Journal of the American Heart Association

SYSTEMATIC REVIEW AND META-ANALYSIS

Omega-3 Polyunsaturated Fatty Acids Intake and Blood Pressure: A Dose-Response Meta-Analysis of Randomized Controlled Trials

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BACKGROUND: Current evidence might support the use of omega-3 fatty acids (preferably docosahexaenoic acid and eicosapentaenoic acid) for lowering blood pressure (BP), but the strength and shape of the dose-response relationship remains unclear.

METHODS AND RESULTS: This study included randomized controlled trials published before May 7, 2021, that involved participants aged ≥18 years, and examined an association between omega-3 fatty acids (docosahexaenoic acid, eicosapentaenoic acid, or both) and BP. A random-effects 1-stage cubic spline regression model was used to predict the average dose-response association between daily omega-3 fatty acid intake and changes in BP. We also conducted stratified analyses to examine differences by prespecified subgroups. Seventy-one trials were included, involving 4973 individuals with a combined docosahexaenoic acid+eicosapentaenoic acid dose of 2.8 g/d (interquartile range, 1.3 g/d to 3.6 g/d). A nonlinear association was found overall or in most subgroups, depicted as J-shaped dose-response curves. The optimal intake in both systolic BP and diastolic BP reductions (mm Hg) were obtained by moderate doses between 2 g/d (systolic BP, −2.61 [95% CI, −3.57 to −1.65]; diastolic BP, −1.64 [95% CI, −2.29 to −0.99]) and 3 g/d (systolic BP, −2.61 [95% CI, −3.52 to −1.69]; diastolic BP, −1.80 [95% CI, −2.38 to −1.23]). Subgroup studies revealed stronger and approximately linear dose-response relations among hypertensive, hyperlipidemic, and older populations.

CONCLUSIONS: This dose-response meta-analysis demonstrates that the optimal combined intake of omega-3 fatty acids for BP lowering is likely between 2 g/d and 3 g/d. Doses of omega-3 fatty acid intake above the recommended 3 g/d may be associated with additional benefits in lowering BP among groups at high risk for cardiovascular diseases.

Key Words: docosahexaenoic acid ■ eicosapentaenoic acid ■ hypertension ■ long-chain fatty acids ■ 1-stage regression

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Epidemiologic and experimental studies indicate that omega-3 polyunsaturated fatty acids (ω3 PUFAs), preferably including docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), may have cardiovascular health benefits by reducing modifiable risk factors. For example, intake of EPA was associated with reduced risks of major vascular events in JELIS (Japan Eicosapentaenoic Acid Lipid Intervention Study)[1] and REDUCE-IT (Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial).[2]

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Supplemental Material for this article is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.121.025071

For Sources of Funding and Disclosures, see page 11.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- Intake of omega-3 fatty acids has a nonlinear association with reductions in blood pressure.
- The optimal daily intake of omega-3 fatty acid for blood pressure control appears to be 3 g.

What Are the Clinical Implications?

- An optimal dose of omega-3 fatty acids is potentially needed for blood pressure control in the general population, but individuals who are at high risk of developing cardiovascular diseases may benefit from higher doses.

Nonstandard Abbreviations and Acronyms

DBP	diastolic blood pressure
DHA	docosahexaenoic acid
EPA	eicosapentaenoic acid
JELIS	Japan Eicosapentaenoic Acid Lipid Intervention Study
REDUCE-IT	Reduction of Cardiovascular Events With Icosapent Ethyl–Intervention Trial
SBP	systolic blood pressure
ω3 PUFA	omega-3 polyunsaturated fatty acid

However, recently completed clinical studies and meta-analyses[5,6] showed that supplementation of ω3 PUFAs did not offer significant favorable impacts on cardiovascular events, such as the risk of cardiovascular disease, myocardial infarction, or stroke. Previous meta-analyses have also examined the association between ω3 PUFA intake and blood pressure (BP),[7–11] but have been unable to reveal a significant dose-response relationship[8,10,12] or have shown conflicting trends.[7,11] These past meta-analyses examined the dose-response relationship using pooled meta-regression[8,10] or, by grouping categories of exposure into separate meta-analyses,[7,11] approaches that are prone to biases and do not take into account the correlations among effects at different dose levels.[13]

These limitations warrant further examination of the effects of ω3 PUFAs on changes in BP among randomized controlled trials (RCTs). To fully capture the dose-response effect and reflect heterogeneity among the studies, we utilized a 1-stage cubic spline regression model, recently developed[13] and used for dose-response meta-analyses in 2 BP systematic reviews.[14,15] The 1-stage spline mixed model is advantageous since it allows estimation of nonlinear dose-response curves, including J or L shape, and allows for the inclusion of studies with <3 exposure levels, in comparison to 2-stage methods.[13] Following a comprehensive literature review for RCTs, this study aimed to more precisely characterize the dose-response effect of ω3 PUFAs (DHA, EPA, or both) on BP in the general population and relevant subgroups.

METHODS

The study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for the conduct of meta-analysis of randomized trials and a checklist was attached (Table S1). The data that support the findings of this study are available from the corresponding author on reasonable request. This meta-analysis was performed with the previously published trials. Therefore, ethical review or institutional review board approval was not applicable.

Literature Review

A systematic literature search was conducted for articles published before May 7, 2021, using PubMed and Embase databases (Table S2). Manual searches were undertaken to screen the reference lists of relevant studies, reviews, and meta-analyses for additional studies. Two reviewers (X.Z. and X.L.) screened each study independently and discrepancies were resolved through discussion. The prespecified eligibility criteria were parallel or crossover RCTs that examined the association between intake of DHA/EPA (combined or individual) and systolic BP (SBP) and/or diastolic BP (DBP) in adults (aged ≥18 years). Studies were eligible if they examined intake of DHA/EPA through diet or fatty oil supplementation. We excluded trials in which: (1) concurrent inactive placebo controls were lacking; (2) intervention duration was <4 weeks; (3) a washout period of <4 weeks was applied between treatments in crossover trials; (4) patients with hypertension received concurrent BP-lowering medications[11,12]; and (5) studies were conducted in pregnant and nursing women, or individuals with preexisting cardiovascular events (eg, those with myocardial infarction or heart failure), renal diseases, or secondary hypertension. Assessment of the methodological quality was performed independently using the Cochrane risk-of-bias tool 2.[16]

Data Extraction

For each eligible study, information was extracted independently by 2 of the authors (N.Z. and X.Z.) and confirmed by a third author (X.L.) using a standardized form. The effects of each dose of exposure were extracted individually in our study. In experiments with

multiple follow-up time points, only changes in SBP and DBP levels at the end of the treatment versus pretreatment were extracted, avoiding multiple measurements from the same trial. If an SD was not provided directly, we calculated it from the SE, interquartile range, or CI.[17]

Exposure and Outcome Assessment

Most studies that examined the effects of omega-3 fatty acids used a combined supplementation of EPA and DHA. The exposure levels were expressed by DHA+EPA combined or DHA/EPA alone. For intake of DHA/EPA through diet, the exposure level was determined by the fraction of pure DHA/EPA amount over the food consumed daily. For fatty oil supplementation trials, the exposure level was determined by the pure DHA/EPA content as claimed by the researchers or the manufacturers. We determined the net mean difference in BP ($\Delta BP_{between}$) between the exposure levels of each RCT as the difference at the end of the intervention minus the corresponding pretreatment value ($\Delta BP_{intragroup}$).

Publication Bias Assessment

Publication bias was examined visually using funnel plots to assess the SE as a function of effect size, and performing Egger regression test to examine small-study bias using R *metafor* functions.[18] We also used the trim-and-fill method to estimate the number of potential missing studies caused by publication bias. A leave-one-out strategy was applied for sensitivity analyses, where we repeatedly ran the dose-response analysis to assess the missing study's influence on overall mean BP change.

Dose-Response Analysis

The placebo dose (0 g/d) was used as the reference for all analyses. A 1-stage random-effects dose-response model[13] was performed to predict the average dose-response relationship between administration of DHA+EPA and changes in SBP and DBP levels. We tested the linearity assumption underlying the dose-response relationship by fitting a restricted cubic spline model with 3 knots (10th, 50th, and 90th percentiles) of the doses.[19] Included studies were pooled into a continuous dose-response curve, and then the predicted effect of omega-3 on BP was estimated from the curve at given doses (ie, 1 g/d, 2 g/d, 3 g/d, 4 g/d, and 5 g/d). Additionally, subgroup analyses were conducted by stratifying studies according to study design (crossover versus parallel), hypertension (SBP ≥140 mm Hg or DBP ≥90 mm Hg), or hyperlipidemia (total cholesterol ≥200 mg/dL or triglycerides ≥150 mg/dL) status, intervention (supplementation versus diet), exposure composition (fish oil versus purified ethyl ester), duration of treatment (≥12 weeks or not), sex, and average age (≥45 years or <45 years). We also conducted subgroup analyses by baseline SBP (≥130 mm Hg versus <130 mm Hg), according to the new cut point suggested in a recent American Heart Association hypertension guideline.[20] The 1-stage cubic spline regression model was conducted using the *dosresmeta* R packages (https://github.com/alecri/dosresmeta).[13,21,22]

RESULTS

Study Characteristics

After removing duplicates, the systematic search retrieved 3066 relevant articles. The title and abstract review further excluded 2897 articles. Full-text examination of 169 articles yielded 71 eligible RCTs (references 23 and 24 and references 36 to 104 in the Supplemental Material) that were included in the analyses. A PRISMA flow diagram of the literature screening is shown in Figure 1. Study characteristics of the included trials are shown in Table S3. These trials, published between 1987 and 2020, reported an overall sample size of 4973 participants with an average age between 22 to 86 years. A parallel design was adopted predominantly in 60 trials, and only 11 trials used a crossover design. These trials were conducted in Europe (n=27), North America (n=25), Oceania (n=16), and Asia (n=3). More than a half of the trials (43 of 71) included both men and women, whereas 25 included only men and 3 included only women. Most trials were restricted to participants without hypertension (n=56 [79%], average baseline SBP <140 mm Hg) and without hyperlipidemia (n=57 [80%], average total cholesterol<200 mg/dL [5.2 mmol/L] and triglycerides <150 mg/dL [1.7 mmol/L]). In terms of outcome measurement, BP was measured either manually (n=13), automatically (n=44), or not reported (n=14), in ambulatory (n=5), rest (n=8), seated (n=32), supine (n=12), or unknown (n=14) modalities. The average intervention duration was 10 weeks (interquartile range, 6–12 weeks) (Figure S1A), and the duration was longer than 12 weeks (ranging from 12 to 52 weeks) in 29 trials and <12 weeks in 42 trials. In the majority of studies (n=64), interventions of supplementation were accomplished by capsuled fish oil, algal oil, or purified fish oil ethyl esters. The remainder of studies (n=7) used a dietary intervention that included intake of fish meals (eg, mackerel, salmon, trout, and tuna) and other fish oil–fortified foods, either cooked at home or by a dietitian. The most commonly used placebo was olive oil, along with the remainder consisting of types of vegetable oils, such as safflower, sunflower, corn, soybean, and palm oils. Fifty-three of 71 trials reported the combined effects of DHA and EPA, with an average combined dose of 2.8 g/d (interquartile range, 1.3–3.6; range 0.2–15

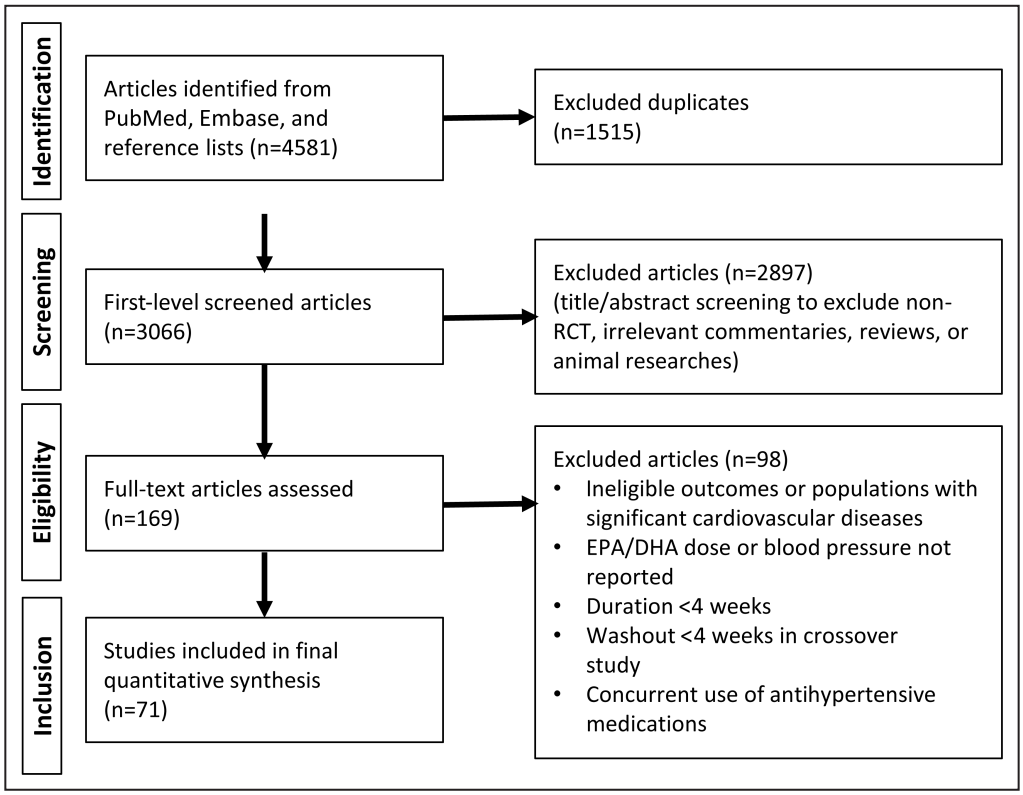

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of systematic literature search and screening for randomized controlled trials published through May 2021 that met the study inclusion and exclusion criteria.
DHA indicates docosahexaenoic acid; and EPA, eicosapentaenoic acid.

g/d) (Figure S1B), DHA dose of 1.4 g/d (range, 0 to 6 g/d), and EPA dose of 1.8 g/d (range, 0 to 9 g/d); only 11 and 6 trials observed the effects of individual DHA or EPA, respectively.

Overall Dose-Response Analysis

The Table summarizes the impact of combined doses of DHA+EPA at 1 g/d, 2 g/d, 3 g/d, 4 g/d, and 5 g/d on average changes in BP, compared with the placebo or control group (combined dose=0 g/d). We found a significant nonlinear dose-response relationship for both SBP and DBP models (Figure 2) (z=3.87 [P=0.0001] and z=2.68 [P=0.0073], respectively). The J-shaped curves suggest that dosages of DHA+EPA at 2 g/d to 3 g/d are associated with the strongest changes in both SBP and DBP relative to the reference dose (0 g/d). The estimated average dose-response curves and corresponding CIs also indicate that the dose region of apparent improvement for SBP and DBP is from 0 g/d to 5 g/d. When compared with the reference (0 g/d), the average mean changes in SBP were –2.61 mm Hg (95% CI, –3.57 to –1.65) for 2 g/d of DHA+EPA, and –2.61 mm Hg (95% CI, –3.52 to –1.69) for 3 g/d of DHA+EPA. The average mean changes in DBP were –1.64 mm Hg (95% CI, –2.29 to –0.99) for 2 g/d of DHA+EPA, and –1.80 mm Hg (95% CI, –2.38 to –1.23) for 3 g/d of DHA+EPA (Table). In both SBP and DBP models, combined doses >3 g/d were associated with weaker or null changes in BP (Table). The width of the CIs was wider at exposure levels >6 g/d for both SBP and DBP. Only 2 trials[23,24] examined a dose >7 g/d (specifically, at 15 g/d). Removal of these 2 trials did not change the shape of the dose-response curve, despite the narrower CIs (Figure S2).

Subgroup Analyses

For studies including an average baseline SBP of ≥ 130 mm Hg, we found evidence that DHA+EPA supplementation had an approximately linear trend with BP, where increasing supplementation resulted in stronger reductions in SBP and DBP (Figure 3, Table). This trend was not evident among those with a baseline SBP of <130 mm Hg, although a similar optimal intake of 2 g/d to 3 g/d as our original findings was found. Similar findings were also seen when stratified by hypertension status (SBP ≥140 mm Hg, as defined in most included trials), where patients with hypertension showed greater reductions in SBP and DBP, compared with those without hypertension (Table, Figure S3). When stratifying by the presence of hyperlipidemia, we found

Table. Estimated Average Dose-Response Relationship Between DHA+EPA Consumption and BP Reduction

BP	Participants	No*	1.0 g/d		2.0 g/d		3.0 g/d		4.0 g/d		5.0 g/d	
			MD	(95% CI)	MD	(95% CI)	MD	(95% CI)	MD	(95% CI)	MD	(95% CI)
SBP	All	70	−1.81	(−2.52 to −1.10)	−2.61	(−3.57 to −1.65)	−2.61	(−3.52 to −1.69)	−2.15	(−3.08 to −1.22)	−1.57	(−2.79 to −0.34)
DBP	All	69	−1.07	(−1.57 to −0.57)	−1.64	(−2.29 to −0.99)	−1.80	(−2.38 to −1.23)	−1.73	(−2.27 to −1.19)	−1.59	(−2.34 to −0.84)
Baseline SBP, mm Hg												
SBP	≥130	19	−1.53	(−2.67 to −0.40)	−2.57	(−4.32 to −0.81)	−3.22	(−5.21 to −1.23)	−3.62	(−5.64 to −1.59)	−3.88	(−5.88 to −1.88)
	<130	44	−1.73	(−2.72 to −0.75)	−2.38	(−3.62 to −1.13)	−2.20	(−3.29 to −1.10)	−1.65	(−2.79 to −0.51)	−1.07	(−2.65 to 0.51)
DBP	≥80	19	−1.46	(−2.14 to −0.78)	−2.49	(−3.58 to −1.40)	−3.18	(−4.48 to −1.87)	−3.64	(−5.03 to −2.25)	−3.99	(−5.41 to −2.58)
	<80	45	−0.83	(−1.50 to −0.16)	−1.31	(−2.13 to −0.49)	−1.54	(−2.21 to −0.87)	−1.66	(−2.36 to −0.95)	−1.76	(−2.83 to −0.69)
Hypertension status, SBP ≥140 mm Hg or DBP ≥90 mm Hg												
SBP	Hypertension	16	−2.56	(−3.46 to −1.65)	−3.99	(−5.29 to −2.70)	−4.54	(−6.02 to −3.05)	−4.42	(−6.33 to −2.52)	−3.89	(−6.62 to −1.16)
	No hypertension	55	−1.66	(−2.52 to −0.80)	−2.22	(−3.30 to −1.14)	−1.97	(−2.90 to −1.03)	−1.35	(−2.32 to −0.39)	−0.70	(−2.06 to 0.66)
DBP	Hypertension	16	−1.23	(−1.90 to −0.55)	−2.14	(−3.25 to −1.03)	−2.81	(−4.18 to −1.45)	−3.30	(−4.80 to −1.81)	−3.68	(−5.25 to −2.10)
	No hypertension	55	−0.94	(−1.55 to −0.33)	−1.42	(−2.18 to −0.67)	−1.57	(−2.18 to −0.95)	−1.55	(−2.15 to −0.96)	−1.53	(−2.41 to −0.64)
Hyperlipidemia status, total cholesterol ≥200 mg/dL or triglycerides ≥150 mg/dL												
SBP	Hyperlipidemia	14	−1.84	(−3.00 to −0.69)	−3.17	(−4.82 to −1.52)	−3.78	(−5.21 to −2.35)	−4.03	(−5.65 to −2.41)	−4.24	(−6.75 to −1.73)
	No hyperlipidemia	56	−1.68	(−2.52 to −0.84)	−2.36	(−3.50 to −1.21)	−2.26	(−3.35 to −1.17)	−1.72	(−2.73 to −0.71)	−1.06	(−2.26 to 0.13)
DBP	Hyperlipidemia	14	−1.55	(−2.71 to −0.39)	−2.42	(−4.03 to −0.80)	−2.34	(−3.61 to −1.07)	−1.80	(−3.18 to −0.43)	−1.21	(−3.54 to 1.13)
	No hyperlipidemia	55	−0.94	(−1.50 to −0.39)	−1.48	(−2.22 to −0.75)	−1.69	(−2.34 to −1.03)	−1.70	(−2.32 to −1.09)	−1.65	(−2.50 to −0.81)
Study duration, wk												
SBP	≥12	29	−0.76	(−2.09 to 0.57)	−1.28	(−2.42 to −0.15)	−1.66	(−3.10 to −0.23)	−2.02	(−4.96 to 0.91)	−2.38	(−6.99 to 2.24)
	<12	41	−2.46	(−3.52 to −1.39)	−3.50	(−4.87 to −2.12)	−3.39	(−4.56 to −2.22)	−2.52	(−3.53 to −1.51)	−1.28	(−2.85 to 0.30)
DBP	≥12	29	−0.91	(−1.93 to 0.11)	−1.51	(−2.51 to −0.51)	−1.91	(−2.63 to −1.20)	−2.29	(−3.51 to −1.06)	−2.66	(−4.70 to −0.62)
	<12	40	−0.99	(−1.60 to −0.38)	−1.56	(−2.42 to −0.70)	−1.76	(−2.56 to −0.95)	−1.70	(−2.35 to −1.05)	−1.52	(−2.24 to −0.79)
Study design												
SBP	Crossover	11	−1.35	(−3.21 to 0.50)	−1.80	(−4.39 to 0.78)	−1.52	(−4.19 to 1.14)	−0.71	(−3.62 to 2.20)	0.44	(−3.54 to 4.41)
	Parallel	59	−1.95	(−2.75 to −1.16)	−2.75	(−3.78 to −1.71)	−2.67	(−3.61 to −1.73)	−2.20	(−3.14 to −1.25)	−1.68	(−2.90 to −0.46)
DBP	Crossover	11	−1.67	(−3.30 to −0.05)	−2.43	(−4.72 to −0.14)	−2.44	(−4.66 to −0.22)	−1.91	(−3.69 to −0.12)	−1.03	(−2.71 to 0.65)
	Parallel	58	−0.91	(−1.46 to −0.36)	−1.45	(−2.14 to −0.77)	−1.70	(−2.27 to −1.12)	−1.81	(−2.41 to −1.20)	−1.90	(−2.79 to −1.01)
Mean age, y												
SBP	≥45	35	−1.76	(−2.82 to −0.71)	−2.58	(−3.79 to −1.37)	−2.82	(−3.91 to −1.73)	−2.87	(−4.28 to −1.45)	−2.91	(−5.00 to −0.81)
	<45	21	−1.10	(−2.48 to 0.29)	−1.50	(−3.50 to 0.51)	−1.29	(−3.27 to 0.69)	−0.67	(−2.26 to 0.91)	0.14	(−1.04 to 1.33)
DBP	≥45	33	−0.61	(−1.26 to 0.04)	−1.17	(−1.93 to −0.40)	−1.68	(−2.31 to −1.05)	−2.18	(−2.85 to −1.51)	−2.68	(−3.66 to −1.70)
	<45	22	−1.22	(−2.03 to −0.41)	−1.75	(−2.92 to −0.58)	−1.68	(−2.85 to −0.51)	−1.21	(−2.17 to −0.24)	−0.53	(−1.34 to 0.27)

(*Continued*)

Table. Continued

BP	Participants	No*	1.0 g/d		2.0 g/d		3.0 g/d		4.0 g/d		5.0 g/d	
			MD	(95% CI)	MD	(95% CI)	MD	(95% CI)	MD	(95% CI)	MD	(95% CI)
Fish oil composition												
SBP	Ethyl ester	12	−0.57	(−1.68 to 0.53)	−1.36	(−3.03 to 0.31)	−2.41	(−4.22 to −0.60)	−3.57	(−5.69 to −1.45)	−4.75	(−7.50 to −2.00)
	Fish oil	58	−1.97	(−2.76 to −1.18)	−2.71	(−3.74 to −1.68)	−2.49	(−3.43 to −1.55)	−1.70	(−2.65 to −0.74)	−0.72	(−2.06 to 0.63)
DBP	Ethyl ester	12	−1.11	(−1.64 to −0.58)	−1.69	(−2.40 to −0.98)	−1.84	(−2.49 to −1.19)	−1.73	(−2.36 to −1.10)	−1.53	(−2.39 to −0.66)
	Fish oil	57	−1.12	(−1.66 to −0.58)	−1.69	(−2.4 to −0.99)	−1.84	(−2.49 to −1.20)	−1.74	(−2.37 to −1.10)	−1.54	(−2.42 to −0.67)
Intervention type												
SBP	Diet	8	−2.05	(−4.13 to 0.04)	−2.54	(−4.99 to −0.09)	−2.02	(−4.07 to 0.04)	−1.07	(−3.40 to 1.25)	−0.10	(−3.59 to 3.39)
	Supplementation	64	−1.78	(−2.53 to −1.03)	−2.58	(−3.59 to −1.57)	−2.62	(−3.59 to −1.65)	−2.24	(−3.22 to −1.25)	−1.75	(−3.02 to −0.47)
DBP	Diet	7	0.34	(−0.37 to 1.05)	−0.05	(−1.07 to 0.97)	−0.94	(−2.75 to 0.88)	−2.08	(−5.19 to 1.03)	−3.27	(−7.83 to 1.29)
	Supplementation	64	−1.16	(−1.69 to −0.63)	−1.76	(−2.45 to −1.06)	−1.90	(−2.51 to −1.29)	−1.78	(−2.35 to −1.22)	−1.60	(−2.39 to −0.82)
Sex												
SBP	Men	24	−1.28	(−2.32 to −0.23)	−2.12	(−3.89 to −0.36)	−2.19	(−4.10 to −0.28)	−1.59	(−3.18 to 0.00)	−0.54	(−1.70 to 0.62)
	Women	3	1.37	(−6.26 to 9.00)	1.00	(−4.77 to 6.76)	−0.31	(−2.61 to 2.00)	−1.74	(−11.28 to 7.80)	−3.17	(−20.45 to 14.11)
DBP	Men	25	−1.13	(−1.71 to −0.55)	−1.89	(−2.85 to −0.93)	−2.01	(−3.03 to −1.00)	−1.60	(−2.46 to −0.75)	−0.85	(−1.63 to −0.07)
	Women	3	3.86	(−2.99 to 10.70)	2.39	(−3.04 to 7.82)	−1.92	(−5.90 to 2.05)	−6.62	(−16.60 to 3.36)	−11.32	(−28.27 to 5.63)
Individual effect of DHA or EPA												
SBP	DHA only	11	−1.95	(−3.52 to −0.38)	−2.37	(−3.86 to −0.88)	−2.03	(−4.08 to 0.03)	−1.56	(−5.21 to 2.09)	−1.10	(−6.56 to 4.37)
	EPA only	6	1.42	(−2.52 to 5.35)	1.02	(−3.30 to 5.33)	−0.58	(−3.24 to 2.08)	−2.68	(−5.14 to −0.21)	−4.82	(−9.89 to 0.25)
DBP	DHA only	11	−1.10	(−3.06 to 0.86)	−1.04	(−2.66 to 0.57)	−0.40	(−2.03 to 1.23)	0.34	(−3.04 to 3.71)	1.07	(−4.35 to 6.50)
	EPA only	6	2.73	(1.72 to 3.74)	2.48	(1.27 to 3.68)	0.26	(−1.18 to 1.70)	−2.78	(−5.06 to −0.49)	−5.89	(−9.28 to −2.49)

BP indicates blood pressure; DHA, docosahexaenoic acid; DBP, diastolic blood pressure; EPA, eicosapentaenoic acid; MD, mean difference, mm Hg; and SBP, systolic blood pressure. Note: *Numbers may not sum to group totals because of missing data or unspecified subgroups in the trials. The total number is >71 because of the multiple intervention types in 1 trial.

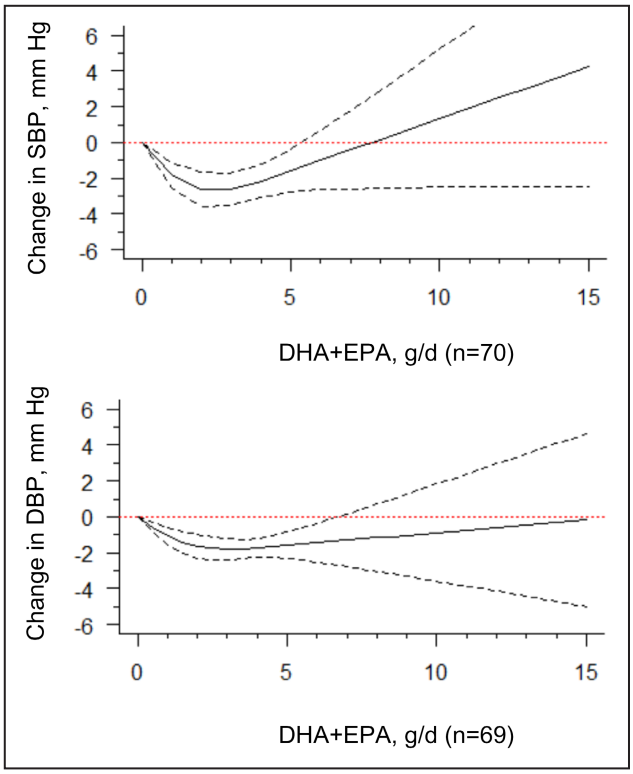

Figure 2. Dose-response relationship between changes in blood pressure and combined docosahexaenoic acid (DHA)+eicosapentaenoic acid (EPA) intake.
Marginal average dose-response curve (solid line) with 95% point-wise CIs (dashed lines) estimated by a 1-stage random-effects restricted cubic spline model, using 0 g/d as the referent. Studies included n=70 for systolic blood pressure (SBP) and n=69 for diastolic blood pressure (DBP).

an approximately linear relationship among those with hyperlipidemia for SBP, suggesting that increasing supplementation was associated with greater reductions in SBP. Again, this trend was not evident among those without hyperlipidemia for SBP, but an optimal intake of 2 g/d to 3 g/d could be seen. For DBP, there was also some indication that patients with hyperlipidemia may have greater reductions in DBP at 2 g/d to 3 g/d, compared with those without hyperlipidemia (Table, Figure 4).

We also found stronger effects among studies examining study participants with an average age of ≥45 years (Table, Figure 5). The negligible departure from linearity between DHA+EPA and reductions in BP appeared to be limited to ≥45 years in both SBP and DBP models, while studies in patients with a mean age of <45 years showed null effects. When examining by study duration, studies conducted <12 weeks tended to show stronger findings for SBP at 2 g/d to 3 g/d. However, in studies with a duration of ≥12 weeks, DHA+EPA intake was found to lower BP in a fashion with a minor departure from linearity across the entire range of doses (Table, Figure S4). In a subgroup analysis stratified by study design (crossover versus parallel), we found slightly stronger effects among studies with a parallel design, in which relatively narrower CIs were estimated (Table, Figure S5).

We found no strong differences when stratifying by intervention type (diet versus supplementation), sex, and fish oil consumption (natural fish oil versus purified ethyl ester), possibly attributable to few studies that reported relationships for diet, women, and use of ethyl esters (Table, Figures S6 through S8). We retrieved few trials that evaluated DHA (n=11) or EPA (n=6) as individual fatty acids. There was insufficient statistical power to detect a meaningful difference between individual EPA and DHA on lowering either SBP or DBP (Table, Figure S9).

Risk of Study Bias and Publication Bias

One and 5 trials were ranked as high and moderate risk of bias, respectively, while the remainder of trials were ranked as low risk of bias (Table S4). Exclusion of moderate and high risk-of-bias trials did not appreciably change the shape of the dose-response curve (results not shown). The funnel plot and Egger regression test indicated asymmetry in the overall SBP model (z=−3.05, P=0.002). There was no evidence of plot asymmetry in pooled DBP and stratified models (Figures S10 and S11). This suggests that publication bias, if present because of small-study effects, did not strongly impact our overall findings. The leave-one-out sensitivity analyses in 1-stage regression models proved that overall effects were not driven by a small number of specific trials, but reflected the global effect of the included trials (Figures S12 and S13).

DISCUSSION

Using a new 1-stage strategy, we examined the strength and shape of the dose-response association between DHA+EPA intake and BP with up-to-date literature and multiple subgroup analyses. We found evidence of a J-shaped dose-response curve, where the greatest reductions of SBP and DBP occurred at moderate DHA+EPA doses between 2 g/d and 3 g/d. These findings were slightly stronger in studies where the average participant age was ≥45 years for SBP. We also found evidence of a stronger, approximately linear dose-response relationship among hyperlipidemic and hypertensive populations, suggesting that this is a population that could be more responsive to the beneficial impacts of ω3 PUFA intake on reductions in BP. Moreover, our data also demonstrated that ω3 PUFA intake above the recommended intake of 3 g/d was not associated with additional benefits, particularly in normotensive subgroups.

Our findings are different from other meta-analyses that examined the relationship between ω3

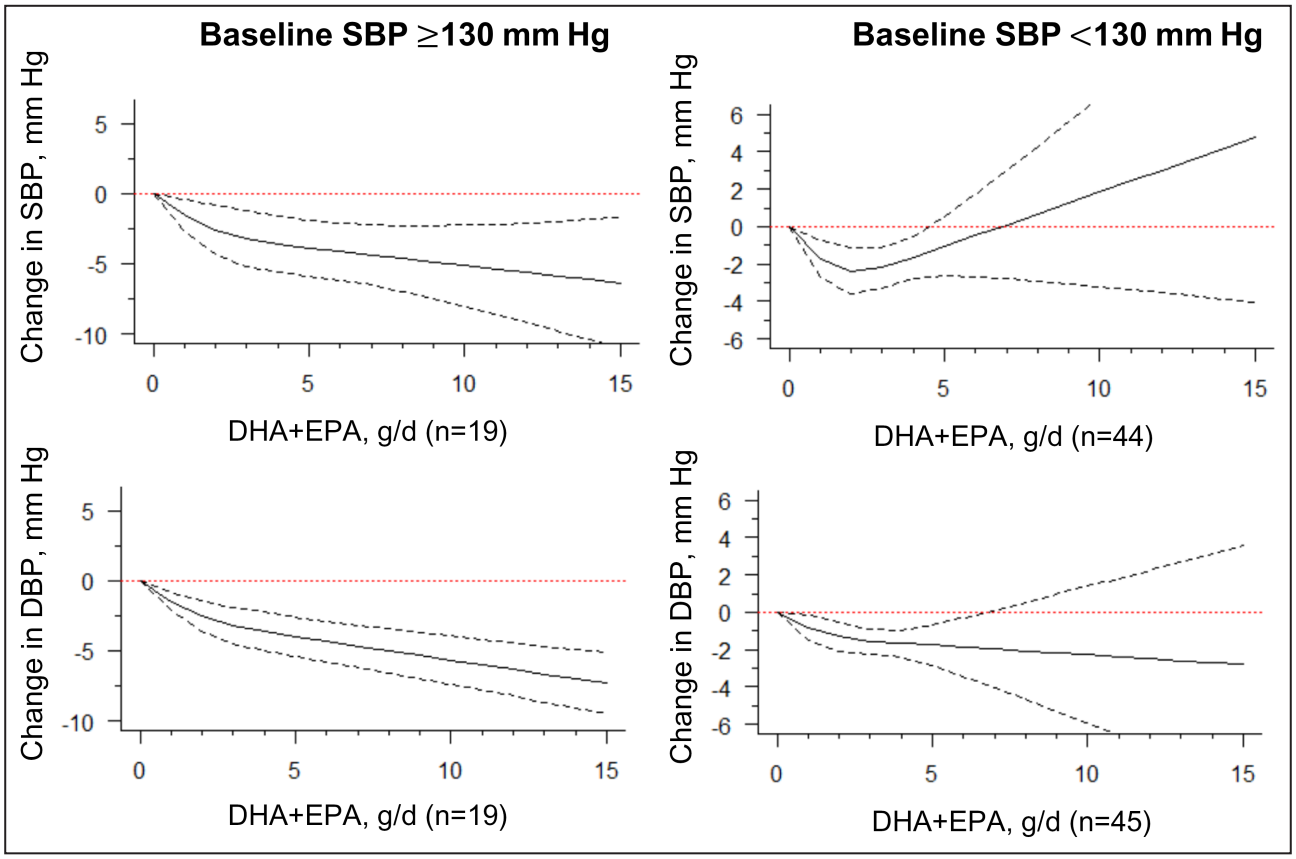

Figure 3. Dose-response relationship between changes in blood pressure and combined docosahexaenoic acid (DHA)+eicosapentaenoic acid (EPA) intake of the studies stratified by the baseline systolic blood pressure (SBP) level.
Marginal average dose-response curve (solid line) with 95% point-wise CIs (dashed lines) estimated by a 1-stage random-effects restricted cubic spline model, using 0 g/d as the referent, in participants with baseline SBP ≥130 mm Hg or <130 mm Hg. DBP indicates diastolic blood pressure; and n, number of the included study.

PUFA intake and changes in BP among RCT studies. Previous meta-analyses assumed a linear function.[8,12] These studies found that BP reductions were not associated with DHA+EPA intake within a dose range of 0.2 g/d to 15 g/d. Morris et al[7] attempted to test a dose-response effect with a meta-regression model with varying doses from 2 g/d to 6 g/d. They proposed a linear dose-response effect among the hypertensive studies, but the absence of doses between 7 g/d and 15 g/d seemed to put disproportionately more weight on the trial that used a dosage of 15 g/d. Similar to our study, Campbell et al[10] later demonstrated that the BP-lowering effect was diminished with the increasing dose between 1 g/d and 6 g/d. Another effort was made a decade later by categorizing the ω3 PUFA intake.[11] The stratum of 3 g/d to 4 g/d exerted the strongest effect of –3.85 mm Hg on SBP and –1.86 mm Hg on DBP, respectively, suggesting the existence of a dose threshold.[11] Overall, although they have been unable to smoothly shape the relationship between fish oil intake and BP over the entire range of exposure, these studies suggested a nonlinear association and sparked further investigations. Our study builds on past evidence by examining the relationship using up-to-date literature, and novel methods that allow for the estimation of a nonlinear trend that accounts for the correlation between studies.

In our study, using overall and subgroup analyses we found a consistent J-shaped curve in our models. The optimal or threshold doses were estimated to fall between 2 g/d and 3 g/d in our models, which coincided with the range of EPA and DHA dose exhibiting maximal effects on BP.[8,10,11] We also observed a minor departure from linearity of BP decline in participants with baseline SBP ≥130 mm Hg and a wider beneficial range in participants with hypertension compared with normotensive populations.[8,11] Moreover, our findings are consistent with previous synthesized results in which DBP reductions were significantly greater in older populations (mean age ≥45 years) compared with younger populations.[8] Considering cardiometabolic comorbidities, we further compared the effects of fish oil between participants with and those without hyperlipidemia. Our

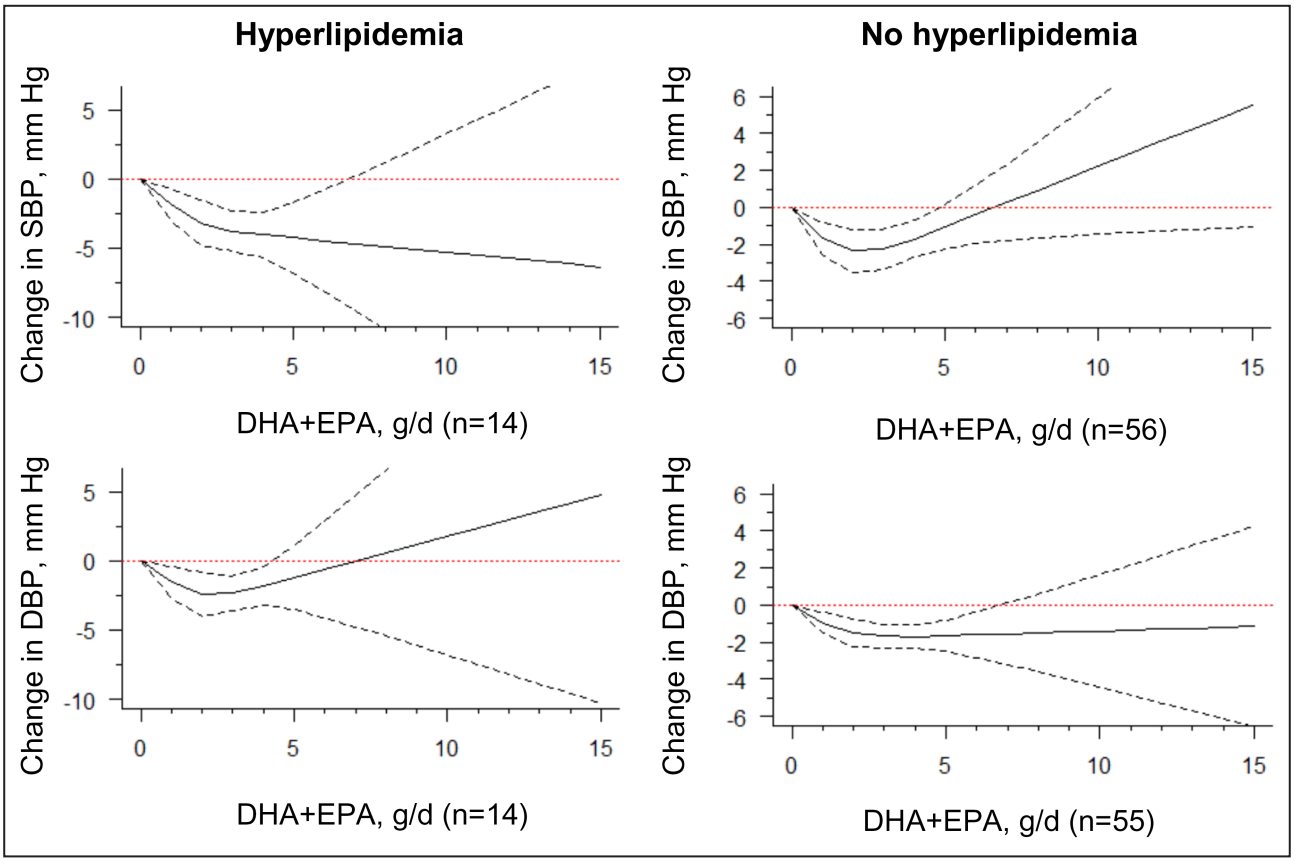

Figure 4. Dose-response relationship between changes in blood pressure and combined docosahexaenoic acid (DHA)+eicosapentaenoic acid (EPA) intake of the studies stratified by the status of hyperlipidemia.
Marginal average dose-response curve (solid line) with 95% point-wise CIs (dashed lines) estimated by a 1-stage random-effects restricted cubic spline model, using 0 g/d as the referent, in participants with or without hyperlipidemia. n indicates the number of the included study.

data suggested that ω3 PUFA intake had larger reductions in SBP in populations with hyperlipidemia, which made our models more applicable given the increasing prevalence of metabolic syndromes.

Our analyses showed a positive and approximately linear (or L-shaped) dose-response association in respective subgroups of hypertensive, hyperlipidemic, and older participants. The approximately linear association could be interpreted as there is no dose threshold, particularly in the hypertensive subgroup. It is unclear why approximately linear associations were evident for these subgroups, in comparison to the J-shaped curves seen in the main analyses. It could be that high-risk population, such as those with hypertension and hyperlipidemia, could benefit differently from ω3 PUFA intake supplementation in comparison to younger and healthier populations, particularly since ω3 PUFA is hypothesized to interact with many pathways, such as triglycerides, inflammation, and heart rate.[25,26] Additionally, there could be mechanistic differences in bioavailability and efficacy of ω3 PUFA intake in these populations.[25,26] However, given that few studies have investigated the relationship at higher doses (ie >7 g/d), more research is needed to elucidate this relationship, including biological mechanisms.

We are not the first to propose a nonlinear model for the dose-response of fish oil intake on the BP effect. The J-shaped dose-response effects have been tentatively proposed in prospective cohort studies and clinical trial meta-analyses. For example, summarized data of 6 selected independent prospective cohort studies indicated that there was also a J-shaped association between the increment of ω3 PUFA intake and risk of hypertension within the low dose range of 0 g/d to 2 g/d.[27] A nonlinear negative and L-shaped association between ω3 PUFA intake and the risk of hypertension was later proposed, with a dose at ≈3.4 g/d reaching the maximal BP risk-lowering effect in a cross-sectional study.[28] In these 2 reports, an apparent J-shaped relationship between ω3 PUFA intake and hypertension risk was indicated with restricted cubic splines, a finding that is supported in our dose-response analysis examining changes in BP.

Our findings of a curvilinear relationship between BP effects and fish oil intake may have considerable implications in the cardioprotection of ω3 PUFAs.

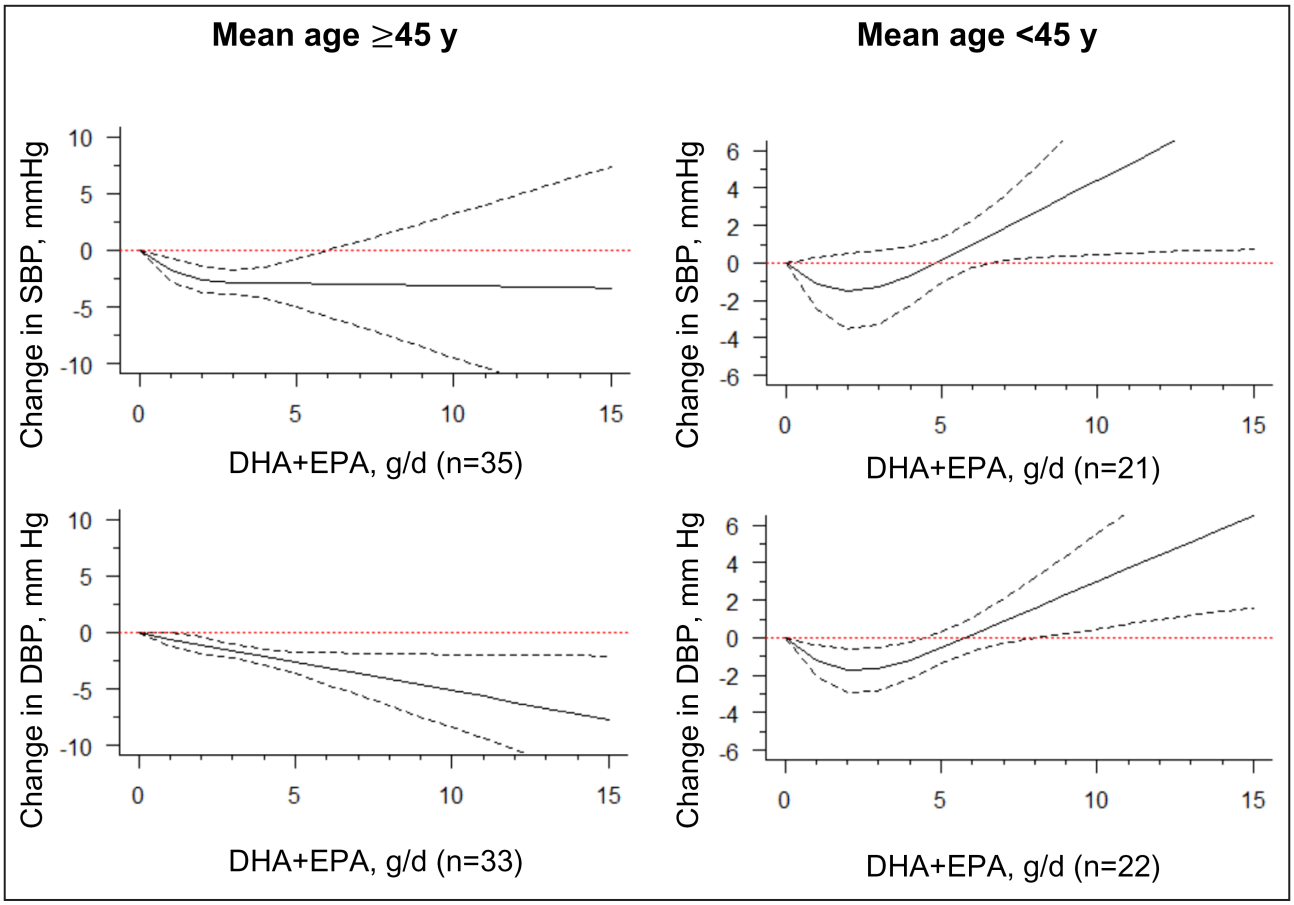

Figure 5. Dose-response relationship between changes in blood pressure and combined docosahexaenoic acid (DHA)+eicosapentaenoic acid (EPA) intake of the studies stratified by the mean of age.
Marginal average dose-response curve (solid line) with 95% point-wise CIs (dashed lines) estimated by a 1-stage random-effects restricted cubic spline model, using 0 g/d as the referent, among participants with a mean age ≥45 years or <45 years. n indicates the number of the included study.

Given the moderate dose at 3 g/d, as shown in our dose-response relationship, both a fish oil diet or supplementation resulted in a decrease in BP ≈2 mm Hg to 3 mm Hg in overall and most stratified effects. In 2009, the European Food Safety Authority recommended that an intake of EPA and DHA of ≈3 g/d was required to bring out the claimed hypotensive effects.[29] Our findings seem to support this suggested daily dosage. Moreover, we found associations among both hypertensive and nonhypertensive groups, suggesting that ω3 PUFAs intake could be beneficial for controlling BP even before the onset of hypertension. This means that the intake of ω3 PUFAs could have implications on a person's future risk of stroke, ischemic heart disease,[30,31] and all-cause mortality.[32]

We recognize that there are some potential limitations to the conclusion that can be drawn from the current studies. The intrinsically significant variations among original trials, such as the device of BP measurement (automatic versus manual), the year of study (conducted 1987–2020), and the type of intervention (diet versus supplementation) are likely to bring some uncertainty to our results and potentially weaken the conclusion. Although we attempted to examine the influence of these factors on our overall findings in subgroup analyses, we acknowledge it is not possible to account for this heterogeneity directly in our analyses. Future research could benefit from examining a more biologically relevant exposure, such as the use of the absorbed DHA/EPA amount as the active exposure levels, use of standardized BP methods to ensure strict quality control, and further examination of how intervention type may influence the relationship. There are several other limitations. First, the absence of doses between 7 g/d and 15 g/d increases the uncertainty in the effect estimates at higher doses. However, the removal of these extreme data points did not strongly change our trends in overall and stratified effects. Second, we did not perform analyses based on the binary outcomes to predict the risk ratio because of the limited studies retrieved. Third, the mechanism of these J-shaped

relationships is not clear. The appearance of the response plateau might reflect a saturating status of fatty acid incorporation into the cell membrane.[33] The change point towards possibly increasing BP may indicate the enhanced α-adrenergic vasoconstriction[34] or disrupted ion exchanges.[35] Nevertheless, attention should be focused on the selection of optimal fish oil intake in the management of hypertension. Finally, because of the few available studies, we could not assess the impact of DHA+EPA on changes in BP by sex, DHA- or EPA-only, or diet-only effects. Future studies should further investigate these issues.

CONCLUSIONS

We conducted a dose-response meta-analysis to characterize the effects of DHA+EPA supplementation and dietary enrichment on BP levels using updated literature. This research helps to improve our understanding of the moderate effects of omega-3 fatty acids on BP reduction. The use of the new model suggests that an optimal dose of 3 g/d in overall and subgroup analyses may yield the greatest BP-lowering performance. The seemingly J-shaped associations between DHA+EPA dose and BP reduction in many subgroups might help reform preventive strategies for reducing cardiovascular risks in the general adult population. However, individuals who are at high risk for developing cardiovascular diseases, such as those with hypertension, may be more responsive to the beneficial impacts of ω3 PUFA intake on reductions in BP.

ARTICLE INFORMATION

Received December 15, 2021; accepted March 24, 2022.

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Sources of Funding

This work was supported by the Macau Science and Technology Development Fund (FDCT) (0123/2020/A and 0053/2021/A1) and the Faculty Research Grants of Macau University of Science and Technology (FRG-21-038-SP).

Disclosures

None.

Supplemental Material

Tables S1–S4
Figures S1–S13
References 36–104

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SUPPLEMENTAL MATERIAL

Table S1. Checklist: PRISMA 2020 Main Checklist.

Topic	No.	Item	Location where item is reported
TITLE			
Title	1	Identify the report as a systematic review.	Line 1
ABSTRACT			
Abstract	2	See the PRISMA 2020 for Abstracts checklist	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of existing knowledge.	Line 50-64
Objectives	4	Provide an explicit statement of the objective(s) or question(s) the review addresses.	Line 69-72
METHODS			
Eligibility criteria	5	Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.	Line 81-89
Information sources	6	Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.	Line 77-80
Search strategy	7	Present the full search strategies for all databases, registers and websites, including any filters and limits used.	Line 77-78 and Table S2
Selection process	8	Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.	Line 80-81
Data collection process	9	Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process.	Line 92-93
Data items	10a	List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.	Line 93-96
	10b	List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.	Line 96-97
Study risk of bias assessment	11	Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.	Line 89-90

Topic	No.	Item	Location where item is reported
Effect measures	12	Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results.	Line 99-102
Synthesis methods	13a	Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item 5)).	Line 125-128, Table S3
	13b	Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.	Line 107-108; Line 110-114
	13c	Describe any methods used to tabulate or visually display results of individual studies and syntheses.	Line 110-114
	13d	Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.	Line 110-114 and Line 120-121
	13e	Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis, meta-regression).	Line 114-120
	13f	Describe any sensitivity analyses conducted to assess robustness of the synthesized results.	Line 107-108
Reporting bias assessment	14	Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).	Line 104-107
Certainty assessment	15	Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.	N/A
RESULTS			
Study selection	16a	Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.	Line 125-128 Figure 1
	16b	Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.	Line 125-128, Figure S1
Study characteristics	17	Cite each included study and present its characteristics.	Supp. references and Table S3
Risk of bias in studies	18	Present assessments of risk of bias for each included study.	Table S4
Results of individual studies	19	For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.	Line 129-149 and Table 1, S3
Results of syntheses	20a	For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.	Line 198-199

Topic	No.	Item	Location where item is reported
	20b	Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect.	Line 151-196
	20c	Present results of all investigations of possible causes of heterogeneity among study results.	Line 168-196
	20d	Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.	Line 203-205
Reporting biases	21	Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.	Line 198-203
Certainty of evidence	22	Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.	Line 151-166
DISCUSSION			
Discussion	23a	Provide a general interpretation of the results in the context of other evidence.	Line 208-262
	23b	Discuss any limitations of the evidence included in the review.	Line 263-273
	23c	Discuss any limitations of the review processes used.	Line 263-273
	23d	Discuss implications of the results for practice, policy, and future research.	Line 274-282
OTHER INFORMATION			
Registration and protocol	24a	Provide registration information for the review, including register name and registration number, or state that the review was not registered.	N/A
	24b	Indicate where the review protocol can be accessed, or state that a protocol was not prepared.	N/A
	24c	Describe and explain any amendments to information provided at registration or in the protocol.	N/A
Support	25	Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.	Line 284-285
Competing interests	26	Declare any competing interests of review authors.	Line 286
Availability of data, code and other materials	27	Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review.	N/A

PRIMSA Abstract Checklist

Topic	No.	Item	Reported?
TITLE			
Title	1	Identify the report as a systematic review.	Yes
BACKGROUND			
Objectives	2	Provide an explicit statement of the main objective(s) or question(s) the review addresses.	Yes
METHODS			
Eligibility criteria	3	Specify the inclusion and exclusion criteria for the review.	Yes
Information sources	4	Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched.	Yes
Risk of bias	5	Specify the methods used to assess risk of bias in the included studies.	No
Synthesis of results	6	Specify the methods used to present and synthesize results.	Yes
RESULTS			
Included studies	7	Give the total number of included studies and participants and summarise relevant characteristics of studies.	Yes
Synthesis of results	8	Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured).	Yes
DISCUSSION			
Limitations of evidence	9	Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision).	No
Interpretation	10	Provide a general interpretation of the results and important implications.	Yes
OTHER			
Funding	11	Specify the primary source of funding for the review.	No
Registration	12	Provide the register name and registration number.	No

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. MetaArXiv. 2020, September 14. DOI: 10.31222/osf.io/v7gm2. For more information, visit: www.prisma-statement.org

Table S2. Literature retrieval strategies for online databases.

Database	Search Strategy
PubMed	#1 (“Dietary fats, unsaturated” [MH] OR “fish oils” [MH] OR “fish oil” [tiab] OR “fatty acids, omega-3”[MH] OR "Docosahexaenoic Acids" [tiab] OR “PUFA” [tiab] OR “DHA” [tiab] OR “EPA” [tiab] OR “long chain omega-3 fatty acids” [tiab] OR “polyunsaturated fatty acid” [tiab] OR "Docosahexaenoic Acids" [tiab] OR “eicosapentaenoic acid” [tiab]) #2 (“blood pressure”[MH] OR “blood pressure determination”[MH] OR “arterial pressure”[MH] OR “hypertension”[MH] OR “blood pressure”[tiab] OR “hypertension”[tiab]) #1 AND #2 AND “human study”
Embase	#1 (‘fish oils’:ab,ti) OR (‘omega-3 fatty acids’:ab,ti) OR (‘docosahexaenoic acids’:ab,ti) OR (‘PUFA’:ab,ti) OR (‘DHA’:ab,ti) OR (‘EPA’:ab,ti) OR (‘ALA’:ab,ti) OR (‘long chain omega-3 fatty acids’:ab,ti) OR (‘polyunsaturated fatty acid’:ab,ti) OR (‘eicosapentaenoic acid’:ab,ti) OR (‘alpha linolenic acid’:ab,ti) #2 (‘blood pressure’:ab,ti) OR (‘blood pressure determination’:ab,ti) OR (‘arterial pressure’:ab,ti) OR (‘hypertension’:ab,ti) #1 AND #2 AND 'human'/de

Table S3. Summary of study characteristics of 71 trials.

Author	Year	Country	n, M/F	Age[a], y Mean (SE/SD) range	Design	HTN	HL	Device	Intervention type	DHA dose d/day	EPA dose d/day	Total dose d/day	Control	Duration, week
Albert [36]	2015	Australia	M47	35-55	Crossover	No	No	Automatic	Supplementation	0.15	0.23	0.38	Canola oil	8
Armstrong [37]	2012	United States	M35/F81	20-59	Parallel	No	No	Automatic	Supplementation	1.00	2.00	3.00	Corn + soy oil	6
Bach[38]	1989	United States	M16/F14	31(9)	Parallel	No	Yes	NR	Supplementation	1.44	1.08	2.52	Neutral oil	5
Barcelo-Coblijn[39]	2008	Canada	MF62	36-44	Parallel	No	No	NR	Supplementation	0.13	0.25	0.38	Sunflower oil	12
					Parallel	No	No	NR	Supplementation	0.25	0.50	0.76	Sunflower oil	12
Blonk[40]	1990	Netherland	M45	22-48	Parallel	No	No	Manual	Supplementation	0.60	0.90	1.50	Not specified	12
					Parallel	No	No	Manual	Supplementation	1.20	1.80	3.00	Not specified	12
					Parallel	No	No	Manual	Supplementation	2.40	3.60	6.00	Not specified	12
Bonaa[41]	1990	Netherland	MF156	20-61	Parallel	Yes	No	Automatic	Supplementation	1.82	3.26	5.08	Corn oil	10
Buckley[42]	2009	Australia	M25	22(1)	Parallel	No	No	Automatic	Supplementation	1.56	0.36	1.92	Sunflower oil	5
Burgin-Maunder[43]	2015	Australia	M23/F19	45-58	Parallel	No	No	Automatic	Supplementation	0.84	1.68	2.52	Canola oil	12
					Parallel	Yes	No	Automatic	Supplementation	0.84	1.68	2.52	Canola oil	12
Carter[44]	2012	United States	M18/F20	24(2)	Parallel	No	No	Automatic	Supplementation	1.10	1.60	2.70	Olive oil	8
Chin[45]	1993	Australia	M29	18-32	Parallel	No	No	Manual	Supplementation	0.58	0.89	1.47	Palm+safflower+olive oil	4
					Parallel	No	No	Manual	Supplementation	1.16	1.78	2.94	Palm+safflower+olive oil	4
					Parallel	No	No	Manual	Supplementation	2.32	3.56	5.88	Palm+safflower+olive oil	4
Cobiac[46]	1991	Australia	M31	30-60	Parallel	No	Yes	Automatic	Diet	3.00	1.50	4.50	Vegetable oil	5
					Parallel	No	Yes	Automatic	Supplementation	1.74	3.08	4.82	Vegetable oil	5
Cobiac[47]	1992	Australia	M36/F19	60-80	Parallel	No	No	Automatic	Supplementation	1.70	2.50	4.20	Sunflower oil	4
Conquer[48]	1999	Canada	M19	30(2)	Parallel	No	No	NR	Supplementation	1.70	1.30	3.00	Vegetable oil	6
Dart[49]	1989	United Kingdom	M14/F7	46(2)	Crossover	No	Yes	NR	Supplementation	2.50	3.52	6.02	Olive oil	8.5
Demke[50]	1988	United States	M8/F23	18-60	Parallel	No	Yes	NR	Supplementation	0.79	0.93	1.72	Safflower oil	4
Derosa[51]	2009	Italy	M164/F169	≥18	Parallel	No	Yes	Manual	Supplementation	1.50	0.90	2.40	Sucrose, mannitol and mineral salt	26
Derosa[52]	2012	Italy	M82/F85	18-75	Parallel	No	Yes	NR	Supplementation	1.35	1.20	2.55	Sucrose, mannitol and mineral salt	26

Dewell[53]	2011	United States	M64/F36	50(10)	Parallel	No	No	NR	Supplementation	0.50	0.70	1.20	Soybean oil	6
					Parallel	No	No	NR	Supplementation	1.50	2.10	3.60	Soybean oil	6
Dyerberg[54]	2004	Denmark	M51	20-60	Parallel	No	No	Automatic	Supplementation	1.40	2.20	3.60	Palm oil	8
Flaten[55]	1990	Norway	M56	35-45	Parallel	No	No	Manual	Supplementation	2.87	3.60	6.47	Olive oil	6
Geelen[56]	2003	Netherland	M36/F38	50-70	Parallel	No	No	Automatic	Supplementation	0.56	0.70	1.26	Sunflower oil	12
Grieger[57]	2014	Australia	MF80	70(6)	Parallel	No	No	Automatic	Diet	NR	NR	0.80	Usual diet	8
Grimsgaard[58]	1998	Norway	M234	36-56	Parallel	No	No	Automatic	Supplementation	—	3.80	3.80	Corn oil	7
					Parallel	No	No	Automatic	Supplementation	3.60	—	3.60	Corn oil	7
Grundt[59]	1995	Norway	M51/F6	18-70	Parallel	No	Yes	Manual	Supplementation	1.28	2.07	3.35	Corn oil	12
Hallund[60]	2010	Denmark	M45	40-70	Parallel	No	No	Automatic	Diet	2.00	0.90	2.90	Chicken	8
Harris[61]	2008	United States	M9/F13	21-70	Parallel	No	No	NR	Supplementation	—	0.98	0.98	Soybean oil	16
Hellsten[62]	1993	Sweden	MF40	30-60	Parallel	No	Yes	NR	Supplementation	NR	NR	2.00	Corn oil	21
Hill[63]	2007	Australia	M28/F53	25–65	Parallel	Yes	Yes	Automatic	Supplementation	1.56	0.36	1.92	Sunflower oil	12
Howe[64]	2018	Australia	M26/F12	40-85	Parallel	Yes	No	Automatic	Supplementation	1.60	0.40	2.00	Corn oil	20
Huerta[65]	2015	Spain	F77	20-50	Parallel	No	No	Manual	Supplementation	0.04	1.30	1.34	Sunflower oil	10
Hughes[66]	1990	United States	M13	32(9)	Crossover	No	No	Automatic	Supplementation	1.50	3.50	5.00	Wheat germ oil	4.3
					Crossover	Yes	No	Automatic	Supplementation	1.50	3.50	5.00	Wheat germ oil	4.3
Jones[67]	2014	United States and Canada	M60/F70	46(14)	Crossover	No	No	Automatic	Supplementation	0.35	0.01	0.36	Oleic acid	4
Kelley[68]	2007	United States	M34	39-66	Parallel	No	Yes	Automatic	Supplementation	3.00	—	3.00	Olive oil	14
Kestin[69]	1990	Australia	M33	46(2)	Parallel	No	No	Automatic	Supplementation	1.30	2.10	3.40	Linoleic acid	6
Knapp[23]	1989	United States	M36	30-71	Parallel	Yes	No	Automatic	Supplementation	1.20	1.80	3.00	Safflower oil	4
					Parallel	Yes	No	Automatic	Supplementation	6.00	9.00	15.00	Safflower oil	4
Kristensen[70]	2016	Denmark	M60/F83	52(12)	Parallel	No	No	Automatic	Supplementation	1.50	1.50	3.00	Olive oil	24
Lee[71]	2019	Canada	M45/F45	18-30	Parallel	No	No	Automatic	Supplementation	—	0.81	0.81	Olive oil	12
					Parallel	No	No	Automatic	Supplementation	0.81	—	0.81	Olive oil	12
Levinson[24]	1990	United States	MF17	18-75	Parallel	Yes	No	Automatic	Supplementation	6.00	9.00	15.00	Vegetable oil	6
Lindqvist[72]	2009	Sweden	M35	35-60	Crossover	No	No	NR	Diet	NR	NR	1.20	Baked lean pork + chicken	6
Lofgren[73]	1993	United States	M23	≤60	Crossover	No	No	Manual	Supplementation	2.40	3.60	6.00	Safflower oil	12
					Crossover	Yes	No	Manual	Supplementation	2.40	3.60	6.00	Safflower oil	12

Logan[74]	2015	Canada	F26	60-76	Parallel	No	No	Automatic	Supplementation	1.00	2.00	3.00	Olive oil	12
Maki[75]	2009	United States	M13/F63	35-64	Parallel	No	No	Automatic	Supplementation	0.09	0.22	0.31	Olive oil	4
					Parallel	No	No	Automatic	Supplementation	0.18	0.21	0.39	Olive oil	4
Meland[76]	1989	Norway	M40	26-66	Parallel	Yes	No	Manual	Supplementation	2.40	3.60	6.00	Corn + olive oil	6
Mills[77]	1990	Canada	M29	19-31	Parallel	No	No	Automatic	Supplementation	0.51	0.81	1.32	Safflower oil	4
Monahan[78]	2004	United States	M10/F8	18-35	Parallel	No	No	Automatic	Supplementation	2.00	3.00	5.00	Olive oil	4
Mori[79]	1999	Australia	M56	20-65	Parallel	No	Yes	Automatic	Supplementation	—	3.84	3.84	Olive oil	6
					Parallel	No	Yes	Automatic	Supplementation	3.68	—	3.68	Olive oil	6
Murphy[80]	2007	Australia	M41/F43	20-65	Parallel	No	No	Automatic	Diet	0.60	0.40	1.00	Control diet	26
Neff[81]	2011	United States	M15/F21	18-65	Parallel	No	No	Automatic	Supplementation	2.00	—	2.00	Corn + soybean oil	16
Nestel[82]	2002	Australia	M21/F17	40-69	Parallel	No	Yes	Automatic	Supplementation	—	3.04	3.04	Olive oil	7
					Parallel	No	Yes	Automatic	Supplementation	2.83	—	2.83	Olive oil	7
Noreen[83]	2012	United States	M14/F26	19-55	Parallel	No	No	Automatic	Supplementation	0.80	1.60	2.40	Safflower oil	6
Pase[84]	2015	Australia	M75/F85	50-70	Parallel	No	No	Automatic	Supplementation	0.48	0.48	0.96	Monounsaturated acid	16
Passfall[85]	1993	Germany	M4/F6	40-61	Crossover	Yes	No	Automatic	Supplementation	0.90	1.26	2.16	Olive oil	6
Prisco[86]	1998	Italy	M16	33-56	Parallel	Yes	No	Automatic	Supplementation	1.40	2.04	3.44	Olive oil	17
Radack[87]	1991	United States	M19/F14	≥18	Crossover	Yes	No	Manual	Supplementation	0.80	1.20	2.00	Safflower oil	12
Ryu[88]	1990	United States	M20	20-39	Parallel	No	No	Manual	Supplementation	0.90	2.10	3.00	Wheat germ oil	4
Sagara[89]	2011	United Kingdom	M38	45-59	Parallel	Yes	Yes	Automatic	Supplementation	2.00	—	2.00	Olive oil bread	5
Sanders[90]	2006	United Kingdom	M39/F40	33	Parallel	No	No	Automatic	Supplementation	1.50	—	1.50	Olive oil	4
Sanders[91]	2011	United Kingdom	M142/F225	45-70	Parallel	No	No	Automatic	Supplementation	0.18	0.27	0.45	Olive oil	52
					Parallel	No	No	Automatic	Supplementation	0.36	0.54	0.90	Olive oil	52
					Parallel	No	No	Automatic	Supplementation	0.72	1.08	1.80	Olive oil	52
Shabrina[92]	2020	China	M21	>30	Parallel	Mixed	No	Automatic	Supplementation	0.85	1.28	2.13	Caloric restriction	12
Shen[93]	2017	China	M48/F49	63(10)	Parallel	No	No	NR	Supplementation	0.20	0.31	0.51	Soybean oil	12
Sjoberg[94]	2010	Australia	M36/F31	53(2)	Parallel	No	No	Automatic	Supplementation	0.52	0.10	0.62	Sunola oil	12
					Parallel	No	No	Automatic	Supplementation	1.04	0.20	1.24	Sunola oil	12
					Parallel	No	No	Automatic	Supplementation	1.56	0.30	1.86	Sunola oil	12

Stark[95]	2004	Canada	F32	45-70	Crossover	No	No	Automatic	Supplementation	2.80	—	2.80	Corn and soy oil	4
Sveinsdottir[96]	2016	Iceland	M30/F69	>50	Parallel	Mixed	No	NR	Diet	0.50	1.00	1.50	Olive oil	4
Theobald[97]	2007	United Kingdom	M20/F19	45-65	Crossover	No	No	NR	Supplementation	0.70	—	0.70	Olive oil	13
Toft[98]	1995	Norway	M50/F28	21-61	Parallel	Yes	No	Manual	Supplementation	1.20	2.10	3.30	Corn oil	16
TOHP[99]	1992	United States	MF350	30-54	Parallel	No	No	Manual	Supplementation	0.90	2.10	3.00	Olive oil	24
Vandongen[100]	1993	Australia	M51	30-60	Parallel	No	No	Automatic	Supplementation	0.90	1.30	2.20	Olive, palm, safflower oils	12
					Parallel	No	No	Automatic	Supplementation	1.70	2.60	4.30	Olive, palm, safflower oils	12
					Parallel	No	No	Automatic	Diet	0.90	1.30	2.20	Olive, palm, safflower oils	12
Vericel[101]	1999	France	MF20	70-83	Parallel	Yes	No	NR	Supplementation	0.15	0.03	0.18	Sunflower oil	6
von Houwelingen[102]	1987	Norway and Netherland	M82	20-45	Parallel	No	No	Manual	Diet	3.00	1.70	4.70	Meat paste	6
Wang[103]	2008	China	M37/F6	42(3)	Parallel	Yes	Yes	Manual	Supplementation	0.36	0.54	0.90	Vegetable oil	8
Wu[104]	2014	United Kingdom	M29/F55	21-65	Crossover	No	No	Automatic	Supplementation	0.60	0.90	1.50	Corn oil	8

Abbreviations: DHA, docosahexaenoic acid; DBP, diastolic blood pressure; EPA, eicosapentaenoic acid; HTN, hypertension; HL, hyperlipidemia; NR, not reported; —, not administered.

Note: a, The age is expressed as Mean (SD/SE), SD, standard deviation and SE, standard error.

Table S4. Risk of bias of included trials.

Author	Year	Randomiz-ation	Blinding	Missing outcome	Measure-ment	Selection of results	Overall
Albert [36]	2015	low	low	low	low	low	low
Armstrong [37]	2012	some concern	some concern	low	low	low	low
Bach[38]	1989	some concern	low	low	some concern	low	low
Barcelo-Coblijn[39]	2008	some concern	some concern	low	some concern	low	low
Blonk[40]	1990	some concern	medium	low	moderate	some concern	moderate
Bonaa[41]	1990	low	low	low	low	low	low
Buckley[42]	2009	some concern	some concern	low	low	low	low
Burgin-Maunder[43]	2015	some concern	some concern	low	some concern	low	low
Carter[44]	2012	some concern	some concern	low	low	low	low
Chin[45]	1993	some concern	some concern	low	low	low	low
Cobiac[46]	1991	low	some concern	low	low	low	low
Cobiac[47]	1992	some concern	some concern	low	low	low	low
Conquer[48]	1999	moderate	some concern	low	some concern	low	moderate
Dart[49]	1989	moderate	some concern	low	some concern	low	moderate
Demke[50]	1988	some concern	low	low	some concern	low	low
Derosa[51]	2009	low	low	low	low	low	low
Derosa[52]	2012	low	some concern	low	some concern	low	low
Dewell[53]	2011	some concern	low	low	some concern	low	low
Dyerberg[54]	2004	low	some concern	low	some concern	low	low
Flaten[55]	1990	some concern	some concern	low	low	low	low
Geelen[56]	2003	some concern	some concern	low	some concern	low	low
Grieger[57]	2014	some concern	low	low	low	low	low
Grimsgaard[58]	1998	low	some concern	low	low	low	low
Grundt[59]	1995	some concern	high	low	low	low	low
Hallund[60]	2010	low	low	low	low	low	low
Harris[61]	2008	some concern	some concern	some concern	some concern	low	moderate
Hellsten[62]	1993	some concern	low	low	some concern	low	low
Hill[63]	2007	low	low	low	low	low	low
Howe[64]	2018	some concern	some concern	low	low	low	low
Huerta[65]	2015	low	some concern	some concern	some concern	low	moderate
Hughes[66]	1990	some concern	low	low	low	low	low
Jones[67]	2014	low	low	low	some concern	low	low
Kelley[68]	2007	some concern	low	low	some concern	low	low
Kestin[69]	1990	some concern	low	some concern	low	low	low
Knapp[23]	1989	low	low	low	low	low	low
Kristensen[70]	2016	low	low	low	some concern	low	low
Lee[71]	2019	some concern	low	low	low	low	low
Levinson[24]	1990	some concern	high	low	low	low	low
Lindqvist[72]	2009	some concern	some concern	low	some concern	low	low

Lofgren[73]	1993	some concern	medium	low	low	low	low
Logan[74]	2015	some concern	some concern	low	low	low	low
Maki[75]	2009	some concern	some concern	low	low	low	low
Meland[76]	1989	some concern	low	low	low	low	low
Mills[77]	1990	low	some concern	low	low	low	low
Monahan[78]	2004	some concern	low	low	low	low	low
Mori[79]	1999	some concern	low	low	low	low	low
Murphy[80]	2007	some concern	some concern	low	low	low	low
Neff[81]	2011	some concern	some concern	low	some concern	low	low
Nestel[82]	2002	low	some concern	low	some concern	low	low
Noreen[83]	2012	some concern	low	low	some concern	low	low
Pase[84]	2015	low	some concern	low	low	low	low
Passfall[85]	1993	some concern	some concern	low	low	low	low
Prisco[86]	1998	some concern	low	low	low	some concern	low
Radack[87]	1991	low	some concern	low	low	low	low
Ryu[88]	1990	low	some concern	low	low	low	low
Sagara[89]	2011	some concern	low	low	some concern	low	low
Sanders[90]	2006	low	low	low	low	low	low
Sanders[91]	2011	some concern	some concern	low	low	low	low
Shabrina[92]	2020	some concern	low	low	some concern	low	low
Shen[93]	2017	low	some concern	low	some concern	low	low
Sjoberg[94]	2010	some concern	low	low	low	low	low
Stark[95]	2004	low	some concern	low	low	low	low
Sveinsdottir[96]	2016	some concern	low	low	low	low	low
Theobald[97]	2007	some concern	low	low	low	low	low
Toft[98]	1995	low	low	low	low	low	low
TOHP[99]	1992	some concern	some concern	low	low	low	low
Vandongen[100]	1993	some concern	high	low	low	low	low
Vericel[101]	1999	high	medium	low	some concern	low	high
von Houwelingen[102]	1987	some concern	some concern	low	low	low	low
Wang[103]	2008	some concern	some concern	low	low	low	low
Wu[104]	2014	low	low	low	low	low	low

Note: Two review authors independently assessed risk of bias of each included trials in the domains of randomization (random sequence generation); blinding (allocation concealment, blinding of participants and personnel, and blinding of outcome assessors); missing outcome (incomplete outcome data); measurement (method and measurement bias); and selection of results (reporting bias).

Figure S1. Histogram of dose and duration distribution. A, Histogram of trial duration (week). B, Histogram of the total dose (DHA+EPA, g/day).

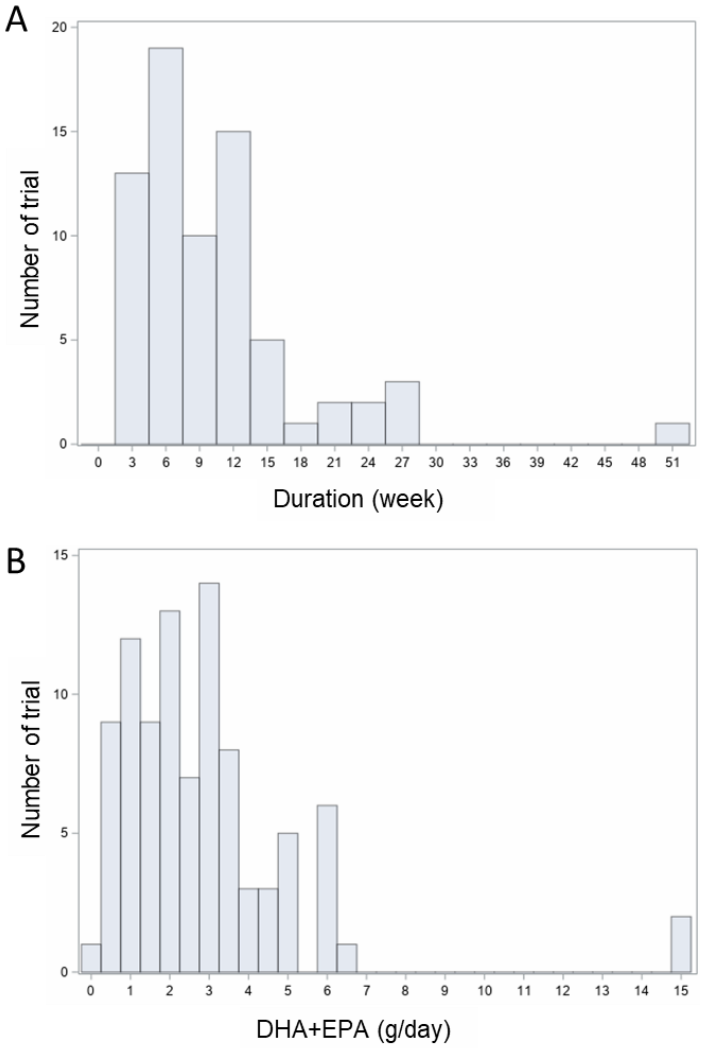
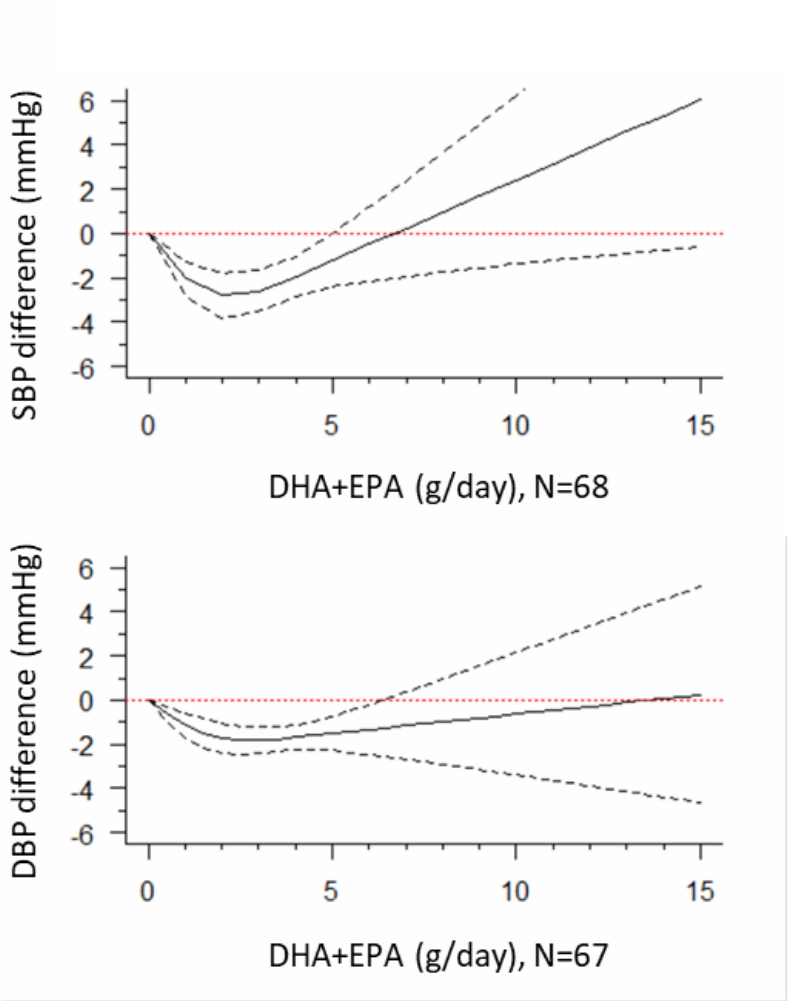
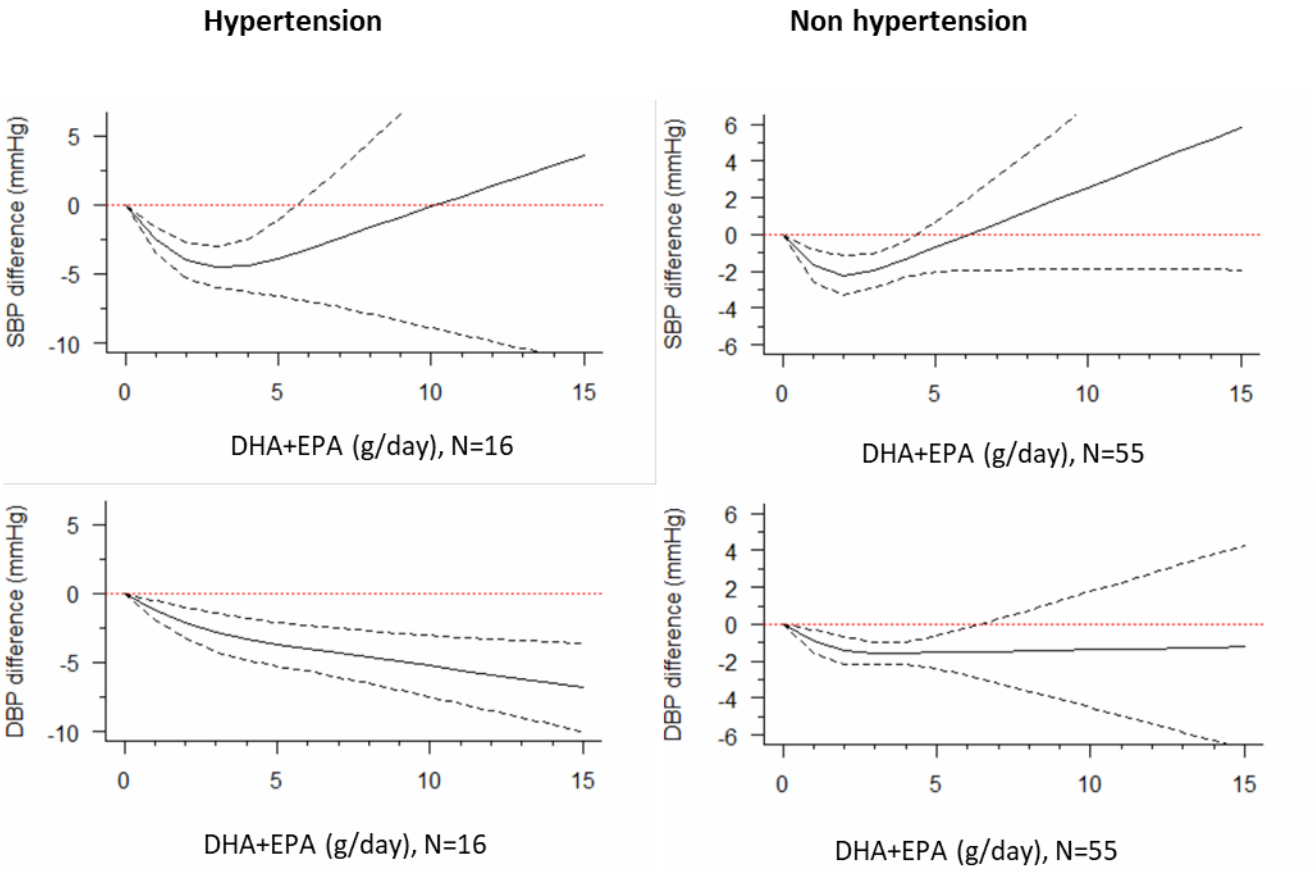


Figure S2. Dose-response relation between changes in blood pressure and combined DHA+EPA intake, after excluding the two trials with a dose of 15 g/day.



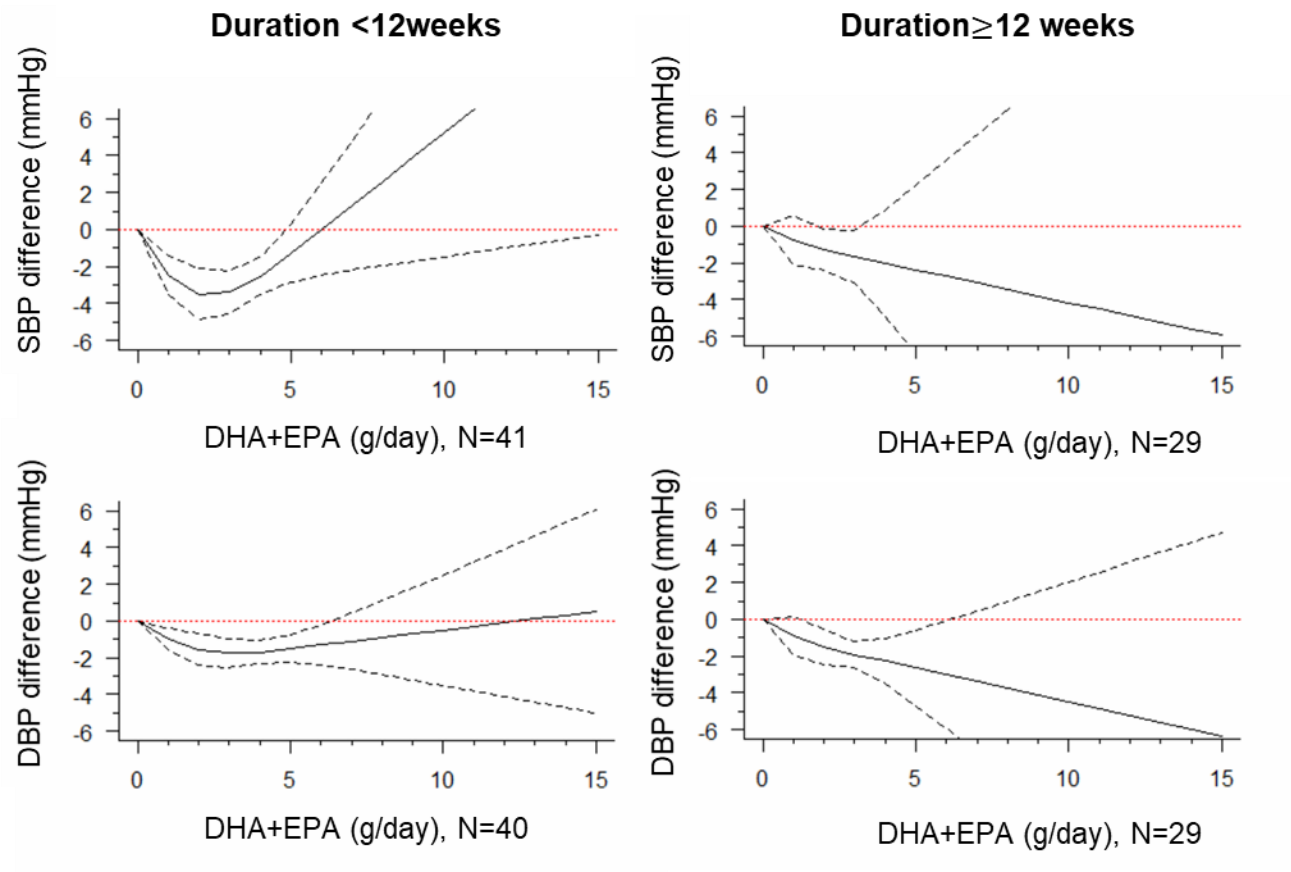
Marginal average dose-response curve (solid line) with 95% point-wise confidence intervals (dashed lines) estimated by a one-stage random-effects restricted cubic spline model, using 0 g/day as the referent. DBP, diastolic blood pressure; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; SBP, systolic blood pressure. Studies included N=69 for SBP and N=68 for DBP.

Figure S3. Dose-response relation between changes in blood pressure and combined DHA+EPA intake of the studies stratified by the status of hypertension



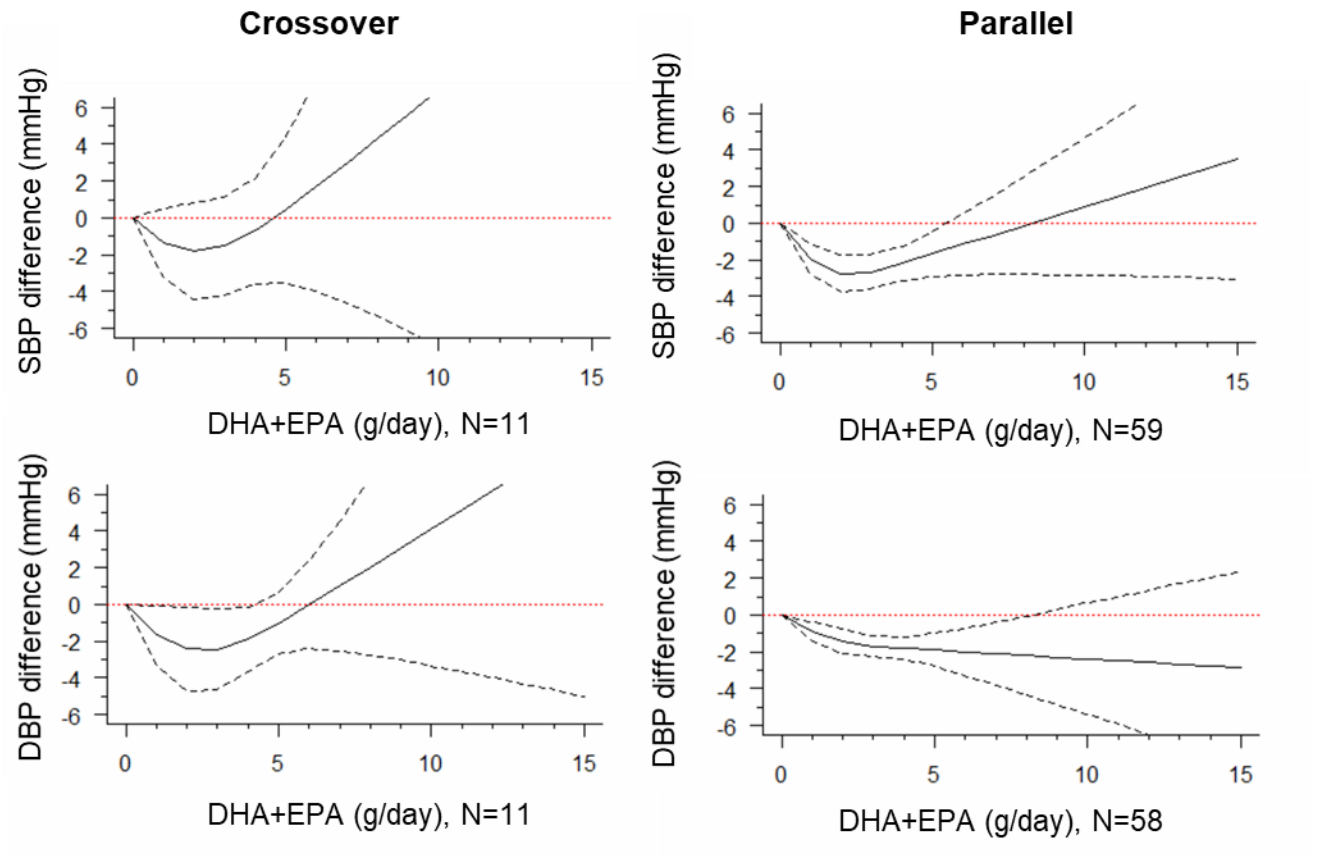
Marginal average dose-response curve (solid line) with 95% point-wise confidence intervals (dashed lines) estimated by a one-stage random-effects restricted cubic spline model, using 0 g/day as the referent, in participants with or with on hypertension, baseline SBP ≥ 140 mmHg or DBP ≥ 90 mmHg. DBP, diastolic blood pressure; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; SBP, systolic blood pressure. N, number of the included study.

Figure S4. Dose-response relation between changes in blood pressure and combined DHA+EPA intake of the studies stratified by trial duration.



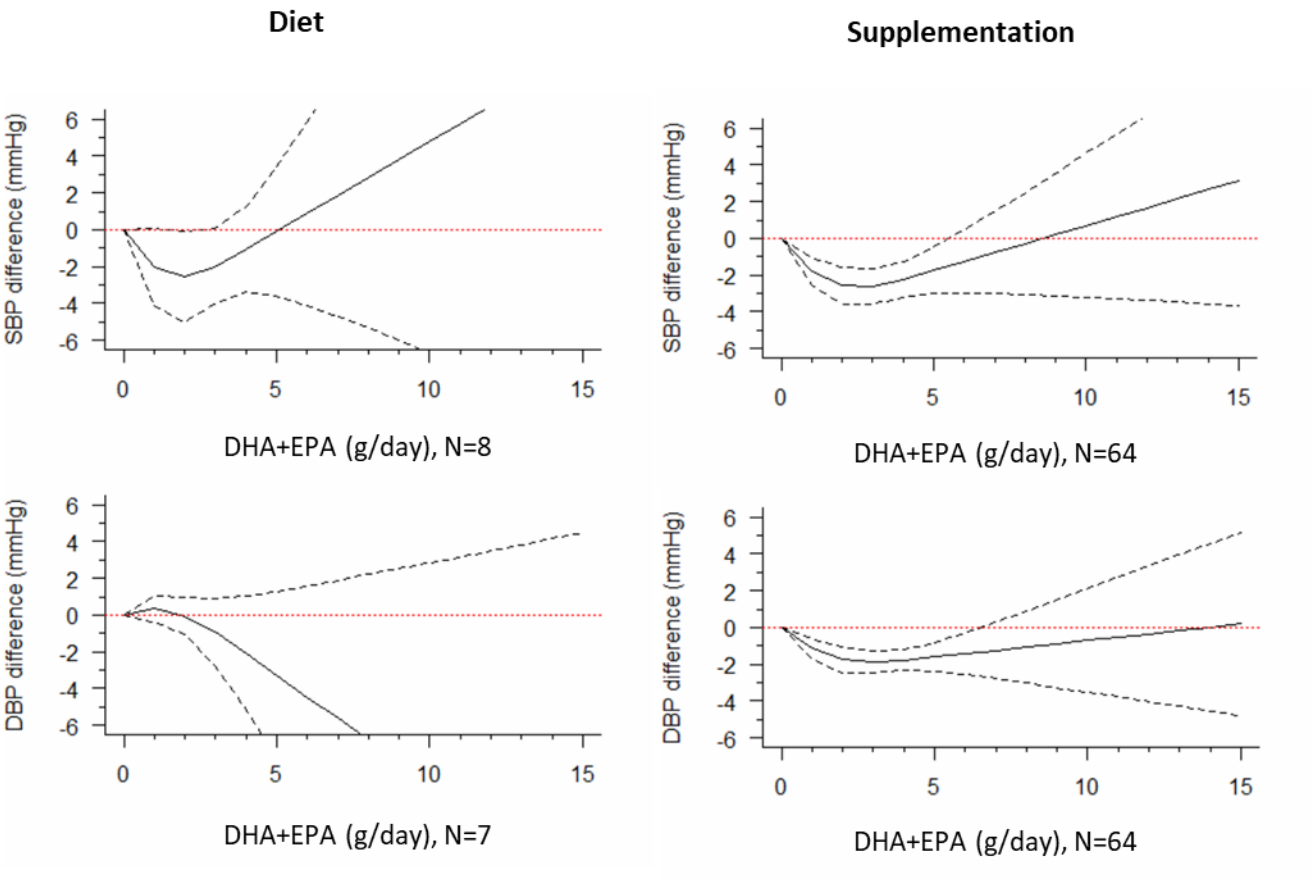
Marginal average dose-response curve (solid line) with 95% point-wise confidence intervals (dashed lines) estimated by a one-stage random-effects restricted cubic spline model, using 0 g/day as the referent, in participants with trial duration ≥ or <12 weeks. DBP, diastolic blood pressure; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; SBP, systolic blood pressure. N, number of the included study.

Figure S5. Dose-response relation between changes in blood pressure and combined DHA+EPA intake in studies stratified by study design.



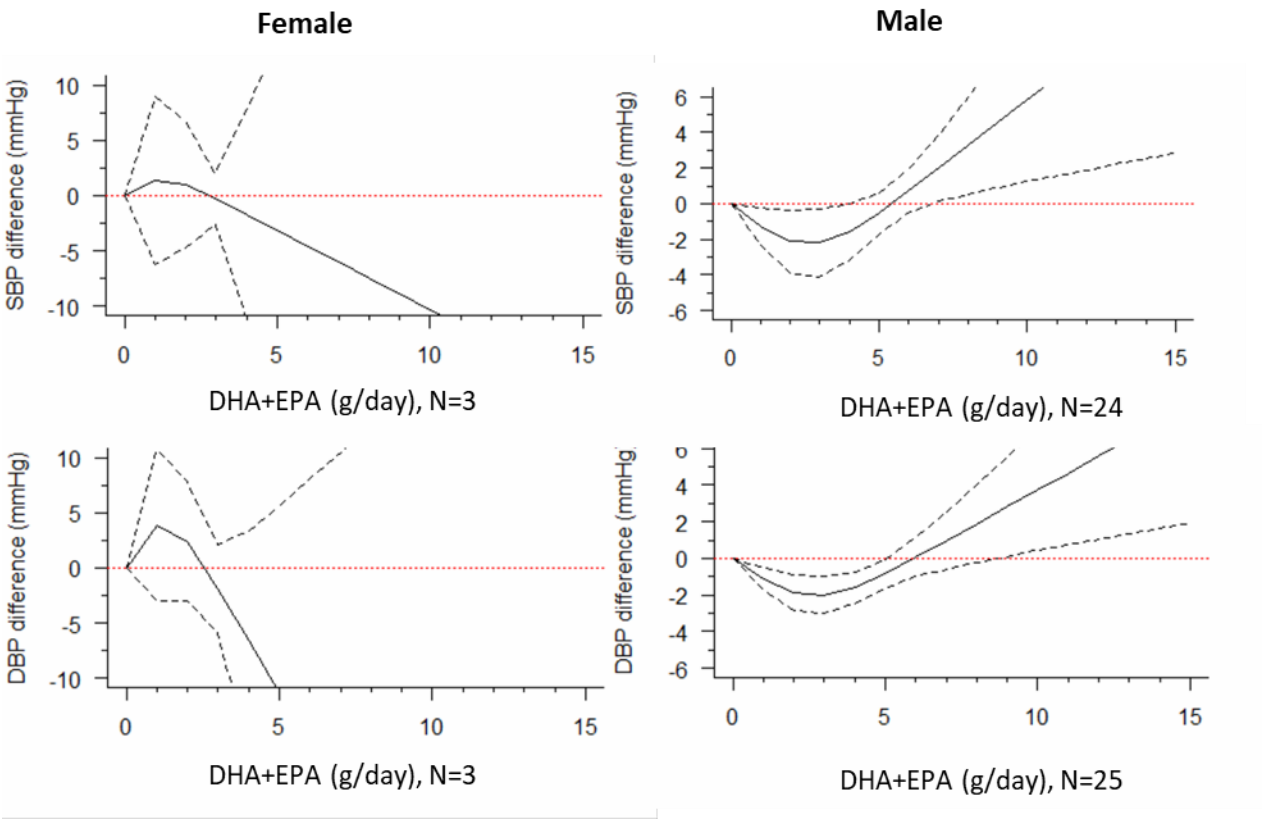
Marginal average dose-response curve (solid line) with 95% point-wise confidence intervals (dashed lines) estimated by a one-stage random-effects restricted cubic spline model, using 0 g/day as the referent, in studies stratified by study design (crossover or parallel). DBP, diastolic blood pressure; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; SBP, systolic blood pressure. N, number of the included study.

Figure S6. Dose-response relation between changes in blood pressure and combined DHA+EPA intake of the studies stratified by the intervention type.



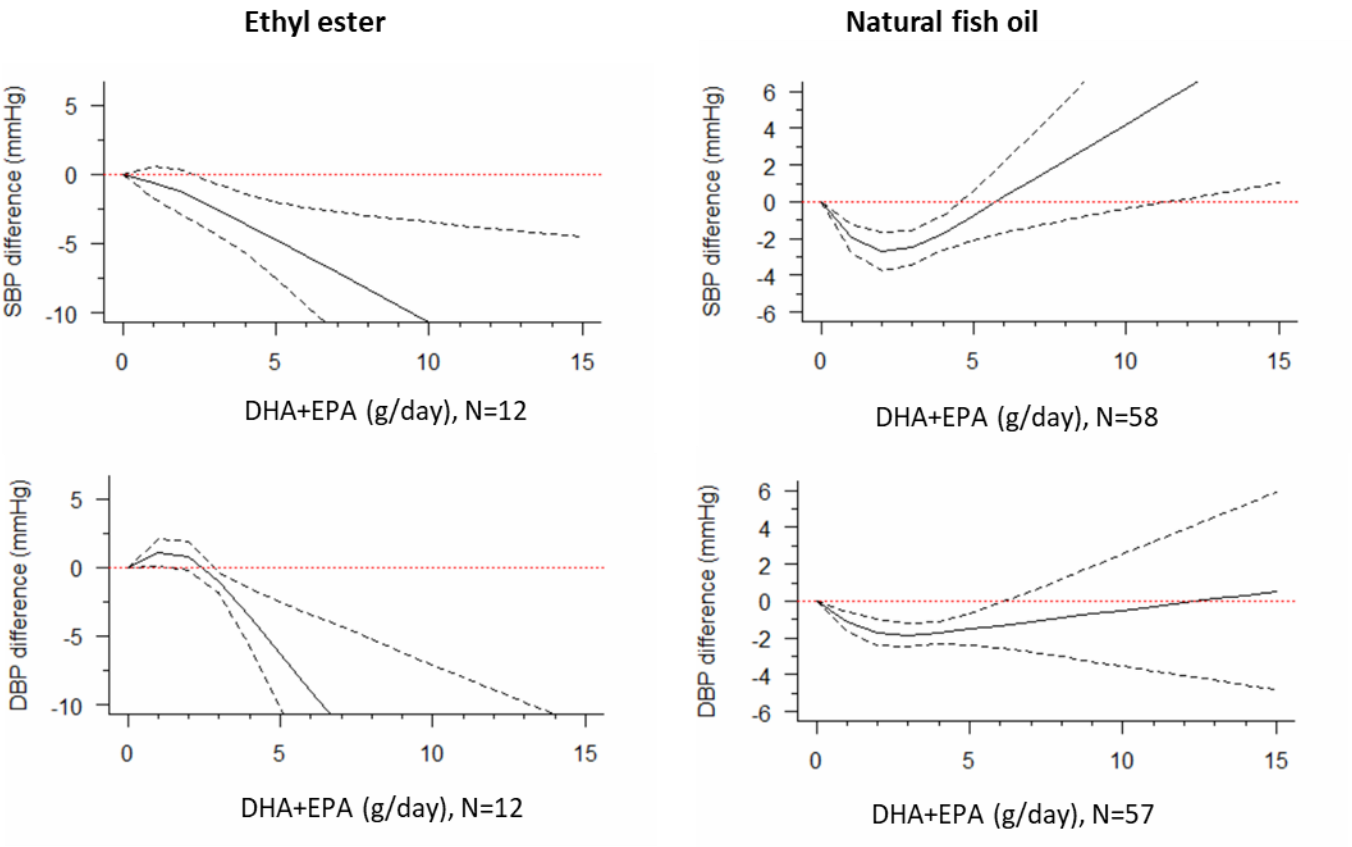
Marginal average dose-response curve (solid line) with 95% point-wise confidence intervals (dashed lines) estimated by a one-stage random-effects restricted cubic spline model, using 0 g/day as the referent, in studies restricted to different intervention types (diet-based or supplementation). DBP, diastolic blood pressure; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; SBP, systolic blood pressure. N, number of the included study.

Figure S7. Dose-response relation between changes in blood pressure and combined DHA+EPA intake of the studies stratified by sex.



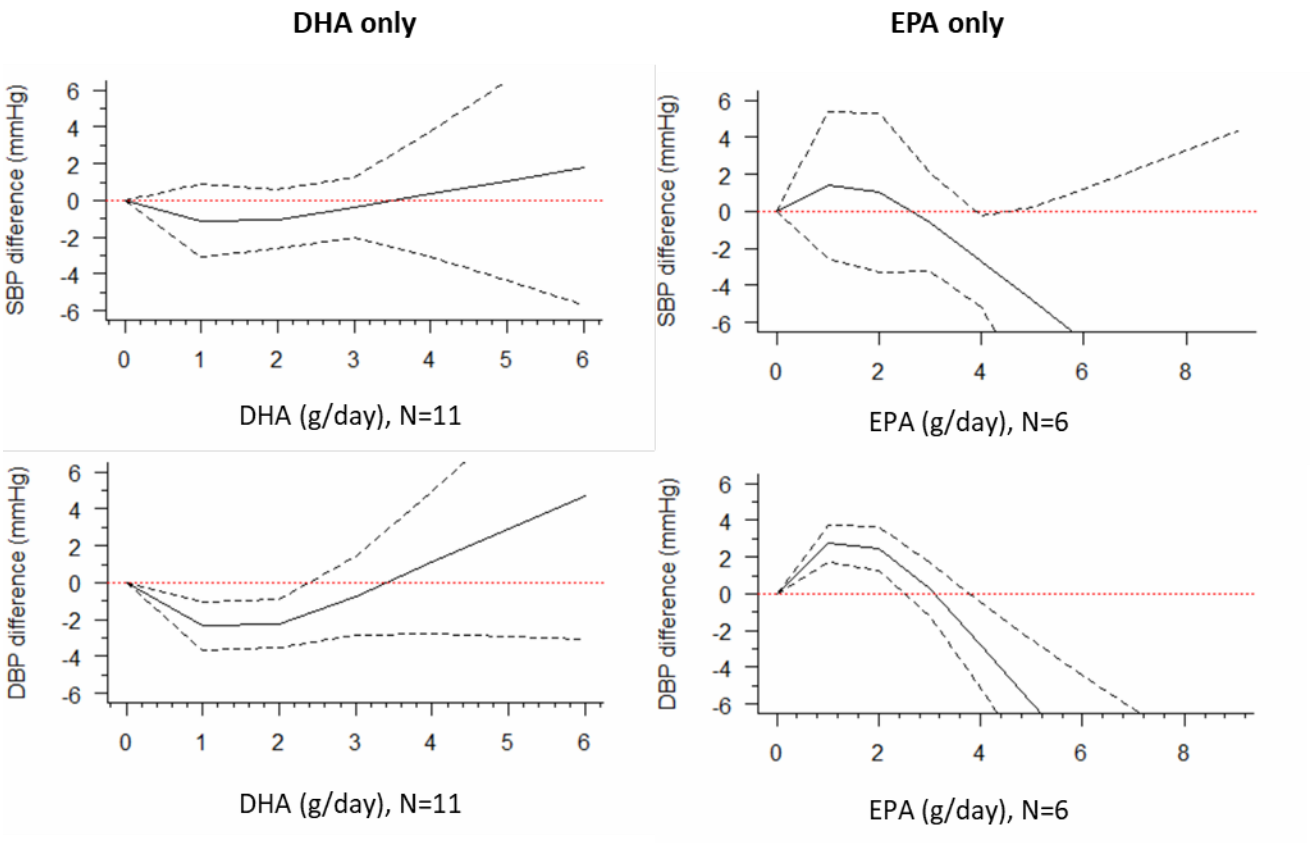
Marginal average dose-response curve (solid line) with 95% point-wise confidence intervals (dashed lines) estimated by a one-stage random-effects restricted cubic spline model, using 0 g/day as the referent, among female- or male-only participants. DBP, diastolic blood pressure; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; SBP, systolic blood pressure. N, number of the included study.

Figure S8.Dose-response relation between changes in blood pressure and combined DHA+EPA intake of the studies stratified by the fish oil composition.



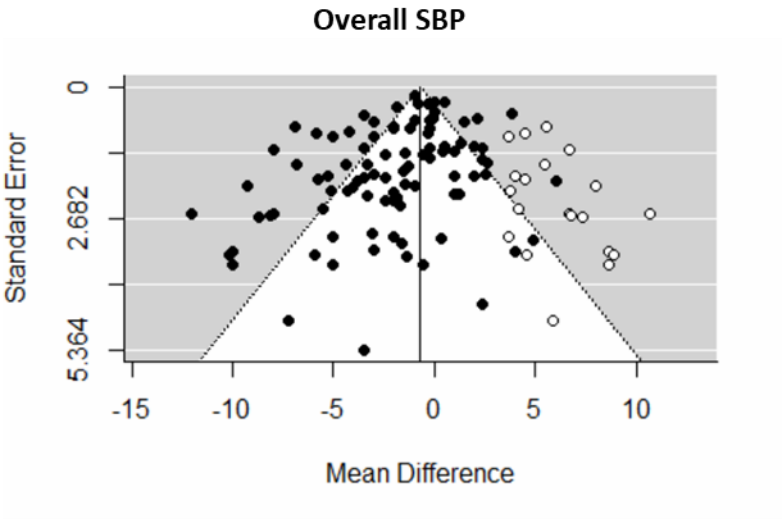
Marginal average dose-response curve (solid line) with 95% point-wise confidence intervals (dashed lines) estimated by a one-stage random-effects restricted cubic spline model, using 0 g/day as the referent, in studies either using purified ethyl esters or natural fish oils. DBP, diastolic blood pressure; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; SBP, systolic blood pressure. N, number of the included study.

Figure S9. Dose-response relation between changes in blood pressure and DHA/EPA intake of the studies stratified by the individual fish oils.

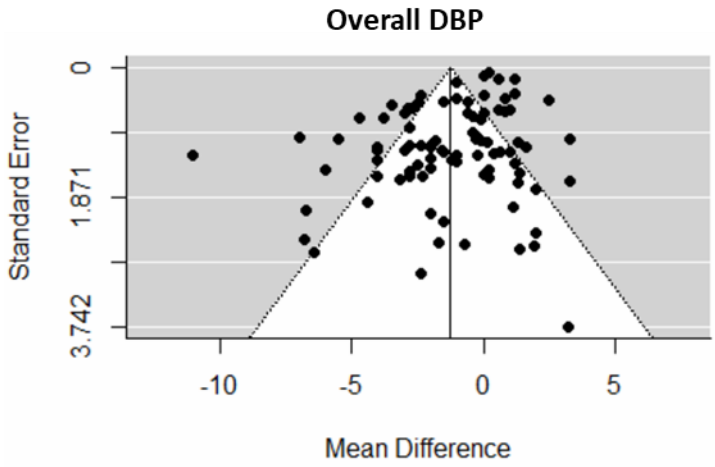


Marginal average dose-response curve (solid line) with 95% point-wise confidence intervals (dashed lines) estimated by a one-stage random-effects restricted cubic spline model, using 0 g/day as the referent, in studies using DHA or EPA alone. DBP, diastolic blood pressure; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; SBP, systolic blood pressure. N, number of the included study.

Figure S10. Funnel plot for assessment of overall publication bias.



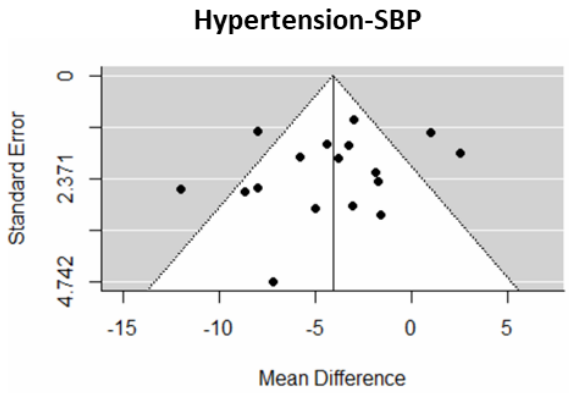
Estimated number of missing studies: 20 ;
Test for funnel plot asymmetry: : z = -3.05, p = 0.002



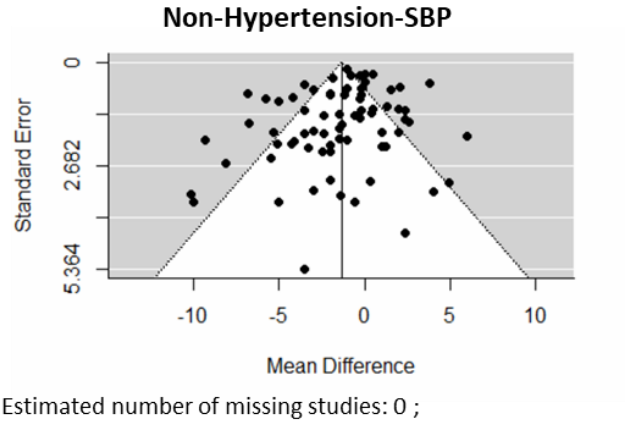
Estimated number of missing studies: 0 ;
Test for funnel plot asymmetry: z = -1.38, p = 0.17

The plots are generated for the mean difference of changes in systolic (SBP) and diastolic (DBP) blood pressure levels as mmHg and its standard error using the trim-and-fill method. No imputed studies are predicted in both plots. Filled dots indicate observed studies. The Grey area indicates $p \leq 0.05$. The plot asymmetry analysis was performed by Egger's regression test.

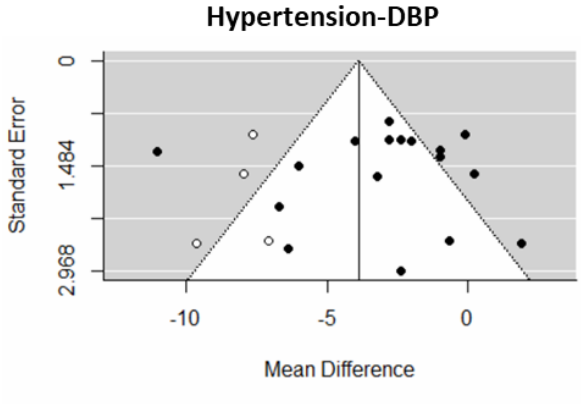
Figure S11. Funnel plot for assessment of publication bias in studies with stratification of hypertension status.



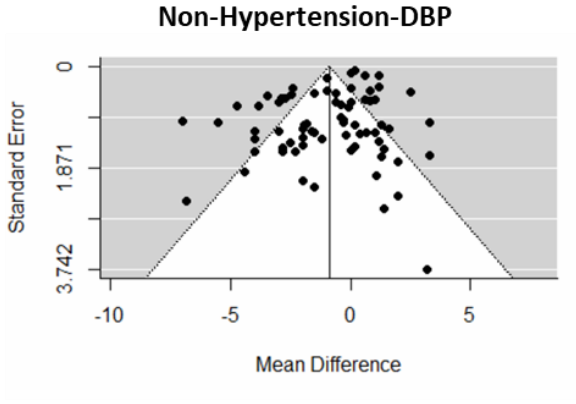
Estimated number of missing studies: 0 ;
Test for funnel plot asymmetry: z = -1.08, p = 0.28



Estimated number of missing studies: 0 ;
Test for funnel plot asymmetry: z = -1.70, p = 0.09



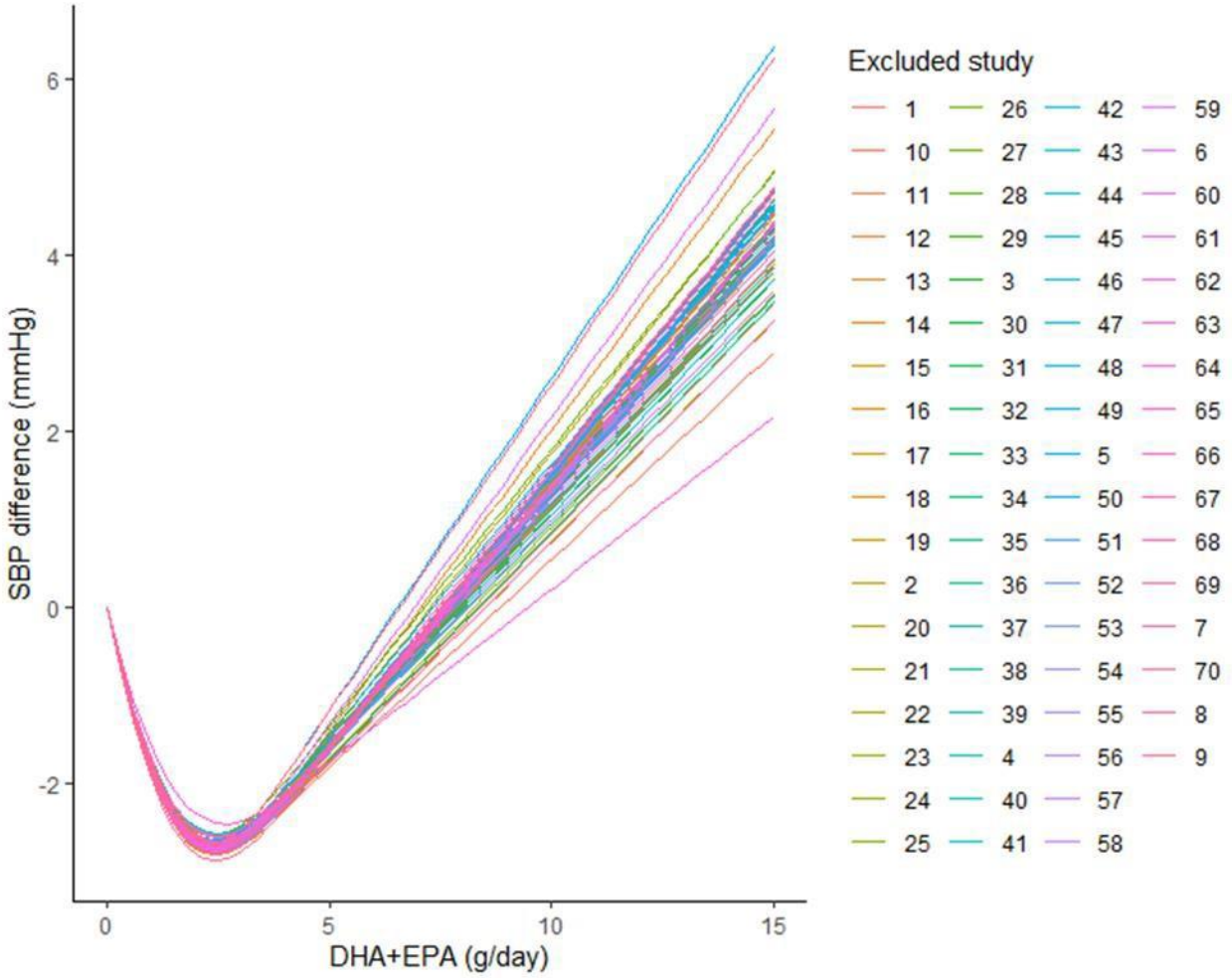
Estimated number of missing studies: 4 ;
Test for funnel plot asymmetry: z = 0.14, p = 0.89



Estimated number of missing studies: 0;
Test for funnel plot asymmetry: z = -0.63, p = 0.53

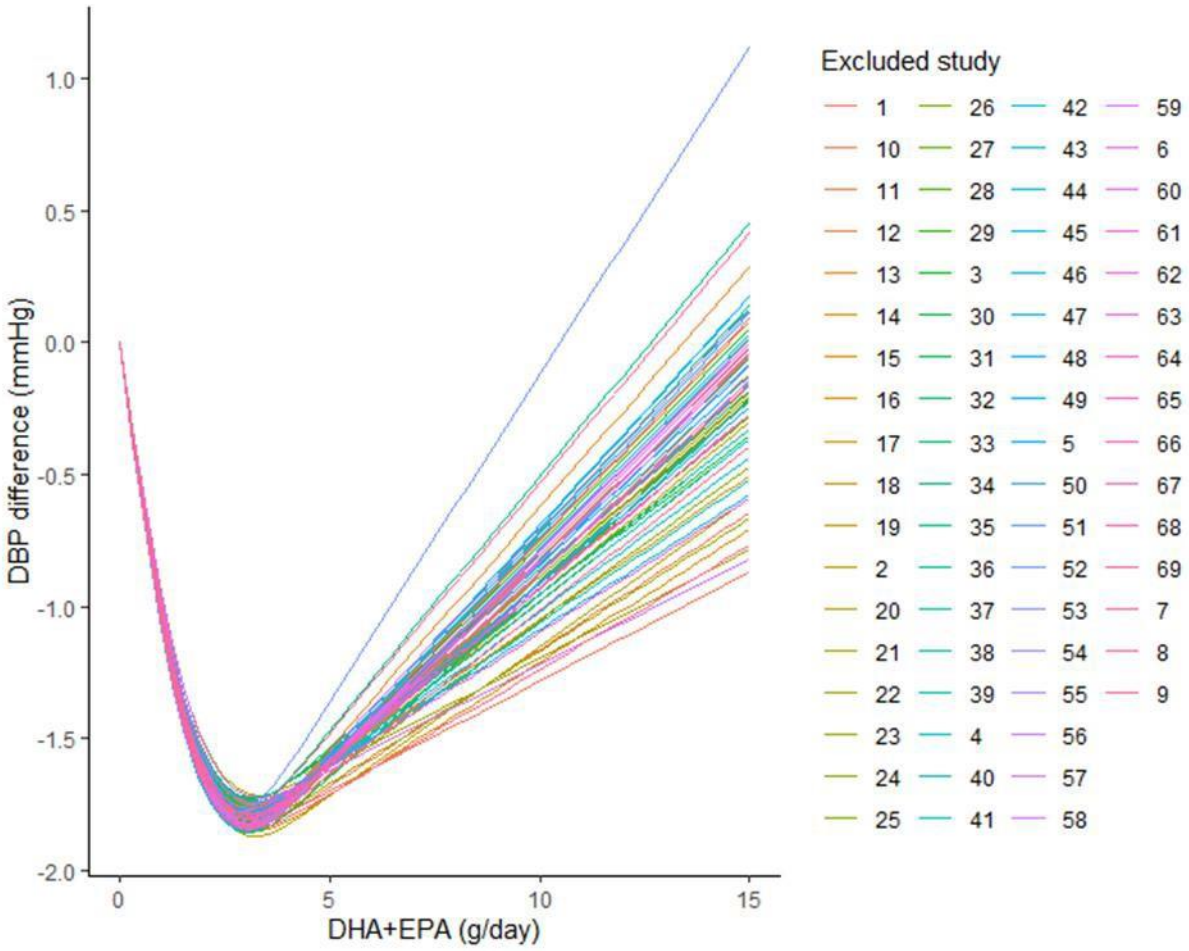
The plots are generated for the mean difference of changes in systolic (SBP) and diastolic (DBP) blood pressure levels as mmHg and its standard error using the trim-and-fill method for studies divided by hypertension status. Imputed studies are shown as empty dots. Solid dots indicate observed studies. The Grey area indicates $p \leq 0.05$. The asymmetry analysis was performed by Egger's regression test.

Figure S12. Sensitivity analysis of overall effects of EPA+DHA on SBP.



Sensitivity analysis of mean difference for changes in systolic blood pressure (SBP) levels between DHA+EPA treatment and placebo groups, using the leave-one-out method where each time one study is omitted to compute the pooled estimate in the one-stage regression model.

Figure S13. Sensitivity analysis of overall effects of EPA+DHA on DBP.



Sensitivity analysis of mean difference for changes in diastolic blood pressure (DBP) levels between DHA+EPA treatment and placebo groups, using the leave-one-out method where each time one study is omitted to compute the pooled estimate in the one-stage regression model.