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Persistent organic pollutants in young adults and changes in glucose related metabolism over a 23-year follow-up

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ABSTRACT

Objectives: Substantial evidence associates persistent organic pollutants (POP) with metabolic disturbances related to diabetes, but longitudinal studies with repeated measures are scarce. We aimed to characterize the association between background exposures to POPs with repeated measures of glucose homeostasis over 23-years.

Methods: Within the Coronary Artery Risk Development in Young Adults study (year 0 ages: 18–30 years), we measured POPs in serum obtained in 1987–88 (follow-up year 2) in 90 non-diabetic controls and 90 cases diabetes-free at year 2 who became diabetic by year 20. We analyzed 32 POPs detectable in $\geq 75\%$ of participants and created summary scores for 32 POPs, 23 polychlorinated biphenyls (PCB), and 8 organochlorine pesticides (OCP). Dependent variables were measures of glucose homeostasis at years 0–25 (up to 8 examinations). We explored associations using repeated measures regression adjusted for race, sex, concurrent body mass index (BMI), examination center and period, separately for cases and controls.

Results: The associations between the three summary scores and measures of glucose homeostasis were present for observations at ages 40–55 years, and particularly between 48–55 years: the 23 PCB summary was associated with HbA1c (never-diabetics: slope [value per unit of summary score], $\beta=0.008$, $p=0.02$; diabetics: $\beta=0.03$, $p=0.07$), fasting glucose (never-diabetics: $\beta=0.24$, $p=0.003$; diabetics: $\beta=1.10$, $p=0.03$), and insulin sensitivity% (never-diabetics: $\beta=-2.82$, $p<0.001$, diabetics: $\beta=-0.31$, $p=0.30$). No associations were observed at younger ages.

Conclusions: Glucose homeostasis may worsen after decades of exposure to PCBs and OCPs at background environmental levels, independent of BMI and after participants reached the 5th decade of life.

1. Introduction

There is substantial in-vitro and in-vivo evidence that persistent organic pollutants (POPs) can act as endocrine disruptors and promote metabolic dysregulation (Lee et al., 2014). Recent studies showed that rats fed high-fat diets with POPs-contaminated salmon oils (compared to decontaminated salmon oil) (Ruzzin et al., 2010), and mice fed commercially farmed salmon filets contaminated with background POPs (compared to salmon specially raised to avoid POPs exposure) (Ibrahim et al., 2011) developed greater insulin resistance, abdominal obesity, and hepatosteatosis. In various population-based cross-sectional studies worldwide, exposure to several POPs at background concentrations (particularly polychlorinated biphenyls (PCB) and organochlorine pesticides) has been found to have strong positive associations with insulin resistance, pre-diabetes and diabetes after adjustment for confounders (Codru et al., 2007; Gasull et al., 2012; Lee et al., 2006, 2007a, 2007b; Uemura et al., 2008). Longitudinal studies in the

Abbreviations: AChE, acetylcholinesterase; POPs, persistent organic pollutants; PCB, polychlorinated biphenyl; CARDIA, Coronary Artery Risk Development in Young Adults; HbA1c, Hemoglobin-A1c; HOMA, Homeostasis Model Assessment; BMI, Body mass index; YALTA, Young Adults Longitudinal Trends in Atherosclerosis; OCP, organochlorine pesticides; PCB, polychlorinated biphenyl congeners; PBDE, polybrominated diphenyl ether; PBB, polybrominated biphenyl

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USA, Sweden, Taiwan and Italy have also reported significant associations of organochlorine pesticides and PCBs with incidence of diabetes (Lee et al., 2011a; Turyk et al., 2009; Vasiliu et al., 2006; Wang et al., 2008) and diabetes-related deaths (Bertazzi et al., 2001). Nevertheless, longitudinal studies with repeated measures are scarce. Such studies could greatly contribute to establish the temporal sequence of metabolic events following POPs exposure.

We previously described non-monotonic (specifically, inverted U-shaped) associations of organochlorine pesticide and PCB blood concentrations with diabetes in a case (diabetes)-control study nested within the Coronary Artery Risk Development in Young Adults (CARDIA) study ($n=180$) (Lee et al., 2010). Among controls, organochlorine pesticides and PCBs also had positive quadratic associations with BMI, triglycerides and insulin resistance, and negative associations with HDL-cholesterol 18 years after the measurement of POPs (Lee et al., 2011b). The reported inverted U-shaped associations of organochlorine pesticides and PCBs with diabetes support the hypothesis that high body burdens of endocrine disrupting chemicals can exert inhibitory effects on processes that are stimulated at much lower doses.

The present investigation further characterizes the associations between blood concentrations of POPs from background exposures in 1987–1988 and glucose dysregulation over the following 23 years among participants with and without diabetes of the CARDIA nested case-control study. Given the possibility of varying associations between POP exposures and glucose dysregulation at different stages of life (Lee et al., 2014), and considering increasing accumulation of POPs in tissues and higher prevalence of cardiovascular and endocrine alterations with age (particularly, after age 40) (National Center for Health Statistics, 2013), we tested the hypothesis that the associations between POPs and glucose dysregulation would be strongest among older individuals.

2. Materials and methods

2.1. Participant selection

In 1985–1986 (CARDIA year 0), CARDIA examined 5115 black and white participants 18–30 years of age, recruited from the general populations of Birmingham, AL, Minneapolis, MN, and Chicago, IL and from the Kaiser Permanente Medical Care Plan in Oakland, CA (Friedman et al., 1988; Hughes et al., 1987). Since year 0, there have been 7 follow-up examinations at years 2, 5, 7, 10, 15, 20 and 25 (2010–2011). The study was approved by the institutional review boards of the University of Minnesota, University of Alabama at Birmingham, Northwestern University, and the Division of Research at Kaiser Permanente Health Care Plan. Participants signed informed consent at every examination.

We included participants in the CARDIA nested case-control study (Lee et al., 2010). Ninety cases were randomly selected from among 116 people having taken anti-diabetic medications or having fasting glucose ≥ 126 mg/dl at two or more examinations after POPs exposure measurement in year 2 (CARDIA years 7, 10, 15 and 20), but having had no diagnosis of diabetes at years 0 and 2. Ninety controls were selected from those who had fasting glucose below 100 mg/dL at follow-up years 0, 7, 10, 15, and 20. Controls were frequency matched to cases, selected at random within several year 0 body mass index (BMI) categories (<20, 20–24.9, 25–29.9, 30–39.9, and 40+ kg/m^2).

Because the definition of controls required attendance at years 0, 7, 10, 15, and 20, they had little missing data in the current analyzes: only 6% ($n=5$) of controls did not attend the year 25 examination. Cases could be identified earlier than year 20, and missing follow-up examinations occurred in 11% ($n=10$) at year 7, 10% ($n=9$) at year 10, 17% ($n=15$) at year 15, 12% ($n=11$) at year 20 and 20% ($n=18$) at year 25.

2.2. Measures

Information regarding demographics, health behaviors and anthropometrics was obtained at baseline and follow-up examinations. Participants with diabetes were allowed to follow their usual diabetes treatment before and during the examination. Blood samples were collected after an overnight fast of at least 8 h. Hemoglobin-A1c (HbA1c), expressed as percent, was measured at the University of Minnesota using ion-exchange high-performance liquid chromatography at years 20 and 25. Fasting plasma glucose concentrations were determined using a hexokinase-ultraviolet method at Linco Research Inc. (now Millipore Inc., Billerica, MA, USA) at years 0, 7, 10, 15 and 20, and at the Molecular Epidemiology and Biomarker Research Laboratory (University of Minnesota) at year 25. Fasting insulin concentrations were measured at Linco Research at years 0, 7, 10, 15 and 20 by radioimmunoassay with an overnight equilibrium incubation using a high-specificity antibody ($<0.2\%$ cross-reactivity with human proinsulin and Des 31,32 proinsulin) (Haffner et al., 1994). Insulin was measured at the University of Minnesota at year 25 on a Roche Elecsys 2010 Analyzer (Roche Diagnostics, Indianapolis, IN) using a sandwich immunoassay method (Roche Diagnostics). Based on re-assays of glucose in December 2007 in approximately 200 samples stored since year 7, 10, 15, and 20, glucose concentrations were recalibrated to values provided by the National Institute of Standards and Technology. The insulin assay at year 20 was similarly recalibrated based on re-assay of year 15 samples; then all insulin values from years 0, 7, 10, 15, and 20 were further multiplied by 0.7049 to recalibrate to the values of the very precise immunoassay performed at year 25.

Percent insulin sensitivity and β-cell function were estimated using the updated Homeostasis Model Assessment (HOMA-2) calculator (University of Oxford, Oxford, UK, http://www.dtu.ox.ac.uk/homacalculator/). HOMA-2 is a steady-state prediction of insulin resistance and β-cell function for many plausible combinations of fasting glucose and insulin concentrations, which accounts for renal glucose losses and assumes reduced suppression of hepatic glucose production and increased insulin secretion at high glucose concentrations (Muniyappa et al., 2008). We have smaller sample sizes for most exam years when assessing HOMA-2 calculations because of missing insulin or glucose measurements: 19 participants had missing information for year 0, 9 for year 7, 5 for year 10, 2 for year 15, 1 for year 20 and 3 for year 25. We also excluded two participants at year 25 for HOMA-2 calculations for having an insulin value or a glucose value exceeding the accepted range for HOMA-2 calculations (insulin upper limit: 43.2 μIU/ml [300 pmol/L], glucose upper limit: 450 mg/dl [25 mmol/L]). In the present sample, BMI has a correlation of 0.87 with waist circumference. For the purpose of estimating the association between exposures to POPs and (an estimate of) fatness, we considered that presenting results for BMI would suffice given its equivalent correlation with fat mass (≈ 0.90) compared to that of waist circumference (Camhi et al., 2011).

POP concentrations in stored CARDIA year 2 serum samples (collected in 1987 and 1988) were measured in 2008 as part of the Young Adults Longitudinal Trends in Atherosclerosis (YALTA) ancillary study to CARDIA. Analyses were performed using solid-phase extraction and final determination using gas chromatography isotope dilution high-resolution mass spectrometry (Barr et al., 2003; Sjödin et al., 2004) at the Centers for Disease Control Environmental Health Laboratory. A total of 55 POPs were measured: 9 organochlorine pesticides, 35 PCB congeners, 10 polybrominated diphenyl ether (PBDE) congeners, and 1 polybrominated biphenyl (PBB) congener. Of the 55