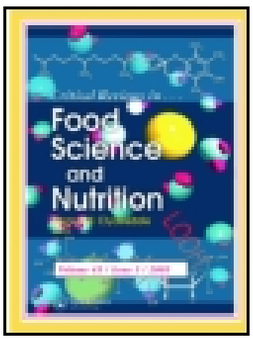

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CRITICAL REVIEWS IN FOOD SCIENCE AND NUTRITION
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REVIEW

Effect of omega-3 fatty acids supplementation on adipokines: a systematic review and meta-analysis of randomized controlled trials

Mahdi Sepidarkish[a], Gholamreza Rezamand[b], Mostafa Qorbani[c,d], Hafez Heydari[e], M. Dulce Estêvão[f], Dalia Omran[g], Mojgan Morvaridzadeh[h], Darren M. Roffey[i], Farnaz Farsi[j], Sara Ebrahimi[k], Fatemeh Shokri[l], and Javad Heshmati[h]

[a]Department of Biostatistics and Epidemiology, School of Public Health, Babol University of Medical Sciences, Babol, Iran; [b]Colorectal Research Center, Iran University of Medical Sciences, Tehran, Iran; [c]Non-communicable Diseases Research Center, Alborz University of Medical Sciences, Karaj, Iran; [d]Chronic Diseases Research Center, Endocrinology and Metabolism Population Sciences Institute, Tehran University of Medical Sciences, Tehran, Iran; [e]Cellular and Molecular Research Center, Sabzevar University of Medical Sciences, Sabzevar, Iran; [f]Universidade do Algarve, Escola Superior de Saúde, Campus de Gambelas, Faro, Portugal; [g]Department of Endemic Medicine and Hepatology, Thabet hospital for Endemic diseases, Faculty of Medicine, Cairo University, Cairo, Egypt; [h]Department of Nutritional Science, School of Nutritional Science and Food Technology, Kermanshah University of Medical Sciences, Kermanshah, Iran; [i]Vancouver General Hospital, Vancouver Coastal Health, Vancouver, Canada; [j]Student Research Committee, Department of Nutrition, School of Public Health, Iran University of Medical Sciences, Tehran, Iran; [k]Institute for Physical Activity and Nutrition, School of Exercise and Nutrition Sciences, Deakin University, Geelong, Australia; [l]Department of Health Education and Promotion, Iran University of Medical Sciences, Tehran, Iran

ABSTRACT

Background: Although a large body of literature reported the beneficial effects of omega-3 fatty acids (omega-3 FAs) consumption on adipokines levels, but recent findings from clinical trials are not univocal. The aim of this systematic review and meta-analysis was to evaluate the effect of omega-3 FAs supplements on adipokines.

Methods: We searched Medline, Web of Science, Scopus, Embase, and Cochrane Library from inception to August 2020 without any particular language limitations. Outcomes were summarized as standardized mean difference (SMD) with 95% confidence intervals (CIs) estimated from Hedge's g and random effects modeling.

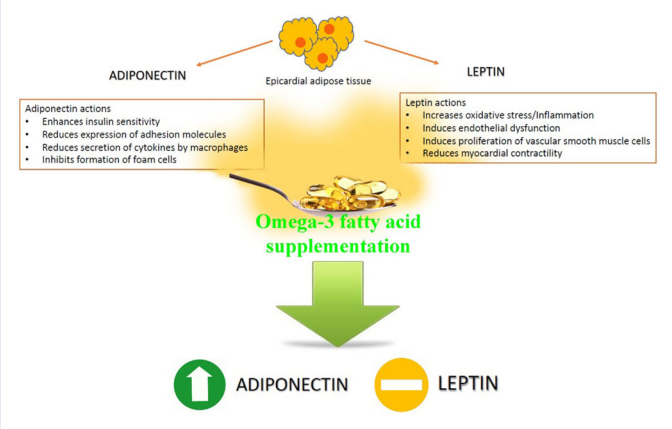
Results: Fifty-two trials involving 4,568 participants were included. Omega-3 FAs intake was associated with a significant increase in plasma adiponectin levels ($n = 43$; 3,434 participants; SMD: 0.21, 95% CI: 0.04, 0.37; $p = 0.01$; $I^2 = 80.14\%$). This meta-analysis indicates that supplementing participants with omega-3 fatty acids more than 2000 mg daily and more than 10 weeks resulted in a significant and more favorable improvement in plasma adiponectin levels. However, omega-3 FAs intake had no significant effect on leptin levels (SMD: −0.02, 95% CI: −0.20, 0.17, $I^2 = 54.13\%$).

Conclusion: The evidence supports a beneficial effect of omega-3 FAs intake on serum adiponectin levels but does not appear to impact on leptin concentrations. Larger well-designed RCTs are still required to evaluate the effect of omega-3 FAs on leptin in specific diseases.

KEYWORDS

Adipokines; adiponectin; meta-analysis; omega-3 FAs; leptin; systematic review

GRAPHICAL ABSTRACT



CONTACT Javad Heshmati javad.heshmati@gmail.com Department of Nutritional Science, School of Nutritional Science and Food Technology, Kermanshah University of Medical Sciences, Isar Square, Next to Farabi Hospital, Kermanshah 6715847141, Iran.

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Introduction

Adipocytes are the cells that primarily compose adipose tissue and are responsible for producing proteins known as adipokines. Regulation and modulation of energy homeostasis and metabolism occurs through the synthesis and secretion of adipokines (Gray et al. 2013). Different types of adipokines, including the protein hormones adiponectin, leptin, resistin, and visfatin, act to stimulate inflammatory and anti-inflammatory responses (von Frankenberg et al. 2014). Unfortunately, in conjunction with the global obesity epidemic, research has shown that an excessive accumulation of lipids in adipose tissue, along with dysregulated adipokines, can result in a multitude of chronic, severe metabolic disturbances (Farimani et al. 2018). Chronic diseases burden are a heavy cost on health systems around the world (Xu and Chen 2019; Chen and Xu 2020), so control and management of chronic disease risk factors from stem cells (Pan et al. 2020) to adulthood through complementary and dietary factors are critical concerns these days (Karimi et al. 2015; Micha et al. 2017).

Dietary lipid intake can influence the production of adipokines, subsequently impacting upon satiety and adiposity (Gray et al. 2013; Ghorabi et al. 2019). Evidence suggests that a dose-dependent relationship exists between omega-3 fatty acids intake and circulating levels of adipokines (D'Angelo, Motti, and Meccariello 2020). Accordingly, the protective and restorative health benefits of consuming omega-3 FAs are the focus of considerable scientific research. The most studied omega-3 FAs are alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). Many observational studies and RCTs have focused on areas of health in which omega-3 FAs might be involved, including: cardiovascular disease (Manson et al. 2019); diabetes (Golpour et al. 2020); infant health and neurodevelopment (Meldrum et al. 2012; Zhu et al. 2020); cancer (Manson et al. 2019); Alzheimer's disease(Zhu et al. 2020), dementia, and cognitive function (Eriksdotter et al. 2015); age-related macular degeneration (Piatti et al. 2020); dry eye disease (Chinnery, Naranjo Golborne, and Downie 2017); and rheumatoid arthritis (Park et al. 2013). In addition omega-3 FAs can change the structure of lipids in cell membrane and are precursors of very metabolically active components (Kidd 2007; Liu et al. 2017).

Nevertheless, despite the plethora of medical literature, mixed results remain in terms of favorable outcomes with omega-3 FAs supplementation. Often, the quality of the study is poor, or the studies are short-termed, and it is difficult to ascertain whether the benefits are due to the omega-3 FAs content of the supplements, the exclusion of less healthy foods, other healthful behaviors, or a combination of these factors. Previous systematic reviews have attempted various methods to mitigate study heterogeneity and publication bias while, at the same time, focusing on populations with specific health disorders (Abdelhamid et al. 2020; Downie et al. 2019; Watson and Stackhouse 2020; Wolbrink et al. 2019; AlAmmar et al. 2019). To differentiate from past efforts, the aim of the present systematic review and meta-analysis was to integrate the findings of RCTs investigating the effects of all kinds of omega-3 FAs supplementation studied on adipokines in adults with any medical conditions.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was applied to conduct and report this systematic review and meta-analysis of the published randomized clinical trials. The protocol of this systematic review and meta-analysis was registered prospectively in PROSPERO (CRD42020212692).

Search strategy and data sources

For identifying published papers, two investigators independently (M.S., J.H.) carried out a comprehensive literature search up to August 2020 through the following electronic databases: PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and Scopus. The MeSH and text keywords used to perform the systematic literature search were as follows: Adipokines OR Leptin OR Adiponectin OR Resistin OR Visfatin OR Fish Oil OR Fatty Acids, Omega-3 OR n-3 Fatty Acids OR n-3 Polyunsaturated Fatty Acid OR n-3 PUFA OR alpha Linolenic Acid OR Linolenic Acid OR Linolenate OR "ALA" OR Docosahexaenoic Acids OR "DHA" OR Eicosapentanoic Acid OR "EPA" OR Timnodonic Acid OR Randomized controlled trial OR controlled clinical trial OR randomized controlled trials OR random allocation OR double blind method OR single blind method OR clinical trial OR clinical trials OR placebos OR placebo OR random. The search strategy is presented in **Supplementary material 1.** Furthermore, a manual search was performed on the reference lists of appropriate reviews, previous systematic reviews, and meta-analyses to find further published papers for relevant RCTs and to complement the electronic search.

Inclusion and exclusion criteria

Primary eligibility criteria to narrow the electronic search were: (i) the studies' design was RCTs either with parallel or cross-over design, (ii) the subjects of the study were related to healthy and unhealthy adult populations (aged >18 years), (iii) the study compared any form of omega-3 FAs supplementation as an intervention with a placebo, (iv) circulating (plasma and serum) adipokines were the primary study outcomes at baseline and at the endpoint of intervention, (v) trials which provide sufficient data means (SDs), standard error of the mean (SEMs). Additionally, we excluded other study designs that were observational studies, animal clinical trials, cell culture case, reports, in vitro studies, nonrandomized trials, studies without a control group, and duplicated publications. Surveys, studies on children, adolescents, and pregnant or lactating women or included interventions carried out in combination with other drugs/supplements or

reported incomplete results of primary outcomes were also excluded.

Study selection data extraction

The systematic evaluation of all included studies and the screen process were carried out carefully by two separate researchers (J.H. and M.M.) under the supervision of a third reviewer (M.S.), who first reviewed and screened the titles and abstracts of each included studies in accordance with the eligibility criteria. To detect the final eligible studies, reviewers read and investigated the full text of eligible articles in the same way. All relevant information was extracted from the included trials by two trained investigators (M.S., D.R.) using a predesigned data abstraction form which includes the following items: the name of the first author of the study, total sample size, study design (parallel/crossover), year of publication, location, trial duration of follow up, number of participants in control and intervention groups, type and dose of daily omega-3 FAs supplementation, and mean baseline and post intervention primary outcome measures, age range or mean age of the participants, and participants' characteristics (including, sex, race, disease status, mean of body mass index). Any disagreement between the authors in all processes was eliminated by referring the senior reviewer (M.S.).

Quality assessment

To assess the methodological quality of each clinical trial, the Cochrane collaboration risk of bias (The CochraneCollaboration, Oxford, UK) tool was used for determining their eligibility to be included in this meta-analysis. The risk of bias of the selected RCTs were investigated by two researchers independently (D.E., M.S.) in terms of six domains of bias: "the adequacy of random sequence generation, allocation concealment, blinding of participants and outcome assessment, the handling of drop-outs and incomplete outcome data, selective outcome reporting, and other potential sources of bias." Eventually, quality of primary studies was illustrated using the proportion of obtained information as follows: "low risk," "high risk," or "unclear risk."

Data synthesis

Effect sizes of pooled studies were estimated by using Standardized Mean Differences (SMDs) and 95% CI estimated from Hedge's g and random effects modeling to determine the effects of omega-3 FAs supplementation on adipokines levels as per the Cochrane guidelines. To quantify statistical heterogeneity across the included studies, Higgin's I-square statistics and Cochran's Q test were also applied so that the p-value was less than 0.10 or $I^2 > 50\%$ was deemed significant heterogeneity. After detecting significant heterogeneity and to identify the possible source of heterogeneity, pre-specified subgroup analyses were also carried out according to the potential moderator variables, such as follow up duration, population characteristics, dosage of omega-3 FAs supplementation, age and gender of participants. Furthermore, Egger's weighted regression tests were conducted to determine publication bias across the included trials. Statistical analyses were carried out all through Review Manager 5.3 (The CochraneCollaboration, Oxford, UK) and Stata 16.0 (Stata Corp, College Station, TX).

Results

Search results

Initially a total of 900 publications was identified in the literature search (155 from PubMed, 211 from Embase, 279 from Scopus, 121 from Web of Science, 124 from Cochrane and 10 from other sources), from which 435 articles were screened based on the title or abstract. Of these, 325 irrelevant publications were deleted after screening the titles and abstracts. Finally, 52 trials met the inclusion criteria and 58 were excluded for the following reasons: 5 were nonrandomized, clinical trials; 17 did not reported appropriate outcomes; 13 did not provide enough information; 11 had no appropriate control group; 8 had no appropriate treatment; 2 did not provide oral administration; and 2 were short term evaluations (Figure 1).

Study characteristics

Table 1 outlines the main characteristics of the 52 included trials. Trials were conducted between 2007 and 2020, of which 18 trials were published after 2015. The trials were conducted in Brazil (5 trials), Italy (4 trials), Spain (3 trials), Denmark (2 trials), Iran (11trials), USA (4 trials), China (3 trials), Mexico (2 trials), Poland (4 trials), Greece (2 trials), Australia (2 trials), Japan (2 trial), Czech Republic (2 trials), Norway (1 trial), Taiwan (1 trial), France (1 trial), Venezuela (1 trial), South Korea (1 trial), and UK (1 trial). The sample size ranged from 20 to 563 participants. The duration of intervention ranged from 4 to 156 weeks. The duration of intervention in most trials was 12 weeks (34.61%). Twelve trials (23.07%) included only women and ten trials (19.23%) included only men, while the rest involved both sexes (57.70%). Five trials were performed on healthy individuals (9.62%) and the remaining were intervene on diseased participants (90.38%). The included diseases were as follows: diabetes mellitus type 2 (10 trials), obesity/overweight (9 trails), cardiovascular diseases (3 trials), systemic lupus erythematosus (1 trial), acquired immune deficiency syndrome (1 trial), hemodialysis (1 trial), pregnancy (2 trials), myocardial infraction (1 trial), end-stage renal disease (1 trial), nonalcoholic fatty liver disease (3 trials), atrial fibrillation (1 trial), polycystic ovary syndrome (4 trials), dyslipidemia (4 trial), myocardial infraction (1 trial), spinal cord injury (1 trial), nonalcoholic steatohepatitis (1 trial), metabolic syndrome (1 trial), and insulin resistant (1 trial).

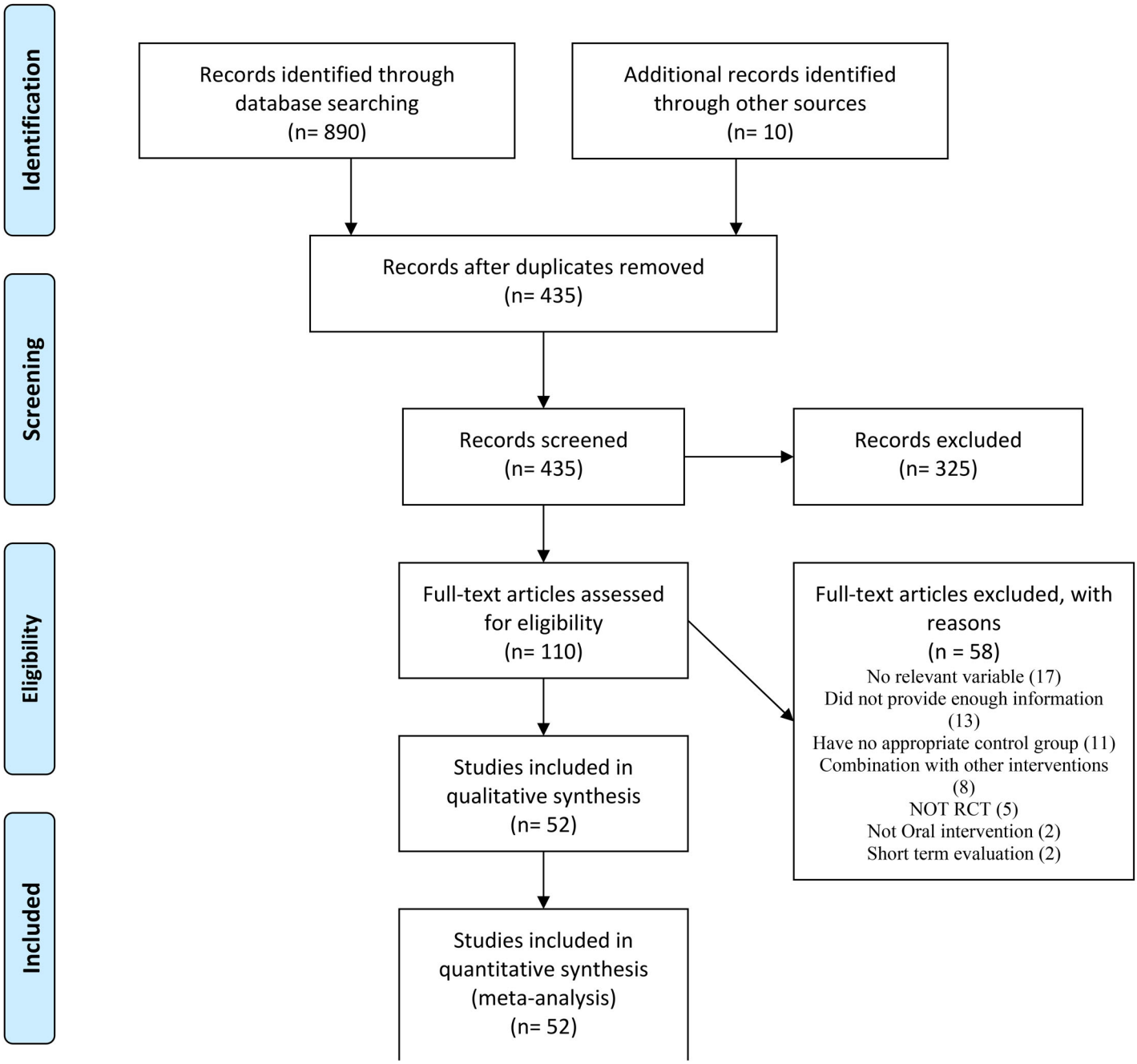

Figure 1. PRISMA flow diagram of study selection.

Risk of bias assessment

Although all included studies were randomized trials, most of trials did not appropriately described the method of random allocation ($n = 27$, 51.92%). Consequently, the allocation concealment was judged to be unclear for seven trials (13.46%) but, in majority of trials ($n = 33$, 63.46%), assessed at high risk. The blinding of outcome assessment was adequate in approximately two-thirds of trials (n = 31, 59.61%). Eighteen trials (34.61%) used appropriate methods for blinding of participants and personnel and were judged to be at low risk of bias for performance bias. Only ten trials (19.23%) used intention-to-treat approach for data analysis and the remaining trials ($n = 42$, 80.77%) categorized as having a high risk of attrition bias because they utilized per-protocol analysis. There was a lack of information regarding "reporting bias" and "other bias" in most of the included trials ($n = 27$, 51.92%), so they were judged to be unclear regarding these two type of biases. The summary of risk of bias assessments is shown in Figure 2.

Effect of omega-3 FAs therapy on plasma adiponectin concentrations

Pooling results from 43 trials, including 3,434 participants (1,705 cases and 1,729 controls), showed a significant

Table 1. Main characteristics of included studies.

Study (ref)	Country	Subjects	Sample size	Amount/day	n-3 fatty acids Dosage (per day)				Duration (week)	Gender (% females)	Age (years)		BMI (kg/m^2)		Main outcome[¥]
					n-3 Dose (mg)	EPA (mg)	DHA (mg)	ALA (mg)			Intervention Mean ± SD	Placebo Mean ± SD	Intervention Mean ± SD	Placebo Mean ± SD	
Barbosa, de Melo, and Damasceno (2017)	Brazil	CVD patients	80	3 capsules (1000 mg) daily	3000	–	–	–	8	55	52.0 ± 9.0	51.5 ± 11	29.8 ± 6.3	31.8 ± 6.3	↑ADP
Borges et al. (2017)	Brazil	SLE patients	49	2 tablets (600 mg) daily	1200	1080	200	–	12	100	37 (29–48)	37 (29–48)	–	–	↔ LEP ↔ADP
Derosa et al. (2011)	Italy	Dyslipidemia patients	167	3 capsules (1000 mg) daily	3000	–	–	–	24	51	–	–	26.0 ± 1.3	27.2 ± 1.9	↑ADP
Domingo et al. (2018)	Spain	HIV infected patients	84	Drinkable vials (7000 mg) daily	–	–	4000	–	48	–	44	45	26.2	25.1	↔ADP ↓TNF-α
Gammelmark et al. (2012)	Denmark	Overweight subjects	50	Fish oil (2000 mg) daily	1100	640	480	–	6	52	58.0 ± 7.4	55.4 ± 9.5	30.82 ± 4.18	29.53 ± 3.31	↑ADP ↔ TNF-α ↔ hs-CRP
Gharekhani et al. (2016)	Iran	Hemodialysis patients	54	6 gel capsules (300 mg)	1800	1080	720	–	12	37	56.8 ± 13.09	57.2 ± 15.19	–	–	↔Lep ↔ hs-CRP
Gomes et al. (2015)	Brazil	T2DM patients	20	–	–	–	–	3000	8	60	47 ± 8.4	50.1 ± 5.8	76.9 ± 11.7	86.3 ± 9.2	↑ADP
Haghiac et al. (2015)	USA	Overweight/ obese pregnant women	120	4 capsules daily	2000	1200	800	–	From 10-16 week to term	100	27 ± 5	27 ± 5	33 ± 6	32 ± 6	↓ hs-CRP
Haidari et al. (2015)	Iran	MI patients	42	3 capsules (1000 mg) daily	3000	540	360	–	10	–	–	–	29.30 ± 3.74	28.79 ± 3.75	↓*Lep* ↑*ADP*
Hajianfar et al. (2011)	Iran	T2DM patients	71	2 capsules (1000 mg) daily	2000	720	480	–	8	100	–	–	27.7 ± 3.4	28 ± 3.8	↑visfatin
Harving et al. (2015)	Denmark	ESRD patients	162	2 capsules daily	1700	–	–	–	12	43	65.5 ± 11	68 ± 11	–	–	↔*ADP* ↔*hs-CRP*
Hua et al. (2020)	China	T2DM patients	173	2 capsules (1000 mg) daily	2000	500	–	–	12	50	44.3 ± 6.2	43.7 ± 8.6	25.28 ± 2.35	25.15 ± 2.5	↑*ADP*
Huang et al. (2019)	Mexico	Obese adolescents	139	5 capsules daily	3000	200	1000	–	12	–	12.5 ± 1.8	12.7 ± 1.5	28.3 ± 4.3	18.9 ± 2.1	↓ *Lep*
Huerta, Navas-Carretero, et al. (2015)	Spain	Overweight/ obese women	97	3 capsules (433.3 mg) daily	–	1300	41.4	–	10	100	38 ± 8	39 ± 8	–	–	↓ *Lep* ↔*Ghrelin*
Huerta, Prieto-Hontoria, et al. (2015)	Spain	Healthy women	73	3 capsules (433.3 mg) daily	–	1300	41.4	300	10	100	–	–	–	–	↓*hs-CRP* ↔*ADP*
Jacobo-Cejudo et al. (2017)	Mexico	T2DM patients	65	2 capsules (520 mg) daily	1040	320	200	–	24	77	50.4 ± 6.3	48.1 ± 6.8	25.6 ± 2.4	26 ± 1.6	↓*Lep* ↔*ADP* ↑*Resistin*
Jafari Salim et al. (2017)	Iran	CAD patients	42	4 capsules daily	1200	720	480	–	8	0	54.86 ± 6.05	57.76 ± 6.26	28.56 ± 3.45	27.53 ± 3.43	↓*hs-CRP*
Janczyk et al. (2015)	Poland	NAFLD children patients	76	Twice a day	450-1300	–	–	–	24	15	13.2	12.8	28.6	28.86	↑*ADP* ↔*Lep* ↔*hs-CRP*
Kabir et al. (2007)	France	T2DM patients	27	–	3000	1080	720	–	8	–	55 ± 2	55 ± 1	30 ± 2	30 ± 2	↔*ADP* ↔*Lep*
Khorrami et al. (2020)	Iran	AF patients	80	2 capsules (1000 mg) daily	2000	600	400	–	8	54	68.6 ± 8.3	69.7 ± 7.7	29 ± 4.9	29.2 ± 4.2	↑*ADP*
	Iran	PCOS patients	28		1000	360	280	–	8	100	22.82 ± 1.77	22.96 ± 2.34	28.34 ± 2.72	25.84 ± 2.21	↑*visfatin*

(*continued*)

Table 1. Continued.

Study (ref)	Country	Subjects	Sample size	Amount/day	n-3 fatty acids Dosage (per day)				Duration (week)	Gender (% females)	Age (years)		BMI (kg/m^2)		Main outcome[¥]
					n-3 Dose (mg)	EPA (mg)	DHA (mg)	ALA (mg)			Intervention Mean ± SD	Placebo Mean ± SD	Intervention Mean ± SD	Placebo Mean ± SD	
Khoshkam, Taghian, and Jalali Dehkordi (2018)				1 capsule (1000 mg) daily											
Kontogianni et al. (2013)	Greece	Healthy young adults	37	15 ml daily	13800	–	–	–	6	–	–	–	22 ± 2.6	21.9 ± 2.5	↔*ADP* ↔*hs-CRP*
Lee et al. (2014)	USA	T2DM patients	59	9 capsules	–	3580	2440	860	8	59	56.2 ± 8.7	59.9 ± 9.8	33.2 ± 4.8	34.8 ± 5.3	↔*Lep*
Machado et al. (2015)	Brazil	Overweight adolescents	75	3 times per week	28,000 flax seed	–	–	–	11	56	–	–	23.38 ± 2.33	23.71 ± 2.01	↔*ADP* ↔*hs-CRP*
Mazaherioun et al. (2017)	Iran	T2DM patients	88	3 capsules daily	2700	1800	900	–	10	36	51.15 ± 7.45	50.56 ± 7.21	29.22 ± 3.58	29.21 ± 2.90	↑*ADP*
Mizia-Stec et al. (2011)	Poland	AMI patients	38	1000 mg daily	1000	465	375	–	4	21	56 ± 8	62 ± 9	27.2 ± 3.2	27.5 ± 2.9	↔*ADP* ↔*resistin*
Mohammadi et al. (2012)	Iran	Overweight, obese PCOS patients	64	4 capsules (1000 mg) daily	4000	720	480	–	8	100	27.3 ± 4.27	27.7 ± 4.53	28.7 ± 3.21	28.8 ± 2.90	↑*ADP* ↔*hs-CRP*
Mejia-Montilla et al. (2018)	Venezuela	PCOS patients	195	–	–	180	120	–	12	100	23.6 ± 3.4	23.3 ± 3.9	26.4 ± 3	26 ± 2.7	↑*ADP*
Mostowik et al. (2013)	Poland	CAD patients	48	–	1000	460	380	–	4	25	62.5 ± 10	63.4 ± 8.4	29	28.5	↑*ADP* ↓*Lep*
Munro and Garg (2013)	Australia	Healthy adults	33	6 capsules (1000 mg) daily	2160	420	1620	–	12	67	39.94 ± 11.70	41.11 ± 11.27	32.55 ± 2.07	32.53 ± 3.58	↔*Lep* ↔*ADP* ↔*hs-CRP*
Nadjarzadeh et al. (2015)	Iran	PCOS patients	84	3 capsules daily	–	540	360	–	8	100	26.9 ± 5.9	26.9 ± 5	31.46 ± 5.74	31.88 ± 3.86	↔*visfatin* ↑*ADP*
Nishi et al. (2020)	Taiwan	Pregnant women	108	9 capsules daily	1800	1206	609	–	12	100	32.8 ± 5.3	32.6 ± 5.3	–	–	↔*ADP* ↔*hs-CRP*
Oh et al. (2014)	South Korea	hypertriglyceridemia	173	–	4000	–	–	–	8	47	55 ± 8	54 ± 9	26.18 ± 3.21	26.50 ± 2.72	↔*hs-CRP* ↔*ADP*
Paoli et al. (2015)	Italy	Overweight subjects	34	2 capsules daily	230	115	65	–	16	0	58.1 ± 6	56.3 ± 5.1	29.17 ± 2.37	29.34 ± 2.4	↓TNF-α ↑ADP
Paschos et al. (2007)	Greece	Dyslipidemia patients	35	–	–	–	–	8100	12	0	49 ± 7	54 ± 10	28 ± 3	28 ± 4	↔*ADP* ↔ TNF-α
Patel et al. (2007)	UK	Post MI patients	35	–	1000	–	–	–	12	0	65.3 ± 7.6	59.7 ± 9.5	27.4 ± 3.7	27.7 ± 5.7	↔*ADP* ↔*Lep* ↔ TNF-α
Payahoo et al. (2017)	Iran	Obese subjects	60	2 capsules (1000 mg) daily	2000	360	240	–	4	75	31.93 ± 8.5	33.56 ± 8.79	34.73 ± 4.32	34.25 ± 4.22	↔*Lep*
Poreba et al. (2017)	Poland	T2DM and atherosclerosis patients	74	–	2000	1000	1000	–	12	35	64.4 ± 6.7	66.7 ± 6.8	30.9	31.1	↔*Lep* ↔*ADP*
Qin et al. (2015)	China	NAFLD	70	4 capsules (1000 mg) daily	4000	728	516	–	12	27	46 ± 10.68	44.3 ± 10.9	26.4 ± 3.9	26 ± 2.8	↑*ADP* ↓ TNF-α ↔hs-CRP
Rizza et al. (2009)	Italy	T2DM patients	50	2 capsules (1000 mg) daily	2000	–	–	–	12	50	–	–	26.1 ± 5.9	25.8 ± 4.6	↓ TNF-α ↑ADP
Sabour et al. (2015)	Iran	SCI patients	104	2 capsules daily	–	126	930	–	56	18	51.15 ± 13.43	54.12 ± 11.76	24.11 ± 4.89	23.64 ± 3.78	↔*lep* ↓*ADP*
Sanyal et al. (2014)	USA	NASH and NAFL patients	243	3 divided dosage in a day	–	2700	–	–	48	61	47.8 ± 11.1	50.5 ± 12.5	35 ± 6.3	33.6 ± 5.9	↔*ADP* ↔*hs-CRP*

(*continued*)

Table 1. Continued.

Study (ref)	Country	Subjects	Sample size	Amount/day	n-3 fatty acids Dosage (per day)				Duration (week)	Gender (% females)	Age (years)		BMI (kg/m^2)		Main outcome¥
					n-3 Dose (mg)	EPA (mg)	DHA (mg)	ALA (mg)			Intervention Mean ± SD	Placebo Mean ± SD	Intervention Mean ± SD	Placebo Mean ± SD	
Satoh et al. (2009)	Japan	Metabolic syndrome patients	92	1 capsule daily	–	1800	–	–	12	58	51.3 ± 2.1	52.2 ± 2.1	30 ± 0.7	30 ± 0.6	↓*hs-CRP* ↑*ADP*
Sedláček et al. (2018)	Czech Republic	Overweight subjects	34	–	1500	–	–	–	12	100	42.6 ± 9.8	51.4 ± 10.8	26.3 ± 1	28 ± 1	↔*Lep*
Lozovoy et al. (2012)	Brazil	Metabolic syndrome patients	65	10 capsules daily	3000	1800	1200	–	12	100	47.5 ± 9.2	47.1 ± 8.8	32.93	35.36	↑*ADP*
Sofi et al. (2010)	Italy	NAFLD patients	11	6.5 ml daily	830	470	240	–	48	3	55	54	29.3 ± 4.1	29.3 ± 3.9	↑*ADP*
Song et al. (2018)	China	Healthy subjects	210	4 capsules daily	1240	–	–	–	12	69	61 ± 8	61 ± 7	23.5 ± 2.9	22.8 ± 2.8	↓*hs-CRP* ↑*ADP*
Spencer et al. (2013)	USA	Insulin resistant patients	33	–	4000	–	–	–	12	67	48.8 ± 2.3	53.3 ± 2.2	33.4 ± 2.3	33.4 ± 1.1	↔*ADP*
Trøseid et al. (2009)	Norway	Healthy subjects	563	–	2400	–	–	–	156	0	–	–	26.4	26.6	↔*ADP* ↔*hs-CRP*
Veleba et al. (2015)	Czech Republic	T2DM patients	69	1000 mg capsule	5000	–	–	–	24	34	59.5	62	34.0	30.9	↔*ADP* ↔*Lep*
Wong et al. (2013)	Australia	Obese and dyslipidemic subjects	25	–	4000	–	–	–	16	44	–	–	34 ± 2	33 ± 1	↑*ADP*
Yamamoto et al. (2014)	Japan	Hyperlipidemic patients	60	–	–	900	–	–	–	24	71 ± 8.4	70.5 ± 7.9	25 ± 4.5	25.7 ± 3.9	↑*ADP* ↓*hs-CRP* ↔*Lep* ↔*Visfatin*

↓Symbol is a sign of decreasing variables in the intervention group, ↑ means increasing variables in the intervention group, ↔ indicates that there is no difference between the two groups. NR: not reported.

¥EPA: eicosapentaenoic acid, DHA: docosahexaenoic acid, ALA:alpha-linolenic acid, ADP: adiponectin, LEP: leptin, Vis: visfatin, Res: resistin, CVD: cardiovascular disease, SLE: systemic lupus erythematosus, AF: atrial fibrillation, HLP: hyperlipidemia, AMI: acute myocardial infraction, CAD: coronary artery disease, MI: myocardial infraction, NAFLD: nonalcoholic fatty liver disease, MDD: major depressive disorder, SCI: spinal cord injury, NASH: nonalcoholic steatohepatitis, IFG: impaired fasting glucose.

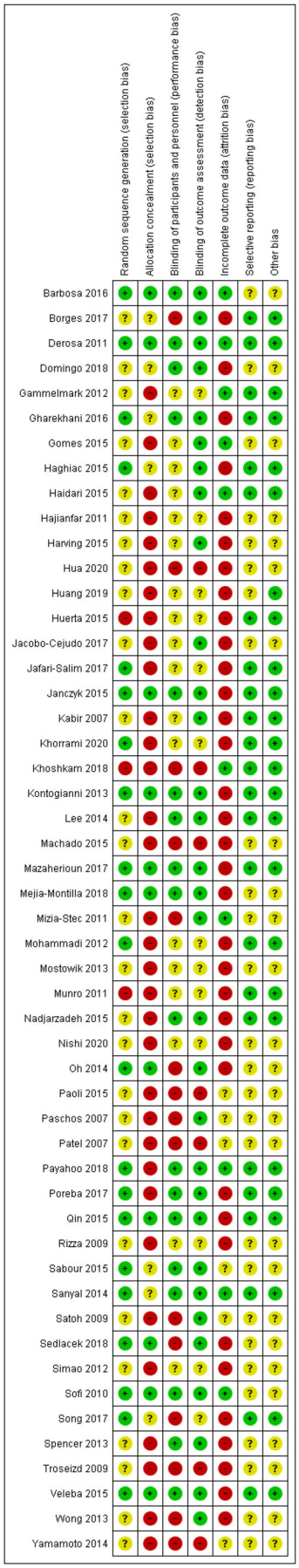

Figure 2. Risk of bias assessment of included studies.

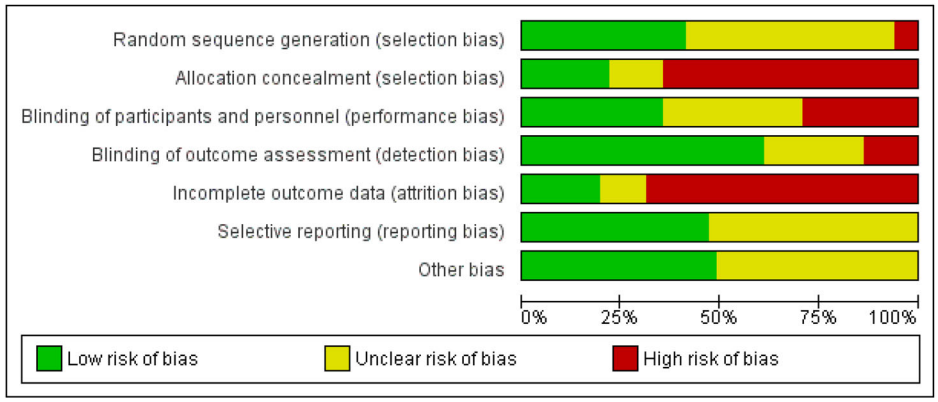

Figure 2. Continued.

Table 2. Pooled standardized mean difference of trials on the effect of omega-3 on adiponectin.

Adiponectin (sub-group analysis)	No. of studies	Total population	Pooled SMD (95% CI)	I^2	Adiponectin (sub-group analysis)	No of studies	Total population	Pooled SMD (95% CI)	I^2
Total	43	3,343	0.21 (0.04, 0.37)	80.14	Dosage				
Control type					<2000 mg/day	16	1,159	0.25 (−0.08, 0.59)	86.56
Sunflower oil	34	247	−0.12 (−0.63, 0.38)	74.71	≥2000 mg/day	27	2,184	0.19 (0.02, 0.36)	72.15
Sucrose	1	187	0.35 (0.07, 0.64)	–	Age categories				
Olive oil	4	479	0.14 (−0.01, 0.39)	38.76	Adolescent (10–19)	4	1,159	−0.01 (−0.45, 0.42)	52.26
Corn oil	4	825	0.45 (−0.21, 1.10)	92.22	Young adults (20–30)	4	2,184	0.68 (0.17, 1.20)	81.64
Paraffin	6	541	0.42 (−0.02, 0.87)	83.38	Middle-aged adults (31–50)	12	1,159	0.24 (−0.11, 0.59)	83.21
Soy bean	1	113	0.24 (−0.12, 0.61)	–	Senior adults (>50)	23	2,184	0.12 (−0.05, 0.31)	71.43
Wheat bran	1	50	−0.49 (−1.04, 0.05)	–	Gender				
Placebo	2	314	−0.14 (−0.36, 0.08)	–	Male	4	671	0.06 (−0.38, 0.52)	69.44
No intervention	10	587	0.28 (−0.10, 0.67)	80.93	Female	9	626	0.27 (−0.17, 0.71)	85.82
Disease type					Both	30	2,046	0.20 (0.01, 0.39)	76.60
Healthy	4	748	0.37 (−0.20, 0.94)	86.87	Omega-3 type				
Unhealthy	39	2,595	0.19 (0.02, 0.37)	79.71	Animal	40	3,201	0.25 (0.08, 0.42)	81.06
Duration (week)					Herbal	3	142	−0.34 (−0.73, 0.05)	7.81
<10	13	677	0.22 (−0.01, 0.45)	50.93					
≥10	30	2,666	0.19 (0.01, 0.40)	84.23					

increase in plasma adiponectin levels after omega-3 FAs therapy (SMD: 0.21, 95% CI: 0.04, 0.37; $p = 0.01$, Table 2). There was non-ignorable heterogeneity among studies ($p < 0.001$; $I^2 = 80.14\%$). Egger test did not provide evidence of publication bias (Egger's regression intercept: 0.63, 95%CI: −1.39, 2.66, $p = 0.528$). A significant difference was observed in the subset of trials that compared the adiponectin levels between cases with different controls: sunflower oil, sucrose, olive oil, corn oil, paraffin, soy bean, wheat bran, placebo and no intervention ($Chi^2 = 17.72$, df = 8, $P = 0.023$). There was a significant increase in plasma adiponectin levels in the subset of trials that compared omega-3 FAs with sucrose (SMD: 0.35, 95% CI: 0.07, 0.64; Table 2) but not in the other subsets. With respect to dosage of treatment, there was a significant increase in plasma adiponectin levels in the subset of trials that administered equal and more than 2000 mg daily of omega-3 FAs (SMD: 0.19, 95% CI: 0.02, 0.36, $I^2 = 72.15\%$) but not in the subset of trials that administered less than 2000 mg daily of omega-3 FAs (SMD: 0.25, 95% CI: −0.08, 0.59, $I^2 = 86.56\%$). We found a significant effect in the subset of trials in which omega-3 FAs were administered for equal and more than10 weeks (SMD: 0.19, 95% CI: 0.01, 0.40, $I^2 = 84.23\%$) and not in the subset of trials in which omega-3 FAs were administered for lower than10 weeks (SMD: 0.22, 95% CI: −0.01, 0.45, $I^2 = 50.93\%$). Higher levels of circulating adiponectin were observed in young adults (SMD: 0.68, 95% CI: 0.17, 1.20, $I^2 = 81.64\%$) but not in the other age categories. In the subgroup analysis of population type, higher serum adiponectin levels were detected in unhealthy population (SMD: 0.19, 95% CI: 0.02, 0.37, $I^2 = 79.71\%$), while no significant difference was identified in healthy population (SMD: 0.37, 95% CI: −0.20, 0.94, $I^2 = 86.87\%$).

Table 3. Pooled standardized mean difference of trials on the effect of omega-3 on leptin.

Leptin (sub-group analysis)	No. of studies	Total population	Pooled SMD (95% CI)	I^2	Leptin (sub-group analysis)	No of studies	Total population	Pooled SMD (95% CI)	I^2
Total	20	1,038	−0.02 (−0.20, 0.17)	54.13	Dosage				
Control type					<2000 mg/day	8	445	−0.12 (−0.50, 0.26)	74.45
Sunflower oil	4	214	0.17 (−0.23, 0.57)	53.81	≥2000 mg/day	12	603	0.05 (−0.10, 0.21)	0.69
Olive oil	1	40	0.50 (−0.12, 1.31)	–	Age categories				
Corn oil	3	124	0.01 (−0.56, 0.58)	60.94	Adolescent (10–19)	2	129	−0.16 (−0.51, 0.17)	–
Paraffin	4	122	0.05 (−0.44, 0.53)	43.17	Young adults (20–30)	1	49	0.21 (−0.34, 0.76)	–
Soy bean	2	113	−0.44 (−0.86, −0.02)	22.14	Middle-aged adults (31–50)	7	325	0.20 (−0.09, 0.51)	46.16
Placebo	2	109	0.31 (−0.05, 0.69)	–	Senior adults (>50)	10	545	−0.15 (−0.42, 0.12)	59.78
No intervention	5	326	−0.24 (−0.58, 0.09)	55.41	Gender				
Duration (week)					Male	1	35	−0.70 (−1.37, −0.03)	–
<10	5	251	0.07 (−0.35, 0.49)	63.81	Female	4	133	0.29 (−0.12, 0.72)	35.27
≥10	15	797	−0.04 (−0.25, 0.16)	52.14	Both	15	880	−0.04 (−0.23, 0.15)	51.61

Effect of omega-3 FAs therapy on plasma leptin concentrations

Twenty trials with 1,038 participants (520 in cases and 518 in controls) compared circulating leptin between participants who were supplemented with omega-3 FAs and those who were supplemented with placebo or other treatment. As showed in Table 3, the results using the random effects model indicated that serum leptin levels between participants who were supplemented with omega-3 FAs and controls were similar (SMD: −0.02, 95% CI: −0.20, 0.17, I^2= 54.13%). In the subgroup analysis of control type, lower serum leptin concentration was detected in the subset of trials that compared omega-3 FAs with soy bean (SMD: −0.44, 95% CI: −0.86, −0.02, I^2= 22.14%), but not in the other subsets. We further conducted subgroup analysis by age categories, duration, and dosage but there were no significant differences between studies.

Discussion

The present systematic review and meta-analysis gathers a total of 52 studies, which included 4,568 subjects, to assess the effect of omega-3 FAs intake on the plasma levels of the main known adipokines, adiponectin, and leptin. In this analysis, healthy and unhealthy participants were included covering the impact of omega-3 FAs in patients suffering from several different diseases. The omega-3 FAs administered in the different studies included single fatty acids or different combinations of the three main omega-3 FAs, eicosapentaenoic acid (EPA, 20:5(n-3)), docosahexaenoic acid (DHA, 22:6(n-3)), and alpha-linolenic acid (ALA, 18:3(n-3)). Moreover, the high number of studies included permitted that a large range of omega-3 FAs doses and a wider range of intervention intervals were also considered and contribute to an updated set of data since the search was carried until August 2020. Our results indicate that omega-3 FAs intake significantly increase adiponectin levels and have no significant effect on leptin levels. To the best of our knowledge this is the most comprehensive systematic review and meta-analysis about the effect of all sources of omega-3 FAs intake on adipokines. Current results are in line to those presented in a previous meta-analysis (Wu, Cahill, and Mozaffarian 2013) which reported that fish oil consumption increases circulating adiponectin. However, Wu et al included less trials (14 RCTs) compared to the current review (52 RCTs), and they only included fish oil sources of omega-3 FAs, whereas we included both plant and animal sources of omega-3 FAs that were used in the included studies. Our results are also in accordance with the Farimani et al. (2018) study (Farimani et al. 2018) which reports that omega-3 FAs intake significantly increase adiponcetin and decrease leptin levels in type 2 diabetes patients. In addition to the Farimani et al. (2018) review, there are other systematic reviews that evaluated the effects of omega-3 FAs on adipokines as, for example, Bahreini et al. (2018) which indicates that omega-3 FAs intake significantly increases adiponectin levels in type 2 diabetic patients. However, our results cover the outcome of omega-3 FAs on adipokines also in patients with other metabolic diseases and in healthy subjects. In contrast with our results, Hariri et al. (2015) shows that omega-3 FAs intake significantly decrease leptin levels but they included fewer studies in comparison to current review and they did not evaluate the effect of omega-3 FAs intake on adiponectin levels.

Adiponectin is the most abundant adipokine and a pleiotropic molecule acting not only in the adipocytes but also in many other cell types. It is well recognized by its benefits including anti-inflammatory, anti-diabetic, and insulin-sensitizing and cardioprotective properties (Hafiane, Gasbarrino, and Daskalopoulou 2019; Izadi and Azadbakht 2015; Swanson, Block, and Mousa 2012). Adiponectin has also been associated with a possible reduction of hypertension risk (Kim et al. 2013), with anti-carcinogenic effects (Perrier and Jarde 2012) and with the mediation between bone and bone adiposity (Jafari Nasabian et al. 2017).

Most of adiponectin effects associated to lipid metabolism seem to be related to its direct action in the regulation of cholesterol efflux and high density lipoproteins (HDL) homeostasis (increased synthesis and decreased degradation) probably after binding to specific receptors (Adipo R1 and Adipo R2) which induce several signaling pathways in the target cells (Hafiane, Gasbarrino, and Daskalopoulou 2019). On the other hand, obesity induces increased levels of inflammatory markers (e.g. IL-6 and TNF-a), which are associated to decreased levels of adiponectin (Weihe et al. 2020; Wang et al. 2014).

Currently, it is broadly accepted that the amount and type of fat consumed has an important impact in our immune system, which may lead to inflammatory diseases. Although the processes by which this might happens are not fully understood, it should be considered that both acute and chronic effects may occur (Fritsche 2015). The consumption of unsaturated fatty acids, including omega-3 FAs, is usually associated with the idea of "healthy diets" as it is widely demonstrated that these fatty acids have antidyslipidemic, anti-diabetic, and anti-inflammatory effects (reviewed by Moreno-Aliaga, Lorente-Cebrian, and Martinez 2010). Omega-3 FAs, being able to bind to peroxisome proliferation activated receptor γ (PPARγ) may stimulate the synthesis and secretion of adiponectin which, in turn, contribute to regulate lipid metabolism (Izadi and Azadbakht 2015). An in vitro study carried out in human adipocytes demonstrated that EPA and DHA may increase adiponectin secretion through mechanisms that not always involve the PPARγ pathway (at least for EPA) (Tishinsky, Ma, and Robinson 2011). In addition, several studies have demonstrated that omega-3 FAs (in particular, DHA and EPA, mainly present in fish oils) may suppress fatty acid synthesis and induce b-oxidation in several human tissues (Moreno-Aliaga, Lorente-Cebrian, and Martinez 2010) which also contributes to regulate lipid metabolism. Omega-3 fatty acids are also recognized by their anti-diabetic effect which may be due to the prevention of insulin resistance associated to a decrease in the expression of muscle and hepatic glucose transporter 4 (GLUT-4) and the regulation of the hepatic glucose-6-phosphatse expression and activity (Moreno-Aliaga, Lorente-Cebrian, and Martinez 2010). The anti-inflammatory action of omega-3 FAs may be explained by their role as substrates for the production of protectins and resolvins, lipid compounds involved in the resolution of inflammation (Kohli and Levy 2009; Serhan and Levy 2018), and by reducing the formation of pro-inflammatory eicosanoids, derived from arachnoid acid (Calder 2006).

The results obtained in this meta-analysis show that omega-3 FAs significantly increases adiponectin levels. As shown in Table 2, this is particularly noticeable when omega-3 FAs interventions are compared with the administration of sucrose as a control (only one study). Using other controls, such as different vegetable oils that may have these or other beneficial fatty acids in their composition, placebo or no intervention does not result in significant differences on the determined adiponectin levels. The intake of higher doses of omega-3 FAs (more than 2000 mg/day) and longer interventions (more than 10 weeks) also induced significant increases in adiponectin. In addition, young adults seem to be more susceptible to the intervention with omega-3 FAs as they are the only sub-group (considering age) presenting a significant increase of adiponectin levels. These findings corroborate what has already been presented in other studies which reported evidences related to the beneficial effect of omega-3 FAs on adiponectin levels, in subjects with variable weight range (normal, overweight and obese individuals) as well as in both healthy and unhealthy subjects (for example Gray et al. 2013; von Frankenberg et al. 2014), with DHA and EPA inducing similar effects on these levels (Vors et al. 2020).

However, the mechanisms underlying omega-3 FAs specific effects on adiponectin levels remain unclear, especially at the genetic and post-transcriptional level via microRNA (miRNA) (Qu, Wei, and Zou 2019). In vitro studies have demonstrated that omega-3 FAs conduct several of their effects through miRNAs (Sam, Tavakoli-Mehr, and Safaralizadeh 2018). It has been shown that genetic modifications have a great impact on metabolic risk factors (Jiang et al. 2017; Akbari et al. 2016; Jiang et al. 2020). miRNAs are a massive type of small noncoding RNAs, which participate as regulators in several health and disease situations (Emami, Nekouian, et al. 2019; Zou et al. 2019; Emami, Akbari, et al. 2019). It has been reported that miRNA-21 regulate gene expression of adiponectin in adipose tissues (Kang et al. 2013), and it is well established that omega-3 FAs are one of the miRNA-21regulators (LeMay-Nedjelski et al. 2018; Mandal et al. 2012), so the effect of omega-3 FAs intake on miRNA levels may be one of the mechanism through which it increases adiponectin levels .

Leptin is released from white adipose tissue and is recognized by its effect in the promotion of satiety by inhibiting the hypothalamus region controlling hunger. Plasmatic leptin levels correlate with adiposity and influence brain regulation of food intake and energy consumption (Smitka and Maresova 2015). Moreover, leptin is also involved in the regulation of body fat storage and insulin signaling (Moreno-Aliaga, Lorente-Cebrian, and Martinez 2010). Elevated body fat levels are associated with increased leptin concentration in the blood which may induce leptin resistance that may, in turn, influence obesity status (Maher and Clegg 2019). In fact, leptin is an important component of the afferent network that send information to the central nervous system allowing an adequate control of energy balance and feeding behavior (Dunn and Adams 2014). The state of insulin resistance may be defined by the impairment of reduction in food intake and body weight in response to the administration of leptin (Vasselli et al. 2013). A recent systematic review and meta-analysis have shown that leptin levels may vary with age, with higher levels being found in healthy older adults that also presented lower energy intake and hunger perception (Johnson et al. 2020). Data on the effect of omega-3 FAs in leptin levels is still scarce and controversial although it has been reported that dietary fatty acid composition may change plasmatic leptin levels (Reseland et al. 2001). In vitro studies with adipocytes have shown that both DHA and EPA did not increased leptin secretion while in vivo studies carried out with several animal models resulted in various outcomes, including decreased leptin levels in patients with stable coronary artery disease after 1 month treatment (Tortosa-Caparros et al. 2017).

In the present work, no significant changes were observed in leptin levels as consequence of omega-3 FAs supplementation. However, when the administration of omega-3 FAs is compared with the intake of soybean as a control, a significant decrease is observed. This was the only subgroup with

a different and significant outcome regarding leptin levels (Table 2).

Omega-3 FAs (DHA and EPA) are unsaturated fatty acids that cannot be synthesized in human cells and the main source of these nutrients are fish oils (Maher and Clegg 2019). For this reason, and for many people, the adequate intake of these fatty acids, which have an important impact in human health, are not met by the consumed diet. The current knowledge of the benefits of these compounds makes it relevant to evaluate the effect of omega-3 FAs supplementation. In this systematic review and meta-analysis, the influence of omega-3 FAs intake was assessed defining the blood levels of adiponectin and leptin, important hormones associated with the adipose tissue and, consequently, with obesity and metabolic syndrome, for example. Results showed that a significant increase in adiponectin was observable but only in some specific subgroups while leptin levels were not affected which may be due to the highly variable conditions defined in the included studies. It is important to remind that impact of supplementation at cellular level needs to be considered as the concentration of omega-3 FAs in the cells will condition the cellular responses (Fritsche 2015). More studies, with well-defined interventions (duration, dose of omega-3 FAs, controls used, baseline parameters and outcomes assessed) are necessary to better define the advantages of omega-3 fatty acids supplementation.

Disclosure statement

The authors have no conflict of interest to declare.

Statement of ethics

This systematic review is accordance with the World Medical Association Declaration of Helsinki.

Author contributions

J.H. and M.S. contributed to the study design and interpretation; and drafted and edited the manuscript. M.M., M.D.E. and M.Q. contributed to the statistical analysis and edited the draft. D.M.R., GH.R. and F.F. contributed to interpretation of the work and revised it critically for important intellectual content. S.E. and F.SH. contributed to performing search and data collection. J.H. and M.S. contributed to edited manuscript and preparing the final article version. H.H. and GH.R. contributed to the revision of the manuscript.

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