Nutrition Research 85 (2021) 135–152

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/NTR

Review Article

Systematic review of marine-derived omega-3 fatty acid supplementation effects on leptin, adiponectin, and the leptin-to-adiponectin ratio

Jamie Rausch[a,*], *Shannon Gillespie*[b], *Tonya Orchard*[c], *Alai Tan*[b], *Jodi C. McDaniel*[b]

[a] *Indiana University Fort Wayne, School of Nursing, Fort Wayne, IN, 46805, USA*
[b] *Ohio State University, College of Nursing, Columbus, OH, 43210, USA*
[c] *Ohio State University, College of Education and Human Ecology, Columbus, OH, 43210, USA*

ARTICLE INFO

Article history:
Received 12 March 2020
Revised 22 October 2020
Accepted 10 November 2020

Keywords:
Leptin
Adiponectin
Omega-3
Unsaturated fatty acids
Fish oils
Systematic review
Inflammation

ABSTRACT

Increasing evidence suggests that adipokines, leptin and adiponectin, produced and secreted by adipocytes, are involved in regulating systemic inflammation and may be important targets for interventions to reduce the chronic systemic inflammation linked to some conditions common in aging (e.g., atherosclerosis). Lower leptin levels and higher adiponectin levels in peripheral circulation have been associated with less systemic inflammation. While some studies have shown that marine-derived omega-3 fatty acids (eicosapentaenoic acid [EPA] and/or docosahexaenoic acid [DHA]) have effects on leptin and adiponectin in the context of inflammation, the extent of their effects remain unclear. The purpose of this systematic review was to summarize findings from randomized, controlled trials that measured effects of EPA+DHA supplementation on circulating levels of leptin and adiponectin to determine the state of the science. PubMed, CINAHL, Web of Science, Scopus, and Cochrane Trials were searched up to June 2018 for studies meeting inclusion criteria. Thirty-one studies included in this review were conducted in 16 countries. Eighteen studies reported lower leptin and/or higher adiponectin levels with EPA+DHA supplementation versus placebo at study end point (9 reported statistically significant differences), but doses, supplementation duration, and population characteristics varied across studies. In 9 studies reporting significantly lower leptin and/or higher adiponectin levels the EPA+DHA dose was 0.52 to 4.2 g/day for 4 to 24 weeks. Additional studies are warranted which assess dose parameters and patient populations similar to studies reporting significant effects of EPA+DHA on leptin or adiponectin in order to evaluate the extent of reproducibility before recommending EPA+DHA as a therapy to target these adipokines.

Abbreviations: EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; PUFAs, polyunsaturated fatty acids; TNF-α, tumor necrosis factor-alpha; IL-1β, interleukin-one beta; IL-6, interleukin-six; LAR, leptin to adiponectin ratio; PRISMA, preferred reporting items for systematic reviews and meta-analyses; REDCap, research electronic data capture; RCTs, randomized controlled trials; g/d, gram per day; BMI, body mass index.

* Corresponding author at: School of Nursing, Indiana University Fort Wayne, LA-309b, 2101 E Coliseum Blvd, Fort Wayne, IN 46805, USA.
E-mail address: annijr08@outlook.com (J. Rausch).

https://doi.org/10.1016/j.nutres.2020.11.002

1. Introduction

More than half of all older adults (≥65 years of age) in the United States have 3 or more chronic conditions with an inflammation component to their pathobiology [1]. Studies show that unlike acute inflammation, chronic low-grade systemic inflammation associated with aging increases risk for developing or exacerbating many of these chronic conditions (e.g., cardiovascular disease, diabetes, arthritis, and certain cancers) [2-5]. Humans are susceptible to inflammation in aging because of body composition changes (e.g., decreased muscle mass, increased adipose tissue mass), imbalances between availability and demand of energy, and weakened immune systems that occur over time [3,6]. Compared to younger individuals, those 50 and older have 2 to 4 times higher circulating levels of activated leukocytes and proinflammatory mediators, such as tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β) and interleukin-6 (IL-6) [4,7]. Moreover, emerging evidence suggests that 2 circulating adipokines, leptin and adiponectin, are also mediators of inflammation and may be novel targets for interventions to temper the chronic systemic inflammation that occurs with aging and is detrimental to health [8-10].

Leptin is a peptide hormone primarily produced and secreted by adipocytes (fat cells) located in adipose tissue [8]. It is a strong indicator of total body fat status and a key regulator of appetite, metabolism, and behavior. Additionally, recent evidence indicates that leptin exhibits proinflammatory actions, including regulating T-cells, upregulating phagocytic function of macrophages, increasing production of proinflammatory cytokines, and stimulating reactive oxygen species [11-13]. Adiponectin, one of the most abundant peptide hormones in the human body, is produced and secreted primarily by the mitochondria of adipocytes in adipose tissue [9,14-16]. Recent studies show that adiponectin has potent anti-inflammatory actions, including inhibiting production of proinflammatory cytokines (e.g., TNF-α, IL-6), inhibiting adhesion molecules, and increasing anti-inflammatory cytokine production (e.g., IL-10) [9,13,16]. After secretion, both leptin and adiponectin circulate in blood as hormones that act on the immune system [9,10,15,17]. The proposed actions of leptin and adiponectin on immune cells involved in regulating inflammation are depicted in Fig. 1. While measuring leptin or adiponectin levels in peripheral circulation may be helpful in determining the status of systemic inflammation, recent studies indicate that considering the leptin-to-adiponectin ratio (LAR) may be more valuable [18-20]. Human studies show that higher LARs indicates higher levels of systemic inflammation and may be a more accurate indicator of inflammatory disease risk than leptin or adiponectin individually [21-25]. Given the increasing evidence that inflammation in aging contributes to the development of multiple chronic diseases in aging and that leptin and adiponectin are involved in modulating systemic inflammation, it is important to evaluate safe, low cost interventions that could potentially target these hormones. Findings from animal and human studies suggest that marine-derived omega-3 fatty acids, eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA), long known for their anti-inflammatory actions, may lower leptin levels and increase adiponectin levels [26,27].

A diet rich in marine-derived omega-3 polyunsaturated fatty acids (PUFAs) was first reported to reduce the risk of cardiovascular disease by Dyerberg and colleagues who studied diets of Greenland Eskimos [28]. Since then, EPA+DHA supplementation has been shown to reduce triglyceride levels and plaque formation and improve symptoms or outcomes of other chronic conditions with an inflammatory component to their pathobiology (e.g., cardiovascular disease) [29]. It has been hypothesized that EPA+DHA may alter leptin and adiponectin levels in terms of tempering inflammation by (1) altering gene expression of *Lep* and *Adipoq* (genes that encode for leptin and adiponectin respectively) [30,31], (2) reducing adipocyte size [32-34], (3) decreasing weight and total adiposity [32,34], and/or 4) improving insulin sensitivity [32,34,35].

While EPA+DHA supplementation has long been associated with anti-inflammatory outcomes [36,37], their mechanisms of action are not entirely known. While some human studies report that EPA+DHA supplementation may have favorable effects on leptin and adiponectin, in terms of reducing inflammation, it is important to evaluate the collective evidence from current literature about this important topic using a systematic approach.

The purpose of the present study was to evaluate and synthesize findings from recent randomized controlled trials (RCTs) that reported the effects of EPA+DHA supplementation on levels of leptin and adiponectin in peripheral circulation by performing a systematic review. We searched PUBMED, CINAHL, Scopus, Web of Science, and Cochrane Trials and the reference lists of pertinent review articles [38-45] up to June 10, 2018 using the keywords: "leptin OR adiponectin" AND "inflammation" AND "PUFAs OR fish oil OR fish oils OR polyunsaturated fatty acids OR omega 3 OR DHA OR EPA OR eicosapentaenoic acid OR docosahexaenoic acid."

2. Approach

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [46,47] guidelines and checklist throughout design, implementation, data extraction, analysis, and reporting.

2.1. *Search methods for study identification*

Five electronic databases (PUBMED, CINAHL, Scopus, Web of Science, and Cochrane Trials) and citation lists of pertinent review articles [38-45] were searched using predesigned search strategies. The search was not limited by date to include all relevant studies published up to the final search date of June 10, 2018. Databases were searched using related keywords of MeSH and non-MeSH terms for marine omega-3 fatty acids, inflammation, and adipokines. The search string used in all databases was "leptin OR adiponectin" AND "inflammation" AND "PUFAs OR fish oil OR fish oils OR polyunsaturated fatty acids OR omega 3 OR DHA OR EPA OR eicosapentaenoic acid OR docosahexaenoic acid."

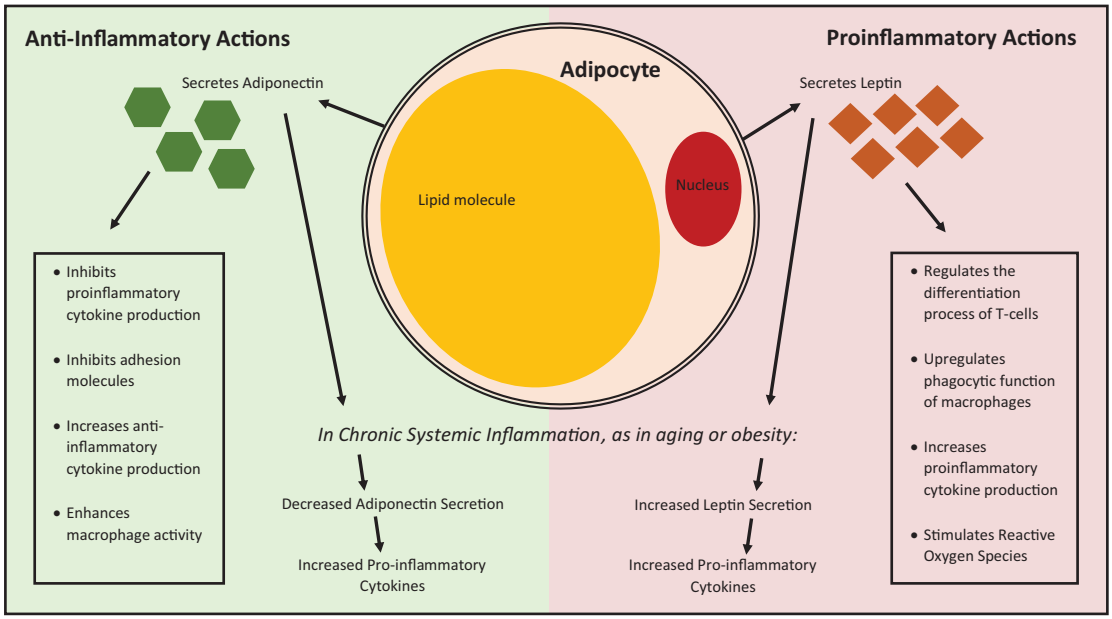

Fig. 1 – Role of leptin and adiponectin in inflammation. Proposed effects of leptin and adiponectin on immune cells are shown. Adipocytes produce and secrete leptin and adiponectin which circulate as hormones. The left side of the diagram shows the anti-inflammatory effects of adiponectin while the right side of the diagram shows the proinflammatory effects of leptin. In chronic systemic inflammation, as seen in obesity and aging, adiponectin levels are decreased, and leptin levels are increased. This imbalance of leptin and adiponectin levels results in increased stimulation of proinflammatory immune cells and decreased stimulation of anti-inflammatory cells, which promotes inflammation.

2.2. *Eligibility criteria*

We included all prospective studies that included a supplementation of EPA or DHA and reported measures of leptin, adiponectin, or LAR in blood. Studies were included in this review if they were: (1) peer-reviewed, (2) randomized trials of human adults, (3) contained leptin or adiponectin measures, and (4) used an intervention of EPA and/or DHA supplementation. Studies were excluded that included (1) animals, (2) children, or (3) pregnant women.

2.3. *Study selection*

Two investigators, J.R. and J.M., independently screened titles and abstracts of all articles that were identified for eligibility. They independently reviewed the full texts of the remaining articles to establish inclusion or exclusion. Corresponding authors of studies without sufficient data for meta-analysis were contacted for additional information. When articles included overlapping data, the most comprehensive articles were chosen. Disagreements were resolved through discussions until consensus was reached.

2.4. *Data extraction and quality assessment*

Data from all articles that met inclusion criteria were extracted independently by investigators J.R. and S.G. and managed using Research Electronic Data Capture (REDCap) [48]. Data retrieved included country of origin, study design, blinding, study population characteristics, duration of follow-up, intervention dose, placebo substance and dose, leptin, adiponectin, LAR, and attrition.

J.R. and S.G. assessed studies that met inclusion criteria for risk of bias using the Cochrane Risk of Bias Tool for Randomized Trials as outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* [49]. The Risk of Bias Tool for Randomized Trials assesses risk of biases associated with participant selection, performance, attrition biases, selective outcome reporting, and blinding. Reviewers reached consensus through discussions when disagreements occurred during bias assessment. Despite risks of bias, all studies were included to fully gage the state of the science (Table 1).

2.5. *Outcomes assessed*

The primary outcome measures investigated in this systematic review were leptin, adiponectin, and the LAR.

3. Results

3.1. *Study characteristics*

The electronic search was conducted in June 2018. A total of 714 records were identified through searching electronic databases. An additional 118 records were identified through hand searching references in pertinent reviews, resulting in a total of 832 records. After removing duplicates ($n = 276$), 556 records remained. By screening titles and abstracts, 494 records were excluded for not meeting inclusion criteria. Full

Table 1 – The Cochrane Risk of Bias Tool for Randomized Trials as outlined in the Cochrane Handbook for Systematic Reviews of Interventions was used to evaluate bias. The Risk of Bias summary for all articles included in the systematic review is listed below

Reference (citation)	Sequence generation	Allocation concealment	Blinding	Incomplete outcome data	Selective outcome reporting	Other sources of bias
Allaire et al. (2016) [50]	L	L	L	L	L	L
Gammelmark et al. (2012) [51]	L	N	L	L	L	L
Guebre-Egziabher et al. (2013) [52]	N	H	H	L	L	L
Haidari et al. (2015) [53]	N	L	L	L	L	N
Harving et al. (2015) [54]	N	L	L	N	L	N
Huerta et al. (2016) [55]	N	N	L	H	L	L
Itariu et al. (2012) [56]	L	N	H	L	L	L
Ito et al. (2014) [57]	L	H	H	H	N	H
Jacobo-Cejudo et al. (2017) [58]	N	N	H	L	L	L
Koh et al. (2012) [59]	L	L	H	L	L	L
Krantz et al. (2015) [60]	N	N	L	H	L	H
Krebs et al. (2006) [61]	N	N	L	L	L	L
Lee et al. (2014) [62]	N	N	L	L	L	L
Masson et al. (2013) [63]	N	N	L	N	N	N
Micallef and Garg. (2009) [64]	L	L	L	N	L	N
Mizia-Stec et al. (2011) [65]	N	N	H	L	L	L
Mohammadi et al. (2012) [66]	L	N	L	N	L	L
Munro and Garg (2012) [67]	L	L	L	L	L	N
Munro and Garg (2013) [68]	L	N	L	N	L	L
Patel et al. (2007) [69]	N	N	H	L	L	L
Poreba et al. (2017) [70]	L	H	L	L	L	L
Qin et al. (2015) [71]	L	L	L	L	L	L
Rizza et al. (2009) [72]	N	N	L	L	L	L
Sanyal et al. (2014) [73]	L	N	L	L	L	L
Satoh et al. (2009) [74]	N	N	N	L	L	L
Satoh-Asahara et al. (2012) [75]	N	N	H	L	L	N
Simao et al. (2012) [76]	N	N	N	N	L	L
Spencer et al. (2013) [77]	N	N	N	N	L	L
Troseid et al. (2009) [78]	N	N	N	H	L	L
Vargas et al. (2011) [79]	N	N	L	N	L	L
Yamamoto et al. (2014) [80]	N	H	H	N	L	L

H = High risk of bias; *L* = Low risk of bias; *N* = Neutral risk of bias.

texts of 62 remaining records were reviewed for eligibility. As a result, 31 records were excluded. Flow of articles, including reasons for full-text exclusion, are shown in the PRISMA diagram in Fig. 2. Thirty-one studies met criteria for inclusion in this systematic review [50-80].

Ten of 31 studies included in the review used more than two arms in their designs [55,59,61,62,64,73,76,78-80]. Data were reported from only arms that tested EPA, DHA, or EPA+DHA supplementation and the control arm most like the intervention group. For example, in the study by Micallef and Garg (2009), data from the arms that also received plant sterols were not included in this review.

Characteristics of the 31 RCTs included in this review are shown in Table 2. Fourteen studies were conducted in the United States ($n = 5$) or Europe ($n = 9$). Five studies were conducted in Asia, 3 in Australia, 2 in Iran, and 1 each in Mexico and Brazil. Five studies did not report locations. Twenty-nine studies used parallel designs. Remaining studies used a crossover design [50] and a 2 × 2 factorial design [64]. Double blinding (participants and researchers) occurred in 17 studies (53%). Five studies were single-blinded, and nine studies did not implement blinding.

Populations of interest in studies included in this review varied. Some studies focused on participants who were overweight/obese [50,51,55-57,67,68] or were at risk for or currently had cardiac disorders [53,60,63,65,69,78], lipid disorders [59,64,80], diabetes mellitus type 2 [58,72], metabolic syndrome [76,77], liver disorders [73], kidney disorders [52], or polycystic ovarian syndrome [79]. Eight studies investigated 2 or more of the above conditions [54,61,62,66,70,71,74,75]. Additionally, the length of the studies varied from as few as 3 weeks [64] to as long as 3 years [78].

Researchers used various approaches for control groups. For example, some studies used no intervention for the control group [57,80], some used a dietary supplementation intervention other than marine-derived fatty acids [74,78], while others used usual or standard care or diet alone as the control [65,69,75,76]. Twenty-five of 31 studies used an oil/fat as the control substance, such as corn oil [50,60,62,71,77], olive oil [51,54,63,72], sunola oil [64,67,68], soybean oil [79], sunflower oil [55], and butterfat [56]. One study used cornstarch as the control substance [58], and 2 used edible paraffin [53,66]. Two studies did not report control substance [59,73]. One study used an unnamed control substance in addition to a biweekly support group, where physical activity and low energy diet recommendations were made for the control group [61]. One study used supplement drinks as interventions. The active group used Smartfish drink (Smartfish, Oslo, Norway) that

Table 2 – Characteristics of articles included in systematic review

Reference; Country (citation)	Study Design	Blinding	Population	Duration (Weeks)	Intervention, dose in g/d	Age mean (SD)	% Males	BMI mean (SD)	Sample size total	% Attrition
Allaire et al. (2016), NR [50]	Crossover, 3-arm	Double	Men/ Women with Abdominal Obesity, CRP 1-10 mg/L	10	Corn Oil	NR	NR	29.3 (4.1)	125	18.8
					EPA, 2.7	NR	NR	29.3 (4.3)	121	21.4
					DHA, 2.7	NR	NR	29.4 (4.4)	123	20.1
Gammelmark et al. (2012); Denmark [51]	Parallel, 2-arm	Double	Overweight Men/ Women with increased WC	6	Olive Oil	NR	NR	NR	24	4
					EPA+DHA, 0.64+0.48	58 (7.4)	48	30.8 (4.2)	25	0
Guebre-Egziabher et al. (2013); France [52]	Parallel, 2-arm	None	Men/ Women with Chronic Kidney Disease, GFR < 20 mL/min, BMI <27	10	Moderate EPA+DHA, 1.08+0.72	50.5 (10.8)	66.7	23.2 (6.7)	6	0
					High EPA+DHA, 2.16+1.44	50.2 (6.7)	33.3	23.4 (3.8)	6	0
Haidari et al. (2015); Iran [53]	Parallel, 2-arm	Double	Men/ Women with BMI <30, recent Acute MI	10	Paraffin	NR	NR	28.8 (3.8)	21	0
					EPA+DHA, 0.54+0.36	NR	NR	24.8 (4.4)	21	0
Harving et al. (2015); Denmark [54]	Parallel, 2-arm	Double	Men/Women w/ESRD on HD, CVD	12	Olive Oil	68 (11)	64.6	24.5 (4.3)	79	23.3
					EPA+DHA, 0.76+0.6375	65.5 (11)	66.3	24.8 (4.4)	83	19.4
Huerta et al. (2016); Spain [55]	Parallel, 4-arm	Double	Caucasian, Sedentary Women w/BMI 27.5–40	10	Sunflower Oil + LA	38.9 (1.7)	0	33.2 (1.3)	21	NR
					EPA+DHA, 1.3+0.414	36.9 (2)	0	33 (0.8)	16	NR
Itariu et al. (2012); Austria [56]	Parallel, 2-arm	None	Severely Obese Men/ Women, nonDM, scheduled for Wt reduction surgery	8	Butterfat	38 (2)	17.9	44.6 (NR)	28	12.5
					EPA+DHA, 1.84+1.52	39 (2)	14.8	48.7 (NR)	27	10
Ito et al. (2014); Japan [57]	Parallel, 2-arm	None	Japanese Obese Men/Women with BMI >25	12	No Intervention	55.6 (12.7)	55.8	29.1 (4.2)	NR	NR
					EPA, 1.8	52.7 (13.5)	53.3	29.6 (4.4)	NR	NR
Jacobo-Cejudo et al. (2017); Mexico [58]	Parallel, 2-arm	Single	Men/Women with DM2, BMI <29.9 without other chronic diseases	24	Cornstarch	48.1 (6.8)	20	26 (1.6)	25	19.4
					EPA+DHA, 0.32+0.2	50.4 (6.3)	24.1	25.6 (2.4)	29	14.7
Koh et al. (2012); Korea [59]	Parallel, 3-arm	Single	Men/Women with HTCD	8	NR	54 (1)	59.2	25.2 (0.3)	49	2
					EPA+DHA 2**	55 (1)	56	25.5 (0.4)	50	0
Krantz et al. (2015); United States [60]	Parallel, 2-arm	Double	Caucasian Men/ Women with at least one risk factor for CVD, without a diagnosis of CVD	12	Corn Oil	60.2 (10.8)	37.1	31.5 (7.1)	35	NR
					EPA+DHA, 1.86+1.5	62.3 (9.7)	33.3	33.9 (8.6)	27	NR
Krebs et al. (2006); United Kingdom [61]	Parallel, 3-arm	Double	Overweight Women, BMI >27, hyper-insulinemia	24	Placebo + Wt Loss	NR	0	34.6 (5.3)	32	15.8
					EPA+DHA + Wt Loss, 1.3+2.9	NR	0	35.3 (5.6)	35	10.3
Lee et al. (2014); United States [62]	Parallel, 3-arm	Single	Men/ Women with early-stage DM2 or MetS	8	Corn Oil	59.9 (9.8)	28.6	34.8 (5.3)	21	16
					EPA+DHA, 3.58+2.44	56.2 (8.7)	37.5	33.2 (4.8)	16	20
Masson et al. (2013); NR [63]	Parallel, 2-arm	Double	Men/ Women with Chronic Heart Failure	12	Olive Oil	NR	79.6	NR	544	12.5
					EPA+DHA, 0.85+0.882	NR	80.1	NR	537	13.5
Micallef and Garg (2009); Australia [64]	Parallel, 4-arm, 2 × 2 Factorial	Double	Men/ Women with established combined HLPD	3	Sunola Oil	54.9 (2.6)	46.7	26.6 (1)	15	0
					EPA+DHA, 0.32+1.12	56.6 (2)	40	26.4 (1.3)	15	0

(continued on next page)

Table 2 (*continued*)

Reference; Country (citation)	Study Design	Blinding	Population	Duration (Weeks)	Intervention, dose in g/d	Age mean (SD)	% Males	BMI mean (SD)	Sample size total	% Attrition
Mizia-Stec et al. (2011); Poland [65]	Parallel, 2-arm	None	Men/Women with Acute MI & successful coronary stent placement	4	Standard Treatment	62 (NR)	84.2	27.5 (2.9)	19	0
					EPA+DHA, 0.465+0.375	56 (8)	73.7	27.2 (3.2)	19	0
Mohammadi et al. (2012); Iran [66]	Parallel, 2-arm	Double	Women w/PCOS, BMI 25-40	8	Paraffin	27.7	0	28.8 (2.9)	31	3.1
					EPA+DHA, 0.72+0.48	27.3 (4.3)	0	28.7 (3.2)	30	6.3
Munro and Garg (2012); Australia [67]	Parallel, 2-arm	Double	Men/ Women with BMI 30-40	14	Sunola Oil	42.3 (9.1)	21.4	33 (3.2)	14	30
					EPA+DHA, 0.42+1.62	40.5 (10.9)	16.7	32.7 (3.3)	18	10
Munro and Garg (2013); Australia [68]	Parallel, 2-arm	Double	Men/Women with BMI 30-40	12	Sunola Oil	41.1 (11.3)	33.3	32.5 (3.6)	18	NR
					EPA+DHA, 0.42+1.62	39.9 (11.7)	33.3	32.6 (2.1)	15	NR
Patel et al. (2007); NR [69]	Parallel, 2-arm	None	Men at least 3 months post MI	12	Usual Care	59.7 (9.5)	100	27.7 (5.7)	19	0
					EPA+DHA, 0.465+0.375	65.3 (7.6)	100	27.4 (3.7)	16	0
Poreba et al. (2017); NR [70]	Parallel, 2-arm	Double	Men/Women w/ DM2 & history of CAD or PAD	12	No EPA+DHA	66.7 (6.8)	68.4	NR	38	0
					EPA+DHA, 1+1	64.4 (6.7)	61.1	NR	36	5.3
Qin et al. (2015); China [71]	Parallel, 2-arm	Double	Men/Women with NAFLD & HLPD	12	Corn Oil	44.3 (10.9)	73.5	26 (2.8)	34	15
					EPA+DHA, 0.728+0.516	46 (10.7)	72.2	26.4 (3.9)	36	10
Rizza et al. (2009); Italy [72]	Parallel, 2-arm	Double	Adult Men/ Women offspring of persons with DM2 (1 or more parent)	12	Olive Oil	NR	NR	NR	24	0
					EPA+DHA, 1**	NR	NR	NR	26	0
Sanyal et al. (2014); United States [73]	Parallel, 3-arm	Double	Men/Women with biopsy-confirmed NASH within six months	48	NR	NR	NR	NR	55	NR
					High EPA, 2.7	NR	NR	NR	64	NR
Satoh et al. (2009); Japan [74]	Parallel, 2-arm	Single	Japanese Men/ Women with DLPD and MetS	12	Diet Only	52.2 (2.1)	41.3	30 (0.6)	46	0
					Diet + EPA, 1.8	51.3 (21)	31.3	30 (0.7)	46	0
Satoh-Asahara et al. (2012); Japan [75]	Parallel, 2-arm	Single	Overweight Japanese Men/ Women w/DLPD	12	Usual Care	54 (13)	66.7	29.1 (5.3	39	0
					EPA, 1.8	52.3 (13)	51.2	29.9 (4.9)	43	0
Simao et al. (2012); Brazil [76]	Parallel, 4-arm	None	Women with MetS	12	Usual Diet	47.1 (8.8)	0	NR	15	0
					EPA+DHA, 1.8+1.2	47.5 (9.2)	0	NR	19	0
Spencer et al. (2013); United States [77]	Parallel, 2-arm	Single	Men/ Women non-DM2 with impaired glucose tolerance, impaired fasting glucose or ≥ 3 features of MetS	12	Corn Oil	53.3 (2.2)	35.7	33.4 (1.1)	14	NR
					EPA+DHA, 4**	48.8 (2.3)	31.6	33.4 (2.3)	19	NR
Troseid et al. (2009); Norway [78]	Parallel, 4-arm	None	Men with a high risk of CVD	156	Diet Only	NR	100	NR	NR	NR
					EPA+DHA+ Diet, 1.8+1.2	NR	100	NR	NR	NR
Vargas et al. (2011); United States [79]	Parallel, 3-arm	Double	Women with PCOS	6	Soybean Oil	28.9 (1)	0	33.2 (1.8)	17	5.6
					EPA+DHA, 2.148+1.452	31.7 1.9)	0	36.3 (1.9)	17	19
Yamamoto et al. (2014); Japan [80]	Parallel, 4-arm	None	Men/ Women with HLPD	18	No Treatment	70.5 (7.9)	44.8	25 (4.5)	29	NR
					EPA, 0.9	71 (8.4)	58.1	25.7 (3.9)	31	4.5

Abbreviations: ALA, alpha-linoleic acid; BMI, body mass index, reported as kg/m^2; CAD, coronary artery disease; CVD, cardiovascular disease; DLPD, dyslipidemia; DM2, Type 2 Diabetes Mellitus; HLPD, hyperlipidemia; HTCD, hypertriglyceridemia; LA, linoleic acid; MetS, metabolic syndrome; MI, myocardial infarction; NAFLD, Nonalcoholic Fatty Liver Disease; NASH, Non-alcoholic steatohepatitis; NR, not reported in original manuscript or supplemental materials available; PAD, peripheral artery disease; PCOS, polycystic ovary syndrome. Age reported in years. **Did not specify amount of EPA or DHA individually in original manuscript.
Table includes study arms of the fish oil supplementation group and a control group; other arms of studies were not included for simplification of effects of fish oil compared to a control group.

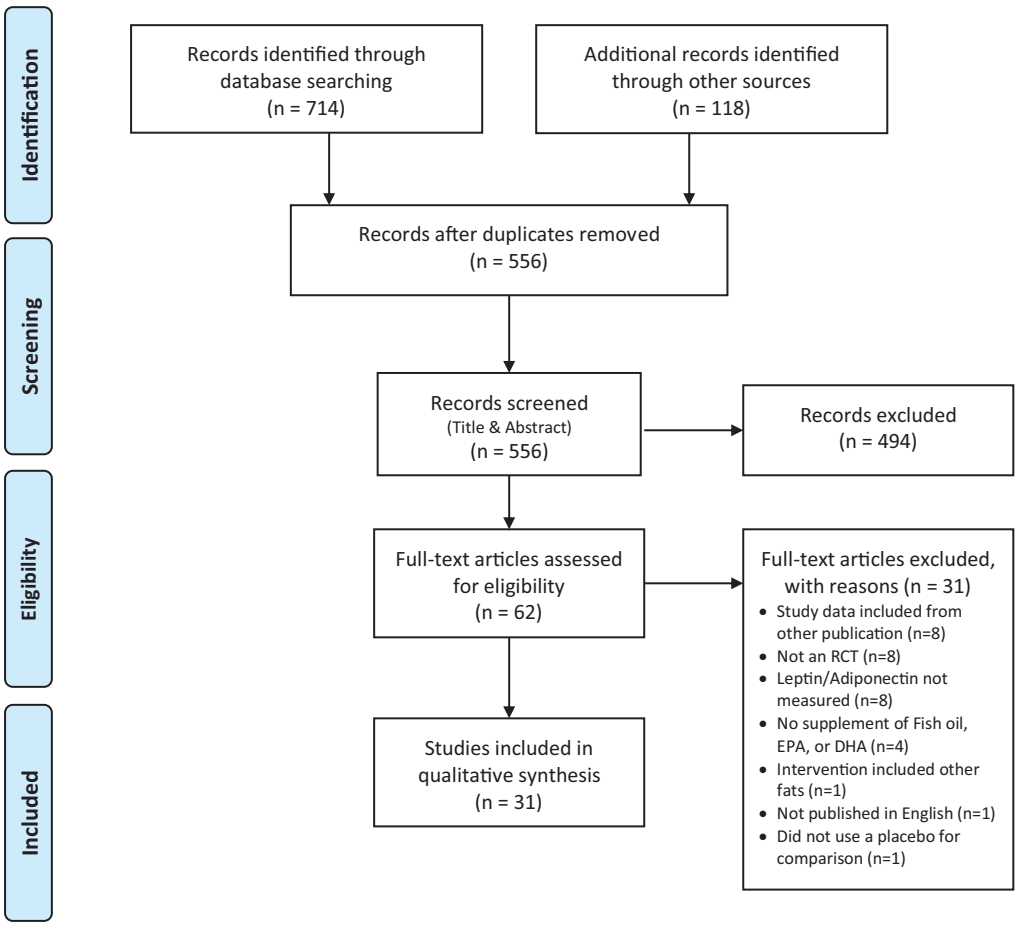

Fig. 2 – Selection process for article inclusion. The PRISMA diagram for the selection process of articles for inclusion. Thirty-one articles met eligibility requirements and were included in this systematic review. DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; RCT, randomized controlled trial.

included 1 gram per day (g/d) each of EPA+DHA plus botanical additives (pomegranate, chokeberry, and transresveratrol) to reduce oxidation. In that study, the placebo group received supplement drinks that included the same ingredients minus EPA+DHA [70]. One study compared a moderate dose of EPA+DHA to a higher dose of EPA+DHA [52].

Five studies assessed effects of EPA only versus control [57,73-75,80], and one study examined effects of EPA versus DHA versus control [50]. No studies examined DHA alone versus control. Most studies (n = 25) used a combined EPA+DHA intervention [51-56,58-72,76-79]. Diverse doses of EPA+DHA were used across studies. The lowest dose consisted of 0.32 g/d of EPA and 0.2 g/d of DHA for combined dose of 0.52 g/d [58]; the highest dose consisted of 3.5 g/d of EPA and 2.44 g/d of DHA for combined dose of 6.02 g/d [62].

Of the 31 studies included in this review, four reported the mean age of the participants as <40 years [55,56,66,79], 21 studies reported the mean age of participants as >40 years at the final study time point [50-52,54,57-65,67-71,74-77,80]. Four studies did not report the mean age per treatment group at final study time points [53,72,73,78]. Sample sizes of studies ranged from 12 [52] to 1081 [63] participants. Three studies did not disclose the sample size per treatment group at the study end point [57,78,80]. Five study samples included only women [55,61,66,76,79], and 2 studies included only men [69,78]. However, the majority of studies (n = 24) included both men and women.

Of studies that reported body mass index (BMI) (n = 26), most (n = 25) reported that participants had a mean BMI >25, which is considered overweight or obese by the Centers for Disease Control [81]. Four studies did not report mean BMI per treatment group at the study endpoint [70,73,76,78].

3.2. *Withdrawal*

Participant withdrawal rates in studies reporting attrition (n = 24) ranged from 0% [52,53,64,65,69,72,74-76] to 30% [67]. Only 3 studies reported withdrawal rates higher than 20% [50,54,67]. Although rates of withdrawal higher than 20% can indicate threats to validity, it is common to see higher rates when the duration of a trial is longer [82]. Studies with higher attrition rates had study durations of 10 [50], 12 [54], and 14 weeks [67], respectively. Seven studies did not disclose withdrawal rates at study end per treatment group [55,57,60,68,73,77,78].

3.3. Risk of bias

As shown in Table 1, most studies had a low or neutral risk of bias. One study had a high risk of bias in 4 categories of the Cochrane Risk of Bias Tool for Randomized Trials [57]. Other studies had a high risk of bias in one category [55,56,58,59,65,69,70,75,79], or 2 categories [52,60,80]. Remaining studies had low or neutral risk of bias in every category. Overall, the category with the most studies showing a high risk of bias was in blinding [52,56,57,60,61,65,69,75,80]. There was a high risk of bias in the allocation category in four studies [52,57,60,78]. Four studies displayed a high risk of bias in the incomplete outcome data category [55,57,60,78]. Other sources of bias were identified in 2 studies [57,60]. The 2014 Ito et al. study did not report baseline data for randomized groups to determine that groups were balanced. The 2015 Krantz et al. study stated that the dose of medication given might not have been adequate to decrease pulse wave velocity "particularly if compliance was suboptimal," however, the study did not discuss if or how compliance was measured. By not determining compliance within the study, a degree of bias was introduced. All studies had either a low or neutral risk of bias in the categories of sequence generation and selective outcome reporting. It is important to note that in some countries (e.g., Japan), comparing a placebo to an effective treatment such as EPA or DHA is not permitted [83]. Rather, the comparison must be between standard therapy and the drug being tested. In the included studies that were subject to this rule [57,74,75,80], randomization was implemented, however blinding was either single (researchers blinded to participant allocation in analyses), or there was no blinding.

3.4. Study findings

Eighteen of the 31 studies reported lower leptin levels or higher adiponectin levels with EPA+DHA supplementation when compared to the control group at the study endpoint. Nine of these studies reported that the between group differences at the study endpoint were statistically significant. Fourteen studies reported no effects of EPA and/or DHA supplementation on leptin, adiponectin, or LAR when compared to the control group at the study end point. However, doses, duration of supplementation, and populations of interest varied widely across studies.

Leptin and adiponectin data are often skewed and, therefore, analyzed on a transformed scale [84,85]. Of the 31 included articles, only nine reported that the leptin and/or adiponectin data distribution was checked for normality [51,53-56,66,71,72,77]. Of those 9, only 4 studies reported that the results for leptin and/or adiponectin data were normally distributed [56,71,72,77]. Additional information was requested from corresponding authors of studies wherein it was not clear if the leptin and adiponectin data were normalized before the analyses [52,57-65,67-70,73,75,76,78,79]. Responses were received from 3 corresponding authors [63,70,76]. Thus, a meta-analyses and effect size analyses for the studies were not conducted.

3.4.1. Effects of EPA and/or DHA on leptin

Sixteen studies reported effects of EPA or EPA+DHA on levels of leptin in peripheral circulation. Of those 16 studies, 12 reported lower levels of leptin in the EPA or EPA+DHA group compared to the control group at study end points [53,56-58,61,62,64,67,68,74,77,79] and 2 of those 12 studies reported that the differences were statistically significant [53,61]. Of the 16 studies reporting leptin levels as an outcome variable, 3 studies used only EPA supplementation (no DHA) and reported no significant differences in leptin levels between groups at the study end point [57,74,80]. Thirteen of the 16 studies used an EPA+DHA supplementation and of those 13 studies, 2 reported significantly lower leptin levels at study endpoints in the EPA+DHA groups compared to the control groups [53,61] (Table 3).

3.4.2. Effects of EPA and/or DHA on adiponectin

Thirty studies reported effects of EPA and/or DHA on levels of adiponectin in peripheral circulation. Eighteen of those 30 studies reported higher adiponectin levels in the treatment group compared to the control group at study endpoints, and 8 of those 18 studies reported that the between group differences were statistically significant [50,51,53,61,66,71,74,75]. Five of the 30 studies including adiponectin as an outcome variable used only EPA supplementation (no DHA) [57,73-75,80]. Two of those 5 studies reported significantly higher adiponectin levels in the treatment groups compared to the control groups at study endpoints [74,75]. Twenty-three studies evaluated effects of a combined EPA+DHA supplementation on adiponectin levels over time; 5 reported significantly higher adiponectin levels in EPA+DHA groups compared to control groups at study end points [51,53,61,66,71]. Allaire et al. (2016) compared effects of EPA versus DHA versus control on adiponectin levels and reported that the group receiving DHA supplementation had significantly higher levels of adiponectin compared to the EPA group and the control group at the study end point (Table 4).

3.4.3. Effects of EPA and/or DHA on leptin to adiponectin ratio

Only one study reported the LAR and in that study the LAR was significantly lower in the EPA+DHA group at the study endpoint compared to the LAR at the study onset [58]. There were no significant differences in the LAR between groups at the study end point. This study used a combined EPA+DHA dose of 0.52 g/d for 24 weeks (Table 5).

4. Discussion

This systematic review summarizes current evidence from RCTs about the effects of EPA or EPA+DHA supplementation on circulating levels of leptin and/or adiponectin, hormones involved in the regulation of systemic inflammation. Nearly all immune cells contain leptin receptors, indicating that leptin may be involved in all stages of the immune response [8]. For example, leptin has been shown to facilitate the production of the proinflammatory cytokines IL-1β, IL-6, and TNF-α by stimulating macrophage migration inhibitory factor [10]. Additionally, Loffreda et al. showed that leptin enhances the synthesis of proinflammatory cytokines by cultured macrophages [86].

Table 3 – Effect of marine omega-3 PUFAs on leptin reported in included studies

Reference (citation)	Method for leptin	Group name	Leptin baseline (ng/mL)	Leptin at study end (ng/mL)	Change in leptin mean	Reported findings (between groups), analysis used	Treatment group significantly higher (+), significantly lower (-) or no difference (ND) than Placebo group
Guebre-Egziabher et al. (2013) [52]	ELISA	Moderate EPA+DHA	20.3 (12.7)	23.4 (14.9)	3.1	No significant differences, np.	ND
		High EPA+DHA	19.8 (6.6)	23.8 (8.5)	4		
Haidari et al. (2015) [53]	ELISA	Paraffin	15.2 (3.9)	9.1 (2.7)	−6.1	Significantly lower in EPA+DHA group ($p = 0.007$), pm.	↓
		EPA+DHA	14.2 (4.8)	6.9 (2.7)	−7.3		
Itariu et al. (2012) [56]	RIA	Butterfat	66 (4.6)	70.3 (4.1)	4.3	No significant differences, pm.	ND
		EPA+DHA	69.7 (3.6)	69 (3.6)	−0.7		
Ito et al. (2014) [57]	NR	No Intervention	9.9 (6.3–19.4)	10.9 (5.8–19.6)	UTD	No significant differences, np.	ND
		EPA	11.2 (6.6–19.2)	9.5 (6.7–16.5)	UTD		
Jacobo-Cejudo et al. (2017) [58]	Luminometry	Cornstarch	18.4 (13.2)	3.5 (2.3)	−14.9	No significant differences, pm.	ND
		EPA+DHA	21.7 (15.5)	3.9 (2.5)	−17.8		
Krebs et al. (2006) [61]	ELISA	Placebo + Wt Loss	25.9 (16.8)	13.6 (11.5)	−12.3	Significantly lower in EPA+DHA + Wt Loss group ($p = 0.0007$), np.	↓
		EPA+DHA + Wt Loss	26.7 (14.9)	16.8 (10.3)	−9.9		
Lee et al. (2014) [62]	NR	Corn Oil	53.5 (6.8)[e]	44.2 (5.3)[e]	−9.3	No significant differences, np.	ND
		EPA+DHA	45.1 (11)[e]	40.6 (7.2)[e]	−4.5		
Micallef and Garg (2009) [64]	EIA	Sunola Oil	15.1 (2.7)	NR	UTD	No significant differences, NR.	ND
		EPA+DHA	19.1 (5.2)	16.1 (4.6)	−3		
Munro and Garg (2012) [67]	ELISA	Sunola Oil	32.2 (14.4)	20.9 (9.8)	−11.3	No significant differences, NR.	ND
		EPA+DHA	32.1 (20.2)	18.2 (11.5)	−13.9		
Munro and Garg (2013) [68]	EIA	Sunola Oil	34.3 (13.5)	35.8 (19.4)	1.5	No significant differences, NR.	ND
		EPA+DHA	36.3 (20)	35.4 (20.6)	−0.9		
Patel et al. (2007) [69]	ELISA	Usual Care	NR	NR	−1.9^	No significant differences, np.	ND
		EPA+DHA	NR	NR	−0.2^		
Poreba et al. (2017) [70]	RIA	No EPA+DHA	6.6 (5.1)	8 (5.5)	1.4	No significant differences, np.	ND
		EPA+DHA	4.9 (4.7)	5 (4.5)	0.1		
Satoh et al. (2009) [74]	RIA	Diet Only	15.2 (1.6)	14 (0.4)	−1.2	No significant differences, pm.	ND
		Diet + EPA	16.1 (1.6)	13.8 (0.5)	−2.3		
Spencer et al. (2013) [77]	Luminex	Corn Oil	34.5 (3.8)	36.2 (5.9)	1.7	No significant differences, pm.	ND
		EPA+DHA	52.5 (10.8)	48.2 (9.1)	−4.3		
Vargas et al. (2011) [79]	RIA	Soybean Oil	28.1 (3.4)	30.6 (4.3)	2.5	No significant differences, np.	ND
		EPA+DHA	29.8 (3.5)	29.4 (3.2)	−0.4		
Yamamoto et al. (2014) [80]	NR	No Treatment	11.1 (7)	10.8 (6.5)	−0.3	No significant differences, pm.	ND
		EPA	10.8 (9.7)	12.3 (14.6)	1.5		

Abbreviations: EIA, Enzyme Immunometric Assay; IFMA, Immunoflourometric Assay; np, Nonparametric testing used in original study; NR, Not reported; pm, parametric testing used in original study; QIA, Quantikine Immunoassay; RIA, Radioimmunoassay; UTD, Unable to Determine; Wt, Weight; e, unit not reported.
Leptin levels are listed as mean (SD) or median (interquartile range), as reported in original manuscript. Leptin was converted to ng/mL when reported under different measures.
^Change as reported in original manuscript.

Table 4 – Effect of marine omega-3 PUFAs on adiponectin reported in included studies

Reference (citation)	Method for adiponectin measurement	Group name	Adiponectin baseline (mcg/mL)	Adiponectin study end (mcg/mL)	Adiponectin CHANGE	Reported findings (between groups), analysis used	Treatment group significantly Higher (+), significantly Lower (-), or no difference (ND) than placebo group
Allaire et al. (2016) [50]	ELISA	Corn Oil	7.2 (5.5)	7 (0.5)	−0.2	Significantly higher in DHA group compared to control group, ($P = .047$) and compared to EPA group ($P < .001$) at study end, pm.	↑
		EPA	7 (5.5)	NR	UTD		
		DHA	7 (5.2)	NR	UTD		
Gammelmark et al. (2012) [51]	ELISA	Olive Oil	9.1 (5.3)	9.1 (5.4)	0	Significantly higher in EPA+DHA group compared to control ($P = .04$), pm.	↑
		EPA+DHA	7.1 (4.8)	7.6 (5.7)	0.5		
Guebre-Egziabher et al. (2013) [52]	QIA	Moderate EPA+DHA	15.4 (4.6)	17.1 (4.6)	1.7	No significant differences, NR.	ND
		High EPA+DHA	19.5 (3)	20.8 (1.3)	1.3		
Haidari et al. (2015) [53]	ELISA	Paraffin	5.1 (2.8)	6.6 (4.1)	1.5	Significantly higher in EPA+DHA group compared to control ($P = .026$), pm.	↑
		EPA+DHA	5.3 (2.7)	7.2 (3.5)	1.9		
Harving et al. (2015) [54]	IFMA	Olive Oil	20.8 (12)	20.8 (13.2)	0	No significant differences, NR.	ND
		EPA+DHA	18.6 (11.7)	18.8 (12.1)	0.2		
Huerta et al. (2016) [55]	ELISA	Sunflower Oil + LA	12.8 (1.3)	13.2 (1.2)	0.4	No significant differences, np.	ND
		EPA	12.1 (0.9)	12 (1.4)	−0.1		
Itariu et al. (2012) [56]	RIA	Butterfat	8.9 (0.6)	8.3 (0.6)	−0.6	No significant differences, pm.	ND
		EPA+DHA	8.4 (0.7)	8.3 (0.6)	−0.1		
Ito et al. (2014) [57]	NR	No Intervention	5.5 (3.8–7.6)	6.1 (3.9–7.7)	UTD	No significant differences, np.	ND
		EPA	5.2 (3.8–6.6)	6.5 (4.6–8.3)	UTD		
Jacobo-Cejudo et al. (2017) [58]	Luminometry	Cornstarch	22.8 (10.5)	24.3 (13.3)	1.5	No significant differences, np.	ND
		EPA+DHA	23.6 (20.3)	24.5 (13)	0.9		
Koh et al. (2012) [59]	ELISA	NR	2.4 (1.7–3.5)	2.4 (1.8–3.1)	UTD	No significant differences, np.	ND
		EPA+DHA	2.5 (1.7–3.3)	2.2 (1.8–3.4)	UTD		
Krantz et al. (2015) [60]	NR	Corn Oil	10.6 (8.3)	NR	0.3	No significant differences, np.	ND
		EPA+DHA	12.2 (7.8)	NR	−0.4		
Krebs et al. (2006) [61]	RIA	Placebo + Wt Loss	11.4 (7.6)	11.2 (6)	−0.2	Significantly higher in EPA+DHA + Wt Loss group ($P = .0012$), np.	↑
		EPA+DHA + Wt Loss	10.5 (5.1)	12.9 (6.3)	2.4		
Masson et al. (2013) [63]	Time-resolved IFMA	Olive Oil	10.8	10.5	−0.3	No significant differences, np.	ND
		EPA+DHA	11.0	10.7	−0.3		
Micallef and Garg (2009) [64]	ELISA	Sunola Oil	2.1 (0.1)	NR	UTD	No significant differences, NR.	ND
		EPA+DHA	1.5 (0.2)	1.7 (0.2)	200		
Mizia-Stec et al. (2011) [65]	ELISA	Standard Treatment	12,100 (9700)	19,400 (12,700)	7300	No significant differences, np.	ND
		EPA+DHA	12,500 (7800)	14,100 (8000)	1600		

(*continued on next page*)

Table 4 (*continued*)

Reference (citation)	Method for adiponectin measurement	Group name	Adiponectin baseline (mcg/mL)	Adiponectin study end (mcg/mL)	Adiponectin CHANGE	Reported findings (between groups), analysis used	Treatment group significantly Higher (+), significantly Lower (-), or no difference (ND) than placebo group
Mohammadi et al. (2012) [66]	ELISA	Paraffin	12.3 (3.6)	12 (3.1)	−0.3	Significantly higher in EPA+DHA group ($P < .05$), NR.	↑
		EPA+DHA	11.8 (3.2)	13.5 (2.4)	1.7		
Munro and Garg (2012) [67]	ELISA	Sunola Oil	10.2 (5.7)	12 (8.3)	1.8	No significant differences, NR	ND
		EPA+DHA	10 (6)	9.1 (5.2)	−0.9		
Munro and Garg (2013) [68]	ELISA	Sunola Oil	12.2 (6.4)	13.4 (7.3)	1.2	No significant differences, NR	ND
		EPA+DHA	13.3 (4.9)	13 (6.4)	−0.3		
Patel et al. (2007) [69]	ELISA	Usual Care	NR	NR	0.044	No significant differences, np.	ND
		EPA+DHA	NR	NR	0.17		
Poreba et al. (2017) [70]	RIA	No EPA+DHA	4.89 (2.40)	4.67 (2.26)	−0.22	No significant differences, np.	ND
		EPA+DHA	3.62 (1.93)	3.73 (1.96)	0.11		
Qin et al. (2015) [71]	ELISA	Corn Oil	5.1 (0.6)	5.2 (0.8)	0.1	Significantly higher in EPA+DHA group ($P < .001$), pm.	↑
		EPA+DHA	5.1 (0.5)	6.4 (0.4)	1.3		
Rizza et al. (2009) [72]	ELISA	Olive Oil	10.6 (5.4)	8.4 (4.7)	−2.2	No significant differences, pm.	ND
		EPA+DHA	7.8 (4.5)	9.5 (5.1)	1.7		
Sanyal et al. (2014) [73]	NR	NR	4.4 (3, 6.8)	NR	0.16 (−0.28, 0.97)	No significant differences, np.	ND
		High EPA - E	4.2 (3.3, 6.4)	NR	0.01 (−0.49, 0.770)		
Satoh et al. (2009) [74]	RIA	Diet Only	7 (0.5)	7 (0.4)	0	Significantly higher in EPA group ($P < .01$), pm.	↑
		Diet + EPA	7 (0.5)	7.5 (0.5)	0.5		
Satoh-Asahara et al. (2012) [75]	NR	Usual Care	6.5 (4.3–8.7)	6.2 (4.3–8)	UTD	Significantly higher in EPA group ($P < .05$), np.	↑
		EPA	6.1 (4.3–7.2)	6.6 (4.4–8.8)	UTD		
Simao et al. (2012) [76]	ELISA	Usual Diet	112.2 (56.6–136.8)	112.6 (74.7–162.9)	UTD	No significant differences, np.	ND
		EPA+DHA	68.2 (47–78.9)	86.6 (51.4–131.6)	UTD		
Spencer et al. (2013) [77]	ELISA	Corn Oil	0.004 (0.0008)	0.0039 (0.0007)	−0.0001	No significant differences, pm.	ND
		EPA+DHA	0.0043 (0.0008)	0.0041 (0.0006)	−0.0002		
Troseid et al. (2009) [78]	EIA	Diet Only	9.3 (5.5–13.4)	8.5 (5.2–13.6)	UTD	No significant differences, np.	ND
		EPA+DHA + Diet	9 (5.3–13.8)	8.3 (5.2–13.8)	UTD		
Vargas et al. (2011) [79]	RIA	Soybean Oil	0.0065 (0.0012)	0.0062 (0.0011)	−0.0003	No significant differences, np.	ND
		EPA+DHA	0.0075 (0.001)	0.0085 (0.0013)	0.001		
Yamamoto et al. (2014) [80]	NR	No Treatment	14.5 (3.5)	14.8 (5)	0.3	No significant differences, pm.	ND
		EPA	10.4 (7.1)	12.5 (8.5)	2.1		

Abbreviations: EIA, Enzyme Immunometric Assay; IFMA, Immunoflourometric Assay; NR, Not reported; np, Nonparametric testing used in original study; pm, parametric testing used in original study; QIA, Quantikine Immunoassay; RIA, Radioimmunoassay; UTD, Unable to Determine: due to missing data from original manuscript. Adiponectin was converted to mcg/mL when reported under different measures.
Adiponectin levels are listed as mean (SD) or median (interquartile range), as reported in original manuscript.

Table 5 – Effect of marine omega-3 PUFAs on leptin to adiponectin ratios (LARs) reported in included studies

Reference (citation)	Group name	LAR baseline	LAR Study end	LAR CHANGE	Treatment group significantly higher (+), significantly lower (-), or no difference (ND) than placebo group
Jacobo-Cejudo et al. (2017) [58]	Cornstarch EPA+DHA	0.88 (0.68) 1.3 (1.2)	0.17 (0.12) 0.24 (0.26)	−0.71 −1.06[a]	ND

The final column indicates that LARs between groups were not statistically different.
[a] Within group comparison from baseline to study end in the EPA+DHA treated group.

Thus, leptin may play a significant role in triggering and maintaining high levels of proinflammatory cytokines in systemic circulation that have been associated with chronic systemic inflammation in aging [2,3,87]. Conversely, adiponectin has been shown to act on proinflammatory mediators by decreasing monocyte production of TNF-α and IL-6 [10,16]. Additionally, Ouchi et al. reported adiponectin enhances anti-inflammatory cytokines by stimulating macrophage production of interleukin-10 [16]. As such, adiponectin actions may play an important role in reducing or preventing the persistent inflammation in peripheral circulation that has been linked to multiple chronic diseases common to the aging population.

In terms of the effect of EPA or EPA+DHA supplementation on leptin, we report that 12 of 16 studies included in this review that measured leptin levels reported lower leptin levels in the EPA or EPA+DHA groups compared to the control groups by the study end points [53,56,58,61,62,64,67-69,74,77,79]. However, only 2 of these studies found the between-group differences to be statistically significant [53,61]. The 2 studies that found statistically significant differences at study endpoints both used combined EPA+DHA supplements and were conducted over 10 and 24 weeks, respectively.

Fifteen of the 31 studies included in this review included adiponectin as a primary outcome variable and reported that adiponectin levels in peripheral circulation were higher in the EPA or EPA+DHA supplementation group by study end point [50-54,58,61,64,65,69-72,74,75]. Eight of those studies reported that the between-group differences were statistically significant [50,51,53,61,66,71,74,75]. All 8 studies reporting statistically significant increases in adiponectin had a study duration of $\geq$ 6 weeks, and all but 3 [50,74,75] used a combination EPA+DHA intervention.

4.1. *Effect of intervention on the LAR and clinical outcomes*

Using the LAR as a marker of inflammation status and/or as a method to predict inflammatory disease risk in younger populations may be more effective than considering leptin or adiponectin levels alone [19,21,25]. Only 1 study out of the 31 studies included in this review reported the LAR [58]. The EPA+DHA group in this study showed a significant reduction in the LAR at the study end point compared to baseline and greater improvements in clinical outcomes. This study population consisted of men and women (mean age of 49 years) with Type II diabetes, a BMI <29.9 and no other chronic diseases. In this sample, there were significant improvements reported for blood lipids, blood glucose, waist circumference, hemoglobin A1c, and atherogenic index.

4.2. *Effect of study duration*

Studies that showed significant reductions to leptin levels in the intervention group compared to the control group ranged from 10 weeks [53] to 24 weeks [61] duration. Similarly, studies that showed significant increases to adiponectin levels in the intervention group compared to the control group, durations ranged from 6 weeks [51] to 24 weeks [61]. Studies that showed no significant changes in leptin or adiponectin ranged from 4 weeks [65] to 156 weeks [78]. The study reporting LAR was 24 weeks in duration [58].

4.3. *Effect of dose*

The daily dose of EPA or EPA+DHA used in studies included in this review varied widely. The average dose of EPA+DHA in studies reporting significant reductions in leptin at study end compared to baseline was 2.8 g/d (0.9 g/d-4.2 g/d) [53,61]. In the 2 studies reporting significantly lower levels of leptin in the EPA+DHA group versus control group by study end, one used a dose of EPA+DHA of 4.2 g/d for 24 weeks [61], while the other used a dose of EPA+DHA of 0.9 g/d for 10 weeks [53].

The average dose of EPA+DHA in studies reporting significant increases in adiponectin at study endpoint compared to baseline was 1.87 g/d (0.9 g/d-4.2 g/d) [50,51,53,61,66,71,74,75]. Similarly, of 8 studies that reported significantly higher levels of adiponectin in the EPA or EPA+DHA group compared to control group, 4 used doses of EPA or EPA+DHA $\geq$1.8 g/d [50,61,74,75], and three used combined doses $\geq$1 g/d [51,66,71]. The eighth study used 0.9 g/d of combined EPA+DHA [53]. Of the studies reporting significantly higher levels of adiponectin in the EPA+DHA group at the study end point compared to the control group, study duration ranged from 6 weeks [51] to 24 weeks [61]. These findings align with current literature suggesting that an EPA+DHA dose of $\geq$2 g/d for 4 weeks or more may be needed to maximize anti-inflammatory actions [88,89].

4.4. *Side effects*

Side effects associated with EPA or EPA+DHA supplementation were reported in five studies included in this review [50,56,62,67,76]. Side effects included fishy taste, gastrointestinal irregularities, psychotic episode ($n = 1$), and a "reaction" to

supplements. In the Allaire et al. (2016) study, researchers reported that there were no differences in reported side effects between groups. The low incidence of side effects reported by the collective studies included in this review is aligned with previous literature showing that EPA+DHA supplementation in doses of up to 3 g/d is safe for the general public and thus is considered a low-risk dietary intervention [90]. Moreover, some studies testing even higher doses of EPA+DHA (up to 8 g/d) have reported no side effects or adverse outcomes associated with the intervention [88,91].

4.5. *Strengths*

There are several strengths to this review. By using multiple databases, broad search terms, and alternative search methods, this systematic review provides a thorough synthesis of published literature. Additionally, this systematic review included all articles meeting inclusion criteria up to the date searches were conducted, June 10, 2018. Authors were contacted when further information was needed; however, only 3 of 19 replied. The review was limited to RCTs, and most ($n = 17$) employed double-blind designs. The analysis of quality of studies revealed most studies were conducted with low risk of bias in all categories of the Cochrane Risk of Bias Tool for Randomized Trials. Only one study showed a high risk of bias in more than 2 categories [57].

4.6. *Limitations*

There were some limitations to this review. First, a degree of bias may have been introduced by excluding papers not written in English or not published in a peer-reviewed journal. Additionally, manuscripts yet to be published on electronic databases may have been missed during the search. There is also a potential for nonpublication of trials with negative results as well as selective reporting among published studies, particularly when either leptin or adiponectin levels were reported alone. Although the LAR has been recently identified as a better indicator of inflammatory status than leptin or adiponectin alone [92-94], only one study included LAR calculations. Including LAR calculations into future studies would facilitate comparison of this important metric across studies. Finally, we could not perform a meta-analysis of pooled data because not all studies included in this review reported whether the leptin and/or adiponectin data had been normalized.

Given that chronic conditions with an inflammatory component (e.g., cardiovascular diseases, diabetes, and cancer) are a growing concern in aging populations [1], it is important to determine effective, low risk, low cost interventions to help prevent, reduce risk for, or improve control of these conditions. Dietary supplementation with EPA+DHA has been found to improve symptoms and outcomes for multiple chronic inflammatory conditions, including cardiovascular diseases, diabetes, and cancer [26,28,39,95], but their mechanisms of action are not definitively known. Collective findings of this systematic review suggest that EPA+DHA supplementation may help balance circulating levels of leptin and adiponectin, peptide hormones involved in regulating systemic inflammation.

Although the 31 RCTs included in this systematic review, evaluated the effects of EPA and/or DHA on circulating levels of leptin and/or adiponectin, missing knowledge remains. First, the exact mechanisms of EPA+DHA action on leptin and adiponectin are not completely known. Second, the optimal dose and duration of EPA+DHA supplementation needed to affect a change in levels of leptin and/or adiponectin individually has not been determined. Third, the omega-3 fatty acids have been shown to have anti-inflammatory actions through other mechanisms, such as via the metabolic pathway that leads to the synthesis of endocannabinoids [96-98]. Yet, to our knowledge, the effect of these novel metabolites on leptin and adiponectin production and secretion have not been fully elucidated. Finally, identification of normal levels of leptin, adiponectin and LARs in all BMI groups have not been definitively determined.

In summary, this systematic review of RCTs was conducted to determine what is currently known about effects of EPA+DHA on circulating levels of leptin and adiponectin. Several studies included in this review (18 of 32) reported that EPA+DHA supplementation decreased leptin levels and LARs and/or increased adiponectin levels (Table 6).

5. Recommendations for future research

Given the variation in EPA+DHA dose, duration of supplementation, and population characteristics across the studies included in this review, additional RCTs are warranted which assess dose parameters and patient populations similar to the previous RCTs reporting significant effects of EPA+DHA supplementation on leptin and adiponectin in order to evaluate the extent of reproducibility. Other factors, including the placebo form, background dietary omega-3 intakes, and use of statins and other therapies might also explain the conflicting findings among studies in this review. Therefore, it is recommended that scientists involved in future RCTs consider these factors during the design phase. It is also suggested that future studies measure levels of all fatty acids in blood in study participants, preferably in blood cells (e.g., erythrocytes, adipocytes) at all study time points. This would be helpful for determining the effect of other fatty acids in the context of EPA+DHA supplementation and for ascertaining if there are differences in individual responses to supplementation.

In summary, additional studies are needed to clarify the extent to which EPA+DHA supplements modulate circulating levels of leptin and adiponectin and their impact on the chronic systemic inflammation linked to various common diseases in aging.

Author contributions

JR was responsible for conceptualization, writing – original draft review and editing, investigation, methodology, and visualization. JM was responsible for supervision, conceptualization, writing – original draft review and editing, investigation, methodology, and visualization. SG was responsible for writing – original draft review and editing, investigation, methodology, and visualization. TO was responsible

Table 6 – Summary of treatment group characteristics and the effects of n-3 PUFAs from RCTs with significant between-group findings

Reference (citation)	Sample size	BMI	Percentage of males	Mean age	Dose of EPA+DHA g/day	Duration (Weeks)	Blinding	Bias (# of low risk categories out of 6)	Effect on Leptin (L), Adiponectin (A), or LAR
Allaire et al. (2016) [50]	123	29.4	NR	NR	0 + 2.7	10	Double	6	↑A
Gammelmark et al. (2012) [51]	25	30.4	58	58	0.64 + 0.48	6	Double	5	↑A
Haidari et al. (2015) [53]	21	26.8	NR	NR	0.54 + 0.36	10	Double	4	↓L + ↑A
Jacobo-Cejudo et al. (2017) [58]	29	25.6	24.1	50.4	0.32 + 0.2	24	Single	3	↓LAR
Krebs et al. (2006) [61]	35	35.3	0	NR	1.3 + 2.9	24	Double	4	↓L + ↑A
Mohammadi et al. (2012) [66]	30	28.7	0	27.3	0.465 + 0.375	4	Double	4	↑A
Qin et al. (2015) [71]	36	26.4	72.2	46	0.728 + 0.516	12	Double	6	↑A
Satoh et al. (2009) [74]	46	30	31.3	51.3	1.8 + 0	12	Single	3	↑A
Satoh-Asahara et al. (2012) [75]	43	29.9	51.2	52.3	1.8 + 0	12	Single	2	↑A
TOTALS - 9 ARTICLES	**Mean 43.1; Range 21 - 123**	**Mean 29.17; Range 25.6 - 35.3**	**Mean 59.2%; Range 0 - 72.2%**	**Mean 47.55; Range 27.3 - 58***	**Range EPA - 0 - 1.8; DHA - 0 - 2.9**	**Mean 12.67; Range 4 - 24**	**6 Double/ 3 Single**	**Mean 4.1; Range 2 - 6**	**(↓L x 2), (↑A x 8), (↓LAR x 1)**

Abbreviations: A, Adiponectin; BMI, Body mass index; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; L, Leptin; LAR, Leptin-to-adiponectin ratio; NR, Not reported.

for writing – original draft review and editing. AT was responsible for writing – original draft review and editing, and methodology.

Acknowledgment

Authors acknowledge the assistance of Anna Biszaha for the valuable methodological support. Authors (JR, SG, TO, AT, and JM) declare they have no conflicts of interest concerning this manuscript. This paper presents independent research funded by The Robert Wood Johnson Foundation (RWJF), Future of Nursing Scholars (FNS) program in collaboration with The Ohio State University (OSU). This paper was completed without input from funders and expresses views of the authors and not necessarily those of the RWJF FNS or OSU.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nutres.2020.11.002.

REFERENCES

[1] Raghupathi Rullianallur, Raghupathi Viju. An empirical study of chronic diseases in the united states: a visual analytics approach to public health. Int J Environ Res Public Health 2018:15. doi:10.3390/ijerph15030431.
[2] Leonardi Giulia, Accardi Giulia, Monastero Roberto, Nicoletti Ferdinando, Libra Massimo. Ageing: from inflammation to cancer. Immun Ageing A 2018;15:1. doi:10.1186/s12979-017-0112-5.
[3] Bektas Arsun, Bektas Shepherd, Sen Ranjan, Ferrucci Luigi. Aging, inflammation and the environment. Exp Gerontol 2017. doi:10.1016/j.exger.2017.12.015.
[4] Freund Adam, Freund Arturo, Desprez Pierre-Yves, Desprez Judith. Inflammatory networks during cellular senescence: causes and consequences. Trends Mol Med 2010;16:238–46. doi:10.1016/j.molmed.2010.03.003.
[5] Zuo Li, Prather Evan R, Stetskiv Mykola, Garrison Davis E, Meade James R, Peace Timotheus I, et al. Inflammaging and oxidative stress in human diseases: from molecular mechanisms to novel treatments. Int J Mol Sci 2019:20. doi:10.3390/ijms20184472.
[6] Franceschi Claudio, Campisi Judith. Chronic inflammation (inflammaging) and its potential contribution to age-associated diseases. J Gerontol A Biol Sci Med Sci 2014;69(Suppl 1):S4–9. doi:10.1093/gerona/glu057.
[7] Zhao Ruilong, Liang Helena, Clarke Elizabeth, Jackson Christopher, Xue Meilang. Inflammation in chronic wounds. Int J Mol Sci 2016:17. doi:10.3390/ijms17122085.
[8] Dagogo-Jack Sam (editor). Leptin: Regulation and Clinical Applications, Switzerland: Springer International Publishing; 2015. ISBN: 9783319099149.
[9] Litwack (editor) Gerald. Adiponectin, 90, Oxford, UK: Elsevier, Inc; 2012. ISBN: 9780123983138.
[10] Fantuzzi Giamila, Mazzone Theodore editors. Adipose tissue and adipokines in health and disease. Adipose tissue and adipokines in health and disease. 2nd edition. New York, USA: Humana Press; 2014. ISBN: 9781627037693.
[11] La Cava Antonio. Leptin in inflammation and autoimmunity. Cytokine 2017;98:51–8. doi:10.1016/j.cyto.2016.10.011.
[12] Vernooy Juanita HJ, Ubags Niki DJ, Brusselle Guy G, Tavernier Jan, Suratt Benjamin T, Joos Guy F, et al. Leptin as regulator of pulmonary immune responses: involvement in respiratory diseases. Pulm Pharmacol Ther 2013;26:464–72. doi:10.1016/j.pupt.2013.03.016.
[13] Candido Giovanna Z, Silva Isabelle LZ, Martins Laysa T, Koczicki Leticia, Kubo Karen S, et al. Specific obesity-related adipokines. Immunochem Immunopathol 2015 01. doi:10.4172/2469-9756.1000108.
[14] Ghantous CM, Azrak Z, Hanache S, Hanache W, Zeidan A. Differential role of leptin and adiponectin in cardiovascular system. Int J Endocrinol 2015:534320. doi:10.1155/2015/534320.
[15] Scotece Morena, Conde Javier, Lopez Veronica, Lago Francisca, Pino Jesus, Gomez-Reino Juan J, et al. Adiponectin and leptin: new targets in inflammation. Basic Clin Pharmacol Toxicol 2014;114:97–102. doi:10.1111/bcpt.12109.
[16] Ouchi Noriyuki, Walsh Kenneth. Adiponectin as an anti-inflammatory factor. Clin Chim Acta 2007;380:24–30. doi:10.1016/j.cca.2007.01.026.
[17] Gairolla Jitender, Gairolla Rupinder, Modi Manish, Modi Dheeraj. Leptin and adiponectin: pathophysiological role and possible therapeutic target of inflammation in ischemic stroke. Rev Neurosci 2017;28:295–306. doi:10.1515/revneuro-2016-0055.
[18] Sardu Celestino, D'Onofrio Nunzia, Torella Michele, Portoghese Michele, Loreni Francesco, Mureddu Simone, et al. Pericoronary fat inflammation and Major Adverse Cardiac Events (MACE) in prediabetic patients with acute myocardial infarction: effects of metformin. Cardiovasc Diabetol 2019;18:126. doi:10.1186/s12933-019-0931-0.
[19] Chou Hsin-Hua, Hsu Lung-An, Wu Semon, Teng Ming-Sheng, Sun Yu-Chen, Ko Yu-Lin. Leptin-to-adiponectin ratio is related to low grade inflammation and insulin resistance independent of obesity in non-diabetic taiwanese: a cross-sectional cohort study. Acta Cardiol Sin 2014;30: 204–214 PMID: 27122790.
[20] Angin Yeliz, Arslan Nur, Kuralay Filiz. Leptin-to-adiponectin ratio in obese adolescents with nonalcoholic fatty liver disease. Turk J Pediatr 2014;56:259–66 PMID: 25341597.
[21] Golbahar Jamal, Das Nagalla M, Al-Ayadhi Maha A, Al-Ayadhi Khalid. Leptin-to-adiponectin, adiponectin-to-leptin ratios, and insulin are specific and sensitive markers associated with polycystic ovary syndrome: a case-control study from Bahrain. Metab Syndr Relat Disord 2012;10:98–102. doi:10.1089/met.2011.0075.
[22] Lekva Tove, Michelsen Annika E, Aukrust Pal, Henriksen Tore, Bollerslev Jens, Ueland Thor. Leptin and adiponectin as predictors of cardiovascular risk after gestational diabetes mellitus. Cardiovasc Diabetol 2017;16:5. doi:10.1186/s12933-016-0492-4.
[23] Otelea Marina, Streinu-Cercel Adrian, Baicus Cristian, Nitescu Maria. The adipokine profile and the cardiometabolic risk in non-obese young adults. Balk Med J 2019;36:155–61. doi:10.4274/balkanmedj.galenos.2018.2018.0789.
[24] Sarray Sameh, Madan Samira, Saleh Layal, Mahmoud Naeema, Almawi Wassim Y. Validity of adiponectin-to-leptin and adiponectin-to-resistin ratios as predictors of polycystic ovary syndrome. Fertil Steril 2015;104:460–6. doi:10.1016/j.fertnstert.2015.05.007.
[25] Fruhbeck Gema, Catalan Victoria, Rodriguez Amaia, Gomez-Ambrosi Javier. Adiponectin-leptin ratio: a promising index to estimate adipose tissue dysfunction. Relation with obesity-associated cardiometabolic risk. Adipocyte 2018;7:57–62. doi:10.1080/21623945.2017.1402151.
[26] Ford Nikki A, Rossi Emily L, Barnett Kelsey, Yang Peiying, Bowers Laura W, Hidaka Brandon H, et al. Omega-3-Acid

Ethyl Esters Block the Protumorigenic Effects of Obesity in Mouse Models of Postmenopausal Basal-like and Claudin-Low Breast Cancer. Cancer Prev Res Phila Pa 2015;8:796–806. doi:10.1158/1940-6207.CAPR-15-0018.
[27] Mostowik Magdalena, Gajos Grzegorz, Zalewski Jaroslaw, Nessler Jadwiga, Undas Anetta. Omega-3 polyunsaturated fatty acids increase plasma adiponectin to leptin ratio in stable coronary artery disease. Cardiovasc Drugs Ther 2013;27:289–95. doi:10.1007/s10557-013-6457-x.
[28] Dyerberg J, Bang HO, Stoffersen E, Moncada S, Vane JR. Eicosapentaenoic acid and prevention of thrombosis and atherosclerosis? Lancet Lond Engl 1978;2:117–19. doi:10.1016/s0140-6736(78)91505-2.
[29] Siscovick David S, Barringer Thomas A, Fretts Amanda M, Wu Jason HY, Lichtenstein Alice H, Costello Rebecca B, et al. Omega-3 polyunsaturated fatty acid (Fish Oil) supplementation and the prevention of clinical cardiovascular disease: a science advisory from the American Heart Association. Circulation 2017;135:e867–84. doi:10.1161/CIR.0000000000000482.
[30] Drevon Christian A. Fatty acids and expression of adipokines. Biochim Biophys Acta 2005;1740:287–92. doi:10.1016/j.bbadis.2004.11.019.
[31] Kroll Caroline, Mastroeni Silmara SBS, Veugelers Paul J, Mastroeni Marco F. Associations of ADIPOQ and LEP Gene Variants with Energy Intake: a Systematic Review. Nutrients 2019:11. doi:10.3390/nu11040750.
[32] Lombardo Yolanda B, Hein Gustavo, Chicco Adriana. Metabolic syndrome: effects of n-3 PUFAs on a model of dyslipidemia, insulin resistance and adiposity. Lipids 2007;42:427–37. doi:10.1007/s11745-007-3039-3.
[33] Skurk T, van Harmelen V, Lee Y-M, Wirth A, Hauner H. Relationship between IL-6, leptin and adiponectin and variables of fibrinolysis in overweight and obese hypertensive patients. Horm Metab Res 2002;34:659–63. doi:10.1055/s-2002-38253.
[34] Huang Chao-Wei, Chien Yi-Shan, Chen Yu-Jen, Ajuwon Kolapo M, Mersmann Harry M, Ding Shih-Torng. Role of n-3 polyunsaturated fatty acids in ameliorating the obesity-induced metabolic syndrome in animal models and humans. Int J Mol Sci 2016:17. doi:10.3390/ijms17101689.
[35] Selenscig Dante, Selenscig Andrea, Chicco Adriana, Chicco Yolanda B. Increased leptin storage with altered leptin secretion from adipocytes of rats with sucrose-induced dyslipidemia and insulin resistance: effect of dietary fish oil. Metabolism 2010;59:787–95. doi:10.1016/j.metabol.2009.09.025.
[36] Calder Philip C. Omega-3 fatty acids and inflammatory processes. Nutrients 2010;2:355–74. doi:10.3390/nu2030355.
[37] Miles EA, Calder PC. Fatty acids, lipid emulsions and the immune and inflammatory systems. World Rev Nutr Diet 2015;112:17–30. doi:10.1159/000365426.
[38] Abbott Kylie A, Burrows Tracy L, Thota Rohith N, Acharya Shamasunder, Garg Manohar L. Do omega-3 PUFAs affect insulin resistance in a sex-specific manner? A systematic review and meta-analysis of randomized controlled trials. Am J Clin Nutr 2016;104:1470–84. doi:10.3945/ajcn.116.138172.
[39] Ellulu Mohammed S, Khaza'ai Huzwah, Abed Yehia, Rahmat Asmah, Ismail Patimah, Ranneh Yazan. Role of fish oil in human health and possible mechanism to reduce the inflammation. Inflammopharmacology 2015;23:79–89. doi:10.1007/s10787-015-0228-1.
[40] Gray B, Steyn F, Davies PSW, Vitetta L. Omega-3 fatty acids: a review of the effects on adiponectin and leptin and potential implications for obesity management. Eur J Clin Nutr 2013;67:1234–42. doi:10.1038/ejcn.2013.197.
[41] Paniagua Juan A. Nutrition, insulin resistance and dysfunctional adipose tissue determine the different components of metabolic syndrome. World J Diabetes 2016;7:483–514. doi:10.4239/wjd.v7.i19.483.
[42] Robinson Lindsay E, Mazurak Vera C. N-3 polyunsaturated fatty acids: relationship to inflammation in healthy adults and adults exhibiting features of metabolic syndrome. Lipids 2013;48:319–32. doi:10.1007/s11745-013-3774-6.
[43] Thota Rohith N, Ferguson Jessica JA, Abbott Kylie A, Dias Cintia B, Garg Manohar L. Science behind the cardio-metabolic benefits of omega-3 polyunsaturated fatty acids: biochemical effects vs. clinical outcomes. Food Funct 2018;9:3576–96. doi:10.1039/C8FO00348C.
[44] Wu Jason HY, Cahill Leah E, Mozaffarian Dariush. Effect of fish oil on circulating adiponectin: a systematic review and meta-analysis of randomized controlled trials. J Clin Endocrinol Metab 2013;98:2451–9. doi:10.1210/jc.2012-3899.
[45] Xin Wei, Wei Wei, Li Xiaoying. Effects of fish oil supplementation on inflammatory markers in chronic heart failure: a meta-analysis of randomized controlled trials. Bmc Cardiovasc Disord 2012;12:77. doi:10.1186/1471-2261-12-77.
[46] Kearney Margaret H. Hoping for a TREND toward PRISMA: the variety and value of research reporting guidelines. Res Nurs Health 2014;37:85–7. doi:10.1002/nur.21591.
[47] Liberati Alessandro, Altman Douglas G, Tetzlaff Jennifer, Mulrow Cynthia, Gotzsche Peter C, Ioannidis John P, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339 b2700–b2700. doi:10.1136/bmj.b2700.
[48] Harris Paul A, Taylor Robert, Thielke Robert, Payne Jonathon, Gonzalez Nathaniel, Conde Jose G. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009;42:377–81. doi:10.1016/j.jbi.2008.08.010.
[49] . In: Higgins JPT, Higgins S, editors. Cochrane handbook for systematic reviews of interventions version 5.1.0 [updated march 2011]. The Cochrane Collaboration; 2011. p. 2011. Available from http://handbook.cochrane.org..
[50] Allaire Janie, Couture Patrick, Leclerc Myriam, Charest Amelie, Marin Johanne, Lepine Marie-Claude, et al. A randomized, crossover, head-to-head comparison of eicosapentaenoic acid and docosahexaenoic acid supplementation to reduce inflammation markers in men and women: the Comparing EPA to DHA (ComparED) Study. Am J Clin Nutr 2016;104:280–7. doi:10.3945/ajcn.116.131896.
[51] Gammelmark Anders, Madsen Trine, Varming Kim, Lundbye-Christensen Soren, Schmidt Erik B. Low-dose fish oil supplementation increases serum adiponectin without affecting inflammatory markers in overweight subjects. Nutr Res 2012;32:15–23. doi:10.1016/j.nutres.2011.12.007.
[52] Guebre-Egziabher Fitsum, Debard Cyril, Drai Jocelyne, Drai Laure, Pesenti Sandra, Bienvenu Jacques, et al. Differential dose effect of fish oil on inflammation and adipose tissue gene expression in chronic kidney disease patients. Nutrition 2013;29:730–6. doi:10.1016/j.nut.2012.10.011.
[53] Haidari F, Tavakoli M, Heybar H, Helli B, Mohammadshahi M. The effect of omega-3 on the level of serum lipid profile, adipocytokines, and indicator of vascular inflammation in patients diagnosed with myocardial infarction. J Babol Univ Med Sci 2015;17:7–17 EMBASE 618673959.
[54] Harving Frederik, Svensson My, Flyvbjerg Allan, Schmidt Erik B, Jorgensen Kaj A, Eriksen Helle H, et al. n-3 polyunsaturated fatty acids and adiponectin in patients with end-stage renal disease. Clin Nephrol 2015;83:279–85. doi:10.5414/CN108285.
[55] Huerta Ana, Prieto-Hontoria Pedro L, Sainz Neira, Martinez J Alfredo, Moreno-Aliaga Maria. Supplementation with

alpha-lipoic acid alone or in combination with eicosapentaenoic acid modulates the inflammatory status of healthy overweight or obese women consuming an energy-restricted diet. J Nutr 2016;146:889S–896S. doi:10.3945/jn.115.224105.
[56] Itariu Bianca K, Zeyda Maximilian, Hochbrugger Eva E, Neuhofer Angelika, Prager Gerhard, Schindler Karin, et al. Long-chain n-3 PUFAs reduce adipose tissue and systemic inflammation in severely obese nondiabetic patients: a randomized controlled trial. Am J Clin Nutr 2012;96:1137–49. doi:10.3945/ajcn.112.037432.
[57] Ito Ryo, Satoh-Asahara Noriko, Yamakage Hajime, Sasaki Yousake, Odori Shinji, Kono Shigeo, et al. An increase in the EPA/AA ratio is associated with improved arterial stiffness in obese patients with dyslipidemia. J Atheroscler Thromb 2014;21:248–60. doi:10.5551/jat.19976.
[58] Jacobo-Cejudo M Gorety, Valdes-Ramos Roxana, Guadarrama-Lopez Ana L, Pardo-Morales Rosa-Virgen, Martinez-Carrillo Beatriz E, Harbige Laurence S. Effect of n-3 polyunsaturated fatty acid supplementation on metabolic and inflammatory biomarkers in Type 2 diabetes mellitus patients. Nutrients 2017:9. doi:10.3390/nu9060573.
[59] Koh Kwang Kon, Quon Michael J, Shin Kwen-Chul, Lim Soo, Lee Yonghee, Sakuma Ichiro, et al. Significant differential effects of omega-3 fatty acids and fenofibrate in patients with hypertriglyceridemia. Atherosclerosis 2012;220:537–44. doi:10.1016/j.atherosclerosis.2011.11.018.
[60] Krantz Mori J, Havranek Edward P, Pereira Rocio I, Beaty Brenda, Mehler Philip S, Long Carlin S. Effects of omega-3 fatty acids on arterial stiffness in patients with hypertension: a randomized pilot study. J Negat Results Biomed 2015;14:21. doi:10.1186/s12952-015-0040-x.
[61] Krebs JD, Browning LM, McLean NK, Rothwell JL, Mishra GD, Moore CS, et al. Additive benefits of long-chain n-3 polyunsaturated fatty acids and weight-loss in the management of cardiovascular disease risk in overweight hyperinsulinaemic women. Int J Obes 2006;30:1535–44. doi:10.1038/sj.ijo.0803309.
[62] Lee Tammy C, Ivester Priscilla, Hester Austin, Sergeant Susan, Case Larry D, Morgan Timothy, et al. The impact of polyunsaturated fatty acid-based dietary supplements on disease biomarkers in a metabolic syndrome/diabetes population. Lipids Health Dis 2014. doi:10.1186/1476-511X-13-196.
[63] Masson Serge, Marchioli Roberto, Mozaffarian Dariush, Bernasconi Roberto, Milani Valentina, Dragani Luana, et al. Plasma n-3 polyunsaturated fatty acids in chronic heart failure in the GISSI-Heart Failure Trial: relation with fish intake, circulating biomarkers, and mortality. Am Heart J 2013;165 208. doi:10.1016/j.ahj.2012.10.021.
[64] Micallef Michelle A, Garg Manohar L. Anti-inflammatory and cardioprotective effects of n-3 polyunsaturated fatty acids and plant sterols in hyperlipidemic individuals. Atherosclerosis 2009;204:476–82. doi:10.1016/j.atherosclerosis.2008.09.020.
[65] Mizia-Stec Katarzyna, Haberka Maciej, Mizia Magdalena, Chmiel Artur, Gieszczyk Klaudia, Lasota Bartosz, et al. N-3 Polyunsaturated fatty acid therapy improves endothelial function and affects adiponectin and resistin balance in the first month after myocardial infarction. Arch Med Sci 2011;7:788–95. doi:10.5114/aoms.2011.25553.
[66] Mohammadi Elahe, Rafraf Maryam, Farzadi Laya, Asghari-Jafarabadi Mohammad, Sabour Siamak. Effects of omega-3 fatty acids supplementation on serum adiponectin levels and some metabolic risk factors in women with polycystic ovary syndrome. Asia Pac J Clin Nutr 2012;21:511–18 PMID: 23017309.
[67] Munro Irene A, Garg Manohar L. Dietary supplementation with n-3 PUFA does not promote weight loss when combined with a very-low-energy diet. Br J Nutr 2012;108:1466–74. doi:10.1017/S0007114511006817.
[68] Munro Irene A, Garg Manohar L. Dietary supplementation with long chain omega-3 polyunsaturated fatty acids and weight loss in obese adults. Obes Res Clin Pract 2013;7:e173–81. doi:10.1016/j.orcp.2011.11.001.
[69] Patel Jeetesh V, Lee Kaeng W, Tomson Joseph, Dubb Kiran, Hughes Elizabeth A, Lip Gregory YH. Effects of omega-3 polyunsaturated fatty acids on metabolically active hormones in patients post-myocardial infarction. Int J Cardiol 2007;115:42–5. doi:10.1016/j.ijcard.2006.04.004.
[70] Poreba Malgorzata, Mostowik Magdalena, Siniarski Aleksander, Golebiowska-Wiatrak Renata, Malinowski Krzysztof P, Haberka Maciej, et al. Treatment with high-dose n-3 PUFAs has no effect on platelet function, coagulation, metabolic status or inflammation in patients with atherosclerosis and type 2 diabetes. Cardiovasc Diabetol 2017:16. doi:10.1186/s12933-017-0523-9.
[71] Qin Yu, Zhou Yong, Chen Shi-Hui, Zhao Xiao-Lan, Ran Li, Zeng Xiang-Long, et al. Fish oil supplements lower serum lipids and glucose in correlation with a reduction in plasma fibroblast growth factor 21 and prostaglandin E2 in nonalcoholic fatty liver disease associated with hyperlipidemia: a randomized clinical trial. PLoS ONE 2015;10:e0133496. doi:10.1371/journal.pone.0133496.
[72] Rizza Stefano, Tesauro Manfredi, Cardillo Carmine, Galli Angelica, Iantorno Micaela, Gigli Fabrizio, et al. Fish oil supplementation improves endothelial function in normoglycemic offspring of patients with type 2 diabetes. Atherosclerosis 2009;206:569–74. doi:10.1016/j.atherosclerosis.2009.03.006.
[73] Sanyal Arun J, Abdelmalek Manal F, Suzuki Ayako, Cummings Oscar W, Chojkier Mario, EPE-A Study Group. No significant effects of ethyl-eicosapentanoic acid on histologic features of nonalcoholic steatohepatitis in a phase 2 trial. Gastroenterology 2014;147 377-384.e1. doi:10.1053/j.gastro.2014.04.046.
[74] Satoh Noriko, Shimatsu Akira, Kotani Kazuhiko, Himeno Akihiro, Majima Takafumi, Yamada Kazunori, et al. Highly purified eicosapentaenoic acid reduces cardio-ankle vascular index in association with decreased serum amyloid A-LDL in metabolic syndrome. Hypertens Res Off J Jpn Soc Hypertens 2009;32:1004–8. doi:10.1038/hr.2009.145.
[75] Satoh-Asahara Noriko, Shimatsu Akira, Sasaki Yousuke, Nakaoka Hidenori, Himeno Akihiro, Tochiya Mayu, et al. Highly purified eicosapentaenoic acid increases interleukin-10 levels of peripheral blood monocytes in obese patients with dyslipidemia. Diabetes Care 2012;35:2631–9. doi:10.2337/dc12-0269.
[76] Simao Andrea NC, Lozovoy Marcell AB, Bahls Larissa D, Morimoto Helena K, Simao Tathiana NC, Matsuo Tiemi, et al. Blood pressure decrease with ingestion of a soya product (kinako) or fish oil in women with the metabolic syndrome: role of adiponectin and nitric oxide. Br J Nutr 2012;108:1435–42. doi:10.1017/S0007114511006921.
[77] Spencer Michael, Finlin Brian S, Unal Resat, Zhu Beibei, Morris Andrew J, Shipp Lindsey R, et al. Omega-3 fatty acids reduce adipose tissue macrophages in human subjects with insulin resistance. Diabetes 2013;62:1709–17. doi:10.2337/db12-1042.
[78] Troseid Marius, Arnesen Harald, Hjerkinn Elsa M, Seljeflot Ingebjorg. Serum levels of interleukin-18 are reduced by diet and n-3 fatty acid intervention in elderly high-risk men. Metabolism 2009;58:1543–9. doi:10.1016/j.metabol.2009.04.031.
[79] Vargas M Luisa, Almario Rogelio U, Buchan Wendy, Kim Kyoungmi, Karakas Sidika E. Metabolic and endocrine

effects of long-chain versus essential omega-3 polyunsaturated fatty acids in polycystic ovary syndrome. Metab-Clin Exp 2011;60:1711–18. doi:10.1016/j.metabol.2011.04.007.
[80] Yamamoto Tsuyoshi, Kajikawa Yutaka, Otani Satoru, Yamada Yuki, Takemoto Syunji, Hirota Minoru, et al. Protective effect of eicosapentaenoic acid on insulin resistance in hyperlipidemic patients and on the postoperative course of cardiac surgery patients: the possible involvement of adiponectin. Acta Med Okayama 2014;68:349–61. doi:10.18926/AMO/53024.
[81] CDC. Defining adult overweight and obesity | overweight & obesity | CDC 2019. https://www.cdc.gov/obesity/adult/defining.html (Accessed September 6, 2019).
[82] Fewtrell Mary S, Kennedy Kathy, Singhal Atul, Martin Richard M, Ness Andy, Hadders-Algra Mijna, et al. How much loss to follow-up is acceptable in long-term randomised trials and prospective studies? Arch Dis Child 2008;93:458–61. doi:10.1136/adc.2007.127316.
[83] Skierka Antonia-Sophie, Michels Karin B. Ethical principles and placebo-controlled trials – interpretation and implementation of the Declaration of Helsinki's placebo paragraph in medical research. BMC Med Ethics 2018:19. doi:10.1186/s12910-018-0262-9.
[84] Jaakkola Johanna M, Pahkala Katja, Viitala Marika, Ronnemaa Tapani, Viikari Jorma, Niinikoski Harri, et al. Association of adiponectin with adolescent cardiovascular health in a dietary intervention study. J Pediatr 2015;167:353–60 e1. doi:10.1016/j.jpeds.2015.04.044.
[85] Thomas T, Burguera B, Melton LJ, Atkinson EJ, O'Fallon WM, Riggs BL, et al. Relationship of serum leptin levels with body composition and sex steroid and insulin levels in men and women. Metabolism 2000;49:1278–84. doi:10.1053/meta.2000.9519.
[86] Loffreda S, Yang SQ, Lin HZ, Karp CL, Brengman ML, Wang DJ, et al. Leptin regulates proinflammatory immune responses. FASEB J Off Publ Fed Am Soc Exp Biol 1998;12:57–65 PMID: 9438411.
[87] Frasca Daniela, Blomberg Bonnie B. Inflammaging decreases adaptive and innate immune responses in mice and humans. Biogerontology 2016;17:7–19. doi:10.1007/s10522-015-9578-8.
[88] Calder Philip C. Marine omega-3 fatty acids and inflammatory processes: effects, mechanisms and clinical relevance. Biochim Biophys Acta 2015;1851:469–84. doi:10.1016/j.bbalip.2014.08.010.
[89] Harris William S. The omega-3 index as a risk factor for coronary heart disease. Am J Clin Nutr 2008;87:1997S–2002S. doi:10.1093/ajcn/87.6.1997S.
[90] U.S. Food and Drug Administration Center for Food Safety and Applied Nutrition Office of Nutritional Products Labeling and Dietary Supplements (FDA/CSFAN). Letter regarding dietary supplement health claim for omega-3 fatty acids and coronary heart disease. (Docket No. 91N-0103) 2000.
[91] Leaf Alexander, Jorgensen Michael B, Jacobs Alice K, Cote Gilles, Schoenfeld David A, Scheer Judy, et al. Do fish oils prevent restenosis after coronary angioplasty? Circulation 1994;90:2248–57. doi:10.1161/01.cir.90.5.2248.
[92] Chen Vincent C-H, Chen Chun-Hsin, Chiu Yi-Hang, Chiu Tsang-Yaw, Li Feng-Chiao, Li Mong-Liang. Leptin/Adiponectin ratio as a potential biomarker for metabolic syndrome in patients with schizophrenia. Psychoneuroendocrinology 2018;92:34–40. doi:10.1016/j.psyneuen.2018.03.021.
[93] Rasmussen-Torvik Laura J, Wassel Christina L, Ding Jingzhong, Carr Jeffrey, Cushman Mary, Jenny Nancy, et al. Associations of BMI and insulin resistance with leptin, adiponectin, and the leptin to adiponectin ratio across ethnic groups: the Multi-Ethnic Study of Atherosclerosis (MESA). Ann Epidemiol 2012;22:705–9. doi:10.1016/j.annepidem.2012.07.011.
[94] Zhang Meixian, Cheng Hong, Zhao Xiaoyuan, Hou Dongqing, Yan Yinkun, Cianflone Katherine, et al. Leptin and leptin-to-adiponectin ratio predict adiposity gain in nonobese children over a six-year period. Child Obes Print 2017;13:213–21. doi:10.1089/chi.2016.0273.
[95] Kromhout Daan, Kromhout Satoshi, Geleijnse Johanna M, Geleijnse Hiroaki. Fish oil and omega-3 fatty acids in cardiovascular disease: do they really work? Eur Heart J 2011;33:436–43. doi:10.1093/eurheartj/ehr362.
[96] Durham Holiday, Wood Jodi T, Williams John S, Geaghan James P, Makriyannis Alexandros, Lammi-Keefe Carol J. How do plasma endocannabinoids and inflammatory markers respond to docosahexaenoic acid (DHA) supplementation in pregnancy? FASEB J 2011:25. doi:10.1096/fasebj.25.1_supplement.777.4.
[97] McDougle Daniel R, Watson Josephine E, Abdeen Amr A, Adili Reheman, Caputo Megan P, Krapf John E, et al. Anti-inflammatory ω-3 endocannabinoid epoxides. Proc Natl Acad Sci 2017;114:E6034–43. doi:10.1073/pnas.1610325114.
[98] Chilton Floyd H, Dutta Rahul, Reynolds Lindsay M, Sergeant Susan, Mathias Rasika A, Seeds Michael C. Precision nutrition and omega-3 polyunsaturated fatty acids: a case for personalized supplementation approaches for the prevention and management of human diseases. Nutrients 2017:9. doi:10.3390/nu9111165.