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Combining plasma measurements and mechanistic modeling to explore the effect of POPs on type 2 diabetes mellitus in Norwegian women

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ABSTRACT

The number of studies on persistent organic pollutants (POPs) and type 2 diabetes mellitus (T2DM) is growing steadily. Although concentrations of many POPs in humans have decreased substantially, only some studies consider temporal and inter-individual changes in POP concentrations when assessing exposure. Here we combined plasma measurements with mechanistic modeling to generate complementary exposure measures to our single blood draw after disease diagnosis.

Blood was collected between 2003–2006 from 106 subjects with T2DM and 106 age-matched controls, and POP concentrations were compared after adjustment for relevant risk factors and multiple testing. Area under the curve (AUC) of PCB-153 from birth until age 18, representing early-life exposure, and AUC from birth until time of diagnosis were generated as well as examples of life-time exposure trajectories using a mechanistic exposure model. The rank sum of polychlorinated biphenyls (PCBs) and organochlorine pesticides (OCPs, OR=16.9 (95% CI: 3.05–93.6)) as well as β-hexachlorocyclohexane (β-HCH, OR=203.8 (95% CI: 11.5–3620)) and 1, 1-dichloro-2,2-bis(*p*-chlorophenyl) ethylene (*p,p′*-DDE, OR=11.3 (95% CI: 2.55–49.9)) were associated with T2DM. Neither of the AUCs reflecting early life exposure and total life-time exposure at the time of diagnosis were associated with the disease. The predicted life course trajectories display clear differences within and between individuals in the past and suggest that a single blood draw provide limited information on POP exposure earlier in life. The predicted AUCs for PCB-153 did not support the positive association between T2DM and measured blood concentration of certain POPs. This may suggest that the model is either too simplistic and/or that strength of the association may vary through life and with time to/past diagnosis.

1. Introduction

The prevalence of type 2 diabetes mellitus (T2DM) has increased in epidemic proportions during the last decades, and so have overweight and obesity, which are important risk factors for T2DM. Despite that, studies indicate that the obesity epidemic cannot fully explain the observed increase in T2DM prevalence, and that background exposure to persistent organic pollutants (POPs), may contribute to this global health challenge (Airaksinen et al., 2011; Lee et al., 2010 and reviewed by Magliano et al. (2014)). Studies of the general population using both cross-sectional and prospective design have reported an increased risk of T2DM with various POPs (Airaksinen et al., 2011; Everett et al., 2007; Lee et al., 2006, 2010, 2011; Rignell-Hydbom et al., 2009; Son et al., 2010; Turyk et al., 2009a, 2009b; Uemura et al., 2008; Vasiliu et al., 2006; Wang et al., 2008; Wu et al., 2013). However, there is inconsistency between studies with regards to which POP is being linked to T2DM, where some observe significant findings for e.g. 1,1-dichloro-2,2-bis(*p*-chlorophenyl) ethylene (*p,p′*-DDE) (Rignell-Hydbom et al., 2009; Turyk et al., 2009a), others do not (Gasull et al., 2012; Wu et al., 2013). Reported associations between POPs and T2DM are often strong (Lee et al., 2006; Rignell-Hydbom et al., 2009), and the most commonly used study design is cross-sectional, where POP concentrations are assessed in blood samples drawn after disease diagnosis. This study design can

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explore the association between POP concentrations and health outcome, yet establishing causality is not feasible. Although the majority of studies in general populations suggest a positive association between various POPs and T2DM, there was a lack of association between POP concentration and indicators of insulin resistance in a group of highly exposed Greenlandic Inuit (Jorgensen et al., 2008). Results from occupationally exposed subjects to dioxins are also inconsistent (Bertazzi et al., 1998; Calvert et al., 1999; Kerger et al., 2012).

At the same time as the numbers of studies on T2DM and POPs have increased, the concentrations of several POPs have decreased in the environment and in humans (Hagmar et al., 2006; Haug et al., 2009; Hovinga et al., 1992; Nost et al., 2013). The human body burden of PCB-153 is for example highly dependent on birth year, as the environmental concentrations have changed considerably over the last 40 years (Quinn and Wania, 2012). Because of these large changes, the importance of considering age, period and cohort effects in studies of POPs in humans, has been highlighted (Alcock et al., 2000; Nost et al., 2013; Porta et al., 2008; Quinn and Wania, 2012; Ritter et al., 2009). Changes in POP concentrations over time are also expected to be unique for each individual, especially for women, where the loss of POPs during pregnancy and breastfeeding is estimated to have a strong influence on total body burden (Quinn et al., 2011). It is therefore uncertain how well a single blood sample donated prior to, or after, time of diagnosis reflect life-long exposure, or exposure during etiologically relevant periods (Bachelet et al., 2010; Hoyer et al., 2000; Verner et al., 2011). It is further not well understood which life-stages that are most sensitive to POP exposure in relation to T2DM, but *in utero* exposure, early life exposure (Boekelheide et al., 2012) and adult exposure (Suarez-Lopez et al., 2015) have been suggested as etiologically relevant periods. As humans are exposed to a large number of POPs, the collective effects of mixtures of POPs are also of concern, but with limited data on mechanisms of action, this is a challenging task undertaken by few epidemiological studies. Due to the combination of these challenges related to temporal, intra- and interindividual changes in POP concentrations and limited knowledge about etiologically sensitive time windows for POP exposure in relation to T2DM, it has been highlighted that researchers have to make every effort to improve the exposure assessment in future studies (Porta, 2014). In this study, we aimed to supplement traditional plasma measurements of POPs with predictions from mechanistic modeling to explore the effects of POPs on T2DM using exposure measures that also reflect past exposure. We also generated individual life-course diagrams of PCB-153 to enhance our understanding of changes in life-time exposure to POPs.

2. Material and methods

2.1. The Norwegian Women and Cancer study

The Norwegian Women and Cancer study (NOWAC) is a prospective population based cohort study consisting of more than 170,000 Norwegian women (aged 30–70 years) with the aim of exploring life-style-related diseases with emphasis on carcinomas (Lund et al., 2008). More than 50,000 of the NOWAC participants have also donated a blood sample (Dumeaux et al., 2008). The participants have answered an extensive questionnaire regarding their current health status, diet, use of medication and life-style. In addition, they answered a two-page questionnaire at the time of blood sampling concerning use of medication, smoking, alcohol consumption and anthropometric measures. The external validity of NOWAC has been found satisfactory (Lund et al., 2003).

We recently validated self-reported diabetes (from the main questionnaire) with satisfactory results (Rylander et al., 2014), and it is from among these women we recruited the participants for the current study. In the validation study, 379 women were asked to confirm their T2DM diagnosis and we also asked for permission to contact their general practitioner in order to validate the diagnosis. A total of 97 subjects with confirmed T2DM and sufficient volume of blood samples for contaminants analysis were identified. In addition, we identified 11 cases from their self-reported use of glucose-lowering medication at the time of blood sampling, in addition to a positive answer on self-reported diabetes on their main questionnaire. Thus, in total, 108 cases, all free of cancer, were identified. Blood samples were taken between September 2003 and October 2006, and year of diagnosis ranged between 1980 and 2008. Four patients had blood samples taken between one month and two years prior to diagnosis. As it is possible to live with undiagnosed T2DM for a long time, and the blood samples were donated close to diagnosis, we did not exclude those samples, knowing they could increase the noise level in our analyses. We also randomly selected 108 age-matched controls. All controls had responded negatively to the question of whether they had diabetes; they did not use anti-diabetic medicine and were free from cancer.

Of the 216 blood samples, six lacked information on the donor's body mass index (BMI) at the time of blood sampling. Four of these participants had filled out height and weight in their main questionnaire ($\sim$1 year before blood sampling). As the agreement in self-reported BMI between the main questionnaire and the blood sampling questionnaire was almost perfect (weighted Cohen's $\kappa = 0.89$), we used the information from the main questionnaire to calculate BMI for these four individuals. Two samples were excluded due to missing information on BMI in both questionnaires. Their subsequent paired samples were also filtered out. The total number of samples included in the study was therefore 212.

2.2. Questionnaire data

From the two questionnaires, we extracted information on covariates. Calculated BMI was used as a continuous variable. Information on smoking (yes/no the week before blood sampling) was extracted from the blood sampling questionnaire. One person had left that question blank and was assigned smoking status "No". Information on self-reported hypertension (yes/no) was extracted from the main questionnaire, of which 36 had left that question blank, which was interpreted as a negative answer. We have previously shown that interpreting a missing answer on hypertension as a negative response, did not change the effect estimates in a large cohort study of fish consumption and T2DM (Rylander et al., 2014). This way we may underestimate the risks related to hypertension, but we consider this limitation acceptable.

2.3. Chemical analyses

Selected polychlorinated biphenyls (PCBs) and organochlorine pesticides (OCPs) were analyzed at Centre de Toxicologie de Quebec, Institut National de santé publique de Québec in Canada using a liquid–liquid extraction method, florisil column clean-up and GC–MS determination (POP-method E-446, ISO 17025 accreditation). In brief, 0.5–1 mL of plasma sample was extracted using hexane (2×6 mL), ethanol (2 mL) and saturated ammonium sulfate solution (2 mL); this is a slight modification of the method described by Sandanger et al. (2003). The POP extracts were cleaned up using 1 g of activated florisil and an automated system before GC–MS determination (Sandanger et al., 2007). Limit of detection (LoD) varied between 10 and 90 pg/mL plasma and the detection frequency were 100% for all measured PCBs and OCPs except for *p, p′*-DDE where it was 99%.

The analyses of perfluoroalkyl acids (PFAAs) has previously been described in detail (Hanssen et al., 2013). In brief, 200 μL plasma was mixed with 20 μL of mixture of mass-labeled internal standards (0.1 ng/μL of $^{13}C_4$PFOS, $^{13}C_4$PFOA, $^{13}C_5$PFNA, Wellington Laboratories Inc.) as well as with 1 mL of methanol. After extraction, 0.8 mL of the supernatant was transferred to a new centrifugation tube and centrifuged with 25 mg acidified ENVI-Carb 120/400 (Supelco, PA, USA). As a recovery standard, 20 μL of branched perfluorodecanoic acid (0.102 ng/μL) was added. Prior to analysis an aliquot of 100 μL of plasma was transferred to a vial and mixed with an equal amount of 2 mM aqueous ammonium acetate (NH_4OAc, ≥99%, Sigma-Aldrich, St. Louis, MO, USA). PFAAs were analyzed by ultrahigh pressure liquid chromatography triple-quadrupole mass-spectrometry (Thermo Fisher Scientific Inc., Waltham, MA, USA). Analytical specifications are described by Hanssen et al. (2013). The quantification was conducted with the LC Quan software, version 2.6.0 (Thermo Fisher Scientific Inc, Waltham, MA, USA). The internal-standard addition method with isotope-labeled PFAAs was used to quantify the contaminants. Concentrations of PFAAs in all samples were within the linear range of the instrument and the calibration curve. Participation in the AMAP ring test program indicated that the uncertainties of the analysis were within ± 15–20% of the assigned values. LoD varied between 10 and 23 pg/mL and the presented PFAAs were detected in concentrations above LoD in more than 99% of all samples.

The lipid content was determined enzymatically and total amounts of lipids were calculated according to the equation presented in Akins et al. (1989).

2.4. Predicting accumulated life-time PCB-153 concentrations

To generate complementary exposure measures to the plasma measurements, we used the mechanistic model CoZMoMAN (Breivik et al., 2010) to predict PCB-153 concentrations in the study subjects at various time points. Based on estimates of time-variant historical emissions, the CoZMoMAN model calculates environmental fate and human bioaccumulation of PCB-153 and estimates age-specific concentrations in individuals. In brief, the model was supplied with person-specific parameters for year of birth, reproductive history (date of birth and breastfeeding duration for each child up to a maximum of four children), and daily intake of meat (grams lipid weight), dairy products (grams lipid weight) and fish (grams fresh weight). Individual input information was derived from the questionnaire responses and is summarized in Supplementary Table S1. The information that can be incorporated in the model simulation of each individual is further described in detail in Nost et al. (2015). Further model parameterization for the time period from 1930 to 2010 was identical to that described in Nost et al. (2013) and references therein. From these simulations, we predicted the PCB-153 concentration at the time of blood sampling as well as from birth until blood sampling, which are presented for selected individuals in the life-course diagrams. The life-course trajectories reflect both historical emissions and the persistent property of PCB-153. As the peak in emissions of several POPs (Breivik et al., 2007; Li, 1999; Schenker et al., 2008) occurred in similar time periods in many industrialized countries, the life-course trajectories could also provide crude indications for certain other legacy POPs.

Area under the curve (AUC) of PCB-153 from birth until age 18 (AUC_{0-18}) and from birth until time of diagnosis ($AUC_{0\text{-diagnosis}}$), was obtained by integrating the area under natural cubic spline interpolations of the life-course concentration profiles using the MESS package for R. The women included in this study were all born during a time period of early productions of PCBs and many pesticides (1943–1957). Thus, concentrations at birth, reflecting *in utero* exposure, were expected to be similar between women and we therefore rather assessed AUC_{0-18} as a measure of early-life exposure. We further hypothesized that $AUC_{0\text{-diagnosis}}$ reflected life-time exposure until the time of diagnosis. Predictions were only available for 79 matched pairs, as the remaining 27 pairs had limited dietary information. Thus, predicted values and measured values were only compared for 79 pairs.

2.5. Data treatment and statistical methods

We used the freely available software R, version 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria), for the statistical analyses. Predictors for the contaminants were explored for cases and controls separately, as well as for the entire study group, using linear regression models. The association between T2DM prevalence and quartiles of contaminant concentration was assessed using conditional logistic regression. Each model was adjusted for known and significant risk factors for T2DM (BMI, smoking, hypertension) as well as for breastfeeding. We adjusted the models for multiple testing by calculating the false discovery rate (FDR) (Benjamini and Hochberg, 1995). To estimate the effect of the collective body burden of PCBs and OCPs, we calculated the rank sum of PCBs and OCPs using a slight modification of the method described by Lee et al. (2006). For every measured PCB and OCP, subjects were ranked according to their concentration. The individual with lowest concentration was assigned the rank "1" and the subject with highest concentration was given the rank "212". The ranks were subsequent summarized and the new rank sum variable was divided into quartiles. As the rank sum of PFAAs was highly correlated with linear PFOS concentration (r_s=0.89), we did not evaluate the rank sum of PFAAs further.

3. Results

3.1. Study group characteristics and POP concentrations

The 212 study subjects were born between 1943 and 1957. Cases and controls were matched on age so the effect of age on T2DM was already accounted for by the study design. Fifty-four percent of the cases and 20% of the controls reported being hypertensive and 32% of cases and 20% of controls reported having smoked during the last week before blood sampling. In Table 1, body mass index (BMI), breastfeeding, total cholesterol, triglycerides, total lipids and contaminant concentrations are provided for cases and controls, in addition to the difference between the matched pairs. Cases had significantly higher BMI, higher blood concentrations of triglycerides and significantly lower blood concentration of total cholesterol than the controls. There was no difference in total lipid concentrations between cases and controls. Cases had also on average breastfed for 6 months less than the controls (95% CI: 3.4–8.6 months). Use of glucose-lowering drugs containing Metformin was reported by 57% of cases. For all PCBs and OCPs, except PCB-180, the concentrations in cases were significantly higher than in controls. For the PFAAs there were no differences in concentrations between cases and controls except for branched PFOS, which was found at higher concentrations in cases.

3.2. POP concentrations and T2DM

Crude and adjusted Odds Ratios (ORs) for quartiles of measured, lipid-normalized POPs and AUCs are provided in Table 2. After adjusting for relevant risk factors (BMI, hypertension and smoking) and confounders (breastfeeding), all PCBs and OCPs were associated with T2DM prevalence. After correction for multiple testing, only β-HCH, *p, p′*-DDE and the rank sum of PCBs and

Table 1
Characteristics and POP concentrations in cases and controls, and the differences between matched pairs.

Variable		Cases ($n=106$)	Controls ($n=106$)	Mean difference between matched pairs (case-control) and 95% CI around the mean
Body mass index (kg/m^2)	Mean	31.4	25.8	5.6 (4.20, 7.04)
	Median	31.6	24.9	5.6
	Min–Max	21.3–51.8	19.8–41.2	−15.6 to 26.7
Breastfeeding (months)	Mean	7.80	13.8	−6 (-8.59, −3.35)
	Median	5.00	11.5	−5.00
	Min–Max	0–39	0–58	−41 to 39
Total cholesterol (mmol/L)	Mean	4.65	5.54	−0.90 (−1.16, −0.64)
	Median	4.54	5.61	−0.88
	Min–Max	2.51–8.81	3.64–7.69	−3.86 to 3.31
Triglycerides (mg/dL)	Mean	169	106	62.3 (34.9, 89.6)
	Median	137	92.9	39.0
	Min–Max	4.42–886	4.42–302	−220 to 743
Total lipids (mg/dL)	Mean	615.8	627.8	−12.0 (−55.1, 31.0)
	Median	568	615	−40.9
	Min–Max	334–1590	414–1000	−524 to 945
OCPs (ng/g lipid)				
HCB	Mean	31.7	23.9	7.8 (5.16, 10.4)
	Median	29.6	22.9	7.00
	Min–Max	10.1–74.0	7.2–43.8	−23.9 to 55.8
oxy-CD	Mean	8.00	6.40	1.6 (0.70, 2.49)
	Median	7.20	5.90	1.5
	Min–Max	1.90–22.8	2.10–15.3	−10.1 to 17.6
p,p′-DDE	Mean	362	180	182 (120, 244)
	Median	280	125	123
	Min–Max	16.8–2090	10.9–895	−590 to 1360
β-HCH	Mean	20.3	10.0	10.4 (6.71, 14.0)
	Median	17.5	8.50	7.9
	Min–Max	3.90–181	3.50–48.5	−27.8 to 177
t-NC	Mean	16.7	12.3	4.4 (2.15, 6.58)
	Median	13.3	10.8	3.30
	Min–Max	3.1–53.9	3.4–32.5	−29.2 to 45.5
PCBs (ng/g lipid)				
PCB-118	Mean	22.4	15.2	7.2 (4.62, 9.87)
	Median	19.1	13.0	5.20
	Min–Max	3.7–62.6	3.1–50.8	−31.8 to 49.6
PCB-138	Mean	61.8	44.1	17.7 (10.6, 24.8)
	Median	56.4	39.7	14.2
	Min–Max	2.80–211	1.80–120	−112 to 164
PCB-153	Mean	110	87.6	22.6 (11.3, 33.9)
	Median	101	78.8	14.4
	Min–Max	13.3–323	12.2–233	−187 to 222
PCB-180	Mean	66.9	61.0	5.9 (−0.28, 12.2)
	Median	61.5	55.1	3.1
	Min–Max	20.3–151	28.6–135	−92.8 to 98.1
PFAAs (ng/ml)				
PFOA	Mean	3.10	3.30	−0.20 (−0.54, 0.23)
	Median	3.00	2.90	−0.10
	Min–Max	0.50–7.40	1.20–11.0	−8.90 to 5.10
Branched PFOS	Mean	8.40	7.40	0.9 (0.84, 1.05)
	Median	6.80	6.40	1.50
	Min–Max	0.008–96.2	0.72–26.9	−22.4 to 89.9
Linear PFOS	Mean	12.3	13.2	−0.90 (−3.19, 1.37)
	Median	11.3	11.4	−0.10
	Min–Max	0.45–66.9	1.10–80.1	−52.2 to 52.7
PFNA	Mean	0.70	0.70	0.00 (−2.09, 2.05)
	Median	0.60	0.60	0.00
	Min–Max	0.05–2.00	0.13–2.50	−2.30 to 1.30
Predicted AUCs of PCB-153 (ng/g lipid)				
AUC_{0-18}	Mean	407	380	27.0 (−14.4, 68.4)
	Median	246	277	7.70
	Min–Max	8.65–2760	35.0–1740	−724 to 2200
$AUC_{0\text{-diagnosis}}$	Mean	5060	4860	201 (−299, 701)
	Median	4900	3500	186
	Min–Max	161–12300	1060–18600	−14500 to 11100

Abbreviations: POPs, persistent organic pollutants; OCPs, Organochlorine pesticides: HCB, Hexachlorobenzene; oxy-CD, oxy-chlordane; *p,p′*-DDE, 1,1-dichloro-2,2-bis(*p*-chlorophenyl) ethylene; *β*-HCH, beta-hexachlorocyclohexane; t-NC, trans-nonachlor; PCB, polychlorinated biphenyls; PFAAs, perfluoroalkyl acids; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonic acid; PFNA, perfluorononanoic acid, AUC: Area under the curve.

Table 2
Crude and adjusted Odds Ratios (OR) for risk of type 2 diabetes mellitus according to lipid-normalized POP concentrations.

POP[a]		Crude OR (95% CI)	Adjusted OR[b] (95% CI)	*p*-Value	FDR[c]
HCB	1Q	1.00	1.00	–	–
	2Q	1.34 (0.56, 3.20)	3.03 (0.71, 13.0)	0.14	0.68
	3Q	3.52 (1.47, 8.43)	3.19 (0.84, 12.1)	0.09	0.66
	4Q	6.74 (2.47, 18.4)	7.00 (1.59, 30.8)	0.01	0.15
β-HCH	1Q	1.00	1.00	–	–
	2Q	4.21 (1.38, 12.9)	3.63 (0.67, 19.7)	0.14	0.68
	3Q	18.8 (4.44, 79.7)	16.8 (2.00, 141)	0.009	0.07
	4Q	136.2 (21.0, 882)	203.8 (11.5, 3620)	< 0.001	0.02
t-NC	1Q	1.00	1.00	–	–
	2Q	1.80 (0.81, 4.02)	2.22 (0.53, 9.35)	0.278	1.00
	3Q	2.39 (1.11, 5.15)	5.06 (1.21, 21.1)	0.026	0.20
	4Q	4.11 (1.65, 10.2)	6.56 (1.57, 27.5.)	0.01	0.15
oxy-CD	1Q	1.00	1.00	–	
	2Q	1.02 (0.47, 2.23)	1.33 (0.37, 4.8)	0.66	1.00
	3Q	2.64 (1.16, 6.01)	3.61 (0.96, 13.6)	0.058	0.44
	4Q	4.12 (1.64, 10.31)	7.22 (1.60, 32.58)	0.01	0.15
p,p′-DDE	1Q	1.00	1.00	–	
	2Q	2.68 (1.05, 6.83)	1.58 (0.44, 5.63)	0.48	1.00
	3Q	4.68 (1.74, 12.6)	3.44 (0.87, 13.66)	0.08	0.59
	4Q	15.4 (5.06, 46.6)	11.3 (2.55, 49.9)	0.001	0.02
PCB-118	1Q	1.00	1.00	–	
	2Q	1.31 (0.55, 3.1)	1.55 (0.41, 5.89)	0.52	1.00
	3Q	3.65 (1.56, 8.52)	4.05 (1.09, 15.0)	0.04	0.27
	4Q	7.03 (2.61, 19.0)	8.71 (1.99, 38.1)	0.004	0.06
PCB-138	1Q	1.00	1.00	–	
	2Q	2.41 (1.03, 5.64)	2.06 (0.57, 7.48)	0.27	1.00
	3Q	3.42 (1.41, 8.31)	2.03 (0.52, 7.95)	0.31	1.00
	4Q	7.37 (2.77, 19.7)	7.02 (1.80, 27.4)	0.005	0.08
PCB-153	1Q	1.00	1.00	–	
	2Q	1.50 (0.71, 3.20)	0.86 (0.22, 3.30)	0.82	1.00
	3Q	1.77 (0.8, 3.94)	1.11 (0.27, 4.53)	0.88	1.00
	4Q	5.26 (1.99, 13.9)	6.44 (1.50, 27.7)	0.012	0.18
PCB-180	1Q	1.00	1.00	–	
	2Q	1.12 (0.48, 2.62)	1.10 (0.27, 4.38)	0.90	1.00
	3Q	1.15 (0.52, 2.56)	2.53 (0.61, 10.5)	0.20	1.00
	4Q	2.03 (0.87, 4.74)	4.23 (1.04, 17.3)	0.005	0.75
Ranksum PCBs + OCPs	1Q	1.00	1.00	–	
	2Q	1.96 (0.86, 4.49)	2.34 (0.56, 9.74)	0.24	1.00
	3Q	4.22 (1.59, 11.2)	4.08 (0.81, 20.5)	0.09	0.68
	4Q	16.07 (4.7, 55.0)	16.9 (3.05, 93.6)	0.001	0.02
PFOA	1Q	1.00	1.00	–	
	2Q	0.61 (0.27, 1.37)	0.62 (0.2, 1.94)	0.41	1.00
	3Q	0.83 (0.38, 1.83)	0.19 (0.34, 4.13)	0.79	1.00
	4Q	0.82 (0.37, 1.82)	1.52 (0.44, 5.23)	0.51	1.00
Branched PFOS	1Q	1.00	1.00		
	2Q	1.46 (0.66, 3.23)	0.78 (0.24, 2.54)	0.68	1.00
	3Q	1.27 (0.59, 2.72)	1.20 (0.38, 3.77)	0.76	1.00
	4Q	1.79 (0.79, 4.03)	2.8 (0.72, 11.0)	0.14	1.00
Linear PFOS	1Q	1.00	1.00	–	–
	2Q	0.81 (0.36, 1.84)	0.95 (0.28, 3.24)	0.93	1.00
	3Q	0.99 (0.44, 2.21)	1.19 (0.1, 4.50)	0.80	1.00
	4Q	0.71 (0.31, 1.65)	1.09 (0.29, 4.07)	0.89	1.00
PFNA	1Q	1.00	1.00	–	–
	2Q	1.41 (0.65, 3.05)	1.42 (0.43, 4.68)	0.56	1.00
	3Q	1.98 (0.88, 4.44)	2.66 (0.77, 9.11)	0.12	1.00
	4Q	1.09 (0.49, 2.41)	1.21(0.39, 3.79)	0.74	1.00
AUC_{0-18} of PCB-153	1Q	1.00	1.00	–	
	2Q	1.95 (0.78, 4.89)	7.93 (1.72, 36.6)	0.008	0.12
	3Q	0.67 (0.24, 1.89)	2.12 (0.5, 9.06)	0.31	1.00
	4Q	1.83 (0.49, 6.77)	4.21 (0.51, 34.8)	0.18	1.00
$AUC_{0\text{-diagnosis}}$ of PCB-153	1Q	1.00	1.00	–	
	2Q	0.8 (0.33, 1.9)	0.36 (0.08, 1.53)	0.17	1.00
	3Q	1.93 (0.76, 4.93)	3.37 (0.65, 17.4)	0.15	1.00
	4Q	1.97 (0.76, 5.09)	2.45 (0.46, 13.2)	0.30	1.00

[a] For compound abbreviations, see Table 1.
[b] Adjusted for body mass index, breastfeeding, hypertension and smoking. Effect estimates for the AUCs were not adjusted for breastfeeding
[c] FDR: false discovery rate.

OCPs were significantly associated with T2DM prevalence. The associations between measured concentrations and T2DM were consistent also in the sub-sample of 79 pairs used for predictions of historical exposures (results not shown). The crude and adjusted ORs for the plasma-weight concentrations are provided in Supplementary Table S2.

3.3. Measured and predicted values of PCB-153

The predicted median concentration of PCB-153 at the time of

blood sampling in the sub-sample of 79 matched pairs was 79.1 ng/g lipid weight (86.7 and 66.9 ng/g lipid weight for cases and controls, respectively) as compared to the measured concentrations of 85.5 ng/g lipids. Median discrepancy between predicted and measured concentrations was −8.5 ng/g lipids and the Spearman's rank correlation was 0.2 ($p=0.01$). When comparing predicted and measured quartile affiliations, the weighted Cohen's κ was 0.2 ($p=0.008$). The rank correlation between measured PCB-153 concentration at blood sampling and predicted $AUC_{0\text{-diagnosis}}$ and AUC_{0-18} was 0.18 ($p=0.03$) and −0.17 ($p=0.03$), respectively.

3.4. Predicted life-course trajectories of Pcb-153

Predicted concentrations of PCB-153 by the exposure model from birth until 2010 are presented for four matched case-control pairs. Fig. 1A displays two women born in 1943, where the case was diagnosed with T2DM in 2001. Neither had any children and the case reported higher consumption of fish than the control, resulting in higher concentration of PCB-153 throughout her life. The pair displayed in Fig. 1B was born in 1947 and the case was diagnosed in 1998. Both women had two children in similar years (the dips in the lines represent loss of PCB-153 during pregnancy and breastfeeding) and the case had higher fish intake than the control. In Fig. 1C, the women displayed were born in 1950 and the case was diagnosed with T2DM in 2001. The women's daily intake of fish was comparable, whereas the intake of meat and milk was higher for the control, resulting in higher PCB-153 concentrations from birth until 1985. Both women had two children, but they gave birth at different times; before and after peak emissions. In Fig. 1D, both women were born in 1944 and had comparable diets. The case was diagnosed with T2DM in 2002 and gave birth to two children in the late 1970s, whereas the control gave birth to three children already in the 1960s. Both women gave birth and breastfed before the PCB emission peak, however childbirth and breastfeeding had a larger effect on PCB-153 concentration in the case as she reproduced closer in time to the emission peak.

4. Discussion

In this cross-sectional case-control study, we explored whether measured plasma concentrations of POPs and predicted accumulated life-time concentrations of PCB-153 at age 18 and at the time of diagnosis were related to T2DM prevalence. Our results showed that (i) measured β-HCH, *p, p′*-DDE and the rank sum of PCBs and OCPs were associated with T2DM after appropriate adjustments for covariates and FDR corrections and (ii) the simulated AUC_{0-18} and $AUC_{0\text{-diagnosis}}$ of PCB-153 were not associated with T2DM diagnosis. All PCBs and OCPs measured were associated with T2DM before corrections for multiple testing, which is also reflected in Table 1 where higher concentrations of measured PCBs and OCPs are displayed in cases, as compared to controls. As many PCBs and OCPs are highly correlated, the significant findings for β-HCH and *p, p′*-DDE might as well reflect the effect of other POPs. The rank sum of PCBs and OCPs can be regarded as a measure of effects for the sum of the measured POPs and may as such be informative. Our positive associations are in line with a large number of other studies of POPs and T2DM with both cross-sectional and prospective design as reviewed by Lee et al. (2014). Despite that many studies indicate a link between background exposure to POPs and T2DM, it is not fully understood how intra- and inter-individual changes in POP concentration prior to diagnosis, related to for example weight change, reproductive history and changing environmental concentrations, affect the association with T2DM (reviewed in Lee et al., 2014; Wolff et al., 2007). In an attempt to address some of these challenges, we generated examples of individual life-course diagrams for PCB-153, provided in Fig. 1. These life-course trajectories show how much the individual

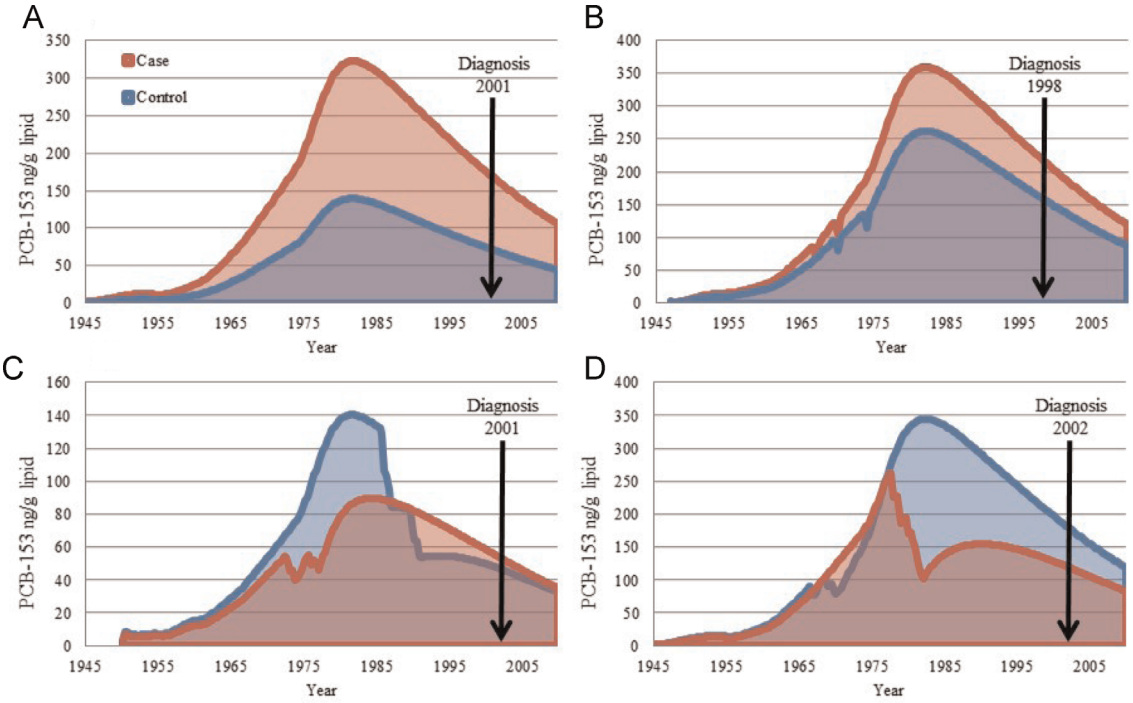

Fig. 1. Predicted concentrations of PCB-153 are displayed for four matched case-control pairs from their birth until 2010. **A:** Both born in 1943, no children, case diagnosed in 2001. **B:** Both born in 1947 and both have two children (case: children born in 1967 and 1970; control: 1970 and 1974), case diagnosed in 1998. **C:** Both born in 1950 and both have two children (case: 1973 and 1976; control: 1986 and 1990), case diagnosed in 2001. **D:** Both born in 1944, the case had two children (born in 1978 and 1980) and the control had three children (born in 1967, 1969 and 1970), case diagnosed in 2002.

concentrations can change through life and that the rank order of individuals in terms of PCB concentration can vary at different time points. Thus, the timing of blood sampling in relation to PCB emission history and the birth year of the study subjects and their reproductive history will strongly influence inter-individual differences in concentrations. As can be seen in Fig. 1B–D, the effects of breastfeeding on the maternal POP concentrations is substantial, but highly dependent on whether the breastfeeding period was before or after the peak emissions, and how much time passed between peak emissions and childbirths.

The blood samples used in the present study were collected in 2003–2006, and the study subjects were diagnosed with T2DM between 1980 and 2008. Considering the decrease in human concentrations in Norway for a number of POPs since the 1980s until today (Nost et al., 2013) and the crossing life-course diagrams (Fig. 1C and D), it appears that a blood sample drawn in 2003–2006 might provide limited information on past exposures. The rank order of individuals will also be highly dependent on sampling year, which may further affect the associations between POP concentration and T2DM. This is in line with conclusions from Verner et al. (2011) and Bachelet et al. (2010) who indicated that non-differential exposure misclassification might be present in human health effect studies based on a single blood sample as exposure measure. If the exposure is dichotomous, bias towards the null is expected, however if exposure is classified into several categories, as usually in studies of POPs, bias can occur both towards and away from the null (Rothman, 2012). However, Vo et al. (2008) concluded that a single blood draw provides considerable information on previous exposure, especially if information on reproductive history and baseline BMI is available after measuring PCB and *p, p′*-DDE concentrations at baseline and at follow-up in women.

For most health outcomes of concern, it is not clear if exposure during a sensitive time window is relevant for the disease development or if exposure above a specific threshold is more important (peak events/accumulated life-time concentration). Different etiologically relevant time periods have been suggested for T2DM, e.g. the early life period, the in utero stage and the period of pregnancy (Boekelheide et al., 2012). Recently, exposure during adulthood was also suggested as highly relevant for T2DM (Suarez-Lopez et al., 2015). The life-course trajectories (Fig. 1) provide valuable information about predicted exposure during the different time periods in life. Women included in this study were mainly born during the 1940s and 1950s when the *in utero* and early life exposure were low and comparable between individuals, which is also confirmed by the life-course diagrams (Fig. 1). For later birth cohorts, the *in utero* and early life exposure is considerably higher than for the women in this study (Quinn et al., 2011). If *in utero* exposure to POPs contributes to the development of T2DM, we can expect a continued increase in T2DM incidence for many years to come (Boekelheide et al., 2012), as this exposure peaked in the late 1970s and during the 1980s (Quinn et al., 2011). This may provide a plausible explanation for the contradiction pointed out in other studies: that human POP concentration is decreasing at the same time as the prevalence of T2DM is increasing (Lee et al., 2010). At the same time, humans are exposed to an increasing number of contaminants, complicating the issue further. To explore the hypothesis of early life exposure and accumulated life-time exposure being relevant for T2DM, we calculated AUC_{0-18} and $AUC_{0\text{-diagnosis}}$ for PCB-153. None of these supplementary exposure measures were significantly associated with T2DM. The AUCs and the measured PCB-153 concentration were weakly correlated and the predicted individual concentrations of PCB-153 did not demonstrate convincing agreement with those measured at the time of sampling. This was expected due to the reduced sample size (79 matched pairs in the predictions) and model simplifications (e.g. predictions did not account for individual differences in BMI, metabolic capacity, intake of seagull eggs etc.). However, the median group estimate of 79.1 ng/g lipids in the sub-sample of 79 matched pairs is comparable with the measured median concentration of 85.5 ng/g lipids in the same group and demonstrates that overall model performance is consistent with the measurements. We did not expect strong correlations between AUC_{0-18} and measured PCB-153 at blood draw, since the main events affecting POP concentrations (childbirth, breastfeeding and peak emission history) occurred between the age 18 and time of blood sampling, which is also exemplified in the life-course trajectories (Fig. 1). Additionally, it is plausible that exposure varies according to the included factors (birth year, reproductive history and diet) and that these differentiate between individuals in their life-course concentrations, although the estimates for time at blood sampling were imprecise. As such, the AUCs are interesting as complementary exposure measures and the fact that they were only weakly correlated with measured concentrations does not undermine their potential value.

In addition to the above mentioned challenges related to exposure measures and etiologically relevant time periods, a number of physiological changes linked to T2DM may confound the associations between POPs and T2DM. These include for example obesity and weight change that may affect the half-life and concentrations of POPs in humans (De Roos et al., 2012; Lind et al., 2013; Thomaseth and Salvan, 1998; Wolff et al., 2007) and dyslipidemia, a key feature of metabolic disorders (Chateau-Degat et al., 2008) that may result in increased plasma concentrations of POPs (Hansen et al., 2010). The complexity of the latter issue is exemplified in the study by Gauthier et al. (2014b) who observed lower POP concentrations in metabolically healthy but obese people as compared to metabolically abnormal obese subjects. In a comment to that article (Ayotte et al., 2014) pointed out that the authors had not taken into account the distinctly different triglyceride concentrations across study groups, which could explain the observed difference. This statement was however later refuted by Gauthier et al. (2014a). The fact that PCBs and OCPs are distributed in lipids whereas PFAAs are mainly distributed in blood may be a possible explanation to why PFAAs seems unrelated to T2DM (Table 2) and may further indicate that there is an urgent need to disentangle the relationships between lipid-soluble POPs, obesity, weight change and dyslipidemia. As some studies have indicated that POPs may disturb the lipid metabolism, it has been suggest that wet-weight concentrations should be used instead of lipid-normalized concentrations when assessing POPs in relation to T2DM (Lee et al., 2014; Schisterman et al., 2005). Therefore, we repeated our analyses with wet-weight concentrations of POPs (Supplementary Table S2) adjusting for plasma lipids. The results were slightly different for some of the individual POPs but remained significant for the rank sum of PCBs and OCPs, β-HCH and *p, p′*-DDE. The fact that many patients with T2DM use Metformin as the glucose-lowering drug, which also lowers blood cholesterol concentration, adds additional complexity to the interrelationships between POPs, lipids and T2DM especially in cross-sectional studies. This was reflected in the present dataset where cases had significantly lower cholesterol concentrations than the controls (Table 1). Further, it is possible to live with undiagnosed T2DM for several years and the time of diagnosis is often arbitrary and influenced by factors such as frequencies of visits to the general practitioner. Together the above mentioned challenges stress the importance of sampling time relative to weight gain and the development of dyslipidemia and highlight the complexity of studying T2DM in relation to POPs.

In the present study, we observed large point estimates and wide confidence intervals for the associations between POPs and T2DM (β-HCH: OR=203.8 (95% CI: 11.5, 3620), *p, p′*-DDE: 11.3 (95%

CI: 2.55, 49.9 for) and the rank sum of PCBs and OCPs: 16.9 (95% CI: 3.05, 93.6)), which indicate imprecision of the effect estimates (Rothman, 2012). The results strongly propose a positive, significant association between the rank sum of PCBs and OCPs, β-HCH, *p, p′*-DDE and T2DM at the time of blood sampling. However, it seems likely that the point estimates are over-estimated due to (i) the small sample size ($n=212$), (ii) the fact that the controls had breastfed for on average 6 more months than the cases and (iii) the controls were selected by cumulative sampling, which often leads to overestimation of point estimates (Rothman, 2012). Large confidence intervals have been an issue in previous studies as well as discussed in a review by Magliano et al. (2014). To overcome the challenge of small data sets, we suggest conducting a pooled analysis of original data from a large number of previous studies. This kind of study design has previously been used for e.g. exploring the effect of exogenous hormone use on thyroid cancer (La Vecchia et al., 1999).

A strength of this study relates to that cases and controls were nested in a large population based cohort, which ensures generalizability of the results. Also, we tried to address previous exposure to POPs through mechanistic modeling despite that our study design was cross-sectional. Limitations of this study include small sample size, only one blood sample collected after disease onset and poor precision of simulated, individual point estimates.

In summary, in an attempt to address intra-individual changes in POP concentration over time, we complemented our single plasma measurements from T2DM cases and controls with simulations of accumulated life-time concentrations of PCB-153 at various time points. The predicted concentrations indicate no associations between T2DM and PCB-153 (indicator substance), which is in contradiction to the measured results. Still, the combination of traditional plasma measurements and mechanistic modeling of past exposure has enhanced our understanding of the temporal changes in POP concentrations. Future model studies should be further expanded to include additional POPs (β-HCH and *p, p′*-DDE) and explore alternative exposure measures reflecting suspected etiological relevant time windows or peak exposure events. In addition to support previous findings on positive associations between POPs and T2DM, this study also shows the importance of temporal aspects when studying the effects of exposure to POPs in general populations, and emphasizes the need for studies assessing the association between POP exposure and T2DM in multiple blood samples prior to diagnosis.

5. Conclusions

Our findings of strong positive associations between the rank sum of PCBs and OCPs, β-HCH, *p, p′*-DDE, and T2DM were not supported by the predicted concentrations of PCB-153, reflecting early-life exposure and accumulated concentrations until the time of diagnosis. The lack of associations for the predicted exposure measures could be a result of current model simplifications or it might indicate that the strength of the associations varies through life and across time prior to and after time of diagnosis. Nevertheless, the time-variant modeling may inform the design and interpretation of future empirical studies.

Competing financial interests declaration

None of the contributing authors has any competing financial interests.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.envres.2015.07.002.

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