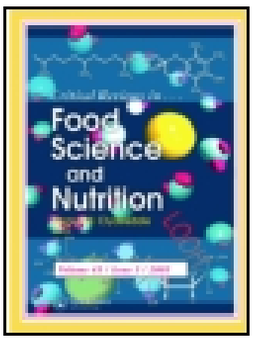

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REVIEW

The effects of probiotic/synbiotic supplementation compared to placebo on biomarkers of oxidative stress in adults: a systematic review and meta-analysis of randomized controlled trials

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ABSTRACT

Background and aims: During the last decades, there has been a burst of scientific literature hypothesizing the antioxidant effect of probiotics. However, the results of these studies are inconsistent and a final conclusion has yet to be reached. Thus, the aim of this study was to assess the effects of probiotic/synbiotic supplementation on serum total antioxidant capacity (TAC), glutathione (GSH), malondialdehyde (MDA) and nitric oxide (NO) levels in adults.

Methods and Results: The following online databases were searched until August 26th 2020: PubMed/Medline, Scopus, Clarivate Analytics Web of Science, Cochrane Central Register of Controlled Trials, Science Direct, Google Scholar and Igaku Chuo Zasshi. The effect sizes were expressed as the weighted mean difference (WMD) with 95% confidence intervals (CI). A total of 31 eligible trials with 1681 participants (839 cases and 842 controls) were included in this meta-analysis. The results revealed that the supplementation with probiotics/synbiotics, significantly increased serum TAC (WMD: 54.14 mmol/L, 95% CI: 27.87, 80.40, $P < 0.001$), GSH (WMD: 40.38 μmol/L, 95% CI: 20.72, 60.03, $P < 0.001$) and NO (WMD: 3.54 μmol/L, 95% CI: 1.73, 5.34, $P < 0.001$) levels. In addition, MDA levels were significantly reduced (WMD: -0.45 μmol/L, 95% CI: -0.58,-0.32, $P < 0.001$) following probiotic/synbiotic supplementation. None of the variables showed a significant change in the sensitivity analysis.

Conclusion: Available evidence suggests that probiotic/synbiotic supplementation can significantly increase serum TAC, GSH and NO, as well as reduce MDA levels in adults. Therefore, probiotic/synbiotic supplementation may play a role in improving antioxidant indices and reducing oxidative stress in the body.

KEYWORDS

Probiotic; synbiotic; oxidative stress; TAC; GSH; MDA; NO; systematic review; meta-analysis

Highlights

- Probiotics/synbiotics are said to play a role in improving antioxidant indices and reducing oxidative stress levels in the body.
- We reviewed the effects of probiotic/synbiotic supplementation on several oxidative stress biomarkers in adults.
- According to our findings, probiotic/synbiotic supplementation significantly increased serum glutathione (GSH), nitric oxide (NO) and the total antioxidant capacity (TAC) and significantly reduced malondialdehyde (MDA) levels in the body.

Introduction

In physiological conditions, the body maintains a balance between pro-oxidants and antioxidants (Roshan et al. 2019). Oxidative stress, which has been associated with a myriad of non-communicable diseases (e.g. cardiovascular diseases, cancer, and diabetes), can be induced by any factor that alters the pro-oxidant/antioxidant balance if the levels of oxidant molecules exceeds the scavenging capacity of available antioxidants (Jones 2006). The main oxidants constantly produced in body are reactive oxygen and nitrogen species (RONS) (Roshan et al. 2019). RONS are produced by all aerobic cells and play an important role in aging and age-related diseases, extraction of energy from organic molecules, immune defense, and signaling pathways (Pizzino et al. 2017). It is generally believed that improving the body's antioxidant capacity, which has undergone extensive changes due to oxidative reactions, can play an important role in preventing oxidative stress by inhibiting oxidation (Halliwell and Gutteridge 1990). Oxidative stress can be measured using several oxidative stress markers such as nitric oxide (NO), superoxide dismutase (SOD), glutathione (GSH), malondialdehyde (MDA) and the total antioxidant

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capacity (TAC). Recently, several reports have postulated the potential antioxidant properties of probiotics and synbiotics (Amaretti et al. 2013), stressing out that their effects in gut pH reduction, decrease in superoxide and hydroxyl radicals levels, increase in glutathione peroxidase levels and others might prevent oxidative stress-related damage (Peran et al. 2006; Ouwehand et al. 2000).

Prebiotics, defined as the live microorganism, are indigestible oligosaccharides with recognized clinical benefits in the prevention and management of ailments associated with low-grade chronic inflammation, such as type 2 diabetes mellitus, obesity, nonalcoholic fatty liver disease, and cardiovascular disorders (Ceriello and Motz 2004; Muriel and Gordillo 2016, Asmat, Abad, and Ismail 2016). In addition, synbiotics contain a combination of prebiotics and probiotics that possess a synergistic effect (Wichansawakun and Buttar 2019). Several experimental rat models have confirmed the potential of probiotics and (or) synbiotics to decrease the levels of oxidative stress markers in the body (Zhao et al. 2017; Lutgendorff et al. 2008). However, the findings derived from clinical research are controversial. Some studies have shown that the effect of probiotics and (or) synbiotics on oxidative stress markers is beneficial, whereas other papers have not endorsed this hypothesis. Although the available scientific literature contains previously conducted systematic reviews which have evaluated the effects of probiotics on oxidative stress based on data collected from randomized controlled trials (Heshmati et al. 2018; Roshan et al. 2019; Zamani et al. 2020; Salehi-Abargouei, Ghiasvand, and Hariri 2017), these papers have had several shortcomings and limitations and have produced inconsistent results as they investigated the effects of probiotics or synbiotics in any form, e.g. capsules, yogurt, milk (Heshmati et al. 2018; Roshan et al. 2019; Salehi-Abargouei, Ghiasvand, and Hariri 2017; Zheng et al. 2019), had missing sub-group analyses regarding the health status of the subjects (if the subjects suffered from any disease or if the women involved in the studies were pregnant) (Heshmati et al. 2018; Salehi-Abargouei, Ghiasvand, and Hariri 2017; Zamani et al. 2020), had missing sub-group analyses for probiotics and synbiotics (Roshan et al. 2019; Salehi-Abargouei, Ghiasvand, and Hariri 2017) and used studies in which probiotic/synbiotic supplements were evaluated together with another antioxidant molecule (Salehi-Abargouei, Ghiasvand, and Hariri 2017; Heshmati et al. 2018). Subsequently, all of these studies have reviewed the articles published until 2016 (Heshmati et al. 2018; Salehi-Abargouei, Ghiasvand, and Hariri 2017) or 2017 (Roshan et al. 2019; Zamani et al. 2020) and, therefore, the recent randomized clinical trials available after 2017 have not been reviewed, except for one paper which has included research manuscripts involving diabetic subjects and has reviewed the literature up to 2018 (Zheng et al. 2019).

Thus, the purpose of this study was to evaluate the effects of probiotic/synbiotic supplementation compared to placebo on biomarkers of oxidative stress (TAC, GSH, MDA and NO) in adults.

Methods

The current systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Shamseer et al. 2015) in every stage of the processing, analyzing, and reporting of the data. The study protocol is registered in the Prospective Register of Systematic Reviews (PROSPERO) [ID: CRD42020148489].

Search strategy

PubMed/Medline, Scopus, Clarivate Analytics Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL), Science Direct, Google Scholar and Igaku Chuo Zasshi online databases were searched until August 26th 2020 to identify relevant studies published before this date, without language, time or any other restrictions. In the Igaku Chuo Zasshi database, the search was done both in Japanese and in English languages. The type of article was limited to randomized controlled trials (RCTs) or clinical trials. The following keywords were used: ((probiotic*) OR (Lactobacillus) OR (Bifidobacterium) OR (Synbiotic*) OR (Symbiotic*) OR (Prebiotic*)) AND ((("oxidative stress") OR ("Free Radicals") OR (Malondialdehyde) OR (MDA) OR ("nitric oxide") OR (NO) OR ("total antioxidant capacity") OR (TAC) OR (antioxidant*) OR (Glutathione) OR (GSH) OR ("reactive oxygen species") OR (ROS) OR ("metabolic profile") OR ("metabolic status") OR ("metabolic response") AND (("clinical trial") OR ("randomized clinical trial") OR (RCT)) AND NOT ((child) OR (infant) OR (children) OR (neonatal) OR (animal) OR ("in vitro") OR (mouse) OR (rat) OR (rabbit) OR (hamster) OR (systematic review) OR (meta-analysis)).

Study selection and eligibility criteria

The screening of the titles and abstracts and the subsequent assessment of the full-texts of the eligible articles were carried out by two independent researchers (B.P. & S.F). All the published controlled clinical trials (either with a parallel or a cross-over design) that reported the effect of probiotic or synbiotic supplementation (in the form of capsules and sachets) on serum oxidative and antioxidant markers (TAC, GSH, MDA or NO) in adults (aged $\geq$ 18 years) were considered. Language limits and specific time frames were not taken into account for the search and all the studies published on this topic before August 26th 2020 were reviewed. We contacted the authors by e-mail to ask for additional explanations if there was any potentially eligible article with unclear data. However, one of them (Aghamohammadi et al. 2019) did not respond. The exclusion criteria of this study were: 1) animal and in vitro studies; 2) studies investigating the effects of probiotics or synbiotics without mentioning the dose and type of probiotic bacteria; 3) articles that examined the effects of prebiotics merely; 4) studies conducted on children or adolescents; 5) studies investigating enriched food with probiotics or synbiotics; 6) studies that

examined the effect of probiotic or synbiotic supplementation along with other agents; 7) articles that studied people with cancer; 8) studies which did not have sufficient information about TAC, GSH, MDA and NO levels at baseline and at the end of the trial; 9) studies that examined other oxidative stress factors than the ones explored in our study; 10) articles with other study designs except for a clinical trial design; 11) studies that examined non-serum biomarkers.

Data extraction

The studies were selected by two independent researchers (B.P.) and (S.F.) on the basis of the inclusion and exclusion criteria. Any disagreement between the researchers was resolved by consulting with the third researcher (F.S.H.). The following information was collected: author's name, study location, study design, study population, mean age, gender, sample size, intervention group, control group, probiotic dosage, probiotic strain, and duration of intervention. This information is shown in Table 1.

Quality assessment

The quality of the studies was independently evaluated by 2 researchers (B.P.) and (F.S.H.) according to the Cochrane Handbook for Systematic Reviews of Interventions, version 5.1.0 (Higgins 2008) and by using the following criteria: 1) random sequence generation, 2) allocation concealment, 3) blinding of participants and personnel, 4) blinding of outcome assessment, 5) incomplete outcome data, and 6) selective outcome reporting.

There were six key domains according to which each study was graded in terms of overall risk of bias: low risk (low for all key domains), high risk (high for one or more key domains) and unclear risk (unclear for one or more key domains).

Data synthesis and statistical analysis

For all outcomes, the effect sizes were measured by the mean difference between the intervention and the control group at follow-up. Where the effect size was not reported, the difference in the mean values at the baseline and at the end of the study were used. We extracted the mean and the standard deviation (SD) from the reviewed studies and where the data were reported in a different format. This method was used by Hozo et al. as follows: SD = square root [(SD pretreatment) 2 + (SD post-treatment) 2 – (2 R × SD pretreatment × SD post-treatment)] (Hozo, Djulbegovic, and Hozo 2005). The groups were combined by applying a weighted average when we had >1 control group to enable a single pairwise comparison. In order to estimate effect sizes, the random effects model (DerSimonian and Laird method) was used and the results were provided across weighted mean difference (WMD) and 95% confidence intervals (CI). We used Plot digitizer software when the results were only presented in the graphic form. Heterogeneity was calculated by the I^2 index (Fatahi et al. 2018). We considered a I^2 index greater than 50% as an indicator of substantial heterogeneity among the trials. Subgroup analysis was performed to identify factors for high heterogeneity. We considered the values less or more than median as the cutoff values for each aforementioned quantitative parameter of subgroups. The sensitivity analysis was done by using the leave-one-out method (Iyengar and Greenhouse 2009) to examine the impact of each study on the results. The funnel plot was used to determine publication bias, by either Beggs' rank correlation or Eggers' regression test. We used trim-and-fill method for estimating the number of missing studies that might exist in a meta-analysis. STATA version 11.0 was used for statistical analysis (Stata Corp, College Station, TX) and P-values < 0.05 were considered statistically significant.

Results

Study selection

A flow chart depicting the literature search and selection is presented in Figure 1. Using the key terms of the study, we identified 3565 articles *via* the database inspection and three additional articles through other sources. First, duplicate articles (n = 2129) were removed. In addition, a number of 1358 articles, which were recognized as irrelevant to our research topic, was removed after the assessment of the titles and abstracts. Furthermore, we evaluated the full-texts of the remaining 81 articles of which 50 articles were excluded for the following reasons: 1. the results were not properly reported (Hütt et al. 2009; Aghamohammadi et al. 2019; Lamprecht et al. 2012; Valentini et al. 2015); 2. only the prebiotic was evaluated (Aliasgharzadeh, Dehghan, et al. 2015; Aliasgharzadeh, Khalili, et al. 2015; Kellow et al. 2014; Chen et al. 2013); 3. the study was conducted on cancer patients (Navaei et al. 2020); 4. the study examined the effects of foods fortified with probiotics or synbiotics (Bakhshimoghaddam et al. 2018; Asemi et al. 2012; Akbari et al. 2016; Ejtahed et al. 2012, مأذنی et al. 2018; Kullisaar et al. 2003; Naruszewicz et al. 2002; Songisepp et al. 2005; Arani et al. 2018; Miraghajani et al. 2017; Hariri et al. 2015; Bahmani et al. 2016; Mohammadi et al. 2015; Ito et al. 2017; Iwasa et al. 2013, Fabian et al. 2008); 5. the study did not report on the outcome of interest (Fuentes et al. 2013; Ishikawa et al. 2011; Kleniewska et al. 2016; Kleniewska and Pawliczak 2018; Mikelsaar et al. 2008; Rossi et al. 2014; Tamtaji et al. 2017; Tonucci et al. 2017; Valimaki et al. 2012); 6. non-serum factors were evaluated (Kuka et al. 2019; Mahdavi et al. 2017; Nikniaz et al. 2013; Lee et al. 2015); 7. the study evaluated probiotics or synbiotics along with other agents (Tamtaji, Heidari-soureshjani, et al. 2019; Reda et al. 2018; Raygan, Ostadmohammadi, et al. 2018; Ostadmohammadi et al. 2019; Önning et al. 2003; Kullisaar et al. 2016; Kang et al. 2012; Jamilian et al. 2018; Ghaderi et al. 2019; Asemi et al. 2016; Raygan, Ostadmohammadi, and Asemi 2019); 8. the results of the examined studies reported our target unit (mmol/L for TAC), but the depicted values were very different numerically from those described

Table 1. Characteristics of the randomized clinical trials that were included in the systematic review.

	Author (year) (reference)	Country	Clinical Trial Design	Population	Mean Age (year)	Gender	Sample Size Case/Placebo	Intervention group	**Control group**	Probiotic dose (cfu)	Probiotic strain	Period (week)
1	(Agahi et al. 2018)	Iran	Randomized-double blind and placebo controlled	Alzheimer's disease	77.5	Male/female	25/23	Probiotic	Maltodextrine	$3*10^9$	1,2,3,14,15,16	12
2	(Akkasheh et al. 2016)	Iran	Randomized-double blind and placebo controlled	major depressive disorder	37.25	Male/female	20/20	Probiotic	Starch	$6*10^9$	3,4,15	8
3	(Babadi et al. 2019)	Iran	Randomized-double blind and placebo controlled	Gestational Diabetes Mellitus	28.9	female	24/24	Probiotic	Corn starch	$8*10^9$	3,4,15,1	6
4	(Badehnoosh et al. 2018)	Iran	Randomized-double blind and placebo controlled	Gestational Diabetes Mellitus	29	female	30/30	Probiotic	Starch	$6*10^9$	3,4,15	6
5	(Borzabadi et al. 2018)	Iran	Randomized-double blind and placebo controlled	Parkinson's Disease	66.8	Male/female	25/25	Probiotic	–	8×10^9	3,15,5,1	12
6	(Farrokhian et al. 2019)	Iran	Randomized-double blind and placebo controlled	Overweight, Diabetes,and Coronary Heart Disease	64.1	Male/female	30/30	Synbiotic	Starch	$6*10^9$	3,4,15	12
7	(Hajifaraji et al. 2018)	Iran	Randomized-double blind and placebo controlled	Gestational Diabetes Mellitus	27.3	female	27/29	Probiotic	–	$4*10^9$	3,6,17,20	8
8	(Jamilian, Amirani, and Asemi 2019)	Iran	Randomized-double blind and placebo controlled	Gestational diabetes	30.55	female	29/27	Probiotic	Starch	$8*10^9$	3,15,5,1	6
9	(Karamali, Eghbalpour, et al. 2018)	Iran	Randomized-double blind and placebo controlled	Polycystic Ovary Syndrome	27.45	female	30/30	Probiotic	Starch	$6*10^9$	3,4,15	12
10	(Karamali, Nasiri, et al. 2018)	Iran	Randomized-double blind and placebo controlled	Gestational Diabetes	29	female	30/30	Synbiotic	–	$6*10^9$	3,4,15	6
11	(Kouchaki et al. 2017)	Iran	Randomized-double blind and placebo controlled	Multiple sclerosis	34.1	Male/female	30/30	Probiotic	Starch	8×10^9	3,4,15,1	12
12	(Mafi et al. 2018)	Iran	Randomized-double blind and placebo controlled	Diabetic nephropathy	59.9	–	30/30	Probiotic	Starch	8×10^9	3,15,5,1	12
13	(Jamilian et al. 2016)	Iran	Randomized-double blind and placebo controlled	Pregnant Women	27.75	female	30/30	Probiotic	Starch	$6*10^9$	3,4,15	12
14	(Mohseni et al. 2018)	Iran	Randomized-double blind and placebo controlled	Diabetic foot ulcer	60.55	Male/female	30/30	Probiotic	–	8×10^9	3,4,1,15	12
15	(Nasri et al. 2018)	Iran	Randomized-double blind and placebo controlled	Polycystic ovary syndrome	25.8	female	30/30	Synbiotic	–	$6*10^9$	3,4,15	12
16	(Raygan et al. 2018)	Iran	Randomized-double blind and placebo controlled	Type 2 diabetes with coronary heart disease	61.25	–	30/30	Probiotic	–	$6*10^9$	3,4,15	12
17	(Salami et al. 2019)	Iran	Randomized-double blind and placebo controlled	Multiple sclerosis	35.66	Male/female	24/24	Probiotic	Maltodextrine	$12*10^9$	14,18,5,4,1,2	16
18	(Soleimani et al. 2017)	Iran	Randomized-double blind and placebo controlled	diabetic hemodialysis	56.7	Male/female	30/30	Probiotic	–	$6*10^9$	3,4,15	12
19	(Soleimani et al. 2018)	Iran	Randomized-double blind and placebo controlled	diabetic hemodialysis	62.8	Male/female	30/30	Synbiotic	Corn starch	$6*10^9$	3,4,15	12
20	(Tamtaji et al. 2019)	Iran	Randomized-double blind and placebo controlled	Parkinson's Disease	67.95	–	30/30	Probiotic	–	8×10^9	3,15,5,1	12
21	(Zamani et al. 2017)	Iran		Rheumatoid arthritis	49.4	Male/female	27/27	Synbiotic	Starch	$6*10^9$	3,4,15	8

(*continued*)

Table 1. Continued.

	Author (year) (reference)	Country	Clinical Trial Design	Population	Mean Age (year)	Gender	Sample Size Case/Placebo	Intervention group	**Control group**	Probiotic dose (cfu)	Probiotic strain	Period (week)
22	(Asemi et al. 2014)	Iran	Randomized-double blind and placebo controlled randomized double-blinded cross-over controlled	Diabetes	53.1	Male/female	62/62	Synbiotic	Isomalt, Sorbitol, Stevia	$27*10^7$	7	6
23	(Gomes et al. 2017)	Brazil	Randomized-double blind and placebo controlled	Excess weight or obesity	38.5	female	21/22	Probiotic	–	$2*10^{10}$	3,4,14,15,8	8
24	(Kleniewska and Pawliczak 2017)	Poland	randomized controlled clinical trial	Healthy volunteers	–	Male/female	16/16	Synbiotic	Nothing	$4*10^8$	4	7
25	(Mazloom, Yousefinejad, and Dabbaghmanesh 2013)	Iran	Randomized single-blind and placebo controlled	Type 2 diabetes	53.6	Male/female	16/18	Probiotic	Magnesium stearate,FOS	10^9,10^6	3,4,15,9	6
26	(Mokhtari et al. 2019)	Iran	Randomized-double blind and placebo controlled	Patients undergoing Gastric Bypass Surgery	34.65	female	23/23	Probiotic	–	10^8,10^9, 10^{10}	4,11,19,20,3,9,16	16
27	(Ebrahimi-Mameghani et al. 2013)	Iran	Randomized-double blind and placebo controlled	Critically ill patients admitted to the intensive care unit	34.6	Male/female	20/20	Probiotic	–	$9*10^{11}$	4,2,3,6,16,18,19,21	1
28	(Taghizadeh et al. 2014)	Iran	Randomized-double blind and placebo controlled	Pregnant Women	26.5	female	26/26	Synbiotic	Isomalt, Sorbitol	$18*10^7$	7	9
29	(Vaghef-Mehrabany et al. 2016)	Iran	Randomized-double blind and placebo controlled	Rheumatoid Arthritis	42.71	female	22/24	Probiotic	Maltodextrine	10^8	4	8
30	(Ekhlasi et al. 2017)	Iran	Randomized-double blind and placebo controlled	Nonalcoholic Fatty liver Disease	44	Male/female	15/15	Synbiotic	Corn starch	$4*10^9$	4,20,3,9,11,16,19	8
31	(Asemi et al. 2013)	Iran	randomized double-blinded controlled clinical trial	types 2 diabetes	51.55	Male/female	27/27	Probiotic	fructo-oligosaccharide with lactose	10^8,10^9, 10^{10}	3,4,11,9,19,16,20	8

Probiotic strain: 1- Lactobacillus fermentum, 2- Lactobacillus plantarum, 3- Lactobacillus acidophilus, 4- Lactobacillus casei, 5- Lactobacillus reuteri, 6- Lactobacillus delbrueckii ssp. bulgaricus, 7- Lactobacillus sporogenes, 8- Lactococcus lactis, 9 -Lactobacillus bulgaricus, 10- Lactobacillus gasser, 11- Lactobacillus rhamnosus, 12- Lactobacillus langum, 13- Lactobacillus paracasei, 14- Bifidobacterium lactis, 15- Bifidobacterium bifidum, 16- Bifidobacterium longum, 17- , Bifidobacterium BB-12, 18- Bifidobacterium infantis, 19- Bifidobacterium breve , 20- Streptococcus thermophiles, 21- Streptococcus salivarius subsp.Thermophilus.

-: No Report.

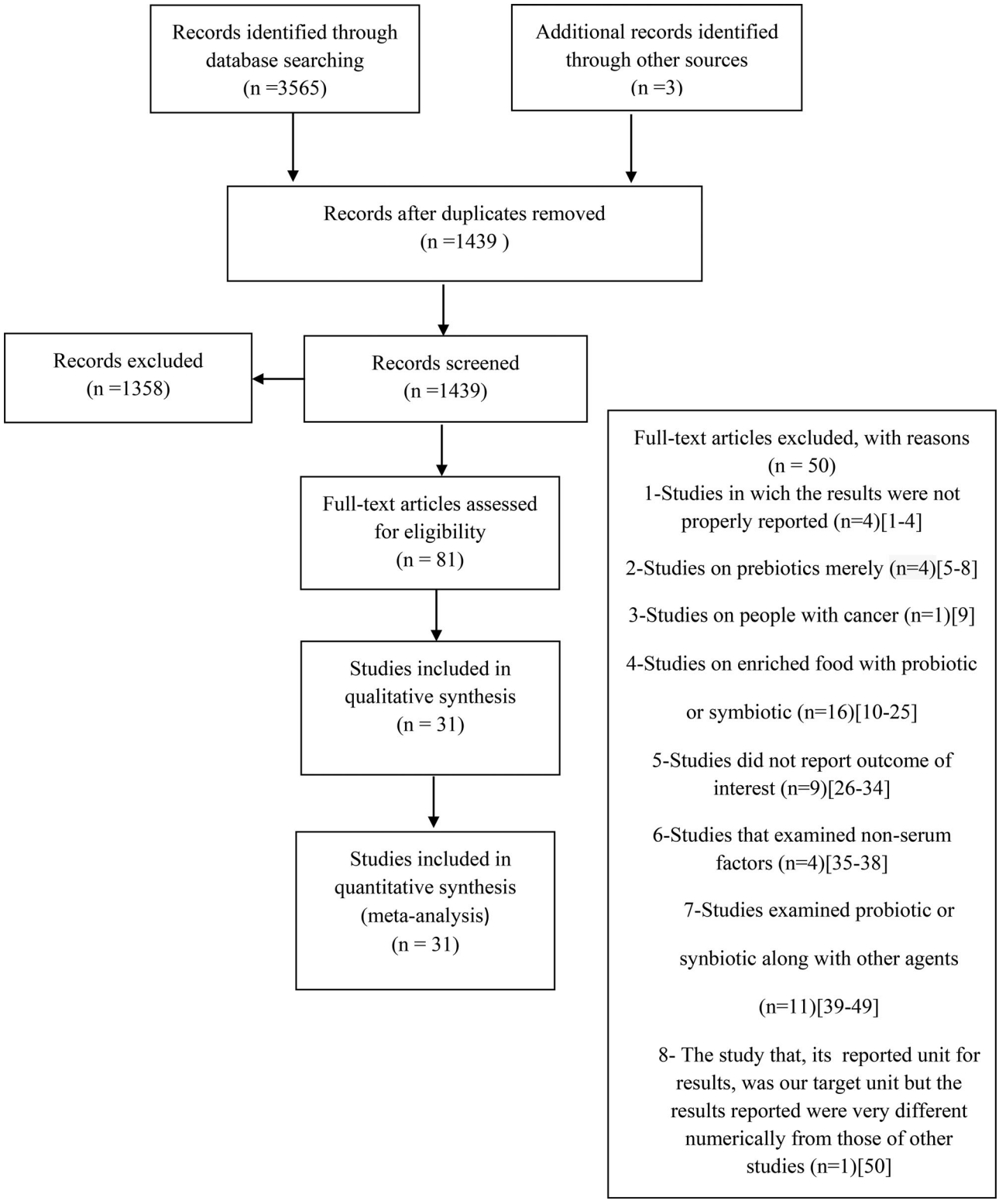

Figure 1. Flow chart of the study selection process.

in the other studies (Nabhani et al. 2018). Two of the studies that evaluated TAC and GSH levels (Vaghef-Mehrabany et al. 2016; Hajifaraji et al. 2018) were included in the GSH meta-analysis but not in the TAC meta-analysis, since the reported results for TAC were very different numerically from the other studies with similar units. Two articles (Taghizadeh et al. 2014; Asemi et al. 2014) mentioned that the subjects received synbiotic food as an intervention, but while evaluating the full-text we discovered that in fact the synbiotic was provided as a supplement/sachet and not as a synbiotic-enriched food. Thus, these two research papers were included in our study and meta-analysis. The two reviewers (B.P.) and (F.Sh.) agreed on the study screening procedure and finally the analysis involved 31 articles.

Study and participant characteristics

The characteristics of the studies included in the present systematic review and meta-analysis are shown in Table 1. Twenty nine studies were conducted in Iran (Agahi et al. 2018; Akkasheh et al. 2016; Babadi et al. 2019; Badehnoosh et al. 2018; Borzabadi et al. 2018; Farrokhian et al. 2019; Hajifaraji et al. 2018; Jamilian, Amirani, and Asemi 2019; Karamali, Eghbalpour, et al. 2018; Karamali, Nasiri, et al. 2018; Kouchaki et al. 2017; Mafi et al. 2018; Jamilian et al. 2016; Mohseni et al. 2018; Nasri et al. 2018; Raygan, Rezavandi, et al. 2018; Salami et al. 2019; Soleimani et al. 2017; Soleimani et al. 2018; Tamtaji, Taghizadeh, et al. 2019; Zamani et al. 2017; Asemi et al. 2014; Mazloom, Yousefinejad, and Dabbaghmanesh 2013; Mokhtari et al. 2019; Ebrahimi-Mameghani et al. 2013; Taghizadeh et al. 2014; Vaghef-Mehrabany et al. 2016; Ekhlasi et al. 2017; Asemi et al. 2013) and two others were conducted in Brazil (Gomes et al. 2017) and Poland (Kleniewska and Pawliczak 2017), respectively. From the total of 31 studies, one study was crossover in design and consisted of 62 participants(Asemi et al. 2014), one study was single-blinded with 34 participants (Mazloom, Yousefinejad, and Dabbaghmanesh 2013) and one study with 32 participants was not blinded (Kleniewska and Pawliczak 2017). The intervention duration was 1 week in one study (Ebrahimi-Mameghani et al. 2013), 6 weeks in six studies (Babadi et al. 2019; Badehnoosh et al. 2018; Jamilian, Amirani, and Asemi 2019; Karamali, Nasiri, et al. 2018; Asemi et al. 2014; Mazloom, Yousefinejad, and Dabbaghmanesh 2013), 7 weeks in one study (Kleniewska and Pawliczak 2017), 8 weeks in seven studies(Akkasheh et al. 2016; Hajifaraji et al. 2018; Zamani et al. 2017; Gomes et al. 2017; Vaghef-Mehrabany et al. 2016; Ekhlasi et al. 2017; Asemi et al. 2013), 9 weeks in one study (Taghizadeh et al. 2014), 12 weeks in thirteen studies (Agahi et al. 2018; Borzabadi et al. 2018; Farrokhian et al. 2019; Karamali, Eghbalpour, et al. 2018; Kouchaki et al. 2017; Mafi et al. 2018; Jamilian et al. 2016; Mohseni et al. 2018; Nasri et al. 2018; Raygan, Rezavandi, et al. 2018; Soleimani et al. 2017; Soleimani et al. 2018; Tamtaji, Taghizadeh, et al. 2019) and 16 weeks in two studies (Mokhtari et al. 2019; Salami et al. 2019). Among these studies, 22 had examined the effects of probiotics (Agahi et al. 2018; Akkasheh et al. 2016; Babadi et al. 2019; Badehnoosh et al. 2018; Borzabadi et al. 2018; Hajifaraji et al. 2018; Jamilian, Amirani, and Asemi 2019; Karamali, Eghbalpour, et al. 2018; Kouchaki et al. 2017; Mafi et al. 2018; Jamilian et al. 2016; Mohseni et al. 2018; Raygan, Rezavandi, et al. 2018; Salami et al. 2019; Soleimani et al. 2017; Tamtaji, Taghizadeh, et al. 2019; Gomes et al. 2017; Mazloom, Yousefinejad, and Dabbaghmanesh 2013; Mokhtari et al. 2019; Ebrahimi-Mameghani et al. 2013; Vaghef-Mehrabany et al. 2016; Asemi et al. 2013) and 9 the effect of synbiotics (Farrokhian et al. 2019; Karamali, Nasiri, et al. 2018; Nasri et al. 2018; Soleimani et al. 2018; Zamani et al. 2017; Asemi et al. 2014; Kleniewska and Pawliczak 2017; Taghizadeh et al. 2014; Ekhlasi et al. 2017). The probiotic dosage was, in the majority of the analyzed studies, 10^9 CFU. It was 10^7 CFU in 2 studies (Asemi et al. 2014; Taghizadeh et al. 2014), 10^8 CFU in 3 studies (Ekhlasi et al. 2017; Vaghef-Mehrabany et al. 2016; Kleniewska and Pawliczak 2017), 10^8-10^{10} CFU in 4 studies (Mokhtari et al. 2019; Asemi et al. 2013), and $10^9$and 10^6 CFU (Mazloom, Yousefinejad, and Dabbaghmanesh 2013), 10^{10} CFU (Gomes et al. 2017) and 10^{11} CFU (Ebrahimi-Mameghani et al. 2013) in one study each. A total of 3 studies did not report the gender of the participants (Mafi et al. 2018; Raygan, Rezavandi, et al. 2018; Tamtaji, Taghizadeh, et al. 2019), 16 studies included both males and females (Kleniewska and Pawliczak 2017; Mazloom, Yousefinejad, and Dabbaghmanesh 2013; Ebrahimi-Mameghani et al. 2013; Ekhlasi et al. 2017; Salami et al. 2019; Soleimani et al. 2017; Soleimani et al. 2018; Zamani et al. 2017; Asemi et al. 2014; Kouchaki et al. 2017; Mohseni et al. 2018; Agahi et al. 2018; Akkasheh et al. 2016; Borzabadi et al. 2018; Farrokhian et al. 2019; Asemi et al. 2013) and 13 other studies only involved adult females. Overall, the age range of the participants was 25–77 years. All the studies used the 24-hour food recall questionnaire at the beginning and at the end of the intervention period to estimate the individual nutrients and energy intake, except for four studies (Agahi et al. 2018; Kleniewska and Pawliczak 2017; Ebrahimi-Mameghani et al. 2013; Mazloom, Yousefinejad, and Dabbaghmanesh 2013) that failed to mention whether the questionnaire was used. Moreover, thirteen studies (Agahi et al. 2018; Badehnoosh et al. 2018; Karamali, Nasiri, et al. 2018; Mafi et al. 2018; Tamtaji, Taghizadeh, et al. 2019; Asemi et al. 2013; Asemi et al. 2014; Kleniewska and Pawliczak 2017; Mazloom, Yousefinejad, and Dabbaghmanesh 2013; Mokhtari et al. 2019; Ebrahimi-Mameghani et al. 2013; Taghizadeh et al. 2014; Ekhlasi et al. 2017) did not mention the use of a physical activity questionnaire. The run-in period was only mentioned in five studies (Gomes et al. 2017; Asemi et al. 2014; Taghizadeh et al. 2014; Ekhlasi et al. 2017; Asemi et al. 2013).

Risk of bias assessment

As shown in Table 2, with the exception of five studies that were evaluated as unclear risk in terms of the random sequence generation (Agahi et al. 2018; Asemi et al. 2014; Kleniewska and Pawliczak 2017; Ebrahimi-Mameghani et al. 2013; Asemi et al. 2013), the other papers explicitly mentioned the random sequence generation methods. Therefore, they were regarded as low risk of bias. One study was assessed as low risk in the allocation concealment (Mokhtari et al. 2019), whereas the other 30 studies were rated as unclear in this section. There were two studies which were single-blinded (Mazloom, Yousefinejad, and Dabbaghmanesh 2013) and not blinded (Kleniewska and Pawliczak 2017) and were thus considered as unclear risk of bias and high risk of bias for the blinding of the participants and personnel, respectively. None of the trials provided a clear description of the blinding of outcome assessment. Three studies were not clear in providing incomplete outcomes and were subsequently considered as having an unclear risk of bias (Kleniewska and Pawliczak 2017;

Table 2. Risk of bias assessment according to the Cochrane collaboration's risk of bias assessment tool.

Study, Year (reference)	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Overall assessment of risk of bias
(Agahi et al. 2018)	Unclear	Unclear	Low	Unclear	Unclear	Low	Unclear
(Akkasheh et al. 2016)	Low	Unclear	Low	Unclear	Low	Unclear	Unclear
Babadi et al. 2019	Low	Unclear	Low	Unclear	Low	Low	Unclear
(Badehnoosh et al. 2018)	Low	Unclear	Low	Unclear	Low	Low	Unclear
(Borzabadi et al. 2018)	Low	Unclear	Low	Unclear	Low	Low	Unclear
(Farrokhian et al. 2019)	Low	Unclear	Low	Unclear	Low	Low	Unclear
(Hajifaraji et al. 2018)	Low	Unclear	Low	Unclear	Low	Low	Unclear
(Jamilian, Amirani, and Asemi 2019)	Low	Unclear	Low	Unclear	Low	Low	Unclear
(Karamali, Eghbalpour, et al. 2018)	Low	Unclear	Low	Unclear	Low	Low	Unclear
(Karamali, Nasiri, et al. 2018)	Low	Unclear	Low	Unclear	Low	Low	Unclear
(Kouchaki et al. 2017)	Low	Unclear	Low	Unclear	Low	Unclear	Unclear
(Mafi et al. 2018)	Low	Unclear	Low	Unclear	Low	Low	Unclear
(Jamilian et al. 2016)	Low	Unclear	Low	Unclear	Low	Low	Unclear
(Mohseni et al. 2018)	Low	Unclear	Low	Unclear	Low	Low	Unclear
(Nasri et al. 2018)	Low	Unclear	Low	Unclear	Low	Low	Unclear
(Raygan et al. 2018)	Low	Unclear	Low	Unclear	Low	Low	Unclear
(Salami et al. 2019)	Low	Unclear	Low	Unclear	Low	Low	Unclear
(Soleimani et al. 2017)	Low	Unclear	Low	Unclear	Low	Low	Unclear
(Soleimani et al. 2018)	Low	Unclear	Low	Unclear	Low	Low	Unclear
(Tamtaji et al. 2019)	Low	Unclear	Low	Unclear	Low	Low	Unclear
(Zamani et al. 2017)	Low	Unclear	Low	Unclear	Low	Low	Unclear
(Asemi et al. 2014)	Unclear	Unclear	Low	Unclear	Low	Low	Unclear
(Gomes et al. 2017)	Low	Unclear	Low	Unclear	Low	Low	Unclear
(Kleniewska and Pawliczak 2017)	Unclear	Unclear	High	Unclear	Unclear	Low	High
(Mazloom, Yousefinejad, and Dabbaghmanesh 2013)	Low	Unclear	Unclear	Unclear	Unclear	Low	Unclear
(Mokhtari et al. 2019)	Low	Low	Low	Unclear	Low	Low	Unclear
(Ebrahimi-Mameghani et al. 2013)	Unclear	Unclear	Low	Unclear	Low	Low	Unclear
(Taghizadeh et al. 2014)	Low	Unclear	Low	Unclear	Low	Low	Unclear
(Vaghef-Mehrabany et al. 2016)	Low	Unclear	Low	Unclear	Low	Low	Unclear
(Ekhlasi et al. 2017)	Low	Unclear	Low	Unclear	Low	Low	Unclear
(Asemi et al. 2013)	Unclear	Unclear	Low	Unclear	Low	Low	Unclear

Mazloom, Yousefinejad, and Dabbaghmanesh 2013; Agahi et al. 2018). Two studies were assessed as unclear risk in the selective reporting (Akkasheh et al. 2016; Kouchaki et al. 2017), and the other 29 studies as low risk of bias, with the exception of one study that was assessed as high risk in quality (Kleniewska and Pawliczak 2017). Since the other studies were considered as having an unclear risk of bias for at least one of the six key domains, we evaluated the quality of these studies as "unclear".

Meta-analysis

Total antioxidant capacity (TAC)

There were 23 studies with 1344 participants (case = 670, and control = 674) which reported TAC as an outcome measure. The combined results of the random-effects model showed a significant increase in TAC following the probiotic/synbiotic supplementation (weight mean difference (WMD): 54.14 mmol/L, 95% CI: 27.87, 80.40, $P < 0.001$). There heterogeneity was significantly high between the included studies (I^2 = 74.1%; P = 0.000) (Figure 2). Thus, we stratified the studies to identify the possible sources of heterogeneity and the results displayed that the study population, gender, BMI, duration of intervention and type of intervention were possible sources of heterogeneity. The subgroup analyzes showed that probiotic/synbiotic supplementation increased TAC significantly in women with gestational diabetes (WMD: 74.59 mmol/L, 95% CI: 40.63, 108.55), diabetic subjects (WMD: 88.03 mmol/L, 95% CI: 20.93, 155.13) and critically ill patients admitted to the intensive care unit (WMD: 64.16 mmol/L, 95% CI: 28.99, 99.33) (Supplementary Figure 2.1). In addition, the elevation in TAC was significant in the studies which included females only (WMD: 77.22 mmol/L, 95% CI: 36.38, 118.07) *versus* those that grouped both females and males (Supplementary Figure 2.2). BMI was another source of heterogeneity, with the increase in TAC reported as significant in the subjects who had a BMI of 25-29.9 kg/m^2 (WMD: 68.18 mmol/L, 95% CI: 34.44, 101.92) (Supplementary Figure 2.3). The sensitivity analysis indicated that no study had a significant impact on the overall effect sizes in terms of

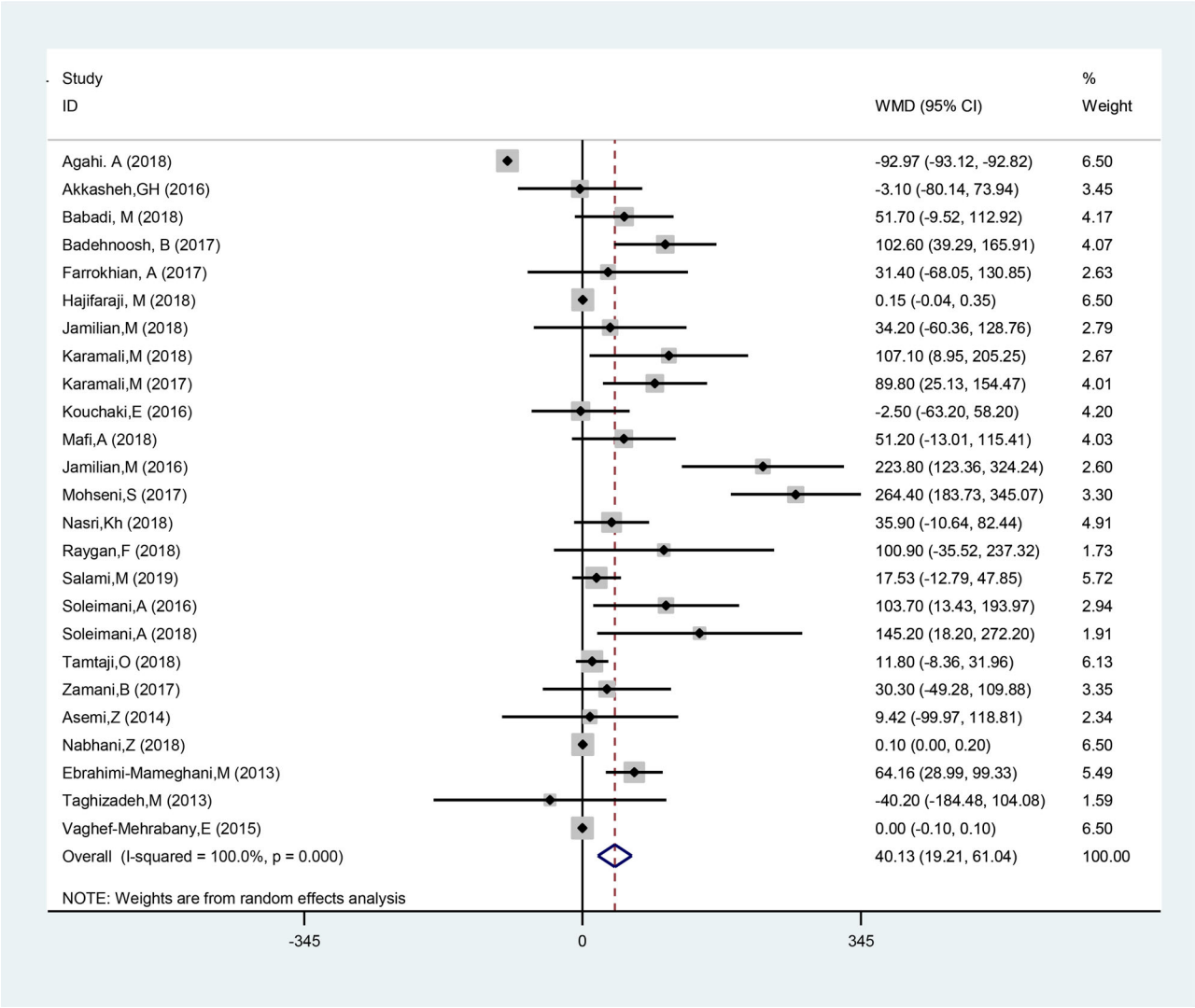

Figure 2. Forest plot of randomized controlled trials investigating the effects of probiotic/ synbiotic on serum TAC.

TAC (Supplementary Figure 2.7). The assessment of the publication bias by visual inspection of the funnel plot did not show any evidence of publication bias in the meta-analysis of probiotic/synbiotic supplementation on TAC (P = 0.10) (Supplementary Figure 2.8).

Glutathione (GSH)

GSH levels were assessed in 24 studies with a total of 1386 participants (cases = 695 and controls = 691). The pooled results from the random-effects model indicated that GSH levels changed significantly after the probiotic/synbiotic supplementation (WMD: 40.38 μmol/L, 95% CI: 20.72, 60.03, P < 0.001, I^2 = 76.4%) (Figure 3). Study population, gender, BMI and age were possible sources of heterogeneity observed for GSH. The subgroup analyzes showed that probiotic/synbiotic supplementation in gestational diabetes (WMD: 30.71 μmol/L, 95% CI: 4.40, 57.03), diabetes (WMD: 74.70 μmol/L, 95% CI: 24.10, 125.30), rheumatoid arthritis (WMD: 95.10 μmol/L, 95% CI: 32.13, 158.07) patients and healthy volunteers (WMD: 5.57 μmol/L, 95% CI: 2.75, 8.39) was more effective in increasing GSH levels versus other conditions (Supplementary Figure 3.1). Also, the elevation in GSH levels was significantly higher in subjects with a BMI of 25-29.9 kg/m^2 (WMD: 51.97 μmol/L, 95% CI: 23.76, 80.19) *versus* subjects with a BMI outside of this range (Supplementary Figure 3.3). The sensitivity analysis revealed that no study had a significant impact on the overall effect sizes in terms of GSH (Supplementary Figure 3.7). The assessment of the publication bias by the visual inspection of the funnel plot provided evidence of publication bias in the meta-analysis of probiotic/synbiotic supplementation on GSH (P = 0.001) (Supplementary Figure 3.8). Therefore, we applied the meta trim-and-fill method to identify which study was responsible for this bias, but we discovered none of the studies lead to this bias.

Malondialdehyde (MDA)

In total, MDA levels were assessed as an outcome measure in 1361 participants recruited for 26 studies (cases = 679 controls = 682). The overall results from the random-effects model indicated that probiotic/synbiotic administration resulted in a significant change in MDA levels (WMD: −0.45 μmol/L, 95% CI: −0.58,-0.32 P < 0.001; I^2 = 76.9%)

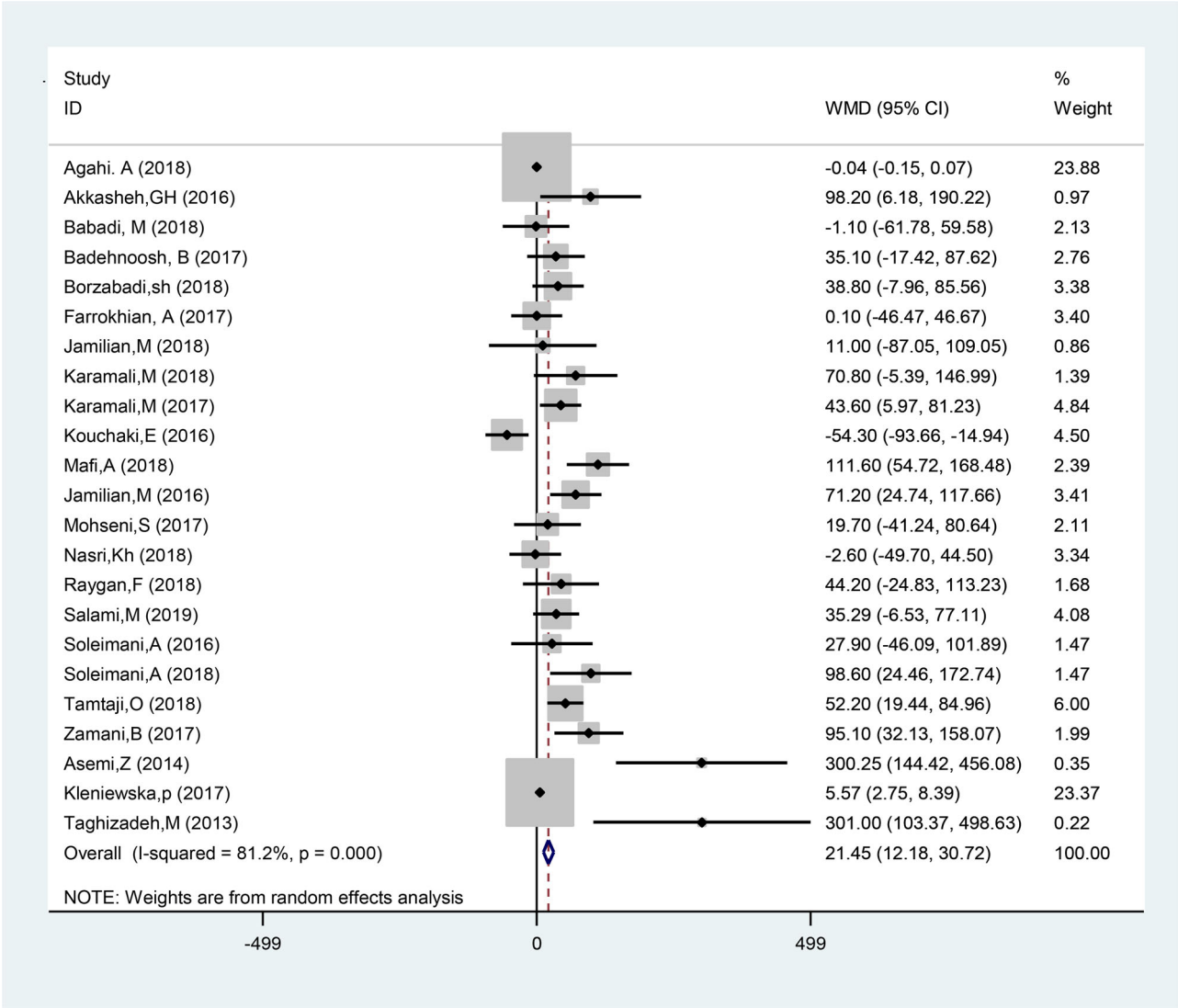

Figure 3. Forest plot of randomized controlled trials investigating the effects of of probiotic/ synbiotic on serum GSH.

(Figure 4). We identified the study population as a source of heterogeneity. The sensitivity analysis indicated that no study had a significant impact on the overall effect sizes in terms of MDA (Supplementary Figure 4.7). The assessment of the publication bias by the visual inspection of the funnel plot provided evidence of publication bias in the meta-analysis regarding the effect of probiotic/synbiotic supplementation on MDA levels ($P < 0.001$) (Supplementary Figure 4.8). Therefore, we applied the meta trim-and-fill method which found no studies responsible for the bias.

Nitric oxide (NO)

A total of 18 studies, including 1006 participants (case = 505 and control = 501), investigated the effects of probiotic/ synbiotic supplementation on NO levels. The pooled results from the random-effects model indicated that NO levels increased significantly after the intervention (WMD: 3.54 μmol/L, 95% CI: 1.73, 5.34, $P < 0.001$; $I^2 = 82.5\%$) (Figure 5). The study population, gender and duration of intervention were identified as potential sources of heterogeneity. The subgroup analyzes displayed that NO increased in diabetes (WMD: 5.67 μmol/L, 95% CI: 2.75, 8.58), healthy pregnancy (WMD: 11.50 μmol/L, 95% CI: 7.25, 15.75) and rheumatoid arthritis (WMD: 3.40 μmol/L, 95% CI: 1.03, 5.77) in a significant manner *versus* other conditions (Supplementary Figure 5.1). Moreover, the elevation in NO was significant when the intervention lasted >8 weeks (WMD: 4.55 μmol/L, 95% CI: 1.62, 7.49) versus <=8 weeks (Supplementary Figure 5.5). The sensitivity analysis indicated that no study had a significant impact on the overall effect sizes in terms of NO (Supplementary Figure 5.7). The assessment of the publication bias by the visual inspection of the funnel plot did not show any evidence of publication bias in the meta-analysis evaluating the effects of probiotic/ synbiotic supplementation on NO levels ($P = 0.43$) (Supplementary Figure 5.8).

Disscusion

The aim of this meta-analysis was to evaluate the effects probiotic/synbiotic supplementation on the serum levels of some antioxidant and oxidative factors in adults. The results

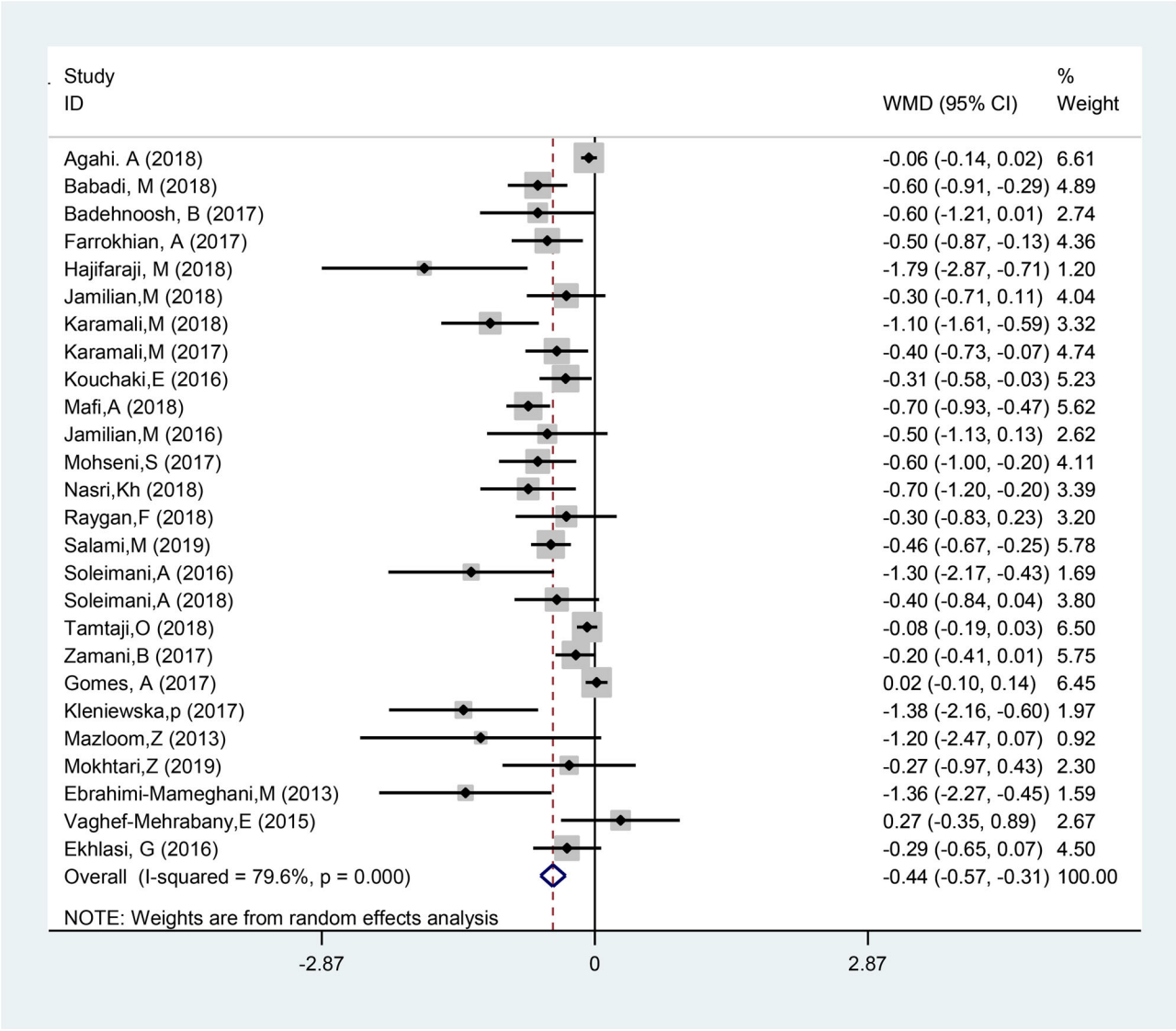

Figure 4. Forest plot of randomized controlled trials investigating the effects of of probiotic/ synbiotic on serum MDA.

of this study showed a significant increase in the serum levels of TAC, GSH and NO, as well as a significant decrease in MDA levels following probiotic/synbiotic supplementation. Based on our investigation, several meta-analyzes have previously investigated the effects of probiotics/synbiotics on serum oxidative and antioxidant factors. However, these reports have produced inconsistent results and, thus, failed to reach a final conclusion. Similarly to our findings, Heshmati et al. found a significant increase in TAC, GSH (0.44 μmol/L), and NO (0.57 μmol/L) and a significant decrease in MDA (−0.45 μmol/L) (Heshmati et al. 2018). However, this study was performed in children and adults taking fortified probiotic/synbiotic supplements and also evaluated studies which investigated the effects of probiotics in association with other antioxidants. In this respect, the aforementioned paper had a different methodology in comparison to the one described in our meta-analysis.

Moreover, Zheng et al. also observed a significant decrease in MDA and an increase in TAC, NO and GSH following the intake of probiotics/synbiotics, confirming our findings (Zheng et al. 2019). However, in the aforementioned research, the subjects were given foods fortified with probiotic/synbiotic supplements and, in addition, the study population was different than ours, since they recruited only diabetic patients. However, there are reports that this hypothesis. For example, Roshan et al. showed that probiotics could significantly increase GSH levels without exhibiting a significant effect on TAC (Roshan et al. 2019). A possible reason for this finding is that they analyzed research papers that included both probiotic/synbiotic supplements and fortified foods which might have led to this effect on TAC levels. In another study, Zamani et al. observed that probiotic supplementation significantly increased TAC and reduced MDA levels, but had no significant effect on GSH levels (Zamani et al. 2020). This interesting effect on GSH levels might have derived from the gender of the participants included in the meta-analysis. The manuscript mentioned above, in which probiotics did not increase GSH levels, included subjects of both sexes. Interestingly, in our gender subgroup analysis regarding the effects of probiotics/

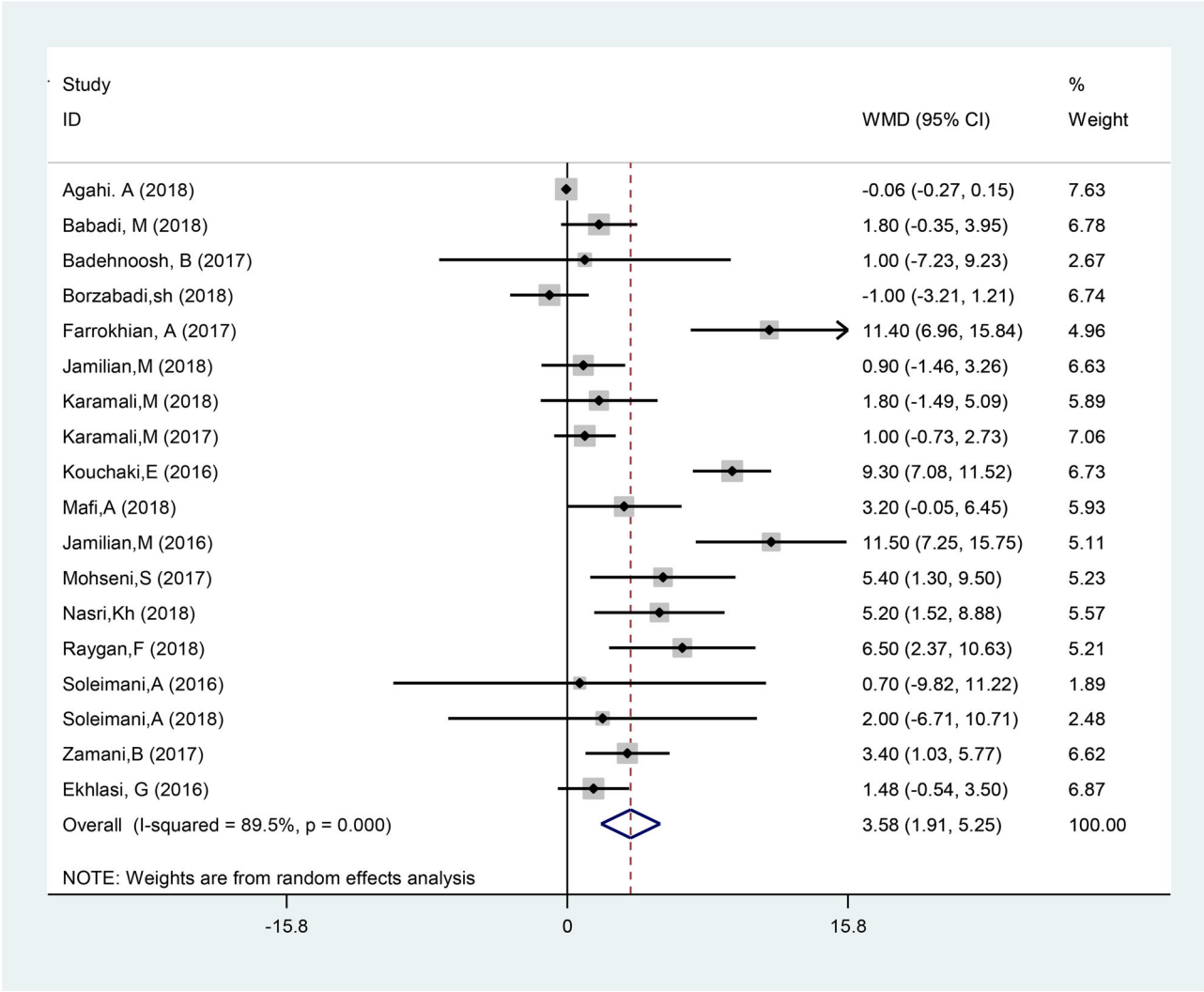

Figure 5. Forest plot of randomized controlled trials investigating the effects of probiotic/ synbiotic on serum NO.

synbiotics on GSH levels, these molecules significantly caused an increase in GSH levels in females rather than males. Also, the high heterogeneity seen in this study (Zamani et al. 2020), in addition to the lack of subgroup analyses, have affected the accuracy and generalizability of the results. Moreover, in a recent report, Ghaderi et al. detected that probiotic supplementation improved TAC and MDA levels (Ghaderi et al. 2019). However, since they administered the supplement in combination with vitamin D and, thus, the action of probiotics was not evaluated separately, it is difficult to extrapolate their findings.

The antioxidant properties of probiotics have been explored for a long time and continue to spark interest for researchers, mostly due to their safe administration and potential therapeutic benefits (Mishra et al. 2015). Different probiotic bacteria strains could exert antioxidant effects and increase TAC by a myriad of possibilities, with several suggested mechanisms including: 1. Probiotics capture metal ions (ferrous and cupric ions) and prevent metal ions from catalyzing oxidation processes; 2. Probiotics make use of their own antioxidant enzymatic systems (superoxide dismutase and catalase) or stimulate the antioxidant system of the host; 3. Probiotics produce various metabolites with antioxidant properties, e.g. GSH, butyrate and folate; 4. Probiotics protect against oxidative stress *via* regulation of the Nrf2-Keap1-ARE, mitogen activated protein kinase (MAPK), nuclear factor kB (NF-kB) and protein kinase C (PKC) pathways; 5. Probiotics also regulate the enzymes responsible for the production of ROS, e.g. they decrease the activity of the NADPH oxidase (NOX), decrease the expression of cyclooxygenase (COX) and lower the activity of cytochrome P450 (CYP) enzymes; 6. Probiotics regulate the composition of intestinal microbiota and inhibit the excessive proliferation of harmful bacteria which may contribute to a reduction in oxidative stress levels in the body (Wang et al. 2017). Moreover, it seems that probiotics can increase GSH levels by inducing its synthesis or secretion. In particular, strains such as *L. fermentum*, *Lactobacillus reuteri*, *Bifidobacterium* and *Lactococcus* have been reported to partake in the release of GSH from the tissues. In addition, probiotics can produce short chain fatty acids (SCFAs), particularly butyrate, which could be involved in the

production of NADPH production for the synthesis of GSH (Roshan et al. 2019). Additionally, the reported effect of synbiotics/probiotics supplementation on pre-inflammatory cytokines, the reduction of the expression of oxidative stress-related genes and of the Toll-like receptor (TLR) pathway might be linked to their properties of increasing serum GSH levels (Heshmati et al. 2018).

MDA is a metabolite extensively employed as an indicator of lipid peroxidation (Kleniewska and Pawliczak 2017). The effect of probiotics/synbiotics in decreasing MDA levels might be linked to changes in the serum lipid profile, since there are reports in which the properties of probiotics to improve the lipid profile have been hypothesized (Zamani et al. 2020). Intestinal lactobacilli may lower serum cholesterol levels by incorporating cholesterol within the cell membrane to prevent the formation of intestinal cholesterol micelles as well as the uptake of cholesterol by growing cells, and the production of bile salt hydrolase (BSH) that catalyzes the hydrolysis of conjugated bile salts to free bile acids (Zhuang et al. 2012; St-Onge, Farnworth, and Jones 2000). Also, the benefits of supplementation with probiotics and synbiotics can improve the NO status of the body *via* various mechanisms, many of which are still debated (Heshmati et al. 2018). A great deal of studies has suggested that probiotics and synbiotics can improve the endothelial function by modulating the intestinal microbiota and subsequently reducing the generation of ROS and increasing NO bioavailability (Vasquez et al. 2019).

The subgroup analyzes showed that the intake of probiotics/synbiotics caused a significant increase in TAC in females rather than in males. Moreover, there was a significant elevation in TAC and NO in subjects aged $<=50$ years versus those aged >50 years. In addition, participants with a BMI between 25 and 29.9 kg/m^2 benefited from a significant increase in TAC and GSH levels. Furthermore, the increase in NO levels was also significant in patients with a calculated BMI of 25–29.9 kg/m^2 and 30-34.9 kg/m^2 and when the intervention lasted >8 weeks. Finally, the subgroup analysis showed a significant increase in NO levels when synbiotics rather than probiotics were employed.

Since most of the studies in our meta-analysis used probiotics with a concentration of 10^9 CFU, whereas some papers employed a different dose (Mazloom, Yousefinejad, and Dabbaghmanesh 2013; Mokhtari et al. 2019; Asemi et al. 2013), we were unable to perform a subgroup analysis on this matter as to clarify the effect of different dosages. Finally, we were unable to perform a subgroup analysis for the probiotic strains due to the relatively large variety of probiotics used in the included reports.

The present study has several strengths. Firstly, there were no time or language limitations for the inclusion of the studies that investigated the effects of probiotic/synbiotic supplementation on serum oxidative and antioxidant factors. Secondly, the number of studies and the study populations evaluated in our meta-analysis were relatively large and the duration of the interventions were also acceptable for all the studies except one (Ebrahimi-Mameghani et al. 2013) which had a duration of 1 week. Thirdly, the effects of probiotics/synbiotics might have been influenced by the participants' diets and their physical activities. As for the studies we analyzed, the participants were asked not to change their regular diet and physical activity prior to the beginning of the study. However, there are some limitations to this meta-analysis as well. Firstly, we analyzed both cross-over and parallel studies which were different in terms of methods and biases. However, there was only one cross-over study (Asemi et al. 2014). Secondly, in three studies (Mohseni et al. 2018; Asemi et al. 2014; Gomes et al. 2017), the patients in both groups were using antibiotics, and in eight studies (Raygan, Rezavandi, et al. 2018; Soleimani et al. 2017; Zamani et al. 2017; Mokhtari et al. 2019; Vaghef-Mehrabany et al. 2016; Ekhlasi et al. 2017; Asemi et al. 2013; Hajifaraji et al. 2018), the patients were not taking antibiotics. Unfortunately, since most of the studies did not mention whether the subjects were taking antibiotics or not, it was not possible to perform a subgroup analysis in this area either. Thirdly, in the study conducted by Gomes et al. the patients were given probiotics and followed an isocaloric diet (Gomes et al. 2017). However, since the diet was prescribed both to the intervention and control group, we included this report in our meta-analysis, but it was not feasible to perform a subgroup analysis between the studies which did not include an isocaloric diet and this study. Finally, given that most of the studies included in our meta-analysis have been conducted in Iran, it appears that the results can be only applicable to the Asian population and may increase the possibility of a selection bias. In this respect, the generalizability of the results to Eastern populations and other communities is still questionable and more research is needed in this area.

Conclusion

The results of our meta-analysis show that probiotic/synbiotic supplementation can significantly increase serum TAC, GSH and NO, as well as reduce MDA levels in adults. In addition, the results of this analysis showed a significant increase in TAC and NO in subjects aged ≤ 50 years versus subjects aged >50 years. In the participants with a BMI of 25–29.9 kg/m^2, TAC, NO and GSH levels significantly increased *versus* subjects with other BMI ranges. In addition, the increase in NO levels was also significant when the intervention exceeded 8 weeks. Therefore, probiotic/synbiotic supplementation might be effective in reducing oxidative stress levels and thus preventing or ameliorating diabetes, cardiovascular disease, cancer and other chronic diseases. However, for accuracy and a higher generalizability of the results, future investigations, with larger sample sizes, different populations (including healthy subjects), doses and probiotic strains are required in order to clarify the effect of probiotic/synbiotic supplementation on oxidative stress biomarkers.

Acknowledgments

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Disclosure statement

All authors have no conflicts of interest to declare.

Authors' contributions

F.S.H. and B.P. conceived the study and designed the search strategy; B.P. and S.F. conducted the study selection; B.P. and S.F. conducted data extraction; B.P. and F.S.H. evaluated the risk of bias of included studies; S.F. and F.S.H. conducted the data analysis and interpretation of results; B.P. wrote the first draft of the manuscript; F.S.H. and M.-A.G. and M.H.S. revised the manuscript. All authors read and approved the final version of the manuscript.

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