Extended Analyses of the Association Between Serum Concentrations of Persistent Organic Pollutants and Diabetes

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We recently reported on serum concentrations of six persistent organic pollutants (POPs) and prevalence of diabetes in a random U.S. sample (1). Most previous epidemiological studies were restricted from studying several POPs given cost and serum amounts needed. Focus on selected POPs may be appropriate in occupational or accidental high exposure, but, in the general population with only background POP exposure, there is a need to study the concentrations of many interrelated POPs.

Our initial approach to risk characterization was to calculate a summary to accumulate risk of exposure across six POPs (1). Even though the summary of six POPs was strongly associated with diabetes, individual POPs had substantial differences in strength of association (1). Thus, it is also of interest to estimate risk within subclasses of POPs that have similar physical and chemical properties. All POPs measured in the National Health and Nutrition Examination Survey (NHANES) can be divided into five subclasses: polychlorinated dibenzo-*p*-dioxins (PCDDs), polychlorinated dibenzofurans (PCDFs), dioxin-like polychlorinated biphenyls (PCBs), nondioxin-like PCBs, and organochlorine (OC) pesticides. Such specificity about diabetogenicity of POP subclasses would be especially important from the viewpoints of both toxicology and regulation. Therefore, in this article we report on the diabetes associations of 19 POPs within five POP subclasses, each detected among at least 60% of study subjects, i.e., in a manner identical to our most recent analysis of POPs and insulin resistance in the NHANES dataset (2).

RESEARCH DESIGN AND METHODS

— We used the NHANES 1999–2002 public use dataset. Serum concentrations of POPs were measured by high-resolution gas chromatography/high-resolution mass spectrometry. There were 1,721 persons aged ≥20 years with all information on the selected 19 POPs (Table 1).

For each POP, subjects with serum concentrations under the limit of detection were the reference, and remaining subjects with detectable values (minimally 60% of those assayed for each POP) were put in quartiles. To yield a cumulative measure of three PCDDs, we summed the ranks of the three PCDDs, then divided into quartiles. We assigned and cumulated POP subclasses similarly for the three PCDFs, the four dioxin-like PCBs, the five nondioxin-like PCBs, and the four OC pesticides.

Diabetes (n = 179) was defined as follows: *1*) fasting plasma glucose ≥126 mg/dl or nonfasting plasma glucose ≥200 mg/dl or *2*) reported history of physician-diagnosed diabetes. Exclusion of nonfasting subjects did not greatly change the findings, but we retained the criteria in our previous article for consistency. Logistic regression was used to calculate multivariable-adjusted odd ratios (ORs), with adjusting variables (Table 1). All statistical analyses were performed with SAS (version 9.0; SAS Institute, Cary, NC)

RESULTS

— In separate models of each POP individually, most POPs belonging to all five subclasses of POPs were positively associated with the prevalence of diabetes but differed substantially across POP subclasses. Specific PCDDs or PCDFs were weakly associated with diabetes, while POPs belonging to PCBs or OC pesticides were strongly associated.

After adjusting for age, there were positive pairwise correlations (r = 0.23–0.73) among serum concentrations of the five POP subclasses. Thus, although etiological relationships with diabetes could be restricted to several specific POPs, the correlation between POPs could lead to positive epidemiologic associations with diabetes for most POPs. When the five POP subclasses were modeled simultaneously, only dioxin-like PCBs and OC pesticides were statistically significantly associated with diabetes; PCDDs and nondioxin-like PCBs were not associated with diabetes. PCDFs were weakly associated with diabetes. Further adjustment for dietary fiber intake, total sugar intake, saturated fat intake, exercise, or place of residence did not materially change the results. In addition, inclusion of both BMI and waist circumference may overadjust, but elimination of either variable from the model did not change the results.

CONCLUSIONS

— Among ~50 POPs measured in NHANES datasets, we previously examined only the 6 POPs detected among at least 80% of

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Abbreviations: NHANES, National Health and Nutrition Examination Survey; OC, organochlorine; PCB, polychlorinated biphenyls; PCDD, polychlorinated dibenzo-*p*-dioxins; PCDF, polychlorinated dibenzofurans; POP, persistent organic pollutants.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Adjusted OR* (95% CI) of prevalence of diabetes* (n/n = *179/1,721*) *by categories of POPs*

Analytes	Detectable (%)	Nondetectable	Detectable				P_{trend}
			<25th	25th to <50th	50th to <75th	≥75th	
Separate models†							
D03	76	Referent	0.5 (0.2–1.0)	1.0 (0.6–1.8)	1.1 (0.7–1.9)	1.5 (0.9–2.5)	0.09
D05§	88	Referent	0.9 (0.4–2.2)	1.8 (0.8–3.8)	1.8 (0.8–3.8)	2.1 (1.0–4.6)	<0.01
D07§	80	Referent	1.8 (0.9–3.9)	2.3 (1.1–4.7)	1.9 (0.9–3.9)	2.5 (1.2–5.3)	0.04
All PCDDs summed‡		—	Referent	0.9 (0.5–1.7)	1.5 (0.8–2.6)	1.8 (1.0–3.3)	<0.01
F03	61	Referent	2.6 (1.5–4.5)	1.6 (0.9–2.9)	2.4 (1.4–4.1)	2.7 (1.5–4.7)	<0.01
F04	70	Referent	2.3 (1.3–4.2)	1.4 (0.7–2.6)	2.8 (1.6–4.9)	2.4 (1.4–4.3)	<0.01
F08	77	Referent	1.4 (0.8–2.5)	1.9 (1.1–3.2)	1.5 (0.8–2.6)	2.4 (1.4–4.0)	<0.01
All PCDFs summed‡		—	Referent	2.3 (1.2–4.3)	2.6 (1.4–4.9)	3.7 (2.0–7.1)	<0.01
074	62	Referent	3.5 (1.8–6.5)	3.4 (1.8–6.4)	4.1 (2.1–7.9)	4.2 (2.0–8.6)	<0.01
118	66	Referent	5.1 (2.3–11.0)	6.9 (3.2–14.9)	7.5 (3.5–16.2)	12.6 (5.6–28.3)	<0.01
126	79	Referent	0.9 (0.4–1.9)	1.4 (0.7–2.7)	2.0 (1.0–3.7)	4.2 (2.3–7.8)	<0.01
156	79	Referent	1.1 (0.6–2.2)	1.9 (1.0–3.5)	2.0 (1.0–3.9)	2.2 (1.1–4.4)	<0.01
All DPCBs summed‡		—	Referent	9.0 (2.7–30.3)	18.6 (5.5–62.7)	24.3 (7.0–84.5)	<0.01
138	76	Referent	2.2 (1.0–4.8)	4.0 (2.0–8.0)	5.6 (2.7–11.5)	6.5 (3.1–13.6)	<0.01
153§	80	Referent	2.8 (1.2–6.6)	4.5 (2.0–10.3)	6.2 (2.7–14.3)	6.8 (2.8–16.1)	<0.01
170	68	Referent	2.2 (1.2–4.2)	2.3 (1.2–4.6)	3.4 (1.7–6.8)	4.4 (2.1–9.2)	<0.01
180	78	Referent	3.0 (1.3–6.7)	5.2 (2.3–11.8)	5.3 (2.2–12.4)	8.2 (3.4–20.2)	<0.01
187	63	Referent	2.2 (1.2–4.0)	2.2 (1.1–4.2)	4.4 (2.3–8.5)	4.3 (2.1–8.5)	<0.01
All NPCBs summed‡		—	Referent	3.0 (1.5–6.1)	4.2 (2.0–8.8)	6.2 (2.8–13.6)	<0.01
PDE§	100	—	Referent	1.3 (0.7–2.6)	1.6 (0.6–3.2)	2.9 (1.5–5.6)	<0.01
OXY§	82	Referent	0.8 (0.3–1.8)	1.5 (0.7–3.4)	3.0 (1.4–6.6)	4.6 (2.0–10.4)	<0.01
TNA§	89	Referent	1.1 (0.3–3.7)	2.3 (0.8–7.1)	4.5 (1.5–13.6)	8.0 (2.6–24.8)	<0.01
BHC	77	Referent	2.5 (1.0–6.6)	3.0 (1.2–7.9)	5.7 (2.2–14.7)	7.0 (2.7–18.1)	<0.01
All OC pesticides summed‡		—	Referent	3.8 (1.4–10.5)	6.4 (2.3–17.4)	13.9 (5.0–38.7)	<0.01
Simultaneous models†							
PCDDs	—	—	Referent	0.4 (0.2–0.8)	0.5 (0.3–1.0)	0.5 (0.2–0.9)	0.25
PCDFs	—	—	Referent	1.8 (0.9–3.6)	1.7 (0.–3.5)	2.2 (1.1–4.7)	0.08
DPCBs	—	—	Referent	8.6 (2.3–31.8)	16.0 (2.3–31.8)	15.7 (3.4–71.2)	<0.01
NPCBs	—	—	Referent	0.7 (0.3–1.7)	0.6 (0.2–1.5)	0.6 (0.2–1.7)	0.45
OC pesticides	—	—	Referent	2.4 (0.8–7.0)	3.4 (1.1–10.0)	6.8 (2.2–21.3)	<0.01

*Adjusted for age, sex, race, poverty income ratio, BMI, and waist circumference. †Separate model: each POP or summary of subclasses of POPs was modeled one by one; simultaneous model: five subclasses of POPs were included in one model. ‡Detectable values of each POP were individually ranked, and the rank orders of the individual POPs in each subclass were summed to arrive at the subclass value. All undetectable values were ranked as 0. The summary values were categorized by cutoff points of 25th, 50th, 75th, and 90th values of the sum of ranks. §Detectable in >80% of participants and previously reported (ref. 1). 074: 2,4,4′,5-tetrachlorobiphenyl; 118: 2,3′,4,4′,5-pentachlorobiphenyl; 126: 3,3′,4,4′,5-pentachlorobiphenyl; 156: 2,3,3′,4,4′,5-hexachlorobiphenyl; 138: 2,2′,3,4,4′,5-hexachlorobiphenyl; 153: 2,2′,4,4′,5,5′-hexachlorobiphenyl; 170: 2,2′,3,3′,4,4′,5-heptachlorobiphenyl; 180: 2,2′,3,4,4′,5,5′-heptachlorobiphenyl; 187: 2,2′,3,4′,5,5′, 6-heptachlorobiphenyl; BHC: Beta-hexachlorocyclohexane; DPCB: dioxin-like PCBs; D03: 1,2,3,6,7,8,-hexachlorodibenzo-*p*-dioxin; D05: 1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin; D07: 1,2,3,4,6,7,8,9-octachlorodibenzo-*p*-dioxin; F03: 2,3,4,7,8-pentachlorodibenzofuran; F04: 1,2,3,4,7,8-hexachlorodibenzofuran; F08: 1,2,3,4,6,7,8-heptachlorodibenzofuran; NPCB: nondioxin-like PCBs; PDE: p,p′-Dichlorodiphenyltrichloroethane; OXY: oxychlordane; TNA: trans-nonachlor.

study subjects (1). This analytic strategy was carefully chosen to assure that the reference group reliably had low levels of POPs, to yield a valid reference group risk estimate and at the same time a valid relative estimate for those with detectable POPs compared with this reference group (3). Given sufficient serum, POPs would be detectable in almost all humans. The problem of a valid reference arises because POP serum concentrations are generally low, but nondetectable concentrations are not necessarily 0, given limited amounts of serum for analysis.

Although our previous restriction to the six POPs detectable among at least 80% of study subjects may avoid this bias, it limited inference about other POPs that may be also important. Among the six POPs we investigated (1), two are PCDDs, one is a nondioxin-like PCB, and three are OC pesticides; none were PCDFs or dioxin-like PCBs. One recent study (4) using the same NHANES dataset (1) examined associations of diabetes with three other POPs that were not included in our analyses (D03 [1,2,3,6,7,8,-hexachlorodibenzo-*p*-dioxin], PCB126, and p,p′-DDT), detectable in 76, 79, and 41% of the sample aged ≥20 years. Considering the probable importance of POPs in relation to diabetes, relaxing the criterion for the reference category to include more POPs in comprehensive and systemic analyses that reflect all five subclasses is needed.

The extended analyses presented here found that the dioxin-like PCB and OC-pesticide subclasses were the most strongly associated with diabetes. The interpretation of current findings as causal is limited because of the cross-sectional design. The apparent contradiction of a dramatic increase in type 2 diabetes incidences coupled with a decreasing pattern of the serum concentrations of POPs in the general population over several de-

cades may be explained by persistence and increased toxicity of POPs in obesity (1,3).

Sorting out exactly which POPs are causal is challenging. Consistency across studies and across conceptually related approaches to the question of POPs and diabetes can be helpful. As an example of consistency, we reported that some PCBs and OC-pesticides were also positively associated with homeostasis model assessment of insulin resistance among participants without diabetes (2). Both PCBs and OC-pesticides may be primary targets of further toxicological and epidemiological studies.

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References

1. Lee DH, Lee IK, Song KE, Steffes M, Toscano W, Baker BA, Jacobs DR Jr: A strong dose-response relation between serum concentrations of persistent organic pollutants and diabetes: results from the National Health and Examination Survey. *Diabetes Care* 29:1638–1644, 2006
2. Lee DH, Lee IK, Jin SH, Steffes M, Jacobs DR: 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* 30:622–628, 2007
3. Lee DH, Jacobs DR, Porta M: Could low level background exposure to persistent organic pollutants contribute to the social burden of type 2 diabetes? *J Epidemiol Community Health* 60:1006–1008, 2006
4. 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* 103:413–418