# Journal Pre-proof


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Omid Reza Tamtaji, Alireza Milajerdi, Željko Reiner, Zatollah Asemi, Ehsan Dadgostar, Reza Heidari-Soureshjani, Peyman Mamsharifi, Elaheh Amirani, Hamed Mirzaei, Jamal Hallajzadeh, Amir Ghaderi

PII: S0965-2299(20)30508-2

DOI: https://doi.org/10.1016/j.ctim.2020.102507

Reference: YCTIM 102507

To appear in: *Complementary Therapies in Medicine*

Received Date: 9 March 2020

Revised Date: 8 July 2020

Accepted Date: 8 July 2020

Please cite this article as: { doi: https://doi.org/

# A systematic review and meta-analysis: The effects of probiotic supplementation on metabolic profile in patients with neurological disorders

Omid Reza Tamtaji[1] tamtaji@gmail.com, Alireza Milajerdi[2] Alimila66@gmail.com, Željko Reiner[3] zeljko.reiner@kbc-zagreb.hr, Zatollah Asemi[1] Asemi_r@yahoo.com, Ehsan Dadgostar[4] dadghostar.eh@yahoo.com, Reza Heidari-Soureshjani[5] Heidari.r@yahoo.com, Peyman Mamsharifi[6] Peymanmamsharifi@gmail.com, Elaheh Amirani[1] elahe.amirani@rocketmail.com, Hamed Mirzaei[1] h.mirzaei2002@gmail.com, Jamal Hallajzadeh[7]† jamal.hallaj@yahoo.com, Amir Ghaderi[*8, 9] gaderiam@gmail.com

[1] *Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, I.R. Iran*

[2] *Students' Scientific Research Center, Tehran University of Medical Sciences, Tehran, Iran; Department of Community Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran*

[3] *Department of Internal Medicine, University Hospital Centre Zagreb, School of Medicine, University of Zagreb, Zagreb, Croatia*

[4] *Halal Research Center of IRI, FDA, Tehran, Iran*

[5] *Student Research Committee, Shahrekord University of Medical Sciences, Shahrekord, Iran*

[6] *Department of Psychology, Allameh Tabataba'i University, Tehran, Iran*

[7] *Department of Biochemistry and Nutrition, Research Center for Evidence-Based Health Management, Maragheh University of Medical Sciences, Maragheh, Iran*

[8] *Department of Addiction studies, School of Medical, Kashan University of Medical Sciences, Kashan, Iran*

[9] *Clinical Research Development Unit-Matini/Kargarnejad Hospital, Kashan University of Medical Sciences, Kashan, Iran*

**Running Title:** Probiotic and neurological disorders

* Corresponding Author. Amir Ghaderi, PhD. Tel: +98-31-55463378; E-mail addresses: gaderiam@gmail.com (A.Ghaderi).

† Co-correspondence: Jamal Hallajzadeh, PhD. Research Center for Evidence-Based Health Management, Maragheh University of Medical Sciences, Maragheh, Iran, E-mail addresses: jamal.hallaj@yahoo.com.

**Number of words (Text): 1954**

**Number of words (Abstract): 238**

**Number of Tables: 3**

**Number of Figures: 2**

**Highlights**

- Probiotic supplementation on metabolic status in patients with neurological disorders was evaluated.
- Probiotic supplementation improved CRP, MDA, insulin and HOMA-IR.
- Probiotic supplementation decreased triglycerides and VLDL-cholesterol, and HDL-cholesterol levels increased.
- Further trials are needed to recruit more participants, and to evaluate the long-term efficacy and safety of probiotic in management of patients with neurological disorders.

**Abstract**

**Background and objective:** The objective of meta-analysis of randomized controlled trials (RCTs) was to evaluate the effects of probiotic supplementation on metabolic status in patients with neurological disorders.

**Methods:** The following databases were search up to April 2019: MEDLINE, EMBASE, Web of Science, and Cochrane Central Register of Controlled Trials. The quality of the relevant extracted data was assessed according to the Cochrane risk of bias tool. Data were pooled by the use of the inverse variance method and expressed as mean difference with 95% Confidence Intervals (95% CI).

**Results:** Nine studies were included in this meta-analysis. The findings suggested that probiotic supplementation resulted in a significant reduction in C-reactive protein (CRP) [Weighted Mean Difference (WMD): -1.06; 95% CI: -1.80, -0.32] and malondialdehyde (MDA) levels (WMD: -0.32; 95% CI: -0.46, -0.18). Supplementation with probiotics also significantly reduced insulin (WMD: -3.02; 95% CI: -3.88, -2.15) and homeostatic model assessment for insulin resistance (HOMA-IR) (WMD: -0.71; 95% CI: -0.89, -0.52). Probiotics significantly reduced triglycerides (WMD: -18.38; 95% CI: -25.50, -11.26) and VLDL-cholesterol (WMD: -3.16; 95% CI: -4.53, -1.79), while they increased HDL-cholesterol levels (WMD: 1.52; 95% CI: 0.29, 2.75).

**Conclusion:** This meta-analysis demonstrated that taking probiotic by patients with neurological disorders had beneficial effects on CRP, MDA, insulin, HOMA-IR, triglycerides, VLDL-cholesterol and HDL-cholesterol levels, but did not affect other metabolic parameters.

**Keywords:** Probiotic supplementation, inflammation, oxidative stress, neurological disorders, meta-analysis

## Introduction

Neurological disorders, particularly Alzheimer's disease (AD), Parkinson's disease (PD), multiple sclerosis (MS) and migraine, are very common diseases worldwide [1]. Neurological disorders are one of the important cause of disability and death as well. The burden of neurological disorders has increased during the past 25 years because of increased population size and its ageing [2]. Increased inflammatory markers and oxidative stress, dyslipidemia and impaired glucose metabolism are important components of neurological disorders pathophysiology [3-5]. Current estimates show that neurological diseases will account for 12% of global disability-adjusted life year in 2030 [6].

The gut microbiota is a population of microorganisms that inhabits the gut. It influences different aspects of host physiology, including central nervous system (CNS) and immune system [7]. Intestinal microbes are involved in the regulation of brain function and behavior through modulation of multiple neurochemical and neurometabolic pathways [8, 9]. Based on the preliminary research, microbiota might be clinical biomarker of some neurological disorders , disease activity and phenotype variability [10]. Probiotics are non-pathogenic microorganisms which can interact with the gut microbiota and induce beneficial effects [11, 12] on neurological disorders through modulation of oxidative stress, inflammation and apoptosis [13, 14]. Several pre-clinical and clinical studies have indicated a promising effect of probiotics supplementation on biomarkers of inflammation, oxidative stress, serum lipoproteins and glycemic control in patients with some neurological disorders. In a study by Lavasani et al.[15], administration of probiotic had beneficial effects in an animal model of MS mediated by an interleukin-10 (IL-10)-dependent mechanism producing regulatory T cells. In a randomized clinical trial (RCT) probiotic supplementation for 12 weks in patients with PD decreased C-reactive protein (CRP),

malondialdehyde (MDA), insulin levels and insulin resistance, and enhanced insulin sensitivity and glutathione (GSH) levels, but did not affect total antioxidant capacity (TAC), fasting plasma glucose (FPG) and nitric oxide (NO) [16]. Martami et al.[17] showed that probiotic supplementation for 10 weeks in patients with migraine has improved migraine headache in both chronic and episodic migraines, but did not improve their inflammatory status.

Several meta-analyses have evaluated the effects of probiotics supplementation on oxidative stress and inflammatory markers in different diseases. Recently, a meta-analysis showed that probiotic and synbiotic supplementation in patients with diabetes significantly increased NO, and reduced CRP and tumor necrosis factor-α (TNF-α), while interleukin-6 (IL-6) concentrations remained unchanged [18]. Wang et al.[19] demonstrated that in overweight/obesity subjects probiotics significantly improved FPG, insulin, HOMA-IR, total cholesterol and LDL-cholesterol levels, while other lipoproteins were unchanged. Another meta-analysis by Roshan et al.[20] found that probiotic and synbiotic supplementation increased GSH levels, but did not affect TAC and superoxide dismutase (SOD) levels. The differences in design of the studies, patients' characteristics, the dosage and type of probiotics, as well as the duration of intervention might explain the discrepancies between the results of published trials. This meta-analysis was performed to analyze the available evidence based upon RCTs and to clarify the effects of probiotics supplementation on markers of inflammation and oxidative stress, serum lipoproteins and glycemic control in patients with some neurological disorders.

**Methods**

The present study was based upon the Preferred Reporting Items of Systematic Reviews and Meta-Analysis (PRISMA) statement guideline for performing and reporting [21].

**Search strategy**

Eligible RCTs were identified using Cochrane Library, Embase, Medline, and Web of Science databases for relevant articles published from inception until April 2019, and by manually searching the reference list of the articles. Databases of International Standard Randomized Controlled Trial Number Register and Meta-register for RCTs were also searched for all ongoing trials. Studies were taken into consideration which evaluated the impact of probiotic and/or symbiotic supplementation on parameters of mental health, and biomarkers of inflammation and oxidative stress by using the following MeSH and text words: patients ["neurological disorder" OR "nervous system disorder" OR "Alzheimer's disease" OR "Parkinson disease" OR "multiple sclerosis" OR "migraine"], intervention [("probiotic and/or synbiotic" OR "symbiotic" AND "supplementation" OR "intake")], and outcomes ["IL-6" OR "IL-10" OR "TNF-α" OR "CRP" OR "nitric oxide (NO)" OR "malondialdehyde (MDA)" OR "total antioxidant capacity (TAC)" OR "glutathione (GSH)" OR "FPG" OR "insulin" OR "HOMA-IR" OR "quantitative insulin-sensitivity check index (QUICKI)" OR "triglycerides (TG)" OR "VLDL-cholesterol (VLDL-C)" OR "total cholesterol (TC)" OR "LDL-cholesterol (LDL-C)" OR "HDL-cholesterol (HDL-C)"]. Additional manual searches including reference lists of related studies. They were performed to increase sensitivity of search strategy. Studies included in this meta-analysis had to fulfill the following criteria: 1) original trials, 2) trials on humans, 3) intervention and control groups had to receive probiotic and/or symbiotic supplementation, and placebo, respectively and 4) the trials had

to report mean changes or mean difference of body composition and/or metabolic profiles with standard deviation (SD) for the intervention and control groups.

**Data extraction and quality assessment**

Two authors (O-RT and ED) independently extracted the data and assessed its quality using standard forms and the Cochrane Collaboration risk of bias tool [22, 23]. This tool is based on information on the following domains: randomization generation, allocation concealment, blinding of subjects and outcome assessment, incomplete outcome data, and selective outcome reporting, and other sources of bias. When there was disagreement between these two authors, it was resolved by third author (ZA). The data from eligible studies were abstracted: 1) first authors' name 2) publication year 3) metabolic profiles of study participants and associated measures of variance 4) study location 5) number of subjects in the intervention and control groups 6) study design 7) duration of the intervention.

**Data analysis**

**Heterogeneity and publication biases**

The statistical heterogeneity of the results of included studies was tested using chi-square test [24], and quantified by the $I^2$ statistic [25]. Publication bias was assessed by the funnel plot and tested for statistical significance using the Egger's test [26].

**Summary measures**

We calculated the mean difference for the effects of probiotic supplementation on metabolic status for each included study. The change score approach was used to obtain the effect sizes, because

the correlations between baseline and end measurements were more than 1/2 [27]. A meta-analysis was performed to obtain the summary measures for the effect of probiotic supplementation on metabolic status using the inverse variance method. The random effects model was used to report the pooled mean difference with 95 % confidence interval (CI). P-values <0.05 were considered as statistically significant. Statistical analyses were performed using both Stata version 11.0 (Stata Corp., College Station, TX) and Review Manager 5.3.

## Results

### Study characteristics

Flow diagram of study selection for this systematic review and meta-analysis is shown in **Fig.1.** 9 studies met the inclusion criteria and were included in this study. Summarized characteristics of these studies are presented in **Table 1**. These studies were published between 2016 and 2019. A total of 511 subjects, 261 persons in intervention group, participated in these studies. Mean age of the participants was 58 years. All studies used probiotic capsules containing different types of bacteria. Duration of taking the probiotics varied from 8 to 16 weeks. Markers of inflammation, oxidative stress, glycemic control and serum lipoproteins were measured as the outcome.

### The effect of probiotic supplementation on markers related to inflammation

Pooling 8 effect sizes from 7 studies, a significant reduction in CRP concentrations following probiotic supplementation was found (WMD: -1.06; 95% CI: -1.80, -0.32) (**Table 2 & Fig.2A**). This finding remained unchanged in all subgroups, except for studies with a sample size of ≤50 subjects, in which no significant difference was found (WMD: -0.29; 95% CI: -0.65, 0.06) (**Table 3**). Probiotic supplementation had no significant effect on TNF-α (WMD: -0.60; 95% CI: -1.42,

0.22) and IL-6 levels (WMD: -0.11; 95% CI: -0.36, 0.15), as found in meta-analysis of 4 studies (with 5 effect sizes) and 3 studies, respectively **(Table 2 & Fig.2B & Fig.2C).** Meta-analysis of 3 studies analyzing the effects of probiotics on IL-10 concentrations, failed to find any statistically significant effects (WMD: 0.08; 95% CI: -0.33, 0.50) (Table 2 & **Fig.2D)**.

Combining data from the same studies for the effects of probiotic supplementation on NO concentrations resulted a non-significant change (WMD: 0.84; 95% CI: -1.52, 3.20) **(Table 2 & Fig.2E).** This finding was also non-significant in all subgroups, except for studies on patients aged <45 years, in which a significant increase in this marker after intake of probiotics was seen (WMD: 5.52; 95% CI: 2.91, 8.12) **(Table 3).**

**The effect of probiotic supplementation on oxidative stress**

Meta-analysis of 6 studies on TAC, failed to find any statistically significant effects of probiotics (WMD: 5.45; 95% CI: -36.59, 47.49) **(Table 2 & Fig.2F).** Subgroup analysis was done for the effects of probiotics on TAC, but it did not change this result, although, a significant increase in TAC after probiotic supplementation was seen in studies with a sample size of >50 (WMD: 21.31; 95% CI: 4.66, 37.95) **(Table 3).** Combining findings from 7 studies, no significant effect of probiotic supplementation on GSH concentrations was found (WMD: 30.85; 95% CI: -1.60, 63.29) **(Table 2 & Fig.2J).** Although similar findings were seen in some subgroups, stratification showed a significant elevation of GSH levels in studies on those aged <45 years (WMD: 23.48; 95% CI: -12.40, 59.35), studies on patients with neuromuscular disorders (WMD: 38.96; 95% CI: 22.32, 55.60), and studies with both ≤50 (WMD: 23.82; 95% CI: 5.23, 42.41) or >50 (WMD: 50.17; 95% CI: 28.04, 72.30) participants **(Table 3).** A significant reduction in MDA levels was also seen in

6 studies after supplementation with probiotics (WMD: -0.32; 95% CI: -0.46, -0.18) **(Table 2 & Fig.2H)**. This did not change in the subgroup analyses **(Table 3).**

**The effect of probiotic supplementation on glycemic control**

The pooled analysis of data from 5 studies showed no significant effect of probiotic supplementation on FPG concentrations (WMD: -1.68; 95% CI: -3.75, 0.38) **(Table 2 & Fig.2K).** A significant reduction of FPG was only seen in studies performed on patients aged ≥45 years (WMD: -4.23; 95% CI: -7.89, -0.57) **(Table 3).** Combined analysis of data from 4 and 5 studies, showed a significant effect of probiotics on reducing insulin (WMD: -3.02; 95% CI: -3.88, -2.15) and HOMA-IR (WMD: -0.71; 95% CI: -0.89, -0.52) **(Table 2, Fig.2L & Fig.2M).** A subgroup analysis had no influence on those findings **(Table 3).** Pooling findings from 5 studies, showed a marginally significant increase in QUICKI after intake of probiotics (WMD: 0.07; 95% CI: 0.00, 0.15) **(Table 2 & Fig.2N).** A significant elevation of QUICKI was also seen in all subgroup analyses **(Table 3).**

**The effect of probiotic supplementation on serum lipoproteins**

We combined data from 4 studies evaluating the effects of probiotics on serum concentrations of triglycerides, total cholesterol, LDL-cholesterol, VLDL-cholesterol and HDL-cholesterol. Probiotics supplementation resulted in a significant reduction of triglycerides (WMD: -18.38; 95% CI: -25.50, -11.26) and VLDL-cholesterol (WMD: -3.16; 95% CI: -4.53, -1.79) concentrations, while it increased HDL-cholesterol levels (WMD: 1.52; 95% CI: 0.29, 2.75) **(Table 2, Fig.2O, P and Q).** However, no significant changes were seen in total cholesterol (WMD: -4.41; 95% CI: -10.16, 1.35) or LDL-cholesterol (WMD: -2.27; 95% CI: -7.43, 2.90) concentrations **(Table 2,**

**Fig.2R-S).** A subgroup analysis based on participants' age did not change these findings. However, there was a significant reduction in total cholesterol levels (WMD: -8.83; 95% CI: -17.03, -0.63) and no significant changes in HDL-cholesterol concentrations (WMD: 1.75; 95% CI: -0.61, 4.10) following intake of probiotics in studies done on patients with mental defects **(Table 3).**

## Discussion

In this meta-analysis, for the first time, we pooled data on probiotic supplementation in patients with different neurological disorders. The results of this study showed that probiotic supplementation improved CRP, MDA, insulin, HOMA-IR, triglycerides, VLDL-cholesterol and HDL-cholesterol levels, but did not affect other metabolic parameters.

### Effects on biomarkers of oxidative stress and inflammation

The results of this study showed that probiotic supplementation significantly improved CRP and MDA levels, but did not influence NO, TAC, GSH, IL-6, IL-10 and TNF-α levels. The beneficial effects of probiotics on metabolic profiles in patients with metabolic disorders were already reported [28, 29]. Our previous work indicated that supplementation with probiotics plus selenium during 12 weeks in patients with AD significantly reduced MDA and CRP, but did not change NO, GSH and TAC levels [30]. De Roos et al.[31] showed that probiotic supplementation during 12 weeks in patients with migraine also failed to improve CRP, IL-6, IL-10 and TNF-α levels but they could neither confirm any significant benefit from probiotic supplementation when compared with placebo on the outcome parameters of migraine. Another study also reported that administration of probiotic supplementation did not affect biomarkers of inflammation and oxidative stress in patients with AD [32]. Neurological disorders are characterized by oxidative damage to DNA, proteins and lipids [33]. Oxidative stress also causes neuronal death and neurodegeneration [33].

Therefore, antioxidant therapy might be an appropriate treatment strategy for some neurological disorders [34]. The evidence suggests that antioxidant mechanisms of probiotics may be due to ROS scavenging, the inhibition of ascorbate autoxidation and metal ion chelation [35]. In addition, microglia is activated in some neurological disorders that causes an increased production of cytotoxic factors such as TNF-α, IL-1 and NO [35]. These cytotoxic factors are closely correlated with severity and the progression of neurological disorders [36, 37]. The anti-inflammatory effects of probiotics may occur due to their effects on nuclear factor kappa B pathway and toll-like receptor signaling [38, 39].

**Effects on glycemic control and serum lipoproteins**

The findings of this meta-analysis indicate that probiotic supplementation significantly improved insulin, HOMA-IR, triglycerides, VLDL-cholesterol and HDL-cholesterol but it did not affect total cholesterol, LDL-cholesterol, QUICKI and FPG levels. In a RCT study, a significant decrease in insulin levels and HOMA-IR was seen following probiotic intake during 16 weeks in patients with MS, but probiotics did not influence QUICKI and FPG [40]. In another study, probiotic supplementation during 12 weeks in patients with MS significantly reduced insulin, HOMA-IR and total-/HDL-cholesterol, while it increased QUICKI and HDL-cholesterol levels [41]. Athari Nik Azm et al.[42] reported that administration of probiotic supplements reduced insulin levels and HOMA-IR in an animal model of AD, but these supplements did not change glucose and triglycerides levels. Insulin resistance affects the expression of high-mobility group box 1 protein (HMGB1) and releasing of HMGB1 which increases inflammation by up-regulating toll- like receptor (TLR)- 4- interleukin (IL)- 6 (TLR4-IL-6) pathway [43, 44]. Cholesterol balance in the brain is altered in several neurodegenerative diseases, although no causal link between

dysregulated cholesterol homeostasis and neurodegeneration has been established except the well-known fact that inheritance of the E4 isoform of apolipoprotein E (APOE), a cholesterol-carrying protein, markedly increases the risk of developing AD [45]. Probiotics may modulate serum lipoproteins by increasing cholesterol 7α-hydroxylase and liver X receptor alpha as well as cholesterol 7α-hydroxylase (CYP7α1) enzyme activity. This might be the mechanism by which they reduce total cholesterol and triglycerides, increase the production of short-chain fatty acids and modulate the expression of lipogenic and glucogenic genes for substances such as glucose-6-pohspahtase and glucose transporter type 4 [46, 47]. The difference in type of bacteria used in probiotic supplementation , different design of the studies, and basic clinical characteristics of study populations are some of the possible reasons which could explain discrepant results regarding the effects of probiotics on inflammation, oxidative stress, glycemic control and serum lipoproteins in different studies.

This meta-analysis tried to summarize findings from earlier studies on the effects of supplementation with probiotics on metabolic profiles in patients with neurological disorders. This study has some limitations. Due to the heterogeneity between studies, different duration of probiotics intake, differences in the dosage and frequency of probiotics, the results of this meta-analysis should be interpreted with caution. The number of studies and number of participant's that finally were included in the meta-analysis was low.

**Conclusions**

This meta-analysis demonstrated that taking probiotics by patients with some neurological disorders had beneficial effects on CRP, MDA, insulin, HOMA-IR, TG, VLDL-cholesterol and HDL-cholesterol levels, but did not affect other metabolic parameters.

## Abbreviations

AD, Alzheimer disease; CRP, C-reactive protein; HDL, High-density lipoprotein; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; IL-6, Interleukin-6; IL-10, Interleukin-10; GSH, Glutathione; LDL, low-density lipoprotein; MS, Multiple sclerosis; NO, Nitric oxide; PD, Parkinson disease; TAC, Total antioxidant capacity; TG, Triglyceride; TC, Total cholesterol; TNF-α, Tumor necrosis factor-α

## Declarations

### Acknowledgements

Not applicable.

### Funding

Not applicable.

### Availability of data and material

The primary data for this study is available from the authors on direct request.

### Author contributions

AG and JH contributed in conception, design, statistical analysis and drafting of the manuscript. O-RT, AM, ZA, ED, RH-S, EA, HM, JH contributed in data collection and manuscript drafting and ZR contributed in manuscript drafting. All authors approved the final version for submission. AG supervised the study.

### Ethics approval and consent to participate

Not applicable.

**Consent for publication**

Not applicable.

**Competing interests**

The authors declare no conflict of interest.

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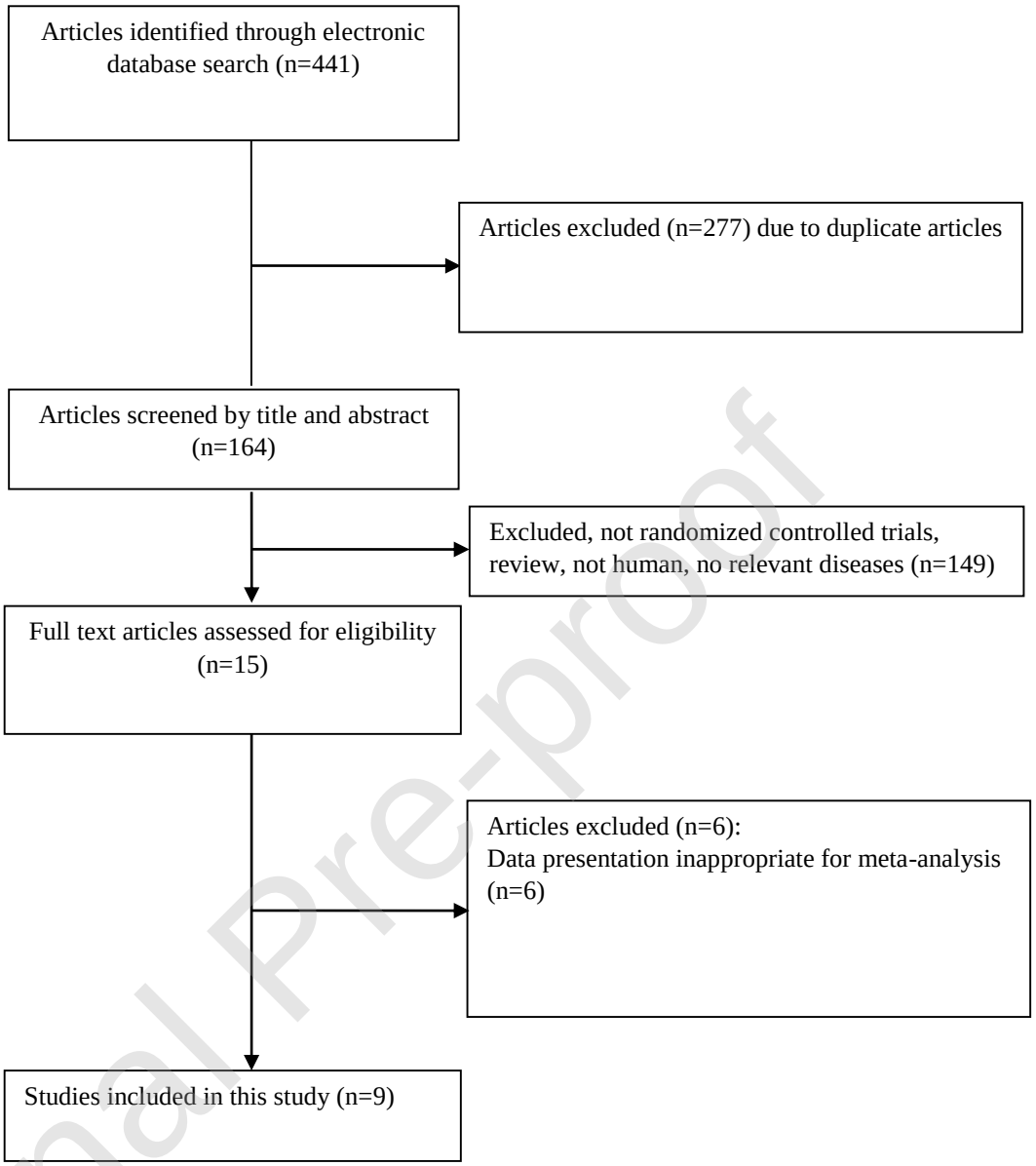
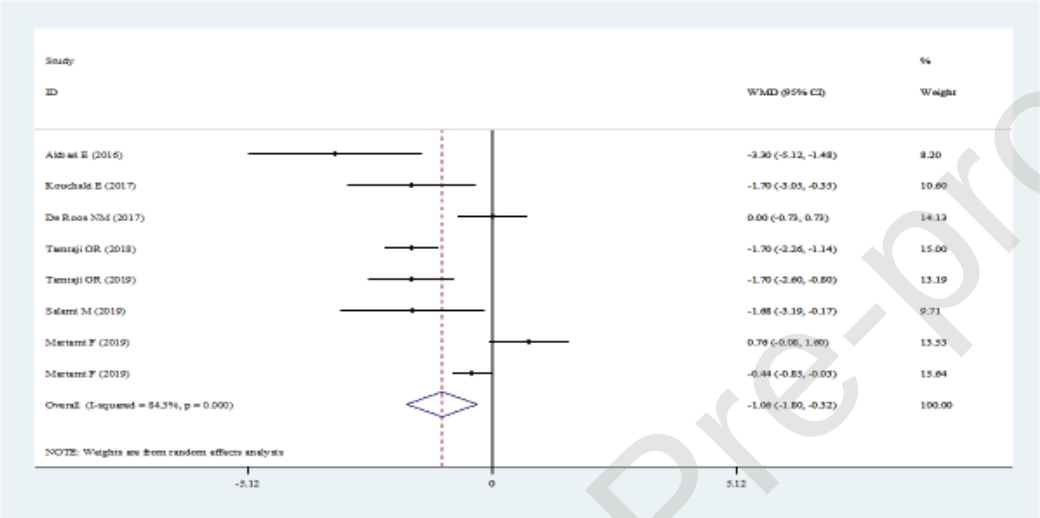
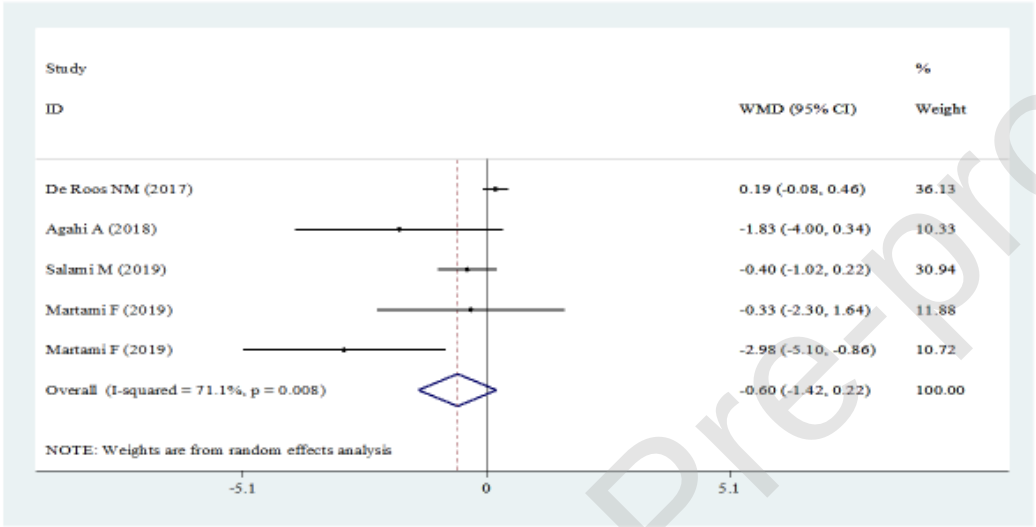



**Fig.1.** Literature search and review flowchart for selection of studies

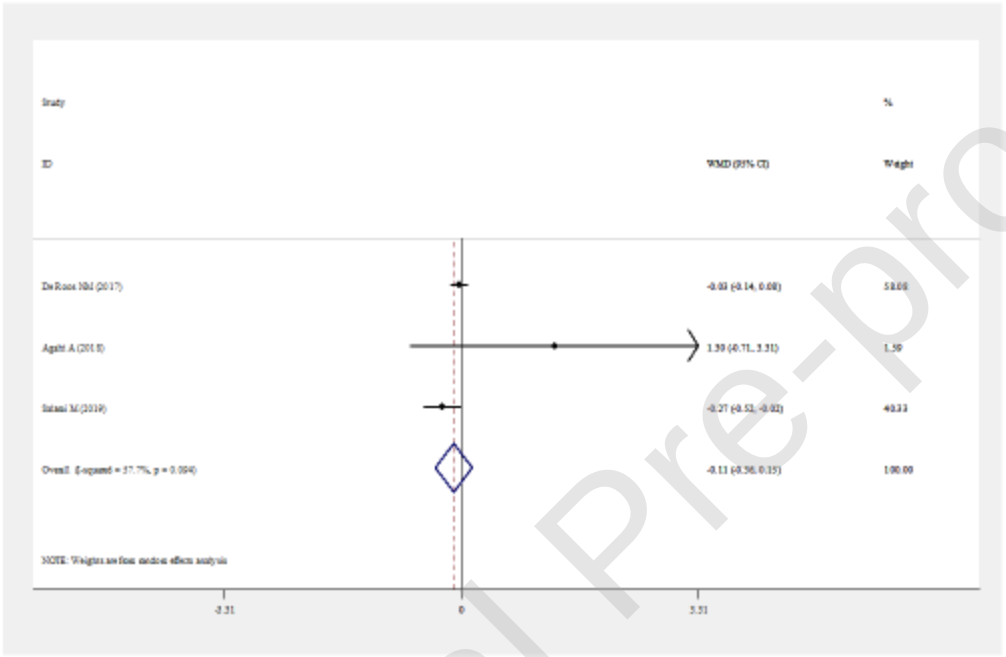
**Fig.2A-S. Meta-analysis biomarkers of inflammation and oxidative stress, glycemic control and serum lipids weighted mean difference estimates in the probiotics supplements and placebo groups (CI=95%).**



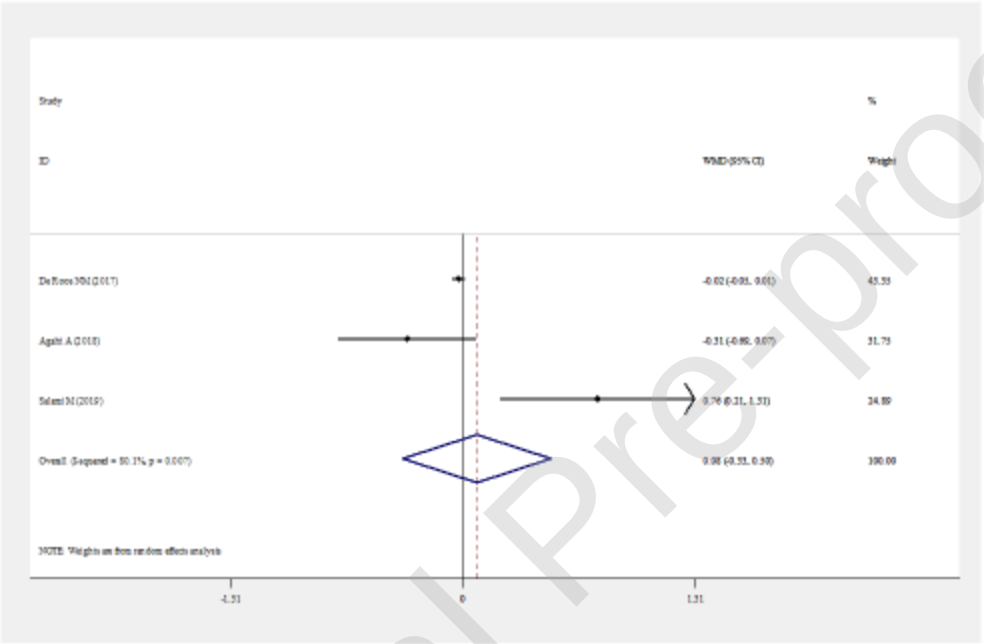

**A: CRP**



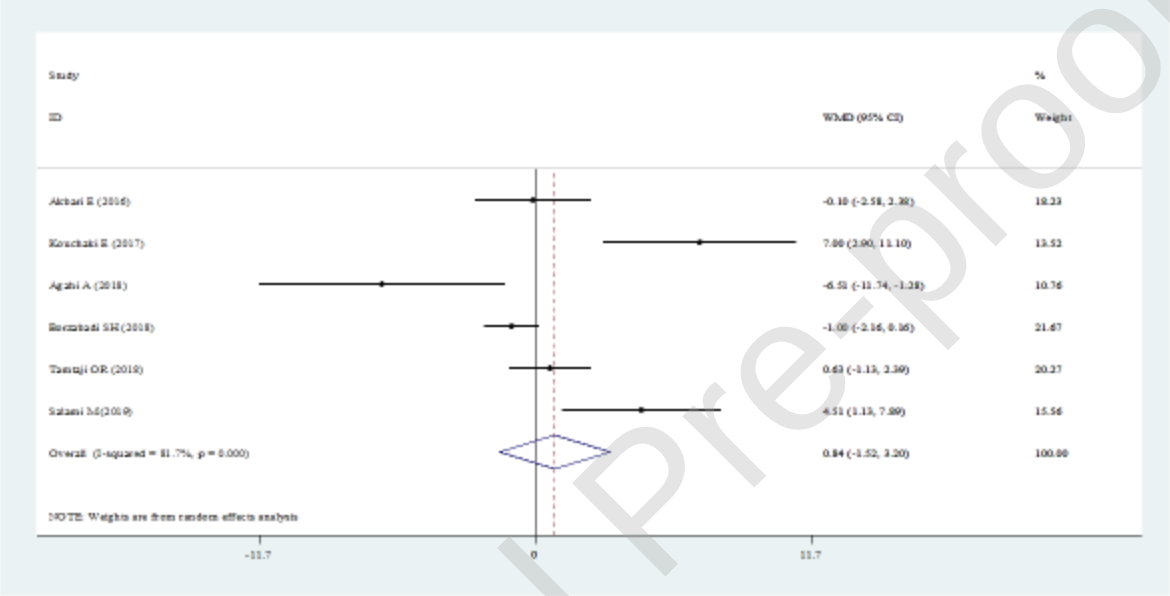

**B: TNF-α**



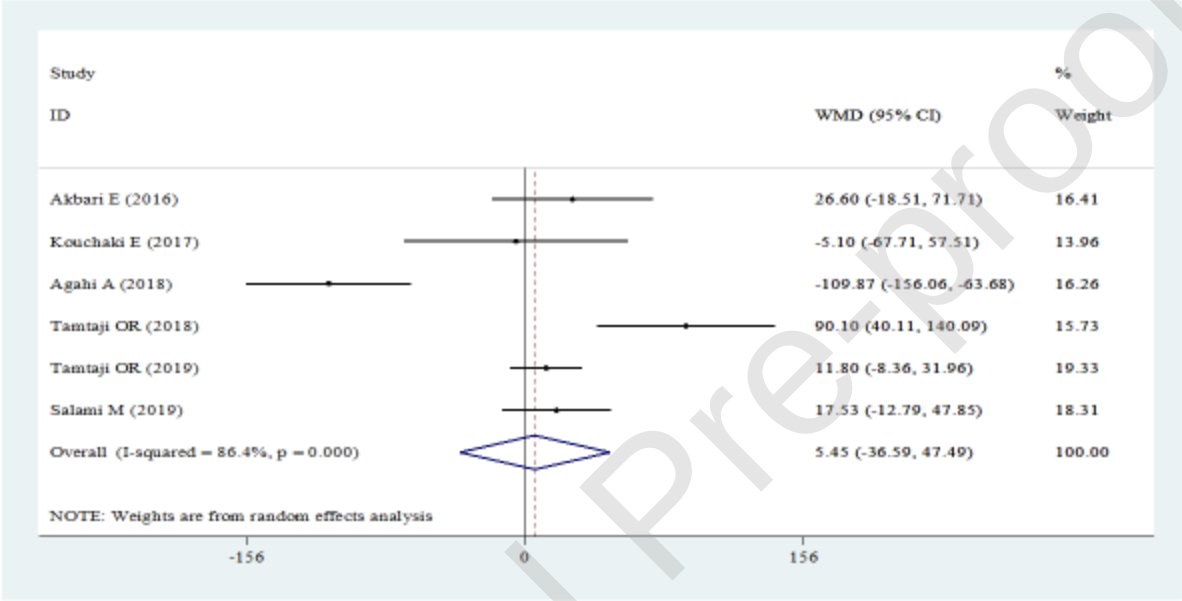

C: IL-6



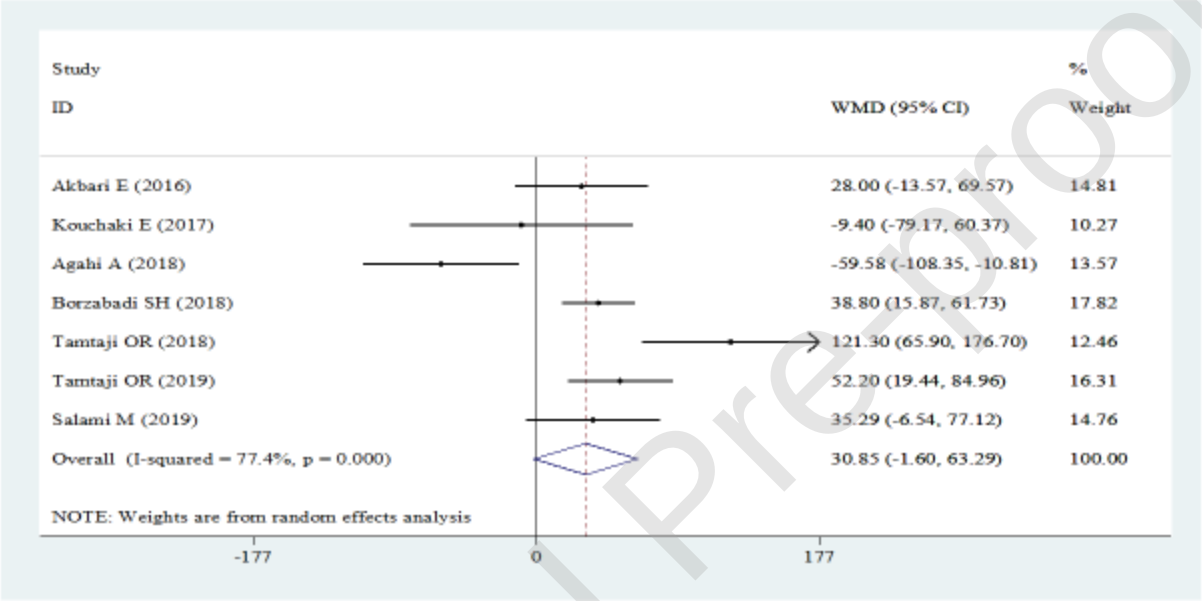

D: IL-10



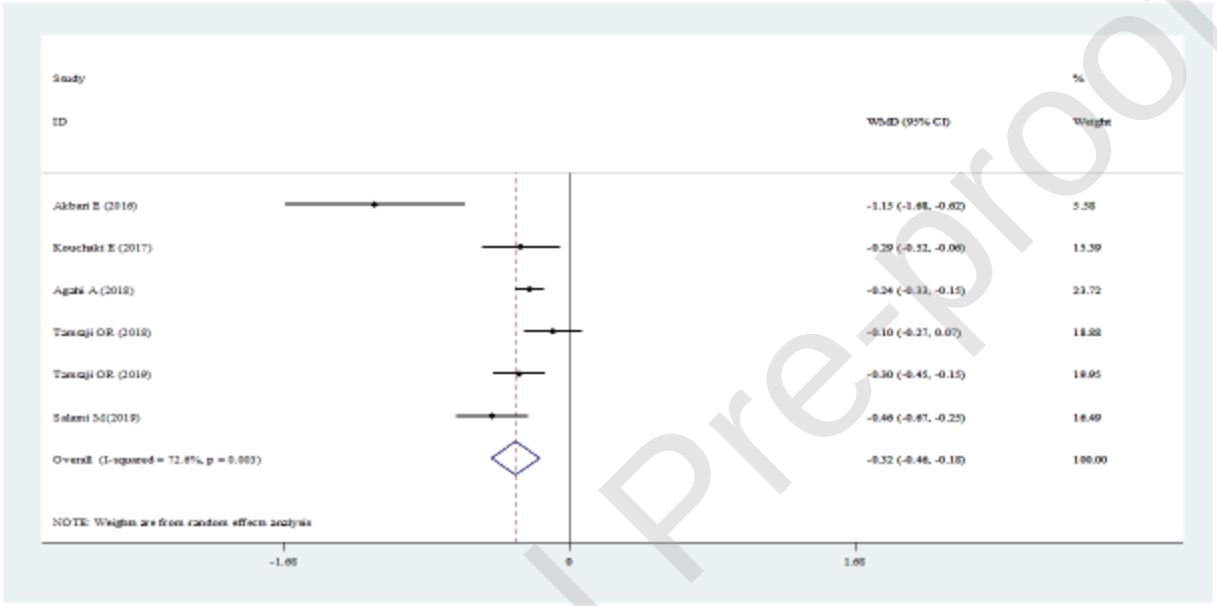

**E: NO**



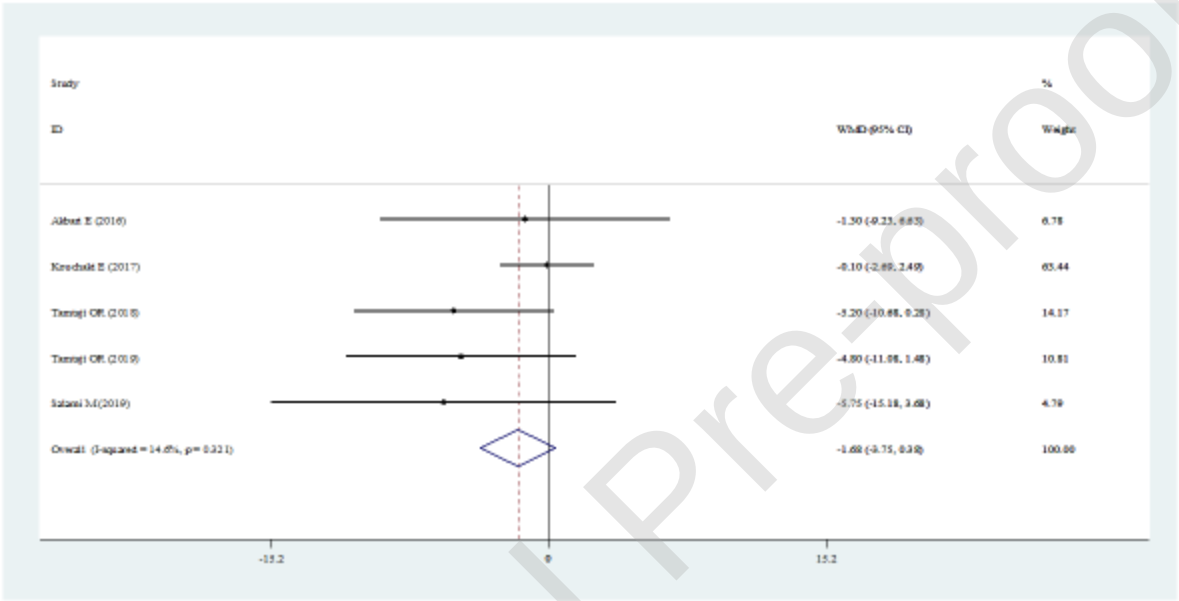

**F: TAC**



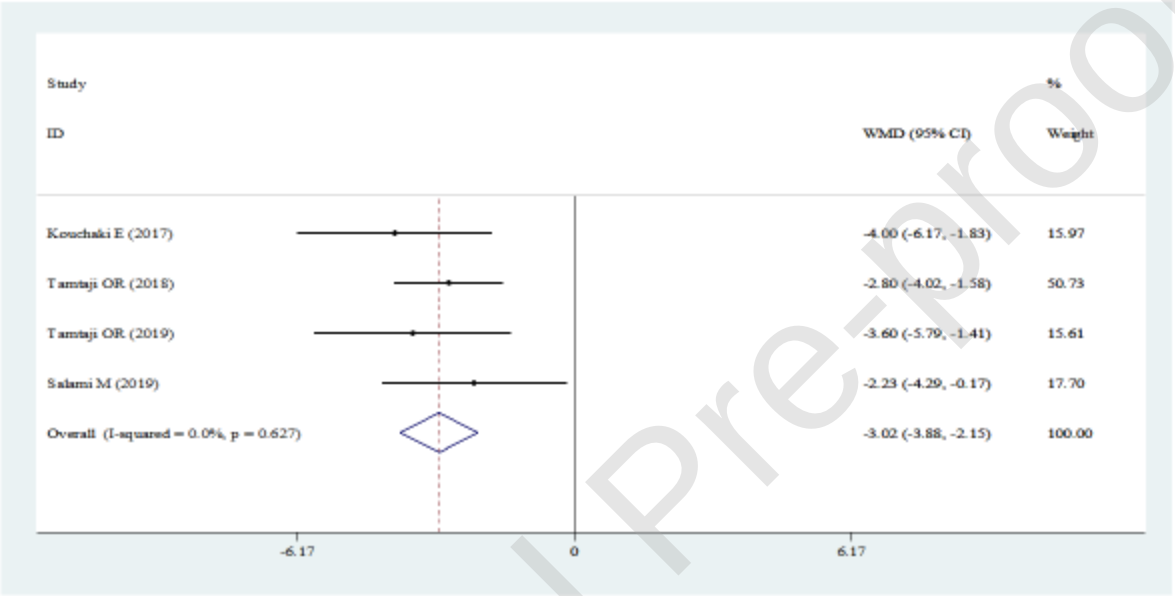

**J: GSH**



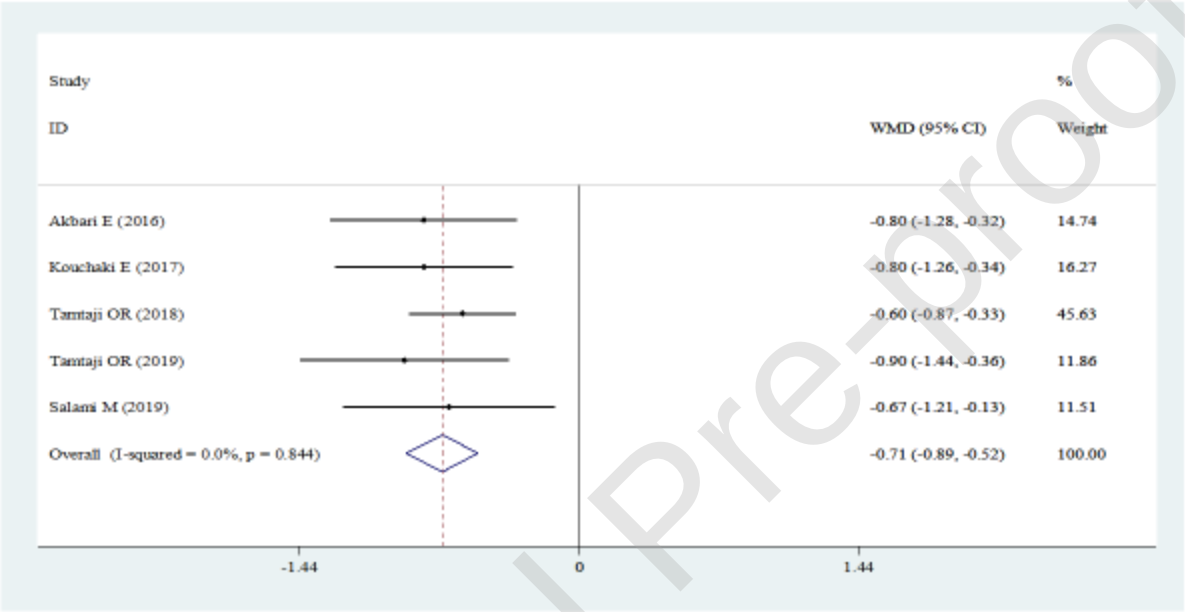

**H: MDA**



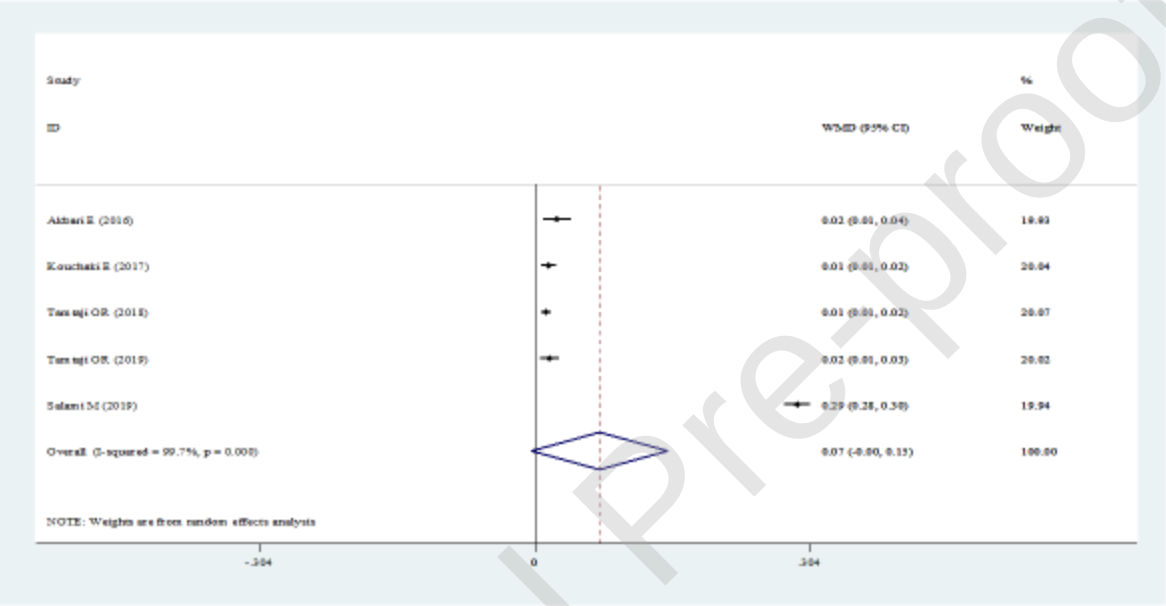

**K: FPG**



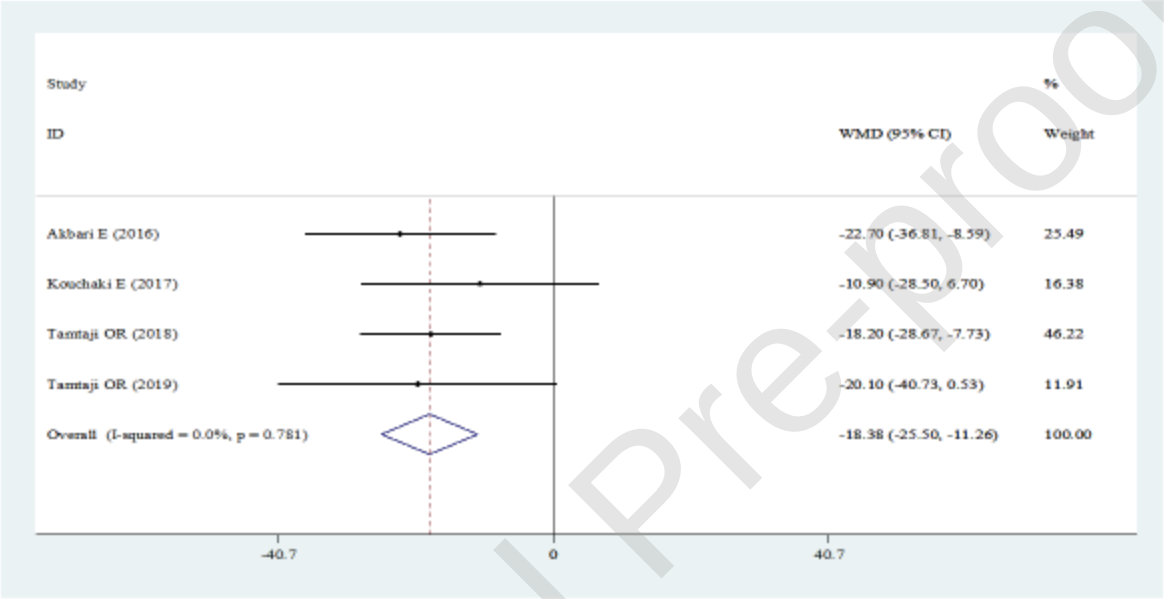

**L: Insulin**



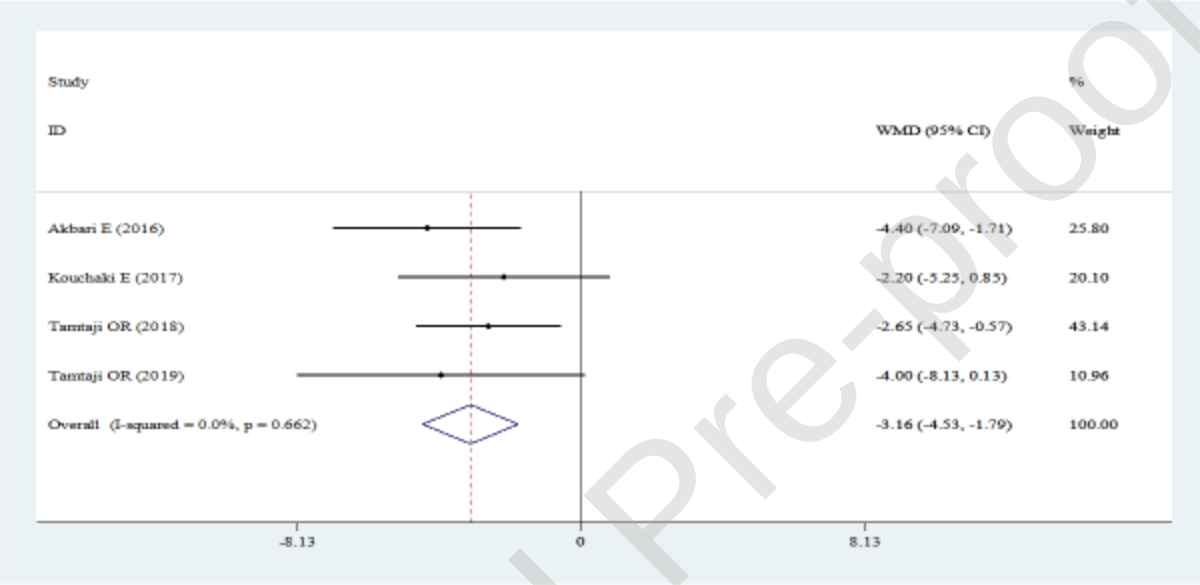

**M: HOMA-IR**



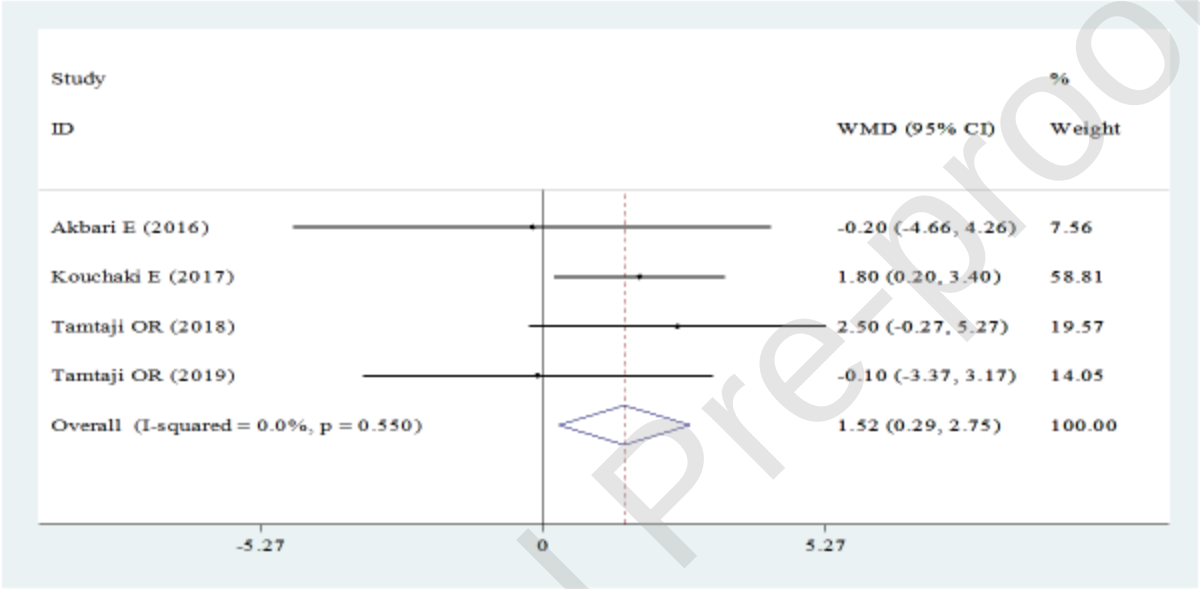

**N: QUICKI**



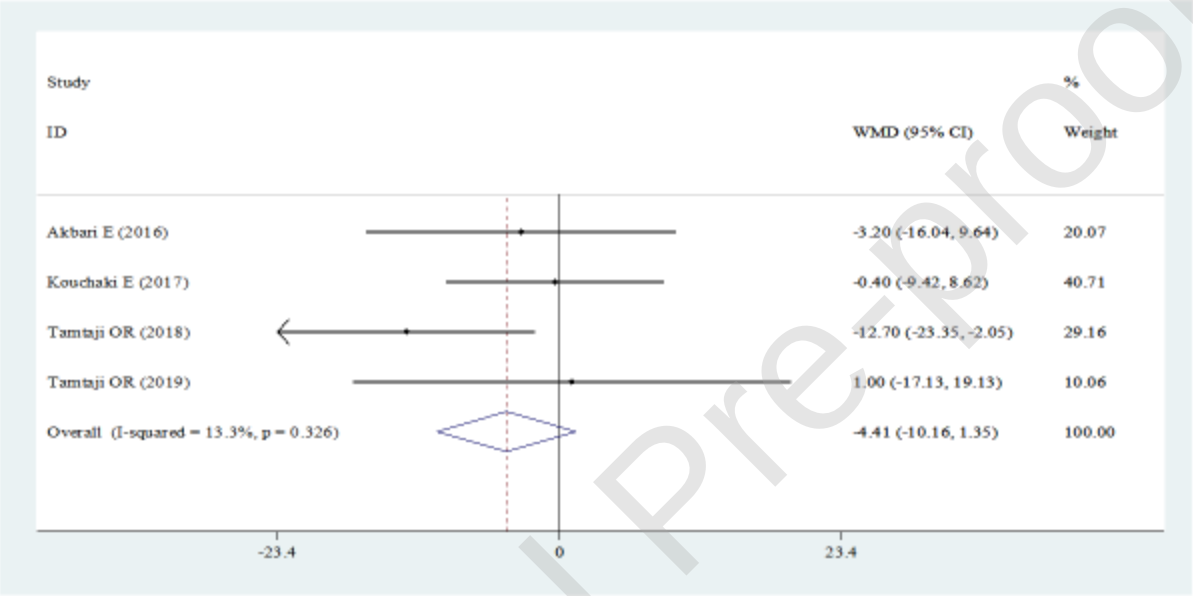

**O: TG**



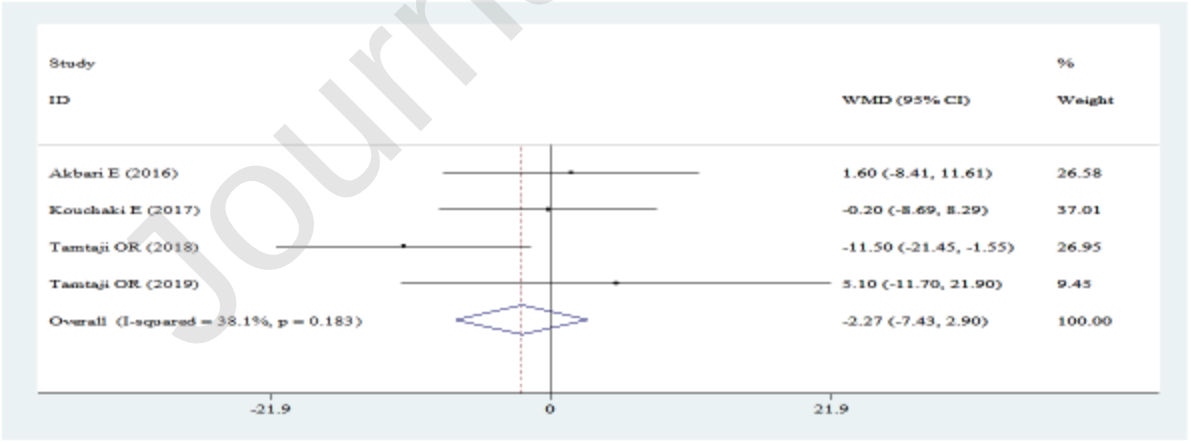

**P: VLDL**




Q: HDL




**R: TC**




**S: LDL**

**Table 1.** Characteristics of included studies

| Authors (Ref) | Publication year | Sample size (control/ intervention) | Country/population | Intervention/ daily dose | Duration | Presented data | Age (y) (control, intervention) |
|---|---|---|---|---|---|---|---|
| Agahi et al.[32] | 2018 | 23/25 | Iran/AD | Probiotic capsule containing *L.fermentum*, *L.plantarum*, *B.lactis*, *L.acidophilus*, *B.bifidum*, and *B.longum* (total $3\times10^9$ CFU) | 12 Weeks | TAC, MDA, GSH, IL-6, IL-10, TNF-α, NO | 80.57 ± 8.5, 79.70 ± 8.6 |
| Akbari et al.[30] | 2016 | 30/30 | Iran/AD | Probiotic milk (200 ml) *containing L.acidophilus*, *L.casei*, *B.bifidum* and *L.fermentum* (each $2\times10^9$ CFU/g) | 12 Weeks | TAC, MDA, GSH, CRP, NO, HOMA-IR, QUICKI, FPG, TG, TC, LDL, HDL, VLDL | 82.00 ± 9.25, 77.67 ± 14.35 |
| Borzabadi et al.[48] | 2018 | 25/25 | Iran/PD | Probiotic capsule containing *L.acidophilus*, *B.bifidum*, *L.reuteri*, and *L.fermentum* (total $8\times10^9$ CFU) | 12 Weeks | GSH, NO | 66.7±10.7, 66.9±7.0 |
| Kouchaki et al.[41] | 2017 | 30/30 | Iran/MS | Probiotic capsule containing *L.acidophilus*, *L.casei*, *B.bifidum* and *L.fermentum* (each $2\times10^9$ CFU) | 12 Weeks | TAC, MDA, GSH, CRP, NO, HOMA-IR, QUICKI, FPG, Insulin, TG, TC, LDL, HDL, VLDL | 33.8±8.9, 34.4±9.2 |
| Tamtaji et al.[49] | 2018 | 26/27 | Iran/AD | Probiotic capsule containing *L.acidophilus*, *B.bifidum*, and *B.longum* (each $2\times10^9$ CFU) plus selenium (200 µg) | 12 Weeks | TAC, MDA, GSH, CRP, NO, HOMA-IR, QUICKI, FPG, Insulin, TG, TC, LDL, HDL, VLDL | 78.5±8.0, 76.2±8.1 |
| Tamtaji et al.[16] | 2019 | 30/30 | Iran/PD | Probiotic capsule containing *L.acidophilus*, *B.bifidum*, *L.reuteri*, and *L.fermentum* (each $2\times10^9$ CFU) | 12 Weeks | TAC, MDA, GSH, CRP, HOMA-IR, QUICKI, FPG, Insulin, TG, TC, LDL, HDL, VLDL | 67.7±10.2, 68.2±7.8 |
| Salami et al.[40] | 2019 | 24/24 | Iran/MS | Probiotic capsule containing *B.infantis*, *B.lactis*, *L.reuteri*, *L.casei*, *L.plantarum* and *L.fermentum* (each $2\times10^9$ CFU) | 16 Weeks | TAC, MDA, GSH, CRP, IL-6, IL-10, TNF-α, HOMA-IR, QUICKI, Insulin, NO | 36.54 ± 7.05, 34.79 ± 5.19 |
| De Roos et al.[31] | 2017 | 26/27 | Netherlands/Migraine | Probiotic capsule containing *B.bifidum*, *B.lactis*, *L.acidophilus*, *L.brevis*, *L.casei*, *L.salivarius*, and *L.lactis* (total $5\times10^9$ CFU) | 12 Weeks | CRP, IL-6, IL-10, TNF-α | 18–70, 18–69 |
| Martami et al.[50] | 2019 | 18/21 | Iran/Chronic migraine | Probiotic capsule containing *B.subtilis*, *B.bifidum*, *B.breve*, *B.infantis*, *B.longum*, *L.acidophilus*, *L.delbrueckii ssp. bulgaricus*, *L.casei*, *L.plantarum*, *L.rhamnosus*, *L.helveticus*, *L.salivarius*, *L.lactis ssp. lactis*, and *S.thermophilus* (total $4\times10^9$ CFU) | 8 Weeks | CRP,TNF-α | 39.28±9.36, 37.57±10.89 |
| Martami et al.[50] | 2019 | 18/22 | Iran/Episodic migraine | Probiotic capsule containing *B.subtilis*, *B.bifidum*, *B.breve*, *B.infantis*, *B.longum*, *L.acidophilus*, *L.delbrueckii ssp. bulgaricus*, *L.casei*, *L.plantarum*, | 10 Weeks | CRP,TNF-α | 39.22±8.11, 36.27±6.99 |

| | |
|---|---|
| | *L.rhamnosus, L.helveticus, L.salivarius, L.lactis ssp. lactis*, and *S.thermophilus* (total $4\times10^9$ CFU) |

AD, Alzheimer disease; CRP, C-reactive protein; HDL, High-density lipoprotein; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; IL-6, Interleukin-6; IL-10, Interleukin-10; GSH, Glutathione; LDL, low-density lipoprotein; MS, Multiple sclerosis; NO, Nitric oxide; PD, Parkinson disease; TAC, Total antioxidant capacity; TG, Triglyceride; TC, Total cholesterol; TNF-α, Tumor necrosis factor-α

**Table 2.** The effects of probiotic supplementation on metabolic profiles

| Variables | Number of effect sizes | Weighted mean difference | CI 95% | Heterogeneity | |
|---|---|---|---|---|---|
| | | | | $I^2$ (%) | P- value heterogeneity |
| CRP | 8 | -1.06 | -1.80, -0.32 | 84.3 | <0.001 |
| TNF-α | 5 | -0.60 | -1.42, 0.22 | 71.1 | <0.01 |
| IL-6 | 3 | -0.11 | -0.36, 0.15 | 57.7 | 0.09 |
| IL-10 | 3 | 0.08 | -0.33, 0.50 | 80.1 | <0.01 |
| NO | 6 | 0.84 | -1.52, 3.20 | 81.7 | <0.001 |
| TAC | 6 | 5.45 | -36.59, 47.49 | 86.4 | <0.001 |
| GSH | 7 | 30.85 | -1.60, 63.29 | 77.4 | <0.001 |
| MDA | 6 | -0.32 | -0.46, -0.18 | 72.6 | <0.01 |
| FPG | 5 | -1.68 | -3.75, 0.38 | 14.6 | 0.32 |
| Insulin | 4 | -3.02 | -3.88, -2.15 | 0.0 | 0.62 |
| HOMA-IR | 5 | -0.71 | -0.89, -0.52 | 0.0 | 0.84 |
| QUICKI | 5 | 0.07 | 0.00, 0.15 | 99.7 | <0.001 |
| TG | 4 | -18.38 | -25.50, -11.26 | 0.0 | 0.78 |
| VLDL | 4 | -3.16 | -4.53, -1.79 | 0.0 | 0.66 |
| TC | 4 | -4.41 | -10.16, 1.35 | 13.3 | 0.32 |
| LDL | 4 | -2.27 | -7.43, 2.90 | 38.1 | 0.18 |
| HDL | 4 | 1.52 | 0.29, 2.75 | 0.0 | 0.55 |

CRP: C - reactive protein; MDA: Malondialdehyde; NO: Nitric Oxide; TNF-α: Tumor Necrosis Factor-α; IL-6: Interleukin-6; GSH: Glutathione; IL-10: Interleukin-10; TAC: Total Antioxidant Capacity; FPG: Fasting Plasma Glucose; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; QUICKI: Quantitative Insulin-sensitivity Check Index; TG: Triglyceride; TC: Total Cholesterol; LDL: Low Density Lipoprotein; VLDL: Very Low Density Lipoprotein; HDL: High Density Lipoprotein

**Table 3.** Subgroup analyses for the effects of probiotic supplementation on metabolic profiles

| Variables | | Subgroups | Number of effect sizes | Pooled WMD | 95% CI | $I^2$ (%) | Between-study $I^2$ (%) |
|---|---|---|---|---|---|---|---|
| CRP | Participants' age | <45 year | 5 | -0.32 | -0.63, -0.00 | 72.4 | <0.001 |
| | | ≥45 year | 3 | -1.80 | -2.26, -1.34 | 27.8 | |
| | Participants' disease | Mental defects | 5 | -0.62 | -0.90, -0.34 | 89.0 | <0.01 |
| | | Neuromuscular disorders | 3 | -1.70 | -2.37, -1.02 | 0.0 | |
| | Study sample size | ≤50 | 3 | -0.29 | -0.65, 0.06 | 79.4 | <0.001 |
| | | >50 | 5 | -1.32 | -1.70, -0.95 | | |
| NO | Participants' age | <45 year | 2 | 5.52 | 2.91, 8.12 | 0.0 | <0.001 |
| | | ≥45 year | 4 | -0.63 | -1.52, 0.26 | 59.4 | |
| | Participants' disease | Mental defects | 3 | -0.10 | -1.49, 1.29 | 68.9 | 0.84 |
| | | Neuromuscular disorders | 3 | 0.07 | -0.99, 1.13 | 90.4 | |
| | Study sample size | ≤50 | 3 | -0.68 | -1.75, 0.39 | 85.9 | 0.04 |
| | | >50 | 3 | 1.11 | -0.25, 2.47 | 78.1 | |
| TAC | Participants' age | <45 year | 2 | 13.23 | -14.05, 40.52 | 0.0 | 0.69 |
| | | ≥45 year | 4 | 6.98 | -9.20, 23.16 | 91.7 | |
| | Participants' disease | Mental defects | 3 | -1.74 | -28.85, 25.37 | 94.4 | 0.38 |
| | | Neuromuscular disorders | 3 | 12.31 | -3.91, 28.52 | 0.0 | |
| | Study sample size | ≤50 | 2 | -20.82 | -46.17, 4.52 | 95.1 | <0.01 |
| | | >50 | 4 | 21.31 | 4.66, 37.95 | 66.2 | |
| GSH | Participants' age | <45 year | 2 | 23.48 | -12.40, 59.35 | 13.7 | 0.50 |
| | | ≥45 year | 5 | 36.82 | 21.31, 52.33 | 84.0 | |
| | Participants' disease | Mental defects | 3 | 23.16 | -4.32, 50.63 | 91.4 | 0.33 |
| | | Neuromuscular disorders | 4 | 38.96 | 22.32, 55.60 | 0.0 | |
| | Study sample size | ≤50 | 3 | 23.82 | 5.23, 42.41 | 84.8 | 0.07 |
| | | >50 | 4 | 50.17 | 28.04, 72.30 | 70.7 | |
| MDA | Participants' age | <45 year | 2 | -0.38 | -0.54, -0.23 | 12.2 | 0.10 |
| | | ≥45 year | 4 | -0.24 | -0.31, -0.18 | 79.4 | |
| | Participants' disease | Mental defects | 3 | -0.23 | -0.31, -0.16 | 85.6 | 0.10 |
| | | Neuromuscular disorders | 3 | -0.34 | -0.45, -0.23 | 0.0 | |
| | Study sample size | ≤50 | 2 | -0.27 | -0.35, -0.19 | 72.5 | 0.86 |
| | | >50 | 4 | -0.26 | -0.36, -0.16 | 79.4 | |
| FPG | Participants' age | <45 year | 2 | -0.50 | -3.00, 2.00 | 22.0 | 0.09 |
| | | ≥45 year | 3 | -4.23 | -7.89, -0.57 | 0.0 | |
| | Participants' disease | Mental defects | 2 | -3.94 | -8.45, 0.57 | 0.0 | 0.27 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| | | Neuromuscular disorders | 3 | -1.09 | -3.41, 1.24 | 29.6 | |
| Insulin | Participants' age | <45 year | 2 | -3.07 | -4.56, -1.58 | 25.7 | 0.93 |
| | | ≥45 year | 2 | -2.99 | -4.05, -1.92 | 0.0 | |
| HOMA-IR | Participants' age | <45 year | 2 | -0.75 | -1.10, -0.40 | 0.0 | 0.79 |
| | | ≥45 year | 3 | -0.69 | -0.91, -0.47 | 0.0 | |
| | Participants' disease | Mental defects | 2 | -0.65 | -0.89, -0.41 | 0.0 | 0.45 |
| | | Neuromuscular disorders | 3 | -0.79 | -1.09, -0.50 | 0.0 | |
| QUICKI | Participants' age | <45 year | 2 | 0.08 | 0.07, 0.09 | 99.9 | <0.001 |
| | | ≥45 year | 3 | 0.01 | 0.01, 0.02 | 14.7 | |
| | Participants' disease | Mental defects | 2 | 0.01 | 0.01, 0.02 | 53.1 | <0.001 |
| | | Neuromuscular disorders | 3 | 0.06 | 0.05, 0.06 | 99.8 | |
| TG | Participants' disease | Mental defects | 2 | -19.80 | -28.21, -11.39 | 0.0 | 0.53 |
| | | Neuromuscular disorders | 2 | -14.77 | -28.16, -1.39 | 0.0 | |
| VLDL | Participants' disease | Mental defects | 2 | -3.30 | -4.95, -1.66 | 1.8 | 0.75 |
| | | Neuromuscular disorders | 2 | -2.84 | -5.29, -0.38 | 0.0 | |
| TC | Participants' disease | Mental defects | 2 | -8.83 | -17.03, -0.63 | 19.7 | 0.13 |
| | | Neuromuscular disorders | 2 | -0.12 | -8.20, 7.95 | 0.0 | |
| LDL | Participants' disease | Mental defects | 2 | -5.00 | -12.05, 2.06 | 69.8 | 0.26 |
| | | Neuromuscular disorders | 2 | 0.88 | -6.70, 8.45 | 0.0 | |
| HDL | Participants' disease | Mental defects | 2 | 1.75 | -0.61, 4.10 | 1.5 | 0.82 |
| | | Neuromuscular disorders | 2 | 1.43 | 0.00, 2.87 | 4.4 | |

CRP: C - reactive protein; MDA: Malondialdehyde; NO: Nitric Oxide; GSH: Glutathione; TAC: Total Antioxidant Capacity; FPG: Fasting Plasma Glucose; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; QUICKI: Quantitative Insulin-sensitivity Check Index; TG: Triglyceride; TC: Total Cholesterol; LDL: Low Density Lipoprotein; VLDL: Very Low Density Lipoprotein; HDL: High Density Lipoprotein