International Journal of Hygiene and Environmental Health 249 (2023) 114148

Contents lists available at ScienceDirect

International Journal of Hygiene and Environmental Health

journal homepage: www.elsevier.com/locate/ijheh

Polybrominated diphenyl ethers in type 2 diabetes mellitus cases and controls: Repeated measurements prior to and after diagnosis

Dolley Charles [a], Vivian Berg [b,c], Therese Haugdahl Nøst [a,d], Tom Wilsgaard [a], Ingvar A. Bergdahl [e], Sandra Huber [c], Pierre Ayotte [f,g], Maria Averina [c,h], Torkjel Sandanger [a,i], Charlotta Rylander [a,*]

[a] Department of Community Medicine, Faculty of Health Sciences, UiT, The Arctic University of Norway, NO-9037, Tromsø, Norway
[b] Department of Medical Biology, Faculty of Health Sciences, UiT, The Arctic University of Norway, NO-9037, Tromsø, Norway
[c] Department of Laboratory Medicine, Division of Diagnostic Services, University Hospital of North Norway, NO-9038, Tromsø, Norway
[d] Department of Community Medicine and Nursing, Norwegian University of Science and Technology, NO-7491, Trondheim, Norway
[e] Department of Public Health and Clinical Medicine, Section of Sustainable Health, Umeå University, Umeå, Sweden
[f] Department of Social and Preventive Medicine, Laval University, Québec, QC, Canada
[g] Centre de Toxicologie du Québec, INSPQ, Québec, QC, Canada
[h] Department of Clinical Medicine, Faculty of Health Sciences, UiT, The Arctic University of Norway, NO-9037, Tromsø, Norway
[i] NILU-Norwegian Institute for Air Research, NO-9007, Tromsø, Norway

ARTICLE INFO

Keywords:
Polybrominated diphenyl ethers
Type 2 diabetes mellitus
Time trends
Repeated measurements
Pre- and post-diagnostic associations

ABSTRACT

Background: Previous studies have reported associations between certain persistent organic pollutants (POPs) and type 2 diabetes mellitus (T2DM). Polybrominated diphenyl ethers (PBDEs) are a class of POPs that are found in increasing concentrations in humans. Although obesity is a known risk factor for T2DM and PBDEs are fat-soluble, very few studies have investigated associations between PBDEs and T2DM. No longitudinal studies have assessed associations between repeated measurements of PBDE and T2DM in the same individuals and compared time trends of PBDEs in T2DM cases and controls.

Objectives: To investigate associations between pre- and post-diagnostic measurements of PBDEs and T2DM and to compare time trends of PBDEs in T2DM cases and controls.

Methods: Questionnaire data and serum samples from participants in the Tromsø Study were used to conduct a longitudinal nested case-control study among 116 T2DM cases and 139 controls. All included study participants had three pre-diagnostic blood samples (collected before T2DM diagnosis in cases), and up to two post-diagnostic samples after T2DM diagnosis. We used logistic regression models to investigate pre- and post-diagnostic associations between PBDEs and T2DM, and linear mixed-effect models to assess time trends of PBDEs in T2DM cases and controls.

Results: We observed no substantial pre- or post-diagnostic associations between any of the PBDEs and T2DM, except for BDE-154 at one of the post-diagnostic time-points (OR = 1.65, 95% CI: 1.00, 2.71). The overall time trends of PBDE concentrations were similar for cases and controls.

Discussion: The study did not support PBDEs increasing the odds of T2DM, prior to or after T2DM diagnosis. T2DM status did not influence the time trends of PBDE concentrations.

Abbreviations: BDE, bromodiphenyl ether; BMI, Body Mass Index; CI, confidence interval; CVs, coefficients of variation; DAG, Directed Acyclic Graph; GC-MS/MS, gas-chromatography tandem mass-spectrometry; HbA1c, glycated hemoglobin; K_{ow}, n-octanol-water partition coefficient; MDL, method detection limit; OR, odds ratio; PBDEs, polybrominated diphenyl ethers; PCBs, polychlorinated biphenyls; POPs, persistent organic pollutants; r_s, correlation coefficients; SD, standard deviation; T, time point; T2DM, Type 2 Diabetes Mellitus.

* Corresponding author.
E-mail address: charlotta.rylander@uit.no (C. Rylander).

https://doi.org/10.1016/j.ijheh.2023.114148
Received 11 November 2022; Received in revised form 24 February 2023; Accepted 27 February 2023
Available online 5 March 2023

1. Introduction

Type 2 Diabetes Mellitus (T2DM) is considered the world's fastest-growing chronic disease. In 2021, the global prevalence of T2DM was estimated to be 10.5%, i.e., 536.6 million people (Sun et al., 2022). T2DM is a chronic metabolic condition that occurs when the body either cannot produce enough insulin or becomes resistant to the normal effects of insulin. Well-known risk factors for T2DM include obesity, older age, a sedentary lifestyle, and genetic predisposition. In addition, research has addressed the associations between T2DM and factors such as epigenetics, stress, and environmental pollutants (Bellou et al., 2018).

Polybrominated diphenyl ethers (PBDEs) are a group of organohalogen flame retardants that have been widely used in electronics, plastics, textiles, and furniture to reduce flammability. Primary routes of PBDE exposure for humans are diet and dust inhalation (Costa and Giordano, 2014; Daso et al., 2010). As PBDEs resist degradation, are lipophilic and accumulate in adipose tissues of living organisms (Siddiqi et al., 2003), they have been detected in human samples, such as blood, placental tissue and breast milk (Daso et al., 2010). There are several possible molecular mechanisms linking POPs and T2DM, including endocrine disruption, DNA methylation and mitochondrial dysfunction (Yang et al., 2017). For instance, PBDEs are suspected to be endocrine disrupting chemicals (Birnbaum and Staskal, 2004), are structurally similar to thyroxine 4 (Birnbaum and Staskal, 2004; McDonald, 2002), and have been associated with altered thyroid hormone homeostasis that plays a key role in, for example, adipocyte differentiation and energy storage processes relevant for metabolic disorders such as T2DM (Song et al., 2016). Studies of associations between PBDEs and T2DM have reported inconsistent results: non-linear associations (Lim et al., 2008; Ongono et al., 2019); positive associations (Zhang et al., 2016), and no associations (Airaksinen et al., 2011; Turyk et al., 2009). Most of these studies are cross-sectional in design (Airaksinen et al., 2011; Lim et al., 2008; Turyk et al., 2009; Zhang et al., 2016), and only two studies were prospective; one measured PBDEs in a single blood sample collected prior to disease development and reported inverse, non-significant results (Turyk et al., 2015); and the other estimated the dietary exposure to PBDEs measured in food products and observed increased risk of T2DM only for the second and fourth, versus the first quintile groups (Ongono et al., 2019). Studies with repeated pre-diagnostic PBDE measurements are non-existent in the published literature. Thus, even though intensive research has focused on associations between different groups of persistent organic pollutants and T2DM, knowledge about how PBDEs relate to T2DM is still limited. Additionally, even though PBDEs are persistent, the time trends of individual PBDEs have varied over the years in adult general populations; some concentrations have declined over time, while others have increased, depending on the birth year, study population and sampling time (Thomsen et al., 2002; Toms et al., 2018). PBDEs are stored in adipose and liver tissues, and blood concentrations may therefore be affected by factors related to disease progression, hence time trends of PBDEs may differ in individuals according to T2DM status. In the present study, we thus used a nested case-control design with repeated measurements of PBDEs to i) investigate the associations between PBDEs and T2DM in samples obtained before and after T2DM diagnosis, and ii) compare time trends of PBDEs in serum from T2DM cases and controls.

2. Materials and methods

2.1. The Tromsø Study

The Tromsø Study is an ongoing population-based health survey conducted within the municipality of Tromsø in northern Norway. It was initiated in 1974 and seven surveys have been conducted approximately every seventh year between 1974 and 2015/16 (Jacobsen et al., 2012). It was initially established to investigate increased mortality from cardiovascular diseases among men living in northern Norway and has expanded to include men and women and other chronic diseases in the later surveys. More than 15,000 of the participants took part in three or more Tromsø surveys and answered questionnaires, underwent clinical examination, and donated blood samples for each survey. Participation in the study was voluntary, and an informed consent was provided by all participants. The study was approved by the Regional Committees for Medical Research Ethics.

2.2. Study design, study participants and data collection

We used a longitudinal, nested case-control study design, with repeated measurements from the same individuals participating in up to five Tromsø surveys: 1986/87 (T1), 1994/95 (T2), 2001 (T3), 2007/08 (T4) and 2015/16 (T5) (Fig. 1). A detailed version of the study design, study participants and data collection has been published (Charles et al., 2022). Briefly, to be included in the study, cases had to have a confirmed T2DM diagnosis recorded in the local diabetes registry between time-points T3 and T4 and also have available pre-diagnostic serum samples (T1, T2, and T3). 76 women and 69 men fulfilled these criteria. If post-diagnostic samples were available for the cases (T4 and/or T5), they were also included in the study sample. We then randomly selected the same number of men and women who had participated in at least the same surveys as the cases, had no T2DM diagnosis recorded in the local diabetes registry, and had available serum samples. They were considered the controls. The participants had also answered questionnaires at each survey with information on participant characteristics, use of medications, parity, breastfeeding (in women, only available for T2-T5), and physical activity. Health professionals measured height and weight and collected blood samples at the clinical examinations. The Tromsø Study has glycated hemoglobin (HbA1c%) results for all included participants for T2-T5. We excluded twenty-nine cases with HbA1c $\geq$ 6.5% in pre-diagnostic samples, and five controls with HbA1c $\geq$ 6.5% at one of the time-points as HbA1c $\geq$ 6.5% is considered one of the diagnostic criteria for T2DM (International Expert, 2009). In total, 990 blood samples from 116 T2DM cases and 139 T2DM-free controls were included. The number of samples at each time-point were 255 at T1 and T3, 252 at T2, 120 at T4 and 108 at T5 (Fig. 1).

2.3. Chemical analyses, and data handling

Frozen serum samples were thawed on ice and split into two aliquots in separate vials (Sarstedt, cat.nr 72.694.600). One aliquot was used for lipid analyses, which were performed immediately after aliquoting, while the other aliquot was stored at −30 °C for another 3–6 months, until PBDEs were determined. Both the PBDE analyses and lipid analyses were performed at the Department of Laboratory Medicine, University Hospital of North Norway. A detailed description of the lipid analysis has been described previously (Charles et al., 2022).

A gas-chromatography tandem mass-spectrometry (GC-MS/MS) was used to analyse the PBDEs together with the polychlorinated biphenyls (PCBs). A detailed version of the chemical analyses procedure has been described elsewhere (Huber et al., 2020). Briefly, the serum samples were prepared in a Freedom Evo 200 (Tecan, Männedorf, Switzerland) liquid handling workstation. Diluted serum samples (150 μL) were extracted and cleaned up by automated solid phase extraction. The instrumental analyses of PBDEs were performed using gas chromatography atmospheric pressure ionization coupled to tandem mass spectrometers (Waters, Milford, MA, USA). Atmospheric pressure ionization was conducted in positive mode under charge transfer conditions. The mass spectrometers were run in multiple reaction monitoring mode using two specific transitions for the individual analytes. Masslynx and Targetlynx software (Version 4.1, Waters) was used for quantification achieved by the internal-standard method with isotope-labeled compounds. 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 ninety-six

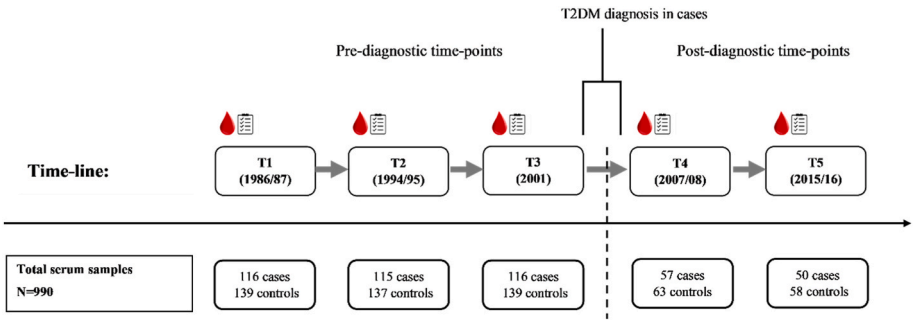

Fig. 1. Overview of the study design and sample size in the pre- and post-diagnostic time-points (T) of the Tromsø Study.

samples, to control for background and carry-over effects as a measure of quality assurance. The accuracy and precision of the established method was estimated from recovery experiments on three different days by analysing replicates of bovine serum spiked at low, medium, and high concentrations. The intra-day and inter-day relative standard deviations (RSD%) ranged between 2-18% and 5–28% which were within the acceptable limits (Huber et al., 2020). The samples from the same participants were analytically determined in the same batch under identical conditions. Each batch had the same number of T2DM cases and controls, and men and women, from identical time-points with randomized positions. The lab staff were blinded to any information that could identify the samples. The measured bromodiphenyl ether (BDE) congeners had coefficients of variation (CVs) ranging between 4% and 26%, which is within previously established acceptable limits (Huber et al., 2020). BDE-47, BDE-99, BDE-100, BDE-153, BDE-154 and BDE-183 were detected above the method detection limit (MDL) in the instrumental analyses (Supplementary Table S1). The PBDE concentrations were lipid-normalized (ng/g lipid) by dividing the wet-weight concentrations (pg/mL) by the total lipid concentrations (g/L) where, total lipids = 2.27*total cholesterol + triglycerides + 0.623 (g/L) (Phillips et al., 1989).

2.4. Statistical analyses

In the present study, the PBDE concentrations were right-skewed, with some individuals having high concentrations, and a large proportion of the PBDE concentrations were below the sample-specific MDL. These sample results (<MDL concentrations) were therefore replaced using distribution-based interval regression multiple imputation (Royston, 2007). We imputed values between zero and the individual MDL of each participant at each time-point using the "mi impute chained (intreg)" STATA code. We used twenty imputed datasets for all the statistical analyses presented in this paper.

Descriptive statistics for lipid-normalized concentrations of BDE-47, BDE-99, BDE-100, BDE-153, BDE-154, BDE-18 and ∑BDEs (sum of BDE-47 + 99+100 + 153+154 + 183) are presented as means and standard deviations (SD) as well as medians and standard errors (SE) for each time-point (T). We calculated the mean differences and 95% confidence intervals (CIs) for participant characteristics and PBDE concentrations between T2DM cases and controls. The mean and median concentrations of PBDEs are also presented as box plots for the different time-points. We used Spearman's rank order correlations to assess monotonic relationships at each time-point between the different PBDEs and other legacy POPs measured in the same samples and previously published (Charles et al., 2022).

To investigate linear associations between PBDE concentrations (independent variable) and T2DM status (dependent variable) at each time-point, we used multivariable logistic regression models. We have presented all results from logistic regression models as odds ratios (ORs) and 95% CIs per 1-SD increase in PBDE concentrations. The SDs were estimated from T2DM-free controls. No exclusions in cases were made based on the time of diagnosis since the aim of the paper was to study both pre-diagnostic and post-diagnostic associations. Thus, we could also assess possibilities of reverse causation in the PBDE-T2DM associations. Based on previous literature, we drew a directed acyclic graph (DAG) depicting the hypothesized relationship between PBDEs and T2DM, to determine which covariates to include in the regression models (Aune et al., 2014; Bellou et al., 2018; Li et al., 2016). Age and increased blood lipids are well-known risk factors for T2DM (Bellou et al., 2018), and determinants of PBDE concentrations in the body (Daniels et al., 2010; Thomsen et al., 2002; Zhao et al., 2021). Obesity is an established risk factor for T2DM, however, the role of body mass index (BMI) in the PBDEs-T2DM association is unclear as the research on it is limited. A recent systematic review examining prenatal POPs exposure in relation to obesity development in children found no evidence to support an obesogenic role for PBDEs (Stratakis et al., 2022). Epidemiologic studies in adults were mostly cross-sectional and did not provide consistent evidence for a relation of PBDEs with increased obesity (Daniels et al., 2010; Lee et al., 2012; Lim et al., 2008; Turyk et al., 2010). Therefore, we hypothesized that BMI is a confounder and not in the causal pathway between PBDEs and T2DM. Some previous studies have shown that breastfeeding and parity influence PBDE concentrations in women (Mehta et al., 2020; Zhang et al., 2017). Previous studies have shown that low breastfeeding and increased parity also increase the risk of T2DM (Aune et al., 2014; Li et al., 2016). Sex directly influences concentrations of PBDEs in the body (Zhao et al., 2021), and may increase the risk of T2DM (Huebschmann et al., 2019). Decreased physical activity is a known risk factor of T2DM (Bellou et al., 2018), and may influence PBDE concentrations through changes in weight/BMI associated with physical activity. Diet (consumption of foods containing PBDEs) directly influences PBDE concentrations (Daso et al., 2010), although its effect on T2DM may be mediated through BMI/weight change. Therefore, adjusting for BMI/weight change also implies controlling for diet, as well as other lifestyle factors. Based on the DAG, we included sex, age (in years), parity, breastfeeding (months), physical activity (categorized into active/inactive), total lipids (g/L), weight change (kg), and BMI (kg/m^2) in the analyses (Supplementary Fig. S1). Including serum biomarkers such as serum lipids in complex scenarios such as the present study are challenging. The DAG shows a complex network of physiological factors associated with both PBDEs and T2DM. Previous simulation studies have shown that in such complex models, it may be more beneficial to include a serum biomarker as a covariate in addition to standardizing the exposure (PBDEs) (Gaskins and Schisterman, 2010; Schisterman et al., 2005, 2011) in the regression model to sufficiently control for confounding and block any open backdoor pathways from the exposure to outcome (O'Brien et al., 2016). Therefore, in our study, we have both lipid-normalized the PBDE concentrations and included total lipids as a covariate in the models. However, as the total lipids are calculated based on a formula and all adjustments are imperfect and regressions with only wet-weight concentrations are warranted by some researchers, we also provide regression results for the wet-weight concentrations. We calculated weight change 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]). Since we had no information on weight from any previous Tromsø survey, we set weight change at T1 to zero. We summed the reported number of months of breastfeeding per child to calculate the cumulative breastfeeding at each time-point. We also assessed the associations between PBDEs and T2DM using multivariable logistic regression based on PBDE concentrations divided into tertiles as the independent variable and T2DM as the dependent variable. Furthermore, to compare how different substitution methods of PBDE concentrations < MDL influenced associations between PBDE and T2DM, in addition to the imputation method described above, we also performed multivariable logistic regressions by, i) dividing PBDE concentrations into 2 categories (above/below MDL) and ii) substituting PBDE concentrations below MDL by MDL divided by the square root of 2 and compared these to estimates observed in the multiple imputed data set. The latter methods (MDL/$\sqrt{(2)}$) are commonly used in epidemiological studies of POPs (Airaksinen et al., 2011; Ongono et al., 2019; Turyk et al., 2009) but have been discouraged if the percentages of non-detects are >15% (EPA, 2000).

We assessed the time trends of PBDEs in cases and controls from T1 (1986/87) to T5 (2015/16) using multivariable linear mixed-effect models with a random intercept for individuals, while accounting for the dependencies between repeated measures. Log-transformed PBDE concentrations were considered dependent variables. T2DM status, age at baseline (T1), and sex were time-constant; while indicator variable of each Tromsø survey, weight change, parity, breastfeeding, total lipids, and BMI categories (normal: ≤24.9 kg/m^2, overweight: ≥25.0 to ≤29.9 kg/m^2, obese: ≥30 kg/m^2) were time-varying independent variables. We included interaction terms between T2DM status and time to examine whether the time trends of PBDEs in cases differed from that of controls. We plotted the multivariable-adjusted predicted PBDE concentrations for T2DM cases and controls at each time-point.

All statistical analyses were performed using STATA software, version 16 (StataCorp, 4905 Lakeway Drive, College Station, TX, USA).

3. Results

3.1. Participant characteristics

In our study sample, 54% of the cases and 52% of the controls were females. The mean age at T1 was 47.5 ± 7.63 years in cases and 45.0 ± 9.85 years in controls. At T1, the cases were ~7.9 (95% CI: 4.63, 11.2) kg heavier and had a BMI that was 3.15 (95% CI: 2.25, 4.04) kg/m^2 higher than the controls, and this trend continued through the study period. No differences in parity or breastfeeding between female cases and controls were observed. Cases had higher pre-diagnostic total lipid concentrations compared to controls, but there were no post-diagnostic differences (T4-T5). A detailed description of the participant characteristics has been described previously (Charles et al., 2022).

3.2. Detection frequencies and PBDE concentrations at each time-point

BDE-47 and BDE-153 were the most frequently detected compounds, >65% and >42%, respectively, in both cases and controls at all five time-points. The detection frequency for BDE-153 increased with time, while BDE-47 decreased. BDE-154 and BDE-183 were the least detected compounds (<42% and <45%, respectively). The detection frequencies for BDE-99 and BDE-100 were higher in the pre-diagnostic time-points compared to the post-diagnostic time-points (Fig. 2, Supplementary Table S1).

Cases had higher pre-diagnostic detection frequencies of BDE-153 (T1), BDE-154 (T3), BDE-100, and BDE-183 (T1-T3), compared to controls, and lower detection frequencies of BDE-153 at T2 and T3. In post-diagnostic samples, cases had a higher proportion with concentrations > MDL for BDE-47 and BDE-154 (T4-T5) compared to controls, and a lower proportion for BDE-99 and BDE-183 at T4 (Fig. 2).

Spearman correlations between PBDEs and chlorinated POPs (PCBs, organochlorine pesticides) at each time-point had coefficients (r_s) ranging between −0.50 and 0.56. The strongest positive correlations were observed between BDE-47 and ∑PCB (0.56) at T1, BDE-100 and ∑PCBs (0.56) at T2, and BDE-153 and *trans*-nonachlor (0.48) at T4

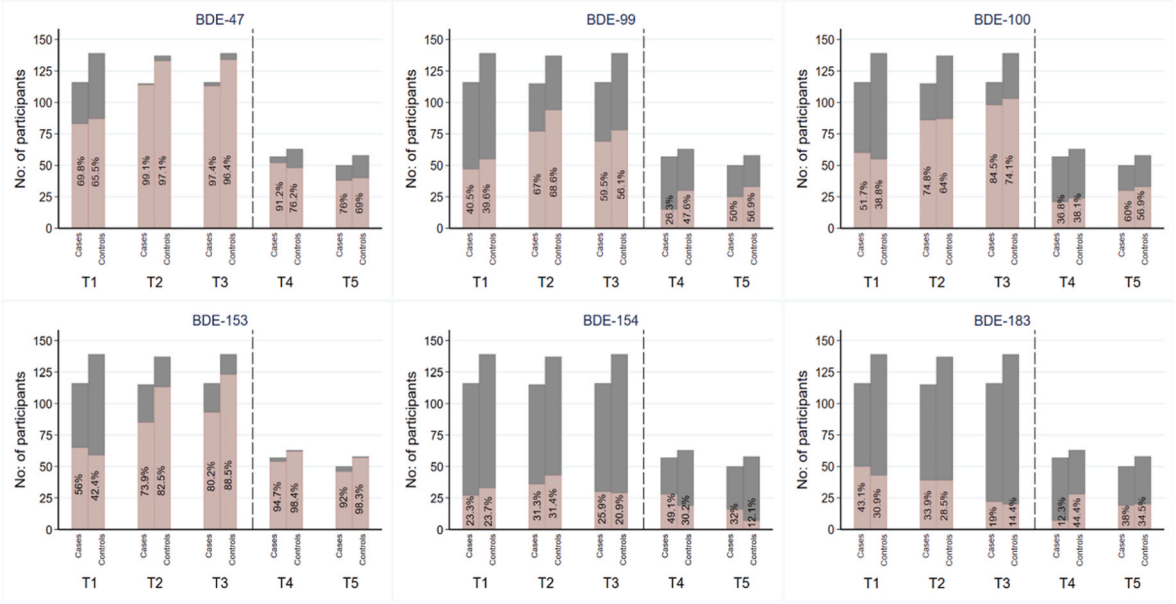

Fig. 2. Detection frequencies for polybrominated diphenyl ethers (PBDEs) for type 2 diabetes mellitus cases and controls at different time-points (T) in the Tromsø Study (1986–2016). The pink color represents the proportion of participants with concentrations > the method detection limit (MDL), while the grey color represents the proportion < MDL with the percentages (%) for detected concentrations within each bar for the cases and controls in each survey. The vertical dashed line on the x-axis separates the pre-diagnostic from the post-diagnostic samples. T1, T3: cases: n = 116; controls: n = 139; T2: cases: n = 115, controls: n = 137; T4: cases: n = 57, controls: n = 63; T5: cases: n = 50, controls: n = 58. Abbreviations: BDE: bromodiphenyl ether. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

(Supplementary Tables S2–S6). Cases and controls had similar mean PBDE concentrations at all time-points except for BDE-99 at T1, and BDE-100 and BDE-183 at T4, for which controls had higher concentrations compared to cases (Fig. 3, Supplementary Tables S7 and S8).

3.3. Associations between PBDEs and T2DM

After adjusting for age, sex, total lipids (g/L), parity, breastfeeding, BMI, weight change, and physical activity, we did not observe increased odds for T2DM for any of the PBDEs at any of the time-points, except for BDE-154 at T5 (OR = 1.65, 95% CI: 1.00, 2.71). Decreased odds for T2DM were observed for BDE-183 at T4 (OR = 0.32, 95% CI: 0.15, 0.68). Generally, the ORs had wide CIs including 1.0 (Fig. 4, Supplementary Table S9). Similar results were observed for the wet-weight concentrations (Supplementary Table S10). On dividing the PBDE concentrations into tertiles, we observed increased odds for T2DM for BDE-153 at T5, but with poor precision of the point estimates (tertile 2 vs 1: OR = 4.25, 95% CI: 1.13, 15.9; tertile 3 vs 1: OR = 4.52, 95% CI:1.02, 20.0) (results not shown).

The choice of substitution method for concentrations < MDL had a minor impact on the estimated associations between PBDEs and T2DM. The results from the different regression models were similar in terms of direction and strength. BDE-154 showed an association with T2DM at T5 in all three substitution methods, and at T4 in the dichotomized substitution method (Fig. S2).

3.4. Time trends of PBDEs

Similar time trends for PBDE concentrations were observed for cases and controls from 1986 to 2016, after adjusting for sex, age at baseline (T1), weight change, parity, breastfeeding, total lipids, BMI categories (normal: ≤24.9 kg/m^2, overweight: ≥25.0 to ≤29.9 kg/m^2, obese: ≥30 kg/m^2) and interaction between T2DM status and time (survey). There was one exception: cases showed a faster decline for BDE-183 from T1 to T4 compared to controls (Fig. 5, Supplementary Tables S11 and S12).

4. Discussion

This is the first study to assess repeated associations between pre- and post-diagnostic concentrations of PBDEs and T2DM, as well as differences in time trends of PBDEs in T2DM cases and controls. Pre-diagnostic PBDE concentrations did not increase the odds of T2DM substantially. Our findings thus do not support the hypothesis of background exposure to PBDEs as being a risk factor for T2DM. The time trends of PBDEs from 1986 to 2016 were also similar for cases and controls, proposing no differences in metabolism or bioaccumulation of PBDEs according to T2DM status. We did, however, observe increased odds for T2DM for BDE-154 at one of the post-diagnostic time-points. As no similar associations were observed for the pre-diagnostic samples, this finding reflects a physiological change related to the disease itself, an effect of a lifestyle change following the disease, or just a random result.

The lack of association between PBDEs and T2DM in pre-diagnostic samples is in line with one previous prospective study based on concentrations of PBDEs in serum samples (Turyk et al., 2015). The other prospective study by Ongono et al., (2019) found a non-linear association, although this study related exposure to PBDEs (as measured in commonly consumed food products) to T2DM, and several studies have shown poor agreement between dietary intake of POPs and circulating concentrations (Ongono et al., 2019). The null findings in the post-diagnostic (cross-sectional) samples are also in line with previous cross-sectional studies, although the mean concentrations of PBDEs in our post-diagnostic study samples were relatively low or similar compared to both these studies (Airaksinen et al., 2011; Turyk et al., 2009). The other cross-sectional study found positive associations between BDE-47 and prevalent T2DM, although this study measured higher median concentrations of BDE-47, and this could have contributed to the positive associations reported in the study. Another contributing factor could be the lack of adjustment of potential confounders such as parity, breastfeeding, weight change, and physical activity in this study (Zhang et al., 2016).

Our previous study addressing associations between chlorinated POPs and T2DM in the same samples showed slower declines in T2DM

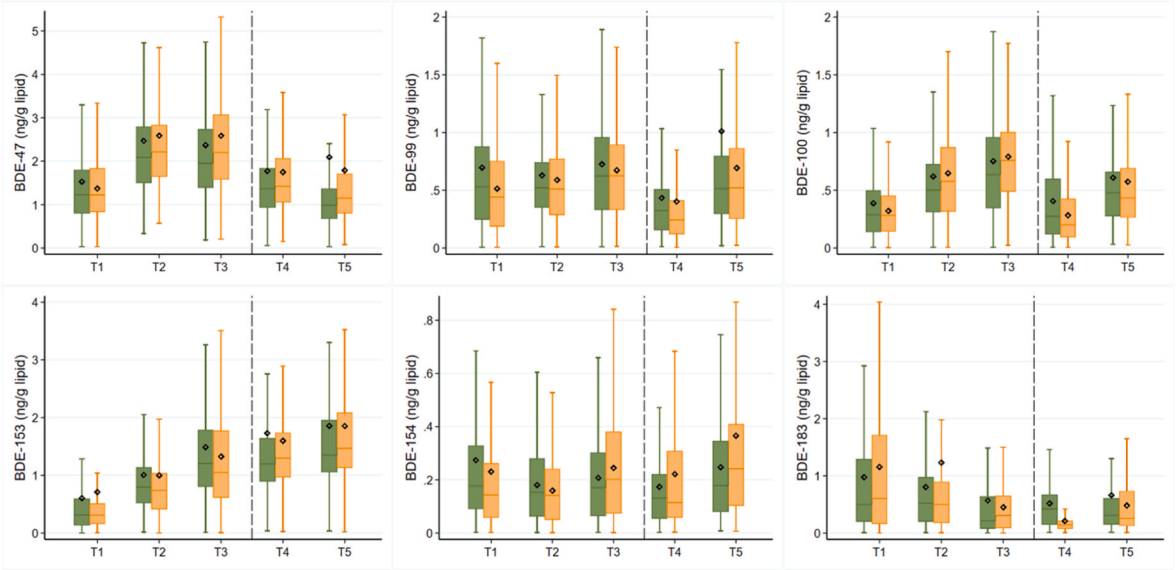

Fig. 3. Lipid normalized concentrations (using imputed concentrations) of polybrominated diphenyl ethers (PBDEs) for controls (green boxes) and type 2 diabetes cases (orange boxes) at different time-points (T) in the Tromsø Study (1986–2016). Boxes represent the 25th–75th percentiles, horizontal lines within the boxes denote the median, and whiskers indicate 1.5 times the length of the interquartile range above and below the 75th and 25th percentiles, respectively, and ◊ denotes the mean. The vertical dashed line on the x-axis separates the pre-diagnostic from the post-diagnostic samples. T1: n = 255; T2: n = 252; T3: n = 255; T4: n = 120; T5: n = 108. Abbreviations: BDE: bromodiphenyl ether. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

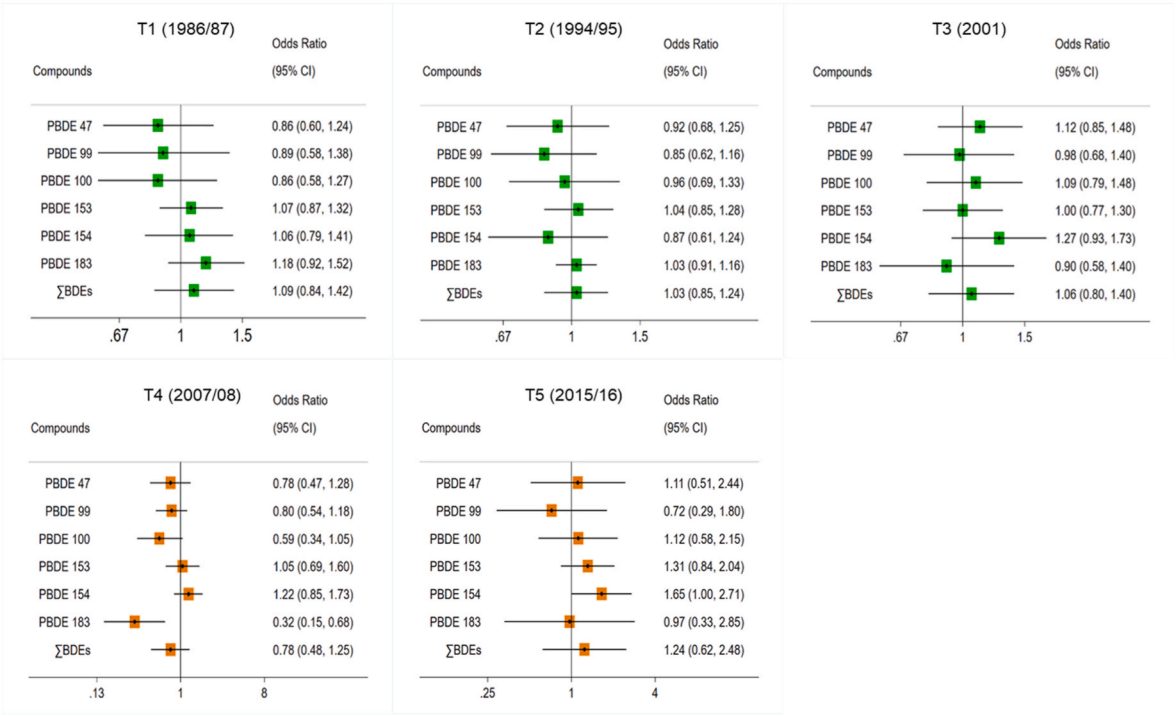

Fig. 4. Odds ratios (ORs) with 95% confidence intervals (CIs) for the associations between a one-standard deviation (SD) increase in lipid-normalized concentrations of PBDEs (among controls) and type 2 diabetes mellitus at different time-points (T) in the Tromsø Study (1986–2016). T1: (n = 254); T2: (n = 235); T3: (n = 225); T4: (n = 100); T5: (n = 93). The ORs are adjusted for age, sex, weight change, parity, breastfeeding, total lipids, physical activity, and BMI (except for weight change and breastfeeding at T1). Abbreviations: BDE: bromodiphenyl ether.

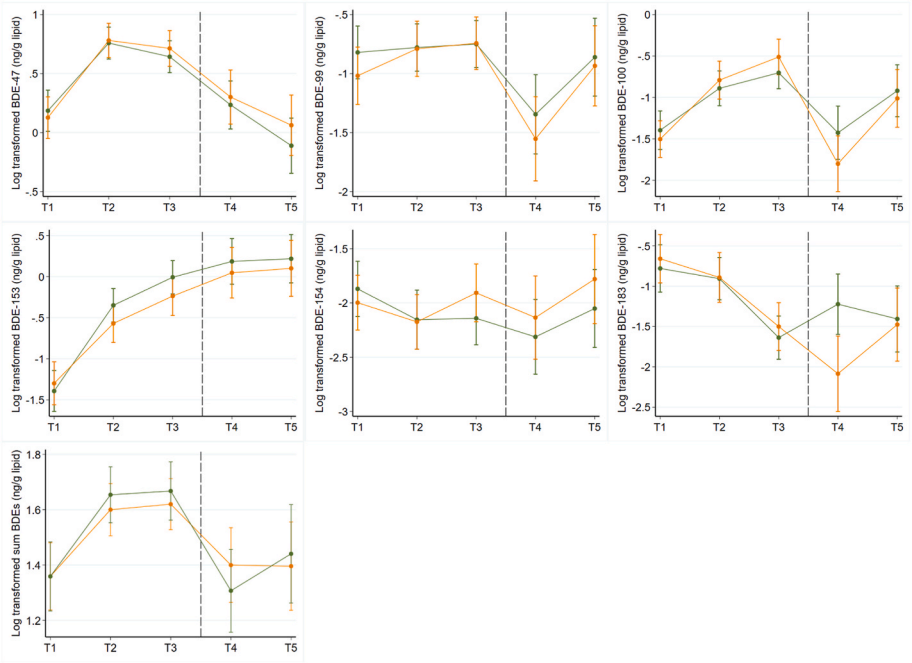

Fig. 5. Predicted lipid-normalized polybrominated diphenyl ether concentrations in type 2 diabetes mellitus cases (in orange) and controls (in green) after adjusting for covariates at different time-points (T) in the Tromsø Study (1986–2016) (N = 990). The vertical dashed line on the x-axis separates the pre-diagnostic from the post-diagnostic samples. Abbreviations: BDE: brominated diphenyl ether. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

cases compared to controls which could explain why prospective T2DM cases experience higher body burdens of chlorinated POPs than healthy controls (Charles et al., 2022). However, both cases and controls had comparable PBDE concentrations in our study. Although PBDEs may be structurally similar to PCBs, have similar log K_{OW} (PCB congeners: 6.04–8.35; PBDE congeners: 6.81–8.27) (ATSDR, 2017, 2000), and be metabolized by the same class of enzymes (Feo et al., 2013; Gross et al., 2015), the time trends for most PBDEs were similar between cases and controls throughout the entire study period. This may be attributed to distinctive characteristics of PBDEs compared to PCBs. For instance, the correlations between PBDEs and the chlorinated POPs ranged from −0.50 to 0.56, depending on the congeners. The fact that these compounds were not correlated to any great extent thus supports the differences in associations and time trends observed in our previous study

(Charles et al., 2022), compared to this. Others have also reported weak or moderate correlations between PBDEs and PCBs in human breast milk (She et al., 2007). Furthermore, some studies measuring both PCBs and PBDEs in adipose tissues and the liver from the same individuals showed higher PBDE concentrations in the liver, compared to adipose tissues, in some of the samples (Meironyte Guvenius et al., 2001). This may suggest that the bioaccumulation and metabolism of PBDEs are not affected by changes in body fatness and differs from that of PCBs and organochlorine pesticides. This is further supported by the fact that most of the T2DM cases in our study had either overweight or obesity at T1, although their mean PBDE concentrations were similar to that of controls. In fact, it was the controls that had highest mean concentrations for some PBDEs at certain time-points (Supplementary Table S7). In line with this, few previous studies have reported no association between BDE-47 and measures of body fatness (Lee et al., 2012; Ronn et al., 2011; Roos et al., 2012).

In the present study, one compound, BDE-183, declined faster among cases compared to controls. From T1 to T3, the detection frequencies for BDE-183 were higher or similar between cases and controls, while, at T4, the detection frequencies for cases and controls were 12.3% and 44.4%, respectively. This suggests that most cases had BDE-183 concentrations that were <MDL at T4, depicting a more rapid decline in the same group, compared to controls (Figs. 2 and 5). The smaller sample size at T4 may also have contributed to this difference between the two groups.

A challenge when working with PBDEs is the large proportion of samples with concentrations < MDL. There are different ways of handling non-detects during data analysis. We have assumed that the <MDL concentrations are missing at random (MAR) and have used multiple imputation. Previous simulation studies have shown that a correctly specified multiple imputation improves efficiency and reduces bias for analysis of MAR data with any proportion of missing data, given that sufficient auxiliary information is provided to the model (Madley-Dowd et al., 2019). Checking the fraction of missingness (FMI) is an efficient indicator for the severity of missing data problems (Li et al., 1991). In our study, the maximum FMI was 0.30 (moderate-high severity) for BDE-154 at T3 in the logistic regression models of the 20 imputed datasets. To the best of our knowledge, we have provided all the necessary auxiliary variables and correctly specified the imputation for our data. Further, but reassuringly, independent of the method used (multiple imputation, MDL/$\sqrt{2}$, dichotomization), we observed similar results for the associations between PBDEs and T2DM. Previous research has shown that MDL/$\sqrt{2}$ substitution of left-censored data may produce less precise estimates (Baccarelli et al., 2005), but we did not observe any considerable differences in associations between using this method and the multiple imputation. Thus, irrespective of the method of substitution used, our overall conclusions remain the same.

The nested longitudinal case-control study design is a major strength of the present study, including three to five repeated PBDE measurements for each study participant. To date, this is the first study to examine both pre- and post-diagnostic associations between PBDEs and T2DM. We could also assess time trends of PBDEs over a period of 30 years within T2DM cases and controls. All T2DM cases were identified and confirmed for diabetes status using a local diabetes registry and HbA1c% measurements of the individuals from the different time-points. Another important strength is that even though we had high non-detects for some of the PBDEs (>20%) at different time-points, we accounted for the <MDL concentrations using multiple imputation, imputing values between 0 and the individual MDL at the respective time-point for each participant. We had complete data for most of the covariates for which we adjusted. Otherwise, missing values were imputed using multiple imputation. To the best of our knowledge, we identified all potential confounders and adjusted for them in both the logistic regression and mixed-model analyses. However, in any observational studies, unmeasured confounding is always present, for example measurement errors from self-reported data. Additionally, we used two other substitution methods for the <MDL concentrations, to compare the consistencies in results. Comprehensive 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, not all participants had post-diagnostic measurements, resulting in smaller sample sizes at T4 and T5. This had an impact on the precision of the effect estimates of the post-diagnostic associations. Also, it should be considered that the study sample may be relatively small and may not have the statistical power to detect small differences. Animal studies suggest that PBDEs may be obesogens (Bondy et al., 2013; Suvorov et al., 2009). If so, then the DAG in our study with BMI as a confounder is wrong. However, previous research has shown no consistent evidence of PBDEs having obesogenic roles in humans thereby rather supporting BMI being a confounder and not a mediating factor (Stratakis et al., 2022). We did not account for multiple testing, i.e., we did not adjust p-values, even though we calculated ORs for six PBDEs at five time-points. With the present overall negative results, adjustments for multiple testing would strengthen the picture of negative findings. The generalization of these findings may be limited to populations similar to the adult Norwegian population, or populations with similar PBDE concentrations. Nevertheless, this study takes advantage of a well-established cohort and is one of the first studies to explore the relationship between PBDEs and T2DM risk.

Our study results support PBDEs not being associated with T2DM before or after T2DM diagnosis. Furthermore, our results show that, despite PBDEs being similar in molecular structure to PCBs, there may be intra- and inter-individual differences in the bioaccumulation and/or metabolism of PBDEs resulting in similar time trends between cases and controls.

5. Conclusion

Our results indicate that exposure to PBDEs does not increase the odds of developing T2DM.The time trends were similar for cases and controls, indicating no effect of T2DM-related factors on PBDE concentrations.

Funding

The project received funding from the Northern Norway Regional Health Authority (project number: SFP1289); the Department of Laboratory Medicine, UNN, and the Tromsø Study, UiT. The funders had no influence on the design of the study.

Acknowledgements

We thank the staff at the Department of Laboratory Medicine, University Hospital of North Norway, who contributed to the laboratory analysis; especially Tone F. Aune, Christina R. Hansen, and Julie S. Strømberg. We would also like to thank the participants in the Tromsø Study for their willingness to participate and donate blood.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijheh.2023.114148.

References

Airaksinen, R., Rantakokko, P., Eriksson, J.G., Blomstedt, P., Kajantie, E., Kiviranta, H., 2011. Association between type 2 diabetes and exposure to persistent organic pollutants. Diabetes Care 34 (9), 1972–1979. https://doi.org/10.2337/dc10-2303.

ATSDR, 2017. Toxicological Profile for Polybrominated Diphenyl Ether. Agency for Toxic Substances and Disease Registry. Retrieved 31 May from. https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=901&tid=183.

ATSDR, 2000. Toxicological Profile for Polychlorinated Biphenyls (PCBs). Agency for Toxic Substances and Disease Registry. Retrieved 31 May from. https://wwwn.cdc.gov/TSP/ToxProfiles/ToxProfiles.aspx?id=142&tid=26.

Aune, D., Norat, T., Romundstad, P., Vatten, L.J., 2014. Breastfeeding and the maternal risk of type 2 diabetes: a systematic review and dose-response meta-analysis of cohort studies. Nutr. Metabol. Cardiovasc. Dis. 24 (2), 107–115. https://doi.org/10.1016/j.numecd.2013.10.028.

Baccarelli, A., Pfeiffer, R., Consonni, D., Pesatori, A.C., Bonzini, M., Patterson Jr., D.G., Bertazzi, P.A., Landi, M.T., 2005. Handling of dioxin measurement data in the presence of non-detectable values: overview of available methods and their application in the Seveso chloracne study. Chemosphere 60 (7), 898–906. https://doi.org/10.1016/j.chemosphere.2005.01.055.

Bellou, V., Belbasis, L., Tzoulaki, I., Evangelou, E., 2018. Risk factors for type 2 diabetes mellitus: an exposure-wide umbrella review of meta-analyses. PLoS One 13 (3), e0194127. https://doi.org/10.1371/journal.pone.0194127.

Birnbaum, L.S., Staskal, D.F., 2004. Brominated flame retardants: cause for concern? Environ. Health Perspect. 112 (1), 9–17. https://doi.org/10.1289/ehp.6559.

Bondy, G.S., Lefebvre, D.E., Aziz, S., Cherry, W., Coady, L., Maclellan, E., Armstrong, C., Barker, M., Cooke, G., Gaertner, D., Arnold, D.L., Mehta, R., Rowsell, P.R., 2013. Toxicologic and immunologic effects of perinatal exposure to the brominated diphenyl ether (BDE) mixture DE-71 in the Sprague-Dawley rat. Environ. Toxicol. 28 (4), 215–228. https://doi.org/10.1002/tox.20713.

Charles, D., Berg, V., Nost, T.H., Bergdahl, I.A., Huber, S., Ayotte, P., Wilsgaard, T., Averina, M., Sandanger, T., Rylander, C., 2022. Longitudinal changes in concentrations of persistent organic pollutants (1986-2016) and their associations with type 2 diabetes mellitus. Environ. Res. 204 (Pt B), 112129 https://doi.org/10.1016/j.envres.2021.112129.

Costa, L.G., Giordano, G., 2014. Polybrominated diphenyl ethers. In: Wexler, P. (Ed.), Encyclopedia of Toxicology, third ed. Academic Press, pp. 1032–1034. https://doi.org/10.1016/B978-0-12-386454-3.00422-X.

Daniels, J.L., Pan, I.J., Jones, R., Anderson, S., Patterson, D.G., Needham, L.L., Sjodin, A., 2010. Individual characteristics associated with PBDE levels in U.S. Human milk samples. Environ. Health Perspect. 118 (1), 155–160. https://doi.org/10.1289/ehp.0900759.

Daso, A.P., Fatoki, O.S., Odendaal, J.P., Okonkwo, J.O., 2010. A review on sources of brominated flame retardants and routes of human exposure with emphasis on polybrominated diphenyl ethers. Environ. Rev. 18 (NA), 239–254. https://doi.org/10.1139/A10-010.

EPA, 2000. Guidance for Data Quality Assessment. Practical Methods for Data Analysis. QA00 Version, Washington, DC. Retrieved from. https://www.epa.gov/sites/default/files/2015-06/documents/g9-final.pdf.

Feo, M.L., Gross, M.S., McGarrigle, B.P., Eljarrat, E., Barcelo, D., Aga, D.S., Olson, J.R., 2013. Biotransformation of BDE-47 to potentially toxic metabolites is predominantly mediated by human CYP2B6. Environ. Health Perspect. 121 (4), 440–446. https://doi.org/10.1289/ehp.1205446.

Gaskins, A.J., Schisterman, E.F., 2010. The effect of lipid adjustment on the analysis of environmental contaminants and the outcome of human health risks. In: Armstrong, D. (Ed.), Lipidomics: Volume 2: Methods and Protocols. Humana Press, pp. 371–381. https://doi.org/10.1007/978-1-60761-325-1_20.

Gross, M.S., Butryn, D.M., McGarrigle, B.P., Aga, D.S., Olson, J.R., 2015. Primary role of cytochrome P450 2B6 in the oxidative metabolism of 2,2',4,4',6-pentabromodiphenyl ether (BDE-100) to hydroxylated BDEs. Chem. Res. Toxicol. 28 (4), 672–681. https://doi.org/10.1021/tx500446c.

Huber, S., Averina, M., Brox, J., 2020. Automated sample preparation and GC-API-MS/MS as a powerful tool for analysis of legacy POPs in human serum and plasma. Anal. Methods 12 (7), 912–929. https://doi.org/10.1039/c9ay02400j.

Huebschmann, A.G., Huxley, R.R., Kohrt, W.M., Zeitler, P., Regensteiner, J.G., Reusch, J.E.B., 2019. Sex differences in the burden of type 2 diabetes and cardiovascular risk across the life course. Diabetologia 62 (10), 1761–1772. https://doi.org/10.1007/s00125-019-4939-5.

International Expert, C., 2009. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 32 (7), 1327–1334. https://doi.org/10.2337/dc09-9033.

Jacobsen, B.K., Eggen, A.E., Mathiesen, E.B., Wilsgaard, T., Njolstad, I., 2012. Cohort profile: the tromso study. Int. J. Epidemiol. 41 (4), 961–967. https://doi.org/10.1093/ije/dyr049.

Lee, D.H., Lind, L., Jacobs Jr., D.R., Salihovic, S., van Bavel, B., Lind, P.M., 2012. Associations of persistent organic pollutants with abdominal obesity in the elderly: the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. Environ. Int. 40, 170–178. https://doi.org/10.1016/j.envint.2011.07.010.

Li, K.H., Raghunathan, T.E., Rubin, D.B., 1991. Large-sample significance levels from multiply imputed data using moment-based statistics and an F reference distribution. J. Am. Stat. Assoc. 86 (416), 1065–1073. https://doi.org/10.2307/2290525.

Li, P., Shan, Z., Zhou, L., Xie, M., Bao, W., Zhang, Y., Rong, Y., Yang, W., Liu, L., 2016. Mechanisms in endocrinology: parity and risk of type 2 diabetes: a systematic review and dose-response meta-analysis. Eur. J. Endocrinol. 175 (5), R231–R245. https://doi.org/10.1530/EJE-16-0321.

Lim, J.S., Lee, D.H., Jacobs Jr., D.R., 2008. Association of brominated flame retardants with diabetes and metabolic syndrome in the U.S. population, 2003-2004. Diabetes Care 31 (9), 1802–1807. https://doi.org/10.2337/dc08-0850.

Madley-Dowd, P., Hughes, R., Tilling, K., Heron, J., 2019. The proportion of missing data should not be used to guide decisions on multiple imputation. J. Clin. Epidemiol. 110, 63–73. https://doi.org/10.1016/j.jclinepi.2019.02.016.

McDonald, T.A., 2002. A perspective on the potential health risks of PBDEs. Chemosphere 46 (5), 745–755. https://doi.org/10.1016/s0045-6535(01)00239-9.

Mehta, S.S., Applebaum, K.M., James-Todd, T., Coleman-Phox, K., Adler, N., Laraia, B., Epel, E., Parry, E., Wang, M., Park, J.-S., Zota, A.R., 2020. Associations between sociodemographic characteristics and exposures to PBDEs, OH-PBDEs, PCBs, and PFASs in a diverse, overweight population of pregnant women. J. Expo. Sci. Environ. Epidemiol. 30 (1), 42–55. https://doi.org/10.1038/s41370-019-0173-y.

Meironyte Guvenius, D., Bergman, A., Noren, K., 2001. Polybrominated diphenyl ethers in Swedish human liver and adipose tissue. Arch. Environ. Contam. Toxicol. 40 (4), 564–570. https://doi.org/10.1007/s002440010211.

O'Brien, K.M., Upson, K., Cook, N.R., Weinberg, C.R., 2016. Environmental chemicals in urine and blood: improving methods for creatinine and lipid adjustment. Environ. Health Perspect. 124 (2), 220–227. https://doi.org/10.1289/ehp.1509693.

Ongono, J.S., Dow, C., Gambaretti, J., Severi, G., Boutron-Ruault, M.C., Bonnet, F., Fagherazzi, G., Mancini, F.R., 2019. Dietary exposure to brominated flame retardants and risk of type 2 diabetes in the French E3N cohort. Environ. Int. 123, 54–60. https://doi.org/10.1016/j.envint.2018.11.040.

Phillips, D.L., Pirkle, J.L., Burse, V.W., Bernert Jr., J.T., Henderson, L.O., Needham, L.L., 1989. Chlorinated hydrocarbon levels in human serum: effects of fasting and feeding. Arch. Environ. Contam. Toxicol. 18 (4), 495–500. https://doi.org/10.1007/BF01055015.

Ronn, M., Lind, L., van Bavel, B., Salihovic, S., Michaelsson, K., Lind, P.M., 2011. Circulating levels of persistent organic pollutants associate in divergent ways to fat mass measured by DXA in humans. Chemosphere 85 (3), 335–343. https://doi.org/10.1016/j.chemosphere.2011.06.095.

Roos, V., Rönn, M., Salihovic, S., Lind, L., Bavel, B.v., Kullberg, J., Johansson, L., Ahlström, H., Lind, P.M., 2012. Circulating levels of persistent organic pollutants in relation to visceral and subcutaneous adipose tissue by abdominal MRI. Obesity. https://doi.org/10.1038/oby.2012.123.

Royston, P., 2007. Multiple imputation of missing values: further update of ice, with an emphasis on interval censoring. STATA J. 7 (4), 445–464. https://doi.org/10.1177/1536867x0700700401.

Schisterman, E., Whitcomb, B., Bowers, K., 2011. Invited commentary: causation or "noitasuac"? Am. J. Epidemiol. 173 (9), 984–987. https://doi.org/10.1093/aje/kwq499 reply 988-989.

Schisterman, E.F., Whitcomb, B.W., Louis, G.M., Louis, T.A., 2005. Lipid adjustment in the analysis of environmental contaminants and human health risks. Environ. Health Perspect. 113 (7), 853–857. https://doi.org/10.1289/ehp.7640.

She, J., Holden, A., Sharp, M., Tanner, M., Williams-Derry, C., Hooper, K., 2007. Polybrominated diphenyl ethers (PBDEs) and polychlorinated biphenyls (PCBs) in breast milk from the Pacific Northwest. Chemosphere 67 (9), S307–S317. https://doi.org/10.1016/j.chemosphere.2006.05.154.

Siddiqi, M.A., Laessig, R.H., Reed, K.D., 2003. Polybrominated diphenyl ethers (PBDEs): new pollutants-old diseases. Clin. Med. Res. 1 (4), 281–290. https://doi.org/10.3121/cmr.1.4.281.

Song, Y., Chou, E.L., Baecker, A., You, N.C., Song, Y., Sun, Q., Liu, S., 2016. Endocrine-disrupting chemicals, risk of type 2 diabetes, and diabetes-related metabolic traits: a systematic review and meta-analysis. J. Diabetes 8 (4), 516–532. https://doi.org/10.1111/1753-0407.12325.

Stratakis, N., Rock, S., La Merrill, M.A., Saez, M., Robinson, O., Fecht, D., Vrijheid, M., Valvi, D., Conti, D.V., McConnell, R., Chatzi, V.L., 2022. Prenatal exposure to persistent organic pollutants and childhood obesity: a systematic review and meta-analysis of human studies. Obes. Rev. 23 (Suppl. 1), e13383 https://doi.org/10.1111/obr.13383.

Sun, H., Saeedi, P., Karuranga, S., Pinkepank, M., Ogurtsova, K., Duncan, B.B., Stein, C., Basit, A., Chan, J.C.N., Mbanya, J.C., Pavkov, M.E., Ramachandaran, A., Wild, S.H., James, S., Herman, W.H., Zhang, P., Bommer, C., Kuo, S., Boyko, E.J., Magliano, D. J., 2022. IDF Diabetes Atlas: global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. Diabetes Res. Clin. Pract. 183, 109119 https://doi.org/10.1016/j.diabres.2021.109119.

Suvorov, A., Battista, M.C., Takser, L., 2009. Perinatal exposure to low-dose 2,2',4,4'-tetrabromodiphenyl ether affects growth in rat offspring: what is the role of IGF-1? Toxicology 260 (1–3), 126–131. https://doi.org/10.1016/j.tox.2009.03.018.

Thomsen, C., Lundanes, E., Becher, G., 2002. Brominated flame retardants in archived serum samples from Norway: a study on temporal trends and the role of age. Environ. Sci. Technol. 36 (7), 1414–1418. https://doi.org/10.1021/es0102282.

Toms, L.L., Sjodin, A., Hobson, P., Harden, F.A., Aylward, L.L., Mueller, J.F., 2018. Temporal trends in serum polybrominated diphenyl ether concentrations in the Australian population, 2002-2013. Environ. Int. 121 (Pt 1), 357–364. https://doi.org/10.1016/j.envint.2018.09.014.

Turyk, M., Anderson, H.A., Knobeloch, L., Imm, P., Persky, V.W., 2009. Prevalence of diabetes and body burdens of polychlorinated biphenyls, polybrominated diphenyl ethers, and p,p'-diphenyldichloroethene in Great Lakes sport fish consumers. Chemosphere 75 (5), 674–679. https://doi.org/10.1016/j.chemosphere.2008.12.035.

Turyk, M., Fantuzzi, G., Persky, V., Freels, S., Lambertino, A., Pini, M., Rhodes, D.H., Anderson, H.A., 2015. Persistent organic pollutants and biomarkers of diabetes risk in a cohort of Great Lakes sport caught fish consumers. Environ. Res. 140, 335–344. https://doi.org/10.1016/j.envres.2015.03.037.

Turyk, M.E., Anderson, H.A., Steenport, D., Buelow, C., Imm, P., Knobeloch, L., 2010. Longitudinal biomonitoring for polybrominated diphenyl ethers (PBDEs) in residents of the Great Lakes basin. Chemosphere 81 (4), 517–522. https://doi.org/10.1016/j.chemosphere.2010.07.037.

Yang, C., Kong, A.P.S., Cai, Z., Chung, A.C.K., 2017. Persistent organic pollutants as risk factors for obesity and diabetes. Curr. Diabetes Rep. 17 (12), 132. https://doi.org/10.1007/s11892-017-0966-0.

Zhang, J., Chen, L., Xiao, L., Ouyang, F., Zhang, Q.-Y., Luo, Z.-C., 2017. Polybrominated diphenyl ether concentrations in human breast milk specimens worldwide. Epidemiology 28, S89–S97. https://doi.org/10.1097/EDE.0000000000000714.

Zhang, Z., Li, S., Liu, L., Wang, L., Xiao, X., Sun, Z., Wang, X., Wang, C., Wang, M., Li, L., Xu, Q., Gao, W., Wang, S.L., 2016. Environmental exposure to BDE47 is associated with increased diabetes prevalence: evidence from community-based case-control studies and an animal experiment. Sci. Rep. 6, 27854 https://doi.org/10.1038/srep27854.

Zhao, X., Yang, X., Du, Y., Li, R., Zhou, T., Wang, Y., Chen, T., Wang, D., Shi, Z., 2021. Polybrominated diphenyl ethers in serum from residents living in a brominated flame retardant production area: occurrence, influencing factors, and relationships with thyroid and liver function. Environ. Pollut. 270, 116046 https://doi.org/10.1016/j.envpol.2020.116046.