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Prenatal exposure to persistent organic pollutants and cognition and motor performance in adolescence

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ABSTRACT

Background: Prenatal exposure to persistent organic pollutants (POPs), such as polychlorinated biphenyls (PCBs), was found to be associated with poorer neurological development in children. Knowledge about the effects on outcomes until adolescence is limited.

Objectives: To determine whether prenatal exposure to POPs, particularly hydroxylated PCBs (OH-PCBs), is associated with cognitive and motor development in 13- to 15-year-old children.

Methods: This prospective observational cohort study is part of the Development at Adolescence and Chemical Exposure (DACE)-study, a follow-up of two Dutch birth cohorts. Maternal pregnancy serum levels of PCB-153 and three OH-PCBs were measured, in part of the cohort also nine other PCBs and three OH-PCBs, and in another part five polybrominated diphenyl ethers (PBDEs), dichloroethene (DDE), pentachlorophenol (PCP) and hexabroomcyclododecane (HBCDD). Of the 188 invited adolescents, 101 (53.7%) participated, 55 were boys. Cognition (intelligence, attention, verbal memory) and motor performance (fine motor, ball skills, balance) were assessed. Scores were classified into 'normal' (IQ > 85; scores > P15) and '(sub)clinical' (IQ ≤ 85; scores ≤ P15). We used linear and logistic regression analyses, and adjusted for maternal education, maternal smoking, maternal alcohol use, breast feeding, and age at examination.

Results: Several OH-PCBs were associated with more optimal sustained attention and balance. PCB-183 was associated with lower total intelligence (OR: 1.29; 95%CI:0.99–1.68; *P* = .060), and HBCDD with lower performance intelligence (OR: 3.62; 95%CI:0.97–13.49; *P* = .056). PCBs, OH-PCBs and PBDEs were negatively associated with verbal memory.

Conclusions: Prenatal background exposure to several POPs can influence neuropsychological outcomes in 13- to 15-year-old Dutch adolescents, although exposure to most compounds does not have clinically relevant consequences at adolescence.

1. Introduction

Persistent organic pollutants (POPs) are man-made chemicals, used for application in a variety of products like flame-retardants, solvents, and pesticides. Despite the fact that the production and use of these chemicals are banned by law, there is still exposure to these compounds. Because POPs, for example polychlorinated biphenyls (PCBs), can be transferred from the mother to the fetus during pregnancy, fetuses are exposed to these chemicals during a critical time of development of the brain (Soechitram et al., 2004). Follow-up studies showed conflicting results, with some studies indicating associations between prenatal exposure to POPs and neurodevelopmental outcome in children whereas other studies found no associations (Berghuis et al., 2015).

Prenatal exposure to PCBs was found to be associated with an increase of attention-deficit/hyperactivity disorder (ADHD)-like behaviors in children (Neugebauer et al., 2015; Polańska et al., 2013), less optimal long-term memory in adolescents (Newman et al., 2009), and lower intelligence levels in children (Chen et al., 1992; Lai et al., 2002). In contrast, some other studies found no associations between prenatal exposure to PCBs and attention in adolescents (Lee et al., 2007; Newman et al., 2014; Strøm et al., 2014), memory in children at school

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; AVLT, Auditory Verbal Learning Test DDE: dichloroethene; HBCDD, hexabroomcyclododecane; Movement-ABC, Movement Assessment Battery for Children; OH-PCB, hydroxylated polychlorinated biphenyl; PBDE, polybrominated diphenyl ether; PCB, polychlorinated biphenyl; PCP, pentachlorophenol; POP, persistent organic pollutant; TEA-Ch, Test of Everyday Attention for Children; WISC, Wechsler Intelligence Scale for Children

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age (Orenstein et al., 2014), and learning in 12- to 15-year-old adolescents (Lee et al., 2007).

Prenatal exposure to polybrominated diphenyl ethers (PBDEs) was found to be associated with lower intelligence levels (Zhang et al., 2017) and reduced motor speed (Kicinski et al., 2012). Prenatal exposure to dichlorodiphenyldichloroethylene (DDE) was found to be associated with ADHD-like behaviors in 7- to 11-year-old children (Sagiv et al., 2010), and several other studies found no association with intelligence after higher exposure to DDE (Gaspar et al., 2015; Lee et al., 2007).

Previously, in children included in the cohort of this study, we observed less optimal motor development and poorer visuomotor function at three months of age, and poorer fine manipulative skills at the age of five to six years after higher prenatal exposure to the hydroxylated metabolites of PCBs (OH-PCBs) (Berghuis et al., 2013; Berghuis et al., 2014; Roze et al., 2009). Because we observed negative effects of prenatal exposure to OH-PCBs, we aimed to determine whether the observed effects persist until adolescence. To our knowledge, no study has been published on the associations between prenatal exposure to OH-PCBs and cognitive and motor outcome in adolescence. Studies on the long-term effects into adolescence of prenatal exposure to POPs, particularly on motor outcome, are sparse. Therefore, the aim of this exploratory study was to investigate whether prenatal exposure to POPs, including OH-PCBs, is associated with cognitive and motor outcome in 13- to 15- year-old adolescents.

2. Materials and methods

2.1. Cohort and study design

This longitudinal cohort study is part of the Development at Adolescence and Chemical Exposure (DACE)-study, in which we followed-up two Dutch cohorts. In the cohort of the Risk of Endocrine Contaminants on human health (RENCO)-study, 104 mother-infant pairs were included between 1998 and 2000 (Soechitram et al., 2004). In the cohort of Groningen-Infant-COMPARE (Comparison of Exposure-Effect Pathways to Improve the Assessment of Human Health Risks of Complex Environmental Mixtures of Organohalogens)-study, also known as GIC-study, 90 mother-infant pairs were included between 2001and 2002 (Meijer et al., 2008). Children of both cohorts were invited for participation in the DACE-study during adolescence. Six children were not invited: four had no available prenatal POP-levels, one had been diagnosed with a congenital syndrome after initial inclusion in the cohort, and one had moved abroad. A reminder was sent in case of no response. The children were all singleton children, and born at term (37–42 weeks' gestation) without congenital anomalies or diseases. Their mothers are of Western European origin, and had no serious illnesses or complications during pregnancy or delivery. At time of follow-up, all children were between 13 and 15 years (inclusion periods were between April 2014 and December 2014, and between October 2015 and August 2016). All adolescents and their parents provided their written informed consent before participation in the follow-up program. The follow-up and the original study were approved by the Medical Ethics Committee of the University Medical Center Groningen.

2.2. Measurement of prenatal POP-levels

Levels of several POPs were measured in maternal serum samples collected during the second and/or third trimester of pregnancy. Detailed descriptions of the analyses have been published previously (Meijer et al., 2008; Soechitram et al., 2004). In both cohorts, levels of PCB-153, 4-OH-PCB-107, 4-OH-PCB-146, and 4-OH-PCB-187 were measured. In the RENCO-study, also nine other PCBs (105; 118; 138; 146; 156; 170; 180; 183; 187) and three other OH-PCBs (3-OH-PCB-153; 3′-OH-PCB-138; 4′-OH-PCB-172) were measured, and the sums of all measured 10 PCBs and 6 OH-PCBs were calculated. In the GIC-study, in addition, the following POPs were measured: five different 2,2′,4,4′-tetrabromodiphenyl ethers (BDEs), 2,2′-bis-(4 chlorophenyl)-1,1′-dichloroethene (*p*,*p*′-DDE), pentachlorophenol (PCP), and hexabroomcyclododecane (HBCDD). PCBs and OH-PCBs were numbered according to Ballschmiter et al. (1993) and to Letcher et al. (2000) respectively. PCB-levels are given in nanograms per gram lipid, and OH-PCB-levels in picograms per gram fresh weight.

2.3. Cognitive and motor outcomes

Total, verbal and performance intelligence were assessed using a shortened form of the Wechsler Intelligence Scale for Children, third edition, Dutch version (WISC-III-NL) (Kort et al., 2002). Verbal intelligence quotients (IQ) were calculated based on subtests on vocabulary and analogies; performance IQs were calculated based on subtests on organizing pictures and block design assembly. Auditory-verbal memory was assessed using a standardized Dutch version of the Rey's Auditory Verbal Learning Test (AVLT) (van den Burg and Kingma, 1999). This test consists of five learning trials with immediate recall (learning capacity), a delayed recall trial (long-term retrieval) and a delayed recognition trial (long-term recognition). Sustained auditory attention and selective visual attention were measured using the subtests ‘Score!’ and ‘Sky Search’ of the Test of Everyday Attention for Children, Dutch Version (TEA-Ch-NL), respectively (Schittekatte et al., 2007). Sustained attention involves maintaining attention over an extended period of time. Selective attention refers to the ability to select target information from an array of distracters. Motor outcome was assessed using the Movement Assessment Battery for Children (Movement-ABC), a standardized test of motor skills for children 4 to 12 years of age (Smits-Engelsman and Niemeijer, 1998). This test yields a score for total movement performance based on separate scores for fine motor skills (manual dexterity), ball skills (object control), and static and dynamic balance (postural control). The cognitive and motor tests were administered by author SAB, trained by author KNJAVB (child neuropsychologist), or administered by a trained research assistant under supervision of author SAB. All children were seen at the same research site. The total duration of the cognitive and motor assessment was typically approximately 3 h, including breaks. One hour before the behavior assessment part of the follow-up program of the DACE-study, the children were seen at the clinic for physical examination (including assessment of pubertal stage), venipuncture and breakfast.

2.4. Statistical analyses of data

To compare POP-levels between the included and excluded children, we used the independent samples Student *t*-test. Regarding outcomes on the WISC-III-NL, we converted the raw scores into scaled scores using age-specific norms according to the instructions in the manual. IQs were calculated by taking the mean of the scores on the verbal and performance subtests. We classified the scores into ‘normal’ (IQ > 85), ‘subclinical’ (IQ 70–85) and ‘clinical’ (IQ < 70). Regarding outcomes on the TEA-Ch-NL, we converted the raw scores on the subtest ‘Score’ into age-specific percentiles using the instruction manual. For the subtest ‘Sky Search’ we chose to use the raw scores, since no normed percentiles are available in the instruction manual. Regarding outcomes on the AVLT and Movement ABC, we used the Dutch norms for children of 12 years of age, because these tests were not normed for children older than 12 years. However, the study in which the norms of the AVLT were published indicated a ceiling effect between 10 and 12 years of age indicating no further improvement is expected after 12 years of age. Despite no norms for children of 13 to 15 years were available, we chose to use these tests because the same tests were used previously in our cohort at early school age, which provides us with the opportunity to compare the results on verbal memory and motor performance. We classified the scores on cognitive