



# Prenatal phthalate exposure and placental size and shape at birth: A birth cohort study



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## ABSTRACT

**Objective:** There is concern over the potential placental effects of prenatal phthalate exposure, and the potential adverse effects of prenatal phthalate exposure require further study; however, few data are available in humans. We investigated the associations between phthalate exposure in each trimester and both placental size and shape at birth.

**Methods:** We measured the urinary concentrations of phthalate metabolites among 2725 pregnant women in the Ma'anshan Birth Cohort. Before collecting urine samples from each of the three trimesters, the pregnant women were interviewed via questionnaires. Placental information was obtained from hospital records. We estimated the sex-specific associations between urinary phthalate concentrations in each trimester and both placental size and shape at birth using adjusted multiple regression. A linear mixed model was used for the repeated measures analysis with subject-specific random intercepts and slopes for gestational age at sample collection to test the effect of phthalate levels on placental size and shape and to estimate the effect sizes.

**Results:** Overall, placental breadth increased by 0.148 cm (95% CI: 0.078, 0.218) with each 1 ln-concentration increase in MBP in the first trimester. The difference between placental length and breadth (length–breadth) decreased by 0.086 cm (95% CI: –0.159, –0.012) and 0.149 cm (95% CI: –0.221, –0.076) with each 1 ln-concentration increase in MMP and MBP, respectively, in the first trimester. In the second trimester, placental thickness increased by 0.017 cm (95% CI: 0.006, 0.027), 0.020 cm (95% CI: 0.004, 0.036), 0.028 cm (95% CI: 0.007, 0.048), and 0.035 cm (95% CI: 0.018, 0.053) with each 1 ln-concentration increase in MMP, MBP, MEOHP, and MEHHP, respectively. In the third trimester, placental thickness increased by 0.037 cm (95% CI: 0.019, 0.056) and 0.019 cm (95% CI: 0, 0.037) with each 1 ln-concentration increase in MBP and MEHP, respectively. Multiple linear regression for each offspring sex indicated that prenatal phthalate exposure increased placental thickness in both the first and second trimesters in males, whereas the corresponding relationship was close to null in females. Linear mixed models (LMMs) yielded similar results.

**Conclusion:** Our results suggest the presence of associations between prenatal phthalate exposure and placental size and shape. Exposure to certain phthalates may cause the placenta to become thicker and more circular. Associations appeared stronger for the subsample representing male offspring than those for the subsample representing female offspring. Given the few studies on this topic, additional research is warranted.

## 1. Introduction

Phthalate acid esters (PAEs), also known as phthalates, are a group of chemicals that have been widely used since 1933 for manufacturing

flexible vinyl and polyvinyl chloride plastic. PAEs are the predominant plasticizer used worldwide and appear in numerous products such as personal care products, pharmaceuticals, textiles, PVC applications, children's toys, food packaging, and medical supplies (Zhao et al., 2016;

**Abbreviations:** PAEs, phthalate acid esters; MMP, mono-methyl phthalate; MEP, mono-ethyl phthalate; MBP, mono-butyl phthalate; MBzP, mono-benzyl phthalate; MEHP, mono-2-ethylhexyl-phthalate; MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; DEHP, di-2-ethylhexyl phthalate; HMWP, high-molecular-weight phthalates; LMWP, low-molecular-weight phthalates; pre-BMI, prepregnancy body mass index

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**Table 1**  
Descriptive statistics [mean ± SD (range) or n (%)] for demographics and placenta in the final sample (n = 2725).

Characteristics	Total (n = 2725)	Boys (n = 1399)	Girls (n = 1326)	p
<b>Pregnant women</b>				
Maternal age(years)	26.09 ± 3.59(18–43)	26.09 ± 3.70(18–42)	26.10 ± 3.49(18–43)	0.933
Prepregnancy BMI (kg/m <sup>2</sup> )	20.86 ± 2.84(14.2–36.4)	20.80 ± 2.83(15.1–36.4)	20.92 ± 2.85(14.3–36.1)	0.246
Pregnancy weight gain (kg)	15.29 ± 5.22(2.1–49)	15.26 ± 5.188(2.1–49)	15.30 ± 5.25(2.1–42)	0.863
Gestational age(weeks)	39.50 ± 1.31(29.1–42.4)	39.43 ± 1.33(29.1–42)	39.57 ± 1.29(29.7–42.4)	0.008
Parity				
0	2476(91.2)	1269(46.7)	1207(44.5)	0.405
≥ 1	239(8.8)	125(4.6)	114(4.2)	
Education(years)				
< 9	535(19.6)	285(10.5)	250(9.2)	0.484
9–12	610(22.4)	307(11.3)	333(11.1)	
> 12	1580(58)	807(29.6)	773(28.4)	
Residence (last half year)				
Urban	2169(79.6)	1118(79.9)	1051(79.2)	0.704
Rural	556(20.4)	281(20.1)	275(20.7)	
Incomes(Yuan)				
< 1000	45(1.7)	30(1.1)	15(0.6)	0.456
1000–2500	657(24.1)	340(12.5)	317(11.6)	
2500–4000	1182(43.4)	596(21.9)	586(21.5)	
> 4000	841(30.9)	433(15.9)	408(15.0)	
Pregnancy willingness				
Prepared	749(27.5)	387(14.2)	362(13.3)	0.616
Random	1575(57.8)	812(29.8)	763(28.0)	
Unexpected	401(14.7)	200(7.3)	201(7.4)	
Sunscreen use				
First trimester	344(12.6)	171(6.3)	173(6.4)	0.517
Second trimester	251(9.2)	129(4.8)	122(4.5)	
Third trimester	212(7.8)	95(3.6)	117(4.4)	
Cigarette smoking				
No	2616(96.0)	1339(49.1)	1227(46.9)	0.236
Yes	109(4.0)	60(2.2)	49(1.8)	
Alcohol consumption				
No	2506(92.0)	1283(47.1)	1223(44.9)	0.615
Yes	219(8.0)	116(4.2)	103(3.8)	
<b>Placental indicator</b>				
Length (cm)	18.94 ± 2.09(10–29.5)	18.94 ± 2.08(10–29.5)	18.93 ± 2.10(12.5–28.4)	0.899
Breadth (cm)	16.54 ± 1.87(7.2–23.8)	16.55 ± 1.90(8.5–23)	16.52 ± 1.83(7.2–23.8)	0.658
Thickness (cm)	2.34 ± 0.45(0.2–4.8)	2.33 ± 0.44(0.3–4.8)	2.36 ± 0.46(0.2–4.2)	0.120
length–breadth (cm)	2.40 ± 1.92(0–18)	2.39 ± 1.93(0–18)	2.41 ± 1.91(0–12.5)	0.778
Surface area (cm <sup>2</sup> )	247.64 ± 48.96(66.8–461.4)	247.96 ± 49.17(66.8–442.6)	247.31 ± 48.74(93.3–461.4)	0.728

Abbreviation: SD = standard deviation; BMI = body mass index.

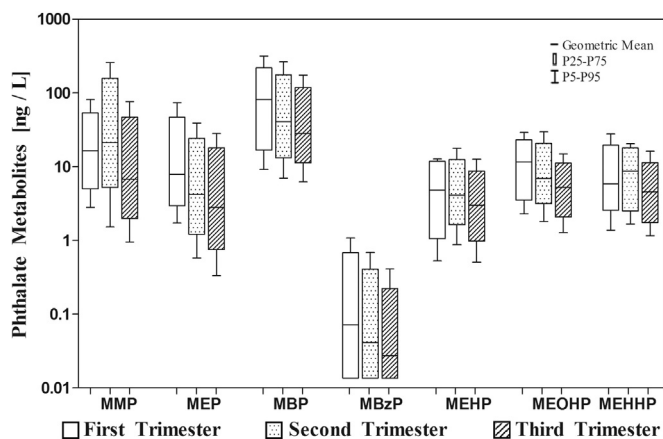


Fig. 1. Phthalate metabolites in urine of the different trimester investigated.

Zota et al., 2014). In recent years, phthalate production has reportedly reached five million tons (Campioli et al., 2014). Under certain circumstances, phthalates are not chemically bound to products and are released into the environment, from where they can enter the human body via ingestion, inhalation, or dermal absorption (Meeker et al., 2009).

Consistent scientific data have demonstrated the exposure to phthalates in pregnant women, as biomarkers for phthalate compounds are routinely found in human fluids (Bornehag and Nanberg, 2010; Botton et al., 2016; Casas et al., 2016; Lenters et al., 2016). In addition,

phthalates have been shown to cross the foetoplacental barrier, with detectable levels found in foetal circulation, cord blood (Huang et al., 2014), placenta (Kim et al., 2016), human amniotic fluid (Tellez-Rojo et al., 2013), meconium (Li et al., 2013), and neonate urine (Enke et al., 2013; Kim et al., 2016). The available evidence suggests that di-2-ethylhexyl phthalate (DEHP) disrupts the labyrinth vascularization of the placenta, inhibits the proliferation of and induces the apoptosis of placenta cells, and disrupts the growth and development of the placenta and affect placental growth. Animal studies have demonstrated that prenatal phthalate exposure reduces placental volume and weight (Zong et al., 2015), but similar data have not been reported for humans.

The placenta plays an essential role in foetal development and maternal health (Guttmacher and Spong, 2015). A growing body of evidence underscores the importance of placental development in the life-long health of both mother and offspring; thus, the lack of knowledge regarding placental structure and function is concerning (Guttmacher et al., 2014). Both animal and clinical studies have demonstrated that decreased placental volume is evident before any decline in foetal growth rate is observed (Jansson and Powell, 2007). As the shape of the placental surface is established at approximately 8–12 weeks of gestation (Barker et al., 2013), these life stages likely represent critical windows of vulnerability to phthalate exposure. Many questions exist regarding the developmental effects of phthalates on the placenta. Considering all the data, we hypothesized that long-term prenatal phthalate exposure might affect the development of placental size and shape.

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