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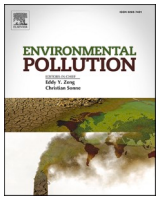

Review

# Phthalate exposure and subclinical carotid atherosclerosis: A systematic review and meta-analysis☆

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ABSTRACT

Phthalates may be associated with an increased risk of cardiometabolic diseases by interfering with glucose and lipid metabolism and by promoting adipogenesis. This study aimed to perform a systematic review and meta-analysis of the association between phthalate exposure and subclinical carotid atherosclerosis, using surrogate markers such as carotid intima-media thickness (IMT) and carotid plaques. The literature search was performed using four databases (Web of Science, Medline, PubMed, and Scopus), and this systematic review includes all available observational studies until July 6th, 2023. The Joanna Briggs Institute critical appraisal tool was used to assess the risk of bias. Meta-analyses were performed, and random effects models were used. Six high-quality cross-sectional studies and 2570 participants aged 12 to 70 were included. Six phthalate metabolites showed significant associations with subclinical carotid atherosclerosis. Exposure to MBzP, ΣDEHP, and MnBP was associated with increased carotid IMT. Exposure to MEP was associated with a higher prevalence of carotid plaques, and MiBP was associated with a lower prevalence. Mixed results were observed for MMP in older adults. The meta-analyses showed a high degree of heterogeneity, and the results are based on single studies. This study accurately describes the evidence of this association to date, suggesting that phthalates are associated with increased carotid IMT and a higher prevalence of carotid plaques. Further research is needed to elucidate this association, as phthalates are still used in the manufacture of everyday products, humans continue to be exposed to them, and atherosclerosis is a public health concern.

## 1. Introduction

Atherosclerosis is a chronic inflammatory disease of the arteries that initiates with the activation of the endothelium, followed by the formation of fatty streaks and atherosclerotic plaques (Jebari-Benslaiman et al., 2022). It is also the most common pathophysiological process underlying cardiovascular disease (CVD)(Singh et al., 2018), of which myocardial infarction and stroke are the two primary leading causes of death worldwide (Vaduganathan et al., 2022). In most cases, the subclinical phase of atherosclerosis remains undetected throughout life

*Abbreviations:* IMT, Intima-media thickness; CVD, cardiovascular disease; MBzP, Mono-benzyl phthalate; MEHP, Mono(2-ethylhexyl) phthalate; ΣDEHP, Molar sum of DEHP; MEP, Mono-ethyl phthalate; MnBP, Mono-n-butyl phthalate; MiBP, Mono-isobutyl phthalate; MMP, Mono-methyl phthalate.

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until a major cardiovascular event occurs (Singh et al., 2018). There are several well-known early markers of this subclinical phase, including carotid intima-media thickness (IMT)(Yang et al., 2020), and the presence of carotid plaques (Yang et al., 2020; Sillesen et al., 2012). Increased IMT is one of the first structural changes detected in atherosclerosis (Lusis, 2000; Fernández-Alvarez et al., 2022), and both IMT and carotid plaques have been used to predict cardiovascular events (IhleHansen et al., 2023; Cao et al., 2007), and as surrogate markers of CVD in clinical trials (Stein et al., 2008; OLeary and Bots, 2010; Willeit et al., 2020).

The impact of the traditional risk factors on the development of atherosclerosis is well established (Fruchart et al., 2004; Ji et al., 2019). However, these risk factors are not sufficient to clearly understand the increased risk of atherosclerosis, and the non-traditional determinants of cardiometabolic health may help to elucidate it. Among these non-traditional determinants (Lechner et al., 2020), lifestyle and environmental risk factors are of increasing interest, including exposure to air pollution (Brauer et al., 2021), heavy metals (Wang et al., 2023a), and certain endocrine-disrupting chemicals, particularly phthalates (Mariana and Cairrao, 2020).

Phthalates are chemicals widely used as solvents, fixatives, and adhesives in cosmetics and personal care products (Giuliani et al., 2020), as well as plasticizers in polyvinyl chloride (PVC) materials, including food packaging, flooring, and medical devices (Giuliani et al., 2020; Serrano et al., 2014). As a result of the widespread use of plastic-based everyday products, people are constantly exposed to phthalates by inhalation, dermal contact, and through diet. After exposure, phthalates can disrupt glucose metabolism and insulin secretion, promote adipogenesis (Kowalczyk et al., 2023), interfere with lipid metabolism, and accelerate the process of atherosclerosis (Liu et al., 2022), which could explain their harmful impact on human health.

Comprehensive reviews have synthesized the cardiometabolic effects of phthalates (Mariana et al., 2023; Mariana and Cairrao, 2023; Perez-Diaz et al., 2024), and meta-analyses have reported positive associations between phthalates and a higher risk of obesity (Wu et al., 2023), insulin resistance (Shoshtari-Yeganeh et al., 2019), the metabolic syndrome (Mérida et al., 2023), diabetes mellitus (Zhang et al., 2022), as well as a higher prevalence of CVD (Fu et al., 2020). However, most of the studies have focused on cardiovascular risk factors and CVD, but the relationship between phthalates and atherosclerosis as an early stage of CVD is still unclear, and it has been barely evaluated. Therefore, the aim of this study was to perform a systematic review and meta-analysis of the association between phthalate exposure and subclinical carotid atherosclerosis, based on surrogate markers such as carotid IMT and the presence of carotid plaques.

## 2. Material and methods

This systematic review and meta-analysis are reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA)(Page et al., 2021). The protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (PROSPERO) (registry number: CRD42023411892).

### 2.1. Search strategy

The literature search was performed by three co-authors (DMM, JA-R, and PG-C) using four different databases: Clarivate (Web of Science), Medline, PubMed, and Scopus, with no restrictions on the year of publication or language. The last search was conducted on July 6th, 2023. The following keywords were used to identify the articles: ((“subclinical atherosclerosis” OR “carotid” OR “coronary calcium” OR “atherosclerosis” OR “plaques” OR “intima-media thickness”) AND “phthalates”).

### 2.2. Study selection

Study selection was performed by two co-authors (DMM and PG-C). After a bibliographic search and identification, the studies were imported into EndNote Web to remove duplicates. The title and the abstract of the published studies were evaluated. After screening, full-text articles were read to identify eligible studies based on the following inclusion criteria: (1) observational analytical studies (including cross-sectional and longitudinal cohort studies); (2) studies analyzing the general population, including children, adolescents, and adults, regardless of their health status; (3) studies with quantitative measurements of phthalate metabolites either in urine or in blood samples; (4) studies comparing extreme categories of exposure or mean values, also providing their 95% confidence intervals (CI) or *p*-value; (5) studies that included the assessment of the carotid artery such as the carotid IMT and/or the presence of carotid plaques. Exclusion criteria were: (1) animal studies; (2) reviews and commentaries; and (3) studies that did not report primary data. Finally, the bibliographic references of the studies included were also reviewed.

### 2.3. Outcomes

The main outcomes of this review were: (1) the carotid IMT as a continuous variable (Yang et al., 2020), (2) the carotid IMT as a categorical variable (Stein et al., 2008; Doyon et al., 2013) (defined as carotid IMT $\geq$75th or $\geq$95th percentile, depending on the cut-off used in the study), and (3) the presence of atherosclerotic plaques in the carotid arteries (Sillesen et al., 2012), all of which are considered as early markers of subclinical carotid atherosclerosis.

### 2.4. Data extraction

Data extraction was performed by two independent co-authors (DMM and PG-C). The following information was collected from the studies: first author, year of publication, country and sample, study design, sample characteristics (size, percentage of men, and age of inclusion of the participants), phthalate measurement, and the carotid ultrasound technique used, the carotid IMT and/or carotid plaques assessment, and confounders. Finally, the mean/median of carotid IMT, the statistical analysis used, phthalate exposure concentrations, as well as results reported as linear regression coefficients or adjusted Odds Ratios (OR) were extracted from each study.

### 2.5. Risk of bias

The risk of bias of the studies included was assessed by using the Joanna Briggs Institute (JBI) critical appraisal tools for cross-sectional studies (JBI Critical Appraisal Tools |; Stone et al., 2023), which consist of eight questions with the following answers: yes/no/unclear. The overall risk of bias was established according to the percentage of positive answers (the higher the score, the lower the risk of bias). A high risk of bias was considered if the score was less than 49%, a moderate risk if the score was 50–69%, and a low risk if the score was more than 70%. Discrepancies were solved by mutual agreement between three co-authors (DMM, JA-R, and PG-C).

### 2.6. Data synthesis and data transformation

When phthalate exposure (mostly expressed as ln-transformed values) and IMT were both continuous variables, data transformation was required for comparability. To homogenize the results, carotid IMT was expressed in micrometers (μm). Effect sizes were standardized and expressed as the absolute change in carotid IMT for a 50% increase in phthalate levels (Rodríguez-Barranco et al., 2017).

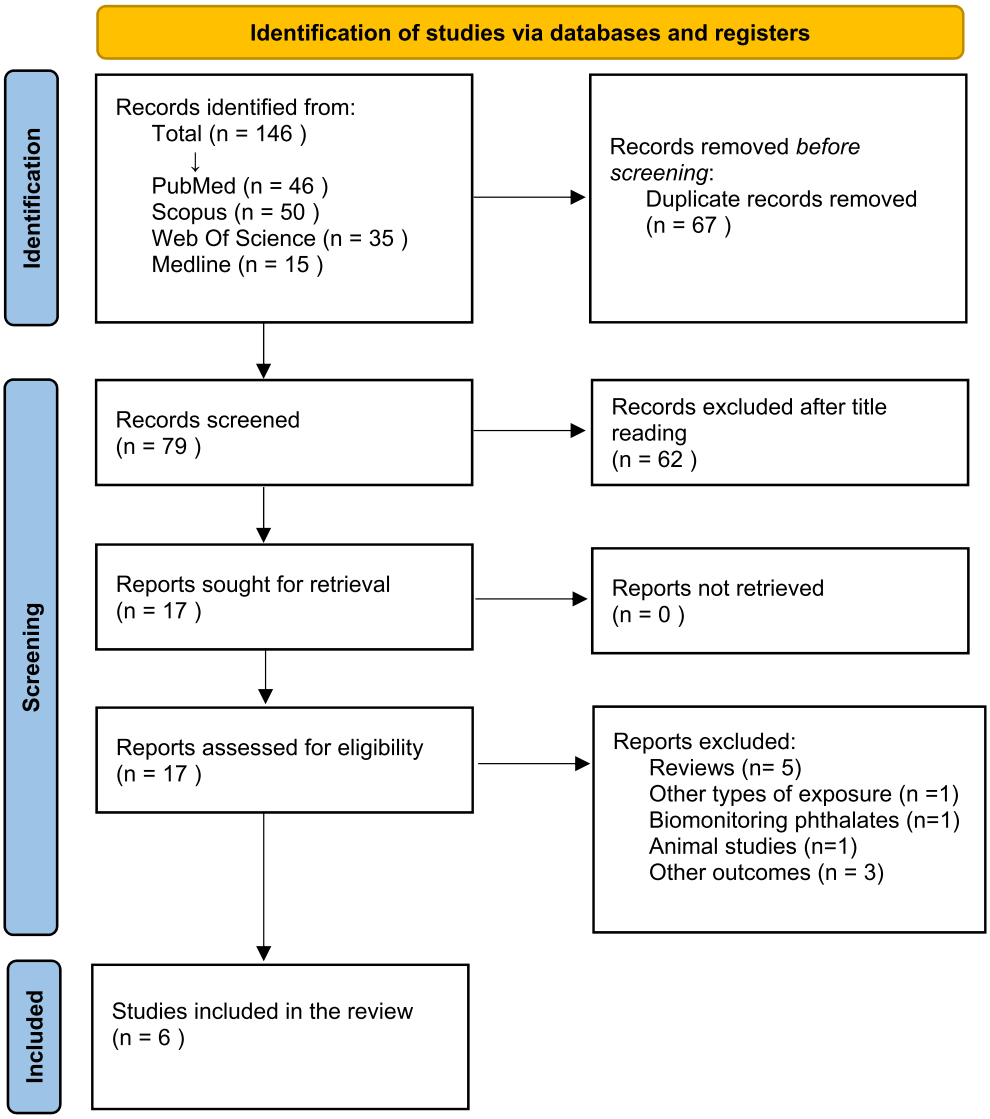


**Fig. 1.** PRISMA flow diagram of literature search and study selection.

### *2.7. Meta-analysis for the association between phthalates exposure and carotid IMT as a continuous variable*

When several models were reported, the standardized association estimates from the most adjusted model were meta-analyzed. Also, when the studies reported the *p*-value of the association instead of the CIs, the standard error was calculated assuming a t-Student distribution (Salanti, 2013). After standardization, the combined result of the meta-analysis could be interpreted as the absolute change in the carotid IMT (expressed in μm) for a 50% increase in phthalate levels.

### *2.8. Meta-analysis for the association between phthalates and carotid IMT/carotid plaques as categorical variables*

The adjusted ORs and their 95% CIs from the most saturated models were extracted from each study when comparing extreme categories of exposure. When the studies reported the *p*-value of the association instead of the CIs, the standard error was calculated assuming a normal distribution (Chapter 6). Pooled OR and their 95% CI for the association between phthalate exposure and the carotid IMT as a categorical variable were calculated by using the inverse-variance weighted method (Chapter 10).

The Inconsistency Index ($I^2$) was used to evaluate the heterogeneity among studies. Random-effects models were used when the $I^2$ was ≥30%. Analyses were performed using Review Manager version 5.4.1.

## 3. Results

### *3.1. Study selection*

Of the 146 studies identified in the primary search, 67 were duplicates and removed, leaving 79 studies for the title and abstract reading (Fig. 1). After the title reading, 62 studies were excluded, and 17 were retained for abstract and/or full text reading. Of these, 11 were excluded for the following reasons (Supplemental table 1): 5 were reviews (Mariana and Cairrao, 2020; Lind and Lind, 2012; Chang et al., 2021; Monica Lind and Lind, 2020; Mariana et al., 2016), 1 evaluated the exposure and the outcome in different participants 10 years apart (phthalate exposure during pregnancy and the carotid intima-media thickness in children at the age of 10) (Blaauwendraad et al., 2022), 1 biomonitoring study on phthalates in mother-child pairs but the association with atherosclerosis was not considered (Carli et al., 2022), 1 animal study (Jaimes et al., 2017), and 3 studies evaluating other outcomes, such as CVD in the general population (Zhu et al., 2021), insulin resistance and endothelial dysfunction in children (Kataria et al., 2017), and coronary heart disease and atherothrombotic biomarkers (Su et al.,

**Table 1**
Characteristics of the studies included assessing the association between phthalate exposure and subclinical carotid atherosclerosis.

| Author (year) | Country (sample) | Study design | Sample characteristics | | | Exposure | Outcome | | | Confounders |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Sample size | Men (%) | Age | Phthalate measurement technique | Carotid ultrasonography technique | Carotid IMT assessment | Carotid plaques assessment | |
| Lind and Lind (2011) | Uppsala, Sweden (Older adults from the population-based Prospective of the Vasculature in Uppsala Seniors study) | Cross-sectional | 1016 | 506 (49.8) | 70 y | Atmospheric Pressure Ionization (API) 4000 liquid chromatograph/ tandem mass spectrometer. Phthalate metabolites measured in serum. | External B-mode ultrasound imaging (Acuson XP128, Mountain View, California, USA) with a 10 MHz linear transducer. | Carotid IMT was evaluated in the far wall of the CCA 1–2 cm proximal to the bulb. A maximal 10 mm segment with good image quality was chosen for IMT analysis from the carotid artery. The carotid IMT is the mean value from both sides. | The CCA, the bulb, and the ICA at both sides were evaluated for the presence of plaque. A plaque was present in a particular carotid artery if a local thickening or the carotid IMT was seen that was more than 50% thicker than the surrounding IMT in any part of the carotid artery investigated, and if the atherosclerosis was extensive (IMT >1.2 mm in all carotid segments) without focally thickened parts. The number of carotid arteries with plaques was considered. | Gender, smoking, BMI, systolic and diastolic blood pressure, HDL and LDL-cholesterol, triglycerides, fasting blood glucose, antihypertensive treatment, and statin use |
| Wiberg et al. (2014) | Uppsala, Sweden (Older adults from the population-based Prospective of the Vasculature in Uppsala Seniors study) | Cross-sectional | 1003 | 499 (49.8) | 70 y | Atmospheric Pressure Ionization (API) 4000 liquid chromatograph/ tandem mass spectrometer. Phthalate metabolites measured in serum. | External B-mode ultrasound imaging (Acuson XP128, Mountain View, California, USA) with a 10 MHz linear transducer. | Carotid IMT was evaluated in the far wall of the CCA 1–2 cm proximal to the bulb. A maximal 10 mm segment with good image quality was chosen for IMT analysis from the carotid artery. The carotid IMT is the mean value from both sides. | The CCA, the bulb, and the ICA at both sides were evaluated for the presence of plaque. A plaque was present in a particular carotid artery if a local thickening or the carotid IMT was seen that was more than 50% thicker than the surrounding IMT in any part of the carotid artery investigated, and if the atherosclerosis was extensive (IMT >1.2 mm in all carotid segments) without focally thickened parts. The number of carotid arteries with plaques was considered. | Gender, smoking BMI, blood pressure, HDL and LDL-cholesterol, triglycerides, blood glucose, and waist circumference |
| Su et al. (2019b) | Taiwan (Young Taiwanese | Cross-sectional | 787 | 313 (39.8) | 12-30 y | Liquid chromatography with tandem mass | High-resolution B-mode ultrasonography | Carotid IMT of the posterior wall of the | Not evaluated | Gender, smoking, BMI, cholesterol, hypertension, |

(*continued on next page*)

**Table 1** (*continued*)

| Author (year) | Country (sample) | Study design | Sample characteristics | | | Exposure | Outcome | | | Confounders |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Sample size | Men (%) | Age | Phthalate measurement technique | Carotid ultrasonography technique | Carotid IMT assessment | Carotid plaques assessment | |
| | Cohort, YOTA) | | | | | spectrometric (LC-MS/MS) system. Phthalate metabolites measured in urine | (GE Vivid ultrasound system, Horten, Norway) equipped with a 3.5–10 MHz real-time B-mode scanner | distal CCA was measured from the leading edge of the first echogenic line (interface between the lumen and vascular intima) to the leading edge of the second line (interface between the vascular media and adventitia). The maximum and mean values of the IMT were calculated bilaterally for the CCA proximal to the carotid bifurcation, bulb, and ICA. | | creatinine, age, drinking habit, Hs-CRP, and household income |
| Lin et al. (2020) | Taiwan (Young Taiwanese Cohort, YOTA) | Cross-sectional | 793 | 295 (37.2) | 12-30 y | Thermo Fisher-Accela ultra-performance liquid chromatography (UPLC) system. Phthalate metabolites measured in urine | High-resolution B-mode ultrasonography (GE Vivid ultrasound system, Horten, Norway) equipped with a 3.5–10 MHz real-time B-mode scanner | Carotid IMT was the distance from the front edge of the first echogenic line (i.e., lumen-intima interface) to the front edge of the second echogenic line (i.e., media-adventitia interface) in the far wall of the vessel. The carotid IMTs of the CCA proximal to the carotid bifurcation, bulb, and ICA were obtained bilaterally. The mean carotid IMT was determined by averaging four measurements on bilateral CCAs. | Not evaluated | Gender, smoking, BMI, systolic blood pressure, LDL-cholesterol, triglycerides, creatinine, age, and HOMA-IR |
| Zhang et al. (2021) | Shanghai, China (Chinese type 2 diabetic adults from the METAL study) | Cross-sectional | 675 | 325 (48.1) | ≥18 y | Ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS). Phthalate metabolites measured in urine | High-resolution B-mode with a Mindray M7 ultrasound system (MINDRAY, Shenzhen, China) ultrasound imaging, with a linear 10 MHz transducer (Wang et al., 2019). | Carotid IMT was measured on the far wall of the CCA. The bilateral mean value of the carotid IMT was used for the analyses. | Plaque in the CCA was identified as focal thickening (≥1.5 mm) of the artery wall. | Gender, smoking, BMI, hypertension, creatinine, age, duration of diabetes, and dyslipidemia |
| Yalçin et al. | Ankara, Turkey (Adolescents | Cross-sectional | 86 | 43 (50) | 12-15 y | Waters Acquity ultra-performance liquid | Affiniti 70G ultrasound system (Philips Medical | Five measures of the carotid IMT were taken. | Not evaluated | Gender, BMI-SDS, creatinine, age, and eGFR |

(*continued on next page*)

**Table 1** (*continued*)

| Author (year) | Country (sample) | Study design | Sample characteristics | | | Exposure | Outcome | | | Confounders |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Sample size | Men (%) | Age | Phthalate measurement technique | Carotid ultrasonography technique | Carotid IMT assessment | Carotid plaques assessment | |
| (2022) | from the Child Health Checkup Study) | | | | | chromatography-tandem mass spectrometry (UPLC-MS/MS) system. Phthalate metabolites measured in urine. | System, Holland) Using 5–18 MHz linear probe. | The average was converted to SDS using least mean squares values for gender and height. | | |

*MHz*, megahertz; *IMT*, intima-media thickness; *CCA*, common carotid artery; mm, millimeters; *ICA*, internal carotid artery; *SDS,* standard deviation score; *BMI,* Body Mass Index; *Hs-CRP,* high-sensitivity C-reactive protein; *HOMA-IR,* Homeostatic Model Assessment of Insulin Resistance; *eGFR,* estimated glomerular filtration rate.

2019a). Finally, 6 studies were included in this systematic review (Lind and Lind, 2011; Wiberg et al., 2014; Su et al., 2019b; Lin et al., 2020; Zhang et al., 2021; Yalçin et al., 2022) (Table 1).

### 3.2. Characteristics of the studies

The studies were conducted in Sweden (n = 2), Taiwan (n = 2), China (n = 1), and Turkey (n = 1) and published from 2011 to 2022. Lind et al. (Lind and Lind, 2011) and Wiberg et al. (2014) analyzed the same sample population from Sweden but different phthalate metabolites were assessed. Su et al. (2019b) and Lin et al. (2020) also analyzed the same sample population from Taiwan. Su et al. (2019b) provided information on 8 different phthalate metabolites, while Lin et al. (2020) reported information on 3 of them (MEHP, MEHHP, and MEOHP) based on the same sample but with a different statistical approach. Results were taken from one or the other as required for statistical purposes without duplicating information in the same analysis. All the studies had a cross-sectional design. The sample sizes ranged from 86 to 1016 participants, with a total of 2570 participants aged 12 to 70, 47.2% were men (Table 1).

All studies measured phthalates in spot urine samples, except for the Swedish studies (Lind and Lind, 2011; Wiberg et al., 2014), which analyzed serum. Different techniques were used to assess phthalates. Most of the studies used ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) system (Su et al., 2019b; Lin et al., 2020; Zhang et al., 2021; Yalçin et al., 2022). Information on phthalate identification and the specific parent compound of each metabolite is available in the Supplementary Material (Supplemental table 2).

Most of the studies used B-mode ultrasound with a range of 3.5–10 MHz linear transducer (Lind and Lind, 2011; Wiberg et al., 2014; Su et al., 2019b; Lin et al., 2020; Zhang et al., 2021). The arterial segments examined varied, but most of the studies calculated the carotid IMT in the far wall of the common carotid artery (CCA)(Lind and Lind, 2011; Wiberg et al., 2014; Lin et al., 2020; Zhang et al., 2021). All the studies reported estimates adjusted for creatinine, except for the Swedish studies (Lind and Lind, 2011; Wiberg et al., 2014). Additional adjustments for sociodemographic factors and CVD risk factors were also performed (Table 1).

### 3.3. Risk of bias assessment

After using the JBI critical appraisal tool for cross-sectional studies, all the included studies were classified as having a low risk of bias with more than 87.5% of positive answers (Supplemental table 3).

### 3.4. Association between phthalates and subclinical carotid atherosclerosis

A total of six phthalate metabolites showed significant associations with subclinical carotid atherosclerosis, with the following results.

### 3.5. Phthalates and carotid IMT as a continuous variable

Higher exposure to MBzP, ΣDEHP, and MnBP was significantly associated with an increase in carotid IMT of 2.54 μm for MBzP, 2.11 μm for ΣDEHP, 1.83 μm for MnBP for every 50% increase in the exposure to these phthalates. On the other hand, higher exposure to MMP was associated with a decrease in carotid IMT of −3.90 μm for every 50% increase in MMP exposure (Table 2).

Four studies were included in the meta-analysis for the association between phthalates and carotid IMT as a continuous variable. A non-statistically significant association was observed (Fig. 2), with high heterogeneity among the studies ($I^2 = 67\%$). The funnel plot showed no evidence of publication bias (Supplemental fig. 1).

### 3.6. Phthalates and carotid IMT as a categorical variable

Higher exposure to ΣDEHP and MnBP was associated with increased carotid IMT. When comparing the highest versus the lowest quartiles in adolescents and young adults from Taiwan, the ORs (95% CI) for carotid IMT ≥75th percentile were: 2.46 (1.46, 4.14) for ΣDEHP, and 2.8 (1.65, 4.75) for MnBP, both with a positive linear trend. When comparing ≥100 versus <100 μg/L of ΣDEHP exposure in Turkish adolescents, the OR for a carotid IMT ≥95th percentile was 3.05 (1.16, 8.02) (Table 3).

Only two studies were included in the meta-analysis analyzing phthalates and carotid IMT as a categorical variable. The pooled OR for an increased carotid IMT was 2.67 (95% CI: 1.89, 3.78), with a low heterogeneity among the studies ($I^2 = 0\%$) (Supplemental fig. 2).

### 3.7. Phthalates and carotid plaque prevalence

Higher exposure to MEP and MMP was associated with a higher prevalence of carotid plaques in older adults from Sweden. When comparing the extreme quintiles of MEP, the OR was 1.54 (p-value: 0.018). For MMP exposure, the intermediate quintiles (Q2-Q4) showed significant associations with a higher prevalence of carotid plaques (reaching an OR of 1.75 in Q4), but not for the highest quintile, showing an inverted U-shaped dose-response relationship (no linear trend was observed). On the other hand, higher exposure to MiBP was associated with a lower prevalence of carotid plaques. When comparing extreme quintiles of MiBP exposure, the OR for the prevalence of carotid plaques was 0.64 (p-value: 0.011) with a negative linear trend (Table 4).

In the meta-analysis for the association between phthalates and carotid plaques included only two studies, both conducted in the same sample from Sweden. No statistically significant associations were observed (Supplemental fig. 3), with a high heterogeneity among the studies ($I^2 = 72\%$).

**Table 2**
Association between phthalates exposure and carotid intima-media thickness as a continuous variable.

| Study (year) | Mean (SD) carotid IMT (mm) | Statistical analysis | Phthalate metabolite | Median concentration (IQR) | Main results | |
|---|---|---|---|---|---|---|
| | | | | | Linear regression coefficient | Standardized effect size (95% CI) [a] |
| Lind et al. (2011). (Lind and Lind, 2011) | 0.88 (0.16) | Linear regression coefficients by a unit increase in *ln*-transformed values; carotid IMT analyzed in millimeters (mm). | **MEHP** | 4.53 ng/mL (2.04–15.5) | ln (MEHP): 0.0051 (*p*-value: 0.15) | 2.07 (−0.75, 4.88) |
| | | | **MEP** | 11.6 ng/mL (7.2–17.5) | ln (MEP): −0.0032 (*p*-value: 0.88) | −1.30 (−18.14, 15.54) |
| | | | **MiBP** | 13.5 ng/mL (9.3–29.3) | ln (MiBP): −0.0045 (p-value: 0.14) | −1.83 (−4.25, 0.60) |
| | | | **MMP** | 1.49 ng/mL (0.8–3.1) | ***ln* (MMP): 0.0096 (*p*-value: 0.005)** | **−3.90 (-6.60, -1.18)** |
| Wiberg et al. (2014) (Wiberg et al., 2014) | 0.88 (0.16) | Linear regression coefficients; carotid IMT analyzed in millimeters (mm). | **MBzP** | 0.39 ng/mL (<LOD, 0.68) | **MBzP: 0.013 (*p*-value: 0.034)** | **2.54 (0.20, 4.87)** |
| Su et al. (2019). (Su et al., 2019b) | NA | Multiple linear regression coefficients for *ln*-transformed values; carotid IMT analyzed in millimeters (mm) | MEHP | NA | ***ln* (MEHP): 0.0034 (SE: 0.0007)** | **1.38 (0.82, 1.94)** |
| | | | MEHHP | | ln (MEHHP): 0.001 (SE: 0.0018) | 0.41 (−1.03, 1.84) |
| | | | MEOHP | | ln (MEOHP): 0.0017 (SE: 0.0018) | 0.69 (−0.74, 2.12) |
| | | | ΣDEHP | | ***ln* (ΣDEHP): 0.0052 (SE: 0.0018)** | **2.11 (0.68, 3.54)** |
| | | | MnBP | | ***ln* (MnBP): 0.0045 (SE: 0.0018)** | **1.83 (0.39, 3.26)** |
| | | | MMP | | ln (MMP): 0.0036 (SE: 0.0023) | 1.46 (−0.37, 3.29) |
| | | | MEP | | ln (MEP): −0.0005 (SE: 0.0014) | 0.20 (−0.91, 1.32) |
| | | | MBzP | | ln (MBzP): −0.0003 (SE: 0.0015) | 0.12 (−1.07, 1.31) |
| Lin et al. (2020) (Lin et al., 2020) | 0.45 (0.05) | Linear regression coefficients by a unit increase in *ln*-transformed values; carotid IMT analyzed in micrometers (μm). | **MEHP** | 6.1 μg/g-cr (5.1–7.3) | ***ln* (MEHP): 6.29 (SE: 0.68) (*p*-value: <0.001)** | **2.55 (2.01, 3.10)** |
| | | | **MEHHP** | 27.9 μg/g-cr (26.1–30.0) | ln (MEHHP): 0.13 (SE:1.89) (*p*-value: 0.944) | 0.05 (−1.45, 1.56) |
| | | | **MEOHP** | 17.5 μg/g-cr (16.4–18.5) | ln (MEOHP): −0.76 (SE: 2.00) (*p*-value: 0.704) | −0.31 (−1.90, 1.28) |
| Zhang et al. (2021) (Zhang et al., 2021) | Median (IQR) 0.80 (0.70, 0.85) | Linear regression coefficients for *ln*-transformed values; carotid IMT analyzed in millimeters (mm). | **MiBP** | 86.04 μg/g-cr (53.1–139.4) | ln (MiBP): 0.024 (95% CI: 0.005–0.043) (*p*-value: 0.014) [b] | 9.73 (2.02, 17.44) |
| | | | **MnBP** | 141.6 μg/g-cr (78.8–251.1) | ln (MnBP): −0.019 (95% CI: −0.036, −0.002) (*p*-value: 0.025) [b] | −7.70 (−14.62, −0.79) |

*SD,* standard deviation; *IQR*, interquartile range; *ln*, natural logarithm; *IMT*, intima-media thickness. Phthalate metabolites: *MEHP*, Mono(2-ethylhexyl) phthalate; *MEP*, Mono-ethyl phthalate; *MiBP*, Mono-isobutyl phthalate; *MMP*, Mono-methyl phthalate; *MBzP*, Mono-benzyl phthalate; *MEHHP*, Mono(2-ethyl-5-hydroxyhexyl) phthalate; *MEOHP*, Mono(2-ethyl-5-oxohexyl) phthalate; *MnBP*, Mono-n-butyl phthalate. *LOD*, limit of detection; ng/mL; *ng/mL*, nanograms per milliliter; *NA*, not available; *μg/g-cr*, microgram/gram creatinine-corrected; *CI*, confidence interval; *SE*, standard error.

[a] Carotid IMT (expressed in μm) increment per every 50% increase in phthalate metabolites. Values in **bold** indicate statistically significant results.

[b] Non-statistically significant results after Bonferroni correction.

## 4. Discussion

In this systematic review and meta-analysis of six cross-sectional studies from four different countries and cultures, the association between phthalate exposure and subclinical carotid atherosclerosis was assessed using surrogate markers (carotid IMT and carotid plaques). Exposure to MBzP, ΣDEHP, and MnBP was associated with increased carotid IMT. Exposure to MEP was associated with a higher prevalence of carotid plaques, and MiBP was associated with a lower prevalence of carotid plaques. Mixed results were also observed for MMP in older adults. The meta-analyses showed a high degree of heterogeneity among the studies, and some of the results in this review are based on single studies. For these reasons, until more evidence is available, each metabolite should be considered individually, and conclusions should be drawn with caution.

The cardiovascular system may be affected by long-term exposure to phthalates, as extensively detailed in a review that explored the cardiovascular outcomes related to phthalate exposure (Mariana et al., 2023). Thus, a meta-analysis showed that phthalates were associated with an 11% increased prevalence of CVD in the general population (Fu et al., 2020). The NHANES study (a US population-based cohort study) also found that exposure to MnBP, MBzP, and specific metabolites of DEHP (MECPP, MEHHP, and MEOHP) was associated with a 23–29% higher risk of CVD mortality, and exposure to MEP with a 10% higher risk (Di et al., 2023).

Apart from mortality, the importance of studying phthalates, is that they could operate in the earliest stages of CVD. Exposure may begin in childhood and adolescence, as exposure to phthalates is universal and

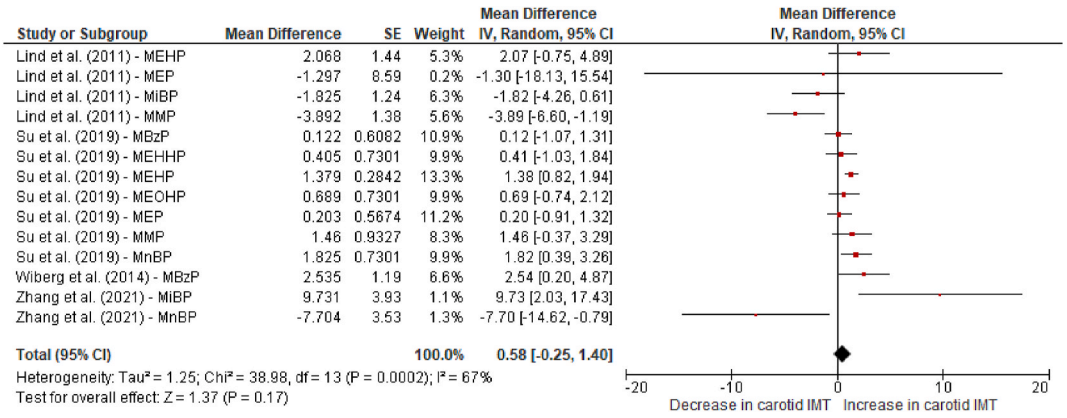


**Fig. 2.** Forest plot of the association between phthalates exposure and carotid intima-media thickness as a continuous variable.

depends on cultural and commercial factors. Phthalates are used in the manufacture of everyday products that people come into contact with from birth, including toys (already restricted since 2007 in the European Union (Ftalatos), and 2008 in the US (Phthalates Business Guidance)), household products, and food packaging. The latter is currently one of the most important sources of phthalate exposure in the general population (Tumu et al., 2023). Thus, the parent compounds of the phthalates that showed positive associations with subclinical carotid atherosclerosis in this review were commonly found in food packaging, such as BzBP, DEHP, DBP, and DEP, the parent compounds of MBzP, MEHP, MnBP, and MEP, respectively (Wang et al., 2023b; Fierens et al., 2012; Li et al., 2019). In 2022, the Food and Drug Administration (FDA) revoked food contact approvals for 23 phthalates (including BzBP, DBP, and DEP)(FDA Limits the Use of). However, despite the widely known harmful effects of some phthalates, DEHP and eight others are still approved for use in the manufacture of food contact materials.

Several mechanisms may explain the relationship between phthalate exposure and atherosclerosis. In mice, DEHP has been shown to induce the development of atherosclerosis by several mechanisms, such as increasing the expression of matrix metalloproteinases (MMP), particularly MMP-2 and MMP-9 (Shih et al., 2015), accelerating the progression of atherosclerosis by promoting LDL oxidation and exacerbating the inflammatory response (Zhao et al., 2016), as well as inducing vascular smooth muscle cell damage and proliferation and increasing foam cell formation (Liu et al., 2022). In humans, the impact of phthalates on the cardiovascular system has been explored, and most of the studies have examined their effects on the fetoplacental vasculature (Lorigo and Cairrao, 2022). Phthalates may be involved in the initiation of the atherosclerotic process as they may contribute to endothelial dysfunction by inducing oxidative stress and apoptosis (Ban et al., 2014), and by disrupting the regulation of certain inflammatory cytokines (Jadhao et al., 2022).

The explanation for the mixed results found for MMP in older adults from Sweden is not easy to elucidate and may be related to the onset and duration of exposure in this population. This suggests that MMP may be related to later stages of the atherosclerotic process. However, a study conducted with the same participants showed that MMP was positively associated with cardiovascular risk factors, such as increased levels of LDL-cholesterol, higher BMI, and a higher Framingham risk score (Olsén et al., 2012). In addition, MMP was associated with a higher risk of hyperlipidemia in middle-aged participants from the general population (Dong et al., 2017). Therefore, further research is needed to elucidate the association of specific phthalates and subclinical carotid atherosclerosis in unselected populations, as mixed results are observed in older adults who may have suffered from different phthalate exposures throughout their lives.

The social relevance of our study lies in the potential for reducing exposure to phthalates as a strategy for CVD primary prevention. Individuals are exposed to phthalates from an early age, and younger individuals may have a longer history of exposure to these chemicals. Furthermore, global public health policies should regulate the use of phthalates in the manufacture of plastics, as the EU and the US have done (Ftalatos; Phthalates Business Guidance), given the global sale and purchase of manufactured plastic products. Continuous research is crucial in this field as the industry is constantly evolving. This includes not only biomonitoring but also the study of associations with the early stages of disease. Our review emphasizes the need for longitudinal studies in this field. However, cross-sectional findings suggest that exposure to phthalates is harmful to cardiovascular health.

Our study has many strengths. First, this is the first systematic review and meta-analysis evaluating the association between phthalate exposure and early markers of atherosclerosis. Second, many relevant databases were used for the literature search. Third, the methods for assessing subclinical carotid atherosclerosis were thoroughly described, studying an early stage of clinical CVD events, and providing results of interest for primary prevention. Finally, although the results were mixed and varied in some populations at high risk of CVD, the main findings are relevant enough to encourage further research on phthalates and atherosclerosis.

This systematic review and meta-analysis also have some limitations. First, only cross-sectional studies were found, so causality should be investigated in the future. Second, a high degree of heterogeneity was observed in the meta-analyses, which could be explained by differences in the characteristics of the samples, such as age, presence of cardiovascular risk factors, racial differences, differences in the time and type of exposure, as well as differences in the outcome measurement, and the diversity of statistical approaches. Third, the main conclusions are based on a limited number of studies and populations, and the results may differ for each phthalate.

In conclusion, exposure to six phthalate metabolites is associated with subclinical carotid atherosclerosis in participants aged 12–70. Of these, MBzP, ΣDEHP, and MnBP are associated with an increased carotid IMT. MEP is associated with a higher prevalence of carotid plaques, and MiBP with a lower prevalence of carotid plaques. MMP showed mixed results in older adults. There is a high degree of heterogeneity among the studies. The results are mainly based on single studies and conclusions must be drawn with caution. Further research is needed to clearly understand the causal relationship between phthalate exposure and subclinical carotid atherosclerosis.

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**Table 3**
Association between phthalates and carotid intima-media thickness as a categorical variable.

| Study (year) | Statistical analysis | Phthalate metabolite | Quartile concentrations (μg/g-cr) | Main results OR (95% CI) for increased carotid IMT |
|---|---|---|---|---|
| Su et al. (2019) (Su et al., 2019b) | Multivariate logistic regression, OR (95% CI) for carotid IMT ≥75th percentile. | **MEHP** | Q1: <1.89<br>Q2: 1.89–12.76<br>Q3: 12.76–37.59<br>Q4: ≥37.59 | Ref.<br>**2.13 (1.18, 3.84)**<br>**4.02 (2.26, 7.15)**<br>**7.39 (4.16, 13.12)**<br>***p*-trend: <0.001** |
| | | **MEHHP** | Q1: <15.50<br>Q2: 15.50–24.12<br>Q3: 24.12–44.14<br>Q4: ≥44.14 | Ref.<br>1.13 (0.69, 1.86)<br>1.15 (0.70, 1.89)<br>1.05 (0.64, 1.72)<br>*p*-trend: 0.868 |
| | | **MEOHP** | Q1: <9.92<br>Q2: 9.92–15.37<br>Q3: 15.37–25.5<br>Q4: ≥25.5 | Ref.<br>1.05 (0.64, 1.73)<br>1.01 (0.61, 1.66)<br>1.01 (0.62, 1.64)<br>*p*-trend: 0.618 |
| | | **ΣDEHP** | Q1: <0.12<br>Q2: 0.12-0.21<br>Q3: 0.21-0.38<br>Q4: ≥0.38 | Ref.<br>1.28 (0.74, 2.20)<br>2.75 (1.65, 4.57)<br>**2.46 (1.46, 4.14)**<br>***p*-trend: <0.001** |
| | | **MnBP** | Q1: <22.27<br>Q2: 22.27–37.49<br>Q3: 37.49–63.91<br>Q4: ≥63.91 | Ref.<br>1.09 (0.62, 1.92)<br>**1.84 (1.08, 3.15)**<br>**2.80 (1.65, 4.75)**<br>***p*-trend: <0.001** |
| Yalçin et al. (2022) (Yalçin et al., 2022) | Logistic regression, OR (95% CI) for carotid IMT-SDS ≥95th percentile. | **ΣDEHP** | Median ΣDEHP (IQR)<br>IMT <95th percentile 60.2 (37.6, 91.7)<br>IMT ≥95th percentile 76.7 (50.0, 114.9) | ΣDEHP (≥100 vs < 100 μg/L)<br>**OR: 3.05 (1.16, 8.02)**<br>*p*-value: NA |

*OR*, Odds Ratio; *CI*, confidence interval; *IMT*, intima-media thickness; *SDS,* standard deviation score. Phthalate metabolites: *MEHP*, Mono(2-ethylhexyl) phthalate; *MEHHP*, Mono(2-ethyl-5-hydroxyhexyl) phthalate; *MEOHP*, Mono (2-ethyl-5-oxohexyl) phthalate; *ΣDEHP*, Molar sum of DEHP; *MnBP*, Mono-n-butyl phthalate. *μg/g-cr*, microgram/gram creatinine-corrected; *IQR*, interquartile range; *NA*, not available. Values in **bold** indicate statistically significant results.

**Table 4**
Association between phthalates and carotid plaque prevalence.

| Study (year) | Statistical analysis | Phthalate metabolite | Median (IQR) concentrations (ng/mL) | Main results OR (*p*-value) for carotid plaques |
|---|---|---|---|---|
| Lind et al. (2011) (Lind and Lind, 2011) | Ordinal logistic regression models. ORs and 95% CI for the presence of carotid plaques. | **MEHP** | 4.53 (2.04–15.5) | Q1: Ref<br>Q2: 0.90 (*p*-value: 0.80)<br>Q3: 0.83 (*p*-value: 0.57)<br>Q4: 0.91 (*p*-value: 0.90)<br>Q5: 0.79 (*p*-value: 0.22) *p*-trend: 0.20 |
| | | **MEP** | 11.6 (7.2–17.5) | Q1: Ref<br>Q2: 1.24 (*p*-value: 0.16)<br>Q3: 1.07 (*p*-value: 0.86)<br>Q4: 1.35 (*p*-value: 0.13)<br>**Q5: 1.54 (*p*-value: 0.018)**<br>*p*-trend: 0.059 |
| | | **MiBP** | 13.5 (9.3–29.3) | Q1: Ref<br>Q2: 0.70 (*p*-value: 0.059)<br>Q3: 0.74 (*p*-value: 0.17)<br>Q4: 1.00 (*p*-value: 0.78)<br>**Q5: 0.64 (*p*-value: 0.011)**<br>***p*-trend: 0.007** |
| | | **MMP** | 1.49 (0.8–3.1) | Q1: Ref<br>**Q2: 1.51 (*p*-value: 0.036)**<br>**Q3: 1.41 (*p*-value: 0.028)**<br>**Q4: 1.75 (*p*-value: 0.008)**<br>Q5: 1.15 (*p*-value: 0.63) *p*-trend: 0.80 |
| Wiberg et al. (2014) | Ordinal logistic regression models. ORs and 95% CI for the presence of carotid plaques. | **MBzP** | 0.39 (<LOD, 0.68) | T1: Ref<br>T2: 1.13 (*p*-value: 0.42)<br>T3: 1.12 (*p*-value: 0.42) *p*-trend: 0.43 |
| Zhang et al. (2021) (Zhang et al., 2021) | Logistic regression models. | **MEP**<br>**MiBP**<br>**MnBP**<br>**MBzP**<br>**MEHP**<br>**MECPP**<br>**MEHHP** | 15.45 (7.44, 39.27)<br>54.41 (30.88, 91.48)<br>90.77 (48.52, 159.90)<br>0.59 (0.28, 1.11)<br>2.43 (0.74, 6.56)<br>21.02 (10.66, 37.89)<br>16.45 (8.80, 29.68) | No significant associations were observed (data not shown) |

*OR*, Odds Ratio; *CI*, confidence interval. Phthalate metabolites: *MEHP*, Mono(2-ethylhexyl) phthalate; *MEP*, Mono-ethyl phthalate; *MiBP*, Mono-isobutyl phthalate; *MMP*, Mono-methyl phthalate; *MBzP*, Mono-benzyl phthalate; *MnBP*, Mono-n-butyl phthalate; *MECPP*, Mono(2-ethyl-5-carboxypentyl) phthalate; *MEHHP*, Mono(2-ethyl-5-hydroxyhexyl) phthalate. *IQR,* interquartile range; *ng/mL*, nanograms per milliliter; *LOD*, limit of detection. Values in **bold** indicate statistically significant results.

## CRediT authorship contribution statement

**Jorge Acosta-Reyes:** Writing – review & editing. **Ana Bayán-Bravo:** Writing – review & editing. **Belén Moreno-Franco:** Writing – review &

editing. **Martín Laclaustra:** Writing – review & editing. **Pilar Guallar-Castillón:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Conceptualization, Diana Mérida, Writing – original draft, Visualization, Software, Methodology, Formal analysis.

## Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used DeepL Write in order to improve readability. After using this tool, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

## 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.

## Data availability

Data will be made available on request.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2024.124044.

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