Published in final edited form as:

Clin Nutr. 2011 December ; 30(6): 702–707. doi:10.1016/j.clnu.2011.08.013.

Omega-3 polyunsaturated fatty acid and insulin sensitivity: A meta-analysis of randomized controlled trials

Akintunde O. Akinkuolie[a,*], **Julius S. Ngwa**[a], **James B. Meigs**[b,c], and **Luc Djoussé**[c,d,e]

[a]Boston University School of Public Health, Boston, MA 02118, USA

[b]General Medicine Division, Massachusetts General Hospital, Boston, MA, USA

[c]Harvard Medical School, Boston, MA, USA

[d]Division of Aging, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA

[e]Massachusetts Veterans Epidemiology and Information Research Center (MAVERIC), VA Boston Healthcare System, Boston, MA, USA

SUMMARY

Background &aim—n-3 PUFA has been shown to decrease the risk of several components of the metabolic syndrome; however, the role of n-3 PUFA on glucose metabolism is not clear. Our aim was to systematically review the effect of n-3 PUFA on IS by conducting a meta-analysis of available RCTs.

Methods—We followed the guidelines of Cochrane's review of systematic interventions. We searched MEDLINE, EMBASE, CENTRAL and clinicaltrials.gov from the beginning of each database until October 2010. Meta-analysis was performed using a random effects model to estimate a pooled SMD and the corresponding 95% CI.

Results—From 303 screened citations, 11 RCTs ($n = 618$) were eligible for inclusion in the analysis. In a pooled estimate, n-3 PUFA intervention had no effects on IS compared to placebo (SMD 0.08, 95% CI −0.11 −0.28). Similarly, n-3 PUFA had no effects on IS in sub-group analyses (Type 2 diabetes vs. other population; QUICKI and other test subgroups). In the HOMA subgroup, n-3 PUFA was associated with a statistically significant increase in IS (SMD 0.30, CI 0.03–0.58) when compared to placebo.

Conclusion—This meta-analysis is consistent with a lack of n-3 PUFA effects on IS.

Keywords

Insulin sensitivity; Diabetes; Omega-3 polyunsaturated fatty acids; Randomized controlled trials; Meta-analysis

[*]Corresponding author. Tel.: +1 8577192351. tunde@bu.edu (A.O. Akinkuolie).

Statement of authorship

The author's responsibilities were as follows – AOA and LD were involved in designing the study; AOA and JSN carried out literature search and data analysis; AOA drafted the manuscript; AOA, JSN, JBM and LD critically appraised the manuscript; and LD supervised the study. All authors read and approved the final manuscript.

Conflict of interest

The authors declare no conflict of interest.

Intake of omega-3 polyunsaturated fatty acids (n-3 PUFA) has been shown to decrease the risk of CVD[1] as well as produce a favorable effect on many markers of the metabolic syndrome.[2–5] These beneficial effect of omega-3 fatty acids have also been established for certain proinflammatory cytokines which are markers of both CVD and metabolic syndrome.[6–8] Despite these known benefits, the role of omega-3 fatty acid on insulin resistance is still marred by controversy. Clinical parameters used to study the role of n-3 PUFA on glucose metabolism include fasting glucose, HbA1C, and insulin sensitivity (IS). While some studies have reported an unfavorable effect of n-3 PUFA on glucose metabolism[9–13] other studies have reported no effects of n-3 PUFA on glucose metabolism.[14–16]

Insulin sensitivity (IS) is a measure of insulin responsiveness as well as insulin resistance, a disorder estimated to affect about 35% of US adults[17] and it plays a significant role in the development of type 2 diabetes (T2D).[18–20] Hence the effect of n-3 PUFA on IS will provide substantial information on how n-3 PUFA affects glucose-insulin homeostasis while further elucidating the role of n-3 PUFA on the risk of T2D. We therefore tested the hypothesis that n-3 PUFA is associated with a better Insulin sensitivity (IS) by conducting a meta-analysis of randomized controlled trials (RCT).

1. Methods

The present systematic review and meta-analysis was performed according to the guidelines published in the Cochrane handbook for systematic reviews of intervention.[21]

1.1. Inclusion/exclusion criteria

In order to minimize publication bias, our primary search identified all trials that measured and reported the effect of n-3 PUFA, irrespective of the type, on insulin sensitivity assessed either directly or indirectly. Studies were included if they were randomized control trials with fish oil or n-3 PUFA as the only active intervention. Cross-over trials were included if data at the end of the first intervention phase were available. Studies that measured insulin sensitivity as either the reciprocal of fasting insulin or glucose-insulin ratio were excluded as these methods of assessing insulin sensitivity leads to erroneous results in subjects with glucose intolerance or T2D.[22]

1.2. Search strategy

We performed a comprehensive electronic literature search of: MEDLINE using the Cochrane sensitivity- and precision-maximizing approach,[23] Embase using the McMaster Hedges Team search filter for optimizing sensitivity and specificity,[24] the Cochrane Central Register of Controlled Trials, and clinicaltrials.gov. All databases were searched from the beginning of each database until October 2010. Our comprehensive search was performed using the following key words in combination as both MeSH terms and text words: [omega-3 fatty acids or alpha-Linolenic Acid or Docosahexaenoic Acids or Eicosapentaenoic Acid] and [Avignon index or Stumvollindex or Matsuda index or HOMA or homeostasis model assessment or QUICKI or quantitative insulin sensitivity check index or modified insulin suppression test or IST or insulin suppression test or FSIVGTT or

MINMOD or minimal model analysis or minimal model or glucose disposal rate or hyperinsulinemic euglycemia clamp or euglycemic clamp or glucose clamp or index of insulin sensitivity or insulin resistance or insulin sensitivity]. This was done with no language restriction. Study selection began through review of titles and abstracts. Full texts were pulled when the abstract could not be used to make sufficient judgment for inclusion. In addition, all studies that met our inclusion criteria had their references manually searched to locate additional studies. Conflicting opinions in making a decision was resolved through discussion amongst study authors. Full articles retrieved were examined independently by two investigators to identify relevant studies. For the purpose of this analysis we treated the data for the MUFA and SAFA diet subgroups in the KANWU study[25] as independent data denoting them as Rosalba (MUFA diet) 2006 and Rosalba (SAFA diet) 2006 respectively (Table 1)

1.3. Data extraction

Two investigators (A.O.A and J.S.N) independently extracted all data through the use of a standardized form; the validity of data extraction was assessed by comparing the independently abstracted results for concordance and any disagreement was resolved by reaching a consensus through discussion. Integrity of extracted data was evaluated by comparing data across studies. Information extracted from each trial included: author identification, year of publication, funding source, country, study design, inclusion/exclusion criteria, type of intervention and placebo, duration of intervention, dose/mode of administration of intervention, baseline characteristics (age, sex, total cholesterol, LDL cholesterol, HDL cholesterol, fasting glucose, fasting insulin, insulin sensitivity), after-intervention report for insulin sensitivity, method used to assess insulin sensitivity and directionality of scale used to measure insulin sensitivity. Dr. Ingrid L Mostad was contacted to provide the after-intervention data for the variables listed in Table 1 of his published study[26] similarly Dr. Rosalba Giacco was contacted to provide the needed data for the variables listed in Fig. 1 of her study.[25]

1.4. Quality assessment

We used the Cochrane Collaboration's tool for assessing risk of bias,[27] which emphasizes a domain based approach using the domains of adequate sequence generation, allocation concealment, blinding, incomplete outcome data, selective reporting and other risk of bias.

1.5. Missing data

Study authors were contacted for information on missing data and other relevant information needed to complete this review.

1.6. Statistical analysis

Meta-analysis was conducted to ascertain the effect of n-3 PUFA exposure on insulin sensitivity. Differences in post-intervention values between intervention and control groups were analyzed as standardized mean difference (SMD) and the corresponding 95% CI were computed using the DerSimonian-laird random effects model, which takes into account the assumption that individual studies are measuring different effects.[28] When the standard

deviation (SD) was not reported, this was calculated from the Standard error of mean (SEM), p values or the confidence intervals (CI). Where the intervention was given to more than one group, we combined the data for such group.[29] To ensure uniformity in the direction of the varying metrics used to measure insulin sensitivity, we reversed this for some studies. The likelihood of statistical heterogeneity was tested for using the χ^2 test. The amount and statistical significance of this were reported as I^2 and P value. $I^2 > 50\%$ was considered substantial amount of statistical heterogeneity. To evaluate publication bias, a funnel plot of the treatment effect versus SE was visually inspected. Further evaluation of publication bias was assessed with the Begg[30] and Egger test.[31]

We sought to detect the source of statistical heterogeneity if any, by performing subgroup analysis. Subgroup analysis was performed for: (1) study with population setting of T2D and others; (2) measures of IS which we grouped according to: HOMA, QUICKI and other measurement of insulin sensitivity. Sensitivity analysis was performed for studies with low risk of bias in domains of randomization, blinding and incomplete outcome data reporting. Estimated SMD were re-expressed into a quantifiable IS metric by multiplying with the baseline SD of one of the included trials using a method suggested by Cochrane.[32] We chose QUICKI for this purpose based on available literature suggesting the use of QUICKI in defining IS.[33,34] The baseline IS measure in the trial by Rizza S et al[35] was used to provide an estimate of the baseline variation for IS since this value was reported for their entire study population, moreover their trial had a relatively large sample size amongst included trials.

Where more than one method for measuring IS was used to assess IS in a trial, we chose the method(s) inputting all study subjects. Based on this, Josune 2010[36] had 2 different IS measurements that qualified to be used for our review which were treated separately during sub-group analysis of IS measurement. Woodman 2002 et al.[37] had 2 different n-3 PUFA arms (EPA and DHA). Since EPA and DHA are alternative forms of n-3 PUFA[38] we pooled the data for the DHA and EPA sub groups into one n-3 PUFA group using the approach suggested by Cochrane.[23] The 1-study removed method was used to investigate the cause of heterogeneity. Significant level was set at 0.05 and all P values were two tailed ($\alpha = 0.05$). All analysis were conducted using RevMan 5.[39]

2. Results

Search strategy and study selection are depicted in Fig. 1. A total of 11 RCT's were included in these analyses.[25,26,35–37,40–45] Table 1 highlights study details. IS was a direct focus in 5 of the trials.[24,26,42,44,45] Most studies used 0.138–4 g/d of n-3 PUFA as intervention except in the study by Abete et al.[45] where the intervention was fatty fish. When all 11 trials were pooled, n-3 PUFA had no effect on IS (SMD = 0.08, 95% CI –0.11 to 0.28, Fig. 2a). In a sensitivity analysis, these findings were not altered when analyses were restricted to studies with a low risk of bias (Fig. 2b), T2D population vs. other populations (Fig. 2b), and type of IS test. The only exception is the HOMA subgroup where we observed that compared to placebo, n-3 PUFA was associated with a statistical significant increase in IS (Fig. 2b). There was no evidence for heterogeneity for the effect of n-3 PUFA on IS ($I^2 = 32\%$, $P = 0.14$) nor publication bias as revealed by a symmetrical funnel plot (Fig. 3) and non-statistically significant Begg's test ($p = 0.78$) and Egger's test ($p = 0.95$).

3. Discussion

This meta-analysis shows no overall association between intake of n-3 PUFA and IS. To the best of our knowledge, this is the first study to review systematically the effects of n-3 PUFA on IS in RCTs. Hartweg J et al.[46] however conducted a meta-analysis for the effect of n-3 PUFA on fasting insulin release using a population of T2D. Under normal conditions, a comparison of their results to ours can be made on the basis of glucose-insulin homeostasis; rising blood glucose stimulates insulin release, the result of which is an insulin mediated action of enhanced glucose utilization in striated and adipose tissues as well as inhibition of hepatic glucose production.[47] With IS being a measure of insulin responsiveness, we anticipate that a change in IS would lead to an adaptive change in insulin secretion. Hence a decrease in IS should reflect an increase in insulin secretion levels. This hypothesis is supported by published data.[48–50] Hartweg J et al.[46] reported that n-3 PUFA was associated with a statistically non-significant reduction in fasting insulin. However, their study population of T2D subjects makes a comparison to our data difficult since insulin levels could be erroneously high in T2D subjects.[22]

Importantly, since we found no overall association between n-3 PUFA and IS, this suggests that n-3 PUFA may not be a risk factor for disorders of glucose metabolism. Other authors have also suggested thesame.[9–12] A meta-analysis by Montori et al.[51] showing that fish oil supplementation in T2D had no significant effect on fasting glucose is consistent with our findings. Furthermore, the fact that n-3 PUFA consumption may not play a role in the development of glucose metabolism disorders is evident from two meta-analysis reporting that compared to control, n-3 PUFA was not associated with a significant change in glycated hemoglobin.[46,51] Similar findings have been reported in related observational studies. In one instance, the ARIC study[52] found no association between the intake of marine omega-3 fatty acids and the risk of T2D after a nine year follow-up; similar conclusion was reached by the investigators of the Kouopio study[53] and Hodge et al.[54] with both concluding that incident T2D was not associated with polyunsaturated fatty acids and dietary long-chain n-3 fatty acids respectively. Furthermore, a recent study by Djoussé et al.[55] showed that after a median follow-up of 10.6 years, plasma phospholipids n-3 fatty acids were not associated with a higher incidence of T2D. These reports are in support of our result. Thus, n-3 PUFA may not perturb glucose-insulin homeostasis.

Conversely, there are varying results from published data. The Nurses' Health Study[56] found an increased risk of T2D when the highest to the lowest quintiles of long-chain omega-3 fatty acids were compared. Investigators from the Women's Health Study[57] also documented an increased risk of T2D with the intake of long-chain omega-3 fatty acids. Meanwhile, using data from the Cardiovascular Health Study, Djoussé et al.[55] observed that individuals with the highest concentration of Plasma phospholipids n-3 fatty acids had a lower risk of T2D. Similarly, a recent publication from the Singapore Chinese Health Study[58] showed that amongst 43,176 participants, increased intake of omega-3 fatty acids was associated with a decreased risk of T2D. We note however that our findings are contrary to this.

The present meta-analysis has some limitations. First, we may not have identified unpublished reports; however, our comprehensive literature search and the absence of

publication bias suggest that our meta-analysis results are not driven by a selective publication of positive findings. Second, we had a limited number of randomized clinical trials; hence, our analysis did not address issues relating to dose and duration of intervention. Third, the quality of methodological approach varied across randomized trials included; however sensitivity analysis of trials with high quality maintained the robustness of our data. Furthermore, we did not identify any statistical heterogeneity between included trials. Lastly, we note the relative non-comparability of the different IS measured used in disorders of glucose metabolism.[22] Nevertheless, our statistical approach was based on computation of SMD's using a random effects model, which is a valid method to pool studies with different metrics for the same outcome measure. The strengths of our analysis also deserve mention. As in other meta-analysis, we pooled several trials which provide strong statistical power to detect small differences. Our strict inclusion criteria as well as abstraction of data by two independent investigators are additional strengths of our analysis.

In conclusion, we found that n-3 PUFA consumption did not affect IS. Larger scale trials may provide more conclusive result of n-3 PUFA consumption and IS.

Acknowledgments

We thank Dr. Ingrid L Mostad and Dr. Rosalba Giacco for providing data on their respective study for inclusion in the current meta-analysis.

Abbreviations

CAD	coronary artery disease
CI	confidence interval
CVD	cardiovascular disease
EPA	eicosapentaenoic acid
DHA	docosahexaenoic acid
FSIVGTT	frequently sampled intravenous glucose tolerance
HDL	high density lipoprotein
HOMA	homeostasis model assessment
IR	insulin resistance
IS	insulin sensitivity
IST	insulin suppression test
LDL	low density lipoprotein
Mesh	medical subject headings
MINMOD	minimal modal analysis
n-3 PUFA	Omega-3 polyunsaturated fatty acid

NAFLD	non-alcoholic fatty liver disease
QUICKI	quantitative insulin sensitivity check index
RCTs	Randomized Controlled Trials
SD	standard deviation
SMD	standardized mean difference
T2D	type 2 diabetes

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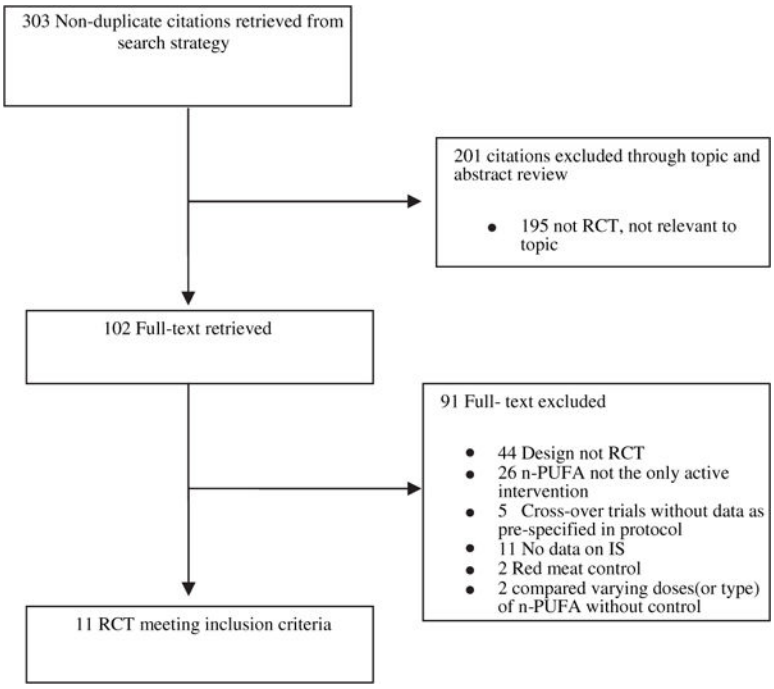

Fig. 1.

Flow diagram of study identification, inclusion and exclusion.

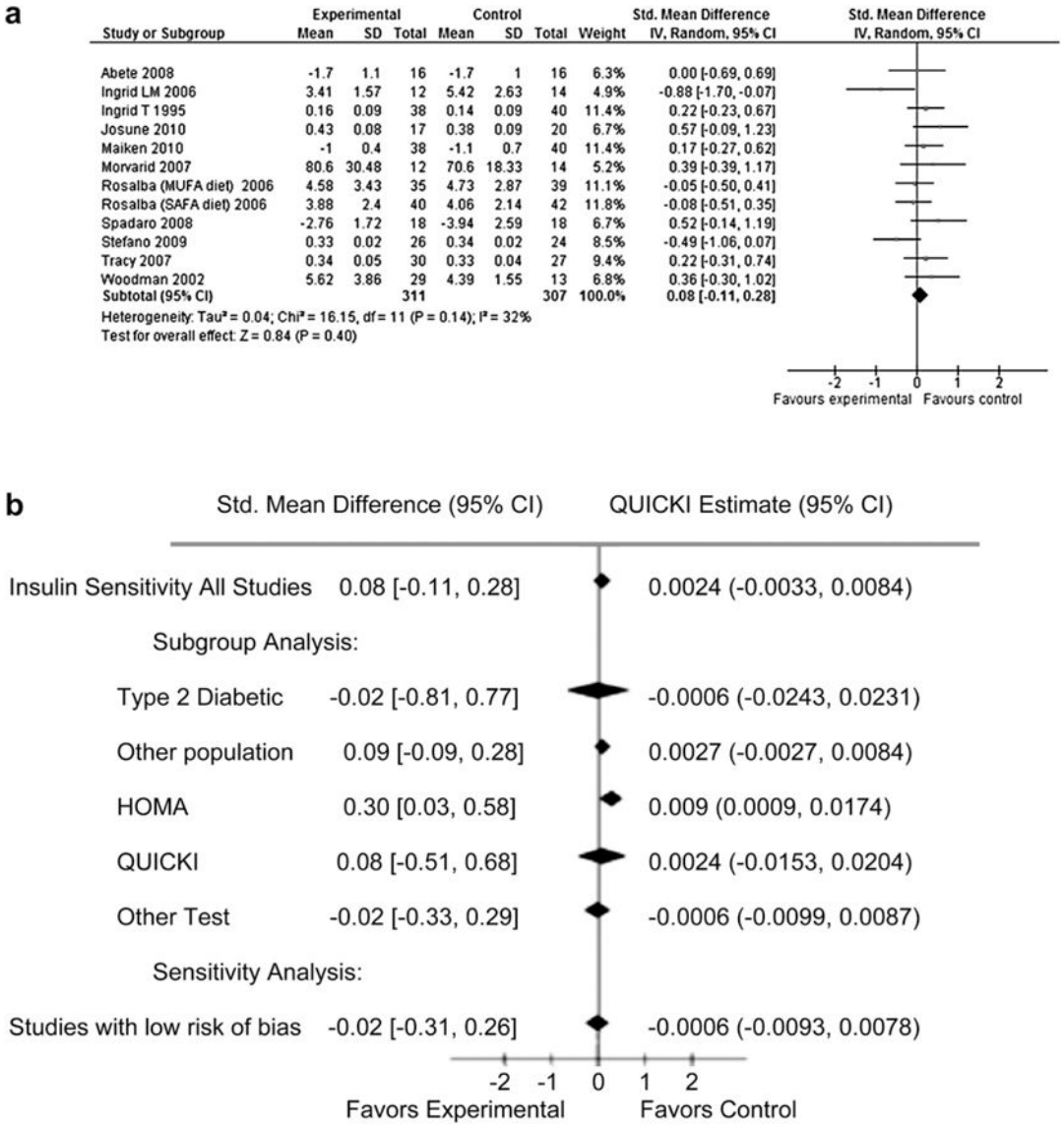

Fig. 2.

a: Forest plot showing all included trials. b: Subgroup and Sensitivity analysis.

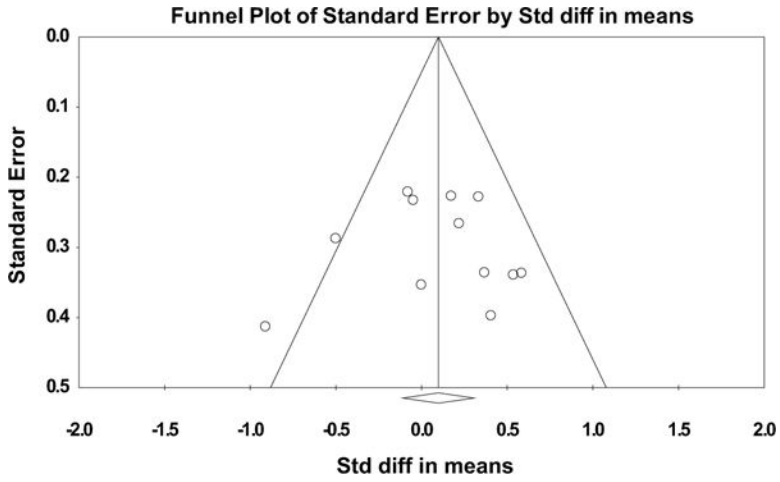

Fig. 3.

Funnel Plot to detect publication bias of included trials.

Clin Nutr. Author manuscript; available in PMC 2016 October 17.

Table 1

Characteristics of eligible studies.

Study	Mean Age (Range), Years	% Male	Participants	n-PUFA dose grams/day	Trial duration	Control oil	IS Measure	Mean Baseline IS	Dropout
Abete 2008[45]	36	56.20%	Non-diabetic, obese subjects $n_e^* - 16$ $n_c^* - 16$	Experimental group had fish based diet 3 days a week, while control did not.	8 weeks	NA	HOMA IR	2.65	E -20% C-20%
Ingrid LM 2006[26]	(40–75)	50%	Type 2 Diabetic $n_e^* - 12$ $n_c^* - 14$	2.42 g per day	9 weeks	Corn oil	Glucose utilization measured by hyperinsulinemic isoglycemic clamp	NA	E -7.7% C-0%
Ingrid T 1995[40]	53.67	64%	Non-diabetic, untreated HTN $n_e^* - 38$ $n_c^* - 40$	4 g per day	16 weeks	Corn oil	ISI -hyperglycemic clamps	0.17	E -9.5% C-4.8%
Josune 2010[36]	75	20%	Required TEN $n_e^* - 17$ $n_c^* - 20$	0.138 g per day	6 months	NA	HOMA IR, QUICKI	$a_{1.14}$ $b_{0.41}$	E -47% C-39%
Maiken 2010[41]	14.3	100%	Slightly over weight $n_e^* - 38$ $n_e^* - 40$	1.5 g per day	16 weeks	Mixture of Palm, soy and rapseed oil	HOMA IR	1.1	10.3% combined
Morvarid 2007[42]	55	0%	Type 2 Diabetic $n_e^* - 12$ $n_c^* - 14$	1.8 g per day	2 months	Paraffin oil	HOMA S	69.1	10.3% overall
Spadaro 2008[43]	50.73	52.80%	NAFLD $n_e^* - 18$ $n_c^* - 18$	2 g per day	6 months	NA	HOMA IR	3.75	E -10% C-10%
Stefano 2009[35]	29.9	50%	OPD $n_e^* - 26$ $n_c^* - 24$	2 g per day	12 weeks	Olive oil	QUICKI	0.35	E -0% C-0%
Tracy 2007[44]	38.49	20%	Abdominally obese	c_{11} g per day	8 weeks	NA	QUICKI	0.34	E -0% C-3.6%

Study	Mean Age (Range), Years	% Male	Participants	n-PUFA dose grams/day	Trial duration	Control oil	IS Measure	Mean Baseline IS	Dropout
Woodman 2002[37]	61.2	76%	Type 2 Diabetic with treated HTN $n_e^* - 29^d$ $n_c^* - 13$	4 g per day	6 weeks	Olive oil	ISI measured by low-dose insulin and glucose infusion test	5.46	28.8% overall
Rosalba 2006[25] (MUFA and SAFA diet groups combined)	48.74	53%	Healthy subjects, non-diabetic MUFA: $n_e^* - 35$ $n_c^* - 39$ SAFA: $n_e^* - 40$ $n_c^* - 42$	3.6 gper day	3 months	Olive oil	ISI measured with MINMOD program	4.44	3.7% overall

n_c^* – subjects in experimental group who completed the trials, n_c^* – subjects in the control group who completed the trials, E - Intervention group, C – Control group, HTN – Hypertension, NA – Not Available, ISI – Insulin sensitivity index, OPD – Offspring of patients with type 2 diabetes, TEN – Total Enteral Nutrition, NAFLD – Non-alcoholic Fatty Liver Disease.

[a] – HOMA IR score.

[b] – QUICKI score.

[c] – Flaxseed oil.

[d] – Combined EPA and DHA groups.