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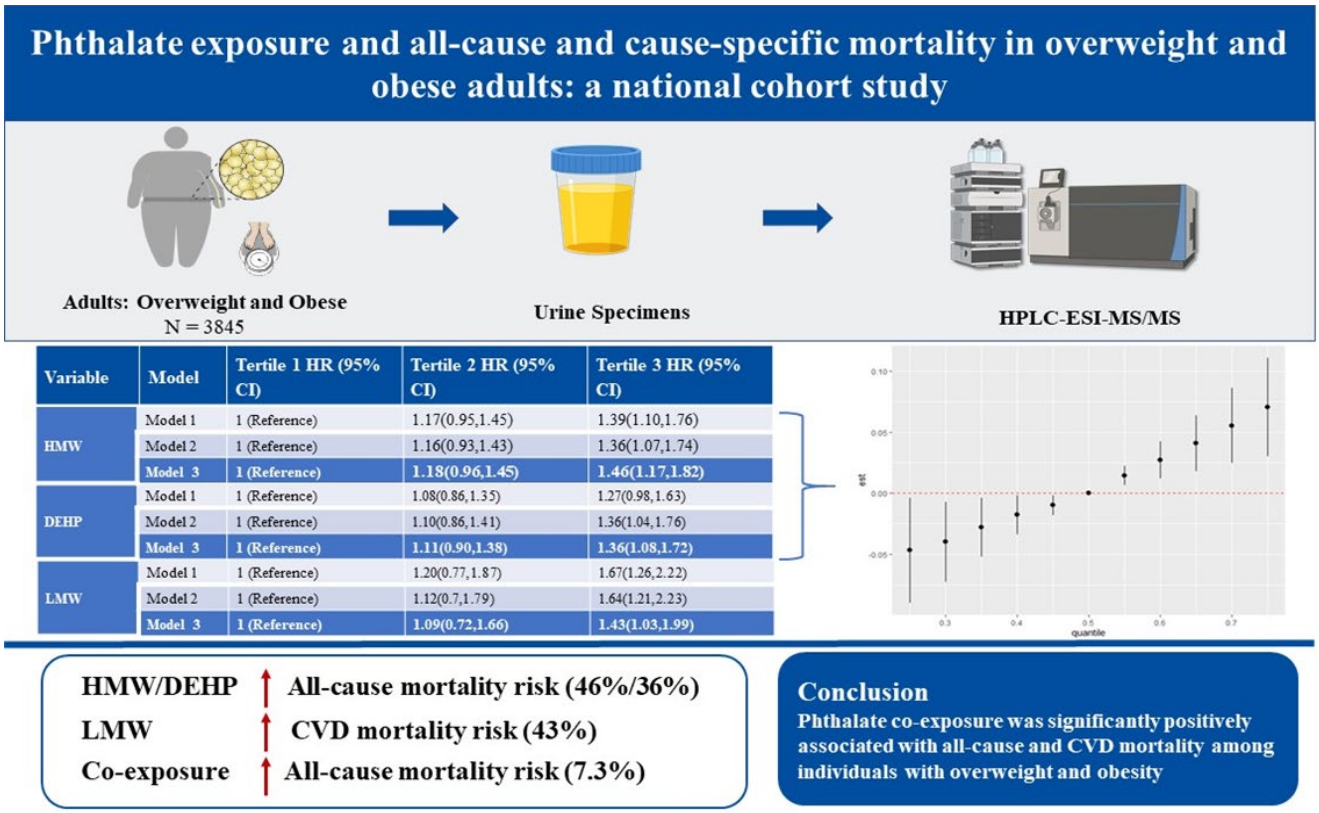
Graphical Abstract



Highlights:

- Urinary phthalate exposure was associated with higher mortality in overweight/obese adults.
- HMW phthalates and DEHP exposure were linked to higher all-cause mortality in overweight/obese adults.
- LMW phthalates were associated with higher CVD mortality in overweight/obese adults.

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Phthalate exposure and all-cause and cause-specific mortality in overweight and obese adults: a national cohort study

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Abstract: **Importance:** Phthalate exposure has been found to be associated with an increased risk of obesity. It remains unknown whether exposure to phthalates further impact the health of individuals who are already obese. **Objective:** To examine the risk of mortality associated with phthalate exposure among individuals with overweight and obesity. **Design:** A nationally representative sample of adults aged 40 years or older who participated in the US National Health and Nutrition Examination Survey 2001–2010 and provided urine samples for phthalate metabolite measurements. These participants were linked to mortality data from the survey date through December 31, 2019. **Exposures:** Phthalate metabolites in urine samples were measured by high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry. **Main Outcome Measures:** Mortality from all causes, cardiovascular disease (CVD), and cancer. **Results:** This cohort study included 3,845 adults aged 40 years or older (mean age 56.5 [0.3] years). During 46,261 person-years of follow-up (median 12 years; maximum 19 years), 990 deaths occurred, of which 304 were from CVD and 246 were from cancer. Elevated concentrations of high-molecular-weight (HMW) urinary phthalate metabolites and di-2-ethylhexylphthalate (DEHP) were associated with a 46% and 36% increased risk of all-cause mortality, respectively. Regarding low-molecular-weight (LMW) phthalates, higher exposure was specifically linked to a 43% excess risk of CVD mortality. Bayesian kernel machine regression (BKMR) analyses indicated a 7.3% increase in all-cause mortality associated with phthalate co-exposure (75th *vs.* 50th percentile). **Conclusions and Relevance:** In this nationally representative study, phthalate co-exposure was significantly positively associated with all-cause and CVD mortality among individuals with overweight and obesity. Higher levels of HMW and DEHP exposure were linked to increased all-cause mortality, while high LMW exposure was associated with elevated CVD mortality. Further studies are necessary to confirm these findings and investigate the underlying mechanisms.

Keywords: phthalate; mortality; overweight; obesity; co-exposure

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1. Introduction

Obesity, a prevalent chronic disease globally, is associated with numerous health issues such as cardiovascular diseases, type 2 diabetes, and non-alcoholic fatty liver disease. The World Health Organization defines obesity as excessive fat deposits that can impair health [1]. According to the World Obesity Federation's World Obesity Report, it is projected that by 2035, the proportion of overweight/obese adults worldwide will increase from 42% in 2020 to 54%. High BMI will lead to a reduction in the global economy of over4 trillion U.S. dollars, nearly 3% of the global gross domestic product [2]. Therefore, it is crucial to explore the risk factors that affect the health outcomes of individuals with obesity.

Phthalates, a class of widely used plasticizers, are ubiquitous in products such as children's toys, household items, and medical devices [3]. Phthalates are non-covalently bound to plastics and thus easily released into environmental media such as water, air, and dust. They enter the human body through dietary intake, inhalation, and dermal contact [4]. Metabolites of phthalates have been detected in various biological matrices (blood, urine, amniotic fluid, breast milk, *etc.*) [5,6]. Epidemiological studies indicate that phthalates significantly contribute to the development of chronic diseases such as obesity [7], hypertension [8], and other cardiovascular diseases [9–11]. Experimental studies have shown that phthalate metabolites may interfere with the endocrine system, particularly by activating peroxisome proliferator-activated receptors (PPARs), promoting adipocyte differentiation and fat formation, and causing oxidative stress and dysfunction in mature adipocytes, thereby being associated with the occurrence of obesity [12,13]. In addition to endocrine disruption, a recent study has found that phthalates can non-covalently bind to DNA, which may lead to genotoxicity [14].

Although numerous studies have provided evidence showing that phthalate exposure is associated with an increased risk of obesity in the general population, it remains unknown whether exposure to phthalates further impacts the health of individuals who are already obese. In this study, we investigated a nationally representative cohort of adults in the United States to assess the association between phthalate exposure, as measured by urinary phthalate levels, and all-cause and cause-specific mortality among individuals with overweight and obesity.

2. Methods

2.1. Study population

The study utilized data from the National Health and Nutrition Examination Survey (NHANES), a nationally representative survey conducted by the US Centers for Disease Control and Prevention. NHANES collects data biennially demographic, socioeconomic, lifestyle, dietary, medical information, and laboratory samples. Details on NHANES procedures have been previously described [15]. NHANES received ethical approval from the National Center for Health Statistics Ethics Review Board, with written informed consent obtained from all participants. As this study used publicly available de-identified data, it was exempt from further ethical review. The STROBE guidelines for observational studies were followed.

Adults aged ≥ 40 years from the NHANES 2001–2010 cycles were included based on the availability of available urinary phthalate metabolite data and a BMI > 25 kg/m² [16]. Participants with CVD or cancer at baseline were excluded to minimize reverse causality (potential exposure changes due to disease management) and survival bias, ensuring a more valid estimation of long-term mortality risks. Participants were linked to mortality data up to 2019, providing approximately 20 years of follow-up.

2.2. Measurement of phthalate metabolites

Urinary phthalate metabolites were quantified using high-performance liquid chromatography-electrospray ionization-tandem mass spectrometry (HPLC-ESI-MS/MS), with laboratory protocols publicly documented on the NHANES website. Metabolite measurements were conducted by CDC's National Center for Environmental Health in one-third of randomly selected NHANES participants. Metabolites detectable in > 50% of samples across the study period were included, with values below the limit of detection (LOD) imputed as LOD divided by the square root of 2.

Phthalate metabolites were categorized based on chemical properties and applications: low molecular weight (LMW) phthalates (mono-ethyl phthalate [MEP], mono-n-butyl phthalate [MnBP], mono-isobutyl phthalate [MiBP]), primarily used in personal care products; high molecular weight (HMW) phthalates (mono-benzyl phthalate [MBzP], mono-(3-carboxypropyl) phthalate [MCPP], mono-2-ethyl hexyl phthalate [MEHP], mono-(2-ethyl-5-hydroxyhexyl) phthalate [MEHHP], mono-(2-ethyl-5-oxohexyl) phthalate [MEOHP], mono-(2-ethyl-5-carboxypentyl) phthalate [MECPP]), found commonly in flooring and food packaging; and di-(2-ethylhexyl) phthalate (DEHP) metabolites (MEHP, MEHHP, MEOHP, MECPP), mainly present due to food and medical device contamination [17].

2.3. Mortality data

Mortality status was determined using the NHANES Public-Use Linked Mortality File through December 31, 2019, matched with the National Death Index [18]. Causes of death were categorized according to ICD-10 codes [19], classifying cardiovascular (I00–I09, I11, I13, I20–I51, I60–I69) and cancer-related mortality (C00–C97). This approach has been used in previous reports [17,19].

2.4. Assessment of covariates

Self-reported questionnaires provided data on age, sex, race/ethnicity, education, income, smoking, alcohol consumption, physical activity, and diet. Race/ethnicity included non-Hispanic white, non-Hispanic black, Hispanic, and other. Education was classified into three levels: < high school, high school, and ≥ college. Family income-to-poverty ratios were categorized as ≤ 1.30, 1.31–3.50, and > 3.50.

Smoking was categorized as never, former, or current based on lifetime cigarette use. Alcohol consumption was classified into none, moderate, or heavy drinking. Physical activity was categorized based on weekly moderate-to-vigorous activity minutes: below 150, meeting (150–300), and exceeding 300. Dietary data, including total energy intake and Healthy Eating Index-2010 scores, were collected via 24-hour dietary recalls [20].

2.5. Statistical analysis

NHANES used a complex, multistage probability sampling design to represent the civilian non-institutionalized US population. Weighted estimates were used to adjust for the differential probability of selecting population controls and non-response. The Taylor series linearization method was applied for variance estimation to account for stratification and clustering, following the NHANES Analytic Guidelines. Baseline characteristics were compared using weighted linear regression (continuous variables) and Chi-square tests (categorical variables). Weighted means and proportions of baseline characteristics were compared by using linear regression.

Primary analyses examined the association between tertiles of urinary phthalate metabolite concentrations (LMW, HMW, DEHP) and mortality risk using Cox proportional hazards regression. Models were progressively adjusted for age, sex, urinary creatinine levels, demographic factors, socioeconomic status, smoking, alcohol use, physical activity, diet, and BMI. Trend analyses involved treating median metabolite levels within tertiles as continuous variables. We also evaluated linear associations using log-transformed continuous metabolite concentrations. Interactions were tested through stratified analyses by age (< 60 or ≥ 60 years), sex, race/ethnicity (white or non-white), diet quality (high or low), and physical activity levels (high or low), with heterogeneity assessed via multiplicative interaction terms.

Additionally, we performed sensitivity analyses to interrogate the robustness of our associations. Because mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP) was not available in NHANES 2001–2002, we excluded MECPP from analyses to evaluate the effect of data availability on the observed associations [21]. Given the observed association between bisphenol A (BPA) and mortality [22], we included BPA in the final model to verify whether the link between phthalates and mortality persisted. We also conducted an alternative definition of excess adiposity using standard clinical criteria as the presence of at least two of the following: BMI ≥ 30 kg/m², waist circumference ≥ 85 cm (women) or ≥ 90 cm (men), and waist-to-height ratio > 0.5 [23] .

2.6. Mixture analysis

Besides aggregating phthalates into the three different molar sums categories, we applied a mixtures analysis framework to examine the associations of the nine individual phthalates with all-cause and cause-specific mortality.

For this purpose, we utilized Bayesian Kernel Machine Regression (BKMR) with hierarchical variable selection to evaluate the joint effect of the phthalate mixture on mortality. To address multicollinearity, the nine metabolites were assigned to six structural groups (e.g., grouping DEHP metabolites). The model was fitted using the km bayes function with a binomial kernel, utilizing 50 knots to efficiently approximate the exposure-response surface. We estimated posterior inclusion probabilities (PIPs) and exposure-response functions based on 15,000 Markov chain Monte Carlo (MCMC) iterations. In this analysis, due to the absence of mono-(2-ethyl-5-carboxypentyl) phthalate in the first cycle, the exposure mixture was implemented in the subsequent four cycles.

All statistical analyses were performed with SAS software (version 9.4; SAS Institute) and R (version 4.3.0, R Foundation).

3. Results

This study included 3,845 adults who were overweight and obese (weighted mean [SE] age, 56.5 [0.3] years). During 46,261 person-years of follow-up (median follow-up, 12 years; maximum follow-up, 19 years), 990 deaths occurred, including 304 deaths from CVD and 246 deaths from cancer. Participants with higher levels of high molecular weight (HMW) and di(2-ethylhexyl) phthalate (DEHP) were more likely to be younger, male, more educated, drinkers, obese, have lower diet quality, and have higher energy intake. In contrast, those with higher levels of low molecular weight (LMW) phthalates were more likely to be younger and obese (Table 1).

Among individuals with overweight and obesity, the levels of HMW and DEHP were associated with increased risk of all-cause mortality (Table 2). For HMW, the HR (95% CI) of all-cause mortality was 1.00 for tertile 1, 1.18 (0.96–1.45) for tertile 2, and 1.46 (1.17–1.82) for tertile 3 (P for trend 0.00). For DEHP, the corresponding HR was 1.00, 1.11 (0.90,1.38), and 1.36 (1.08,1.72), respectively (P for trend 0.01). A positive but non-significant association between LMW and all-cause mortality was observed (HR, 1.19 [0.98–1.45] for tertile 3 compared to tertile 1) (Table 2). However, higher LMW level was associated with increased risk of CVD mortality, with the HR of 1.09 (0.72–1.66) for tertile 2 and 1.43 (95% CI: 1.03–1.99) for tertile 3, compared to those in the lowest tertile (P for trend 0.03). The association of HMW and DEHP with CVD mortality was positive but non-significant (Table 2). When specific metabolites were examined, elevated CVD mortality was observed in the highest tertiles of mono-ethyl phthalate (MEP; HR: 1.38, 95% CI: 1.01–1.87), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP; HR: 1.61, 95% CI: 1.06–2.44), and mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP; HR: 1.79, 95% CI: 1.19–2.68) (eTable 1). No significant associations were observed between cancer mortality and higher levels of LMW (multivariable-adjusted HR: 1.05, 95% CI: 0.67–1.65), HMW (multivariable-adjusted HR: 1.00, 95% CI: 0.62–1.62), DEHP (multivariable-adjusted HR: 0.83, 95% CI: 0.46–1.49), or specific metabolites (Table 2, eTable 1). Similar results were also observed in populations with excess adiposity, except that the HR for all-cause mortality associated with LMW was 1.28 (1.04,1.58) (eTable 2).

Table 1. Characteristics of the study population.

Characteristic	No.	LMW			HMW			DEHP		
		Tertile 1	Tertile 2	Tertile 3	Tertile 1	Tertile 2	Tertile 3	Tertile 1	Tertile 2	Tertile 3
Median level (SE), μmol/L		**0.32**	**1.13**	**5.30**	**0.08**	**0.24**	**0.66**	**0.06**	**0.18**	**0.53**
Number of participants	3845	1281	1282	1282	1282	1281	1282	1282	1281	1282
Age, years, mean ± SE		**57.7 (0.4)**	**56.1 (0.3)**	**55.4 (0.4)**	**58 (0.5)**	**56 (0.4)**	**55.5 (0.3)**	**57.6 (0.4)**	**56.4 (0.4)**	**55.4 (0.4)**
Sex, % (SE)										
Male		51.33 (1.81)	51.11 (1.70)	51.72 (1.66)	**46.33 (1.79)**	**53.17 (1.49)**	**54.46 (1.83)**	**45.23 (1.85)**	**55.54 (1.83)**	**53.43 (1.85)**
Female		48.67 (1.81)	48.89 (1.70)	48.28 (1.66)	**53.67 (1.79)**	**46.83 (1.49)**	**45.54 (1.83)**	**54.77 (1.85)**	**44.46 (1.83)**	**46.57 (1.85)**
Race/ethnicity, % (SE)										
Hispanic		6.94 (1.04)	9.77 (1.27)	13.77 (1.40)	9.04 (1.14)	11.59 (1.49)	9.19 (1.06)	8.61 (1.17)	11.84 (1.51)	9.43 (1.06)
Non-Hispanic whites		83.4 (1.53)	74.96 (1.80)	65.22 (2.35)	77.33 (1.71)	73.19 (1.89)	74.98 (1.91)	78.18 (1.54)	72.19 (2.10)	75.01 (1.92)
Non-Hispanic black		5.68 (0.61)	12.00 (1.09)	17.84 (1.63)	9.24 (0.95)	12.53 (1.16)	12.41 (1.17)	9.03 (0.93)	12.87 (1.18)	12.35 (1.18)
Other		3.97 (0.74)	3.27 (0.59)	3.17 (0.72)	4.39 (0.82)	2.69 (0.62)	3.42 (0.72)	4.19 (0.75)	3.10 (0.75)	3.21 (0.71)
Education, % (SE)										
Less than high school		16.49 (1.23)	19.54 (1.12)	22.56 (1.73)	**19.86 (1.35)**	**19.76 (1.44)**	**18.39 (1.49)**	**20.22 (1.26)**	**19.57 (1.33)**	**18.22 (1.61)**
High school		24.49 (1.50)	27.21 (1.63)	26.41 (1.81)	**24.92 (1.72)**	**26.01 (1.6)**	**26.89 (1.65)**	**26.61 (1.70)**	**24.97 (1.64)**	**26.23 (1.53)**
College or higher		59.03 (1.69)	53.24 (1.81)	51.03 (2.34)	**55.22 (1.92)**	**54.23 (1.94)**	**54.73 (1.95)**	**53.16 (1.86)**	**55.46 (1.92)**	**55.55 (1.96)**
Family income to poverty ratio, % (SE)										
< 1		8.00 (0.87)	9.35 (0.95)	11.00 (1.16)	8.40 (0.84)	10.34 (1.15)	9.31 (0.92)	8.96 (0.77)	9.92 (1.20)	9.18 (0.88)
1–1.9		14.49 (1.20)	16.9 (1.18)	18.29 (1.19)	18.28 (1.35)	16.34 (1.40)	14.74 (1.09)	18.81 (1.29)	16.31 (1.45)	14.23 (1.12)
2–3.9		30.75 (1.93)	27.74 (1.81)	25.33 (1.56)	28.53 (1.75)	28.34 (1.44)	27.56 (1.74)	29.02 (1.73)	27.75 (1.53)	27.63 (1.73)
≥ 4		40.95 (2.04)	39.17 (1.85)	38.09 (1.99)	37.88 (2.11)	39.06 (1.96)	41.46 (1.83)	36.38 (2.18)	39.55 (2.03)	42.46 (1.76)
missing		5.81 (0.74)	6.84 (1.07)	7.30 (0.91)	6.91 (0.93)	5.91 (0.76)	6.94 (0.84)	6.82 (0.91)	6.46 (0.93)	6.49 (0.81)
Alcohol drink, %(SE)										
Non-drinker		74.32 (1.56)	71.05 (1.78)	71.11 (1.69)	**74.8 (1.76)**	**73.28 (1.83)**	**68.98 (1.65)**	**74.44 (1.75)**	**72.2 (1.67)**	**70.3 (1.52)**
Moderate drinking		8.09 (0.81)	11.16 (1.22)	9.67 (1.11)	**7.52 (0.92)**	**10.36 (1.21)**	**10.77 (1.04)**	**7.64 (0.79)**	**10.22 (1.12)**	**10.82 (0.97)**
Heavy drinking		14.79 (1.53)	14.48 (1.46)	16.44 (1.33)	**14.67 (1.40)**	**13.85 (1.33)**	**16.91 (1.39)**	**15.04 (1.47)**	**14.72 (1.46)**	**15.74 (1.30)**
Missing		2.80 (0.71)	3.31 (0.57)	2.79 (0.53)	**3.01 (0.67)**	**2.51 (0.51)**	**3.34 (0.61)**	**2.88 (0.66)**	**2.86 (0.58)**	**3.13 (0.69)**
Smoke, % (SE)										
Never smoker		52.47 (1.72)	50.27 (1.87)	46.14 (1.82)	50.46 (1.47)	50.17 (1.64)	48.96 (1.86)	49.76 (1.55)	49.21 (1.73)	50.51 (1.91)
Ever smoker		31.99 (1.70)	33.46 (1.61)	33.71 (1.75)	33.53 (1.65)	30.68 (1.44)	34.64 (1.65)	32.85 (1.66)	32.40 (1.46)	33.66 (1.73)
Current smoker		15.54 (1.24)	16.27 (1.61)	20.15 (1.59)	16.00 (1.19)	19.15 (1.54)	16.4 (1.29)	17.39 (1.26)	18.39 (1.46)	15.83 (1.21)
Physical activity, % (SE)										
Below		42.73 (1.61)	40.38 (1.42)	42.93 (2.05)	40.72 (1.77)	43.19 (1.72)	42.15 (1.69)	42.73 (1.82)	41.79 (1.74)	41.55 (1.62)
Meet		12.71 (1.08)	15.48 (1.51)	12.91 (1.21)	13.76 (1.35)	14.55 (1.17)	12.78 (1.45)	12.76 (1.32)	14.22 (1.28)	14.07 (1.48)
Exceed		44.56 (1.88)	44.14 (1.57)	44.16 (1.93)	45.52 (1.81)	42.26 (1.88)	45.07 (1.89)	44.52 (1.88)	43.99 (1.85)	44.38 (1.83)
BMI, % (SE)										
25–29.9 kg/m^2		**51.91 (1.46)**	**49.43 (2.13)**	**44.92 (1.74)**	**55.1 (1.68)**	**47.55 (1.53)**	**44.58 (1.78)**	**55.01 (1.78)**	**47.33 (1.61)**	**44.77 (1.76)**
≥ 30 kg/m^2		**48.09 (1.46)**	**50.57 (2.13)**	**55.08 (1.74)**	**44.9 (1.68)**	**52.45 (1.53)**	**55.42 (1.78)**	**44.99 (1.78)**	**52.67 (1.61)**	**55.23 (1.76)**
HEI2010 score, mean ± SE		**50.96 (0.68)**	**49.31 (0.48)**	**48.24 (0.58)**	**51.84 (0.65)**	**49.02 (0.52)**	**48.03 (0.56)**	**51.50 (0.62)**	**48.99 (0.52)**	**48.35 (0.53)**
Total energy intake, kcal/d, mean ± SE		2079.28 (33.78)	2076.87 (31.33)	2134.97 (36.60)	**1985.22 (35.72)**	**2144.54 (33.20)**	**2153.07 (36.17)**	**2001.33 (39.54)**	**2132.40 (33.76)**	**2151.29 (37.87)**

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); HEI-2010, Healthy Eating Index 2010; MET, metabolic equivalent of task.
Values are weighted mean (SE) for continuous variables and weighted percentages (SE) for categorical variables, except the number of participants.
Boldface indicates statistically significance.

Table 2. Association of urinary phthalate metabolites with all-cause mortality, CVD mortality and cancer mortality among individual with overweight and obesity (n = 3845).

Variable	Model	Tertile 1 HR (95% CI)	Tertile 2 HR (95% CI)	Tertile 3 HR (95% CI)	P for trend	Ln(X)
All-cause mortality						
	Model 1	1 (Reference)	1.08 (0.87,1.34)	**1.34 (1.11,1.61)**	**0.00**	**1.08 (1.01,1.14)**
LMW	Model 2	1 (Reference)	1.01 (0.81,1.25)	**1.28 (1.04,1.58)**	**0.02**	**1.06 (1.00,1.13)**
	Model 3	1 (Reference)	0.97 (0.77,1.20)	1.19 (0.98,1.45)	0.07	1.04 (0.98,1.10)
	Model 1	1 (Reference)	1.17 (0.95,1.45)	**1.39 (1.10,1.76)**	**0.01**	**1.11 (1.02,1.21)**
HMW	Model 2	1 (Reference)	1.16 (0.93,1.43)	**1.36 (1.07,1.74)**	**0.00**	**1.13 (1.03,1.23)**
	Model 3	1 (Reference)	1.18 (0.96,1.45)	**1.46 (1.17,1.82)**	**0.00**	**1.14 (1.05,1.25)**
	Model 1	1 (Reference)	1.08 (0.86,1.35)	1.27 (0.98,1.63)	0.07	1.08 (0.99,1.17)
DEHP	Model 2	1 (Reference)	1.10 (0.86,1.41)	**1.36 (1.04,1.76)**	**0.02**	**1.11 (1.03,1.21)**
	Model 3	1 (Reference)	1.11 (0.90,1.38)	**1.36 (1.08,1.72)**	**0.01**	**1.12 (1.04,1.21)**
CVD mortality						
	Model 1	1 (Reference)	1.2 (0.77,1.87)	**1.67 (1.26,2.22)**	**0.00**	**1.13 (1.02,1.25)**
LMW	Model 2	1 (Reference)	1.12 (0.7,1.79)	**1.64 (1.21,2.23)**	**0.00**	**1.12 (1.01,1.23)**
	Model 3	1 (Reference)	1.09 (0.72,1.66)	**1.43 (1.03,1.99)**	**0.03**	1.09 (0.98,1.20)
	Model 1	1 (Reference)	1.32 (0.93,1.86)	**1.57 (1.01,2.44)**	**0.05**	1.08 (0.93,1.24)
HMW	Model 2	1 (Reference)	1.29 (0.89,1.87)	1.53 (0.93,2.52)	0.09	1.10 (0.94,1.29)
	Model 3	1 (Reference)	1.37 (0.90,2.08)	1.49 (0.95,2.32)	0.09	1.15 (0.96,1.38)
	Model 1	1 (Reference)	1.03 (0.72,1.47)	1.37 (0.91,2.07)	0.13	1.04 (0.92,1.18)
DEHP	Model 2	1 (Reference)	1.07 (0.72,1.58)	1.49 (0.91,2.44)	0.11	1.08 (0.94,1.25)
	Model 3	1 (Reference)	1.24 (0.84,1.83)	1.50 (0.98,2.31)	0.06	1.14 (0.97,1.35)
Cancer mortality						
	Model 1	1 (Reference)	0.89 (0.56,1.43)	1.03 (0.64,1.65)	0.90	1.02 (0.91,1.15)
LMW	Model 2	1 (Reference)	0.84 (0.53,1.33)	0.94 (0.58,1.52)	0.82	1.00 (0.88,1.13)
	Model 3	1 (Reference)	0.83 (0.52,1.30)	1.05 (0.67,1.65)	0.81	1.02 (0.91,1.14)
	Model 1	1 (Reference)	0.82 (0.54,1.25)	0.85 (0.52,1.38)	0.54	0.97 (0.79,1.2)
HMW	Model 2	1 (Reference)	0.82 (0.52,1.29)	0.85 (0.51,1.43)	0.58	0.99 (0.79,1.22)
	Model 3	1 (Reference)	0.83 (0.55,1.24)	1.00 (0.62,1.62)	0.95	1.03 (0.86,1.25)
	Model 1	1 (Reference)	0.65 (0.42,1.02)	0.76 (0.43,1.34)	0.38	0.95 (0.77,1.17)
DEHP	Model 2	1 (Reference)	0.63 (0.38,1.02)	0.77 (0.42,1.42)	0.47	0.97 (0.77,1.21)
	Model 3	1 (Reference)	0.69 (0.44,1.06)	0.83 (0.46,1.49)	0.59	1.01 (0.83,1.22)

Abbreviations: CVD, cardiovascular disease.
Model 1: adjustment for age, sex, and urinary creatinine.
Model 2: model 1 + race/ethnicity, family income, education, smoking, alcohol drinking, physical activity, total energy intake, HEI2010 score, survey year.
Model 3: model 2 + BMI.

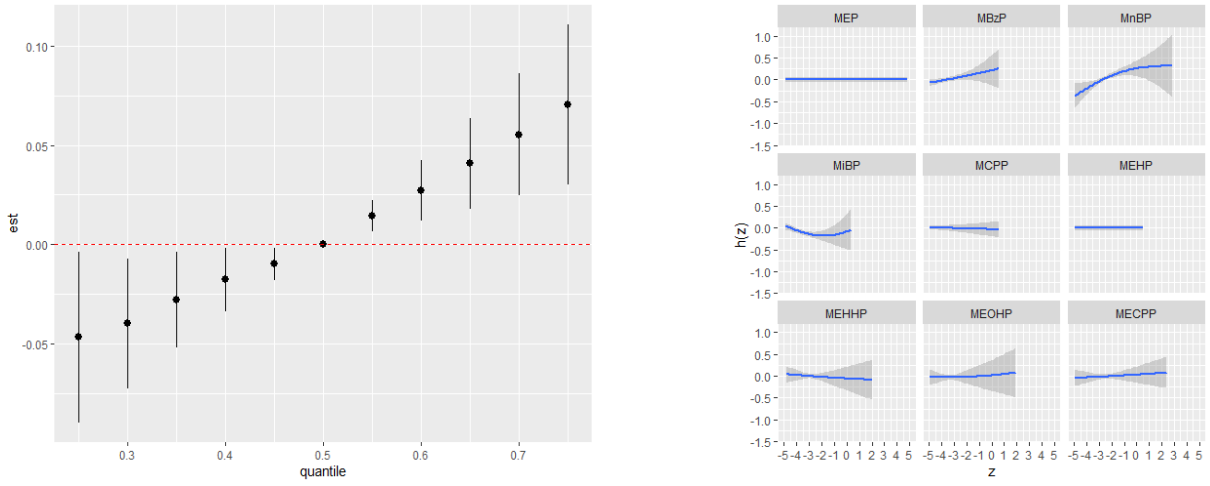
Stratified analysis showed that, compared with the lowest tertile, higher levels of phthalate exposure increased the risk of all-cause mortality by 32% in individuals with low physical activity, while no such effect was observed in those with high physical activity. This effect modification suggests that physical activity may attenuate phthalate toxicity (eTable 3). Similarly, LMW exposure was associated with increased CVD mortality among White individuals (eTable 4). No significant association was observed between LMW exposure and cancer mortality in any subgroup, nor were there significant differences in the associations between HMW and DEHP exposure and all-

cause or cause-specific mortality across strata of age, sex, race/ethnicity, diet quality, and physical activity (eTable 3, eTable 4, eTable 5). Sensitivity analysis showed that after excluding NHANES 2001–2002 participants, the association between DEHP and all-cause mortality disappeared, whereas the associations of HMW with all-cause mortality and LMW with CVD mortality remained significant (eTable 6). After further adjustment for BPA, the link between LMW and CVD mortality vanished, yet the association of HMW with all-cause mortality persisted (eTable 7).

BKMR results provided strong support for the six group classification (Table 3, eTable 8, eTable 9) based on the observed correlation among the nine phthalate esters (eFigure 1). The group posterior inclusion probability for all-cause mortality was 0.644 (Table 3). Mono-n-butyl phthalate (MnBP) was identified as the primary factor in this group, while group 6 showed the highest conditional posterior inclusion probability of 0.53 for mono-2-ethyl-5-oxohexyl phthalate (MEOHP). The other seven phthalate esters were not selected (Table 3). The mono-n-butyl phthalate (MnBP) showed a nearly linear positive exposure-response relationship with all-cause mortality (Figure 1A). Overall, simultaneous exposure to 9 phthalate esters was positively associated with all-cause mortality (Figure 1B). Specifically, the mixture phthalate level was 7.3% higher (95% CI, 4.32–11.67) when fixing all exposures at the 75th percentile compared to the median (Figure 1B). Additionally, the mixture analysis showed no significant associations with mortality from CVD or cancer mortality (eFigure 2, eFigure 3). Similarly, hierarchical BKMR did not identify joint associations between specific phthalates and CVD or cancer mortality (eTable 8, eTable 9).

Table 3. Hierarchical posterior inclusion probabilities (PIPs) from BKMR for all-cause mortality.

Variable	Group	GroupPIP	CondPIP
mono-ethyl phthalate (MEP)	1	0.00	0.00
mono-benzyl phthalate (MBzP)	2	0.415	1.00
mono-n-butyl phthalate (MnBP)	3	0.644	1.00
mono-isobutyl phthalate (MiBP)	4	0.473	1.00
mono-(3-carboxypropyl) phthalate (MCPP)	5	0.003	1.00
mono-2-ethyl hexyl phthalate (MEHP)	6	0.067	0.00
mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP)	6	0.067	0.182
mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP)	6	0.067	0.582
mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP)	6	0.067	0.236



(A) (B)

Figure 1. Phthalate exposure and all-cause mortality. **(A)** Overall association (percentage change and 95% credible intervals) of the individual phthalate exposure to all-cause mortality; **(B)** Exposure–response curves for phthalates exposure and all-cause mortality. Note: mono-ethyl phthalate (MEP), mono-benzyl phthalate (MBzP), mono-n-butyl phthalate (MnBP), mono-isobutyl phthalate (MiBP), mono-(3-carboxypropyl) phthalate (MCPP), mono-2-ethylhexyl phthalate (MEHP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP).

4. Discussion

In this US nationally representative cohort study, we found that mixed phthalate exposure was significantly and positively associated with all-cause mortality among individuals with overweight and obesity. Additionally, high levels of HMW and DEHP exposure were significantly associated with an increased risk of all-cause mortality. Higher levels of LMW exposure were significantly associated with an elevated risk of CVD mortality.

To the best of our knowledge, this is the first study to examine the health hazards of phthalate exposure on individuals with overweight and obese from the perspective of molecular weight classifications and mixed exposure scenarios, all with a focus on mortality as the outcome. We found that higher levels of phthalate exposure were associated with an increased risk of all-cause and CVD mortality in individuals with overweight and obesity. These findings are consistent with previous studies conducted in general populations considering molecular weight classifications [17,24,25] and limited studies considering mixture exposure [26,27]. However, inconsistencies exist. For example, one study found no association between phthalate exposure and the risk of cardiovascular death in general US adults [28]. This is probably because earlier studies had relatively short follow-up (≈ 7 years on average). With such limited follow-up, too few outcome events may accrue, resulting in insufficient statistical power to detect meaningful associations. Moreover, subgroup characteristics, such as the proportion of overweight and obese individuals in the study population, could also play a role, as our sensitivity analysis indicated that among non-obese individuals, there was no association between phthalate exposure and the risk of death. Furthermore, we identified mono-n-butyl phthalate (MnBP) as a key contributor to increased mortality, which is consistent with findings from a longitudinal study showing that doubling creatinine-adjusted MnBP levels was linked to a faster annual decline in forced vital capacity [29] and with increased carotid intima-media thickness [30].

Experimental studies have shown that treatment with phthalates, such as DEHP, can stimulate the release of TNF-α, enhance oxidative stress, and reduce the secretion of functional markers like adipokine in adipose tissue [31,32]. It can also aggravate hyperlipidemia, promote systemic inflammation, and accelerate the development of atherosclerosis [33]. In addition, experiments in mice and zebrafish embryo models have found that phthalates can produce cardiotoxicity by increasing the expression of peroxisome proliferator-activated receptor γ (PPARγ) or downregulating Nkx2.5 and Tbx5 [34,35]. In vitro studies showed that DEHP can cause changes in the gene expression profile of kinesin, TGFβ2, α-tubulin, and α1&β1 integrins in mouse cardiomyocytes, leading to arrhythmias [36]. All these mechanisms may play a role in exacerbating obesity-related health problems and increasing the risk of death.

Phthalates are classified into low molecular weight phthalates and high molecular weight phthalates (with ≥ 7 carbon atoms) based on the length of the alkyl chain. The physicochemical properties and molecular docking results of phthalates and their metabolites show that as the alkyl chain lengthens, the octanol-water partition coefficient increases, hydrophobicity increases, and the binding efficiency with peroxisome proliferator-activated receptors (PPARs) and retinoid X receptors (RXRs) ligands is higher [37,38]. PPAR and RXR receptors play an important regulatory role in fatty acid metabolism and energy metabolism and are closely related to the occurrence and development of various chronic diseases (such as diabetes, hypertension, *etc.*) [39,40]. These factors may explain the difference in the strength of the association between phthalates and all-cause mortality and cardiovascular mortality.

This study has significant public health implications. Obesity is a major global public health challenge. With the continuous growth of the obese population, finding ways to promote their health has become a crucial scientific issue. We found that for individuals who are already overweight or obese, exposure to phthalates may further increase their risk of death. Specifically, higher exposure to HMW and DEHP was associated with a 46% and 36% increase in the risk of all-cause mortality, respectively; LMW exposure was associated with a 43% increase in the risk of CVD mortality. These findings underscore the importance of considering phthalate exposure when assessing the health risks of obese patients. Health providers may consider ways advising patients to reduce the use of certain plastic products, cosmetics or canned foods that may contain or be contaminated by phthalate [41].

4.1. Strengths and limitations

This study has several strengths. Briefly, we utilized nationally representative data from NHANES, which allows us to generalize our findings to a broader population. Secondly, the rich data from NHANES, including comprehensive information on demographics, socioeconomics, anthropometrics, and diet and lifestyle factors, provided opportunities to adjust for various potential confounding factors. Third, we systematically explored the risk of phthalate exposure and death from the perspectives of individual phthalate metabolites, molecular weight categories, and mixed exposures, and consistently found that phthalate exposure was associated with an increased risk of all-cause mortality and CVD mortality among individuals with overweight and obesity. There are also limitations in this study. First, spot urine samples are not ideal for assessing chronic, long-term cardiovascular mortality due to the short half-life of phthalates [42]. However, previous evidence indicates that a single spot-sampling approach can sufficiently represent average population exposure, provided urine samples are collected from a sufficiently large population with randomized meal consumption and bladder-emptying times [43]. Second, although linking to mortality data up to 2019 establishes a prospective cohort design for this study, the cross-sectional nature of the NHANES survey means there is no longitudinal data on participants. Owing to the inherently cross-sectional design, we are unable to examine association between phthalate exposure

and mortality among individuals with new-onset obesity. Individuals who are already obese may have modified their lifestyles in ways that indirectly alter their phthalate exposure, thereby introducing further uncertainty into the observed associations. This prevents us from further analyzing the mechanisms of phthalate exposure and mortality among individuals with obesity. Longitudinal studies are needed to confirm our findings. Third, overweight and obesity were defined based on height and weight measurements taken at the time of the NHANES survey, without information about the duration of obesity and any changes in body weight over time. Consequently, it is not possible to determine whether the duration of obesity affects the association between exposure and death. Fourth, while this study focused exclusively on phthalate metabolites, these compounds represent only one component of the complex environmental chemical mixture to which humans are commonly exposed. It remains plausible that unmeasured co-exposures or other clinically relevant risk factors—if distributed analogously to phthalate concentrations across exposure categories—could partially drive or confound the observed associations. Addressing this critical limitation will require future studies to: assess joint effects of multi-chemical mixtures through high-dimensional approaches integrating granular clinical data (e.g., longitudinal biomarkers, detailed comorbidity records), thereby rigorously mitigating residual confounding.

5. Conclusion

In this nationally representative cohort study, phthalate exposure was significantly associated with an increased risk of all-cause mortality and CVD mortality among individuals with overweight and obesity. Further studies are needed to replicate the findings and determine the underlying mechanisms.

Data availability statement

The data analyzed in this study are publicly available in the National Health and Nutrition Examination Survey (NHANES) repository at https://www.cdc.gov/nchs/nhanes/.

Declaration of generative AI and AI-assisted technologies

The authors did not use generative AI or AI-assisted technologies in the writing of this manuscript.

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Authors' contribution

Conceptualization, Buyun Liu; formal analysis, Xing Yuan, Yang Ge, Yi Wang, and Mingxiao Liu; validation, Xing Yuan, Yang Ge, Yi Wang, and Mingxiao Liu; writing—original draft preparation, Xing Yuan and Yang Ge; writing—review and editing, Hans-Joachim Lehmler, Leonardo Trasande, Robert B. Wallace, Guifeng Xu, Shuang Rong, Buyun Liu, and Wei Bao; visualization, Xing Yuan, Yang Ge, Yi Wang, and Mingxiao Liu; supervision, Buyun Liu and Wei Bao; funding acquisition, Buyun Liu and Wei Bao. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

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