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Longitudinal changes in concentrations of persistent organic pollutants (1986–2016) and their associations with type 2 diabetes mellitus

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ABSTRACT

Background: Positive associations have been reported between persistent organic pollutants (POPs) and type 2 diabetes mellitus (T2DM); however, causality has not been established. Over the last decades, environmental exposure to legacy POPs has decreased, complicating epidemiological studies. In addition, physiological risk factors for T2DM may also influence POP concentrations, contributing to a complex network of factors that could impact associations with T2DM. Longitudinal studies on this topic are lacking, and few have assessed prospective and cross-sectional associations between repeated POP measurements and T2DM in the same individuals, which may shed light on causality.

Objectives: To compare longitudinal trends in concentrations of polychlorinated biphenyls (PCBs) and organochlorine pesticides (OCPs) in T2DM cases and controls, and to examine prospective and cross-sectional associations between PCBs, OCPs and T2DM at different time-points before and after T2DM diagnosis in cases.

Methods: We conducted a longitudinal, nested case-control study (1986–2016) of 116 T2DM cases and 139 controls from the Tromsø Study. All participants had three blood samples collected before T2DM diagnosis in cases, and up to two samples thereafter. We used linear mixed-effect models to assess temporal changes of POPs within and between T2DM cases and controls, and logistic regression models to investigate the associations between different POPs and T2DM at different time-points.

Results: PCBs, *trans*-nonachlor, *cis*-nonachlor, oxychlordane, *cis*-heptachlor epoxide, *p,p'*-DDE, and *p,p'*-DDT declined more slowly in cases than controls, whereas *β*-HCH and HCB declined similarly in both groups. Most POPs showed positive associations between both pre- and post-diagnostic concentrations and T2DM, though effect estimates were imprecise. These associations were most consistent for cis-heptachlor epoxide.

Discussion: The observed positive associations between certain POPs and T2DM may be because of higher POP concentrations within prospective T2DM cases, due to slower temporal declines as compared to controls.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a global health challenge, affecting nearly 463 million people worldwide (prevalence: 9.3%) in 2019 (Saeedi et al., 2019). Conventional risk factors for T2DM include older age, obesity, genetic predisposition, and sedentary lifestyle. Recent research has also focused on other risk factors, like persistent organic pollutants (POPs), and has established positive associations between T2DM and several polychlorinated biphenyls (PCBs) and organochlorine pesticides (OCPs) (Magliano et al., 2014; Taylor et al.,

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2013), although causality has not been established. PCBs and OCPs are classified as endocrine disrupting chemicals; they circulate in the human body and are stored in adipose tissue. Researchers have proposed several endocrine mechanisms that may link POPs and T2DM, including endocrine disruption of estrogen, androgen, thyroid hormone, and glucocorticoid homeostasis. Other proposed mechanisms include disruption of mitochondrial function, which results in the accumulation of diacylglycerol and other metabolites of fatty acid metabolism. This eventually suppresses the insulin signaling pathways, leading to insulin-resistance (Howell and Mangum, 2011; Yang et al., 2017).

Although positive associations between several POPs and T2DM have been reported in many published studies, including some meta-analyses (Song et al., 2016; Tang et al., 2014), discrepancies between them reflect the fact that there are many challenges in the study of POPs and T2DM. One of these is the overall declining time-trend in human concentrations of legacy POPs (Abass et al., 2018; Nost et al., 2013). Also, the vast majority of previous studies investigated the association between POPs and T2DM in a single blood sample collected either before or after T2DM diagnosis, which does not necessarily reflect life-long exposure to POPs, or past peak exposure, which could be relevant for disease etiology. Physiological factors related to T2DM, like age (birth year), weight change, and adiposity have also been shown to influence POP concentrations (Nost et al., 2013; Schade and Heinzow, 1998; Stubleski et al., 2018; Tornevi et al., 2019), thus affecting POPs-T2DM associations. Additionally, individuals with T2DM usually change their lifestyle after diagnosis, often resulting in stabilized or decreased body weight and improved lipid profiles (Ford et al., 2013). These factors could also influence POP concentrations, thereby affecting cross-sectional associations between POPs and prevalent T2DM. Until now, only two studies have assessed intra-individual changes in POPs within T2DM cases and controls using repeated samples from the same individuals (one pre- and one post-diagnostic sample) (Berg et al., 2021; Tornevi et al., 2019). Both studies suggested that lifestyle changes related to T2DM at least partly affect POP concentrations and their associations with T2DM. Thus, having repeated POP measurements from the same individuals taken several years apart may extend our knowledge of how POPs are associated with T2DM before and after T2DM diagnosis.

To explore the above-mentioned knowledge gaps, we designed a longitudinal, nested case-control study with three to five repeated POP measurements per participant over a period of 15–30 years. The present study aimed to compare longitudinal trends in POP concentrations between T2DM cases and controls, and to examine prospective and cross-sectional associations between POP concentrations and T2DM at different time-points before and after T2DM diagnosis in cases.

2. Materials and methods

2.1. The Tromsø Study

The Tromsø Study, initiated in 1974, is an ongoing population-based health survey conducted within the Tromsø municipality in Northern Norway. At present, the study consists of seven surveys conducted from 1974 to 2015/16, with a survey conducted approximately every 7 years (Jacobsen et al., 2012). Over 15,000 participants have participated in three or more surveys. At each survey, the participants answered a questionnaire, gave a blood sample, and submitted to a thorough physical examination.

2.2. Study design and participants

We used a longitudinal, nested case-control study design, with repeated blood samples collected from the same individuals at up to five surveys: 1986/87 (T1), 1994/95 (T2), 2001 (T3), 2007/08 (T4) and 2015/16 (T5). To be included, cases had to have a T2DM diagnosis recorded in a local diabetes registry between T3 and T4, and available pre-diagnostic serum samples (T1, T2, and T3). These criteria were fulfilled by 76 women and 69 men. If cases also had post-diagnostic samples (T4 and/or T5) available, they were also included. We randomly selected 76 women and 69 men as controls who had participated in at least the same surveys as the cases, had no T2DM diagnosis recorded in a local diabetes registry, and had available serum samples. The Tromsø Study has HbA1c% results for all included participants for T2-T5. Twenty-nine cases had HbA1c $\geq$ 6.5% in pre-diagnostic samples, and five controls had HbA1c $\geq$ 6.5% at one of the time-points; therefore, they were excluded from the study. Participation in the different surveys is represented by four sample sets (Fig. 1). Two controls and one case had insufficient serum at T2. Thus, the number of samples at each time-point was 255 at T1 and T3, 252 at T2, 120 at T4, and 108 at T5, adding up to 990 samples in total, of which the maximum number of cases and controls at any one time-point was 116 and 139, respectively (at T1 and T3) (Fig. 1).

2.3. Questionnaire, clinical examinations, and laboratory data

Tromsø Study participants completed and underwent clinical examinations at each survey. Questionnaires collected information on participant characteristics, use of medications, parity, and breastfeeding (in women, only available for T2-T5), and physical activity. Health professionals took measures of height and weight and collected blood samples by venous puncture at the clinical examinations. Samples were kept at room temperature for 30 min, after which the coagulated samples were centrifuged at 2000 *g* for 10 min. Aliquots of serum were transferred to secondary plastic sample containers within 1 h and stored at −70 °C (Eggen et al., 2013; Jacobsen et al., 2012).

2.4. Chemical analyses, and data handling

For the POPs and lipids analyses, serum samples of included participants were thawed on ice and aliquoted into two separate vials (Sarstedt, cat.nr 72.694.600). Lipid analyses were performed immediately, whereas the other aliquot was stored at −30 °C for another 3–6 months, until POP analyses were performed. Serum concentrations of triglycerides, total cholesterol, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol were analyzed with coulometric methods on a Cobas® 8000 platform (Roche diagnostics) at the Department of Laboratory Medicine, University Hospital of North Norway, which is certified according to ISO 151189 (Accredition, 2020). The analyses are routinely used in the clinic for diagnostic purposes. Quality control samples of three different concentrations were ran each day and their CVs were <3%. The laboratory also participates in the Lab Quality external quality assessment program, and results have been within the acceptance limits (Labquality, 2020). HbA1c% was measured after each survey by high-performance liquid chromatography on a Tosoh G8 analyzer (Tosoh Bioscience); CV was <3%.

All POP analyses were also performed at the Department of Laboratory Medicine, University Hospital of North Norway. The samples from the same individuals were measured in the same batch and processed under identical conditions. Each batch had same number of cases and controls, men and women, from the same time-point with randomized positions. Any information that could identify the samples were blinded to the lab staff.

The method for POP analysis has been described in detail elsewhere (Huber et al., 2020). The procedure includes a Freedom Evo 200 (Tecan, Männedorf, Switzerland) liquid handling workstation, which is used for sample preparation. Laboratory personnel extracted 150 μL of the diluted serum samples and cleaned them using automated solid phase extraction. Gas chromatography atmospheric pressure ionization coupled to tandem mass spectrometers (Waters, Milford, MA, USA) were used for the instrumental analyses of PCB congeners and OCPs. Atmospheric pressure ionization was conducted in positive mode under charge transfer conditions. The multiple reaction monitoring mode with

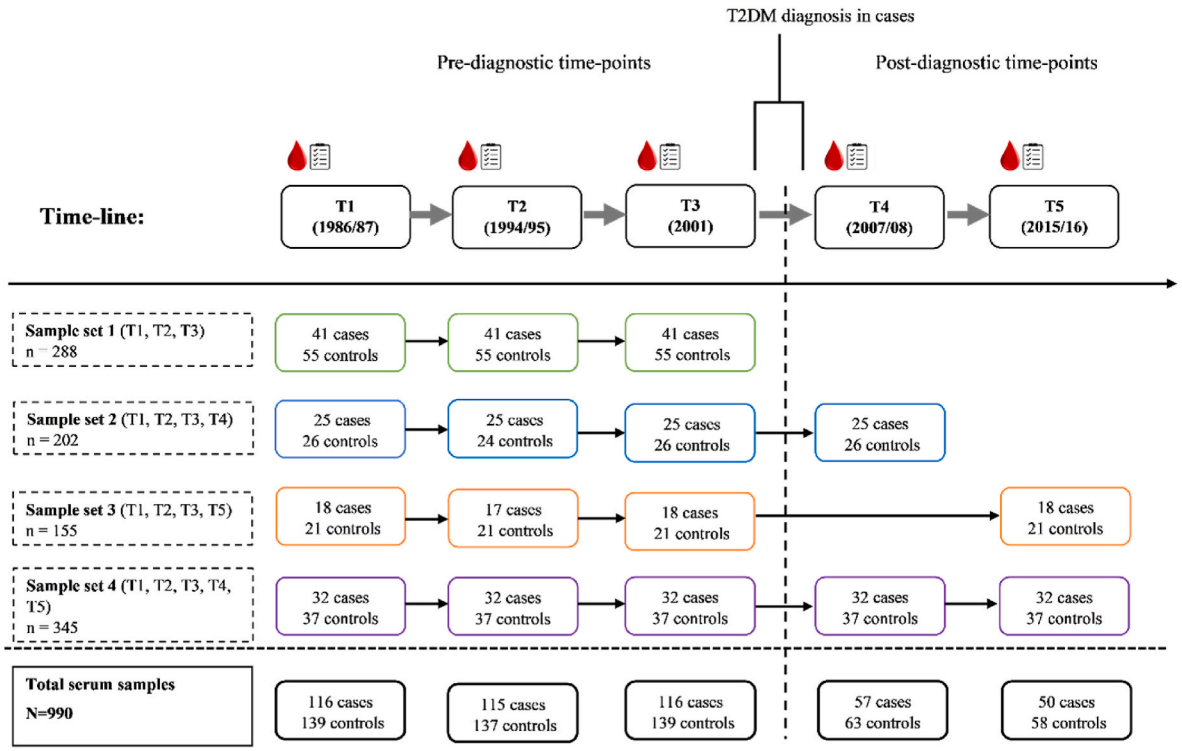

Fig. 1. Overview of the study design, sample size, and sample sets (mutually exclusive groups) based on participation in different surveys (time-points, T) of the Tromsø Study. Abbreviations: T2DM: type 2 diabetes mellitus.

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. For quality assurance, four blank samples, four SRM 1957/1958 (NIST, Gaithersburg, MD, USA) samples, and three bovine serum samples (Sigma Aldrich, Steinheim, Germany) were analyzed within each batch of 96 samples to control for background and carry-over effects. The coefficients of variation (CVs) for the measured POPs ranged from 6 to 24% in the present study, which was within previously established acceptable limits (Huber et al., 2020). All concentrations of the measured POPs were within ±20% of the certified reference materials from the National Institute of Standards and Technology. The laboratory successfully participates in the Arctic Monitoring and Assessment Ring Test for Persistent Organic Pollutants in Human Serum, organized by the Laboratoire de Toxicologie, Institut National de Santé Publique du Québec, Canada, which ensures that the measured POP concentrations are comparable across laboratories.

A total of 13 PCB congeners (PCB-28, 52, 74, 99, 118, 138, 153, 156, 170, 180, 183, 187, and 194) and 13 OCPs (alpha-hexachlorocyclohexane [α-HCH], beta-hexachlorocyclohexane [β-HCH], gamma-hexachlorocyclohexane [γ-HCH], *trans*-chlordane, *cis*-chlordane, *trans*-nonachlor, *cis*-nonachlor, oxychlordane, heptachlor, *cis*-heptachlor epoxide, hexachlorobenzene [HCB], 1,1,1-trichloro-2,2-bis-(4-chlorophenyl) ethane [*p,p'*-DDT], and 1,1-bis-(4-chlorophenyl)-2,2-dichloroethene [*p,p'*-DDE]) were detected in the analyses (Supplementary Table S1). Concentrations below the sample-specific method of detection limit (MDL) were replaced by MDL divided by the square root of 2. Only those PCBs and OCPs with a detection frequency over 70% at each time-point were included in the present study (Supplementary Table S1). The sum of PCB 118 and 156 is referred to as 'dioxin-like PCBs' ($\sum$DL-PCBs). The sum of all PCB congeners (PCB 74, 99, 118, 138, 153, 156, 170, 180, 183, 187, and 194) included in the analyses is presented as $\sum$PCBs. POP concentrations were lipid-normalized (ng/g lipid) by dividing the wet weight concentrations (pg/mL) by the total lipid concentrations (g/L) according to the formula by Phillips et al.: Total lipids = 2.27*total cholesterol + triglycerides + 0.623 (g/L) (Phillips et al., 1989).

2.5. Statistical analyses

Descriptive statistics of lipid-normalized and wet-weight POP concentrations at each time-point (T1-T5) are presented as means and standard deviations (SD). The mean and median of the different POPs at the different time-points are also presented as box plots. We calculated the mean differences and 95% confidence intervals (CIs) for participant characteristics and POP concentrations between cases and controls, and between men and women, at each time-point. Spearman's rank order correlations were used to assess monotonic relationships between the different POPs at each time-point and also between POPs and BMI at the different time-points.

To assess the time trends in POPs from T1 (1986/87) to T5 (2015/16) in cases and controls, we used multivariable linear mixed-effect models with a random intercept for individuals, while accounting for the dependencies between repeated measures. As the number of samples was considerably larger than the number of measurement occasions, no assumptions were made on the covariance pattern of the random effect; therefore, we fitted an unstructured variance covariance matrix (Fitzmaurice, 2008). Log-transformed POP concentrations were considered dependent variables. Among the independent variables, T2DM status and sex were considered to be constant over time, whereas time-indicator variables of each survey, age, weight change, parity, breastfeeding, total lipids, physical activity, and BMI (normal: $\leq$24.9 kg/m^2, overweight: $\geq$25.0 to $\leq$29.9 kg/m^2, obese: $\geq$30 kg/m^2) were considered to be time-dependent. Interaction terms between T2DM status and time were included to assess whether the time-trends of POPs were different in cases compared to controls. We also included interaction terms between sex and time to assess whether the time-trends of POPs were different between men and women. Predicted POP concentrations after adjusting for the above-mentioned covariates were plotted

for T2DM cases and controls at each time-point.

We used logistic regression models to assess linear associations between POP concentrations (independent variable) and T2DM status (dependent variable) for the different time-points. As our outcome variable (T2DM) is non-time-varying, methods like generalized estimating equations (GEE) that accounts for repeated measurements of POPs is not possible to use (Chen et al., 2015). Instead, we calculated the area under the curve (AUC) for the three pre-diagnostic measurements to quantify the cumulative exposure to POPs. AUCs were then used as independent variables in the logistic regression models. To further take advantage of our repeated measurement design, we modelled the pre-diagnostic POP concentrations as a function of time, using linear mixed effects models with random intercepts and random slopes and unstructured covariance patterns. From the models, we extracted the best linear unbiased prediction (BLUP) of POP concentrations of each individual and used the subject-specific predicted slope as independent variables in logistic regression models. The predicted subject-specific slope then represents a measure of each individual's pre-diagnostic time-trend in POP concentrations. We have presented all results from the logistic regression models as odds ratios (ORs) per 1-SD increase in POP measure in controls along with 95% CIs. To determine which covariates to include in the regression models, we drew a directed acyclic graph (DAG) depicting the hypothesized relationship (based on previous literature) between POPs and T2DM, and the covariates considered (Aune et al., 2014; Bellou et al., 2018; Li et al., 2016). Based on the DAG, covariates included in the regression models were sex, age (in years), weight change (kg), parity, breastfeeding (months), total lipids (g/L), physical activity (categorized into active/inactive), and body mass index (BMI, kg/m^2) (Supplementary Figure S1). Weight change was calculated for time-points T2-T5 using weight information from two adjacent time-points (for example: weight change at T2 = [weight at T2] - [weight at T1]). Weight change at T1 was set to zero, as we had no information on weight from the previous Tromsø survey. Cumulative breastfeeding at each time-point was calculated by summing the reported number of months of breastfeeding per child. As some previous studies have demonstrated sex-specific associations, we also assessed the relationship between POPs and T2DM stratified by sex. Since many analyses were conducted in this work, we controlled for multiple comparisons, and present 99.5% CIs as well, which corresponds to a Bonferroni correction for 10 tests. All statistical analyses were performed using STATA software, version 16 (StataCorp, 4905 Lakeway Drive, College Station, TX, USA).

3. Results

3.1. Sample characteristics

Our study sample consisted of 54% and 52% of females among cases and controls, respectively. The mean age of cases and controls at T1 was 47.5 ± 7.63 and 45.0 ± 9.85 years, respectively. At T1, the cases were ~7.9 (CI: 4.63, 11.2) kg heavier and had a BMI that was 3.15 (CI: 2.25, 4.04) kg/m^2 higher than controls, and this trend persisted through all time-points. There were no differences in parity or breastfeeding between female cases and controls. Total lipids were higher in cases compared to controls in pre-diagnostic time-points, but not in post-diagnostic time-points (Table 1). Men and women showed no differences in BMI or total lipids, except at T1, where men had higher total lipids than women (Supplementary Table S2).

At T1, concentrations of ∑PCBs, *β*-HCH, *trans*-nonachlor, *cis*-nonachlor, oxychlordane, HCB, and *p,p'*-DDE were similar between cases and controls, whereas concentrations of ∑DL-PCBs, *cis*-heptachlor epoxide, and *p,p'*-DDT were higher in cases. However, from T2 to T5, cases had higher mean concentrations of several lipid-normalized POPs compared to controls (Fig. 2, Supplementary Table S3). Similarly, cases experienced higher mean wet-weight concentrations of all POPs at pre-diagnostic time-points, but concentrations were more comparable at post-diagnostic time-points for several POPs (Supplementary Table S4). Cases had in general higher cumulative pre-diagnostic exposure of most

Table 1
Participant characteristics presented as means and standard deviations (SD) for cases and controls, and mean differences (Δ) between type 2 diabetes mellitus cases and controls at each time-point (T). The Tromsø Study (1986–2016).

Characteristics		Pre-diagnostic time-points						Post-diagnostic time-points			
		T1 (1986/87)		T2 (1994/95)		T3 (2001)		T4 (2007/08)		T5 (2015/16)	
		Mean ± SD	ΔMean (95% CI)	Mean ± SD	ΔMean (95% CI)	Mean ± SD	ΔMean (95% CI)	Mean ± SD	ΔMean (95% CI)	Mean ± SD	ΔMean (95% CI)
Age (years)	Cases	47.5 ± 7.63	2.49 (0.28, 4.69)	55.5 ± 7.65	2.48 (0.25, 4.71)	62.5 ± 7.63	2.49 (0.28, 4.69)	65.9 ± 7.38	2.58 (0.50, 5.67)	73.6 ± 7.02	3.72 (0.27, 7.16)
	Controls	45.0 ± 9.85		53.0 ± 9.90		60.0 ± 9.85		63.4 ± 9.44		69.9 ± 10.4	
Weight (kg)	Cases	78.0 ± 14.2	7.91 (4.63, 11.2)	82.1 ± 14.6	9.02 (5.54, 12.5)	86.0 ± 15.2	10.0 (6.38, 13.6)	84.5 ± 14.2	7.50 (1.88, 13.1)	84.5 ± 16.5	7.63 (1.61, 13.7)
	Controls	70.0 ± 12.3		73.1 ± 13.4		76.0 ± 14.1		77.0 ± 16.7		76.8 ± 15.0	
Parity[a]	Cases	2.88 ± 1.56	0.46 (−0.08, 0.99)	2.97 ± 1.50	0.42 (−0.09, 0.93)	2.97 ± 1.50	0.37 (−0.14, 0.87)	2.89 ± 1.28	0.24 (−0.47, 0.95)	2.66 ± 1.32	−0.11 (−0.80, 0.58)
	Controls	2.43 ± 1.54		2.55 ± 1.46		2.60 ± 1.45		2.65 ± 1.75		2.76 ± 1.39	
Breastfeeding[b] **(months)**	Cases	–	–	12.7 ± 11.0	0.64 (−3.40, 4.67)	13.5 ± 12.1	−0.49 (−4.77, 3.79)	13.3 ± 13.3	−0.86 (−7.88, 6.16)	11.3 ± 8.87	−6.75 (−13.2, −0.27)
	Controls			12.0 ± 11.1		14.0 ± 11.7		14.1 ± 14.7		18.0 ± 14.8	
Total Lipids (g/L)	Cases	8.05 ± 1.84	0.90 (0.51, 1.30)	8.30 ± 1.82	0.72 (0.23, 1.20)	7.53 ± 1.33	0.43 (0.11, 0.76)	7.33 ± 1.49	0.08 (−0.42, 0.59)	6.35 ± 1.47	−0.24 (−0.75, 0.27)
	Controls	7.15 ± 1.39		7.58 ± 2.05		7.10 ± 1.29		7.25 ± 1.31		6.59 ± 1.21	
Body Mass Index (kg/m^2)	Cases	27.3 ± 3.91	3.15 (2.25, 4.04)	29.0 ± 4.27	3.61 (2.59, 4.63)	30.6 ± 4.79	4.05 (2.94, 5.15)	30.8 ± 4.78	3.46 (1.70, 5.21)	30.5 ± 5.82	3.33 (1.36, 5.30)
	Controls	24.2 ± 3.34		25.4 ± 3.97		26.5 ± 4.15		27.3 ± 4.91		27.1 ± 4.48	

T1: n = 255, 116 cases; T2: n = 252, 115 cases; T3: n = 255, 116 cases; T4: n = 120, 57cases; T5: n = 108, 50 cases.
[a] Only in women: T1-T3 = 135, 60 cases.
[b] T4 = 76, 36 cases; T5 = 63, 29 cases.

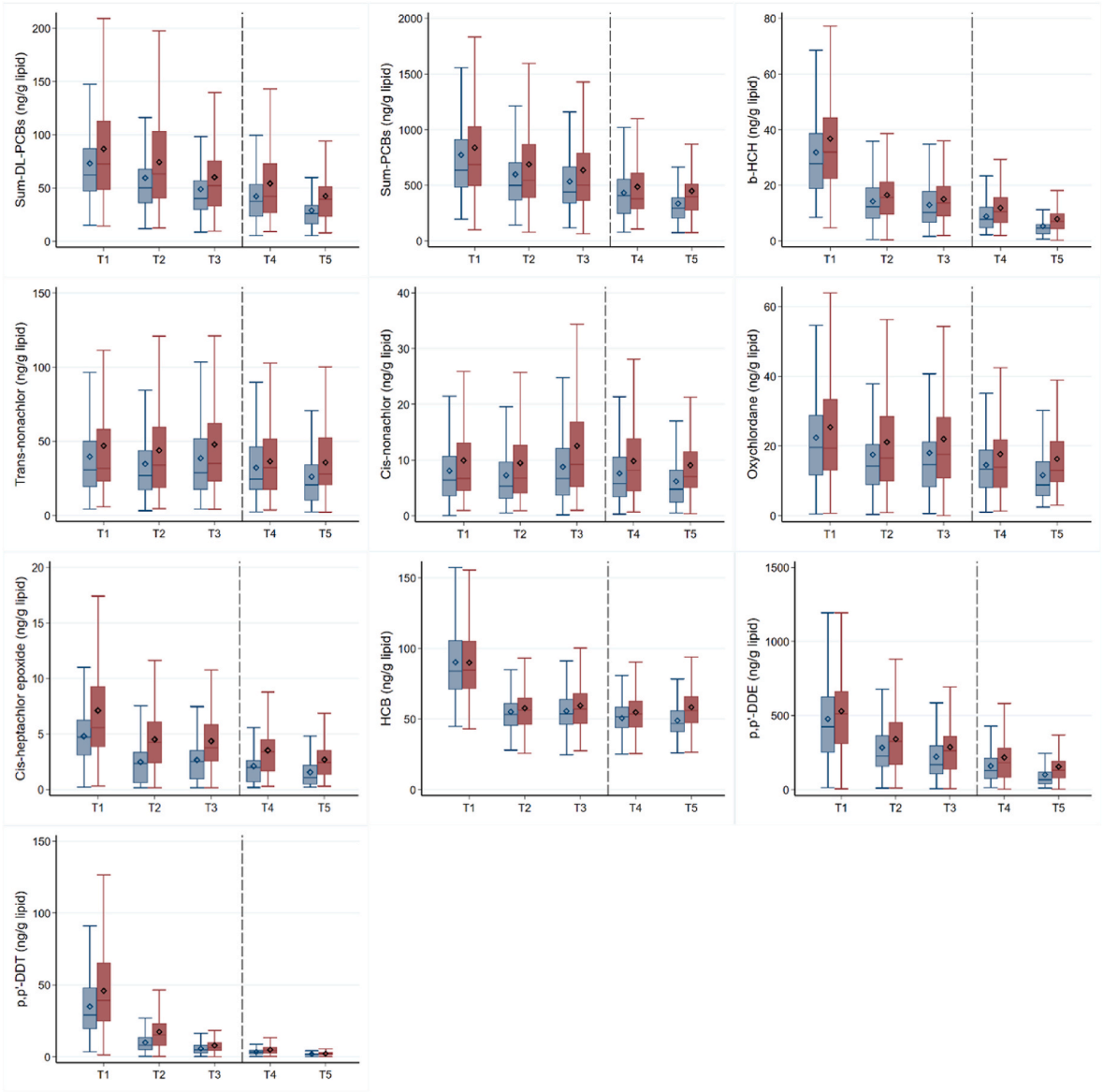

Fig. 2. Lipid-normalized persistent organic pollutant concentrations for type 2 diabetes mellitus cases (red boxes) and controls (blue boxes) at different time-points (T) in the Tromsø Study (1986–2016). Abbreviations: ∑DL-PCBs: dioxin-like polychlorinated biphenyls (PCB 118,156); ∑PCBs: sum polychlorinated biphenyls (PCB 74, 99, 118, 138, 153, 156, 170, 180, 183, 187 and 194); *β*-HCH: beta-hexachlorocyclohexane; HCB: hexachlorobenzene; *p,p'*-DDE: 1,1-bis-(4-chlorophenyl)-2,2-dichloroethene; *p,p'*-DDT: 1,1,1-trichloro-2,2-bis(4-chlorophenyl) ethane. T1-1986/87 (n = 255, 116 cases); T2-1994/95 (n = 252, 115 cases); T3-2001 (n = 255, 116 cases); T4-2007/08 (n = 120, 57 cases); T5-2015/16 (n = 108, 50 cases). Boxes represent the 25th–75th percentiles, horizontal lines within the boxes represent the median, whiskers indicate 1.5 times the length of the interquartile range above and below the 75th and 25th percentiles, respectively, ◊ denotes the mean. The vertical stifled line on the x-axis separates the pre-diagnostic samples from the post-diagnostic samples. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

POPs as estimated by the AUC (year * ng/g lipid). The predicted subject-specific pre-diagnostic slopes were negative for most individuals, however less for cases than controls.

Positive correlations were observed between the different POPs at each time-point, with correlation coefficients (r_s) ranging between 0.09 and 0.98. The highest correlations were seen between *trans*-nonachlor, *cis*-nonachlor and oxychlordane (>0.85) at all time-points, and the lowest correlation coefficient were seen between HCB and *p,p'*-DDT (0.09) at T5 (Supplementary Tables S5-S9). There were also positive correlations between BMI and POPs at the different time points ranging between 0.01 for ∑PCBs at T3 and 0.42 for *cis*-heptachlor epoxide at T2 (Supplementary Table S10). We observed sex differences in mean lipid-normalized concentrations of most POPs at both pre- and post-diagnostic time-points, except for HCB and *p,p'*-DDE, which were similar in men and women at all time-points (Supplementary Table S2).

3.2. Longitudinal changes in POPs from T1 to T5 in cases versus controls

In both cases and controls, concentrations of all POPs declined from T1 (1986/87) to T5 (2015/16), also after adjusting for sex, age, previous weight change, parity, breastfeeding, total lipids, physical activity, BMI, interaction between T2DM status and time (survey) and interaction between sex and time (Fig. 3). However, the overall decline in POP concentrations was smaller in T2DM cases than in controls, except for *β*-HCH and HCB, which declined similarly in cases and controls (Fig. 3, Supplementary Table S11). Adjusting for weight or BMI as a continuous predictor (instead of applying BMI categories) did not change overall findings. Similar results for all POPs were observed for the wet-weight

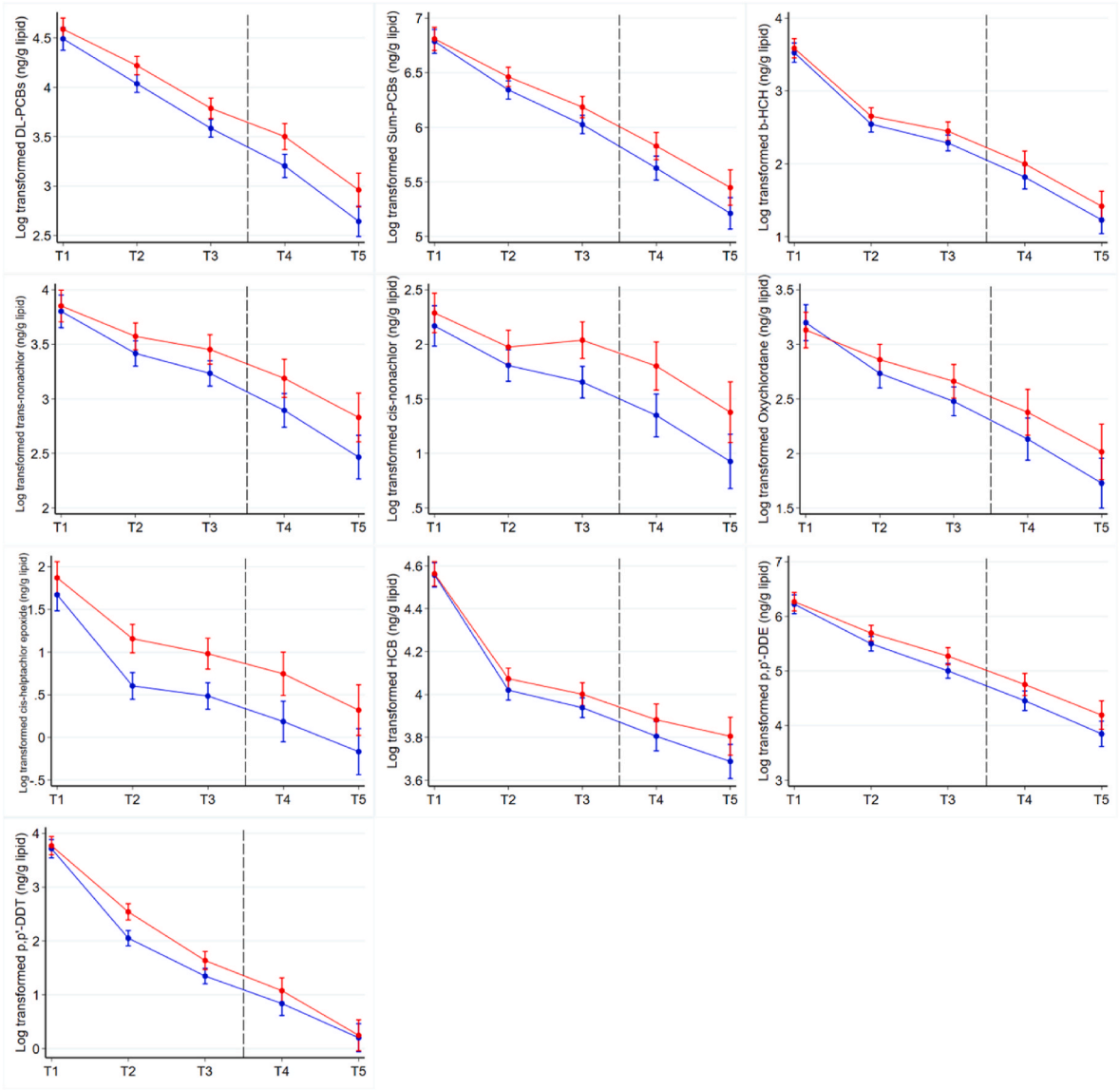

Fig. 3. Predicted lipid-normalized persistent organic pollutant concentrations in type 2 diabetes mellitus cases (in red) and controls (in blue) after adjusting for covariates at different time-points (T) in the Tromsø Study (1986–2016) (n = 990). T1-1986/87; T2-1994/95; T3-2001; T4-2007/08; T5-2015/16. Abbreviations: ∑DL-PCBs: dioxin-like polychlorinated biphenyls (PCB 118,156); ∑PCBs: sum polychlorinated biphenyls (PCB 74, 99, 118, 138, 153, 156, 170, 180, 183, 187 and 194); *β*-HCH: beta-hexachlorocyclohexane; HCB: hexachlorobenzene; *p,p'*-DDE: 1,1-bis-(4-chlorophenyl)-2,2-dichloroethene; *p,p'*-DDT: 1,1,1-trichloro-2,2-bis(4-chlorophenyl) ethane. The vertical stifled line on the x-axis separates the pre-diagnostic time-points from the post-diagnostic time-points. The models are adjusted for time (survey), sex, age, weight change, parity, breastfeeding, total lipids, BMI, interaction between T2DM status and time (survey) and interaction between sex and time (survey). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

concentrations as well (Supplementary Figure S2; Supplementary Table S12). However, when adjusting the confidence intervals and p-values for multiple testing, the stricter criteria for the precision of the estimates still indicated significant differences in longitudinal trends between cases and controls for several of the POPs, except for *β*-HCH, HCB, oxychlordane, *cis*-heptachlor epoxide and *p,p'*-DDT. There were indications of sex differences in temporal trends of all POPs except for *cis*- and *trans*-nonachlor, oxychlordane, and *p,p'*-DDT, with women experiencing slower declines than men. In addition to T2DM status and time, sex, age, weight change, parity, total lipids, physical activity, and BMI were important predictors of POP concentrations, although their relative importance varied according to the compound (Supplementary Tables S11 & S12).

Cases experienced a smaller decrease in lipid-normalized concentrations of ∑DL-PCBs, ∑PCBs, *trans*-nonachlor, oxychlordane, *cis*-heptachlor epoxide, *p,p'*-DDE, and *p,p'*-DDT from T1 to both subsequent pre-diagnostic time-points (T2 and T3) in comparison to controls. A smaller decline in cases was also observed for *cis*-nonachlor, specifically, from T1 to T3. The decline in *β*-HCH and HCB at all pre-diagnostic time-points and for *cis*-nonachlor from T1 to T2 were similar between cases and controls (Fig. 3, Supplementary Table S11). Similar results for the time-trends were observed when only the pre-diagnostic time-points were used in the linear mixed models (data not shown). After controlling for multiple testing, significant differences in declines were still evident for *cis*-heptachlor epoxide, and *p,p'*-DDT from T1 to T2; for ∑DL-PCBs, *trans*-nonachlor, *cis*-nonachlor and *p,p'*-DDE from T1 to T3; and ∑PCBs to both T2 and T3 (Supplementary Table S11 & S12).

When considering the longitudinal changes in POP concentrations from T1 to the post-diagnostic time-points (T4 and T5), cases experienced slower declines in lipid-normalized concentrations of ∑DL-PCBs, ∑PCBs, *trans*-nonachlor, *cis*-nonachlor, oxychlordane, and *p,p'*-DDE compared to controls. The decline for *cis*-heptachlor epoxide (from T1 to

T4) and HCB (from T1 to T5) was smaller in cases than controls, but similar for the other post-diagnostic time-point. Both cases and controls showed similar decreases in concentrations of *p,p'*-DDT and *β*-HCH from T1 to both post-diagnostic time-points (Fig. 3, Supplementary Table S11). After adjusting for multiple comparisons, there were no longer evidence of significant differences in declines between cases and controls for *β*-HCH, oxychlordane, *cis*-heptachlor epoxide, HCB and *p,p'*-DDT to both post-diagnostic time-points. However, there were still significantly slower declines in cases for ∑DL-PCBs, ∑PCBs, *trans*-nonachlor, *cis*-nonachlor and *p,p'*-DDE from T1 to both post-diagnostic time-points compared to controls (Supplementary Tables S11 & S12).

3.3. Associations between POPs and T2DM

After adjusting for confounding factors, several pre-diagnostic POP concentrations were positively associated with subsequent development of T2DM: *cis*-heptachlor epoxide (at T1, T2, and T3), *p,p'*-DDT (at T2), and *cis*-nonachlor (at T3) had 95% CIs around the effect estimates that did not include 1.0 (Fig. 4, Supplementary Table S13). The strengths of the positive associations varied from OR = 1.00 to OR = 1.98 and were stronger closer to the time of diagnosis (T1<T2<T3). The strongest association was observed for *cis*-nonachlor at T3 (OR = 1.98, 95% CI: 1.27–3.08). The wet-weight concentrations demonstrated similar results (Supplementary Figure S3; Supplementary Table S14). The conclusions were similar after adjusting the CIs (at level 99.5%) for multiple testing, except for *cis*-heptachlor epoxide at T1 which now had a wide CI including 1.0 (Supplementary Tables S13 & S14). In the models stratified by sex, we observed comparable results, but the associations were stronger for men for *cis*-nonachlor at T3, and *cis*-heptachlor epoxide and *p,p'*-DDT at T2 (data not shown). Results from the models estimating the associations between cumulative exposure to POPs, measured as AUC, and T2DM, showed similar results as the logistic regression models done separately at T1, T2 and T3. In the multivariable AUC models, only cis-heptachlor epoxide (OR = 1.75, CI: 1.29, 2.37) and *p,p'*-DDT (OR = 1.46, CI:1.12, 1.91) were relatively strongly associated with T2DM with CI intervals not including 1.0, also after controlling for multiple testing (Supplementary Table S15). The predicted pre-diagnostic time-trends of POPs were positively associated with T2DM, indicating that a slower decline was associated with T2DM. The 95% and 99.5% CIs indicated though poor precision of the estimates, which limited further interpretations (Supplementary Table S15).

Positive associations between POPs and T2DM were observed in the post-diagnostic time-points (except for ∑PCBs, *trans*-nonachlor, and oxychlordane), but corresponding 95% CIs were wide and included 1.0, except for *cis*-heptachlor epoxide at T4 (OR = 1.74, 95% CI: 1.07–2.83) (Fig. 4, Supplementary Table S13). Wet-weight concentrations of the same POPs were also positively associated with T2DM; however, the CIs indicated low precision of the point estimates (Supplementary Figure S3; Supplementary Table S14). After controlling for multiple comparisons, all POPs showed very wide CIs, indicating imprecise effect estimates (Supplementary Tables S13 & S14). Associations at post-diagnostic time-points stratified by sex demonstrated positive point estimates similar to those in the overall study sample, but the 95% CIs suggested poor precision, which hampered further interpretations (data not shown).

4. Discussion

This is the first study to fully embrace the chronologic aspects of the complexity of the relationship between POPs and T2DM by including repeated POP measurements from the same individuals collected before and after T2DM diagnosis. We observed a slightly smaller decline in the concentration of several POPs during the observation period (1986–2016) in T2DM cases compared to controls. The difference in decline between cases and controls was consistent in both pre- and post-diagnostic time-points. Our study sample also demonstrated evidence that *cis*-nonachlor, *cis*-heptachlor epoxide, and *p,p'*-DDT are positively associated with T2DM up to 7 years before diagnosis (*cis*-heptachlor epoxide and *p,p'*-DDT), and the strength of these associations increased closer to time of diagnosis. However, after T2DM diagnosis, none of the POPs were associated with T2DM after Bonferroni correction for

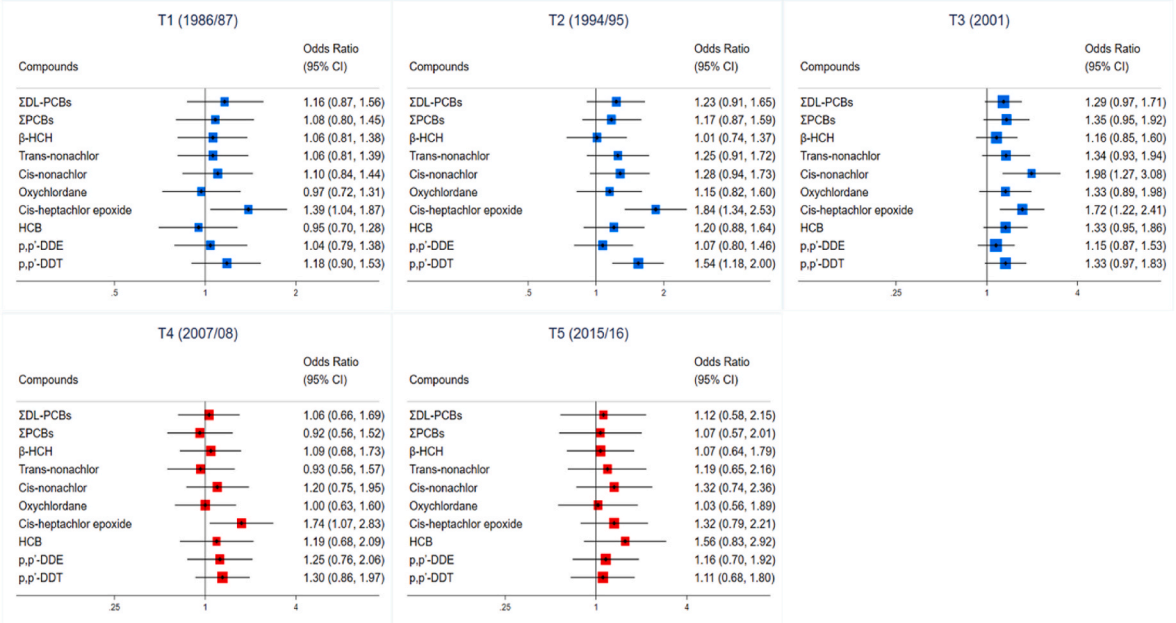

Fig. 4. Odds ratios and 95% confidence intervals (CIs) for the associations between a one-standard deviation (SD) increase in lipid-normalized concentrations of persistent organic pollutants (among controls) and type 2 diabetes mellitus at different time points (T) in the Tromsø Study (1986–2016). T1: (n = 254); T2: (n = 235); T3: (n = 225); T4: (n = 100); T5: (n = 93). Abbreviations: ∑DL-PCBs: Dioxin-like Polychlorinated biphenyls (PCB 118,156); ∑PCBs: Sum Polychlorinated biphenyls (PCB 74, 99, 118, 138, 153, 156, 170, 180, 183, 187 and 194); *β*-HCH: beta-hexachlorocyclohexane; HCB: hexachlorobenzene; *p,p'*-DDE: 1,1-bis-(4-chlorophenyl)-2,2-dichloroethene; *p,p'*-DDT: 1,1,1-trichloro-2,2-bis(4-chlorophenyl) ethane. Odds ratios are adjusted for sex, age, weight change, parity, breastfeeding, total lipids, physical activity, and BMI (except for weight change and breastfeeding at T1).

multiple comparisons. Overall, we observed higher POP concentrations in T2DM cases before diagnosis, and slower temporal declines of several POPs in the same individuals. Our observations suggest that the biological mechanisms related to T2DM or risk factors for the disease also lower the elimination rate of POPs. Thus, increased retention of POPs in individuals at high risk for T2DM could explain the positive associations between POPs and T2DM we observed as early as 15 years before clinical diagnosis of T2DM. Indeed, several factors associated with T2DM can influence POP concentrations, their metabolism, and/or excretion. For instance, toxicokinetic modelling indicates that the greater the BMI, the slower the decline of POP concentrations in the body (Wolff et al., 2007; Wood et al., 2016). Other factors that determine temporal trends of POPs include age (birth year), weight change, and blood lipid levels (Nost et al., 2013; Schade and Heinzow, 1998; Stubleski et al., 2018; Tornevi et al., 2019). In our study, T2DM cases were heavier and had higher BMIs than controls throughout the study period. This may be attributed to dietary habits and other lifestyle factors that influenced body weight before T1. The fact that cases had smaller decreases in the concentrations of several POPs after controlling for differences in sex, age, weight change, parity, breastfeeding, total lipids, physical activity, and BMI, and adjusting for multiple testing suggests that additional mechanisms may be entangled in the underlying mechanisms behind the time-trends of POPs. For instance, physiological factors associated with obesity and T2DM may alter several molecular mechanisms within the body, which further affect elimination rates of POPs. Accordingly, obesity is associated with cytochrome P450 (CYP) enzyme activities (Tomankova et al., 2017; Zanger and Schwab, 2013), processes that are critical for the detoxification of xenobiotics and the metabolism of numerous drugs. Particularly, CYP 3A (a subfamily of CYP), the most plentiful phase I drug-metabolizing enzyme which is found abundantly in the liver and intestines of humans, has been shown to have reduced metabolizing capacity in obese individuals (Krogstad et al., 2021; Zanger and Schwab, 2013). Reduced metabolizing capacity of these enzymes in prospective T2DM cases years before clinical manifestation of the disease could partly explain smaller decreases in POP concentrations, as several cases were already overweight or obese at the start of the study. It is also possible that the adjustment for BMI in our models do not fully account for all aspects of overweight and obesity.

Only two prior studies have compared POP measurements in one pre- and one post-diagnostic sample from the same T2DM cases and controls (Berg et al., 2021; Tornevi et al., 2019). In line with our observations for ∑PCBs, Tornevi and colleagues (Tornevi et al., 2019) reported that T2DM cases experienced smaller declines compared to the controls. Conversely, in our recently published pilot study (Berg et al., 2021), we observed that lipid-normalized concentrations of several OCPs and PCBs increased from the pre-to the post-diagnostic time-point in cases (~4 years), whereas a declining trend based on environmental exposure or a slight increase was observed in controls. The wet-weight concentrations in the same study did not demonstrate an increasing trend. We hypothesized that lifestyle changes provoked by T2DM diagnosis could lead to rapid improvements in lipid profiles and at least partly explain these observations. However, the present study does not support that hypothesis, as we observed weaker associations in post-diagnostic samples. Instead, our study suggests that differences in POP concentrations between cases and controls are present years before T2DM diagnosis.

Our results further suggest that men and women had different temporal trends for several POPs, with a slower decline observed in women, even though most women were above childbearing age at T1. However, this interaction did not affect the overall observations of slower declines in cases compared to controls. This aspect still deserves further in-depth study, as this is beyond the scope of the present publication. In addition to sex, time, and T2DM status, other factors such as age, weight change, total lipids, physical activity, and BMI influenced the time-trends of POPs, clearly emphasizing the complex network of factors that both influence POP concentrations and are independent risk factors of T2DM. To move the research forward in the field of POPs and T2DM, longitudinal studies with repeated measurements like this one are important.

We observed overall positive associations between pre-diagnostic concentrations of many POPs and T2DM with variations in the size and precision of effect estimates at the different time-points. In fact, *cis*-heptachlor epoxide, *p,p'*-DDT, and *cis*-nonachlor were the only compounds that displayed relatively strong and precise associations (with 95% and 99.5% CIs that did not include 1.0) after adjusting for confounding factors and multiple testing. Of these, *cis*-heptachlor epoxide and *p,p'*-DDT were consistently associated with T2DM at T2 and T3 and had distinctly higher concentrations among cases compared to controls even at T1. In addition, our results indicate differential elimination rates of *cis*-heptachlor epoxide and *p,p'*-DDT between cases and controls in the pre-diagnostic period, but not overall after controlling for multiple testing. Also, for unknown reasons, the concentrations of *cis*-nonachlor increased from T2 to T3 among cases, which could explain the strong positive association between *cis*-nonachlor and T2DM at T3. Our measures of cumulative exposure to POPs prior to T2DM diagnosis (AUCs) and the subject-specific pre-diagnostic time-trends confirmed the results observed at the separate pre-diagnostic time-points, as well as our analysis of differences in time-trends between cases and controls. Former prospective studies based on background exposure in general populations have reported an increased risk of T2DM with increasing concentrations of *p,p'*-DDE (Rignell-Hydbom et al., 2009; Turyk et al., 2009); *trans*-nonachlor, oxychlordane, and highly chlorinated PCBs (Lee et al., 2010); heptachlor and *cis*-heptachlor epoxide (Everett and Matheson, 2010; Montgomery et al., 2008); and HCB (Tornevi et al., 2019; Wu et al., 2013); or that gender modifies the association between POPs and T2DM (Vasiliu et al., 2006; Zong et al., 2018). However, the most recently published case-cohort study reported no associations between POPs and incident T2DM (Magliano et al., 2021). Additionally, when comparing results across studies, there is no uniform consistency about which POPs are positively associated with T2DM, which is an important, but not exclusive criteria for causality. Our observations of positive associations between *cis*-heptachlor epoxide and T2DM at two out of three pre-diagnostic time-points, as well as *p,p'*-DDT at T2 add to the range of publications that have reported positive associations between one or several POPs and T2DM. This could reflect a causal association; however, based on the lack of consistency in previous research and our indications of differential elimination rates of POPs according to T2DM status, there are also other explanations that need to be considered. Additionally, very few previous publications control for multiple comparisons, and our work highlight the necessity of this.

Differences in the timing of blood collection with respect to T2DM diagnosis in different studies could affect the final results. Our study is the first to investigate repeated pre-diagnostic measurements of POPs within the same individuals, and our results suggest that the associations between POPs and T2DM vary over time. Therefore, studies with only one pre-diagnostic measurement could reach different conclusions depending on how long before T2DM diagnosis blood samples were collected. Other factors that could influence study results include sample size, selection of confounders, and statistical modeling. Stratification by sex did not change our overall findings. However, the associations were stronger in men compared to women, which could also be a result of smaller sample size and less precision of effect estimates in women.

Our study also assessed the relationship between POPs and T2DM at two post-diagnostic time-points. All post-diagnostic POP measurements showed mainly positive associations, but 95% CIs were wide, exhibiting no evidence for increased odds of prevalent T2DM after Bonferroni correction. Previous reviews of epidemiological studies have consistently indicated that POPs are associated with increased odds of prevalent T2DM (Evangelou et al., 2016; Lee et al., 2014; Taylor et al., 2013). In cross-sectional studies of prevalent T2DM, it is not certain whether elevated concentrations of POPs preceded T2DM diagnosis. Thus, it is important to remember that, in these studies, POPs were measured after clinical manifestations of T2DM. In the present study, cases showed no

major weight loss. However, they showed stable post-diagnostic weight and BMI, and decreased total lipids, and weak positive post-diagnostic associations were demonstrated. Thus, as previously mentioned, our results do not support that lifestyle changes after T2DM diagnosis affect POP concentrations, thereby creating strong positive associations, as has been proposed in previous studies (Berg et al., 2021; Tornevi et al., 2019). However, slower declines in POP concentrations in cases compared to controls was observed even at post-diagnostic time-points. Therefore, our findings must be interpreted with caution, as the weakened associations in our post-diagnostic samples may also be attributed to the smaller sample sizes at T4 and T5.

The most unique feature of this study is the study design itself, with three to five repeated POP measurements for every individual, which has enabled us to examine temporal trends of POPs over a period of 30 years and to assess repeated associations between the different POPs and T2DM. These aspects have not been explored in previously published epidemiological studies. All T2DM cases in our study were identified using a local diabetes registry. Additionally, HbA1c% measurements from the individuals were available at the different time-points, which further enabled us to confirm T2DM status. Another important strength is that height and weight of all participants were objectively measured at each survey by health care professionals and were not self-reported. In addition, complete data were available on most of covariates for which we adjusted. Therefore, to the best of our knowledge, we adjusted for all potential confounders in both the logistic regression and mixed-model analyses. Meticulous laboratory quality control measures for the chemical analyses are an added strength of the present study. However, there are limitations that also need to be considered. For instance, there were fewer participants with post-diagnostic measurements, which may have influenced the strength and precision of effect estimates of the post-diagnostic POP concentrations and T2DM. Another limitation to be considered is that we could not investigate the interactions between POP concentrations and BMI in relation to T2DM as several of the cases were already either overweight/obese at T1 leaving very few participants in the stratified BMI categories. It is also important to remember that BMI does not necessarily reflect fat mass, but also muscle mass. Including a better measure of body fat mass than BMI and a larger sample size so that stratification by BMI status could be possible is highly relevant for future research in this field. This would be particularly interesting as the different POPs clearly displayed different correlations with BMI. It should also be noted that the generalization of these findings may be limited to populations similar to the adult Norwegian population.

Taken together, our results indicate that POPs have an extremely complex relationship with T2DM, as factors related to T2DM also affect POP concentrations. We suggest that slower elimination rates of POPs in people who develop T2DM can explain the observed positive associations between POPs and T2DM. The higher retention is not necessarily caused only by obesity as previously suggested (Wolff et al., 2007) but could also be a result of reduced activity in detoxifying enzymes or other molecular events related to risk factors for T2DM. We hope this study will trigger further longitudinal assessments on the relationship between T2DM and POPs, along with studies of factors such as obesity, lipids, and enzyme activities, which may play key roles in the temporal changes of POPs in individuals with T2DM, thereby influencing POPs-T2DM associations.

5. Conclusion

Our results suggest that higher retention of POPs in people that later develop T2DM can explain the observed positive associations between POP concentrations and T2DM.

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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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Abbreviations

AUC	area under the curve
BLUP	best linear unbiased prediction
BMI	body mass index
CI	confidence interval
CVs	Coefficients of variations
CYP	cytochrome P450
DAG	directed acyclic graph
DL-PCBs	dioxin-like polychlorinated biphenyls
γ-HCH	gamma-hexachlorocyclohexane
HCB	hexachlorobenzene
MDL	method of detection limit
OCPs	Organochlorine pesticides
OR	odds ratio
p,p'-DDE	1,1-bis-(4-chlorophenyl)-2,2-dichloroethene
p,p'-DDT	1,1,1-trichloro-2,2-bis-(4-chlorophenyl) ethane
PCBs	Polychlorinated biphenyls
POPs	Persistent Organic Pollutants
r_s	correlation coefficients
SD	standard deviation
T	time-point
T2DM	Type 2 Diabetes Mellitus
α-HCH	alpha-hexachlorocyclohexane
β-HCH	beta-hexachlorocyclohexane

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2021.112129.

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