Phthalate exposure from plastics and cardiovascular disease: global estimates of attributable mortality and years life lost

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Summary

Background New evidence has emerged that plastic polymers and their chemical additives, particularly di-2-ethylhexylphthalate (DEHP), contribute to cardiovascular disease (CVD). Phthalates are commonly used in the production of plastic materials and have been linked to increased oxidative stress, metabolic dysfunction, and cardiovascular disease. Estimates of phthalate-attributable cardiovascular mortality have been made for the US, but global estimates are needed to inform ongoing negotiations of a Global Plastics Treaty.

Methods Cardiovascular mortality data from the Institute for Health Metrics and Evaluation (IHME) and regional DEHP exposure estimates from several sources were used to estimate burden. Hazard ratios of CV mortality were calculated using published exposure estimates, and country-level cardiovascular mortality rates were used to calculate excess deaths and years of life lost (YLL) due to DEHP exposure.

Findings In 2018, an estimated 356,238 deaths globally were attributed to DEHP exposure, representing 13.497% of all cardiovascular deaths among individuals aged 55–64. Of these, 349,113 were attributed to the use of plastics. Geographic disparities were evident, with South Asia and the Middle East suffering the greatest percentage of cardiovascular deaths attributable to DEHP exposure (16.807%). The Middle East, South Asia, East Asia, and the Pacific accounted for the largest shares of DEHP-attributable CVD deaths (73.163%). Globally, DEHP resulted in 10.473 million YLL.

Interpretation Plastics pose a significant risk to increased cardiovascular mortality, disproportionately impacting regions which have developing plastic production sectors. The findings underscore the need for urgent global and local regulatory interventions to kerb mortality from DEHP exposure.

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Keywords: Phthalates; Plastics; DEHP; Mortality; Cardiovascular disease

Introduction

Cardiovascular disease (CVD) has been the leading cause of death in the United States of America (US) since 1921,[1] and in 2011, the UN formally recognised CVD as a major global health concern.[2] The decline in CVD morbidity and mortality arguably represents one of the major public health victories over the past fifty years. Deaths rates from CVD have declined by 60% since 1950 and age-adjusted death rates attributable to CVD have decreased by 4.7% from 2010 to 2020.[1,3] These hard fought gains can be credited to efforts to address key risk factors,[4] including high blood pressure, elevated cholesterol, obesity, unhealthy diet and physical activity,[5] smoking,[6] second-hand smoke exposure,[7] outdoor air pollution,[8] and heavy metal exposures.[9,10]

Despite this effort, the epidemic of CVD remains a global health threat that leads to premature and preventable deaths. CVD death rates have recently trended upward, with age-standardised CVD mortality increasing between 2015 and 2022.[11] Over one billion people are affected by CVD, which was responsible for more than 17 million deaths in 2019—nearly one-third

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Research in context

Evidence before this study

Before undertaking this study, a comprehensive review of the literature was conducted using several databases, including Web of Science and PubMed. Studies that related to the health impacts of phthalates were examined, specifically di-2-ethylhexylphthalate (DEHP), with search terms such as "DEHP," "phthalates," "cardiovascular disease," "cardiovascular", "mortality," "plastic," and "exposure." The existing evidence consistently linked DEHP exposure to metabolic disturbances, oxidative stress, and cardiovascular events, but no global estimate of cardiovascular disease mortality attributable to DEHP exposure had been calculated. No pooled analyses had yet quantified the worldwide burden of DEHP exposure on cardiovascular mortality.

Added value of this study

Our study provides, to the best of our knowledge, a previously unknown global estimation of the burden of cardiovascular mortality attributable to DEHP exposure. The present disease burden model not only quantifies DEHP-related cardiovascular deaths but also highlights significant geographic disparities, showing that regions such as Africa, the Middle East, and South Asia bear the highest burden of DEHP-attributable deaths. By focussing on plastic production, consumption, and disposal our findings demonstrate the wide-reaching public health implications of DEHP exposure and how plastic-related chemicals disproportionately impact countries on the Asian continent. This study provides crucial data that can inform regulatory interventions and global policy discussions on plastic pollution and chemical exposure, offering new understanding of the environmental contributions to cardiovascular mortality.

Implications of all the available evidence

The combined evidence from this study and previous research underscores the need for urgent global policy interventions aimed at reducing exposure to phthalates like DEHP, particularly in countries with high plastic production and consumption as well as ageing populations. Our findings reveal that plastic-related chemicals significantly contribute to cardiovascular mortality in the 55–64 age group, highlighting an under-recognised but critical environmental health issue. The global burden of DEHP exposure, especially in vulnerable populations, calls for immediate regulatory action to mitigate these risks. Reducing phthalate exposure through regulatory interventions could lead to a significant decrease in global cardiovascular mortality, particularly in regions facing the greatest burden of cardiovascular disease from DEHP. Future research and monitoring of environmental exposures to phthalates is needed across most of the world.

of all deaths worldwide.[12] This reflects global population growth and a growing ageing population, as well as contribution from preventable metabolic behavioural and emerging environmental risks, which pose new global challenges in reducing CVD risk.[12,13]

The past decade has presented a new and previously unrecognised risk for CVD: exposure to plastic polymers and their chemical additives. Of particular concern are phthalates, particularly one class of phthalates di-2-ethylhexylphthalate (DEHP), which are used to soften polyvinylchloride (PVC) plastics. DEHP is used in this disease burden model to estimate cardiovascular (CV) burden because it is one of the most widely used and studied phthalates, with extensive human exposure leading to robust data from regional biomonitoring surveys and epidemiological studies in comparison to other phthalates.[14] In addition to data availability, strong epidemiological and mechanistic evidence links DEHP to adverse CV outcomes. DEHP and other phthalates are antiandrogens,[15] increase expression of peroxisome-proliferator activated receptors crucial for lipid and carbohydrate metabolism,[16–21] and are oxidative stressors.[22,23] Cohort studies have identified phthalates to be associated with weight gain,[24] incident diabetes,[25,26] accelerated atherosclerosis,[27–30] and CVD mortality.[31] Studies of human specimens have also detected micro- and nano plastics (MNP), which possibly act as physical irritants to the body, similar to the physical effects of particulate matter in air,[32] and enhance delivery of phthalates and other toxic chemicals, just as nano-particles are widely used for targeted delivery of pharmaceuticals to cells for direct benefit.[33] MNPs can also accumulate phthalates and other chemicals not routinely used in their manufacture.[34–37] A recent observational cohort of endarterectomy patients identified increases in the composite of myocardial infarction, stroke and death with presence of microplastics measured in carotid artery plaque,[38] though challenges in MNP research remain, including distinguishing true microplastics from artefacts, isolating their effects from diffused polymers, and determining the impact of particle size.

These studies highlight an evolving cardiovascular risk factor landscape that present new global health challenges but also offer opportunities for improving the prevention of CVD globally. By recognising emerging environmental risk factors posed by plastic exposure and reducing the production and consumption of plastic, new interventions have successfully reduced phthalate exposure in low-as well as high-income sub-populations.[39,40] In the US, a previous investigation estimated that 50,200 CVD deaths were attributed to 2008 levels of DEHP.[41] The concentrations of four DEHP metabolites mono (2-ethylhexyl) phthalate (MEHP), mono (2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono (2-ethyl-5-carboxypentyl)

phthalate (MECPP), and mono (2-ethyl-5-oxohexyl) phthalate (MEOHP) have been detected almost ubiquitously in all countries around the world, regardless of characteristics of the region.[14]

In February 2022, the UN Environment Assembly announced plans to negotiate an internationally legal binding instrument to end plastic pollution.[42] As negotiations have ensued, petrochemical-producing countries have resisted efforts to kerb plastic production and consumption, arguing that there are few health effects of chemicals used in plastic. To inform ongoing negotiations, this study therefore leveraged existing data on phthalate exposure to create a global disease burden model which estimates the country-specific burden of CVD mortality linked to DEHP, and specifically those attributable to plastic production and consumption.

Methods

Study population

All countries recognised by the World Bank were originally considered by this analysis. To be included in the analytic sample for this study, it was necessary that values for World Bank 2018 population estimates for 55–64-year-olds and Institute for Health Metrics and Evaluation (IHME) cardiovascular mortality rates be publicly available for each country. If these data were not available for a country they were excluded. A list of all countries or territories included (n = 200) as well as their UN standardised geographic regions, CV mortality rates, and population size can be found in Supplement 1.

Measurement/estimation of phthalate metabolites

Four DEHP metabolites of interest were identified: MEHP, MEHHP, MEOHP, and MECPP. This analysis relied on estimates from a previous investigation on global phthalate exposures. Concentrations of phthalate exposure for 5 global areas were estimated in Acevedo et al.,[14] which estimated DEHP metabolite concentrations in areas of the world that suffer from lack of centralised or publicly available data on chemical exposures. The team performed a systematic review and meta-analysis including data from studies on phthalate exposures from different regions across the globe broadly covering Australia, Eastern Asia and the Pacific, The Middle East and South Asia, Latin America, and Africa. The researchers utilised a mixed-effects regression model to examine phthalate metabolite concentrations across time. A regression model weighted for study-specific standard error was used to quantify the change in phthalate metabolite concentrations after controlling for potential modifiers such as age group, region, and pregnancy status. The analysis was further stratified by region to investigate the regional trends in phthalate metabolite exposure over time. The team further conducted a covariate-adjusted meta-regression by including the quadratic term for time (time^2) in the models. The results of this analysis were pooled mean concentration and 95% CI for each phthalate metabolite by region, and projected mean and standard deviation of phthalate metabolite concentrations across five periods, including 2008. These projected mean concentrations were produced for the 10th, 25th, 50th, 75th, and 90th percentiles of exposure, and values from 2008 were used in the present analysis. Details of analytic procedures used to estimate phthalate exposure percentiles in 2008 can be found in the methods of Acevedo et al., 2025.[14] In this systematic review, there was not sufficient evidence to calculate regional concentrations of MEHP for Australia. For the development of the present disease burden model, MEHP concentrations for Australia were therefore estimated by calculating the ratio of average global MEOHP concentrations to global MEHP concentrations excluding Australia and then multiplying this ratio by the concentration of MEOHP in Australia to impute regional estimates for each population quantile.

Based on the UN statistics division standardised country geographic regions,[43] the percentiles of phthalate concentrations from Acevedo et al., 2025 were assigned to eligible countries included in this analysis.[14] Per the UN classification, Latin America and the Caribbean were classified as Latin America. Northern Africa and Sub-Saharan Africa per UN classification was classified as Africa. Central Asia, Eastern Asia, and South-Eastern Asia per UN classification were classified as Eastern Asia and the Pacific (Asia-EPA). Southern Asia & Western Asia per UN classification were classified as the Middle East and South Asia (Asia-MESA). Lastly, Australia was considered its own region while New Zealand, and countries in the sub-regions of Melanesia, Micronesia, and Polynesia were classified as Asia-EPA.

For those regions which do have robust population surveys that allow for measurements of estimates of DEHP metabolites, DEHP exposure data was collected directly from study records. MEHP, MEHHP, MEOHP, and MECPP concentrations for Canada, the US, Europe, and any associated territories were sourced from the Canadian Health Measures Survey (CHMS) Biomonitoring Dashboard,[44] the USA's National Health and Nutrition Examination Survey (NHANES),[45] and the European Consortium to Perform Human Biomonitoring on a European Scale (COPHES)/DEMOCOPHES (its pilot study of feasibility) project's European Human Biomonitoring Dashboard, respectively.[46] When analysing biomonitoring survey data, exposure data for all age groups, both sexes, and unadjusted for creatinine and specific gravity was utilised. NHANES is publicly available, and study staff utilised laboratory data from the 2007–2008 cycle available on the Centres for Disease Control and Prevention National Centre for Health Statistics NHANES webpage. Data from COPHES/DEMCOPHES had to be requested

from the European Institute for Technological Research's European Human Biomonitoring Dashboard, as not all data was available on public webpages. COPHES/DEMCOPHES data from 2008 was requested. CHMS data from cycle 1 (2007–2009) was utilised. When analysing the data from European countries, available median values and standard deviations from country-level samples were utilised to calculate a standard error-weighted regression model in order to estimate regional metabolite concentrations, a method adapted from previous efforts to incorporate heterogeneity of effects.[47] Once beta coefficients were obtained, concentration estimates at the 10th, 25th, 50th, 75th, and 95th percentiles were computed using the inverse of the normal cumulative distribution for the mean and standard deviation between 2007 and 2009. Measures to obtain percentiles of DEHP exposure in Europe were completed in STATA (version 16.0). Data on all metabolites and percentiles of exposure in 2008 from the Canadian Biomonitoring Dashboard was requested from Health Canada. The CHMS did not gather data on MECPP in cycle 1. MECPP concentrations for Canada was therefore estimated by calculating the ratio of average global MEOHP concentrations to global MECPP concentrations excluding Canada and then multiplying this ratio by the concentration of MEOHP in Canada to impute regional estimates for each population quantile. For the United States, standard NHANES sample weights were utilised to calculate the percentiles of exposure in the US population in 2008. Estimated and exact DEHP metabolite concentrations for each world region can be found in Supplement 2.

Estimating hazard for cardiovascular mortality due to DEHP

Throughout all calculations, non-rounded (exact) numbers were utilised. Tables and Supplemental Materials reported in this analysis report rounded values for simplicity.

In methodological alignment with previous studies,[31] exposures were assessed for the year 2008, and mortality outcomes were evaluated for the year 2018, resulting in a ten-year lag between exposure measurement and the observed outcome. To estimate the number of CVD-related excess mortality and number of years of life lost in 2018 due to phthalate exposure in 2008, it was first necessary to calculate the hazard ratio of CV mortality due to phthalate exposure.

Once global estimates of concentrations of four phthalate metabolites were obtained, each compound's concentration was divided by its molecular weight (g/mol) and then added together. Then to weight all concentrations to MEHP, this summed molar mass was further multiplied by the molecular weight of MEHP to create an MEHP equivalent ng/mL. In the end, this value (concentration in nanogrammes of metabolite per millilitre) was further divided by the molecular weight of MEHP to calculate the final molar concentration value of nanomole (nmol) of phthalate metabolite per mL.

To calculate hazard ratios for CV mortality across different quantiles, values were extrapolated from Trasande et al., 2022.[31] This study linked phthalate metabolite measurements in urine from the US National Health and Nutrition Examination Survey 2001–2010 data for 55–64 year olds to the National Death Index through the end of 2015, to assess hazard ratios for mortality observed ten years after the exposure period. In multivariable models in this analysis, the hazard ratio for continuously measured, log transformed DEHP metabolite concentration was 1.10 (95% CI 1.03–1.19), with a median exposure level in the first tertile of 0.05 (HR of 1.0, as the reference group). No effects were therefore assumed below 0.05 μmol/L.

To calculate the HR for CV mortality due to phthalate exposure different quantiles, if the concentration of a given metabolite was less than a threshold of 0.05 ng per mL, this hazard ratio was set to 1, and effect was therefore not estimated for values lower than this threshold. If the calculated value exceeded 0.05, the hazard ratio for CV mortality for each phthalate exposure quantile in each region was estimated:

$$HR_{Region,Quantile} = 1.10^{\ln\left(\frac{nmol\ per\ mL_{Region,Quantile}}{0.05}\right)}$$

Estimated hazard ratios for ten-year CV mortality for each world region can be found in Supplement 3.

Mortality data

IHME Global Burden of Disease (GBD) country-level CV mortality rates (CVMR) were used to estimate baseline CV mortality rates in each country in this analysis.[48] To obtain the dataset, the IHME global health index VizHub results tool was searched for "GBD Estimate: Cause of Death or Injury," "Measure: Deaths and YLLs (Years of Life Lost)," "Cause: Cardiovascular Diseases," "Location: Select all countries and territories," "Age: 55–59 years and 60–64 years," "Sex: Both," and "Year: 2021". This dataset includes estimated number of deaths of 55–64-year-olds from CVD in 2018 in each country. For this analysis, the mean of rates per 100,000 in 55–69-year-olds and 60–64-year-olds were calculated to arrive at one CV mortality rate per country. Details on data input sources and information on how the IHME produces population estimates can be found in documentation for the Global Burden of Diseases study.[48]

Country and territory population estimates from the World Bank were used to estimate the population size of each country.[49] In order to obtain this dataset, the World Bank Group online Population estimates and projections databank was searched, and fields specified were "Database: World Development Indicators," "Country: All Countries," "Series: Population ages

55–59, female, Population ages 55–59, male, Population 60–64, female, and Population 60–64, male," and "Time: 2018". This dataset includes population estimates for each country, disaggregated by gender and age group (55–59 and 60–64) for 2018. Values for both sexes and age groups were added together by country or territory to compute a country or territory-specific population count of 55–64-year-olds. The age group was restricted to 55–64 years to maintain consistency with the primary investigation on which this study is based,[31] ensuring alignment with the data used to extrapolate the Hazard Ratio calculation in the present analysis.

Calculation of population attributable deaths due to DEHP exposure

To calculate the excess CV mortality rate due to phthalate exposure for each country or territory, the population attributable fraction was used, which is defined as the proportional increase in the number of deaths with an increase in the risk factor or exposure:[50]

$$\text{excess CVMR} = \left(\left(HR_{region,quantile} - 1\right) / HR_{region,quantile}\right) * CVMR_{country}$$

HR was considered to be the hazard ratio for CV mortality due to phthalate exposure for each world region for which phthalate exposures for 2008 was estimated, and CVMR was considered to be the baseline IHME-estimated country-specific CV mortality for 55–64-year-olds.

Next, baseline number of CVD-related deaths & excess number of CV-related deaths (phthalate-attributable deaths) in each country were calculated through the following procedure:

$$\text{Baseline number of CV deaths} = \text{CVMR}_{\text{country}} * \text{Population estimate}_{\text{country}}$$

$$\text{Excess deaths} = \text{excess CVMR}_{\text{country,quantile}} * \left(\text{Population estimate} * \text{quantile size}\right)$$

The population estimates used for these calculations were derived from the World Bank's 2018 data for individuals aged 55–64. Quantiles represented the distribution of the population at specific levels of phthalate exposure, enabling hazard ratios to be applied selectively to specific population segments based on their exposure quantile. The lowest 10th of the population in phthalate exposure was considered a control group and values were not calculated for this percentile of the population. In these analyses, the 10th percentile phthalate exposure was applied to the 11th–25th percentile of country-level populations, 25th to the 26–50th, 50th to the 51–75th, 75th to the 76th–95th, and 95th to the 96th–100th percentile of country-level populations. Once number of excess deaths was calculated for each percentile, this total was summed to result in the total number of deaths across the population in entirety.

Lastly, percent excess mortality due to DEHP was calculated:

$$\%\ \text{excess mortality} = \left(\frac{\text{excess number of CV deaths}_{\text{country,quantile}}}{\text{baseline number of CV deaths}_{\text{country,quantile}}}\right) * 100\%$$

Baseline number of deaths was standardised to the aforementioned quantiles, with percent excess mortality for any given exposure group being calculated from the same percent of the overall population.

Calculation of excess cardiovascular-related years of life lost due to phthalate exposure

YLL (premature mortality measured in years) was calculated by using the IHME's years life lost to CVD measures. The IHME calculates cause-specific YLL by multiplying CV deaths by the standard life expectancy at the age of death in a given area, where this life expectancy is derived from a life table that records the lowest observed mortality rate at each age in populations exceeding 5 million. For the purposes of this analysis, excess YLL due to phthalate exposure (phthalate attributable YLL) was calculated in the following manner:

$$\text{Phthalate YLL}_{\text{country,quantile}} = \%\ \text{excess CVMR}_{\text{country,quantile}} * \text{CVD YLL}_{\text{country}} * \text{size of quantile}$$

Percent increase in years of life lost was calculated as the following:

$$\%\ \text{excess YLL} = \left(\frac{\text{excess number of YLL}_{country,quantile}}{\text{Baseline number of CVr YLL}_{country,quantile}}\right) * 100\%$$

Estimates of attributable mortality due to plastics

In order to quantify attributable mortality due to the percentage of DEHP exposure that come from plastics, the attributable phthalate deaths and YLL for each quantile of exposure were multiplied by the approximate percentage of DEHP that come from plastics, estimated by Trasande et al., 2024.[41] In this investigation, a plastics-related fraction of 98% (sensitivity analyses applied a range of 96–99%) was utilised for DEHP metabolites.

Worked example: estimation of excess cardiovascular (CV) deaths in India due to phthalate exposure

In this working example, the number of excess cardiovascular (CV) deaths in India was calculated using available data for the 95th quantile of phthalate exposure.

Attributable deaths (Step 1). IHME cardiovascular mortality data

- CV mortality for ages 55–59: 490.966305 per 100,000 individuals, which equates to a mortality rate of 0.00490966305.
- CV mortality for ages 60–64: 696.0470472 per 100,000 individuals, equating to a mortality rate of 0.006960470472.
- Mean CV mortality rate: (0.00490966305 + 0.006960470472)/2 = 0.00593506676

Attributable deaths (Step 2). Hazard ratios

First, the concentration at the 95th percentile for each phthalate was processed as per section 2.3 to get a final nmol per mL DEHP metabolite concentration:

$$\frac{\left(\frac{30.01437}{278.34}+\frac{62.47058}{294.34}+\frac{39.99131}{292.33}+\frac{55.91116}{308.33}\right)*278.34}{278.34}=0.63821$$

The hazard ratio was calculated as 1.274713 using the formula below:

$$\mathrm{HR}=1.10^{\ln\left(\frac{0.63821}{0.05}\right)}$$

Attributable deaths (Step 3). Calculation of excess cardiovascular mortality rate (CVMR)

The excess CVMR due to phthalate exposure was calculated as follows:

$$\text{excess CVMR}=\left(\frac{(1.274713-1)}{1.274713}\right)*0.00593506676$$
$$=0.00127906438$$

Attributable deaths Step 4. Population data

Using the World Bank population estimates, the total population in India in 2008 for both age groups (55–64) and genders was calculated as 103,846,506.

Attributable deaths (Step 5). Baseline cardiovascular deaths

The baseline number of CV deaths was calculated using the mean CV mortality rate:

$$\text{Baseline CV Deaths}$$
$$=0.00593506676\times 103,846,506=616,335.945903$$

Additionally, 5% of this baseline death was calculated in order to calculate the expected number of CV deaths above the 95th percentile:

$$616,335.945903\times 0.05=30816.79729$$

Finally, the excess number of CV deaths due to phthalate exposure was determined as follows:

$$\text{Excess CV deaths}$$
$$=0.00127906438\times(103,846,506\times 0.05)=6,641.3183406$$

Calculating attributable YLL

$$\text{Phthalate attributable YLL}_{\text{country,quantile}}$$
$$=0.215510230089221*17280928.49*0.05$$
$$=186,210.843752$$

Sensitivity analyses

To assess the impact of multiple variables in modelling on the results obtained, a series of sensitivity analyses were performed. Alternate estimates of excess YLL due to DEHP exposure were computed using an alternate dataset of the World Health Organization life expectancy at 60,[51] which is generic to the entire population and not specific to those with CVD. Data was downloaded directly from the World Health Organization Global Health Observatory Indicators: Life expectancy at 60 (years) webpage. Both genders and all countries were included in this dataset.

In order to run sensitivity on model selection for the generation of estimated phthalate concentrations in global regions without robust population estimates of exposure, alongside the linear estimations, percentiles of phthalate exposure derived from the quadratic model used by Acevedo et al., 2025 were applied to estimate metabolite concentrations.[14]

Finally, the range of plastic attributable fractions for DEHP exposure obtained by Trasande et al., 2024 was utilised to calculate a range for the number of deaths and years life lost inclusive of the true plastics related fraction of disease burden.[41]

Ethics

This investigation is a global burden model which only uses summary-level data; therefore, no ethical approval for human subject research was required. The principal investigator signed a New York University School of Medicine Institutional Review Board attestation form documenting the nature of the research activity conducted as research not involving humans.

Statistics

All analytical methods used in this disease burden model have been described in detail. No inferential statistical comparisons were conducted, and only descriptive statistics were calculated and reported.

Role of funders

Funding sources for this study had no role in study design; collection, analysis, and interpretation of data; writing of the report; and decision to submit the paper for publication.

Results

From the main estimates calculated in this analysis, a total of 356,238 deaths due to DEHP exposure were identified (Table 1), of which over 349,000 were plastic-attributable deaths. Exposure to MEHP, MEHHP, MEOHP, and MECPP contributed 13.497% of all CV deaths in 2018 worldwide, with plastics contributing 98% of these deaths, comprising 13.227% of all CV deaths globally. Sensitivity analyses revealed the actual range of DEHP-attributable mortality to likely be between 356,238 and 356,602 deaths (13.497–13.511% of CV deaths globally), with 349,113–349,469 deaths (13.227–13.241% of CV deaths globally) due to plastic production, consumption, and waste in 2008.

DEHP exposures in 2008 varied greatly among world region (Supplement 2). In the case of MEHP, the Middle East and South Asia led in exposure with a percentile weighted average exposure of 19.460 µmol/L, while the lowest region in terms of exposure, Europe, had a weighted-average of only 3.243 µmol/L, representing an approximate 6-fold decrease. The highest MEHHP exposure was again found in the Middle East and South Asia, with an average exposure of 46.107 µmol/L, in this case closely followed by Africa, with an average exposure of 43.199 µmol/L. The lowest exposure levels for MEHHP were found in Europe (18.413 µmol/L). A similar pattern is seen in MEOHP, where levels are highest in the Middle East and South Asia (26.193 µmol/L) and lowest in Europe (11.935 µmol/L). A slight variation in concentration of MECPP was found, with the highest concentration of 65.452 µmol/L in Africa outstripping all other regions, while the lowest levels were again in Europe (15.304 µmol/L). Overall, across all four DEHP metabolites, the Middle East, South Asia, and Africa bore the most exposure burden, and Europe consistently had comparably low exposures. A detailed breakdown of regional estimated exposures to each chemical and methods for calculating percentile weighted average exposures can be found in Supplement 2.

Geographic disparities in DEHP-attributable CV mortality were notable, with the Middle East and South Asia accounting for 41.678–41.699% of all DEHP-related CV deaths (148,474–148,699 deaths) worldwide (Table 1, Supplement 4). East Asia and the Pacific also experienced notable mortality, with an estimated excess 111,871–112,160 deaths due to DEHP exposure (Table 1, Supplement 4), accounting for 31.399–31.485% of all DEHP-related CV deaths. This suggests that approximately 73.098–73.163% of all global deaths

World region	Deaths						Years of life lost						% Attributable outcome					
	10	25	50	75	95	Total	10	25	50	75	95	Total	10	25	50	75	95	Average
Africa	0	3011	14,382	15,380	4496	37,269	0	86,783	414,516	443,299	129,598	1,074,196	0.000	3.827	18.282	24.439	28.579	11.844
Asia-EPA	16,392	29,625	31,850	27,043	7250	112,160	503,793	910,463	978,869	831,129	222,807	3,447,061	12.668	13.736	14.768	15.674	16.807	13.001
Asia-MESA	21,699	39,319	42,214	35,723	9519	148,474	609,557	1,104,526	1,185,838	1,003,495	267,406	4,170,822	16.375	17.803	19.114	20.219	21.551	16.807
Australia	41	80	91	80	22	314	1243	2443	2762	2419	665	9532	10.560	12.449	14.077	15.409	16.937	12.144
Canada	67	176	237	239	82	801	2012	5281	7116	7184	2464	24,057	7.065	11.125	14.990	18.916	26.951	12.669
Europe	0	4828	9612	9836	2961	27,237	0	148,819	296,243	303,164	91,248	839,474	0.000	5.938	11.821	15.121	18.205	8.374
Latin America	2777	5159	5647	4849	1312	19,744	83,201	154,544	169,185	145,261	39,312	591,503	12.659	14.109	15.446	16.577	17.945	13.500
USA	26	1611	3217	3876	1509	10,239	817	49,860	99,590	119,989	46,720	316,976	0.179	6.557	13.097	19.724	30.720	10.421
Global	41,002	83,809	107,250	97,026	27,151	356,238	1,200,623	2,462,719	3,154,119	2,855,940	800,220	10,473,621	10.357	12.701	16.254	18.380	20.574	13.497

Estimates for number of deaths and years of life lost (YLL) are shown, as well as percent attributable cardiovascular mortality associated with DEHP exposure in each region and quantile of the exposed population. Estimates for Africa, Asia-EPA, Asia-MESA, Latin America, and Australia have been estimated using values for DEHP metabolite concentrations calculated from linear models constructed from meta-analysis in Acevedo et al., 2024. Estimates for the USA, Europe, and Canada (MEHP, MEHHP, MEOHP) have been calculated using values for DEHP metabolite concentrations measured in regional biomonitoring surveys. Estimates for MEHP in Australia and MECPP in Canada have been estimated using imputation from concentration data in all other regions derived from linear models constructed from meta-analysis in Acevedo et al., 2024. Global totals represent the sum of linear estimates from Africa, Asia-EPA, Asia-MESA, Latin America, and Australia & regional estimates for USA, Canada, and Europe. Average percent attributable cardiovascular mortality for each region, and globally, was calculated by dividing the total number of attributable deaths in the given world region by the total number of expected baseline cardiovascular deaths per the IHME in that world region, and multiplying by 100. Global percent attributable mortality for each percentile was calculated by dividing the total number of global attributable deaths in the given percentile by the total number of globally expected baseline cardiovascular deaths per the IHME in that percentile of the population, and multiplying by 100. Baseline expected cardiovascular deaths for specific percentiles were calculated by multiplying total number of expected cardiovascular deaths per the IHME by each percentile's given weight in this anlaysis (0.15 for the 10-24th percentile, 0.25 for the 25-49th percentile, 0.25 for the 50-74th percentile, 0.2 for the 75-94th percentile, and 0.05 for the 95-100th percentile. Deaths and YLL have been rounded to the nearest whole number, and percent attributable deaths have been rounded to three decimal places.

Table 1: **Aggregate cardiovascular mortality burden due to DEHP, main estimates.**

from DEHP in 2018 occurred in the continent of Asia (Fig. 1a). These trends were driven by these regions' large population sizes within the 55–64-year-old age group. South Asia and the Middle East had the highest percentage of CV deaths attributable to DEHP exposure (an average of 16.807%), followed by Latin America (13.500%), East Asia and the Pacific (13.001%), Canada (12.669%), Australia (12.144%), and Africa (11.844%), indicating a disproportionate burden of disease on these areas (Table 1, Fig. 1b). In comparison, lower percent attributable mortality was found in USA (10.421%) and Europe (8.374%) (Table 1, Fig. 1b). With a range of around 8 percentage points, there is a large disparity in cardiovascular burden due to differences in DEHP exposure between different areas of the world. Overall, regions containing a higher proportion of populations from low- and middle-income countries bear the brunt of this burden while regions containing more high-income countries face less exposure to DEHP, and thus less attributable mortality. However, this trend is not seen universally and each regions' profile of exposure between population percentiles and population size of 55–64-year-olds determines the level of risk of excess CV mortality.

Within regions, countries with large ageing populations such as India, China, and Indonesia experienced the highest numbers of DEHP-attributable deaths, with estimated mortality figures of 103,587, 60,937, and 19,761, respectively. Complete country-level estimates for DEHP-attributable deaths and YLL can be found in Supplement 5. However, when adjusting for population size, even very populous countries within this age group differ greatly in burden depending on region. From the aforementioned countries alone, China (with 157,232,453 individuals aged 55–64 in 2018) experienced 60,937 deaths due to DEHP exposure, while India, with a population of approximately 103,846,506 people aged 55–64 (approximately 66% the size of China's) experienced 103,587 deaths, approximately 70% more than China (Supplement 1, Supplement 5).

Globally, DEHP exposure resulted in a total of over 10.473 million YLL among individuals aged 55–64. The distribution of YLL followed the same patterns as overall

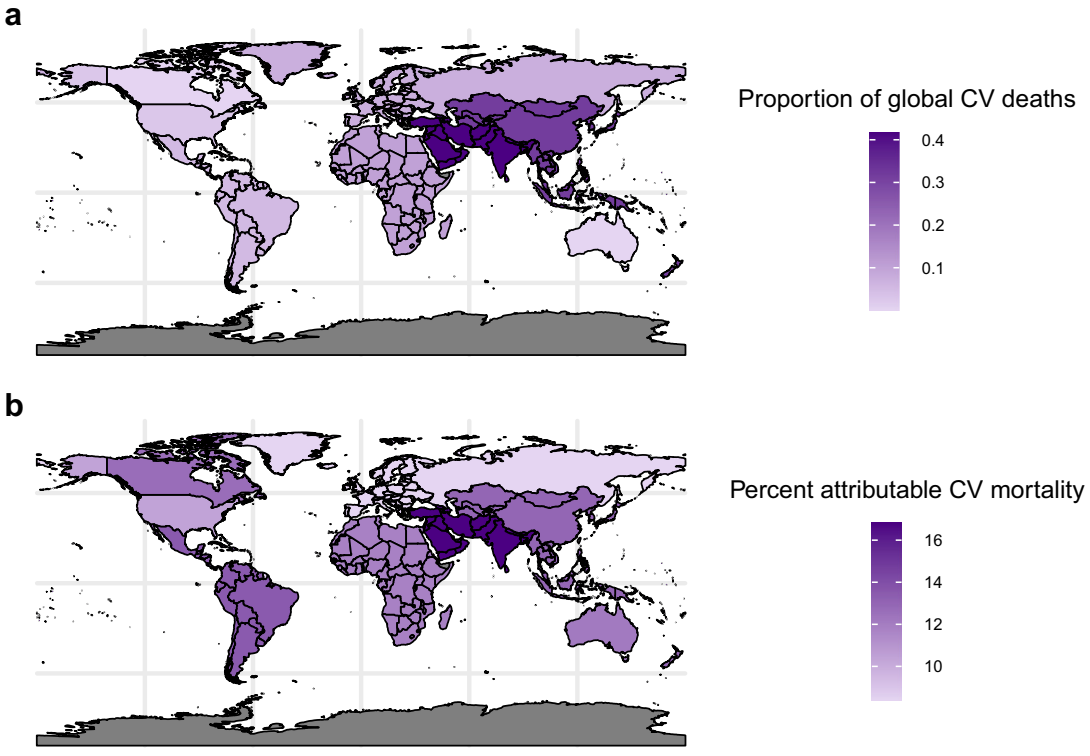

Fig. 1: Aggregate DEHP-attributable mortality world maps among 200 countries and eight world regions. Plot labelled a. represents proportion of global excess CV deaths, or "global share" of mortality burden in each continent. The legend gradient represents the global range of proportion of global shares of death that occur in any one region. Plot labelled b. represents the average disease burden map for percent DEHP-attributable cardiovascular mortality across all world regions. The legend gradient represents the global range of average percent attributable mortality (%). Average percent attributable cardiovascular mortality for each region was calculated by dividing the total number of attributable deaths in the given world region by the total number of expected baseline cardiovascular deaths per the IHME in that world region, and multiplying by 100.

mortality. Asia-MESA and Asia-EPA exhibited the highest YLL totals, with India, China, and Indonesia bearing the greatest burden in this age group, losing 2,904,389, 1,935,961, and 587,073 years of life, respectively, due to phthalate exposure (Supplement 5). Regionally, the Middle East and South Asia lost 4,170,822–4,177,123 years of life, 4,087,406–4,093,581 of which can be attributable to plastics (Table 1, Supplement 4). East Asia and the Pacific lost 3,447,061–3,441,245 years of life due to DEHP in 2018 (Table 1, Supplement 4), 3,378,120–3,372,420 of which can be attributable to plastics.

In addition to these aggregate findings, when regions were broken into percentiles of exposure, patterns of disparity became clearer. These patterns over percentiles are visualised in Fig. 2. In certain regions, there is a greater disparity in percent attributable mortality between the lowest and highest quantiles of exposure. In the USA, the difference between the 95th quantile of exposure and the 10th quantile of exposure is 30.541 percentage points, followed by Africa (28.579% difference), Canada (19.886%), Europe (18.205%), Australia (6.377%), Latin America (5.286%), the Middle East and South Asia (5.176%), and East Asia and the Pacific (4.139%). Those in the highest exposure quantile in the USA and Africa experience a much higher burden of attributable CV mortality (30.720 and 28.579%) than other regions, while those at the lowest exposure quantile experience barely any additional burden due to DEHP exposure, indicating that burden inequality is high in these regions. In other regions such as the Middle East and South Asia, East Asia and the Pacific, and Latin America, those even at the lowest levels of exposure experience burden due to DEHP (16.375, 12.668, and 12.659 percent attributable mortality, respectively, with only 3–4% difference attributable mortality when comparing the lowest and highest exposure percentiles) which indicates that those across all exposure levels are more consistently burdened.

Sensitivity analyses using quadratic exposure models yielded higher mortality estimates compared to the

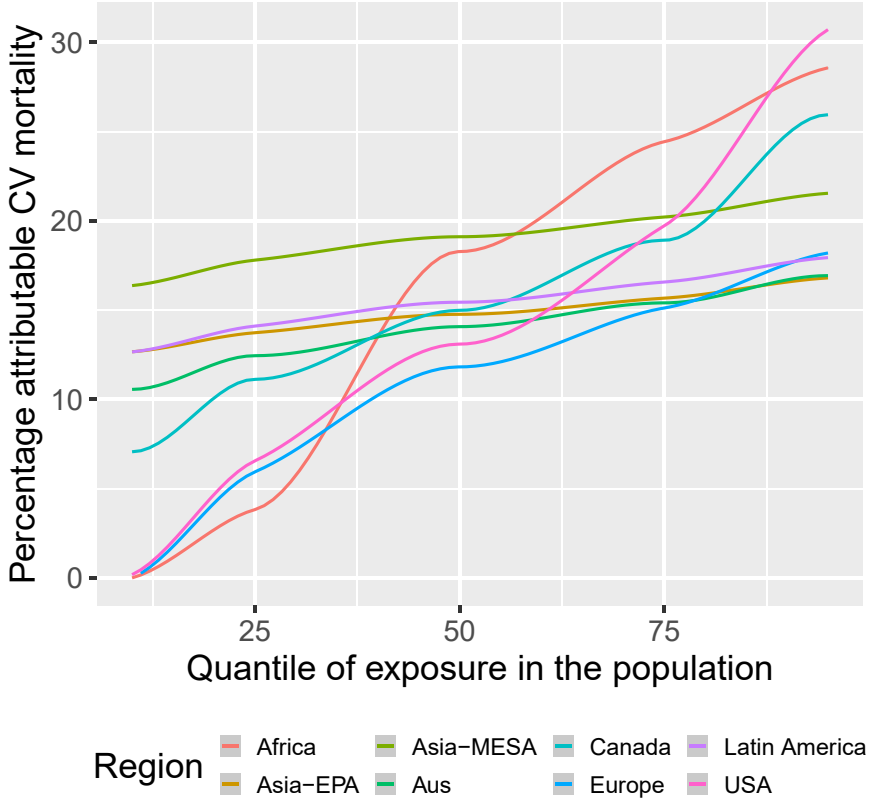

Fig. 2: Percent change in attributable cardiovascular mortality due to DEHP exposure by quantile in across eight world regions. Individual plots represent the change in the percent attributable cardiovascular mortality due to DEHP-metabolite exposure for each region, as quantile of the exposed population increases. Only linear estimates of percent change in attributable mortality are shown alongside regional estimates for the USA, Canada, and Europe. The smoothed curves illustrate illustrates the smoothed relationships between the quantile of exposure in the population and the percentage attributable mortality across various regions using LOESS regression. The LOESS smoothing method applies localised regression to capture non-linear trends in the data, enabling a detailed depiction of regional variations. The x-axis denotes the quantiles of exposure in the population, while the y-axis shows the corresponding percentage of attributable mortality.

primary disease burden model. Aggregate-level findings are presented in Supplement 4, with detailed country-level results available in Supplement 6. Quadratic models projected an increase of approximately 0.1% in deaths and YLLs, along with a 0.014% increase in the global percent attributable mortality, relative to the main estimates (Supplement 4; Supplement 6). In contrast, sensitivity analysis using WHO estimates for YLL at age 60 produced lower results than the main model (Supplement 7), estimating 6.7 million global excess YLLs from DEHP exposure based on linear models, compared to 10.5 million YLLs in the main analysis.

Discussion

In the present disease burden model, it was identified that a total of just over 356,000 global deaths, or 13.497% of worldwide CV mortality in 2018 among 55–64-year-olds was attributable to plastics exposure. The effects of DEHP metabolite exposures on CVD outcomes were disproportionately experienced by countries in the Middle East and South Asia as well as East Asia and the Pacific, posing significant health risk that must be addressed by both local and global governmental bodies. This study found that the South Asian and Middle Eastern regions had higher exposure to DEHP metabolites compared to other regions. However, within Africa and the USA, there were the highest levels of disparity in exposure among different percentiles of the population, with the highest percentiles of exposure experiencing the greatest percent attributable mortality difference. Although phthalate exposure varied greatly between world regions, it was found ubiquitously and contributed to CV mortality in every region on earth. The burden was heightened, not only in countries with developing plastics industries and waste management systems, but also in countries with ageing populations. CVD is clearly associated with older age,[13] and as exposure to phthalates exacerbate these conditions,[25–31] this is of high concern for countries with large numbers of older adults. In such regions, the public health burden of CVD linked to phthalates could be particularly severe, amplifying existing health disparities and placing additional strain on healthcare systems.

Industries pursue the production of plastic for profit, and the adverse consequences are not widely considered in economic tradeoffs about the societally optimal amount. As a proxy for the social cost of a year of life lost (SCYLL) many investigators use a $50,000 measure for the US.[52] Some researchers extrapolate to elsewhere on the globe from this value using a purchasing power parity correction,[53] but this implies a difference in the value of human life based upon place. We have therefore not executed such an extrapolation here but present a range of estimates of the potential societal costs of the YLL identified in this manuscript for consideration. If all the YLLs are valued equally at $50,000 each, then the social costs of plastic-induced mortality would total $510 billion. A more conservative valuation of $1000/YLL would place the social cost at $10.2 billion. An alternative to SCYLL is using the value of a statistical life (VSL) to estimate the economic cost of lives lost due to DEHP exposure. Based on the U.S. Department of Transportation's 2018 definition where VSL is valued at $10.5 million,[54] the total cost for 356,238 deaths would amount to $3.74 trillion. Alternatively, using the U.S. Environmental Protection Agency's 2006 value of mortality risk reduction at $7.4 million,[55] the estimated cost would be $2.6 trillion.

The implications of our findings are particularly relevant for countries with high levels of industrialisation and plastic consumption. This analysis aligns with global trends in plastics production and regulation. For example, India has a rapidly expanding plastics industry, and faces substantial phthalate exposure risks due to plastic waste and the extensive use of commonly DEHP-inclusive plastics, such as PVC in manufacturing of consumer goods.[56] In 2018, China was a major importer of plastic waste,[57] and its plastics industry produced over 29% of global plastics in 2018.[58] A recent 2024 study found that India emitted the highest volume of plastic emissions, totalling 9.3 million metric tons per year. The regions with the highest plastic emissions globally were identified as Southern Asia, Sub-Saharan Africa, and Southeastern Asia,[59] findings that suggest consistency with the global disease burden model. While this analysis does not investigate the origins of exposure within each country and region, higher exposure levels to DEHP may attributed to more industrial manufacturing of plastics, less regulation in products, high rates of plastic product use, and large amounts of plastic waste with underdeveloped waste management sectors.

Findings from this disease burden model also align with expectations when considering the regulatory landscape in the 2008–2018 period. Globally, phthalate regulations targeting DEHP have primarily been implemented on a country-by-country or small regional basis. Prior to 2008, regulations were scarce, with only a few leading countries taking significant action. Japan instituted phthalate restrictions early, introducing a prohibition in 2003 on products containing DEHP within the food packaging and childcare sectors, reflecting Japan's early commitment to reducing exposure to harmful substances.[60] The EU implemented regulations designating DEHP as a restricted phthalate and placing bans on certain quantities of the chemical in childcare and food sectors as early as 2006.[61–63] Between 2008 and 2018, Canada enforced limits on DEHP in children's toys and products related to childcare domestically in 1999 and banned items containing over 0.1% concentration by weight of DEHP in childcare sectors,[64] the USA exacted a prohibition of DEHP childcare articles and toys containing more than 0.1% DEHP,[65] and Australia put in place bans over toxic levels

of DEHP in certain products.[66] Since 2018, the Chinese government reports it has banned 24 categories of foreign waste including plastics waste,[67] while India has incorporated DEHP restrictions into its food packaging sector,[68] but these regulations have been very recent.

These recent regulatory measures reflect a growing awareness of the harmful effects of DEHP. However, it is notable that many of these regulations were not in place at the time of data acquisition for the present study and their effect is not reflected in our results. Despite the increase in regulatory actions, inconsistencies persist across countries, industries, and specific chemicals. Many countries to this day do not have comprehensive regulations. Collaboration among nations to harmonise regulatory standards is essential for reducing global phthalate exposure. Developing economies face the dual burden of expanding their economic and industrial development while also managing waste from industrialised nations. Efforts to regulate major polluters should be supported, with an equitable focus on the immense plastic waste generated by post-industrial nations and now disposed of in developing economies, which undoubtedly contributes to exposure to DEHP in these nations.[69]

This disease burden model provides key insights about the global burden to humans of phthalate exposure, including the disproportionate impact on regions with developing plastics sectors. It highlights the urgent need for both global and local policy interventions and offers evidence to support targeted regulations in countries with high phthalate exposures. To mitigate the impact of phthalates on CV mortality, multi-modal interventions are necessary at both regional and global levels. Limiting exposure to DEHP should involve regulation such as banning or restricting DEHP-use in certain products or improving labelling requirements, improvement of waste management practices, promoting changes in consumer habits, and increasing public awareness about the risks of exposure to DEHP.

This study also provides evidence to support regulations and initiatives targeting those with the highest percentiles of exposure in highly burdened regions, as these groups account for the vast majority of excess deaths. In addition, while previous investigations have been limited in scope due to lack of public data from national biomonitoring surveys in many parts of the world outside of the United States,[45] Canada,[44] and Europe,[46] this study is strengthened by the unique inclusion of phthalate exposure measures estimated for every region on earth.[14] Given that the greatest health effects from phthalates have been found to be in regions without robust national surveys on chemical exposures and in countries with rapidly developing industrial sectors, it is crucial that these regions are included in future investigations.

The present study has limitations that warrant consideration. To estimate the global health effects due to plastics, it was necessary to rely on regional estimates from meta-analysis rather than country-specific chemical exposure data. In this meta-analysis, certain regions, such as Africa, had fewer studies available on phthalates, which may result in higher error of estimated values. For example, while Australia had estimates for three DEHP metabolites, it did not have any available estimates for MEHP, and thus concentrations for this MEHP was estimated from other metabolites. Even among regions with public data available from biomonitoring surveys such as Europe, there are limitations. The COPHES/DEMOCOPHES project only sampled from certain European countries, and some studies excluding adult age groups, limiting the generalisability of their exposure measurements. Larger, and more comprehensive studies will need to be conducted by scientists within nations in these regions, and the present study can serve as further evidence of the importance of funding national research on phthalate exposures.

In addition, heterogeneity of data sources warrants discussion. To the extent possible, the IHME sources data from databases using territorial composition definitions within UN 2008 boundaries. Because IHME compiles data from several different sources it should be noted that there may be slight variations in territorial composition between datasets, which may contribute to increased variance from true population measures for reported health estimates. Additionally, as the IHME integrates data from multiple national and international sources, discrepancies may arise when comparing IHME-compiled estimates with studies conducted within individual countries. For instance, in our previous analysis using NHANES and CDC Wide-ranging Online Data for Epidemiologic Research (WONDER),[31] the estimated number of attributable deaths differed from the results of this disease burden model. This discrepancy is mostly driven by the higher CV mortality rate reported in WONDER (965.2 per 100,000) compared to the IHME-derived more conservative estimate (232.49 per 100,000), as well as differences in the reference years—our previous analysis estimated mortality for 2014, whereas this disease burden model reflects data for 2018. Similarly, sensitivity analyses in our own analysis using quadratic models produced higher estimates than the main, linear model, suggesting that this disease burden model may be conservative in its estimates of the cardiovascular mortality attributable to DEHP exposure. These findings imply that the true burden could be even greater than initially estimated. Alternatively, a sensitivity analysis utilising WHO data for YLL yielded a lower estimate of 6.7 million YLLs, compared to the main model. This discrepancy reflects methodological differences between the WHO and the Institute for Health Metrics and Evaluation (IHME), particularly in their data sources and definitions and calculations of YLL.[48,51] Overall, given that various

studies and institutions apply different approaches to estimating exposure and mortality, comparative disease burden models using multiple data sources are essential. This analysis involved harmonising data from various sources, leading to inherent heterogeneity in the variability of statistics as there are difference sources of uncertainty when working with global data from multiple sources. This burden model is the initial analysis of its kind as is subject to recalculation for reliability.

The present study was also limited in its investigation of only four DEHP metabolites. Other plastic-related chemicals such as bisphenols, DEHP replacements, and microplastics have been suggested by previous investigations to be associated with increased CV mortality.[38,70] These were not accounted for in calculation of attributable mortality, potentially underestimating the overall mortality burden due to plastic exposure. Additionally, plastic production and consumption are also known to contribute to climate change,[71] and associated CV risks,[72] which were not considered in the present calculations.

It is additionally important to acknowledge the uncertainties in accurately quantifying the relationship between DEHP exposure and CVD mortality. While estimates in this model are primarily based on findings from a single study from the US,[41] they are supported by laboratory research findings and epidemiological studies. For example, an Italian study documented associations between PVC microplastics, which commonly contain phthalates, and adverse CV outcomes, including heart attack, strokes, and mortality.[38] However, this single country analysis was not confirmed in another industrialising country to extrapolate exposure-response relationships, which may have different dietary habits, cigarette smoke exposure, physical activity and other cardiovascular risks. More meta-analyses on a global scale are needed to confirm these findings. Additionally, sex reporting for this paper was not possible as exposure data is not disaggregated on sex. Lastly, as this study utilised aggregate data at the country level, it is impossible to incorporate potential individual-level confounders which may bias the magnitude of attributable mortality. Within country variation in socio-economic status and stress may cause variant rates of CVD, with those being the most exposed to DEHP also having the highest baseline CV mortality rates.

This study uncovers a substantial global health burden attributable to DEHP exposure. DEHP exposure in 2008 was responsible for more than 13% of CV deaths among 55–64-year-olds worldwide in 2018, with the most pronounced effects observed in the Middle East and South Asia. These data highlight critical global disparities in loss of life due to plastics pollution. The large mortality burden disproportionately borne in Asia and Africa, which are simultaneously experiencing growth in plastics consumption and production, should raise alarm in nations in these regions. These findings underscore the critical need for enhanced regulatory measures and international cooperation to mitigate the health impacts of phthalates, particularly in regions characterised by high levels of industrialisation and plastic consumption. While this global disease burden model cannot make claims about causality, and policymakers may choose to dismiss the larger body of evidence documenting negative health effects of phthalates,[73,74] this model provides feasible estimates of those risks to CV mortality. Data from human exposure studies are being used to assess the health impacts of plastic use worldwide, informing decisions about the trade-offs involved in reducing plastic production and consumption. This model provides concrete estimates of only a small fraction of those risks, emphasising the urgent need for comprehensive strategies to address the health impacts of plastic exposure.

Contributors

Ms. Sara Hyman contributed to all parts of the project and sections of the manuscript, excluding funding acquisition. Mr. Jonathan Acevedo contributed to conceptualisation, data curation, formal analysis, investigation, methodology, software, writing in the review & editing stages. Dr. Giannarelli contributed intellectual contributions, as well as to the writing in the review and editing stages. Dr. Leonardo Trasande contributed to conceptualisation, data curation, funding acquisition, investigation, methodology, project administration, resources, supervision, validation, writing on the original draft and review and editing stages. Ms. Sara Hyman and Dr. Leonardo Trasande accessed and verified all underlying data. Mr. Jonathan Acevedo also accessed and verified underlying data from the Canadian Health Measures Survey and the European Consortium to Perform Human Biomonitoring on a European Scale project. All authors read and approved the final version of the manuscript for submission.

Data sharing statement

Most of the data utilised in this study is publicly available and no individual-level data was collected as a part of this investigation. Data used in this study are available through the data publisher's websites, and there is no end date to the availability of these datasets as far as the investigators are aware. The IHME necessitates users to sign a data agreement upon releasing data to the public, and therefore investigators interested in acquiring this dataset must go through the IHME website and complete this agreement to be granted access to this public dataset. Data from the European COPHES/DEMOCOPHES project is available to the public at request of the project staff. Data from NHANES is available on a publicly accessible webpage. The only other data utilised in this study was information on the 25th and 75th percentiles of metabolite concentrations from Health Canada. These datapoints were acquired through formally requesting data from Health Canada and will be made available upon request to the corresponding author for this manuscript. This study was not associated with an institutional protocol and did not require consent.

Declaration of interests

Leonardo Trasande, MD. MPP has received royalties or licences from Houghton Mifflin Harcourt, Audible, Paidos and Kobunsha, unrelated to the present work. He has received support for travel or meetings from the Endocrine Society, World Health Organization, the United Nations Environment Programme, Japan Environment and Health Ministries, and the American Academy of Paediatrics, unrelated to the present work. He has served in leadership or fiduciary roles at Beauty counter, Ahimsa, and Grassroots Environmental Education and Footprint, unrelated to the present work. Dr. Chiara Giannarelli has received support

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.ebiom.2025.105730.

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