ORIGINAL ARTICLE

Serum long-chain omega-3 polyunsaturated fatty acids and risk of orthostatic hypotension

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Long-chain omega-3 polyunsaturated fatty acids (PUFAs) from fish have been shown to lower blood pressure. However, there is little information about the association with orthostatic hypotension, for which hypertension is a risk factor. We investigated the associations between serum long-chain omega-3 PUFAs and orthostatic hypotension in 1666 middle-aged or older men and women free of cardiovascular disease (CVD), diabetes or hypertension in 1998–2001 in the Kuopio Ischemic Heart Disease Risk Factor Study (KIHD) in eastern Finland. We also investigated the associations with mercury exposure, a major source of which is fish, and which has been associated with higher CVD risk in KIHD. Orthostatic hypotension was defined as decrease in systolic blood pressure of at least 20 mm Hg or diastolic blood pressure of at least 10 mm Hg within 1 min of standing. Orthostatic hypotension was found in 146 participants (8.8%). The mean serum concentrations were 1.67% (s.d. 0.92) for eicosapentaenoic acid, 0.79% (s.d. 0.16) for docosapentaenoic acid (DPA) and 2.78 (s.d. 0.92) for docosahexaenoic acid of all serum fatty acids. The mean pubic hair mercury concentration was $1.5 \mu\text{g g}^{-1}$ (s.d. 1.6). We did not find statistically significant associations between the serum long-chain omega-3 PUFAs or pubic hair mercury and risk of orthostatic hypotension, except for DPA. Those in the highest vs. the lowest serum DPA tertile had multivariate-adjusted 41% lower odds for orthostatic hypotension (95% confidence interval 7–63%, P -trend = 0.02). Serum long-chain omega-3 PUFAs or mercury exposure were not associated with the risk of orthostatic hypotension, except for the inverse association with DPA.

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INTRODUCTION

Orthostatic hypotension is common in the elderly, occurring in 15–30% among those >65 years of age, and it is associated with higher levels of mortality and morbidity, including cardiovascular disease (CVD), falls and fractures.^{1,2} Orthostatic hypotension can occur acutely secondary to, for example, medication use or fluid or blood loss, or it can be a chronic condition as a result of altered blood pressure regulation mechanisms, CVD or autonomic nervous system dysfunction.^{1–3} Increase in systolic blood pressure with increasing age is one of the major determinants of orthostatic hypotension development.^{1,2}

The long-chain omega-3 polyunsaturated fatty acids (PUFAs) from fish, eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been associated with lower risk of hypertension in population studies.^{4–9} In addition, fish oil supplementation has been shown to lower blood pressure, especially in hypertensive subjects who were not taking hypertension medication.¹⁰ The beneficial effects of the long-chain omega-3 PUFAs on blood pressure regulation may be explained by, for example, improved vasodilation and vasoreactivity and arterial compliance.¹¹

Based on the potential benefits of the long-chain omega-3 PUFAs in hypertension prevention, we hypothesized that these fatty acids might

also be associated with lower risk of orthostatic hypotension in older people. Currently, there is very little information on the association between the long-chain omega-3 PUFAs and orthostatic hypotension. Therefore, the aim of this study was to investigate the associations between serum long-chain omega-3 PUFA concentrations, an objective biomarker of exposure, and orthostatic hypotension in middle-aged or older men and women in the Kuopio Ischemic Heart Disease Risk Factor Study (KIHD) population in Eastern Finland. Previously, higher serum long-chain omega-3 PUFA concentration was associated with lower blood pressure in this study population.⁸ We also investigated the association between mercury exposure and risk of orthostatic hypotension, because fish is the major source of methylmercury and mercury exposure has been associated with a higher risk of CVD in the KIHD cohort.^{9,12} The previous findings for the association between mercury exposure and hypertension have been mixed,^{11,13–19} but little evidence exists for the association with orthostatic hypotension.

METHODS

Study population

The KIHD is an ongoing population-based cohort study designed to investigate risk factors for CVD and other chronic diseases in middle-aged and older men

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and women in Eastern Finland.²⁰ The study protocol was approved by the Research Ethics committee of the University of Kuopio. All subjects gave their written informed consent. The KIHd complies with the principles of the Declaration of Helsinki.

The baseline examinations of the KIHd were conducted between 1984 and 1989 to a random sample of men living in the city of Kuopio and neighboring rural communities. A total of 2682 men aged 42, 48, 54 or 60 years at baseline were recruited into two cohorts. The first cohort consisted of 1166 men (83.3% of those eligible) aged 54 years, enrolled between 1984 and 1986, and the second cohort included 1516 men (82.6%) aged 42, 48, 54 or 60 years, enrolled between 1986 and 1989. During the years 1998–2001, all men from the second cohort were invited to the 11-year re-examinations of the study, and 854 men (85.6%) participated. These examinations were also the baseline for 920 postmenopausal women (78.4% of the 1173 eligible women) from the same area, aged 53–73 years. For the present study, we excluded those with missing data on orthostatic hypotension ($n=6$) or on serum fatty acids ($n=16$) or pubic hair mercury ($n=86$) at the 11-year re-examinations, leaving 1666 participants (837 men and 829 women) for the analyses.

Blood pressure measurements

All blood pressure measurements were performed by specially trained nurses. Resting blood pressure was measured between 0800 and 1000 hours on the first examination day by one nurse with a random-zero mercury sphygmomanometer (Bodenseewerk Perkin-Elmer GmbH, Überlingen, Germany) with cuff-size of $120 \times 350 \text{ mm}^2$ or $150 \times 430 \text{ mm}^2$. The measuring protocol included, after a supine rest of 5 min, three measurements in supine position with 5-min intervals, one measurement in standing position 1 min after standing and two

measurements in sitting position with 5-min intervals. The mean of all six systolic pressure values was used in the present analyses as the systolic blood pressure and the mean of all six diastolic measurements as diastolic blood pressure. Hypertension was defined as blood pressure $>140/90 \text{ mm Hg}$ at the follow-up examinations or treatment for hypertension. Orthostatic hypotension was defined as a decrease in systolic blood pressure of at least 20 mm Hg or diastolic blood pressure of at least 10 mm Hg within 1 min of standing.

Serum fatty acids

Serum total fatty acids were determined from frozen samples with a NB-351 capillary column (HNU-Nordion, Helsinki, Finland) by a Hewlett-Packard 5890 Series II gas chromatograph (Hewlett-Packard Company, Avondale, PA, USA, since 1999 Agilent Technologies, USA) with a flame ionization detector. Serum was extracted with chloroform–methanol and fatty acids were methylated with methanol and sulfuric acid prior to gas chromatography. Each analyte had an individual reference standard and the analytes were quantified with an internal standard method using eicosane. Results for fatty acids were obtained in $\mu\text{mol l}^{-1}$ and in the data analyses proportion of a fatty acid from the total fatty acids was used. The coefficient of variation for repeated measurements of fatty acids ranged from 7% (palmitic acid 16:0) to 16% (lignoceric acid 24:0).

Other measurements

The subjects gave fasting blood samples between 0800 and 1000 hours on the examinations in 1998–2001. They were instructed to abstain from ingesting alcohol for 3 days and from smoking and eating for 12 h prior to giving the

Table 1 Baseline characteristics of the Kuopio Ischemic Heart Disease Risk Factor Study (KIHd) population

Characteristics	Serum EPA+DPA+DHA tertile (percentage of serum fatty acids)			P-value for trend
	1 (<3.53)	2 (3.53–4.72)	3 (>4.72)	
Number of participants	555	556	555	
Age (years)	62.5 (6.5)	62.7 (6.5)	63.2 (6.5)	0.24
Male sex (%)	56	48	47	0.002
Systolic blood pressure, mm Hg	137 (18)	135 (17)	135 (17)	0.30
Diastolic blood pressure, mm Hg	81 (9)	81 (9)	81 (9)	0.79
Body mass index (kg m^{-2})	27.9 (4.5)	27.9 (4.3)	27.6 (4.4)	0.31
Income (Euro)	15 276 (9154)	16 032 (10 083)	17 647 (14 237)	0.002
Education (years)	9.2 (3.1)	9.6 (3.5)	9.9 (3.6)	0.003
Leisure-time physical activity (kcal per day)	175 (197)	192 (224)	185 (176)	0.36
Pubic hair mercury ($\mu\text{g g}^{-1}$)	1.0 (1.3)	1.4 (1.6)	2.0 (1.8)	<0.001
Urinary potassium (mmol per day)	78.6 (23.5)	80.9 (23.1)	85.5 (24.5)	<0.001
Urinary sodium (mmol per day)	145.8 (55.5)	142.1 (53.2)	151.1 (58.0)	0.03
Current smoker (%)	18	10	11	0.001
Hypertension in family (%)	58	59	59	0.90
Aspirin use (%)	22	25	25	0.39
Number of drugs used	2.6 (2.5)	2.6 (2.4)	2.6 (2.3)	0.99
Medication use (%) ^a	47	47	45	0.66
Multivitamin use (%)	5	7	8	0.16
<i>Dietary intakes</i>				
Total energy (kcal per day)	1929 (612)	1816 (561)	1808 (557)	0.001
Fish (g per day)	24 (38)	40 (53)	77 (71)	<0.001
Meat and meat products (g per day)	135 (86)	130 (80)	116 (80)	0.001
Fruits and berries (g per day)	195 (174)	204 (161)	202 (143)	0.61
Vegetables (g per day) ^b	256 (113)	275 (126)	290 (123)	<0.001
Dairy (g per day)	507 (305)	479 (258)	464 (263)	0.04
Alcohol (g per week)	45 (198)	46 (83)	56 (114)	0.17

Abbreviations: DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid.

All values are mean (s.d.) or percentage.

^aMedications include drugs associated with orthostatic hypotension: angiotensin-converting enzyme inhibitors, diuretics, antihypertensives, beta-blockers, calcium channel blockers, vasodilators, nitrates, antidepressants, benzodiazepines, antipsychotics and antidepressants.

^bExcluding potatoes.

Table 2 Associations of serum n-3 polyunsaturated fatty acids and hair mercury with risk of orthostatic hypotension

	Serum long-chain omega-3 polyunsaturated fatty acid tertile			P for trend
	1 (n = 555)	2 (n = 556)	3 (n = 555)	
EPA+DPA+DHA, %	<3.53	3.53–4.72	>4.72	
Number of events	52	46	48	
Model 1	1	0.88 (0.58–1.34)	0.90 (0.59–1.37)	0.67
Model 2	1	0.89 (0.58–1.37)	0.87 (0.56–1.34)	0.55
EPA, %	<0.90	0.90–1.39	>1.39	
Number of events	61	39	46	
Model 1	1	0.61 (0.40–0.93)	0.73 (0.49–1.10)	0.20
Model 2	1	0.62 (0.40–0.95)	0.69 (0.45–1.05)	0.13
DPA, %	<0.62	0.62–0.76	>0.76	
Number of events	58	48	40	
Model 1	1	0.79 (0.53–1.20)	0.63 (0.41–0.98)	0.04
Model 2	1	0.79 (0.52–1.20)	0.59 (0.37–0.93)	0.02
DHA, %	<1.87	1.87–2.58	>2.58	
Number of events	50	41	55	
Model 1	1	0.82 (0.53–1.27)	1.12 (0.74–1.68)	0.52
Model 2	1	0.80 (0.51–1.24)	1.08 (0.71–1.66)	0.62
Hair mercury, $\mu\text{g g}^{-1}$	<0.29	0.29–0.93	>0.93	
Number of events	52	38	56	
Model 1	1	0.66 (0.42–1.02)	0.96 (0.64–1.44)	0.71
Model 2	1	0.67 (0.43–1.05)	0.91 (0.59–1.38)	0.98

Abbreviations: EPA, eicosapentaenoic acid; DPA, docosapentaenoic acid; DHA, docosahexaenoic acid.

Values are odds ratio (95% confidence interval).

Model 1 adjusted for age, gender and examination year.

Model 2 adjusted for the Model 1 and the history of hypertension in family, leisure-time physical activity, body mass index, alcohol intake, years of education, urinary potassium, urinary sodium, smoking status, history of cardiovascular disease, type 2 diabetes or cancer, systolic and diastolic blood pressure, number of drugs and drugs associated with orthostatic hypotension (angiotensin-converting enzyme inhibitors, diuretics, antihypertensives, beta-blockers, calcium channel blockers, vasodilators, nitrates, antidepressants, benzodiazepines, antipsychotics and antidepressants).

sample. Detailed descriptions of the determination of blood glucose, assessment of medical history and medications, family history of diseases, smoking and alcohol consumption have been published.²¹ Diabetes was defined as self-reported diabetes mellitus or fasting plasma glucose of $>6.9 \text{ mmol l}^{-1}$ or 2-h oral glucose tolerance test plasma glucose $>11.0 \text{ mmol l}^{-1}$ at the study examinations. Education was assessed in years by using self-administered questionnaire. Physical activity was assessed using the KIHD 12-Month Leisure-Time Physical Activity Questionnaire.²² Body mass index was computed as the ratio of weight in kilograms to the square of height in meters. Dietary intake of foods and nutrients was assessed at the time of blood sampling using 4-day food recording.²³ Mercury in pubic hair was determined by flow injection analysis–cold vapor atomic absorption spectrometry and amalgamation, as described.²⁴

Statistical analysis

After confirming that gender did not modify the associations between the serum fatty acids or pubic hair mercury and orthostatic hypotension (P -interactions >0.2), the associations were investigated in the whole study population. The relationships between baseline characteristics and serum EPA+docosapentaenoic acid (DPA)+DHA were explored by means and linear (for continuous variables) or logistic regression (for dichotomous variables). The associations between serum fatty acids and hair mercury with orthostatic hypotension were analyzed with logistic regression. Odds ratios were used to estimate the risk of orthostatic hypotension. The Model 1 was adjusted for age, gender and examination year. The Model 2 included the Model 1 and the history of hypertension in family, leisure-time physical activity, body mass index, alcohol intake, years of education, urinary potassium, urinary sodium, smoking status, history of CVD, type 2 diabetes or cancer, systolic and

diastolic blood pressure, number of drugs and drugs associated with orthostatic hypotension (angiotensin-converting enzyme inhibitors, diuretics, antihypertensives, beta-blockers, calcium channel blockers, vasodilators, nitrates, antidepressants, benzodiazepines, antipsychotics and antidepressants).

The cohort mean was used to replace missing values of covariates ($<5.2\%$ of values). Few participants reported using fish oil supplements ($n < 10$). Tests of linear trend across tertiles of serum fatty acids or hair mercury were conducted by assigning the median values for each category of exposure variable and treating those as a single continuous variable. Statistical significance of the interactions on a multiplicative scale was assessed by likelihood ratio tests with a cross-product term. All P -values were two-tailed ($\alpha = 0.05$). Data were analyzed with SPSS 21.0 for Windows (IBM, Armonk, NY, USA).

RESULTS

The mean serum concentrations were 1.67% (s.d. 0.92) for EPA, 0.79% (s.d. 0.16) for DPA and 2.78% (s.d. 0.92) for DHA of all serum fatty acids. The mean pubic hair mercury concentration was $1.5 \mu\text{g g}^{-1}$ (s.d. 1.6). Table 1 shows the characteristics of the KIHD population at baseline. Those with higher serum EPA+DPA+DHA were more likely to be women, have a higher education with higher income and higher hair mercury content with higher urinary potassium and sodium. They also had higher intake of fish and vegetables (excluding potatoes) and lower intake of dairy and meat and meat products. They were also less likely to smoke.

The number of subjects with orthostatic hypotension was 146 (83 men and 63 women, 8.8% of the study population). We did not find statistically significant associations between the serum long-chain

omega-3 PUFA concentrations and risk of orthostatic hypotension, except for DPA (Table 2). Those in the highest vs. the lowest serum DPA tertile had multivariate-adjusted 41% (95% CI 7–63%) lower odds for orthostatic hypotension (P -trend = 0.02).

We did not find statistically significant associations between pubic hair mercury content and risk of orthostatic hypotension (Table 2). Pubic hair mercury did not modify the associations between serum long-chain omega-3 PUFAs and orthostatic hypotension either (P -interactions > 0.05).

DISCUSSION

The results from this population-based cohort study of middle-aged and older men and women from Eastern Finland suggest that, except for the inverse association with DPA, higher serum concentrations of the long-chain omega-3 PUFAs were not associated with the risk of orthostatic hypotension. No associations were observed with mercury exposure either.

There is little prior information about the impact of the long-chain omega-3 PUFAs on orthostatic hypotension, but these fatty acids have been associated with lower blood pressure in population studies,^{4–8,19} and fish oil supplementation has been shown to lower blood pressure in randomized trials.¹⁰ Also in the KIH cohort, higher total serum long-chain omega-3 PUFA concentration was associated with lower blood pressure and the associations were similar with the individual long-chain omega-3 PUFAs, EPA, DPA and DHA.⁸ One of the major determinants of development of orthostatic hypotension is increase in systolic blood pressure with ageing.^{1,2} Therefore, the long-chain omega-3 PUFAs could also have benefits regarding prevention of orthostatic hypotension. However, in the current analysis we found an inverse association with the risk of orthostatic hypotension only with DPA. DPA can be synthesized endogenously from EPA or obtained from the diet, mainly from seafood.²⁵ Currently, much less is known about the health effects of DPA, when compared with the other long-chain omega-3 PUFAs, EPA and DHA.²⁶ However, in studies that have investigated all three long-chain omega-3 PUFAs, DPA appears to have similar inverse associations with the risk of CVD as EPA and DHA.^{9,27–32} Because so far few studies have evaluated the impact of DPA on blood pressure regulation with mixed findings,^{8,17,33} and even less is known about the impact of EPA, DPA or DHA on the risk of orthostatic hypotension, the results from our study should be interpreted cautiously.

We have previously shown that high hair mercury concentration attenuated the benefits of the long-chain omega-3 PUFAs on the risk of CVD in men in this study population.^{9,12} However, high hair mercury content was not associated with blood pressure, and it did not modify the inverse associations between the serum long-chain omega-3 PUFAs and blood pressure.⁸ Our findings indicate that moderate, long-term mercury exposure is not associated with orthostatic hypotension either. This suggest little effect of mercury on blood pressure regulation, concordant with the findings from other study populations.¹⁹

The main strength of this study is the use of established biomarkers of exposure, the circulating fatty acid concentrations and hair mercury, to investigate the associations with orthostatic hypotension. These biomarkers do not depend on study participants' recall ability, which ensures objectivity of the exposure variables and minimizes the chance of bias through misclassification and recall bias. The serum long-chain omega-3 PUFA concentration is an indicator of exposure during few previous weeks,³⁴ while the hair mercury indicates long-term exposure.³⁵ The additional strengths of this study include

extensive examinations on potential confounders and population-based recruitment.

In conclusion, our findings suggest that the long-chain omega-3 PUFAs or mercury exposure have little impact on the risk of orthostatic hypotension in ageing men and women. The role of DPA in blood pressure regulation warrants further studies.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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