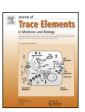
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Journal of Trace Elements in Medicine and Biology

journal homepage: www.elsevier.com/locate/jtemb



Toxicology

Performance IQ in children is associated with blood cadmium concentration in early pregnancy

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ARTICLE INFO

Article history: Received 25 September 2014 Accepted 19 November 2014

Keywords: Blood cadmium Performance IQ WPPSI-R

ABSTRACT

Objective: To investigate whether performance IQ in children is associated with maternal blood cadmium concentration in early pregnancy.

Method: The present study is a component of the Mothers' and Children's Environmental Health (MOCEH) study, a multi-center birth cohort project in Korea that began in 2006. The study cohort consisted of 119 children whose mothers underwent testing of blood cadmium during early pregnancy. All children were evaluated using the Korean version of the Wechsler Preschool and Primary Scale of Intelligence, revised edition (WPPSI-R), at 60 months of age. Multivariate linear regression analysis was performed to analyze the correlation between IQ in children and maternal blood cadmium concentration in early pregnancy, after adjustment for covariates.

Results: Maternal blood cadmium concentration during early pregnancy was inversely associated with performance IQ, after adjustment for covariates such as sex, educational levels of both parents, family income, and maternal BMI. Maternal blood cadmium concentration, however, was not associated with cognitive IQ.

 ${\it Conclusion:} \ Performance \ IQ \ in \ children \ is \ associated \ with \ maternal \ blood \ cadmium \ concentration \ in \ early \ pregnancy.$

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Introduction

Cadmium is a ubiquitous environmental pollutant. In the general population, the primary sources of cadmium exposure are cigarette smoke; ingestion of certain foods, including rice, wheat, potatoes, root vegetables, and leafy vegetables; and ambient air, particularly in urban areas and in the vicinity of industrial settings [1–7]. The diet in Korea is largely based on rice, which takes

up cadmium from the soil and is a dominant source of cadmium exposure. The biological half-life of cadmium in the human body exceeds 10 years. Cadmium levels in the body accumulate with age, as only minute amounts of the body burden (0.01–0.02%) are excreted daily [1]. Blood cadmium is a valid biomarker of recent cadmium exposure [8].

Cadmium is a carcinogenic metal of increasing public health concern [1,3]. Cadmium affects kidney function and bone metabolism, even at exposure levels found in the general population [9,10]. In contrast to the well-reported effects in adults, less is known about the adverse effects of exposure during pregnancy on the developing child. Experimental animal studies have shown

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that cadmium exposure during early development has deleterious neurobehavioral effects. Cadmium was found to be toxic to the fetus prior to and during gestation in rats and mice, resulting in reduced fetal or pup weights, malformation, and impaired neurobehavioral development [11–14]. Several epidemiological studies showed that cadmium exposure of pregnant women may influence pregnancy outcomes and neonatal birth weight [15–21]. However, the relationship between children's IQ and their prenatal cadmium exposure has not been determined [22,23]. This study was therefore designed to assess whether IQ in children is associated with maternal blood cadmium concentration during early pregnancy.

Subjects and methods

Subjects

The present study is a component of the Mothers' and Children's Environmental Health (MOCEH) study, a multi-center prospective birth cohort project involving 1751 pregnant women that was conducted in South Korea from May 2006 to December 2010 [24]. The study cohort consisted of 119 children whose mothers underwent testing of blood cadmium during early pregnancy. All children were tested using the Korean version of the Wechsler Preschool and Primary Scale of Intelligence, revised edition (WPPSI-R), at 60 months of age.

Parents of all participants were interviewed by trained personnel, using a detailed questionnaire, to obtain information about demographic characteristics, socioeconomic status, residential characteristics, medical and reproductive history, exposure to occupational hazards, alcohol consumption, nutritional habits, and exposure to second hand smoke in the home. Each questionnaire was completed on the day on which blood samples were collected.

Prior to the enrolment, all study participants were provided for written informed consent. The study protocol and the consent form were approved by the institutional review boards of Ewha Womans University (Seoul) (approval no. 12-07B-15); Dankook University Hospital (Cheonan) (approval no. 2011-09-0340); and Ulsan University Hospital (Ulsan) (approval no. 06-29); all three hospitals are located in the Republic of Korea.

Laboratory testing

Heparinized venous blood samples were obtained from each mother and child. Special care was taken to avoid skin and equipment contamination. Blood samples for women only were drawn after an overnight fast. Whole blood samples were cooled during storage and shipment. Blood samples were frozen and stored at $-20\,^{\circ}$ C. Prior to analysis, samples were allowed to attain room temperature and were thoroughly vortexed after thawing. Blood samples (each 0.1 mL) were diluted with 1.8 mL of matrix modifier reagent (containing Triton X-100 and ammonium phosphate). Blood cadmium concentrations were measured by graphite furnace atomic absorption spectrometry with Zeeman background correction (GFAAS) (Perkin Elmer AAS800, Perkin Elmer). All samples were analyzed by the Neodin Medical Institute, a laboratory certified by the Korean Ministry of Health and Welfare. For internal quality assurance and control, commercial reference materials were used (Lyphochek® Whole Blood Metals Control; Bio-Rad, Hercules, CA, USA). The coefficients of variation for blood cadmium was within 0.010–0.048 of the three reference samples. The Neodin Medical Institute passed the German External Quality Assessment Scheme of Friedrich-Alexander University (Germany), both in the occupational and environmental medical ranges, the latter with much lower concentrations of toxic substances, as well as passing the Quality Assurance Program operated by the Korean Occupational Safety and Health Agency. The Neodin Medical Institute has

also been certified by the Korean Ministry of Employment and Labor as a designated laboratory for analysis of specific chemicals, including heavy metals and certain organic chemicals. The method detection limits for blood cadmium in the present study were 0.081 μ g/L. Only two samples contained a cadmium level below the detection limit and we considered the level in that sample to be the detection limit divided by the square root of 2.

K-WPPSI

The K-WPPSI is the Korean version of the Wechsler Preschool and Primary Scale of Intelligence, revised edition (WPPSI-R) [25,26], an instrument commonly used to measure intelligence in young children, aged 3 years to 7 years 3 months. The K-WPPSI consists of subtests of verbal (Verbal IQ) and performance (Performance IQ) skills, as well as composite scores that represent Verbal, Performance, and Full Scale IQ. The verbal subtests include those on Information, Comprehension, Arithmetic, Vocabulary, Similarities, and Sentences, and the Performance subtests consist of those on Object Assembly, Geometric Design, Block Design, Mazes, Picture Completion, and Animal Pegs. The WPPSI scores have been standardized for Korean children compared with Western countries [26]. Assessments were performed at the hospital by experienced personnel. The standardized mean of WPPSI-R scores is 100 ± 15 , with scores of 89–80 being low average, 79-70 borderline, and ≤ 69 intellectually deficient.

Statistical analyses

Significant differences in mean maternal blood cadmium concentrations and verbal IQ in children according to categorical variables were determined using Student's *t*-tests. Multivariate linear regression analysis was utilized to assess the correlation between IQ in children and maternal blood cadmium concentration during early pregnancy, after adjustment for covariates, including sex of the child, maternal age and BMI, parents' educational levels, and family income.

Results

Table 1 shows maternal blood cadmium concentrations and verbal IQ of children by various categories. There were no differences in mean blood cadmium concentration and mean performance IQ when subjects were assorted by children's sex, parents' educational level, family income, and maternal age and BMI. Smoking was not used as a variate, since there was no current smoker. Children's verbal IQ was significantly lower in the third than in the first tertile group of maternal blood cadmium concentration. In contrast, cognitive IQ did not differ among the groups (data not shown).

Maternal blood cadmium concentrations during early pregnancy, as both categorical and continuous variables, were inversely associated with performance IQ, after adjustment for covariates such as sex, educational level of both parents, family income, and maternal BMI and age (Table 2, Models 1 and 2).

Discussion

The mean maternal blood cadmium concentration in the 117 Korean participants was 1.49 μ g/L, slightly higher than in cohorts of Taiwanese (1.15 μ g/L) [27] and Japanese (1.04 μ g/L) subjects [28]. In addition, the blood cadmium concentration in our cohort was higher than that observed in a general population of Korean women aged 20 to 40 years (0.81 μ g/L) [29] and in pregnant and non-pregnant women of child-bearing age in a US NHANES sample (0.22–0.33 μ g/L) [30].

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