Original Article: Fish consumption, omega-3 fatty acids, and environmental contaminants in relation to low-grade inflammation and early atherosclerosis

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ABSTRACT

Background Fish consumption and omega-3 polyunsaturated fatty acid (PUFA) intake are shown to protect from cardiovascular diseases (CVD). However, most fish contain environmental contaminants such as dibenzo-*p*-dioxins and dibenzofurans (PCDD/Fs), polychlorinated biphenyls (PCBs), and methylmercury (MeHg) that may have adverse effects on cardiovascular health.

Objective Our aim was to elucidate the associations of fish consumption, omega-3 PUFAs, environmental contaminants with low-grade inflammation, early atherosclerosis, and traditional CVD risk factors.

Methods The Health 2000 survey participants (n=1173) represented the general Finnish population and the Fishermen study participants (n=255) represented a population with high fish consumption and high exposure to environmental contaminants. Model-adjusted geometric means and tests for linear trend were calculated for CVD risk factors by tertiles of fish consumption and serum omega-3 PUFAs, and additionally in the Fishermen study only, by tertiles of serum PCDD/F+PCB, and blood MeHg.

Results Serum triglyceride decreased across omega-3 PUFA tertiles in both sexes and studies. Insulin resistance, C-reactive protein, tumour necrosis factor α, and interleukin 6 decreased across omega-3 PUFA tertiles among the Health 2000 survey participants. Among the Fishermen study men, insulin resistance and arterial stiffness indicated by β-stiffness index tended to increase and the RR estimate for carotid artery plaque tended to decrease across tertiles of PCDD/F+PCB and MeHg.

Conclusion Previously established hypotriglyceridemic and anti-inflammatory effects of omega-3 PUFAs were seen also in this study. The hypothesised favourable effect on insulin sensitivity and arterial elasticity was suggested to be counteracted by high exposure to environmental contaminants but the effect on plaque prevalence appeared not to be harmful.

Keywords: fish; omega-3; dioxin; PCB; methylmercury; inflammation; atherosclerosis

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Ethical approval: The study protocols have been approved by the ethical committee of the Hospital District of Helsinki and Uusimaa, and a written informed consent has been obtained from all participants.

1. Introduction

Many of the traditional risk factors for cardiovascular diseases (CVD) and diabetes, such as hypertension, dyslipidemia, and insulin resistance, are suspected to be favourably affected by high fish consumption and high intake of fish-derived long-chain omega-3 polyunsaturated fatty acids (PUFAs) (Calder and Yaqoob, 2009; Carpentier et al., 2006; Riediger et al., 2009). Further, omega-3 PUFAs have been observed to decrease the production of pro-inflammatory eicosanoids and cytokines and thus, fish consumption is believed to protect from diseases involving inflammatory processes (Calder, 2006; Wall et al., 2010). Fish consumption and omega-3 PUFA intake have also been suggested to slow the progression of atherosclerosis (Massaro et al., 2008) and to reduce arterial stiffness (Hall, 2009).

In contrast, most fish contain bioaccumulative environmental contaminants that have endocrine-disrupting potency and may have an adverse effect on cardiovascular health (Bushkin-Bedient and Carpenter, 2010). For example, high exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), the most toxic congener of polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/Fs), is hypothesised to increase the risk of circulatory diseases and diabetes (Consonni et al., 2008). In addition, PCDD/Fs, polychlorinated biphenyls (PCBs), and methyl mercury (MeHg) are suspected to have a capacity to increase both blood pressure and oxidative stress, alter lipid, glucose and insulin metabolism, and promote inflammatory processes (Everett et al., 2011; Hennig et al., 2007; Mozaffarian, 2009). Especially exposure to PCBs has lately been linked with obesity, dyslipidemia, insulin resistance (Lee et al., 2011) and the risk of diabetes (Airaksinen et al., 2011).

Although the benefits of fish consumption and omega-3 PUFAs have been extensively studied, some controversy still remains (Hooper et al., 2006; Salas-Salvado et al., 2011) and one explanation for conflicting findings might be competing effects of environmental contaminants in fish (He,

2009). More importantly, the benefits of fish consumption and omega-3 PUFA intake have rarely been studied in populations with high exposure to environmental contaminants. Our aim was to study the associations of habitual fish consumption and serum concentrations of fish-derived omega-3 PUFAs and environmental contaminants with chronic low-grade systemic inflammation, early signs of atherosclerosis, and traditional CVD risk factors taking into account the overall effect of beneficial and hazardous compounds in fish. We conducted the analyses in a sub-sample of the general Finnish population and among professional Baltic Sea area fishermen and their family members. The latter is a unique population with high fish consumption and high exposure to environmental contaminants.

2. Methods

2.1. Study populations

The nationally representative Health 2000 health examination survey (the Health 2000 survey) was conducted in 2001–2002 (Heistaro, 2008). A total of 1526 volunteers, aged 45–74 years, and living near the five university hospitals (Helsinki, Turku, Tampere, Kuopio, and Oulu) participated in a cardiovascular and diabetes sub-study and of those, 532 men and 641 women had complete dietary, health interview, and basic health examination data for the present work. Further, of those, 406 men and 499 women had also ultrasound data for the analyses of vascular structure and function.

The Nutrition, environment and health study (the Fishermen study) on professional Baltic Sea area fishermen, their wives, and other family members was conducted in 2004–2005 (Turunen et al., 2008). A total of 309 volunteers, aged 22–74 years, and living near Helsinki and Turku study centres participated in a health examination study and of those, 123 men and 132 women had complete dietary, health questionnaire, and basic health examination data for the present work. Further, of those, 84 men and 90 women had also ultrasound data for the analyses of vascular structure and function.

Both studies were coordinated by the National Institute for Health and Welfare (THL) in Finland. The studies were conducted according to similar study protocols and the guidelines laid down in the Declaration of Helsinki and Uniform Requirements for manuscripts submitted to Biomedical journals. The study protocols were approved by the ethical committee of the Hospital District of Helsinki and Uusimaa, and a written informed consent was obtained from all participants.

2.2. Dietary data

In both studies, diet was assessed by the same calibrated (i.e., determined to have relative validity) self-administered 128-item food frequency questionnaire (FFQ) designed to cover the whole diet and the use of dietary supplements (such as fish oil capsules) over the past 12 months (Männistö et al., 1996; Paalanen et al., 2006). Consumption of fish and other foods and the intakes of alcohol and salt (g/day) were calculated with the national Fineli® Finnish Food Composition Database. Dietary data has been described in detail elsewhere (Turunen et al., 2010).

2.3. Laboratory analyses

Blood samples were drawn from antecubital vein after 10–12 hours of fasting. Serum concentrations of fatty acids were analysed using a gas chromatograph and flame ionisation detector (Jula et al., 2005). The sum of eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA), and docosahexaenoic acid (DHA) (namely omega-3 PUFAs) was calculated as a proportion from all serum fatty acids (% FAs).

Serum total cholesterol and triglyceride concentrations were analysed by spectrophotometric enzymatic method, high-density lipoprotein (HDL, mmol/l) cholesterol by a direct method, glucose (mmol/l) by hexokinase method, and insulin (mU/l) by microparticle enzyme immunoassay. Homeostasis model assessment (HOMA) indexes, namely insulin resistance index (HOMA-IR) and pancreatic β-cell function (HOMA-%B), were calculated using formulas listed in Appendix.

Serum concentrations of highly sensitive C-reactive protein (CRP, mg/l), tumour necrosis factor α (TNF-α, ng/l), and interleukin 6 (IL-6, ng/l) were analysed using a solid-phase enzyme-labelled

chemiluminescent immunometric assay in the Health 2000 survey. In the Fishermen study, CRP was analysed immunoturbidimetrically. Participants with CRP<10 mg/l were included in the study.

In the Fishermen study only, serum concentrations of 17 PCDD/F and 37 PCB congeners were analysed gravimetrically from serum fat using a high resolution mass spectrometer equipped with a gas chromatograph. The method has been described in detail elsewhere (Kiviranta et al., 2002). PCDD/Fs and PCBs were expressed as toxic equivalent quantity (TEq) recommended by the World Health Organization (WHO). The sum of PCDD/F-TEq and PCB-TEq (PCDD/F+PCB-TEq, pg/g fat) was calculated. Blood MeHg concentration (ng/ml) was analysed from whole blood using an isotope dilution-gas chromatograph/mass spectrometer (Airaksinen et al., 2010). Blood samples to analyse environmental contaminants were not available in the Health 2000 survey.

2.4. Vascular measurements

Intima media thickness (IMT, mm) and arterial diameter change according to pulse pressure (ADC, mm) were measured from the right common carotid artery (CCA) at the level of the carotid bifurcation by high-resolution B-mode ultrasound. The method has been described in detail elsewhere (Niiranen et al., 2007; Sipila et al., 2011). The presence of formed atherosclerotic plaques in the carotid artery, defined as a focal raised lesion of >1.5 mm in size in at least one of the images of the carotid bulb, was determined. Measures for arterial stiffness, namely carotid artery compliance (CAC, %/10 mmHg), Young's elastic modulus (YEM, kPa), and β-stiffness index (SI), were calculated based on ADC using formulas listed in Appendix. Participants with all six arterial diameter measurements (approximately 90% of those who had participated in vascular measurements) were included in the analyses concerning ultrasonographic variables.

2.5. Body composition, blood pressure and other basic health characteristics

Body mass index (BMI) was calculated using measured weight and height. Blood pressure was measured three times from the right brachial artery by an electronic sphygmomanometer (OMRON HEM 722C/OMRON M4, Omron Corporation, Japan) in sitting position after a 10 minute rest. For the calculations of the vascular markers, blood pressure was measured again three times in supine position directly before the ultrasound examination. Data on smoking, physical activity, and the use of insulin, oral glucose lowering drugs, lipid modifying drugs (such as statins), and blood pressure lowering drugs were obtained from a structured interview and a self-administered health questionnaire in the Health 2000 survey and from the self-administered health questionnaire in the Fishermen study.

2.6. Statistical analyses

For the primary analyses (Tables 2–5), the participants were categorised into tertiles according to their non-transformed total fish consumption and serum omega-3 PUFAs, and additionally in the Fishermen study only, according to their serum PCDD/F+PCB-TEq and blood MeHg. Due to skewed variable distributions, all continuous variables except for age and blood pressure were transformed according to natural logarithm. After log transformations, the normality of the residuals was satisfactory. Each log-transformed risk factor or marker was treated as a response variable at a time, and their model-adjusted geometric means were calculated by the above mentioned tertiles using GLM procedure in the Statistical Analysis Systems (SAS) and tested for linear trend. Since the geometric means for the tertiles were not equally spaced, the coefficients for linear contrasts were produced by SAS/IML software. Adjusted risk ratio (RR) for the presence of atherosclerotic plaque in the carotid artery wall was calculated by the above mentioned tertiles using a Poisson

regression model with robust error variance and GENMOD procedure in SAS, and tested for linear trend.

To assess the shape of the studied associations and to evaluate the reliability of the results especially in the Fishermen study, an additive model with thin-plate regression spline was applied in the multiple generalised cross-validation package (mgcv) for R Statistical Software (Wood, 2006). The additive model is a non-parametric extension of a linear model for Gaussian response, and it allows the data to "speak for themselves" because a smoothing function does not assume a rigid form for the dependence. Continuous (instead of categorised) fish consumption, serum omega-3 PUFAs, serum PCDD/F+PCB-TEq, and blood MeHg were treated as smoothed predictors. Scatter plots with regression curves and approximate 95% CIs for selected associations are presented in Figure 1.

The geometric means, RRs, and regression splines were adjusted for age, smoking, physical activity, vegetable, fruit, berry, and oil consumption, salt and alcohol intake, and the use of insulin, blood glucose lowering drugs, lipid modifying agents, and antihypertensives. In addition, the means and RRs were adjusted for traditional CVD risk factors (BMI, non-HDL cholesterol, serum triglycerides, insulin resistance, and systolic blood pressure). Vascular markers were additionally adjusted for inflammatory markers. Potential negative confounding was controlled for by adjusting the means and RRs across omega-3 PUFA tertiles for environmental contaminants and geometric means and RRs across tertiles of environmental contaminants for omega-3 PUFAs. The covariates were chosen based on a common knowledge on cardiovascular risk factors. Vegetable, fruit, berry, and oil consumption were included in the models since they were positively associated with fish consumption based on our previous study (Turunen et al., 2011).

3. Results

Compared with the Health 2000 survey men and women, the geometric means for fish consumption and serum omega-3 PUFAs were approximately 80% higher among the Fishermen study men and, respectively, 40% and 70% higher among the Fishermen study women (Table 1).

In the Health 2000 survey, serum HDL cholesterol increased and serum triglyceride decreased in both sexes, and serum insulin and insulin resistance measured by HOMA-IR index decreased among the women across serum omega-3 PUFA tertiles (Table 2). Additionally among the women, BMI, waist circumference and pancreatic β-cell function measured by HOMA-%B index decreased across omega-3 PUFA tertiles. Regarding markers of inflammation and early atherosclerosis, serum TNF-α and IL-6 decreased across omega-3 PUFA tertiles in both sexes whereas serum CRP decreased across omega-3 PUFA tertiles only among the women. Arterial stiffness measured by β-stiffness index decreased across omega-3 PUFA tertiles only among the men (Table 3). Overall, similar but weaker trends were seen across fish consumption tertiles.

In the Fishermen study, many of the observed linear trends were statistically non-significant, and thus, they are referred here to as tendencies towards a linear trend. Serum triglyceride decreased across serum omega-3 PUFA tertiles among the men, and there was a tendency towards a decreasing trend among the women (Table 2). Among the men, serum CRP had a tendency to decrease across fish consumption tertiles (Table 2), and the RR estimate for atherosclerotic plaque in the carotid artery decreased across blood MeHg tertiles and had a tendency to decrease across tertiles of serum PCDD/F+PCB-TEq (Table 5).

Some unhealthy trends were also observed in the Fishermen study. Among the men, serum glucose, serum insulin, and HOMA-IR index had a tendency to increase especially across fish consumption, serum PCDD/F+PCB-TEq, and blood MeHg tertiles (Tables 3 and 5). Additionally, carotid artery compliance decreased and β-stiffness index increased across omega-3 PUFA, PCDD/F+PCB-TEq, and MeHg tertiles among the men (Tables 3 and 5). Among the women, serum glucose concentration increased across MeHg tertiles, HOMA-%B tended to decrease across PCDD/F+PCB-TEq tertiles, and serum CRP tended to increase across MeHg tertiles (Table 4).

In both studies, all the above mentioned results stayed essentially the same after additional adjusting for traditional CVD risk factors (BMI, non-HDL cholesterol, serum triglycerides, insulin resistance, systolic blood pressure) and the use of fish oil supplements, and regarding vascular markers, also after additional adjusting for inflammatory markers (data not shown). The only detectable change was seen when the linear trends in serum insulin and insulin resistance slightly attenuated after adjusting for BMI. Furthermore, the observed trends especially in inflammatory markers among the Health 2000 survey men and in the RR estimate for carotid artery plaque among the Fishermen study men were attenuated when obese (BMI≥30) individuals were excluded. To control for negative confounding in the Fishermen study, means across omega-3 PUFA tertiles were additionally adjusted for environmental contaminants and vice versa but it did not change the results.

The regression curves produced by the additive model gave reassurance that a linear trend test could be applied for the studied associations. In addition, the shapes of the curves supported the conclusions made based on the model-adjusted means. Increasing trends in insulin resistance and β-stiffness index and a decreasing trend in the risk of carotid artery plaque across tertiles of environmental contaminants among the Fishermen study men are visualised in Figure 1.

4. Discussion

In the Health 2000 survey, a beneficial decreasing trend along with increasing serum fish-derived omega-3 PUFA concentration was observed in serum triglyceride, inflammatory markers, insulin resistance measured by HOMA-IR index (only among the women), and arterial stiffness measured by β-stiffness index (only among the men). Except for serum triglyceride concentration, these beneficial trends were not clearly seen in the Fishermen study. On the contrary, an increasing trend in insulin resistance and arterial stiffness was observed along with increasing serum omega-3 PUFAs and environmental contaminants among the men. However, the risk of atherosclerotic plaque in the carotid artery tended to decrease along with increasing contaminant concentrations. The results stayed essentially the same regardless of adjustments.

4.1. Strengths and limitations

We utilised two separate study populations of which the larger was a sub-sample of the general population of Finland with an exceptionally high response rate. The smaller was a unique population of professional Baltic Sea area fishermen and their family members. Among the men in this high-exposure population, fish consumption and serum concentrations omega-3 PUFAs and environmental contaminants were almost twofold when compared with the males representing the general population of Finland (Turunen et al., 2011; Turunen et al., 2008). Furthermore, the fishermen's serum TCDD concentration was comparable to that measured among the residents in the second highest exposure zone B in Seveso Italy after the industrial accident (Pesatori et al., 2009). The multidisciplinary data included several exposures and risk factors, and both omega-3 PUFAs and environmental contaminants were simultaneously included into the models to control

for potential negative confounding. In addition to testing for linear trend, we decided to present model-adjusted means by tertiles to enable one to explore also possible non-linear associations.

Due to cross-sectional setting, causality could not be established in the present work. Another limitation was the small size of the Fishermen study population which could, at least partially, explain why some of the hypothesised associations were not detectable or some of the apparent linear tendencies across tertiles did not reach statistical significance. However, the regression curves produced by the additive model supported the conclusions made based on the model-adjusted means suggesting that the results of the primary analyses were reliable. In addition, a decrease in serum triglyceride concentration across serum omega-3 PUFAs was observed also in the Fishermen study which gave reassurance that at least strong associations could be detectable. Another limitation is the lack of blood samples to analyse environmental contaminants from the general population. Additionally, data on cooking method was not available but it may not be a problem since according to unpublished data from the Fishermen study, the only heavily processed fish dish commonly used in Finland, fish fingers, consisted only 1% of the total fish consumption. Pan-frying was the most common single cooking method for fish consisting 25% of all used methods but cooking and oven-baking combined were as common as pan-frying.

4.2. Methodology

The analyses were performed separately for men and women due to potential metabolic and other differences between the sexes. Further, tertiles were considered the most appropriate due to the small size of the Fishermen study. Total fish consumption was preferred since the analyses conducted separately for fatty and lean fish consumption yielded similar results (data not shown). Similarly, total serum omega-3 PUFA concentration was preferred since there were only subtle

differences in the results when EPA and DHA were considered separately (data not shown). More specifically, trends in HDL cholesterol and IMT were more evident across EPA tertiles, and trends in blood pressure, serum glucose, and the risk of carotid artery plaque were more evident across DHA tertiles in the general population sub-sample (data not shown). Many of the trends observed across omega-3 PUFA tertiles were weaker or even non-existent across fish consumption tertiles which is expected since the FFQ measures long-term diet whereas serum concentrations are absolute measures and markers of short-term dietary intake.

The studied associations were adjusted for various combinations of covariates, for example traditional CVD risk factors (BMI, non-HDL cholesterol, serum triglycerides, insulin resistance, and systolic blood pressure). Additionally in the Fishermen study, potential negative confounding (Choi et al., 2008) was controlled for by adjusting means across omega-3 PUFA tertiles for environmental contaminants and vice versa. However, the models were stable regardless of large number of covariates, and the adjustments did not essentially change the results. In addition, we entered fish consumption and omega-3 PUFAs simultaneously into the models. As a result, models remained stable and the estimates for omega-3 PUFAs remained essentially the same. However, when studying the association between fish consumption and cardiovascular risk factors, adjusting for omega-3 PUFAs attenuated some of the observed trends especially in serum triglyceride concentration.

In multiple regression modelling, over-adjustment and multicollinearity are potential problems. For example, BMI is probably an intermediate variable in the causal pathway of many of the studied associations in the present work. Thus, BMI and other traditional CVD risk factors were omitted from the reported model. Regarding multicollinearity, energy intake caused multicollinearity with food consumption variables and thus, it was not included in the models. Otherwise, multicollinearity was not a problem based on pairwise Pearson correlation coefficients between the

covariates (commonly around 0.2 and, at the highest, 0.6–0.7 between oil and salt intake) and the collinearity diagnostics (e.g., condition index).

4.3. Insulin sensitivity

Intervention studies among healthy individuals (Damsgaard et al., 2008; Giacco et al., 2007; Lara et al., 2007; Rizza et al., 2009) and many cohort studies (Dewailly et al., 2002; Lee et al., 2008; Nogi et al., 2007) have seen no association between fish consumption or omega-3 PUFA intake and glucose and insulin metabolism. Intervention studies among high-risk individuals have yielded inconsistent results. For example, among diabetics, both a decrease (Mostad et al., 2006) and an increase (Karlstrom et al., 2011) in insulin sensitivity have been observed. In addition, an increase has also been observed among obese individuals (Ramel et al., 2008) which implies that the beneficial effect might be best observable among individuals with metabolic syndrome (Nigam et al., 2009). The fact that metabolic syndrome and diabetes are common in Finland could explain why beneficial inverse association between fish consumption or serum omega-3 PUFAs and insulin resistance measured by HOMA-IR was observed among women in the Health 2000 survey.

With regard to unhealthy effects, serum insulin concentration and insulin resistance tended to increase along with increasing serum PCDD/F+PCB-TEq and blood MeHg concentrations among the men in the Fishermen study. This contradictory result could be, at least partly explained by environmental contaminants since a similar adverse trend has been observed previously among the Inuit (Ebbesson et al., 2007) who are known to eat a lot of potentially contaminated marine mammals and fish. Regarding non-dietary exposure, an increasing insulin resistance has been observed among residents near a closed pentachlorophenol and chlor-alkali factory along with

increasing serum PCDD/F and blood mercury concentrations (Chang et al., 2010) and among Vietnam veterans (Kern et al., 2004) along with increasing serum TCDD concentration.

Additionally in the present work, a tendency towards a decreasing pancreatic β-cell function measured by HOMA-%B was observed along with increasing fish consumption and serum omega-3 PUFAs among the women in the Health 2000 survey and along with increasing serum PCDD/F+PCB-TEq among the women in the Fishermen study. A similar inverse association between β-cell function and dioxin-like and non-dioxin-like PCBs has been observed among the Greenland Inuit (Jorgensen et al., 2008) who have even higher serum concentrations of omega-3 PUFAs (Thorseng et al., 2009) and environmental contaminants (Bjerregaard et al., 2001; Jorgensen et al., 2008) than in the present work. Regarding the women in the Fishermen study, a weak decreasing trend could be explained by relatively high exposure to environmental contaminants. In contrast, exposure to environmental contaminants was presumably lower among the women in the Health 2000 survey. This was inferred from their lower fish consumption when compared with the Fishermen study women and the fact that in Finland, approximately 95% of dioxin exposure and 80% of PCB exposure originates from fish (Kiviranta et al., 2004). A decrease in their β-cell function could be a compensation after a decrease in serum insulin and an increase in insulin sensitivity along with increasing fish consumption and omega-3 PUFA intake.

4.4. Low-grade systemic inflammation

An inverse association between fish consumption or omega-3 PUFA intake and inflammatory markers have been observed in the majority of the previous studies on the topic (Farzaneh-Far et al., 2009; Ferrucci et al., 2006; He et al., 2009; Kalogeropoulos et al., 2010; Ohsawa et al., 2008). In the present work, the inverse association was strong in the Health 2000 survey especially regarding

TNF-α and IL-6. An absence of a clear beneficial association in the Fishermen study could be due to chance or possibly the exposure to environmental contaminants was high enough to attenuate or even cancel out the anti-inflammatory effect. On the other hand, since fish consumption and serum omega-3 PUFA concentrations were relatively high among the Fishermen study participants, a beneficial effect might have reached a plateau and would no longer be detectable. Furthermore, the anti-inflammatory effect of omega-3 PUFAs might be best observable among high-risk individuals (Ohsawa et al., 2008).

4.5. Early signs of atherosclerosis

In some of the previous intervention studies, omega-3 PUFA supplementation has increased arterial elasticity (Nestel et al., 2002; Sjoberg et al., 2010; Wang et al., 2008). Similarly in the present work, arterial stiffness decreased along with increasing serum omega-3 PUFAs among the men in Health 2000 survey. In contrast, an increase in arterial stiffness measured by β-stiffness index along with increasing contaminant concentrations was observed among the men in the Fishermen study. This contradictory finding is indirectly supported by several previous observational studies where serum PCDD/Fs, serum PCBs, and blood mercury were associated with elevated blood pressure (Chang et al., 2011; Goncharov et al., 2011; Uemura et al., 2009; Valera et al., 2009) which is strongly associated with arterial stiffness. In the present work, there was a tendency towards increasing blood pressure among the men with high fish consumption and in addition, fish consumption was positively correlated with sodium chloride intake (Spearman correlation coefficient around 0.4). Thus, fish-related sodium chloride intake together with high exposure to environmental contaminants and their consequent effect on blood pressure could, at least partially, explain the observed increase in arterial stiffness.

Several observational studies among healthy individuals have reported an inverse association between fish consumption or serum omega-3 PUFAs and IMT (Ebbesson et al., 2008; Sala-Vila et al., 2010) or the prevalence of atherosclerotic plaque in the coronary artery (He et al., 2008; Heine-Broring et al., 2010). In the present work, the risk of carotid artery plaque tended to decrease across tertiles of environmental contaminants among the men in the Fishermen study. This observation implies that despite the potential adverse effects on insulin sensitivity and arterial elasticity, high exposure to environmental contaminants may not be able to cancel out the beneficial effect of omega-3 PUFAs on the plaque formation and the overall effect remains beneficial. Regarding the RR estimates, however, it should be noted that the number of cases was probably underestimated since ultrasonography was performed only from one segment of the right common carotid artery.

4.6. Conclusion

Overall, the results of this cross-sectional study contribute to the growing body of evidence that the hypotriglyceridemic and anti-inflammatory effects of fish-derived omega-3 PUFAs have a pivotal role in the cardiovascular benefits of fish consumption. Other beneficial trends were seen in glucose-insulin metabolism and arterial stiffness. Our results also suggest that high dietary exposure to fish-derived environmental contaminants might decrease insulin sensitivity and arterial elasticity assuming that the exposure is high enough to cancel out the beneficial effect of omega-3 PUFAs. At the same time, the overall effect on carotid artery plaque formation appeared not to be harmful regardless of high exposure to environmental contaminants.

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Table 1. Characteristics of the study participants: unadjusted geometric means and their 95% confidence intervals (CI) for continuous variables or number of participants (n) and percentages (%) for categorical variables

	Health 2000 sub-study				Fishermen sub-study			
	Men (n=532)		Women (n=641)		Men (n=123)		Women (n=132)	
	Mean	95% CI	Mean	95% CI	Mean	95% CI	Mean	95% CI
Dietary data[a]								
Fish consumption, g/day	35	33–38	36	34–38	64	56–72	50	45–56
Vegetable consumption, g/day	189	178–201	256	244–268	169	150–189	255	230–282
Fruit and berry consumption, g/day	114	103–126	186	173–201	139	119–162	180	150–216
Oil consumption, g/day	7.7	7.4–8.1	7.3	7.1–7.6	8.2	7.6–8.9	7.7	7.2–8.3
Alcohol intake, g/day	4.5	4.1–5.0	1.8	1.7–2.0	7.2	5.9–8.6	2.6	2.1–3.2
Salt intake, g/day	11	10–11	9.9	9.6–10	9.6	9.1–10	8.5	8.1–8.9
Serum omega-3 PUFAs[b], % serum FAs	3.6	3.5–3.8	3.7	3.6–3.8	6.3	5.8–6.8	6.4	6.0–6.8
Environmental contaminants								
Serum PCDD/F+PCB-TEq[c], pg/g fat	-	-	-	-	98	84–114	54	47–62
Blood MeHg, ng/ml	-	-	-	-	3.8	3.2–4.4	2.3	2.0–2.6
Traditional risk factors								
Age, years	57	57–58	58	57–58	52	50–54	48	46–50
Smoking, n (%)								
Never smoker	191	(36)	413	(64)	50	(41)	86	(65)
Occasional or former smoker[d]	222	(42)	131	(21)	46	(37)	29	(22)
Daily smoker	119	(22)	97	(15)	27	(22)	17	(13)
Physical activity, n (%)								
Sufficient	199	(37)	246	(38)	37	(30)	41	(31)
Intermediate[e]	147	(28)	190	(30)	33	(27)	42	(32)
Sedentary	186	(35)	205	(32)	53	(43)	49	(37)
BMI, kg/m^2	27	27–28	26	26–27	27	27–28	26	25–27
Waist circumference, cm	99	98–100	87	86–88	98	96–100	85	83–87
Systolic blood pressure, mmHg	140	139–142	134	132–135	134	131–137	122	119–126
Diastolic blood pressure, mmHg	87	86–88	81	81–82	85	83–86	78	77–80
Serum HDL cholesterol, mmol/l	1.4	1.4–1.4	1.7	1.6–1.7	1.5	1.4–1.6	1.7	1.6–1.7
Serum non-HDL cholesterol, mmol/l	4.0	3.9–4.0	3.8	3.7–3.9	4.1	4.0–4.3	3.6	3.4–3.8
Serum triglycerides, mmol/l	1.3	1.3–1.4	1.1	1.1–1.2	1.2	1.1–1.3	1.0	0.97–1.1
Serum glucose, mmol/l	6.0	5.9–6.1	5.5	5.5–5.6	5.7	5.5–5.8	5.3	5.2–5.3
Serum insulin, mU/l	8.9	8.5–9.3	7.6	7.3–7.9	6.0	5.4–6.7	5.9	5.3–6.6
HOMA-IR index[f]	2.4	2.2–2.5	1.9	1.8–1.9	1.5	1.3–1.7	1.4	1.2–1.5
HOMA-%B index[g]	74	71–77	77	75–80	57	52–62	69	63–76
Inflammatory markers								
Serum CRP, mg/l	1.5	1.4–1.6	1.4	1.3–1.5	1.3	1.1–1.5	1.3	1.1–1.6
Serum TNF-α, ng/l	5.6	5.5–5.8	5.3	5.2–5.5	-	-	-	-
Serum IL-6, ng/l	1.6	1.5–1.7	1.4	1.3–1.5	-	-	-	-
Vascular markers[h]								
Carotid artery IMT[gi]	0.82	0.80–0.83	0.77	0.76–0.78	0.80	0.76–0.84	0.74	0.71–0.77
Plaque in carotid artery[j], n (%)	69	(17)	54	(11)	22	(26)	13	(15)
Carotid artery stiffness								
Compliance[k], %/10 mmHg	0.80	0.76–0.84	0.84	0.80–0.88	0.79	0.68–0.92	0.95	0.86–1.1
Elastic modulus[l], kPa	830	788–874	741	707–777	796	683–928	624	565–689
β-stiffness index[m]	3.6	3.6–3.6	3.6	3.6–3.6	3.6	3.5–3.7	3.5	3.4–3.6
Medications, n (%) of users								
Insulin	9	(1.7)[n]	5	(0.78)[n]	5	(4.1)	3	(2.3)
Oral glucose lowering drugs	23	(4.3)[o]	12	(1.9)[o]	6	(4.9)	3	(2.3)
Lipid modifying drugs	73	(14)[p]	67	(10)[p]	22	(18)	16	(12)
Blood pressure lowering drugs	119	(22)[q]	145	(23)[q]	23	(19)	20	(15)

Abbreviations: ATC, anatomical therapeutic chemical; BMI, body mass index; CRP, C-reactive protein; FA, fatty acid; HDL, high density lipoprotein; HOMA, homeostasis model assessment; IMT, intima-media thickness; IR, insulin resistance; IL-6, interleukin 6; MeHg, methyl mercury; PCB, polychlorinated biphenyl;

PCDD/F, polychlorinated dibenzo-*p*-dioxin and dibenzofuran; PUFA, polyunsaturated fatty acid; TEq, toxic equivalent quantity; TNF-α, tumour necrosis factor α

[a] based on a food frequency questionnaire
[b] the sum of eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA)
[c] the sum of World Health Organization's toxic equivalent quantities for dioxins and PCBs
[d] smoked two days ago at the minimum but within previous 10 years
[e] mildly exhausting physical activity on free-time (duration at least 20 minutes) at least 2–3 times/week and physical activity while commuting (duration less than 30 minutes) daily
[f] insulin resistance index
[g] pancreatic beta cell function
[h] Health 2000 sub-study: men n=406, women n=499; Fishermen sub-study: men n=84, women n=90
[i] three end-diastole images from lateral interrogation angle at least 1 cm away from the origin of the bulb
[j] the prevalence of a focal raised lesion of >1.5 mm in size in at least one of the images of the carotid bulb
[k] ability of the artery to expand according to pulse pressure
[l] arterial stiffness independent of arterial wall thickness
[m] arterial stiffness relatively independent of blood pressure
[n] ATC code A10A
[o] ATC code A10B
[p] ATC code C10A
[q] ATC codes C02–C09

Table 2. Model-adjusted* geometric means for traditional CVD risk factors and inflammatory markers by tertiles of fish consumption and serum omega-3 PUFAs in the Health 2000 sub-study and the Fishermen sub-study.

	Health 2000 sub-study								**Fishermen sub-study**							
	Men (n=532)				**Women (n=641)**				**Men (n=123)**				**Women (n=132)**			
	1st tertile[a]	2nd tertile[b]	3rd tertile[c]	p for linear trend	1st tertile[a]	2nd tertile[b]	3rd tertile[c]	p for linear trend	1st tertile[d]	2nd tertile[e]	3rd tertile[f]	p for linear trend	1st tertile[d]	2nd tertile[e]	3rd tertile[f]	p for linear trend
	Fish consumption, g/day															
Traditional risk factors																
BMI, kg/m^2	26.9	27.2	27.5	0.22	26.7	26.0	26.4	0.66	27.0	27.1	28.3	0.15	25.5	26.7	26.7	0.33
Waist, cm	98.2	98.5	99.5	0.31	88.3	86.7	86.9	0.33	95.7	96.9	100	0.07	82.7	86.9	86.0	0.25
Systolic BP, mmHg	143	142	140	0.26	138	134	134	0.07	130	137	137	0.22	121	123	127	0.15
Diastolic BP, mmHg	89	87	86	0.02	82	82	82	0.50	83	88	85	0.52	77	79	81	0.11
HDL, mmol/l	1.41	1.42	1.34	0.10	1.63	1.67	1.74	0.02	1.50	1.54	1.42	0.27	1.64	1.65	1.66	0.82
Non-HDL, mmol/l	4.01	3.97	3.93	0.47	3.92	3.77	3.74	0.11	4.12	4.10	4.24	0.62	3.49	3.65	3.57	0.80
Triglycerides, mmol/l	1.34	1.29	1.32	0.91	1.23	1.10	1.05	<0.01	1.27	1.11	1.15	0.54	1.03	1.00	1.09	0.51
Glucose, mmol/l	5.94	6.05	5.99	0.67	5.53	5.52	5.54	0.92	5.49	5.75	5.81	0.09	5.25	5.28	5.24	0.89
Insulin, mU/l	8.44	9.08	9.22	0.17	8.22	7.44	7.11	<0.01	5.58	5.62	6.89	0.12	5.76	6.56	5.47	0.60
HOMA-IR index	2.23	2.44	2.45	0.19	2.02	1.82	1.75	0.01	1.36	1.44	1.78	0.08	1.34	1.54	1.27	0.62
HOMA-%B index	71.8	73.8	76.3	0.29	82.5	76.2	73.3	0.01	57.2	51.5	62.2	0.38	67.3	76.2	64.8	0.63
Inflammatory markers																
CRP, mg/l	1.53	1.48	1.54	0.93	1.50	1.36	1.31	0.24	1.41	1.27	1.14	0.36	1.41	1.12	1.47	0.75
TNF-α, ng/l	5.89	5.60	5.40	0.05	5.49	5.23	5.29	0.41	-	-	-	-	-	-	-	-
IL-6, ng/l	1.67	1.62	1.57	0.48	1.46	1.33	1.41	0.77	-	-	-	-	-	-	-	-
	Serum omega-3 PUFA concentration, % FAs															
Traditional risk factors																
BMI, kg/m^2	27.0	27.5	27.0	0.67	27.2	26.2	25.7	<0.01	26.5	27.8	28.1	0.10	25.9	25.6	27.5	0.11
Waist, cm	99.0	99.6	97.7	0.18	89.7	86.7	85.5	<0.01	94.3	98.6	100	0.03	84.3	84.4	86.9	0.28
Systolic BP, mmHg	142	143	141	0.53	137	135	134	0.08	131	138	135	0.43	123	121	127	0.33
Diastolic BP, mmHg	89	87	87	0.14	82	82	82	0.64	83	87	85	0.63	79	79	79	0.92
HDL, mmol/l	1.34	1.36	1.46	<0.01	1.58	1.67	1.80	<0.01	1.51	1.49	1.46	0.57	1.64	1.71	1.60	0.60
Non-HDL, mmol/l	4.01	3.91	3.98	0.85	3.94	3.74	3.76	0.08	4.18	4.18	4.09	0.71	3.50	3.75	3.47	0.79
Triglycerides, mmol/l	1.45	1.33	1.17	<0.01	1.28	1.10	1.00	<0.01	1.32	1.26	0.97	0.01	1.10	1.06	0.96	0.13
Glucose, mmol/l	6.00	6.05	5.93	0.33	5.56	5.50	5.52	0.61	5.62	5.69	5.74	0.51	5.22	5.16	5.40	0.07
Insulin, mU/l	8.98	9.58	8.21	0.05	8.14	7.65	6.97	<0.01	5.74	5.79	6.48	0.36	5.87	5.43	6.49	0.39
HOMA-IR index	2.40	2.57	2.17	0.05	2.01	1.87	1.71	<0.01	1.43	1.46	1.65	0.34	1.36	1.24	1.55	0.29
HOMA-%B index	74.3	78.2	69.6	0.12	81.7	78.7	71.7	<0.01	55.2	54.8	60.3	0.44	70.2	66.8	70.9	0.88

Inflammatory markers																
CRP, mg/l	1.57	1.57	1.42	0.26	1.59	1.32	1.28	0.03	1.22	1.38	1.22	0.91	1.12	1.61	1.29	0.68
TNF-α, ng/l	5.81	5.73	5.35	0.03	5.74	5.46	4.84	<0.01	-	-	-	-	-	-	-	-
IL-6, ng/l	1.76	1.72	1.40	<0.01	1.57	1.45	1.20	<0.01	-	-	-	-	-	-	-	-

* Adjusted for age, smoking, physical activity, vegetable, fruit, berry, and oil consumption, salt and alcohol intake, and the use of insulin, blood glucose lowering drugs, lipid modifying agents, and antihypertensives

Abbreviations: BMI, body mass index; CRP, C-reactive protein; FA, fatty acid; HDL, high density lipoprotein; HOMA, homeostasis model assessment; IR, insulin resistance; IL-6, interleukin 6; PUFA, polyunsaturated fatty acid; TNF-α, tumour necrosis factor α

Fish consumption, g/day:

[a] men: n=177, mean=14, range 0–30; women: n=213, mean=16, range 0–31
[b] men: n=178, mean=39, range 31–50; women: n=214, mean=38, range 32–47
[c] men: n=177, mean=77, range 51–276; women: n=214, mean=71, range 48–417

[d] men: n=41, mean=31, range 3.9–47; women: n=44, mean=26, range 0.54–41
[e] men: n=42, mean=65, range 48–89; women: n=44, mean=52, range 42–67
[f] men: n=40, mean=131, range 90–463; women: n=44, mean=93, range 68–282

Serum omega-3 PUFA concentration, % FAs:

[a] men: n=177, mean=2.4, range 1.0–3.0; women: n=213, mean=2.4, range 0.72–3.1
[b] men: n=177, mean=3.5, range 3.1–4.3; women: n=216, mean=3.7, range 3.2–4.3
[c] men: n=178, mean=5.7, range 4.4–12; women: n=212, mean=5.6, range 4.4–12

[d] men: n=41, mean=4.1, range 2.6–5.0; women: n=44, mean=4.4, range 3.2–5.5
[e] men: n=41, mean=6.1, range 5.1–7.4; women: n=44, mean=6.4, range 5.6–7.5
[f] men: n=41, mean=10, range 7.5–23; women: n=44, mean=9.4, range 7.6–23

Table 3. Model-adjusted* geometric means for vascular markers and a risk ratio (RRs) for the presence of carotid artery plaque by tertiles of fish consumption and serum omega-3 PUFAs in the Health 2000 sub-study and the Fishermen sub-study.

	Health 2000 sub-study								**Fishermen sub-study**							
	Men (n=406)				**Women (n=499)**				**Men (n=84)**				**Women (n=90)**			
	1st tertile[a]	2nd tertile[b]	3rd tertile[c]	p for linear trend	1st tertile[a]	2nd tertile[b]	3rd tertile[c]	p for linear trend	1st tertile[d]	2nd tertile[e]	3rd tertile[f]	p for linear trend	1st tertile[d]	2nd tertile[e]	3rd tertile[f]	p for linear trend
	Fish consumption, g/day															
Vascular markers																
IMT (mm)	0.81	0.81	0.80	0.48	0.77	0.77	0.76	0.32	0.78	0.81	0.80	0.90	0.72	0.72	0.77	0.15
Compliance (%/10 mmHg)	0.79	0.76	0.84	0.29	0.83	0.87	0.85	0.80	0.88	0.69	0.81	0.90	0.96	0.91	0.99	0.75
Elastic modulus (kPa)	844	856	792	0.36	746	701	738	0.93	720	903	777	0.89	647	668	562	0.24
β-stiffness index	3.61	3.66	3.55	0.32	3.60	3.58	3.60	0.92	3.56	3.66	3.60	0.88	3.50	3.57	3.49	0.84
RR for plaque	1.00	0.82	1.09	0.71	1.00	0.49	0.54	0.11	1.00	3.06	1.70	0.55	1.00	1.38	1.00	0.96
	Serum omega-3 PUFA concentration, % fatty acids															
Vascular markers																
IMT (mm)	0.81	0.81	0.81	0.79	0.78	0.76	0.76	0.20	0.79	0.81	0.79	0.82	0.72	0.74	0.75	0.40
Compliance (%/10 mmHg)	0.76	0.75	0.89	0.01	0.85	0.83	0.88	0.40	1.07	0.72	0.65	0.03	1.01	0.97	0.88	0.25
Elastic modulus (kPa)	866	889	743	0.01	728	750	708	0.56	597	870	971	0.04	592	617	665	0.36
β-stiffness index	3.67	3.63	3.52	0.01	3.58	3.63	3.57	0.71	3.42	3.63	3.78	0.04	3.50	3.51	3.56	0.58
RR for plaque	1.00	0.81	0.71	0.20	1.00	1.19	1.06	0.92	1.00	1.12	0.64	0.44	1.00	1.26	3.03	0.05

* Adjusted for age, smoking, physical activity, vegetable, fruit, berry, and oil consumption, salt and alcohol intake, and the use of insulin, blood glucose lowering drugs, lipid modifying agents, and antihypertensives

Abbreviations: FA, fatty acid; IMT, intima-media thickness; PUFA, polyunsaturated fatty acid; RR, risk ratio

Fish consumption, g/day:

[a] men: n=135, mean=14, range 0–30; women: n=166, mean=16, range 0–31
[b] men: n=136, mean=38, range 31–49; women: n=167, mean=38, range 32–46
[c] men: n=135, mean=76, range 50–276; women: n=166, mean=67, range 47–417

[d] men: n=28, mean=32, range 3.9–47; women: n=30, mean=23, range 0.54–38
[e] men: n=28, mean=61, range 48–77; women: n=30, mean=52, range 39–67
[f] men: n=28, mean=143, range 78–463; women: n=30, mean=93, range 68–282

Serum omega-3 PUFA concentration, % FAs:

[a] men: n=135, mean=2.4, range 1.0–3.1; women: n=167, mean=2.4, range 0.72–3.1
[b] men: n=136, mean=3.6, range 3.2–4.4; women: n=165, mean=3.7, range 3.2–4.3
[c] men: n=135, mean=5.7, range 4.5–12; women: n=167, mean=5.6, range 4.4–12

[d] men: n=28, mean=3.9, range 2.6–5.0; women: n=30, mean=4.4, range 3.2–5.6
[e] men: n=28, mean=6.1, range 5.1–7.7; women: n=30, mean=6.6, range 5.7–7.9
[f] men: n=28, mean=9.8, range 7.8–23; women: n=30, mean=9.9, range 8.0–23

Table 4. Model-adjusted* geometric means for traditional CVD risk factors and CRP by tertiles of environmental contaminants in the Fishermen sub-study.

	Fishermen sub-study							
	Men (n=123)				Women (n=132)			
	1st tertile[a]	2nd tertile[b]	3rd tertile[c]	p for linear trend	1st tertile[a]	2nd tertile[b]	3rd tertile[c]	p for linear trend
	Serum PCDD/F+PCB-TEq concentration, pg/g fat							
Traditional risk factors								
BMI, kg/m^2	26.4	27.9	28.1	0.18	26.5	25.9	26.5	0.91
Waist, cm	95.5	99.7	97.7	0.60	86.5	84.4	84.8	0.66
Systolic BP, mmHg	131	142	131	0.67	121	123	128	0.10
Diastolic BP, mmHg	83	89	83	0.52	76	80	80	0.14
HDL, mmol/l	1.54	1.47	1.44	0.34	1.68	1.56	1.73	0.42
Non-HDL, mmol/l	4.34	4.06	4.06	0.39	3.79	3.45	3.48	0.41
Triglycerides, mmol/l	1.21	1.21	1.10	0.45	1.14	1.01	0.97	0.19
Glucose, mmol/l	5.61	5.72	5.72	0.62	5.17	5.32	5.28	0.49
Insulin, mU/l	5.19	6.06	6.85	0.07	6.23	6.06	5.47	0.39
HOMA-IR index	1.30	1.54	1.74	0.09	1.43	1.43	1.28	0.49
HOMA-%B index	50.2	57.6	63.2	0.10	77.1	68.2	63.2	0.17
CRP, mg/l	1.30	1.48	1.07	0.29	1.50	1.09	1.42	0.94
	Blood MeHg concentration, ng/ml							
Traditional risk factors								
BMI, kg/m^2	26.8	27.6	28.0	0.26	25.9	25.9	27.2	0.17
Waist, cm	95.1	98.1	99.6	0.10	83.9	84.0	88.0	0.08
Systolic BP, mmHg	135	133	136	0.79	124	121	127	0.30
Diastolic BP, mmHg	85	85	86	0.67	78	78	80	0.30
HDL, mmol/l	1.45	1.51	1.50	0.67	1.64	1.69	1.62	0.73
Non-HDL, mmol/l	4.42	4.00	4.04	0.26	3.49	3.58	3.64	0.57
Triglycerides, mmol/l	1.22	1.10	1.21	0.86	1.08	1.00	1.03	0.77
Glucose, mmol/l	5.47	5.72	5.86	0.04	5.24	5.13	5.41	0.04
Insulin, mU/l	5.60	5.72	6.75	0.15	6.24	5.06	6.56	0.42
HOMA-IR index	1.36	1.46	1.76	0.09	1.45	1.16	1.58	0.30
HOMA-%B index	58.5	52.9	59.1	0.75	73.3	63.5	71.2	0.97
CRP, mg/l	1.46	1.11	1.28	0.75	0.96	1.56	1.59	0.07

* Adjusted for age, smoking, physical activity, vegetable, fruit, berry, and oil consumption, salt and alcohol intake, and the use of insulin, blood glucose lowering drugs, lipid modifying agents, and antihypertensives

Abbreviations: BMI, body mass index; CRP, C-reactive protein; HDL, high density lipoprotein; HOMA, homeostasis model assessment; IR, insulin resistance; IL-6, interleukin 6; MeHg, methylmercury; PCB, polychlorinated biphenyl; PCDD/F, polychlorinated dibenzo-*p*-dioxin and dibenzofuran; TEq, toxic equivalent quantity

Serum PCDD/F+PCB-TEq concentration, pg/g fat:

[a] men: n=41, mean=37, range 6.6–69; women: n=44, mean=22, range 7.3–36
[b] men: n=41, mean=106, range 70–155; women: n=44, mean=54, range 37–74
[c] men: n=41, mean=239, range 156–590; women: n=44, mean=128, range 75–433

Blood MeHg concentration, ng/ml:

[a] men: n=41, mean=1.3, range 0.21–2.6; women: n=46, mean=0.96, range 0–1.5
[b] men: n=42, mean=3.5, range 2.7–5.3; women: n=44, mean=2.2, range 1.6–2.9
[c] men: n=40, mean=9.4, range 5.4–60; women: n=42, mean=5.0, range 3.0–20

Table 5. Model-adjusted* geometric means for vascular markers and a risk ratio (RRs) for the presence of carotid artery plaque by tertiles of environmental contaminants in the Fishermen study.

	Fishermen sub-study							
	Men (n=84)				Women (n=90)			
	1st tertile[a]	2nd tertile[b]	3rd tertile[c]	p for linear trend	1st tertile[a]	2nd tertile[b]	3rd tertile[c]	p for linear trend
	Serum PCDD/F+PCB-TEq concentration, pg/g fat							
Vascular markers								
IMT (mm)	0.82	0.78	0.79	0.66	0.74	0.74	0.73	0.62
Compliance (%/10 mmHg)	1.05	0.70	0.68	0.09	1.13	0.82	0.94	0.38
Elastic modulus (kPa)	589	934	917	0.12	529	713	645	0.32
β-stiffness index	3.43	3.62	3.78	0.07	3.35	3.69	3.53	0.37
RR for plaque	1.00	0.76	0.47	0.13	1.00	2.67	4.07	0.15
	Blood MeHg concentration, ng/ml							
Vascular markers								
IMT (mm)	0.82	0.78	0.80	0.86	0.74	0.74	0.73	0.79
Compliance (%/10 mmHg)	1.14	0.65	0.68	0.03	1.06	0.93	0.88	0.13
Elastic modulus (kPa)	544	1011	895	0.05	564	636	685	0.13
β-stiffness index	3.32	3.74	3.76	0.02	3.43	3.55	3.60	0.13
RR for plaque	1.00	0.90	0.36	0.04	1.00	1.50	2.04	0.14

* Adjusted for age, smoking, physical activity, vegetable, fruit, berry, and oil consumption, salt and alcohol intake, and the use of insulin, blood glucose lowering drugs, lipid modifying agents, and antihypertensives

Abbreviations: IMT, intima-media thickness; MeHg, methylmercury; PCB, polychlorinated biphenyl; PCDD/F, polychlorinated dibenzo-*p*-dioxin and dibenzofuran; TEq, toxic equivalent quantity; RR, risk ratio

Serum PCDD/F+PCB-TEq concentration, pg/g fat:

[a] men: n=28, mean=36, range 11–67; women: n=30, mean=22, range 7.3–39
[b] men: n=28, mean=102, range 68–155; women: n=30, mean=54, range 40–74
[c] men: n=28, mean=234, range 156–590; women: n=30, mean=126, range 75–367

Blood MeHg concentration, ng/ml:

[a] men: n=27, mean=1.1, range 0.21–2.2; women: n=32, mean=0.92, range 0–1.5
[b] men: n=30, mean=3.0, range 2.3–3.5; women: n=29, mean=2.0, range 1.6–2.6
[c] men: n=27, mean=6.2, range 3.6–19; women: n=29, mean=4.4, range 2.7–10

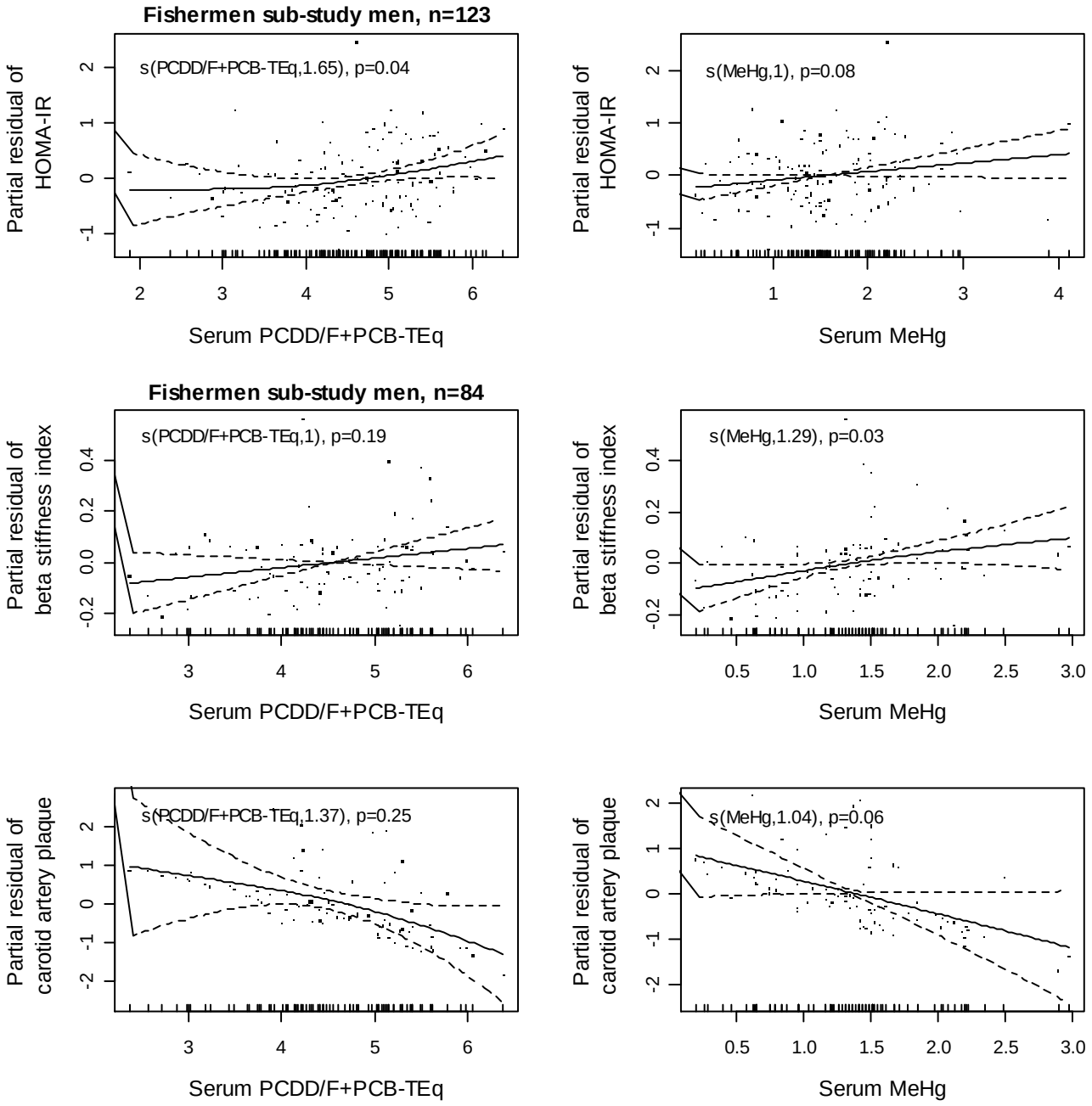

Figure. Smoothed associations between log-transformed serum PCDD/F+PCB-TEq concentration or blood MeHg concentration and log-transformed HOMA-IR index, log-transformed beta stiffness index, and the risk of carotid artery plaque among the Fishermen sub-study men. The figure has been produced by an additive model (AM) with a thin-plate regression spline and adjusted for age, smoking, physical activity, vegetable, fruit, berry, and oil consumption, salt and alcohol intake, and the use of insulin, blood glucose lowering drugs, lipid modifying agents, and antihypertensives. The solid curve is the additive model fit and the dashed curves represent the approximate 95% confidence interval. The fit is named as s(log_PCDD/F+PCB-TEq, edf) or s(log_MeHg, edf), where edf is the estimated degrees of freedom describing the wiggliness of the fit. The plotted points are partial residuals.

Abbreviations: HOMA, homeostasis model assessment; IR, insulin resistance; MeHg, methylmercury; PCB, polychlorinated biphenyl; PCDD/F, polychlorinated dibenzo-*p*-dioxin and dibenzofuran; TEq, toxic equivalent quantity

Appendix 1

Abbreviations and formulas for the parameters of homeostasis model assessment (HOMA) and ultrasonography

HOMA-IR[a,b]	Insulin resistance index	= [serum insulin (mU/l) * serum glucose (mmol/l)] / 22.5
HOMA-%B[a,b]	β-cell function (%)	= [20 x serum insulin (mU/l)] / [serum glucose (mmol/l) - 3.5]
IMT[a]	Intima-media thickness (mm)	= average of three end-diastole CCA IMT measurements
CAC[a,c]	Carotid artery compliance (%/10 mmHg)	= ability of the artery to expand according to pulse pressure (elasticity) = 100*10*[(ADC/DAD)/PP]
YEM[a,c]	Young's elastic modulus (kPa)	= arterial stiffness independent of arterial wall thickness = 0.1333*[EP*DAD/(2*IMT)]
SI[a,c]	β-stiffness index	= arterial stiffness relatively independent of blood pressure = Ln(SBP/DBP)/(ADC/DAD)
ADC	Arterial diameter change (mm)	= SAD–DAD
DAD	Diastolic arterial diameter (mm)	= average of three diastolic CCA diameter measurements
PP	Pulse pressure (mmHg)	= systolic blood pressure–diastolic blood pressure
EP[c]	Peterson's elastic modulus (kPa)	= 0.1333*(PP*DAD)/ADC
SAD	Systolic arterial diameter (mm)	= average of three systolic CCA diameter measurements

[a] reported in the present work

[b] 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.

[c] Selzer RH, Mack WJ, Lee PL, Kwong-Hu H, Hodis HN. Improved common carotid elasticity and intima-media thickness measurements from computer analysis of sequential ultrasound frames. Atherosclerosis 2001; 154:185–193.

Appendix 2

Age-adjusted Spearman's correlation coefficients between fish consumption and serum/blood concentrations of fish-derived fatty acids and environmental contaminants in the Health 2000 sub-study and the Fishermen study

	Spearman correlation coefficients		
	Fish consumption, g/day	Serum omega-3 PUFA concentration, % FAs	Serum PCDD/F+PCB-TEq concentration, pg/g fat
Health 2000 sub-study men (n=532)			
Serum omega-3 PUFA concentration, % FAs	0.35	1	-
Health 2000 sub-study women (n=641)			
Serum omega-3 PUFA concentration, % FAs	0.29	1	-
Fishermen sub-study men (n=123)			
Serum omega-3 PUFA concentration, % FAs	0.36	1	1
Serum PCDD/F+PCB-TEq concentration, pg/g fat	0.47	0.56	1
Blood MeHg concentration, ng/ml	0.41	0.47	0.59
Fishermen sub-study women (n=132)			
Serum omega-3 PUFA concentration, % FAs	0.34	1	1
Serum PCDD/F+PCB-TEq concentration, pg/g fat	0.34	0.18	1
Blood MeHg concentration, ng/ml	0.44	0.26	0.59