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Phthalate exposure and metabolic parameters in Korean girls

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BACKGROUND

- Phthalates are synthetic chemicals produced in extremely large volumes for a wide variety of uses in personal care and consumer products, including building materials, food packaging, medical devices, toys and cosmetics.
- Several in vivo and in vitro studies suggest that phthalates may promote obesity through antiandrogenic effects, antithyroid hormone activities, and/or activation of peroxisome proliferator-activated receptors (PPARs).
- Recently, human studies have been performed to study the association between phthalate exposure and obesity, and some work has shown that that concentrations of phthalate metabolites are associated with obesity and insulin resistance in adults .
- Children are known to be more vulnerable to environmental exposure to phthalates, as compared to adults, because of their hand-to-mouth activity, larger surface area to weight ratio, and enhanced metabolic rate. However, studies on the phthalate exposure and obesity/insulin resistance risk in children and adolescents are scarce.
- Urinary phthalate metabolites are the most useful biomarkers, as they are relatively easy to collect and their levels in a single sample reflect the exposure to phthalates over several weeks or months.

PURPOSE

We aimed to examine the associations of urine levels of phthalate metabolites with obesity status (BMI status, body fat %) and metabolic parameters (ALT, lipid profiles, fasting insulin, and HOMA-IR) in Korean girls.

METHODS

- A total of 139 girls (67 overweight cases and 72 controls, aged 6 to 13yr) were recruited. Anthropometric indices including height, weight, waist circumference were measured and Bioelectrical impedance measures were collected using the Inbody 720 (Biospace 40. Ltd.).
- Fasting blood samples were obtained from the antecubital vein following a 10-hour overnight fast. The fasting plasma concentrations of total cholesterol, low-density lipoprotein (LDL) cholesterol, insulin, glucose, AST, and ALT were measured. The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated using the following formula: fasting plasma glucose (mg dL^{-1}) × fasting insulin (μUmL^{-1})/405.
- First morning urine specimens were collected in all subjects, and stored at -20°C until assayed. Phthalate metabolites (MEP, MiBP, MnBP, MEHP, MEHHP, MEOHP, MBzP) were analyzed in selected ion monitoring mode using gas chromatograph-mass spectrometer (GC-MS, 7890A GC –5975C MS, Agilent, Palo-Alto, CA, USA).
- Associations between phthalate exposure and anthropometric indices/metabolic parameters and their trends were examined by multiple linear regression and logistic regression analyses, respectively.

RESULTS

1. Obesity and urinary concentrations of phthalate metabolites

Di-2-ethylhexyl phthalate (DEHP) metabolites showed the highest detected concentration (82.5 μg/g creatinine, 100%), and mono-benzyl phthalate (MBzP) showed the lowest detected concentration (6.3 μg/g creatinine, 87.8%). There was no significant difference in the concentrations of all phthalate monoesters between overweight and control girls, however percentage fraction of MEOHP among DEHP metabolites (MEOHP%) was significantly lower in overweight girls than in controls.

Table 1. General characteristics and metabolic variables in subjects by obesity status

	BMI status		
	BMI < 85 percentile	BMI ≥ 85 percentile	P-value
N	72	67	
Age (years)	9.0±1.5	8.6±1.5	0.122
Ht (cm)	134.8±9.8	135.8±9.2	0.529
Ht percentile	78.8±12.1	81.9±19.7	0.803
Body mass index (kg/m^2)	17.0±1.8	21.7±2.7	<0.001
BMI percentile	50.1±22.3	91.6±15.2	<0.001
WC (cm)	60.5±5.3	74.3±7.2	<0.001
WC percentile	55.5±23.8	96.2±3.5	<0.001
Body fat mass (kg)	12.2±2.7	13.9±3.3	0.001
Percent body fat (%)	22.6±5.8	33.8±8.1	<0.001
Tanner stage			0.319
1	35(48.6%)	38(57.6%)	
2	20(27.8%)	11(16.7%)	
3	7(9.7%)	11(16.7%)	
4	8(11.1%)	4(6.1%)	
5	2(2.8%)	2(3.0%)	
AST (IU/L)	27.8±6.2	26.6±6.8	0.274
ALT (IU/L)	17.2±16.7	19.8±14.8	0.344
Total cholesterol (mg/dL)	174.7±34.0	178.7±26.9	0.451
Triglyceride (mg/dL)	102.0±43.8	105.2±47.8	0.686
HDL-C (mg/dL)	53.1±9.5	51.4±10.9	0.361
LDL-C (mg/dL)	105.1±28.0	110.3±18.8	0.208
Fasting glucose (mg/dL)	93.5±6.3	94.9±8.3	0.298
Fasting insulin (㎕IU/mL)	9.8±8.4	15.1±10.2	0.002
HOMA-IR	2.3±2.0	3.3±1.8	0.003

Table 2. Urinary phthalate metabolite concentrations (μg/g creatinine) and percentage fractions of DEHP metabolites (%) by obesity status

	BMI status		
	BMI < 85 percentile	BMI ≥ 85 percentile	P-value
LMW phthalates			
MEP	6.1±1.5	4.6±1.5	0.132
MiBP	22.5±6.6	21.4±3.3	0.622
MnBP	34±3.9	28.9±3.1	0.136
Sum of LMW metabolites	68.8±8.8	58.8±5.9	0.716
HMW phthalates			
MEHP	12.4±1.2	12.9±1.5	0.41
MEHHP	43.2±4.5	42.4±11.2	0.888
MEOHP	29.1±3.0	25.8±5.5	0.264
MBzP	7.8±2.5	6.4±2.0	0.528
Sum of DEHP metabolites	88.4±8.3	86.5±17.7	0.627
Sum of HMW metabolites	101.4±9.4	95.7±18.2	0.844
MEHP%	14.0±1.2	15.0±1.6	0.549
MEHHP%	48.9±0.7	49±1.1	0.193
MEOHP%	**34.2±0.8**	**30±0.8**	**0.014**
Values are GM ± SE			

Phthalate metabolite concentrations showed no significant associations with anthropometric indices. After adjusting for age, pubertal stages, and height percentile, MEHHP% was positively associated with waist circumference and MEOHP% was negatively associated with body mass index (BMI) percentile.

Table 3. Regression analyses of associations between phthalate metabolites and anthropometric indicies in subjets

	Height percentile		BMI percentile		WC		BF%	
	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)
LMW phthalates								
MEP	0.006	(-0.08 to 0.092)	0.001	(-0.113 to 0.113)	-0.008	(-0.108 to 0.093)	-0.023	(-0.087 to 0.041)
MiBP	0.051	(-0.079 to 0.18)	-0.116	(-0.287 to 0.055)	-0.018	(-0.183 to 0.146)	0.030	(-0.075 to 0.135)
MnBP	0.002	(-0.146 to 0.149)	-0.108	(-0.301 to 0.086)	-0.062	(-0.232 to 0.107)	-0.057	(-0.165 to 0.051)
Sum of LMW metabolites	-0.016	(-0.139 to 0.107)	-0.114	(-0.276 to 0.047)	-0.075	(-0.222 to 0.07)	-0.044	(-0.137 to 0.05)
HMW phthalates								
MEHP	-0.031	(-0.142 to 0.08)	-0.128	(-0.273 to 0.018)	0.060	(-0.188 to 0.068)	-0.028	(-0.11 to 0.054)
MEHHP	-0.005	(-0.114 to 0.104)	-0.072	(-0.215 to 0.071)	-0.039	(-0.165 to 0.087)	-0.006	(-0.086 to 0.074)
MEOHP	-0.023	(-0.059 to 0.012)	0.010	(-0.102 to 0.123)	-0.001	(-0.105 to 0.103)	-0.010	(-0.076 to 0.056)
MBzP	0.036	(-0.053 to 0.125)	-0.005	(-0.124 to 0.113)	-0.004	(-0.109 to 0.101)	0.021	(-0.045 to 0.088)
Sum of DEHP metabolites	0.002	(-0.134 to 0.138)	-0.117	(-0.295 to 0.062)	-0.064	(-0.228 to 0.09)	-0.020	(-0.121 to 0.08)
Sum of HMW metabolites	-0.005	(-0.141 to 0.131)	-0.123	(0.302 to 0.055)	-0.069	(-0.228 to 0.09)	-0.024	(-0.125 to 0.078)

Regression coefficients were calculated using multivariate linear regression analyses adjusted for age, Tanner stage.
Phthalate metabolite concentrations showed no significant associations with anthropometric indicies.
Log-transformation was applied to phthalate concentrations and each anthropometric indicies.

Table 4. Regression analyses of associations between percentage fractions of DEHP metabolites (%) and obesity markers

	BMI percentile		WC	
	β	(95% CI)	β	(95% CI)
MEHP%	0.107	(-3.24 to 0.529)	-0.003	(-0.612 to 0.102)
MEHHP%	4.160	(-0.251 to 1.094)	**0.206**	**(0.001 to 0.412)***
MEOHP%	**-0.906**	**(-1.420 to -0.093)***	-0.159	(-0.387 to 0.069)

Regression coefficients were calculated using multivariate linear regression analyses adjusted for age, Tanner stage and height percentile.

2. Metabolic parameters and urinary concentrations of phthalate metabolites

Concentrations of MiBP, MnBP, MEHP, MEHHP, sum of DEHP metabolites, and sum of high molecular weight phthalates (HMP) were positively associated with serum ALT. Concentrations of MiBP were also positively associated with total cholesterol/LDL-cholesterol levels.

Table 5. Regression analyses of associations between phthalate metabolites and metabolic biomarkers in subjets

	AST		ALT		Total chole		LDL-C		HDL-C		TG		FBS		Fasting insulin		HOMA-IR	
	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)	β	(95% CI)
LMW phthalates																		
MEP	0.018	(-0.015 to 0.051)	0.040	(-0.029 to 0.109)	0.009	(-0.016 to 0.035)	-0.001	(-0.034 to 0.032)	0.004	(-0.025 to 0.034)	0.056	(-0.013 to 0.125)	-0.006	(-0.019 to 0.006)	-0.022	(-0.101 to 0.058)	-0.029	(-0.113 to 0.055)
MiBP	**0.085**	**(0.036 to 0.134)****	**0.132**	**(0.028 to 0.235)***	**0.047**	**(0.009 to 0.085)***	**0.059**	**(0.01 to 0.108)***	-0.018	(-0.064 to 0.027)	0.056	(-0.051 to 0.162)	-0.016	(-0.035 to 0.003)	-0.030	(-0.165 to 0.105)	-0.048	(-0.191 to 0.094)
MnBP	**0.061**	**(0.004 to 0.118)***	**0.144**	**(0.026 to 0.262)***	0.004	(-0.003 to 0.084)	0.046	(-0.010 to 0.103)	-0.014	(-0.066 to 0.037)	0.055	(-0.066 to 0.176)	-0.020	(-0.042 to 0.002)	-0.015	(-0.155 to 0.125)	-0.036	(-0.184 to 0.112)
Sum of LMW metabolites	0.210	(-0.027 to 0.069)	0.097	(-0.003 to 0.196)	0.021	(-0.016 to 0.058)	0.041	(-0.006 to 0.089)	-0.017	(-0.060 to 0.027)	0.069	(-0.034 to 0.171)	**-0.025**	**(-0.045 to -0.005)***	0.014	(-0.133 to 0.161)	-0.004	(-0.016 to 0.151)
HMW phthalates																		
MEHP	**0.043**	**(0.001 to 0.087)***	**0.131**	**(0.042 to 0.22)****	0.022	(-0.012 to 0.055)	0.030	(-0.013 to 0.073)	-0.021	(-0.060 to 0.018)	0.025	(-0.066 to 0.116)	-0.012	(-0.029 to 0.004)	-0.015	(-0.120 to 0.091)	-0.030	(-0.142 to 0.081)
MEHHP	0.040	(-0.002 to 0.082)	**0.020**	**(0.042 to 0.214)****	0.024	(-0.008 to 0.056)	0.028	(-0.014 to 0.069)	-0.010	(-0.048 to 0.028)	0.043	(-0.046 to 0.131)	-0.014	(-0.030 to 0.002)	0.005	(-0.097 to 0.107)	-0.010	(-0.119 to 0.097)
MEOHP	0.007	(-0.026 to 0.041)	0.033	(-0.036 to 0.102)	0.016	(-0.009 to 0.041)	0.018	(-0.015 to 0.052)	-0.004	(-0.034 to 0.026)	0.009	(-0.067 to 0.081)	-0.007	(-0.020 to 0.006)	-0.008	(-0.091 to 0.076)	-0.017	(-0.105 to 0.071)
MBzP	0.017	(-0.018 to 0.052)	0.062	(-0.010 to 0.134)	0.009	(-0.017 to 0.036)	0.013	(-0.022 to 0.048)	-0.008	(-0.039 to 0.024)	0.035	(-0.040 to 0.109)	-0.009	(-0.022 to 0.004)	-0.026	(-0.113 to 0.060)	-0.045	(-0.136 to 0.046)
Sum of DEHP metabolites	0.044	(-0.008 to 0.097)	**0.161**	**(0.053 to 0.238)****	0.026	(-0.015 to 0.067)	0.035	(-0.017 to 0.087)	-0.020	(-0.067 to 0.028)	0.044	(-0.067 to 0.155)	-0.013	(-0.032 to 0.007)	0.004	(-0.125 to 0.132)	-0.019	(-0.155 to 0.117)
Sum of HMW metabolites	0.048	(-0.005 to 0.101)	**0.164**	**(0.056 to 0.272)****	0.025	(-0.016 to 0.066)	0.035	(-0.017 to 0.087)	-0.022	(-0.069 to 0.026)	0.050	(-0.061 to 0.161)	-0.015	(-0.034 to 0.005)	0.009	(-0.119 to 0.138)	-0.015	(-0.150 to 0.121)

Regression coefficients were calculated using multivariate linear regression analyses adjusted for age, Tanner stage, and BMI percentile
Log-transformation was applied to phthalate concentrations and each metabolic biomarkers
**P<0.01.
*P<0.05.

Figure 1. Regression coefficiA254:F323ents (95% confidence intervals) for a change in ALT (ΔALT) associated tertiles of MiBP, MnBP, sum of LMP, MEHP, MEHHP, MEOHP, and sum of DEHP metabolites, and sum of HMP concentrations (adjusted for age, Tanner stage and BMI percentile).

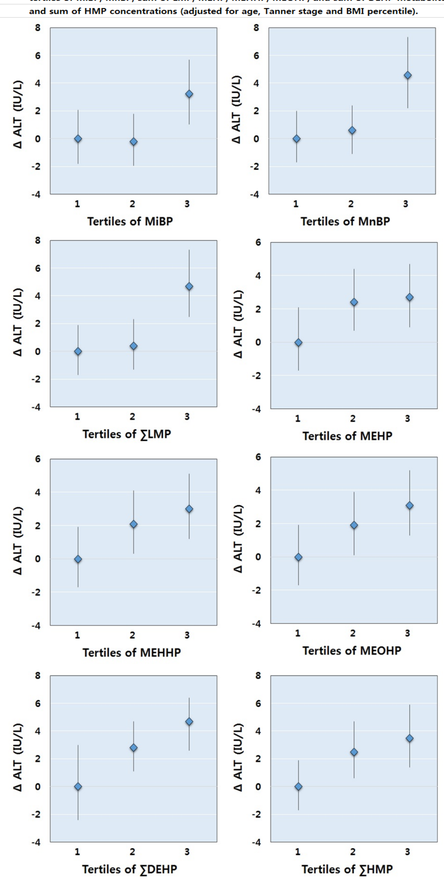
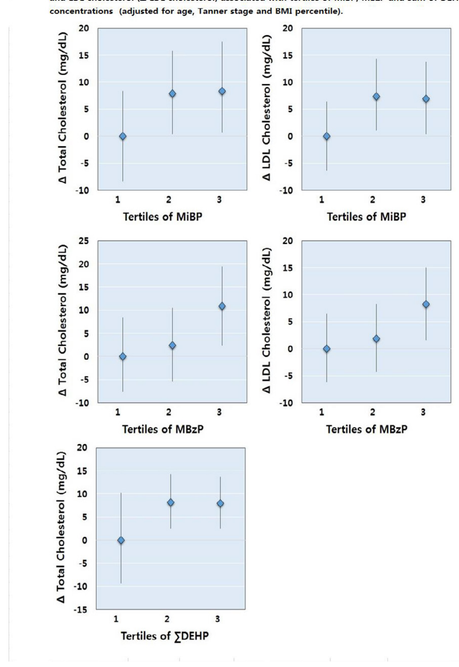


Figure 2. Regression coefficients (95% confidence intervals) for a change in Totoal cholesterol (Δ Total cholesterol) and LDL cholesterol (Δ LDL cholesterol) associated with tertiles of MiBP, MBzP and sum of DEHP concentrations (adjusted for age, Tanner stage and BMI percentile).



3. Indices of insulin resistance and percentage fractions of DEHP metabolites

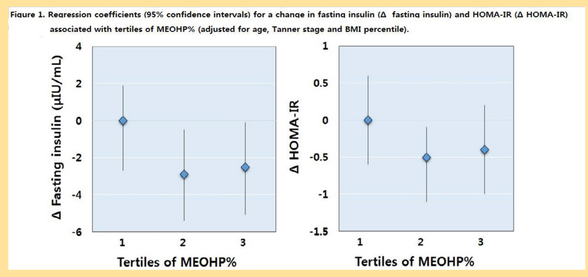
After controlling for age and pubertal stages, MEHHP% was positively associated with fasting insulin and HOMA-IR, whereas MEOHP% was negatively associated with fasting insulin and HOMA-IR. However, after further adjustment for BMI percentile, the significant associations were remained only for MEOHP%.

Table 6. Regression analyses of associations between phthalate metabolites and metabolic biomarkers in subjets

		MEHP%		MEHHP%		MEOHP%	
		β	(95% CI)	β	(95% CI)	β	(95% CI)
AST	Model 1	5.524	(-3.523 to 14.572)	-2.147	(-6.346 to 2.053)	4.19	(-2.714 to 11.904)
	Model 2	5.661	(-3.392 to 14.714)	-2.094	(-6.296 to 2.111)	0.376	(-3.243 to 10.762)
ALT	Model 1	10.776	(-10.870 to 32.421)	-4.978	(-15.000 to 5.050)	3.89	(-12.671 to 20.451)
	Model 2	9.984	(-11.286 to 31.254)	-5.234	(-15.169 to 4.522)	7.273	(-9.161 to 23.706)
Total cholesterol	Model 1	28.39	(-14.156 to 70.935)	2.235	(-17.600 to 22.079)	4.092	(-28.570 to 36.755)
	Model 2	27.74	(-14.826 to 70.307)	1.949	(-17.895 to 21.793)	6.964	(-26.094 to 40.023)
LDL cholesterol	Model 1	11.915	(-21.725 to 45.555)	5.562	(-10.097 to 21.221)	3.103	(-22.591 to 28.797)
	Model 2	11.397	(-22.234 to 45.028)	5.113	(-10.56 to 20.786)	5.661	(-20.364 to 31.686)
HDL cholesterol	Model 1	4.231	(9.982 to 18.444)	0.14	(-6.492 to 6.773)	-1.305	(-12.191 to 9.582)
	Model 2	4.767	(-9.212 to 18.747)	0.426	(-6.102 to 6.953)	-3.336	(-14.161 to 7.488)
TG	Model 1	22.308	(-41.537 to 86.153)	5.708	(24.372 to 35.789)	-13.12	(-61.767 to 35.527)
	Model 2	21.859	(-42.077 to 85.796)	4.923	(-25.258 to 35.105)	-9.969	(-59.380 to 39.442)
FBS	Model 1	1.074	(-9.514 to 11.662)	-1.838	(-6.826 to 3.150)	0.712	(-6.544 to 9.9551)
	Model 2	1.036	(-9.373 to 11.445)	-2.35	(-7.265 to 2.565)	3.196	(-4.820 to 11.212)
Fasting insulin	Model 1	-2.296	(-15.144 to 10.552)	**0.679**	**(0.685 to 12.733)***	**-13.863**	**(-23.308 to -4.419)****
	Model 2	-1.887	(-13.597 to 9.823)	4.954	(-0.619 to 10.527)	**-9.79**	**(-18.691 to -0.889)***
HOMA-IR	Model 1	-0.4	(-3.162 to 2.362)	**1.419**	**(0.122 to 2.716)***	**-3.238**	**(-5.255 to -1.221)****
	Model 2	-0.328	(-2.854 to 2.197)	1.063	(-0.139 to 2.266)	**-2.397**	**(-4.304 to -0.489)***

Regression coefficients were calculated using multivariate linear regression analyses.
Model 1 : adjusted for age and Tanner stage
Model 2: adjusted for age, Tanner stage and BMI percentile
**P<0.01.
*P<0.05.

Figure 1. Regression coefficients (95% confidence intervals) for a change in fasting insulin (Δ fasting insulin) and HOMA-IR (Δ HOMA-IR) associated with tertiles of MEOHP% (adjusted for age, Tanner stage and BMI percentile).



CONCLUSIONS

- Urinary concentrations of phthalate metabolites were not significantly associated with BMI percentile, waist circumference, or percent body fat in Korean girls.
- Urinary concentrations of some phthalate metabolites were positively associated with serum ALT, total cholesterol or LDL-cholesterol levels.
- Percentage fraction of MEOHP among DEHP metabolites (MEOHP%) was significantly decreased in overweight children than in controls, and it was negatively associated with insulin resistance after controlling for age, pubertal stages, and BMI percentile.
- Prospective studies are needed to determine potential causal links between phthalate exposure and metabolic derangement such as NAFLD and insulin resistance in children.

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