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Urinary Phthalate Metabolites and Slow Walking Speed in the Korean Elderly Environmental Panel II Study

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Background: Previous epidemiological studies have suggested that phthalate exposure may contribute to neurocognitive and neurobehavioral disorders and decreased muscle strength and bone mass, all of which may be associated with reduced physical performance. Walking speed is a reliable assessment tool for measuring physical performance in adults age 60 y and older.

Objective: We investigated associations between urinary phthalate metabolites and slowness of walking speed in community-dwelling adults ages 60–98 y.

Methods: We analyzed 1,190 older adults [range, 60–98 y of age; mean ± standard deviation (SD), 74.81 ± 5.99] from the Korean Elderly Environmental Panel II study and measured repeatedly up to three times between 2012 and 2014. Phthalate exposure was estimated using the following phthalate metabolites in urine samples: mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono-*n*-butyl phthalate (MnBP), mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP), and mono-benzyl phthalate (MBzP). Slowness was defined as a walking speed of <1.0 meter/second. We used logistic and linear regression models to evaluate the association between each urinary phthalate metabolite and slowness or walking-speed change. We also used Bayesian kernel machine regression (BKMR) to examine overall mixture effects on walking speed.

Results: At enrollment, MBzP levels were associated with an increased odds of slowness [odds ratio (OR) per doubling increase: 1.15, 95% confidence interval (CI): 1.02, 1.30; OR for the highest vs. lowest quartile: 2.20 (95% CI: 1.12, 4.35) with *p*-trend across quartiles = 0.031]. In longitudinal analyses, MEHHP levels showed an increased risk of slowness [OR per doubling increase: 1.15 (95% CI: 1.02, 1.29), OR for the highest vs. lowest quartile: 1.47 (95% CI: 1.04, 2.06), *p*- trend = 0.035]; whereas those with higher MnBP showed a reduced risk of slowness [OR per doubling increase: 0.84 (95% CI: 0.74, 0.96), OR in the highest (vs. lowest) quartile: 0.64 (95% CI: 0.47, 0.87), *p*-trend = 0.006]. For linear regression models, MBzP quartiles were associated with slower walking speed (*p*-trend = 0.048) at enrollment, whereas MEHHP quartiles were associated with slower walking speed, and MnBP quartiles were associated with faster walking speed in longitudinal analysis (*p*-trend = 0.026 and <0.001, respectively). Further, the BKMR analysis revealed negative overall trends between the phthalate metabolite mixtures and walking speed and DEHP group (MEHHP, MEOHP, and MECPP) had the main effect of the overall mixture.

Discussion: Urinary concentrations of prevalent phthalates exhibited significant associations with slow walking speed in adults ages 60–98 y. https://doi.org/10.1289/EHP10549

Introduction

Walking speed is one of the quickest, most reliable, and simple measurements for monitoring the mobility and physical function of older adults.[1] Along with blood pressure, pulse rate, respiratory rate, body temperature, and pain, walking speed has been recommended as the "sixth vital sign" for assessing functional ability and overall health.[2] Moreover, slowness in walking speed has been associated with adverse health outcomes, including disability, cognitive impairment, hospital admissions, falls, and all-cause mortality in those age 65 y and older.[3,4] Recently, a systematic review has identified potentially modifiable risk factors for slow walking speed in community-dwelling adults age 45 y and older, including physical inactivity, low education, obesity, pain, and depression.[5] Exposure to environmental factors such as lead,[6] cadmium,[7] and cobalt[8] have been suggested to be associated with walking speed declines.

Phthalates are a group of chemicals used to make plastics more flexible and durable and are widely used in industrial materials, consumer products, and personal care products.[9] The high molecular weight phthalates (ester side-chain lengths, five or more carbons) are used widely in polyvinyl chloride (PVC) polymers and plastisol applications, plastics, food packaging and processing materials, vinyl toys and floor coverings, and building products. The most important source of human exposure is diet, particularly foods packaged in plastic or PVC materials.[10] The low molecular weight phthalates are used in non-PVC applications, such as personal care products, adhesives, and enteric-coated tablets, and their major sources of human exposure are reported as cosmetics and

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personal care products.[9] Once in the body, phthalates are both endocrine disruptors[11] and carcinogenic,[12] and their accumulation has been associated with a wide range of health problems, including neurodevelopmental disorders,[13] reproductive outcomes,[14,15] respiratory[16] and cardiovascular diseases,[17] and metabolic outcomes (e.g., diabetes, insulin resistance, obesity, and kidney diseases).[18] In addition, several epidemiological studies suggested that exposure to phthalates might be associated with neurocognitive and neurobehavioral disorders,[19] frailty,[20] and declines in both muscle strength[21,22] and bone mineral density.[23,24] All these outcomes were associated with poor physical performance and disability in adults age 50 y and older.[25–28] *In vivo* experimental studies also showed that phthalate exposure could cause cognitive, neurosensory, and behavioral dysfunction[29,30] and locomotor behavior defects through cellular and DNA damage in the brain.[31,32] Other experimental studies reported that phthalates were associated with musculoskeletal impairment through glucose catabolic reactions in the muscle[33] and developmental malformations in bones.[34,35] Moreover, there is evidence that phthalates are associated with increases in oxidative stress and inflammation biomarkers such as C-reactive protein (CRP), interleukin 6 (IL-6), and tumor necrosis factor-α (TNFα),[36,37] which are considered important mechanisms of age-related physical function decline.[38–40] Despite this epidemiological and experimental evidence, the potential influence of phthalate exposure on walking speed among adults age 60 y and older remains unknown. Therefore, the present study aimed to evaluate whether exposure to phthalates estimated based on urinary mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), mono-*n*-butyl phthalate (MnBP), mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP), and mono-benzyl phthalate (MBzP) concentrations, was associated with slowness of walking speed in adults age ≥60 y who participated in the Korean Elderly Environmental Panel II (KEEP II) study.

Methods

Study Participants

The KEEP II study was designed to examine relationships between environmental exposure and health outcomes in adults age ≥60 y. For this purpose, it conducted repeated interviews, physical examinations, and laboratory testing on participants age 60 y and over who visited two community welfare centers located in Seoul (urban area) and Asan (rural area), South Korea, between 2012 and 2014.[21] At each examination, information on sociodemographic characteristics, medical and family history, and lifestyle behaviors was collected using structured questionnaires. Physical examinations and laboratory testing were conducted by certified health technicians who received intensive training on examination protocols. Detailed data collection structure is described in Table S1. Of 1,251 participants initially recruited without communication impairments, subjects who had no information on urinary phthalate metabolites concentrations ($n=8$) or walking speed ($n=35$) were excluded. Furthermore, we excluded 14 subjects with missing information on weight ($n=10$) or physical activity ($n=4$), as well as four subjects with unreliably high walking speed >1.8 meters/second (m/s), leading to a final sample size of 1,190 participants. During the follow-up, subjects participated in each examination up to three times [450 (37.8%) subjects participated only once, 452 (38.0%) subjects participated twice, and 288 (24.2%) subjects participated three times] with 1-y interval [mean ± standard deviation (SD): 1.10 ± 0.38 y]. The number of participants was 740 at follow-up 1 and 288 at follow-up 2. Details for the enrollment and follow-up of study participants are presented in Figure 1. Additionally, the following subjects with extreme phthalate metabolite values were excluded from their specific analyses: MEHHP >500 μg/L ($n=2$), MEOHP >380 μg/L ($n=2$), MECPP >700 μg/L ($n=1$), MnBP >1,000 μg/L ($n=2$), and MBzP >100 μg/L ($n=1$).

The institutional review board of the Seoul National University Hospital (H-1209-006-424) approved and reviewed the study. All participants provided written informed consent before participation.

Walking Speed

At enrollment and each follow-up visit, participants were asked to walk at their usual pace a distance of 2.5 m (see Table S1). The walking time started when the participant's foot crossed the starting line and fully touched the floor and ended when the participant's foot completely passed the ending line and fully touched the floor. This process was repeated twice using a handheld stopwatch, and the faster value was used in the analyses. Walking speed (m/s) was computed by dividing the walked distance (in meters) by the recorded time of walk (in seconds). Walking speed has been proven to have a test-retest reliability.[1] This measure has been used in previous studies of older adults including the Health and Retirement Study (HRS).[41,42]

For the main analyses, slowness was defined using the current 1.0 m/s cutoff point suggested by the Asian Working Group for Sarcopenia (AWGS) in 2019.[43] Additionally, in sensitivity analyses, slowness was defined using two alternative cutoff points: *a*) 0.8 m/s[44] and *b*) the lowest sex- and height-specific quintiles.[45] The current AWGS definition of slowness (walking speed <1.0 m/s) has been shown to predict mild physical disability and has been associated with a higher risk of hospitalization and lower extremity functional limitations,[3] whereas the other two definitions have been associated with severe physical disability and an increased risk of falls and mortality.[46,47]

Urinary Phthalate Metabolites

Urine samples for all participants were collected at enrollment and at each follow-up visit. Phthalate exposure was estimated based on the following metabolites in the urine: MEHHP, MEOHP, MnBP, MECPP, and MBzP. Although MEHHP, MEOHP, and MnBP metabolites were available at enrollment and each follow-up visit (Exam I, Exam II, and Exam III), MECPP and MBzP metabolites were only measured at Exam II (see Table S1; Figure 1). Spot urine samples were collected from participants during their physical examination between 1000 hours to 1200 hours (10:00 A.M. to 12:00 P.M.) and frozen immediately at −20°C until laboratory analyses. Concentrations of urinary metabolites were analyzed using ultra performance liquid chromatography–tandem mass spectrometry (LC-MS/MS) (Xevo TQ-S; Waters) according to a previously reported method.[21] The limits of detection (LODs) for MEHHP, MEOHP, MECPP, MnBP, and MBzP were 0.32 μg/L, 0.20 μg/L, 0.26 μg/L, 0.35 μg/L, and 0.19 μg/L, respectively. Values below the LOD were replaced by the LOD divided by 2.

Other Covariates

Information on covariates was obtained at enrollment and at each follow-up visit (see Table S1). Based on *a priori* biological and epidemiological knowledge, the following were considered as potential confounders: sociodemographic factors, including age, sex, education level (≤elementary school, middle and high school, and >high school), economic status (household income <USD $450, USD $450–2,659.9, or ≥USD $2,660), living arrangement (living alone, living with spouse, living with child, or others), and city of residence; anthropometric measurements: height and weight measured by certified health technicians; health-related behaviors, such as physical activity and smoking (no, yes); clinical factors, including

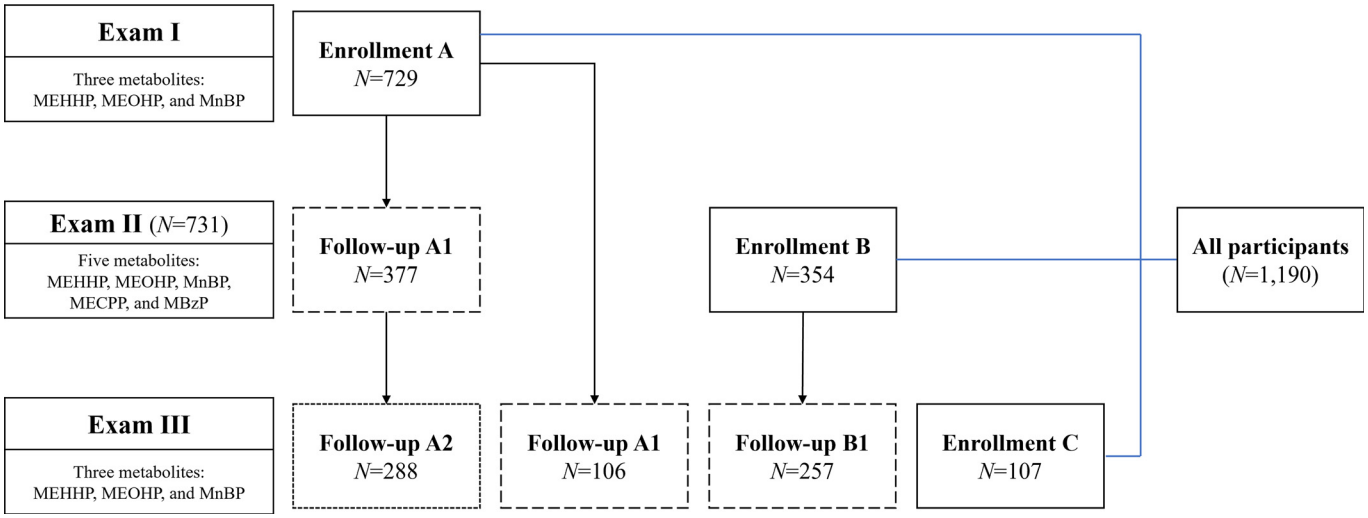

Figure 1. Classification of participants. Solid line box indicates the first visit for each participant ($n = 1,190$ for all participants), and the dashed and dotted line boxes indicate the second ($n = 740$ for follow-up 1 group) and third visits ($n = 288$ for follow-up 2 group), respectively. Two metabolites (MECPP and MBzP) had one measurement at Exam II (Follow-up A1 and Enrollment B). Only cross-sectional analysis was possible. Thus, repeated measurements of MECPP and MBzP were not available.

self-reported depression and self-reported physician diagnosis of osteoarticular disease (osteoporosis and osteoarthritis), cardiovascular disease (angina, myocardial infarction, stroke, and cerebrovascular disease), respiratory disease (asthma and chronic obstructive pulmonary disease), cancer, hypertension, and diabetes; and urinary creatinine as measured using a Hitachi Automatic Analyzer (Hitachi 7600).

Because height and weight are known to affect walking speed,[48] we controlled for these variables separately, instead of adjusting for body mass index. Physical activity [metabolic equivalents per week (METs-hours/week)] was computed as the sum of weekly METs of moderate and vigorous activity, as measured using the Korean version of the International Physical Activity Questionnaire (IPAQ).[49] Individuals were classified into those who engaged in <7.5 (reference) and ≥ 7.5 METs-hours/week, which is recommended for Leisure Time Physical Activity by the World Health Organization.[50] Current and former smokers were not considered separately because the number of current smokers was very low ($n = 57$, 24, and 4 at enrollment and follow-up 1 and follow-up 2 visits). Depression was measured using the Korean version of the Short Form Geriatric Depression Scale (SGDS-K, range 0–15, with higher scores being indicative of more severe depression).[51]

Statistical Analyses

All statistical analyses were performed using SAS software (version 9.4; SAS Institute) and R (version 4.1.1; R Development Core Team). The statistical significance level was set as $p < 0.05$. Characteristics of participants between subjects with and without slowness were compared using *t*-test for continuous variables and the chi-square test for categorical variables. Distributions of phthalate metabolite by participant characteristics were summarized using *t*-test for binomial variables and Wald F-test for categorical variables. We evaluated Spearman's correlations between all phthalate metabolites collected at a single point and Spearman correlations between enrollment and follow-up visits for each metabolite. Correlation between metabolites was analyzed using data at Exam II, the only time when all five metabolites were measured.

We performed a cross-sectional analysis for all five phthalate metabolites with the first measurement data and additionally examined longitudinal analysis for three phthalate metabolites with repeated measurement data. Urinary phthalate metabolite concentrations were modeled as continuous variables (log-transformed to normalize their distributions) and quartiles with *p* for trend. In addition, *p*-values for linear trend across quartiles of phthalate metabolites were computed by modeling categories of the metabolite as an ordinal variable coded using integer values (0–3). Furthermore, we computed estimates by comparing each of the upper three quartiles to the lowest quartile. The cutoff value of each quartile for phthalate metabolite concentration was applied using values obtained at enrollment. To estimate the odds ratios (ORs) of slowness associated with phthalate metabolite levels, logistic regression models (PROC LOGISTIC) for cross-sectional analyses and marginal logistic models based on generalized estimating equations (PROC GENMOD) for longitudinal analyses were used. To evaluate the change in walking speed (meters/second) associated with phthalate metabolite levels, linear regression models (PROC GLM) were used for cross-sectional analysis and linear mixed effect models (PROC MIXED) were used for longitudinal analysis. A random intercept and a random slope for the time elapsed from the first visit were used to account for the heterogeneity across subjects and subject-specific variability of walking speed over time. All models were adjusted for age, sex, education level, city of residence, height, weight, physical activity, smoking status, osteoarticular disease, cardiovascular disease, respiratory disease, cancer, hypertension, and diabetes; potentially time-varying covariates were collected at enrollment and every follow-up. To account for variations in urinary dilution, we fitted creatinine-corrected models dividing phthalate metabolite concentrations by the creatinine concentrations.

We evaluated the overall effect as a mixture of all five phthalate metabolites using Bayesian kernel machine regression (BKMR) while accounting for nonlinear exposure–response relationships and the relative importance of individual metabolites in the association between mixtures and walking speed.[52,53] BKMR analysis was conducted using data at one time point (Exam II) when all five phthalate metabolites were measured to account for overall mixture effects and individual effects on walking speed. First, we evaluated overall mixture effects of phthalate metabolites on changes in walking speed (m/s) when all phthalate metabolites were at specific percentiles (i.e., first to 99th percentile) in comparison with their median values. Second, posterior inclusion

probabilities (PIPs) were used to determine which phthalate metabolites were important contributors to the association between the overall mixture effects and walking speed.[54] We also grouped phthalate exposure according to phthalate metabolite precursors and divided the five phthalate metabolites into three groups (group 1: MEHHP, MEOHP, and MECPP; group 2: MnBP; and group 3: MBzP) to fit hierarchical BKMR models.[53]

For all BKMR analyses, log-transformed creatinine-corrected phthalate metabolites levels were centered to a mean of 0 and scaled to an SD of 1. A PIP value of ≥0.5 was considered meaningful.[54,55] All models were adjusted for age, sex, region, education level, smoking status, weight, height, physical activity, osteoarticular disease, cardiovascular disease, chronic respiratory diseases, cancer, diabetes, and hypertension.

Sensitivity Analyses

The following sensitivity analyses were conducted: First, we examined whether the results were different between the nonadjusted creatinine models and the creatinine-adjusted models, including creatinine concentrations as a covariate in the models.[56] Second, we examined logistic regression models using 0.8 m/s and the lowest quintile of sex- and height-adjusted walking speed as cutoff points for slowness. Third, because socioeconomic status (SES) affects walking speed,[57] we examined whether the results differed after adjustment for additional SES factors, i.e., household income (<USD $450, USD $450–2,659.9, or ≥USD $2,660) and living arrangement (living alone, living with spouse, living with child, or others) in the subset sample with this information available (1,041 subjects with 1,721 observations). Fourth, because phthalate exposure was associated with the risk of depression in older adults[58] and depression might affect walking speed in older adults,[59] we examined whether results differed after adjusting for depression (1,189 subjects with 2,215 observations). Fifth, we conducted stratified models to assess potential effect modification by sex.

Results

Table 1 shows participants' main characteristics by walking speed group. Among a total of 1,190 older adults (range of 60–98 y of age) included at enrollment, 30.67% were males, and their mean ± SD age was 74.81 ± 5.99 y. The participants with slowness ($n = 893$, 75.04%) were significantly older and had lower height, weight, education, and physical activity levels than their counterparts.

The geometric mean (GM) (SD) was 21.25 (2.42) μg/L for MEHHP, 15.44 (2.45) μg/L for MEOHP, 28.50 (2.15) μg/L for MnBP, 25.00 (2.15) μg/L for MECPP, and 2.19 (4.43) μg/L for MBzP. Except for MnBP, metabolite concentrations were higher in participants with slowness at enrollment and at each follow-up visit (Table 1). The overall distribution of phthalate metabolites is presented in Tables S2 and S3. Concentrations of

Table 1. Enrollment and follow-up characteristics of 1,190 older adults from the Korean Elderly Environmental Panel II (2012–2014) by slowness status.

	Total			Slowness <1 m/s			Nonslowness ≥1 m/s			
	n	Mean	± SD	*n*	Mean	± SD	*n*	Mean	± SD	*p*-Value[a]
Demographic characteristics at enrollment										
Age (y)	1,190	74.81	± 5.99	893	75.75	± 5.91	297	71.99	± 5.31	<.001
BMI (kg/m^2)	1,190	23.79	± 3.09	893	23.75	± 3.21	297	23.90	± 2.68	0.434
Height (cm)	1,190	155.96	± 8.59	893	155.61	± 8.75	297	157.02	± 8.01	0.014
Weight (kg)	1,190	57.96	± 9.36	893	57.62	± 9.68	297	58.98	± 8.25	0.019
Sex [*n* (%)]	—	—	—	—	—	—	—	—	—	0.150
Male	365	30.67		264	29.56	—	101	34.01	—	—
Female	825	69.33		629	70.44	—	196	65.99	—	—
Education [*n* (%)]	—	—	—	—	—	—	—	—	—	<.001
≤Elementary school	797	66.97	—	668	74.80	—	129	43.13	—	—
Middle and high school	310	26.05	—	183	20.49	—	127	42.76	—	—
>High school	83	6.97	—	42	4.70	—	41	13.80	—	—
Physical activity (METs-hours/week) [*n* (%)]				—		—	—	—	—	<.001
<7.5	988	83.03	—	785	87.91	—	203	68.35	—	—
≥7.5	202	16.97	—	108	12.09	—	94	31.65	—	—
Phthalate metabolites[b]										
MEHHP (μg/L)										
Enrollment	1,190	21.25	± 2.42	893	22.79	± 2.39	297	17.23	± 2.45	<.001
Follow-up 1	740	17.94	± 2.19	583	18.84	± 2.18	157	14.98	± 2.16	0.001
Follow-up 2	288	15.99	± 2.27	154	17.46	± 2.34	134	14.45	± 2.16	0.050
MEOHP (μg/L)										
Enrollment	1,190	15.44	± 2.45	893	16.37	± 2.39	297	12.95	± 2.56	<.001
Follow-up 1	740	12.38	± 2.39	583	12.97	± 2.39	157	10.41	± 2.30	0.005
Follow-up 2	288	11.51	± 2.23	154	12.58	± 2.30	134	10.39	± 2.12	0.043
MnBP (μg/L)										
Enrollment	1,190	28.50	± 2.15	893	28.65	± 2.16	297	28.02	± 2.10	0.664
Follow-up 1	740	28.43	± 2.21	583	28.08	± 2.21	157	29.74	± 2.23	0.422
Follow-up 2	288	38.15	± 2.16	154	38.60	± 2.22	134	37.64	± 2.10	0.782
MECPP (μg/L)[c]										
Exam II (A1+B)	731	25.00	± 2.15	629	25.62	± 2.15	102	21.45	± 2.17	0.030
MBzP (μg/L)[c]										
Exam II (A1+B)	731	2.19	± 4.43	629	2.32	± 4.45	102	1.53	± 4.15	0.009

Note: All participants: Enrollment A+B+C in Figure 1. No covariate values were missing. —, no data; BMI, body mass index; GM, geometric mean; MBzP, mono-benzyl phthalate; MECPP, mono-(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; MET, metabolic equivalent; MnBP, mono-*n*-butyl phthalate; m/s, meter/second; SD, standard deviation.

[a]*p*-Values were based on *t*-test for continuous variables and chi-square test for categorical variables.

[b]GMs and SDs are presented.

[c]MECPP and MBzP had one measurement ($n = 731$) at Exam II (Follow-up A1 and Enrollment B). Only cross-sectional analysis was possible. Thus, repeated measurements of MECPP and MBzP were not available.

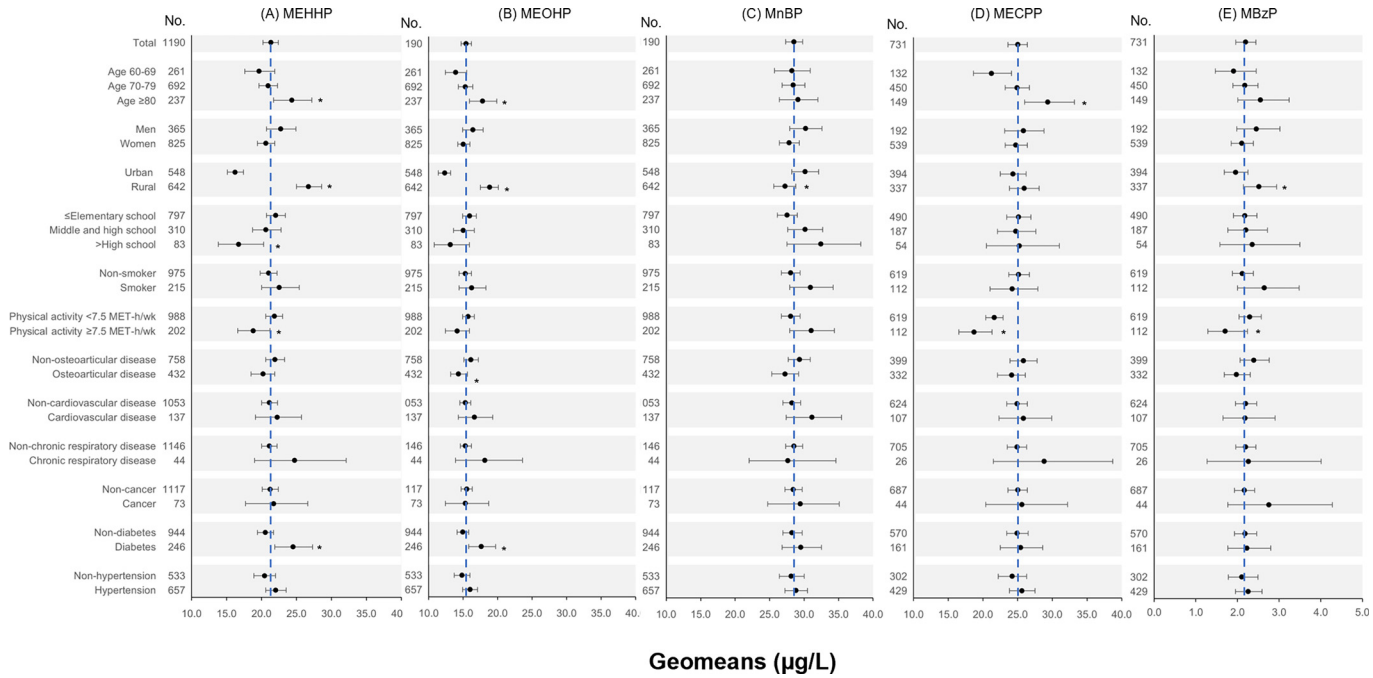

Figure 2. Geometric means (95% CIs) of urinary phthalate concentrations according to participant characteristics at enrollment in the KEEP II study. We used a survey *t*-test for binominal groups and Wald F-test for categorical groups. *Statistical significance at $p < 0.05$. The dotted line includes overall geometric means of phthalate metabolites (numeric values are presented in Table S4). Note: CI, confidence interval.

oxidized metabolites of di(2-ethylhexyl) phthalate (DEHP; i.e., MEHHP, MEOHP, and MECPP) were also higher in older participants, as well as in those who lived in rural areas and had lower physical activity levels; whereas concentrations of MnBP were higher in participants with higher education level, those who lived in urban areas, and those with higher physical activity levels (Figure 2; the numeric values are presented in Table S4). All phthalate metabolites were significantly correlated with each other [all correlation coefficients (r) >0.5 with all $p < 0.001$]; in particular, high molecular weight metabolites (MEHHP, MEOHP, and MECPP from the same parent compound) were strongly correlated with one another ($r = 0.894$, 0.915, and 0.960; all $p < 0.001$; Table 2). Correlations between enrollment and follow-up measures for each metabolite was relatively low (r between 0.296 and 0.463 with $p < 0.001$; Table S5).

Table 3 shows logistic regression results for slowness according to each urinary phthalate metabolite (phthalate levels divided by creatinine and expressed as micrograms per gram creatinine) from cross-sectional analysis at enrollment and longitudinal analysis. In the cross-sectional analysis, we observed a linear trend between MBzP quartiles and slowness (p for trend = 0.031). The OR per doubling of MBzP was 1.15 (95% CI: 1.02, 1.30), and the OR in the highest vs. lowest quartile was 2.20 (95% CI: 1.12, 4.35). We did not observe this trend with slowness in the other phthalate metabolites, although those in the second MECPP quartile and the highest MEHHP quartile (in comparison with those in the lowest) showed higher odds of slowness [OR = 2.21 (95% CI: 1.17, 4.18) and 1.52 (95% CI: 0.96, 2.41), respectively]. In the longitudinal analysis, MEHHP levels were associated with an increased risk of slowness [OR per doubling: 1.15 (95% CI: 1.02, 1.29), OR in the highest quartile (vs. lowest): 1.47 (95% CI: 1.04, 2.06), and p for trend = 0.035], whereas MnBP levels were associated with a decreased risk of slowness [OR per doubling: 0.84 (95% CI: 0.74, 0.96), OR in the highest quartile (vs. lowest): 0.64 (95% CI: 0.47, 0.87), and p for trend = 0.006]. Although MEOHP did not show a linear exposure–response association with slowness, the participants in the highest quartile (vs. lowest) of this metabolite showed an increased risk of slowness [OR = 1.52 (95% CI: 1.09, 2.13)].

Table 4 presents linear regression results of changes in walking speed according to each urinary phthalate metabolite from cross-sectional analysis at enrollment and longitudinal analysis. In the cross-sectional analysis, MBzP quartiles showed a liner trend with slower walking speed (p for trend = 0.048). The change in walking speed with an increased MBzP level was −0.01 m/s (95% CI: −0.02, −0.00) per doubling and −0.05 m/s (95% CI: −0.09, −0.01) in the highest quartile (vs. lowest). Although we did not observe this trend in other phthalate metabolites, MECPP levels were associated with slower walking speeds [change in walking speed: −0.02 m/s (95% CI: −0.04, −0.00) per doubling, −0.06 m/s (95% CI: −0.10, −0.02) and −0.05 m/s (95% CI: −0.09, −0.01)] in the second and third quartiles (vs. lowest),

Table 2. Spearman's coefficients of a single point correlation between phthalate metabolites at Exam II in the Korean Elderly Environmental Panel II study ($n = 731$).

	MEHHP (μg/L)	MEOHP (μg/L)	MnBP (μg/L)	MECPP[a] (μg/L)	MBzP[a] (μg/L)
MEHHP (μg/L)	1	—	—	—	—
MEOHP (μg/L)	0.960 ($p < 0.001$)	1	—	—	—
MnBP (μg/L)	0.576 ($p < 0.001$)	0.594 ($p < 0.001$)	1	—	—
MECPP (μg/L)	0.894 ($p < 0.001$)	0.915 ($p < 0.001$)	0.601 ($p < 0.001$)	1	—
MBzP (μg/L)	0.523 ($p < 0.001$)	0.528 ($p < 0.001$)	0.505 ($p < 0.001$)	0.537 ($p < 0.001$)	1

Note: —, no data; MBzP, mono-benzyl phthalate; MECPP, mono-(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; MnBP, mono-*n*-butyl phthalate.
[a]MECPP and MBzP had one measurement ($n = 731$) at Exam II (Follow-up A1 and Enrollment B). Only cross-sectional analysis was possible. Thus, repeated measurements of MECPP and MBzP were not available.

Table 3. Odds ratios (95% CI) for slowness (<1.0 m/s) according to urinary phthalate metabolite concentrations (micrograms per gram creatinine) from cross-sectional analysis at enrollment ($n = 1{,}190$) and longitudinal analysis ($n = 2{,}218$).

	Cross-sectional analysis at enrollment			Longitudinal analysis		
Phthalate metabolites	No. with slowness/no. of participants	OR (95% CI)		No. with slowness/no. of observations	OR (95% CI)	
MEHHP (μg/g cre)						
Per doubling	—	1.12	(0.96, 1.30)	—	1.15	(1.02, 1.29)
Quartile 1 (1.07, 16.75)	191/299	1	Ref	421/660	1	Ref
Quartile 2 (16.78, 25.89)	228/297	1.14	(0.77, 1.73)	427/580	1.08	(0.83, 1.41)
Quartile 3 (25.98, 41.58)	220/297	0.97	(0.65, 1.44)	404/530	1.16	(0.87, 1.54)
Quartile 4 (41.74, 306.32)	252/296	1.52	(0.96, 2.41)	376/446	1.47	(1.04, 2.06)
p for trend	—	0.198	—	—	0.035	—
MEOHP (μg/g cre)						
Per doubling	—	1.06	(0.92, 1.23)	—	1.05	(0.94, 1.17)
Quartile 1 (0.53, 11.98)	197/298	1	Ref	443/680	1	Ref
Quartile 2 (12.01, 18.66)	231/298	1.26	(0.84, 1.90)	423/573	1.04	(0.79, 1.36)
Quartile 3 (18.67, 30.96)	213/297	0.75	(0.50, 1.12)	387/519	0.91	(0.68, 1.22)
Quartile 4 (30.98, 263.23)	250/296	1.45	(0.92, 2.29)	375/444	1.52	(1.09, 2.13)
p for trend	—	0.555	—	—	0.105	—
MECPP[a] (μg/g cre)						
Per doubling	—	1.20	(0.92, 1.58)	—	NA	NA
Quartile 1 (3.89, 18.65)	142/182	1	Ref	NA	NA	NA
Quartile 2 (18.67, 27.29)	164/183	2.21	(1.17, 4.18)	NA	NA	NA
Quartile 3 (27.29, 41.43)	162/183	1.65	(0.89, 3.06)	NA	NA	NA
Quartile 4 (41.48, 216.94)	160/182	1.39	(0.74, 2.59)	NA	NA	NA
p for trend	—	0.326	—	—	NA	—
MnBP (μg/g cre)						
Per doubling	—	1.03	(0.86, 1.25)	—	0.84	(0.74, 0.96)
Quartile 1 (4.60, 24.63)	231/298	1	Ref	401/521	1	Ref
Quartile 2 (24.65, 33.97)	212/297	0.75	(0.49, 1.14)	380/517	0.72	(0.53, 0.99)
Quartile 3 (33.98, 49.07)	220/298	0.89	(0.58, 1.37)	403/565	0.67	(0.50, 0.91)
Quartile 4 (49.15, 764.57)	229/296	0.99	(0.64, 1.53)	145/614	0.64	(0.47, 0.87)
p for trend	—	0.829	—	—	0.006	—
MBzP[a] (μg/g cre)						
Per doubling	—	1.15	(1.02, 1.30)	—	NA	NA
Quartile 1 (0.04, 1.13)	146/182	1	Ref	NA	NA	NA
Quartile 2 (1.14, 2.76)	158/183	1.32	(0.72, 2.42)	NA	NA	NA
Quartile 3 (2.76, 5.53)	158/183	1.32	(0.72, 2.43)	NA	NA	NA
Quartile 4 (5.61, 66.47)	167/182	2.20	(1.12, 4.35)	NA	NA	NA
p for trend	—	0.031	—	—	NA	—

Note: All participants: Enrollment A+B+C in Figure 1. All observations: Enrollment A+B+C and Follow-up A1+A2+B1 in Figure 1. Logistic regression models were used for cross-sectional analysis and generalized estimating equation models were used for longitudinal analysis. All models were adjusted for age, sex, region, education level, smoking status, weight, height, physical activity, osteoarticular disease, cardiovascular disease, chronic respiratory diseases, cancer, diabetes, and hypertension. —, no data; CI, confidence interval; Cre, creatinine; MBzP, mono-benzyl phthalate; MECPP, mono-(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono (2-ethyl-5-hydroxyhexyl) phthalate; MEOHP, mono (2-ethyl-5-oxohexyl) phthalate; MnBP, mono-*n*-butyl phthalate; m/s, meter/second; NA, not available; Ref, reference.
[a]MECPP and MBzP had one measurement ($n = 731$) at Exam II (Follow-up A1+Enrollment B). Only cross-sectional analysis was possible. Thus, repeated measurements of MECPP and MBzP were not available.

whereas MnBP levels were associated with faster walking speeds [change in walking speed: 0.04 m/s (95% CI: 0.00, 0.07) in the second quartile (vs. lowest)]. In longitudinal analysis, MEHHP quartiles showed a linear trend with slower walking speed, and MnBP quartiles showed a linear trend with faster walking speed (p for trend = 0.026 and <0.001, respectively). The change in walking speed was −0.01 m/s (95% CI: −0.02, −0.00) per doubling of MEHHP, and 0.03 m/s (95% CI: 0.02, 0.04) per doubling of MnBP, and 0.04 m/s (95% CI: 0.02, 0.07), 0.05 m/s (95% CI: 0.03, 0.08), and 0.08 m/s (95% CI: 0.05, 0.10) increases in the second, third, and fourth MnBP quartiles (vs. lowest), respectively.

In the sensitivity analysis, results in the creatinine-unadjusted models, as well as in models adjusted for creatinine by including it as a covariate, were consistent, even though the statistical significances differed between the logistic (Table S6) and linear regression models (Table S7) depending on the metabolites. These results were consistent although when slowness was defined using the alternative proposed cutoff point of 0.8 m/s, results were no longer statistically significant (~49% of the population rated slow; Table S8), or the lowest quintile of walking speed was adjusted for sex and height (Table S9). Additionally, results were also consistent when models were further adjusted for SES factors and depression in subjects where this information was available (Table S10).

In stratified analyses, we observed an effect modification for MnBP with an inverse exposure–response association in women (p for interaction = 0.018; Table S11).

After controlling for all covariates, the BKMR model showed that the overall mixture of five phthalate metabolites was inversely associated with walking speed when all phthalate metabolites were in the first to 99th percentiles in comparison with the median value (Figure 3; numeric values are presented in Table S12). For example, in comparison with the 50th percentile, the subjects with overall phthalate mixtures in the 75th and 95th percentiles had 0.021 m/s [95% credible interval (Crl): −0.035, −0.006] and 0.047 m/s (95% Crl: −0.093, −0.001) decreases in walking speed, respectively. Based on the estimated PIPs, none of the five phthalate metabolites (all PIPs <0.5) was identified as a significantly dominant contributor to the overall association (Table S13). In our hierarchical model, we observed that group 1 (MEHHP, MEOHP, and MECPP) had the highest group PIP, driving the main effect of the overall mixture (group PIP = 0.51), in which MEHHP played the most important role (conditional PIP = 0.72) (Table S13).

Table 4. Change (95% CI) in walking speed (m/s) according to urinary phthalate metabolite concentrations (micrograms per gram cre) from cross-sectional analysis at enrollment ($n = 1{,}190$) and longitudinal analysis ($n = 2{,}218$).

	Cross-sectional analysis at enrollment			Longitudinal analysis		
Phthalate metabolites	No. of participants	Estimate (m/s) (95% CI)		No. of observations	Estimate (m/s) (95% CI)	
MEHHP (μg/g cre)						
Per doubling	—	−0.01	(−0.02, 0.01)	—	−0.01	(−0.02, −0.00)
Quartile 1 (1.07, 16.75)	299	0	Ref	660	0	Ref
Quartile 2 (16.78, 25.89)	297	−0.01	(−0.05, 0.02)	580	0.00	(−0.03, 0.02)
Quartile 3 (25.98, 41.58)	297	−0.01	(−0.05, 0.02)	530	−0.02	(−0.05, 0.00)
Quartile 4 (41.74, 306.32)	296	−0.03	(−0.06, 0.01)	446	−0.03	(−0.05, 0.00)
p for trend	—	0.174	—	—	0.026	—
MEOHP (μg/g cre)						
Per doubling	—	0.00	(−0.01, 0.01)	—	0.00	(−0.01, 0.01)
Quartile 1 (0.53, 11.98)	298	0	Ref	680	0	Ref
Quartile 2 (12.01, 18.66)	298	0.00	(−0.04, 0.03)	573	0.01	(−0.01, 0.04)
Quartile 3 (18.67, 30.96)	297	0.02	(−0.01, 0.06)	519	0.01	(−0.02, 0.03)
Quartile 4 (30.98, 263.23)	296	−0.01	(−0.04, 0.03)	444	−0.01	(−0.04, 0.02)
p for trend	—	0.865	—	—	0.493	—
MECPP[a] (μg/g cre)						
Per doubling	—	−0.02	(−0.04, −0.00)	—	NA	NA
Quartile 1 (3.89, 18.65)	182	0	Ref	NA	NA	NA
Quartile 2 (18.67, 27.29)	183	−0.06	(−0.10, −0.02)	NA	NA	NA
Quartile 3 (27.29, 41.43)	183	−0.05	(−0.09, −0.01)	NA	NA	NA
Quartile 4 (41.48, 216.94)	182	−0.04	(−0.08, 0.00)	NA	NA	NA
p for trend	—	0.112	—	—	NA	—
MnBP (μg/g cre)						
Per doubling	—	0.00	(−0.01, 0.02)	—	0.03	(0.02, 0.04)
Quartile 1 (4.60, 24.63)	298	0	Ref	521	0	Ref
Quartile 2 (24.65, 33.97)	297	0.04	(0.00, 0.07)	517	0.04	(0.02, 0.07)
Quartile 3 (33.98, 49.07)	298	0.02	(−0.01, 0.05)	565	0.05	(0.03, 0.08)
Quartile 4 (49.15, 764.57)	296	0.03	(−0.01, 0.06)	614	0.08	(0.05, 0.10)
p for trend	—	0.284	—	—	<.001	—
MBzP[a] (μg/g cre)						
Per doubling	—	−0.01	(−0.02, −0.00)	—	NA	NA
Quartile 1 (0.04, 1.13)	182	0	Ref	NA	NA	NA
Quartile 2 (1.14, 2.76)	183	−0.04	(−0.08, 0.00)	NA	NA	NA
Quartile 3 (2.76, 5.53)	183	−0.02	(−0.06, 0.02)	NA	NA	NA
Quartile 4 (5.61, 66.47)	182	−0.05	(−0.09, −0.01)	NA	NA	NA
p for trend	—	0.048	—	—	NA	—

Note: All participants: Enrollment A+B+C in Figure 1. All observations: Enrollment A+B+C and Follow-up A1+A1+B1 in Figure 1. Linear regression models were used for cross-sectional analysis and linear mixed-effects models were used for longitudinal analysis. All models were adjusted for age, sex, region, education level, smoking status, weight, height, physical activity, osteoarticular disease, cardiovascular disease, chronic respiratory diseases, cancer, diabetes, and hypertension. —, no data; CI, confidence interval; Cre, creatinine; MBzP, mono-benzyl phthalate; MECPP, mono-(2-ethyl-5-carboxypentyl) phthalate; MEHHP, mono (2-ethyl-5-hydroxyhexyl) phthalate; MEOHP, mono (2-ethyl-5-oxohexyl) phthalate; MnBP, mono-*n*-butyl phthalate; m/s, meters/second; NA, not available; Ref, reference.

[a]MECPP and MBzP had one measurement ($n = 731$) at Exam II (Follow-up A1+Enrollment B). Only cross-sectional analysis was possible. Thus, repeated measurements of MECPP and MBzP were not available.

Discussion

In the current study, we evaluated the association between urinary phthalate metabolite levels and slowness in adults aged ≥60 years using data from the Korean Elderly Environmental Panel II (KEEP II) study. The cross-sectional data showed a positive exposure-response association between creatinine-corrected (micrograms per gram creatinine) MBzP levels and slowness, and higher concentrations of MEHHP were positively associated with the odds of slowness. The association for MEHHP became stronger in longitudinal analyses. MnBP showed a null result in the cross-sectional analysis but an inverse exposure–response association with slowness in the longitudinal analysis. Linear regression models using walking speed (meter/second) showed similar results as well as in MBzP, MEHHP, and MnBP. Furthermore, the current study found an overall joint effect of urinary phthalate metabolites in the association with decreased walking speed. The DEHP group (MEHHP, MEOHP, and MECPP) was observed to have the main effect of the overall mixture, in which MEHHP played the most important role.

Although there is growing evidence on the potential associations between environmental pollutants and declined physical function,[20,60] and in particular on reduction in walking speed,[6–8] this is the first epidemiological study, to our knowledge, that has evaluated the association between phthalate metabolites and slowness.

The associations observed may be explained through several mechanisms. First, phthalates could exert neurological effects on several cognitive, neurosensory, and behavioral abilities, which control walking function.[61] In this respect, *in vivo* studies using Kunming mice, given oral exposure to DEHP and benzyl butyl phthalate (BBP) caused spatial learning and memory dysfunction;[29,30] whereas phthalate exposure in zebrafish induced damage to the primary neurons and reduced the expression of genes associated with central nervous system development.[32] There is also epidemiological evidence in humans suggesting that phthalate exposure may induce declines in memory[62] and hearing.[19] Second, phthalates have been associated with changes in the musculoskeletal system, manifested as reductions in bone mineral density,[24] an increased risk of osteoporosis,[23] and low grip strength.[21,22] In other animal studies, exposure to phthalates has been associated with disruptions to skeletal formation and bone homeostasis.[34,35] Third, a recent literature review has suggested that phthalates are associated with the cardiovascular system (e.g., hypertension, atherosclerosis, diabetes, and obesity),[63] which might cause slower walking speed in adults age 45 y and older.[64,65] However, adjusting for cardiovascular diseases and hypertension

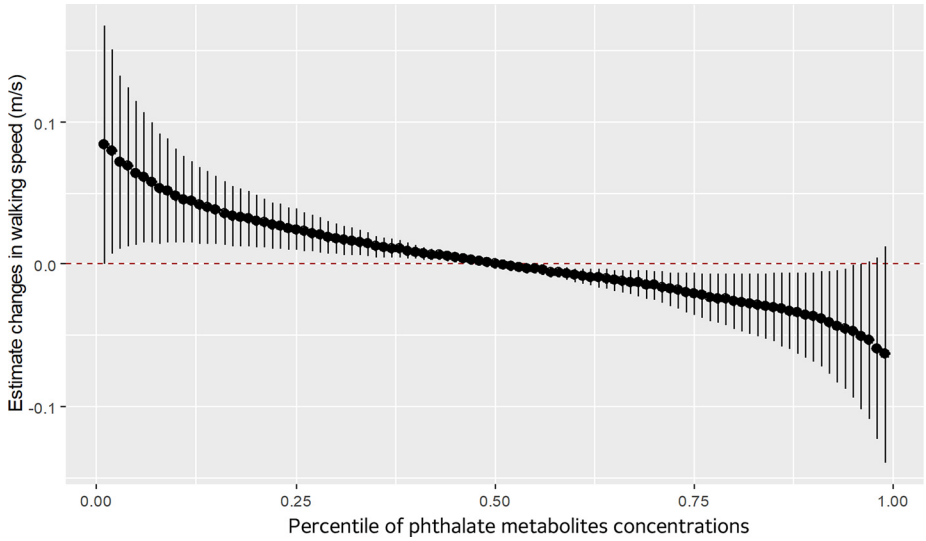

Figure 3. Overall effects of phthalate metabolite mixtures on changes in walking speed (m/s, meters/second) estimated by Bayesian kernel machine regression. Analysis was conducted with data at one time point (Exam II) when all five metabolites were measured ($n = 731$). The model was adjusted for age, sex, region, education level, smoking status, weight, height, physical activity, osteoarticular disease, cardiovascular disease, chronic respiratory diseases, cancer, diabetes, and hypertension. The plot shows the estimated values when all log-transformed phthalates were at the respective percentiles (from the first to the 99th) in comparison with median values. Variation is presented using 95% credible intervals (numeric values are presented in Table S12).

did not alter the observed associations. Fourth, there is evidence that phthalate exposure can induce oxidative stress and inflammation,[36,37] both of which are important mechanisms associated with age-related physical functional decline.[40] Indeed, several epidemiological studies have shown that inflammatory markers such as CRP, IL-6, and TNFα are associated with decreased physical function in the adults age 65 y and older through catabolic effects on muscle[38–40] and through structural brain damage.[66] In addition, Semba et al. have reported an inverse relationship between protein carbonyl level, as an indicator of oxidative damage to protein, and decreased walking speed among women age 65 y and older.[67] Increased concentrations of superoxide anion production by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, another indicator of oxidative stress, have also been associated with slow walking speed in adults ages 76–84 y.[68] Moreover, a growing body of evidence suggests that increased oxidative stress can induce mitochondrial DNA and microglia damage in the aging brain, which may lead to cognitive and neurodegenerative diseases.[69] One *in vivo* study has reported that phthalate exposure can induce neurotoxicity through oxidative stress.[31] Fifth, several *in vitro* studies have shown that phthalates can activate peroxisome proliferation–activated receptors (PPARs) in skeletal muscle, brain, and adipose tissues.[70,71] Moreover, recent literature review and animal studies have suggested that some PPARs can not only be activated by phthalate metabolites but also can modify some adverse effects of phthalates on reproductive,[72] hepatic,[73] neurological,[74] and cardiovascular outcomes.[75] Last, an *in vitro* study using mice has found evidence that DEHP can induce PPARγ overexpression and result in apoptosis of undifferentiated neurons.[76]

However, we found inconsistent results in the association between low molecular weight phthalate metabolites (MnBP and MBzP) and walking speed. MBzP revealed an exposure–response association with slowness in the cross-sectional analysis, and MnBP showed a null result in the cross-sectional analysis but an inverse exposure–response association with slowness in the longitudinal analysis. The observed inverse association between MnBP and slowness might be affected by confounding of socioeconomic status [see directed acyclic graph (DAG)] in Figure S1, because the higher usage of personal care products, a major source of MnBP exposure, was correlated with higher SES (e.g., household income and education level),[77] and individuals with higher SES were associated with better physical function.[57] Therefore, we performed sensitivity analyses adjusting for household income, but the results were virtually the same (Table S10). An interesting finding was that urinary MnBP levels in the current study were marginally correlated with household income in women ($p = 0.054$) but not in men ($p = 0.305$) (Table S14). Silva et al. have reported that concentrations of MnBP used in personal care products, such as perfumes, lotions, cosmetics, and hair care products, are higher in women than in men.[78] Thus, we performed a sensitivity analysis of the association between phthalate metabolites and slowness in subgroups according to sex (Table S11). An inverse exposure–response association was observed only in women but not in men. Taken together, a correlation between SES and personal care product use, one of major sources of MnBP in women, might lead to a change in the estimated association between MnBP and slowness in women (Figure S1B). Because the majority of the participants in the current study were women (69.3%), the associations in women may have driven the results in the overall study population.

Strengths of this study include the use of repeated measures for urinary phthalates and walking speed, the use of several phthalate metabolites, the fact that we adjusted for an important number of potential confounding factors, and the use of different approaches to account for urinary dilution. Another strength of the current study was the use of a sophisticated method, i.e., the BKMR approach, to evaluate the overall mixture effect of urinary phthalate metabolites on walking speed. It is challenging to detect an exposure–response relationship between chemical mixtures and health outcomes, in particular when the chemicals are highly correlated or from the same precursors. Among the potential limitations, we had a relatively low number of participants, which may have limited our ability to observe statistically significant associations. Unfortunately, we do not have information on potential biological mediators (i.e., inflammatory favors) and, due to a short biological half-life (24–48 h),[79] our urinary phthalate metabolite levels could provide only an estimate of recent exposure. However, previous studies have demonstrated that single-spot urine samples of phthalates could be representative of long-term average levels of exposure. Thus, they could reflect an

increased risk of cumulative exposure over time.[80–82] Moreover, within-subject temporal variations are unlikely to be large because an individual's lifestyle does not change significantly over time. Additionally, there might be an issue of healthy worker bias because phthalates exposure might differ in part depending on occupation. However, because most subjects in our study were retired or currently unemployed, their exposure sources were mainly from nonoccupational settings such as leisure or household activities. Thus, our study is unlikely to have a healthy worker bias.

Conclusion

In conclusion, urinary phthalate concentrations were associated with slowness in walking speed, which might reflect decreased functional ability and overall health in adults ages 60–98 y. Our findings add to the growing body of evidence demonstrating phthalate-mediated adverse health effects in the human body and support the need to further reduce the current exposure levels to prevent functional decline and promote healthy aging.

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The funders had no role in this study design, data collection, and analysis and prepared all results.

All authors participated in literature search and data interpretation. Y.C. supervised the study; Y.C. and Y.H. participated in designing the study; H.K., S.K., and K.K. acquired the data; J.Y., J. Kim, and J. Kwak analyzed data; J.Y. wrote the manuscript; E.G.-E., J. Kim, J. Kwak, H.K., Y.H., and Y.C. critically revised the manuscript.

Patient consent was obtained. This study was approved by the institutional review board (IRB) of Seoul National University Hospital/College of Medicine (IRB No. H-1209-004-424).

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