Exposure to Phthalates Is Associated with Overweight or Obesity in 4-Year-Old Children

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Background

Phthalates may act as obesogens.
Possible mechanisms include peroxisome proliferator activated receptors (PPAR) agonist, thyroid hormone axis antagonists, and antiandrogens. Moreover, it has been reported that children are extensively exposed to phthalates and the exposure levels are higher compared with adults.
Limited epidemiologic studies in childhood. Inconsistent results for several phthalate metabolites for the risk of overweight or obesity in children and adults.

Purpose

In Korean 4-year-old children, we investigated the association of urine phthalate metabolite concentrations with overweight or obese status, after adjusting for possible obesity-related confounders

Subjects and Methods

This study was approved by the institutional review boards of Seoul National University Hospital (SNUH).

Between April, 2013 and December, 2014, **413 children aged 4 years (3.8 to 4.6 years), born as appropriate gestational age,** were included in analysis of our study.

- Height, weight and their Z-scores at 4 years of age
- All prepubertal stage
- Body mass index (BMI) category
  - ✓ Normal weight (<85th),
  - ✓ **Overweight (85-95th, n = 41)**
  - ✓ **Obesity (≥95th percentile, n = 6)**

Questionnaires

- Birth weight and Z-scores
- Weekly exercise hours (minutes/week)
- Daily calorie intake (Kcal/day) by dietitian
- Midparental height (MPH)
- Parental BMI and education levels
- Duration of breastfeeding (mons)

Urinary sample collection (early morning, fasting sample**)**

- Mono-(2-ethyl-5-hydroxyhexyl) phthalate **(MEHHP)** mono-(2-ethyl-t-oxohexyl) phthalate **(MEOHP),** and mono-n-butyl phthalate **(MnBP)** were measured.
- MEHHP, MEOHP, and MnBP concentrations under limit of detection (LOD) were assigned as a default value of LOD concentration divided by 2.

Results

Table 1. Characteristics of participants.

	Total	Boys	Girls
N (%)	**413**	**226 (54.7)**	**187 (45.3)**
Age, years	**3.9 (0.1)**	3.9 (0.1)	3.9 (0.1)
Height, cm	**101.6 (3.6)**	102.1 (3.6)*	101 (3.4)*
BMI	**15.6 (1.2)**	15.6 (1.1)	15.6 (1.3)
Height Z-score	**0.17 (0.8)**	0.17 (0.82)	0.16 (0.80)
BMI Z-score	**-0.18 (1.0)**	-0.23 (0.95)	-0.11(1.07)
Overweight or obesity, n (%)	**47 (11.4)**	**18 (8.0)***	**29 (15.5)***
Birth weight, kg	**3.3 (0.3)**	3.3 (0.33)*	3.2 (0.33)*
Birth weight Z-score	**-0.22 (0.67)**	-0.21 (0.65)	-0.24 (0.70
Midparental height, cm		174.1 (4.5)	161.6 (3.8)
Exclusive breastfeeding (≥ 6months), n (%)	**190 (46.0)**	100 (44.2)	90 (48.1)
Maternal obesity, n (%)	**53 (12.8)**	30 (13.3)	23 (12.3)
Paternal obesity, n (%)	**170 (41.4)**	95 (42.0)	75 (40.5)
Parental college graduate, n (%)	**307 (74.5)**	165 (73.0)	142 (76.3)
Daily calorie intake†,, Kcal/day**	**1452.5 (400.9)**	**1515.4 (426.9)***	**1373.5 (350.2)***
Weekly exercise†, minutes/week	**173.8 (178.5)**	**185.8 (191.5)***	**158.1 (158.4)***

*$P < 0.05$, †log-transformed for statistical analysis,
**Total 238 participants were evaluated by dietitian

Table 3. Comparison between normal weight children and overweight or obese children

	Normal weight	Overweight or obesity
N(%)	366 (88.6)	**47 (11.4)**
Age, years	3.9 (0.1)	3.9 (0.1)
Males (%)	**208 (56.8)***	**18 (38.3)***
Height Z-score	0.14 (0.80)*	0.39 (0.88)*
BMI Z-score	-0.37 (0.89)*	1.37 (0.32)*
Birth weight Z-score	**-0.25 (0.67)***	**-0.01 (0.64)***
Exclusive breastfeeding (≥ 6months), n (%)	172 (47.0)	18 (38.3)
Maternal obesity, n (%)	44 (12.0)	9 (19.1)
Paternal obesity, n (%)	145 (39.3)	25 (53.2)
Parental college graduate, n (%)	273 (74.8)	34 (72.3)
Daily calorie intake†,, Kcal/day**	1454.2 (401.7)	1433.7 (391.9)
Weekly exercise†, minutes/week	**177.2 (179.4)***	**147.5 (168.5)***
MEHHP†, ug/L	**62.7 (47.9)***	**78.0 (65.5)***
MEOHP†, ug/L	**48.3 (36.5)***	**58.8 (43.6)***
MnBP†, ug/L	**79.6 (64.4)**	**72.3 (62.1)**

*$P < 0.05$, †log-transformed for statistical analysis,
**Total 238 participants were evaluated by dietitian

Table 4. Risk factors for overweight or obesity at 4 years of age, Univariate (A) and multivariate (B)

Univariate analysis (A)	OR (95%C.I)	P-value
MEHHP†	**1.6 (1.05-2.3)**	**0.030**
MEOHP†	**1.5 (1.02-2.3)**	**0.038**
MnBP†	**1.0 (0.7-1.4)**	**0.922**
Females (vs. males)	**2.1 (1.1-3.9)**	**0.018**
Birth weight Z-score	**1.8 (1.09-2.8)**	**0.021**
Weekly exercise†, minutes/week	**0.7 (0.5-0.99)**	**0.049**
Exclusive breastfeeding ≥ 6mons	0.7 (0.4-1.3)	0.262
Paternal obesity	1.7 (0.9-3.2)	0.083
Maternal obesity	1.7 (0.8-3.8)	0.173
Parental college graduate	0.9 (0.4-1.7)	0.716
Daily calorie intake†, Kcal/day	0.9 (0.2-4.4)	0.858

†log-transformed for statistical analysis

Multivariate analysis (B)	MEHHP			MEOHP		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
	OR (95%C.I)	OR (95%C.I)	OR (95%C.I)	OR (95%C.I)	OR (95%C.I)	OR (95%C.I)
Phthalates (MEHHP or MEOHP) †	**1.9 (1.2-3.3)***	**1.9 (1.1-3.3)***	**2.2 (1.1-4.8)***	**2.0 (1.2-3.5)***	**1.9 (1.1-3.5)***	**2.4 (1.1-5.6)***
Females (vs. males)	2.3 (1.2-4.3)	1.8 (0.8-3.8)	2.2 (0.7-6.5)	1.4 (0.8-3.5)	1.8 (0.9-3.8)	2.2 (0.7-6.6)
Birth weight Z-score	**1.8 (1.1-2.9)***	**2.3 (1.3-4.2)***	2.2 (0.9-5.1)	**2.3 (1.3-4.3)***	**2.3 (1.3-4.2)***	2.1 (0.9-5.1)
Weekly exercise†	**0.7 (0.5-0.9)***	0.7 (0.5-1.0)	0.9 (0.5-1.4)	**0.7 (0.5-0.9)***	0.7 (0.5-1.0)	0.9 (0.5-1.4)
Exclusive breastfeeding		0.8 (0.4-1.7)	0.7 (0.2-2.1)		0.8 (0.4-1.7)	0.7 (0.2-2.1)
Paternal obesity		1.8 (0.8-3.7)	2.7 (0.9-8.1)		1.7 (0.8-3.6)	2.7 (0.9-7.9)
Maternal obesity		1.2 (0.4-3.4)	1.9 (0.5-7.1)		1.3 (0.4-3.5)	1.9 (0.5-7.1)
Parental college graduate		0.7 (0.3-1.7)	0.5 (0.2-1.8)		0.7 (0.3-1.7)	0.5 (0.2-1.8)
Daily calorie intake†, Kcal/day			1.6 (0.2-11.2)			1.6 (0.2-11.2)

*$P < 0.05$, †log-transformed for statistical analysis,

Table 2. Distribution of phthalate metabolites (ug/L)

	Mean (S.D)	LOD	N > LOD (%)	Selected percentiles				
				10th	25th	50th	75th	95th
MEHHP	64.5 (50.4)	0.116	100	15.61	29.93	53.05	83.30	169.69
MEOHP	49.5 (37.5)	0.080	100	12.94	22.99	40.94	66.35	120.17
MnBP	78.8 (64.1)	0.396	100	17.88	33.12	59.31	104.4	208.43

Conclusions

- After adjusting for possible obesity-related confounders, **urinary MEHHP and MEOHP concentrations (Di-2-ethylhexl phthalate (DEHP) metabolites)** are significantly associated with **higher risk for overweight or obesity**, respectively.
- Further well-designed, prospective epidemiologic studies are needed in order to conclude regarding obesogenic effects of phthalates in humans.

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