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Prenatal exposure to phthalates and neuropsychological development during childhood

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ABSTRACT

There is inconsistent evidence regarding the effects of prenatal phthalate exposure on children's neuropsychological development. We evaluate the association between prenatal phthalate exposure and the cognitive, psychomotor and behavioral development of 367 children at repeated ages in a prospective birth cohort study. We measured phthalate metabolites (sum of four DEHP metabolites – Σ_4DEHP, MBzP, MEP, MiBP and MnBP) in urine samples collected during the 1st and 3rd trimesters of pregnancy in women participating in the INMA-Sabadell birth cohort study. We assessed cognitive and psychomotor development of their children at 1 and 4 years, and social competence, ADHD symptoms and other behavioral problems at 4 and 7 years. No associations were observed between prenatal phthalate exposure and cognitive and psychomotor scores at the age of 1 year and at the age of 4 years, except for an association between MBzP and lower psychomotor scores ($\beta = -1.49$ [95% confidence interval (CI) = −2.78, −0.21]). Σ_4DEHP concentrations were associated with increased social competence scores at 4 years and with reduced ADHD symptoms at age 4 and 7 years. Increasing MEP concentrations were associated with a reduced risk of inattention symptoms at 4 years. No associations were observed for MBzP, MiBP or MnBP in relation to behavioral problems. This study, with multiple phthalate exposure measurements and measures of neuropsychological domains at different ages, suggest that prenatal phthalate exposure does not adversely affect children's cognitive, psychomotor or behavioral development.

Abbreviations: ADHD, attention-deficit hyperactivity disorder; ADHD-DSM-IV, attention-deficit hyperactivity disorder – criteria of the diagnostic and statistical manual of mental disorders – 4th edition; BMI, body mass index; BSID, bayley scales of infant development; CPSCS, california preschool social competence scale; CSRS, conners' parent rating scales; DEHP, di-(2-ethylhexyl) phthalate; INMA, *infancia y medio ambiente*; LMWP, low molecular weight phthalates; LOD, limit of detection; MEHHP, mono-(2-ethyl-5-hydroxyl-hexyl) phthalate; MEHP, mono-(2-ethylhexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxo-hexyl) phthalate; MECPP, mono-(2-ethyl-5-carboxy-pentyl) phthalate; MBzP, mono-benzyl phthalate; MEP, mono-ethyl phthalate; MiBP, mono-isobutyl phthalate; MnBP, mono-*n*-butyl phthalate; MSCA, mccarthy scales of children's abilities; SDQ, strengths and difficulties questionnaire.

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Introduction

Phthalates are synthetic chemical compounds produced in large quantities and widely used in a range of consumer products including cosmetics, plastics, carpets, building materials, toys and medical and cleaning products (Bellinger, 2013; Braun et al., 2013; Miodovnik et al., 2014). The general population is exposed to phthalates mainly through diet, which is the most likely exposure route for the high molecular weight phthalates, and personal care products, which are the most likely exposure route for the low molecular weight phthalates (Hoppin et al., 2002; Braun et al., 2013; Miodovnik et al., 2014). Previous studies on animals have suggested that prenatal exposure to phthalates can increase the risk of impaired neurodevelopment (Bellinger, 2013; Martinez-Arguelles et al., 2013; Miodovnik et al., 2014). In humans, several prospective birth cohort studies, most of them including a relatively small study population, have reported adverse effects of prenatal phthalate exposure on the cognitive, psychomotor and behavioral development of children (Table 1). However, reported effects are not consistent across the different phthalate congeners and outcomes assessed and, additionally, there is not a clear gender specificity of the effects observed (Bellinger, 2013; Miodovnik et al., 2014). One of the main limitations of previous studies is that prenatal phthalate exposure was determined in a single spot urine measurement, which can lead to exposure misclassification, as phthalates have a short half-life (of hours) and are rapidly excreted from the body (Hoppin et al., 2002; Braun et al., 2013). Further, the only study with more than one phthalate measurement during pregnancy performed neurological examinations at the age of one month but did not follow-up children at later ages (Yolton et al., 2011). In the present study we collected urine samples in the 1st and the 3rd trimester of pregnancy in order to improve the assessment of phthalate exposure throughout pregnancy, and we conducted neuropsychological tests covering a wide range of cognitive, psychomotor and behavioral domains from the first year of life up to school ages. The aim of the present study, which includes more than 350 participants, is to evaluate whether urine biomarker measurements of phthalates during pregnancy are associated with impaired cognitive, psychomotor and behavioral development of children aged 1, 4 and 7 years in a longitudinal birth cohort study.

Methods

Study population

Pregnant women from the general population were recruited into the INMA-*INfancia y Medio Ambiente* (Environment and Childhood) birth cohort set up in Sabadell (Catalonia, Spain) between 2004 and 2006 ($N = 657$). Protocol details are described elsewhere (Guxens et al., 2012). Briefly, women were recruited during the 1st trimester routine antenatal care visit in the main public hospital or health centre of reference if they fulfilled the inclusion criteria: age ≥ 16 years, intention to deliver in the reference hospital, singleton pregnancy, no assisted conception, and no problems of communication. The study was conducted with the approval of the hospital ethics committee and written informed consent was obtained from the parents of all children.

Cognitive and psychomotor development assessment

At the age of 1 year (mean 14 months, range 12–18 months), we assessed children's cognitive and psychomotor development using the Bayley Scales of Infant Development (BSID) (Bayley, 1977), which includes the mental scale and the psychomotor scale. All testing was done in the health care centre in the presence of the mother by two specially trained psychologists, who followed a strict protocol to limit inter-observer variability (for further information see Forns et al., 2012). Scores were standardized for child's age in days at test administration using a parametric method for the estimation of age-specific reference intervals. The parameters of the distribution were modeled as a fractional polynomial function of age and estimated by maximum likelihood. Residuals were then normalized to a mean of 100 points with a standard deviation of 15 points to homogenize the scales and to be able to compare our results with other studies. At the age of 4 years, children completed a standardized version of the McCarthy Scales of Children's Abilities (MSCA) adapted to the Spanish population (McCarthy, 1972). The global cognitive scale and five subscales (Verbal, Perceptive-Performance, Memory, Quantitative and Motor) were examined. The testing was done by one psychologist. The continuous MSCA scales were standardized to a mean score of 100 with a standard deviation of 15 to homogenize all the scales.

Behavioral development assessment

At the age of 4 years, teachers of children completed an adapted bilingual version (Spanish/Catalan) of the California Preschool Social Competence Scale (CPSCS) to evaluate children's social competence (Julvez et al., 2008). This test consists of 30 items and a single general score is obtained. Teachers also completed a form list of Attention-Deficit Hyperactivity Disorder (ADHD) Criteria of the Diagnostic and Statistical Manual of Mental Disorders – 4th edition (ADHD-DSM-IV), which is used to assess attention-deficit, hyperactivity and impulsivity. A global score and two subscores (Inattention and Hyperactivity/Impulsivity) were created. At the age of 7 years, parents completed the Strengths and Difficulties Questionnaire (SDQ) (Goodman, 1997) and the short form of the Conners' Parent Rating Scales (CSRS) (Gianarris et al., 2001). The SDQ, which covers common areas of emotional and behavioral difficulties, consists of 25 items that allow obtaining a global score and individual scores for five subscales (Emotional symptoms, Conduct problems, Hyperactivity/Inattention, Peer relationship problems and Prosocial behaviour). The short form of the CSRS intends to assess problematic behavior in children and consists of 27 items that result into scores for three subscales (Oppositional, Cognitive Problems/Inattention and Hyperactivity) and an ADHD Index.

In this study, all outcomes were assessed as continuous (score) variables rather than dichotomized according to a clinically relevant cut-off, because our aim was not to detect an effect of exposure on clinically diagnosed cases, but rather on the distribution of symptoms in the general population.

Exposure assessment

We collected spot urine samples of mothers at 12 and 32 weeks of gestation and stored in 10 mL polyethylene tubes at −20 °C. Echevarne laboratory of Barcelona (Spain) determined creatinine by the Jaffé method (kinetic with target measurement, compensated method) with Beckman Coulter© reactive in AU5400 (IZASA®), and the Bioanalysis Research Group at Hospital del Mar Medical Research Institute (IMIM, Barcelona, Spain) quantified urine concentrations of a total of eight phthalate metabolites: mono-(2-ethyl-5-hydroxyl-hexyl) phthalate (MEHHP), mono-(2-ethyl-hexyl) phthalate (MEHP), mono-(2-ethyl-5-oxo-hexyl) phthalate (MEOHP), mono-(2-ethyl-5-carboxy-pentyl) phthalate (MECPP), MBzP, mono-ethyl phthalate (MEP), mono-isobutyl phthalate (MiBP) and mono-*n*-butyl phthalate (MnBP). The LOD for the different congeners ranged from 0.5 to 1 μg/L (further details at Valvi et al., 2015). We adjusted phthalates concentrations for creatinine (μg/g creatinine) to control for urine dilution. Because of the low correlation observed between phthalates concentrations