the overall effect size for mortality in relation to DTAC was calculated using fixed-effects model. When between-study heterogeneity was significant, we also did random-effects analysis to take between-study variation into account. For examining the between-study heterogeneity, we used Cochran's Q test and I^2. In the current study, I^2 values of $\geq 50\%$ were considered between-study heterogeneity [44]. To identify probable sources of heterogeneity, we did subgroup analyses according to the predefined criteria as follows: gender (male vs. female), follow-up duration (≥ 10 vs. <10 years), geographical region (US vs. non-US countries), sample size ($\geq 10{,}000$ vs. $<10{,}000$ individuals), using energy-adjusted DTAC in statistical analysis (used vs. not-used), considering BMI as a covariate (adjusted vs. non-adjusted) and methods used to assess dietary intakes (food recall vs. food frequency questionnaire (FFQ) vs. diet history). In these analyses, fixed-effects model was used. In addition to the main analyses, we carried out sensitivity analysis based on the main exposure and main outcome to find if the overall estimate depended on the effect size from a single study. If this was the case, the analyses were re-done by excluding the mentioned study. Assessing the publication bias was done by visual inspection of the funnel plots as well as the formal test of Egger.

A dose-dependent meta-analysis was used to compute the trend from the correlated log OR/RR/HR estimates across DTAC categories according to the method proposed by Greenland, Longnecker and Orsini et al. [45, 46]. For this purpose, studies that categorized participants based on DTAC (at least 3 categories), reported number of participants in each DTAC category, reported number of mortality in total population and in each DTAC category, and calculated OR, RR and HR with related 95% confidence interval for mortality in each category, were used. The midpoint of the DTAC category was considered as the corresponding OR/RR/HR estimate, while the open-ended categories were considered as same width as the neighbouring categories. Non-linear relationship between DTAC and risk of mortality was explored using the two-stage random-effects dose–response meta-analysis. To this purpose, we used DTAC modelling and restricted cubic splines with 3 knots at fixed percentiles of 10%, 50%, and 90% of the distribution [47]. A restricted cubic spline model was calculated using generalized least square regression taking into account the correlation within each set of published ORs/RRs/HRs [36]. Then, the restricted maximum likelihood method was used to combine the study-specific estimates in a multivariate random-effects meta-analysis [48]. In addition, a linear dose–response relation of 5 mmol/day increments in DTAC with risk of mortality was estimated using the two-stage generalized least squares trend estimation [45, 46, 49]. To estimate an overall average slope, the study-specific slope lines were estimated, then combined with studies in which the slopes were directly reported [46]. Linear and non-linear dose–response meta-analyses were done separately for each method used to assess DTAC (FRAP and ORAC). All statistical analyses were conducted using Stata, version 11.2 (Stata Corp, College Station, TX, USA). P values were considered significant at level of <0.05.

Results

Findings from systematic review

In the current systematic review, five prospective studies were included. Out of these studies, one was carried out in the US [6], one in Sweden [8], two in Spain [9, 10] and one in France [7]. The sample size of studies included in the current review varied from 7015 to 81,994 participants with an age range from 30 to 80 years. In total, 226,297 individuals with 38,449 cases of all-cause mortality, 4470 cases of cancer mortality and 2841 cases of CVD mortality were included. Papers had been published between 2007 and 2017. Mean duration of follow-up ranged from 6.5 to 16.5 years.

Dietary intakes had been assessed by FFQ in two studies [8, 9], using 24 h dietary recall in one study [6] and by diet history in two other studies [7, 10]. To measure DTAC, different methods were applied: one study by VCE [6], one by ORAC [8], one by FRAP [9], one by FRAP and TRAP [7], and one using FRAP, TRAP, TEAC and ORAC [10]. Out of five studies, all reported risk estimates for all-cause mortality, three for cancer mortality [6, 7, 9] and three for CVD mortality [6, 7, 9]. Of five studies, one reported the estimates for men and women separately [8], one only reported them for women [7] and others reported them for both sexes combined [6, 9, 10]. All studies except one [10] used energy-adjusted DTAC

for assessing the association between DTAC and mortality [6–9]. Furthermore, out of five studies, three controlled for BMI [7, 9, 10] and four adjusted for age on the association between DTAC and mortality [6, 7, 9, 10]. All studies reported risk of mortality across categories of DTAC and considered participants in the lowest category as the reference group. In addition, two studies had reported risk estimates for mortality based on one unit (per quintile or log2) increase in DTAC [9, 10]. All studies were of high quality based on the NOS.

Of five studies considering all-cause mortality as main outcome, four found a protective association with DTAC [6–8, 10] and remaining one study reported no significant relationship [9]. Out of three studies in terms of DTAC and cancer mortality [6, 7, 9], only one reached a significant inverse association [7] and two other studies found no significant association [6, 9]. Except one [9], all studies assessing the association between DTAC and CVDs mortality reported significant inverse association [6, 7].

Findings from meta-analysis

Overall, all prospective studies assessed in the systematic review were included in the current meta-analysis. These studies included 226,297 participants, aged 30–80 years old, with 38,449 cases of death. The total number of mortality from cancer and CVDs was 4470 and 2841, respectively.

DTAC and all-cause mortality

Combining six effect sizes from five studies [6–10] revealed a significant inverse association between DTAC and all-cause mortality (combined effect size: 0.62, 95% CI 0.60–0.64) (Fig. 2). However, a significant between-study heterogeneity was seen ($I^2 = 95.5$). Such significant inverse association was also seen when we did random-effects analysis (combined effect size: 0.69, 95% CI 0.58–0.81) (Supplemental Fig. 1) (Table 1). Furthermore, we did subgroup analyses based on gender (males vs. females), follow-up duration (≥ 10 vs. <10 years), sample size (≥ 10,000 vs. <10,000 individuals), geographical

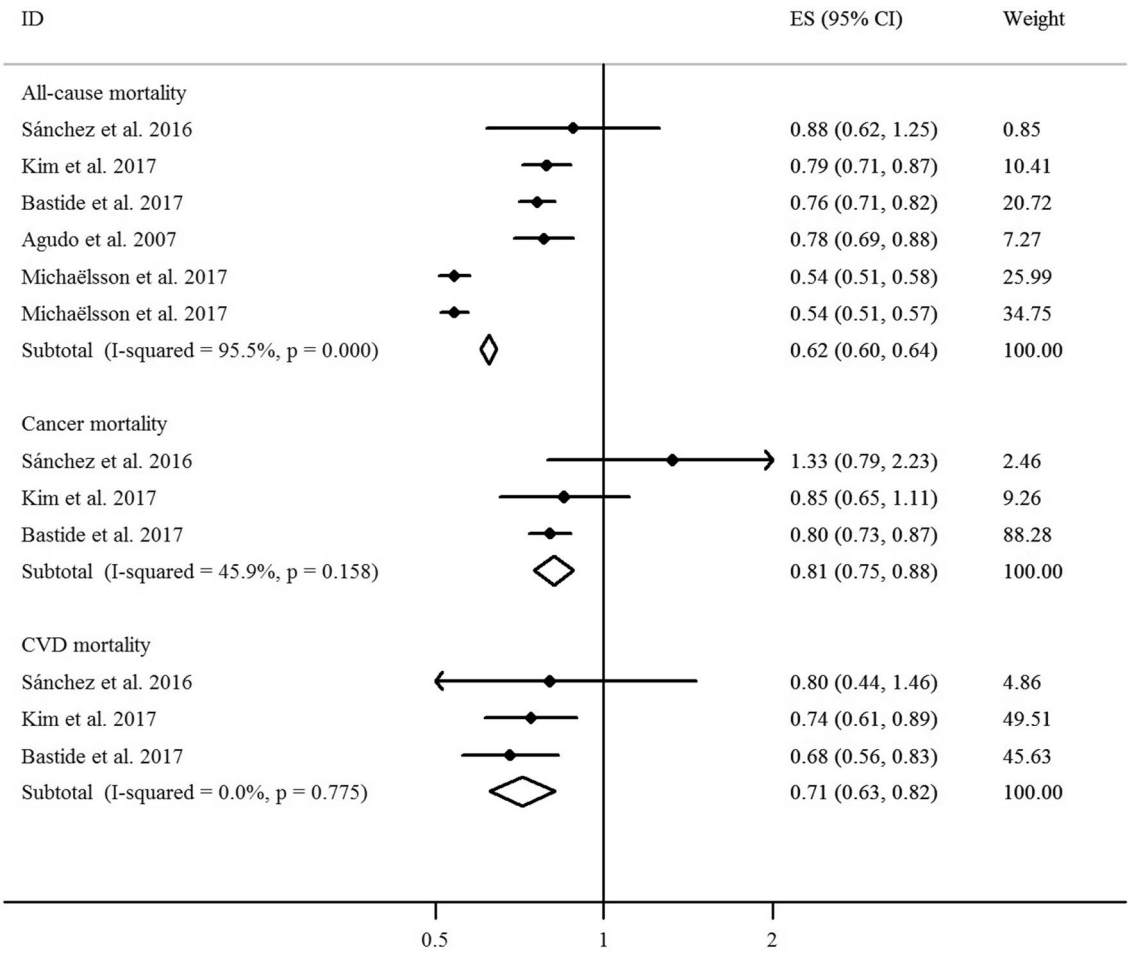

Fig. 2 Forest plot for the association between DTAC and risk of mortality from all-cause, cancer and CVDs using fixed-effects model

Table 1 Summary information of prospective studies on the association between DTAC and mortality from all-cause, cancer and CVDs

Authors	Country	Age range (years)	Gender	Sample size	Cases	Follow-up (years)	Person-year	Exposure	Exposure assessment	Outcome	Outcome assessment	Comparison	OR, RR or HR (95% CI)	Adjustment[a]
Kim et al. 2017	USA	≥ 30	M/F	23,595	7157 1578 2155	13		VCE	24 h dietary recall	All-cause mortality Cancer mortality CVDs mortality	Medical record	Q4 vs. Q1	HR: 0.79 (0.71–0.87) HR: 0.85 (0.65–1.11) HR: 0.74 (0.61–0.89)	1, 2, 4, 11–13, 16
Bastide et al. 2017	France	41–72	F	72,335	4619 2726 584	16.5	1,199,011	FRAP	Diet history	All-cause mortality Cancer mortality CVDs mortality	Medical record	Q4 vs. Q1	HR: 0.75 (0.68–0.83) HR: 0.79 (0.70–0.90) HR: 0.70 (0.52–0.93)	1, 3, 5–7, 11, 12, 15–18
								TRAP	Diet history	All-cause mortality Cancer mortality CVDs mortality	Medical record	Q4 vs. Q1	HR: 0.78 (0.70–0.86) HR: 0.82 (0.72–0.93) HR: 0.66 (0.50–0.87)	
Michaëlsson et al. 2017	Sweden	39–79	F	36,714	10,314	15	581,785	ORAC	FFQ	All-cause mortality	Medical record	Q4 vs. Q1	HR: 0.64 (0.61, 0.67)	16
			M	45,280	15,478	15	687,688	ORAC	FFQ	All-cause mortality	Medical record	Q4 vs. Q1	HR: 0.67 (0.64, 0.69)	

Table 1 (continued)

Authors	Country	Age range (years)	Gender	Sample size	Cases	Follow-up (years)	Person-year	Exposure	Exposure assessment	Outcome	Outcome assessment	Comparison	OR, RR or HR (95% CI)	Adjustment[a]
Sánchez et al. 2016	Spain	55–80	M/F	7015	319 166 102	4.3	31,075	FRAP	FFQ	All-cause mortality Cancer mortality CVDs mortality	Medical record	Q5 vs. Q1	HR: 0.88 (0.62–1.26) HR: 1.33 (0.79–2.23) HR: 0.80 (0.44–1.47)	1–3, 5, 7, 8–10, 12, 13, 14–17, 19–22
										All-cause mortality Cancer mortality CVDs mortality	Medical record	Per one quintile increase	HR: 0.99 (0.97–1.00) HR: 1.01 (0.98–1.03) HR: 1.00 (0.97–1.02)	
Agudo et al. 2007	Spain	30–69	M/F	41,358	562	6.5	268,852	FRAP TRAP TEAC ORAC	Diet history	All-cause mortality	Medical record	Q4 vs. Q1	HR: 0.77 (0.61–0.97) HR: 0.77 (0.61–0.97) HR: 0.78 (0.62-1.00) HR: 0.81 (0.64–1.04)	1–3, 5–7, 16, 17
								FRAP TRAP TEAC ORAC		All-cause mortality	Medical record	Per log2 increase	HR: 0.84 (0.77–0.92) HR: 0.84 (0.77–0.92) HR: 0.85 (0.78–0.93) HR: 0.88 (0.79–0.97)	

region (US vs. non-US countries), methods used to assess dietary intakes (food recall vs. FFQ vs. diet history), use of energy-adjusted scores of DTAC in statistical analysis (used vs. not-used) and adjustment for BMI (adjusted vs. non-adjusted) to find sources of heterogeneity (Table 2). Subgroup analyses based on gender and adjustment for BMI could decrease between-study heterogeneity. From these analyses, a significant inverse association was found between DTAC and all-cause mortality in all subgroups. Sensitivity analysis showed that exclusion of any single study from the meta-analysis did not change the summary association. Furthermore, based on Egger's test, no evidence of publication bias was seen ($P = 0.20$). Such finding was also seen by visual inspection of funnel plot (Supplemental Fig. 4.A).

The association between DTAC and all-cause mortality stratified by methods used to assess DTAC (FRAP and ORAC) is shown in Fig. 3. Considering three effect sizes from three studies in terms of FRAP [7, 9, 10], a significant inverse association was found with all-cause mortality (combined effect size: 0.76, 95% CI 0.70–0.83) with no between-study heterogeneity ($I^2 = 0$). Such inverse association was also seen in random-effects model (combined effect size: 0.76, 95% CI 0.70–0.83) (Supplemental Fig. 2). In case of ORAC, combining three effect sizes from two studies [8, 10] revealed a significant inverse association between DTAC and all-cause mortality (combined effect size: 0.55, 95% CI 0.52–0.57) (Fig. 3). However, there was an evidence of high between-study heterogeneity ($I^2 = 80.8$). Random-effects analysis showed no alteration in observed inverse association (combined effect size: 0.57, 95% CI 0.51–0.64) (Supplemental Fig. 2). Unfortunately, because of the limited number of studies, subgroup analysis was not possible to do. Furthermore, we could not perform meta-analysis based on other methods of DTAC including TRAP and TEAC due to limited studies.

Three studies on the association between DTAC (based on FRAP) and all-cause mortality were included in non-linear dose–response meta-analysis. No significant non-linear association was seen in this regard (P-nonlinearity = 0.66) (Fig. 4a). However, a significant reduction in risk of all-cause mortality was seen when increasing FRAP from 2 to 12 mmol/day (P-nonlinearity = 0.002). Although the risk was decreased when increasing DTAC from 12 mmol/day, the slope was slightly flattening. Furthermore, linear dose–response analysis among mentioned three studies showed that the combined effect size of all-cause mortality per a-5 mmol/day increase in DTAC (based on FRAP) was 0.92 (combined effect size: 0.76, 95% CI 0.91–0.94) (Fig. 5). However, between-study heterogeneity was observed ($I^2 = 50.1$). When we did random-effects analysis, similar result was seen (combined effect size: 0.92, 95% CI 0.89–0.96) (Supplemental Fig. 3).

Table 1 (continued)

FRAP ferric reducing antioxidant power, *VCE* Vitamin C equivalent antioxidant capacity, *TRAP* total radical trapping antioxidant parameter, *TEAC* Trolox equivalent antioxidant capacity, *ORAC* oxygen radical absorbance capacity, *FFQ* food frequency questionnaire, *CVD* cardiovascular disease, *HR* hazard ratio

[a]Adjustment: age (1), sex (2), education (3), race (4), BMI (5), physical activity (6), smoking (7), study center (8), intervention group (9), marital status (10), personal or family history of CVD (11), diabetes mellitus (12), hypertension (13), dyslipidemia (14), cancer (15), dietary intake of energy (16), alcohol (17), fiber (18), saturated fatty acids (19), polyunsaturated fatty acids (20), monounsaturated fatty acids (21), glycemic index (22), dairy intake (23), red meat (24), dietary supplements (25)

Table 2 Subgroup analysis based on fixed effects models for the association between DTAC and risk of all-cause mortality

	Effect sizes (*n*)	I^2	*Q* test	RR (95% CI)	$P_{between}$
Overall	6	95.5	< 0.001	0.62 (0.60–0.64)	
Gender					
Male	1	0	0	0.54 (0.51–0.57)	< 0.001
Female	2	97.9	< 0.001	0.63 (0.60–0.66)	
Both	3	0	0.82	0.79 (0.73–0.85)	
Geographical region					
US	1	0	0	0.79 (0.71–0.87)	< 0.001
Non-US	5	95.4	< 0.001	0.60 (0.58–0.63)	
Methods used to assess dietary intakes					
FFQ	3	72.2	0.02	0.54 (0.52–0.57)	< 0.001
24 h dietary recall	1	0	0	0.79 (0.71–0.87)	
Diet history	2	0	0.71	0.77 (0.72–0.81)	
Using energy-adjusted DTAC					
Used	5	95.9	< 0.001	0.61 (0.59–0.63)	< 0.001
Not-used	1	0	0	0.78 (0.69–0.88)	
Adjustment for BMI					
Adjusted effect size	3	0	0.701	0.77 (0.72–0.82)	< 0.001
Non-adjusted effect size	3	95.6	< 0.001	0.57 (0.55–0.59)	
Sample size					
< 10,000 people	1	0	0	0.88 (0.62–1.25)	0.05
≥ 10,000 people	5	96.3	< 0.001	0.62 (0.60–0.64)	
Follow-up					
< 10 years	2	0	0.52	0.79 (0.70–0.89)	< 0.001
≥ 10 years	4	96.8	< 0.001	0.61 (0.59–0.63)	

For assessing non-linear dose–response association between DTAC (based on ORAC) and all-cause mortality, two studies with complete data were included; however, Michaëlsson study was considered as two separate studies because of presenting gender-stratified effect sizes. On the other hand, three studies were included this analysis. We found a significant inverse non-linear relationship between DTAC (based on ORAC) and all-cause mortality (*P*-nonlinearity = 0.02) (Fig. 4b). This inverse association was mostly seen when increasing ORAC from 5 to 11 mmol/day (*P*-nonlinearity < 0.001); however, it became attenuated in dose of > 11 mmol/day. Based on findings from linear dose–response meta-analysis, a 5 mmol/day increase in DTAC (based on ORAC) was associated with 15% lower risk of death from all-cause (combined effect size: 0.85, 95% CI 0.84–0.86) with a significant between-study heterogeneity ($I^2 = 84.5$) (Fig. 5). However, such significant association was also observed when we did random-effects analysis (combined effect size: 0.85, 95% CI 0.84–0.86) (Supplemental Fig. 3).

DTAC in relation to cancer and CVD mortality

Totally, three effect sizes from three studies [6, 7, 9] with a total of 102,945 participants and 4470 cases of death were extracted for the association between DTAC and cancer mortality. Combining the reported estimates, we found a significant inverse association between DTAC risk of death from cancer (combined effect size: 0.81, 95% CI 0.75–0.88) (Fig. 2). Between-study heterogeneity was not significant in this regard ($I^2 = 45.9$). This association became non-significant when we did random-effects analysis (combined effect size: 0.86, 95% CI 0.71–1.04) (Supplemental Fig. 1).

Considering three effect sizes from three studies [6, 7, 9] that included 102,945 participants and 2841 cases of death from CVDs revealed a significant inverse association between DTAC and CVDs mortality (combined effect size: 0.71, 95% CI 0.63–0.82) (Fig. 2). No between-study heterogeneity was seen ($I^2 = 0$). Such finding was also seen in random-effects model (combined effect size: 0.71, 95% CI 0.63–0.82) (Supplemental Fig. 1). Because of the limited

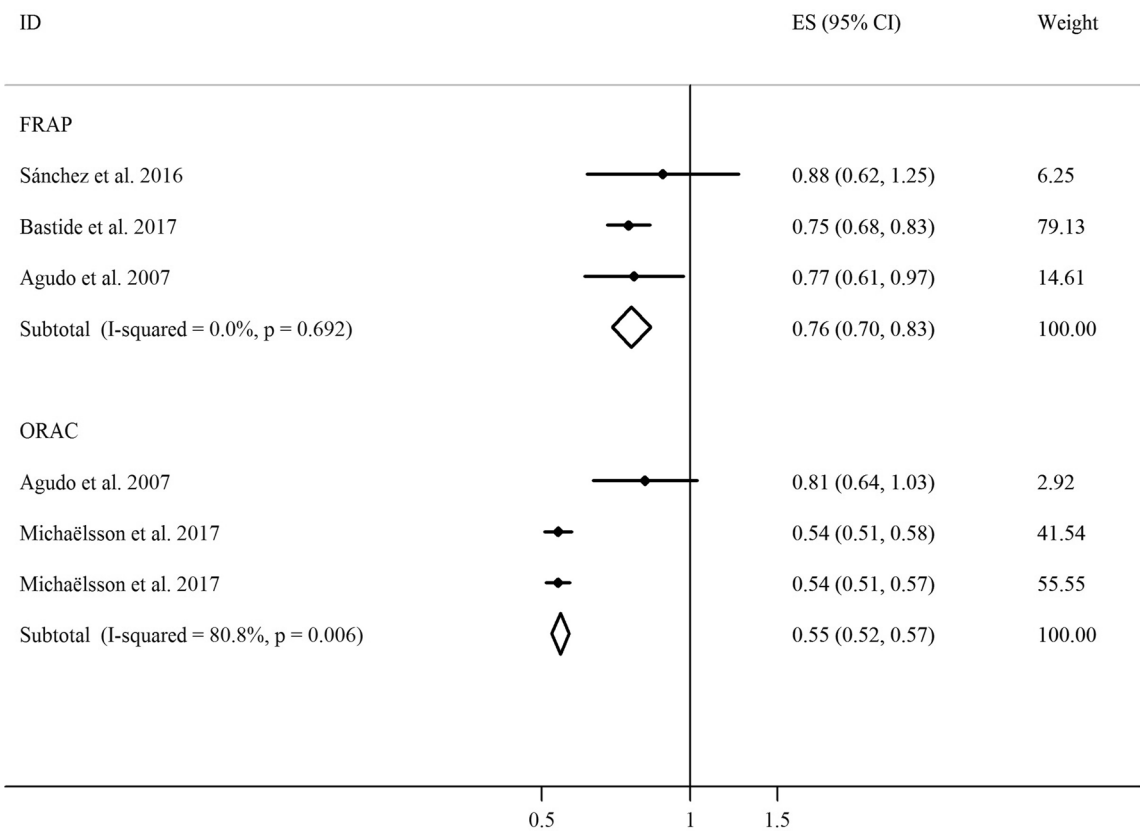

Fig. 3 Forest plot for the association between DTAC (based on FRAP and ORAC) and risk of all-cause mortality using fixed-effects model

number of studies, subgroup analysis (based on methods used to assess DTAC and other variables) as well as dose–response meta-analysis was not conducted for the association of DTAC with cancer and CVDs mortality.

Findings from sensitivity analysis showed that overall estimates on the association of DTAC with cancer and CVD mortality did not depend on a single study. Furthermore, based on visual inspection of funnel plots and also according to the results of Egger's test (cancer mortality; P = 0.29, CVD mortality; P = 0.67), we found no evidence of publication bias (Supplemental Fig. 4.B, C).

Discussion

Findings from the current systematic review and meta-analysis supported the hypothesis that high antioxidant capacity of diet was associated with lower risk of mortality from all-cause, cancer and CVDs. In addition, we found that a 5 mmol/day increment in DTAC, based on FRAP and ORAC, was associated with 7% and 15% lower risk of all-cause mortality, respectively. To the best of our knowledge, current study is the first to summarize earlier prospective studies on the association between DTAC and risk of mortality.

The prevalence of CVD and cancer is increasing at an alarming rate [50–52]. Both of them are associated with a high burden and mortality [53]. Similar to our findings, accumulating evidences from prior studies have shown that fruits' and vegetables' consumption, as important sources of antioxidants, is inversely associated with mortality [11, 12]. Findings from a meta-analysis showed that with increasing intake of fruits and vegetables, the risk of all-cause mortality decreased [12]. Such finding was also seen for whole grains as other source of antioxidants [54]. In contrast, in a prospective study, Wang et al. reported no significant association between fruits plus vegetables consumption and all-cause mortality [55]. It must be kept in mind that studies reaching no significant association between DTAC, antioxidant-rich foods and all-cause mortality had mostly low quality than those reporting significant association. For example, in Wang study, energy intake was not controlled for the association between fruits plus vegetables consumption and all-cause mortality [55]. Furthermore, among five studies included in the current meta-analysis, only one with a low sample size (< 10,000 participants) [9] and low duration of follow-up (< 5 years) [9] reported no significant

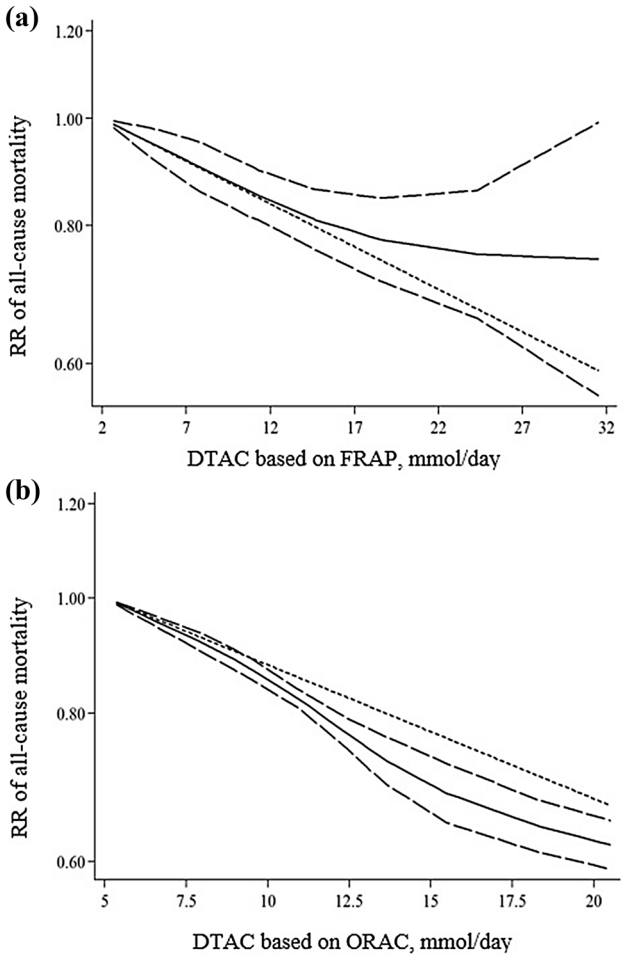

Fig. 4 Non-linear dose–response meta-analysis for the association between DTAC and all-cause mortality: **a** DTAC based on FRAP, **b** DTAC based on ORAC

association between DTAC and all-cause mortality, while others that reached a significant inverse association had a sample size of ≥ 10,000 individuals and ≥ 5 years' duration of follow-up [6–8, 10].

We found a significant inverse association between DTAC and death from cancer. A large number of studies have shown that adherence to a diet rich in antioxidants is associated with decreased risk of cancer [56–58]. In a prospective study, Pantavos et al. reported that high overall dietary antioxidant capacity is associated with a lower risk of breast cancer [56]. In another study that was done on EPIC data, Serafini et al. reported a significant inverse association between DTAC (based on FRAP) and risk of gastric cancer among women [57]. In a systematic review and meta-analysis, high adherence to Mediterranean diet was associated with lower risk of death from cancer [58]. Mediterranean diet is known as an antioxidant-rich dietary pattern [59]. In contrast, some prospective studies had indicated no significant association between DTAC and cancer incidence [60, 61]. However, energy intake and BMI, as important confounders, were not adjusted in mentioned studies. In the current systematic review, out of two studies that reported no significant association between DTAC and cancer mortality, one had a sample size of < 10,000 individuals and follow-up duration of < 5 years [9] and other one had not considered BMI as a covariate [6]. In contrast, one study that reported a significant inverse association had a sample size of ≥ 10,000 individuals, ≥ 5 years' duration of follow-up and also considered BMI as a covariate [7].

In the current study, a significant inverse association was found between DTAC and CVD mortality. Only one study [9], out of three studies [6, 7, 9] on the association between DTAC and CVD mortality, had shown non-significant association. This study had low sample size (< 10,000 participants) and low duration of follow-up (< 5 years) than two studies that reported significant inverse association [9]. Furthermore, a large number of studies have indicated similar findings about CVD risk [29, 38, 41]. In a population-based prospective study on women, adherence to diet with high antioxidant capacity was associated with decreased risk of stroke [38]. Such inverse relationship was also reported for cerebral infarction in another prospective study [41]. Therefore, it seems that diet with high antioxidant capacity decreases risk of CVD in addition to death from it.

It has been shown that adherence to a diet with a high antioxidant capacity is inversely associated with serum levels of oxidative stress indicators, triglyceride, low-density lipoprotein cholesterol (LDL-C) and homocysteine which all are positively associated with risk of cancer and CVDs including hypertension, stroke and myocardial infarction, and also mortality from them [62–65]. Furthermore, intake of antioxidant-rich foods can reduce inflammatory biomarkers which are positively associated with mortality [63].

In the current study, a-5 mmol/day increment in DTAC, based on FRAP and ORAC, was associated with 7% and 15% lower risk of all-cause mortality. Antioxidants can be provided from fruits, vegetables, chocolate, coffee, tea, wine, beer and fresh herbs (Table 3) [15]. Based on the study of Pellegrini et al. [15], a 100 grams of blackberry (a fruit with very high antioxidant capacity) is equivalent to 5.12 mmol DTAC based on FRAP which means that daily consumption of this amount is associated with 7% lower risk of all-cause mortality. Some antioxidant-rich food items are presented in Table 3.

Some strengths and weaknesses of DTAC approach should be considered during the interpretation of our findings. The main strength of this approach is to capture the effects of a wide variety of antioxidants available in foods. It means that DTAC considers known antioxidants as well as those that have not been well characterized, such as flavonoids [19, 66]. In addition, DTAC can evaluate antioxidant's synergistic and complementary effects in a food or the

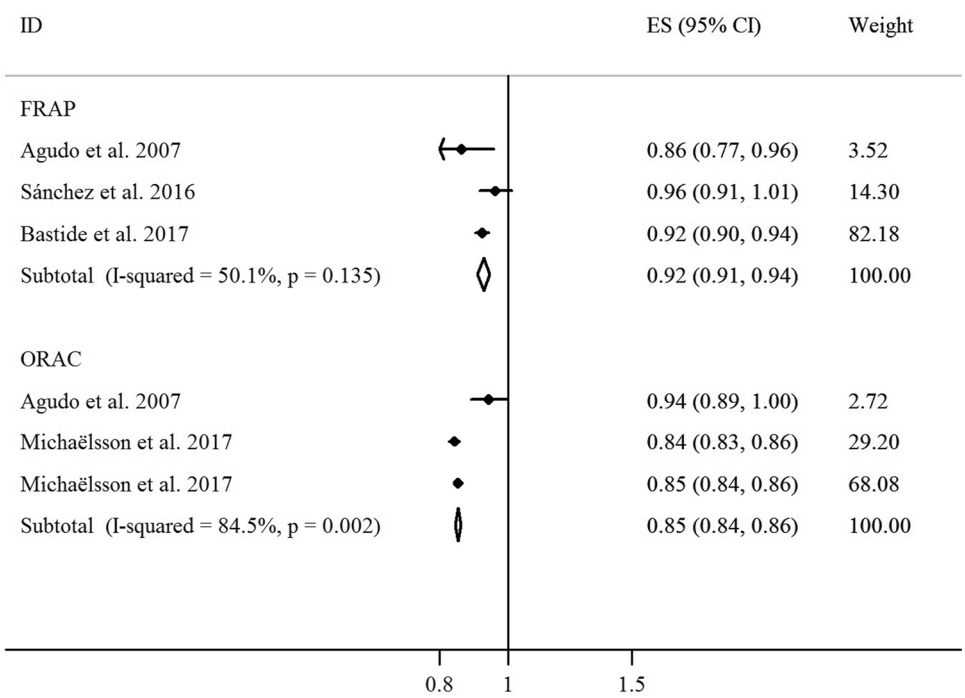

Fig. 5 Forest plot for risk of all-cause mortality based on a 5 mmol/day increment in D-TAC (based on FRAP and ORAC) using fixed-effects model

Table 3 Ranking of selected food items based on their antioxidant content

Vegetables	DTAC (mmol/kg)[a]	Fruits	DTAC (mmol/kg)[a]	Soft beverages	DTAC (mmol/L)[a]	Other food items	DTAC (mmol/L or kg)[a]
Spinach	26.94	Blackberry	51.53	Orange juice	9.44	Coffee (espresso) (per L)	129.38
Pepper (chili)	23.54	Raspberry	43.03	Mixed fruit juice	8.76	Wine (Chianti, red) (per L)	31.53
Pepper (red bell)	20.98	Olive (black)	39.99	Lemon juice	8.37	Tea (green) (per L)	18.00
Mushroom	16.39	Strawberry (wild)	28.00	Grapefruit juice	8.22	Tea (black) (per L)	10.09
Beet	13.13	Olive (green)	24.59	Peach juice	7.79	Vinegar (red) (per L)	9.50
Broccoli	11.67	Strawberry (cultivated)	22.74	Pear juice	7.43	Soybean (per Kg)	2.20
Artichoke	11.09	Orange	20.50	Apricot juice	7.15	Extra virgin olive (per Kg)	1.79
Cabbage (green)	5.79	Blueberry	18.61	Tropical juice	6.18	Corn (per Kg)	1.29
Onion (yellow)	5.28	Pineapple	15.73	Pineapple juice	5.16	Sunflower (per Kg)	1.17
Tomato (salad)	5.12	Plum (red)	12.79	Apple juice	5.01	Olive (per Kg)	0.63
Potato	3.67	Grape (black)	11.09	Cola	0.92	Peanut (per Kg)	0.61

All values were obtained from study of Pellegrini et al. [15] and were reported based on one kg or liter of food items

[a]Based on FRAP values

possible interactions between antioxidants in the food matrix [19]. In contrast, the major weakness of DTAC approach is the weak correlation of DTAC with plasma TAC or biological effects of antioxidants [20, 21]. The chemical structures, biochemical changes of antioxidant molecules in the food matrix or supplements (i.e. free, glycosylated, polymerised or chemically bound to other food components), and also the way of antioxidants consumption (i.e. alone or combined with other foods) might affect the pharmacokinetic parameters of antioxidants [19]. Furthermore, the bioavailability of dietary antioxidants is affected by mechanisms of digestion, absorption and metabolism occurring in human body [19, 22]. The huge inter-individual variability in mentioned mechanisms can easily explain the different responses of plasma TAC to an antioxidants-rich food [19]. The genetic capacity of individuals as well as baseline inflammatory and antioxidant status are other contributors for plasma TAC response to dietary antioxidants [19, 67]. It has been shown that genetic capacity of individuals to retain the redox status in the cells could impact the bioavailability of dietary

antioxidants as well as systemic oxidative status [19, 67]. It seems that in an oxidative stress condition, when the endogenous control of redox condition is unbalanced due to the depletion of antioxidant enzymes and plasma antioxidant compounds, plasma TAC becomes in some way more susceptible to the dietary antioxidants [19]. This may be a reason for the observed correlation between DTAC and plasma TAC in some studies [23–28]. Based on these studies, intake of high TAC foods such as strawberry [23], tea [24], red wine [25] and even solid foods like dark chocolate [26] is capable of enhancing plasma TAC. However, oxidative status was not assessed in these studies. Moreover, similar findings obtained for DTAC, plasma TAC and individual antioxidants in relation to chronic diseases are other reasons for the correlation between DTAC and plasma TAC [29, 30]. Overall, it seems that the validity of DTAC assay is unclear and needs further investigations. Therefore, our findings should be viewed with caution. The observed significant inverse association between DTAC and mortality in the current study may be due to fiber content of foods with high TAC [68]. However, in study of Bastide et al., after adjusting for fiber intake, the inverse association between DTAC and mortality remained significant [7]. Another weakness of DTAC approach is different methods of measurement like FRAP, TRAP, ORAC and TRAP. Each method employs different analytical conditions making the results not comparable to each other and poorly representative of the physiological action of the single antioxidant molecules [19].

Our present systematic review and meta-analysis had some strengths. To the best of our knowledge, this was the first meta-analysis exploring the association between DTAC and mortality. Furthermore, prospective cohort studies were included in this analysis. Studies with prospective design can minimize the possibility of recall or selection bias, which could be of concern in case–control or cross-sectional studies. In addition, this meta-analysis included a large number of cases that provided good statistical power for assessing the association between DTAC and mortality. Assessing the quality of included studies showed that all were of high quality and the majority of studies had controlled for important confounders. Despite mentioned strengths, several limitations also need to be acknowledged. First, some non-differential misclassification of individuals in terms of DTAC may have occurred in each study and, therefore, it may have attenuated any true association between DTAC and mortality in the meta-analysis. Such probable misclassifications may be particularly high for studies with long duration of follow-up assessing DTAC at study baseline only. Although analyses on the association between DTAC and all-cause mortality were separately done for each DTAC method (FRAP and ORAC), it was better to do such stratified analyses for cancer and CVD mortality, but because of limited number of studies, it was not possible. In addition to low number of studies included in the current meta-analysis, they were from some limited countries and, therefore, our findings cannot be generalized. Although studies controlled for different confounders on the associations between DTAC and mortality, we cannot exclude the residual confounders such as psychological disorders, drug use and other dietary factors including intake of trans fatty acids in these associations, particularly those obtained for CVD mortality. Hence, further studies from other populations with considering residual confounders are needed to confirm our findings.

In conclusion, adherence to diet with high capacity of antioxidant was associated with decreased risk of death from all-cause, cancer and CVD. Furthermore, a-5 mmol/day increment in DTAC, based on FRAP and ORAC, was associated with 7% and 15% lower risk of all-cause mortality, respectively.

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Author contributions MN, JAS, MP, SRK and MK contributed to conception, design, statistical analyses, data interpretation and manuscript drafting. OS and MP contributed to data analysis, data interpretation and manuscript drafting. All authors approved the final manuscript for submission.

Compliance with ethical standards

Conflict of interest The author declares that there is no conflict of interest.

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