

Persistent Organochlorine Pollutants in Plasma, Blood Pressure, and Hypertension in a Longitudinal Study

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Abstract—Persistent organochlorine pollutants (POPs) have shown to be involved in the atherosclerotic process and to cause endothelial cell dysfunction. To assess longitudinally whether plasma concentrations of different POPs were associated with blood pressure and risk of hypertension in middle-aged women and men. Study subjects were 850 participants in the VIP (Västerbotten Intervention Programme) with 2 blood samples and blood pressure measurements, 10 years apart, during 1990 to 2003 (baseline) and during 2000 to 2013 (follow-up). Dioxin-like and nondioxin-like polychlorinated biphenyls (DL-PCBs, NDL-PCBs) and p,p'-dichlorodiphenyldichloroethylene (DDE) were measured. Associations were assessed using generalized estimating equations. At baseline sampling 49% and at follow-up 64% had hypertension. DL-PCBs and DDE, but not NDL-PCBs or hexachlorobenzene, were associated with hypertension. Only the association for DL-PCBs remained statistically significant after lipid-standardization and adjustment for body mass index and total serum lipids. The multivariable-adjusted odds ratio of hypertension based on repeated measurements were 1.52 (95% confidence interval, 1.08–2.13) for DL-PCBs (third versus first tertile of lipid-standardized POPs). In stratified adjusted analyses, odds ratio for those born after 1950 increased to 3.99 (95% confidence interval, 2.15–7.43), whereas no association was observed among those born earlier. Based on repeated measurements, the accumulated exposure to DL-PCBs and DDE, although less clear for the latter, may disrupt the normal blood pressure levels and increase the odds of hypertension. Moreover, individuals experiencing early-life POP exposure may be at elevated risk of vascular POP effects. (*Hypertension*. 2018;71:1258-1268. DOI: 10.1161/HYPERTENSIONAHA.117.10691.) • [Online Data Supplement](#)

Key Words: DDE ■ dioxin-like polychlorinated biphenyls ■ early-life exposures
■ exposure via diet ■ hypertension

Over the past few decades, the number of individuals worldwide with systolic blood pressure (BP) ≥ 140 mmHg and the associated deaths have increased substantially.¹ Hypertension is an important risk factor for multiple cardiovascular and renal outcomes and increased knowledge of emergent-suspected risk factors is imperative from a public health perspective. Emerging evidence suggests a potential link between environmental contaminants and cardiometabolic disorders, including hypertension.²

Persistent organochlorine pollutants (POPs) include several groups of synthetic compounds with high lipophilic and bioaccumulative potential extensively used worldwide in agricultural, industrial, and health applications. POPs accumulate in the food chain resulting in an age-dependent body burden in humans.³ Some of the most widely dispersed POPs are the fungicide hexachlorobenzene (HCB), the insecticide dichlorodiphenyltrichloroethane—and its persistent metabolite p,p'-dichlorodiphenyldichloroethylene (DDE)—and the

polychlorinated biphenyls (PCBs), all being chlorinated. Despite their long-term ban, they are still of concern⁴ and the general population is constantly exposed to these pollutants at low doses through diet, mainly via animal fat, that is, fatty fish, meat, milk products, and eggs.^{5,6}

In animal studies, POPs have shown to induce hypertension, vascular dysfunction, and cardiac hypertrophy^{7–9} as well as to alter the expression of genes involved in DNA repair and cell cycling in vascular smooth muscle cells.¹⁰ Despite the biological plausibility and that some studies observed higher prevalence of hypertension in populations highly exposed to POPs,^{11–13} the few available observational studies on the general population considering this potential link, have reported somewhat discordant results.^{14–16} This inconsonance could potentially be explained by limitations related to study design, such as the availability of only a single cross-sectional measurement or the lack of information on relevant factors that may affect the associations, such as serum lipids,¹⁷ diet,¹⁸ adiposity,¹⁹ or the

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consideration of the impact of early exposures to these POPs through placenta transfer and lactation.²⁰ Moreover, different types of POPs have shown distinct mechanisms of action, thus, diverging effects on the vascular system could be anticipated both between and within groups of POPs,²¹ emphasizing the need for mechanistic-based approach to avoid any obscuring of the overall picture. Because of the wide dispersion of POPs and the still prevalent exposure worldwide, additional studies covering these gaps are needed to clarify their potential danger and to be able to assess the need for actions to further reduce the exposure in the population.

The purpose of the present study was to investigate whether plasma concentrations of different types of POPs are associated with BP levels and hypertension in a longitudinal study with repeated measurements in a sample of middle-aged men and women. To fully address the hypothesized relationship between POPs and hypertension, we specifically considered the influence of serum lipids, body mass index (BMI), diet, and early-life exposure to these substances.

Materials and Methods

Analysis methods that support the findings of this study are available from the corresponding author on reasonable requests. Requests for data can be made to the Department of Biobank Research, Umeå University, Sweden (<http://www.biobank.umu.se>) and will be subject to ethical review and assessment by a panel of scientists to grant that use of the data is in line with Swedish and EU legislation.

Design and Study Population

This study used data from the VIP (Västerbotten Intervention Programme), a subcohort in the Northern Sweden Health and Disease Study, one of the world's largest and most comprehensive biobank studies with samples and data sets based on continuous population-based health examinations. VIP was initiated in 1985 with the aim of preventing cardiovascular disease.²² In short, all subjects who become 40, 50, or 60 years (until 1996 also 30 years) in the study area are identified and invited to a health examination, anthropometric measurements, and to complete a questionnaire on lifestyle, including diet. Measurement of blood lipids was gradually introduced as a practice of the health examination. The participation rate exceeds 56% but is often around 70%, of which the vast majority (90.5%) have donated blood samples for research.

The present study was originally initiated to disentangle whether POPs are associated with risk of type 2 diabetes mellitus (T2D), applying a nested case-control study design with repeated sampling. For the purpose of the present analysis on POPs and hypertension, we used data from both cases and controls. T2D cases were identified via the Diabetes Register in Northern Sweden,²³ a register based on ascertainment of diabetes mellitus through computerized linkage to the patient and prescribed drug registers. Participation rate among individuals identified with diabetes mellitus was 74%. We identified 425 VIP participants with T2D included in the Diabetes Register in Northern Sweden register that had given blood samples twice to the biobank and the first one was before T2D diagnosis. These T2D cases were matched with VIP participants without T2D that were alive at time of T2D diagnosis for the case and had given blood sample twice. Matching criteria were gender, age, sample date (± 90 days), and type of questionnaire at baseline examination.

We initially performed the analyses separately for prediabetics and nondiabetics provided as online supplemental material (Table S5 in the [online-only Data Supplement](#)). Because the estimates obtained were mostly the same for both groups and there were no significant interactions between any of the POPs and the prediabetic status on the odds of hypertension, the 2 groups were combined in all assessments hereafter.

Oral/written informed consent has been obtained from the participants and the regional ethics review board approved the study.

Exposure and Covariate Assessment

The first medical examination and blood sampling was performed during 1990 to 2003 (baseline) and the follow-up during 2000 to 2013, with ≈ 10 years between the sampling occasions (Figure 1). All samples were collected after an 8-hour overnight fasting and were immediately centrifuged, separated, and stored at -80°C . POPs were measured at the National Institute for Health and Welfare in Finland by gas chromatography-triple quadrupole mass spectrometry.²⁴ A Reflotron bench-top analyser (Roche Diagnostics) was used for the blood lipid analyses.

The 4 different organochlorine compounds measured in plasma were the nondioxin-like (NDL)-PCBs composed by summation of the following 8 PCB congeners 74, 99, 138, 153, 170, 180, 183, 187; the dioxin-like (DL)-PCBs composed by summation of the 2 PCB congeners 118, 156; and 2 chlorinated pesticides, HCB and DDE. There were no concentrations below the limit of detection for any of the POPs. Concentrations were standardized for total lipids in plasma, by dividing the crude plasma POP concentration by total lipids, and were expressed as ng/g of lipid. The total plasma lipid content was calculated from triglycerides and total cholesterol using the standard formula proposed by Phillips et al.^{25,26} (Total lipid=2.27×total cholesterol+triglycerides+0.623; all expressed in units of g/L).

Samples with missing values for contaminants, total serum lipids, and BP measurements were excluded from analyses (ie, 169 samples at baseline and 20 at follow-up). Hence, out of the total 850 subjects (425 T2D cases and 425 matched nondiabetic controls), 681 had complete data at baseline and 830 at follow-up (1511 observations; Figure 1).

Covariables involved in these analyses were obtained from the life-style and semiquantitative food frequency questionnaires—validated with ten 24-hour diet recalls^{27,28}—completed by participants at the time of the blood sampling; including gender, age, educational level, smoking habits, BMI (calculated in kg/m^2 from the weight and height measured at the medical examinations), Cambridge index for physical activity, BP, and cholesterol-lowering medication, healthy diet score,²⁹ and alcohol consumption. Missing values of nondietary variables in one of the samples were replaced by the corresponding value reported in the other sample (<2%). Missing values on diet and alcohol consumption were slightly higher (3.5%) and were included into the models as a separate missing indicator category.

Outcome Assessment

Systolic and diastolic BP were measured once at both baseline and follow-up with a mercury sphygmomanometer after 5 minutes rest with the subject in a supine or sitting position depending on whether it was measured before September 2009 or after, respectively. To make reliable comparisons before and after 2009, algorithms taking into account gender and age were applied. Hypertension was defined as any of (1) self-reported diagnosis, (2) use of antihypertensive drugs, or (3) measured systolic/diastolic BP ≥ 140 or ≥ 90 mm Hg.

Statistical Analyses

Associations of POP plasma concentrations with systolic and diastolic BP levels (continuous) and with hypertension (dichotomous) were assessed cross-sectionally at the 2 sampling occasions using multivariable linear and logistic regression analyses, generating beta coefficients (β) and odds ratios (OR), with corresponding 95% confidence intervals (CI). Additionally, we performed longitudinal analyses based on both individual sample occasions (repeated measures) using generalized estimating equations (GEE). POPs exposure was assessed as tertiles of the distribution (based on the nondiabetics at each sampling occasion), which relax the linearity assumption, as well as on the continuous scale (per 1 SD increment) to determine if there is an overall trend (presented as P_{trend}). In addition, we prospectively evaluated the associations between POP levels at baseline and odds of hypertension during the follow-up. In these analyses, we excluded prevalent hypertension at baseline ($n=378$) and included participants with available data on wet-weight POPs levels at baseline as well as on BP at both baseline and follow-up (426 participants of which 179 developed hypertension during the

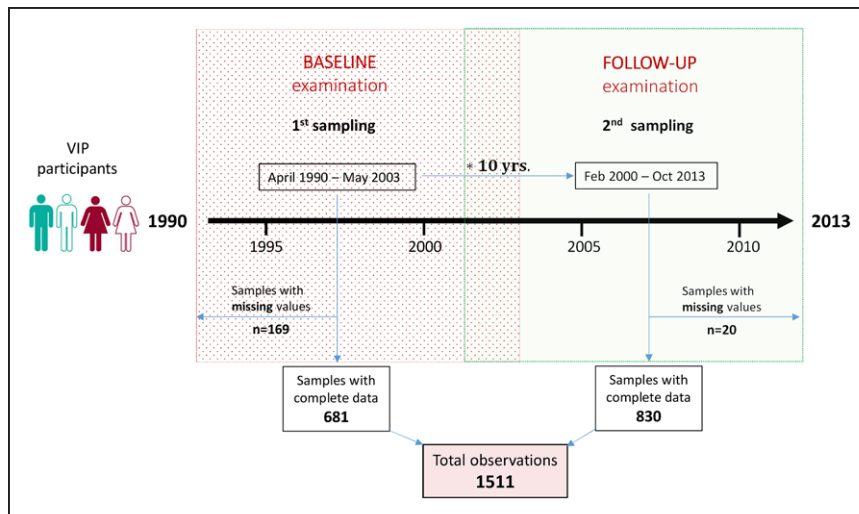


Figure 1. Study population and time of sampling. In each examination, both the exposure (persistent organochlorine pollutants) and the outcome (hypertension/blood pressure [BP]) were measured at the same time. As some subjects had missing values (for contaminants, total serum lipids, and BP measurements) in 1 assessment, there were subjects with only 1 final available observation. The time between both observations varies with an average of 10 y, and almost all of them within 8 to 12 y. VIP indicates Västerbotten Intervention Programme.

follow-up). Pairwise correlations were assessed using the Spearman rank correlation coefficient (ρ). We estimated the strength of agreement between the first and second POP measurement by calculating the intraclass correlation.

For confounder identification and to select the minimal set of covariates needed to control for, we followed a strategy that combined directed acyclic graphs, based on current scientific knowledge, and change-in-estimate procedure. In this procedure, the covariates identified as confounders by the relevant directed acyclic graph were included in the initial full logistic regression model and selected by backward elimination. In each step, the covariate for which removal caused the smallest change in the coefficient for the exposure was removed (if $<10\%$ change) until no covariate's removal met the criterion. Thus, the variables healthy diet score (3 categories), alcohol consumption (<0 , 0.1 – 5.0 , 5.1 – 15 , >15 g/d), smoking habit (current, former, never smoker), physical activity (inactive or active), or education ($>$ or <12 years.) were not included in the final regression model, keeping it as parsimonious as possible. The variables included in all the multivariable-adjusted models were gender, age ($<$ or ≥ 45 years at baseline/ $<$ or ≥ 55 years at follow-up), sample year (1990–1993, 1994–1997, 1998–2003 at baseline and 2000–2003, 2004–2008, 2009–2013 at follow-up), and to have been sampled because of a future T2D diagnosis or instead being a control (hereafter named prediabetics and nondiabetics). We further adjusted for antihypertensive therapy when BP levels were the outcome of interest.

On the other hand, both BMI and plasma lipid concentrations could potentially lie in the causal pathway between POPs and hypertension, acting as mediators.^{9,19,30,31} However, because they are correlated with the exposure—elevated lipid concentrations tend to carry proportionally higher concentrations of lipid-soluble contaminants^{25,32}—and with the outcome^{33,34} (Tables S2 and S3), they might also act as confounders for the associations evaluated. We constructed simple directed acyclic graphs corresponding to 3 main potential causal scenarios (Table S4) and fitted 4 different multivariable-adjusted models using different approaches to control for BMI and serum lipids. Model 1, POP tertiles based on wet-weight and no lipid adjustment; model 2, POP tertiles based on wet-weight adjusted for total serum lipids; model 3, POP tertiles based on wet-weight adjusted for total serum lipids plus BMI; and model 4, lipid-standardized POP tertiles adjusted for total serum lipids plus BMI. All models were adjusted for gender, age, sample year, and prediabetic status.

Because of the high correlations between different POPs, collinearity problems leading to unstable coefficient estimates and a loss of power cannot be ruled out if all POPs are entered simultaneously into a model. Thus, we considered single-pollutants analyses as the main results (ie, on which all the tables have been based), whereas models mutually adjusted for all POPs have been performed only with an exploratory purpose presented in the text for DL-PCBs only.

We conducted stratified analyses to discern whether the effect would be different depending on age ($<$ or ≥ 45 years at baseline/ $<$

or ≥ 55 years at follow-up), gender, and year of sampling (\leq or >1994 at baseline/ \leq or >2004 at follow-up) as well as birth year (≤ 1950 , >1950). We explored possible multiplicative interactions between POPs and these variables for the outcome hypertension using GEE-models and tested for statistical significance using the Wald test ($P_{\text{interaction}}$). In a final assessment, analyses were restricted to the leaner group of participants ($<$ median BMI, ie, 26.7 kg/m² at baseline and 27.9 at follow-up).

In sensitivity analyses, we assessed the associations between POP levels and odds of hypertension by separate adjustment for total cholesterol and triglycerides, instead of total lipids.

The level of statistical significance was set at 0.05 and all tests were 2-tailed. The statistical software STATA/SE version 14.0 (Stata Corp LP, College Station, TX) was used to manage the database of the study and to perform statistical analyses.

Results

At baseline and at follow-up the prevalence of hypertension was 49% and 65%, respectively. Table 1 summarizes the characteristics of the study population by hypertensive status at both occasions. Participants with hypertension were almost twice more likely to belong to the group selected based on a future diagnosis of T2D. In addition, the use of cholesterol-lowering medication at follow-up were much more common in hypertensive (25% of them versus 7%). BMI was also considerably higher in hypertensive than in normotensive participants. In general, no major differences were observed in the main characteristics between baseline and follow-up, with the exception of the use of antihypertensive and cholesterol-lowering drugs, which increased considerably at follow-up. Consequently, the average levels of lipids and diastolic BP were slightly lower at follow-up.

Concentration of POPs standardized to serum lipids was higher in prediabetics than in nondiabetics as well as, with few exceptions, in hypertensive than in normotensive participants. Correlations between the 4 groups of plasma lipid-standardized POPs ranged from ρ 0.64 (DDE versus HCB) to 0.89 (DL-PCBs and NDL-PCBs), $P < 0.05$ for all (Tables S2 and S3). We found that POP concentrations decreased over calendar time with relative changes over the 10-year period of -27% (DL-PCBs), -25% (NDL-PCBs), -41% (HCB), and -39% (DDE). The intraclass correlations between both measures were 0.8 for all except for HCB (0.5).

Table 1. Main Characteristics of the Participants by Sampling Occasion, Number of Subjects (%), or Mean (SD)

Characteristics	Baseline (1990–2003) N=681		Follow-Up (2000–2013) N=830	
	Normotensive n=351	Hypertensive n=330	Normotensive n=291	Hypertensive n=539
Prediabetes mellitus	137 (39)	210 (63)	86 (30)	329 (61)
Female	143 (41)	160 (48)	119 (41)	221 (41)
Age, y	46±6	47±5	55±7	57±5
BMI, kg/m ²	26±4	29±4	26±4	29±5
Education, n				
>12 y	252 (72)	227 (69)	213 (73)	367 (68)
Smoking status				
Current	108 (31)	68 (20)	60 (21)	70 (13)
Former	108 (31)	37 (42)	123 (42)	234 (43)
Physical activity				
(moderately) inactive	197 (56)	182 (56)	150 (51)	279 (52)
Healthy diet				
(1–22 score)	11±4	11±4	13±4	13±4
Alcohol consumption, g/d				
0.1–5	226 (67)	218 (69)	173 (59)	343 (64)
5.1–15	91 (27)	74 (23)	93 (32)	135 (25)
>15	7 (2)	6 (2)	13 (4)	20 (4)
BP lowering medication	0 (0)	88 (27)	0 (0)	318 (59)
Cholesterol-lowering medication	2 (<1)	2 (<1)	21 (7)	136 (25)
Laboratory analyses*				
Total cholesterol	5.8±1.2	5.9±1.2	5.4±1.1	5.2±1.1)
Triglycerides	1.5±0.9	1.9±1.2	1.4±0.8	1.8±1.0)
Clinical examination†				
Systolic BP	120±9	143±16	122±10	143±17
Diastolic BP	76±7	91±10	75±8	86±9
Plasma POP levels‡				
DL-PCBs				
Prediabetics	42±25	44±22	33±17	35±21
Nondiabetics	38±20	42±20	28±15	32±16
NDL-PCBs				
Prediabetics	494±203	500±232	445±235	426±198
Nondiabetics	479±200	487±210	361±160	392±175
HCB				
Prediabetics	36±13	38±16	25±10	24±11
Nondiabetics	35±14	34±14	21±8	22±10
DDE				
Prediabetics	324±204	371±263	241±198	252±206
Nondiabetics	268±195	313±252	157±139	188±149

BMI indicates body mass index; BP, blood pressure; DDE, p,p'-dichlorodiphenyldichloroethylene; DL-PCB, dioxin-like polychlorinated biphenyls; HCB, hexachlorobenzene; NDL-PCB, nondioxin-like polychlorinated biphenyls; and POP, persistent organochlorine pollutants.

*In mmol/L.

†In mm Hg.

‡In ng/g of lipid.

When assessing BP as a continuous outcome (Table S5), all subgroups of wet-weight POPs were associated with higher systolic and diastolic BP levels in the multivariable-adjusted model without consideration of serum lipids (model 1). The significant β coefficients ranged from 3.04 to 4.74 mmHg of systolic BP and 2.00 to 3.39 mmHg of diastolic BP—comparing participants in the third tertile of wet-weight POPs with those in the first. However, only the DL-PCBs remained associated with both systolic and diastolic BP after lipid-standardization and adjusting for both serum lipids and BMI (model 4). Thus, in the longitudinal assessment (using baseline and follow-up measurements), participants in the highest lipid-standardized DL-PCB tertile had a systolic and diastolic BP, 3.30 mmHg (95% CI, 0.86–5.75; overall trend (P_{trend}) was 0.063, determined by assessing POP exposure as continuous scale was) and 2.19 mmHg (95% CI, 0.81–3.58; $P_{\text{trend}} < 0.001$) higher than participants in the lowest tertile, respectively (model 4). Per 1 SD increment of lipid-standardized DL-PCBs, the systolic and diastolic BP increased by 0.80 (95% CI, -0.04–1.65) and 1.03 (95% CI, 0.58–1.49) mmHg, respectively (Figure 2). For DDE, after adjustment for total serum lipids, the association, although mitigated, remained statistically significant ($P_{\text{trend}} = 0.008$ and < 0.001 for systolic and diastolic BP, respectively, model 2); but tended to be attenuated after additional adjustment for BMI (models 3 and 4).

For the odds of hypertension, we did not observe any link for the sum of NDL-PCBs or HCB (Table 2), whereas DL-PCBs were consistently associated with hypertension over the different considerations of lipids and BMI (model 1–4), in line with the observed results for continuous BP. The multivariable-adjusted longitudinal assessment for lipid-standardized DL-PCB (model 4) showed an OR of hypertension of 1.52 (95% CI, 1.08–2.13; $P_{\text{trend}} = 0.051$) comparing subjects in the upper tertile of DL-PCB with those in the lowest tertile. Likewise, high DDE levels were also significantly associated with odds of hypertension when BMI was not included in the model as a covariate (models 1–2).

Additionally, we prospectively assessed the association between wet-weight POPs at baseline and odds of hypertension at follow-up. This prospective approach resulted in OR of 2.00 (95% CI, 1.11–3.62) for DL-PCBs, comparing highest with the lowest tertile. Although similar results were observed for NDL-PCBs, the ORs for HCB and DDE did not reach the statistical significance (Table S6).

In sensitivity analyses, we evaluated the association between wet-weight POP levels and hypertension risk adjusting for total cholesterol (model 2a) and triglycerides (model 2b) disjointedly, instead of for total lipids (model 2 in Table 2). In general, the associations were strengthened by adjustment for total cholesterol and attenuated by adjustment for triglycerides, as compared with the estimates for total lipids (Table S7).

The diet (assessed as a healthy diet score) did not have any influence on the POP-hypertension associations. To test whether residual confounding by parallel decreasing time-trends in the population's BP and DL-PCBs could have affected the results, analysis for model 4 were made with 14 categories for sampling year, instead of only 3. Changes in OR were negligible. Likewise, complementary results based on analyses mutually adjusted for all POPs did not change the overall conclusion. In the longitudinal assessment for DL-PCBs (model 4), the OR of hypertension was 2.17 (95% CI, 1.26–3.74) and the β of BP were 6.57 (95% CI, 2.71–10.43) for systolic and 2.84 (95% CI, 0.65–5.04) for diastolic, comparing third tertile versus the lowest (data not shown in tables).

In essence, for both DL-PCBs and DDE, the standardization and adjustment for lipid concentration somewhat attenuated the associations with BP levels and odds of hypertension, as compared with those based on wet-weight; DDE also showed an even greater attenuation after further adjustment for BMI. To further disentangle the impact of the BMI, when we restricted the DDE analyses to those \leq mean BMI, we observed higher multivariable-adjusted ORs of hypertension in the lean group than for the entire sample: 1.66 (95%

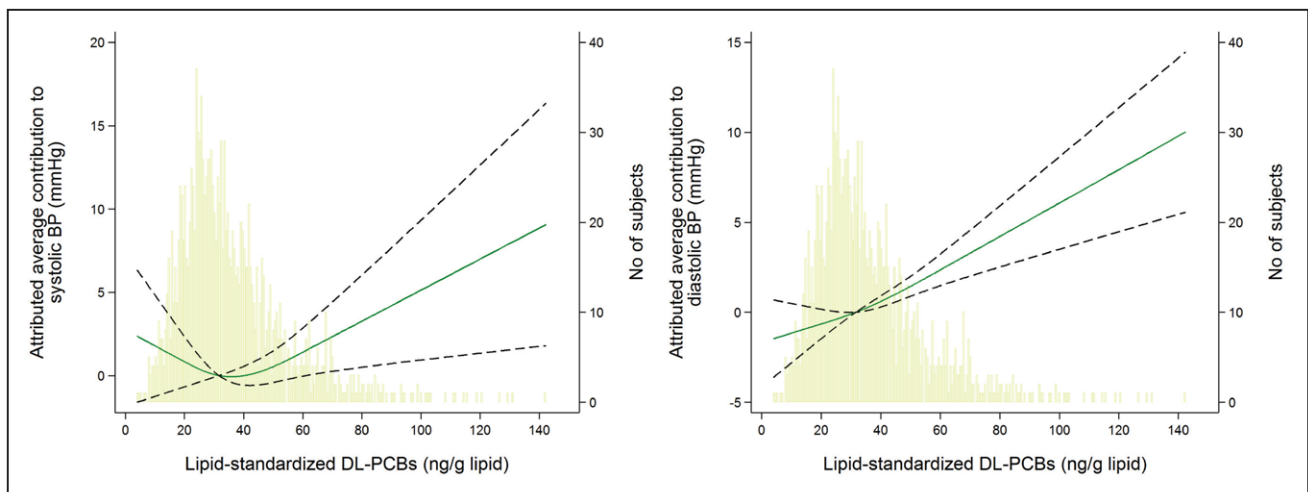


Figure 2. Continuous association between dioxin-like polychlorinated biphenyl (DL-PCBs) and blood pressure (BP). Multivariable-adjusted β coefficients of systolic (A) and diastolic (B) BP (solid lines) and their 95% confidence intervals (CI; dashed lines), as a continuous smooth function of lipid-standardized DL-PCBs. Data included the repeated measurements (both baseline and follow-up) and was fitted using multiple linear regression via generalized estimating equation methodology. Models were adjusted for gender, age, sample year, prediabetic status, total serum lipids, and body mass index. The median (31.7 ng/g lipids) was used as a reference and the histogram shows the distribution of the DL-PCBs. Plasma DL-PCB levels above the 99th percentile were excluded ($n=3$). Estimates are based on a single-pollutants analysis (ie, the different types of persistent organochlorine pollutants [POPs] were not mutually adjusted). Detailed data on the different POPs and different models for adjustment are given in the Table S5.

Table 2. Associations Between Plasma Persistent Organochlorine Pollutants Concentrations and Odds of Hypertension at Baseline, at Follow-Up, and Jointly Assessed in a Longitudinal Analysis (OR and 95% CI)

	Cross-Sectional Logistic Regression						Longitudinal Generalized Estimated Equation		
	Baseline n=681			Follow-Up n=830			Repeated Measurements n=1511		
	T1	T2	T3	T1	T2	T3	T1	T2	T3
DL-PCBs									
Model 1	1 (ref.)	1.06 (0.70–1.61)	1.86 (1.21–2.87)	1 (ref.)	1.43 (0.97–2.12)	1.75 (1.16–2.63)	1 (ref.)	1.16 (0.87–1.55)	1.47 (1.08–2.01)
Model 2	1 (ref.)	0.96 (0.63–1.48)	1.51 (0.95–2.42)	1 (ref.)	1.41 (0.95–2.10)	1.69 (1.09–2.60)	1 (ref.)	1.17 (0.87–1.56)	1.50 (1.08–2.08)
Model 3	1 (ref.)	0.99 (0.64–1.54)	1.65 (1.03–2.66)	1 (ref.)	1.49 (0.99–2.24)	1.73 (1.11–2.71)	1 (ref.)	1.22 (0.90–1.65)	1.65 (1.27–2.32)
Model 4	1 (ref.)	1.08 (0.72–1.62)	1.77 (1.07–2.91)	1 (ref.)	1.34 (0.88–2.03)	1.34 (0.88–2.03)	1 (ref.)	0.97 (0.72–1.30)	1.52 (1.08–2.13)
NDL-PCBs									
Model 1	1 (ref.)	1.07 (0.71–1.62)	1.54 (0.99–2.40)	1 (ref.)	1.58 (1.06–2.36)	1.13 (0.76–1.70)	1 (ref.)	1.16 (0.89–1.53)	1.13 (0.83–1.54)
Model 2	1 (ref.)	0.96 (0.63–1.46)	1.17 (0.72–1.90)	1 (ref.)	1.52 (1.01–2.28)	1.02 (0.66–1.57)	1 (ref.)	1.16 (0.88–1.52)	1.11 (0.80–1.54)
Model 3	1 (ref.)	1.04 (0.67–1.60)	1.36 (0.83–2.25)	1 (ref.)	1.53 (1.01–2.32)	1.10 (0.71–1.72)	1 (ref.)	1.22 (0.92–1.63)	1.28 (0.91–1.81)
Model 4	1 (ref.)	1.06 (0.70–1.62)	1.26 (0.79–2.00)	1 (ref.)	1.23 (0.81–1.86)	1.10 (0.72–1.68)	1 (ref.)	0.98 (0.73–1.30)	1.08 (0.78–1.49)
HCB									
Model 1	1 (ref.)	0.93 (0.61–1.42)	1.55 (0.99–2.43)	1 (ref.)	1.30 (0.87–1.94)	1.59 (1.05–2.39)	1 (ref.)	0.92 (0.69–1.21)	1.28 (0.95–1.73)
Model 2	1 (ref.)	0.84 (0.55–1.30)	1.22 (0.75–1.98)	1 (ref.)	1.27 (0.85–1.91)	1.51 (0.98–2.34)	1 (ref.)	0.92 (0.69–1.22)	1.29 (0.94–1.76)
Model 3	1 (ref.)	0.80 (0.51–1.24)	1.15 (0.70–1.88)	1 (ref.)	1.14 (0.75–1.72)	1.25 (0.80–1.96)	1 (ref.)	0.88 (0.66–1.17)	1.20 (0.86–1.67)
Model 4	1 (ref.)	0.89 (0.59–1.36)	1.09 (0.68–1.76)	1 (ref.)	1.14 (0.75–1.72)	1.14 (0.74–1.76)	1 (ref.)	0.92 (0.69–1.24)	1.05 (0.76–1.45)
DDE									
Model 1	1 (ref.)	1.29 (0.84–1.98)	1.64 (1.06–2.53)	1 (ref.)	1.56 (1.04–2.34)	1.75 (1.15–2.65)	1 (ref.)	1.46 (1.07–1.98)	1.57 (1.13–2.17)
Model 2	1 (ref.)	1.19 (0.77–1.83)	1.44 (0.92–2.24)	1 (ref.)	1.53 (1.02–2.30)	1.69 (1.11–2.57)	1 (ref.)	1.46 (1.07–1.99)	1.57 (1.13–2.18)
Model 3	1 (ref.)	1.09 (0.70–1.69)	1.28 (0.81–2.02)	1 (ref.)	1.33 (0.87–2.02)	1.31 (0.85–2.04)	1 (ref.)	1.30 (0.95–1.79)	1.33 (0.95–1.87)
Model 4	1 (ref.)	1.12 (0.73–1.72)	1.41 (0.90–2.20)	1 (ref.)	1.31 (0.87–1.97)	1.24 (0.81–1.91)	1 (ref.)	1.19 (0.88–1.62)	1.24 (0.89–1.73)

Estimates are based on a single-pollutants analysis (ie, the different types of persistent organochlorine pollutants [POPs] were not mutually adjusted). Model 1: wet-weight (nonlipid standardized) POPs with adjustment for gender, age, sample year, and prediabetic status. Model 2: model 1 additionally adjusted for total serum lipids. Model 3: model 1 additionally adjusted for total serum lipids and body mass index. Model 4: model 3 with lipid-standardized persistent organochlorine pollutants. CI indicates confidence interval; DDE, p,p'-dichlorodiphenyldichloroethylene; DL-PCB, dioxin-like polychlorinated biphenyls; HCB, hexachlorobenzene; NDL-PCB, nondioxin-like polychlorinated biphenyls; OR, odds ratio; POP, persistent organochlorine pollutant; T1, first tertile; T2, second tertile; and T3, third tertile.

CI, 0.90–3.05; $P_{\text{trend}}=0.055$) at baseline and 1.94 (95% CI, 1.11–3.38; $P_{\text{trend}}=0.205$) at follow-up, comparing the highest tertile with the lowest.

When the potential modifying effect of age, gender, birth year, and year of sampling was explored (Figure 3), only birth year and age revealed a significant interaction with DL-PCBs on hypertension ($P_{\text{interaction}}=0.016$ and 0.004, respectively). It should be noted, however, that the categories created for year of birth and age had great overlap. Thus, although no association was observed among those born during 1950 or earlier, DL-PCBs were clearly associated with hypertension in those born after 1950 in the longitudinal assessment: OR of 3.99 (95% CI, 2.15–7.43), comparing the third versus first tertile of DL-PCBs. Likewise, despite POP levels were lower in the younger participants, when stratifying by age, higher odds, 3.71 (95% CI, 1.94–7.12) of hypertension in younger than older subjects was observed for those with higher DL-PCBs concentrations. The higher ORs in those born >1950 and in younger participants were increased substantially when all

POPs were included simultaneously in the models; 5.60 (95% CI, 2.02–15.53) for those born >1950 and 5.31 (95% CI, 1.84–15.34) for the younger and comparing the third versus first tertile of DL-PCBs in longitudinal analysis.

Discussion

In the present study, conducted among middle-aged women and men, longitudinal associations of repeated measurements of 4 different groups of POPs with BP levels and hypertension risk showed to be dependent on type of compound as well as on total lipids in serum, BMI, and the participant's birth year, but not affected by a healthy eating score. All subgroups of wet-weight and lipid-unadjusted POPs showed to be positively associated with higher systolic and diastolic BP levels, and DL-PCBs and DDE also with odds of hypertension. However, only the DL-PCBs remained associated with BP and hypertension after lipid-standardization and adjusting for both serum lipids and BMI. An effect modification by birth year and age may suggest an impact of early-life exposure.

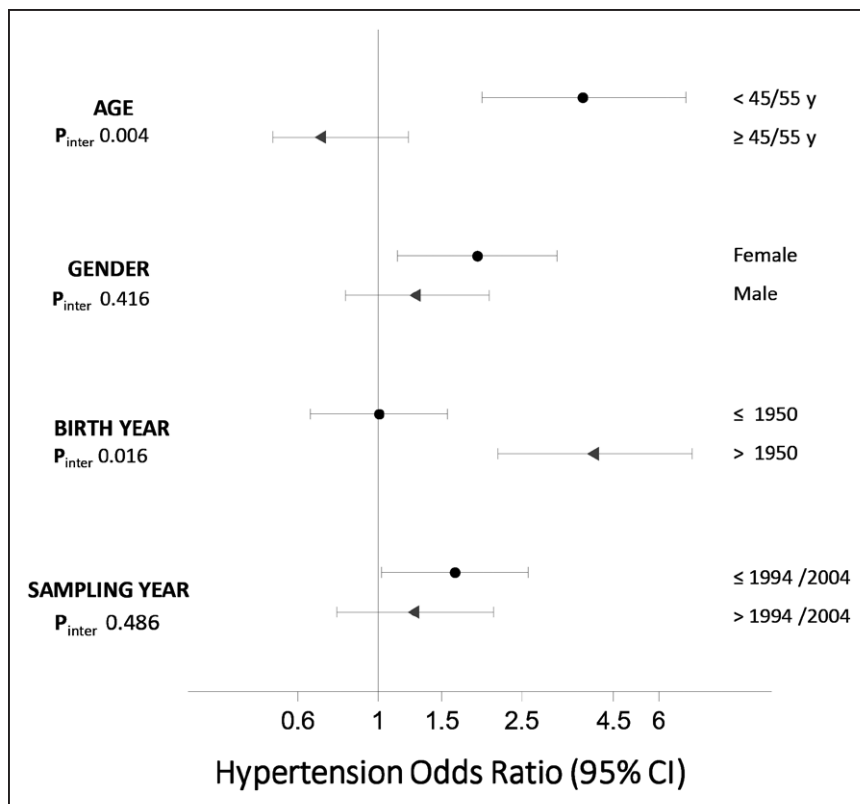


Figure 3. Odds ratio (OR) and 95% confidence intervals (CI) of hypertension for dioxin-like polychlorinated biphenyl (DL-PCBs) stratified by age (< and ≥45/55 years), gender (female, male), birth year (≤ and >1950 and sample year [≤ and > 1994/2004], black and grey respectively). Estimates are based on a single-pollutants analysis (ie, the different persistent organochlorine pollutants were not mutually adjusted).

Prior Evidence on POPs and Hypertension

Our results add to the information from a recent meta-analysis on POP levels in human plasma and hypertension risk in the general population.³⁵ That summarizing work observed a pooled borderline statistically significant OR of hypertension, comparing the highest and lowest POP concentration categories, of 1.45 (95% CI, 1.00–2.12) for the sum of DL-PCBs and 1.10 (95% CI, 1.03–1.18) for DDE, including studies that both lipid standardized/adjusted the exposure and those who did not. The OR for the sum of ND-L-PCBs did not reach statistical significance, and there were not enough studies for HCB.

In a previous cross-sectional study of a Swedish elderly population (132 hypertension cases out of 1016 subjects), where 23 lipid-standardized POPs were assessed in relation to prevalent hypertension, the strongest and most consistent association was observed for DDE (OR, 1.35 for a 1 SD increase; 95% CI, 1.17–1.56). Further adjustments including BMI attenuated all POP associations, whereas it remained only for DDE; OR of 1.23 for a 1 SD increase (95% CI, 1.06–1.43).³⁶ The DL-PCB congeners, 105 and 118, were only associated with the prevalence of hypertension after adjustment for gender alone.

Biological Mechanisms Relating DL-PCBs to BP

PCBs are often categorized into 2 groups based on their number and position of the chlorine atoms, which gives them different biological activity. The non-ortho chlorine-substituted (coplanar) PCB congeners, also including some mono-ortho-substituted congeners, are known as DL-PCBs (dioxin-like PCBs) because they activate the AhR (aryl hydrocarbon receptor), in the same way as dioxins. The ortho-substituted congeners (noncoplanar PCBs) do not bind to AhR (non-DL-PCBs)

and their mechanistic link with specific metabolic end points has not been elucidated. Supporting our findings, experimental^{37–40} and animal^{7–9} evidence reveals that DL-PCBs induce chronic inflammation and dysfunction in the vascular endothelium, potentially leading to hypertension through different AhR-mediated pathways such as via expression of several inflammatory markers^{38,40} and increasing cellular oxidative stress.⁸ The DL-PCB congener 126 showed to stimulate the production of vasoconstriction factors, including COX-2 (cyclooxygenase), prostaglandins, and reactive oxygen species, as well as to inhibit the release of the vasodilator nitric oxide (NO).^{37,39} Experimental or animal studies considering the biological mechanism for potential ND-L-PCB-induced hypertension are still lacking.

Methodological Issues: Dealing With Lipids

There is controversy about the best way to handle BMI and lipids when assessing health outcomes in relation to lipophilic contaminants. As POPs are fat-soluble hydrophobic molecules, they are not soluble in plasma, but in its lipid phase, that is, lipids, lipoproteins, and phospholipids. The concentration of POPs in the lipid phase may be assumed to be in equilibrium with other lipid pools with high blood perfusion, such as muscles and liver. As a consequence, the concentration in the lipid phase of plasma reflects the concentration in other parts of the body.⁴¹ Because elevated blood lipids tend to carry proportionally higher POP concentrations, we therefore standardized the POP concentrations to total lipids. There are indications that some POPs may increase blood lipids and potentially laying in the causal pathway between POPs and hypertension, acting as mediators (9, 17, 29, 30). Although this does not affect the reasoning above, it has implications for whether further corrections and adjustments for blood lipids should be done or avoided because of overadjustment, resulting in biased estimates. Thus, when devising a statistical model for assessing exposure to lipophilic contaminants measured in blood, there is no consensus on the best way to deal with this

relation between POPs, serum lipids, and potential lipid-mediated health outcomes.^{17,42} The appropriate statistical model will depend on the role of blood lipids and BMI on the true causal scenario and, consequently, each method implicitly assume a hypothetical causal model (Table S3). Because real-life scenarios likely involve complicated causal structures, we argue for the rationale recently suggested by O'Brien et al,¹⁷ who found that when assessing the association of lipid-soluble chemical with a health outcome and involving many interrelated covariates, the least biased statistical approach is to both lipid standardize the POP blood concentration and adjust for blood lipids in the model. The main asset of this method is that it showed to keep good performance even when there was a complicated confounding structure.

Existing Evidence on DDEs Effect on BP—Directly, or Indirectly via Adiposity?

The reason why the association between DDE and hypertension became largely attenuated after adjusting for BMI can only be speculated. Existing experimental data^{43,44} support a potential role of BMI as a mediator variable on the causal pathway between DDE and hypertension; that is, DDE might be involved in the increment of adiposity, which ultimately leads to BP disturbance. In line with this possibility raised, *in vitro* studies indicate that DDE exposure at environmentally relevant doses, increases proliferation and differentiation of preadipocytes.⁴³ Likewise, DDE has been associated with increased mRNA expression of the PPAR γ (peroxisome proliferator-activated receptor γ), which constitutes a major regulator of adipogenesis.⁴⁴ Moreover, the revealed DDE antiandrogen activity is suggested to be a likely mechanism whereby DDE directly—independently of adiposity—might disturb BP levels; low testosterone levels are linked to hypertension,⁴⁵ and DDE levels have been found to be inversely related to testosterone levels.⁴⁶ Likewise, experimental evidence suggests that dichlorodiphenyltrichloroethanes (precursor of DDE) can act on several arms of the renin-angiotensin system to possibly increase risk of hypertension.⁴⁷

However, the analysis for DDE excluding subjects with higher BMI, which resulted in higher odds of hypertension than the analyses of the complete sample, could be more in line with a potential confounding by BMI, rather than the proposed intermediate role. If there is confounding by BMI, analyses not adjusting for BMI will overestimate the true associations, whereas if BMI is an intermediate variable, BMI adjustment will underestimate the total effect of DDE. Thus, it is not possible to conclude whether our model 2, resulting in significant associations for DDE, or our model 3, providing no significant association with DDE, is best reflecting cause-effect associations.

Factors Modifying the Associations and Potential Biological Mechanisms

When we further explored these associations by age and birth year, all POPs presented higher odds of hypertension in younger subjects than in older even though the POP concentrations were lower in the younger ones. In line, Valera et al¹³ also observed an increased risk of hypertension linked to DL-PCBs and DDE only among the youngest individuals: the OR for DL-PCBs was 1.34 (95% CI, 1.03–1.74) and the OR for DDE 1.42 (95% CI, 1.08–1.85). A likely partial explanation could be that young people tend to have a more sensitive

physiological system.⁴⁸ This sensitivity decreases with aging and then, in elderly, other age-related physiological factors might be more determinant in the development of hypertension than environmental factors per se.

An alternative explanation is that the younger generation may have experienced epigenetic changes because of early-life exposure to POPs (placental transfer or via breast milk). Some gathered evidence indicates that environmental exposures during key stages of development that may influence crucial cellular functions have an important effect on epigenetic code (ie, durable changes in gene expression patterns) and permanently alter the structure or function of specific organ systems, resulting in increased risk of metabolic disease later in life and even affecting health across generations.²⁰ Epigenetic alterations—for example, through microRNA expression, histone modification, or DNA methylation⁴⁹—have been proposed as one important mechanism in the pathogenesis of atherosclerosis.⁵⁰ Because the environmental POP burden in Sweden had a rapid increase in the early 1950s, peaking in the 1960s,⁵¹ the fetal and postnatal lactation POP exposure was higher in those born later (after 1950 as compared with before). Thus, our observed higher OR in those born after 1950 supports the hypothesis that hypertension risk could be greater because of a sensitization early in life.^{20,52} This interpretation converges with existing studies where pre-/postnatal POP levels are associated with a higher BP in offspring later in life.^{53–55} Likewise, a higher risk of stroke was observed with increasing dietary PCB exposure in women likely exposed to PCBs *in utero* as compared with women born before the industrial use of PCBs began.⁵⁶

This finding raises the question as to whether DL-PCB exposure early in life could be more determinant than the later exposure accumulation over the years. With our data, however, this hypothesis can only be examined to a limited extent because some results lost precision because of the smaller sample sizes. Likewise, we cannot rule out the possibility that unmeasured exposures and other unknown factors occurred early and later in life actually explain the association observed only in the group born after 1950.

Relevance of the Effect Observed

The magnitude of the DL-PCB effect observed—with β of systolic BP ranging from 5.8 mmHg in systolic BP at baseline to 3.0 mmHg as average in the repeated assessment when comparing the third versus first tertile—is more or less comparable to that observed for other known factors affecting hypertension. For instance, the DASH (Dietary Approach to Stop Hypertension) diet significantly decreased systolic BP by 5.2 mmHg and diastolic BP by 2.6 mmHg in a meta-analysis of randomized controlled trials.⁵⁷

Strengths and Limitations

Some limitations need to be considered. First, hypertension was not the primary end point of the original nested case-control study and participants were selected on the basis to assess the link between POPs and T2D. However, all models were adjusted for being prediabetic or not and the results did not change appreciably when we assessed the associations among the nondiabetic subjects alone. We therefore do not think that this selection of study subjects affected the results. Second,

in the prospective assessment of the cumulative incidence of hypertension, sequential of a previous POP exposure, it was not possible to adjust for time-varying confounding as well as it was somewhat constrained by the limited number of non-hypertensive subjects at baseline. These prospective results, however, were fully in line with those from the main longitudinal analysis. Third, although the available high-quality data on diet, anthropometric measurements, and clinical parameters, allowed us to control for important potential confounders that have not been accounted for in other studies; we cannot discard the possibility of residual or unmeasured confounding.

Considering the high cost involved in the analysis of these chemicals, it is particularly noteworthy that the study was based on a fairly large sample size, with adequate statistical power. The longitudinal design with repeated measurements in most of the participants (>80%) during the 10-year follow-up, is a strength because it considers the individual outcome progression and corresponding POP concentrations, whereas at the same time provides the possibility to adjust for time-varying confounding. Likewise, because the long half-life of POP in blood (≈ 8 –15 years)—because of their high liposolubility and chlorination—and the high intraclass correlation between baseline and follow-up POP measurements, it was appropriate to also prospectively examine the association of early POP levels and development of hypertension; which avoids reverse causation bias and takes into account long-term POP exposure. Hence, the major advantage of our study was the consistency of the estimations obtained from both approaches, ensuring that the results are robust.

Perspectives

These findings add to the evidence of chemicals exposures being of importance in cardiovascular disease prevention. Recent findings indicating associations between POPs and hypertension-related adverse outcomes such as stroke,^{56,58} stresses this relevance. Although environmental levels of POPs are declining, they are still present in the food chain, persist in human bodies for decades and consequently, they are currently detected in all citizens worldwide at different concentrations.⁵⁹ Thus, the population impact may be large even if individual risks are low.⁶⁰ Moreover, fatty fish constitutes a major source of POP exposure but also to cardioprotective nutrients such as vitamin D and the long-chain omega-3 fatty acids, which may lower BP and blood triglyceride concentrations, decrease inflammation, and improve vascular function.⁶¹ Hence, balancing the rewards and possible risks of fish, presents a dilemma to consumers and authorities launching dietary guidelines and further knowledge on risk and benefits of fish intake is needed.⁶²

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Disclosures

None.

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Novelty and Significance

What Is New?

- Emerging experimental and animal data suggest that persistent organochlorine pollutants have the potential to cause vascular dysfunction. The few studies considering this potential link in general population report discordant results and exhibit significant methodological limitations. Several of these limitations were overcome by this longitudinal study with valid, reliable, and repeated assessments of both the exposure and the outcome, reducing the likelihood of bias. Equally notable is that the influence of serum lipids, the body mass index, the diet as well as the role of early-life exposure to these substances was specially considered.

What Is Relevant?

- These findings offer further evidence that some widely spread organochlorine compounds are environmental risk factors for cardiovascular disease. As these contaminants are detected in all citizens at different concentrations in many societies worldwide, the population impact may be large even if individual risks are low. This has an impact on both clinical

medicine, as regards interpretation and prognosis of trends in blood pressure, and public health policy, protecting citizens through dietary guidelines and regulatory measures about chemical products. The finding also further encourage mechanistic research.

Summary

This study provides high quality and reliable evidence on the positive associations of the widely spread dioxin-like polychlorinated biphenyls and the pesticide dichlorodiphenyltrichloroethane with hypertension and blood pressure levels in general population. The magnitude of the observed dioxin-like polychlorinated biphenyl association with blood pressure and hypertension is comparable to that observed for other known factors affecting hypertension. These findings underline the importance of integrating knowledge on human chemical contamination in the cardiovascular prevention research.