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SUPPLEMENTAL DATA

Urinary monoester phthalate metabolites and thyroid function in healthy adults: Sex- and obesity-specific associations

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Table S1. Hormonal levels (mean ± SD and median values) for FT3, FT4 and TSH for enrolled participants

Hormone	*n*	Mean ± SD	Median
FT4 (pmol/L)	201	13.20 ± 2.61	13.40
FT3 (pmol/L)	201	4.77 ± 1.24	4.70
TSH (mIU/L)	201	1.97 ± 1.04	1.81

Abbreviations: FT3, free triiodothyronine; FT4, free thyroxine; SD, standard deviation; TSH, thyroid-stimulating hormone.

Table S2. Rankit-transformed hormone values

BMI	Hormone	Exp.	Mean±SD (−)	Mean±SD (+)	Diff [95% CI]	*d*	*p*	*P* (FDR)
Lean	FT4	MEP	*n*=79, 12.93±2.27	*n*=29, 12.70±2.46	−0.23 [−1.23, 0.77]	−0.10	0.699	0.890
Lean	FT4	MEHP	*n*=93, 13.04±2.15	n=15, 11.81±3.01	−1.23 [−2.49, 0.03]	−0.54	0.030	0.282
Lean	FT3	MEP	*n*=79, 4.75±0.85	*n*=29, 4.88±0.52	+0.13 [−0.21, 0.47]	+0.17	0.320	0.848
Lean	FT3	MEHP	*n*=93, 4.77±0.83	n=15, 4.87±0.35	+0.10 [−0.33, 0.53]	+0.13	0.578	0.890
Lean	TSH	MEP	*n*=79, 1.96±1.14	*n*=29, 2.07±1.35	+0.11 [−0.40, 0.63]	+0.09	0.936	0.936
Lean	TSH	MEHP	*n*=93, 2.02±1.24	*n*=15, 1.82±0.84	−0.20 [−0.86, 0.46]	−0.16	0.851	0.928
Ov+Ob	FT4	MEP	*n*=58, 13.21±3.11	*n*=35, 14.20±2.37	+0.98 [−0.23, 2.20]	+0.35	0.047	0.282
Ov+Ob	FT4	MEH	*n*=64, 13.71±2.47	*n*=29, 13.31±3.65	−0.40 [−1.68, 0.89]	−0.14	0.742	0.890

		P						
Ov+Ob	FT3	MEP	*n*=58, 4.69±1.72	*n*=35, 4.83±1.47	+0.15 [−0.55, 0.84]	+0.09	0.603	0.890
Ov+Ob	FT3	MEHP	*n*=64, 4.84±1.89	*n*=29, 4.52±0.71	−0.32 [−1.05, 0.40]	−0.20	0.424	0.848
Ov+Ob	TSH	MEP	*n*=58, 1.90±0.89	*n*=35, 2.04±0.69	+0.14 [−0.21, 0.49]	+0.17	0.285	0.848
Ov+Ob	TSH	MEHP	*n*=64, 1.98±0.73	*n*=29, 1.88±1.00	−0.11 [−0.47, 0.26]	−0.13	0.371	0.848

p values were calculated from Rankit-transformed hormone values, consistent with the regression analyses; descriptive statistics and Cohen's d are reported on the raw scale. Permutation testing (10,000 resamples on raw values) yielded *p*=0.054 and *p*=0.115 for the Lean/MEHP and Overweight+obese/MEP FT4 comparisons, respectively, consistent with the FDR-adjusted results. **Abbreviations**: BMI, body mass index; CI, confidence interval; d, Cohen's d; Diff, difference; Exp., exposure; FDR, false discovery rate; FT3, free triiodothyronine; FT4, free thyroxine; LOQ, limit of quantification; MEHP, mono(2-ethylhexyl) phthalate; MEHP+, MEHP concentration above the LOQ; MEHP−, MEHP concentration below the LOQ; MEP, monoethyl phthalate; MEP+, MEP concentration above the LOQ; MEP−, MEP concentration below the LOQ; Ov+Ob, overweight and obese; SD, standard deviation; TSH, thyroid-stimulating hormone.

Table S3. ANOVA results for hierarchical multiple linear regression models predicting serum FT4, FT3, and TSH concentrations from urinary MEP, sex, BMI, and their interactions

Model		Sum of squares	*df*	Average square	*F*	*p*
Criterial variable FT4						
1	Regression	13.203	3	4.401	4.657	0.004
	Residue	186.183	197	0.945		

	Total	199.386	200			
	Regression	13.203	4	3.301	3.475	0.009
2	Residue	186.183	196	0.950		
	Total	199.386	200			
	Regression	13.712	5	2.742	2.880	0.016
3	Residue	185.675	195	0.952		
	Total	199.386	200			
	Regression	13.898	6	2.316	2.423	0.028
4	Residue	185.488	194	0.956		
	Total	199.386	200			
Criterial variable FT3						
	Regression	12.926	3	4.309	4.654	0.004
1	Residue	185.967	197	0.944		
	Total	198.892	200			
	Regression	14.569	4	3.642	3.873	0.005
2	Residue	184.323	196	0.940		
	Total	198.892	200			
	Regression	16.711	5	3.342	3.577	0.004
3	Residue	182.181	195	0.934		
	Total	198.892	200			
	Regression	16.754	6	2.792	2.974	0.008
4	Residue	182.138	194	0.939		
	Total	198.892	200			
Criterial variable TSH						
	Regression	6.064	3	2.021	2.057	0.107
1	Residue	193.609	197	0.983		
	Total	199.673	200			
	Regression	6.087	4	1.522	1.541	0.192
2	Residue	193.586	196	0.988		
	Total	199.673	200			
	Regression	10.374	5	1.275	1.286	0.271
3	Residue	193.299	195	0.991		
	Total	199.673	200			

	Regression	10.736	6	1.789	1.837	0.094
4	Residue	188.937	194	0.974		
	Total	199.673	200			

For each dependent variable, Model 1 included the main effects of urinary MEP, sex, and BMI. Model 2 additionally included the MEP × sex interaction, Model 3 additionally included the MEP × BMI interaction, and Model 4 additionally included the MEP × sex × BMI interaction. Terms entered in the preceding models were retained at each subsequent step. MEP was mean-centered before the interaction terms were calculated, and sex was entered as a binary variable. **Abbreviations**: ANOVA, analysis of variance; BMI, body mass index; df, degrees of freedom; F, F statistic; FT3, free triiodothyronine; FT4, free thyroxine; MEP, monoethyl phthalate; TSH, thyroid-stimulating hormone.

Table S4. Partial contributions of predictors to urinary MEP concentrations: Sex, BMI, and their interactions with FT4, FT3, and TSH

		dependent variable: FT4			dependent variable: FT3			dependent variable: TSH		
Model		Beta	*t*	*p*	Beta	*t*	*p*	Beta	*t*	*p*
1	Constant		1.674	0.096		3.313	0.001		-2.143	0.033
	MEP	0.155	2.248	0.026	0.022	0.325	0.746	0.060	0.848	0.397
	Sex	-0.122	-1.754	0.081	-0.242	-3.470	0.001	0.159	2.245	0.026
	BMI	0.140	2.013	0.045	-0.116	-1.665	0.098	-0.033	-0.464	0.643
2	Constant		1.670	0.097		3.329	0.001		-2.137	0.034
	MEP	0.152	0.674	0.501	-0.260	-1.158	0.248	0.026	0.115	0.909
	Sex	-0.122	-1.749	0.082	-0.241	-3.456	0.001	0.159	2.240	0.026
	BMI	0.140	1.991	0.048	-0.103	-1.467	0.144	-0.031	-0.437	0.662
	MEP*sex	0.004	0.016	0.987	0.296	1.322	0.188	0.035	0.152	0.879
3	Constant		1.551	0.123		3.517	0.001		-2.187	0.030
	MEP	0.104	0.444	0.658	-0.162	-0.697	0.487	-0.009	-0.039	0.969
	Sex	-0.115	-1.625	0.106	-0.256	-3.657	<0.001	0.165	2.290	0.023
	BMI	0.141	2.000	0.047	-0.105	-1.496	0.136	-0.031	-0.428	0.669

	MEP*sex	0.052	0.220	0.826	0.197	0.848	0.397	0.071	0.297	0.767
	MEP*BMI	0.053	0.731	0.466	-0.109	-1.514	0.132	0.040	0.537	0.592
4	Constant		1.511	0.132		3.515	0.001		-2.045	0.042
	MEP	0.085	0.356	0.722	-0.153	-0.645	0.520	0.083	0.344	0.731
	Sex	-0.114	-1.608	0.110	-0.257	-3.652	<0.001	0.161	2.248	0.026
	BMI	0.132	1.801	0.072	-0.100	-1.379	0.170	0.012	0.158	0.875
	MEP*sex	0.062	0.261	0.795	0.193	0.822	0.412	0.024	0.100	0.921
	MEP*BMI	0.167	0.624	0.533	-0.164	-0.618	0.537	-0.508	-1.888	0.061
	MEP*BMI*sex	-0.117	-0.442	0.659	0.056	0.213	0.831	0.563	2.116	0.036

Abbreviations: BMI, body mass index; FT3, free triiodothyronine; FT4, free thyroxine; MEP, monoethyl phthalate; TSH, thyroid-stimulating hormone.

Table S5. Statistical parameters of urinary MEP, BMI, and sex interactions with TSH as a criterial variable

Sex	BMI		coefficient	*p*
Male	Lean (BMI ≤ 25 kg/m^2)	Kendall Tau B	0.026	0.864
		Kendall Tau C	0.016	0.864
		Gamma	0.044	0.864
		Spearman's	0.044	0.777
		Pearson	0.092	0.551
	Overweight+obese (BMI > 25 kg/m^2)	Kendall Tau B	0.003	0.980
		Kendall Tau C	0.002	0.980
		Gamma	0.003	0.980
		Spearman's	0.009	0.955
		Pearson	-0.045	0.780
Female	Lean (BMI ≤ 25 kg/m^2)	Kendall Tau B	-0.036	0.678
		Kendall Tau C	-0.027	0.678
		Gamma	-0.050	0.678
		Spearman's	-0.044	0.728

		Pearson	-0.068	0.596
	Overweight+obese (BMI > 25 kg/m^2)	Kendall Tau B	0.268	0.012
		Kendall Tau C	0.194	0.012
		Gamma	0.390	0.012
		Spearman's	0.333	0.017
		Pearson	0.289	0.040

Abbreviations: BMI, body mass index; MEP, monoethyl phthalate; TSH, thyroid-stimulating hormone.

Table S6. Analysis of variance results for hierarchical multiple linear regression models examining the main and interaction effects of urinary MEHP, sex, and BMI on serum FT4, FT3, and TSH concentrations

Model		Sum of squares	*df*	Average square	*F*	*p*
Criterial variable FT4						
1	Regression	11.000	3	3.667	3.834	0.011
	Residue	188.386	197	0.956		
	Total	199.386	200			
2	Regression	11.125	4	2.781	2.896	0.023
	Residue	188.261	196	0.961		
	Total	199.386	200			
3	Regression	17.528	5	3.506	3.759	0.003
	Residue	181.858	195	0.933		
	Total	199.386	200			
4	Regression	18.527	6	3.088	3.312	0.004
	Residue	180.860	194	0.932		
	Total	199.386	200			
Criterial variable FT3						
1	Regression	13.079	3	4.360	4.622	0.004
	Residue	185.814	197	0.943		
	Total	198.892	200			

	Regression	13.082	4	3.271	3.450	0.009
2	Residue	185.810	196	0.948		
	Total	198.892	200			
	Regression	14.528	5	2.906	3.073	0.011
3	Residue	184.364	195	0.945		
	Total	198.892	200			
	Regression	19.734	6	3.289	3.561	0.002
4	Residue	179.158	194	0.923		
	Total	198.892	200			
Criterial variable TSH						
	Regression	5.379	3	1.793	1.818	0.145
1	Residue	194.294	197	0.986		
	Total	199.673	200			
	Regression	5.641	4	1.410	1.425	0.227
2	Residue	194.032	196	0.990		
	Total	199.673	200			
	Regression	5.815	5	1.163	1.170	0.325
3	Residue	193.858	195	0.994		
	Total	199.673	200			
	Regression	7.042	6	1.174	1.182	0.317
4	Residue	192.631	194	0.993		
	Total	199.673	200			

For each dependent variable, Model 1 included the main effects of urinary MEHP, sex, and BMI. Model 2 additionally included the MEHP × sex interaction, Model 3 additionally included the MEHP × BMI interaction, and Model 4 additionally included the MEHP × sex × BMI interaction. Terms entered in the preceding models were retained at each subsequent step. MEHP was mean-centered before the interaction terms were calculated, and sex was entered as a binary variable.

Abbreviations: BMI, body mass index; df, degrees of freedom; F, F statistic; FT3, free triiodothyronine; FT4, free thyroxine; MEHP, mono(2-ethylhexyl) phthalate; TSH, thyroid-stimulating hormone.

Table S7. Partial contributions of predictors to urinary MEHP concentrations, sex, BMI and their interactions with FT4, FT3 and TSH as dependent variables

		dependent variable: FT4			dependent variable: FT3			dependent variable: TSH		
Model		Beta	*t*	*p*	Beta	*t*	*p*	Beta	*t*	*p*
1	Constant		1.880	0.062		3.361	0.001		-2.106	0.036
	MEHP	-0.116	-1.641	0.102	-0.036	-0.517	0.605	0.011	0.147	0.883
	Sex	-0.138	-1.970	0.050	-0.245	-3.520	0.001	0.157	2.205	0.029
	BMI	0.164	2.302	0.022	-0.109	-1.535	0.126	-0.034	-0.473	0.637
2	Constant		1.859	0.065		3.352	0.001		-2.122	0.035
	MEHP	-0.044	-0.207	0.836	-0.049	-0.230	0.818	0.115	0.534	0.594
	Sex	-0.138	-1.960	0.051	-0.245	-3.511	0.001	0.157	2.209	0.028
	BMI	0.168	2.325	0.021	-0.109	-1.523	0.129	-0.028	-0.389	0.698
	MEHP*sex	-0.077	-0.361	0.719	0.013	0.062	0.951	-0.112	-0.515	0.607
3	Constant		1.859	0.065		3.352	0.001		-2.122	0.035
	MEHP	-0.115	-0.545	0.586	-0.015	-0.070	0.944	0.127	0.582	0.561
	Sex	-0.157	-2.256	0.025	-0.236	-3.365	0.001	0.161	2.236	0.026
	BMI	0.204	2.813	0.005	-0.126	-1.732	0.085	-0.034	-0.460	0.646
	MEHP*sex	-0.077	-0.366	0.714	0.013	0.062	0.951	-0.112	-0.514	0.608
	MEHP*BMI	0.194	2.620	0.009	-0.092	-1.237	0.218	-0.032	-0.419	0.676
4	Constant		2.087	0.038		3.003	0.003		-2.262	0.025
	MEHP	-0.029	-0.129	0.898	-0.211	-0.935	0.351	0.032	0.136	0.892
	Sex	-0.170	-2.404	0.017	-0.207	-2.931	0.004	0.175	2.399	0.017
	BMI	0.209	2.877	0.004	-0.318	-1.908	0.058	-0.040	-0.535	0.594
	MEHP*sex	-0.157	-0.697	0.486	0.194	0.869	0.386	-0.024	-0.104	0.917
	MEHP*BMI	-0.054	-0.216	0.829	0.476	1.900	0.059	0.243	0.938	0.349
	MEHP*BMI*sex	0.258	1.035	0.302	-0.590	-2.374	0.019	-0.286	-1.111	0.268

Abbreviations: BMI, body mass index; FT3, free triiodothyronine; FT4, free thyroxine; MEHP, mono(2-ethylhexyl) phthalate; TSH, thyroid-stimulating hormone.

Table S8. Statistical parameters of the urinary MEHP and BMI interactions with FT4 as the criterial variable

BMI		coefficient	*p*
Lean (BMI ≤ 25 kg/m^2)	Kendall Tau B	-0.168	0.040
	Kendall Tau C	-0.089	0.040
	Gamma	-0.331	0.040
	Spearman's	-0.207	0.031
	Pearson	-0.185	0.056
Overweight+obese (BMI > 25 kg/m^2)	Kendall Tau B	-0.026	0.749
	Kendall Tau C	-0.019	0.749
	Gamma	-0.036	0.749
	Spearman's	-0.032	0.761
	Pearson	-0.057	0.587

Abbreviations: BMI, body mass index; FT4, free thyroxine; MEHP, mono(2-ethylhexyl) phthalate.

Table S9. Statistical parameters for the interaction effects of urinary MEHP, BMI, and sex on serum FT3 concentrations

Sex	BMI		coefficient	*p*
Male	Lean (BMI ≤ 25 kg/m^2)	Kendall Tau B	-0.164	0.093
		Kendall Tau C	-0.106	0.093
		Gamma	-0.277	0.093
		Spearman's	-0.202	0.189
		Pearson	-0.221	0.149
	Overweight+obese (BMI > 25 kg/m^2)	Kendall Tau B	0.082	0.408
		Kendall Tau C	0.058	0.408
		Gamma	0.125	0.408
		Spearman's	0.100	0.529
		Pearson	0.088	0.579
Female	Lean (BMI ≤ 25 kg/m^2)	Kendall Tau B	0.118	0.160
		Kendall Tau C	0.056	0.160
		Gamma	0.284	0.160

	Spearman's	0.143	0.261
	Pearson	0.140	0.269
Overweight+obese (BMI > 25 kg/m^2)	Kendall Tau B	-0.159	0.170
	Kendall Tau C	0.123	0.170
	Gamma	-0.211	0.170
	Spearman's	-0.208	0.143
	Pearson	-0.222	0.117

Abbreviations: BMI, body mass index; FT3, free triiodothyronine; MEHP, mono(2-ethylhexyl) phthalate.