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Pre- and post-diagnostic blood profiles of chlorinated persistent organic pollutants and metabolic markers in type 2 diabetes mellitus cases and controls; a pilot study

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ABSTRACT

Objective: Several risk factors for type 2 diabetes mellitus (T2DM) are also associated with blood concentrations of persistent organic pollutants (POPs), and factors related to the disease may affect POP concentrations, and subsequent associations between POPs and T2DM. The purpose of this pilot study was to investigate the change in concentrations of lipids, hormones and POPs pre- and post-diagnosis in T2DM cases compared to healthy controls and their associations with T2DM.

Methods: We measured POPs, lipids, and thyroid and steroid hormones in plasma from 44 female cases collected prior to (pre-diagnostic) and following (post-diagnostic) T2DM diagnosis, and in 44 healthy female age-matched controls. We compared cross-sectional differences and longitudinal changes within and between matched cases and controls with t-tests and multivariable linear regression models. Associations between POP concentrations and T2DM were investigated using conditional logistic regression.

Results: Between the pre- and post-diagnostic measurement, cases developed more favorable lipid profiles and the longitudinal changes in lipid-normalized concentrations of non-dioxin-like polychlorinated biphenyls (PCBs), dioxin-like PCBs, beta-hexachlorocyclohexane (HCH), HCB, and 1,1,1-trichloro-2,2-bis(4-chlorophenyl) ethane (p,p'-DDE) differed significantly between cases and controls. The longitudinal changes in POPs were mainly driven by changes in bodyweight, total lipids and T2DM status. Cases had significantly higher pre-diagnostic concentrations of POPs and triglycerides, and lower concentrations of high-density lipoprotein cholesterol and free thyroxin than controls. Pre-diagnostic POP concentrations were not significantly associated with incident T2DM, whereas several post-diagnostic POP concentrations were significantly positively associated with prevalent T2DM.

Conclusions: This pilot study suggests that factors related to T2DM affect blood concentrations of POPs and may partly explain the positive associations between POPs and T2DM.

1. Introduction

Chlorinated persistent organic pollutants (POPs) have received extensive attention due to their lipophilicity, persistency, and chronic toxicity in living organisms. A large number of epidemiological studies with cross-sectional or prospective designs (reviewed in Lee et al., 2014), including our previous contribution (Rylander et al., 2015), have linked background exposure to POPs with type 2 diabetes mellitus (T2DM). Obesity is a well-known risk factor for T2DM, and people with obesity experience larger *in vivo* dilution of POPs in fat mass and slower degradation rates than normal-weight persons (Thomaseth and Salvan 1998). As many POPs are lipophilic, weight change episodes can affect

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POP concentrations in the blood through dilution or enrichment (De Roos et al., 2012). Further, individuals with T2DM often suffer from dyslipidemia, a condition that causes elevated lipid concentrations in the blood, which may affect circulating POP concentrations (Jansen et al., 2017). Accordingly, a number of physiological conditions associated with T2DM are also associated with elevated POP concentrations and becomes a challenge when investigating the association between POPs and T2DM. If T2DM alters POP concentrations, measuring POP concentrations after disease onset will introduce bias due to factors related to the disease progression. Accordingly, studies have reported that individuals who develop T2DM have elevated concentrations of blood lipids and higher BMI, years before being diagnosed with T2DM (Hulsegge et al., 2017; Vazquez et al., 2007). In order to disentangle these complex relationships, longitudinal studies of POPs and T2DM with repeated measurements from the same individuals are needed (Lee et al., 2014). Such studies are costly and require large collections of prospective samples. To increase our knowledge we initiated this pilot study of pre- and post-diagnostic profiles of POPs, lipids, thyroid and steroid hormones, and body weight in T2DM cases and controls. The intention is to use the lessons learnt from this study in the design of larger, future, longitudinal studies of POPs and T2DM.

2. Materials and methods

2.1. Study sample

The women included in the present study were participants of the Norwegian Women and Cancer (NOWAC) study (Lund et al., 2008). Details about the NOWAC study and procedures are published elsewhere (Lund et al., 2008; Waaseth et al., 2008). In brief, 7849 participants donated two blood samples: the first in 2001/02 and the second in 2005/06. Fifty-three incident T2DM cases were identified between these time points from self-administered questionnaires, which included questions about diabetes, age at diabetes diagnosis, and use of glucose lowering drugs. Incident T2DM cases were defined as those who reported no diabetes or age at diabetes diagnosis, and no use of glucose lowering drugs at or before 2001/02 and reported diabetes, age of diabetes diagnosis, and/or use of glucose lowering drugs in 2004/05. Participants reporting use of insulin only were considered to have type 1 diabetes mellitus and were not considered as eligible T2DM cases. Self-reported diabetes in the NOWAC Study has been previously validated against medical journals/doctors confirmation (Rylander et al., 2014). Of the 53 incident T2DM cases, 44 had blood samples available for 2001/02 (pre-diagnostic samples) and for 2005/06 (post-diagnostic samples). We randomly selected two, diabetes-free control groups: control group 1 was matched to T2DM cases on birth year (±1 year) and year of pre-and post-diagnostic blood sample collection; control group 2 was matched on birth year (±1 year), BMI in 2005/06 (±3 kg/m2) and year of pre-and post-diagnostic blood sample collection. There were only 41 available controls that matched the cases both on birth year and BMI, thus case-control group 2 consisted of 41 matched pairs. To facilitate the dissemination in this report, we focus on case-control group 1 as both case-control groups showed comparable results and conclusions. Hereafter, when referring to cases and controls, that means case control group 1, unless other is specified. Thus, the final study sample comprised 44 cases and 44 controls. In addition to donating two blood samples, the participants had completed five detailed questionnaires of varying length and degree of detail (Figure S1 in the Supplemental material).

2.2. Chemical analyses

2.2.1. Persistent organic pollutant analyses

The methods applied for POP analyses have been previously described in detail (Huber et al., 2020). Briefly, a Freedom Evo 200 (Tecan, Männedorf, Switzerland) liquid handling workstation was used for sample preparation. A 150 μL plasma sample was diluted prior to extraction and cleaned-up by automated solid phase extraction. The instrumental analyses of 13 polychlorinated biphenyls (PCB) congeners and 13 organochlorine pesticides (OCPs) (specified in the Supplemental material) were performed by gas chromatography atmospheric pressure ionization coupled to tandem mass spectrometers (Waters, Milford, MA, USA). Standard reference materials and blank samples were prepared alongside the plasma samples and demonstrated concentrations well within reference values and no contamination. The atmospheric pressure ionization was conducted in positive mode under charge transfer conditions. The multiple reaction monitoring (MRM) mode with two specific transitions for the individual analytes was applied for detection on the mass spectrometers. Quantification was performed using Masslynx and Targetlynx software (Version 4.1, Waters) and achieved by the internal-standard method with isotope-labeled compounds.

2.2.2. Analyses of lipids and thyroid hormones

Measurements of plasma concentrations of triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, thyroid stimulating hormone (TSH), free triiodothyronine (FT3) and free thyroxin (FT4) were performed on a Cobas® 8000 platform (Roche Diagnostics, Rotkreuz, Switzerland) by laboratory staff at the University Hospital of North Norway, Department of Laboratory Medicine. The laboratory is certified according to ISO 151189 (Accreditation 2020). Quality controls are run at three different concentrations every day, and the laboratory also participates in the external quality assessment program, Lab Quality (Labquality 2020). Total lipids were calculated according to the formula proposed by Philips et al.: Total lipids = 2.27*total cholesterol + triglycerides +0.623 (g/L) (Phillips et al., 1989).

2.2.3. Analyses of steroid hormones

A detailed sample procedure and information about chemicals, internal standards, quality controls, calibrators, mass spectrometry mode, and MRM transitions are included in the Supplemental material. Briefly, a Freedom Evo 200 (Tecan) liquid handling workstation was used for sample preparation. Concentrations of testosterone, 11-deoxycortisol, corticosterone, androstenedione, cortisol, and dehydroepiandrosterone sulfate (DHEA-S) were measured in the samples by LC-ESI-MS/MS using a Waters Acquity™ *I*-class UPLC system with an autosampler and a binary solvent delivery system (Waters), interfaced to a Waters Xevo TQ-S benchtop tandem quadrupole mass spectrometer (Waters, Manchester, UK). All calibration curves for the steroids were linear ($r^2 \geq 0.99$).

2.3. Statistical analyses

POPs with detection frequencies equal to or above 90% were evaluated in the statistical models. Concentrations below the limit of detection (LOD) were replaced by LOD/$\sqrt{2}$. POP concentrations were lipid-normalized by dividing wet weight concentrations by the total lipid concentrations. We used one-sample t-tests to test whether pre- and post-diagnostic differences in demographics, POP, lipid, and hormone concentrations between matched case-control pairs, differed from zero. One sample *t*-test were also used to assess mean intra-individual longitudinal changes in POP, lipid, and hormone concentrations and body weight as well as comparison of longitudinal trends between cases and controls (longitudinal change in cases-longitudinal changes in controls). In order to control for confounding factors, we used linear regression models with the longitudinal changes in POP, lipid, and hormone concentrations and body weight as dependent variables, and T2DM status, age, pre-diagnostic BMI, and concurrent changes in weight, lipids (for POPs and hormones) and intake of seafood as independent variables. There were no changes in breastfeeding or parity between the two timepoints, so these variables were not included.

We used conditional logistic regression models to study associations between pre- and post-diagnostic POP concentrations and T2DM status. The models included lipid-normalized concentrations of POPs and the

covariates BMI, weight change, breastfeeding, intake of seafood and total lipids. To determine which covariates to include in the regression models, we drew a directed acyclic graph (DAG). A presentation of the DAG and a description of the assumptions behind the DAG are presented in the Supplementary material (Figure S2). Results are presented as odds ratios (ORs) with 95% confidence intervals (CIs). All included variables were modelled as continuous exposure metrics. The statistical analyses were performed in STATA (v 16.1, StataCorp LLC). All p-values were two-sided, and a 5% level of significance was used.

3. Results

Mean time between the collection of pre- and post-diagnostic blood samples was 4 years. At the time of pre-diagnostic blood sample collection, mean age was similar for cases and controls (52 years), whereas cases were heavier (78 versus 72 kg) and had a higher BMI (29 versus 26 kg/m^2) compared to the controls (Table S1 in the Supplemental material). At the time of post-diagnostic blood sample collection, cases were heavier (80 versus 74 kg) and had a higher BMI (29 versus 27 kg/m^2) compared to the controls. There were no significant differences in parity, months of breastfeeding or intake of seafood between cases and controls at either time points (Table S1). Both cases and controls increased their body weight significantly from enrollment in NOWAC in 1991 until last follow-up in 2005/06 (+6.4 kg and +8.7 kg, respectively). Cases increased the most (+4.7 kg) in the period before the pre-diagnostic blood sample collection, whereas controls increased the most in the period between the pre- and the post-diagnostic blood sample collection (Table S2).

T2DM cases had significantly higher pre-diagnostic concentrations of total lipids and triglycerides, and significantly lower HDL cholesterol and FT4 compared to controls (Fig. 1). Post-diagnostic concentrations of triglycerides were significantly higher in T2DM cases than in controls and, they had significantly lower total cholesterol, LDL cholesterol and HDL cholesterol. There were no other differences in hormone concentration between cases and matched controls at any time point. In cases, concentrations of total lipids, triglycerides, total cholesterol, and LDL cholesterol decreased significantly from pre- to post-diagnostic blood sample collection, whereas HDL cholesterol and FT4 increased significantly (Fig. 1). Among the controls, HDL-cholesterol significantly increased and DHEA-S decreased over that same time period. Concentrations of cortisol and corticosterone decreased in both cases and controls. There were significant differences in crude longitudinal changes in total lipid, triglyceride, and total cholesterol and FT4 concentrations between cases and controls (Fig. 1). When adjusting for confounding factors the differences remained significant (Table S3).

T2DM cases had significantly higher pre- (*trans*-nonachlor, *p,p′*-DDE and *p,p′*-DDT) and post-diagnostic (PCBs, *trans*-nonachlor, *p,p′*-DDE, and *p,p′*-DDT) concentrations of several POPs, and significantly lower pre-diagnostic concentrations of ɣ-HCH compared to the controls (Fig. 2 and Table S4). Wet weight concentrations of POPs displayed the same

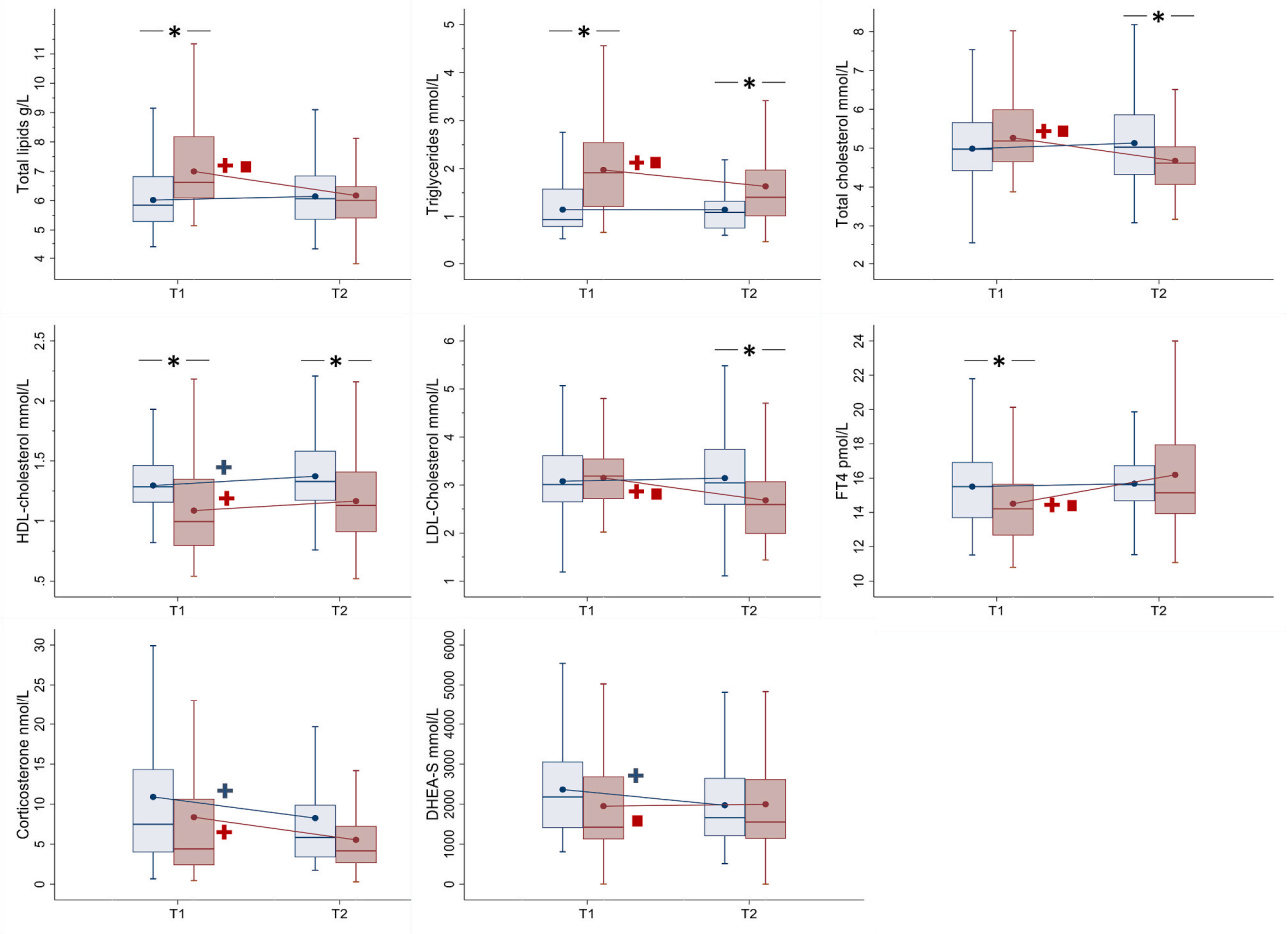

Fig. 1. Lipid and hormone concentrations in cases (red boxes) and controls (blue boxes) at T1 (year 2001/02, pre-diagnosis) and T2 (year 2005/06, post-diagnosis) and the crude longitudinal change in means (represented by lines). Boxes represent the 25th–75th percentiles, horizontal lines represent the median, dots represent the mean, whiskers indicate 1.5 times the length of the interquartile range above and below the 75th and 25th percentiles. * denotes significant difference in mean concentrations between cases and controls; + denotes significant longitudinal change within the group; ■ denotes significant difference in longitudinal change between cases and controls. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

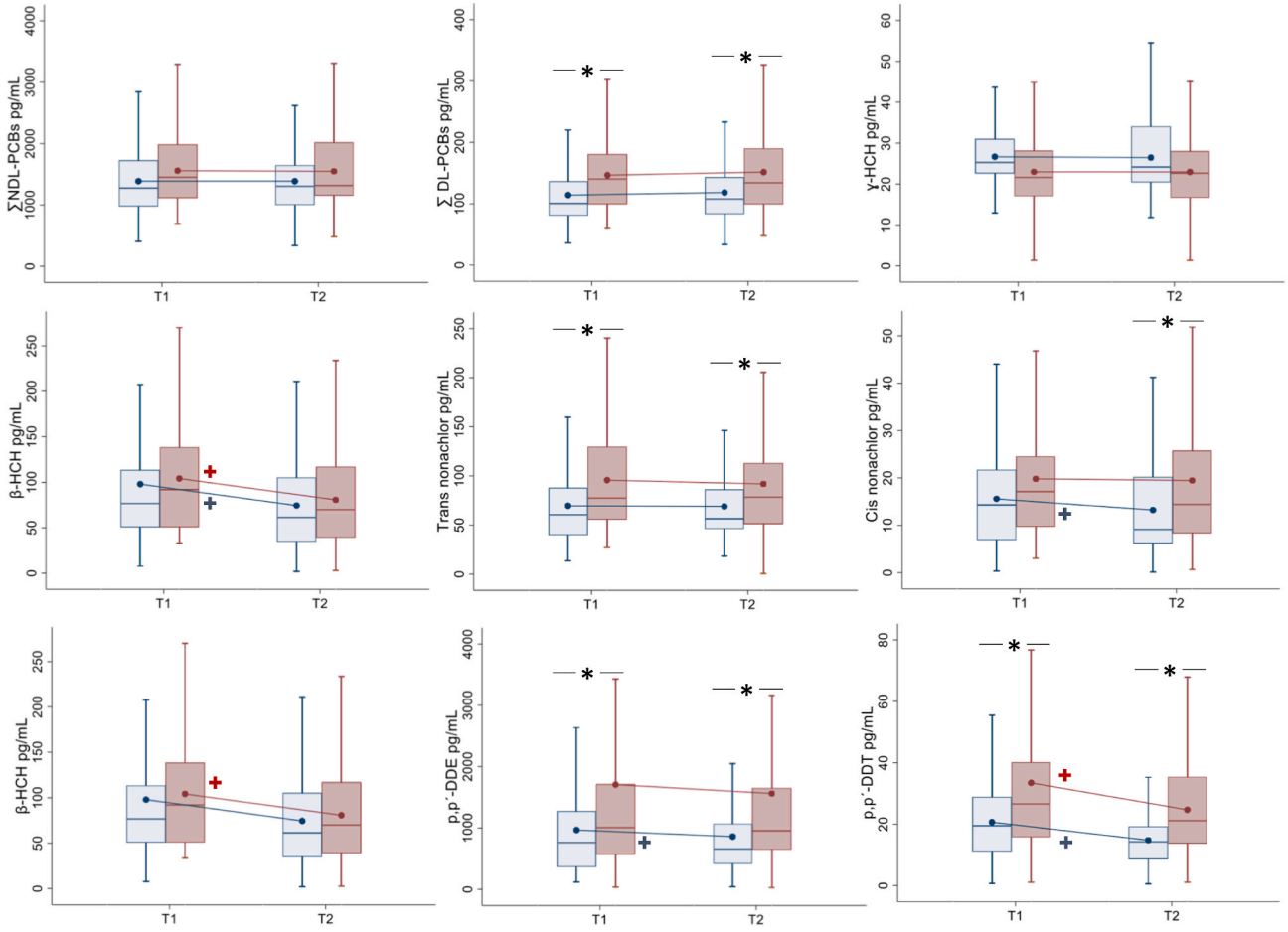

Fig. 2. POP concentrations in cases (red boxes) and controls (blue boxes) at T1 (year 2001/02, pre-diagnosis) and T2 (year 2005/06, post-diagnosis) and the crude longitudinal change in means (represented by lines). Boxes represent the 25th–75th percentiles, horizontal lines represent the median, dots represent the mean, whiskers indicate 1.5 times the length of the interquartile range above and below the 75th and 25th percentiles. * denotes significant difference in mean concentrations between cases and controls; + denotes significant intra-individual longitudinal change; ■ denotes significant difference in longitudinal change between cases and controls. ∑NDL-PCBs: sum of non-dioxin like polychlorinated biphenyls includes PCB-28, 52, 74, 99, 153, 138, 170, 180, 187 and 194; ∑DL-PCBs: sum of dioxine-like polychlorinated biphenyls includes PCB-118 and 156; ɣ-HCH: gamma-hexachlorocyclohexane; β-HCH: beta-hexachlorocyclohexane; HCB: hexachlorobenzene; p,p'-DDE: 1,1,1-trichloro-2,2-bis(4-chlorophenyl) ethane; p,p'-DDT: 1,1,1-trichloro-2,2-bis(4-chlorophenyl) ethane. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

overall differences as the abovementioned lipid-normalized results (Figure S3). In cases, lipid-normalized PCB and HCB concentrations increased significantly from pre- to post-diagnostic blood sample collection (Fig. 2), whereas there were no significant differences in the other measured POPs. In comparison, wet weight concentrations of HCB increased significantly and concentrations of β-HCH and *p,p′*-DDT decreased, whereas there were no differences over time in wet weight concentrations of the other measured POPs (Figure S3). In controls,

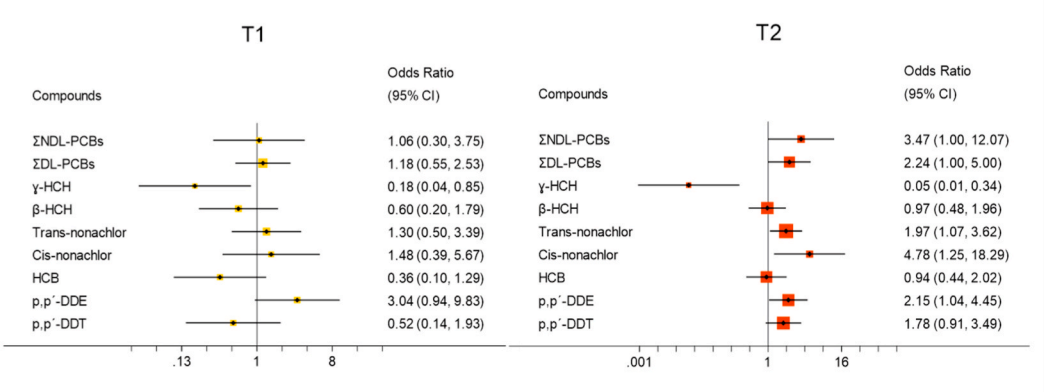

Fig. 3. Odds ratios and 95% confidence intervals (CIs) for the associations between one interquartile range increase in lipid-normalized persistent organic pollutant (POP) concentrations and incident (T1, pre-diagnosis) and prevalent (T2, post-diagnosis) type 2 diabetes mellitus.

lipid-normalized and wet weight *p,p′*-DDE, *p,p′*-DDT and *cis*-nonachlor concentrations decreased significantly from pre- to post-diagnostic blood sample collection. The crude longitudinal changes in lipid-normalized NDL-PCBs, DL-PCBs, β-HCH, HCB, and *p,p′*-DDE were significantly different in cases compared to controls (Fig. 2). When adjusting for confounding factors in linear regression models, these differences remained significant for NDL-PCBs, DL-PCBs, *cis*-nonachlor, *trans*-nonachlor, HCB and *p, p′*-DDE (Table S5).

We observed no significant positive associations between pre-diagnostic POP concentrations and incident T2DM after multivariable adjustments for confounding factors (Fig. 3). However, ɣ-HCH was inversely associated with T2DM. In contrast, we observed significant positive associations between post-diagnostic concentrations of *trans*-nonachlor, *cis*-nonachlor, and *p,p′*-DDE and prevalent T2DM (Fig. 3). Post-diagnostic ɣ-HCH concentrations remained negatively associated with T2DM. Using wet weight concentrations in the regression models gave similar results (Results not presented).

All abovementioned results were similar in case-control group 2 that in addition to age, also was matched on BMI (results not shown).

4. Discussion

In this pilot study of pre- and post-diagnostic blood profiles in T2DM cases and controls, we observed significant differences in the direction and magnitude of longitudinal changes in lipid, hormone and POP concentrations between cases and controls. We observed no significant positive associations between pre-diagnostic POP concentrations and incident T2DM. However, several post-diagnostic POP concentrations were positively and significantly associated with prevalent T2DM. Overall, these results suggest that factors related to lifestyle changes after T2DM diagnosis, for instance changes in weight and lipid profiles may affect POP concentrations and subsequent associations between POPs and prevalent T2DM.

Pre-diagnostic concentrations of several lipid-normalized POP concentrations were higher in cases compared to controls. However, after adjusting for confounding factors, the odds of developing T2DM in relation to elevated POP concentrations were non-significant, clearly emphasizing the role of BMI, lipids, weight change and diet as confounding factors in the POPs-T2DM association. Between the pre- and post-diagnostic blood sample collection, cases maintained a stable weight and developed a more favorable lipid profile (lower triglycerides, lower total and LDL cholesterol, and higher HDL cholesterol). In contrast, controls increased in weight, total lipids, and HDL cholesterol. The improvement in lipid profiles in cases is likely a result of a combination of lifestyle changes and use of diabetes medication following T2DM diagnosis. Overall, these results are supported by the findings of the National Health and Nutrition Examination Survey (NHANES) (Ford et al., 2013), in which T2DM cases improved their lipid profiles after diagnosis compared to healthy controls. In line with the improvement in lipid profiles, cases showed post-diagnostic FT4 concentrations that were higher than pre-diagnostic values. This observation is in accordance with the findings that FT4 concentrations are inversely correlated with triglyceride concentrations and positively correlated with HDL cholesterol concentrations (Roef et al., 2014). During that same time period, cases mainly experienced an increase in lipid-normalized concentrations of POPs (significantly for PCBs and HCB), except for β-HCH, which decreased, whereas controls experienced either a decrease or only a slight increase. One could expect a small decline in legacy POP concentrations in this period, due to past international regulations as reported in several blood monitoring studies (Nost et al., 2017; Thomsen et al., 2007; Vo et al., 2008). However, as our study period covers only 4 years and occurred several years after peak exposure, large differences in pre- and post-diagnostic POP concentrations were not expected. Overall, our findings suggest that the observed differences in longitudinal changes in lipid-normalized POP concentrations in cases compared to controls are largely affected by the improvements in lipid profiles in cases. Thus, a substantial decline in total lipid concentrations over a relatively short time period, concurrent with a relatively small natural decline in POP concentrations, may lead to artificially high POP concentrations, explaining the significant associations between several post-diagnostic POPs and T2DM. These findings are in line with several previous cross-sectional studies (Airaksinen et al., 2011; Lee et al., 2006; Rignell-Hydbom et al., 2009; Rylander et al., 2005; Ukropec et al., 2010) whereas our pre-diagnostic null results contradict those of several other prospective studies (Lee et al., 2011; Rignell-Hydbom et al., 2009; Turyk et al., 2015; Wu et al., 2013). However, there are also inconsistences across prospective studies, for instance about which POPs are positively associated with incident T2DM (Lee et al., 2011; Turyk et al., 2015; Wu et al., 2013; Zong et al., 2018). Blood sample collection also occurred in different calendar years, and the number of years between blood sample collection and T2DM diagnosis varies between studies. Thus, timing, in terms of both calendar year and time between blood sample collection and T2DM diagnosis, seems important to consider when comparing results from different prospective studies of POPs and T2DM. As pre-diabetes may be present long before clinical manifestation of the disease, factors related to T2DM may affect metabolic blood profiles years before T2DM diagnosis and induce disease progression bias in studies (Lee et al., 2014). Hence, there is clearly a need for longitudinal studies assessing pre-diagnostic concentrations of POPs repeated times prior to diagnosis as well as the effects of lifestyle changes and glucose-lowering medication on POP and lipid concentrations. We did, however, observe similar results in the case-control group matched on BMI and can conclude that matching by BMI seems unnecessary in future studies.

To the best of our knowledge, this is the second published study of pre- and post-diagnostic measurements of POP concentrations in T2DM cases and controls; the first was published in 2019 and reported both similar and dissimilar results (Tornevi et al. 2019). Our study has a design that generates hypotheses that can be confirmed or refuted in future larger studies, and is unique as it includes information about a large number of metabolic factors in addition to POP concentrations. This pilot study was based on a relatively small sample size, thus we did not have sufficient power to draw firm conclusions based on all possible associations. However, we have sufficient sample size for detecting the longitudinal difference in concentrations for all the POPs, lipids and hormones (power >80% and the probability of committing a type 1 error of 5%).

5. Conclusions

This pilot study suggests that factors related to T2DM affect blood concentrations of POPs and may partly explain the positive associations between POPs and prevalent T2DM. This pilot study highlight the importance of longitudinal studies with repeated measurements in order to critically assess whether the observed associations between POPs and T2DM actually reflect a causal mechanism.

Authors' contributions

Vivian Berg: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Funding acquisition; Dolley Charles: Conceptualization, Methodology, Investigation, Writing – original draft; Ingvar A Bergdahl: Methodology, Writing – review & editing; Therese H Nøst: Conceptualization, Writing – review & editing; Torkjel M Sandanger: Conceptualization, Writing – review & editing; Andreas Tornevi: Methodology, Writing – review & editing; Sandra Huber: Resources, Investigation, Writing – review & editing; Ole-Martin Fuskevåg: Resources, Investigation, Writing – review & editing; Charlotta Rylander: Conceptualization, Methodology, Writing – original draft, Project administration, Funding acquisition

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Ethics approval and consent to participate

Participation in the NOWAC Study was voluntarily, and a signed consent form was obtained from all participants. The study was approved by the Regional Committee for Medical Research Ethics (REK, case number: 2015/1780).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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List of abbreviations

BMI	body mass index
CI	confidence interval
DAG	directed acyclic graph
DHEA-S	Dehydroepiandrosterone sulfate
DL-PCB	Dioxin like polychlorinated biphenyl
FT3	Free triiodothyronine
FT4	Free thyroxin
HCB	Hexachlorobenzene
HCH	Hexachlorocyclohexane
HDL	High-density lipoprotein
IQR	Inter quartile range
LDL	Low-density lipoprotein
LOD	Limit of detection
MRM	Multiple reaction monitoring
NDL-PCB	Non-dioxin like polychlorinated biphenyl
NOWAC	Norwegian Women and Cancer study
OCP	Organochlorine Pesticides
PCB	Polychlorinated biphenyl
POP	Persistent Organic Pollutants
p,p'-DDE	1,1-bis-(4-chlorophenyl)-2,2-dichloroethene
p,p'-DDT	1,1,1-trichloro-2,2-bis-(4-chlorophenyl) ethane
T2DM	Type 2 Diabetes Mellitus
TSH	Thyroid-stimulating hormone
OR	Odds ratio

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2021.110846.

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