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Association of a polychlorinated dibenzo-*p*-dioxin, a polychlorinated biphenyl, and DDT with diabetes in the 1999–2002 National Health and Nutrition Examination Survey

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Abstract

The association of a polychlorinated dibenzo-*p*-dioxin, a polychlorinated biphenyl, and *p*,*p*′-DDT with diabetes was evaluated using the 1999–2002 National Health and Nutrition Examination Survey. Persons 20 years old and older were included. Relationships with diagnosed diabetes, undiagnosed diabetes (glycohemoglobin (HbA1c) $>6.1\%$), and total diabetes (diagnosed plus undiagnosed) were tested. When all three chemicals were evaluated together for total diabetes, the unweighted number of participants was 1830. All three compounds were significantly associated with diagnosed diabetes. PCB 126 and *p*,*p*′-DDT were significantly associated with undiagnosed diabetes. 1,2,3,6,7,8-hexachlorodibenzo-*p*-dioxin (HxCDD) was not associated with undiagnosed diabetes. When the three chemicals were included in a combined model for total diabetes, PCB 126 >83.8 pg/g lipid adjusted had an odds ratio of 2.57 (95% CI 1.33–4.95) compared to PCB 126 $\leqslant 31.2$ pg/g lipid adjusted. Also significant in a combined model for total diabetes was *p*,*p*′-DDT 20.8–26.6 ng/g lipid adjusted with an odds ratio of 2.52 (95% CI 1.26–5.02) and *p*,*p*′-DDT >26.6 ng/g lipid adjusted with an odds ratio of 2.74 (95% CI 1.44–5.23) both compared to *p*,*p*′-DDT $\leqslant 20.7$ ng/g lipid adjusted. HxCDD was not associated with total diabetes in a combined model. When participants with poor liver function and poor kidney function were removed from the analysis, the combined model for total diabetes produced similar results with PCB 126 and *p*,*p*′-DDT having been significantly associated, and HxCDD not having been associated. These findings add to the list of chemicals found to be associated with diabetes in the 1999–2002 National Health and Nutrition Examination Survey.

Keywords: Dioxin; PCB; DDT; Diabetes

1. Introduction

Polychlorinated dibenzo-*p*-dioxins are chlorinated aromatic chemicals that have no known commercial or natural use, and are commonly referred to as dioxins. They are produced as byproducts in the bleaching of paper products and during certain types of chemical synthesis, but the release of dioxins from these industrial sources are estimated to have decreased by 75% from 1987 to 1995. Regulations put in place in the 1990s should result in a 95% reduction in dioxin emissions from municipal waste combustors and medical waste incinerators. However, dioxins are persistent in the environment, and dioxin emissions will continue from uncontrolled combustion of household waste. Although most soil and water samples contain trace amounts of these compounds, the main source of human exposure is through ingestion of contaminated foods as a result of bioaccumulation in the food chain. The US Environmental Protection Agency (EPA) estimates that over 95% of dioxin intake comes through dietary intake of animal fats (EPA, 2004a,b).

Much toxicologic work has been done with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), which has been shown to dramatically reduce glucose uptake in guinea pigs, mice and rats in vivo and in vitro (Enan and

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Matsumura, 1994). Epidemiological studies have also found associations between dioxin and diabetes (Pazderova-Vejlupkova et al., 1981; Henriksen et al., 1997; Longnecker and Michalek, 2000; Cramner et al., 2000; Lee et al., 2006). These findings have led to the hypothesis that exposure to dioxins is a risk factor for diabetes (Lognecker and Daniels, 2001; Remillard and Bunce, 2002). However, a study by the National Institute for Occupational Safety and Health (NIOSH) did not find an association between serum TCDD and diabetes in 267 chemical workers and 227 referents (Steenland et al., 2001). Remillard and Bunce (2002) suggested that aryl hydrocarbon (Ah) receptor functions may antagonize peroxisome proliferator-activated receptor (PPAR) functions, contributing to the pathophysiology of diabetes as dioxins bind with the Ah receptor. PPARγ plays an important role in adipocyte mediation of glucose homeostasis and is also the target of the anti-diabetic thiazolidinedione drugs (Jones et al., 2005).

Lee et al. (2006) investigated the association of 1,2,3,4,6,7,8-heptachlorodibenzo-*p*-dioxin (HpCDD) and 1,2,3,4,6,7,8,9-octachlorodibenzo-*p*-dioxin (OCDD) with diabetes in the 1999–2002 National Health and Nutrition Examination Survey (NHANES) and found a strong dose–response relationship. We investigated the association of 1,2,3,6,7,8-hexachlorodibenzo-*p*-dioxin (HxCDD) with the occurrence of diabetes in the same nationally representative sample. HxCDD was chosen for evaluation because its 95th percentile was above the limit of detection (referred to as maximum limit of detection) reported in the Third National Report on Human Exposure to Environmental Chemicals (CDC, 2005).

Polychlorinated biphenyls (PCBs) are similar to dioxins and have been shown to be associated with diabetes in several studies (Longnecker et al., 2001; Glynn et al., 2003; Fierens et al., 2003; Rylander et al., 2005; Lee et al., 2006). Lee et al. (2006) investigated a common PCB marker, 2,2′,4,4′,5,5′-hexachlorobiphenyl (PCB 153) in the 1999–2002 NHANES. We investigated a coplanar biphenyl, 3,3′,4,4′,5-pentachlorobiphenyl (PCB 126). While Longnecker et al. (2001) and Fierens et al. (2003) evaluated general classes of serum PCBs, Glynn et al. (2003), Rylander et al. (2005), and Lee et al. (2006) looked specifically at PCB 153.

1,1,1-Trichloro-2,2-bis(*p*-chlorophenyl)ethane (*p,p*′-DDT), and 1,1,1-dichloro-2,2-bis(*p*-chlorophenyl)ethylene (*p,p*′-DDE) are also organochlorine chemicals. DDE is a metabolite of DDT. DDT has been banned in the US since 1972, while it was used in Mexico until the year 2000. Serum DDT levels are known to be high in the Hispanic community (CDC, 2005), but the significance of relatively high concentrations is not well understood. Morgan et al. (1980) found that serum DDT + DDE levels were 29% higher in persons having diabetes than in persons not having diabetes in a study of pesticide-exposed workers. However, serum DDT + DDE concentrations in Morgan et al.'s control group were much higher than those in the general population in 1999–2002 (CDC, 2005), and an assessment made 20 years later than Morgan et al. is warranted. Lee et al. (2006) investigated the association of DDE with diabetes in the 1999–2002 NHANES, and we investigated the relation of DDT with diabetes in the same data set.

2. Methods

Data used for this study were derived from the NHANES, 1999–2002. The NHANES 1999–2002 is a nationally representative sample of the noninstitutionalized US population. The NHANES design includes an oversampling of minorities and an ability to make population estimates. More information on the methodology of the NHANES 1999–2002, including laboratory assessment, can be found at the National Center for Health Statistics (NCHS) website (CDC, 2006a).

We investigated the association of three chemicals with diagnosed diabetes, undiagnosed diabetes and total diabetes (diagnosed plus undiagnosed). Diagnosed diabetes was assessed by self-report answer to the question: "Other than during pregnancy, have you ever been told by a doctor or health professional that you have diabetes or sugar diabetes?" Persons who answered "borderline" were considered to not have diabetes. Persons presumed to have Type 1 diabetes, that is were diagnosed with diabetes before the age of 30 and were only taking insulin, were excluded from our analyses. Undiagnosed diabetes was defined as persons who had glycohemoglobin (HbA1c) $>6.1\%$ who had not been diagnosed as having diabetes. HbA1c $>6.1\%$ predicts fasting plasma glucose $\geqslant 126$ mg/dl, the standard for determining diabetes, with a sensitivity of 63.2% and a specificity of 97.4% (Rohlfing et al., 2000). We did not use fasting plasma glucose for determination of undiagnosed diabetes because glucose was measured on a fasting subsample of participants and would have reduced the number of persons in our analyses by half. Total diabetes was defined as diagnosed plus undiagnosed diabetes.

A polychlorinated dibenzo-*p*-dioxin, a PCB, and *p,p*′-DDT were measured in nonfasting blood samples of a one third, stratified random, subsample of participants age 12 years and older. We evaluated persons in this subsample who were $\geqslant 20$ years old. The unweighted number of participants assessed for total diabetes was 2098 for HxCDD, 2090 for PCB 126, and 2163 for *p,p*′-DDT. When all three chemicals were evaluated together for total diabetes, the unweighted number of participants was 1830. We did not evaluate TCDD because the limit of detection was higher than nearly all of the measurements. HxCDD had a toxic equivalency factor (Van den Berg et al., 1998) less than that of TCDD, but greater than that of OCDD.

HxCDD, PCB 126, and *p,p*′-DDT were measured in serum by high-resolution gas chromatography/isotope-dilution high-resolution mass spectrometry. Values are expressed on a lipid adjusted basis (Akins et al., 1989). The (maximum) limit of detection was 20.1 pg/g lipid adjusted for HxCDD, 23.2 pg/g lipid adjusted for PCB 126, and 20.7 ng/g lipid adjusted for *p,p*′-DDT. For receiver operating characteristic (ROC) curve analyses, and linear regressions, values below the sample-specific limit of detection were set to the limit of detection divided by the square root of 2. For logistic regressions values below the (maximum) limit of detection were assigned to the lowest category.

ROC curve analyses were used to determine cut-points for the logistic regressions. The ROC curve analyses took into consideration the weights associated with each participant. The lower cut-point had the fewest false positive and false negative values for predicting diagnosed diabetes. When this value was below the (maximum) limit of detection (1 case), we used the (maximum) limit of detection as the lower cut-point. The upper cut-point was the value that produced 95% specificity for predicting diagnosed diabetes.

We tested the association of a dioxin, a PCB, and DDT with diagnosed diabetes, undiagnosed diabetes, and total diabetes in logistic regressions adjusted for age, gender, race, country of birth, education, poverty income ratio (PIR), body mass index (BMI), waist circumference, and physical activity. Race was classified as Non-Hispanic White, Non-Hispanic Black,

Mexican American, Other Race/Multi-Racial, and Other Hispanic. Country of birth was designated as being the US, Mexico, or elsewhere. Education was classified as either less than high school, or high school graduate/at least some college. PIR was analyzed as a continuous variable, and was the ratio of a family's income to their appropriate poverty threshold based on family size (US Census Bureau, 2004a). PIR was top coded at 5, and values below 1.00 were below the official poverty threshold (US Census Bureau, 2004b). BMI was derived from height and weight measurements (kg/m^2) collected in the NHANES physical examination. Waist circumference (cm) was also measured in the NHANES physical examination. Physical activity was defined as moderate or vigorous activity over the past 30 days, versus sedentary, from two questions (CDC, 2006a). Country of birth was used as a control variable because exposure to these chemicals differs by country. In particular, DDT was used in Mexico up until 2000, while it was banned in 1972 in the US. BMI and waist circumference were used as control variables because these chemicals are lipophilic.

In addition to testing the association of the three chemicals individually, we also evaluated a combined model predicting total diabetes with all three of the chemicals included at the same time. We then reran the combined model excluding persons with poor liver function and poor kidney function who might have impaired ability to metabolize and excrete one or more of these chemicals. Poor liver function was defined as alanine aminotransferase (ALT) >40 IU/L for men and >31 IU/L for women, or aspartate aminotransferase (AST) >37 IU/L for men and >31 IU/L for women (Clark et al., 2003). Poor kidney function was defined as estimated glomerular filtration rate (GFR) <100 ml/min per $1.73\,m^2$ for pregnant women and <60 ml/min per $1.73\,m^2$ for everyone else. Pregnant women have a GFR 40%–65% higher than prior to pregnancy (Conrad, 2004). Estimated GFR was calculated using the "reexpressed (2005) MDRD study equation" (Stevens et al., 2006) using serum creatinine concentration, age, gender, and race (black or non-black). Serum creatinine from the 1999–2000 NHANES was corrected using an equation developed by the Centers for Disease Control and Prevention (CDC, 2006b). No correction of serum creatinine from the 2001–2002 NHANES was needed. Excluding persons with poor liver function and poor kidney function removed 377 of 1604 unweighted persons without diabetes and 73 of 226 unweighted persons with either diagnosed diabetes or undiagnosed diabetes.

To further address the issue of metabolism and excretion of these chemicals being impaired in persons having diabetes, we performed linear regressions predicting levels of the three chemicals using the number of years the participants has had diabetes. We restricted these analyses to persons with either diagnosed or undiagnosed diabetes and set the number of years with diabetes to zero for persons with undiagnosed diabetes. Beta coefficients for the number of years with diabetes that were significantly greater than zero suggested metabolism and excretion of chemicals in question were increasingly impaired over time in participants having diabetes.

We used SUDAAN software, for most analyses, to allow us to make appropriate estimates from the complex sample design used in the NHANES (Research Triangle Institute, 2005). Our analysis incorporated both the stratification and clustering aspects of the sampling design. The proper weighting procedures include adjustments for nonresponse and poststratification. Since minorities were oversampled and a complex sampling design was employed, sampling weights provided by the NHANES for the dioxins subsample were used to compute population estimates based on weighted parameter estimates and standard errors (CDC, 2006a). Preliminary ROC curve analyses were performed using MedCalc software taking into consideration the weighting of the data.

3. Results

ROC curve analyses indicated an unadjusted (for covariates) association of the dioxin, PCB and DDT with diagnosed diabetes. Areas under the ROC curve were 0.654 for HxCDD, 0.697 for PCB 126 and 0.696 for *p,p′*-DDT. Each area under the ROC curve was significantly different from an area of 0.5. Cut-points selected using the ROC curve analyses are shown in Table 1.

Table 1 describes the adjusted association of the three chemicals with diagnosed diabetes and undiagnosed diabetes. All three compounds were significantly associated with diagnosed diabetes. HxCDD >42.0 pg/g lipid adjusted, PCB 126 >83.8 pg/g lipid adjusted, and *p,p′*-DDT >20.7 ng/g lipid adjusted had odds ratios for diagnosed diabetes of >2 compared to lower levels of these chemicals. HxCDD was not associated with undiagnosed diabetes, but PCB 126 and *p,p′*-DDT were.

Associations of the three chemicals with total diabetes are shown in Table 2. PCB 126 and *p,p′*-DDT were significantly associated with total diabetes. HxCDD was inconclusive in that intermediate level had an odds ratio significantly greater than that of the low level of the chemical, but the high level had an odds ratio that was no different from the low level.

When all three chemicals were included in a combined model, PCB 126 >83.8 pg/g lipid adjusted had an odds ratio of 2.57 (95% CI 1.33–4.95) compared to PCB 126 ⩽31.2 pg/g lipid adjusted. Both intermediate and high levels of *p,p′*-DDT were significantly associated with total diabetes in the combined model. Compared to *p,p′*-DDT ⩽20.7 ng/g lipid adjusted, *p,p′*-DDT of 20.8–26.6 ng/g lipid adjusted had an odds ratio of 2.52 (95% CI 1.26–5.02) and *p,p′*-DDT >26.6 ng/g lipid adjusted had an odds ratio of 2.74 (95% CI 1.44–5.23). HxCDD was not associated with total diabetes in the combined model.

When participants with poor liver function and poor kidney function were removed from the analysis, the combined model for total diabetes produced similar results with PCB 126 >83.8 pg/g lipid adjusted having an odds ratio of 2.45 (95% CI 1.23–4.90) compared to low levels of PCB 126. In addition, *p,p′*-DDT >26.6 ng/g lipid adjusted had an odds ratio of 2.56 (95% CI 1.03–6.33) and *p,p′*-DDT of 20.8–26.6 ng/g lipid adjusted had an odds ratio of 2.70 (95% CI 1.25–5.80) compared to low levels of *p,p′*-DDT when individuals with poor liver function and poor kidney function were excluded.

We also tested the combined model for total diabetes without BMI or waist circumference included as covariates to assess the effect of adiposity on our analysis. Removing BMI and waist circumference from the combined model increased the odds ratios for elevated PCB 126 and *p,p′*-DDT by 10%–30%. Further adjustment of our models for body composition using the NHANES bioelectrical impedance data would have been desirable, however only persons 8–49 years of age were evaluated in this manner.

Table 3 shows regression coefficients for equations relating years a person has had diabetes to levels of the dioxin, PCB and DDT. None of the chemicals had a beta coefficient significantly greater than zero, suggesting metabolism and excretion of these compounds was not increasingly impaired over time in participants having diabetes. PCB 126 had a nonsignificant beta coefficient of

Table 1
Adjusted association of a polychlorinated dibenzo-*p*-dioxin, a polychlorinated biphenyl, and DDT with diagnosed diabetes and undiagnosed diabetes[a]

	Diagnosed diabetes		Undiagnosed diabetes	
	Odds ratio	95% CI	Odds ratio	95% CI
HxCDD[b] pg/g lipid adjusted				
⩽42.0	1.00	—	1.00	—
42.1–99.1	2.43	1.22–4.83	0.87	0.40–1.91
>99.1	2.98	1.07–8.30	0.74	0.22–2.42
PCB 126[c] pg/g lipid adjusted				
⩽31.2	1.00	—	1.00	—
31.3–83.8	1.77	0.91–3.43	1.43	0.60–3.37
>83.8	3.28	1.73–6.22	3.32	1.15–9.58
p,p′-DDT[d] ng/g lipid adjusted				
⩽20.7	1.00	—	1.00	—
20.8–26.6	3.01	1.27–7.11	1.78	0.51–6.15
>26.6	2.14	1.03–4.46	2.58	1.25–5.33

[a]Logistic regressions adjusted for age, gender, race, country of birth, education, poverty income ratio, body mass index, waist circumference, and physical activity.
[b]1,2,3,6,7,8-Hexachlorodibenzo-*p*-dioxin.
[c]3,3′,4,4′,5-Pentachlorobiphenyl.
[d]1,1,1-Trichloro-2,2-bis(*p*-chlorophenyl)ethane.

Table 2
Adjusted association of a polychlorinated dibenzo-*p*-dioxin, a polychlorinated biphenyl, and DDT with total diabetes in separate and combined models[a]

	Total diabetes		Combined model for total diabetes	
	Odds ratio	95% CI	Odds ratio	95% CI
HxCDD[b] pg/g lipid adjusted				
⩽42.0	1.00	—	1.00	—
42.1–99.1	1.77	1.10–2.84	1.33	0.73–2.44
>99.1	1.99	0.91–4.37	1.14	0.49–2.66
PCB 126[c] pg/g lipid adjusted				
⩽31.2	1.00	—	1.00	—
31.3–83.8	1.67	1.03–2.71	1.36	0.78–2.40
>83.8	3.68	2.09–6.49	2.57	1.33–4.95
p,p′-DDT[d] ng/g lipid adjusted				
⩽20.7	1.00	—	1.00	—
20.8–26.6	2.69	1.35–5.36	2.52	1.26–5.02
>26.6	2.46	1.45–4.15	2.74	1.44–5.23

[a]Logistic regressions adjusted for age, gender, race, country of birth, education, poverty income ratio, body mass index, waist circumference, and physical activity. Combined model includes all three compounds as well as control variables.
[b]1,2,3,6,7,8-Hexachlorodibenzo-*p*-dioxin.
[c]3,3′,4,4′,5-Pentachlorobiphenyl.
[d]1,1,1-Trichloro-2,2-bis(*p*-chlorophenyl)ethane.

0.06, indicating PCB 126 levels would rise by only 1.2 pg/g lipid adjusted over 20 years. Nonsignificant beta coefficients for HxCDD and *p,p′*-DDT also indicated that levels of these chemicals would rise slowly if at all over a 20 year period.

4. Discussion

Our results are similar to those of Fierens et al. (2003) who found an association of coplanar PCBs with diabetes among 115 men and 142 women in Belgium. Longnecker (2006) suggested an association found between PCBs and diabetes in a prospective study (Vasiliu et al., 2006) was due to differences in metabolism and excretion. In our study, PCB 126 was significantly associated with undiagnosed diabetes. We assume persons with undiagnosed diabetes represent the most recent cases and would be the least likely to have impaired metabolism and excretion of PCB 126. In addition, PCB 126 remained significantly associated with total diabetes when participants with poor liver function and poor kidney function were removed from the analysis. These persons were the ones most likely

Table 3
Regression coefficients for equations using years a person has had diabetes to predict a polychlorinated dibenzo-*p*-dioxin, a polychlorinated biphenyl, and DDT among persons with diagnosed or undiagnosed diabetes[a]

	Beta[b]	95% CI	*P*[c]
1,2,3,6,7,8-Hexachlorodibenzo-*p*-dioxin	0.11	−0.55 to 0.77	0.74
3,3′,4,4′,5-Pentachlorobiphenyl (PCB 126)	0.06	−0.76 to 0.87	0.89
1,1,1-Trichloro-2,2-bis(*p*-chlorophenyl)ethane (*p,p*′-DDT)	0.06	−0.30 to 0.42	0.74

[a]Number of years a person has had diabetes set to zero for persons with undiagnosed diabetes.
[b]Beta for number of years a person has had diabetes.
[c]*P* value for significant difference from beta = 0.

to have impaired metabolism and excretion of PCB 126. Furthermore, the beta coefficient for the linear regression predicting PCB 126 using the number of years participants has had diabetes was not significant. This fact suggests the metabolism and excretion of PCB 126 was not increasing impaired over time in participants having diabetes.

Our finding that *p,p*′-DDT was associated with undiagnosed diabetes and total diabetes complements the results of Lee et al. (2006) who found *p,p*′-DDE to be associated with diabetes in the NHANES 1999–2002, and the results of Morgan et al. (1980) who evaluated the association of DDT/DDE exposure with diabetes. In the final analysis, we did not find an association of HxCDD with total diabetes. Other studies have shown associations between diabetes and dioxin exposure (Pazderova-Vejlupkova et al., 1981; Henriksen et al., 1997; Longnecker and Michalek, 2000; Cramner et al., 2000; Lee et al., 2006). Our study adds to the literature by reporting on a polychlorinated dibenzo-*p*-dioxin not previously investigated and by reporting associations of PCB 126 and *p,p*′-DDT with diabetes in a large sample of the US population.

Notably, the proportion of the US population having PCB 126 > 83.8 pg/g lipid adjusted was 5.48% and 29.24% of these persons had either diagnosed or undiagnosed diabetes. Similarly, the proportion of the US population having *p,p*′-DDT > 20.7 ng/g lipid adjusted was 7.01% and 28.87% of these persons had either diagnosed or undiagnosed diabetes. While our results suggest elevated levels of PCB 126 and *p,p*′-DDT may contribute to the development of diabetes, we cannot rule out the possibility that persons with diabetes retain more of these pollutants than persons not having diabetes. This study is a cross-sectional exploration; therefore, we cannot determine the temporal relationship or causality of these associations. We have attempted to control for possible differential storage of PCB 126 and *p,p*′-DDT by people with diabetes due to differences in obesity by controlling for BMI and waist circumference in the logistic regressions. These findings do confirm those of other epidemiologic studies that have shown a cross-sectional association between coplanar PCBs and diabetes (Fierens et al., 2003) and an association of DDT/DDE exposure with diabetes (Morgan et al., 1980). In addition, we add the strength of the most recent nationally representative data from the US population.

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