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Effect of seafood mediated PCB exposure on desaturase activity and PUFA profile in Faroese septuagenarians

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Abstract

Polychlorinated biphenyl (PCB) exposure may affect serum concentrations of polyunsaturated fatty acids (PUFAs) by inhibiting desaturases 5 and 6 that drive their synthesis from precursor fatty acids. Such changes in the composition of fatty acids may affect cardiovascular disease risk, which is thought to increase at elevated PCB exposures. This population-based cross-sectional study examined 712 Faroese men and women aged 70–74 years. The serum phospholipid fraction of fasting blood samples was used to determine the PUFA profile, including linoleic acid, dihomo- γ -linolenic acid, arachidonic acid, eicosatrienoic acid, and other relevant fatty acids. Ratios between precursor and metabolite fatty acids were used as proxies for 5 and 6 desaturase activity. Tertiles of serum-PCB concentrations were used in multiple regression analyses to determine the association between the exposure and desaturase activity. In multiple regression models, PCB exposure was inversely related to the estimated 6 desaturase activity resulting in accumulation of precursor fatty acids and decrease in the corresponding product PUFAs. A positive association between PCB and 5 desaturation was also found. A relative increase in EA was also observed, though only in the third tertile of PCB exposure. Non-linear relationships between the exposure and the desaturase activity were not found. Consuming fish and seafood may not be translated into beneficial fatty acid profiles if the diet simultaneously causes exposure to PCBs. Although the desaturase estimates were likely influenced by dietary intakes of product

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Ethical approval

The study protocol was approved by the Faroe Islands ethical review committee and by the Institutional Review Board at the Harvard School of Public Health. All study participants gave their written informed consent.

Competing interests

None of the authors have any conflicts of interests in regard to this study.

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PUFAs, the association between PCB exposure and $\Delta 6$ desaturase activity is plausible and may affect cardiovascular disease risk.

Keywords

Polyunsaturated fatty acids; Desaturase; Polychlorinated biphenyls; Cardiovascular disease; Generalized additive models

Introduction

The positive influences of a high fish intake on cardiovascular health are well established (Mozaffarian and Rimm, 2006). However, consumption of marine foods may also be associated with an increased intake of potentially toxic contaminants, such as the polychlorinated biphenyls (PCBs) (Domingo and Bocio, 2007). Many PCB congeners are persistent, they still remain in the environment and, after absorption, also persist for many years in the human body (Hopf et al., 2012; Ritter et al., 2011). Due to the lipophilic properties, PCB accumulates in fatty fish and marine mammals, and increased body burdens of PCB are associated with high fish consumption (Domingo and Bocio, 2007).

PCB exposure has been linked to adverse health outcomes, including cardiovascular disease (ATSDR, 2000; Bergkvist et al., 2014; Gustavsson and Hogstedt, 1997; Valera et al., 2013). Lately, studies have suggested that PCB exposure may affect the body's ability to synthesize long-chained fatty acids by inhibiting enzymes involved in the elongation and desaturation process from shorter to longer and more unsaturated fatty acids (Grandjean and Weihe, 2003). While previous research focused on the synthesis of arachidonic acid (AA) from the *n*-6 fatty acid family, the ability to synthesize *n*-3 poly unsaturated fatty acids (PUFAs) docosahexaenoic acid (DHA; 22:6n-3) and eicosapentaenoic acid (EPA; 20:5n-3) is crucial, as these PUFAs are thought to reduce serum cholesterol and triglyceride, lower heart rate and blood pressure, and prevent atherosclerosis (Mozaffarian and Rimm, 2006).

We investigated the relationship between PCB exposure and surrogate markers of PUFA synthetic rates in a cohort of Faroese septuagenarians with increased exposures to PCB through the consumption of traditional marine foods, including pilot whale blubber.

1. Methods

2.1. Study population and clinical procedures

The eligible study population consisted of 1131 residents of the Faroe Islands who were 70–74 years of age (Grandjean et al., 2011). Of the 1131 invited, 776 were initially enrolled (response rate 69%), but 14 died before examination could be scheduled, 42 eventually withdrew, 7 were excluded due to incapacities that prevented examinations, and 1 was excluded due to alcoholic pancreatitis. Details of the data collection have been described in detail elsewhere (Grandjean et al., 2011). In short, fasting serum samples were obtained from all subjects, who underwent a thorough physical examination where blood pressure, weight and height were obtained. Characteristics of subjects included age, sex, smoking history, and body mass index (BMI). We also included binary indicators on whether the

subject was taking any heart medicine, suffered from diabetes, and had a history of myocardial infarction (MI), stroke or other cardiovascular disease (CVD). A dietary questionnaire was used to ascertain the intake of traditional and other foods during childhood, adolescence, adulthood, and the most recent year. The questionnaire focused on the amount of local food items, such as fish, whale meat and blubber, and seabirds in the diet.

1.2. Exposure assessment

Serum was analyzed for PCBs by gas chromatography using a dual-capillary column system with micro electron capture detection after solid phase extraction (Halling et al., 2005). The concentrations of congeners CB-138, CB-153, and CB-180 on average accounted for approximately 50% of the total amount of PCB congeners. To avoid problems with congeners not assessed and concentrations below the detection limit, a simplified total PCB concentration was calculated as the sum of these three congeners multiplied by 2 and expressed on a lipid-weight basis ($\mu\text{g/g}$ lipid) (Heilmann et al., 2006).

1.3. Outcome assessment

The serum phospholipid fraction of fasting blood samples was used to analyze members of the *n*-3, *n*-6 and *n*-9 PUFA families. Serum phospholipids were extracted and transmethyated before analysis on a gas chromatograph with a flame ionization detector (Bjerve et al., 1987). The results obtained had a high analytical quality level (Lindberg et al., 2013) and were expressed as relative concentrations in weight percent of total fatty acids.

Regulation of $\Delta 5$ and $\Delta 6$ desaturase activity is considered important for controlling intracellular levels of the different *n*-3 and *n*-6 essential fatty acids. A decreased desaturase activity results in a relative accumulation of precursors and a concomitant reduction in metabolites. Therefore, the ratio between one fatty acid and its corresponding precursor is assumed to reflect the respective desaturase activities (Slagsvold et al., 2009). The $\Delta 5$ desaturase converts dihomo- γ -linolenic acid (DGLA; 20:3n-6) to arachidonic acid (AA; 20:4n-6), the $\Delta 6$ desaturase converts linoleic acid (LA; 18:2n-6) to DGLA, while the conversion of oleic acid (OA; 18:1n-9) to eicosatrienoic (mead) acid (EA; 20:3n-9) depends on both desaturases. We therefore used the ratio AA / DGLA as a proxy for $\Delta 5$ desaturase, the ratio DGLA / LA as a proxy for $\Delta 6$ desaturase, and the ratio EA / OA as a proxy for the sum of $\Delta 5 + \Delta 6$ desaturases. Furthermore, since the relative concentration of EA not only increases in essential fatty acid deficiency (Bjerve et al., 1987) but also as a result of increasing desaturase activity (Ichi et al., 2014), the relative concentration of EA was used as an additional proxy for both desaturases. The metabolic stability and tracking ability of phospholipid fatty acids and their ratios is similar to that found for serum cholesterol (Lindberg et al., 2013). Thus, an inverse association between PCB and the described ratios or EA would be interpreted as an indication of reduced desaturase activity.

1.4. Statistical analysis

Outcome and exposure data were log (base 10) transformed to approximate Gaussian distributions and limit problems with extreme observations. To determine the associations between the exposure and desaturase activity, we used tertiles of serum-PCB concentrations

in the multiple regression analyses, where the first tertile served as the reference group. Residual plots were used to assess the model fit, and the possible significance of second- and third-order terms was determined. In sensitivity analyses, we used fractional polynomials models to identify non-linear associations (Royston and Altman, 1994), and we also used generalized additive models (GAMs) (Hastie and Tibshirani, 1990) to test the fit of smoothing on the effects of PCB exposure.

Potential confounders were identified using directed acyclic graphs (DAGs) (Greenland et al., 1999). All analyses were adjusted for age and sex. As subjects with a high body mass index (BMI) may at first dilute their body burden within a larger distribution volume, but later protect it from elimination (Wolff and Anderson, 1999), analyses were further adjusted for BMI. To account for the competition between *n*-3, *n*-6, and *n*-9 PUFAs for 5- and 6 desaturase (Brenna, 2002) analyses with ratios calculated from *n*-6 PUFAs were adjusted for the sum proportion of *n*-3 and *n*-9 PUFAs. Similarly, analyses with EA as the outcome were adjusted for sum proportions of *n*-3- and *n*-6 PUFAs. All analyses were additionally adjusted for current use of statins, history of CVDs including MI and stroke, and diabetes.

Two-sided tests for statistical significance at $p < 0.05$ were performed. Descriptive analyses and regression models were carried out in STATA (version 11; StataCorp LP; College Station, Texas) and SAS (version 9.4; SAS Institute Inc, Cary, NC). Generalized additive models and fractional polynomial models were developed in R (version 3.1; <http://www.R-project.org>).

2. Results

Table 1 shows the characteristics of the 712 study subjects (360 men and 352 women). Of note, the mean BMI was rather high, and 74% of cohort members were treated with statins. All subjects had eaten traditional food to some degree (notably pilot whale meat and blubber) as well as seabirds, such as fulmar and puffin. The intake was especially high in childhood and adolescence (i.e., from the mid-1930s to early 1950s) and somewhat decreased in adulthood and during the most recent year before the examination.

The geometric mean serum PCB concentration was 8.07 µg/g lipid and covered a range from 0.1 µg/g lipid to a high level of 70.1 µg/g lipid. Due to the long half-time of PCBs and the stability of dietary habits, serum-PCB concentrations were significantly correlated with the history of whale meat and blubber intake in the past as well as currently. However, PCBs correlated poorly with fish intake (results not shown) as previously reported (Grandjean et al., 2011), possibly because the Faroese fish catch primarily involves leaner species, such as cod and haddock (Johansen & Olafsson, 1999). The PCB concentration in males was twice that seen in females, in accordance with the more frequent intake of blubber dinners among the men.

The proportion of *n*-3, *n*-6, and *n*-9 PUFAs in phospholipids as well as mean ratios between metabolite- and precursor PUFAs are shown in Table 2. No significant difference was found between men and women. Table 3 shows the crude and adjusted desaturase activity results in tertiles of lipid adjusted PCB concentrations. We found a statistically significant decrease in 6 desaturase activity with increasing level of PCB exposure. Adjusting for confounders

did not change this relationship. In the crude analyses, the Δ^5 desaturase activity increased at higher tertiles of PCB exposure. The association attenuated slightly when confounders were included, though remained statistically significant. We also observed a covariate-adjusted association between PCB and the combined Δ^5 plus Δ^6 activity, although only in the third tertile. Figure 1 shows the associations between the continuous serum-PCB concentrations ($\mu\text{g/g}$ lipid) as predictor for the average desaturase outcomes after adjustment for covariates. When compared with the linear PCB exposure, the smoothing functions for the exposure in the GAM analyses did not significantly improve the model fit ($p=0.25$ for Δ^5 , 0.26 for Δ^6 , and 0.20 for $\Delta^5 + \Delta^6$ for differences between the fits).

In the fractional polynomials models, non-linear relationships between the desaturase outcomes and PCB exposure were not identified. Similar to the results in Model 4 (Table 3), the PCB linear regression coefficients (95% CI) from the fractional polynomial models were 0.07 (0.05, 0.09) for Δ^5 ; -0.06 (-0.08 , -0.03) for Δ^6 ; and 0.06 (0.03, 0.09) for $\Delta^5 + \Delta^6$, respectively.

3. Discussion

This population-based cross-sectional study of elderly Faroese men and women showed an inverse association between PCB serum concentrations and the estimated activity of desaturase Δ^6 . Such decreases in desaturase activity can unfavorably alter the composition of n -3 PUFAs, such as EPA and DHA, which in turn can increase the risk of cardiovascular disease (Mozaffarian and Rimm, 2006). Our results are in accordance with previous animal and human studies (Grandjean and Weihe, 2003; Guitart et al., 1996; Matsusue et al., 1997, 1999). We also observed a concomitant increase in calculated Δ^5 desaturase activity with increasing PCB exposure. This finding is unexpected, as the mechanisms by which PCB is thought to affect Δ^5 and Δ^6 desaturase would likely be the same. These results must be interpreted in light of the fact that all calculations assumed that dietary intake of the metabolites did not affect the ratios. Estimation of the Δ^5 desaturase activity from the ratio between AA and DGLA would be highly susceptible to dietary AA intake that could bias the ratio toward higher values. Similarly for the Δ^6 desaturase (approximated by ratio between DGLA/LA), any non-assessed dietary DGLA could augment the DGLA concentration, again leading to potential bias. Hence, the observed inverse association between PCB and Δ^6 is possibly of a smaller magnitude than it would have been had we had the possibility to adjust for the dietary DGLA intake. An additional possibility is that PCB may conceivably affect oxidations and other biochemical processes yet to be studied that may affect relative PUFA concentrations.

Despite the shortcomings of these calculations, the advantages of the present study include the total adjustment of n -3 and n -9 PUFA concentrations. Hence, the reduced activity cannot be attributed to internal competition between the fatty acid families for the available desaturases and elongases (Brenna, 2002). Further, we were able to adjust for medications and medical conditions that could potentially affect the synthesis rate (Nakamura et al. 2004). Relative to the PCBs, PUFA concentrations in phospholipids are less stable and vary over time with the diet. Given that this study utilized fasting serum concentrations, long-

term variability of these PUFAs would likely be limited and similar to that observed for serum cholesterol concentrations (Lindberg et al., 2013).

Additional strengths of the study include the minimal social differences among the Faroese elderly, who constitute a unique study population with a high intake of fish and seafood, greatly increased average PCB exposures over the full lifespan, and a surprisingly high rate of cardiovascular disease considering the high intake of heart-beneficial marine fatty acids. While statin treatment was highly prevalent in this population, medication did not seem to affect the findings of this study to any appreciable degree. Furthermore, the study had a high participation rate of 63% that appeared to be fairly representative of the background population.

Analyses were not adjusted for other marine contaminants such as the pesticide metabolite 2,2-bis(4-chlorophenyl)-1,1-dichloroethene (DDE). Similar to PCB, lipophilic DDE primarily accumulates in whale blubber. Sharing the source of exposure, the serum concentrations of two contaminants are highly correlated, which makes adjustments unfeasible. It is therefore impossible to be sure that the effects found in present study are caused by PCB and not by DDE or similar persistent and fat-soluble contaminants. However, in contrast to PCB, human health concerns in regard to elevated DDE exposures do not include effects on fatty acid metabolism (Ezkenazi et al., 2009).

The observed changes in desaturase activity found in the Faroese septuagenarians may have public health relevance, as PUFAs are important for a variety of biochemical functions and cell membrane properties (Mozaffarian and Rimm, 2006). For example, *N*-3 PUFAs are known to regulate hepatic lipid metabolism via the expression of key enzymes involved in lipid synthesis and catabolism by binding and activating peroxisome proliferator-activated receptor- α (PPAR α). Activation of PPAR α results in activation of hepatic fatty acid oxidation. At the same time these PUFAs inhibit hepatic fatty acid synthesis. The net effect of fatty acid control of hepatic lipid metabolism is that the composition as well as the type and quantity of lipids available for LDL synthesis and secretion are affected. Because the liver plays a central role in whole-body lipid metabolism, this regulatory process in turn affects the lipid composition throughout the body and therefore likely contributes to the onset and progression of several chronic diseases, including atherosclerosis, diabetes, and obesity. The liver is, at the same time, a major target organ for PCBs (ATSDR, 2000; Lauby-Secretan et al., 2013). Due to the importance of PUFAs in the pathogenesis of cardiovascular disease (Mozaffarian and Rimm, 2006), the role of PCB effects on fatty acid metabolism should be considered as a potential mode of action in regard to PCB-associated cardiovascular disease and mortality (ATSDR, 2000; Bergkvist et al., 2014; Gustavsson and Hogstedt, 1997; Valera et al., 2013).

4. Conclusions

This population-based cross-sectional study of Faroese septuagenarians demonstrated an inverse association between serum-PCB concentrations and the estimated activity of desaturase 6. Due to lack of adjustment for seafood-derived intake of fatty acid metabolites, bias likely occurred and may explain the positive association with 5 observed.

As PCB-mediated decreased desaturase activity may affect the risk of cardiovascular disease, confirmation of this association deserves attention in future studies.

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Abbreviations

AA	arachidonic acid
BMI	body mass index
CVD	cardiovascular disease
DAG	directed acyclic graph
DGLA	dihomo- γ -linolenic acid
DHA	docosahexaenoic acid
EA	eicosatrienoic (Mead) acid
EPA	eicosapentaenoic acid
GAM	generalized additive model
LA	linoleic acid
MI	myocardial infarction
OA	oleic acid
PCB	Polychlorinated biphenyl
PUFA	polyunsaturated fatty acid

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Highlights

- Polychlorinated biphenyl (PCB) exposure may affect the metabolism of polyunsaturated fatty acids (PUFAs) by inhibiting desaturases
- Ratios between precursor and metabolite fatty acids in serum can be used as proxies for Δ^5 and Δ^6 desaturase activity
- PCB exposure was inversely related to the estimated Δ^6 desaturase activity in 712 Faroese septuagenarians
- A positive association between PCB and Δ^5 desaturation is thought to be affected by dietary intake of metabolite PUFAs
- The results suggest a pathway for PCB exposure to affect cardiovascular disease risk in consumers of contaminated seafood

Figure 1.

Generalized additive models for the serum total PCB concentration ($\mu\text{g/g}$ lipid) (x-axis) as predictor for the average desaturase 5 (1A), desaturase 6 (1B), and desaturase 5+ 6 (1C) , after adjustment for age, sex, BMI, PUFA, statins, CVD, and diabetes.

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Table 1Characteristics of 712 Faroese septuagenarians^a

Variable	N	All	Men	Women	p-value ^b
Age at examination, mean (SD)	712	72.4 [1.2]	72.4 [1.2]	72.5 [1.1]	0.21
Sex, n (%)	712		360 (51)	352 (49)	0.76
Smoke status	712				0.0001
Never-smoker, n (%)		233 (33)	74 (21)	159 (45)	
Ex-smoker, n (%)		353 (49)	228 (63)	125 (36)	
Current smoker, n (%)		126 (18)	58 (16)	68 (19)	
BMI(kg/m ²), mean (SD)	709	28.9 (4.7)	29.1 (4.3)	28.7 (5.0)	0.30
Monthly fish dinners in recent year (0–1/2–4/ >4, %)	712	36/56/8	35/58/7	35/56/9	0.64
Monthly blubber dinners in recent year (0–1/2–4/ >4, %)	712	58/20/22	47/23/30	68/17/15	0.0001
Monthly whale meat dinners in recent year (0–1/2–4/ >4, %)	712	75/13/12	68/16/16	82/10/8	0.0001
Monthly bird dinners in recent year (0–1/2–4/ >4, %)	712	93/4/3	91/6/3	95/2/3	0.02
Serum PCB (µg/g lipid), geometric mean (IQR range)	710	8.07 (4.7; 13.8)	11.3 (7.6; 18.2)	5.7 (3.7; 9.3)	0.0001
1st tertile		3.4 (2.6; 4.7)	5.2 (4.2; 7.6)	2.7 (2.3; 3.7)	
2nd tertile		8.3 (7.1; 9.9)	12.0 (10.3; 13.6)	5.7 (5.0; 6.8)	
3rd tertile		18.8 (13.8; 23.3)	23.4 (18.3; 27.2)	12.3 (9.3; 14.2)	
Statins, n (%) yes	712	528 (74)	259 (72)	269 (76)	0.19
Diabetes, n (%) yes	712	246 (35)	130 (36)	116 (33)	0.38
History of cardiovascular disease, n (%) yes	706	161 (23)	92 (26)	69 (20)	0.06

^aMeans [with standard deviation in brackets] are listed for normally distributed parameters, otherwise the geometric mean (with IQR, interquartile range in parenthesis) and percentages as indicated.^bDifference of characteristics between men and women: two-sample t-test for continuous variables; chi-square tests for categorical variables

Table 2

Relative concentrations of selected n-3, n-6, n-9 PUFAs and ratios in serum phospholipids from 712 Faroese septuagenarians^a

	All	Men	Women
N-3			
Sum	10.4 (8.7; 12.1)	10.9 (9.17; 13.2)	9.77 (8.38; 11.4)
ALA 18:3n-3 (%)	0.23 (0.19; 0.29)	0.23 (0.18; 0.28)	0.24 (0.19; 0.29)
EPA 20:5n-3 (%)	2.42 (1.71; 3.39)	2.69 (1.91; 3.66)	2.16 (1.57; 2.89)
DHA 22:6n-3 (%)	6.40 (5.57; 7.50)	6.67 (5.80; 7.84)	6.12 (5.31; 7.05)
N-6			
Sum	29.0 (27.5; 31.1)	28.2 (26.7; 30.7)	29.8 (28.5; 31.5)
LA 18:2n-6 (%)	16.4 (14.9; 18.5)	16.1 (14.3; 18.5)	16.7 (15.2; 18.5)
DGLA 20:3n-6 (%)	2.66 (2.22; 3.24)	2.46 (2.10; 2.97)	2.88 (2.46; 3.45)
AA 20:4n-6 (%)	8.77 (7.63; 9.89)	8.59 (7.51; 9.68)	8.97 (7.80; 10.2)
N-9			
OA 18:1n-9 (%)	11.1 (10.2; 12.0)	11.3 (10.4; 12.1)	10.9 (10.1; 11.9)
EA 20:3n-9 (%)	0.19 (0.14; 0.34)	0.19 (0.14; 0.25)	0.19 (0.14; 0.26)
Ratio			
5 (AA/DGLA)	3.30 (2.71; 4.01)	3.49 (2.86; 4.29)	3.12 (2.62; 3.78)
6 (DGLA/LA)	0.16 (0.13; 0.20)	0.15 (0.12; 0.20)	0.17 (0.14; 0.21)
5+ 6 (EA/OA)	0.017 (0.013;0.022)	0.017 (0.013;0.021)	0.017 (0.014;0.023)

^aGeometric mean (with 50% range in parenthesis) and percentages as indicated.

Table 3

Associations between tertiles of lipid adjusted serum PCB concentrations and desaturase activity

	Model 1 Unadjusted	Model 2 Age, sex, and BMI	Model 3 + Competing PUFAs ^a	Model 4 + CVDs and Diabetes
	Coef. (95% CI)	Coef. (95% CI)	Coef. (95% CI)	Coef. (95% CI)
5 (AA/DGLA ratio)				
1st	Reference	Reference	Reference	Reference
	0.05	0.04	0.03	0.03
2nd	(0.03; 0.07)**	(0.02; 0.07)**	(0.01; 0.06)**	(0.01; 0.05)**
	0.09	0.08	0.06	0.05
3rd	(0.07; 0.11)**	(0.05; 0.10)**	(0.03; 0.08)**	(0.03; 0.08)**
6 (DGLA/LA ratio)				
1st	Reference	Reference	Reference	Reference
	-0.04	-0.03	-0.03	-0.04
2nd	(-0.07; -0.01)**	(-0.05; -0.001)**	(-0.06; -0.01)	(-0.06; -0.02)**
	-0.05	-0.02	-0.05	-0.05
3rd	(-0.08; -0.03)**	(-0.05; 0.004)	(-0.07; -0.02)**	(-0.07; -0.03)**
5+ 6 (EA/OA)				
1st	Reference	Reference	Reference	Reference
	-0.005	0.004	0.02	0.02
2nd	(-0.04; 0.03)	(-0.03; 0.04)	(-0.02; 0.05)	(-0.02; 0.05)
	0.00002	0.02	0.04	0.04
3rd	(-0.03; 0.03)	(-0.02; 0.05)	(0.00; 0.07)**	(0.003; 0.08)**

^a 5 and 6 adjusted for sum proportions of n3 PUFAs and EA; 5+ 6 adjusted for sum proportions of n3 and n6 PUFAs

** p<0.05 for difference from the first tertile.