Association Between Type 2 Diabetes and Exposure to Persistent Organic Pollutants

Riikka Airaksinen, msc[1]
Panu Rantakokko, phd[1]
Johan G. Eriksson, phd[2,3,4,5,6]
Paul Blomstedt, msc[2]
Eero Kajantie, md, phd[2,7]
Hannu Kiviranta, phd[1]

OBJECTIVE—The prevalence of type 2 diabetes is increasing alarmingly in both developed and developing countries. Recently, exposure to persistent organic pollutants (POPs) has been associated with the prevalence of type 2 diabetes. The purpose of this cross-sectional study is to examine the association between type 2 diabetes and POP exposure in the Helsinki Birth Cohort Study.

RESEARCH DESIGN AND METHODS—The cohort consists of 8,760 people born in Helsinki during 1934–1944, before the global POP emission peak. In 2003, a clinical examination was performed, including blood sampling for laboratory analyses of serum lipids and POPs. Complete data from the examination were available for 1,988 participants. The concentrations of each POP were categorized into four groups on the basis of percentile intervals, and logistic regression was performed to examine diabetes prevalence across the POP categories, adjusting for sex, age, waist circumference, and mean arterial pressure and using the lowest category as the reference group.

RESULTS—Among the participants with the highest exposure to oxychlordane, *trans*-nonachlor, 1,1-dichloro-2,2-bis-(*p*-chlorophenyl)-ethylene (*p,p*'-DDE, and polychlorinated biphenyl 153, the risk of type 2 diabetes was 1.64–2.24 times higher than that among individuals with the lowest exposure (P_{lin} = 0.003–0.050, where P_{lin} is the *P* value for linear trend across POP categories). In the stratified analysis, the associations between type 2 diabetes and oxychlordane and *trans*-nonachlor remained significant and were strongest among the overweight participants. Exposure to 2,2′,4,4′-tetrabromodiphenyl ether (BDE 47) and 2,2′,4,4′,5,5′-hexabromodiphenyl ether (BDE 153) was not associated with type 2 diabetes.

CONCLUSIONS—This study confirms the association between type 2 diabetes and adult-only exposure to organochlorine pesticides in a general urban population.

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The prevalence of type 2 diabetes is increasing alarmingly in both developed and developing countries. The disease has traditionally been regarded as a multifactorial disorder, with a strong genetic component and lifestyle influences. Lately, it has been suggested that, in addition to the conventional risk factors, which include genetic susceptibility, obesity, physical inactivity, and an unhealthy diet, environmental factors may have a significant contribution. Specifically, exposure to persistent organic pollutants (POPs) has been shown to have a strong positive association with type 2 diabetes and related metabolic conditions (1–8).

POPs are a diverse group of ubiquitous environmental contaminants, characterized by toxicity, slow degradation, lipid solubility, and accumulation in the food chain. In numerous cross-sectional studies performed during the last decade, associations between type 2 diabetes and exposure to polychlorinated dibenzo-*p*-dioxins and dibenzofurans (PCDD/Fs), polychlorinated biphenyls (PCBs), brominated flame retardants (polybrominated diphenylethers [PBDEs]), and some organochlorine pesticides (OCPs) were observed (1–8). So far, the strongest indications regarding the positive association between POPs and type 2 diabetes within the general population have been obtained from a cross-sectional study in the U.S. (the National Health and Nutrition Examination Survey [NHANES]) (5–7). Lee et al. (5) observed that the prevalence of type 2 diabetes among the most exposed subgroup was 38 times higher than that among the least exposed group. It is striking that obesity was found to be a risk factor for type 2 diabetes and insulin resistance only in association with increased concentrations of POPs (5). The association between POPs and impaired glucose regulation was confirmed in in vitro and in vivo (9–11) studies.

Human exposure to the majority of POPs occurs mainly through diet and, especially, foods of animal origin. In Finland, the most important source of POPs is Baltic Sea fatty fish, such as Baltic herring (*Clupea harengus membras*) and salmon (*Salmo salar*) (12). Although human exposure to POPs such as PCDD/Fs and PCBs in the Baltic region has been declining during the last 3 decades (13), these compounds are still detectable in human samples. In contrast to PCDD/Fs and PCBs, the concentrations of many emerging chemicals that hold a potential for health threat such as PBDEs, which are widely used as flame retardants, have recently increased in humans (14). POPs are persistent in the body, and measurements from serum are assumed to reflect lifetime exposure.

The purpose of the present cross-sectional study is to examine the association between type 2 diabetes and POP exposure in the Helsinki Birth Cohort Study, which represents a general adult urban Finnish population. The cohort consists of people who were born in the 1930s and 1940s, well before the global POP emissions peaked, and their exposure

From the [1]Department of Environmental Health, Chemical Exposure Unit, National Institute for Health and Welfare, Kuopio, Finland; the [2]Department of Chronic Disease Prevention, Diabetes Prevention Unit, National Institute for Health and Welfare, Helsinki, Finland; the [3]Folkhälsan Research Center, Helsinki, Finland; the [4]Unit of General Practice, Helsinki University Central Hospital, Helsinki, Finland; the [5]Department of General Practice and Primary Health Care, University of Helsinki, Helsinki, Finland; the [6]Vasa Central Hospital, Vasa, Finland; and the [7]Hospital for Children and Adolescents, Helsinki University Central Hospital and University of Helsinki, Helsinki, Finland.
Corresponding author: Riikka Airaksinen, riikka.airaksinen@thl.fi.
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during the fetal and childhood period has probably been very low. However, during their adulthood, they experienced a steep increase in environmental POP concentrations (15). Therefore, this population provides an excellent opportunity to study the association between adult exposure to POPs and type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study population and data collection

The original birth cohort consists of 8,760 people who were born as singletons at the Helsinki University Central Hospital during 1934 and 1944 and who attended child welfare clinics and were residents in Finland in 1971. The majority (77%) also went to school in Helsinki. Details of the cohort have been described previously (16,17).

From the original study cohort, 2,003 men and women were selected at random to attend a clinical examination in 2003. No significant difference in diabetes-related outcomes between individuals selected and not selected was observed. The examination included the measurement of weight, length, and waist circumference and a standard 2-h 75-g oral glucose tolerance test (OGTT), with plasma glucose and insulin concentrations measured at 0 and 120 min. The study was approved by the local ethical committee, and informed written consent was obtained from the participants.

Laboratory analyses of diabetes-related markers

Serum total and HDL cholesterol and triglyceride concentrations were measured using standard enzymatic methods and apolipoprotein B using an immunoturbinometric assay. From the OGTT, plasma glucose was measured by a hexokinase method. The diagnosis of diabetes was based on an OGTT and the World Health Organization 1999 criteria for glucose intolerance. Subjects were considered to have diabetes if their fasting plasma glucose was ≥7.0 mmol/L or their 2-h plasma glucose was ≥11.1 mmol/L or they were on antidiabetic medication. The methods have been described previously (16,17).

Laboratory analyses of POPs

The POP analyses were performed in the National Institute for Health and Welfare, Chemical Exposure Unit, which is accredited for measurement of POPs in serum samples (according to the International Standard ISO/IEC 17025). The compounds analyzed were oxychlordane, *trans*-nonachlor, 1,1-dichloro-2,2-bis-(*p*-chlorophenyl)-ethylene (*p,p′*-DDE), 2,2′,4,4′,5,5′-hexachlorobiphenyl (PCB 153), 2,2′,4,4′-tetrabromodiphenyl ether (BDE 47), and 2,2′,4,4′,5,5′-hexabromodiphenyl ether (BDE 153). Analytical grade *n*-hexane, diethyl ether, ethanol, sodium chloride, *n*-butyl acetate, dichloromethane, Silica Gel 60, silver nitrate, and heptanoic acid were used. For each compound, corresponding ^{13}C-labeled compounds were used as the internal standard. A toluene solution of ^{13}C-PCB 128 was used as the recovery standard.

Serum samples, 2 mL each (the internal standard in a toluene solution), and 3.0 mL ethanol were pipetted into glass test tubes. The samples were shaken mechanically and sonicated for 5 min to precipitate the proteins and equilibrate the internal standards. To extract the analytes, 1.0 mL solid sodium chloride, followed by 3.0 mL diethyl ether and 3.0 mL hexane, were added. The samples were extracted in a carousel extractor for 15 min at 35 rpm and centrifuged for 5 min at 3,500 rpm. During centrifugation, a solid plug was formed in the interface between the organic and water phase, and the organic extract was poured into another glass tube. The extract was evaporated to dryness in a warm water bath under a gentle stream of nitrogen gas with heptanoic acid as a keeper. One milliliter of hexane was added to redissolve the extract. For cleanup, a 6-mL solid phase extraction column was packed with a filter paper, 1.0 mL 44% sulfuric acid–impregnated silica, 1.0 mL activated silica, 1.0 mL 10% silver nitrate–impregnated silica, and a wad of glass wool on top to prevent dusting. The column was precleaned and equilibrated by elution with 3.0 mL 20% dichloromethane:hexane three times, followed by 3.0 mL hexane. The extract reconstituted in hexane was poured into the column, and the analytes were eluted with 12–18 mL 20% dichloromethane:hexane. The eluate was evaporated into 0.5 mL, and *n*-butyl acetate was added as keeper. The recovery standard was added into a conical vial, followed by the sample. The vial was left to evaporate into a few drops.

The determination of the analytes was performed with a Hewlett-Packard 6890 gas chromatograph with a Combi PAL autosampler, connected to an Autospec Ultima high-resolution mass spectrometer (with a resolution of 8,000). The gas chromatograph was equipped with a split-splitless injector and a DB-5MS capillary column (30 m, 0.25-mm internal diameter, 0.25-μm film). The injected volume was 2 μL. Two ions were monitored for each analyte and the corresponding ^{13}C standard. The linearity of the gas chromatograph high–resolution mass spectrometer analysis was checked with calibration solutions that covered the concentration range expected in real samples.

All laboratory analyses and data handling were performed blind. Two laboratory reagent and equipment blank samples and two in-house control samples (human plasma and serum) were analyzed with each batch of ~36 actual samples. The accuracy and precision of the method was verified by analyzing Standard Reference Material 1589a (SRM 1589a) from the National Institute of Standards and Technology (Gaithersburg, MD), which has certified concentrations or reference concentrations for all compounds analyzed. Furthermore, the laboratory participates regularly in the Arctic Monitoring and Assessment Program (AMAP) interlaboratory exercises (Ring Test for Persistent Organic Pollutants in Human Serum, the National Institute of Public Health, Quebec, Canada), offering assigned values for all POPs analyzed.

The concentration of total cholesterol as millimoles per liter was converted into milligram per milliliter by multiplying by the molecular mass of 386.7 g/mol. The concentration of triglycerides as millimoles per liter was converted into milligram per milliliter by multiplying by the molecular mass of triolein (885.5 g/mol). The POP concentrations are presented per gram lipid (total cholesterol plus triglycerides). The limits of quantification were calculated individually for each analyte in each run of samples and varied between 0.012–2.3, 0.0023–0.57, 0.096–47, 0.050–24, 0.033–14, and 0.0040–7.5 ng/g lipid for oxychlordane, *trans*-nonachlor, *p,p′*-DDE, PCB 153, BDE 47, and BDE 153, respectively.

Statistical analysis

Complete data from the clinical examination and the serum POP analyses were available for 1,988 subjects. POP concentrations below the limits of quantification were treated as one-half of the respective limits of quantification (middle bound). Pearson's correlation coefficients were calculated between the six POPs using log-transformed data (nontransformed data were used for other analyses). The

Table 1—*Descriptive statistics of the study population*

		Sex			Diabetes status		
	All	Male	Female	*P**	Yes	No	*P**
n	1,988	921	1,067		308	1,680	
Prevalence of type 2 diabetes (%)	15.5	19.4	12.1				
Sex ratio (% of males)	46.3				58.1	44.2	
Age (years)	62 ± 0.066 (61, 57–70)	62 ± 0.093 (61, 57–69)	62 ± 0.093 (61, 57–70)	0.86	62 ± 0.16 (61, 57–69)	62 ± 0.072 (61, 57–70)	0.93
BMI (kg/m^2)	28 ± 0.10 (27, 15–50)	27 ± 0.13 (27, 19–46)	28 ± 0.15 (27, 15–50)	0.28	30 ± 0.30 (30, 20–50)	27 ± 0.10 (27, 15–50)	<0.001
Waist circumference (cm)	96 ± 0.29 (95, 63–140)	100 ± 0.37 (100, 73–140)	91 ± 0.40 (90, 63–140)	<0.001	110 ± 0.76 (100, 73–140)	94 ± 0.30 (94, 63–140)	<0.001
Serum lipids (mg/dL)							
Total	360 ± 2.5 (350, 160–3,400)	360 ± 3.0 (350, 160–800)	370 ± 4.0 (350, 190–3,400)	0.17	400 ± 12 (370, 180–3,400)	360 ± 2.1 (350, 160–880)	<0.001
Total cholesterol	230 ± 0.93 (230, 85–550)	220 ± 1.3 (220, 85–400)	240 ± 1.3 (230, 120–550)	<0.001	220 ± 2.7 (220, 110–550)	230 ± 0.98 (230, 85–400)	<0.001
Triglycerides	130 ± 2.1 (120, 37–2,800)	140 ± 2.3 (120, 37–530)	130 ± 3.4 (110, 40–2,800)	0.14	180 ± 10 (160, 48–2,800)	130 ± 1.6 (110, 37–580)	<0.001
Serum POPs (ng/g lipid)							
Oxychlordane	12 ± 0.13 (11, 0.73–76)	13 ± 0.21 (12, 0.73–76)	11 ± 0.15 (11, 1.9–42)	<0.001	13 ± 0.35 (11, 0.98–40)	12 ± 0.14 (11, 0.73–76)	0.17
Trans-nonachlor	32 ± 0.40 (28, 0.012–190)	37 ± 0.69 (33, 0.012–190)	27 ± 0.42 (25, 2.4–110)	<0.001	34 ± 1.1 (30, 4.0–130)	31 ± 0.43 (28, 0.012–190)	0.067
p,p′-DDE	610 ± 12 (470, 9.1–10,000)	600 ± 18 (460, 9.5–10,000)	610 ± 16 (480, 9.1–6,900)	0.64	710 ± 28 (620, 23–3,900)	590 ± 13 (450, 9.1–10,000)	<0.001
PCB 153	310 ± 3.4 (290, 6.5–1,600)	350 ± 5.6 (330, 6.5–1,600)	280 ± 3.6 (260, 16–1,100)	<0.001	320 ± 8.7 (300, 58–1,000)	310 ± 3.6 (290, 6.5–1,600)	0.20
BDE 47	8.8 ± 1.6 (2.9, 0.051–2,800)	6.9 ± 0.98 (3.0, 0.054–770)	10 ± 2.8 (2.8, 0.051–2,800)	0.050	8.8 ± 2.4 (2.7, 0.072–590)	8.8 ± 1.8 (2.9, 0.051–2,800)	0.60
BDE 153	2.8 ± 0.39 (1.6, 0.0040–760)	2.6 ± 0.10 (2.0, 0.019–53)	2.9 ± 0.72 (1.4, 0.0040–760)	<0.001	2.2 ± 0.22 (1.5, 0.023–53)	2.9 ± 0.46 (1.7, 0.0040–760)	0.005

Data are means ± SE (median, range), unless otherwise indicated. *Unpaired *t* test (two-tailed) for age, BMI, waist circumference, and serum lipids (normally distributed); Mann-Whitney *U* test (two-tailed) for serum POPs (not normally distributed).

concentrations of each POP were categorized into four groups, on the basis of percentile intervals <10th, 10th to <50th, 50th to <90th, and ≥90th. Logistic regression was performed to obtain the odds ratio (OR) for prevalent type 2 diabetes across the categories of each POP, adjusting for sex, age, waist circumference, and mean arterial pressure using the lowest category (<10th) as the reference group. The adjusting variables were selected to obtain the best-fitting model possible using most relevant risk factors for type 2 diabetes. Mean arterial pressure was used instead of systolic and diastolic pressure to avoid multicollinearity effects. The analysis was performed also without adjusting for mean arterial pressure, which did not considerably change the results (data not shown). Furthermore, we were not able to simultaneously adjust for both waist circumference and BMI because of multicollinearity effects. Therefore, logistic regression was performed stratified by BMI, with the BMI categories being <25, 25 to <30, and ≥30 kg/m^2.

RESULTS—Descriptive statistics of the study population are provided in Table 1. In total, 308 participants were diagnosed with type 2 diabetes, and the total prevalence in the study population was 15.5%. The proportion of men among the participants was 46.3%. The prevalence of type 2 diabetes was higher among men than among women (19.4 and 12.1%, respectively).

The age distribution of the population was narrow (average age 62 years, ranging between 57 and 70 years). The average BMI and waist circumference for men and women were 27 and 28 kg/m^2 and 100 and 91 cm, respectively, and both were higher among the participants diagnosed with type 2 diabetes than among individuals not diagnosed ($P < 0.001$).

The average concentration of serum lipids was 360 mg/dL, of which the majority was accounted for by cholesterol (64%). Men had a slightly lower concentration of serum cholesterol than women (220 and 240 mg/dL, $P < 0.001$). Among the participants with diabetes, the total concentration of serum lipids was higher than among the participants without diabetes (400 and 360 mg/dL, $P < 0.001$).

The median concentrations of oxychlordane, *trans*-nonachlor, *p,p'*-DDE, PCB 153, BDE 47, and BDE 153 were 11, 28, 470, 290, 2.9, and 1.6 ng/g lipid, respectively. The concentrations of oxychlordane, *trans*-nonachlor, and PCB 153 were higher among men than among women ($P < 0.001$). On the contrary, the concentrations of the BDEs were lower among men than women ($P < 0.001$).

Among the participants with diabetes, the concentrations of *trans*-nonachlor and *p,p'*-DDE were higher ($P = 0.067$ and $P < 0.001$, respectively) than among individuals without diabetes, but the concentration of BDE 153 was lower ($P = 0.005$).

Significant associations were observed between all of the analytes, when log-transformed data were studied for bivariate correlation. The associations between oxychlordane, *trans*-nonachlor, *p,p'*-DDE, and PCB 153 (Pearson's correlation coefficient $r = 0.49$–0.93, $P < 0.001$) were strong, but the association of these four compounds with the BDEs was weaker ($r = 0.17$–0.37, $P < 0.001$). However, the BDEs were strongly associated with each other ($r = 0.51$, $P < 0.001$). The associations among the analytes and age, BMI, and waist circumference were weak ($r = -0.053$–0.145, -0.20–0.17, and -0.14–0.13, respectively, P was ≤0.001 in most cases). There was strong correlation between BMI and waist circumference ($r = 0.84$, $P < 0.001$).

In the logistic regression analyses, oxychlordane (P for linear trend across categories = 0.003), *trans*-nonachlor ($P_{lin} = 0.003$, where P_{lin} is the P value for linear trend across POP categories), *p,p'*-DDE ($P_{lin} = 0.020$), and PCB 153 ($P_{lin} = 0.050$) had a statistically significant positive association with prevalent type 2 diabetes (Table 2). The individual ORs in the highest exposure categories were 2.08 (95% CI 1.18–3.69, $P = 0.012$), 2.24 (1.25–4.03, $P = 0.007$), 1.75 (0.96–3.19, $P = 0.069$), and 1.64 (0.92–2.93, $P = 0.097$), respectively, compared with the group with the lowest exposure category. For the BDEs, no association was observed ($P_{lin} = 0.57$ and 0.20, respectively).

In the stratified adjusted logistic regression, none of the POPs showed association with type 2 diabetes among the group with BMI <25 kg/m^2 (normal weight). However, oxychlordane and *trans*-nonachlor were significantly associated with type 2 diabetes among the groups with BMI between 25 and 30 kg/m^2 (overweight, $P_{lin} = 0.011$ and = 0.030, respectively) and those with BMI higher than 30 kg/m^2 (obese, $P_{lin} = 0.020$ and = 0.034). For *p,p'*-DDE and PCB 153, borderline significant associations were observed, only among those with BMI >30 kg/m^2 ($P_{lin} = 0.087$ and = 0.062, respectively). For all of these four POPs, the associations were strongest among the group with BMI between 25 and 30 kg/m^2. For the PBDEs, the stratified analysis revealed no associations. The P values for POP × BMI interaction were nonsignificant for all POPs.

CONCLUSIONS—In the current study, high exposure to OCPs and PCB 153 was associated with an approximately double risk of prevalent type 2 diabetes. Among the participants with the highest levels of the organochlorine pesticide metabolites oxychlordane, *trans*-nonachlor, and *p,p'*-DDE, as well as PCB 153, the prevalence of type 2 diabetes was 1.64–2.24 times higher than among participants with the lowest exposure. Furthermore, the prevalence of type 2 diabetes increased in an exposure-response manner across the increasing categories of these POPs. In contrast, exposure to PBDEs did not seem to be associated with type 2 diabetes. It is generally assumed a single measurement of POPs in the body reflects lifetime exposure, although there is variation in the elimination rate between individuals, caused by, for example, age, lactation, and changes in body weight.

These results are in accordance with previous findings among populations with relatively low exposure (3–8). In particular, among NHANES, Lee et al. (5) found that type 2 diabetes had a strong association with concentrations of oxychlordane, *trans*-nonachlor, *p,p'*-DDE, and PCB 153, with the individual ORs among the highest exposure category being 6.5, 11.8, 4.3, and 6.8, respectively. Furthermore, Lim et al. (7) reported much weaker associations between several PBDE congeners and prevalent type 2 diabetes among NHANES: among the highest exposure group, ORs ranged between 0.8 and 1.7 and were statistically nonsignificant. A similar pattern was also observed by Turyk et al. (8), who reported increased risk of type 2 diabetes among Great Lakes sport fish consumers highly exposed to *p,p'*-DDE, but not among individuals highly exposed to PBDEs.

In the stratified analysis, we observed that among the normal-weight participants (BMI <25 kg/m^2), even high POP exposure did not increase the risk of type 2 diabetes. Additionally, we observed that, among individuals with low POP exposure, overweight and obesity did not seem to increase the prevalence of diabetes as much as among individuals with high POP exposure. This is in line with NHANES (5), where a significant association was observed between type 2 diabetes and a

Table 2—*Serum concentration of POPs and adjusted ORs for type 2 diabetes across categories of each POP*

	Serum concentration (ng/g lipid) (median, range)	Not stratified		Stratified by BMI (kg/m^2)					
				<25		25 to <30		≥30	
		Cases/*n*	Adjusted OR	Cases/*n*	Adjusted OR	Cases/*n*	Adjusted OR	Cases/*n*	Adjusted OR
Oxychlordane									
<10th	5.4, 0.73–6.3	31/199	Reference	3/51	Reference	6/77	Reference	22/71	Reference
10th to <50th	8.9, 6.3–11	108/795	1.03 (0.64–1.65), $P = 0.90$	11/213	0.95 (0.24–3.72), $P = 0.95$	39/373	1.45 (0.58–3.61), $P = 0.42$	58/209	0.92 (0.49–1.72), $P = 0.79$
50th to <90th	14, 11–19	129/795	1.42 (0.89–2.26), $P = 0.14$	19/240	1.69 (0.46–6.22), $P = 0.43$	58/367	2.46 (1.00–6.03), $P = 0.049$	52/188	0.90 (0.48–1.72), $P = 0.76$
≥90th	23, 19–76	40/199	2.08 (1.18–3.69), $P = 0.012$ $P_{lin} = 0.003$	4/73	1.14 (0.23–5.65), $P = 0.88$ $P_{lin} = 0.76$	19/94	3.04 (1.12–8.24), $P = 0.029$ $P_{lin} = 0.011$	17/32	2.68 (1.06–6.80), $P = 0.037$ $P_{lin} = 0.020$
Trans-nonachlor									
<10th	11, 0.012–14	27/199	Reference	2/49	Reference	5/80	Reference	20/70	Reference
10th to <50th	22, 14–28	110/795	1.21 (0.74–1.96), $P = 0.45$	11/217	1.25 (0.26–6.09), $P = 0.78$	41/363	1.89 (0.71–5.01), $P = 0.20$	58/215	0.98 (0.52–1.85), $P = 0.95$
50th to <90th	36, 28–53	128/795	1.51 (0.93–2.46), $P = 0.098$	17/242	1.84 (0.39–8.56), $P = 0.44$	58/373	2.72 (1.04–7.15), $P = 0.042$	53/180	0.98 (0.51–1.88), $P = 0.95$
≥90th	65, 53–190	43/199	2.24 (1.25–4.03), $P = 0.007$ $P_{lin} = 0.003$	7/69	2.56 (0.48–13.67), $P = 0.27$ $P_{lin} = 0.19$	18/95	3.00 (1.03–8.76), $P = 0.044$ $P_{lin} = 0.030$	18/35	2.46 (0.97–6.20), $P = 0.057$ $P_{lin} = 0.034$
p,p′-DDE									
<10th	120, 9.1–170	21/199	Reference	4/71	Reference	7/95	Reference	10/33	Reference
10th to <50th	320, 170–470	89/795	1.00 (0.59–1.69), $P = 0.99$	13/259	0.76 (0.23–2.47), $P = 0.64$	39/380	1.29 (0.55–3.01), $P = 0.56$	37/156	0.89 (0.37–2.11), $P = 0.79$
50th to <90th	710, 470–1,200	157/795	1.62 (0.97–2.69), $P = 0.065$	17/198	1.33 (0.41–4.28), $P = 0.63$	65/356	2.60 (1.14–5.92), $P = 0.023$	75/241	1.04 (0.46–2.36), $P = 0.93$
≥90th	1,500, 1,200–10,000	41/199	1.75 (0.96–3.19), $P = 0.069$ $P_{lin} = 0.020$	3/49	0.88 (0.18–4.35), $P = 0.88$ $P_{lin} = 0.99$	11/80	1.91 (0.69–5.27), $P = 0.21$ $P_{lin} = 0.15$	27/70	1.82 (0.71–4.65), $P = 0.21$ $P_{lin} = 0.087$
PCB 153									
<10th	140, 6.5–160	31/199	Reference	4/48	Reference	7/88	Reference	20/63	Reference
10th to <50th	230, 160–290	116/795	1.00 (0.63–1.58), $P = 0.99$	8/207	0.40 (0.11–1.44), $P = 0.16$	42/354	1.45 (0.62–3.39), $P = 0.39$	66/234	0.92 (0.48–1.75), $P = 0.80$
50th to <90th	360, 290–500	123/795	1.19 (0.75–1.90), $P = 0.47$	19/249	0.93 (0.29–3.01), $P = 0.91$	57/373	2.00 (0.87–4.61), $P = 0.10$	47/173	0.76 (0.38–1.50), $P = 0.43$
≥90th	590, 500–1,600	38/199	1.64 (0.92–2.93), $P = 0.097$ $P_{lin} = 0.050$	6/73	1.03 (0.25–4.18), $P = 0.97$ $P_{lin} = 0.57$	16/96	1.97 (0.75–5.23), $P = 0.17$ $P_{lin} = 0.14$	16/30	2.30 (0.87–6.11), $P = 0.094$ $P_{lin} = 0.062$

Table 2—*Continued*

	Serum concentration (ng/g lipid) (median, range)	Not stratified		Stratified by BMI (kg/m^2)					
				<25		25 to <30		≥30	
		Cases/*n*	Adjusted OR	Cases/*n*	Adjusted OR	Cases/*n*	Adjusted OR	Cases/*n*	Adjusted OR
BDE 47									
<10th	0.11, 0.051–0.13	26/199	Reference	3/69	Reference	13/91	Reference	10/39	Reference
10th to <50th	1.9, 0.13–2.9	136/795	1.29 (0.80–2.09), $P = 0.30$	21/253	1.86 (0.52–6.64), $P = 0.34$	53/348	1.08 (0.55–2.12), $P = 0.82$	62/194	1.35 (0.59–3.07), $P = 0.48$
50th to <90th	4.6, 2.9–12	113/795	0.95 (0.59–1.56), $P = 0.85$	9/208	0.89 (0.23–3.48), $P = 0.86$	45/380	0.82 (0.42–1.62), $P = 0.57$	59/207	1.11 (0.49–2.53), $P = 0.81$
≥90th	21, 12–2,800	33/199	1.24 (0.69–2.23), $P = 0.48$	4/47	1.82 (0.38–8.85), $P = 0.46$	11/92	0.91 (0.38–2.21), $P = 0.84$	18/60	1.40 (0.54–3.64), $P = 0.49$
			$P_{lin} = 0.57$		$P_{lin} = 0.51$		$P_{lin} = 0.82$		$P_{lin} = 0.55$
BDE 153									
<10th	0.71, 0.0040–0.85	44/199	Reference	5/32	Reference	9/75	Reference	30/92	Reference
10th to <50th	1.2, 0.85–1.6	122/795	0.92 (0.60–1.41), $P = 0.69$	11/195	0.50 (0.15–1.67), $P = 0.26$	52/377	1.21 (0.55–2.63), $P = 0.64$	59/223	0.86 (0.48–1.52), $P = 0.59$
50th to <90th	2.2, 1.6–3.9	123/795	1.11 (0.71–1.75), $P = 0.65$	19/269	0.55 (0.17–1.75), $P = 0.31$	53/376	1.21 (0.54–2.70), $P = 0.65$	51/150	1.33 (0.71–2.51), $P = 0.38$
≥90th	5.6, 3.9–760	19/199	0.68 (0.36–1.28), $P = 0.23$	2/81	0.20 (0.03–1.18), $P = 0.075$	8/83	0.82 (0.29–2.36), $P = 0.72$	9/35	0.90 (0.35–2.30), $P = 0.82$
			$P_{lin} = 0.20$		$P_{lin} = 0.10$		$P_{lin} = 0.53$		$P_{lin} = 0.82$

Data are OR (95% CI), unless otherwise indicated. ORs are adjusted for sex, age, waist circumference, and mean arterial pressure.

sum of six POPs among normal-weight participants. Together, these studies suggest that overweight and exposure to POPs may have a synergistic effect on the risk of type 2 diabetes.

Additionally, we observed that exposure to the PBDEs was weakly related to the exposure to the other POPs, suggesting different or additional routes of exposure. It is generally accepted that diet (animal foods, in particular) is the most important source of PCDD/Fs and PCBs for humans. For PBDEs, other sources such as indoor air or dust have been identified, although their contribution to total PBDE intake appears to be higher in North America than in Europe (18). In Finland, the most important dietary source of PCDD/Fs and PCBs is fish, contributing 95 and 80% of total dietary intake, respectively, and for PBDEs, the contribution of fish is much lower (55%) and other sources are more diverse (12). However, the different dietary intake patterns between PCDD/Fs, PCBs, and PBDEs do not explain the weak association observed between the PBDEs and the other POPs. Our findings suggest that, in Finland, exposure to PBDEs through inhalation of indoor air or inhalation or ingestion of dust may be more significant than previously believed.

The associations between POPs and type 2 diabetes observed in the current study were not as striking as those observed in NHANES (5). In their study (5), the ORs for type 2 diabetes in the highest exposure categories of oxychlordane, *trans*-nonachlor, *p,p'*-DDE, and PCB 153 were 6.5, 11.8, 4.3, and 6.8, respectively, whereas the respective ORs in our study were 2.08, 2.24, 1.75, and 1.64. However, in NHANES, participants represented all age-groups ≥20 years of age, and the age of the participants in our study was 57–70 years. Among the subgroup of participants ≥60 years of age, Lee et al. (5) observed that the risk of type 2 diabetes associated with high exposure to the sum of POPs (calculated by adding ranks of the individual POPs) was lower than among younger age-groups, which is more consistent with our findings. One important factor that may explain why the association of POPs and type 2 diabetes was lower among our elderly study group, and among the NHANES subgroup aged ≥60 years, is the lack of exposure during the developmental period. Participants in our study population, who were born in the 1930s and 1940s, probably experienced little exposure in utero

and during childhood, which is often thought to be critical when considering the health effects of POPs. In fact, most of the study population's exposure probably occurred during their adult life. Even so, a statistically significant association between POP exposure and type 2 diabetes was observed here. This, together with an increasing number of studies, suggesting that a causal relationship exists (1–8), might encourage public health professionals concerned with the diabetes epidemic: limiting adult exposure might help to decrease the risk of developing this disorder.

Another significant factor explaining why the associations observed in the current study were not as strong as in NHANES is the clear difference in the level of exposure. Among NHANES, the same POP compounds as in the current study were reported, and with the exception ofPCB 153, their concentrations were systematically higher. In the highest exposure categories (≥90th), in particular, the concentrations of oxychlordane, *trans*-nonachlor, and *p,p'*-DDE were 75–190% higher in NHANES than in the current study, whereas the concentration of PCB 153 was 72% lower (5). The difference in the concentrations of the PBDEs was even more pronounced, with the concentrations of the congeners 47 and 153 in the highest exposure category (≥75th) being 590–650% higher than in the current study (7). This difference is striking, especially when it is considered that, in NHANES, participants from all age-groups are represented, whereas in the current study, participants are all aged 57–70 years, with longer overall exposure history. No studies previously reported serum concentrations of POPs among the general Finnish population, but PCB 153 concentrations of 116 ng/g (range 16.8–958) of lipid were observed in adipose tissue of a general Southern Finnish population aged 13–81 years, which is slightly lower than that in the current study (19).

Because of the cross-sectional study design, we were not able to assess the causal relationship between POPs and type 2 diabetes. Within human populations, studies addressing this question are scarce. In a follow-up study by Rignell-Hydbom et al. (20) within a general female population, the risk of type 2 diabetes among individuals with high baseline exposure to *p,p′*-DDE compared with individuals with low exposure was more pronounced when the lag time between baseline and diagnosis was longer, suggesting that high exposure may predispose individuals to developing type 2 diabetes later in life. In a case-control study nested in a prospective study, Lee et al. (21) observed indications of nonmonotone associations between POPs and type 2 diabetes among a general population, although the cases in this study had elevated baseline concentrations of triglycerides, HDL cholesterol, and fasting glucose. Recently, strong evidence of causality was obtained in in vitro and in vivo studies. That is, Ruzzin et al. (11) showed that low-level chronic POP exposure induced significant impairment of whole-body insulin action in rats. In addition, they showed that, in differentiated adipocytes, POP exposure induced a significant inhibition of insulin-dependent glucose uptake. It is interesting that there were no threshold doses in the inhibition of glucose uptake, suggesting that the risk assessments on the basis of tolerable intakes may not be applicable to insulin resistance.

The biological mechanisms by which POPs are thought to promote diabetogenesis remain obscure. In general, POPs are thought to exert their toxic effects through direct binding and activation of the aryl hydrocarbon receptor (AhR) pathway (22). Based on this assumption, a toxic equivalency concept was developed to assess the risks associated with exposure to dioxins and dioxin-like compounds. However, the diabetogenic effects of POPs might also be mediated through AhR-independent oxidative stress and mitochondrial dysfunction, which is known to play an important role in the etiology of diabetes (23). For example, Fischer et al. (24) demonstrated that an intracellular Ca^{2+} increase and insulin release from RINm5F cells is stimulated by PCB 47 and PCB 153, which have low affinity for the AhR but that such an effect is not produced by the coplanar PCB 77, a congener with moderate affinity for the AhR. In addition, Biswas et al. (25) observed that 2,3,7,8-tetrachlorodibenzo-*p*-dioxin, a high-affinity AhR ligand, induces mitochondrial dysfunction in mouse skeletal muscle C2C12 myoblasts, independent of AhR activation.

We were unable to include some important risk factors for type 2 diabetes in this study, e.g., physical inactivity, dietary composition, and genetic susceptibility. Therefore, we were unable to assess the role of these factors as possible confounders.

In conclusion, the current study confirms the association between adult exposure to OCPs and type 2 diabetes in a general Finnish population. In addition, our results suggest that regarding exposure to PBDEs, a significant contribution from nondietary sources is probable. Furthermore, this is the first study to report serum concentrations of the selected POPs in a population representing the general urban Finnish population.

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