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Persistent organic pollutants and biomarkers of diabetes risk in a cohort of Great Lakes sport caught fish consumers

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ABSTRACT

Background: Exposure to persistent organic pollutants (POPs) is associated with increased diabetes risk, although the mechanism of action is not well delineated.
Methods: We investigated established diabetes biomarkers that could implicate potential mechanistic pathways, including C-reactive protein (CRP), a marker of systemic inflammation; gamma glutamyl transferase (GGT), a liver enzyme associated with oxidative stress; and adiponectin, an adipokine modulating glucose regulation and fatty acid oxidation. These biomarkers as well as hemoglobin A1c (HA1c), and POPs [polychlorinated biphenyls (PCBs), *p,p*-dichlorodiphenyldichloroethylene (DDE) and polybrominated diphenyl ethers (PBDEs)] were measured in a cohort of Great Lakes sport caught fish (GLSCF) consumers. We examined associations of POPs and fish consumption with HA1c and incident diabetes, and evaluated mediation and moderation by the diabetes biomarkers.
Results: Odds of incident diabetes were elevated with exposure to DDE and PCBs. DDE and PCB 118 were positively, and fish meals were inversely, associated with HA1c. CRP was inversely associated with saltwater and total fish meals, particularly in persons with higher adiposity, but did not mediate the associations of fish meals with HA1c. There were few associations of POPs with adiponectin, CRP and GGT, with the exception of positive associations of PCB 118 with GGT, PBDEs with GGT in older persons, and PBDEs with adiponectin. Adiponectin, CRP and GGT did not mediate associations of DDE and PCBs with HA1c or incident diabetes. However, the association of DDE with HA1c was stronger in persons with higher CRP, GGT and BMI, and lower adiponectin, while the association of PCB 118 with HA1c was stronger in persons with higher GGT.
Conclusions: These findings suggest that adiponectin, CRP and GGT did not mediate effects of POPs on diabetes or HA1c. However, POPs may have stronger effects on blood glucose in persons at higher risk for diabetes.

1. Introduction

There is accumulating evidence that environmental contaminants are associated with increased diabetes risk. Many studies have investigated the risk of diabetes with exposure to one or more persistent organic pollutants (POPs), including polychlorinated biphenyls (PCBs), dibenzo-p-dioxins and chemicals with related toxicological properties, and persistent pesticides such as DDT and its metabolite *p,p*-dichlorodiphenyldichloroethylene (DDE) (reviewed by Kuo et al. (2013) and Taylor et al. (2013)). While associations have been noted in many studies, chemicals with multiple modes of action have been implicated.

Possible biologic pathways through which POPs could affect diabetes incidence have been hypothesized, including insulin

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resistance (Kern et al., 2004), pancreatic beta cell destruction (De Tata, 2014), mitochondrial dysfunction (Lee, 2011), alterations in steroid metabolism (Persky et al., 2011; Persky et al., 2012), antagonism of PPARγ expression (Remillard and Bunce, 2002), and induction of low grade chronic inflammation (Fujiyoshi et al., 2006), oxidative stress (Lee et al., 2008), and autoimmunity (Langer et al., 2002). This study explored some of these potential pathways using biomarkers of diabetes risk. Selected biomarkers were C-reactive protein (CRP), adiponectin, and gamma glutamyl transferase (GGT). C-reactive protein is a general marker of systemic inflammation, which is increased in obese persons and associated with increased risk of type 2 diabetes, independent of obesity (Dehghan et al., 2007; Duncan and Schmidt, 2006). Adiponectin, an adipokine, is positively associated with insulin sensitivity, is decreased in obesity and in persons with type 2 diabetes, and has been related to decreased risk of incident diabetes independent of adiposity (Li et al., 2009). Adiponectin has anti-inflammatory properties, including inhibition of tumor necrosis factor α and IL-6 production and induction of anti-inflammatory cytokines (Fantuzzi, 2005). GGT is a liver enzyme associated with oxidative stress that is related to increased type 2 diabetes risk, with stronger effects in persons with higher BMI (Nakanishi et al., 2003).

A significant route of exposure to POPs is through ingestion of contaminated food, in general, and fish in particular. Sport caught fish from the Great Lakes have elevated levels of PCBs and other POPs and frequent consumers of these fish have higher exposures than the general population (Turyk et al., 2012). Increased risk of diabetes with elevated POP levels has been noted in Great Lakes fish consuming populations (Codru et al., 2007;Turyk et al., 2009a), but investigations of the effects of fish consumption on diabetes risk have been inconsistent (reviewed by Wu et al. (2012) and Zhang et al. (2013)). We previously reported a relationship of DDE with incident diabetes (Turyk et al., 2009a) and of DDE and PCB 118 with prevalent diabetes (Turyk et al., 2009b) in participants in the Great Lakes Fish Consumption Study.

Hemoglobin A1c (HA1c), or glycated hemoglobin, is useful as a measure of glucose control over the lifespan of the red blood cell (3–4 months). It therefore represents more long-term glucose regulation than acute fluctuations and recently has been adopted as a test for diabetes ($\geq$6.5%) and prediabetes (5.7–6.4%) (American Diabetes Association, 2010). Because diabetes risk increases for persons with fasting plasma glucose values at the higher end of the normal range, it has been suggested that diabetes risk prediction may be more accurate if glycemic measures are treated as continuous rather than categorical variables (Tabak et al., 2012). Continuous glycemic measurements (i.e. fasting plasma glucose and HA1c) have been analyzed in relation to POP exposures in several investigations (Calvert et al., 1999; Grandjean et al., 2011; Henriksen et al., 1997; Jorgensen et al., 2008; Langer et al., 2014; Michalek et al., 1999; Suarez-Lopez et al., 2015), but the effects of POP exposures on continuous HA1c levels have not yet been evaluated in the Great Lakes Fish Consumption Study.

The current study measured diabetes biomarkers in participants in the Great Lakes Fish Consumption Study. Our purpose was to determine 1) if POPs or fish consumption were related to levels of adiponectin, CRP, and GGT; 2) if adiponectin, CRP, and GGT were related to incident diabetes or to continuous levels of HA1c; and 3) if the associations of POPs or fish consumption with incident diabetes and continuous HA1c were mediated or modified by adiponectin, CRP, and GGT.

2. Methods

2.1. Participants

The Great Lakes Consortium for the Health Assessment of Great Lakes Sport Fish Consumption was organized in 1992 (Anderson et al., 1996), and study design of the Great Lakes Fish Consumption Study through 2004–2005 has been previously described (Turyk et al., 2009b). Briefly, approximately 4,200 participants with frequent and infrequent Great Lakes sport fish consumption were recruited, including Great Lakes fishing charter boat captains, anglers who fished from inland Wisconsin lakes, and infrequent consumers (reporting consumption of fewer than six meals of Great Lakes sport fish in any year of the previous 20 years). Between 1994 and 2005, biological samples were collected at least once from 948 participants and tested for persistent pollutants (Anderson et al., 2008; Hanrahan et al., 1999; Persky et al., 2001). The current analysis incorporates data collected at follow up in 2004–2005 and in 2010.

2.2. Data collection

Self-reported diagnosis of diabetes, date of diagnosis, demographics, height, weight, smoking, alcohol use, medication use, and fish consumption were assessed by survey. In 2004–2005, 515 participants were surveyed (Turyk et al., 2009b) and data on fish meals consumed in the past year was assessed, and summarized as commercial (fresh water and saltwater) fish meals and sport caught fish meals (Great Lake or other body of water). Health data assessed in 2010 was available from 598 participants, of whom 402 also participated in the 2004–2005 data collection.

In 2004–2005, non-fasting blood was collected in red-top vacutainer tubes, allowed to clot for 20 min at room temperature, centrifuged for 15 min, transferred to solvent-rinsed glass vials, and stored at −20 °C until analysis. All laboratory tests were performed by technicians blinded to participant characteristics. Sera samples were analyzed for DDE, and for PCB and PBDE congeners as previously described (Anderson et al., 2008). Briefly, sera were extracted with hexane/ethyl ether, with clean-up and fractionation using Florisil, silica-gel and concentrated sulfuric acid. PBDEs were analyzed by gas chromatography–mass spectrometry and PCBs and DDE by gas chromatography.

Total cholesterol and triglycerides were measured by Quest Diagnostics (Auburn Hills, MI and Wood Dale, IL). Total serum lipids were calculated by the formula:

Total lipid=(total cholesterol mg/dL+2:27*triglycerides mg/dL)+62:3.

HA1c was measured in whole blood by Quest Diagnostics through affinity chromatography, which measured total glycosylated hemoglobin, from which HA1c is calculated.

Stored sera samples were assayed in 2010 for adiponectin, CRP, and GGT. Because sera samples had been through prior freeze-thaw cycles during testing for hormones in 2004–2005, we evaluated the stability of test results for these biomarkers after a series of freeze-thaw cycles in serum obtained from four donors. These tests did not indicate systematic decline in biomarker measurements with increasing freeze-thaw cycles.

Quality control was monitored using internal positive and negative controls. Inter-assay coefficients of variation (CVs) were calculated from repeated assays on 4–5% of the participant samples. For adiponectin and CRP, each participant sample was assayed in duplicate and CVs were calculated for each duplicate pair. The average CV was then calculated for each assay plate and the intra-assay CV was the average of all the plate averages. For GGT, a single measurement was obtained for each participant sample precluding calculation of an intra-assay CV.

Circulating serum levels of adiponectin and CRP were measured using Quantikine ELISA kits from R&D Systems (Minneapolis, MN). The human adiponectin/Acrp30 immunoassay (DRP300) recognizes recombinant and natural (low, middle, and high molecular weight) human total adiponectin, and had a sensitivity of 0.246 ng/mL. Intra and inter-assay CVs for participant samples were 4.8% and 9.9%, respectively. The human CRP immunoassay kit (DCRP00) had a sensitivity of 0.01 ng/mL. Intra- and inter-assay CVs were 7.9% and 13.5%, respectively. GGT was measured by the University of Illinois Hospital, Pathology Laboratory Services by an enzymatic rate method using the SYNCHRON LX® System (Beckman Coulter, Inc.). The assay sensitivity was 5 U/L and the inter-assay CV for repeated measurements of participant samples was 4.6%.

2.3. Statistical analysis

Participants were included in the analysis if data were available from 2004–2005 for POPs exposures, HA1c, serum cholesterol and triglycerides, and at least one of the diabetes biomarkers. Participants were excluded because of missing data and use of hormone medications, including systemic corticosteroids ($n=2$), steroid hormones ($n=26$), steroid hormones and corticosteroids ($n=1$), and thyroid hormones ($n=41$). We excluded participants taking hormone medications (sex steroids, corticosteroid or thyroid) because of potential effects on diabetes biomarkers and HA1c (Brand et al., 2011; Fallah et al., 2012; Sargeant et al., 2000). The final sample size for analysis was 413.

HA1c% was examined as a continuous outcome in these 413 participants. Included in this sample were 349 persons without diagnosed diabetes and with HA1c $<6.5\%$, and 64 persons with diagnosed diabetes and/or HA1c $\geq 6.5\%$: 13 with HA1c $\geq 6.5\%$ and without diagnosis, 11 with HA1c $<6.5\%$ and with diagnosis, and 40 with HA1c $\geq 6.5\%$ and with diagnosis. Subgroup analyses were performed in the 349 persons without diagnosed diabetes and with HA1c $<6.5\%$.

Incident diabetes was investigated in of 287 participants who did not have diagnosed diabetes and did not use thyroid and steroid hormone medications at the 2004–2005 follow up and who also responded to the follow up survey in 2010. Incident diabetes ($n=16$) was defined as no diagnosed diabetes in 2004–2005 and reported diabetes diagnosis in 2010.

POP exposures (DDE, sum PBDEs, PBDE 47, sum PCBs and individual congeners PCB 118, 180, 132/153, 138/163), fish consumption measures, adiponectin, CRP and GGT were analyzed as continuous variables with natural log transformations (Ln). POPs and fish consumption were also modeled as quartiles or tertiles (see Supplemental Tables 3 and 4).

Associations of POPs and fish consumption with adiponectin, GGT and CRP were examined in linear regression models, adjusting for age, BMI, gender, and serum lipids. Education, smoking, alcohol use, and specific types of medication use were considered as covariates, but were not included in the final models because they did not confound the associations. Age, BMI, and gender were evaluated for effect modification in stratified models.

Analyses of the relationships of GGT, CRP, adiponectin, POPs, and fish consumption with incident diabetes and with HA1c were conducted using logistic and ordinary least squares regression models, respectively, adjusting for gender, age, BMI, and serum lipids for POP models only. We also adjusted HA1c models for use of any diabetes medication. Education, smoking, alcohol use, serum lipids, and selected medications (beta blocker, diuretic, calcium channel blocker, antilipemic, angiotensin-converting enzyme inhibitor, any antidepressive) were included in the model if confounding was present ($>10\%$ change in effect estimate). Additional potential confounders available only for incident diabetes models were family history of diabetes and long-term prednisone use. For models with POPs as predictor variables, different types of fish meals were considered potential confounders, and the strongest confounder was selected. For models with fish meals as predictor variables, DDE and sum PCBs were considered potential confounders, and the strongest confounder was selected.

Effect modification by adiponectin, CRP, GGT and BMI was investigated using multiplicative interaction terms. For interaction terms with p-values <0.15, modification was illustrated using estimates of the exposure/outcome association at selected percentiles of the modifier. Gender and age did not modify associations of POPs and fish consumption with HA1c.

Mediation analyses were used to explore the hypothesis that these diabetes biomarkers were partial mediators in associations between POPs and diabetes. Mediation would be supported if the following factors were satisfied 1) diabetes was associated with the POP, 2) the diabetes biomarker was associated with the POP, and 3) the association of diabetes with the POP was attenuated by including the biomarker as a covariate in the regression model.

Information about fasting time prior to blood sample collection was missing for 50 persons. Adiponectin differed by fasting status prior to blood draw, with mean=10.5 mg/L for fasting ≤ 12 h and mean=9.0 mg/L for fasting >12 h ($p=0.03$). However, adjusting final adiponectin models for fasting time did not change results substantially (not shown). Fasting was not associated with GGT, CRP, POPs and fish consumption, nor did adjustment for fasting substantially affect results of cross sectional or prospective models (not shown). All statistical analyses were performed using SAS Version 9.3 (SAS Institute, Inc., Cary, NC).

3. Results

3.1. Associations among diabetes biomarkers, exposures and demographics

Associations of BMI, age, gender, education, smoking, alcohol use, and serum lipids with prevalent and incident diabetes are shown in Supplemental Table 1 and associations of these characteristics with adiponectin, GGT, CRP, HA1c, POPs and fish consumption in Tables 1 and 2. Correlations among diabetes biomarkers, POPs and fish consumption variables are found in Supplemental Table 2.

3.2. Associations of POPs and fish consumption with adiponectin, CRP, and GGT

Associations of POPs and fish consumption with adiponectin, CRP, and GGT, after adjustment for age, gender and BMI, were examined in the full cohort and in models stratified by gender, median age and median BMI (Table 3 and Supplemental Table 3). LnDDE, Lnsum PCBs and individual LnPCB congeners were not significantly associated with Lnadiponectin, LnCRP, or LnGGT (Table 3) with the exception of LnGGT, which was positively associated with tertiles of PCB 118 (Supplemental Table 3).

In stratified models (not shown), LnSum PBDEs and LnPBDE 47 were associated with LnGGT in persons of above median age ($\beta=0.13$, $p=0.02$ and $\beta=0.11$, $p=0.008$, respectively); Lnsum PBDEs was associated with Lnadiponectin in persons with above median BMI ($\beta=0.11$, $p=0.05$) and above median age ($\beta=0.18$, $p=0.003$); and LnPBDE 47 was associated with Lnadiponectin in persons with above median age ($\beta=0.13$, $p=0.009$).

Lnsaltwater fish meals were inversely associated with LnCRP in the full cohort (Table 3), and in males and persons with above median BMI ($\beta=-0.08$, $p=0.005$ and $\beta=-0.08$, $p=0.02$, respectively, not shown). Quartiles of total fish meals were inversely

Table 1
Associations of participant characteristics with diabetes biomarkers, $n=413$.

Characteristic		*LnAdiponectin*, mg/L	*LnCRP*, mg/L	*LnGGT*, U/L	*HA1c*, %
All participants	Mean[a]	10.0	2.2	21.9	5.77
	95% CI	9.4,10.6	2.0, 2.5	20.7, 23.2	5.70,5.84
Men, $n=313$	Mean[a]	8.9	2.4	24.0	5.8
Women, $n=100$	Mean[a]	14.0	1.8	16.7	5.6
	p-value[b]	<0.0001	0.07	<0.0001	0.008
Age <50 years, $n=93$	Mean[a]	8.9	2.0	21.7	5.5
Age 50–64.9 years, $n=219$	Mean[a]	10.2	2.2	22.4	5.8
Age ≥ 65 years, $n=101$	Mean[a]	10.5	2.6	21.1	6.0
	p-value[b]	0.15	0.19	0.69	<0.0001
BMI <25 kg/m^2, $n=74$	Mean[a]	14.2	1.1	17.3	5.5
BMI 25–29.9 kg/m^2, $n=174$	Mean[a]	9.8	2.2	22.2	5.7
BMI ≥ 30 kg/m^2, $n=167$	Mean[a]	8.7	3.0	24.0	5.9
	p-value[b]	<0.0001	<0.0001	0.0004	<0.0001
$\leq$ High School, $n=142$	Mean[a]	9.5	2.7	23.7	5.9
Some College, $n=132$	Mean[a]	10.9	2.1	20.5	5.7
$\geq$ 4-year College, $n=139$	Mean[a]	9.6	1.9	21.6	5.7
	p-value[b]	0.15	0.01	0.11	0.08
Smoker, $n=43$	Mean[a]	9.5	2.7	22.2	5.8
Non-smoker, $n=370$	Mean[a]	10.0	2.2	21.9	5.8
	p-value[b]	0.58	0.22	0.89	0.93
Alcohol use, $n=301$	Mean[a]	10.0	2.2	23.0	5.7
No Alcohol use, $n=107$	Mean[a]	9.9	2.1	19.2	6.0
	p-value[b]	0.83	0.77	0.002	0.003
Prevalent diabetes[c], $n=64$	Mean[a]	8.7	2.2	23.9	6.9
No prevalent diabetes[c],	Mean[a]	10.2	2.4	21.6	5.6
$n=349$	p-value[b]	0.13	0.44	0.14	<0.0001
Incident diabetes[d], $n=16$	Mean[a]	6.8	4.9	26.4	6.3
No incident diabetes[d],	Mean[a]	10.5	2.1	21.2	5.5
$n=271$	p-value[b]	0.003	<0.0001	0.18	0.003
Hemoglobin A1c, %	r	-0.15	0.10	0.10	
	p-value[e]	0.003	0.04	0.05	
Cholesterol, mg/dL	r	0.10	0.04	0.11	-0.13
	p-value[e]	0.04	0.40	0.03	0.009
Triglycerides, mg/dL	r	-0.36	0.18	0.32	0.17
	p-value[e]	<0.0001	0.0002	<0.0001	0.0005

[a] Geometric mean for adiponectin, CRP, GGT, arithmetic mean for HA1c.
[b] *P*-values are from Student's *t*-test or ANOVA.
[c] Diagnosed diabetes reported in 2004–2005 and/or HA1c $\geq$ 6.5%.
[d] No diagnosed diabetes reported in 2004–2005 and reported diabetes diagnosis in 2010.
[e] *P*-values are for Pearson's correlation coefficients.

associated with LnCRP (Supplemental Table 3). Lntotal fish meals and LnGLSCF meals were inversely associated with LnCRP only in persons with above median BMI ($\beta=-0.08$, $p=0.03$, and $\beta=-0.13$, $p=0.02$, respectively, not shown).

3.3. Associations of diabetes biomarkers with incident diabetes and hemoglobin A1c

After adjusting for confounding, Lnadiponectin was inversely associated with incident diabetes and HA1c; LnCRP was positively associated with incident diabetes, but not with HA1c; and GGT quartiles were positively but not significantly associated with incident diabetes, while LnGGT was positively but not significantly associated with HA1c (Tables 4 and 5).

3.4. Associations of POPs and fish consumption with incident diabetes: evaluation of mediation by diabetes biomarkers

Odds of incident diabetes were significantly elevated by LnDDE, LnPCB 118, LnPCB 132153, and LnPCB 138163 exposure, controlling for age, gender, BMI, and serum lipids (Table 4). LnsumPBDEs, LnPBDE 47, Lntotal fish meals and Lnsaltwater fish meals decreased odds of incident diabetes, but these associations did not reach significance (Table 4).

We found no evidence for mediation, as no substantial changes in associations of DDE and PCBs with incident diabetes were seen with adjustment for CRP or GGT, and associations of DDE, sum PCB and PCB congeners with incident diabetes were strengthened with further adjustment for adiponectin (not shown).

Because of the small number of diabetes cases, we did not explore modification of associations of POPs and fish consumption with incident diabetes by BMI, adiponectin, CRP and GGT.

3.5. Associations of POPs and fish consumption with HA1c: evaluation of mediation and moderation by diabetes biomarkers

LnDDE and LnPCB 118 were positively, and Lnsaltwater fish meals, Lntotal fish meals, and LnGLSCF meals were inversely associated with HA1c after adjustment for confounding factors (Table 5). In models that included the subgroup of participants without diabetes and with HA1c $<6.5\%$, Lntotal fish meals and Lnsaltwater fish meals, but not LnDDE, LnPCB 118 and LnGLSCF meals, remained significantly and inversely associated with HA1c (Table 5).

We found evidence for negative confounding, or strengthening of effect, by GLSCF meals for associations of DDE and PCB 118 with HA1c. Furthermore, associations of GLSCF and total fish meals with HA1c were negatively confounded by DDE and PCBs, but not PBDEs. However, associations of saltwater fish meals with HA1c were not confounded by POP exposures. The joint effect of DDE and GLSCF meals on HA1c is illustrated in Fig. 1. Mean percent HA1c was 0.43 higher in persons with the highest tertile of DDE and the lowest tertile of GLSCF meals compared to those with the lowest tertile of DDE and the highest tertile of GLSCF meals.

Table 2
Associations of participant characteristics with POPs and fish consumption, $n=413$.

Characteristic		*LnDDE* ng/g	*LnPCB* 118 ng/g	*Ln∑PCB* ng/g	*Ln∑PBDE* ng/g	*LnGLSCF meals*/yr	*LnSaltwater fish meals*/yr	*LnTotal fish meals*/yr
All participants	Mean[a]	2.0	0.12	2.4	0.30	6.6	11.4	40.2
	95% CI	1.8, 2.1	0.11,0.13	2.2, 2.5	0.28,0.32	5.5, 7.9	9.6,13.5	35.7,45.3
Men, $n=313$	Mean[a]	2.19	0.13	2.71	0.30	8.1	10.8	41.2
Women, $n=100$	Mean[a]	1.39	0.10	1.54	0.30	3.4	13.3	37.1
	p-value[b]	<0.0001	0.004	<0.0001	0.92	<0.0001	0.31	0.46
Age <50 years, $n=93$	Mean[a]	1.19	0.09	1.46	0.25	5.2	11.0	36.5
Age 50–64.9 years, $n=219$	Mean[a]	2.05	0.12	2.50	0.32	6.3	12.9	41.1
Age ≥ 65 years, $n=101$	Mean[a]	2.86	0.15	3.28	0.31	9.0	8.9	41.8
	p-value[b]	<0.0001	<0.0001	<0.0001	0.02	0.10	0.23	0.69
BMI <25 kg/m^2, $n=74$	Mean[a]	1.27	0.10	1.95	0.33	4.1	9.9	35.9
BMI 25–29.9 kg/m^2, $n=174$	Mean[a]	1.99	0.11	2.51	0.27	6.8	10.4	37.8
BMI ≥ 30 kg/m^2, $n=167$	Mean[a]	2.34	0.13	2.42	0.32	7.9	13.2	45.0
	p-value[b]	<0.0001	0.005	0.04	0.08	0.04	0.37	0.30
$\leq$ High School, $n=142$	Mean[a]	2.16	0.13	2.61	0.31	8.5	9.0	44.7
Some College, $n=132$	Mean[a]	1.97	0.11	2.22	0.31	7.1	13.2	42.5
$\geq$ 4-year College, $n=139$	Mean[a]	1.79	0.11	2.28	0.29	4.8	12.6	34.2
	p-value[b]	0.22	0.17	0.13	0.76	0.04	0.23	0.57
Smoker, $n=43$	Mean[a]	1.66	0.10	2.57	0.34	15.4	16.0	57.4
Non-smoker, $n=370$	Mean[a]	2.01	0.12	2.35	0.30	6.0	10.9	38.6
	p-value[b]	0.20	0.14	0.44	0.22	0.001	0.19	0.02
Alcohol use, $n=301$	Mean[a]	2.09	0.12	2.46	0.30	7.6	12.2	44.2
No alcohol use, $n=107$	Mean[a]	1.76	0.11	2.15	0.29	4.3	9.6	30.9
	p-value[b]	0.16	0.10	0.07	0.79	0.005	0.25	0.02
Prevalent diabetes[c], $n=64$	Mean[a]	3.28	0.16	3.03	0.31	6.6	11.1	40.4
No prevalent diabetes[c],	Mean[a]	1.79	0.11	2.27	0.30	6.6	11.4	40.2
$n=349$	*p*-value[b]	<0.0001	0.0009	0.003	0.78	0.99	0.91	0.98
Incident diabetes[d], $n=16$	Mean[a]	3.8	0.22	3.4	0.26	6.7	6.8	32.5
No incident diabetes[d],	Mean[a]	1.8	0.11	2.3	0.30	6.3	12.3	39.7
$n=271$	*p*-value[b]	<0.0001	0.0002	0.03	0.23	0.89	0.19	0.53
Hemoglobin A1c, %	*r*	0.30	0.19	0.17	0.01	-0.04	-0.07	-0.08
	p-value[e]	<0.0001	0.0001	0.0006	0.77	0.40	0.18	0.10
Cholesterol, mg/dL	*r*	0.06	0.11	0.12	0.09	-0.02	0.01	0.002
	p-value[e]	0.25	0.03	0.01	0.07	0.73	0.78	0.97
Triglycerides, mg/dL	*r*	0.21	0.20	0.21	0.08	0.02	-0.02	-0.03
	p-value[e]	<0.0001	<0.0001	<0.0001	0.09	0.76	0.67	0.54

[a] Geometric mean.
[b] *P*-values are from Student's *t*-test or ANOVA.
[c] Diagnosed diabetes reported in 2004–2005 and/or HA1c $\geq$ 6.5%.
[d] No diagnosed diabetes reported in 2004–2005 and reported diabetes diagnosis in 2010.
[e] *P*-values are for Pearson's correlation coefficients.

Mediation was assessed by further adjusting multivariable models for Lnadiponectin, LnCRP, or LnGGT, but little change was observed in the magnitude of associations of LnDDE, LnPCB 118, Lntotal fish meals, Lnsaltwater fish meals, and LnGLSCF meals with HA1c (not shown).

GGT, CRP, adiponectin and BMI modified the positive association of LnDDE with HA1c, with stronger effects in persons with higher GGT, CRP, and BMI and with lower adiponectin (Table 6). Similarly, the effect of LnPCB 118 on HA1c was stronger in persons with higher GGT. Inverse associations of Lntotal fish meals and LnGLSCF meals with HA1c were stronger in persons with higher CRP and GGT, respectively. The decline in HA1c with saltwater fish ingestion was larger in those with lower BMI and adiponectin.

4. Discussion

We previously reported positive associations of DDE and PCB 118, but not PBDEs, with prevalent diabetes in the 2004–2005 cross-sectional data from this cohort (Turyk et al., 2009a, 2009b). The current study extends our investigations of the same dataset, finding positive associations of DDE and PCB 118 with a continuous measure of glycemic control, HA1c. However, associations of DDE and PCB 118 with HA1c did not reach significance in the subgroup analysis that focused on participants without diagnosed diabetes and with HA1c levels below 6.5% [the threshold used to identify potential diabetes for population screening (American Diabetes Association, 2010)], suggesting that the effect of POPs on glucose dysregulation may be more important for development of diabetes than prediabetes. Analyses of cross sectional National Health and Nutrition Examination Survey (NHANES) data that defined prediabetes by HA1c% found that PCB 118 was associated with HA1c% in the higher range (5.9–6.4%), but not in the lower range of 5.7–5.8% (Everett and Thompson, 2012), and that DDE was associated with diabetes but not prediabetes (Everett and Matheson, 2010). However, a 23-year longitudinal investigation found that PCB exposure was associated with increased HA1c% during follow up in persons who became diabetic by year 20 as well as in non-diabetic controls (Suarez-Lopez et al., 2015).

Our findings on elevated incident diabetes risk with DDE exposure are consistent with published results in this cohort based on follow up from 1993 to 2005 (Turyk et al., 2009a). While we did not previously detect an association of PCBs with incident diabetes, the current analysis revealed increased diabetes risk with PCB exposure. The association of PCBs with incident diabetes is consistent with some (Lee et al., 2010, 2011; Vasiliu et al., 2006; Wu et al., 2013), but not all prospective investigations on this topic (Rignell-Hydbom et al., 2009; Zani et al., 2013).

Our past work did not identify any associations of years consuming sport caught fish with incident and prevalent diabetes

Table 3
Association of POPs and fish consumption with adiponectin, CRP and GGT, n=413.

Biomarker	*Exposure*	*Beta-coefficient, p-value*[a]
LnAdiponectin	LnDDE	0.02, 0.68
	LnPCB 118	−0.01, 0.89
	Ln∑PCBs	0.02, 0.68
	LnPBDE 47	0.04, 0.26
	Ln∑PBDEs	0.08, 0.07[b]
	LnGLSCF meals	−0.01. 0.38
	LnSaltwater fish meals	−0.01, 0.71
	LnTotal fish meals	0.03, 0.24
LnCRP	LnDDE	−0.01, 0.90
	LnPCB 118	0.02, 0.82
	Ln∑PCBs	−0.04, 0.64
	LnPBDE 47	0.02, 0.74
	Ln∑PBDEs	0.04, 0.56
	LnGLSCF meals	−0.01, 0.79
	LnSaltwater fish meals	−0.06, 0.045
	LnTotal fish meals	−0.03, 0.54
LnGGT	LnDDE	0.05, 0.12
	LnPCB 118	0.07, 0.10
	Ln∑PCBs	0.04, 0.33
	LnPBDE 47	0.04, 0.13
	Ln ∑PBDEs	0.06, 0.13
	LnGLSCF meals	0.01, 0.68
	LnSaltwater fish meals	0.002, 0.92
	LnTotal fish meals	−0.02, 0.95

PCB 132153, PCB 138163, PCB 180 were not associated with biomarkers and are not shown in table.

[a] Linear regression models adjusted for age, gender, and BMI. Models with POPs also adjusted for serum lipids.

[b] Significant with control for fasting.

(Turyk et al., 2009a, 2009b). The current analysis focused on different fish consumption metrics, namely meals of fish consumed in the past year, including total fish meals, saltwater fish meals and GLSCF meals. Odds of incident diabetes were reduced, but not significantly, with increasing total and saltwater fish meals. HA1c was inversely and significantly associated with total and saltwater fish meals in the full cohort and remained significantly and inversely associated in the subgroup analysis that included only participants without diagnosed diabetes and with HA1c levels below 6.5%, suggesting that fish consumption may affect blood glucose levels in the normal and prediabetic range as well as the diabetic range. In persons without diabetes, eating oily fish was inversely associated with HA1c in women but not men, but the association was attenuated with adjustment for family history of diabetes, smoking, physical activity, alcohol, total energy and fruit and vegetable intake (Harding et al., 2004). Among diabetics, intake of fish has been associated with decreased HA1c (Lee et al., 2012). In the current study we were not able to determine which component of fish could account for its effect on blood glucose. Protective effects of fish consumption on diabetes have been attributed to omega-3 fatty acids, mediated in part through reduction of triglycerides and inflammation (Carpentier et al., 2006), but interventions (Akinkuolie et al., 2011; Fedor and Kelley 2009) and prospective observational studies (Wu et al., 2012; Zhang et al., 2013) have not consistently reported a beneficial effect of marine omega-3 fatty acids on insulin resistance and diabetes.

GLSCF meals were inversely associated with HA1c only after adjustment for DDE exposure, while positive associations of DDE and PCB 118 with HA1c were strengthened after control for GLSCF meals. These findings emphasize the importance of adjusting for both POP exposures and fish intake in investigations of populations ingesting contaminated fish, and are consistent with a study of sport fish consumers that noted elevated odds of diabetes with DDE and PCB exposure, but decreased odds of diabetes with increasing total fish and trout consumption, with adjustment for PCBs (Philibert et al., 2009). On the other hand, a cross sectional investigation of Finnish fishermen did not find that co-adjustment for environmental contaminants, including POPs, and omega-3 fatty acids affected associations of either factor modeled separately with glucose, insulin resistance, or inflammatory markers (Turunen et al., 2013). Inconsistent effects of fish and marine omega-3 fatty acid intake on diabetes risk in prospective observational studies could potentially be confounded by unmeasured contaminant exposures (Wu et al., 2012; Zhang et al., 2013).

Our findings of elevated risk of incident diabetes with elevated CRP and GGT and decreased risk with elevated adiponectin levels were consistent with the literature (Dehghan et al., 2007; Duncan and Schmidt, 2006; Nakanishi et al., 2004). However, we detected few associations of these diabetes biomarkers with POPs and fish ingestion, with the exception of positive associations of GGT with PCB 118 and with PBDEs in older persons, a positive association of adiponectin with PBDEs, and inverse associations of CRP with fish ingestion, particularly in persons with higher adiposity. Furthermore, adiponectin, CRP and GGT did not attenuate associations of

Table 4
Associations of POPs, fish consumption, adiponectin, GGT and CRP with incident diabetes.

Exposure or biomarker	*Odds of incident diabetes: Model 1*[a]			*Odds of incident diabetes: Model 2*[b]			
	OR	*95% CI*	*P value*	*OR*	*95% CI*	*P value*	*Additional confounders*
LnAdiponectin	0.20	0.07, 0.56	0.002	0.20	0.07, 0.56	0.002	None
LnCRP	2.87	1.19, 6.89	0.02	3.22	1.25, 8.29	0.02	Lnsaltwater fish meals
LnGGT	1.75	0.77, 3.96	0.18	1.50	0.57, 3.90	0.41	Family history diabetes
Quartile GGT	1.86	1.04, 3.30	0.04	1.70	0.93, 3.11	0.08	Family history diabetes
LnDDE	2.08	1.01, 4.29	0.05	2.63	1.17, 5.89	0.02	Calcium channel blocker use
LnPCB 118	2.83	1.35, 5.90	0.006	3.28	1.50, 7.18	0.003	Lntotal fish meals
LnPCB 132153	2.59	1.05, 6.40	0.04	3.24	1.17, 9.03	0.02	Calcium channel blocker use, Lntotal fish meals, education
LnPCB 138163	2.64	1.12, 6.24	0.03	3.62	1.38, 9.52	0.009	Calcium channel blocker use, Lntotal fish meals
LnPCB 180	1.89	0.74, 4.87	0.19	2.33	0.86, 6.35	0.10	Lntotal fish meals
Ln∑PCB	2.43	0.96, 6.12	0.06	3.38	1.19, 9.59	0.02	Calcium channel blocker use, Lntotal fish meals
LnPBDE 47	0.71	0.38, 1.34	0.29	0.71	0.38, 1.34	0.29	None
Ln∑PBDE	0.44	0.16, 1.21	0.11	0.44	0.16, 1.21	0.11	None
LnTotal fish meals	0.79	0.51, 1,23	0.30	0.66	0.40, 1,09	0.10	Ln∑ PCBs
LnSaltwater fish meals	0.80	0.59, 1.08	0.14	0.80	0.59, 1.11	0.18	None
LnGLSCF meals	1.02	0.75 1.39	0.89	0.89	0.63, 1.26	0.50	Ln∑ PCBs

N=287, including 16 incident diabetes cases.

[a] Model 1 adjusted for age, BMI, gender and serum lipids for POP models.

[b] Model 2 adjusted for all covariates in Model 1 and for additional covariates determined to be confounders.

Table 5
Cross sectional associations of POPs, fish consumption, adiponectin, GGT, and CRP with hemoglobin A1c.

Group	*Exposure or biomarker*	*Association of exposure with hemoglobin A1c*						
		Model 1[a]			Model 2[b]			
		Beta	*95% CI*	*P-value*	*Beta*	*95% CI*	*P-value*	*Additional confounders*
With and without diabetes $N=413$	LnAdiponectin	−0.159	−0.246, −0.072	0.0004	−0.159	−0.246, −0.072	0.0004	None
	LnCRP	0.027	−0.026, 0.081	0.31	0.011	−0.044, 0.065	0.70	Education, serum lipids, ace inhibitor use
	LnGGT	0.100	0.005, 0.195	0.04	0.076	−0.026, 0.178	0.15	Alcohol use, serum lipids, antilipid use, LnDDE
	LnDDE	0.099	0.034, 0.164	0.003	0.118	0.051, 0.186	0.0006	LnGLSCF meals
	LnPCB 118	0.055	−0.024, 0.133	0.17	0.091	0.007, 0.175	0.03	Alcohol use, LnGLSCF meals
	LnTotal fish meals	−0.059	−0.102, −0.016	0.007	−0.072	−0.115, −0.029	0.001	LnDDE
	LnSaltwater fish meals	−0.030	−0.060, −0.001	0.045	−0.030	−0.060, −0.001	0.045	None
	LnGLSCF meals	−0.019	−0.049, 0.010	0.20	−0.039	−0.069, −0.008	0.01	Smoking, LnDDE
No diabetesand HA1c < 6.5% $N=349$	LnAdiponectin	−0.084	−0.148, −0.019	0.01	−0.074	−0.138, −0.009	0.03	Alcohol use
	LnCRP	0.007	−0.030, 0.044	0.70	−0.011	−0.048, 0.026	0.55	Alcohol use, smoking, lnsaltwater fish, serum lipids, beta-blocker use, ace inhibitor use, diuretic use
	LnGGT	0.037	−0.026, 0.100	0.25	0.035	−0.034, 0.103	0.32	Alcohol use, antilipid use, serum lipids
	LnDDE	0.011	−0.035, 0.057	0.64	0.025	−0.022, 0.071	0.30	Smoking, Lntotal fish meals
	LnPCB 118	0.010	−0.047, 0.067	0.73	0.033	−0.027, 0.093	0.27	Alcohol use, LnGLSCF meals
	LnTotal fish meals	−0.040	−0.070, −0.011	0.008	−0.040	−0.070, −0.011	0.008	None
	LnSaltwater fish meals	−0.029	−0.050, −0.009	0.005	−0.029	−0.050, −0.009	0.005	None
	LnGLSCF meals	−0.008	−0.029, 0.012	0.41	−0.014	−0.036, 0.007	0.18	Smoking, LnDDE

Sum PCB, PCB 132153, PCB 138163, PCB 180, Sum PBDE, PBDE 47 were not associated with HA1c and are not shown in table.

[a] Model 1 adjusted for age, BMI, and gender, for all models; serum lipids for POP models; and diabetes medication use for models for participant group: "with and without diabetes".

[b] Model 2 adjusted for all covariates in Model 1 and for additional covariates determined to be confounders.

POPs with either HA1c or incident diabetes, and this study does not lend support for any of these biomarkers as mediators of associations of POPs and diabetes.

We detected a positive association of sum PBDEs with adiponectin in the entire cohort, and in persons with higher body mass or older age, suggesting improved insulin sensitivity with increased PBDE exposure. Supporting this observation is our finding of a non-significant trend towards reduction of incident diabetes risk with PBDE exposure. To our knowledge, no other epidemiologic studies have investigated effects of PBDEs on adiponectin; however, decreased insulin-stimulated glucose oxidation was observed in adipocytes isolated from penta-BDE treated rats (Hoppe and Carey, 2007). We did not observe associations of DDE or PCBs with adiponectin, overall or by age, gender, or BMI strata. In contrast, three other epidemiological investigations found inverse associations (Lim and Jee, 2014; Mullerova et al., 2008) or trends (Kern et al., 2004) of PCBs or related chemicals with adiponectin, and stronger effects in subgroups with elevated BMI (Lim and Jee, 2014; Mullerova et al., 2008). Evidence that PCB 153 (Taxvig et al., 2012) and DDE (Howell and Mangum, 2011) promote adipocyte dysfunction *in vitro* supports these results. Reasons for differences in the effect of PCBs on adiponectin in these

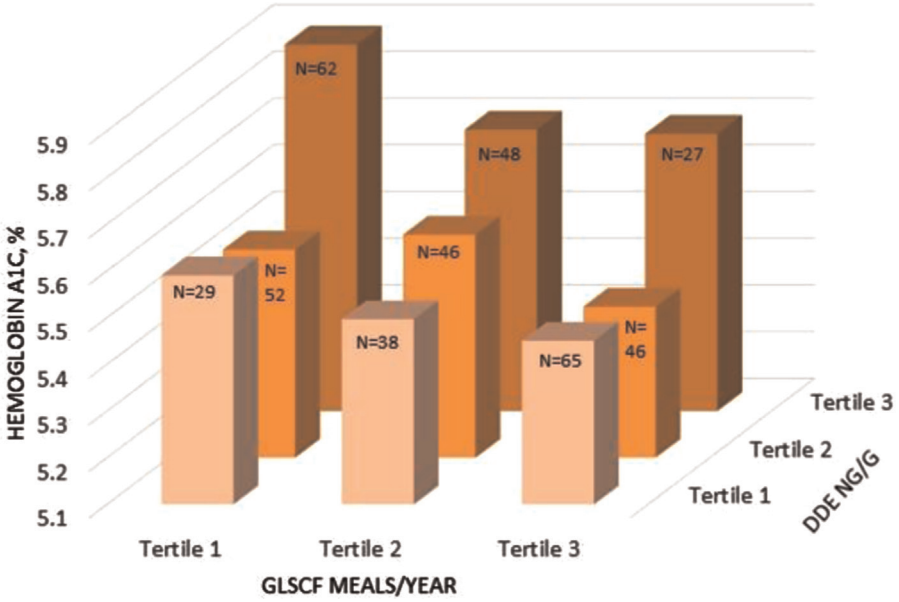

Fig. 1. Joint effect of DDE exposure and GLSCF meals in past year on HA1c levels, adjusted for age centered, gender, BMI centered, diabetes medication use, and serum lipids centered. Total $N=413$, number of participants in each group is shown in on bar.

Table 6
Modification of associations of POPs and fish consumption with HA1c by BMI, adiponectin, CRP and GGT.

Participant group	*Exposure*	*Modifier*	*Interaction p-value*	*Conditional associations of Hemoglobin A1c with POPs and fish consumption at selected percentiles of modifying variable*[a]		
				25th *Percentile Beta*[b], *p-value*	50th *Percentile Beta*[b], *p-value*	75th *Percentile Beta*[b], *p-value*
With and without diabetes, $n=413$	LnDDE	BMI	0.03	0.08, 0.04	0.11, 0.002	0.15, <0.0001
		Adiponectin	0.04	0.16, 0.0002	0.13, 0.0002	0.10, 0.01
		CRP	0.05	0.07, 0.07	0.12, 0.0005	0.15, 0.0001
		GGT	0.09	0.08, 0.05	0.11, 0.002	0.14, 0.0002
	LnPCB 118	GGT	0.05	0.03, 0.56	0.07, 0.09	0.12, 0.01
	LnTotal fish meals	CRP	0.13	−0.06, 0.01	−0.08, 0.0004	−0.10, 0.0007
	LnSaltwater fish meals	BMI	0.11	−0.05, 0.01	−0.03, 0.03	−0.02, 0.38
		Adiponectin	0.02	−0.06. 0.003	−0.03, 0.03	−0.01, 0.54
	LnGLSCF meals	GGT	0.14	−0.03, 0.12	−0.04, 0.01	−0.05, 0.004
No diabetes and HA1c $<6.5\%$, $n=349$	LnDDE	CRP	0.09	−0.001, 0.98	0.32, 0.22	0.05, 0.08
	LnTotal fish meals	GGT	0.12	−0.03, 0.13	−0.04, 0.01	−0.05, 0.001
	LnSaltwater fish meals	BMI	0.03	−0.04, 0.0004	−0.03, 0.002	−0.02, 0.13

[a] A total of 40 models were examined but results shown in table only if *p*-value for interaction of modifier with exposure <0.15.
[b] Adjusted for age, BMI, and gender, for all models; serum lipids for POP models; and diabetes medication use for models for participant group: "with and without diabetes". Additional covariates were included if determined to be confounders (see Table 5)

investigations and in the current study are not clear, but could be related to variability in population characteristics and exposures. Finally, fish ingestion was not related to adiponectin levels, although increased adiponectin has been detected in fish intake intervention studies (Kondo et al., 2010; Lara et al., 2007; Neale et al., 2013; Zhang et al., 2012).

POPs have been associated with increased inflammation, assessed by a variety of biomarkers (Fujiyoshi et al., 2006; Imbeault et al., 2012; Kumar et al., 2014b; Kuwatsuka et al., 2014). In the current study, we did not find any associations of POPs with CRP, and other investigators have inconsistently detected effects of POPs on CRP. Occupational PCB exposure was associated with elevated CRP in women (Persky et al., 2011), but not men (Persky et al., 2012); Organochlorine pesticides were positively and PCBs were inversely associated with CRP in NHANES participants (Ha et al., 2007; Kim et al., 2012); and dioxin-like chemicals, PCBs, and organochlorine pesticides did not affect CRP in two other studies (Kumar et al., 2014b; Turunen et al., 2013). Our findings of inverse associations of saltwater fish meals and total fish meals with CRP are consistent with observational and intervention studies (He et al., 2009; Ouellet et al., 2008; Ramel et al., 2010; Smith et al., 2009).

GGT, an independent risk factor for the development of cardiovascular disease and diabetes, is induced by oxidative stress and catalyzes the first step in the degradation of glutathione, which functions as a conjugating ligand for phase II metabolism of xenobiotics, such as POPs (Lee et al., 2008). Exposures to POPs have been associated with increased GGT, even within the normal reference range in some (Chen et al., 2006; Lee and Jacobs, 2006; Sweeney and Mocarelli, 2000), but not all reports (Kumar et al., 2014a; Persky et al. 2011, 2012). In the current study, PCB 118 was positively associated with GGT, as were PBDEs in persons of above median age.

BMI, adiponectin, GGT and CRP modified the association of DDE with HA1c, with stronger effects of DDE on HA1c in persons with higher levels of risk for diabetes (higher BMI, GGT and CRP and lower adiponectin). Similarly, GGT modified the association of PCB 118 with HA1c. A cross sectional analysis of NHANES data examined modification of the effect of POPs on insulin resistance by CRP, with results similar to ours, namely stronger effects of POPs on insulin resistance in persons with higher concentrations of CRP (Kim et al., 2012). There is also evidence of effect modification of associations of diabetes and POPs by body weight, with stronger effects in persons with higher adiposity (Lee et al., 2014). With respect to fish intake, our findings suggest that the inverse association of fish consumption with HA1c is stronger in persons with higher levels of the diabetes biomarkers. However, this was not the case for adiposity, as the inverse association of saltwater fish meals with HA1c was stronger in those with lower body mass, which is consistent with a meta-analysis concluding that that fish consumption was related to lower risk of diabetes in populations with lower BMI (Wu et al., 2012).

There are several limitations to this study. First, with respect to measurement of biomarkers, there may have been some loss of activity due to long term storage and prior freeze/thaw cycles. However, all of the serum samples were handled similarly, so we do not expect differential bias in statistical estimates. Second, diabetes diagnosis and fish consumption were collected by self report and may be affected by measurement error, although misclassification is unlikely to be differential. Third, there may be residual confounding for variables with measurement errors or for unmeasured variables, such as other dietary factors (Boeing et al., 2000; Harding et al., 2004; Prynne et al., 2009), physical activity, and other contaminants. Fourth, adjustment of POPs models for serum lipids is appropriate for non-fasting samples, but could potentially result in attenuated effect estimates if serum lipids are intermediates in the causal pathway between POPs and diabetes (Taylor et al., 2013). Nevertheless, this study takes advantage of an established, well characterized cohort and is one of the first studies to explore the role of diabetes biomarkers in the effect of POPs on diabetes risk.

5. Conclusions

This investigation found that odds of incident diabetes were elevated with exposure to DDE and PCBs and that DDE and PCB 118 were positively associated with HA1c. Fish intake was inversely associated with HA1c, suggesting the presence of nutrients in fish that modify glucose levels. Co-adjustment for POPs and fish consumption strengthened associations of either factor modeled separately, highlighting the importance of assessing both POP exposures and fish intake in populations ingesting contaminated fish.

Few associations of DDE and PCB exposure with adiponectin, CRP, and GGT were detected, and fish consumption was inversely related to CRP measurements. Diabetes biomarkers did not mediate associations of POPs or fish consumption with HA1c or with incident diabetes. Our findings suggest that while adiponectin, CRP and GGT do not mediate the effect of POPs on HA1c, positive associations of POPs with HA1c are stronger in persons with higher levels of these diabetes risk factors.

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Human subjects research review

This study was conducted in accordance with national and institutional guidelines for the protection of human subjects. Prior to initiation of this study protocol, it was reviewed and approved by both the University of Illinois-Chicago Internal Review Board and University of Wisconsin-Madison Medical School Human Subjects Committee. Informed consent was obtained from each subject prior to participation.

Appendix A. Suplementary Information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2015.03.037.

References

Akinkuolie, A.O., Ngwa, J.S., Meigs, J.B., Djousse, L., 2011. Omega-3 polyunsaturated fatty acid and insulin sensitivity: a meta-analysis of randomized controlled trials. Clin. Nutr. 30, 702–707.

American Diabetes Association, 2010. Standards of medical care in diabetes – 2010. Diabetes Care 33 (Suppl 1), S11–S61. http://dx.doi.org/10.2337/dc10-S011.

Anderson, H., Falk, C., Fiore, B., Hanrahan, L., Humphrey, H.E., Kanarek, M., et al., 1996. Consortium for the health assessment of great lakes sport fish consumption. Toxicol. Ind. Health 12, 369–373.

Anderson, H.A., Imm, P., Knobeloch, L., Turyk, M., Mathew, J., Buelow, C., et al., 2008. Polybrominated diphenyl ethers (PBDE) in serum: findings from a US cohort of consumers of sport-caught fish. Chemosphere 73, 187–194.

Boeing, H., Weisgerber, U.M., Jeckel, A., Rose, H.J., Kroke, A., 2000. Association between glycated hemoglobin and diet and other lifestyle factors in a nondiabetic population: cross-sectional evaluation of data from the Potsdam cohort of the European Prospective Investigation into Cancer and Nutrition Study. Am. J. Clin. Nutr. 71, 1115–1122.

Brand, J.S., Wareham, N.J., Dowsett, M., Folkerd, E., van der Schouw, Y.T., Luben, R.N., et al., 2011. Associations of endogenous testosterone and SHBG with glycated haemoglobin in middle-aged and older men. Clin. Endocrinol. 74, 572–578.

Calvert, G.M., Sweeney, M.H., Deddens, J., Wall, D.K., 1999. Evaluation of diabetes mellitus, serum glucose, and thyroid function among United States workers exposed to 2,3,7,8-tetrachlorodibenzo-p-dioxin. Occup. Environ. Med. 56, 270–276.

Carpentier, Y.A., Portois, L., Malaisse, W.J., 2006. n-3 fatty acids and the metabolic syndrome. Am. J. Clin. Nutr. 83, 1499S–1504S.

Chen, H.L., Su, H.J., Guo, Y.L., Liao, P.C., Hung, C.F., Lee, C.C., 2006. Biochemistry examinations and health disorder evaluation of Taiwanese living near incinerators and with low serum PCDD/Fs levels. Sci. Total Environ. 366, 538–548.

Codru, N., Schymura, M.J., Negoita, S., Rej, R., Carpenter, D.O., 2007. Diabetes in relation to serum levels of polychlorinated biphenyls and chlorinated pesticides in adult Native Americans. Environ. Health Perspect. 115, 1442–1447.

De Tata, V., 2014. Association of dioxin and other persistent organic pollutants (POPs) with diabetes: epidemiological evidence and new mechanisms of beta cell dysfunction. Int. J. Mol. Sci. 15, 7787–7811.

Dehghan, A., Kardys, I., de Maat, M.P., Uitterlinden, A.G., Sijbrands, E.J., Bootsma, A. H., et al., 2007. Genetic variation, C-reactive protein levels, and incidence of diabetes. Diabetes 56, 872–878.

Duncan, B.B., Schmidt, M.I., 2006. The epidemiology of low-grade chronic systemic inflammation and type 2 diabetes. Diabetes Technol. Ther. 8, 7–17.

Everett, C.J., Matheson, E.M., 2010. Biomarkers of pesticide exposure and diabetes in the 1999–2004 national health and nutrition examination survey. Environ. Int. 36, 398–401.

Everett, C.J., Thompson, O.M., 2012. Associations of dioxins, furans and dioxin-like PCBs with diabetes and pre-diabetes: is the toxic equivalency approach useful? Environ. Res. 118, 107–111.

Fallah, S., Sanjary, P.M., Rabbani, C.A., Korani, M., 2012. Adiponectin, leptin and lipid profiles evaluation in oral contraceptive pill consumers. Arch. Gynecol. Obstet. 285, 1747–1752.

Fantuzzi, G., 2005. Adipose tissue, adipokines, and inflammation. J. Allergy Clin. Immunol. 115, 911–919.

Fedor, D., Kelley, D.S., 2009. Prevention of insulin resistance by n-3 polyunsaturated fatty acids. Curr. Opin. Clin. Nutr. Metab. Care 12, 138–146.

Fujiyoshi, P.T., Michalek, J.E., Matsumura, F., 2006. Molecular epidemiologic evidence for diabetogenic effects of dioxin exposure in U.S. Air force veterans of the Vietnam war. Environ. Health Perspect. 114, 1677–1683.

Grandjean, P., Henriksen, J.E., Choi, A.L., Petersen, M.S., Dalgard, C., Nielsen, F., et al., 2011. Marine food pollutants as a risk factor for hypoinsulinemia and type 2 diabetes. Epidemiology 22, 410–417.

Ha, M.H., Lee, D.H., Jacobs, D.R., 2007. Association between serum concentrations of persistent organic pollutants and self-reported cardiovascular disease prevalence: results from the National Health and Nutrition Examination Survey, 1999–2002. Environ. Health Perspect. 115, 1204–1209.

Hanrahan, L.P., Falk, C., Anderson, H.A., Draheim, L., Kanarek, M.S., Olson, J., 1999. Serum PCB and DDE levels of frequent Great Lakes sport fish consumers-a first look. The Great Lakes Consortium. Environ. Res. 80, S26–S37.

Harding, A.H., Day, N.E., Khaw, K.T., Bingham, S.A., Luben, R.N., Welsh, A., et al., 2004. Habitual fish consumption and glycated haemoglobin: the EPIC-Norfolk study. Eur. J. Clin. Nutr. 58, 277–284.

He, K., Liu, K., Daviglus, M.L., Jenny, N.S., Mayer-Davis, E., Jiang, R., et al., 2009. Associations of dietary long-chain n-3 polyunsaturated fatty acids and fish with biomarkers of inflammation and endothelial activation (from the Multi-Ethnic Study of Atherosclerosis [MESA]). Am. J. Cardiol. 103, 1238–1243.

Henriksen, G.L., Ketchum, N.S., Michalek, J.E., Swaby, J.A., 1997. Serum dioxin and diabetes mellitus in veterans of Operation Ranch Hand. Epidemiology 8, 252–258.

Hoppe, A.A., Carey, G.B., 2007. Polybrominated diphenyl ethers as endocrine disruptors of adipocyte metabolism. Obesity 15, 2942–2950.

Howell III, G., Mangum, L., 2011. Exposure to bioaccumulative organochlorine compounds alters adipogenesis, fatty acid uptake, and adipokine production in NIH3T3-L1 cells. Toxicol. In Vitro 25, 394–402.

Imbeault, P., Findlay, C.S., Robidoux, M.A., Haman, F., Blais, J.M., Tremblay, A., et al., 2012. Dysregulation of cytokine response in Canadian First Nations communities: is there an association with persistent organic pollutant levels? PLoS One 7, e39931.

Jorgensen, M.E., Borch-Johnsen, K., Bjerregaard, P., 2008. A cross-sectional study of the association between persistent organic pollutants and glucose intolerance among Greenland Inuit. Diabetologia 51, 1416–1422.

Kern, P.A., Said, S., Jackson Jr., W.G., Michalek, J.E., 2004. Insulin sensitivity following agent orange exposure in Vietnam veterans with high blood levels of 2,3,7,8-tetrachlorodibenzo-p-dioxin. J. Clin. Endocrinol. Metab. 89, 4665–4672.

Kim, K.S., Hong, N.S., Jacobs Jr., D.R., Lee, D.H., 2012. Interaction between persistent organic pollutants and C-reactive protein in estimating insulin resistance among non-diabetic adults. J. Prev. Med. Public Health 45, 62–69.

Kondo, K., Morino, K., Nishio, Y., Kondo, M., Fuke, T., Ugi, S., et al., 2010. Effects of a fish-based diet on the serum adiponectin concentration in young, non-obese, healthy Japanese subjects. J. Atheroscler. Thromb. 17, 628–637.

Kumar, J., Lind, L., Salihovic, S., van, B.B., Ingelsson, E., Lind, P.M., 2014a. Persistent organic pollutants and liver dysfunction biomarkers in a population-based human sample of men and women. Environ. Res. 134, 251–256.

Kumar, J., Lind, P.M., Salihovic, S., van, B.B., Ingelsson, E., Lind, L., 2014b. Persistent organic pollutants and inflammatory markers in a cross-sectional study of elderly swedish people: the PIVUS cohort. Environ. Health Perspect. 122, 977–983.

Kuo, C.C., Moon, K., Thayer, K.A., Navas-Acien, A., 2013. Environmental chemicals and type 2 diabetes: an updated systematic review of the epidemiologic evidence. Curr. Diabetes Rep. 13, 831–849.

Kuwatsuka, Y., Shimizu, K., Akiyama, Y., Koike, Y., Ogawa, F., Furue, M., et al., 2014. Yusho patients show increased serum IL-17, IL-23, IL-1beta, and TNFalpha levels more than 40 years after accidental polychlorinated biphenyl poisoning. J. Immunotoxicol. 11, 246–249.

Langer, P., Tajtakova, M., Guretzki, H.J., Kocan, A., Petrik, J., Chovancova, J., et al., 2002. High prevalence of anti-glutamic acid decarboxylase (anti-GAD) antibodies in employees at a polychlorinated biphenyl production factory. Arch. Environ. Health 57, 412–415.
Langer, P., Ukropec, J., Kocan, A., Drobna, B., Radikova, Z., Huckova, M., et al., 2014. Obesogenic and diabetogenic impact of high organochlorine levels (HCB, p,p'-DDE, PCBs) on inhabitants in the highly polluted Eastern Slovakia. Endocr. Regul. 48, 17–24.
Lara, J.J., Economou, M., Wallace, A.M., Rumley, A., Lowe, G., Slater, C., et al., 2007. Benefits of salmon eating on traditional and novel vascular risk factors in young, non-obese healthy subjects. Atherosclerosis 193, 213–221.
Lee, D.H., Jacobs Jr., D.R., 2006. Association between serum concentrations of persistent organic pollutants and gamma glutamyltransferase: results from the National Health and Examination Survey 1999–2002. Clin. Chem. 52, 1825–1827.
Lee, D.H., Lind, P.M., Jacobs Jr., D.R., Salihovic, S., van, B.B., Lind, L., 2011. Polychlorinated biphenyls and organochlorine pesticides in plasma predict development of type 2 diabetes in the elderly: the prospective investigation of the vasculature in Uppsala Seniors (PIVUS) study. Diabetes Care 34, 1778–1784.
Lee, D.H., Porta, M., Jacobs Jr., D.R., Vandenberg, L.N., 2014. Chlorinated persistent organic pollutants, obesity, and type 2 diabetes. Endocr. Rev. 35, 557–601.
Lee, D.H., Steffes, M.W., Jacobs Jr., D.R., 2008. Can persistent organic pollutants explain the association between serum gamma-glutamyltransferase and type 2 diabetes? Diabetologia 51, 402–407.
Lee, D.H., Steffes, M.W., Sjodin, A., Jones, R.S., Needham, L.L., Jacobs Jr., D.R., 2010. Low dose of some persistent organic pollutants predicts type 2 diabetes: a nested case-control study. Environ. Health Perspect. 118, 1235–1242.
Lee, H.K., 2011. Mitochondrial dysfunction and insulin resistance: the contribution of dioxin-like substances. Diabetes Metab. J. 35, 207–215.
Lee, K.L., Yoon, E.H., Lee, H.M., Hwang, H.S., Park, H.K., 2012. Relationship between food-frequency and glycated hemoglobin in Korean diabetics: using data from the 4th Korea National Health and Nutrition Examination Survey. Korean J. Fam. Med. 33, 280–286.
Li, S., Shin, H.J., Ding, E.L., van Dam, R.M., 2009. Adiponectin levels and risk of type 2 diabetes: a systematic review and meta-analysis. JAMA 302, 179–188.
Lim, JE, Jee, SH, 2014. Association between `serum levels of adiponectin and polychlorinated biphenyls in Korean men and women. Endocrine.
Michalek, J.E., Akhtar, F.Z., Kiel, J.L., 1999. Serum dioxin, insulin, fasting glucose, and sex hormone-binding globulin in veterans of Operation Ranch Hand. J. Clin. Endocrinol. Metab. 84, 1540–1543.
Mullerova, D., Kopecky, J., Matejkova, D., Muller, L., Rosmus, J., Racek, J., et al., 2008. Negative association between plasma levels of adiponectin and polychlorinated biphenyl 153 in obese women under non-energy-restrictive regime. Int. J. Obes. 32, 1875–1878.
Nakanishi, N., Nishina, K., Li, W., Ssato, M., Suzuki, M., Tatara, K., 2003. Serum?-glutamyltransferase and development of impaired fasting glucose or type 2 diabetes in middle-aged Japanese men. J. Intern. Med. 254, 287–295.
Nakanishi, N., Suzuki, K., Tatara, K., 2004. Serum gamma-glutamyltransferase and risk of metabolic syndrome and type 2 diabetes in middle-aged Japanese men. Diabetes Care 27, 1427–1432.
Neale, E.P., Muhlhausler, B., Probst, Y.C., Batterham, M.J., Fernandez, F., Tapsell, L.C., 2013. Short-term effects of fish and fish oil consumption on total and high molecular weight adiponectin levels in overweight and obese adults. Metabolism 62, 651–660.
Ouellet, V., Weisnagel, S.J., Marois, J., Bergeron, J., Julien, P., Gougeon, R., et al., 2008. Dietary cod protein reduces plasma C-reactive protein in insulin-resistant men and women. J. Nutr. 138, 2386–2391.
Persky, V., Piorkowski, J., Turyk, M., Freels, S., Chatterton Jr., R., Dimos, J., et al., 2011. Associations of polychlorinated biphenyl exposure and endogenous hormones with diabetes in post-menopausal women previously employed at a capacitor manufacturing plant. Environ. Res. 111, 817–824.
Persky, V., Piorkowski, J., Turyk, M., Freels, S., Chatterton Jr., R., Dimos, J., et al., 2012. Polychlorinated biphenyl exposure, diabetes and endogenous hormones: a cross-sectional study in men previously employed at a capacitor manufacturing plant. Environ. Health 11, 57.
Persky, V., Turyk, M., Anderson, H.A., Hanrahan, L.P., Falk, C., Steenport, D.N., et al., 2001. The effects of PCB exposure and fish consumption on endogenous hormones. Environ. Health Perspect. 109, 1275–1283.
Philibert, A., Schwartz, H., Mergler, D., 2009. An exploratory study of diabetes in a First Nation community with respect to serum concentrations of p,p'-DDE and PCBs and fish consumption. Int. J. Environ. Res. Public Health 6, 3179–3189.
Prynne, C.J., Mander, A., Wadsworth, M.E., Stephen, A.M., 2009. Diet and glycosylated haemoglobin in the 1946 British birth cohort. Eur. J. Clin. Nutr. 63, 1084–1090.
Ramel, A., Martinez, J.A., Kiely, M., Bandarra, N.M., Thorsdottir, I., 2010. Effects of weight loss and seafood consumption on inflammation parameters in young, overweight and obese European men and women during 8 weeks of energy restriction. Eur. J. Clin. Nutr. 64, 987–993.
Remillard, R.B., Bunce, N.J., 2002. Linking dioxins to diabetes: epidemiology and biologic plausibility. Environ. Health Perspect. 110, 853–858.
Rignell-Hydbom, A., Lidfeldt, J., Kiviranta, H., Rantakokko, P., Samsioe, G., Agardh, C. D., et al., 2009. Exposure to p,p'-DDE: a risk factor for type 2 diabetes. PLoS One 4, e7503.
Sargeant, L.A., Wareham, N.J., Khaw, K.T., 2000. Hormone replacement therapy and glucose tolerance in EPIC-Norfolk: a population-based study. Diabetes Metab. Res. Rev. 16, 20–25.
Smith, K.M., Barraj, L.M., Kantor, M., Sahyoun, N.R., 2009. Relationship between fish intake, n-3 fatty acids, mercury and risk markers of CHD (National Health and Nutrition Examination Survey 1999–2002). Public Health Nutr. 12, 1261–1269.
Suarez-Lopez, J.R., Lee, D.H., Porta, M., Steffes, M.W., Jacobs Jr., D.R., 2015. Persistent organic pollutants in young adults and changes in glucose related metabolism over a 23-year follow-up. Environ. Res. 137, 485–494.
Sweeney, M.H., Mocarelli, P., 2000. Human health effects after exposure to 2,3,7,8-TCDD. Food Addit. Contam. 17, 303–316.
Tabak, A.G., Herder, C., Rathmann, W., Brunner, E.J., Kivimaki, M., 2012. Prediabetes: a high-risk state for diabetes development. Lancet 379, 2279–2290.
Taxvig, C., Dreisig, K., Boberg, J., Nellemann, C., Schelde, A.B., Pedersen, D., et al., 2012. Differential effects of environmental chemicals and food contaminants on adipogenesis, biomarker release and PPARgamma activation. Mol. Cell. Endocrinol.
Taylor, K.W., Novak, R.F., Anderson, H.A., Birnbaum, L.S., Blystone, C., Devito, M., et al., 2013. Evaluation of the association between persistent organic pollutants (POPs) and diabetes in epidemiological studies: a national toxicology program workshop review. Environ. Health Perspect. 121, 774–783.
Turunen, A.W., Jula, A., Suominen, A.L., Mannisto, S., Marniemi, J., Kiviranta, H., et al., 2013. Fish consumption, omega-3 fatty acids, and environmental contaminants in relation to low-grade inflammation and early atherosclerosis. Environ. Res. 120, 43–54.
Turyk, M., Anderson, H., Knobeloch, L., Imm, P., Persky, V., 2009a. Organochlorine exposure and incidence of diabetes in a cohort of Great Lakes sport fish consumers. Environ. Health Perspect. 117, 1076–1082.
Turyk, M., Anderson, H.A., Knobeloch, L., Imm, P., Persky, V.W., 2009b. Prevalence of diabetes and body burdens of polychlorinated biphenyls, polybrominated diphenyl ethers, and p,p'-diphenyldichloroethene in Great Lakes sport fish consumers. Chemosphere 75, 674–679.
Turyk, M.E., Bhavsar, S.P., Bowerman, W., Boysen, E., Clark, M., Diamond, M., et al., 2012. Risks and benefits of consumption of Great Lakes fish. Environ. Health Perspect. 120, 11–18.
Vasiliu, O., Cameron, L., Gardiner, J., Deguire, P., Karmaus, W., 2006. Polybrominated biphenyls, polychlorinated biphenyls, body weight, and incidence of adult-onset diabetes mellitus. Epidemiology 17, 352–359.
Wu, H., Bertrand, K.A., Choi, A.L., Hu, F.B., Laden, F., Grandjean, P., et al., 2013. Persistent organic pollutants and type 2 diabetes: a prospective analysis in the nurses' health study and meta-analysis. Environ. Health Perspect. 121, 153–161.
Wu, J.H., Micha, R., Imamura, F., Pan, A., Biggs, M.L., Ajaz, O., et al., 2012. Omega-3 fatty acids and incident type 2 diabetes: a systematic review and meta-analysis. Br. J. Nutr. 107 (Suppl 2), S214–S227.
Zani, C., Donato, F., Magoni, M., Feretti, D., Covolo, L., Vassallo, F., et al., 2013. Polychlorinated biphenyls, glycaemia and diabetes in a population living in a highly polychlorinated biphenyls-polluted area in Northern Italy: a cross-sectional and cohort study. J. Public Health Res. 2, 2–8.
Zhang, J., Wang, C., Li, L., Man, Q., Meng, L., Song, P., et al., 2012. Dietary inclusion of salmon, herring and pompano as oily fish reduces CVD risk markers in dyslipidaemic middle-aged and elderly Chinese women. Br. J. Nutr. 108, 1455–1465.
Zhang, M., Picard-Deland, E., Marette, A., 2013. Fish and marine omega-3 polyunsatured fatty acid consumption and incidence of type 2 diabetes: a systematic review and meta-analysis. Int. J. Endocrinol. 2013, 501015.