Review

Dietary total antioxidant capacity (TAC), general and central obesity indices and serum lipids among adults: An updated systematic review and meta-analysis

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Abstract: *Background*: In the present meta-analysis, we aimed to summarize the relationship between dietary total antioxidant capacity (TAC), general and central obesity indices and lipid profile in adult population. *Methods*: The electronic databases of Web of Sciences, PubMed, Scopus and Cochrane library were searched for relevant studies from inception to October 2019. The effect size was indicated as weighted mean difference (WMD) and 95% confidence intervals (CI) by using random effects model. The I^2 index and Cochran's Q-test were used for evaluating heterogeneity. *Results*: From 2,469 studies identified, thirty-four studies (nineteen cross-sectional studies, thirteen cohort studies, two case-control studies) were included in the meta-analysis. According to our results, higher categories of TAC were associated with significantly lower serum triglyceride concentartions (TG; WMD: −7.58; CI: −11.42, −3.75; P < 0.001) and waist circumference (WC; WMD: −1.17; 95% CI: −1.47, −0.87; P < 0.001); while no significant change in body mass index (BMI; WMD: −0.17; 95% CI: −0.35, 0.01; P = 0.12), high density lipoprotein cholesterol (HDL-C; WMD: 0.61; 95% CI: −0.16, 1.40; P = 0.12), low density lipoprotein cholesterol (LDL-C; WMD: 1.34; 95% CI: −0.61, 3.30; P = 0.17) and total cholesterol (TC; WMD: 1.19; 95% CI: −1.46, 3.855; P = 0.37) was reported. *Conclusion*: Higher dietary TAC was related to reduced prevalence of central obesity, reduced WC and TG concentrations in the current meta-analysis. Moreover, subgroup analysis showed that TAC measurement index, geographical area, dietary assessment tool, health status and gender were potential sources of heterogeneity.

Keywords: antioxidants, diet, obesity, central obesity, serum lipids, dietary total antioxidant capacity (TAC), meta-analysis

Introduction

Obesity has become a growing public health issue, owing to its high prevalence, mortality and morbidity and economic costs. In 2016, it has been reported that over 650 million adults, 18 years and older, were obese [1]. Obesity is a complex, multifactorial disease that results from an interaction between genetic and environmental factors such as physical activity level and diet [2, 3]. Moreover, according to several studies, overproduction of free radicals plays an important role in the pathogenesis of obesity [4–6]. Therefore, high body fat is accompanied by higher systemic oxidative stress, increased oxidation of proteins, DNA and lipids [7, 8], and the final development of several serious diseases such as cardiovascular disease (CVD), stroke, type 2 diabetes, hypertension and multiple types of cancer [2, 9, 10]. Consequently, exploration of new strategies to decrease free radicals may be beneficial to control the obesity and related diseases. The studies reported that vegetable and fruit juices affect cardiovascular risk factors, such as improving blood lipid profiles and lowering blood pressure [11–15]. The key mechanisms of action include antioxidant effects, improved cardiovascular system, anti-inflammatory effects, suppression of platelet aggregation, and prevention of hyperhomocysteinemia [16]. Dietary total antioxidant capacity (TAC) is a recently developed index frequently used to evaluate the antioxidant status of biological samples and can assess the antioxidant response against the free radicals produced in a given disease. The most common measures of TAC are oxygen radical

absorbance capacity (ORAC), ferric reducing ability of plasma (FRAP), total radical trapping antioxidant parameter (TRAP), vitamin C equivalent antioxidant capacity (VCEA) and Trolox equivalent antioxidant capacity (TEAC) [17]. Several studies revealed the positive association of TAC with dietary folic acid, fiber, vitamins E, A and C even after adjustment for sex, age and daily energy consumption [14, 18–20]. TAC represents the capability of different antioxidants to clear free radicals and represents a biomarker of antioxidant potential, including redox synergistic interactions. Several studies have reported that food items rich in bioactive redox substances, such as fruit juices, chocolate, berries, coffee, lettuce, tea and vegetables modify the plasma total antioxidant capacity [21–23]. Numerous studies have evaluated the role of dietary TAC against general and central obesity indices [24, 25], metabolic syndrome [26–28], pre-diabetes [29], various types of cancers [30] and cardiovascular disease [31–33]. However, there is inconsistency in the results of prior studies that evaluated the association between dietary TAC and obesity. Although several studies have reported a strong negative association between dietary TAC and central obesity [19, 25, 34], other studies have not found any significant association [35–38]. According to our literature review, no summarized systematic review or meta-analysis that evaluated the role of dietary TAC against obesity and obesity-related disorders is available. In the current study, we aimed to evaluate the possible effects of dietary TAC on obesity indices such as waist circumference (WC), body mass index (BMI), waist to hip ratio (WHR) and lipid profile including triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), and total cholesterol (TC) in adult population in a systematic review and meta-analysis.

Methods

This study was conducted according to the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [39] (Table E1 in Electronic Supplementary Material 1).

Search strategy

A systematic literature search using Web of Sciences, PubMed, Scopus and Cochrane electronic databases was performed to find the studies that evaluated the relationship between dietary TAC, central or general obesity indices and serum lipids up to October 2019. No language restriction was used. In the search strategy, we used MESH (Medical Subject Headings) and non-MESH terms including the following: ("dietary antioxidant capacity" OR "total dietary antioxidant capacity" OR "dietary antioxidant index" OR "antioxidant capacity of diet") AND ("body mass index" OR "BMI" OR "obesity" OR "central obesity" OR "waist circumference" OR "waist to hip ratio" OR "WC" OR "WHR" OR "serum lipids" OR "lipid profile" OR "triglyceride" OR "cholesterol" OR "LDL-cholesterol "low density lipoprotein cholesterol" OR "HDL" OR "high density lipoprotein cholesterol" OR "hypertension" OR "cardiovascular risk factors" OR "cardiometabolic risk factors" OR "hypertension" OR "diabetes"). In addition, the reference lists of the relevant studies were screened for additional data sources. The PICO for the current meta-analysis is shown in Table 1. The protocol of the present study has been registered in the International prospective register of systematic reviews (PROSPERO; Identifier: CRD42019123484). Additionally, the ethics committee of Tabriz University of Medical Sciences has approved the study's protocol (Registration number: IR.TBZMED.VCR.REC.1398.176).

Inclusion criteria

In the present meta-analysis, observational studies (cross-sectional, cohort or case control) that evaluated the association between dietary TAC and WC, WHR, BMI, obesity, and serum lipids were included. Accordingly, the studies were included if they reported the mean ± standard deviation (SD) of study outcome in the highest versus lowest dietary TAC categories as the reference group. The studies that were retrieved from the electronic searches were inserted into the EndNote software (version X8, for Windows, Thomson Reuters, Philadelphia, PA, USA). Consequently retrieved studies were combined and the duplications were removed for facilitation of the review process. Two authors (MAF and MV) independently examined the titles and abstracts of all studies to identify potentially relevant studies and reviewed the full text of them. Articles that did not meet the eligibility criteria were excluded. Furthermore, the reference lists of eligible review articles were scanned to identify additional studies and any disagreements were resolved by the third reviewer (PF).

Data collection and extraction

The following data were extracted from included studies using a pre-designed form: first author's name, sample size, year of publication, study location, study design, participants age range, health status of participants, dietary assessment tool, setting, gender, number of case and controls, and information about the adjustment for possible confounders.

Table 1. The PICO criteria used for the present systematic review

PICO criteria	Description
Participants	General apparently healthy population or with obesity related metabolic disorders
Exposure (Interventions)	Highest category of dietary total antioxidant capacity represented by higher scores of TAC as FRAP, TRAP, TEAC, ORAC, VCEA
Comparisons	Lowest category of dietary total antioxidant capacity represented by lower scores of TAC as FRAP, TRAP, TEAC, ORAC, VCEA
Outcome	BMI, WC, LDL, HDL, TG, TC
Study design	Observational studies with the design of cross-sectional, case control or cohort

TAC: total antioxidant capacity; FRAP: ferric reducing ability of plasma; TRAP: total radical trapping antioxidant parameter; TEAC: Trolox equivalent antioxidant capacity; ORAC: oxygen radical absorbance capacity VCEA: vitamin C equivalent antioxidant capacity.

Quality assessment

The quality of included studies were assessed by the Newcastle-Ottawa scale (NOS) criterion. The 9-point NOS scale has scoring ranges from 0 to 9 and is categorized into comparability, selection and ascertaining of outcome. Studies with equal or more than 7 stars were considered as low risk of bias [40].

Data synthesis and analysis

In the present study, two meta-analysis approaches were used: The comparison of the continuous variables including TG, LDL-C, TC, HDL-C, BMI and WC between highest versus lowest categories of dietary TAC was performed by the assessment of unstandardized mean differences as the effect size that was calculated by pooled estimate of weighted mean difference (WMD) with 95% confidence interval (CI), and the random and fixed effects models according to level of heterogeneity. The prevalence of central obesity in highest versus lowest dietary TAC categories was done by re-calculating the proportions of interest from the related denominator and numerator. Between-studies heterogeneity was examined using I^2 test (I^2 = 0–25%: no heterogeneity; I^2 = 25–50%: moderate heterogeneity; I^2 > 50%: extreme heterogeneity) and Cochran's Q test [41]. The heterogeneity was considered significant if either the Q statistic had $p < 0.1$ or $I^2 > 50\%$. In addition, subgroup analysis was done to identify possible sources of heterogeneity among studies. We used a sensitivity analysis to determine the effect of each study on the estimated pooled effect size. Publication bias was evaluated visually by funnel plots and was calculated by Begg's and Egger's tests. The data were analyzed using STATA version 13 (STATA Corp, College Station, Texas), and P-values < 0.05 were considered as statistically significant.

Results

Study selection

The study selection process is presented in Figure 1. In our search we identified 2,469 potentially relevant studies from Scopus, Web of Sciences, PubMed and Cochrane electronic databases. After removing the 596 duplicates, the titles and abstracts of the remaining 1,873 were screened, and 128 articles were reviewed by full text. After full-text review, 94 studies were excluded because of the following reasons: studies that were performed on pregnant women or children, review studies, seminars and conferences and those that did not report relevant data (Figure 1). Finally, 34 articles [14, 19, 20, 24–27, 29, 31, 34–38, 42–61] were included in the current systematic review and meta-analysis.

Study characteristics

Table 2 presents the characteristics of studies that evaluated the relationship between dietary TAC with obesity indices (BMI, WHR, and WC) and serum lipids. These studies were conducted between 2004 and 2019 and the sample size of included articles varied from 33 to 475,999 participants. The studies were conducted in Maryland [19], Spain [20, 24–26, 49], USA [14, 34, 37, 61], Iran [29, 31, 35, 42, 43, 50, 56], Sweden [45, 48, 53, 55, 58], Netherlands [47], Italy [36], China [59], Czech [52], Poland [27], France [44, 54, 60], Japan [51], Brazil [46], South Korea [57] and one study [38] was performed in 10 countries. From these studies, 13 studies [19, 38, 43–45, 47, 48, 53–55, 58, 60, 61] were cohort, 19 were cross-sectional [14, 20, 24–27, 31, 34–37, 42, 46, 49, 51, 52, 56, 57, 59] and two were case-control [29, 50] studies. Twenty-four studies included both genders, nine studies [34, 42, 44, 50, 53, 54, 58–60] included only female participants and one study included only male participants [19]. The included populations were apparently healthy individuals, patients with dysglycemia [43], metabolic syndrome [57], NAFLD [46], breast cancer [50] and candidates for CABG [31, 36]. In our meta-analysis, fifteen studies [20, 24–27, 34, 44–49, 51, 56, 60] used FRAP assay, four studies used TRAP assay [38, 44, 51, 54], ten studies used ORAC assay [29, 31, 35, 42, 43, 50, 51, 53, 55, 58], one study used TEAC assay [36] and four studies used VCEA assay [14, 37, 57, 61] to evaluate dietary TAC.

In total, 34 studies have reported the association between obesity indices (BMI, WHR or WC) and dietary antioxidant

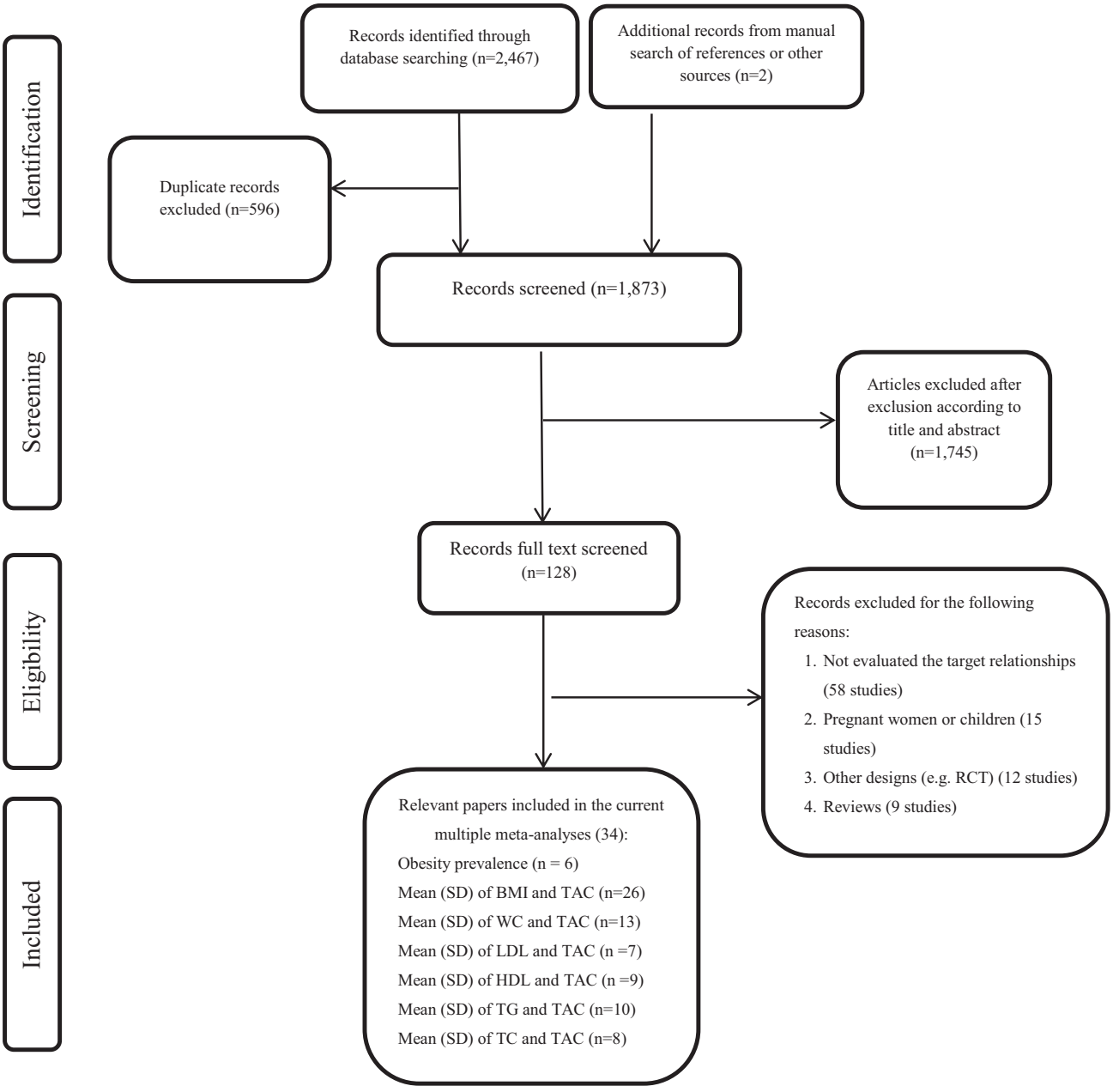

Figure 1. Flow diagram of study screening and selection process.

capacity [14, 19, 20, 24–27, 29, 31, 34–38, 42–61]. While some of these studies were included in the meta-analysis as more than one independent study because of their separate subgrouping according to gender or measurement index; the study by Maugeri et al. [52] evaluated the relationship between TAC and BMI separately for men and women. Several studies also reported gender-specific differences in BMI according to different TAC groupings [27, 31, 45, 55]. Also, several other studies included the TAC-BMI associations differentially according to each of the TAC-measurement indices [44, 51]. Nine studies reported the lower BMI or lower prevalence of obesity (BMI above 30 kg/m^2) in highest versus lowest TAC categories [14, 19, 20, 34, 48, 52, 54, 59, 61]. However, other studies reported no significant difference in the prevalence of obesity or BMI in different TAC categories [24, 25, 27, 29, 31, 36–38, 46, 47, 53]. The prevalence of central obesity (WC > 80 and 90 cm in women and men, respectively) or mean of WC were also reported in 14 studies [24–27, 29, 35, 42, 46, 52, 56–58]; while two studies have reported lower prevalence of central obesity or WC in highest versus lowest TAC categories [25, 58] and others found no statistically significant difference. WHR was only reported in two studies [26, 52].

Table 2. Characteristics of studies included in the systematic review owing to reporting the association between dietary antioxidant index, obesity indices (BMI, WHR and WC) and lipid profile in adults

First author/year	Country	Study design	Sex	Age range	Sample size/ Population	Number of cases/controls	Dietary index/unit	Dietary assessment tool	Result	Adjusted variables	Quality of the study
Wright ME [19]/ 2004	Maryland	Cohort	Men	50–69 y	27110/Apparently healthy smokers	5422/5422	DAI/loading factors of PCA	FFQ	Significantly lower BMI in highest versus lowest DAI quintile ($P < 0.05$).	Energy intake	8
Puchau B [20]/ 2009	Spain	Cross-sectional	Both	20.86 ± 2.7 y	153/Apparently healthy individuals	30/30	TAC/FRAP	FFQ	Significantly lower BMI in highest versus lowest TAC quintile ($P = 0.049$).	–	7
Devore EE [34]/ 2010	USA	Cross-sectional	Women	≥ 70 y	16010/Apparently healthy individuals	3202/3202	TAC/FRAP	FFQ	Significantly lower prevalence of obesity (15 vs 22%) in highest versus lowest quintile of TAC was reported ($P < 0.0001$ and 0.04).	–	7
Puchau B [26]/ 2010	Spain	Cross-sectional	Both	20.86 ± 2.7 y	153/Apparently healthy individuals	77/76	TAC/FRAP	FFQ	No significant difference between WC, WHR, BF% TC, TG, HDL, LDL was reported.	–	7
Hermsdorff HHM [25]/2011	Spain	Cross-sectional	Both	18–35	266/Apparently healthy individuals	90/86	TAC/FRAP	FR	Significantly lower WC, central obesity in highest versus lowest TAC quintile ($P < 0.05$). No significant difference in BMI, obesity prevalence was reported.	–	7
Bahadoran Z [35]/ 2012	Iran	Cross-sectional	Both	19–70 y	1983/Apparently healthy individuals	485/484	TAC/ORAC	FFQ	No significant difference in WC HDL, TG, central obesity, hypertriglyceridemia, MetS in lowest versus highest TAC quintile was reported.	–	6
Wang Y [37]/2012	USA	Cross-sectional	Both	18–25 y	60/Apparently healthy individuals	20/20	TAC/VCEA	30 day-FR	No significant difference in the BMI, TG, TC, HDL-C in lowest versus highest TAC tertiles.	–	7
Devore EE [47]/ 2013	Netherlands	Cohort	Both	≥ 55 y	5395/Apparently healthy individuals	1799/1798	TAC/FRAP	FFQ	No significant difference in the mean BMI in lowest versus highest TAC tertiles.	Age, calorie intake, smoking, HTN, T2DM, MI, supplement USE.	8
Rautiainen S [53]/ 2013	Sweden	Cohort	Women	49 – 83 y	33713/Apparently healthy individuals	6743/6742	TAC/ORAC	FFQ	At baseline, no significant difference in BMI in highest versus lowest quintiles of TAC was reported.	Age, educational, smoking, BMI, PA, HTN, T2DM, family history of MI, alcohol consumption, energy intake, supplement use, incident MI	9
Zamora-Ros R [38]/2013	EPIC*	Cohort	Both	35–70 y	475999/Apparently healthy individuals	158666/158666	TAC/TRAP	FFQ	No significant difference in BMI between different tertiles of TAC was observed.	–	7
Rautiainen S [58]/ 2014	Sweden	Cohort	Women	49–83 y	30607/Apparently healthy individuals	6123/6122	TAC/ORAC	FFQ	Slightly lower WC in highest versus lowest TAC quintile.	–	7
Costanzo S [36]/ 2015	Italy	Cross-sectional	Both	≥ 18 y	217/Patients CABG	73/71	TEAC	FFQ	No significant difference in BMI, prevalence of obesity and hypercholesterolemia in highest versus lowest tertile of TAC.	Age, sex, caloric intake, use of hypoglycemic drug, education, PA	8
Luu HN [59]/2015	China	Cross-sectional	Women	40–70 y	3853/Apparently healthy women	DAQS: 2551/432, CDAI: 1284/1284	DAQS, CDAI	FFQ	DAQS: lower prevalence of obesity in highest versus lowest DAQS tertiels. CDAI: lower prevalence of obesity in highest versus lowest CDAI tertiels.	–	7

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Table 2. (Continued)

First author/year	Country	Study design	Sex	Age range	Sample size/ Population	Number of cases/controls	Dietary index/unit	Dietary assessment tool	Result	Adjusted variables	Quality of the study
Henríquez-Sánchez P [49]/ 2015	Spain	Cross-sectional	Both	55–80 y	7447/Apparently healthy individuals	1489/1490	TAC/FRAP	FFQ	No significant difference in the BMI and higher prevalence of dyslipidemia in highest versus lowest TAC quartiles were reported.	–	7
Kim K [14]/2016	USA	Cross-sectional	Both	≥ 19 y	4039/Apparently healthy individuals	1028/975	TAC/VCEA	24-HR	Lower prevalence of obesity, lower BMI, higher HDL and lower TG in highest versus lowest TAC quartiles were reported. No significant difference in TC and LDL were reported.	–	8
Maugeri A [52]/ 2019	Czech	Cross sectional	Both	25–64	894/Apparently healthy individuals	298/298	CDAI/zinc, selenium, carotenoids and vitamins A, C and E	24-HR	Significantly lower BMI and body fat mass in highest versus lowest CDAI category in women. No significant difference in WHR, TC, TG, HDL, LDL, Hyperlipidemia, in highest versus lowest CDAI category in men and woman.	–	8
Zujko ME [27]/ 2018	Poland	Cross-sectional	Both	>20	5690/Apparently healthy individuals	1896/1897	TAC/FRAP	24-h recall	No significant difference in BMI, WC, TC, TG, LDL, HDL between highest versus lowest TAC category in men.	Age, BMI, educational level, leisure time PA, smoking, alcohol intake	9
Sotoudeh G [29]/ 2018	Iran	Case-control	Both	35–65 y	150/Patients with pre-diabetes and 150 healthy control	150/150	TAC/ORAC	FFQ	No significant difference in BMI, WC between highest versus lowest TAC category.	BMI, education, PA dietary fiber, fat, energy and coffee	9
Mancini FR [60]/ 2018	France	Cohort	Women	40–65 y	64,223/Apparently healthy individuals	12845/12844	TAC/FRAP	DHQ	No significant difference in the prevalence of hypercholesterolemia, and obesity in lowest versus highest TAC quintile.	Intake of energy, coffee, fruit, vegetable, alcohol, smoking, BMI.	8
Kim K [61]/2017	USA	Cohort NHANES two data sets of 1988–1994 and 1999–2004	Both	>30 y	For 1988–1994 data (12453) for 1999–2004 data (11143)	For 1988–1994 data (3113/3113) for 1999–2004 data (2785/2785)	VCEA	24-HR	Significantly lower prevalence of obesity in highest versus lowest TAC quartile.	T2DM, HTN, history of CVD, total energy intake, age, sex, ethnicity.	9
Kashino I [51]/ 2018	Japan	Cross-sectional	Both	20–65 y	513/Apparently healthy individuals	171/171	NEAC/FRAP/ORAC/TRAP	DHQ	No significant difference in BMI of lowest versus highest tertiles of FRAP, ORAC or TRAP.	–	8
Hantikainen E [48]/ 2018	Sweden	Cohort	Both	18–94 y	34543/Apparently healthy individuals	8635/8636	TAC/FRAP	FFQ	Subjects in highest TAC quartile had lower BMI compared with the lowest.	Sex, BMI, PA, alcohol, smoking, education, diabetes history, aspirin, coffee, lipid disturbance, HTN, supplement use.	9
Galarregui C [24]/ 2018	Spain	Cross sectional	Both	40–80 y	112/Overweight or obese NAFLD patients	37/38	TAC/FRAP	FFQ	No significant difference in BMI, WC, TG, TC and LDL-c/ HDL-c ratio between categories.	–	7
Farhangi MA [31]/ 2018	Iran	Cross-sectional	Both	35–80	454/Patients candidates of CABG and hospitalized	74/61	TAC/ORAC	FFQ	No significant difference in BMI and prevalence of Hyperlipidemia between highest versus lowest TAC quintiles in men and women.	Age, gender, BMI, T2DM, MI	9

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Table 2. (Continued)

First author/year	Country	Study design	Sex	Age range	Sample size/ Population	Number of cases/controls	Dietary index/unit	Dietary assessment tool	Result	Adjusted variables	Quality of the study
Oliveira DG de [46]/ 2018	Brazil	Cross-sectional	Both	> 18	33/Outpatients with NAFLD	16/17	TAC/FRAP	FFQ	No significant difference in prevalence of central obesity, dyslipidemia, overweight and BMI, TG, TC, LDL, HDL between highest versus lowest TAC categories.	–	7
Asghari G [43]/ 2017	Iran	Cohort	Both	≥ 30 y	1179/Patients with dysglycemia	393/393	TAC/ORAC	FFQ	No significant difference in BMI between highest versus lowest TAC category.	–	7
Abshirini M [42]/ 2018	Iran	cross-sectional	Women	Middle-aged	400/ Postmenopausal women	100/100	TAC/ORAC	FFQ	No significant difference in BMI and WC between highest versus lowest TAC quartile.	Energy-adjusted TAC	8
Yang F [55]/2017	Sweden	Cohort	Both	Mean age for women 75.7 ± 7.8 and for men 74.6 ± 7.8	84774/Apparently healthy individuals	21193/21194	TAC/ORAC	FFQ	No significant difference in BMI between highest versus lowest TAC quartiles.	–	
Dongwoo H [57]/ 2017	South Korea	Cross-sectional	Both	30–59	346/Subjects with two or more risk factors of metabolic syndrome	115/116	TAC/VCEA	3-day FR	Significantly lower TG, WC and HDL between highest versus lowest TAC category in women. In men, only TG in highest tertile of TAC was significantly lower.	Age, education, monthly income, alcohol, smoking, PA	9
Colarusso L [45]/ 2017	Sweden	Cohort	Both	≥ 18 y	34555/Apparently healthy individuals	Women: 5678/5678, Men 2960/2961	NEAC/FRAP	FFQ	No significant difference in the BMI between highest versus lowest FRAP quartiles.	–	9
Bastide N [44]/ 2016	France	Cohort	Women	40–65 y	74508/Apparently healthy women	18627/18627	NEAC/FRAP, TRAP	DHQ	No significant difference in the BMI between highest versus lowest FRAP or TRAP quartiles.	Age, family history of cancer, CVD, T_2DM, BMI, education, smoking, PA, energy intake, intake of alcohol and fibers	9
Karimi Z [50]/2015	Iran	Case-control	Women	30–65	275/100 breast cancer cases and 175 controls	68/68	TAC/ORAC	FFQ	No significant difference in the BMI between highest versus lowest ORAC quartiles.	Age	9
Aghamohammadi V [56]/2019	Iran	Cross-sectional	Both	18–50 y	263/Apparently healthy individuals	145/144	FRAP	FFQ	No significant difference between weight, WC, HC and serum lipids in highest versus lowest TAC groupings	–	6
Villaverde P [54]/ 2019	France	Cohort	Women	40–65 y	40576/Apparently healthy individuals	8114	TRAP	DHQ	Higher BMI in highest versus lowest TAC quintiles.	–	6

AMI: acute myocardial infarction; BMI: body mass index; WC: waist circumference; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; TC: total cholesterol; TG: triglyceride; WHR: waist–hip-ratio; HC: hip circumference; BF: body fat; MetS: Metabolic syndrome; PCA: Principal Component Analysis; CABG: coronary artery bypass grafting surgery; DAI: Dietary Antioxidant Index; CDAI: composite dietary antioxidant index; CVD: cardiovascular disease; DAQs: dietary antioxidant quality score; DBP: diastolic blood pressure; FBS: fasting blood sugar; DHQ: diet history questionnaire; FFQ: food frequency questionnaire; 24-HR: 24-h dietary recall; FR: Food record; FRAP: ferric reducing ability of plasma; HOMA-IR: homeostatic model assessment of insulin resistance; HTN: hypertension; HR: hazard ratio; MI: myocardial infarction; NAFLD: non-alcoholic fatty liver disease; NHANES: national health and nutrition examination survey; ORAC: oxygen radical absorbance capacity; PA: physical activity; SBP: systolic blood pressure; TAC: total antioxidant capacity; TEAC: Trolox equivalent antioxidant capacity; TRAP: total radical trapping antioxidant parameter; VCEA: vitamin C equivalent antioxidant capacity; T_2DM: type 2 diabetes mellitus.

*Involved countries included Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, UK.

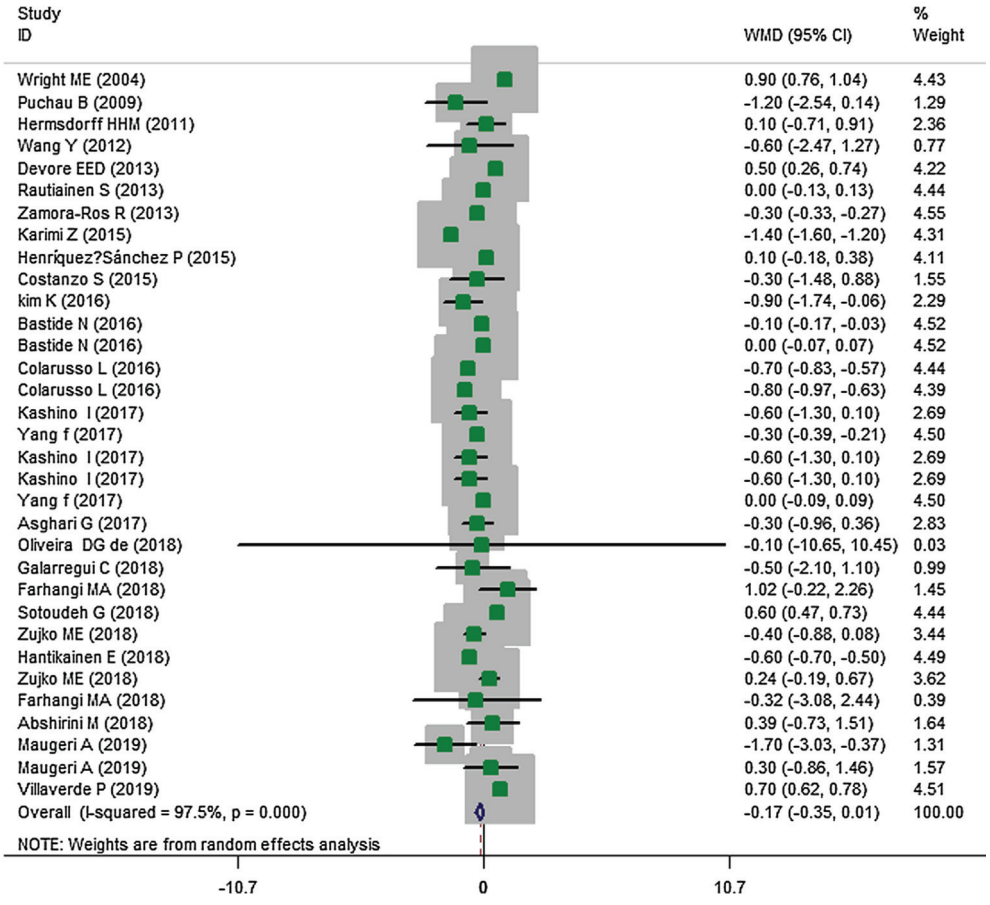

Figure 2. Forest plot illustrating weighted mean difference in body mass index (BMI) in highest versus lowest total antioxidant capacity (TAC) categories.

Lower TG and higher HDL-C concentrations in highest versus lowest quartiles of TAC were reported in a cross-sectional study in USA [61]; while significantly lower TG and HDL-C in highest versus lowest TAC categories in women and lower TG in men were reported in a study by Ham et al. [57]. No statistically significant difference in lipid profile, the prevalence of hyperlipidemia or hypercholesterolemia was reported in studies that were performed by Puchau et al. [26], Hermsdorff et al. [25], Bahadoran et al. [35], Wang et al. [37], Costanzo et al. [36], Kim et al. [14], Maugeri et al. [52], Zujko et al. [27], Galarregui et al. [24], Abbasalizad Farhangi et al. [31] and Oliveira DG de [46].

Meta-analyses results

Body mass Index (BMI)

Twenty-five studies [14, 19, 20, 24, 25, 27, 29, 31, 36–38, 42–55] with thirty-three arms, including a total of 834,763 participants have reported BMI as an outcome measure. The Forest plot is shown in Figure 2. In the fixed-effect model, a high heterogeneity value was observed (I^2 = 97.5%; p < 0.0001). Therefore, the random effect model was used. Our results demonstrated that TAC was not related to a significant reduction in BMI (WMD: −0.17; 95% CI: −0.35, 0.01; P = 0.12). A subgroup analysis was conducted to detect the sources of heterogeneity (Table E2 in ESM 1) and accordingly dietary index, dietary assessment tool and health status were the sources of heterogeneity. In these analyses, being at highest TAC categories was associated with reduced BMI when TAC was sub-grouped according to dietary index (e.g. significant for FRAP and TRAP), geographical area (e.g. significant for studies conducted in Europe) and health status (e.g. significant for studies conducted in general healthy population).

Waist circumference (WC)

Twelve studies [14, 24–27, 29, 35, 42, 46, 56–58] with fourteen arms, including a total of 44,042 participants have reported WC as study outcome. The Forest plot is shown in Figure 3. The findings of the current meta-analysis showed that being at the higher categories of TAC significantly reduces WC (WMD: −1.17; 95% CI: −1.47, −0.87; P < 0.001), with no significant difference between study heterogeneity (I^2 = 44.0%, P = 0.03).

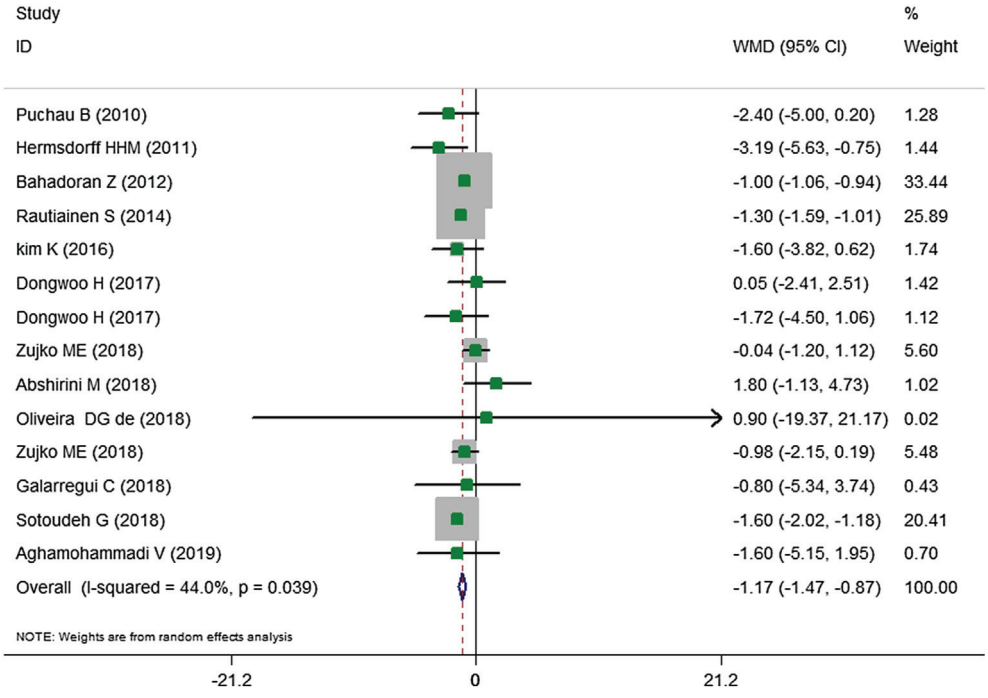

Figure 3. Forest plot illustrating weighted mean difference in waist circumference (WC) in highest versus lowest total antioxidant capacity (TAC) categories.

In the subgroup analysis (Table E3 in ESM 1), being at the highest TAC category was associated with reduced WC when TAC was sub-grouped according to dietary index (e.g. significant for FRAP and ORAC), geographical area (e.g. significant for studies conducted in Asia and Europe), sample size, health status and dietary assessment tool (e.g. significant for studies that used food record as dietary assessment tool).

Total cholesterol (TC)

In comparison of TC between TAC categories, a total of eight studies with ten arms [14, 24, 26, 27, 37, 46, 52, 56] and a total of 11,192 participants were included (Figure 4) while no significant difference was observed (WMD: 1.19; 95% CI: −1.46, 3.85; P = 0.37). There was no significant heterogeneity between the studies (I^2 = 13.0%, P = 0.32). In the subgroup analysis (Table E4 in ESM 1), being at highest TAC category was associated with increased TC when TAC was sub-grouped according to sample size (e.g. significant for studies with number of participants > 1000).

Triglyceride (TG)

In comparison of TG between TAC categories, a total of ten studies (thirteen arms) [14, 24, 26, 27, 35, 37, 46, 52, 56, 57] with a total of 13,573 participants were included. The findings of the current meta-analysis showed that being at higher category of TAC is associated with significantly lower serum TG concentrations (WMD: −7.58; 95% CI: −11.42, −3.75; P < 0.001). There was no significant between-studies heterogeneity (I^2 = 36.1%, P = 0.09) (Figure 5). In the subgroup analysis (Table E5 in ESM 1), being at the highest TAC category was associated with a more pronounced reduction in TG when TAC was sub-grouped according to dietary index (e.g. significant for VCEA and ORAC), geographical area (e.g. significant for studies conducted in USA and Asia), health status (e.g. significant for studies conducted in metabolic disorder population group), dietary assessment tool (e.g. significant for studies used 24-h dietary recall (24-HR) and food frequency questionnaire (FFQ)) and sample size (e.g. significant for studies with number of participants > 1000). Also, studies that were conducted on both genders showed higher reduction in TG concentrations (WMD: −10.96; 95% CI: −11.43, −10.50; P < 0.001).

Low density lipoprotein cholesterol (LDL-C)

In comparison of LDL-C between TAC categories a total of seven studies with ten arms [14, 26, 27, 46, 52, 56, 57] and a total of 11,418 participants were included. No significant association was found between LDL-C and TAC (WMD: 1.34; 95% CI: −0.61, 3.30; P = 0.17). There was no significant heterogeneity between the included studies (I^2 = 0.0%, P = 0.74) (Figure 6). In the subgroup analysis (Table E6 in ESM 1), being at the highest TAC category was associated with increased LDL-C concentrations when TAC was sub-grouped according to health status (e.g. significant for studies carried out in general healthy population)

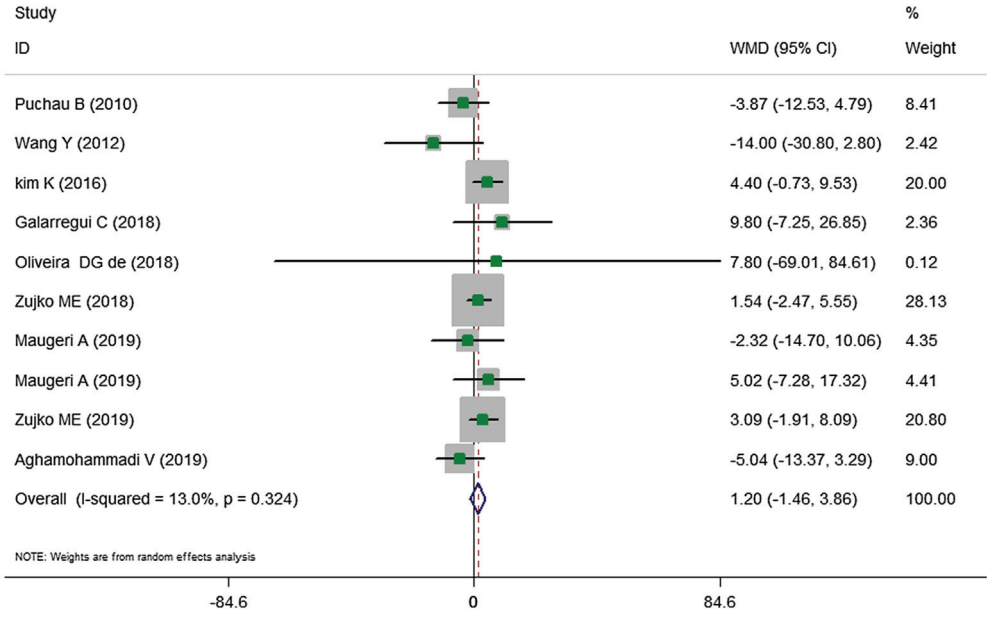

Figure 4. Forest plot illustrating weighted mean difference in total cholesterol (TC) in highest versus lowest total antioxidant capacity (TAC) categories.

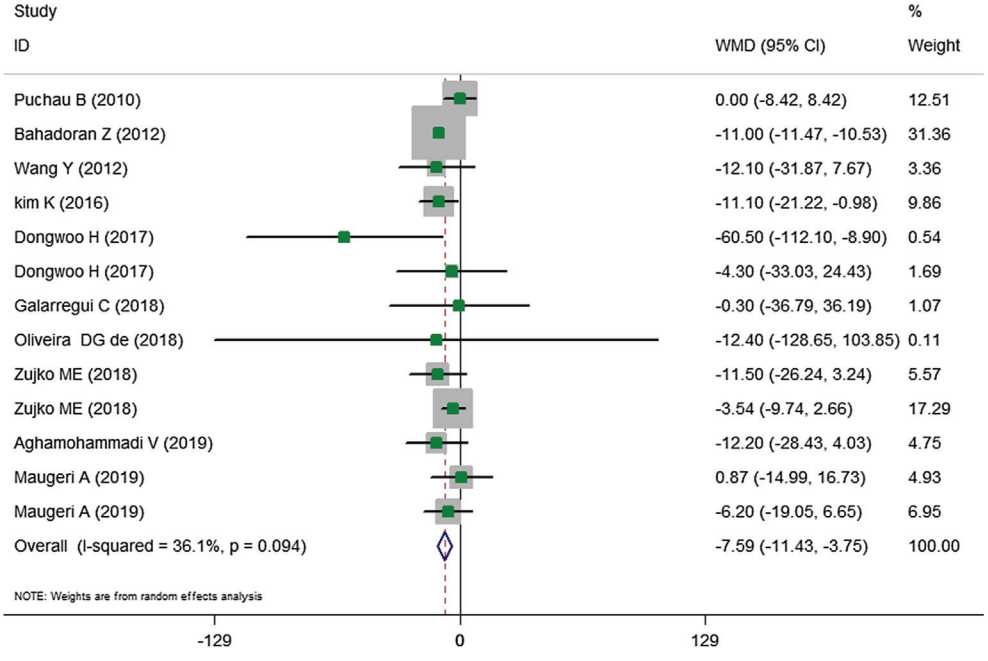

Figure 5. Forest plot illustrating weighted mean difference in triglyceride (TG) in highest versus lowest TAC categories.

and dietary assessment tool (e.g. significant for studies used 24-HR).

High density lipoprotein cholesterol (HDL-C)

In comparison of HDL-C between TAC categories a total of nine studies with twelve arms [14, 26, 27, 35, 37, 46, 52, 56, 57] and a total of 13,461 participants were included. The findings showed no significant association between HDL-C and TAC (WMD: 0.61; 95% CI: −0.16, 1.40; P = 0.12) and no significant heterogeneity between the studies (I^2 = 36.0%, P = 0.10) (Figure 7). In the subgroup analysis (Table E7 in ESM 1), being at the highest TAC category was associated with increased LDL-C when TAC was sub-grouped according to dietary index (e.g. significant for VCEA and ORAC), geographical area (e.g. significant for studies conducted in USA and Asia), health status

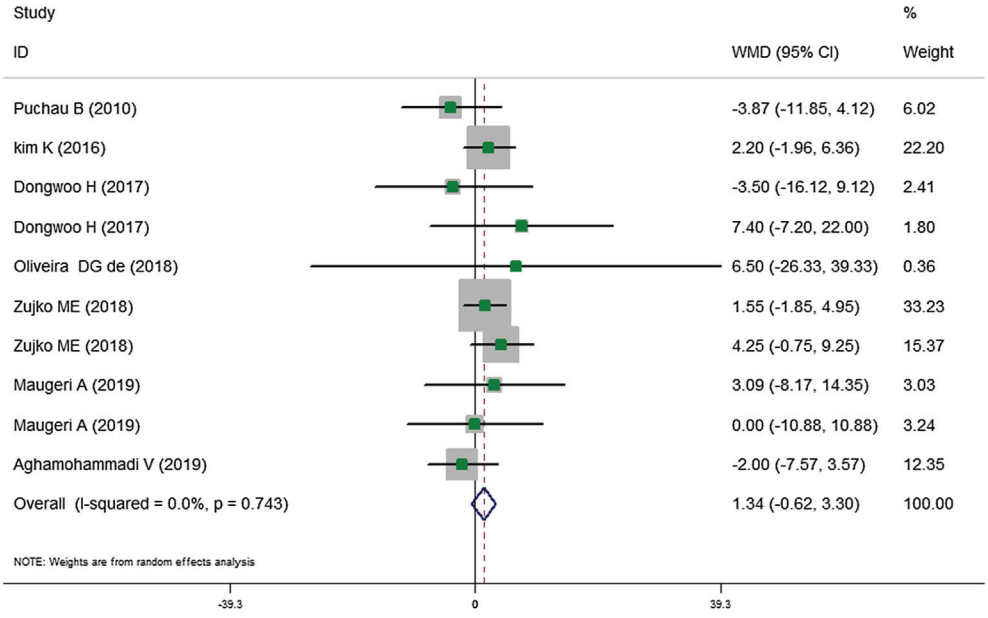

Figure 6. Forest plot illustrating weighted mean difference in low density lipoprotein cholesterol (LDL-C) in highest versus lowest total antioxidant capacity (TAC) categories.

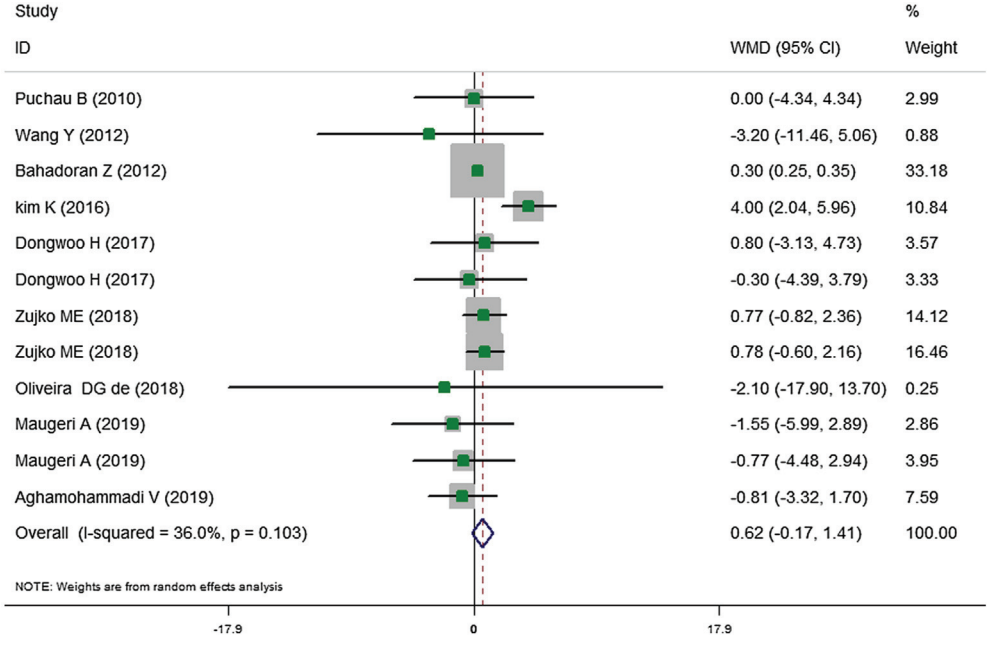

Figure 7. Forest plot illustrating weighted mean difference in high density lipoprotein cholesterol (HDL-C) in highest versus lowest total antioxidant capacity (TAC) categories.

(e.g. significant for studies conducted in general healthy population) and dietary assessment tool (e.g. significant for studies used FFQ and 24-HR), sample size (e.g. significant for studies with number of participants > 1000) and sex (e.g. significant for studies that were conducted on both genders).

Prevalence of central obesity

In total, six studies (eight arms) [25, 34, 36, 59–61] with a total of 108,165 participants reported the prevalence of central obesity (defined by WC > 80 and 90 cm in women and men, respectively) in the highest versus lowest TAC category. The findings showed that the prevalence of

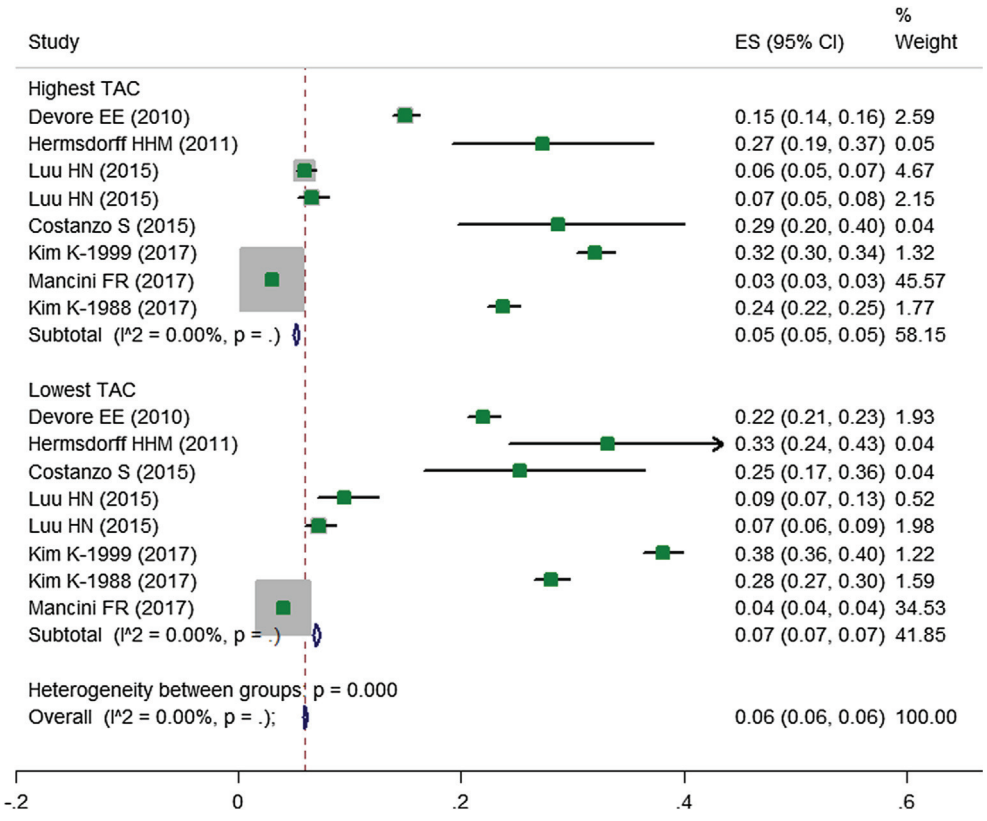

Figure 8. Forest plot illustrating central obesity proportion in highest versus lowest total antioxidant capacity (TAC) categories.

central obesity in the highest category of TAC was lower than the lowest category (5% vs. 7%; P < 0.001). There was no significant heterogeneity between the studies (Figure 8).

Sensitivity analysis and publication bias

The sensitivity analysis was performed to discover the effect of each individual study on the pooled effect size by omitting each study in turn. Sensitivity analysis for BMI revealed that exclusion of the study by Wright et al. [19] changed the overall effect size to be statistically significant (WMD: −0.21; 95% CI: −0.39, −0.03; P = 0.01). (Figure E1 in ESM 1). Also, by removing this study, high heterogeneity I^2 = 97.0%; p < 0.001) between the studies were observed.

The Funnel plots indicated moderate asymmetry (Figures E2 [A-F] in ESM 1). Nevertheless, the Egger's and Begg's tests did not identify substantial publication bias for all of the variables. The provided values are as follows: WC, Begg's test (P = 0.46) and Egger's test (P = 0.53), BMI, Begg's test (P = 0.43) and Egger's test (P = 0.48), TG, Begg's test (P = 0.41) and Egger's test (P = 0.19), LDL-C, Begg's test (P = 0.53) and Egger's test (P = 0.79), HDL-C, Begg's test (P = 0.18) and Egger's test (P = 0.61), TC, Begg's test (P = 0.67) and Egger's test (P = 0.52).

Discussion

The current study represented a relatively comprehensive review of studies that evaluated the relationship between dietary TAC, obesity measurements and serum lipids and reveled that dietary TAC reduced the prevalence of central obesity, WC and serum TG concentrations in adults aged ≥ 18 years old. However, the association between dietary TAC and BMI, TC, HDL-C and LDL-C was not significant in this study. In the subgroup analyses, we found a greater reduction in BMI in general healthy population, in FRAP and TRAP assays and in Europe countries.

Numerous studies have been performed to determine factors that might contribute to the etiology of obesity [4, 28, 62]. One of the most important factors well-known in this field is the diet [62]. In recent years, it has been found that considering TAC of diet in relation to obesity is better than valuation of a single antioxidant of food rich in antioxidant [19, 20]. Dietary TAC takes into consideration both unknown and known antioxidants in foods and thus, reflects total antioxidant capacity of diet. Several studies assessed the relationship between dietary TAC, obesity and lipid profile; however, results in this field are inconsistent [27, 29, 52]. According to results in the present study, dietary TAC was inversely related to central obesity,

WC and TG levels. The protective role of TAC against central obesity in our meta-analysis also was confirmed in previous reports [11, 14]; in the study by Hermsdorff et al. [25] in a cross-sectional study among healthy young adults, a negative association between WC and dietary TAC (based on TEAC assay) was reported. Also, Bahadoran et al. [35] reported that WC was significantly lower in the highest quartile of TAC (based on ORAC assay) compared with the subjects in the lowest quartile at baseline. Chrysohoou et al. [63] in a cross-sectional study reported an inverse relationship between dietary TAC with body fat and central obesity in apparently healthy women and men. In contrast to our results, Puchau et al. [26] found no relationship between dietary TAC (based on FRAP assay) and WC. In agreement with our results, Kim et al. [14] in a cross-sectional population-based study reported that higher TAC was related to lower TG concentrations among 4,039 U.S. adults after adjusting for potential confounders. However, in their study, no significant association between TAC and BMI, WC, LDL-C and TC was observed.

Intake of fruit juices that contain a diversity of polyphenols (phenolic acids, flavanols and flavonoids), vitamins (vitamin E, B and C), and minerals (magnesium, potassium and calcium) from different fruits and vegetables [16] has a potential role in improvement of cardiovascular health. Kim et al. [64] showed a negative association between dietary TAC and dyslipidemia, specifically hypertriglyceridemia. This relationship is often attributed to the antioxidants (vitamin C, E, polyphenols, flavonoids and carotenoids) in foods, which protects LDL-C against oxidation and prevents the atherogenic effects of oxidized LDL-C [65]. Also, these food ingredients exert hypolipidemic effects via increased fecal bile excretion, inhibition of cholesterol synthesis, increased lipoprotein lipase (LPL) [66], LDL receptors activity [25], reduced lipid peroxidation, reduced reactive oxygen species (ROS) activation and increased serum antioxidant capacity [67, 68].

The lipid-modifying effects of dietary anti-oxidants had been proved by numerous studies including clinical trials [11, 12]. The three-week intake of chokeberry juice significantly improved serum antioxidant capacity. Nevertheless, there was no significant change in the serum lipids, except for the participants with a higher level of TG, in whom the intake of chokeberry juice decreased these compounds to normal values [69]. Other authors reported a significant increase in the serum antioxidant capacity in 12 subjects during 1 h after the intake of 1 liter of apple juice [70]. Skoczynska et al. [71] also reported a reduction in TG by 13% during 6 weeks after intake of chokeberry juice. However, no significant effects were observed for HDL-C, TC, and LDL-C. Also, Flammer et al. [72] observed no significant changes in LDL-C, HDL-C and TC after consumption of cranberry juice over a period of four months. These inconsistent findings might be due to evaluation of a single antioxidant or a group of antioxidant foods rather than a dietary antioxidant index.

Dietary antioxidants exert anti-obesity and anti-adipogenic effects via mitogen-activated protein kinase signaling pathways (MAPK) and adenosine monophosphate-activated protein kinase (AMPK), reduced visceral fat mass, leptin and insulin levels [73, 74]. Previous studies proposed that AMPK is a main metabolic regulator involved in the regulation of adipocyte differentiation and energy metabolism [75, 76]. Studies have revealed that activation of AMPK in adipocytes has multiple beneficial effects such as reduced fatty acid synthesis, and TG accumulation by suppression of lipogenic genes such as acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS), peroxisome proliferator-activated receptor gamma (PPAR-γ) and CCAAT/enhancer-binding proteina (C/EBP-α) [76, 77]. The increase of inactive phosphorylated ACC and FAS, in turn, inhibits adipogenesis. In the study by Ahn et al. [73] exposure of 3T3-L1 preadipocytes with quercetin inhibited adipogenesis by increasing AMPKα and β1 phosphorylation and blocking the expression of the adipogenic transcription factors such as PPAR-γ and C/EBP-α. Furthermore, quercetin increases apoptosis of mature adipocytes through suppression of MAPK signaling by inhibiting c-Jun N-terminal kinase (JNK) and extracellular signal-regulated kinases (ERK1/2) phosphorylation [78, 79].

Kim et al. [14] in a cross-sectional, population-based study reported a positive relationship between dietary TAC, vitamin C and fiber. Increased dietary fiber intake promotes weight loss by increased satiety after meals, possibly due to prolongation of the intestinal phase of nutrient digestion and absorption [80–82]. Exposure to high levels of ROS increases adipocyte differentiation both *in vivo* [83] and *in vitro* [84] models. Furthermore, as a result of this differentiation, adipose tissue produces higher ROS amounts and this vicious cycle is a key problem that can worsen obesity-associated consequences [85]. Dietary antioxidants have been proposed as a potential therapeutic target against obesity and its related diseases, because they might suppress fat absorption in the gastrointestinal tract [86], inhibit preadipocyte differentiation [87], stimulate fat catabolism in adipose tissue [88], and prompt apoptosis in adipocytes [89].

It appears that the possible explanation for these inconsistencies is the use of different assays to estimate TAC. Moreover, subgroup analysis showed that TAC measurement index was potential sources of heterogeneity. There are several assays to evaluate dietary TAC and each assay employs different analytical procedures and might give a different value of TAC. This difference in results might be due to the differences in chemical mechanisms. For instance, dietary TAC based on FRAP assay directly

measures reductants or antioxidants in a sample by evaluating the reduction of Fe^{3+} to Fe^{2+} [90]. On the other hand, other assays are commonly indirect because they estimate the inhibition of reactive species produced in the reaction mixture [91]. Halvorsen et al. [92] reported that FRAP is a better assay to measure dietary TAC compared with other assays. In contrast to our results, Villaverde et al. [54] found that the BMI was higher in the highest quintile of TAC (based on TRAP) compared with the lowest quintiles while in the study by Hantikainen et al. [48], participants in the highest quartile of TAC (based on FRAP) presented lower BMI than those in the lowest quartile.

Moreover, some of inconsistencies are attributed to difference in dietary habits, food preferences, or the accuracy of reported dietary intakes [93, 94]. For instance, Puchau et al. [18] found a negative association between FRAP and obesity among 369 children and adolescents. However, in contrast to our results, Mozaffari et al. [95] reported a significant positive relationship between high dietary TAC (TRAP and TEAC assay) and obesity among Iranian women. Additionally, they found no significant relationship between dietary TAC and WC. Moreover, it is possible that increased inflammation in higher ages might hinder the detection of the effects of dietary TAC [96]. Also, some of included studies in this review ignored the effects of confounding variables, such as dietary fiber [14, 25, 26, 35, 58] and vitamin supplementation [25, 26, 35]. Some other differences between studies in terms of origin, sample size, analysis of different outcomes and assay tools might also lead to inconsistent results.

The present study has several limitations and strengths that should be considered. First, the observational design of the included studies does not allow us to conclude causal relationship between dietary TAC and metabolic risk factors. Second, as stated in the results section, geographical area and dietary assessment tool as well as health status could be a source of heterogeneity among studies in the present meta-analyses. In the present study, information about dietary TAC were obtained by FFQ, 24 hours record method or 24 hours recall method which may be susceptible to bias. On the other hand, difference in the items of the FFQ might be a source of heterogeneity; as described previously, the FFQ items ranged from 63 to 168 items and the local foods in the FFQ could also affect the heterogeneity [97], while, almost all of the included articles used valid and reliable FFQs. Another source of heterogeneity, the geographical area, presents the possible role of geographical distribution, cultural factors and genetic background influencing the relationship between dietary TAC and metabolic risk factors [98]. Additionally, studies that were included in the present meta-analysis were different in terms of statistical analyses and assays used to measure dietary TAC. However, to the best of our knowledge, this is the first study that evaluated the relationship between dietary TAC as FRAP, TRAP, TEAC, ORAC and VCEA scores with a wide range of metabolic risk factors including WC, BMI, serum lipids and prevalence of central obesity.

Conclusion

The present meta-analysis summarized the results of 34 observational studies that evaluated the effects of dietary TAC on central obesity, WC, BMI and serum lipids; our findings indicated that dietary TAC significantly reduced the prevalence of central obesity, WC and TG levels. Moreover, subgroup analysis revealed that TAC measurement index, geographical area, dietary assessment tool, health status, gender, and sample size were potential sources of heterogeneity. We propose further interventional studies in this filed for better elucidation of causal inference and for confirmation of the potential role of TAC as a prognostic diet-related clinical marker for prevention of chronic disease.

Electronic Supplementary Material

The electronic supplementary material is available with the online version of the article https://doi.org/10.1024/0300-9831/a000675

ESM 1. Including information about PRISMA checklist, subgroup analysis and Begg's Funnel plots.

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Conflict of interest
The authors declare that there are no conflicts of interest.

Ethical standard disclosure
This study was designed according to the guidelines laid down in the Declaration of Helsinki and the protocol of the study has been approved by the ethics committee of the Tabriz University of Medical Sciences (Registration number: IR.TBZMED.VCR.REC.1398.176).

Authors' contribution statement
All authors have read and approved the manuscript; MAF was the main researcher, designed the hypothesis, wrote the manuscript, revised the manuscript and supervised the project. MAF was also involved in data extraction, manuscripts reading and data analysis, MV and PF were also involved in manuscript writing. MV also performed the revision. All of authors read and approved the final manuscript version.

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