Chemosphere 205 (2018) 674–681

Contents lists available at ScienceDirect

Chemosphere

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

Evaluating effects of prenatal exposure to phthalates on neonatal birth weight: Structural equation model approaches

Qi Song [a, b], Ruzhi Li [c], Yan Zhao [d], Qingyang Zhu [a, b], Bin Xia [a, b], Shangqin Chen [e], Yunhui Zhang [a, b, *]

[a] Key Lab of Health Technology Assessment, National Health Commission of the People's Republic of China (Fudan University), China
[b] Key Laboratory of Public Health Safety, Ministry of Education, School of Public Health, Fudan University, Shanghai, China
[c] Department of Obstetrical, The Obstetrics and Gynecology Hospital of Fudan University, China
[d] Shanghai First Maternity and Infant Hospital, Tongji University School of Medicine, Shanghai, China
[e] Department of Neonatology, The 2nd Affiliated Hospital, Wenzhou Medical College, Wenzhou, China

ARTICLE INFO

Article history:
Received 21 December 2017
Received in revised form
9 April 2018
Accepted 11 April 2018
Available online 21 April 2018

Handling Editor: Myrto Petreas

Keywords:
Phthalates
Birth weight
Structural equation model
Gestational age
Pregnancy syndrome
Mediation

ABSTRACT

Background: A large body of evidence has shown that phthalate exposure can lower birth weight in animals and human beings. However, there are only limited data on whether phthalates could affect birth weight directly or indirectly through gestational age and pregnancy syndrome.
Objectives: To evaluate the effects of prenatal exposure to phthalates on birth weight in neonates and the mediation effects of gestational age and pregnancy syndrome on the association between phthalate exposure and birth weight.
Methods: In this study, 181 mother-newborn pairs were recruited from Wenzhou city. Maternal urine samples were collected during the third trimester and measured for phthalate metabolites by ESI-MS/MS. Structural equation models (SEMs) were used to evaluate effects of phthalate on birth weight controlling for maternal education, monthly income, nutritional supplements, infant gender, and maternal weight gain per week. The potential mediated effects of phthalate exposure through gestational age and pregnancy syndrome on birth weight were also calculated by structural equation modeling.
Results: After adjusting for potential confounders, urinary mono-phthalate levels (including MMP, MBP, MEHP, MEOHP, and MEHHP) were negatively associated with birth weight. A ten-fold increase in the concentration of MEOHP and MEHHP would be directly associated with lower birth weights (reduced to 124 g and 107 g, respectively). However, MBP had mediated effects on birth weight through gestational age, which was associated with an 85-g reduction in birth weight for every ten-fold increase in exposure. Both direct and mediated effects on birth weight were found in MMP and MEHP. The indirect effects of MMP and MEHP were mediated through gestational age and pregnancy syndrome. Thus, prenatal MMP and MEHP exposures were associated with decrease in birth weight.
Conclusions: A negative association exists between prenatal phthalate exposure and birth weight in Chinese neonates. In addition to direct pathway, phthalate exposures could affect birth weight through the mediated effects of gestational age and pregnancy syndrome.

1. Introduction

As a family of synthetic organic chemicals, which are produced in large volumes, phthalates are used in food containers, packaging, children's toys, and clothing, posing harmful effects to human health (Schettler, 2006; Sathyanarayana, 2008; Cao, 2010; Koniecki et al., 2011; Araki et al., 2017). Due to the wide use of phthalates worldwide, they are ubiquitous in the environment (Crinnion, 2010; Bamai et al., 2015). Human exposure to phthalates could be via inhalation, ingestion, skin absorption, or touching medical devices (Hernandez-Diaz et al., 2009; Guo et al., 2014). Recently, a large body of evidence showed that phthalates and their metabolites could pass through placental barrier in pregnant women and

* Corresponding author. Department of Environmental Health, School of Public Health, Fudan University, P.O. Box 249, 138 Yixueyuan Road, Shanghai, 200032, China.
E-mail address: yhzhang@shmu.edu.cn (Y. Zhang).

https://doi.org/10.1016/j.chemosphere.2018.04.063
0045-6535/

Abbreviations

BMI	body mass index
ETS	environmental tobacco smoke
GA	gestational age
HMW	high molecular weight
LMW	low molecular weight
LOAEL	the lowest observed adverse effect level
MBP	mono-*n*-butyl phthalate
MEHHP	mono(2-ethyl-5-hydroxyhexyl) phthalate
MEHP	mono-2-ethylhexyl phthalate
MEOHP	mono (2-ethyl-5-oxohexyl) phthalate
MMP	monomethyl phthalate
SEM	structural equation models

impact fetal intrauterine growth (Mose et al., 2007).

A large number of studies indicated that phthalate exposures result in adverse birth outcomes, including preterm birth, low birth weight, and small for gestational age (Tyl et al., 2004; Gray et al., 2006). In animal models, the reduction of birth weight in offspring was considered as one of the most sensitive endpoints for *in utero* exposure of phthalates (Tanaka, 2005; Boberg et al., 2008). The lowest observed adverse effect level (LOAEL) of di-*n*-butyl phthalate (DBP, one of phthalate esters) for reduced birth weight in F_2 generation rats was 52 and 66 mg/kg/day for males and females, respectively (Marsman, 1995). Human epidemiological studies showed a negative correlation between prenatal phthalate exposures and birth weight in newborn babies (Zhao et al., 2015; Lenters et al., 2016). Being born low birth weight is a well-established risk factor for metabolic and cardiovascular diseases in adulthood. Thus, the adverse outcome of birth weight has raised the public concerns.

Apart from the reduction in birth weight, prenatal exposure to phthalates was also related to shortened gestational age and induced pregnancy syndrome (Vega et al., 1993; Ferguson, 2014). For instance, each interquartile range (IQR) increase in urinary mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP, one of the secondary urinary metabolites of di-2-ethylhexyl phthalate) was associated with a 4.2-day decrease in gestation(Weinberger et al., 2014). Higher urinary monobenzyl phthalate (MBzP) concentrations in early-mid pregnancy also increased the risk (RR = 2.92) of pregnancy-induced hypertensive disease (Werner et al., 2015), which was universally known to affect the fetal weight (Bale et al., 2003; Zhu et al., 2015). However, little evidence is available to estimate whether phthalates decrease birth weight directly or indirectly through other factors, such as gestational age and pregnancy syndrome.

Mediation analysis is a rapid and promising area of epidemiology to evaluate the direct and indirect effects of chemical exposures. Mediation of an observed association between exposure and outcome by variability in a biomarker along the proposed causal pathway, explicitly evaluates the proposed causal mechanism alongside that observed association. As a powerful approach of mediation analysis, structural equation model (SEM) has been widely used to establish the structure between measured and latent variables in many areas, such as financial analysis, management science, sociology, and medical filed (Marsh et al., 2010; Jacobs et al., 2015; Li et al., 2017; Logie et al., 2017). Recently, Kile et al. used SEMs to measure the causal relationship between exposure to arsenic and birth weight and found the potential indirect effects of pregnancy duration and maternal weight gain during pregnancy(Kile et al., 2016). This provides us a new approach to evaluate the relationship between prenatal phthalate exposures and birth weight considering the indirect effects of confounders, for example, gestational age, body weight gain, and pregnancy syndrome.

As SEM provided a solution to explain the relationships among variables, it can be either continuous or discrete (Witt and Meyerand, 2009). From this perspective, this model was utilized to conduct a quantitation of factor analysis and multiple regression analysis or path analysis, which included a large number of complex hypothetical systems (Magiera et al., 2013; Lau et al., 2015). Herein, SEMs were applied to estimate the proposed direct or intermediate effects between phthalate exposures and neonatal birth weight and measure the parameters among each possible pathway. We hypothesized that phthalate exposures would be related to decreased birth weight, and gestational age and pregnancy syndrome might mediate the effects between prenatal phthalate exposures and reduced birth weight.

2. Methods

2.1. Study population

Participants were from a previous study, which was conducted in Wenzhou to investigate the association between prenatal environmental endocrine disrupting chemical (EDC) exposure and birth outcomes (Zhao et al., 2016). During the study period, participants were recruited from the Second Affiliated Hospital of Wenzhou Medical College. We enrolled 181 mother-newborn pairs who provided intact urinary samples and eligible questionnaires in this study. All subjects were residents of Wenzhou and signed written informed consent documents approved by Fudan University's Institutional Review Board before their participation in the study.

All methods were carried out in accordance with the approved guidelines (Xiao et al., 2016). The mothers answered a detailed questionnaire, including maternal weight and height before pregnancy, maternal age, maternal weight when delivery, maternal active smoking, environmental tobacco smoke exposure, history of drinking, nutritional supplements, dietary habits, monthly income, education background, and basic information of husband in two days after delivery. Gestational age, calculated by subtracting the date of the last menstrual period from the date of delivery, was obtained from hospital records. Furthermore, maternal pregnancy syndrome and neonatal birth weight and birth length were gathered from hospital records. Mothers were asked to provide a spot urine sample during their third trimester, and the samples were stored at −20 °C until measurement. During collection and storage of specimens, glass devices were utilized to reduce contamination by phthalates.

2.2. Sample processing and measurement

Urinary phthalate metabolites were analyzed by using the method modified by Guo et al. (2011a, b), and the analytical approach has been described in detail elsewhere (Guo et al., 2011a; b; Zhao et al., 2014). Five urinary phthalate metabolite concentrations were measured in the present study: two low-molecular-weight (LMW) phthalate metabolites, mono-*n*-butyl phthalate (MBP) and monomethyl phthalate (MMP), which are the primary metabolites of dibutyl phthalate (DBP) and dimethyl phthalate (DMP), respectively, and three high-molecular-weight (HMW) phthalate metabolites, namely, mono-2-ethylhexyl phthalate (MEHP), mono (2-ethyl-5-oxohexyl) phthalate (MEOHP), and MEHHP. MEHP is the primary metabolite of DEHP, while MEHHP and MEOHP are the secondary metabolites of DEHP (Koch and Calafat, 2009). The limits of detection (LOD) ranged from 0.25 to 0.50 ng/ml for the detected five metabolites.