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Persistent organic pollutants are related to the change in circulating lipid levels during a 5 year follow-up

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ABSTRACT

When reporting circulating levels of persistent organic pollutants (POPs), usually lipid-normalized values are given. However, animal experiments and some human data indicate that exposure to POPs may change lipid values. The aim of the present study is to investigate if POP levels can predict future changes in levels of circulating lipids. In the population-based Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study, lipids were measured at age 70 and at age 75 in 598 subjects without lipid-lowering medication. Twenty-three different POPs, including 16 polychlorinated biphenyls (PCBs), five organochlorine pesticides, one dioxin (OCDD) and one flame retardant brominated compound (BDE47) were analyzed by high-resolution chromatography coupled to high-resolution mass spectrometry (HRGC/HRMS) at age 70. Strong relationships were seen among the baseline levels of the non-dioxin-like PCBs 194, 206 and 209 and the degree of increase in total serum cholesterol and LDL-cholesterol during the 5 year follow-up. These relationships were generally stronger when lipid-normalized levels were used compared to wet-weight based levels. On the contrary, for two of the pesticides, hexachlorobenzene and trans-nonachlordane, levels were inversely related to the change in LDL-cholesterol, with strongest associations found using wet-weight based levels. PCBs 194, 206 and 209 were inversely related to the change in HDL-cholesterol, in particular for wet-weight based levels. However, these relationships were only significant for wet-weight PCB 194 following adjustment for multiple testing. None of the POPs was related to the change in serum triglycerides. When investigating the association between the change in total serum cholesterol and LDL-cholesterol across different categories of change in BMI, we noted robust results especially in the group with stable BMI, suggesting that the observed relationships were not due to fluctuations in BMI over time. In conclusion, POPs are related to the change in lipids over time, especially LDL-cholesterol. This may explain why POP exposure previously has been linked to atherosclerosis and cardiovascular disease.

1. Introduction

Persistent organic pollutants (POPs) are highly lipophilic chemicals that accumulate in adipose tissues due to long half-lives of the compounds and their metabolites. A number of POPs have been identified as deleterious for health and have been listed at the Stockholm convention. Amongst those are organochlorine pesticides, such as hexachlorobenzene (HCB) (Annex A) and *p*,*p*′-DDE (Annex B), different chlordanes, PCBs, dioxins, brominated flame retardants and fluorinated compounds.

Circulating lipid levels are important biomarkers of the risk to develop atherosclerosis and cardiovascular disease (CVD), and a lowering of population mean cholesterol levels can predict major benefits regarding the risk of death due to coronary heart disease (Huffman et al., 2013). High total cholesterol and LDL cholesterol levels are associated with increased risk of coronary artery disease (CAD), whereas high HDL cholesterol levels have been associated with reduced risk of CAD (Castelli, 1988; Clarke et al., 2007). Therefore, investigating factors that might alter lipid levels should be prioritized in order to reduce and prevent disease.

Abbreviations: BDE, brominated biphenyl ether; BMI, body mass index; HCB, hexachlorobenzene; HRGC/HRMS, high-resolution chromatography coupled to high-resolution mass spectrometry; IQR, interquartile range; OC, organochlorine; POP, persistent organic pollutant; OCDD, octachlorodibenzo-*p*-dioxin; PCB, polychlorinated biphenyl; *p*,*p*′-DDE, 2,2-Bis (4-chlorophenyl)-1,1-dichloroethene; HDL, high density lipoprotein; LDL, low density lipoprotein; TG, triglyceride; TNC, trans-nonachlordane; TSC, total serum cholesterol

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A number of different studies report associations between POP exposure and elevations in serum lipid levels. For example in vitro studies have reported increased levels of lipid parameters in response to exposure to organic pollutants (Rogers et al., 1983; Taxvig et al., 2012). Also animal studies have found increased lipid parameter levels after exposure to PCBs (Bell et al., 1994; Boll et al., 1996; Kato et al., 1981; Lind et al., 2004) although higher PCB levels were found inhibitory on serum lipid levels (Boll et al., 1996). In humans, similar findings have been reported for various organic pollutants (Baker et al., 1980; Goncharov et al., 2008), often in occupationally exposed individuals (Chase et al., 1982; Martin, 1984). Also, epidemiological studies of the general population have addressed the association between organic pollutants and CVD or CVD risk factors (Lee et al., 2012; Lind et al., 2012; Olsen et al., 2012; Sergeev and Carpenter, 2005). Unfortunately, longitudinal studies in humans lack in addressing the association between POP exposures and changes in lipid levels.

By convention, the circulating levels of persistent organic pollutants (POPs) are normalized for lipids, since many of these compounds are lipid soluble, are transported by lipoproteins and accumulate in adipose tissue (Noren et al., 1999; Rylander et al., 2006). However, animal studies suggest that exposure to POPs may alter lipid metabolism and thereby alter the circulating lipid levels and adipose tissue weight (Bell et al., 1994; Lakshman et al., 1988; Lind et al., 2004). In addition, species differences have been observed for the relationship between POP exposure and lipid metabolism and very few data on these possibly negative health effects exist in humans. Therefore, we hypothesized that human subjects with higher POP levels would experience an altered pattern regarding changes in lipid levels over time compared to those with lower POP levels, regardless of POP levels were lipid-normalized or not. To test this hypothesis, we used data from a sample of elderly individuals included in the population-based Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. Circulating levels of 23 different POPs were measured together with circulating lipids at the age of 70. The subjects were invited to a new visit, including measurements of circulating lipids, 5 years later. Specifically, this study investigates the association between baseline circulating POP levels and the 5-year change in serum cholesterol, triglycerides, LDL-cholesterol and HDL-cholesterol concentration, respectively.

2. Material and methods

2.1. Study population

Eligible were all men and women aged 70 living in the community of Uppsala, Sweden. The study subjects were chosen from the register of community living and were invited in a randomized order. They received an invitation by letter within 2 months of their 70th birthday. Of the 2025 men and women invited, 1016 persons (including 50.2% women) participated in the Prospective Investigation of the Vasculature in Uppsala (PIVUS) study, giving a participation rate of 50.1%. The baseline investigation was started in April 2001. Details of the PIVUS study have been presented (Lind et al., 2005). The study was approved by the Ethics Committee of Uppsala University and the participants gave written informed consent prior to their participation in the study.

2.2. Clinical Investigation at enrollment and follow-up

The participants were asked to answer a questionnaire about their medical history, education level, exercise habits, smoking habits and regular medication. All participants were investigated in the morning after an over-night fast and venous blood samples were drawn between 8 and 10 a.m. The blood samples for POP analyses were stored at $-70\ ^{\circ}\mathrm{C}$ until analysis while lipid variables were measured the same day as blood was drawn. No medication or smoking was allowed after midnight. BMI was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Educational level was divided into three groups (<9, 9–12, and >12 years of education). Exercise habits were divided into four groups (less than two times per week of light exercise [no sweat], two or more times per week of light exercise, one to two times per week of heavy exercise [sweat], and more than two times per week of heavy exercise). Smoking status was dichotomized as current smoker at 70 and at 75, respectively; yes/no. Further details have been presented elsewhere (Lind et al., 2005). The lipid variables HDL-cholesterol and triglycerides were measured on an Architect Ci8200 analyzer (Abbott Laboratories, Abbott Park, Ill., USA). LDL-cholesterol was calculated from total serum cholesterol, serum triglycerides and HDL-cholesterol by the Friedewald's formula (Friedewald et al., 1972); LDL-cholesterol = total plasma cholesterol − HDL-cholesterol − (triglycerides/5) where the last term relates to the cholesterol in plasma attributable to very low density lipoprotein (VLDL).

The cohort was invited to a re-examination one month after their 75th birthday, which 827 (81%) individuals attended. From March 2006 to September 2009, when the subjects became 75, reinvestigation of the cohort was performed with follow-up rate of 81.4%. No information was available concerning 1009 nonparticipants. When comparing demographic and clinical characteristics between study participants and subjects lost to follow-up, participants were less likely current smokers at 70 years of age (9% versus 19%), exercised more (categories 3 and 4: 28% versus 17%) and were more educated (category 3: 26% versus 20%) compared to subjects not available for follow-up whereas gender distribution (52% versus 49%) and BMI at 70 (26.9 versus 26.6 kg/m^2) were similar. The plasma concentrations of POPs at baseline were fairly similar between two groups. For example, when comparing participants and subjects not available at follow up PCB 194 levels had a median concentration of 118.9 (IQR 85.2, 157) and 124.4 (IQR 89.6, 158.2), respectively. For PCB 209 the levels were 25.8 (IQR 19.5, 34.7) and 26 (IQR 18.8, 33.2), respectively. The time between the examinations was 5.13 (SD 0.10) years. The baseline examination performed at age 70 was repeated. The 5-year follow-up was completed in September 2009. Following exclusion of subjects on regular medication with lipid-lowering drugs either at age 70 or at age 75 which would distort the evaluation of changes in lipid levels, 598 subjects with lipid data both at ages 70 and 75 years were included in the analysis.

2.3. POP analyses

POPs were measured in stored serum samples collected at baseline. Analyses of POPs were performed using Micromass Autospec Ultima (Waters, Milford, MA, USA) high-resolution chromatography coupled to high-resolution mass spectrometry (HRGC/HRMS). All details on POP analyses have been reported elsewhere (Salihovic et al., 2012). A total of 23 POPs were measured: 16 polychlorinated biphenyls (PCBs), five organochlorine (OC) pesticides, one octachlorodibenzo-*p*-dioxin (OCDD), and one flame retardant, brominated biphenyl ether (BDE). Among the 23 POPs measured, two OC pesticides (*trans*-chlordane and *cis*-chlordane) with detection rates $<10\%$ were not included in the final results/statistical analyses. An established summation formula based on total serum cholesterol and serum triglyceride concentrations was used to calculate the total amount of lipids in each plasma sample (Rylander et al., 2006). Thereafter the wet-weight concentrations of the POPs were divided by this estimation of lipids to obtain lipid-normalized values. Median values and interquartile ranges (IQR) for wet-weight and lipid-normalized levels for the POPs studied are given in Table 2.

2.4. Statistical analyses

All POPs were skewed towards high levels but natural log transformation of the POPs reduced the influence of observations far out in the tails and gave more normally distributed residuals, as assessed visually by distribution plots (data not shown). Relationships between POP levels and changes in lipid levels over the 5 year follow-up period were evaluated by multivariable linear regression models, first using wet-weight concentrations of log transformed POPs, and thereafter lipid-normalized log transformed POP concentrations. The regression analyses were performed with the change in cholesterol, triglycerides, HDL-cholesterol and LDL-cholesterol as dependent variables, respectively, against the independent variables (i.e. wet-weight or lipid-normalized log transformed POP concentrations) adjusting for variables selected as potential factors influencing the change in lipid levels and varying with the POP concentrations; gender, exercise habits at enrollment (4 categories), education level (three categories), smoker at enrollment, BMI at 70 years and change in BMI over the 5 year study period. The potential confounders were evaluated in univariate analysis against the four outcomes. In addition, the regression models were adjusted for percentage of fat intake in the diet and average daily calorie intake (kcal) which was based on data in individual week-long food diaries. In the wet-weight analyses, the linear regression models were further adjusted for total lipid content. Non-linear relationships between the outcomes and the exposures were investigated by adding the squared POP value as an independent variable in the adjusted models. Since a large number of tests were performed, we set the level of significance to $p<0.001$ instead of <0.05 to avoid false positive results due to multiple testing.

Sensitivity analyses were performed for changes in cholesterol and LDL-cholesterol by investigating whether the relationship between lipid-normalized POP levels and changes in lipid levels was affected by the BMI change status over the five year follow-up; stable BMI (± 1 kg/m^2), decreased BMI (>1 kg/m^2 lower BMI), and increased BMI (>1 kg/m^2 higher BMI). The models for each outcome