


Association Between Urinary Phthalate Metabolites and Chronic Obstructive Pulmonary Disease: A Cross-Sectional Study

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Objective: To determine the association of urinary phthalate metabolites with chronic obstructive pulmonary disease (COPD), airflow obstruction, lung function and respiratory symptoms.

Methods: Our study included a total of 2023 individuals aged ≥ 40 years old in the National Health and Nutrition Examination Survey (NHANES). Multivariate logistic regression was conducted to explore the correlation of eleven urinary phthalate metabolites (MCNP, MCOP, MECPP, MnBP, MCP, MEP, MEHHP, MEHP, MiBP, MEOHP, and MBzP) with COPD, airflow obstruction and respiratory symptoms. Linear regression analyses were used to evaluate the relationship between urinary phthalate metabolites and lung function.

Results: When compared to the first tertile, the third tertile of MEHHP was associated with the risk of COPD [OR: 2.779; 95% confidence interval (CI): 1.129–6.840; $P = 0.026$]. Stratified analysis showed that MEHHP increased the risk of COPD by 7.080 times in male participants. Both MCP and MBzP were positively correlated with the risk of airflow obstruction. The third tertile of MBzP increased the risk of cough by 1.545 (95% CI: 1.030–2.317; $P = 0.035$) times. Both FEV1 and FVC were negatively associated with MEHHP, MECPP, MnBP, MEP, MiBP and MEOHP.

Conclusion: Higher levels of MEHHP are associated with increased risk of COPD, and lower measures of FEV1 and FVC. MBzP is positively related to airflow obstruction and cough.

Keywords: chronic obstructive pulmonary disease, phthalate, airflow obstruction, lung function, national health and nutrition examination survey

Introduction

Chronic obstructive pulmonary disease (COPD) is one of the most common chronic lung disorder, and its global health burden is increasing. COPD is the third leading cause of death worldwide.^{1,2} Chronic bronchitis and emphysema are two primary phenotypes of COPD.³ COPD is characterised by progressive airflow obstruction and persistent respiratory symptoms.⁴ Airway obstruction is applied for the diagnosis of COPD and the assessment of disease severity by the Global Initiative for Chronic Obstructive Lung Disease (GOLD).^{5,6} The ratio of forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) < 0.7 is defined as airflow obstruction.⁷ Patients with COPD clinically present with cough, expectoration, wheezing, and dyspnoea.⁴ Long-term exposure to tobacco smoking is the key risk factor associated with COPD. However, only 15–20% of smokers develop the disease in their lifetime.⁸ Other risk factors include noxious agents, pollutants, host genetic factors, childhood respiratory viral infections, history of asthma, dietary intake, and social deprivation.^{9,10}

Phthalates are a class of endocrine-disrupting chemicals that are extensively used in a variety of plastic products, including housing materials, food/beverage containers, cosmetics, and children's playthings.^{11,12} Phthalates are not firmly bound to polymers and thereby are easily released into the surrounding environment. Human beings are widely exposed

to large amounts of phthalates through air inhalation, skin contact, and food intake.^{12,13} Phthalates are metabolized into monoesters in the human body and then excreted in the urine. Exposure to phthalates is usually inferred by the detection of urinary metabolite concentrations.^{14–16}

Current evidence suggests that phthalates exposure may affect the health of the respiratory system.¹⁷ Experimental studies show that phthalates directly impact the role of epithelial cells on airway remodeling.^{18,19} Phthalates may facilitate oxidative stress, which has been shown to deteriorate airway obstruction.^{20–22} Higher exposure to phthalates was correlated with increased respiratory symptoms and COPD exacerbations in a small sample of COPD patients.¹⁵ However, the association between phthalates and the risk of COPD was not understood. In the present study, we aimed to determine associations of urinary phthalate metabolites with COPD, airflow obstruction, lung function and respiratory symptoms using comprehensive data from the National Health and Nutrition Examination Survey (NHANES).

Materials and Methods

Study Population and Data Sources

NHANES is a national survey conducted to assess health and nutritional status of Americans by the US Centers for Disease Control and Prevention. Our study included data from three rounds (2007–2008, 2009–2010, and 2011–2012) of the NHANES project. Ethics approval was accepted by the Ethics Review Committee of the National Center for Health Statistics. All participants signed written consent forms. All data obtained from the NHANES database were de-identified. Therefore, the Ethics Committee of Zhejiang Hospital exempted both ethical approval and written informed consent from subjects of the present study.

A total of 30,442 individuals were identified from NHANES 2007–2012. We excluded missing data, including age, gender, race, education, ratio of family income to poverty, marital status, body measures, FEV1, FVC, smoking, urinary phthalate metabolites, and respiratory symptoms (cough, expectoration, and wheezing). FEV1 or FVC with the quality of C, D or F was also excluded. Finally, 2023 subjects aged ≥ 40 years old were included in our study, and the flow chart of participants selection was shown in [Figure 1](#).

Study Variables

We collected the following data of subjects, including age, gender (female and male), race (Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, and other races), education level (less than 9th grade, 9–11th grade, high school graduates, some college/AA degrees, and college graduates/above), ratio of family income to poverty (≤ 1 , 1–2, 2–4, and > 4), marital status (married, divorced, widowed, separated, never married, and living with partner) and body mass index (BMI, kg/m^2) (< 18.5 , 18.5–25, 25–30, and ≥ 30). Smoking status was defined according to participants' answers to the question "smoked at least 100 cigarettes in their lifetime". Subjects who are diagnosed with "chronic bronchitis and/or emphysema" by a doctor or other healthcare provider are considered to have COPD. The ratio of FEV1 to FVC < 0.7 was defined as airflow obstruction. FEV1 and FVC were obtained from pre-bronchodilator spirometry. Cough was defined according to the answer to the question "usually cough on most days for 3 consecutive months or more during the year". The definition of expectoration was based on the problem of "bring up phlegm on most days for 3 consecutive months or more during the year". We defined wheezing according to the participants' answers to the question "wheezing or whistling in chest in the past 12 months".

Measurements of Urinary Phthalate Metabolites

Urine samples were collected and frozen at -20°C by the National Center for Environmental Health. High-performance liquid chromatography-electrospray ionization tandem mass spectrometry (HPLC-ESI-MS/MS) was used to quantitatively detect the concentrations of urine phthalate metabolites. The levels below the limit of detection (LOD) were replaced by the LOD divided by the square root of two. All urinary phthalate metabolites were creatinine-standardized ($\mu\text{g}/\text{g}$ creatinine). We selected eleven urinary phthalate metabolites with a detection frequency of more than 60%, including mono (carboxynonyl) phthalate (MCNP), mono (carboxyoctyl) Phthalate (MCOP), mono-2-ethyl-5-carboxypentyl phthalate (MECPP), mono-n-butyl phthalate (MnBP), mono-(3-carboxypropyl) phthalate (MCP), mono-ethyl

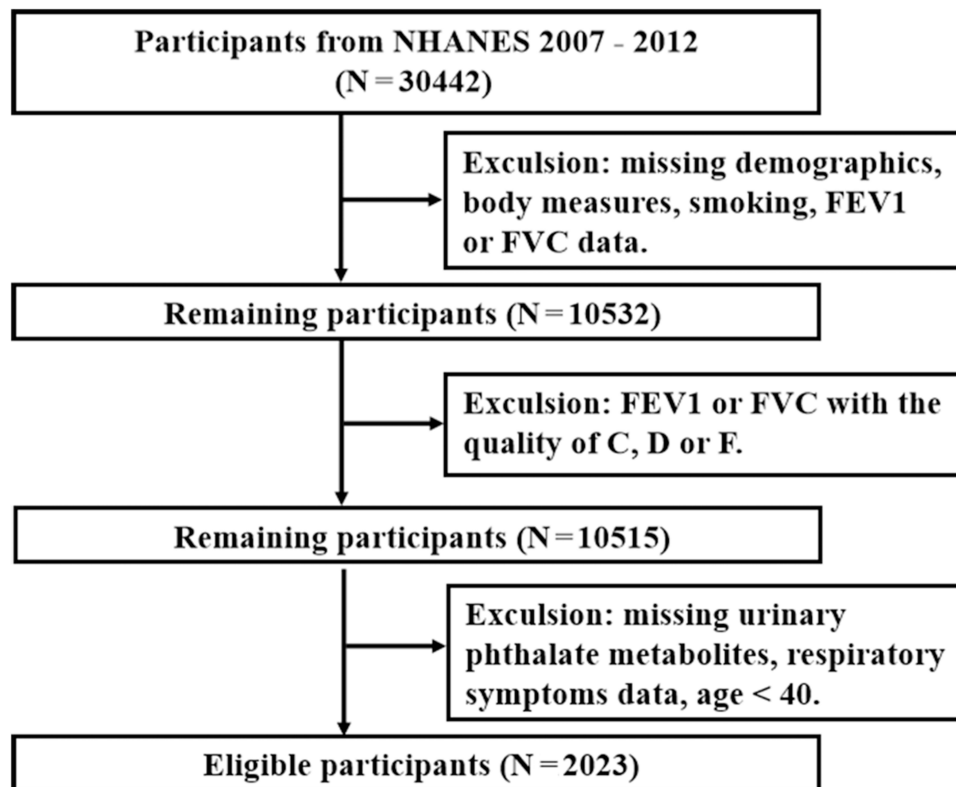


Figure 1 Flow chart of the screening process.

Abbreviations: NHANES, National Health and Nutrition Examination Survey; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity.

phthalate (MEP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-hexyl) phthalate (MEHP), mono-isobutyl phthalate (MiBP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono-benzyl phthalate (MBzP). Urinary phthalate metabolites were categorized into tertiles, with the lowest tertile set as the reference category.

Statistical Analysis

All data analyses were performed using Statistical Package for the Social Sciences version 19.0 software (SPSS Inc., Chicago, IL, USA). Categorical data were represented as numbers (percentages) and chi-square tests were performed to compare differences between groups. Normally distributed variables were expressed as mean \pm standard deviation (SD), and comparisons between groups were analyzed by *t*-test. Multi-group comparisons were examined by one-way ANOVA analysis. Multivariate logistic regression was conducted to explore the associations of urinary phthalate metabolites with COPD, airflow obstruction and respiratory symptoms. The variables of the adjusted model included age, race, gender, education, marital status, ratio of family income to poverty, BMI and smoking. Linear regression analyses were used to evaluate the correlation between urinary phthalate metabolites and lung function. The *P*-value < 0.05 was considered with statistical significance.

Results

Demographic Characteristics

A total of 2023 individuals were enrolled in our study, including 153 COPD and 1870 non-COPD participants (Table 1). There were no significant differences between the COPD and non-COPD group in age and marital status. Individuals with COPD had lower FEV1 (2292.0 vs 2794.6 mL), lower FVC (3229.1 vs 3678.1 mL), and higher proportion of smokers (67.0 vs 44.1%), airflow obstruction (34.0 vs 17.6%), cough (27.5 vs 8.2%), expectoration (20.3 vs 6.6%) and wheezing (53.6 vs 9.8%). Significant differences were observed between the two groups in gender, education, race, ratio of family income to poverty and BMI.

Table I Basic Characteristics of American Population with or Without COPD

Variables	COPD (N = 153)	No COPD (N = 1870)	P-value
Age	58.0 ± 10.6	56.5 ± 10.6	0.102
Gender			0.001
Male	57 (37.3%)	951 (50.9%)	
Female	96 (62.7%)	919 (49.1%)	
Race			0.001
Mexican American	11 (7.2%)	274 (14.7%)	
Other Hispanic	11 (7.2%)	180 (9.6%)	
Non-Hispanic White	93 (60.8%)	864 (46.2%)	
Non-Hispanic Black	34 (22.2%)	402 (21.5%)	
Other Race	4 (2.6%)	150 (8.0%)	
Education level			0.004
Less than 9th grade	13 (8.5%)	191 (10.2%)	
9–11th grade	28 (18.3%)	260 (13.9%)	
High school graduate	37 (24.2%)	429 (22.9%)	
Some college or AA degree	54 (35.3%)	495 (26.5%)	
College graduate or above	21 (13.7%)	495 (26.5%)	
Ratio of family income to poverty			0.001
≤ 1.00	38 (24.8%)	282 (15.1%)	
1.01–2.00	46 (30.1%)	465 (24.9%)	
2.01–4.00	36 (23.5%)	469 (25.1%)	
> 4.00	33 (21.6%)	654 (35.0%)	
Marital status			0.107
Married	80 (52.3%)	1147 (61.3%)	
Widowed	15 (9.8%)	144 (7.7%)	
Divorced	34 (22.2%)	287 (15.3%)	
Separated	7 (4.6%)	61 (3.3%)	
Never married	13 (8.5%)	144 (7.7%)	
Living with partner	4 (2.6%)	87 (4.7%)	
BMI (kg/m ²)			0.008
< 18.5	5 (3.3%)	15 (0.8%)	
18.5–25	30 (19.6%)	450 (24.1%)	
25–30	47 (30.7%)	653 (34.9%)	
≥ 30	71 (46.4%)	752 (40.2%)	
Smoking			< 0.001
Yes	111 (72.5%)	884 (47.3%)	
No	42 (27.5%)	986 (52.7%)	
Airflow obstruction			< 0.001
Yes	52 (34.0%)	329 (17.6%)	
No	101 (66.0%)	1541 (82.4%)	
Cough			< 0.001
Yes	42 (27.5%)	153 (8.2%)	
No	111 (72.5%)	1717 (91.8%)	
Expectoration			< 0.001
Yes	31 (20.3%)	124 (6.6%)	
No	122 (79.7%)	1746 (93.4%)	
Wheezing			< 0.001
Yes	82 (53.6%)	183 (9.8%)	
No	71 (46.4%)	1687 (90.2%)	
FEV1 (mL)	2292.0 ± 765.2	2794.6 ± 786.0	< 0.001
FVC (mL)	3229.1 ± 919.0	3678.1 ± 1019.2	< 0.001

Abbreviations: COPD, chronic obstructive pulmonary disease; BMI, body mass index; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity.

Association Between Urinary Phthalate Metabolites and COPD

When using the lowest tertile of urinary phthalate metabolites as a reference, the second tertile of MCNP and third tertile of MEHHP increased the risk of COPD by 1.587 [95% confidence interval (CI): 1.037–2.431; $P = 0.034$] and 2.779 (95% CI: 1.129–6.840; $P = 0.026$) times, respectively (Table 2). The third tertile of MEHP [odds ratio (OR): 0.455; 95% CI: 0.267–0.775; $P = 0.004$] and MEOHP (OR: 0.298; 95% CI: 0.114–0.776; $P = 0.013$) reduced the risk of COPD. These significant differences were robust after adjustment of gender, age, race, education, ratio of family income to poverty, BMI, marital status, and smoking ($P < 0.05$).

Table 2 Multivariate Regression Analysis of Association Between Urinary Phthalate Metabolites and COPD

Variables	Unadjusted Model		Adjusted Model ^a	
	OR (95% CI)	P-value	OR (95% CI)	P-value
MCNP ($\mu\text{g/g}$ creatinine)				
Tertile 1 (≤ 0.02)	1.0 (Reference)		1.0 (Reference)	
Tertile 2 (0.03–0.04)	1.587 (1.037–2.431)	0.034	1.764 (1.138–2.735)	0.011
Tertile 3 (> 0.04)	1.230 (0.757–1.998)	0.403	1.392 (0.845–2.293)	0.195
MCOP ($\mu\text{g/g}$ creatinine)				
Tertile 1 (≤ 0.05)	1.0 (Reference)		1.0 (Reference)	
Tertile 2 (0.06–0.17)	1.141 (0.748–1.740)	0.540	1.071 (0.695–1.652)	0.756
Tertile 3 (> 0.17)	0.827 (0.487–1.404)	0.482	0.776 (0.452–1.330)	0.356
MECPP ($\mu\text{g/g}$ creatinine)				
Tertile 1 (≤ 0.13)	1.0 (Reference)		1.0 (Reference)	
Tertile 2 (0.14–0.27)	1.411 (0.817–2.436)	0.217	1.478 (0.846–2.583)	0.170
Tertile 3 (> 0.27)	1.990 (0.983–4.026)	0.056	2.251 (1.085–4.672)	0.029
MnBP ($\mu\text{g/g}$ creatinine)				
Tertile 1 (≤ 0.10)	1.0 (Reference)		1.0 (Reference)	
Tertile 2 (0.11–0.20)	1.032 (0.635–1.678)	0.898	0.980 (0.596–1.611)	0.936
Tertile 3 (> 0.20)	1.138 (0.659–1.964)	0.644	0.962 (0.550–1.682)	0.891
MCCP ($\mu\text{g/g}$ creatinine)				
Tertile 1 (≤ 0.02)	1.0 (Reference)		1.0 (Reference)	
Tertile 2 (0.03–0.05)	1.102 (0.710–1.709)	0.666	1.079 (0.687–1.693)	0.742
Tertile 3 (> 0.05)	1.058 (0.624–1.793)	0.835	1.065 (0.620–1.828)	0.820
MEP ($\mu\text{g/g}$ creatinine)				
Tertile 1 (≤ 0.42)	1.0 (Reference)		1.0 (Reference)	
Tertile 2 (0.43–1.53)	0.982 (0.650–1.483)	0.930	0.884 (0.577–1.353)	0.570
Tertile 3 (> 1.53)	0.869 (0.566–1.336)	0.523	0.809 (0.520–1.259)	0.348
MEHHP ($\mu\text{g/g}$ creatinine)				
Tertile 1 (≤ 0.08)	1.0 (Reference)		1.0 (Reference)	
Tertile 2 (0.09–0.18)	1.082 (0.567–2.066)	0.811	1.207 (0.620–2.350)	0.579
Tertile 3 (> 0.18)	2.779 (1.129–6.840)	0.026	3.515 (1.365–9.055)	0.009
MEHP ($\mu\text{g/g}$ creatinine)				
Tertile 1 (≤ 0.01)	1.0 (Reference)		1.0 (Reference)	
Tertile 2 (0.02–0.03)	1.128 (0.749–1.700)	0.564	1.086 (0.712–1.655)	0.702
Tertile 3 (> 0.03)	0.455 (0.267–0.775)	0.004	0.482 (0.278–0.833)	0.009
MiBP ($\mu\text{g/g}$ creatinine)				
Tertile 1 (≤ 0.05)	1.0 (Reference)		1.0 (Reference)	
Tertile 2 (0.06–0.11)	0.816 (0.514–1.295)	0.388	0.860 (0.534–1.384)	0.533
Tertile 3 (> 0.11)	1.239 (0.766–2.003)	0.383	1.213 (0.740–1.988)	0.445

(Continued)

Table 2 (Continued).

Variables	Unadjusted Model		Adjusted Model ^a	
	OR (95% CI)	P-value	OR (95% CI)	P-value
MEOHP ($\mu\text{g/g}$ creatinine)				
Tertile 1 (≤ 0.05)	1.0 (Reference)		1.0 (Reference)	
Tertile 2 (0.06–0.11)	0.518 (0.267–1.006)	0.052	0.455 (0.230–0.898)	0.023
Tertile 3 (> 0.11)	0.298 (0.114–0.776)	0.013	0.214 (0.080–0.574)	0.002
MBzP ($\mu\text{g/g}$ creatinine)				
Tertile 1 (≤ 0.04)	1.0 (Reference)		1.0 (Reference)	
Tertile 2 (0.05–0.08)	0.974 (0.618–1.535)	0.911	0.957 (0.601–1.524)	0.854
Tertile 3 (> 0.08)	1.295 (0.815–2.060)	0.274	1.142 (0.706–1.849)	0.588

Notes: ^aAdjusted for gender, age, race, education, ratio of family income to poverty, BMI, marital status and smoking.

Abbreviations: COPD, chronic obstructive pulmonary disease; OR, odds ratio; CI, confidence interval; MCNP, mono (carboxynonyl) phthalate; MCOP, mono (carboxyoctyl) Phthalate; MECPP, mono-2-ethyl-5-carboxypentyl phthalate; MnBP, mono-n-butyl phthalate; MCP, mono-(3-carboxypropyl) phthalate; MEP, mono-ethyl phthalate; MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono-(2-ethyl-hexyl) phthalate; MiBP, mono-isobutyl phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; MBzP, mono-benzyl phthalate.

Stratified analysis was performed based on categories of gender (Table S1) and smoking (Table S2). When compared to the first tertile, the third tertile of MEHHP increased the risk of COPD by 7.080 (95% CI: 1.834–27.330; $P = 0.005$) times in male participants. However, there was no statistically significant correlation between MEHHP and COPD in women. Male individuals in the third tertile of MEOHP showed a decreased prevalence of COPD (OR: 0.058; 95% CI = 0.012–0.294; $P = 0.001$). The OR for the third tertile of MEHP was 0.155 (95% CI: 0.050–0.476) in non-smoking individuals ($P = 0.001$).

Association Between Urinary Phthalate Metabolites and Airflow Obstruction

This study included 381 subjects with airflow obstruction and 1642 individuals without airflow obstruction. When compared to the first tertile, the second and third tertile of MCPP increased the risk of airflow obstruction by 1.556 (95% CI: 1.154–2.099; $P = 0.004$) and 1.918 (95% CI: 1.346–2.733; $P < 0.001$) times, respectively (Table 3). The third tertile of MBzP was significantly associated with the risk of airflow obstruction (OR: 1.522; 95% CI: 1.113–2.081; $P = 0.009$). The third tertile of MCOP reduced the risk of airflow obstruction by 0.522 (95% CI: 0.368–0.741; $P < 0.001$) times. These significant differences persisted after adjustment of gender, age, race, education, ratio of family income to poverty, BMI, marital status, and smoking ($P < 0.05$).

Association Between Urinary Phthalate Metabolites and Lung Function

Linear regression analysis suggested that FEV1 was negatively associated with MECPP ($\beta = -0.082$, $P < 0.001$), MnBP ($\beta = -0.149$, $P < 0.001$), MEP ($\beta = -0.126$, $P < 0.001$), MEHHP ($\beta = -0.069$, $P = 0.002$), MiBP ($\beta = -0.099$, $P < 0.001$), and MEOHP ($\beta = -0.089$, $P < 0.001$) (Table 4). Negative correlations were found between FVC and MECPP ($\beta = -0.103$, $P < 0.001$), MnBP ($\beta = -0.167$, $P < 0.001$), MEP ($\beta = -0.140$, $P < 0.001$), MEHHP ($\beta = -0.084$, $P < 0.001$), MiBP ($\beta = -0.127$, $P < 0.001$), and MEOHP ($\beta = -0.101$, $P < 0.001$).

Association Between Urinary Phthalate Metabolites and Respiratory Symptoms

The study included 195 participants with cough, 1828 without cough, 155 with expectoration, 1868 without expectoration, 265 with wheezing, and 1758 without wheezing. The third tertile of MBzP increased the risk of cough by 1.545 (95% CI: 1.030–2.317; $P = 0.035$) times (Table S3). However, MBzP was not significantly related to the risk of cough after adjustment of all covariates of interest. The second tertile of MECPP (OR: 0.440; 95% CI: 0.257–0.752; $P = 0.003$) and MBzP (OR: 0.539; 95% CI: 0.338–0.858; $P = 0.009$) reduced the risk of expectoration (Table S4). There were no significant association between urinary phthalate metabolites and wheezing (Table S5).

Table 3 Multivariate Regression Analysis of Association Between Urinary Phthalate Metabolites and Airflow Obstruction

Variables	Unadjusted Model		Adjusted Model ^a	
	OR (95% CI)	P-value	OR (95% CI)	P-value
MCNP				
Tertile 1	1.0 (Reference)		1.0 (Reference)	
Tertile 2	1.174 (0.884–1.559)	0.269	1.108 (0.814–1.507)	0.514
Tertile 3	0.921 (0.667–1.271)	0.616	0.949 (0.669–1.346)	0.767
MCOP				
Tertile 1	1.0 (Reference)		1.0 (Reference)	
Tertile 2	0.676 (0.508–0.899)	0.007	0.765 (0.562–1.040)	0.087
Tertile 3	0.522 (0.368–0.741)	< 0.001	0.582 (0.399–0.849)	0.005
MECPP				
Tertile 1	1.0 (Reference)		1.0 (Reference)	
Tertile 2	0.959 (0.678–1.356)	0.813	0.965 (0.661–1.410)	0.855
Tertile 3	0.929 (0.582–1.484)	0.758	1.145 (0.685–1.915)	0.605
MnBP				
Tertile 1	1.0 (Reference)		1.0 (Reference)	
Tertile 2	0.878 (0.645–1.195)	0.409	0.880 (0.632–1.225)	0.447
Tertile 3	0.763 (0.530–1.099)	0.146	0.770 (0.521–1.139)	0.191
MCPP				
Tertile 1	1.0 (Reference)		1.0 (Reference)	
Tertile 2	1.556 (1.154–2.099)	0.004	1.529 (1.106–2.113)	0.010
Tertile 3	1.918 (1.346–2.733)	< 0.001	1.979 (1.348–2.904)	< 0.001
MEP				
Tertile 1	1.0 (Reference)		0.1.0 (Reference)	
Tertile 2	1.070 (0.812–1.410)	0.630	1.103 (0.818–1.486)	0.521
Tertile 3	0.857 (0.640–1.148)	0.302	0.926 (0.675–1.271)	0.633
MEHHP				
Tertile 1	1.0 (Reference)		1.0 (Reference)	
Tertile 2	1.125 (0.741–1.709)	0.580	1.168 (0.742–1.837)	0.503
Tertile 3	0.693 (0.362–1.329)	0.270	0.753 (0.368–1.539)	0.437
MEHP				
Tertile 1	1.0 (Reference)		1.0 (Reference)	
Tertile 2	0.988 (0.745–1.311)	0.934	0.967 (0.710–1.316)	0.830
Tertile 3	0.836 (0.592–1.179)	0.307	0.861 (0.592–1.254)	0.436
MiBP				
Tertile 1	1.0 (Reference)		1.0 (Reference)	
Tertile 2	0.913 (0.683–1.222)	0.541	0.979 (0.715–1.340)	0.893
Tertile 3	0.775 (0.555–1.083)	0.136	0.824 (0.578–1.176)	0.287
MEOHP				
Tertile 1	1.0 (Reference)		1.0 (Reference)	
Tertile 2	1.036 (0.673–1.595)	0.873	1.010 (0.634–1.609)	0.968
Tertile 3	1.371 (0.705–2.666)	0.353	1.119 (0.543–2.309)	0.760
MBzP				
Tertile 1	1.0 (Reference)		1.0 (Reference)	
Tertile 2	1.159 (0.860–1.562)	0.332	1.229 (0.893–1.691)	0.206
Tertile 3	1.522 (1.113–2.081)	0.009	1.637 (1.166–2.297)	0.004

Notes: ^aAdjusted for gender, age, race, education, ratio of family income to poverty, BMI, marital status and smoking.

Abbreviations: OR, odds ratio; CI, confidence interval; MCNP, mono (carboxynonyl) phthalate; MCOP, mono (carboxyoctyl) Phthalate; MECPP, mono-2-ethyl-5-carboxypentyl phthalate; MnBP, mono-n-butyl phthalate; MCPP, mono-(3-carboxypropyl) phthalate; MEP, mono-ethyl phthalate; MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono-(2-ethyl-hexyl) phthalate; MiBP, mono-isobutyl phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; MBzP, mono-benzyl phthalate.

Table 4 Linear Regression Analysis of Association Between Urinary Phthalate Metabolites and Lung Function

Variables	FEV1			FVC		
	β	t	P-value	β	t	P-value
MCNP	-0.001	-0.067	0.947	0.000	-0.018	0.985
MCOP	-0.020	-0.890	0.374	-0.037	-1.665	0.096
MECPP	-0.082	-3.684	< 0.001	-0.103	-4.673	< 0.001
MnBP	-0.149	-6.766	< 0.001	-0.167	-7.625	< 0.001
M CPP	-0.042	-1.905	0.057	-0.036	-1.612	0.107
MEP	-0.126	-5.696	< 0.001	-0.140	-6.375	< 0.001
MEHHP	-0.069	-3.099	0.002	-0.084	-3.793	< 0.001
MEHP	-0.010	-0.429	0.668	-0.036	-1.612	0.107
MiBP	-0.099	-4.491	< 0.001	-0.127	-5.770	< 0.001
MEOHP	-0.089	-3.998	< 0.001	-0.101	-4.579	< 0.001
MBzP	-0.037	-1.663	0.096	-0.021	-0.923	0.356

Abbreviations: FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; MCNP, mono (carboxynonyl) phthalate; MCOP, mono (carboxyoctyl) Phthalate; MECPP, mono-2-ethyl-5-carboxypentyl phthalate; MnBP, mono-n-butyl phthalate; M CPP, mono-(3-carboxypropyl) phthalate; MEP, mono-ethyl phthalate; MEHHP, mono-(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono-(2-ethyl-hexyl) phthalate; MiBP, mono-isobutyl phthalate; MEOHP, mono-(2-ethyl-5-oxohexyl) phthalate; MBzP, mono-benzyl phthalate.

Discussion

COPD is one of the common global health problems.³ Phthalates are generally used in a variety of plastic products. Human beings are widely exposed to large amounts of phthalates.^{11,12} As far as we know, this is the first study to investigate the association between phthalates and the risk of COPD. Our study suggested that the third tertile of MEHHP increased the risk of COPD. The third tertile of MEHP and MEOHP reduced the risk of COPD. The second and third tertile of M CPP were correlated with the increased risk of airflow obstruction. MBzP was positively related to airflow obstruction and cough. Both FEV1 and FVC were negatively associated with MEHHP, MECPP, MnBP, MEP, MiBP and MEOHP.

Accumulating evidence suggested that exposure to phthalates was associated with an increased risk of respiratory disease.²³ A cross-sectional study demonstrated that exposure to certain phthalates was related to respiratory morbidity in COPD individuals.¹⁵ Gascon et al²⁴ reported that prenatal phthalate exposure may increase the risk of asthma symptoms and respiratory infections throughout childhood. Epidemiological studies suggested that exposure to phthalates was correlated with increased airway inflammation.²⁵ Phthalates elevated levels of oxidative stress and accelerated the recruitment and activation of lung neutrophils, which contribute to pulmonary inflammation.²⁶ Oxidative stress is the result of an imbalance of ROS and antioxidants in the body and plays a crucial role in the pathogenesis of COPD.^{15,27} In the present study, MEHHP was associated with the risk of COPD (OR = 2.779). Stratified analysis showed that MEHHP increased the risk of COPD by 7.080 times in male participants. However, both MEHP and MEOHP reduced the risk of COPD. The parent phthalate of MEHHP is di-(2-ethylhexyl) phthalate (DEHP). Animal experiments suggested that DEHP not only affected alveolar formation of mammalian lungs, but also had toxic effects on pulmonary tissues.^{28,29}

The main feature of COPD is progressive and irreversible airflow obstruction.^{30,31} Small airway dysfunction in patients with COPD results in luminal narrowing, which further causes airflow obstruction.^{5,6,32} The GOLD employs airway obstruction as one of the criteria for diagnosing COPD.^{33,34} In the current study, both MBzP and M CPP increased the risk of airflow obstruction. MBzP and M CPP are the phthalate metabolites of benzyl butyl phthalate (BBzP).³⁵ The concentration of urinary BBzP metabolites in children was positively correlated with airway inflammation.³⁶ Ferguson et al³⁷ observed that the concentrations of urinary BBzP metabolites were positively related to serum levels of C-reactive protein. The metabolites of BBzP were inversely associated with the levels of the strong antioxidant bilirubin.³⁸ These findings indicated that MBzP and M CPP may be involved in inducing airway inflammation and oxidative stress.

Phthalates can leach into airborne dust and particulate matter, which can then be absorbed and cause lung damage.²⁷ In residential district near a petrochemical complex, phthalates on forehead skin wipes have been reported to be inversely correlated with reduced lung function.³⁹ Our study showed that both FEV1 and FVC were negatively associated with MEHHP, MECPP, MnBP, MEP, MiBP and MEOHP. These findings are consistent with previous reports.^{40–42}

Our study has some limitations. Firstly, the nature of cross-sectional design makes it difficult to determine a causal relationship between phthalates and the risk of COPD. Secondly, the definition of COPD was determined by participants' self-reporting. This may contribute to some bias in our study. However, similar criteria were used in the previous studies investigating COPD data from the NHANES survey.^{43–45} Thirdly, the current study only included US participants from the NHANES database. Thus, further studies are needed to validate our findings in other populations.

Conclusions

The present study suggests that higher levels of MEHHP are associated with increased risk of COPD, and lower measures of FEV1 and FVC. MBzP is positively related to airflow obstruction and cough. Lung function is negatively associated with MEHHP, MECPP, MnBP, MEP, MiBP and MEOHP. These findings suggest that phthalate may be associated with COPD and lung function in the general population. Targeted interventions may be beneficial in reducing the risk of COPD.

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Disclosure

The authors report no conflicts of interest in this work.

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