The possible association of phthalates with coronary heart disease: A case-control study

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Abstract

Background: Phthalates have been linked to numerous adverse health effects, yet, the relationship between phthalate exposure and coronary heart disease (CHD) remains unclear. This study aims to investigate the possible association between phthalate exposure, indicated by urinary concentrations of Mono-2-ethylhexyl phthalate, and CHD.

Subjects & Methods: This case-control study included 110 participants divided into two groups; Group (A) comprised 55 patients with CHD, and Group (B) comprised 55 healthy participants. Urinary concentrations of MEHP were measured using high-performance liquid chromatography.

Results: There was a highly significant difference between groups (A and B) regarding the urinary level of MEHP (p-value < 0.001). Also, significant relationships were observed between MEHP urinary level and the number of coronaries affected (p-value= 0.001) and the coronary lesion type (p-value <0.001).

Conclusions: This study indicated that urinary MEHP levels are associated with CHD. Exposure to phthalates could be linked to the development of hypertension and atherosclerosis as leading causes of CHD.

Keywords: Coronary heart disease, Phthalates exposure, Mono-2-ethylhexyl phthalate, Endocrine disrupting chemicals.

Introduction

1. Introduction

With an estimated 17.9 million deaths in 2019, cardiovascular diseases (CVDs) are the ultimate cause of death worldwide (WHO 2021). Among CVDs, coronary heart disease (CHD), also known as coronary artery disease or ischemic heart disease, is the most prevalent (CDC 2021 and Khan et al. 2020). The key risk factors for CVDs include modern lifestyle and practices, such as smoking, sedentary behavior, and improper dietary habits, along with diabetes and obesity. The detrimental effects of environmental contaminants on human health have also been identified as a contributing factor in CVDs, with studies linking phthalates exposure and CVDs (Mariana and Cairrao 2020 and Su et al. 2019).

Due to their exceptional flexibility and durability, phthalates are widely utilized in personal-care products, detergents, medical equipment, adhesives, electronics, agricultural adjuncts, construction supplies, and other everyday items. The most often used plasticizer is di-(2-ethylhexyl)-phthalate (DEHP) (Su et al. 2019). Mono-2-ethylhexyl phthalate (MEHP) is the main active metabolite of DEHP (Franken et al. 2017).

People are exposed to environmental phthalates by ingestion, inhalation, cutaneous, and intravenous contact. Phthalates are quickly metabolized and eliminated in urine and feces, with the majority of metabolites expelled in urine within 24 hours (Franken et al. 2017).

Phthalates have been linked to the development of hypertension (HTN) (Zhang et al. 2018), atherosclerosis (Su et al. 2019 and Lind and Lind 2011), and cardiometabolic risk factors (Amin et al. 2018 and Milosevic 2017); however, there is still inadequate information on the cardiovascular consequences of phthalates.

This study aimed to find out the possible link between phthalates exposure, indicated by urinary MEHP level, and CHD.

2. Participants and methods

2.1. Study design and setting:

This is an observational case-control study carried out at the intensive care department at Kasr Alainy Hospital, in collaboration with the Lab of Forensic Medicine and Clinical Toxicology department and the Biochemistry and Molecular Biology department.

Before commencing the study, all participants provided their informed consent. The study design was approved by the Faculty of Medicine's Research Ethics Committee, Cairo University (IRB code: MD-167-2021).

2.2. Study participants:

The study participants (n=110) were divided into two groups; group A (cases) included fifty-five patients admitted to the intensive care department at Kasr Alainy Hospital. The inclusion criteria for the cases were adults aged between 18 and 60 years, of both sexes, and diagnosed with CHD. Patients with congenital heart disease, smokers, and individuals who abused drugs (specifically stimulants) were excluded from the study. Group B (controls) comprised fifty-five healthy adults of the same age and sex of group A, and we excluded those with CHD, congenital heart disease, smokers, drug abusers (stimulants), and previous history of surgical operations or hospitalization and IV fluid administration.

All participants provided the following data: socio-demographic data (age, sex, residence, educational level, and occupation) and routes of exposure to phthalates (dietary, environmental, occupational, and medical exposure). They also provided blood and urine specimens and were assessed regarding cardiovascular risk factors; HTN, body mass index (BMI), and diabetes (DM).

2.3. Assessment of cardiovascular risk factors:

After five minutes of rest in a seated position, blood pressure was measured using a mercury sphygmomanometer, and the mean of two readings was recorded. HTN was diagnosed as systolic blood pressure> 140 mmHg and/or diastolic blood pressure> 90 mmHg or taking anti-hypertension medications. By dividing the kilogram weight by the square of the height in meters, the BMI was calculated. Fasting glucose ≥126 mg/dl and/or a history of managing DM are considered signs of prevalent DM

2.4. Samples collection:

In spotless glass containers labeled with the personal identity code, urine samples were collected. Turbid or blood-contained samples were disqualified. At a temperature of -20 degrees Celsius, all specimens were kept frozen. Then, samples were examined using high-performance liquid chromatography (HPLC).

2.5. Echocardiography and Coronary Angiography:

2.5.1. Cardiac ultrasound: Cardiac function measurement was done using the cardiac probe of Siemens Acuson X300 PE Ultrasound Machine. From the parasternal long axis, standard 2D echocardiography was used along with M-mode to obtain standard heart chambers quantification and estimation of ejection fraction.

2.5.2. Coronary angiography: All patients are subjected to Coronary angiography, using standard Procedures, either trans-radial or transfemoral approaches, GE Innova Cath system was used. Angiography was observed with Special Emphasis on the number of vessels affected, which is considered when stenosis is 50% or above.

2.6. Measuring MEHP level in urine by HPLC:

2.6.1. Instruments: A high-pressure isocratic system was used, consisting of a Dionex UltiMate 3000 UHPLC, RS pump, autosampler, column compartment, and Diode array detector.

Chromatographic column reversed-phase 150mm× 4.6 mm Hypersil BDS, C18 particle size 5u were utilized. Data acquisition and interpretation were done using Chromeleon 7 software. MEHP (>97%), was purchased from SIGMA- ALDRICH.

2.6.2. Extraction: 3 ml of urine was buffered with 180µL of 3.0M sodium acetate buffer (pH 5.2). Then, hydrolyzed enzymatically with β-glucuronidase at 40°C in a shaking water bath. After that, 1000µL of 2N HCl was added, and the hydrolysate was extracted with 6 mL of hexane containing benzyl benzoate. After centrifugation, 4mL of supernatant was transferred to a new tube and evaporated. The residue was dissolved with 1ml acetonitrile and filtered with a syringe filter then 20µL of the solution was injected into HPLC (Jung et al. 2005).

2.6.3. Chromatographic conditions: Mobile phase bottle A was prepared by adding 1.0mL of acetic acid to 999mL HPLC grade acetonitrile, while mobile phase bottle B was prepared by adding 1.0mL of acetic acid to 999mL HPLC grade water. Then, the mobile phase was prepared by mixing 70% from bottle A with 30% from bottle B in isocratic mode. The column temperature was set at 40 °C. The sample injection volume was 20 µL, and the flow rate was 1 mL/min. UV was set from 240-280nm maximum absorbance of 254nm (Silva et al. 2004 and EL-Desouky et al. 2022).

2.6.4. Validation: Urine samples with a series of concentrations (0.1, 0.25, 0.5, 1, 5, 25ug/ml) of standard MEHP, were prepared. Phthalate metabolite concentrations were adjusted for urine dilution by measuring urinary creatinine.

2.7. Statistical Analysis:

Data were coded and entered using the statistical package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, USA) and GraphPad Prism. For quantitative data, the mean, standard deviation, median, minimum, and maximum were used and frequency and relative frequency for categorical data. The non-parametric Kruskal-Wallis and Mann-Whitney tests were used to compare quantitative variables (Chan 2003a), and the Chi-square ((c2)) test to compare categorical data. When the anticipated frequency is less than 5, an exact test was applied instead (Chan 2003b). Statistical significance was determined by P-values less than 0.05.

3. Results:

The socio-demographic data of the study participants (cases and controls) are demonstrated in Table (1). A statistically significant difference was observed between the two study groups as regards age (p-value= 0.002) .

Comparison between the studied groups regarding routes of exposure to phthalates showed statistically significant differences in using plastic containers for fat food storage (50.9% of group A used them weekly, compared to 45.5% of group B) and eating canned food (54.5% of group A compared to 30.9% of group B). Also, significant differences were observed between the two groups regarding chronic use of intravenous preparations, operative history, hospitalization, and occupational exposure (p-value < 0.05) (Table 2).

Table (3) shows the comparison between the studied groups regarding cardiovascular risk factors; significant differences were observed between the two groups in BMI, HTN, and DM, with the majority (83.7%) of group A being overweight and obese compared to (45.4%) of group B, (50.9%) of group A being diabetic compared to (5.5%) of group B, and (58.2%) of group A were hypertensive compared to none of group B).

Comparison of MEHP levels in urine between the study groups showed a highly significant difference with higher mean values among group A (1.23 ± 3.37 µg /ml) compared to group B (0.4 ± 0.53 µg /ml) (Table 4).

Table (5) displays the echocardiography and coronary angiography findings of the cases, where (76.4%) have normal ejection fraction and only (7.3%) have reduced function, (3.6%) have diastolic dysfunction grade 3, and (29.1%) have significant valve lesions. The majority of cases (80.0%) have a significant lesion in the left anterior descending coronary (LAD) that mostly shows (50- 99%) occlusion, (67.3%) have a significant lesion in the right coronary (RCA) that mostly shows (100%) occlusion, and (41.8%) of cases have a significant lesion in the left circumflex (LCX)that mostly shows (50- 99%) occlusion.

Concerning the relation between routes of exposure to phthalates and adjusted MEHP levels in urine, a statistical significance was observed between using plastic containers for fat food storage and MEHP levels (p< 0.001). The post hoc pairwise comparison showed significant differences between the monthly use of plastic containers and the weekly and daily and between the weekly and daily use. Also, significant differences were detected between MEHP urinary levels and eating canned food at least weekly (p< 0.001), using scents at least weekly (p< 0.001), chronic use for IV preparations (p=0.003), hospitalization (p=0.003), operative history (p=0.026) and occupational exposure (p-value <0.001) (Table 6).

Regarding the relation between cardiovascular risk factors and MEHP in urine, a highly statistically significant relation was observed between MEHP level and HTN with (p-value <0.001), while no significance was observed with DM or BMI (P=0.245 and 0.057, respectively) as shown in (Table 7).

Concerning the relation between the echocardiography and coronary angiography findings and adjusted MEHP levels in urine, there was a significant relation (p-value= 0.001) between MEHP level, and the number of vessels affected (single VD with multiple VD). Also, a significant (p-value <0.001) relation was found between MEHP level and the coronary lesion type (100% occlusion with <50% occlusion and 50-99% occlusion). However, no significance was observed between MEHP level and echocardiography findings (ejection fraction, diastolic dysfunction, and significant valve lesion) (Table 8).

Table (1): Comparison between studied groups as regards distribution of socio-demographic data

		Cases (group A)		Controls (group B)		P value
		Count	%	Count	%	
Age	**18- 30y**	0	0.00%	4	7.30%	0.002**
	>30- 45y	14	25.50%	26	47.30%	
	>45- 60y	41	74.50%	25	45.50%	
Sex	**Male**	36	65.5%	26	47.3%	0.055
	Female	19	34.5%	29	52.7%	
Residence	**Urban**	26	47.3%	31	56.4%	0.357
	Rural	22	40.0%	21	38.2%	
	Industrial	7	12.7%	3	5.5%	
Education	**Illiterate**	8	14.5%	12	21.8%	0.318
	Read and write	8	14.5%	12	21.8%	
	Primary or secondary school	26	47.3%	17	30.9%	
	High school	13	23.6%	14	25.5%	
Occupation	**Not working**	16	29.1%	21	38.2%	0.344
	Hand workers	4	7.3%	4	7.3%	
	Employment	20	36.4%	17	30.9%	
	Health care workers	2	3.6%	6	10.9%	
	Workers in plastic manufacturing	7	12.7%	2	3.6%	
	Others	6	10.9%	5	9.1%	

Chi square ($\chi 2$) test.

**P < 0.01 were considered highly statistically significant.

Table (2): Comparison between studied groups as regards routes of exposure to phthalates

Routes of exposure to phthalates			Cases (group A)		Controls (group B)		P value
			Count	%	Count	%	
Dietary and environmental exposure	Use of plastic containers for fat food storage	Never	4	7.3%	3	5.5%	0.001**
		Daily	17	30.9%	5	9.1%	
		Weekly	28	50.9%	25	45.5%	
		Monthly	6	10.9%	22	40.0%	
	Eating canned food at least weekly	Yes	30	54.5%	17	30.9%	0.012*
		No	25	45.5%	38	69.1%	
	Use of scents at least weekly	Yes	33	60.0%	26	47.3%	0.181
		No	22	40.0%	29	52.7%	
	Use of Cosmetics, nail polishes at least weekly	Yes	12	21.8%	16	29.1%	0.381
		No	43	78.2%	39	70.9%	
Medical exposure	Chronic use IV preparation	Yes	16	29.1%	5	9.1%	0.008**
		No	39	70.9%	50	90.9%	
	Hospitalization	No	8	14.5%	41	74.5%	< 0.001**
		≤1w	35	63.6%	11	20.0%	
		> 1w	12	21.8%	3	5.5%	
	Operative history	Yes	35	63.6%	10	18.2%	< 0.001**
		No	20	36.4%	45	81.8%	
Occupational exposure		Yes	17	30.9%	7	12.7%	0.021*
		No	38	69.1%	48	87.3%	

Chi square ($\chi 2$) test.
*P values ≤ 0.05 were considered significant.
**P < 0.01 were considered highly statistically significant.
IV: Intra venous.

Table (3): Comparison between studied groups as regards distribution of cardiovascular risk factors

Cardiovascular risk factors		Cases (group A)		Controls (group B)		P value
		Count	%	Count	%	
BMI	Normal	9	16.4%	30	54.5%	< 0.001**
	Overweight	25	45.5%	19	34.5%	
	Obese	21	38.2%	6	10.9%	
DM	Yes	28	50.9%	3	5.5%	< 0.001**
	No	27	49.1%	52	94.5%	
HTN	Yes	32	58.2%	0	0.0%	< 0.001**
	No	23	41.8%	55	100.0%	

Chi square ($\chi 2$) test.
**P < 0.01 were considered highly statistically significant
HTN: Hypertension, DM: Diabetes mellites, BMI: Body mass index

Table (4): Comparison between studied groups as regards adjusted MEHP in urine

	Cases (group A)			Controls (group B)			P value
	Mean	**SD**	**Median**	**Mean**	**SD**	**Median**	
Adjusted MEHP (µg /ml)	1.23	3.37	0.55	0.40	0.53	0.33	< 0.001**

Non-parametric Kruskal-Wallis and Mann-Whitney tests.
**P < 0.01 were considered highly statistically significant.
MEHP: Mono-2-ethyl hexyl phthalate, SD: Standard deviation.

Table (5): Percentage of echocardiography and coronary angiography findings among cases.

			Cases (group A)	
			Count	**%**
Echocardiography findings	**Ejection fraction**	**Normal function >50%**	42	76.4%
		Fair 40-50 %	9	16.4%
		Reduced <40%	4	7.3%
	Diastolic Dysfunction	**Grade 1**	36	65.5%
		Grade 2	17	30.9%
		Grade 3	2	3.6%
	Significant Valve lesion	**Yes**	16	29.1%
		No	39	70.9%
Coronary angiography findings	**LAD**	**Yes**	44	80.0%
	LAD type %	**< 50% Occlusion**	3	5.5%
		50- 99% Occlusion	32	58.2%
		100% Occlusion	9	16.4%
	Diagonal	**Yes**	13	23.6%
	Diagonal type %	**< 50% Occlusion**	0	0.0%
		50- 99% Occlusion	12	21.8%
		100% Occlusion	1	1.8%
	LCX	**Yes**	23	41.8%
	LCX type %	**< 50% Occlusion**	5	9.1%
		50- 99% Occlusion	14	25.5%
		100% Occlusion	4	7.3%
	OM	**Yes**	18	32.7%
	OM type %	**< 50% Occlusion**	2	3.6%
		50- 99% Occlusion	13	23.6%
		100% Occlusion	3	5.5%
	RCA	**Yes**	37	67.3%
	RCA type %	**< 50% Occlusion**	4	7.3%
		50- 99% Occlusion	15	27.3%
		100% Occlusion	18	32.7%
	PDA	**Yes**	5	9.1%
	PDA type %	**< 50% Occlusion**	0	0.0%
		50- 99% Occlusion	5	9.1%
		100% Occlusion	0	0.0%

LAD: left anterior descending, LCX: Left circumflex, OM: Obtuse marginal
RCA: Right coronary artery, PDA: posterior descending artery

Table (6): Relation between routes of exposure to phthalates and MEHP in urine

Routes of exposure to phthalates			Adjusted MEHP in urine microgram/ml			
			Mean	SD	Median	P value
Dietary and environmental exposure	Use of plastic containers for fat food storage	Never [a]	0.44	0.15	0.40	< 0.001**
		Daily [b]	2.74[c, d]	5.85	1.00	
		Weekly [c]	0.65[b, d]	0.50	0.48	
		Monthly [d]	0.20[b, c]	0.09	0.18	
	Eating canned food at least weekly	Yes	1.85	4.48	0.63	< 0.001**
		No	0.50	0.47	0.32	
	Use of scents at least weekly	Yes	1.81	4.27	0.71	< 0.001**
		No	0.37	0.21	0.32	
	Use of Cosmetics, nail polishes at least weekly	Yes	1.01	0.69	0.79	0.055
		No	1.29	3.80	0.47	
Medical exposure	Chronic use of IV preparation	Yes	1.05	0.57	0.99	0.003**
		No	1.31	3.99	0.44	
	Hospitalization	No	0.31	0.14	0.29	0.003**
		≤1w	1.48	4.19	0.55	
		> 1w	1.13	0.65	1.02	
	Operative history	Yes	1.65	4.17	0.62	0.026*
		No	0.51	0.38	0.44	
Occupational exposure		Yes	2.64	5.87	0.78	0.001**
		No	0.60	0.54	0.40	

Non-parametric Kruskal-Wallis and Mann-Whitney tests.

Each frequency of using plastic for fat food storage was assigned a letter (a: never, b: daily, c: weekly, d: monthly). Letters present above the mean indicate significance with the assigned category.

*P values ≤ 0.05 were considered significant.

**P < 0.01 were considered highly statistically significant.

MEHP: Mono-2- ethylhexyl phthalate, IV: intravenous, SD: Standard deviation.

Table (7): Relation between cardiovascular risk factor and MEHP in urine

		Adjusted MEHP in urine microgram/ml			
		Mean	**Standard Deviation**	**Median**	**P value**
HTN	**Yes**	1.9	4.3	0.82	<0.001**
	No	0.29	0.11	0.32	
DM	**Yes**	0.65	0.53	0.45	0.245
	No	1.84	4.74	0.58	
BMI	**Normal**	1.06	2.09	0.42	0.057
	Overweight	1.83	4.81	0.62	
	Obese	0.60	0.48	0.44	

Non-parametric Kruskal-Wallis and Mann-Whitney tests.
**P < 0.01 were considered highly statistically significant
HTN: Hypertension, DM: Diabetes mellites, BMI: Body mass index

Table (8): Relation between Echocardiography and coronary angiography findings and MEHP in urine

Echocardiography and coronary angiography findings		**Adjusted MEHP in urine microgram/ml**			
		Mean	**SD**	**Median**	**P value**
Ejection fraction	**Normal function >50%**	0.82	1.07	0.47	0.383
	Fair 40-50 %	0.69	0.19	0.63	
	Reduced <40%	6.80	11.98	1.18	
Diastolic Dysfunction	**Grade 1**	1.57	4.13	0.57	0.208
	Grade 2	0.56	0.48	0.51	
	Grade 3	0.94	0.24	0.94	
Significant Valve lesion	**Yes**	0.89	0.61	0.62	0.133
	No	1.37	3.98	0.47	
Lesion site (Number of vessels affected)	**Single VD[a]**	0.33[c]	0.25	0.23	0.001**
	Two VD[b]	1.78	5.57	0.44	
	Multiple VD[c]	1.18[a]	1.26	0.77	
Lesion type%	**< 50% Occlusion[d]**	0.27[f]	0.14	0.24	< 0.001**
	50- 99% Occlusion[e]	0.45[f]	0.28	0.35	
	100% Occlusion[f]	2.38[d, e]	5.03	1.06	

Non-parametric Kruskal-Wallis and Mann-Whitney tests.
Each lesion site and type were assigned a letter (a: single VD, b: two VD, c: multiple VD, d: <50% Occlusion, e: 50-99% Occlusion, f: 100% Occlusion). Letters present above the mean indicate significance with the assigned category.
*P values ≤ 0.05 were considered significant.
**P < 0.01 were considered highly statistically significant.
MEHP: Mono-2- ethylhexyl phthalate, IV: intravenous, SD: Standard deviation.

4. Discussion

Egypt is the most populous country in the Middle East and North Africa, where cardiovascular fatalities are highly prevalent. Despite governmental primary prevention measures, the prevalence and characteristics of CAD among Egyptian patients are insufficiently understood (Reda et al. 2019).

Phthalates are more frequently associated with an increased risk of several chronic health conditions. Because these synthetic chemicals are widely used in consumer goods (such as cosmetics, nail polish, perfumes, shampoos, dentures, adhesives, cleaning supplies, nutritional supplements, and food packaging), human exposure is common (Vieyra et al. 2023). This study aimed to find any potential links between phthalates exposure, as detected by urine MEHP levels and CHD.

In terms of age distribution among the study participants, a statistically significant difference was observed between the two study groups (cases and controls), with about three-fourths of the cases group in the age range (>45-60). Similarly, Zhu et al. (2021) in China found a significantly higher age among the CHD group than the non-CHD group. Also, Su et al. (2019) reported a mean age of (46.2 ± 6.9 years) among cases with CHD. Wang (2020) stated that age appears to play a role in CHD development, and each additional decade of life was linked to a rough doubling of the risk of CHD (51–60 years 3.5%, 61–70 years 7.15%, and 71–80 years 13%).

Regarding sex distribution, males were more common in group A (65.5%) than in group B, without significant differences between the two groups. Similarly, Millett et al. (2018) found that the incidence of CHD was higher in men than women. According to Wang (2020), women had a 20% lower risk than men for all major cardiovascular outcomes, such as cardiovascular death, myocardial infarction, and hospitalization for heart failure. Park et al. (2021) explained that the primary factor influencing the difference in CHD risk between the sexes was the difference in the HDL/total cholesterol ratio. Also, estrogen may protect against heart disease in women by regulating their glucose metabolism.

In the setting of residence distribution, no significant difference was observed between the study groups. Likewise, Krishnan et al. (2016) did not find differences in CAD prevalence between urban and rural populations in India, despite some risk factors, as smoking was higher in rural areas, whereas general and abdominal obesity were higher in urban areas.

Concerning educational level among the studied groups, the school (primary or secondary) level was the most common in both groups with no significant difference. That was comparable with Dégano et al. (2017) who reported that education is inversely associated with CHD and its risk factors such as smoking, blood pressure, obesity, and diabetes. Education is frequently linked to healthy habits like eating fruit and vegetables and quitting smoking.

There was no significant difference between the two study groups (cases and controls) regarding occupation, which is similar to Tayyem et al. (2018).

Our study revealed significant differences between groups A and B regarding using plastic containers for fat food storage and eating canned food. In agreement with our study, Wang (2020) reported that higher risks of CHD have been associated with higher red meat and high-fat dairy product consumption, especially if preserved in plastic containers. Also, CHD patients usually take multiple drugs. Many medications, herbal medicines, and nutritional supplements are covered with films formed of synthetic polymers containing phthalates, making consumption of these substances a potential source of phthalate exposure (Jaimes et al. 2017).

Regarding medical exposure among the studied groups, there was a significant difference between groups A and B. Hab et al. (2018) demonstrated that using polyvinylchloride (PVC) medical devices may lead to higher exposure to DEHP. Numerous procedures, including the use of catheters, haemodialysis, enteral nutrition for adults, heart transplantation or coronary artery bypass graft surgery, massive blood transfusions, peritoneal dialysis, respiratory masks, and endotracheal tubes, could result in high exposure to DEHP that could be released from the equipment used. The type of device, the quantity, and length of medical operations all play a significant role in the level of exposure.

Our results revealed that more than half of group A (58.2%) had hypertension which was statistically significant with group B. Similarly, Zhu et al. (2021) reported a significantly higher prevalence of hypertension among the CHD group than the non-CHD group. Hypertension worsens the atherosclerosis process causing endothelial dysfunction and making the atherosclerotic plaque more unstable. In addition, left ventricular hypertrophy, the usual complication of hypertension, promotes increased myocardial oxygen demand and decreases coronary reserve, which leads to myocardial ischemia (Wang 2020).

Also, a statistically significant difference was observed between groups A and B regarding the prevalence of DM, with more than half of group A being diabetics, compared to only (5.5%) of group B. Likewise, Su et al. 2019 reported a significantly higher prevalence of DM in CHD patients compared to the control. Multiple mechanisms of DM were described by Glovaci et al. in 2019, including abnormalities in the composition and concentration of lipoproteins, insulin resistance, hyperinsulinemia, protein glycosylation in plasma and the arterial wall, lipid oxidation, pro-coagulation, and pro-inflammatory states, and abnormal endothelial function.

Regarding BMI, a significant difference was found between the study groups, with nearly half of the CHD cases being overweight. Similarly, Su et al. 2019 reported that CHD patients had a higher prevalence of high BMI than the controls. Maradonna and Carnival 2018, explained that obesogenic endocrine disrupting chemicals like phthalates stimulate adipogenesis and fat storage and increase the chances for obesity by activating peroxisome proliferator-activated receptor (PPAR) that promotes adipogenesis.

According to creatinine-adjusted MEHP levels in urine among studied groups, there was a highly significant difference between groups A and B, which is consistent with Su et al. (2019), who reported significantly higher creatinine-adjusted urinary levels of MEHP in CHD patients. Some researchers have found an association between phthalates and an increased risk of coronary heart disease in elderly populations. They examined over 1000 participants to determine their cardiovascular risk factors and blood levels of four phthalate metabolites (MiBP, MMP, MEP, and MEHP). They concluded that phthalate concentration increases the risk of coronary heart disease (Mariana et al. 2016).

The relation between dietary and environmental exposure and the level of MEHP in urine showed a statistical significance between using plastic containers for fat food storage and MEHP in urine, which was consistent with Pacyga et al. (2019), who reported that using plastic containers was associated with higher urinary phthalate metabolites. Fweja (2020) stated that packed foods containing high lipid content as milk, butter, and processed meat, have high concentrations of DEHP. Furthermore, DEHP is capable of migration from plastic containers into foods, particularly when heated.

This study showed a statistically significant relation between eating canned food at least weekly with MEHP level in urine. Similar findings were made by Colacino et al. (2011), who found that people who admitted to eating canned food had considerably higher levels of MiBP and MEHP. Higher urine concentrations of a number of phthalate metabolites have been linked to canned food (meat, dairy, and seafood items) and fast food, but not to fresh fruit and vegetable consumption, according to food monitoring studies (Huang et al. 2021).

The current study showed a highly significant relationship between using scents at least weekly and MEHP in urine, but there was no significant relation between MEHP level and using cosmetics and nail polishes at least weekly. Berger et al. (2019) reported a positive relationship between using scents and cosmetic products and urine concentrations of phthalate metabolites. Due to chemical combinations that enhance dermal penetration, skin care products can occasionally boost cutaneous absorption by up to 100 times. Phthalates are used as solvents in fragrances because they stabilise and prolong the life of the scent (Caporossi et al. 2021).

This study demonstrated a statistically significant relationship between occupational exposure and urinary MEHP level. Similarly, Fréry et al. 2020 reported that people exposed to phthalates in their work had a higher level of urinary MEHP than the general population.

Regarding the relation between medical exposure and the level of MEHP in urine, there were statistically significant relations between chronic use for IV preparations and MEHP in urine and between hospitalization for >1w and MEHP in urine. Several medical devices used in hospitals are made of flexible

PVC, such as bags for intravenous fluids and blood, which contain 30-40% DEHP. The PVC matrix of the devices contains a variety of plasticizers that can leak into the infused solutions in varying concentrations (Bernard et al. 2017).

Concerning the relation between cardiovascular risk factors and urinary MEHP, there was a highly statistically significant relation between MEHP level and HTN. According to Zhang et al.'s 2018 study, participants in the DEHP group with the median exposure experienced a significant 2.96 mmHg rise in systolic blood pressure (Zhang et al. 2018). These findings can be attributed to phthalates' ability to block the bradykinin-NO pathway and raise levels of the angiotensin-converting enzyme (ACE) and angiotensin II type I receptor (AT1R). Phthalates may also contribute to insulin resistance, which can result in microvascular alterations and hypertension (Mariana and Cairrao 2020). Additionally, elevated systolic blood pressure may be caused by DEHP-induced oxidative stress. Increased serum C-reactive protein, a measure of inflammation, oxidative stress indicators, gamma-glutamyl transferase, and malondialdehyde have all been linked to higher levels of human urinary DEHP metabolite. The latter is a biomarker of the generation of free radicals, which can change the tone of the arteries and raise blood pressure (Ramadan et al. 2020)

Our results did not reveal any significant relation between MEHP level and DM, which is consistent with a meta-analysis conducted by Zhang et al. (2022), who reported no significant association between DM and MEP or MEHP. Also, no significant association was found between MEHP level and BMI, which is contrary to Amin et al. (2018), who reported a positive correlation between phthalate metabolites and BMI.

There was a highly statistically significant correlation between MEHP level and coronary artery lesion site, which reflects the number of damaged vessels, and lesion type, which represents the severity of lesion stenosis, in terms of the relationship between coronary angiography findings and MEHP level. Similar findings were observed by Su et al. (2019), who discovered a significant correlation between CHD and phthalate metabolites (DEHP and Di-n-butyl phthalate). They claimed that the elevated levels of atherothrombotic markers point to the possibility that phthalate exposure and the risk of subclinical atherosclerosis are related via inflammatory and haemostatic pathways, which would raise the risk of arterial stenosis and coronary heart disease (Su et al. 2019). Additionally, Zhang et al. 2021 discovered that urine phthalate metabolites, particularly MEHP and mono-isobutyl phthalate, were favourably linked with CVD in Chinese people. Additionally, they discovered that males with type 2 diabetes may be more vulnerable to CVD when exposed to phthalates, making it crucial to reduce exposure.

5. Conclusion

This study demonstrated that urinary MEHP levels are associated with CHD. Exposure to phthalates could be linked to the development of hypertension and atherosclerosis as leading causes of CHD. To avoid the adverse health effects of DEHP, its use as a plasticizer should be strictly regulated. Also, its replacement in medical-related devices is warranted. More comprehensive studies investigating the long-term effects of phthalates and possible mechanisms of toxicity have to be conducted.

6. Disclosure of interest

The authors declare that they have no competing interest.

7. Funding statement

The study is funded by Cairo university, Egypt.

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