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Association between phthalate exposure and lower lung function in an urban elderly population: A repeated-measures longitudinal study

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ABSTRACT

Background: Lung function is a major predictor of morbidity and mortality. Only a few studies have explored the association between phthalate exposure and lung function.
Objective: To evaluate the association between phthalate exposure and lung function in the elderly.
Methods: A total of 3 repeated-measures surveys were conducted in 559 elderly individuals aged ≥60 years in Seoul, Korea, at 1-year intervals (2012–2015). During each survey, urinary mono-(2-ethyl-5-hydrohexyl) phthalate (MEHHP) (geometric mean, 15.68 μg/L), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP) (11.97 μg/L), and mono-*n*-butyl phthalate (MnBP) (2.09 μg/L) levels were measured; moreover, lung function tests and a structured questionnaire interview were performed. We constructed linear mixed models to assess the association between urinary phthalate metabolite levels and lung function.
Results: A doubling of creatinine-adjusted urinary phthalate metabolite levels was inversely associated with forced expiratory volume in 1 s (L) (β = −0.01, 95% confidence interval [CI]: −0.02, 0.004 for MEHHP; β = −0.02, 95% CI: −0.03, −0.01 for MEOHP; β = −0.01, 95% CI: −0.03, −0.003 for MnBP) and forced vital capacity (L) (β = −0.02, 95% CI: −0.03, −0.001 for MEHHP; β = −0.02, 95% CI: −0.03, −0.004 for MEOHP; β = −0.02, 95% CI: −0.03, −0.001 for MnBP). A doubling of creatinine-adjusted MnBP levels was associated with increased rates of annual decline in forced vital capacity (L/year) (β = −0.01, 95% CI: −0.02, −0.001).
Conclusions: Urinary phthalate metabolite levels were associated with lower lung function and an increased rate of decline in lung function in an elderly population.

1. Background

Lung function is a major predictor of morbidity and mortality in the general population (Kannel et al., 1983; Schünemann et al., 2000). In elderly individuals, in particular, lung function is critical in terms of their functional status and quality of life (Peruzza et al., 2003). Impairments in lung function can lead to a decline in physical activity, muscle strength, and mobility in this population; this might further decrease lung function and thus create a vicious cycle (Buchman et al., 2009; Sillanpää et al., 2014). The rates of a decline in lung function and subsequent lung function levels can differ across elderly individuals of a similar age (Sharma and Goodwin, 2006; Sillanpää et al., 2014) due to factors such as smoking status (Vestbo et al., 2011) or body mass index (Casanova et al., 2011).

Phthalates, which are widely used chemicals used as plasticizers or scent preservatives in various consumer and industrial products (Zota et al., 2014), were shown to be associated with lower lung function in a limited number of epidemiological studies (Cakmak et al., 2014; Hoppin et al., 2004). The association between phthalate exposure and lower lung function may be due to the pro-oxidative and inflammatory properties of phthalates that can adversely affect the respiratory system (Cakmak et al., 2014; Hoppin et al., 2004; Park et al., 2013).

However, a majority of previous studies on the association between phthalate exposure and lung function used a cross-sectional study

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; DBP, dibutyl phthalate; DEHP, di-(2-ethylhexyl) phthalate; $FEF_{25–75}$, forced expiratory flow at 25–75% of the forced vital capacity; FEV_1, forced expiratory volume in 1 s; FEV_1/FVC, ratio of forced expiratory volume in 1 s to forced vital capacity; FVC, forced vital capacity; MEHHP, mono-(2-ethyl-5-hydrohexyl) phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; MnBP, mono-*n*-butyl phthalate

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design, and therefore, a single measurement of phthalates and lung function (Cakmak et al., 2014; Hoppin et al., 2004). A cross-sectional study design with a single measurement of exposure may have problems such as reverse causality and measurement error, especially when the temporal variability of biomarker levels is high, as in the case of phthalates (Hoppin et al., 2002).

Elderly individuals are potentially susceptible to environmental risk factors including phthalates, due to their increased age-associated oxidative stress (Andriollo-Sanchez et al., 2005) and decreased capacity to retain physiological homeostasis (Geller and Zenick, 2005). In the present study, we hypothesized that urinary phthalate metabolite levels are associated with lower lung function and an increased rate of lung function decline in an elderly population. To obtain accurate estimators of the associations between phthalate exposure and lung function as well as the rate of lung function decline, we conducted repeated-measures analyses using a cohort from a community-dwelling elderly population.

2. Methods

2.1. Study design and population

We conducted 3 repeated-measures surveys at approximately 1-year intervals between 2012 and 2015. A total of 559 elderly citizens aged ≥60 years who had the ability to communicate with the survey technicians were recruited at 2 elderly welfare centers in Seoul, Republic of Korea. During the study period, 244 (43.7%), 151 (27.0%), and 164 (29.3%) subjects participated in all 3, 2, and only 1 survey(s), respectively. Each survey consisted of urine and blood sampling; physical examinations including lung function tests (spirometry); anthropometric measurements; and a structured questionnaire interview asking questions on sociodemographic characteristics, medical history, and lifestyle factors. All study participants provided written informed consent, and the Institutional Review Board of the Seoul National University Hospital approved the study protocol (C-1209-006-424).

2.2. Lung function test

Lung function was assessed by a trained technician using a Viasys Microlab portable spirometer (MicroMedical Ltd., Rochester, Kent, UK) according to the 2005 European Respiratory Society/American Thoracic Society recommendations (Miller et al., 2005). For each survey, three lung function tests that met the quality criteria standards (such as an acceptable start of test) were measured from up to 8 maneuvers and the greatest value was recorded. Forced expiratory volume in 1 s (FEV_1, L), forced vital capacity (FVC, L), ratio of FEV_1 to FVC (FEV_1/FVC, %), and forced expiratory flow at 25–75% of the FVC ($FEF_{25–75}$, L/s) were calculated from the tests.

2.3. Exposure assessment

Three phthalate metabolites representing two parent phthalate compounds were measured using urine samples collected during each survey. Urinary levels of mono-(2-ethyl-5-hydrohexyl) phthalate (MEHHP) and mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), which are monoester metabolites of di-(2-ethylhexyl) phthalate (DEHP), and those of mono-*n*-butyl phthalate (MnBP), which is a monoester metabolite of dibutyl phthalate (DBP), were analyzed using ultra-high-performance liquid chromatography tandem mass spectrometry (NexeraX2; Shimadzu, Kyoto, Japan). Of the numerous phthalate metabolites, we chose to measure MEHHP, MEOHP, and MnBP due to their widespread use. Lead, cadmium, and mercury levels in blood were measured from venous whole blood samples that were collected in trace-metal-free tubes. Detailed methods are presented in the Supplementary Material.

2.4. Covariates

During every survey, information on the participants' age, sex, monthly household income, educational level, active smoking status, pack-years of smoking, passive smoking status, alcohol consumption, physical activity (such as fast walking, swimming, table tennis, badminton, bare-handed gymnastics, stretching, dancing, and yoga), and comorbidity was obtained using structured questionnaires. Anthropometric indices such as the participants' standing height and weight were measured by trained survey staff.

2.5. Statistical analysis

We adjusted urinary phthalate metabolite levels for urinary creatinine levels by dividing phthalate metabolite levels by creatinine levels, to account for the effect of different urine dilutions. As MEHHP and MEOHP are metabolites of the same parent phthalate DEHP and reflect the same exposure, we summed the molar concentrations of MEHHP and MEOHP and used the summed values in the analysis (referred to as ΣDEHP). We then log2-transformed the values of creatinine-adjusted urinary phthalate metabolite (MEHHP, MEOHP, ΣDEHP, and MnBP) levels based on their log-normal distributions.

To evaluate the associations between the levels of each phthalate metabolite (MEHHP, MEOHP, ΣDEHP, and MnBP) and the lung function indices (FEV_1, FVC, FEV_1/FVC, and $FEF_{25–75}$), we constructed linear mixed models adjusted for potential confounders with a random intercept for each participant to account for the repeated-measures study design. The linearity of the associations was investigated by conducting semiparametric analysis using generalized additive mixed models.

We also assessed the association between phthalate metabolite levels and the progression of lung function decline during the study period. In the progression analysis (Gassett et al., 2015; Kaufman et al., 2016), we constructed linear mixed models with random intercepts and slopes, including covariates and phthalate metabolite levels assessed at baseline, time from baseline at each observation (in years), interaction between time-varying covariates and time, and interaction between time-varying phthalate metabolite levels and time. The regression coefficient for the interaction term between time-varying phthalate metabolite levels and time was interpreted as a change in the annual decline rate of lung function by a doubling of phthalate metabolite levels (Gassett et al., 2015; Kaufman et al., 2016).

Detailed methods regarding covariate selection and modeling approach are presented in the Supplementary Material.

We conducted the same analysis stratified by chronic obstructive pulmonary disease (COPD) status (defined as FEV_1/FVC < 0.7), because COPD is an important respiratory condition with high prevalence and substantial disease burden in an elderly population and potentially moderates the association between phthalate exposure and lung function.

We performed sensitivity analyses to confirm the robustness of the results. First, we constructed models that were further adjusted for heavy metal levels (lead, cadmium, and mercury) measured from venous blood samples that were collected during each survey. We conducted this analysis because blood heavy metal levels were reported to be associated with lower lung function in recent cross-sectional studies using representative samples of U.S. (Rokadia and Agarwal, 2013) and Korean populations (Leem et al., 2015). Second, as the participants completed differing numbers of surveys, which could be a source of selection bias, we performed the analyses after weighting the observation by the inverse probability of participation in each follow-up survey. Third, because information on the smoking status was obtained only through questionnaire and not confirmed by biomarker such as cotinine, we conducted analyses excluding each smoking status variables (active smoking, pack-years, and passive smoking status) sequentially. In addition, we conducted analysis restricted to those who