Environment International 129 (2019) 221–228

Contents lists available at ScienceDirect

Environment International

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

Persistent organic pollutants and the incidence of type 2 diabetes in the CARLA and KORA cohort studies

Kathrin Wolf[a,b,*], Brenda W.C. Bongaerts[b,c], Alexandra Schneider[a,b], Cornelia Huth[a,b], Christa Meisinger[e], Annette Peters[a,b], Andrea Schneider[a], Jürgen Wittsiepe[f], Karl-Werner Schramm[g], Karin Halina Greiser[b,h,i], Saskia Hartwig[b,h], Alexander Kluttig[b,h], Wolfgang Rathmann[b,c,d]

[a] Institute of Epidemiology, Helmholtz Zentrum München, Germany
[b] German Center for Diabetes Research (DZD), München-Neuherberg, Germany
[c] Institute for Biometrics and Epidemiology, German Diabetes Center, Leibniz Center for Diabetes Research at Heinrich Heine University Düsseldorf, Germany
[d] Medical Faculty, Heinrich Heine University, Düsseldorf, Germany
[e] Chair of Epidemiology, LMU Munich, UNIKA-T Augsburg, Germany
[f] Former: Department of Hygiene, Social and Environmental Medicine, Ruhr-University Bochum, Germany
[g] Molecular EXposomics, Helmholtz Zentrum München, Germany
[h] Institute of Medical Epidemiology, Biostatistics, and Informatics, Martin-Luther-University Halle-Wittenberg, Halle (Saale), Germany
[i] Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany

ARTICLE INFO

Handling Editor: Olga-Ioanna Kalantzi

Keywords:
Type 2 diabetes
Incidence
Environmental contaminates
Case-control study
Epidemiology

ABSTRACT

Background: Associations between several persistent organic pollutants (POPs) and type 2 diabetes have been found in humans, but the relationship has rarely been investigated in the general population. The current nested case-control study examined internal exposure to polychlorinated biphenyls (PCB) and pesticides and the incidence of type 2 diabetes among participants of two population-based German cohort studies.

Methods: We retrospectively selected 132 incident cases of type 2 diabetes and 264 age- and sex-matched controls from the CARdiovascular Living and Aging in Halle (CARLA) study (2002–2006, East Germany) and the Cooperative Health Research in the Region of Augsburg (KORA) study (1999–2001, South Germany) based on diabetes status at follow-up examinations in 2007–2010 and 2006–08, respectively (60% male, mean age 63 and 54 years). We assessed the association between baseline POP concentrations and incident diabetes by conditional logistic regression adjusted for cohort, BMI, cholesterol, alcohol, smoking, physical activity, and parental diabetes. Additionally, we examined effect modification by sex, obesity, parental diabetes and cohort.

Results: In both cohorts, diabetes cases showed a higher BMI, a higher frequency of parental diabetes, and higher levels of POPs. We observed an increased chance for incident diabetes for PCB-138 and PCB-153 with an odds ratio (OR) of 1.50 (95%CI: 1.07–2.11) and 1.53 (1.15–2.04) per interquartile range increase in the respective POP. In addition, explorative results suggested higher OR for women and non-obese participants.

Conclusions: Our results add to the evidence on diabetogenic effects of POPs in the general population, and warrant both policies to prevent human exposure to POPs and additional research on the adverse effects of more complex chemical mixtures.

1. Introduction

Traditional lifestyle risk factors such as physical inactivity, smoking and obesity, are not sufficient to fully explain the current epidemic of type 2 diabetes. Attempts to identify novel risk factors beyond the traditional ones have mounted evidence on the contribution of environmental contaminants to the rapid rise in the incidence of type 2 diabetes. Associations between persistent organic pollutants (POPs) and the development of type 2 diabetes have been shown for over ten years now (Lee et al., 2006; Porta, 2006; Lee et al., 2007; Jones et al., 2008) and several reviews (Taylor et al., 2013; Magliano et al., 2014; Ngwa et al., 2015; Jaacks and Staimez, 2015; Yang et al., 2017; Lind and Lind, 2018) and one meta-analysis of epidemiological studies (Wu et al., 2013) combined the findings corroborating the initial assumption.

* Corresponding author at: Helmholtz Zentrum München, Institute of Epidemiology, Ingolstädter Landstr. 1, 85764 Neuherberg, Germany.
E-mail address: kathrin.wolf@helmholtz-muenchen.de (K. Wolf).

https://doi.org/10.1016/j.envint.2019.05.030
Received 6 February 2019; Received in revised form 10 May 2019; Accepted 11 May 2019

POPs are a class of ubiquitous environmental compounds, either used as pesticides or generated as by-products of industrial or combustion processes. Typical examples include chlorinated compounds such as polychlorinated biphenyls (PCBs), organochlorine pesticides and dioxins (Lee et al., 2014). Since resistant to any kind of environmental degradation, POPs persist in the environment and can subsequently accumulate in the food chain (Grün and Blumberg, 2009). Most POPs were banned several decades ago in many countries. Yet, humans are still exposed to these chemicals through contaminated food, especially fatty animal products like fish, meat, and milk (Grün and Blumberg, 2009; Verner et al., 2013). When POPs enter the human body, they are primarily stored in adipose tissue and are slowly released into the circulation to be eliminated over several years (Milbrath et al., 2009).

The mechanisms that link POP exposure to diabetes are not fully understood. Nevertheless, several pathways have been proposed including endocrine-disrupting processes and mechanisms related to mitochondrial dysfunction (Alonso-Magdalena et al., 2006; Newbold et al., 2009; Meyer et al., 2013). While animal studies reported deleterious effects of POPs with respect to obesity, insulin sensitivity and glucose absorption (Ruzzin et al., 2010; Enan and Matsumura, 1994), a recent experimental paper suggested that chronic exposure to low doses of POPs may increase the risk of type 2 diabetes by primarily affecting pancreatic ß-cell function rather than insulin resistance (Lee et al., 2017).

Though the number of epidemiological studies investigating POPs and type 2 diabetes is already quite large, the overall evidence is still suggestive since most of these studies were limited by either a highly selected population, a low number of study participants and/or cross-sectional study designs precluding the assertion of a causal relationship (Taylor et al., 2013; Magliano et al., 2014; Ngwa et al., 2015; Yang et al., 2017; Lind and Lind, 2018).

Several prospective studies have reported positive associations between POPs and the risk of diabetes ruling out reverse causation, yet with inconsistent findings for individual POPs (Wu et al., 2013; Lee et al., 2011a; Lee et al., 2010; Rignell-Hydbom et al., 2009; Turyk et al., 2009; Vasiliu et al., 2006; Wang et al., 2008; Grice et al., 2017; Zong et al., 2018; Turyk et al., 2015). Also, most of these studies were from the U.S. (Wu et al., 2013; Lee et al., 2010; Turyk et al., 2009; Vasiliu et al., 2006; Grice et al., 2017; Zong et al., 2018; Turyk et al., 2015), based on highly exposed participants (Turyk et al., 2009; Vasiliu et al., 2006; Wang et al., 2008; Turyk et al., 2015) or restricted to females (Wu et al., 2013; Rignell-Hydbom et al., 2009; Zong et al., 2018) or the elderly (Lee et al., 2011a). Therefore, the current nested case-control study aimed to investigate the relationship between serum concentrations of POPs and incident type 2 diabetes in the general population by selecting participants of two large German population-based cohort studies.

2. Material and methods

2.1. Study population and case definition

We combined data from two population-based cohort studies: the CARdiovascular Disease, Living and Ageing in Halle (CARLA) and the Cooperative Health Research in the Region of Augsburg (KORA) study. Details on study design have been described elsewhere (Greiser et al., 2005; Rathmann et al., 2003; Holle et al., 2005). Briefly, the CARLA study was conducted in the urban area of Halle, Eastern Germany, between 2002 and 2006. The 1779 participants, aged 45–83 years, were followed-up between 2007 and 2010. Data collection included a detailed standardized computer-assisted interview, self-administered questionnaires, physical examination, and blood sampling. Incidence of diabetes was based on a hemoglobin A1c (HbA1c) level ≥ 6.5% at follow-up (and HbA1c < 6.5% at baseline), a self-reported physician's diagnosis between the baseline and the follow-up examination, or on newly prescribed glucose-lowering medication (ATC-Code A10). The age- and sex-matched controls did not report having diabetes and had normal glucose metabolism with HbA1c levels < 5.7% at both baseline and follow-up examination.

The KORA S4 survey (1999–2001) was conducted in the region of Augsburg, Southern Germany including a cluster-random sample of all inhabitants of the study region of German nationality aged 25–74 years. From the initial 4261 participants, 3080 (72%) participated in the follow-up examination KORA F4 in 2006–2008. Data collection included standardized computer-assisted personal interviews, self-administered questionnaires, physical examination, and blood sampling. A standard 75 g oral glucose tolerance test (OGTT) was performed among S4 and F4 participants who did not report having diabetes; in KORA S4 the OGTT was only conducted in participants aged 55 years and older. According to the 1999/2006 WHO criteria (WHO, 2006) normal glucose metabolism was defined as fasting glucose < 6.1 mmol/l and 2 h glucose < 7.8 mmol/l and diabetes as fasting glucose ≥7.0 mmol/l or 2 h glucose ≥11.1 mmol/l. All incident diabetes cases at baseline (S4) did report being nondiabetic, did not use glucose-lowering medication (ATC-Code A10), had HbA1c levels < 6.3% and had neither fasting nor 2 h glucose in the diabetic range if an OGTT had been conducted. At follow-up (F4) they had either 1) HbA1c levels ≥6.3% and a self-reported diabetes diagnosis that occurred later than one year after S4 and that could be validated by the responsible physician or medical chart review, or 2) HbA1c levels > 6.5% and OGTT-diagnosed diabetes. The age- and sex-matched controls did not report having diabetes and had normal glucose metabolism with HbA1c levels < 5.7% and according to OGTT if an OGTT had been conducted at both baseline and follow-up examination.

The current study population consisted of 77 incident cases of diabetes and 154 age- and sex-matched controls with normal glucose metabolism from CARLA plus 55 incident diabetes cases and 110 age- and sex-matched controls with normal glucose metabolism from KORA. The studies were approved by the local ethics committees, and informed written consent was obtained from the participants.

2.2. Blood samples

In the CARLA study non-fasting blood sampling was performed in sitting position. Immediately after sampling, all serum and plasma samples were centrifuged at 4 °C in-house by specially trained study. The cooled samples were shipped to the Institute of Laboratory Medicine, Clinical Chemistry and Molecular Diagnostics (ILM) at the Leipzig University Clinics. For the analysis of HbA1c in EDTA anticoagulated blood, the High Performance Liquid Chromatography (HPLC) method was used with the Variant II system (BIO-RAD, Munich, Germany).

For KORA, blood was collected with minimal stasis, refrigerated at 4–8 °C, and shipped in refrigerant packaging within 2–4 h to the laboratory of Augsburg Central Hospital. Fasting venous blood glucose was sampled in the morning (7:00 A.M. to 11:00 A.M.). HbA1c was measured using a turbidimetric immunological method (Tinaquant; Roche Diagnostics, Mannheim, Germany) with a Hitachi 717 analyser in KORA S4 and with a reverse-phase cation-exchange high-performance liquid chromatography (HPLC) method using the Menarini–Arkray analyser HA-8160 (Menarini Diagnostics, Florence, Italy) in KORA F4. Total cholesterol, high-density lipoprotein (HDL) and triglycerides were measured by enzymatic methods (Roche Diagnostics) (Rathmann et al., 2003).

2.3. Determination of POP concentrations

Using solid-phase extraction and gas chromatographic high-resolution mass spectrometry as described previously (Wittsiepe et al., 2014), concentrations of the following six POPs were measured in baseline serum samples stored at −80 °C for CARLA: polychlorinated biphenyl

(PCB) 138, PCB-153, PCB-180, hexachlorobenzene (HCB), beta-hexachlorocyclohexane (β-HCH), and 4,4′-dichlorodiphenyldichloroethylene (4,4′-DDE). As not enough serum samples were available for KORA, we determined the same POPs in KORA S4 plasma samples, which were stored at −70 °C until analysis. For 17 controls, serum concentrations were also available. Based on these duplicates, we conducted univariate linear regression to adjust the plasma concentrations.

2.4. Statistical analyses

Both confounding and mediating effects of blood lipids have been suggested when investigating causal effects of POPs and type 2 diabetes (Lee et al., 2014). However, there is still an ongoing debate how to best approach this complex interplay methodologically. Since POPs are predominantly carried by blood lipids, lipid-standardized concentrations have been suggested (initially to correct for differences in lipid concentrations between fasting and non-fasting individuals) to reflect the body's POP-burden better than wet-weight concentrations as (Lopez-Carrillo et al., 1999). On the other hand, both experimental and epidemiological studies have indicated that POPs can interfere with the lipid metabolism leading to dyslipidemia, obesity and changes in metabolic phenotype (Yang et al., 2017; Ruzzin et al., 2010; Lee et al., 2011b; Gasull et al., 2018). Being involved in the pathological mechanisms to type 2 diabetes, lipid concentrations (and maybe even body mass index (BMI)) would thus represent intermediate factors through which POPs might cause diabetes (Lee et al., 2014; Gasull et al., 2018) In this case, adjusting for lipid-levels would underestimate the true associations between POP concentrations and diabetes, whereas not adjusting for lipid levels would overestimate the true associations (Lee et al., 2014) (similar methodological work has been recently published for pancreatic cancer (Gasull et al., 2019)). Therefore, we a priori decided to use the wet-weight concentrations (POPs concentrations in μg/l not divided by lipids) adjusting for total cholesterol and BMI as our main analysis, but also present the results for lipid-standardized concentrations (ng/g lipid) as has been suggested previously (Lee et al., 2014).

To assess differences in baseline characteristics between cases and controls within each cohort, we performed Pearsons's Chi-square test for categorical variables and *t*-test for continuous variables. As POP concentrations strongly deviated from a normal distribution, we applied Wilcoxon rank sum test to test for differences between cases and controls but also between men and women separately for cases and controls of each cohort. We used multivariable conditional logistic regression to assess the association between serum POP concentrations and the odds of type 2 diabetes. A priori, we specified two multivariable models based on previous studies and availability of data in the two cohorts. The minimum model included only an indicator variable for cohort (CARLA/KORA) as age and sex were already adjusted for by design. The main model additionally included baseline information on BMI (kg/m^2), serum total cholesterol (mmol/l), average alcohol consumption (g/d), smoking status (current-, ex-, never-smoker), physical activity (regularly ≥1 h/week vs. unregularly/never), and parental diabetes (yes, no, unknown). Each POP was then included in the regression model separately as a linear term. We also applied two-pollutant models by adding a second POP variable if Spearman's correlation coefficient was < 0.7.

On an explorative basis, we investigated potential effect modification by including interaction terms of the continuous POP concentrations and: (i) the cohort indicator, since type 2 diabetes incidence was different for Eastern and Western Germany (Schipf et al., 2014) but also since the exposure to POPs might have been different due to the different living conditions; (ii) sex, since a higher susceptibility to POPs has been reported for women in previous studies (Vasiliu et al., 2006; Wang et al., 2008); (iii) obesity defined by BMI ≥ 30 vs. < 30 kg/m^2, since POPs are stored in the adipose tissue (Lee et al., 2006; Everett et al., 2007); and (iv) parental diabetes indicating potential differences in the underlying baseline risk (Lee et al., 2014).

2.5. Sensitivity analyses

We conducted several sensitivity analyses to check the robustness of our results. First, we left out total cholesterol as well as BMI since an over-adjustment has been suggested if lipid levels are in the causal pathway leading to an underestimation of the true association. (Lee et al., 2014; Gasull et al., 2018; Gasull et al., 2019).

As an overestimation might also be the case if lipid levels are not considered as well as to increase comparability with previous studies (Lee et al., 2014), we also applied an extended confounder model adjusting for high-density lipoprotein cholesterol (mmol/l) instead of total cholesterol and additionally for fasting triglycerides (mmol/l). As triglycerides were not measured in 75 KORA participants (25 cases and 50 controls), we had to exclude these. For reasons of comparison, we also reran the minimum and main model with the reduced data set (N = 320). In addition, also only feasible for the reduced data set, we calculated lipid-standardized POP concentrations by dividing the serum POP concentrations by the total serum lipid content according to the Phillips formula (Phillips et al., 1989) and investigated the association with type 2 diabetes adjusting for the minimum and main confounder model (the latter without total cholesterol). Fourth, we conducted stratified analyses since some fundamental differences between the two cohorts existed, such as non-fasting (CARLA) vs fasting status (KORA), or serum (CARLA) vs plasma (KORA) to measure the POPs. Fifth, we excluded participants with extremely high POP concentrations identified based on visual inspection. Finally, we investigated the linearity assumption of the dose-response function by incorporating each POP separately as a smooth function (P-Spline with three degrees of freedom).

All *p*-values were two-sided, and values < 0.05 were considered statistically significant. All statistical analyses were performed with R version 3.4.0 (The R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Baseline characteristics

Mean follow-up time for CARLA was four years and seven years for KORA. Table 1 presents the baseline characteristics and serum POP concentrations of the cases and controls stratified by cohort. There was an age difference between the participants of the two cohorts, with an average age of 63.4 ± 9.6 years in CARLA versus 54.5 ± 9.0 years in KORA. Within both cohorts, the diabetes cases tended to have a higher BMI, higher levels of HbA1c, lower HDL-cholesterol, and they more often reported parental diabetes. Cases in KORA had higher serum concentrations of PCB-153, HCB, and β-HCH than controls in KORA, whereas in CARLA only higher β-HCH concentrations were observed in cases versus controls. Comparing the two cohorts, PCB-138 and PCB-180 levels, as well as the sum of the three PCBs, were considerably higher in KORA participants, while PCB-153 concentrations were slightly higher in CARLA participants. HCB, β-HCH and 4,4′-DDE showed much higher concentrations in CARLA participants. A description of the reduced data set and the lipid-standardized POP concentrations can be found in Supplementary Table S1. The KORA participants were on average five years older than in the full KORA sample and displayed slightly lower triglyceride levels but higher total lipid concentrations than CARLA participants. For both cohorts, spearman correlation coefficients indicated high correlations between the PCBs, especially between PCB-138 and PCB-153 with a coefficient of 0.93 for CARLA and 0.94 for KORA (Supplementary Table S2). The comparison of internal POPs concentrations between women and men indicated higher HCB and β-HCH levels for women compared to men for both cases and controls of the CARLA cohort and for HCB for KORA cases and controls (Supplementary Table S3). In both cohorts, PCB-180 concentrations were increased in male controls compared to female controls.

Table 1
Baseline characteristics and POP concentrations[a] of type 2 diabetes cases and controls (matched on age and sex) from the population-based cohort studies CARLA (2002–2005) and KORA (1999–2001).

	CARLA		KORA	
Baseline characteristics	Cases	Controls	Cases	Controls
	Mean ± SD or N (%)		Mean ± SD or N (%)	
N	77	154	55	110
Age (years)	63.4 ± 9.6	63.4 ± 9.5	55.1 ± 8.8	54.2 ± 9.2
Sex (male)	46 (59.7)	92 (59.7)	33 (60)	66 (60)
HbA1c (%)	5.9 ± 0.4	5.5 ± 0.4*	5.8 ± 0.3	5.3 ± 0.3*
HbA1c (mmol/mol)	41 ± 4.4	37 ± 4.4	40 ± 3.3	34 ± 3.3
BMI (kg/m^2)	29.9 ± 5.4	27.4 ± 4.1*	31.2 ± 4.2	26.8 ± 4*
Cholesterol (mmol/l)	5.3 ± 1	5.6 ± 1.1*	6.2 ± 1.3	6 ± 1
HDL (mmol/l)	1.3 ± 0.4	1.5 ± 0.4*	1.3 ± 0.4	1.5 ± 0.4*
Alcohol (g/day)	11.6 ± 17.9	13.6 ± 17.6	28.8 ± 37.6	20.3 ± 19.9
Physical activity (regular ≥ 1 h/week)	25 (32.5)	70 (45.5)	28 (50.9)	74 (67.3)
Parental diabetes				
Yes	24 (31.2)	35 (22.7)	24 (43.6)	23 (21.1)*
No	37 (48.1)	88 (57.1)	21 (38.2)	72 (66.1)
Unknown	16 (20.8)	31 (20.1)	10 (18.2)	14 (12.8)
Smoking status				
Current	18 (23.4)	20 (13)	11 (20)	26 (23.6)
Ex	28 (36.4)	68 (44.2)	22 (40)	47 (42.7)
Never	31 (40.3)	66 (42.9)	22 (40)	37 (33.6)
POPs (µg/l)	**Median (Q1-Q3)**		**Median (Q1-Q3)**	
PCB-138	0.51 (0.39–0.79)	0.48 (0.33–0.66)	1.47 (1.17–1.86)	1.36 (0.99–1.76)
PCB-153	0.93 (0.70–1.35)	0.94 (0.68–1.26)	0.86 (0.59–1.09)	0.70 (0.50–0.92)†
PCB-180	0.77 (0.57–1.07)	0.79 (0.63–1.11)	1.21 (0.95–1.67)	1.23 (0.89–1.60)
Sum of PCBs 138, 153, 180	2.17 (1.62–3.19)	2.22 (1.65–2.97)	3.66 (2.76–4.46)	3.29 (2.42–4.26)
HCB	1.02 (0.56–1.55)	0.77 (0.46–1.32)	0.59 (0.24–1.08)	0.39 (0.27–0.64)†
β-HCH	0.47 (0.32–0.66)	0.40 (0.23–0.63)†	0.24 (0.15–0.37)	0.19 (0.14–0.31)†
4,4′-DDE	6.82 (3.45–13.9)	6.25 (3.22–11.47)	2.83 (1.56–5.28)	1.89 (1.20–3.46)

N: total number; BMI: body mass index; HDL: high-density lipoprotein; SD: standard deviation; POPs: persistent organic pollutants; PCB: polychlorinated biphenyl; HCB: hexachlorobenzene; β-HCH: beta-hexachlorocyclohexane; 4,4′-DDE: 4,4′-dichlorodiphenyldichloroethylene; Q1, Q3: first and third quartile.

[a] POP concentrations were measured in serum for CARLA and plasma in KORA which were subsequently calibrated based on 17 duplicates.

* *p*-value < 0.05 for comparison between cases and controls within each cohort: Pearson's Chi-square test for categorical variables and *t*-test for continuous variables.

† *p*-value < 0.05 of Wilcoxon rank sum test for comparison between cases and controls within each cohort.

3.2. Regression models

Multivariable conditional logistic regression modeling showed that serum POP concentrations were associated with an increased odds of having incident diabetes (Table 2). Increased odds ratios (ORs) were observed for PCB-138, PCB-153 and the sum of the three PCBs with higher effect estimates for the main adjustment set compared to the minimum model. Contrarily, for HCB the estimates decreased with the stricter adjustment and the association with diabetes was only significant in the minimum adjustment model. For 4,4′-DDE, the association was also positive though only borderline statistically significant and effect estimates remained stable when adding additional covariates. We observed no evident relationship between PCB-180 or β-HCH and incident diabetes. The two-pollutant models showed mainly robust results (Supplementary Fig. S1).

Table 2
Associations between POP concentrations (per interquartile increase) and incident type 2 diabetes within the population-based cohort studies CARLA (2002 − 2013) and KORA (1999–2008) – full sample (N = 395[a]; 132 cases and 263 controls).

POPs (µg/l)	IQR	Minimum model[b] OR (95% CI)	Main model[c] OR (95% CI)	Model without cholesterol[d] OR (95% CI)	Model without BMI & cholesterol[e] OR (95% CI)
PCB-138	0.8	1.34 (1.00, 1.78)*	1.50 (1.07, 2.11)*	1.36 (0.98;1.88)	1.33 (0.98;1.81)
PCB-153	0.6	1.32 (1.04, 1.67)*	1.53 (1.15, 2.04)*	1.38 (1.06;1.80)*	1.32 (1.03;1.70)*
PCB-180	0.6	1.00 (0.86, 1.15)	1.08 (0.93, 1.26)	1.06 (0.91;1.23)	1.01 (0.87;1.17)
Sum of PCBs 138, 153, 180	1.8	1.14 (0.93, 1.40)	1.29 (1.01, 1.64)*	1.21 (0.96;1.51)	1.15 (0.93;1.42)
HCB	0.8	1.43 (1.12, 1.84)*	1.22 (0.93, 1.59)	1.17 (0.91;1.52)	1.42 (1.11;1.82)*
β-HCH	0.3	1.00 (0.94, 1.07)	1.00 (0.93, 1.08)	1.00 (0.93;1.08)	1.00 (0.94;1.07)
4,4′-DDE	6.9	1.21 (0.99, 1.48)	1.22 (0.99, 1.49)	1.18 (0.98;1.43)	1.22 (1.00;1.48)*

POPs: persistent organic pollutants; PCB: polychlorinated biphenyl; HCB: hexachlorobenzene; β-HCH: beta-hexachlorocyclohexane; 4,4′-DDE: 4,4′-dichlorodiphenyldichloroethylene; IQR: interquartile range; OR: odds ratio; CI: confidence interval.

[a] One control had to be excluded due to missing information on parental diabetes.

[b] Multivariable conditional logistic regression analysis adjusted for cohort (CARLA/KORA) only.

[c] Multivariable conditional logistic regression analysis adjusted for cohort, body mass index, total cholesterol levels, alcohol consumption, smoking status, physical activity , and parental diabetes.

[d] Main model without adjustment for total cholesterol levels.

[e] Main model without adjustment for total cholesterol levels and body mass index.

* *p*-value < 0.05.

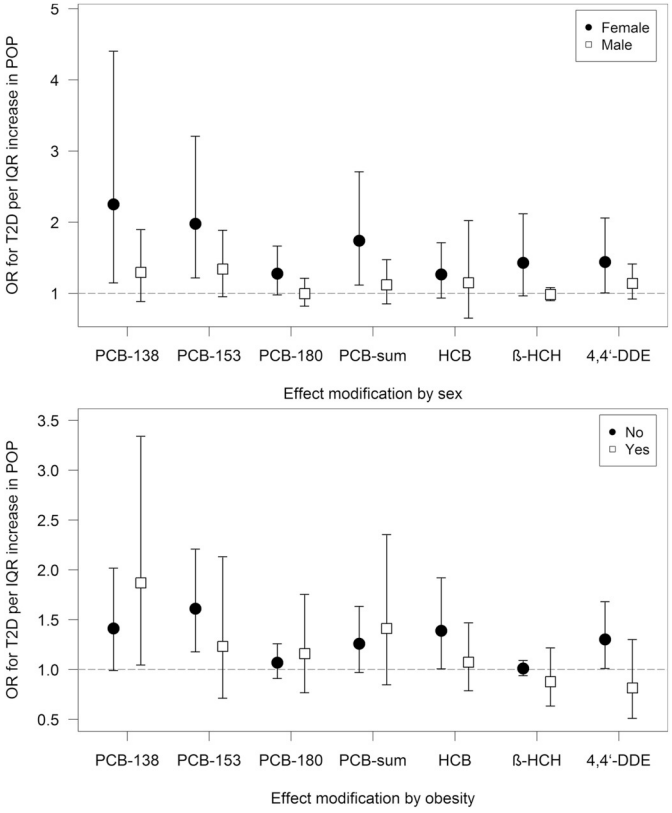

Fig. 1. Adjusted odds ratios (OR) with 95%-confidence intervals for the association of POP concentrations and incident type 2 diabetes (T2D): effect modification by sex (top; black circles = Females; white squares = Males) and obesity (bottom; black circles = No (BMI < 30 kg/m^2); white squares = Yes (BMI ≥ 30)). All models were adjusted for cohort, body mass index, total cholesterol, alcohol consumption, smoking status, physical activity, and parental diabetes (main model). POP: persistent organic pollutant; PCB: polychlorinated biphenyl; PCB-sum: sum of PCBs 138, 153, 180; HCB: hexachlorobenzene; β-HCH: beta-hexachlorocyclohexane; 4,4′-DDE: 4,4′-dichlorodiphenyldichloroethylene.

3.3. Effect modification

The explorative investigation of effect modification by the inclusion of interaction terms indicated higher effect estimates for females for most POPs except HCB compared to males though the interaction terms were not statistical significant (Fig. 1). Non-obese participants showed a positive association of PCB-153, HCB and 4,4′-DDE with diabetes whereas no association was observed for these POPs for obese participants (Fig. 1). No clear pattern was observed for an effect modification by parental diabetes (Supplementary Fig. S1). The KORA cohort showed a significantly increased OR for PCB-153 and HCB but interaction terms for the cohort indicator were not significant (Supplementary Fig. S2).

3.4. Sensitivity analyses

Not adjusting for total cholesterol led to slightly decreased effect estimates compared to the main adjustment set (Table 2). When leaving out BMI as well, the effect sizes were similar to the minimal adjustment set indicating that the other covariates did not affect the POPs-diabetes associations (Table 2). Both, the model with extended confounder control adjusting for high-density lipoprotein cholesterol and triglycerides and the model with lipid-standardized POP concentrations showed largely reduced effect sizes without significant associations (Supplementary Table S4 and Table 3). Except for 4,4′-DDE, the minimum and main adjustment model for the reduced data set

Table 3
Associations between lipid-standardized POP concentrations (per interquartile increase) and incident type 2 diabetes, reduced data set (N = 320; 107 cases and 213 controls).

POPs (ng/g lipid)	IQR	Minimum model[a] OR (95% CI)	Main model[b] OR (95%CI)
PCB-138	102	1.02 (0.73;1.43)	1.04 (0.73;1.49)
PCB-153	72	1.04 (0.79;1.36)	1.14 (0.85;1.54)
PCB-180	79	0.88 (0.70;1.10)	0.96 (0.81;1.15)
Sum of PCBs 138, 153, 180	228	0.93 (0.73;1.19)	1.01 (0.79;1.28)
HCB	123	1.22 (0.96;1.56)	1.06 (0.80;1.39)
β-HCH	46	1.01 (0.94;1.09)	1.00 (0.91;1.08)
4,4′-DDE	1089	1.19 (0.93;1.52)	1.17 (0.90;1.52)

POPs: persistent organic pollutants; PCB: polychlorinated biphenyl; HCB: hexachlorobenzene; β-HCH: beta-hexachlorocyclohexane; 4,4′-DDE: 4,4′-dichlorodiphenyldichloroethylene; IQR: interquartile range; OR: odds ratio; CI: confidence interval.

[a] Multivariable conditional logistic regression analysis adjusted for cohort (CARLA/KORA).

[b] Multivariable conditional logistic regression analysis adjusted for cohort, body mass index, alcohol consumption, smoking status, physical activity , and parental diabetes but not total cholesterol.

(Supplementary Table S4) resulted, however, in similar though slightly lower odds compared to the main results implicating that the reduced number of observations is not responsible for the decreased effect size but the more stringent lipid adjustment. The stratified analyses showed significant positive odds for PCB-138, PCB-153, β-HCH and 4,4′-DDE for CARLA whereas no significant associations were seen for KORA in the full sample (Supplementary Table S5). Our main results did not change when excluding three cases and three controls with extremely high POP concentrations (data not shown). The investigation of the dose-response function by including the POP concentrations as smooth functions indicated no deviation from linearity (Supplementary Fig. S3).

4. Discussion

In this first population-based nested case-control study on POP exposure and type 2 diabetes in Germany, we have found a positive association between serum PCB-138 and PCB-153 concentrations and incident type 2 diabetes. In addition, our results indicated a higher odds for the total sum of the three PCB and 4,4′-DDE. The effects were mostly more pronounced in females. These results are in overall agreement with findings from a limited number of prospective studies that have reported associations between some POPs, or combinations of POPs, and incident diabetes (Wu et al., 2013; Lee et al., 2011a; Lee et al., 2010; Rignell-Hydbom et al., 2009; Turyk et al., 2009; Vasiliu et al., 2006; Wang et al., 2008; Grice et al., 2017; Zong et al., 2018; Turyk et al., 2015). Findings for individual POPs, however, were not consistent across the studies. Since the methods and especially the presentation of results differed a lot among the studies, precluding direct comparison of the effect estimates, the following comparison is qualitative in nature.

The PCBs analyzed in this study (PCB-138, PCB-153 and PCB-180) were all higher chlorinated PCBs which reflect long-term contamination mainly through food as they decompose very slowly and accumulate strongly in organisms and the food chain (UBA and German Environment Agency, 2018). PCBs were previously used as hydraulic fluids, insulating and cooling liquids, plasticizers and flame retardants but are also substantially emitted as by-products of thermal processes. Only one study from Sweden among seniors (Lee et al., 2011a) and another study from the US among two female subcohorts (Wu et al., 2013) investigated PCB-138 separately. However, while we saw a clear relationship with incident diabetes, the Swedish study reported a positive but non-significant association, whereas the two US cohorts

pointed to no association at all. PCB-153 was additionally examined in two case-control studies from the US among African Americans and Whites (Lee et al., 2010) as well as American Indians (Grice et al., 2017) and one case-control study among Swedish women (Rignell-Hydbom et al., 2009). None of them found an association with diabetes, whereas the above mentioned studies (Wu et al., 2013; Lee et al., 2011a) and our study suggested an increased risk. For PCB-180, the Swedish seniors showed a highly increased risk which is not supported by other studies (Wu et al., 2013; Lee et al., 2011a; Lee et al., 2010; Grice et al., 2017; Turyk et al., 2015) including our results. Previous studies also suggested to analyze the sum of PCBs as well as selected groupings of PCB congeners either based on biological characteristics or previous findings (Lee et al., 2010; Zong et al., 2018). We therefore additionally analyzed the sum of the three PCBs available for our studies, although we were aware that the respective sum estimates cannot be directly compared to the sum estimates of other PCB combinations as has been shown previously (Lee et al., 2010). Studies with a similar grouping reported positive but non-significant associations (Wu et al., 2013; Lee et al., 2010; Zong et al., 2018).

HCB is a fungicide but was also used as flame retardant and plasticizer and is emitted substantially by thermal processes (UBA and German Environment Agency, 2018). Due to its comparatively high vapor pressure it is very mobile in the environment. While previous studies reported a significantly decreased risk (Grice et al., 2017) or no association (Lee et al., 2010; Zong et al., 2018), others observed an increased risk (Wu et al., 2013) or at least an indication for an increased risk (Lee et al., 2011a) similar to our results. β-HCH is an isomeric compound among the group of chlorinated hydrocarbons and a by-product of the production of the insecticide lindane (γ-HCH). Similar to our results, previous studies did not see an association for this POP with type 2 diabetes (Lee et al., 2010; Grice et al., 2017; Zong et al., 2018). 4,4′-DDE is the main metabolite of dichlorodiphenyltrichloroethane (DDT) and even more persistent than DDT (UBA and German Environment Agency, 2018). Our results indicated a positive association robust for confounder adjustment, which was also seen by others (Turyk et al., 2009; Zong et al., 2018; Turyk et al., 2015). However, there are also other investigations who did not observe an association (Lee et al., 2010; Rignell-Hydbom et al., 2009; Grice et al., 2017; Zong et al., 2018).

Differences in population characteristics, POP exposure distributions, outcome ascertainment, covariate adjustment, and the varying laboratory and analytical approaches may partly explain these inconsistencies. A further issue of discussion is how to methodologically approach the complex interplay between blood lipids, fasting status, and body mass index when estimating possible causal effects of POPs since both confounding and mediating effects have been suggested (Lee et al., 2014; Gasull et al., 2019). Among the prospective studies on POP exposure and risk of diabetes, two studies (Wu et al., 2013; Zong et al., 2018) used lipid-standardized POP concentrations as opposed to ten (Lee et al., 2011a; Lee et al., 2010; Rignell-Hydbom et al., 2009; Turyk et al., 2009; Vasiliu et al., 2006; Wang et al., 2008; Grice et al., 2017; Turyk et al., 2015) that used wet-weight POP concentrations, of which five adjusted the applied statistical models for serum lipid levels (Lee et al., 2011a; Lee et al., 2010; Turyk et al., 2009; Grice et al., 2017; Turyk et al., 2015). Since lipid-standardized concentrations have been initially suggested to correct for differences in lipid concentrations between fasting and non-fasting individuals (Phillips et al., 1989) and fasting status was indirectly a matching factor in our study (CARLA participants were non-fasting whereas KORA participants were fasting), we a priori decided to mainly focus on wet-weight concentrations but also to conduct several sensitivity analyses in terms of lipid and BMI adjustment. Interestingly, our effect estimates slightly decreased when we did not adjust for total cholesterol and BMI compared to the main adjustment set. When additionally adjusting for triglycerides or investigating lipid-standardized POP concentrations which were however only available for a subgroup of participants, all associations between serum POP levels and risk of diabetes disappeared. Nevertheless, the reduced sample size seemed not to be responsible for the decrease in effect size. In contrary, a recent matched case-control study among 793 pairs of middle aged (mean: 45 years) US women reported significant positive associations of HCB, β-HCH, p,p′-DDE and dioxin-like PCBs on type 2 diabetes with similar effect sizes for wet-weight and lipid-standardized POP concentrations though the latter decreased considerably and turned mostly non-significant when additionally adjusted for BMI (Zong et al., 2018). Interestingly, all of the mutually investigated plasma POP concentrations were much lower compared to the serum concentrations of our study participants, with e.g. lipid-standardized median concentrations for cases of 39 ng/g lipid for PCB-153 and 18 ng/g lipid for HCB compared to 132 and 122 ng/g lipid for PCB-153 and 142 and 70 ng/g lipid for HCB for CARLA and KORA, respectively. Our duplicate measurements indicated slightly lower plasma than serum POP concentrations and correction factors for KORA samples ranged from 1.10 for HCB to 1.26 for PCB-180 with intercepts of 0.0 for β-HCH to 0.08 for PCB-138 (R^2 of 0.87 for HCB to 0.99 for β-HCH and 4,4′-DDE). Another case-control study from the US pooling two female subcohorts observed mostly positive but non-significant associations between several POPs (also measured in plasma) and type 2 diabetes which were in general slightly stronger pronounced when using wet-weight concentrations adjusting for total cholesterol and triglycerides than lipid-standardized levels (Wu et al., 2013). Lipid-standardized median levels of PCB-153 with 117 and 98 ng/g lipid among participants with incident diabetes of the two cohorts were actually quite similar to the concentrations we observed in our KORA participants whereas HCB levels were also much lower with 34 and 41 ng/g lipid. Since wet-weight concentrations are partly not stated (Wu et al., 2013) or reported in quartiles (Lee et al., 2010; Vasiliu et al., 2006), quintiles (Lee et al., 2011a) or as geometric mean (Turyk et al., 2009; Wang et al., 2008; Grice et al., 2017; Turyk et al., 2015). However, a recent multi-center study on methodological issues of plasma POP concentrations and pancreatic cancer risk reported huge differences in wet-weight concentrations from 1533 participants aged 35–70 years old for the eight study regions (Gasull et al., 2019). For example, median plasma PCB-153 levels ranged from 0.34 μg/l in Greece to 1.35 μg/l in Germany, including our median serum concentrations of 0.93 and 0.89 μg/l for CARLA and KORA cases. Median plasma HCB levels ranged from 0.24 μg/l in participants from the UK to 4.40 μg/l in participants from Spain, also covering our median serum levels of 1.02 and 0.59 μg/l for CARLA and KORA cases. Also, the other POPs concentrations of our cohorts lay within the ranges reported for the eight countries except for PCB-138 in KORA cases with a median level of 1.47 μg/l compared to median plasma levels of 0.22 in Greece to 0.87 μg/l in Sweden.

The investigation of effect modifications by the inclusion of interaction terms has to be treated with caution and should rather serve as an indication since inference is limited due to the small samples size. Our results suggested an increased risk for women which has also been reported for stratified analyses of total PCB for a highly exposed US cohort (Vasiliu et al., 2006) and a Taiwanese study (Wang et al., 2008), whereas a study among US fish consumers reported no evidence for an effect modification by sex for total PCB or 4,4′-DDE (Turyk et al., 2009). Furthermore, our results indicated a higher risk for non-obese participants for some of the POPs. Contrary, previous studies observed an association only in obese participants for PCBs (Lee et al., 2010) or 4,4′-DDE (Turyk et al., 2009) while no effect modification by obesity was seen in Swedish seniors (Lee et al., 2011a) or middle aged US women (Zong et al., 2018). Regional differences in diabetes incidence have been described for Germany with highest rates in the East (16.9% (95% CI: 13.3–21.8%) per 1000 person years) and lowest rates in the South (9.3% (95% CI: 7.4–11.1%) per 1000 person years) (Schipf et al., 2014). Since this variation could only partly be explained by regional differences in common risk factors for type 2 diabetes, including age, sex, BMI and socioeconomic status, we hypothesized that the degree of POP

exposure might also play a role due to differences in regulation and handling between the former German Democratic Republic (East Germany) and the Federal Republic of Germany (West Germany). Indeed, with the exception of PCB-138, PCB-180 and the sum of PCBs 138, 153 and 180, participants from CARLA (representing the northeast German population) showed higher POP concentrations compared to participants from KORA (representing the Southwestern German population). However, we did not observe a clear pattern indicating an effect modification of the observed associations by cohort.

The main strengths of this study include the prospective study design, the use of incident diabetes cases and the selection of cases and controls from population-based cohort studies permitting generalizability of our results to the general population. Some limitations need to be considered as well. First, the study sample is relatively small, resulting in limited statistical power. Especially the inspection of effect modifications should be regarded as rather exploratory. Second, POP concentrations from KORA participants were assessed in plasma samples. We converted these plasma values to serum values based on univariate linear regression models of 17 duplicate samples. Third, while we observed associations with development of diabetes for PCB-138 and PCB-153, it might be that these associations are attributable to other unmeasured POP subclasses like dioxins or organochlorine pesticides. During the entire lifetime, people are exposed to a mixture of several hundred POPs with various distributions. Given the correlations between POPs, and the large array of POPs in background exposure, patients with low levels of a specific POP likely also have higher levels of other POPs (Porta et al., 2012). Therefore, one specific POP may partly reflect the influence of other POPs rather than that of itself, and caution should be taken not to over-interpret findings for single POPs. In addition, we could also not consider chemical mixtures of rather new toxicants like brominated flame retardants, perfluoroalkyl and polyfluoroalkyl substances, phthalates, or bisphenols for which diabetogenic effects have been suggested and which might be correlated with POPs as well due to mixing in the environment and food chain (Lind and Lind, 2018).

5. Conclusions

In conclusion, our results support a positive association between POP exposure and development of type 2 diabetes. However, larger longitudinal studies are needed to gain further insights into the (dose-dependent) effect of POPs on diabetes. Preferably, studies using real-world populations are required that not only consider exposure to a broad range of POPs, but also other types of diabetogenic environmental pollutants and chemicals to study additive or even multiplicative interactions between the various substances. Furthermore, serial POP measurements are recommended over single measurement, since serum POP levels fluctuate with fluctuating body weight. Serial measurements may also shed further light on the complex interactions that have been suggested between POPs and obesity. In addition, there is a clear need for several agents to become more aware of and active on the available evidence on the environmental causes of type 2 diabetes. Therefore, policy-makers (in public institutions and private companies), citizens, clinicians, and the media need to act effectively and in joint efforts to reduce the environmental burden of disease.

Declaration of Competing Interest

The authors declare they have no actual or potential competing financial interests.

Acknowledgements

Funding

The work was supported by a grant from the German Federal Ministry of Education and Research (BMBF) to the German Center for Diabetes Research (DZD e.V.). The German Diabetes Center (DDZ) was supported by the Ministry for Culture and Science of the State of North Rhine-Westphalia, Germany and the German Federal Ministry of Health, Germany. CARLA was funded by a grant from the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) as part of the Collaborative Research Center 598 “Heart failure in the elderly–cellular mechanisms and therapy” at the Medical Faculty of the Martin-Luther-University Halle-Wittenberg; by a grant of the Wilhelm-Roux Programme of the Martin-Luther-University Halle-Wittenberg; by the Federal Employment Office; and by the Ministry of Education and Cultural Affairs of Saxony-Anhalt. The KORA research platform and the MONICA Augsburg studies were initiated and financed by the Helmholtz Zentrum München, Germany, German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education, Science, Research, and Technology, Germany and by the State of Bavaria, Germany.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.05.030.

References

Alonso-Magdalena, P., Morimoto, S., Ripoll, C., Fuentes, E., Nadal, A., 2006. The estrogenic effect of bisphenol A disrupts pancreatic beta-cell function in vivo and induces insulin resistance. Environ. Health Perspect. 114 (1), 106–112.

Enan, E., Matsumura, F., 1994. 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD)-induced changes in glucose transporting activity in guinea pigs, mice, and rats in vivo and in vitro. J. Biochem. Toxicol. 9 (2), 97–106.

Everett CJ, Frithsen IL, Diaz VA, Koopman RJ, Simpson WM, Jr., Mainous AG, 3rd. Association of a polychlorinated dibenzo-p-dioxin, a polychlorinated biphenyl, and DDT with diabetes in the 1999-2002 National Health and Nutrition Examination Survey. Environ. Res.. 2007;103(3):413–8.

Gasull, M., Castell, C., Pallares, N., Miret, C., Pumarega, J., Te Llez-Plaza, M., et al., 2018. Blood concentrations of persistent organic pollutants and unhealthy metabolic phenotypes in normal-weight, overweight, and obese individuals. Am. J. Epidemiol. 187 (3), 494–506.

Gasull, M., Pumarega, J., Kiviranta, H., Rantakokko, P., Raaschou-Nielsen, O., Bergdahl, I.A., et al., 2019. Methodological issues in a prospective study on plasma concentrations of persistent organic pollutants and pancreatic cancer risk within the EPIC cohort. Environ. Res. 169, 417–433.

Greiser, K.H., Kluttig, A., Schumann, B., Kors, J.A., Swenne, C.A., Kuss, O., et al., 2005. Cardiovascular disease, risk factors and heart rate variability in the elderly general population: design and objectives of the CARdiovascular disease, Living and Ageing in Halle (CARLA) Study. BMC Cardiovasc. Disord. 5, 33.

Grice, B.A., Nelson, R.G., Williams, D.E., Knowler, W.C., Mason, C., Hanson, R.L., et al., 2017. Associations between persistent organic pollutants, type 2 diabetes, diabetic nephropathy and mortality. Occup. Environ. Med. 74 (7), 521–527.

Grün, F., Blumberg, B., 2009. Endocrine disrupters as obesogens. Mol. Cell. Endocrinol. 304 (1–2), 19–29.

Holle, R., Happich, M., Lowel, H., Wichmann, H.E., 2005. KORA–a research platform for population based health research. Gesundheitswesen 67 (Suppl. 1), S19–S25.

Jaacks, L.M., Staimez, L.R., 2015. Association of persistent organic pollutants and non-persistent pesticides with diabetes and diabetes-related health outcomes in Asia: a systematic review. Environ. Int. 76, 57–70.

Jones, O.A.H., Maguire, M.L., Griffin, J.L., 2008. Environmental pollution and diabetes: a neglected association. Lancet 371 (9609), 287–288.

Lee, D.H., Lee, I.K., Song, K., Steffes, M., Toscano, W., Baker, B.A., et al., 2006. A strong dose-response relation between serum concentrations of persistent organic pollutants and diabetes: results from the National Health and Examination Survey 1999-2002. Diabetes Care 29 (7), 1638–1644.

Lee DH, Lee IK, Jin SH, Steffes M, Jacobs DR, Jr. Association between serum concentrations of persistent organic pollutants and insulin resistance among nondiabetic adults: results from the National Health and Nutrition Examination Survey 1999-2002. Diabetes Care. 2007;30(3):622–8.

Lee DH, Steffes MW, Sjodin A, Jones RS, Needham LL, Jacobs DR, Jr. Low dose of some persistent organic pollutants predicts type 2 diabetes: a nested case-control study. Environ. Health Perspect.. 2010;118(9):1235–42.

Lee, D.H., Lind, P.M., Jacobs Jr., D.R., Salihovic, S., van Bavel, B., Lind, L., 2011a. Polychlorinated biphenyls and organochlorine pesticides in plasma predict development of type 2 diabetes in the elderly: the prospective investigation of the vasculature in Uppsala Seniors (PIVUS) study. Diabetes Care 34 (8), 1778–1784.

Lee, D.H., Steffes, M.W., Sjodin, A., Jones, R.S., Needham, L.L., Jacobs Jr., D.R., 2011b. Low dose organochlorine pesticides and polychlorinated biphenyls predict obesity, dyslipidemia, and insulin resistance among people free of diabetes. PLoS One 6 (1), e15977.

Lee, D.H., Porta, M., Jacobs Jr., D.R., Vandenberg, L.N., 2014. Chlorinated persistent organic pollutants, obesity, and type 2 diabetes. Endocr. Rev. 35 (4), 557–601.
Lee, Y.M., Ha, C.M., Kim, S.A., Thoudam, T., Yoon, Y.R., Kim, D.J., et al., 2017. Low-dose persistent organic pollutants impair insulin secretory function of pancreatic beta-cells: human and in vitro evidence. Diabetes 66 (10), 2669–2680.
Lind, P.M., Lind, L., 2018. Endocrine-disrupting chemicals and risk of diabetes: an evidence-based review. Diabetologia 61 (7), 1495–1502.
Lopez-Carrillo, L., Torres-Sanchez, L., Lopez-Cervantes, M., Blair, A., Cebrian, M.E., Uribe, M., 1999. The adipose tissue to serum dichlorodiphenyldichloroethane (DDE) ratio: some methodological considerations. Environ. Res. 81 (2), 142–145.
Magliano, D.J., Loh, V.H., Harding, J.L., Botton, J., Shaw, J.E., 2014. Persistent organic pollutants and diabetes: a review of the epidemiological evidence. Diabetes Metab. 40 (1), 1–14.
Meyer, J.N., Leung, M.C., Rooney, J.P., Sendoel, A., Hengartner, M.O., Kisby, G.E., et al., 2013. Mitochondria as a target of environmental toxicants. Toxicol. Sci. 134 (1), 1–17.
Milbrath, M.O., Wenger, Y., Chang, C.W., Emond, C., Garabrant, D., Gillespie, B.W., et al., 2009. Apparent half-lives of dioxins, furans, and polychlorinated biphenyls as a function of age, body fat, smoking status, and breast-feeding. Environ. Health Perspect. 117 (3), 417–425.
Newbold, R.R., Padilla-Banks, E., Jefferson, W.N., 2009. Environmental estrogens and obesity. Mol. Cell. Endocrinol. 304 (1–2), 84–89.
Ngwa, E.N., Kengne, A.P., Tiedeu-Atogho, B., Mofo-Mato, E.P., Sobngwi, E., 2015. Persistent organic pollutants as risk factors for type 2 diabetes. Diabetology & Metabolic Syndrome 7, 41.
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.
Porta, M., 2006. Persistent organic pollutants and the burden of diabetes. Lancet 368 (9535), 558–559.
Porta, M., Pumarega, J., Gasull, M., 2012. Number of persistent organic pollutants detected at high concentrations in a general population. Environ. Int. 44, 106–111.
Rathmann, W., Haastert, B., Icks, A., Lowel, H., Meisinger, C., Holle, R., et al., 2003. High prevalence of undiagnosed diabetes mellitus in Southern Germany: target populations for efficient screening. The KORA survey 2000. Diabetologia 46 (2), 182–189.
Rignell-Hydbom, A., Lidfeldt, J., Kiviranta, H., Rantakokko, P., Samsioe, G., Agardh, C.D., et al., 2009. Exposure to p,p'-DDE: a risk factor for type 2 diabetes. PLoS One 4 (10), e7503.
Ruzzin, J., Petersen, R., Meugnier, E., Madsen, L., Lock, E.J., Lillefosse, H., et al., 2010. Persistent organic pollutant exposure leads to insulin resistance syndrome. Environ. Health Perspect. 118 (4), 465–471.
Schipf, S., Ittermann, T., Tamayo, T., Holle, R., Schunk, M., Maier, W., et al., 2014. Regional differences in the incidence of self-reported type 2 diabetes in Germany: results from five population-based studies in Germany (DIAB-CORE consortium). J. Epidemiol. Community Health 68 (11), 1088–1095.
Taylor, K.W., Novak, R.F., Anderson, H.A., Birnbaum, L.S., Blystone, C., Devito, M., et al., 2013. Evaluation of the association between persistent organic pollutants (POPs) and diabetes in epidemiological studies: a national toxicology program workshop review. Environ. Health Perspect. 121 (7), 774–783.
Turyk, M., Anderson, H., Knobeloch, L., Imm, P., Persky, V., 2009. Organochlorine exposure and incidence of diabetes in a cohort of Great Lakes sport fish consumers. Environ. Health Perspect. 117 (7), 1076–1082.
Turyk, M., Fantuzzi, G., Persky, V., Freels, S., Lambertino, A., Pini, M., et al., 2015. Persistent organic pollutants and biomarkers of diabetes risk in a cohort of Great Lakes sport caught fish consumers. Environ. Res. 140, 335–344.
UBA. German Environment Agency. Environmental monitoring with human and environmental samples 2018 [Available from: https://www.umweltprobenbank.de/en/documents/profiles/analytes.
Vasiliu, O., Cameron, L., Gardiner, J., Deguire, P., Karmaus, W., 2006. Polybrominated biphenyls, polychlorinated biphenyls, body weight, and incidence of adult-onset diabetes mellitus. Epidemiology 17 (4), 352–359.
Verner, M.A., Sonneborn, D., Lancz, K., Muckle, G., Ayotte, P., Dewailly, E., et al., 2013. Toxicokinetic modeling of persistent organic pollutant levels in blood from birth to 45 months of age in longitudinal birth cohort studies. Environ. Health Perspect. 121 (1), 131–137.
Wang, S.L., Tsai, P.C., Yang, C.Y., Guo, Y.L., 2008. Increased risk of diabetes and polychlorinated biphenyls and dioxins: a 24-year follow-up study of the Yucheng cohort. Diabetes Care 31 (8), 1574–1579.
WHO, 2006. Definition and Diagnosis of Diabetes Mellitus and Intermediate Hyperglycaemia: Report of a WHO/IDF Consultation. World Health Organization & International Diabetes Federation, Geneva.
Wittsiepe, J., Nestola, M., Kohne, M., Zinn, P., Wilhelm, M., 2014. Determination of polychlorinated biphenyls and organochlorine pesticides in small volumes of human blood by high-throughput on-line SPE-LVI-GC-HRMS. J. Chromatogr. B 945-946, 217–224.
Wu, H., Bertrand, K.A., Choi, A.L., Hu, F.B., Laden, F., Grandjean, P., et al., 2013. Persistent organic pollutants and type 2 diabetes: a prospective analysis in the nurses' health study and meta-analysis. Environ. Health Perspect. 121 (2), 153–161.
Yang, C., Kong, A.P.S., Cai, Z., Chung, A.C.K., 2017. Persistent organic pollutants as risk factors for obesity and diabetes. Current Diabetes Reports 17 (12), 132.
Zong, G., Valvi, D., Coull, B., Goen, T., Hu, F.B., Nielsen, F., et al., 2018. Persistent organic pollutants and risk of type 2 diabetes: a prospective investigation among middle-aged women in Nurses' Health Study II. Environ. Int. 114, 334–342.