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Mixture effects of 30 environmental contaminants on incident metabolic syndrome—A prospective study

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ABSTRACT

Background: Several cross-sectional studies have linked different environmental contaminants to the metabolic syndrome (MetS). However, mixture effects have not been investigated and no prospective studies exist regarding environmental contaminants and the MetS.

Objectives: To study mixture effects of contaminants on the risk of incident MetS in a prospective fashion.

Methods: Our sample consisted of 452 subjects from the Prospective Study of the Vasculature in Uppsala Seniors (PIVUS) study (50% women, all aged 70 years) free from the MetS at baseline, being followed for 10 years. At baseline, 30 different environmental contaminants were measured; 6 polychlorinated biphenyls (PCBs), 3 organochlorine (OC) pesticides, one dioxin, one polybrominated diphenyl ether (all in plasma), 8 perfluoroalkyl substances (in plasma) and 11 metals (in whole blood). The MetS was defined by the ATPIII/NCEP criteria. Gradient boosted Classification and Regression Trees (CARTs) was used to evaluate potential synergistic and additive mixture effects on incident MetS.

Results: During 10-year follow-up, 92 incident cases of the MetS occurred. PCB126, PCB170, hexachlorobenzene (HCB) and PCB118 levels were all associated with incident MetS in an additive fashion (OR 1.73 for a change from 10th to 90th percentile (95%CI 1.24–3.04) for PCB126, OR 0.63 (0.42–0.78) for PCB170, OR 1.44 (1.09–2.20) for HCB and OR 1.46 (1.13–2.43) for PCB118). No synergistic effects were found.

Conclusion: A mixture of environmental contaminants, with PCB126, PCB170, HCB and PCB118 being the most important, showed associations with future development of the MetS in an additive fashion in this prospective study. Thus, mixture effects of environmental contaminants could contribute to the development of cardio-metabolic derangements.

1. Introduction

The metabolic syndrome (MetS) is a term used to define subjects with multiple cardiovascular (CV) risk factors, like hypertension, diabetes/impaired glucose tolerance, visceral obesity, low HDL-cholesterol and high serum triglycerides. The MetS was described in the late 1980s by different groups (Reaven, 1988) (Lind et al., 1988), and the clustering of the CV risk factors have been suggested to be due to visceral obesity and/or insulin resistance. Having the MetS approximately doubles your risk of future CV disease (Sundstrom et al., 2006).

In the last decade it has become apparent that environmental contaminants could play a role in the development of cardio-metabolic diseases (Lind and Lind, 2012; Lind et al., 2016). A number of environmental contaminants have been linked to obesity, diabetes, hypertension and disturbances in lipid metabolism (Goncharov, Haase et al., 2008, Gaskins and Schisterman, 2009, Lee et al., 2011, Lee et al., 2012, Lind et al., 2012, Patel et al., 2012, Fisher et al., 2013, Lind, Zethelius et al. 2014, Lind, Penell et al. 2014, Penell et al., 2014), as well as to the metabolic syndrome in itself (Lee et al., 2007; Uemura et al., 2009; Park et al., 2010; Teppala et al., 2012; Fisher et al., 2013; Lind et al., 2013).

However, previous reports on a link between environmental contaminants and the MetS have used a cross-sectional design, which has the possibility of being biased by reverse causation. Furthermore, these studies have not taken into account that multiple environmental contaminants interfere with each other in the population setting; in previous studies the contaminants are usually evaluated one by one.

In the present study, we addressed some of these shortcomings of

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previous investigations in that we studied the effect of a mixture of environmental contaminants on incident MetS in a prospective fashion. We used the Prospective Study of the Vasculature in Uppsala Seniors (PIVUS) study (Lind et al., 2005), in which we have evaluated 30 different environmental contaminants and have followed the cohort for 10 years regarding the development of the MetS. The hypothesis tested was that several contaminants would be associated with incident MetS, either in an additive or a synergistic fashion. We tested this hypothesis by using gradient-boosted CARTs, a statistical method previously deemed suitable for studies of mixture effects of environmental contaminants (Lampa et al., 2014).

2. Material and methods

2.1. Subjects

Eligible subjects were all aged 70 and lived in the city of Uppsala, Sweden, a city of 185,000 inhabitants. The subjects were randomly chosen from the register of community living. A total of 1016 subjects participated, entailing a participation rate of 50.1%. The prevalence of the MetS at baseline was 23% in the total cohort. These subjects were invited to a follow-up examination 10 years later, and 606 individuals participated in this follow-up. Following exclusion of 154 subjects who showed the MetS at baseline, 452 subjects were included in the final analyses (being free from the MetS at baseline and participating in the 10-year follow-up).

The study was approved by the Ethics Committee of Uppsala University, and all the participants gave their informed consent prior to the study.

All subjects were investigated in the fasting state in the morning after an overnight fast. Between 8 and 10 am venous samples of whole blood, serum and plasma were collected. The whole blood and plasma samples were collected in EDTA-tubes, while serum was collected in tubes free from additives. After approximately 1 h, the serum was removed to plastic tubes free from additives and the samples were put into a −80C freezer. The plasma tubes were spinned and plasma was removed to plastic tubes free from additives and the samples were put into a −80C freezer within 1 h. Whole blood was removed from the EDTA-tubes to plastic tubes free from additives and the samples were put into a −80C freezer within 1 h. The samples were kept in −80C until analysis. The samples were later shipped to different laboratories using dry ice to keep them in the frozen state.

No medication or smoking was allowed after midnight. The participants were asked to answer a questionnaire about their medical history, smoking habits and regular medication.

Blood pressure was measured three times by a calibrated mercury sphygmomanometer to the nearest mmHg following at least 30 min of rest. The mean of these three recordings were used. Lipid variables and fasting blood glucose were measured by standard laboratory techniques the same day using unfrozen samples (Carlsson et al., 2010).

These examinations were performed in the same fashion both at age 70 and at age 80 years.

Basic characteristics are presented in Table 1 in the Results section.

Results of the measurements of the 30 environmental contaminants at age 70 are shown in Table 2 in the Results section. The collection of blood samples for the measurements of the environmental contaminants and the other examinations at age 70 was performed on the same day.

2.2. Chemical analysis

2.2.1. Metals

All 11 metal elements in this study were determined in whole blood at a commercial laboratory (ALS Scandinavia, Luleå, Sweden). The analysis was performed using inductively coupled plasma-sector field mass spectrometry, ICP-SFMS, after microwave-assisted digestion with

Table 1
Means (and SD) or proportions (in %) for major cardiovascular risk factors at age 70 and 80 years in the sample. n = 452. NE = not evaluated. For more detailed definitions of exercise levels, please see the Methods section.

	Age 70	Age 80
Variable	Mean (SD)	Mean (SD)
Systolic blood pressure (mm Hg)	147.1 (22.4)	145.7 (19.1)
Diastolic blood pressure (mm Hg)	77.9 (9.8)	73.5 (8.9)
Fasting blood glucose (mmol/L)	5.0 (0.8)	5.1 (1.1)
Waist circumference (cm)	89.1 (10)	94.6 (11.1)
HDL-cholesterol (mmol/L)	1.6 (0.4)	1.4 (0.4)
Serum triglycerides (mmol/L)	1.1 (0.4)	1.1 (0.5)
LDL-cholesterol (mmol/L)	3.4 (0.8)	3.2 (0.9)
Current smoking (%)	8.4	3.4
Education level	< 10 years: 51% 10–12 years: 19% > 12 years: 30%	NE
Exercise habits (per week)	Sedentary: 9% Light exercise only: 56% 1–2 times heavy exercise per week: 27% > 2 times heavy exercise per week: 8%	NE
Alcohol intake (g/day)	7.6 (8.1)	NE
Energy intake (kcal/day)	1921 (481)	NE
Fat intake (% of total energy intake)	32	NE
Metabolic syndrome (%)	0	20
Antihypertensive treatment (%)	22	55

Table 2
Medians and 10th and 90th percentile for the 30 evaluated environmental contaminants in the present sample (n = 452). Wet-weight data are given.

Variable	Median (10th and 90th percentile)
PCB-118 (2,3′,4,4′,5-pentachlorobiphenyl) (pg/mL)	197.2 (92, 364.2)
PCB-126 (3,3′,4,4′,5-pentachlorobiphenyl) (pg/mL)	39.8 (12.4, 112.6)
PCB-153 (2,2′,4,4′,5,5′-hexachlorobiphenyl) (pg/mL)	1394 (809, 2289.8)
PCB-169 (3,3′,4,4′,5,5′-hexachlorobiphenyl (pg/mL)	173 (102.6, 289)
PCB-170 (2,2′,3,4,4′,5,5′-heptachlorobiphenyl) (pg/mL)	494 (302.2, 787.6)
PCB-209 (2,2′,3,3′,4,4′,5,5′,6,6′-decachlorobiphenyl) (pg/mL)	26.6 (14.6, 44.8)
HCB (hexachlorobenzene) (pg/mL)	245.4 (145.2, 424.8)
OCDD (octachlorodibenzo-*p*-dioxin) (pg/mL)	2.4 (1.3, 5.8)
TNC (*trans*-nonachlor) (pg/mL)	132.4 (60, 270.8)
p,p′-DDE (pg/mL) (2,2-bis (4-chlorophenyl)-1,1-dichloroethene)	1613.6 (475.2, 5265.8)
BDE-47 (bromodiphenyl ether) (pg/mL)	12.6 (9, 32.4)
PFHpA (perfluoroheptanoic acid) (ng/mL)	0.1 (0, 0.1)
PFHxS (perfluorohexane sulfonic acid) (ng/mL)	2.2 (1.2, 8.5)
L-PFOS (linear-perfluorooctane sulfonic acid isomer) (ng/mL)	13.8 (7.7, 25.4)
PFOA (perfluorooctanoic acid) (ng/mL)	3.5 (2, 5.7)
PFNA (perfluorononanoic acid) (ng/mL)	0.7 (0.4, 1.4)
PFDA (perfluorodecanoic acid) (ng/mL)	0.3 (0.2, 0.6)
PFOSA (perfluorooctane sulfonamide) (ng/mL)	0.1 (0.1, 0.3)
PFUnDA (perfluoroundecanoic acid) (ng/mL)	0.3 (0.1, 0.5)
Al (aluminium) (μmol/L)	0.6 (0.4, 1)
Cd (cadmium) (nmol/L)	2.3 (1.3, 5.1)
Co (cobalt) (nmol/L)	1.4 (0.8, 2.8)
Cr (chromium) (nmol/L)	11.7 (8.1, 29.4)
Cu (copper) (nmol/L)	12.6 (10.6, 15.3)
Hg (mercury) (nmol/L)	9.7 (4.1, 22.4)
Mn (manganese) (nmol/L)	138.5 (93.7, 200)
Mo (molybdenum) (nmol/L)	9.7 (6.6, 15.3)
Ni (nickel) (nmol/L)	89.4 (15.7, 429)
Pb (lead) (μmol/L)	0.1 (0, 0.1)
Zn (zink) (μmol/L)	95.5 (78, 113)