

Systematic Review

Dietary Total Antioxidant Capacity and Risk of Gastrointestinal Cancers: A Systematic Review and Meta-analysis of Observational Studies

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Background: Gastrointestinal (GI) cancers are common types of cancers. Among different factors that affect the etiology of GI cancers, diet has an important contribution. Dietary antioxidants decrease oxidative stress which plays a pivotal role in carcinogenesis. Several studies assessed the relation between dietary total antioxidant capacity (TAC) and risk of GI cancers. Dietary TAC was measured by three indices including FRAP (ferric ion reducing antioxidant power), TRAP (total radical-trapping antioxidant parameter), and TEAC (trolox equivalent antioxidant capacity). We performed a systematic review and meta-analysis of published studies to determine the association between dietary TAC and GI cancers risk.

Methods: Eligible studies were selected from PubMed, ISI Web of Science and Scopus databases from inception until May 2018. Case-control and cohort studies that reported GI cancer risk estimates for dietary TAC were included. We ignored the distinction between case-control and cohort studies. We applied random-effects to estimate pooled relative risks. Subgroup analysis was done based on study design.

Results: Among the seven observational studies that were included, four were cohort studies and three were case-control studies. Dietary FRAP, TRAP, and TEAC reduced GI cancer risk: FRAP; 0.71; 95% CI: 0.58–0.85, TRAP; 0.65; 95% CI: 0.57–0.75, TEAC; 0.70; 95% CI: 0.59–0.83, respectively.

Conclusion: This study indicated that dietary TAC significantly decreased the risk of GI cancers. Nevertheless, further prospective studies are required to clarify the association between dietary TAC and risk of GI cancers.

Keywords: Cancer risk, Dietary total antioxidant capacity, FRAP, Gastrointestinal cancers, TEAC, TRAP

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Introduction

Cancer has been a serious problem in public health.¹ It is counted as the second cause of mortality in the world and the third one in Iran. Almost 17.5 million individuals were diagnosed with cancer and 8.7 million died of these lethal diseases in 2015.^{2,3} The cancer incidence rate is increasing in developing countries and its outbreak is predicted to double by 2030.¹ Among different types of cancers, GI cancers have been considered to be one of the common types.⁴ Inherited and environmental factors have a significant contribution to the pathogenesis of cancers.⁵ Among environmental factors, diet has an important role in the etiology of GI cancers.⁶

Some studies showed that high consumption of red meat and fat is associated with the increased risk of GI cancers.^{7,8} While fruit and vegetable intake could reduce the risk of GI cancers.⁹ A western diet which is identified by high consumption of fat, meat, and low fiber intake

enhances colorectal cancer risk.¹⁰ Mediterranean diet has an inverse association with GI cancer risk, which may be due to the antioxidant-rich plant foods of this diet.^{11,12} A meta-analysis indicated that soy intake, as a rich antioxidant food, decreases the risk of digestive tract cancers.¹³ Some components existing in fruits, vegetables, and other plant foods have antioxidant properties. These bioactive compounds inhibit reactive oxygen species (ROS) and reduce oxidative stress.^{14,15} Oxidative stress elevates carcinogenesis and can induce GI cancer. The digestive tract is the main site in which antioxidants are most active because carotenoids and flavonoids have lower absorption compare with some antioxidants such as vitamin C and E, consequently concentration of these antioxidants increase in GI tract.¹⁶⁻¹⁸

Plant foods comprise different antioxidants. It is best to consider all antioxidants existing in a diet together, because of their synergistic and cooperative effects. Dietary

total antioxidant capacity (TAC) considers the entire antioxidants of the diet.^{19,20} Studies showed significant relations between Dietary TAC and plasma TAC.²¹ To calculate dietary TAC, several assays were used, which include Trolox equivalent antioxidant capacity (TEAC), which measures the ability of antioxidant molecules to quench the long-lived ABTS⁺ compared to that of 6-hydroxy-2,5,7,8-tetramethylchroman-2-carboxylic acid, Trolox, the total radical-trapping antioxidant parameter (TRAP) which measures the protection provided by antioxidants on the fluorescence decay of R-phycoerythrin (lag-phase) during a controlled peroxidation reaction and ferric ion reducing antioxidant power (FRAP) which measures in vitro the reduction of the Fe³⁺ (ferric ion) to Fe²⁺ (ferrous ion) in the presence of antioxidants.²² Many studies have concluded that dietary TAC has a positive effect on the reduction of GI cancer risk. On the other hand, some studies have not found a significant association between dietary TAC and them.

Several observational studies evaluated relations between dietary TAC and different GI cancers. Because of inconsistent results, we performed a meta-analysis to determine the role of dietary TAC in GI cancer risk. The PICOS eligibility criteria were applied. Adults, with or without GI cancers, were compared based on highest vs. lowest ntiles of DTAC among cohort and case-control studies.

Materials and Methods

We conducted a systematic review and meta-analysis of observational (cohort and case-control) studies that evaluated the association between dietary TAC and gastrointestinal (GI) cancers. The methodology of preferred reporting items for systematic reviews and meta-analyses (PRISMA) were used for this study (Table 1).²³

Search Strategy

We identified studies by searching in PubMed, ISI Web of Science and Scopus databases. The following terms were applied: (“Dietary total antioxidant capacity” OR “Dietary TAC” OR “Non enzymatic antioxidant capacity”) AND (“gastrointestinal cancers” OR “esophageal cancer” OR “gastric cancer” OR “colorectal cancer” OR “pancreatic cancer” OR “liver cancer”) from inception to May 2018. Language limitation was not exerted. We also checked the cited references of the retrieved articles to find potentially eligible studies.

Study Selection

Only studies were included that had prospective cohort and case-control study design, determined dietary TAC score, related to GI cancers and report risk estimates (relative risk, odds ratios, or hazard ratio) with 95% CIs or must report sufficient information to estimate data. We

excluded studies that had a clinical trial design, animal or *in vitro* studies and review papers. Studies that examined the effect of single antioxidants or antioxidants of a specific food on GI cancers risk were excluded. Also, the studies in which supplementary sources of antioxidants are considered as part of total antioxidant capacity (TAC) were not included.

Quality Assessment

For quality assessment of included studies, Newcastle–Ottawa Scale (NOS) was used. This assessment tool uses for observational studies such as case-control and cohort studies. NOS score is between zero to nine.²⁴ A study with 6 scores or more is considered a high-quality study.²⁵

Data Extraction

Two investigators (BZ and ED) extracted data, which was checked by one other (LA). We extracted the following information from each study: first authors name, years of publication, follow up period (if study was prospective cohort), design of the study, mean or range of age, gender, food intake evaluation tool and assay used, cancer site and risk estimates (relative risk, odds ratios, or hazard ratio).

Statistical Analysis

We ignored the distinction between case-control and cohort studies.²⁶ For this meta-analysis, we used hazard ratios (HR), relative risks (RR) and odds ratio (OR) of GI risks according to highest ntiles of dietary TAC assays compared to lowest ntiles in cohort and case-control studies. We used a random effects model because of variation between included studies. Heterogeneity between studies was assessed using I-squared tests (significant by $P < 0.1$). Formal statistical assessment of publication bias was done with Egger’s test. All statistical analyses were performed using STATA, version 12. $P < 0.05$ was considered statistically significant.

Results

Study Characteristics

A total of 1852 studies were identified after a primary search. After deleting 346 duplicates, 1507 studies remained. We assessed title and if needed the abstract of the studies. In this step, 1209 irrelevant, 30 clinical trials, 126 animal, and 135 review studies were excluded. Eventually, seven studies were included in the systematic review and meta-analysis (Figure 1).²⁷⁻³³ Of the seven studies, four were prospective cohort^{27,30,32,33} and three were case-control.^{28,29,31} All the studies were published between 2010 and 2016. All included studies were conducted in both male and female²⁸⁻³³ except one that was conducted in male.²⁷ Six studies were from Europe²⁸⁻³³ (4 from Italy and 2 from 10 European countries including Denmark, France, Germany, Greece, Italy, the Netherlands, Norway,

Table 1. Characteristics of Observational Studies Eligible in the Systematic Review and Meta-analysis

Code	Author (y)/Country	Study Design	Sample Size and Gender	Age Range (y)	Follow-up Period	Assay Used	Quality Assessment	Effect Size	Cancer Site	Adjusted Variables
1	Praud et al (2015)/ Italy	Case-control	Case=230 Control=547 (male and female)	22-80	—	TEAC TRAP FRAP	8	OR	Gastric	Sex, age, year of interview, education, BMI, family history, smoking, total energy intake
2	Serafini et al (2011)/ Europe	Cohort	521457 (male and female)	35-70	14	TRAP FRAP	9	HR	Gastric	Sex, educational level, BMI, red meat intake and total energy intake
3	Mekary et al (2010)/USA	Cohort	47339 (men)	40-75	18	FRAP	7	RR	Colorectal	Age, aspirin use, family history of colorectal cancer, history of the previous endoscopy, supplement use containing antioxidants, BMI, energy intake, alcohol intake, physical activity, red meat consumption, total calcium intake, dietary folate intake, dietary vitamin D intake, smoking, and race
4	Vece MM et al (2015)/ Italy	Cohort	45194 (male and female)	35-70	15	TEAC	9	HR	Colorectal	Age, sex, study center, BMI, height, smoking status, education and total physical activity, intakes of alcohol, non-alcohol energy intake, red meat, processed meat, calcium, and dietary fiber
5	La Vecchia et al (2013)/ Italy	Case-control	Cases=1953 Control=4154 (male and female)	19-74	—	TEAC TRAP FRAP	8	OR	Colorectal	Sex, age, study center, education, alcohol consumption, BMI, family history, physical activity, TAC from coffee, and energy intake
6	Lucas AL et al (2016)/Italy	Case-control	Case=326 Control=652 (male and female)	34-80	—	TEAC TRAP FRAP	8	OR	Pancreatic	Study center, sex, age, year of interview, education, BMI, tobacco smoking, alcohol intake, diabetes, and energy intake
7	Zamora-Ros et al (2013)/ Europe	Cohort	477206 (male and female)	35-70	19	FRAP TRAP	9	HR	Liver	Study center, sex, age, total energy, educational level, smoke intensity, alcohol lifetime and alcohol baseline, BMI, self-reported diabetes at baseline, physical activity, fiber intake

TEAC, Trolox equivalent antioxidant capacity; TRAP, Trolox, the total radical-trapping antioxidant parameter; FRAP, ferric ion reducing antioxidant power; OR, odds ratio; HR, hazard ratio; RR, relative risk

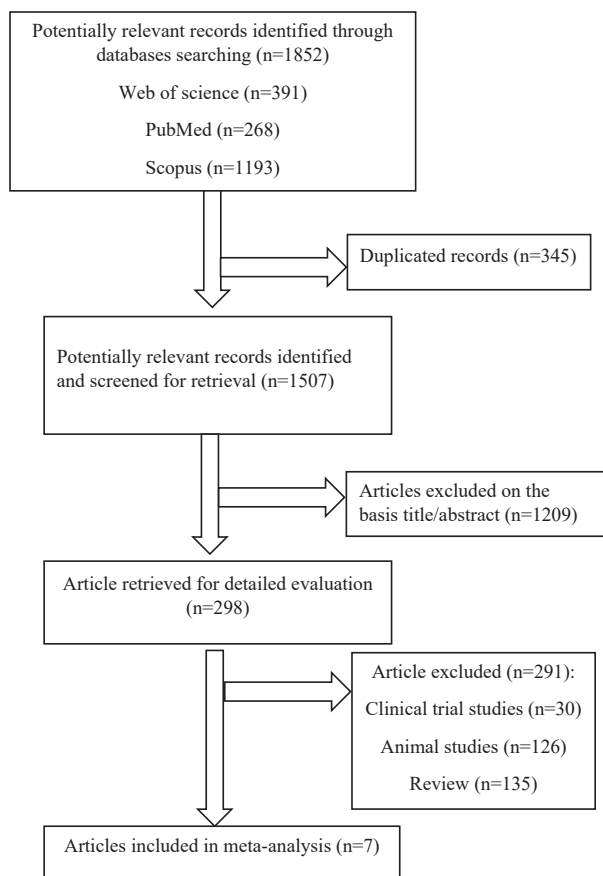


Figure 1. Flow Diagram of Study Selection.

Spain, Sweden, and the United Kingdom) and one other was from the United States.²⁷ To evaluate dietary TAC of three case-control studies, three assays of FRAP, TRAP, and TEAC were applied.^{28,29,31} Also, in cohort studies, two studies applied two assays (FRAP and TRAP),^{30,33} one just applied FRAP²⁷ and one applied TEAC³² to evaluate dietary TAC. The follow-up period of cohort studies varied from 14 to 19 years, sample size ranged from 45194 to 521457 and the participants ranged from 35 to 70 years. In case-control studies, participants' age was between 19 to 80 years, a sample size of cases ranged from 230 to 1953 and control ranged from 547 to 4154. Included studies had a quality score of 7–9, which was high quality. Characteristics of the seven included studies in the meta-analysis are summarized in Table 1. A meta-analysis was performed in all seven included articles.

Meta-analysis

FRAP and Gastrointestinal Cancers Risk

Among seven studies that were included in this meta-analysis, six studies used dietary FRAP to measure dietary TAC that three of them were case-control and three others were a cohort. We conducted a subgroup analysis by the design of the study. Subgroup analysis for case-control studies indicated that FRAP associated significantly with

low GI cancers risk (0.67; 95% CI: 0.57–0.79, $P < 0.001$) and there was no significant heterogeneity between studies ($I^2 = 0\%$, $P = 0.952$). Also, a meta-analysis of cohort studies indicated that there was no association between FRAP and GI cancers risk (0.72; 95% CI: 0.48–1.06; $P = 0.098$) and significant heterogeneity was observed in this subgroup ($I^2 = 74.3\%$, $P = 0.020$). A forest plot of six datasets showed significant inverse association between FRAP and GI cancers risk (0.71; 95% CI: 0.58–0.85; $P < 0.001$) and heterogeneity was significant ($I^2 = 51.2\%$, $P = 0.068$) (Figure 2). There is no publication bias for FRAP ($P = 0.375$).

TRAP and Gastrointestinal Cancers Risk

Subgroup analysis was conducted based on the study design. Subgroup analysis for case-control studies indicated that TRAP have significant inverse relation with risk of GI cancers (0.68; 95% CI: 0.58–0.80; $P < 0.001$) and Significant heterogeneity was not evident ($I^2 = 0.0\%$, $P = 0.630$). As well as, subgroup analysis for cohort studies depicted that there is an inverse association between TRAP and GI cancers risk (0.56; 95% CI: 0.43–0.75; $P < 0.001$) without heterogeneity ($I^2 = 0.0\%$, $P = 0.463$). A forest plot of five datasets depicted significant inverse association between TRAP and GI cancers risk (0.65; 95% CI: 0.57–0.75; $P < 0.001$) and we did not observe significant heterogeneity in overall ($I^2 = 0.0\%$, $P = 0.588$) (Figure 3). Publication bias did not exist for TRAP ($P = 0.359$).

TEAC and Gastrointestinal Cancers Risk

The effect of the TEAC on GI cancers risk was evaluated in four studies of which three were case-control and only one was a cohort. We conducted a subgroup analysis based on the study design. Subgroup analysis for three case-control studies indicated inverse association between TEAC and GI cancers risk (0.66; 95% CI: 0.56–0.78; $P \leq 0.001$) with no statistically significant heterogeneity ($I^2 = 0.0\%$, $P = 0.612$). We cannot identify meta-analysis and heterogeneity for a cohort study in the TEAC assay because it was only a single study. A forest plot of four datasets depicted significant inverse association between TEAC and GI cancers risk (0.70; 95% CI: 0.59–0.83; $P < 0.001$) with a minimum heterogeneity ($I^2 = 18.2\%$, $P = 0.300$) (Figure 4). For TEAC, no publication bias existed ($P = 0.665$).

Discussion

The present meta-analysis showed that high dietary TAC was associated with decreased GI cancer risk. To the best of our knowledge, this article is the first systematic review and meta-analysis that examined the relationship between dietary TAC and GI cancer risk.

This meta-analysis of prospective cohort and case-control studies showed a more credible outcome than an

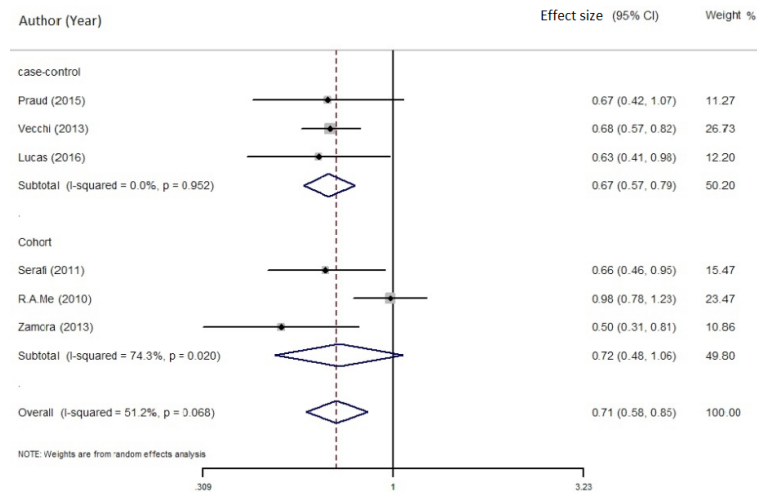


Figure 2. Forest Plot Showing Overall Association of FRAP with Gastrointestinal Cancers Risk and Subgroup Analysis Based on Study Design (Cohort and Case-Control Studies) Using Random Effects Model.

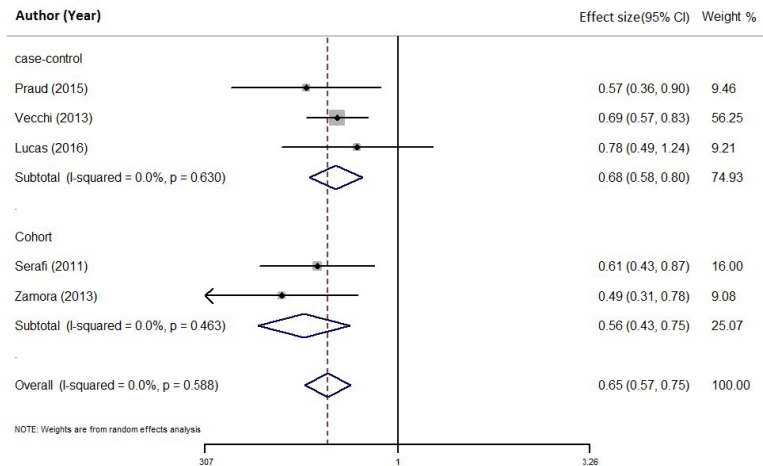


Figure 3. Forest Plot Showing Overall Association of TRAP with Gastrointestinal Cancers Risk and Subgroup Analysis Based on Study Design (Cohort and Case-Control Studies) Using Random Effects Model.

assessment of separate individual studies. As it has been shown in a meta-epidemiological study, no significant difference was reported regarding treatment effect estimates between case-control and cohort studies.³⁴ Besides, previous studies did not consider the differences between case-control and cohort studies as well.³⁵ Similar to the results of this meta-analysis, several studies have depicted inverse association between intake of dietary antioxidants and different cancers such as breast, endometrial, and prostate.³⁶⁻³⁸ A review study by want et al indicated that the Mediterranean diet is related to decreasing of GI cancers risk.¹¹ A Mediterranean diet that is characterized by high consumption of fruits, vegetables, whole grains, nuts, legumes, and olive oil is high in antioxidants³⁹ and have a positive relationship with plasma TAC.⁴⁰ Other studies showed that intake of fruits, vegetables, coffee and tea

which are important components of dietary antioxidants play a protective role against cancers of the digestive system.^{9,41,42} Furthermore, multiple studies investigated the relation between dietary TAC and health outcomes, indicated an inverse association between dietary TAC and chronic diseases such as cancers, cardiovascular diseases, and metabolic syndrome.⁴³⁻⁴⁵

On the contrary, there are several studies that revealed inconsistent results. A meta-analysis of 14 randomized trials showed that not only antioxidant supplements did not decrease GI cancers risk but also apparently increased total mortality.⁴⁶ A randomized trial study depicted that high consumption of fruits and vegetables have not had relation with risk of colorectal cancer⁴⁷; however, these findings may be due to people in intervention group over-reported the consumption of fruit and vegetables or other

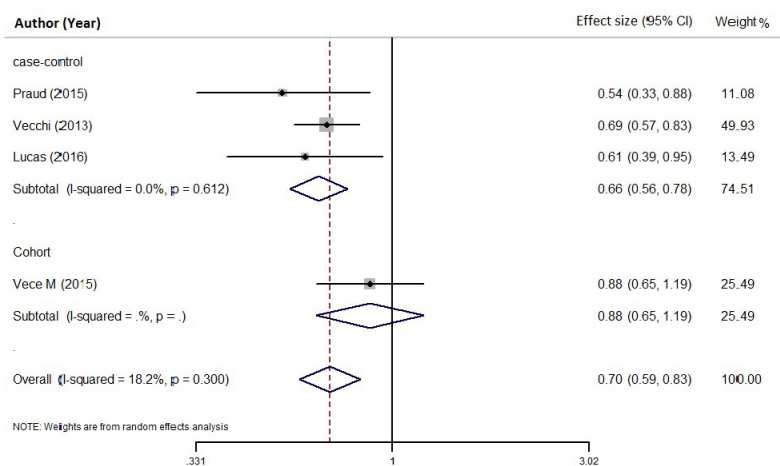


Figure 4. Forest Plot Showing Overall Association of TEAC with Gastrointestinal Cancers Risk and Subgroup Analysis Based on Study Design (Cohort and Case-Control Studies) Using a Random Effects Model.

dietary interventions were too low to result in a reduction of risk of recurrent adenomas.

There are several investigations that evaluated the association of single antioxidant and risk of cancers⁴⁸⁻⁵⁰ but obviously, it is better to examine total antioxidants intake because of the synergistic interactions between different antioxidants which prevent carcinogenesis.⁵¹ There are several methods to evaluate dietary TAC and each method may give a different score of dietary TAC.^{52,53} The most common assays that are used to measure dietary TAC, include FRAP, TRAP, and TEAC.⁴³ Hence, studies included in this meta-analysis were analyzed based on dietary TAC assays.

In this meta-analysis, six of the studies have used FRAP assay, five studies used TRAP assay and four studies used TEAC assay to evaluate dietary TAC. Most studies used two or three of these methods. GI cancers risk was reduced in the highest vs. lowest ntiles of all three indices of FRAP, TRAP, and TEAC in these studies. Heterogeneity of TRAP and TEAC assays were not significant but the heterogeneity of FRAP assay was significant. When we conducted subgroup analysis based on the study design, heterogeneity of case-control studies was not significant but in the cohort studies, heterogeneity was significant that may relate to sample size, cancer site, and the difference in population. Because of the few numbers of studies in each subgroup, we could not characterize the source of heterogeneity. In most studies, the main contributors to dietary TAC were coffee, fruits, vegetables, and wine.

Oxidative stress that results from increased ROS production, induce DNA damage, gene mutation, and consequently carcinogenesis.⁵⁴⁻⁵⁷ Dietary antioxidants are able to neutralize ROS, decrease DNA damage and consequently have a protective role against cancers.⁵⁸ Antioxidants have a more important role in GI cancers because the digestive tract is more accessible to ROS product.¹⁸ Furthermore, Antioxidants play an important

role in cell differentiation and DNA replication, prevent the function of phase I metabolic enzymes which may increase ROS product or activate phase II enzymes which eliminate residual toxic metabolites produced by the phase I enzymes.^{59,60}

This meta-analysis has some strong points. All of the studies used a valid and reproducible food frequency questionnaire (FFQ) to evaluate food intake. In most studies, participants were from both gender except one that was from males. Four cohort studies included in this meta-analysis had a large sample size and long follow-up periods. Also, some limitations existed, such as all three indices applied for measurement of dietary TAC that does not measure *in vivo* antioxidant capacity and merely measures *in vitro* antioxidant capacity. TRAP and FRAP assays do not calculate lipophilic antioxidants that may underestimate dietary TAC. Despite controlling for various population demographic confounders, some of the included studies did not adjust for other components of diet such as fiber, calcium, folate, red and processed meat, and alcohol. Also, serum TAC was not considered as a confounder in included studies.

In conclusion, the results of this meta-analysis suggested that high dietary TAC is inversely associated with GI cancer risk. Further well-designed studies or randomized clinical trials can determine the relationship between DTAC and GI cancer risks.

Authors' Contribution

BZ designed and LA supervised the study. BZ, ED, and LA conducted the literature search, data extraction, and independent search and review. ED performed the statistical analyses and BZ prepared a first draft of the manuscript, and ED and LA finalized it.

Conflict of Interest Disclosures

The authors declare that they have no conflict of interest.

Ethical Statement

Not applicable.

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