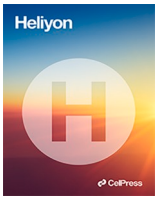
Heliyon 9 (2023) e20343

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Associations of urinary di(2-ethylhexyl) phthalate metabolites with lipid profiles among US general adult population

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A R T I C L E I N F O

Keywords:
Phthalate
Di(2-ethylhexyl) phthalate (DEHP)
Serum lipid
WQS
NHANES

A B S T R A C T

Background: Di(2-ethylhexyl) phthalate (DEHP) a parent compound that is metabolized into 4 phthalate metabolites, which correlate to adverse cardio-metabolic risk factors. This study aimed to explore the links between urinary DEHP metabolites and serum lipids in the U.S. general adult population.

Methods: In this cross-sectional study, data on 11 urinary phthalate metabolites from the 2005–2018 National Health and Nutrition Examination Surveys (NHANES) were analyzed. Multivariate linear regression and restricted cubic spline (RCS) were used to examine the relationship between phthalate metabolites [specific DEHPs: mono-(2-ethyl-5-carboxy-pentyl) phthalate (MECPP), mono-(2-ethyl-5-hydroxy-hexyl) phthalate (MEHHP), mono-(2-ethylhexyl) phthalate (MEHP), mono-(2-ethyl-5-oxo-hexyl) phthalate (MEOHP)] and serum lipids (triglycerides [TG], total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C], and high-density lipoprotein cholesterol [HDL-C]). To identify mixed exposure effects of phthalate metabolites, quantile g-computation (QG-C) and weighted quantile sum (WQS) regression were employed for the lipid profiles.

Results: A total of 9141 adults were included in the analysis. MECPP, MEHHP, MEHP, and MEOHP in the highest quartile had a negative relationship with HDL-C compared to the lowest quartile (All P for trend <0.05). TG showed a significant positive relation with MECPP, MEHHP, and MEOHP (All P for trend <0.05), but there was no notable association with MEHP. RCS demonstrated a linear relationship of DEHP metabolites with HDL-C, TC, TG, and LDL-C (all P for nonlinearity >0.05). The WQS index of DEHP metabolites showed independent correlations with HDL-C [$\beta = -0.26$, 95%CI (-0.43, -0.09), $P = 0.002$], TC [$\beta = 0.55$, 95%CI (0.13, 0.98), $P = 0.011$], and TG [$\beta = 2.40$, 95%CI (0.85, 3.96), $P = 0.003$].

Conclusion: Our study suggests that environmental DEHP exposure may affect serum HDL-C and TG levels in the general adult population. Further research is warranted to confirm these findings and illuminate the underlying mechanisms of DEHP exposure on lipids.

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https://doi.org/10.1016/j.heliyon.2023.e20343
Received 22 December 2022; Received in revised form 14 September 2023; Accepted 19 September 2023
Available online 21 September 2023

1. Introduction

Due to population aging and modern lifestyle, cardiovascular diseases (CVDs) have become the leading cause of mortality worldwide. Dyslipidemia, a major cardiovascular risk factor, plays a crucial role in the pathogenesis and development of atherosclerotic cardiovascular disease (ASCVD) [1]. Recently, environmental contaminants such as phthalates have been proposed as potential risk factors for CVD [2].

Notably, phthalates are widely used in various consumer products such as personal care items, plastics, and food packaging, leading to widespread exposure to these substances [3,4]. Numerous studies have shown that various phthalate metabolites are closely associated with adverse cardio-metabolic outcomes in both children and adolescents [2,4–7]. Phthalates have also been shown to interfere with hormone homeostasis and lipid metabolism [8–11]. However, these studies only provide limited evidence of the cardiovascular effects of phthalate exposure, and the mixture effect of different types of phthalates limits the generalization of the results.

Di(2-ethylhexyl) phthalate (DEHP), a commonly used plasticizer, is recognized as an endocrine-disrupting chemical (EDC) and is easily leached out as persistent pollutants. Studies have suggested that DEHP exposure may be linked to several CVDs, such as hypertension, atherosclerosis (AS), coronary artery disease (CAD), and myocardial infarction [12–15]. Moreover, DEHP exposure has been shown to cause oxidative stress, inflammation, and damage to blood vessels, and the DEHP-induced atherosclerosis might be associated with metabolism disruption, vascular smooth muscle cell damage, and inflammation throughout the pathological development [16–18].

Among the different metabolites used to measure DEHP exposure, mono-(2-ethylhexyl) phthalate (MEHP), mono-(2-ethyl-5-hydroxy-hexyl) phthalate (MEHHP), mono-(2-ethyl-5-carboxy-pentyl) phthalate (MECPP), and mono-(2-ethyl-5-oxo-hexyl) phthalate (MEOHP) are commonly measured in urine samples.

It is important to note that evidence of whether DEHP and its metabolites participate in the increased prevalence of dyslipidemia in adults is limited. The current study aims to explore the possible pathophysiological effects of exposure to these substances and further clarify the individual correlation of DEHP metabolites and lipid profiles by analyzing data from the National Health and Nutrition Examination Survey (NHANES) from 2005 to 2018.

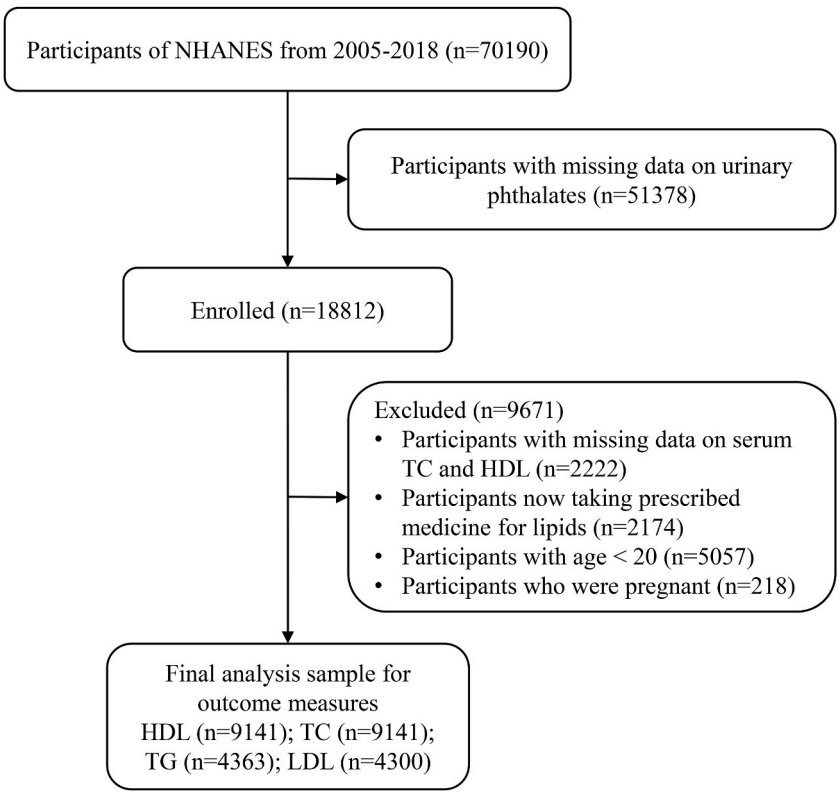

Fig. 1. Eligible participants in the evaluation of the influence between urinary phthalate metabolites and serum lipid profiles in the general adult population.

2. Methods

2.1. Study participants and baseline characteristics

This cross-sectional epidemiological study utilized publicly available data from NHANES, conducted by the US National Center for Health Statistics. The authors were not involved in the collection or production of the database. Publicly available information on the survey design, methods, and data protocols can be accessed at https://www.cdc.gov/nchs/nhanes/about_nhanes.htm [19]. The National Center for Health Statistics (NCHS) Research Ethics Review Board approved the research protocols, and all participants provided written informed consent.

A representative sample of 9141 adult participants was selected from NHANES 2005–2018, which included 7 survey cycles with 70,190 total adult participants. The excluded participants lacked urinary phthalate data and were under 18 years of age (Fig. 1).

The mean age of the participants was 46.1 (17.0) years, and 4491 (49.1%) were male. The mean BMI of the study population was 28.9 (7.1) kg/m2. The prevalence of comorbidities was 1.7% for congestive heart failure (n = 153), 1.8% for coronary heart disease (n = 164), 1.2% for angina (n = 113), 2.2% for heart attack (n = 205), and 2.5% for stroke (n = 226). The mean levels of TG, TC, LDL-C, and HDL-C were 117.8 (80.1) mg/dL, 194.7 (40.7) mg/dL, 115.5 (34.7) mg/dL, and 53.1 (16.2) mg/dL, respectively. The demographic characteristics of the participants are shown in Table 2.

2.2. Phthalates metabolites assessment

In this study, a total of 12 urinary phthalate metabolites were continuously measured and documented in NHANES 2005–2018 using high-performance liquid chromatography-tandem mass spectrometry (LC-MS/MS) for a subsample of NHANES participants. To estimate the limits of detection (LOD) in this analysis, the highest reported LOD for any given metabolite across all survey years was used. All concentrations below the LOD, except MEHP (40%), were replaced by an LOD value divided by two square root values (LOD/$\sqrt{2}$) [20]. Creatinine was included as a covariate in all models to adjust for urine concentration. The detailed protocol can be found at https://wwwn.cdc.gov/nchs/data/nhanes/2007-2008/labmethods/phthte_e_met_phthalate_metabolites.pdf, Accessed June 06, 2021.

Monoisononyl phthalate (MINP) was excluded due to low detectable concentrations. The analysis initially included 11 phthalate biomarkers, of which at least 65% of study subjects had concentrations above the LOD and are shown in Table 1: mono (carboxynonyl) phthalate (MCNP), mono (carboxyoctyl) phthalate (MCOP), MECPP, mono-*n*-butyl phthalate (MBP), mono-(3-carboxypropyl) phthalate (MCPP), mono-ethyl phthalate (MEP), MEHHP, MEHP, mono-isobutyl phthalate (MiBP), MEOHP, and mono-benzyl phthalate (MBzP). The molar sum of DEHP metabolites (MEHP, MECPP, MEHHP, and MEOHP) was also calculated and expressed as ΣDEHP.

2.3. Lipid profiles

The lipid profiles in this cross-sectional epidemiological study were measured using enzymatic assays for total cholesterol (TC) and triglyceride (TG), and immunoassays for high-density lipoprotein cholesterol (HDL-C). Low-density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald calculation method. Detailed instructions on these procedures can be found in the Laboratory Procedures Manual corresponding to each NHANES cycle (https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx).

2.4. Covariates

Demographic characteristics such as age, sex, educational levels, race/ethnicity, and poverty income ratio (PIR), as well as lifestyle factors like smoking status, alcohol use, and body mass index (BMI), medication use (including lipid-lowering agents), and

Table 1
Concentrations and detection rate of the eleven urinary phthalates (ng/mL).

Metabolite	N	LODmax	≥LODmax(%)[a]	5th	25th	50th	75th	95th
MCNP	9141	0.2	95.4	0.4	1.0	2.1	4.2	13.8
MCOP	9141	0.3	98.4	1.1	3.5	7.8	21.7	126.7
MECPP	9141	0.4	99.8	2.2	6.9	14.6	31.1	127.0
MBP	9141	0.4	98.2	1.4	6.2	13.5	26.7	72.8
MCPP	9141	0.4	90.8	0.3	0.8	1.8	4.1	16.5
MEP	9141	1.2	99.8	5.1	19.9	54.4	174.8	1062.3
MEHHP	9141	0.4	99.4	1.2	4.3	9.5	21.2	92.0
MEHP	9141	0.8	66.5	0.4	0.6	1.4	3.32	14.1
MiBP	9141	0.8	98.0	0.9	3.7	8.0	15.4	40.8
MEOHP	9141	0.2	99.0	0.8	2.7	5.9	12.8	53.3
MBzP	9141	0.3	97.5	0.5	2.1	5.1	12.3	42.0

N, number of urinary samples; LOD, limit of detection; 5th, 5th percentile; 25th, 25th percentile; 50th, 50th percentile; 75th, 75th percentile; 95th, 95th percentile.

[a] Percentage of metabolite concentrations at or above the maximum limit of detection (<LODmax). All concentrations below the LODmax (<LODmax) were substituted with a value of LODmax divided by square root of two ($\sqrt{2}$).

Table 2
Characteristics of the study population.

Variable	Total (n = 9141)
Age, years	46.1 (17.0)
Male, %	4491 (49.1%)
Education level, %	
Below high school	2227 (24.4%)
High school	2071 (22.7%)
Above high school	4843 (53.0%)
Race/ethnicity, %	
Mexican American	1488 (16.3%)
Other Hispanic	913 (10.0%)
Non-Hispanic White	3711 (40.6%)
Non-Hispanic Black	1946 (21.3%)
Other race	1083 (11.8%)
Poverty, %	2035 (22.3%)
Smoker, %	3889 (42.5%)
Alcohol use, %	6596 (72.2%)
Body mass index, kg/m^2	28.9 (7.1)
Sedentary time, hrs	
<3 h	2427 (26.6%)
3–6 h	3056 (33.4%)
>6 h	3658 (40.0%)
Urinary creatinine, mg/dL	115.0 [66.0, 174.0]
Serum calcium, mg/dL	9.4 (0.36)
Serum phosphorus, mg/dL	3.7 (0.56)
Energy intake, kcal/day	1985.0 [1480.0, 2623.0]
Systolic pressure, mmHg	122.8 (17.2)
Diastolic pressure, mmHg	70.8 (11.6)
Diabetes, %	706 (7.7%)
Congestive heart failure, %	153 (1.7%)
Coronary heart disease, %	164 (1.8%)
Angina, %	113 (1.2%)
Heart attack, %	205 (2.2%)
Stroke, %	226 (2.5%)
Triglyceride, mg/dL	117.8 (80.1)
Total cholesterol, mg/dL	194.7 (40.7)
Low-density lipoprotein cholesterol, mg/dL	115.5 (34.7)
High-density lipoprotein cholesterol, mg/dL	53.1 (16.2)

Data are presented as mean (SD) or n (%).

comorbidities information (e.g., hypertension, diabetes, congestive heart failure, coronary heart disease, etc.) were obtained from physical examination and standardized medical condition questionnaire administered by trained interviewers. The corresponding questionnaires can be accessed on the each NHANES cycle website (https://wwwn.cdc.gov/nchs/nhanes/continuousnhanes/default.aspx?BeginYear=2007).

The criteria set for identifying a smoker was someone who smoked at least 100 cigarettes in their lifetime. An alcohol user was defined as an individual who consumed at least 12 alcoholic drinks in any one year. Educational levels were classified into three categories: below high school, high school, and above high school, while race and ethnicity were classified into five categories: Mexican American, other Hispanic, non-Hispanic white, non-Hispanic black, and other race groups (including multi-racial). Family PIR was utilized to assess the ratio of family income to the poverty threshold, with poverty defined as a family PIR below 1. Height and weight measurements were taken without shoes using the anthropometry procedures manual, and BMI was calculated as weight divided by height squared (kg/m^2).

2.5. Statistical analysis

Study used descriptive statistics to present continuous variables as means (standard deviations, SDs) with normal distribution or medians with interquartile ranges (IQRs) with non-normal distribution, while categorical variables were reported as numbers (%). To normalize the distribution of urinary phthalate metabolites, log2-transformation was applied. Spearman's rank correlation was used to calculate the correlation coefficients between urinary phthalate exposures and creatinine. The missing data were multiply interpolated for the covariates by the "mice" package based on the random forest algorithm.

Linear regression analyses were further conducted to determine the associations between urinary phthalate metabolites (as continuous variables in 11 phthalate metabolites and as category variables in DEHP metabolites) and lipid profiles. Furthermore, the restricted cubic spline (RCS) regression model with knots at the (10th, 50th, and 90th) percentiles of each DEHP metabolite was used to explore the shape of relationship and nonlinearity between lipid parameters and urinary DEHP metabolites. Quantile g-computation (QG-C) model was applied to comprehensively assess the effect of DEHP exposure on serum lipids, which combines the inferential simplicity of weighted quantile regression (WQS) regression with the flexibility of g-computation without requiring directional

homogeneity [21]. WQS regression was applied to determine the mixed effect of the correlated exposure variables on lipid parameters by using the "gWQS" package. This method involved calculating a WQS index by assigning weights to each DEHP metabolite concentration through bootstrap sampling. To obtain the WQS index, DEHP metabolite were divided into deciles. The data were then split into training (40%) and validation (60%), and 2000 bootstrap samplings were set. Model was adjusted with age, sex, race, education level, poverty, urinary creatinine, smoking, alcohol use, BMI, energy intake levels, sedentary time, systolic pressure, diastolic pressure, diabetes, congestive heart failure, coronary heart disease, angina, heart attack, and stroke.

Stratified analysis was conducted to assess the stability of these associations across different populations. We stratified the data based on several important variables, including age (<40, 40–59, or ≥60) and sex (female and male). SPSS (version 24.0; IBM) and R software (version 4.1.0; The R Foundation for Statistical Computing) were used for data analysis. A two-sided P-value of less than 0.05 was considered statistically significant.

3. Results

3.1. Correlation for phthalate exposures to lipids

Correlation analysis of the urinary phthalate metabolites showed that most of the metabolites were moderately correlated with the other 10 metabolites and urine creatinine (Spearman r ≥ 0.3). Specifically, the correlation coefficients between the four oxidative phthalates metabolites of DEHP, including MECPP, MEHHP, MEHP, and MEOHP, were all ≥0.75 (Fig. 2).

3.2. Association of urinary phthalate metabolites and lipid profiles

The study also analyzed the association between individual exposure to each phthalate and lipid profiles (Table 3). Multiple linear regression analysis demonstrated that the study targets - MECPP, MEHHP, MEHP, and MEOHP - were significantly associated with

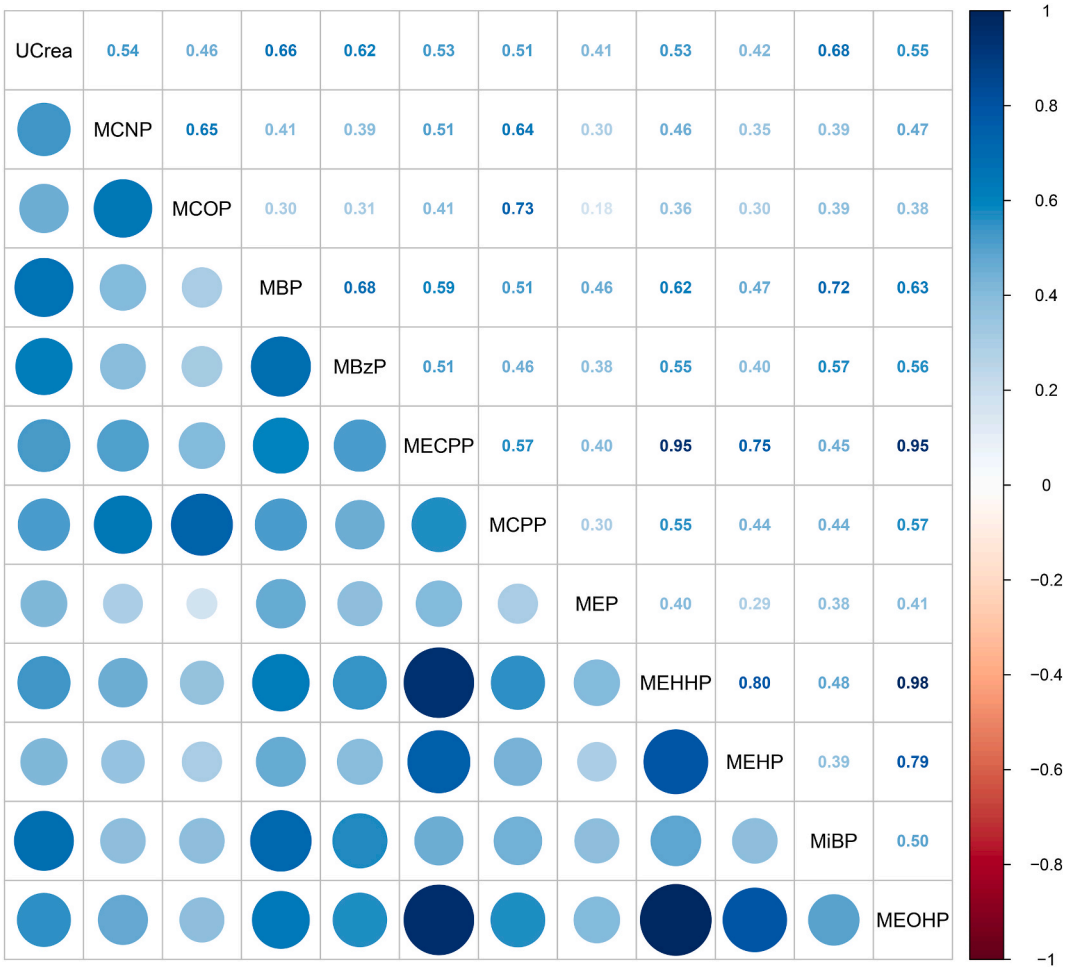

Fig. 2. Pairwise Spearman's rank correlation coefficients among urinary phthalate metabolites concentrations in the general population.

Table 3
Multiple linear regression associations of eleven urinary phthalates metabolites with lipid profiles in adults.

Phthalates	Model	HDL-C		TC		TG		¹LDL-C	
		β (95%CI)	*P*-value	β (95%CI)	*P*-value	β (95%CI)	*P*-value	β (95%CI)	*P*-value
MCNP	Model1	−0.03 (−0.26, 0.20)	0.810	−0.32 (−0.91, 0.28)	0.298	−0.23 (−2.34, 1.88)	0.831	−0.45 (−1.19,0.28)	0.226
	Model2	0.04 (−0.18, 0.25)	0.742	−0.19 (−0.76, 0.39)	0.526	−0.35 (−2.44, 1.74)	0.742	−0.41 (−1.13, 0.31)	0.265
MCOP	Model1	−0.37 (−0.54, −0.20)	<0.001	−0.47 (−0.92, −0.02)	0.039	−0.38 (−1.97, 1.21)	0.639	0.14 (−0.41, 0.70)	0.616
	Model2	−0.25 (−0.41, −0.09)	0.003	−0.31 (−0.75, 0.12)	0.159	−0.53 (−2.11, 1.05)	0.511	0.24 (−0.30, 0.78)	0.387
MBP	Model1	0.03 (−0.21, 0.27)	0.806	−0.02 (−0.66, 0.62)	0.949	0.86 (−1.53, 3.25)	0.480	−0.66 (−1.49, 0.17)	0.121
	Model2	−0.09 (−0.32, 0.14)	0.445	0.17 (−0.44, 0.79)	0.581	1.07 (−1.29, 3.44)	0.374	−0.24 (−1.05, 0.58)	0.569
MBzP	Model1	−0.29 (−0.50, −0.08)	0.007	−0.51 (−1.06, 0.04)	0.069	2.45 (0.44, 4.46)	0.017	−0.68 (−1.38, 0.02)	0.058
	Model2	−0.15 (−0.35, 0.05)	0.149	−0.33 (−0.87, 0.20)	0.225	2.10 (0.10, 4.09)	0.039	−0.36 (−1.04, 0.33)	0.310
MECPP	Model1	−0.33 (−0.54, −0.13)	0.002	−0.11 (−0.65, 0.43)	0.691	4.59 (2.67, 6.51)	<0.001	−0.43 (−1.10, 0.24)	0.211
	Model2	−0.30 (−0.49, −0.10)	0.003	0.20 (−0.33, 0.72)	0.468	4.76 (2.86, 6.65)	<0.001	−0.11 (−0.77, 0.55)	0.747
MCPP	Model1	−0.30 (−0.50, −0.10)	0.003	−0.39 (−0.92, 0.13)	0.141	1.42 (−0.45, 3.30)	0.138	−0.41 (−1.07, 0.24)	0.218
	Model2	−0.28 (−0.47, −0.09)	0.004	−0.18 (−0.69, 0.33)	0.482	1.42 (−0.44, 3.28)	0.134	−0.20 (−0.84, 0.45)	0.551
MEP	Model1	0.15 (−0.01, 0.30)	0.057	0.11 (−0.28, 0.50)	0.583	−0.64 (−2.12, 0.83)	0.392	−0.04 (−0.56, 0.47)	0.867
	Model2	0.12 (0.11, −0.03)	0.112	0.09 (−0.30, 0.47)	0.664	−0.72 (−2.17, 0.74)	0.333	−0.01 (−0.50, 0.50)	0.994
MEHHP	Model1	−0.25 (−0.45, −0.05)	0.012	0.45 (−0.06, 0.96)	0.081	5.01 (3.21, 6.81)	<0.001	−0.23 (−0.86, 0.40)	0.470
	Model2	−0.25 (−0.43, −0.07)	0.008	0.62 (0.12, 1.12)	0.014	5.04 (3.26, 6.82)	<0.001	0.04 (−0.57, 0.66)	0.890
MEHP	Model1	−0.36 (−0.56, −0.17)	<0.001	−0.32 (−0.86, 0.23)	0.258	1.82 (−0.05, 3.70)	0.056	−0.29 (−0.99, 0.41)	0.420
	Model2	−0.23 (−0.42, −0.03)	0.024	−0.04 (−0.57, 0.49)	0.877	2.33 (0.34, 4.31)	0.021	0.14 (−0.55, 0.83)	0.684
MiBP	Model1	−0.23 (−0.49, 0.04)	0.094	−0.80 (−1.49, −0.10)	0.024	−1.24 (−3.76, 1.29)	0.338	−0.02 (−0.89, 0.86)	0.969
	Model2	−0.15 (−0.41, 0.10)	0.228	−0.64 (−1.32, 0.04)	0.063	−1.57 (−4.07, 0.92)	0.216	0.16 (−0.70, 1.02)	0.714
MEOHP	Model1	−0.31 (−0.51, −0.10)	0.003	−0.22 (−0.75, 0.31)	0.419	3.69 (1.83, 5.56)	<0.001	−0.51 (−1.16, 0.15)	0.129
	Model2	−0.29 (−0.48, −0.10)	0.003	0.08 (−0.43, 0.60)	0.749	3.76 (1.91, 5.61)	<0.001	−0.18 (−0.82, 0.46)	0.577

Model 1 was adjusted as age, sex, race, education level, poverty, urinary creatinine; Model 2 was adjusted as model 1 plus smoking, alcohol use, BMI, energy intake levels, sedentary time, systolic pressure, diastolic pressure, diabetes, congestive heart failure, coronary heart disease, angina, heart attack, and stroke. HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; CI, confidence interval.

lipid profiles, indicating the feasibility of further analysis. Fig. 3 showcases the weights of each phthalate metabolite and the positive and negative effects of the separate phthalates regarding the HDL-C (Fig. 3A), TC (Fig. 3B), TG (Fig. 3C), and LDL-C (Fig. 3D). In the QG-C model, the total effect of phthalate metabolites mixture was only significantly and negatively associated with HDL-C [Difference per quartile increase = −0.76, 95% CI (−1.34, −0.18), Table 4].

3.3. Association of DEHP metabolites and lipid profiles

Upon further analysis, it was found that all four separated DEHP metabolites - namely MECPP, MEHHP, MEHP, and MEOHP - as well as ΣDEHP were associated with HDL-C across increasing quartiles ($\beta = -1.86$, 95% CI (−2.84, −0.88), $P < 0.001$; $\beta = -1.80$, 95% CI (−2.77, −0.83), $P < 0.001$; $\beta = -1.12$, 95% CI (−2.04, −0.21), $P < 0.05$; and $\beta = -1.73$, 95% CI (−2.71, −0.74), $P < 0.01$ respectively) (All P for trend <0.01, Table 5). Additionally, TG showed significant association with MECPP, MEHHP, MEOHP, and ΣDEHP (All P for trend <0.005), but not with MEHP (P for trend = 0.401). It is worth noting that TC was associated exclusively with MEHHP (Q4: $\beta = 3.32$, 95%CI (0.71, 5.94), $P < 0.05$), with no significant differences observed in the remaining parameters of TC and LDL-C in all quartiles (All $P > 0.05$).

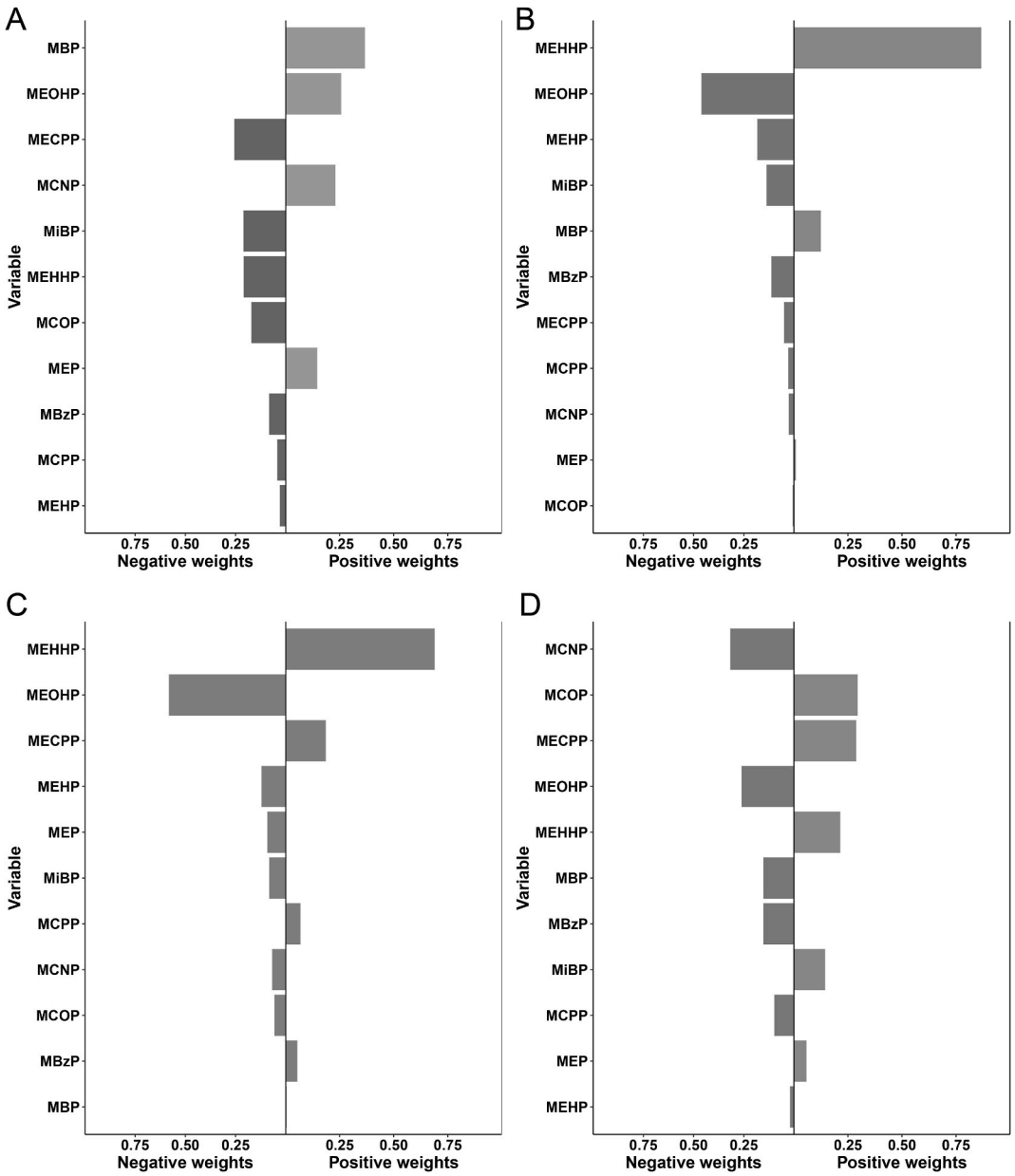

Fig. 3. - Contribution of each compound to the mixture effect of urinary phthalate metabolites on (A) HDL-C, (B) TC, (C) TG, and (D) LDL-C. Quantile g-computation model adjusting for age, sex, race, education level, poverty, urinary creatinine, smoking, alcohol use, BMI, energy intake levels, sedentary time, systolic pressure, diastolic pressure, diabetes, congestive heart failure, coronary heart disease, angina, heart attack, and stroke.

These associations were then analyzed using restricted cubic splines (RCS) with a multivariate linear regression model. Results demonstrated similar trends as the above results and suggested that DEHP metabolites have a linear association with HDL-C and TG (all P for nonlinearity >0.05, Fig. 4).

The relationships between urinary DEHP metabolites and lipid profile were further analyzed using weighted quantile sum (WQS) regression analysis. The WQS index of the four DEHP metabolites was independently correlated with HDL-C ($\beta = -0.26$, 95%CI (-0.43, -0.09), $P = 0.002$), TC ($\beta = 0.55$, 95%CI (0.13, 0.98), $P = 0.011$), and TG ($\beta = 2.40$, 95%CI (0.85, 3.96), $P = 0.003$) (Table 6). In the WQS model, MEHPP was the most heavily weighted component in HDL-C (weight = 0.35), TC (weight = 0.94), and TG (weight = 0.83). The weights for MEHP were 0.77 and for MEHHP were 0.15 in LDL-C (Fig. 5).

Table 4
Quantile g-computation model to assess the association of the mixture of eleven urinary phthalate metabolites with lipid profiles in adults.

Outcomes	Difference (95% CI)	p-value	Sum of positive coefficients	Sum of negative coefficients
HDL-C	−0.76 (−1.34, −0.18)	0.010	1.47	−2.23
TC	−1.02 (−2.58, 0.54)	0.201	7.16	−8.18
TG	0.12 (−5.50, 5.74)	0.966	35.6	−35.5
LDL-C	−0.43 (−2.38, 1.52)	0.663	3.70	−4.14

Model was adjusted as age, sex, race, education level, poverty, urinary creatinine, smoking, alcohol use, BMI, energy intake levels, sedentary time, systolic pressure, diastolic pressure, diabetes, congestive heart failure, coronary heart disease, angina, heart attack, and stroke.
HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; CI, confidence interval.

Table 5
Multiple linear regression associations of DEHP metabolites with lipid profiles in adults.

Outcomes	Phthalates	Quartile 1	Quartile 2	Quartile 3	Quartile 4	*p-t*
		β	β (95%CI)	β (95%CI)	β (95%CI)	
HDL-C (n = 9141)	MECPP	0.00 (Ref.)	−1.21(-2.10, −0.33) **	−1.71(-2.66, −0.77) ***	−1.86(-2.84, −0.88) ***	<0.001
	MEHHP	0.00 (Ref.)	−1.39(-2.27, −0.51) **	−1.77(-2.71, −0.84) ***	−1.80(-2.77, −0.83) ***	0.001
	MEHP	0.00 (Ref.)	−0.17(-1.03, 0.68)	−0.75(-1.61, 0.12)	−1.12(-2.04, −0.21) *	0.008
	MEOHP	0.00 (Ref.)	−1.52(-2.40, −0.63) **	−1.75(-2.69, −0.80) ***	−1.73(-2.71, −0.74) **	0.002
	ΣDEHP	0.00 (Ref.)	−1.14(-2.04, −0.25) *	−1.42(-2.37, −0.46) **	−1.81(-2.80, −0.82) ***	0.001
TC (n = 9141)	MECPP	0.00 (Ref.)	−0.46(-2.85, 1.93)	0.92(-1.63, 3.48)	1.06(-1.59, 3.71)	0.290
	MEHHP	0.00 (Ref.)	1.78(-0.60, 4.15)	3.50(1.00, 6.01) **	3.32(0.71, 5.94) *	0.009
	MEHP	0.00 (Ref.)	0.01(-2.29, 2.32)	0.51(-1.82, 2.84)	−1.61(-4.07, 0.86)	0.195
	MEOHP	0.00 (Ref.)	0.50(-1.90, 2.90)	0.98(-1.57, 3.54)	1.01(-1.65, 3.67)	0.437
	ΣDEHP	0.00 (Ref.)	1.40(-1.01, 3.80)	1.91(-0.66, 4.48)	2.17(-0.50, 4.83)	0.126
TG (n = 4363)	MECPP	0.00 (Ref.)	4.50(-4.15, 13.16)	12.59(3.44, 21.73) **	18.45(9.01, 27.90) ***	<0.001
	MEHHP	0.00 (Ref.)	9.37(0.74, 17.99) *	14.51(5.44, 23.58) **	24.28(14.88, 33.69) ***	<0.001
	MEHP	0.00 (Ref.)	2.42(-8.84, 13.67)	−2.40(-14.80, 10.00)	5.97(-6.55, 18.49)	0.401
	MEOHP	0.00 (Ref.)	7.39(-1.30, 16.07)	4.64(-4.59, 13.87)	15.90(6.32, 25.48) ***	0.002
	ΣDEHP	0.00 (Ref.)	6.76(-1.96, 15.48)	12.45(3.25, 21.66) **	18.96(9.43, 28.50) ***	<0.001
LDL-C (n = 4300)	MECPP	0.00 (Ref.)	0.360(-2.63, 3.35)	0.73(-2.44, 3.90)	0.43(-2.84, 3.69)	0.795
	MEHHP	0.00 (Ref.)	0.83(-2.14, 3.81)	2.15(-0.98, 5.29)	−0.06(-3.31, 3.19)	0.998
	MEHP	0.00 (Ref.)	0.11(-3.77, 3.98)	2.74(-1.53, 7.01)	−1.53(-4.19, 4.44)	0.784
	MEOHP	0.00 (Ref.)	0.78(-2.22, 3.78)	1.59(-1.60, 4.77)	−0.33(-3.63, 2.97)	0.831
	ΣDEHP	0.00 (Ref.)	1.23(-1.78, 4.24)	1.49(-1.69, 4.66)	0.60(-2.68, 3.89)	0.816

Model was adjusted as age, sex, race, education level, poverty, urinary creatinine, smoking, alcohol use, BMI, energy intake levels, sedentary time, systolic pressure, diastolic pressure, diabetes, congestive heart failure, coronary heart disease, angina, heart attack, and stroke.
HDL, high-density lipoprotein; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein; CI, confidence interval; *p-t*: *p* for trend; $^{*}p < 0.05$, $^{**}p < 0.01$ and $^{***}p < 0.001$.

3.4. Stratified analysis

Table 7 presents the results of the comprehensive stratified analyses examining the associations between DEHP metabolites and lipid profiles among the general adult population. Stratification was performed based on several important variables, including age (<40, 40–59, or ≥60 years) and sex (female and male). Across all subgroups, we observed consistent associations between DEHP metabolites and lipid profiles, indicating the robustness and generalizability of these findings (all *P* for interaction >0.05).

4. Discussion

In this general population-based observational study, urinary DEHPs were negatively associated with serum HDL-C level and positively associated with serum TG level. DEHP metabolites were independently correlated with HDL-C, TC, and TG, with the greatest influence being from MEHHP on each lipid profile.

EDCs, such as phthalates, are known to interfere the lipid profile by interfering with the metabolic processes of the liver, which can ultimately impact lipid circulation, and have been implicated in altering the lipid profile by interfering with hepatic fatty acid metabolism [22–25]. The mechanism of phthalates in lipid disruption appears to involve both direct effects on the peroxisome proliferator-activated receptor (PPAR) system [26] and indirect effects caused by oxidative stress-induced cell damage [27]. Given that lipids play an essential role in many physiological processes, including the maintenance of cell membrane structure and hormonal regulation, disruptions in lipid metabolism can have far-reaching consequences for human health.

As the most frequently used plasticizer in the daily necessities and agricultural products, studies showed that DEHP involves the PPAR system in various ways, and prompts varying effects on lipid metabolism by promoting fatty acid uptake, oxidation, and autophagy [26,28,29]. DEHP exposure can also disrupt the expression of other genes involved in lipid metabolism, such as those

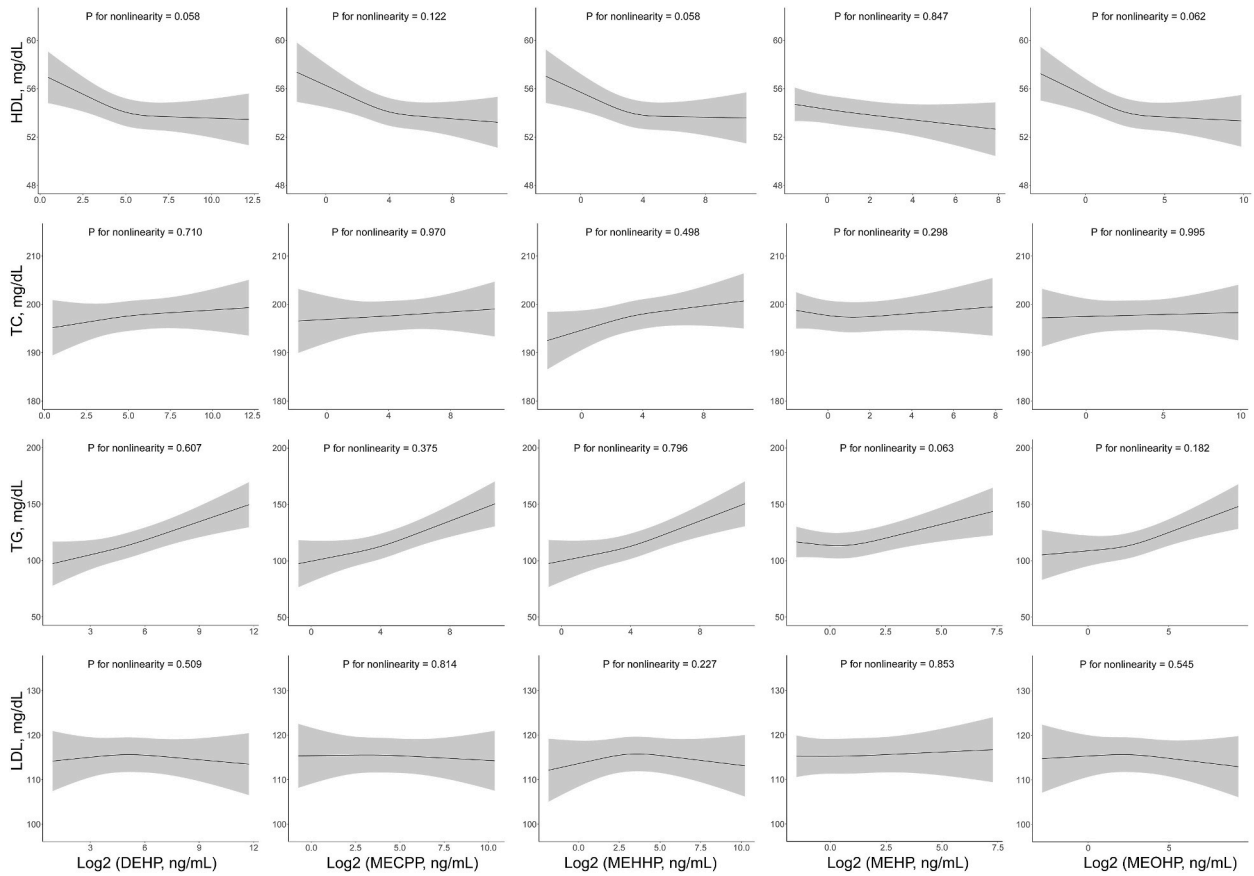

Fig. 4. - Restricted cubic spline (RCS) plots of the association of DEHP metabolites with serum lipid profiles. Vertical columns refer to the each DEHP metabolites labeled on the bottom. Horizontal columns refer to the serum lipid profiles labeled on the left. Adjusted for age, sex, race, education level, poverty, urinary creatinine, smoking, alcohol use, BMI, energy intake levels, sedentary time, systolic pressure, diastolic pressure, diabetes, congestive heart failure, coronary heart disease, angina, heart attack, and stroke. HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol.

Table 6
WQS regression model to assess the association of the sum of DEHP metabolites with lipid profiles in adults.

Outcomes	β (95% CI)	*p* value	Direction of WQS
HDL-C	−0.26 (−0.43, −0.09)	0.002	Negative
TC	0.55 (0.13, 0.98)	0.011	Positive
TG	2.40 (0.85, 3.96)	0.003	Positive
LDL-C	−0.33 (−0.87, 0.22)	0.242	Positive

CI, confidence interval; HDL, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein cholesterol; WQS, weighted quantile sum. WQS regression model was adjusted as age, sex, race, education level, poverty, urinary creatinine, smoking, alcohol use, BMI, energy intake levels, sedentary time, systolic pressure, diastolic pressure, diabetes, congestive heart failure, coronary heart disease, angina, heart attack, and stroke.

encoding lipases and transport proteins [30]. These effects might be mediated by DEHPs to act as an endocrine disruptor, interfering with the function of hormones such as insulin and thyroid hormones that regulate lipid metabolism [17]. Furthermore, the lipometabolic disruption might involve in DEHP-induced atherosclerosis associate to the metabolism disruption, vascular smooth muscle cells damage, inflammation in the initiation and progression of CVDs [16,18,24]. In the epidemiology aspect, however, the effects of DEHPs on the lipid profile have been inconsistent. For instance, study showed that DEHP exposure may disrupt lipid metabolism and correlated with lower LDL-C level in a peripubertal Mexican youth population [8]. In contrast, urine DEHP metabolites levels did not exhibit a direct association with lipids but correlated with adverse health outcomes in young Taiwanese population [7].

To explore this corresponding effect of DEHP metabolites and lipid, current study utilized the U.S. national general population dataset included 11 phthalates for a comprehensive weight analysis. The study found that all DEHPs (MECPP, MEHHP, MEHP, and MEOHP) among the 11 phthalates demonstrated a significant association with the lipid profile. The closest association was observed

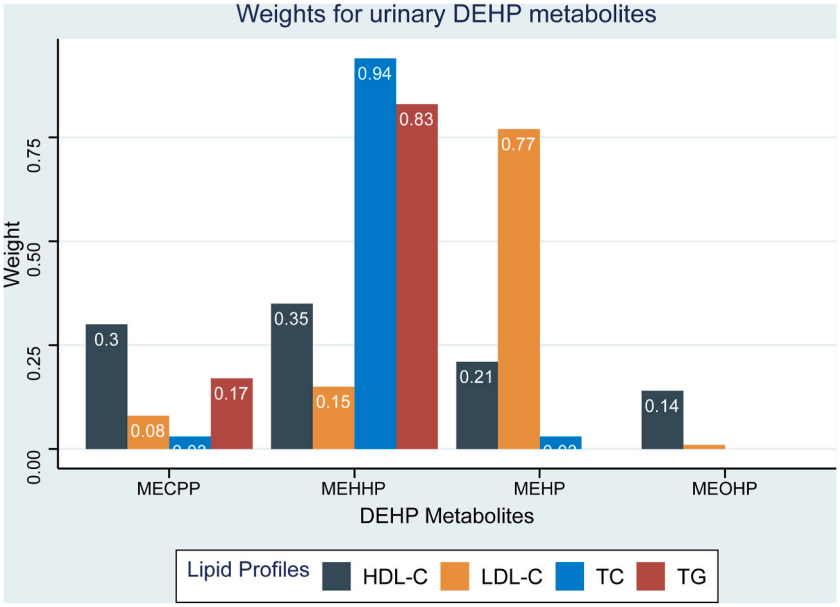

Fig. 5. - Contribution of each compound to the mixture effect of DEHP metabolites on serum lipid profiles. Weighted quantile sum (WQS) regression was adjusted for age, sex, race, education level, poverty, urinary creatinine, smoking, alcohol use, BMI, energy intake levels, sedentary time, systolic pressure, diastolic pressure, diabetes, congestive heart failure, coronary heart disease, angina, heart attack, and stroke.

between HDL-C and TG with MECPP, MEHHP, and MEOHP, consistent with previous studies on different specific populations [31,32], suggests that exposure to DEHP is a dyslipidemic factor due to the observed changes in TC, TG and HDL-C [28,33–35]. However, the study did not find a satisfactory association between LDL-C and DEHP, which might be attributed to the effects of non-DEHP phthalates [6,36], indirect sampling, and relatively small sample size.

Limitations of the study include its observational nature, the lack of information regarding potential confounders such as dietary information, occupation, and comorbidity, as well as the inclusion of only adults with different life stages and sexes, which should be considered such effects of phthalates target hormonal mechanisms in future analysis. Additionally, the study was limited in its exploration of DEHPs and did not include other environmental factors that may be important confounders for the outcomes, thus restricting certain ability to evaluate the overall impact of phthalates.

5. Conclusion

In conclusion, results demonstrated the association of DEHP exposures to HDL-C and TG in general population. Among, MECPP, MEHHP, and MEOHP might be major contributor of these effects. These findings support the need for additional studies to investigate whether the concurrent exposure to DEHP is associated with dyslipidemia and its impact on the internal metabolic environment.

Ethics statement

All participants provided written informed consent and study procedures were approved by the National Center for Health Statistics Research Ethics Review Board (Protocol Number: Protocol #2005-06 and Protocol #2011-17). The requirement of ethical approval for this study was waived by the Institutional Review Board of The First Affiliated Hospital of Nanjing Medical University, as the current study solely used publicly available data from NHANES for research. All methods were carried out in accordance with NHANES guidelines and ethical principles (declaration of Helsinki).

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Author contribution statement

Xu Zhu: Conceived and designed the experiments; Analyzed and interpreted the data.
Iokfai Cheang: Conceived and designed the experiments; Wrote the paper.
Ziqi Chen: Analyzed and interpreted the data.
Mengsha Shi: Analyzed and interpreted the data.

Table 7
Stratified analyses of the associations between eleven urinary phthalates metabolites and lipid profiles by age and gender in adults.

Phthalates	Subgroups	HDL-C		TC		TG		LDL-C	
		β (95%CI)	*p-int*	β (95%CI)	*p-int*	β (95%CI)	*p-int*	β (95%CI)	*p-int*
MECPP	<39	−0.17(-0.44, 0.09)	0.877	0.89(0.17, 1.61) *	0.067	6.64(3.38, 9.90) ***	0.345	0.283(-0.62, 1.19)	0.215
	40–59	−0.45(-0.79, −0.11)*		−0.37(-1.30, 0.56)		4.31(1.60, 7.03) **		−0.54(-1.67, 0.60)	
	≥60	−0.26(-0.72, 0.21)		−0.01(-1.19, 1.17)		2.82(-1.57, 7.21)		−0.06(-1.57, 1.45)	
	Male	−0.45(-0.71, −0.20) ***	0.249	0.02(-0.73, 0.77)	0.491	5.60(2.48, 8.71) ***	0.125	−0.22(-1.10, 0.68)	0.827
	Female	−0.11(-0.40, 0.19)		0.40(-0.33, 1.12)		3.39(1.32, 5.47) **		−0.06(-1.02, 0.91)	
MEHHP	<39	−0.14(-0.39, 0.11)	0.751	1.10(0.41, 1.78) **	0.129	6.24(3.19, 9.30) ***	0.277	0.18(-0.67, 1.02)	0.260
	40–59	−0.35(-0.67, −0.03) *		−0.04(-0.90, 0.83)		4.74(2.19, 7.28) ***		−0.26(-1.32, 0.81)	
	≥60	−0.33(-0.77, 0.11)		0.53(-0.57, 1.64)		2.98(-1.14, 7.11)		−0.11(-1.52, 1.31)	
	Male	−0.42(-0.67, −0.18) ***	0.200	0.52(-0.19, 1.22)	0.324	5.44(2.52, 8.36) ***	0.221	0.04(-0.79, 0.87)	0.482
	Female	−0.05(-0.33, 0.22)		0.70(0.02, 1.38) *		4.16(2.22, 6.11) ***		−0.06(-0.97, 0.84)	
MEHP	<39	−0.16(-0.43, 0.11)	0.403	0.05(-0.68, 0.77)	0.43	3.40(-0.03, 6.84)	0.258	−0.09(-1.02, 0.84)	0.367
	40–59	−0.54(-0.89, −0.20) **		−0.87(-1.81, 0.06)		2.40(-0.40, 5.20)		−0.37(-1.57, 0.83)	
	≥60	0.11(-0.37, 0.60)		0.62(-0.59, 1.83)		−1.62(-6.41, 3.17)		0.72(-0.93, 2.37)	
	Male	−0.38(-0.64, −0.13) **	0.379	−0.10(-0.86, 0.65)	0.098	2.64(-0.58, 5.86)	0.138	−0.02(-0.94, 0.90)	0.280
	Female	−0.03(-0.32, 0.27)		0.05(-0.69, 0.78)		1.58(-0.62, 3.78)		0.22(-0.81, 1.24)	
MEOHP	<39	−0.12(-0.39, 0.14)	0.706	0.72(0.01, 1.43) *	0.146	5.30(2.11, 8.50) **	0.084	−0.06(-0.94, 0.82)	0.463
	40–59	−0.45(-0.79, −0.11) **		−0.54(-1.44, 0.36)		4.12(1.47, 6.77) **		−0.41(-1.52, 0.70)	
	≥60	−0.35(-0.80, 0.10)		0.11(-1.02, 1.25)		0.24(-3.99, 4.47)		−0.06(-1.52, 1.39)	
	Male	−0.51(-0.76, −0.26) ***	0.097	−0.03(-0.76, 0.71)	0.452	4.10(1.06, 7.13) **	0.257	−0.18(-1.05, 0.68)	0.536
	Female	−0.04(-0.32, 0.25)		0.30(-0.40, 1.01)		3.10(1.07, 5.12) **		−0.21(-1.15, 0.73)	
ΣDEHP	<39	−0.16(-0.43, 0.11)	0.900	0.95(0.21, 1.68) *	0.123	6.59(3.28, 9.89) ***	0.285	0.15(-0.76, 1.07)	0.284
	40–59	−0.44(-0.79, −0.09) *		−0.28(-1.22, 0.66)		4.52(1.78, 7.26) **		−0.40(-1.55, 0.75)	
	≥60	−0.27(-0.74, 0.21)		0.25(-0.95, 1.45)		2.51(-1.98, 6.99)		−0.11(-1.65, 1.43)	
	Male	−0.47(-0.73, −0.21) ***	0.186	0.16(-0.60, 0.92)	0.459	5.43(2.29, 8.57) ***	0.182	−0.18(-1.08, 0.72)	0.712
	Female	−0.06(-0.36, 0.24)		0.57(-0.17, 1.30)		3.81(1.69, 5.92) ***		−0.04(-1.02, 0.94)	

Analyses were adjusted for covariates age, sex, race, education level, poverty, urinary creatinine, smoking, alcohol use, BMI, energy intake levels, sedentary time, systolic pressure, diastolic pressure, diabetes, congestive heart failure, coronary heart disease, angina, heart attack, and stroke when they were not the strata variables. HDL-C, high-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; CI, confidence interval; *p-int*: *p* for interaction; *$p < 0.05$, **$p < 0.01$ and ***$p < 0.001$.

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Yanli Zhou: Conceived and designed the experiments; Wrote the paper.
Xinli Li: Conceived and designed the experiments; Wrote the paper.
1 - Conceived and designed the experiments.
2 - Performed the experiments.
3 - Analyzed and interpreted the data.
4 - Contributed reagents, materials, analysis tools or data.

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Data availability statement

Data associated with this study has been deposited at https://www.cdc.gov/nchs/nhanes/index.htm.

Consent for publication

Not applicable.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

Authors appreciate all participants and National Center for Health Statistics (NCHS) of the Centers for Disease Control and Prevention (CDC) in the NHANES study.

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