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Long-Chain Omega-3 Fatty Acids Eicosapentaenoic Acid and Docosahexaenoic Acid and Blood Pressure: A Meta-Analysis of Randomized Controlled Trials

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Abstract

BACKGROUND

Although a large body of literature has been devoted to examining the relationship between eicosapentaenoic and docosahexaenoic acids (EPA+DHA) and blood pressure, past systematic reviews have been hampered by narrow inclusion criteria and a limited scope of analytical subgroups. In addition, no meta-analysis to date has captured the substantial volume of randomized controlled trials (RCTs) published in the past 2 years. The objective of this meta-analysis was to examine

the effect of EPA+DHA, without upper dose limits and including food sources, on blood pressure in RCTs.

METHODS

Random-effects meta-analyses were used to generate weighted group mean differences and 95% confidence intervals (CIs) between the EPA+DHA group and the placebo group. Analyses were conducted for subgroups defined by key subject or study characteristics.

RESULTS

Seventy RCTs were included. Compared with placebo, EPA+DHA provision reduced systolic blood pressure (−1.52mm Hg; 95% confidence interval (CI) = −2.25 to −0.79) and diastolic blood pressure (−0.99mm Hg; 95% CI = −1.54 to −0.44) in the meta-analyses of all studies combined. The strongest effects of EPA+DHA were observed among untreated hypertensive subjects (systolic blood pressure = −4.51mm Hg, 95% CI = −6.12 to −2.83; diastolic blood pressure = −3.05mm Hg, 95% CI = −4.35 to −1.74), although blood pressure also was lowered among normotensive subjects (systolic blood pressure = −1.25mm Hg, 95% CI = −2.05 to −0.46; diastolic blood pressure = −0.62mm Hg, 95% CI = −1.22 to −0.02).

CONCLUSIONS

Overall, available evidence from RCTs indicates that provision of EPA+DHA reduces systolic blood pressure, while provision of ≥2 grams reduces diastolic blood pressure.

Keywords: blood pressure, docosahexaenoic acid, eicosapentaenoic acid, fish oil, hypertension, meta-analysis, omega-3, randomized controlled trials, systematic review

Topic: hypertension , systolic blood pressure , omega-3 fatty acids , blood pressure , eicosapentaenoic acid , docosahexaenoic acids , food , diastolic blood pressure

Issue Section: State of the Art

Thirty-one percent of Americans are hypertensive, 30% are prehypertensive, and approximately 20% are hypertensive yet unaware of their status.[1,2] Only 47% of those with hypertension are adequately controlled.[1] Prior research shows that diet and lifestyle modifications, including physical activity, sodium reduction, and fish oil supplementation, can reduce blood pressure (BP), enhance antihypertensive drug efficacy, and decrease cardiovascular disease (CVD) risk.[3]

The active ingredients in fish oil considered responsible for its antihypertensive effect are the long-chain omega-3 fatty acids eicosapentaenoic acid (EPA; 20:5 n-3) and docosahexaenoic acid (DHA; 22:6 n-3). Although previous meta-analyses of fish oil supplementation and BP have been published,[4–7] none have been designed with inclusion criteria sufficient to examine the extensive scope of literature available in this active area of investigation. For example, the most recently published meta-analysis excluded trials that examined food sources of EPA and DHA (herein referred to as EPA+DHA) and those that were less than 8 weeks in duration.[7] Therefore, our main objective was to update the state of the science by conducting the most comprehensive meta-analysis of its kind of randomized controlled trials (RCTs) that examined EPA+DHA in relation to BP.

METHODS

Literature review

A comprehensive literature search was conducted by the University of Colorado Denver Health Science Library using Ovid/Medline, Embase, and the Cochrane Library. A PubMed search was performed in February 2013 to identify any publications not yet indexed by Ovid/Medline. Literature

searches covered studies published from 1946 through February 2013 and published in all languages. Level 1 screening included review of all titles and/or abstracts. Full-text publications of any studies not eliminated at level 1 were retrieved for complete review at level 2 screening. Supplementary literature searches included examining the reference lists of all relevant studies, pertinent review articles, and meta-analyses.

Eligibility criteria for study selection

Included studies were RCTs that examined the effect of EPA+DHA on BP in nonhospitalized adults (aged ≥18 years). Eligible outcomes were systolic and diastolic BP values (SBP and DBP, respectively). The exclusion criteria in this review were as follows:

1. Hypertensive subjects treated with BP-lowering medications;
2. Less than 3-week treatment duration;
3. Crossover RCTs with less than a 4-week washout period between treatments;
4. Studies that did not specify the amount of EPA+DHA provided or without required data to be used meta-analytically (all authors of otherwise eligible studies were contacted for missing data); and
5. Studies conducted in populations not representative of the general adult population, including pregnant and nursing women and individuals with preexisting CVD or significant disease process (e.g., renal disease or cancer) or secondary hypertension.

Data extraction and quality assessment

The following qualitative and quantitative information was extracted from all RCTs: publication year, population demographic characteristics, geographic location, baseline hypertensive status, other relevant baseline health

characteristics, medication use, sample size, the specific dose of EPA+DHA, the type of food or supplement, outcome assessment method, and means and SDs for BP outcomes.

Data synthesis

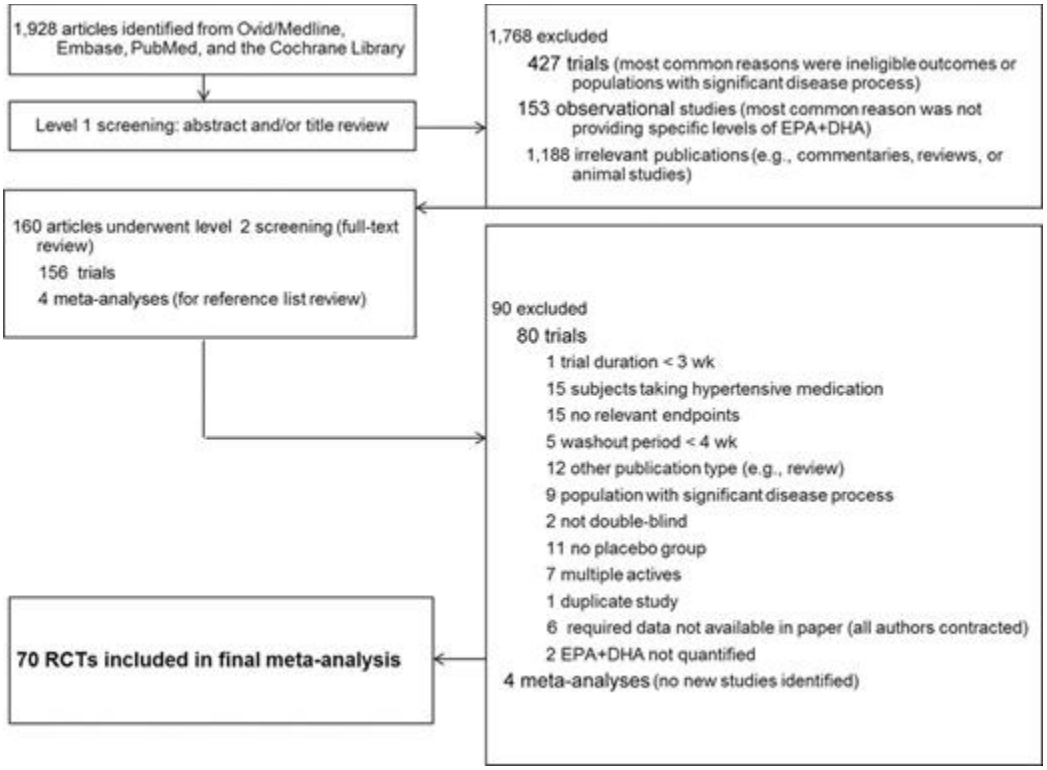
Random-effects meta-analysis models were used to calculate weighted group mean differences (postintervention minus preintervention), 95% confidence intervals (CIs), and corresponding *P* values for heterogeneity between the EPA+DHA group and the placebo group. The weight of each study was based on the inverse of the variance, which is a measure that accounts for the sample size in each group. The macro-level models included data on all subjects at all dose levels. Subgroup analyses were conducted to identify potential sources of heterogeneity or between-study variability and to estimate the effect of EPA+DHA according to key study characteristics. Categorical dose–response analyses were performed to discern potential patterns or thresholds of effect. Sensitivity and influence analyses were conducted by evaluating the impact of adding or removing studies based on important study characteristics and outlier status. The relative weight of each study was appreciated for each meta-analysis model to determine the influence that each study had on the overall summary effect. The presence of publication bias was assessed visually by examining a funnel plot measuring the SE as a function of effect size, as well as performing Egger's regression method and the Duval and Tweedie imputation method.[8] All analyses were performed using Comprehensive Meta-Analysis (version 2.2.046; Biostat, Englewood, NJ).

RESULTS

Study Characteristics

A flow diagram of the search strategy, including reasons for exclusion, is shown in Figure 1. A total of 70 RCTs[9–78] met all eligibility criteria and were included in the meta-analysis. The main study characteristics are shown in Table 1 (hypertensive populations) and Table 2 (normotensive populations, with 1 prehypertensive population).[17] Ramel *et al.*[63] examined hypertensive and normotensive subjects combined; these data are included in Table 1 but were not meta-analyzed in the subgroup analyses by hypertension status. Approximately 40% of the included RCTs were conducted in North America, with the remaining distributed primarily between Nordic countries (20%), European countries other than the Nordic countries (27%), and Australia (13%). The mean study duration was 69 days, the mean EPA+DHA dose was 3.8g/day, and sources of EPA+DHA included different types of seafood, EPA+DHA–fortified foods, fish oil, algal oil, and purified ethyl esters. Olive oil was the most commonly used placebo, with the remainder consisting predominately of other vegetable oils (e.g., safflower, corn, and sunflower oils).

Figure 1.



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Flow diagram of literature search and selection of randomized controlled trials (RCTs) for meta-analysis of eicosapentaenoic and docosahexaenoic acids (EPA+DHA) and blood pressure.

Table 1.

Characteristics of the randomized controlled trials in hypertensive study populations[a]

First author	Year	Country	Age, y[b]	Sex, M/F[c]	Duration, d	Intervention r
						Intervention type
Bonaa[14]	1990	Norway	20–61	156 (M+F)	70	Fish oil (EE)
Hill[38]	2007	Australia	25–65	28/53	84	Fish oil
Hughes[39]	1990	United States	NR	26/0	30	Fish oil
Knapp[41]	1989	United States	30–71	36/0	28	Fish oil
Landmark[42]	1993	Norway	33–64	18/0	28	Fish oil (EE)
Levinson[43]	1990	United States	18–75	17 (M+F)	42	Fish oil
Meland[48]	1989	Norway	26–66	40/0	42	Fish oil
Mundal[54]	1993	Norway	33–64	18/0	28	Fish oil

First author	Year	Country	Age, y[b]	Sex, M/F[c]	Duration, d	Intervention regi
						Intervention type
Passfall[60]	1993	Germany	40–61	4/6	42	Fish oil
Prisco[61]	1998	Italy	33–57	32/0	120	Fish oil (EE)
Radack[62]	1991	United States	≥ 18	19/14	84	Fish oil
Ramel[63,f]	2010	Iceland, Spain, Ireland	20–40	138/186	56	Fish oil
						Cod
						Salmon
Sagara[65]	2011	United Kingdom	45–59	38/0	35	DHA-enriched bread
Steiner[69]	1989	Switzerland	44 (13)	17/11	28	Fish oil
Toft[71]	1995	Norway	20–61	50/28	112	Fish oil (EE)
Wang[77]	2008	China	42 (3)	14/7	56	Fish oil

Abbreviations: DHA, docosahexaenoic acid; EE, ethyl esters; EPA, eicosapentaenoic acid; F, female; M, male; NR, not reported.

[a] Two study populations (Hughes *et al*. 1990[39] and Steiner *et al*. 1989[69]) were stratified by hypertensive status; therefore, only study

characteristics for hypertensives are shown here.

[b] Mean (SD) is shown when range was not provided.

[c] The total sample size is shown plus M+F to indicate both men and women were included when the distribution by sex was not provided.

[d] Dose of entire fish oil supplement or food.

[e] May include small amounts of docosapentaenoic acid.

Table 2.

Characteristics of the randomized controlled trials in normotensive study populations[a]f Not included in hypertensive-only meta-analysis because only a portion of the population (32%) was hypertensive

First author	Year	Country	Age, y[b]	Sex, M / F[c]	Duration, d	Intervention r
						Intervention type
Armstong[10]	2012	United States	20 –59	35/81	42	Fish oil (EE)
Atar[11]	2012	Iran	45 –65	0/78	56	Fish oil
Bach[12]	1989	United States	31 (9)	16/14	35	Fish oil
Barcelo-Coblijn[13]	2008	Canada	36 –43	50/3	84	Fish oil
Browning[15]	2007	United Kingdom	< 50	0/33	84	Fish oil
Buckley[16]	2009	Australia	22 (1)	25/0	35	Fish oil

First author	Year	Country	Age, y[b]	Sex, M / F[c]	Duration, d	Intervention r
						Intervention type
Carter[17,f]	2012	United States	24 (2)	18/20	56	Fish oil
Cazzola[18]	2007	Italy	18 –42	100/0	84	Fish oil
Chin[19]	1993	Australia	18 –32	29/0	28	Fish oil
Cobiac[20]	1991	Australia	30 –60	31/0	35	Salmon + sardines
						Fish oil
Conquer[21]	1999	Canada	30 (2)	19/0	42	Seal oil
Croset[22]	1990	France	86 (4)	NR	60	Fish oil (EE)
Demke[23]	1988	United States	18 –60	8/23	28	Fish oil
Derosa[25]	2009	Italy	≥18	164/169	180	Fish oil (EE)

First author	Year	Country	Age, y[b]	Sex, M / F[c]	Duration, d	Intervention r
						Intervention type
Derosa[24]	2012	Italy	18 –75	82/85	180	Fish oil (EE)
Deslypere[26]	1992	Belgium	21 –90	58/0	365	Fish oil
Dewell[27]	2011	United States	50 (10)	64/36	60	Fish oil
Dyerberg[28]	2004	Denmark	20 –60	87/0	56	Fish oil
Finnegan[29]	2003	United Kingdom	25 –72	87/63	120	EPA+DHA-enriched margarine
						EPA+DHA –enriched margarine + fish oil capsules
Flaten[30]	1990	Norway	35 –45	56/0	42	Fish oil
Geelen[31]	2003	Nether-	50	36/38	84	Fish oil

First author	Year	Country	Age, y[b]	Sex, M / F[c]	Duration, d	Intervention r
						Intervention type
Ginty[32]	2012	United States	NR	8/26	21	Fish oil
Grimsgaard[33]	1998	Norway	36 –56	224/0	49	Fish oil (EE)
Gustafsson[34]	1996	Sweden	48 (9)	24 (M+F)	21	EPA+DHA-enriched food products
Hallund[35]	2010	Denmark	40 –70	45/0	56	Marine trout
Harris[36]	2008	United States	21 –70	14 /19	112	Fish oil (EE)
Hellsten[37]	1993	Sweden	30 –60	40 (M+F)	150	Cod liver oil
Hughes[39]	1990	United States	NR	26/0	30	Fish oil
Kelley[40]	2007	United States	54 (2)	34/0	90	Fish oil
Lindqvist[78]	2009	Sweden	35 –60	35/0	42	Baked herring
Lofgren[44]	1993	United States	40 –60	23/0	84	Fish oil
Mackness[45]	1994			55/24	98	Fish oil

First author	Year	Country	Age, y[b]	Sex, M / F[c]	Duration, d	Intervention r
						Intervention type
		7 European countries	30 –71			
Maki[46]	2009	United States	35 –64	8/42	28	Krill oil
						Fish oil
McVeigh[47]	1994	Ireland	45 –61	16/4	42	Fish oil
Mills[50]	1989	Canada	22 –34	20/0	28	Fish oil
Mills[49]	1990	Canada	19 –31	29/0	28	Fish oil
Monahan[51]	2004	United States	18 –35	10/8	30	Fish oil
Mori[52]	1999	Australia	20 –65	56/0	42	Fish oil (EE)
Mortensen[53]	1983	Denmark	25 –40	20/0	28	Fish oil
Murphy[55]	2007	Australia	20 –65	35/39	190	EPA+DHA –enriched foods
Neff[56]	2010	United States	18 –65	15/21	112	Algal oil

First author	Year	Country	Age, y[b]	Sex, M / F[c]	Duration, d	Intervention r
						Intervention type
Nestel[57]	2002	United States	40 –69	21/17	49	Fish oil (EE)
Nordoy[58]	2001	Norway	28 –61	32/10	35	Fish oil (EE)
Noreen[59]	2012	United States	19 –55	14/26	42	Fish oil
Ryu[64]	1990	United States	20 –39	20/0	28	Fish oil
Sanders[66]	2006	United Kingdom	33 (13)	39/40	28	Fish oil
Sjoberg[67]	2010	Australia	53 (17)	17/16	84	Fish oil
Stark[68]	2004	Canada	45 –70	0/32	28	Fish oil
Steiner[69]	1989	Switzer-land	44 (13)	17/11	28	Fish oil
Theobald[70]	2007	United Kingdom	45 –65	20/19	90	Fish oil
THPCRG[9]	1992	United States	30 –54	245/105	180	Fish oil

First author	Year	Country	Age, y[b]	Sex, M / F[c]	Duration, d	Intervention reg
						Intervention type
Vakhapova[72]	2011	Israel	50 –90	67/63	105	Fish oil
Vandongen[73]	1993	Australia	30 –60	51/0	84	Fish oil
Vericel[74]	1999	France	70 –83	6/14	42	Fish oil
von Houwelingen[75]	1987	Nether-lands	20 –45	82/0	42	Mackarel paste
Walser[76]	2008	United States	20 –51	14/7	42	Fish oil

Abbreviations: DHA, docosahexaenoic acid; EE, ethyl esters; EPA, eicosapentaenoic acid; NFS, not further specified; NR, not reported; THPCRG, Trials of Hypertension Prevention Collaborative Research Group.

[a] Two study populations (Hughes *et al*.[39] and Steiner *et al*.[69]) were stratified by hypertensive status; therefore, only study

characteristics for normotensives are shown here.

[b] Mean (SD) is shown when range was not provided.

[c] The total sample size is shown plus M+F to indicate both men and women were included when the distribution by sex was not provided.

[d] Dose of entire fish oil supplement or food.

[e] May include small amounts of docosapentaenoic acid.

[f] Population includes normotensive and prehypertensive subjects.

Results from meta-analysis

Meta-analysis results for all analyses are reported in Table 3, and results for selected analyses are illustrated in Figures 2 and 3 and

Supplementary Figures S1
and
S2
.

Table 3.

Summary of meta-analysis results

Model	No. of data points	WGMD	Lower 95% CI	Upper 95% CI	*P* value for heterogeneity
Systolic blood pressure					
All studies[a]	93	−1.52	−2.25	−0.79	0.001
Supplement only	82	−1.75	−2.55	−0.94	0.001
Food only	11	0.10	−1.31	1.50	0.50
US studies	25	−1.78	−3.33	−0.23	0.03
Non-US studies	68	−1.33	−2.16	−0.50	0.007
Duration ≥60 days	41	−1.63	−2.67	−0.59	0.08
Dose 0 to <1 g	12	−2.38	−5.14	0.38	0.009
Dose 1 to <2 g	19	−1.81	−3.59	−0.03	0.47
Dose 2 to <3 g	18	−0.21	−1.85	1.43	0.007

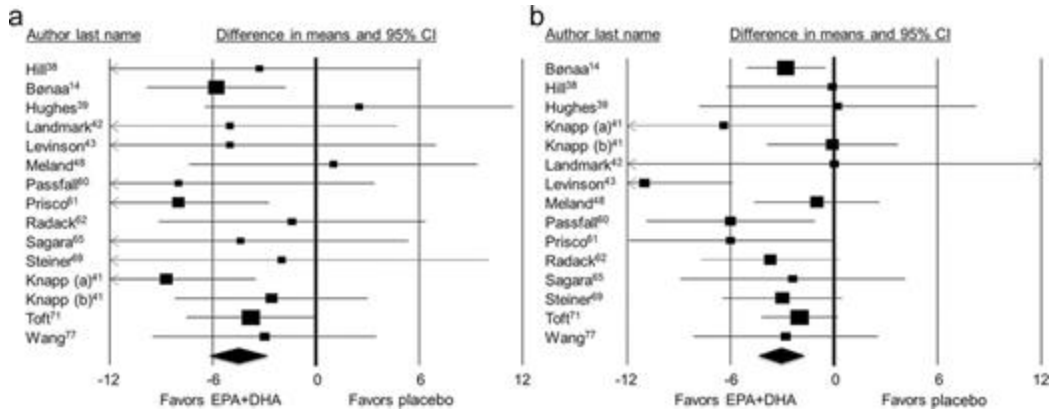
Model	No. of data points	WGMD	Lower 95% CI	Upper 95% CI	*P* value for heterogeneity
Dose 3 to <4 g	22	−3.85	−5.55	−2.15	0.05
Dose 4 to <5 g	11	−0.86	−1.84	0.13	0.97
Dose ≥5 g	10	−0.36	−2.95	2.23	0.17
Hypertensive subjects	15	−4.51	−6.12	−2.83	0.72
Normotensive subjects	73	−1.25	−2.05	−0.46	0.01
EPA only	7	−4.61	−8.35	−0.86	0.01
DHA only	8	−1.27	−3.37	0.84	0.28
Ethyl ester	15	−2.24	−3.72	−0.76	0.002
Other marine oils	67	−1.45	−2.39	−0.50	0.007
Diastolic blood pressure					
All studies[a]	92	−0.99	−1.54	−0.44	0.00
Supplement only	81	−1.11	−1.72	−0.50	0.00
Food only	11	−0.38	−1.46	0.70	0.75
US studies	24	−1.35	−2.48	−0.21	0.02
Non-US studies	68	−0.88	−1.52	−0.25	0.00
Duration ≥60 days	41	−0.95	−1.56	−0.34	0.31

Model	No. of data points	WGMD	Lower 95% CI	Upper 95% CI	*P* value for heterogeneity
Dose 0 to <1 g	10	0.04	−1.48	1.56	0.78
Dose 1 to <2 g	21	0.40	−1.10	1.91	0.001
Dose 2 to <3 g	18	−1.09	−2.08	−0.11	0.16
Dose 3 to <4 g	22	−1.86	−2.67	−1.06	0.36
Dose 4 to <5 g	11	−0.59	−1.37	0.19	0.94
Dose ≥5 g	10	−1.97	−3.96	0.02	0.06
Hypertensive subjects	15	−3.05	−4.35	−1.74	0.17
Normotensive subjects	72	−0.62	−1.22	−0.02	0.002
EPA only	5	−0.81	−1.99	−0.37	0.55
DHA only	8	−0.84	−2.29	0.62	0.32
Ethyl ester	16	−0.80	−1.49	−0.11	0.28
Other marine oils	64	−1.20	−2.02	−0.37	0.00

Abbreviations: CI, confidence interval; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; WGMD, weighted group mean difference.

[a] Includes all studies, regardless of dose, duration, region, hypertensive status, and source of EPA+DHA (supplement or food).

Figure 2.



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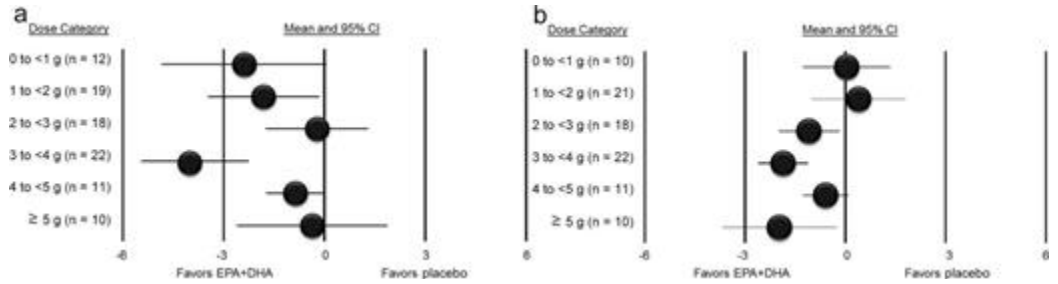
Results from meta-analyses of randomized controlled trials examining eicosapentaenoic and docosahexaenoic acids (EPA+DHA) provision and (**a**) systolic blood pressure and (**b**) diastolic blood pressure among hypertensive subjects. The squares represent average change in blood pressure in individual randomized controlled trials, or individual trial strata, with 95% confidence intervals (CIs). The diamond represents the pooled summary estimate. Knapp (a) is a higher-dose subgroup, and Knapp (b) is a lower-dose subgroup.

Figure 3.



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Results from meta-analyses of randomized controlled trials examining eicosapentaenoic and docosahexaenoic acids (EPA+DHA) and (**a**) systolic blood pressure and (**b**) diastolic blood pressure by EPA+DHA dose category. The circle represents the pooled summary estimate across all studies within each dose category, with 95% confidence intervals (CIs). n indicates the number of data points in each dose category, which may be greater than the number of individual studies.

In the overall meta-analysis model of 93 data points from 70 RCTs, SBP decreased by 1.52mm Hg (95% CI = −2.25 to −0.79) and DBP by 0.99mm Hg (95% CI = −1.54 to −0.44), compared with placebo, after EPA+DHA provision (Table 3;

Supplementary Figures S1
and
S2
). Studies with multiple entries in the meta-analysis models reflect results presented separately by the authors for different subgroups (e.g., low-dose and high-dose EPA+DHA). In the meta-analysis of hypertensive subjects, significant reductions in SBP (−4.51mm Hg; 95% CI = −6.12 to −2.83) and DBP (−3.05mm Hg; 95% CI = −4.35 to −1.74) were observed (Figure 2). The meta-analysis of studies among normotensive subjects also found a significant reduction of SBP (−1.25mm Hg; 95% CI = −2.05 to −0.46) and DBP (−0.62mm Hg; 95% CI = −1.22 to −0.02) (Table 3). The summary estimates were modified by source of EPA+ DHA and by study region (Table 3). In the meta-analysis of supplement-only studies, SBP decreased by 1.75mm Hg (95% CI = −2.55 to −0.94) and DBP by 1.11 (95% CI = −1.72 to −0.50) after EPA+DHA provision, compared with placebo. Among US-only studies, reductions of 1.78mm Hg (95% CI = −3.33 to −0.23) in SBP and 1.35mm Hg (95% CI = −2.48 to −0.21) in DBP were observed. Because relatively few studies evaluated EPA+DHA as individual fatty acids, there was insufficient statistical power to detect a meaningful difference between EPA and DHA separately on lowering either SBP or DBP.

The subgroup analyses by dose are depicted in Figure 3. There was no clear pattern of dose–response between EPA+DHA and SBP. Significant reductions were observed with doses of 1 to <2g/d (−1.81; 95% CI = −3.59 to −0.03) and 3 to <4g/d (−3.85; 95% CI = −5.55 to −2.15). No apparent effect on DBP was observed for dose levels <2g/day, whereas significant reductions were observed for 2 to <3g/day (−1.09; 95% CI = −2.08 to −0.11) and 3 to <4g/day (−1.86; 95% CI = −2.67 to −1.06).

An examination of potential publication bias indicated a modest proclivity for published studies that found a significant SBP reduction with EPA+DHA provision (

Supplementary Figure S3
). There was a slight indication of publication bias with a proclivity for publication of results that showed a significant DBP reduction with EPA+DHA provision, which was modified by study region. Non-US studies were more

likely to publish findings showing DBP reduction with EPA+DHA provision, whereas US studies were more likely to publish null findings or an increase in DBP with EPA+DHA provision.

DISCUSSION

This meta-analysis of RCTs that examined EPA+DHA provision and BP provides the most comprehensive quantitative summary of the evidence to date. Before this meta-analysis, the most recent published meta-analysis[7] excluded studies <8 weeks in duration and those that examined food sources of EPA+DHA. By liberalizing the duration restriction to 3 weeks, including RCTs conducted with EPA+DHA–rich and –fortified foods, and capturing recent RCTs published in the past 2 years, our meta-analysis evaluated an additional 53 studies not included by Campbell *et al.*[7] The considerably larger volume of studies enhanced the statistical power to perform important subgroup analyses by factors such as dose, geographic region, hypertensive status, and source of EPA+DHA.

The results from our analysis demonstrate that EPA+DHA are as effective, and in some cases more effective, than other lifestyle-related interventions, including increasing physical activity and restricting alcohol and sodium,[79] for lowering BP among hypertensive populations not taking antihypertensive medication. These results are consistent with findings from Campbell *et al.*[7] as well as other earlier meta-analyses.[80,81] Lowered systemic vascular resistance through changes in endothelial function is considered a primary mechanism by which EPA+DHA may lower BP.[82] Recent systematic reviews and a meta-analysis of RCTs found improved endothelial function in response to EPA+DHA, particularly among patients with risk factors for CVD, including hypertension, but not consistently among healthy young and middle-aged subjects.[83,84] This observation may explain the greater response of unmedicated hypertensive subjects when compared with normotensive subjects in our meta-analysis.

The reductions in BP observed in this analysis are not only statistically significant but also are clinically meaningful. Among adults, SBP rises by approximately 0.6mm Hg per year; among those aged ≥50 years, the lifetime risk of hypertension is 90%.[85] Furthermore, only 1mm Hg SBP separates each stage of hypertension. The statistically significant reduction in SBP of 1.25mm Hg noted among normotensive individuals in our analysis would represent a delay of age-related SBP increase by 2 years and progression from prehypertensive to hypertensive status. The 4.51mm Hg decrease observed among hypertensive populations not taking antihypertensive medication could prevent an individual from requiring medication to control their hypertension or could help maintain an individual in a lower stage of progressive hypertension. Lowered systemic vascular resistance and BP can reduce risk of coronary plaque rupture, stroke, and complications of stroke, including related cognitive decline, thus improving clinical outcomes for higher-risk populations.[82]

Overall, there was no clear discernible pattern of a dose–response effect for EPA+DHA on BP, which is similar to findings from past meta-analyses.[7,81,86] Although less data are available that examine EPA+DHA–rich or –fortified food and BP outcomes (n = 8 studies in this meta-analysis), EPA+DHA–rich or –fortified foods were less effective than supplements with regards to lowering BP. It is important to note, however, that there are barriers to frequent fish consumption, which may explain in part the discrepant findings between food and supplement studies. Among the general population, barriers to frequent fish consumption include dislike of taste, unpleasant smell, and "concerns about bones."[87,88] Five of the 8 food studies in the current meta-analysis required daily consumption of oily fish, including sardines, mackerel, and salmon. Although compliance was not routinely reported among all food studies, von Houwelingen *et al.*,[75] who provided subjects with mackerel, reported compliance of only 78%. In addition, the researchers noted that a tendency for compliance decreased over the course of the study, as assessed by urinary lithium excretion. Only 3 studies of EPA+DHA–fortified foods (e.g., margarine and bread)[29,55,65] were

identified for inclusion in our meta-analysis, which challenges efforts to fully investigate the role of these EPA+DHA sources as part of an overall healthy dietary pattern.

Collectively, the evidence from RCTs indicates that provision of ≥2g/d EPA+DHA may reduce both SBP and DBP, with the strongest benefits observed among hypertensive individuals who are not on antihypertensive medication. In addition, a lower dose (between 1 and 2g/d) may reduce SBP but not DBP. From a clinical and public health perspective, provision of EPA+DHA may lower BP and ultimately reduce the incidence of associated chronic diseases.

DISCLOSURE

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