Published in final edited form as:
Am J Hypertens. 2011 October ; 24(10): 1121–1126. doi:10.1038/ajh.2011.120.

LONG-CHAIN OMEGA-3 FATTY ACIDS AND BLOOD PRESSURE

J. C. Liu, MD[1], **S. M. Conklin, PhD**[2], **S. B. Manuck, PhD**[3], **J. K. Yao, PhD**[4], and **M. F. Muldoon, MD, MPH**[1]

[1]Department of Medicine, University of Pittsburgh School of Medicine

[2]Department of Psychology and Neuroscience Program, Allegheny College

[3]Department of Psychology, University of Pittsburgh

[4]Pittsburgh VA Healthcare System

Abstract

Objective—High dose fish oil supplementation reduces blood pressure (BP) in hypertensive patients. The current study examines how modest variations in omega-3 fatty acid intake may affect BP in a healthy community sample.

Methods—Study participants included 265 Pittsburgh-area adults 30–54 years of age (11% black, 51% female) not taking omega-3 fatty acid supplements or antihypertensive medications. Standardized assessments of clinic and 24-hour ambulatory BP, and pulse rate were obtained. Docosahexanenoic acid (DHA) and eicosapentaenoic acid (EPA) in fasting serum phospholipids were measured by capillary gas chromatography. Regression analyses controlled for age, gender, race, BMI, self-reported sodium intake and physical activity.

Results—Participants included 181 (68%) normotensives, 64 (25%) prehypertensives, and 18 (7%) persons with untreated hypertension. DHA was inversely associated with clinic diastolic (β= −0.121, p= 0.03), awake ambulatory diastolic BP (β=−0.164, p= 0.004), and 24-hour diastolic BP (β=−0.135, p=0.02). A two standard deviation greater DHA was associated with 2.1 mm Hg lower clinic and 2.3 mm Hg lower awake ambulatory diastolic BP. In addition, DHA was inversely associated with pulse rate measured at rest in the clinic. EPA was related to clinic pulse rate but not clinic or ambulatory BP.

Conclusion—In this sample of American adults not on antihypertensive medications, a modest, inverse association was found between DHA exposure and both clinic and ambulatory diastolic BP. Therefore, increasing DHA consumption through diet modification rather than large dose supplementation represents a candidate strategy for future studies of hypertension prevention.

Keywords

hypertension; blood pressure monitoring, ambulatory; docosahexaenoic acid; eicosapentaenoic acid; omega-3 fatty acids

Omega-3 polyunsaturated fatty acids (n-3 PUFAs) are required for normal human development and metabolic function [1, 2]. The three most commonly ingested n-3 PUFAs

Corresponding Author*:* Matthew F. Muldoon, MD, MPH, 506 Old Engineering Hall, University of Pittsburgh, Pittsburgh, PA 15260, Telephone: 412-624-8798, Fax: 412-624-5407, mfm10@pitt.edu.

Disclosure: Drs Conklin, Yao and Muldoon received a $9,000 grant from Isodis Natura in 2008 to support serum fatty acid analyses for a separate study. The authors have no other potential conflicts of interest to disclose.

Disclaimer:
The contents of this article do not represent the views of the United States Government or the Department of Veterans Affairs.

are α-linolenic acid (18:3 ω-3, ALA), docosahexaenoic acid (20:5 ω-3, DHA), and eicosapentaenoic acid (22:6 ω-3, EPA). The primary source of ALA is certain seeds and nuts, whereas most dietary EPA and DHA come from seafood. EPA and DHA comprise less than 0.2% of total calories in many countries, yet are inversely associated with cardiovascular morbidity and mortality [3],[4]. The two largest randomized clinical trials of fish oil supplementation, GISSI-Prevenzione and JELIS, revealed 10% and 19% reductions in major cardiovascular events, respectively [5, 6].

Several mechanisms for these cardiovascular benefits have been proposed, including blood pressure (BP) reduction [7, 8]. Across numerous studies, raised EPA and DHA consumption lowers resting or clinic BP [9, 10]. However, the general applicability of such evidence for hypertension prevention and treatment is limited for several reasons. The median intake of EPA and DHA among US citizens is less than 150 mg/day [11, 12] whereas most trials examining antihypertensive effects have tested the efficacy of 3 grams or more per day [9, 10, 13, 14]]. Consumption of such large doses through diet modification is extremely impractical, since eating fatty fish twice a week – as recommended by the American Heart Assocaition for patients with ischemic heart disease -- provides only approximately 1 gram per day. To reach an intake of 3 grams of EPA and DHA requires between 4 and 10 fish oil capsules at a cost of $1 or more per day [15]. Finally, high-dose supplementation frequently causes fishy belching, limiting acceptance for chronic use.

What remains unclear is whether such large doses are necessary. The public health importance of n-3 PUFA consumption would be substantial if, as opposed to “pharmacologic dosing,” normative variability in dietary intake of EPA, DHA or both were found to affect BP. If that were the case, modest diet modifications might represent a practicable means of preventing or treating hypertension. The few randomized trials of low dose EPA and DHA supplementation suggest a benefit related specifically to DHA intake. Theobald and colleagues studied the effects of supplementation with 700 mg DHA among largely normotensive 40–65 y/o men and women. Compared to placebo, DHA reduced diastolic BP by an average of 3.3 mm Hg ($p = 0.01$) [16]. In another randomized and double-blind trial conducted in similar “at risk” volunteers, supplementation with 480 mg of EPA (and 120mg of gamma-linoleic acid, an n-6 fatty acid) had no effect on resting, seated BP [17].

With respect to observational studies of n-3 PUFA consumption and BP, the large INTERMAP study found that individuals reporting relatively high intake of n-3 fatty acids had lower resting BP than other participants [18]. This investigation used four 24-hour dietary recalls but was unable to identify a significant association for EPA and DHA separately. Also, the study lacked data on 24-hour ambulatory BP data, whereas such measures predict cardiovascular disease events more accurately than clinic or resting BP [19, 20].

In summary, variation EPA and/or DHA intake that may achieved by modified dietary intake of these long-chain n-3 fatty acids could well be relevant to the prevention of hypertension and, secondarily, cardiovascular disease events. However, research to date on non-pharmacologic dosing or diet modification has been inconclusive, and preliminary evidence points to differences between DHA and EPA. The current investigation studied a sample of 265 generally healthy adults taking neither antihypertensive medication nor fish oil supplements. BP was measured with standardized clinical assessments and also by 24-hour ambulatory monitoring. Serum phospholipid fatty acid composition was utilized as a biomarker of individual differences in dietary EPA and DHA intake. We hypothesized that increasing levels of serum n-3 fatty acids would be correlated inversely with blood pressure, and that this association would be stronger for DHA than for EPA.

Methods

The study utilized data from the Adult Health and Behavioral project, which is comprised of behavioral and biological information collected from generally healthy individuals between the ages of 30 to 54 years old living in the Pittsburgh metropolitan area. Participants were recruited via mass mailing of study information. Contributing to the present analyses were all participants free of clinically-evident atherosclerotic vascular disease, diabetes, known liver or kidney disease, cancer and major neuropsychiatric disorder and not taking any anti-hypertensive, lipid-lowering or psychotropic medication. Additional exclusion criteria for subjects participating in the current substudy included a resting BP ≥ 180/110 mm Hg, a body mass index (weight/height^2, BMI) greater or equal to 40 kg/m^2, average daily alcohol consumption greater than 21 drinks per week (ethanol > 273 g/ wk), and use of fish oil supplements. These methods permitted the enrollment of individuals with untreated hypertension provided their BP was less than 180/110. A total of 308 volunteers met these criteria and participated in a phase of the study which included ambulatory BP monitoring and dietary assessments. Of these, 26 were missing serum fatty acids data and 19 were missing ambulatory BP data, resulting in a sample of 265 individuals for the current analyses. Participants gave signed consent in accordance with the regulations of the University of Pittsburgh Institutional Review Board and were compensated for their involvement in the study.

Clinic BP and Pulse Rate Measurement

BP and pulse were measured on two occasions, separated by an average of 35 days. Participants sat quietly for at least 5 minutes and arm circumference was measured to determine the appropriate cuff size. Two BP readings were auscultated with a mercury manometer at 2 minute intervals by certified staff, between which pulse rate was palpated for 30 seconds. BP readings were averaged across the two appointments and are referred to hereafter as “clinic” systolic and diastolic BP.

24-hour Ambulatory BP and Pulse Rate Measurement

Participants wore an ambulatory BP device (Accutracker DX monitor) for 24 hours. The device was programmed to automatically record BP every 30 minutes between 7 AM and 11 PM and every hour between 11 PM and 7 AM. Subjects noted the time they went to bed at night and the time of arising in the morning. Using this information, device data were averaged during “awake” and “asleep” time periods. Ten of the 265 participants were missing asleep BP and pulse rate data due to device malfunction or removal by the participant.

Serum lipid analyses

On the same day as the first clinic BP measurement, phlebotomy was performed after an overnight fast and a serum aliquot was frozen at −80 C until analysis. As described elsewhere in greater detail [21], serum phospholipids were initially separated from total lipids by Sep-Pak silica cartridge. The fatty acid composition of the extracted phospholipids was then determined by capillary gas chromatography and flame ionization. Intra- and interassay coefficients of variation were 2.0% to 9.2% and 1.9% to 9.6%, respectively, for all major serum fatty acids and polyunsaturated fatty acids. EPA and DHA are expressed as percent of total fatty acids (mole %). Serum HDL cholesterol, and triglyceride concentrations were measured by the Heinz Nutrition Laboratory, School of Public Health, University of Pittsburgh, which has met criteria for the Centers for Disease Control and Prevention–National Heart, Lung, and Blood Institute Standardization Program since 1982

Diet and Physical Activity

Two unannounced 24-hour diet recall interviews were conducted with each subject and analyzed using the Nutritional Data System for Research software developed by the Nutrition Coordinating Center at the University of Minnesota. This system converted the dietary information into estimates of daily nutrient consumption. Daily dietary sodium (mg/100kg/d) was treated as a covariate in statistical analyses. Usual physical activity was estimated from the Paffenbarger survey [22].

Statistical Analysis

Statistical analysis was conducted using SPSS v 17. Dietary sodium, physical activity, serum DHA and EPA distributions were skewed and log transformation reduced skewness. Because findings were virtually identical whether or not DHA and EPA were logged, results using untransformed DHA and EPA are presented for ease of interpretation. Separate linear regression models were analyzed for the dependent measures of: a) clinic systolic and diastolic BP and pulse rate; b) 24-hour ambulatory systolic and diastolic BP and pulse rate; c) ambulatory awake systolic and diastolic BP and pulse rate; d) asleep systolic and diastolic BP and pulse rate; and e) nocturnal BP and pulse dipping (calculated as the fall during sleep as a proportion of the awake value). Covariates for step 1 in all models were age, gender, race, BMI, dietary sodium, and physical activity. Age, BMI, dietary sodium and physical activity were entered as continuous variables, and gender (male, female) and race (white and non-white) as categorical variables. In step 2, DHA and EPA were entered in separate models. Effect sizes were calculated from linear regression alayses using standardized DHA levels.

The Sobel test for mediation of the association between DHA and clinic BP by clinic pulse was conducted using the online calculator created by Preacher & Leodarnelli [23]. Analyses included unstandardized coefficients from regression models and their respective standard errors, as well as standard covariates listed above.

Results

Characteristics of the study population are provided in Table 1. Approximately half of the participants were female, the sample was predominantly Caucasian, and, on average, participants were mildly overweight. Based on clinical BP readings, 18 (7%) of the 265 participants had untreated hypertension, 66 (25%) were pre-hypertensive, and 181 (68%) were normotensive.

Linear regression models predicting clinic BP measurements and controlling for age, gender, race, BMI, dietary sodium and physical activity revealed a statistically significant inverse relationship between DHA and clinic diastolic BP (Table 2). One standard deviation (SD) above, relative to one SD below the mean DHA level in serum phospholipids (0.86 versus 2.20 mol %) was associated with a 2.1 mm Hg lower clinic diastolic BP. Additionally, both DHA and EPA were significantly and inversely related to clinic pulse rate.

In analyses of 24-hour BP data, greater DHA was again associated with lower diastolic BP (Table 3). This same associationwas evident in analysis restricted to awake periods, whereas DHA was unrelated to either BP during sleep (Tables 4 and 5). One SD above, compared to one SD below, the mean serum phospholipid DHA was associated with a 2.3 mm Hg lower awake ambulatory diastolic BP. Inclusion of insulin resistance (estimated using fasting insulin and glucose in the Homeostatic Model Assessment) [24] in the regression models does not alter the findings. Participants whose nocturnal BP declined less than 10% (“non-dippers”) did not differ from other participants with respect to DHA or EPA levels. Regression models using the fatty acids ratios, AA/DHA and AA/EPA, in step 2 in place of

DHA and EPA yields results very similar to those reported in Tables 2–5 with the exception that the sign of beta is reversed(results not shown).

Because DHA was related to both clinic BP and clinic pulse rate, any BP effects of DHA may be mediated by alterations in cardiovascular autonomic control. Pulse rate is a function of cardiac autonomic input with higher pulse reflecting greater sympathetic, relative to parasympathetic, control. Based on the Sobel test for statistical mediation, resting pulse rate accounted for 36% of the variance between DHA and clinic diastolic BP ($Z = -2.5$, $P = 0.01$).

Discussion

The role of practicable increases in consumption of the long-chain n-3 fatty acids in hypertension prevention is promising but understudied. In the current analyses of mid-life adults not taking antihypertensive medications or fish oil supplements, higher serum phospholipid DHA wass associated with lower clinic or resting diastolic BP and also with lower 24 hour diastolic BP. Furthermore, a higher serum DHA was associated with lower clinic pulse rate whereas serum EPA was associated only with clinic pulse rate.

Across INTERMAP's 17 population-based samples, total n-3 fatty acid consumption was also associated with resting BP [18]. One SD above compared to one SD below the mean in intake corresponded to only −0.55 / −0.57 mm Hg for systolic and diastolic, respectively, and effects of the individual n-3 fatty acids were not significant. Whereas INTERMAP used self-reported diet to estimate n-3 fatty acid consumption, here fatty acid composition of serum phospholipids was employed as a biomarker of dietary intake. Among the major long-chain n-3 fatty acids, DHA was found to be uniquely related to BP, with an effect size about 4-fold larger than that estimated from INTERMAP. Both investigations suggest that normal variability between individuals in n-3 fatty acid consumption – rather than pharmacologic dosing – may affect BP.

Differential effects of EPA and DHA on BP have been examined in a small clinical trial literature. As noted, of two trials of low dose supplementation of either DHA or EPA, only DHA reduced BP significantly [16], [17]. Mori and colleagues directly compared large doses EPA and DHA (4 g/d) for 6 weeks in overweight men [25] and, similarly, found that BP declined uniquely in those assigned to DHA supplementation. These investigators also conducted a randomized trial in which BP fell following increased consumption of oily fish [26]. Oils from fish contain both EPA and DHA, whereas DHA can be harvested from marine algae. Since algae are far more plentiful than fish, additional research to define the differential cardiovascular effects of EPA and DHA would inform utilization of these ecological resources.

Current literature suggests a range of mechanisms through which n-3 fatty acids may affect blood pressure, including but not limited to: a) interacting with the nitric oxide pathway and endothelial function, b) lowering vascular tone via blockade of the angiotensin pathway, c) inhibition of thromboxane production and thromboxane-induced vasoconstriction, and d) modulating autonomic tone [27]. Evidence of effects on these pathways tends to be greater for DHA than EPA [14]. Radaelli, et al studied the effects of PUFA supplementation in heart failure patients using carotid baroreceptor stimulation and found increases in reflex response and the alpha index [28]. Other research suggests that n-3 fatty acids modulate the parasympathetic and sympathetic interaction through observed changes in heart rate and, in murine models, n-3 fatty acids increase dopaminergic activity to reduce sympathetic tone [29]. Prior research has implicated impaired baroreflexes in hypertension both in the young and in the elderly, and n-3 fatty acids may ameliorate this abnormality [30].

Autonomic modulation of BP is further supported by our observation that pulse rate measured in the seated position, an index of resting autonomic tone, accounting for a substantial portion of the DHA – BP association. Finally, rodents fed diets deficient in n-3 fatty acids often develop high BP and do so specifically when consuming relatively large amounts of casein-based protein [31]. Protein consumption in the US tends to be high and derives predominantly from animal sources, paralleling this rodent experiment.

Our analyses revealed that DHA was related to diastolic but and not systolic BP. This pattern was also found in the DHA supplementation trial by Theobald and colleagues [16]. In contrast to isolated systolic hypertension in the elderly, primary hypertension developing early to mid-adulthood typically involves elevations in diastolic BP and is often associated with a hyperadrenergic state [32], [33]. Therefore, our noted associations between DHA and both diastolic BP and resting pulse (and near significant trends for ambulatory pulse) may reflect this early phase of hypertension development. While an association with systolic BP might also be expected, the observed relationship between DHA and specifically diastolic BP parallels a greater effect of beta blocker medications on diastolic BP when compared to thiazide diuretics and calcium channel blockers [34, 35].

The current findings are limited by their derivation from data collected in an observational study. Serum phospholipid analyses were utilized as biomarkers of dietary consumption of long-chain polyunsaturated fats because self-reported dietary data tend to be unreliable. However, individual variations in n-3 fatty acid absorption, metabolism, and excretion would make direct extrapolations from blood levels to dietary patterns imprecise. Multiple statistical tests inflate a study's risk of type 1 error. Tables 2–5 report on the findings of analyses to detect associations between either DHA or EPA with either BP or pulse rate in either a clinic and ambulatory setting. Together, we find significant associations in 5 of 24 analyses (21%). Some consistency is noteworthy for DHA in relation to diastolic BP, for which 3 of 4 analyses reveal significant associations. The magnitude of the reported association may be viewed as small since a diastolic BP difference of only 2.1–2.3 mm Hg was found in comparison of individuals having phospholipid DHA content of 0.86 versus 2.20 mol % (12^{th} versus 87^{th} percentiles). However, Americans consume much less fish than many other populations, resulting in a rather limited range of n-3 PUFA exposure. Also, in order to avoid confounding, individuals receiving antihypertensive medications were excluded. This constrained the BP range of our sample. For these reasons and based on preliminary trial data [16] [26], one may posit that increasing DHA consumption via diet modification, as opposed to large dose supplementation, may lower BP and prevent hypertension. Additional studies involving randomized, controlled trials of diet modification or low dose supplementation of EPA or DHA would more directly test and quantify any effect on clinic and ambulatory BP.

In conclusion, this investigation of generally healthy adults taking neither antihypertensive medications nor fish oil supplements revealed a correlation between greater DHA content in serum phospholipids and lower BP in both clinic and ambulatory settings. Such findings suggest of novel paradigm for the management of hypertension risk which may be tested in future studies involving modest increases in DHA consumption.

Acknowledgments

This research was supported by U.S. Public Health Service grants P01 HL40962 and T32 HL007560 and by grants from the Department of Veterans Affairs, Veterans Health Administration, Office of Research and Development (Senior Research Career Scientist Award), and VA Pittsburgh Healthcare System . The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

The authors are grateful to Mr. Jack Haflett for his technical assistance.

REFERENCES

1. Innis SM. Dietary (n-3) fatty acids and brain development. The Journal of nutrition. 2007 Apr; 137(4):855–859. [PubMed: 17374644]
2. Yashodhara BM, Umakanth S, Pappachan JM, Bhat SK, Kamath R, Choo BH. Omega-3 fatty acids: a comprehensive review of their role in health and disease. Postgraduate medical journal. 2009 Feb; 85(1000):84–90. [PubMed: 19329703]
3. Harris WS, Kris-Etherton PM, Harris KA. Intakes of long-chain omega-3 fatty acid associated with reduced risk for death from coronary heart disease in healthy adults. Current atherosclerosis reports. 2008 Dec; 10(6):503–509. [PubMed: 18937898]
4. Saravanan P, Davidson NC, Schmidt EB, Calder PC. Cardiovascular effects of marine omega-3 fatty acids. Lancet. 2010 Aug 14; 376(9740):540–550. [PubMed: 20638121]
5. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto miocardico. Lancet. 1999; 354(9177):447–455. [PubMed: 10465168]
6. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, et al. Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet. 2007 Mar 31; 369(9567):1090–1098. [PubMed: 17398308]
7. Massaro M, Scoditti E, Carluccio MA, De Caterina R. Basic mechanisms behind the effects of n-3 fatty acids on cardiovascular disease. Prostaglandins, leukotrienes, and essential fatty acids. 2008 Sep–Nov; 79(3–5):109–115.
8. Kris-Etherton PM, Harris WS, Appel LJ. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. Circulation. 2002; 106(21):2747–2757. [PubMed: 12438303]
9. Mori TA, Beilin LJ. Long-chain omega 3 fatty acids, blood lipids and cardiovascular risk reduction. Current opinion in lipidology. 2001 Feb; 12(1):11–17. [PubMed: 11176197]
10. Borghi CC, Arrigo FG. Recent evidence of the role of omega-3 polyunsaturated faty acids on blood pressure control and hypertension-related complications. Future Lipidology. 2006; 1(5): 569–577.
11. Agriculture USDo. What We Eat In America. 2011. [website] [cited 12/10/10]; Available from: http://www.ars.usda.gov/Services/docs.htm?docid=13793
12. What We Eat In America, NHANES. 2010. cited Available from: http://www.ars.usda.gov/Services/docs.htm?docid=13793
13. Mori TA. Omega-3 fatty acids and blood pressure. Cellular and molecular biology (Noisy-le-Grand, France). 56(1):83–92.
14. Mori TA. Omega-3 fatty acids and blood pressure. Cellular and molecular biology (Noisy-le-Grand, France). 2010; 56(1):83–92.
15. Search on DHA and tablet supplements. 2011. [website] [cited 2011 04/01]; website]. Available from: http://www.amazon.com
16. Theobald HE, Goodall AH, Sattar N, Talbot DC, Chowienczyk PJ, Sanders TA. Low-dose docosahexaenoic acid lowers diastolic blood pressure in middle-aged men and women. The Journal of nutrition. 2007 Apr; 137(4):973–978. [PubMed: 17374663]
17. Dokholyan RS, Albert CM, Appel LJ, Cook NR, Whelton P, Hennekens CH. A trial of omega-3 fatty acids for prevention of hypertension. The American journal of cardiology. 2004 Apr 15; 93(8):1041–1043. [PubMed: 15081453]
18. Ueshima H, Stamler J, Elliott P, Chan Q, Brown IJ, Carnethon MR, et al. Food omega-3 fatty acid intake of individuals (total, linolenic acid, long-chain) and their blood pressure: INTERMAP study. Hypertension. 2007 Aug; 50(2):313–319. [PubMed: 17548718]
19. Verdecchia P, Porcellati C, Schillaci G, Borgioni C, Ciucci A. Ambulatory blood pressure monitoring in mild hypertension. Circulation. 1995 Jun 1; 91(11):2852–2853. [PubMed: 7758194]
20. Staessen JA, Thijs L, Fagard R, O'Brien ET, Clement D, de Leeuw PW, et al. Predicting cardiovascular risk using conventional vs ambulatory blood pressure in older patients with systolic hypertension. Systolic Hypertension in Europe Trial Investigators. Jama. 1999 Aug 11; 282(6): 539–546. [PubMed: 10450715]

21. Yao JK, Leonard S, Reddy RD. Membrane phospholipid abnormalities in postmortem brains from schizophrenic patients. Schizophrenia research. 2000; 42(1):7–17. [PubMed: 10706981]
22. Paffenbarger RS Jr, Hyde RT, Wing AL, Lee IM, Jung DL, Kampert JB. The association of changes in physical-activity level and other lifestyle characteristics with mortality among men. The New England journal of medicine. 1993 Feb 25; 328(8):538–545. [PubMed: 8426621]
23. Preacher, KLG. Calculation for the Sobel Test. 2010. [cited; Available from: http://peopl.ku.edu/~preacher/sobel/sobel.htm
24. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985; 28:412–419. [PubMed: 3899825]
25. Mori TA, Bao DQ, Burke V, Puddey IB, Beilin LJ. Docosahexaenoic acid but not eicosapentaenoic acid lowers ambulatory blood pressure and heart rate in humans. Hypertension. 1999 Aug; 34(2):253–260. [PubMed: 10454450]
26. Bao DQ, Mori TA, Burke V, Puddey IB, Beilin LJ. Effects of dietary fish and weight reduction on ambulatory blood pressure in overweight hypertensives. Hypertension. 1998 Oct; 32(4):710–717. [PubMed: 9774368]
27. Cicero AF, Ertek S, Borghi C. Omega-3 polyunsaturated fatty acids: their potential role in blood pressure prevention and management. Current vascular pharmacology. 2009 Jul; 7(3):330–337. [PubMed: 19601857]
28. Radaelli A, Cazzaniga M, Viola A, Balestri G, Janetti MB, Signorini MG, et al. Enhanced baroreceptor control of the cardiovascular system by polyunsaturated Fatty acids in heart failure patients. Journal of the American College of Cardiology. 2006 Oct 17; 48(8):1600–1606. [PubMed: 17045894]
29. Kimura SMMTMHN, Endo T, Hirafuji M, Yamada M. Antihypertensive effect of dietary docosahexa-enoic acide in stroke-prone spontaneously hypertensive rats. Bigenic amines. 1995; 11(3):195–203.
30. Grassi G, Seravalle G, Bertinieri G, Turri C, Dell'Oro R, Stella ML, et al. Sympathetic and reflex alterations in systo-diastolic and systolic hypertension of the elderly. Journal of hypertension. 2000 May; 18(5):587–593. [PubMed: 10826562]
31. Begg DP, Sinclair AJ, Stahl LA, Garg ML, Jois M, Weisinger RS. Dietary protein level interacts with omega-3 polyunsaturated fatty acid deficiency to induce hypertension. Am J Hypertens. 2010 Feb; 23(2):125–128. [PubMed: 19893499]
32. Grassi G. Sympathetic neural activity in hypertension and related diseases. Am J Hypertens. 2010 Oct; 23(10):1052–1060. [PubMed: 20651696]
33. Palatini P, Julius S. The role of cardiac autonomic function in hypertension and cardiovascular disease. Current hypertension reports. 2009 Jun; 11(3):199–205. [PubMed: 19442329]
34. Chen JM, Heran BS, Perez MI, Wright JM. Blood pressure lowering efficacy of beta-blockers as second-line therapy for primary hypertension. Cochrane database of systematic reviews (Online). 2010; (1):CD007185. [PubMed: 20091622]
35. Chen JM, Heran BS, Perez MI, Wright JM. Blood pressure lowering efficacy of beta-blockers as second-line therapy for primary hypertension. Cochrane database of systematic reviews (Online). (1):CD007185.

Table 1

Participant Characteristics (n=265)[1]

	Mean	SD
Age	**44.7**	**±6.7**
Gender (% male)	**49%**	**--**
Race (% Caucasian)	**89%**	**--**
BMI (kg/m^2)	**26.1**	**±4.3**
Total cholesterol (mg/dl)	**200**	**±35**
Clinic BP (mm Hg)	**114.7/75.5**	**±11.8/8.7**
Clinic HR (BPM)	**67.7**	**±9.3**
24 hr Ambulatory BP (mm Hg)	**121.9/72.2**	**±14.0/7.1**
24 hr Ambulatory HR (BPM)	**76.5**	**9.6**
Ambulatory Awake BP (mm Hg)	**124.7/75.2**	**±14.0/7.1**
Ambulatory Awake HR (BPM)	**80.2**	**±10.3**
Ambulatory Sleep BP (mm Hg)	**113.6/63.5**	**±17.1/9.2**
Ambulatory Sleep HR (BPM)	**65.8**	**±10.2**
Physical Activity (calorie/week)	**2402**	**±1690**
Dietary Sodium (mg/day)[2]	**3654 (3355)**	**±1615 (2149)**
Dietary Potassium (mg/day)[2]	**2971 (2705)**	**±1177 (1564)**
Dietary Magnesium (mg/day)[2]	**335 (297)**	**±146 (170)**
EPA (mol %)[2]	**0.50 (0.40)**	**±0.40 (0.27)**
DHA (mol %)[2]	**1.53 (1.38)**	**±0.67 (0.83)**

[1] Residents of the Pittsburgh metropolitan area and enrolled between 2001 and 2005.

[2] Due to skewed distribution, median and interquartile range are provided in parentheses.

Table 2

Regression Models of Fatty Acids in relation to Clinic BP and Pulse Rate

	Systolic BP (mm Hg)			Diastolic BP (mm Hg)			Pulse (BPM)		
	β	**P**	**Adjusted R^2**	**β**	**P**	**Adjusted R^2**	**β**	**P**	**Adjusted R^2**
Step 1			0.247			0.214			0.093
Sex	−0.358	<0.001		−0.278	<0.001		0.159	0.02	
Age	0.188	0.001		0.156	<0.001		−0.136	0.03	
Race	0.135	0.020		0.153	0.008		−0.026	0.67	
BMI	0.225	<0.001		0.264	<0.001		0.088	0.18	
Sodium	−0.042	0.48		−0.063	0.30		−0.020	0.76	
Physical Activity	−0.006	0.91		−0.008	0.89		−0.277	<0.001	
Step 2 (entered in separate models)									
DHA	−0.049	0.37	0.247	**−0.121**	**0.03**	0.225	**−0.179**	**0.003**	0.121
EPA	−0.032	0.56	0.246	−0.082	0.15	0.218	**−0.124**	**0.04**	0.105

Table 3

Regression Models of Fatty Acids in relation to 24-hour Ambulatory BP and Pulse Rate

	Systolic BP (mm Hg)			Diastolic BP (mm Hg)			Pulse (BPM)		
	β	**P**	**Adjusted R^2**	**β**	**P**	**Adjusted R^2**	**β**	**P**	**Adjusted R^2**
Step 1			0.253			0.190			0.120
Sex	−0.436	<0.001		−0.329	<0.001		0.274	<0.001	
Age	−0.002	0.97		0.172	0.003		−0.049	0.41	
Race	0.094	0.09		0.174	0.003		0.062	0.31	
BMI	0.138	0.02		0.156	0.01		0.164	0.01	
Sodium	0.075	0.21		0.005	0.93		−0.019	0.77	
Physical Activity	0.061	0.28		0.001	0.99		−0.209	0.001	
Step 2 (entered in separate models)									
DHA	−0.052	0.35	0.253	**−0.135**	**0.02**	0.204	−0.110	0.07	0.129
EPA	−0.004	0.94	0.250	−0.056	0.32	0.190	−0.013	0.83	0.117

Table 4

Regression Models of Fatty Acids in relation to Ambulatory Awake BP and Pulse Rate

	Systolic BP (mm Hg)			Diastolic BP (mm Hg)			Pulse (BPM)		
	β	**P**	**Adjusted R^2**	**β**	**P**	**Adjusted R^2**	**β**	**P**	**Adjusted R^2**
Step 1			0.254			0.163			0.099
Sex	−0.468	<0.001		−0.338	<0.001		0.244	<0.001	
Age	0.002	0.97		0.163	0.005		−0.047	0.43	
Race	0.059	0.29		0.149	0.01		0.055	0.37	
BMI	0.102	0.08		0.104	0.10		0.127	0.05	
Sodium	0.048	0.42		−0.010	0.88		−0.027	0.68	
Physical Activity	0.043	0.44		−0.015	0.80		−.208	0.001	
Step 2 (entered in separate models)									
DHA	−0.062	0.25	0.260	**−0.164**	**0.004**	0.187	−0.109	0.070	0.107
EPA	−0.015	0.78	0.256	−0.055	0.34	0.163	−0.008	0.90	0.096

Table 5

Regression Models of Fatty Acids in relation to Asleep BP and Pulse Rate

	Systolic BP (mm Hg)			Diastolic BP (mm Hg)			Pulse (BPM)		
	β	**P**	**Adjusted R^2**	**β**	**P**	**Adjusted R^2**	**β**	**P**	**Adjusted R^2**
Step 1			0.162			0.176			0.099
Sex	−0.270	<0.001		−0.244	<0.001		0.258	<0.001	
Age	0.005	0.93		0.202	0.001		−0.040	0.51	
Race	0.168	0.006		0.219	<0.001		0.054	0.39	
BMI	0.185	0.004		0.199	0.002		0.167	0.01	
Sodium	0.114	0.08		0.006	0.93		−0.052	0.44	
Physical Activity	0.102	0.09		0.046	0.20		−0.159	0.01	
Step 2 (entered in separate models)									
DHA	0.016	0.79	0.159	−0.040	0.50	0.174	−0.084	0.17	0.102
EPA	0.025	0.67	0.160	−0.039	0.51	0.174	0.006	0.93	0.095