Environmental Research 142 (2015) 671–679

Contents lists available at ScienceDirect

Environmental Research

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

Exposure to bisphenol A during pregnancy and child neuropsychological development in the INMA-Sabadell cohort

Maribel Casas [a,b,c,*], Joan Forns [a,b,c,d], David Martínez [a,b,c], Claudia Avella-García [a,b,c,e,f], Damaskini Valvi [a,b,c,g], Ana Ballesteros-Gómez [h], Noelia Luque [h], Soledad Rubio [h], Jordi Julvez [a,b,c], Jordi Sunyer [a,b,c], Martine Vrijheid [a,b,c]

[a] Centre for Research in Environmental Epidemiology (CREAL), Barcelona, Spain
[b] Universitat Pompeu Fabra (UPF), Barcelona, Spain
[c] CIBER Epidemiología y Salud Pública (CIBERESP), Barcelona, Spain
[d] Department of Genes and Environment, Division of Epidemiology, Norwegian Institute of Public Health, Oslo, Norway
[e] Unitat Docent de Medicina Preventiva i Salut Publica H. Mar-UPF-ASPB, Barcelona, Spain
[f] IMIM (Hospital del Mar Medical Research Institute), Barcelona, Spain
[g] Department of Environmental Health, Harvard T.H. Chan School of Public Health, Boston, MA, US
[h] Department of Analytical Chemistry, University of Cordoba, Cordoba, Spain

ARTICLE INFO

Article history:
Received 11 May 2015
Received in revised form
16 July 2015
Accepted 31 July 2015

Keywords:
Bisphenol A
Cognitive development
Behavior
ADHD
Birth cohort

ABSTRACT

Background: Bisphenol A (BPA) may be a neurodevelopmental toxicant, but evidence is not consistent in terms of the sex-specific patterns of the associations and the specific behavioral or cognitive domains most affected.
Objective: To examine the effects of prenatal BPA exposure on cognitive, psychomotor, and behavioral development in 438 children at 1, 4 and 7 years of age.
Methods: BPA was measured in spot urine samples collected in trimester 1 and 3 of pregnancy from women participating in the INMA-Sabadell birth cohort study. Cognitive and psychomotor development was assessed at 1 and 4 years using psychologist-based scales. Attention deficit hyperactivity disorder (ADHD) symptoms and other behavioral problems were assessed at 4 years by teachers and at 7 years by parents using questionnaire-based rating scales.
Results: Geometric mean creatinine-adjusted BPA concentration of the averaged samples was 2.6 μg/g creatinine. BPA exposure was not associated with the cognitive scores or their subscales at 1 and 4 years of age. At 1 year of age, exposure in the highest tertile of BPA concentrations was associated with a reduction of psychomotor scores (T3 vs T1 $\beta = -4.28$ points, 95% CI: -8.15, -0.41), but there was no association with psychomotor outcomes at 4 years. At 4 years, BPA exposure was associated with an increased risk of ADHD-hyperactivity symptoms (Incidence Rate Ratio (IRR) per $\log_{10}$ μg BPA/g creatinine increase = 1.72; 1.08, 2.73) and this association was stronger in boys than in girls. Further, boys had an increased risk of ADHD-inattention symptoms whereas girls showed a reduced risk (p for interaction < 0.1). At 7 years, these associations were not statistically significant nor were any other behavioral problems.
Conclusions: These results suggest that prenatal BPA exposure does not affect cognitive development up to age 4 years. Associations are observed with psychomotor development and ADHD-related symptoms at early ages, but these do not appear to persist until later ages.

Abbreviations: ADHD, attention deficit hyperactivity disorder; ADHD-DSM-IV, attention deficit hyperactivity disorder - Criteria of Diagnostic and Statistical Manual of Mental Disorders-4th Edition; BMI, body mass index; BPA, Bisphenol A; BSID, Bayley Scales of Infant Development; CI, confidence interval; CPRS, Conner's Parent Rating Scales; DAGs, directed acyclic graphs; GAMs, generalized additive models; GM, geometric mean; Hg, mercury; HOME, Health Outcomes and Measures of the Environment Study; INMA, INfancia y Medio Ambiente; IQ, intelligence quotient; IRR, incidence rate ratio; LOD, limit of detection; MSCA, McCarthy Scales of Children's Abilities; p,p'-DDE, dichlorodiphenyldichloroethylene; PCBs, polychlorinated biphenyls; SD, standard deviation; SDQ, Strengths and Difficulties Questionnaire; WAIS-III, Similarities subtest of the Weschler Adult Intelligence-Third Edition

* Correspondence to: Centre for Research in Environmental Epidemiology, Doctor Aiguader, 88, 08003 Barcelona, Spain.
E-mail address: mcasas@creal.cat (M. Casas).

http://dx.doi.org/10.1016/j.envres.2015.07.024
0013-9351/

1. Introduction

Neuropsychological disabilities including attention deficit hyperactivity disorder (ADHD) and subclinical cognitive impairments have increased worldwide during the last decades (Polanczyk et al., 2007; Visser et al., 2014). Although genetic factors play an important role, the etiology of neuropsychological disabilities remains largely unknown (Grandjean and Landrigan, 2014). A total of 11 industrial chemicals widely distributed in the environment have been recognized as neurodevelopmental toxicants but there are 200 more chemicals with the capacity to affect the human brain (Grandjean and Landrigan, 2014).

Bisphenol A (BPA) has been recently recognized as a suspected agent causing developmental neurotoxicity (Grandjean and Landrigan, 2014). BPA is an organic chemical produced in very large quantities worldwide to make polycarbonate plastics and epoxy resins. Although US and Europe banned the use of BPA in infant feeding bottles in 2011, it is still used to make a variety of common consumer goods such as water bottles, sports equipment, CDs and DVDs, and food and beverage cans (Vandenberg et al., 2007). The primary source of exposure to BPA is through the diet and BPA has been detected in urine samples of $>95\%$ of the general population in the US and Europe, with similar levels of exposure (Casas et al., 2013a; Vandenberg et al., 2007).

BPA has weak estrogenic properties and the wide range of potential reproductive and developmental effects suggested by experimental and some human studies encompasses potential effects on the developing brain (Kundakovic and Champagne, 2011; Rochester, 2013). Experimental studies in rats and mice have observed altered neuronal differentiation, positioning and connectivity, anxiety related behavior, impairments in learning, memory, and motor activity and modification of sexual differentiation in the brain leading to behavioral changes (Kundakovic and Champagne, 2011). Previous studies, generally in relatively small populations, have reported associations between BPA exposure and behavioral and cognitive development outcomes in children (Braun et al., 2009; Braun et al., 2011; Evans et al., 2014; Harley et al., 2013; Hong et al., 2013; Maserejian et al., 2012a; Maserejian et al., 2012b; Perera et al., 2012; Roen et al., 2015; Yolton et al., 2011). However, the evidence of these studies is characterized by discrepancies in the exposure assessment (biomarker or dental composite), the time window of exposure (pre or postnatal), the sex-specific directions of the associations, the specific behavioral domain affected, and/or the sociodemographic characteristics of the populations (reviewed by Mustieles et al. (2015)). Psychomotor development in relation to BPA exposure has not yet been assessed in epidemiological studies.

In this study, we examined the effects of prenatal BPA exposure on cognitive, psychomotor, and behavioral development in three follow-up settings during childhood from the Spanish INMA-INfancia y Medio Ambiente (Childhood and Environment) birth cohort. Based on previous studies (Braun et al., 2009; Braun et al., 2011; Evans et al., 2014; Harley et al., 2013; Perera et al., 2012; Roen et al., 2015) we specifically examined effect modification by sex.

2. Methods

2.1. Study population

A population-based birth cohort was established in the city of Sabadell (Catalonia, Spain) as part of the INMA Project (Guxens et al., 2012). Between July 2004 and July 2006, 657 pregnant women who visited the primary health center of Sabadell for an ultrasound in the 1st trimester were recruited. Inclusion criteria were: age at least 16 years, intention to give birth in the reference hospital, no problems in communication, singleton pregnancy, and no assisted conception (Guxens et al., 2012). Informed consent was signed and the study was approved by the ethics committee of the Institut Municipal d'Investigació Mèdica (IMIM), Barcelona, Spain.

Of 657 mother–infant pairs initially enrolled, 622 participated in the follow-up conducted at the time of delivery. Of 479 children with prenatal urinary BPA concentrations in both the 1st and 3rd pregnancy trimesters, 438 had available information on at least one neuropsychological outcome at 1, 4 and/or 7 years of age and were included in the present analysis (see Supplemental material, Table S1).

2.2. Prenatal BPA exposure

Mothers provided a spot urine sample in the 1st and the 3rd trimesters of pregnancy and they were stored in polypropylene tubes at $-20\,^{\circ}C$ prior analysis. Total BPA (free plus conjugated) was quantified by liquid chromatography mass spectrometry in the Department of Analytical Chemistry laboratory, University of Cordoba (Spain) (Casas et al., 2013b). The limit of detection (LOD) was 0.1 μg/L. Only 3 samples in the 3rd trimester of pregnancy had BPA levels below the LOD and they were replaced by LOD/2. Creatinine determination was carried out at the Echevarne laboratory of Barcelona (Spain) by using the Jaffé method (kinetic with target measurement, compensated method) with Beckman Coulter© reactive in AU5400 (IZASA®). BPA concentrations were divided by urinary creatinine concentrations to control for urine dilution. Due to the short biological half-life of BPA (Völkel et al., 2002) we used the average of the creatinine-adjusted concentrations measured in the 1st and 3rd trimester to provide a better estimation of exposure throughout pregnancy. Average creatinine-adjusted BPA concentrations were $\log_{10}$-transformed to obtain normal distributions as the original distributions were right skewed.

2.3. Cognitive and psychomotor development assessment

At 1 year of age (range 12–17 months), child cognitive and psychomotor development were assessed using the Bayley Scales of Infant Development (BSID) (Bayley, 1993) version I. The BSID cognitive development scale (163 items) assesses age-appropriate cognitive development, including performance abilities, memory, and first verbal learning. The BSID psychomotor scale (81 items) assesses fine and gross motor development. At 4 years of age (range 4.1–5.6 years), child cognitive and motor development were assessed using the McCarthy Scales of Children's Abilities (MSCA) adapted to the Spanish population (McCarthy, 2009). The general cognitive index and 5 subscales (verbal, perceptual-performance, quantitative, memory, and motor) were examined. Raw BSID scores were standardized for age of the child in days at test administration. Then, the BSID and MSCA index scores were computed based on the assumption of a normal distribution with a mean of 100 corresponding to the mean of the raw scores, and a standard deviation (SD) of 15 was equivalent to 1 SD of the raw score. Both tests were performed at the primary health center, in the presence of the mother, by trained psychologists. The psychologists were not aware of any exposure information. BSID and MSCA tests of children that presented less than optimal cooperation, behavioral problems or were under influential conditions during the test performance were excluded in the corresponding BSID and MSCA analyses ($n=27$) but not in the analyses with behavioral outcomes. Excluded children presented no differences in BPA concentrations with the children included (Wilcoxon $p=0.47$). BSID and MSCA have been validated and used previously in the Spanish context (Bayley, 1993; McCarthy, 2009).