Plasticisers chemical mixture, vitamin status, and mortality in US adults: a prospective population-based cohort

Yu Zhang, Qi Sun, Yi-Xin Wang, Yang Sun, Mariana F Fernández, Carmen Messerlian, Vicente Mustieles

Summary

Background Plastic pollution is a major environmental and health issue. To cover knowledge gaps, this study aimed to examine the association between population exposure to plasticiser mixtures and mortality, estimate the attributable public health burden, and explore potential nutritional mitigation measures.

Methods This prospective population-based study included non-pregnant US adults aged 20 years or older free from cardiovascular diseases and cancer at baseline from the US National Health and Nutrition Examination Survey 2005–16. The main outcome was mortality status and cause of death, which was confirmed using ICD-9 and ICD-10 codes. Baseline urinary concentrations of eight phthalate metabolites and bisphenol A were selected a priori based on a comprehensive review of the toxicological and epidemiological evidence and modelled as a plasticiser mixture by quantile-based g-computation. Vitamin concentrations were examined as effect modifiers.

Findings 8378 adults were included. Over 71 127 person-years of follow-up (average 8·5 years per person), 633 deaths occurred. Each tertile increase in the mixture concentration was positively associated with all-cause mortality (hazard ratio 1·35, 95% CI 1·02–1·78), cancer mortality (1·79, 1·06–3·03), and cardiovascular disease mortality (1·83, 1·04–3·22). An estimated 10·31% (95% CI 0·78–20·38) of total deaths were attributable to a tertile increase in the mixture, equating to 256 471 annual excess deaths in the USA. The mixture association with all-cause, cancer, or cardiovascular disease mortality was observed only in individuals with serum vitamin D or red blood cell folate concentrations in the lowest tertile, but not in the upper tertiles.

Interpretation Exposure to a mixture of common plasticisers was associated with increased all-cause, cancer, and cardiovascular disease mortality risk. Vitamin D and folate appeared to mitigate these associations. The findings underscore the need to reduce plasticiser exposure, optimise vitamin intake, and regulate chemicals by class.

Funding Instituto de Salud Carlos III (Spain) and NextGeneration EU.

Lancet Planet Health 2025

Published Online
https://doi.org/10.1016/j.lanplh.2025.101394

MEEKL-AERM, College of Environmental Sciences and Engineering, and Center for Environment and Health, Peking University, Beijing, China (Y Zhang PhD); **Department of Nutrition** (Q Sun PhD), **Department of Epidemiology** (Q Sun, C Messerlian PhD), **and Department of Environmental Health** (C Messerlian), **Harvard T H Chan School of Public Health, Boston, MA, USA; Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA** (Q Sun); **Department of Environmental Health, School of Public Health, Shanghai Jiao Tong University School of Medicine, Shanghai, China** (Prof Y-X Wang PhD); **Department of Otolaryngology-Head and Neck Surgery, Shanghai Sixth People's Hospital Affiliated to Shanghai Jiao Tong University, Shanghai, China** (Y Sun MD); **Center for Biomedical Research, University of Granada, Granada, Spain** (Prof M F Fernández PhD, V Mustieles PhD); **Instituto de Investigación Biosanitaria de Granada (ibs GRANADA), Granada, Spain** (Prof M F Fernández, V Mustieles); **Consortium for Biomedical Research in Epidemiology and Public Health, Granada, Spain** (Prof M F Fernández, V Mustieles); **Hospital Universitario Clínico San Cecilio, Servicio de Radiodiagnóstico, Granada, Spain** (V Mustieles)

Correspondence to:
Dr Vicente Mustieles, Instituto de Investigación Biosanitaria de Granada (ibs GRANADA), Granada 18012, Spain
vmustieles@ugr.es

Introduction

Plastic pollution is a major environmental issue.[1] More than 1500 plastic-associated chemicals are known to leach from plastics,[2] leading to universal human exposure throughout life.[3–5] Among plastic-associated chemicals, phthalates and phenols are two major chemical groups used as plasticisers and additives to enhance the flexibility and durability of plastic materials. Ubiquitous in consumer products such as food packaging and cosmetics, they contribute to widespread human exposure.[6,7] Some phthalates and phenols are well established endocrine-disrupting chemicals known to interfere with the human endocrine system,[8] and observational studies have linked their exposure to cardiometabolic diseases and cancer,[8] with health-care costs estimated to be millions of dollars annually.[9]

Life expectancy in the USA has been declining since 2014.[10,11] Apart from medical and lifestyle factors, exposure to plasticiser chemicals could play an inadvertent role. Previous studies have shown that exposure to individual plasticisers, such as di-2-ethylhexyl phthalate[12] and bisphenol A,[13] is associated with higher mortality risk in the general US population. However, although humans are exposed to complex mixtures of plasticiser chemicals that share common exposure sources and can interact with each other leading to synergistic or antagonistic actions,[14] no previous study has examined the contribution of plasticiser mixture exposure to mortality risk.

Since achieving a zero-pollution scenario is unrealistic, identifying modifiable factors that can mitigate the health effects of plasticiser chemical exposure is crucial to inform public health interventions. Experimental animal studies show that certain vitamins, including folate and vitamins D, B6, and B12, could mitigate the adverse health impacts of exposure to phthalates and bisphenol A.[15] However, this hypothesis has not yet been tested in population studies.

Leveraging data from a prospective cohort of the general US population, this study aimed to: investigate the association between exposure to a mixture of bisphenol A and phthalate plasticisers and mortality risk; estimate the mortality burden attributable to this plasticiser mixture; and identify potential nutritional mitigation strategies. To enhance biological plausibility and real-world relevance, an evidence-based mixture of phenols and phthalate

Research in context

Evidence before this study

Before conducting the statistical analysis, we did a comprehensive search in the PubMed and MEDLINE databases to identify, out of the phenols and phthalate metabolites measured in the US National Health and Nutrition Examination Survey 2005–16 cycles, the chemicals supported by a higher weight of toxicological and epidemiological evidence for an effect on chronic diseases and mortality. Given the large scope of our literature research question, we adapted the main points of the navigation guide systematic review methodology, including a structured and reproducible comprehensive search, prioritising meta-analyses, systematic reviews, reviews, and individual studies (in that order). Searches included exposure terms for specific phthalate and phenol chemicals, along with effect terms ("all-cause mortality" OR "cancer" OR "cardiovascular" OR "obesity" OR "diabetes" OR "hypertension" OR "metabolic syndrome"). No time restrictions were applied to the search and only works published in English were considered. Between Nov 15th, and Nov 28th, 2024, 1307 references were screened, of which 172 relevant studies and reviews were identified and used to formulate the weight-of-evidence considering both toxicological and epidemiological data. Based on the weight-of-evidence, the literature search output justified the prioritisation and analysis as a mixture of the plastic-associated chemicals bisphenol A, monoethyl phthalate, monobutyl phthalate, mono-isobutyl phthalate, monobenzyl phthalate, and di-2-ethylhexyl phthalate metabolites. Results of the literature search also showed that most previous epidemiological studies examined phthalates and phenols one at a time as single-pollutant exposures, failing to account for the fact that human beings are exposed to complex mixtures of chemicals with common exposure sources. Additionally, although experimental animal studies suggest that certain vitamins can mitigate the adverse health impacts of exposure to various phthalates and bisphenol A, no population study has examined whether these vitamins can attenuate the contribution of exposure to these chemicals on human mortality risk.

Added value of this study

Leveraging data from a prospective cohort of the general US population, this study observed that exposure to a mixture of eight phthalate metabolites and bisphenol A, selected based on a priori toxicological and epidemiological evidence, was associated with a higher risk of all-cause, cancer, and cardiovascular disease mortality. An estimated 10% of all-cause mortality in the USA can be attributed to a tertile increase in the plasticiser mixture exposure, showing a lower contribution than tobacco exposure but higher than physical inactivity in the examined dataset. The deleterious associations between mixture exposure and mortality risk were only found among participants in the lowest tertile of serum vitamin D or red blood cell folate concentrations.

Implications of all the available evidence

Human exposure to mixtures of plastic-associated chemicals poses an enormous health burden. Efforts are needed to intervene and reduce exposure levels, as well as regulate chemicals on a mixture basis. Optimisation of folate and vitamin D status could be a target for individual-level and population-level interventions aimed at mitigating the harmful health impacts of plastic-associated chemicals.

metabolites was identified a priori through a comprehensive literature review.

Methods

Study design and population

In this prospective population-based cohort, we used participant data from the National Health and Nutrition Examination Survey (NHANES), which is a nationwide representative study designed to assess the health and nutritional status of children and adults in the general population of the USA.[16] A detailed survey description can be found elsewhere.[17] Our study population is a subsample of adults aged 20 years or older who were not pregnant at the time of examination, reported no history of cardiovascular diseases or cancer, and had valid data of death status during the NHANES 2005–16 cycles. These cycles were selected because urinary phthalate metabolites and phenols were quantified in the same subpopulation, allowing us to investigate the two plastic-associated chemical groups simultaneously. A participant inclusion diagram is shown in the appendix (p 2). The study protocol for the NHANES was approved by the NHANES institutional review board and the National Center for Health Statistics Research Ethics Review Board. All participants provided written informed consent.

See Online for appendix

Exposure

In each NHANES cycle, urinary chemical biomarkers were randomly measured in one-third of the participants at the Centers for Disease Control and Prevention (Atlanta, GA, USA) under strong quality control measures. Quantification methods of urinary plasticiser concentrations are described in the appendix (p 3).

To increase the biological plausibility of our analysis, a comprehensive literature search in the PubMed and MEDLINE databases was done to prioritise the chemicals supported by the highest weight of toxicological and epidemiological evidence in relation to chronic diseases and mortality (appendix pp 4–21). Consequently, this analysis examined an evidence-based mixture composed of urinary concentrations of bisphenol A, monoethyl phthalate (MEP), monobutyl phthalate (MBP), mono-isobutyl phthalate (MiBP), monobenzyl phthalate (MBzP), and the four di-2-ethylhexyl phthalate metabolites: mono(2-ethylhexyl)

phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP).

All analysed biomarkers were detected in more than 90% of participants except for MEHP (detection rate 68·3%; appendix p 22). Values below the limit of detection were imputed with values randomly selected between 0 and the limit of detection based on a log-normal distribution.[18] All exposure biomarkers were standardised by urinary creatinine concentrations using the covariate standardised creatinine adjusted method described by O'Brien and colleagues.[19] A detailed description of the imputation and standardised creatinine adjusted method is presented in the appendix (pp 22–23).

Outcome

Mortality data until Dec 31, 2019 (latest update) were ascertained by death certificate records in the National Death Index, which was linked to NHANES data by the National Center for Health Statistics.[20] Causes of mortality were ascertained by ICD-9 and ICD-10 codes. The National Center for Health Statistics classifies cardiovascular disease mortality as death from heart disease (codes I00–I09, I11, I13, and I20–I51) or cerebrovascular disease (codes I60–I69), and cancer mortality as death from malignant neoplasms (codes C00–C97). Time-to-event was calculated as person-months from the recruitment date to death or follow-up end. In the 2015–16 cycle, cerebrovascular disease and accident deaths were not categorised by causes due to the small number of cases. Thus, we excluded 2015–16 cycle data in the cause-specific analyses for cardiovascular disease and accident mortality.[20]

Covariates

Demographic and socioeconomic data were collected through questionnaires and included age, sex, race and ethnicity, education, marital status, and household income. The income–poverty ratio was calculated as household income to the regional poverty line.[21] Bodyweight and height were measured by trained staff and BMI was calculated as weight divided by the square of height. Alcohol intake and the Alternative Healthy Eating Index 2010 (AHEI-2010) score were estimated as the average intake from two 24-h recalls that spanned 3–10 days. The AHEI-2010 score is a composite measure of overall diet quality, with a higher score representing better diet quality.[22] We categorised alcohol intake as 45 g or more per day versus less than 45 g per day based on a meta-analysis showing elevated mortality beyond this cutoff.[23] Physical activity was assessed through a questionnaire from which we calculated the metabolic equivalent of task in minutes per week. Because this questionnaire has changed since the 2007 cycle, we categorised the population into quartiles of estimated metabolic equivalent of task for each cycle. We categorised participants with serum cotinine concentrations of 10 ng/mL or more as exposed to tobacco.[24,25] The calendar month at recruitment was reported as a binary season variable (November–April and May–October) in NHANES. Vitamin biomarkers included red blood cell folate concentrations (2005–16 cycles), and serum concentrations of total 25-hydroxy-vitamin D (25[OH]D; 2005–16 cycles), vitamin B12 (2005–06 and 2011–14 cycles), and vitamin B6 (2007–10 cycles).

Random forest with single imputation[26] was used to impute missing covariate values that ranged from 0·06% (marital status) to 21·3% (physical activity, metabolic equivalent of task; appendix p 24).

Statistical analysis

Descriptive analyses for population characteristics and chemical biomarker concentrations accounted for the NHANES sampling stratification, clustering, and subsample weighting. We used Cox proportional hazards models with a penalised spline term to assess the linearity of chemical-mortality associations. After finding no significant departures from linearity (appendix pp 25–26), we specified exposure variables as linear terms in regression models. In the main analysis, we first used quantile-based g-computation (QGC) accounting for sampling weights to examine hazard ratios (HRs) and 95% CIs for all-cause, cardiovascular disease, and cancer mortality, respectively, per tertile increase in chemical mixture concentrations. The mixture included bisphenol A, MEP, MBP, MiBP, MBzP, MEHP, MEHHP, MEOHP, and MECPP. Adjusted covariates were selected a priori as confounders based on a directed acyclic graph (appendix p 27), and included age, sex, education, race and ethnicity, marital status, BMI, serum cotinine concentration, income–poverty ratio, AHEI-2010 score, alcohol consumption, survey cycle, season, quartiles of metabolic equivalent of task, and urinary creatinine concentrations. Based on our literature search, we hypothesised that exposure to the plasticiser chemical mixture might increase the risk of cancer, cardiometabolic diseases, and mortality (appendix pp 4–21). Thus, we used accident mortality as a negative control outcome as we did not expect chemical exposure to causally lead to accident-related mortality.[27]

We estimated the population attributable fraction,[28] and the associated number of excess deaths for a tertile change in the plasticiser mixture concentration and for other major modifiable lifestyle factors including obesity, excessive alcohol consumption, tobacco exposure, poor diet, and physical inactivity (appendix p 28). We examined effect measure modification by red blood cell folate concentrations, and serum concentrations of vitamins B6, B12, and D, as well as diet quality (AHEI-2010 score) on mixture-mortality associations. We used QGC models including interaction terms between the chemical mixture and tertiles of vitamins or AHEI-2010 score, adjusting for the same covariates described above. We used tertiles to stratify groups based on exploratory results from Generalised Additive Models, which flexibly examined the interaction term (appendix pp 28–32), as well as to preserve power within each stratified group.[29,30] Vitamin supplementation,

especially at high doses, has shown contradictory results on cardiovascular disease, cancer, and mortality endpoints in randomised controlled trials,[31–33] and can lead to heterogeneous increases in the vitamin biomarkers investigated, potentially obscuring true associations. Therefore, we restricted the effect measure modification analyses on vitamins to the population who did not report taking corresponding vitamin supplements in the two 24-h recalls (supplement intake information available in cycle 2007–08 and onwards; percent of supplement users in either of the recalls: 27% for folic acid, 31% for vitamin D, 29% for vitamin B6, and 28% for vitamin B12). Nevertheless, we also examined the effect measure modification, including participants who reported dietary supplement use, as a sensitivity analysis.

Several sensitivity analyses were performed. First, because the four di-2-ethylhexyl phthalate metabolites were moderately to highly correlated, we repeated QGC mixture models, grouping the four di-2-ethylhexyl phthalate metabolites as a molar sum. Second, we conducted adjusted and survey-weighted Cox proportional hazards models for each individual chemical (natural log-transformed) with all-cause, cardiovascular disease, and cancer mortality, to compare with QGC mixture results. Third, we restricted analyses to participants aged 55 years and older to reduce the influence of person-time at low risk of death. Fourth, analyses were stratified by participant sex. Fifth, we calculated E-values, which represent the minimum association between a potential unmeasured confounder with both the exposure and outcome that could explain away the observed results.

All statistical analyses were done in R (version 4.3.0). Random forest imputation was done by the missForest (version 1.5) package. QGC and effect measure modification analyses were done by qgcomp (version 2.10.1) and qgcompint (version 0.7.0) packages.

Role of the funding source

The funders had no role in data collection, analysis, interpretation, writing of the manuscript, or the decision to submit for publication.

	N=8378
Number of deaths	633
Years of follow-up	8·5 (3·4)
Age, years	44·4 (15·7)
BMI, kg/m^2	28·8 (6·8)
Sex	
Male	4127 (51·1%)
Female	4251 (48·9%)
Race or ethnicity	
Hispanic	2230 (15·0%)
Non-Hispanic White	1913 (65·3%)
Non-Hispanic Black	3297 (12·0%)
Other	938 (7·7%)
Highest education	
Less than middle school	856 (5·6%)
Middle school	1230 (11·1%)
High school degree	1925 (22·6%)
College degree	2431 (31·5%)
College graduate or higher	1926 (29·2%)
Household income-poverty ratio	
<1	1670 (14·6%)
≥1 to <1·5	1186 (10·9%)
≥1·5	4793 (74·5%)
Marital status	
Married or living with partner	4994 (63·8%)
Widowed, divorced, or separated	1638 (16·4%)
Never married	1741 (19·8%)
Serum cotinine concentration ≥10 ng/mL	2091 (26·1%)
Alcohol consumption ≥45 g per day	290 (5·2%)
Survey season	
May–October	3977 (42·9%)
November–April	4401 (57·1%)
Alternative Healthy Eating Index, 2010 score	33·45 (10·49)
Metabolic equivalent of task, min per week	480 (120–1200)

Data are n (%), mean (SD), or median (quartile 1–quartile 3), unless otherwise specified. The mean (SD) and percentages in this table were US nationally representative.

Table 1: **Population characteristics of adults aged ≥20 years, National Health and Nutrition Examination Survey 2005–16**

Results

8378 participants were included with a mean of 8·5 years of follow-up (SD 3·4; table 1). The mean age was 44·4 years (SD 15·7) and the mean BMI was 28·8 kg/m^2. Most of the participants were Non-Hispanic White (n=1913 [US representative percentage 65%]), obtained a college degree or higher (n=4357 [61%]), and were married or living with a partner (n=4994 [64%]). About one-fourth of the participants were exposed to tobacco (n=2091 [26%]), while 290 (5%) of the population consumed 45 g or more per day of alcohol. 633 deaths occurred in 71 127 person-years of follow-up. Except the four di-2-ethylhexyl phthalate metabolites that were moderately to highly correlated among them (*r* for cratio-adjusted concentrations 0·57–0·97), low to moderate Spearman correlations were observed among other chemical biomarkers (0·05–0·51; appendix p 23).

Each tertile increase in the mixture concentration was associated with a 35% higher hazard for all-cause mortality (HR 1·35, 95% CI 1·02–1·78), a 79% higher hazard for cancer mortality (1·79, 1·06–3·03), and an 83% higher hazard for cardiovascular disease mortality (1·83, 1·04–3·22; table 2). No association was found for accident-related mortality (0·96, 0·30–3·05). MECPP contributed the most to the overall association between the mixture and all-cause mortality, with a weight of 36%, followed by MEP (19%), MBP (18%), and MBzP (16%; appendix p 33). MEHHP had the highest contribution (35%) for the cancer mortality association, followed by MEP (27%). MECPP contributed the most (57%) to the cardiovascular disease mortality

association, followed by MBzP (15%) and bisphenol A (14%; appendix p 33).

We estimated that 10·31% (95% CI 0·78–20·38) of total deaths, 21·51% (1·34–42·27) of cancer deaths, and 20·77% (2·03–40·10) of cardiovascular disease deaths were attributable to a tertile change in mixture concentrations, which translates to an average of 256 471 total death cases, 126 798 cancer deaths, and 127 920 cardiovascular disease deaths annually in the USA. The estimated population attributable fraction of total deaths due to a tertile increase in mixture exposure was lower than that of tobacco exposure (population attributable fraction 16·49%, 95% CI 11·89–21·10), while higher than the population attributable fraction due to physical inactivity (ie, metabolic equivalent of task in the lowest quartile range; 3·61%, 0·06–7·19; figure).

Among participants who did not use vitamin D supplements, the positive associations between the mixture and all-cause, cancer, and cardiovascular disease mortality were observed among participants in the lowest tertile of serum total 25(OH)D (all-cause mortality HR 2·09, 95% CI 1·27–3·47; cancer mortality HR 4·88, 1·70–13·96; and cardiovascular disease mortality HR 12·48, 3·26–47·75), while no deleterious associations were found among those in the second or third vitamin D tertiles (table 3). Similarly, among participants who did not use folic acid supplements, the positive association between the mixture and cancer mortality was only observed among those in the lowest tertile of red blood cell folate concentrations (HR 4·06, 95% CI 1·20–13·80), while not in the upper tertiles (table 3). In contrast, a positive association between the mixture and all-cause mortality was only found in the highest tertile of serum vitamin B12 concentrations (5·09, 1·19–21·71), while not in the lower tertiles. No obvious effect measure modification was observed for serum vitamin B6 or AHEI-2010 score (table 3).

In sensitivity analyses, using the sum of di-2-ethylhexyl phthalate metabolites in the mixture did not change results for all-cause or cancer mortality but slightly attenuated estimates for cardiovascular disease mortality (appendix p 34). Single-pollutant Cox models showed positive associations for MBP, MEP, MBzP, and MECPP with all-cause mortality, for MBP, MEP, and MiBP with cancer mortality, and for MECPP with cardiovascular disease mortality (appendix pp 35–36). After restricting to age 55 years and older, results were consistent with primary results in the total population, where the mixture exposure was positively associated with all-cause, cancer, and cardiovascular disease mortality (appendix p 37). Mixture associations with all-cause mortality were similar but slightly stronger among females than among males. The mixture–cardiovascular disease mortality association was stronger in females (HR 2·14, 95% CI 1·18–3·89) than males (1·55, 0·69–3·44), while the association with cancer mortality was predominantly observed in males (2·75, 1·29–5·83) but not females (1·23, 0·60–2·55; appendix p 38). However, interaction terms were not statistically significant (p for interaction=0·50 for both all-cause and cardiovascular disease mortality and 0·11 for cancer mortality; appendix p 38). The estimated E-values for the observed associations between the mixture and all-cause, cancer, and cardiovascular disease mortality were 1·16, 1·31, and 1·24 for the lower 95% CIs and 2·04, 2·98, and 3·06 for the point estimates, representing the strength of confounding required to reduce the associations to null (appendix p 39). When participants using vitamin supplements were included in the effect measure

	Mixture (N=8378)	
	Cases per person-month	Hazard ratio (95% CI)
All-cause mortality	633/853 519	1·35 (1·02–1·78)
Cancer mortality	153/853 519	1·79 (1·06–3·03)
Cardiovascular disease mortality*	160/788 692	1·83 (1·04–3·22)
Accident mortality*	27/788 692	0·96 (0·30–3·05)

Mixture included urinary concentrations of creatinine-ratio-adjusted bisphenol A, monoethyl phthalate, monobutyl phthalate, mono-isobutyl phthalate, monobenzyl phthalate, mono(2-ethylhexyl) phthalate, mono(2-ethyl-5-hydroxyhexyl) phthalate, mono(2-ethyl-5-oxohexyl) phthalate, and mono(2-ethyl-5-carboxypentyl) phthalate. Models were adjusted for age (continuous), sex (female or male), highest education attainment (less than middle school, middle school, high school degree, college degree, college graduate, or higher), race and ethnicity (Hispanic, Non-Hispanic White, Non-Hispanic Black, or Other), marital status (married or living with a partner; widowed, divorced, or separated; or never married), BMI (continuous), serum cotinine concentration (continuous), ratio of household income to regional poverty line (continuous), Alternative Healthy Eating Index-2010 score (continuous), alcohol consumption (<45 g per day *vs* ≥45 g per day), cycle (categorical), season (May–October or November–April), quartiles of the metabolic equivalent of task (categorical), and natural-log transformed urinary creatinine concentrations (continuous). *Analyses on cardiovascular disease and accident mortality did not include 2015–16 cycle data because the National Health and Nutrition Examination Survey categorised cerebrovascular disease and accident mortality into other causes of death due to the small number of cases in this cycle. N=7004 for cardiovascular and accident mortality.

Table 2: **Hazards ratio (95% CI) of mortality per tertile increase in urinary concentration of the mixture of plasticiser chemicals, National Health and Nutrition Examination Survey 2005–16**

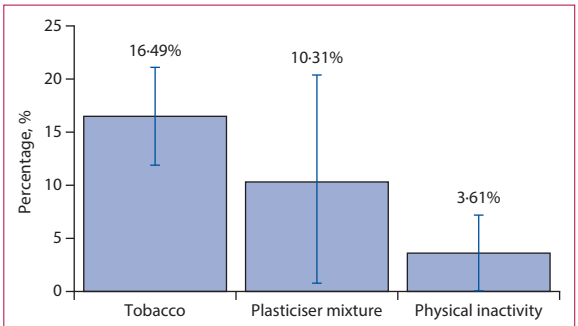

Figure: **Population attributable fraction of all-cause mortality due to modifiable factors in the US general population**

Tobacco exposure was defined as a serum cotinine concentration of ≥10 ng/mL; physical inactivity was defined as a metabolic equivalent of task in the lowest quartile of each cycle. Other examined modifiable factors were not significantly associated with all-cause mortality and were not presented in the plot, including obesity (ie, a BMI of ≥30 kg/m^2; hazard ratio 1·03, 95% CI 0·92–1·16), excessive alcohol consumption (ie, ≥45 g per day; 0·95, 0·68–1·34), and poor diet (ie, an Alternative Healthy Eating Index score of <25; 1·08, 0·91–1·28). Models were adjusted for age (continuous), sex (binary), highest education attainment (categorical), race and ethnicity (categorical), marital status (categorical), BMI (continuous), ratio of household income to regional poverty line (continuous), cycle (categorical), season (binary), Alternative Healthy Eating Index–2010 score (continuous), alcohol intake (<45 g per day *vs* ≥45 g per day), cotinine concentration (continuous, not adjusted in models for tobacco exposure), and physical activity (metabolic equivalent of task quartiles, not adjusted in physical inactivity models). The plasticiser mixture model was additionally adjusted for natural log-transformed urinary creatinine concentrations (continuous).

	Tertile 1		Tertile 2		Tertile 3		p for interaction
	Cases per person-month	HR (95%CI)	Cases per person-month	HR (95%CI)	Cases per person-month	HR (95%CI)	
Serum total 25-hydroxy-vitamin D, 2007–16 cycles							
All-cause mortality	89/134 410	2·09 (1·27–3·47)	80/133 802	0·70 (0·36–1·37)	62/135 460	0·73 (0·40–1·33)	0·0046
Cancer mortality	22/134 410	4·88 (1·70–13·96)	12/133 802	0·98 (0·18–5·38)	14/135 460	0·89 (0·29–2·76)	0·064
Cardiovascular disease mortality*	22/120 236	12·48 (3·26–47·75)	26/119 879	0·40 (0·06–2·66)	15/121 539	0·07 (0·02–0·29)	<0·0001
Red blood cell folate, 2007–16 cycles							
All-cause mortality	85/148 273	1·29 (0·61–2·71)	65/153 701	0·75 (0·38–1·46)	131/142 064	1·02 (0·63–1·63)	0·52
Cancer mortality	23/148 273	4·06 (1·20–13·80)	16/153 701	0·89 (0·29–2·69)	25/142 064	1·46 (0·51–4·13)	0·18
Cardiovascular disease mortality*	23/133 281	0·86 (0·36–2·06)	19/137 952	0·35 (0·07–1·64)	32/127 752	1·26 (0·40–3·97)	0·42
Serum vitamin B6, 2007–10 cycles							
All-cause mortality	96/77 464	1·31 (0·67–2·57)	45/80 153	0·64 (0·25–1·69)	34/80 754	0·84 (0·35–2·01)	0·41
Cancer mortality	25/77 464	NA	10/80 153	NA	5/80 754	NA	..
Cardiovascular disease mortality	30/77 464	NA	11/80 153	NA	5/80 754	NA	..
Serum vitamin B12, 2011–14 cycles							
All-cause mortality	27/49 231	0·98 (0·36–2·64)	22/48 979	1·36 (0·41–4·57)	23/49 584	5·09 (1·19–21·71)	0·14
Cancer mortality	10/49 231	NA	3/48 979	NA	7/49 584	NA	..
Cardiovascular disease mortality	6/49 231	NA	7/48 979	NA	8/49 584	NA	..
Alternative Healthy Eating Index–2010 score, 2007–16 cycles							
All-cause mortality	154/210 810	1·04 (0·65–1·65)	160/211 053	1·20 (0·69–2·09)	128/210 249	1·11 (0·69–1·79)	0·91
Cancer mortality	45/210 810	1·48 (0·65–3·35)	34/211 053	0·89 (0·38–2·11)	39/210 249	1·17 (0·48–2·81)	0·71
Cardiovascular disease mortality*	37/189 506	0·88 (0·36–2·12)	38/192 048	2·43 (0·98–6·05)	30/190 612	0·90 (0·28–2·83)	0·17

Mixture included urinary concentrations of creatinine-ratio-adjusted bisphenol A, monoethyl phthalate, monobutyl phthalate, mono-isobutyl phthalate, monobenzyl phthalate, mono(2-ethylhexyl) phthalate, mono(2-ethyl-5-hydroxyhexyl) phthalate, mono(2-ethyl-5-oxohexyl) phthalate, and mono(2-ethyl-5-carboxypentyl) phthalate. Models were adjusted for age (continuous), sex (female or male), highest education attainment (less than middle school, middle school, high school degree, college degree, college graduate, or higher), race and ethnicity (Hispanic, Non-Hispanic White, Non-Hispanic Black, or other), marital status (married or living with a partner; widowed, divorced, or separated; and never married), BMI (continuous), serum cotinine concentration (continuous), ratio of household income to regional poverty line (continuous), Alternative Healthy Eating Index–2010 score (continuous, not adjusted in models stratified by tertiles of Alternative Healthy Eating Index–2010 score), alcohol consumption (<45 g per day *vs* ≥45 g per day), cycle (categorical), season (May–October or November–April), quartiles of the metabolic equivalent of task (categorical), and natural-log transformed urinary creatinine concentrations (continuous). Models on nutrient tertiles were restricted to those who did not report taking respective nutrient supplements in the two 24-h diet recalls. To preserve power and reduce chance findings, we did not run regression models when the number of death cases was less than 10. HR=hazard ratio. NA=not analysed. *Analyses on cardiovascular disease mortality did not include 2015–16 cycle data because National Health and Nutrition Examination Survey categorised cerebrovascular disease mortality into other causes of death due to the small number of cases in this cycle.

***Table 3*: Hazards ratio (95% CI) of mortality per tertile increase in urinary plasticisers mixture concentration across tertiles of vitamin biomarkers or Alternative Healthy Eating Index-2010 scores among participants who did not report taking dietary supplements, National Health and Nutrition Examination Survey 2005–16**

modification analysis, evidence of modification was also observed across vitamin D, folate, vitamin B12, and B6 tertiles, but more complex relationships emerged, such as the U-shape patterns observed across tertiles of most vitamin concentrations (appendix p 40).

Discussion

In this US nationally representative study, exposure to a mixture of phthalate metabolites and bisphenol A was associated with a higher risk of all-cause, cardiovascular disease, and cancer mortality, but not with accident mortality. The deleterious associations were only found among participants in the lowest tertile of serum vitamin D or red blood cell folate concentrations. In contrast, higher serum B12 concentrations strengthened the mixture-mortality association.

Previous NHANES studies have only evaluated exposure to individual phthalates or phenols and mortality risk using single-chemical models. In general, they found consistent evidence that exposure to higher urinary concentrations of di-2-ethylhexyl phthalate metabolites, MBP, MBzP, and bisphenol A were associated with a higher risk of all-cause mortality.[12,13,34–36] However, associations with cause-specific mortality were less consistent, of which bisphenol A was reported to be associated with cardiovascular disease mortality in some studies,[13,36] while not in others.[35] Higher MBzP, MBP, and MiBP urinary concentrations were associated with higher cancer mortality risk,[34] while the association was null when metabolites were grouped by molecular weight and analysed together.[12] One study consistently reported sex-specific findings for which MBP was associated with higher cancer mortality among males but not females,[36] whereas other studies reported no heterogeneity by sex.[12,13,34] The inconsistencies in cause-specific and sex-specific findings can be due to varying sample sizes, a reduced number of cases, and heterogeneity in the examined NHANES cycles and individual chemicals. Notably, all previous studies handled urine dilution by simply including creatinine concentration in regression models or dividing chemical concentration by the original creatinine concentration,[12,13,34–36] which might not sufficiently control for confounding arising from factors related to both creatinine concentration and death risk factors.[19] Other limitations included an absence of control for physical activity[35,37] and diet,[34,36] and potential selection bias by restricting to subpopulations with complete covariate data.[36]

To the best of our knowledge, our study is the first to explore the mitigation potential of vitamin biomarkers on the plasticiser mixture-mortality association. Our findings suggest that an optimal status of vitamin D and folate could counteract the adverse effects of plastic-associated chemicals. Vitamin D status has indeed been associated with a lower mortality risk in previous population studies.[38–41] However, there is mixed evidence regarding the association between folate status and mortality, and some studies even show that excessive folic acid intake from supplements was associated with higher cancer mortality.[33,42] The inconsistencies might be due to the differential effects of natural folate compared with folic acid through fortification or supplementation. Indeed, when participants using folic acid supplements were included in the analysis (appendix p 40), we found more complex and U-shape effect measure modification patterns. Notably, previous epidemiological and toxicological studies support the idea that folate and vitamin D might interact with phthalates and bisphenol A exposure,[43,44] being able to mitigate their deleterious effects on adverse pregnancy and birth outcomes,[45] child neurodevelopmental impairments,[46] and metabolic alterations in both pregnant mothers and children.[47] Although the mechanisms remain speculative, these vitamins might act by counteracting elevated oxidative stress associated with exposure to plasticiser chemicals.[15] In contrast, we found that vitamin B12 concentrations showed a synergistic interaction with chemical mixture exposure on mortality, which is not surprising since elevated B12 concentrations have been associated with a higher mortality risk.[48,49] We did not find effect measure modification between the mixture and AHEI-2010 diet score, consistent with two previous studies reporting no interaction between bisphenol A and diet quality on mortality risk.[50,51]

We estimated that 10·3% of annual deaths in the USA could be attributable to the mixture of eight phthalate metabolites and bisphenol A. If the mixture concentration was reduced by a tertile (a realistic objective based on previous lifestyle intervention studies),[52,53] an average of 256 471 death cases could be prevented annually. Although a single observational study cannot attain definitive causal evidence,[54] there is ample toxicological and epidemiological evidence supporting a likely causal effect of exposure to the examined phthalate metabolites and bisphenol A on human chronic diseases that are potential causes of death. Indeed, we prioritised the chemicals showing a higher weight-of-evidence, increasing the biological plausibility of our findings (appendix pp 4–21). The null association between mixture exposure and accident mortality (the negative control outcome) also strengthened the plausibility of our findings. The potential for public health prevention appears enormous, since our data show that the number of deaths attributable to the plasticiser mixture is lower than tobacco exposure, but similar or higher than other well known risk factors such as physical inactivity. Apart from regulatory and community-level interventions to reduce exposure to these plasticisers, our results also open the door to nutritional interventions aimed at optimising folate and vitamin D concentrations to mitigate the adverse effects of plastic-associated chemicals. Notably, the chemicals investigated in this study could also correlate with overall exposure to plastics including micro-plastics and nano-plastics (as preliminary environmental data shows),[55] and therefore we hypothesise that the estimated death burden associated with the current mixture exposure could also partially reflect the overall burden of plastics exposure in the population. In any case, a general reduction in exposure to plastics is expected to reduce exposure to both plastic-associated chemicals and micro-plastics and nano-plastics. Considering the evidence as a whole and with previously estimated costs,[9,12,36] our results support the urgent need for the expected UN Global Plastics Treaty, which should establish a global limit on plastic production, restrict single-use plastics, and implement stricter regulations for plastic-associated chemicals.[56,57]

Our study is the first to analyse several phthalate metabolites and bisphenol A as a mixture based on previous evidence of their potential health impacts and common exposure sources from plastics. This study is also the first time that vitamins have been examined as a potential mitigation measure to reduce the impact of chemicals on mortality risk. The representative and large sample size, and relatively long follow-up period are notable strengths. We also used state-of-the-art methods to impute chemical non-detected values, correct for urine dilution using the novel standardised creatinine adjusted method,[19] and impute missing covariate values to maximise our sample size and avoid selection bias. Of note, our study is the first to apply the standardised creatinine adjusted approach to this topic, which can control for urine dilution and also reduce bias and confounding from factors influencing both creatinine concentrations and death risk factors. Multiple sensitivity analyses were done, in all cases supporting the robustness of our findings. Nevertheless, our study is not without limitations. Firstly, although NHANES is the best dataset to test our hypothesis since it has the most abundant data on chemicals, vitamin biomarkers, and long-term mortality follow-up, urinary chemical concentrations were assessed at only one timepoint. Because the investigated plasticisers are short-lived chemicals, one measurement might not be fully representative of the individual's overall exposure pattern. However, we expect this error to be non-differential, which would tend to drive our results towards the null,[58] underestimating rather than overestimating associations. Secondly, although we controlled for the most important known risk factors, unmeasured confounding is still possible. Nevertheless, we believe this possibility is small as E-values for the observed point estimates were large (2·04–3·06).[27]

In this US nationally representative study, we observed that exposure to a mixture of eight phthalate metabolites and bisphenol A, selected based on a priori evidence, was associated with a higher risk of all-cause, cancer, and cardiovascular disease mortality. If exposure to this mixture

was reduced by a tertile, hundreds of thousands of deaths could be prevented in the USA each year. The deleterious associations were only found among participants in the lowest tertile of vitamin D or folate concentrations. These findings highlight the enormous health burden posed by human exposure to mixtures of plastic-associated chemicals, urging efforts to intervene and reduce exposure levels, optimise folate and vitamin D status, and regulate chemicals on a mixture basis.

Contributors

YZ contributed to the conceptualisation, data curation, formal analysis, investigation, methodology, software, data visualisation, writing of the original draft, and review and editing subsequent drafts. VM contributed to the conceptualisation, data curation, funding acquisition, investigation, methodology, supervision, writing of the original draft, and review and editing subsequent drafts. QS, YW, YS, MFF, and CM contributed to the investigation and review and editing subsequent drafts. All authors had access to the data and code, and YZ and VM accessed and verified the data and analysis. All authors critically revised the manuscript for important intellectual content and were responsible for the decision to submit the manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Declaration of interests

We declare no competing interests.

Data sharing

All data used in this study are open access and can be found at the official website of the National Health and Nutrition Examination Survey. Analytical codes can be found at the GitHub repository.

For the **National Health and Nutrition Examination Survey website** see https://wwwn.cdc.gov/nchs/nhanes/default.aspx

For the **analytical codes** see https://github.com/YZhang9719/Plasticizer-mixture-and-mortality

Acknowledgments

The work was supported in part by research grants from Instituto de Salud Carlos III, the Government of Spain, NextGeneration EU funds (FIS-PI23/01884 awarded to VM), and CIBER de Epidemiología y Salud Pública. VM is supported by a grant (CD22/00176) from the Instituto de Salud Carlos III and NextGeneration EU. We acknowledge funding support from the PAIDI-CTS-206 group "Oncología Básica y Clínica" from the University of Granada, Spain. We thank Tong Zhu and Jicheng Gong from Peking University for their valuable insights and suggestions on the manuscript. We also thank the National Health and Nutrition Examination Survey investigators and participants.

References

1 Seewoo BJ, Goodes LM, Thomas KV, et al. How do plastics, including microplastics and plastic-associated chemicals, affect human health? *Nat Med* 2024; **30:** 3036–37.
2 Wagner M, Monclús L, Arp HPH, et al. State of the science on plastic chemicals—identifying and addressing chemicals and polymers of concern. 2024. https://zenodo.org/records/10701706 (accessed Nov 18, 2025).
3 Seewoo BJ, Goodes LM, Mofflin L, et al. The plastic health map: a systematic evidence map of human health studies on plastic-associated chemicals. *Environ Int* 2023; **181:** 108225.
4 Landrigan PJ, Raps H, Cropper M, et al. The Minderoo-Monaco Commission on Plastics and Human Health. *Ann Glob Health* 2023; **89:** 23.
5 Symeonides C, Aromataris E, Mulders Y, et al. An umbrella review of meta-analyses evaluating associations between human health and exposure to major classes of plastic-associated chemicals. *Ann Glob Health* 2024; **90:** 52.
6 Hauser R, Calafat AM. Phthalates and human health. *Occup Environ Med* 2005; **62:** 806–18.
7 Vandenberg LN, Chahoud I, Heindel JJ, Padmanabhan V, Paumgartten FJ, Schoenfelder G. Urinary, circulating, and tissue biomonitoring studies indicate widespread exposure to bisphenol A. *Cien Saude Colet* 2012; **17:** 407–34.
8 La Merrill MA, Vandenberg LN, Smith MT, et al. Consensus on the key characteristics of endocrine-disrupting chemicals as a basis for hazard identification. *Nat Rev Endocrinol* 2020; **16:** 45–57.
9 Kassotis CD, Vandenberg LN, Demeneix BA, Porta M, Slama R, Trasande L. Endocrine-disrupting chemicals: economic, regulatory, and policy implications. *Lancet Diabetes Endocrinol* 2020; **8:** 719–30.
10 Yan BW, Arias E, Geller AC, Miller DR, Kochanek KD, Koh HK. Widening gender gap in life expectancy in the US, 2010–2021. *JAMA Intern Med* 2024; **184:** 108–10.
11 Woolf SH, Schoomaker H. Life expectancy and mortality rates in the United States, 1959–2017. *JAMA* 2019; **322:** 1996–2016.
12 Trasande L, Liu B, Bao W. Phthalates and attributable mortality: a population-based longitudinal cohort study and cost analysis. *Environ Pollut* 2022; **292:** 118021.
13 Bao W, Liu B, Rong S, Dai SY, Trasande L, Lehmler H-J. Association between bisphenol A exposure and risk of all-cause and cause-specific mortality in US adults. *JAMA Netw Open* 2020; **3:** e2011620–2011620.
14 Kortenkamp A, Faust M. Regulate to reduce chemical mixture risk. *Science* 2018; **361:** 224–26.
15 Mo HY, Shan CH, Chen LW, et al. Antioxidant vitamins' modification of the adverse health effects induced by phthalate exposure: a scoping review of epidemiological and experimental studies. *Ecotoxicol Environ Saf* 2024; **286:** 117190.
16 Centers for Diseases Control and Prevention. National Health and Nutrition Examination Survey. 2024. https://www.cdc.gov/nchs/nhanes/about/index.html (accessed Nov 18, 2025).
17 Zhang Y, Mustieles V, Wang Y-X, et al. Folate concentrations and serum perfluoroalkyl and polyfluoroalkyl substance concentrations in adolescents and adults in the USA (National Health and Nutrition Examination Study 2003–16): an observational study. *Lancet Planet Health* 2023; **7:** e449–58.
18 Lubin JH, Colt JS, Camann D, et al. Epidemiologic evaluation of measurement data in the presence of detection limits. *Environ Health Perspect* 2004; **112:** 1691–96.
19 O'Brien KM, Upson K, Cook NR, Weinberg CR. Environmental chemicals in urine and blood: improving methods for creatinine and lipid adjustment. *Environ Health Perspect* 2016; **124:** 220–27.
20 National Center for Farmworker Health Statistics. Continuous NHANES public-use linked mortality files. National Center for Health Statistics, 2019.
21 Johnson CL, Paulose-Ram R, Ogden CL, et al. National health and nutrition examination survey: analytic guidelines, 1999–2010. *Vital Health Stat 2* 2013; **161:** 1–24.
22 Wang DD, Leung CW, Li Y, et al. Trends in dietary quality among adults in the United States, 1999 through 2010. *JAMA Intern Med* 2014; **174:** 1587–95.
23 Zhao J, Stockwell T, Naimi T, Churchill S, Clay J, Sherk A. Association between daily alcohol intake and risk of all-cause mortality: a systematic review and meta-analyses. *JAMA Netw Open* 2023; **6:** e236185–236185.
24 Florescu A, Ferrence R, Einarson T, Selby P, Soldin O, Koren G. Methods for quantification of exposure to cigarette smoking and environmental tobacco smoke: focus on developmental toxicology. *Ther Drug Monit* 2009; **31:** 14–30.
25 Vartiainen E, Seppälä T, Lillsunde P, Puska P. Validation of self reported smoking by serum cotinine measurement in a community-based study. *J Epidemiol Community Health* 2002; **56:** 167–70.
26 Shah AD, Bartlett JW, Carpenter J, Nicholas O, Hemingway H. Comparison of random forest and parametric imputation models for imputing missing data using MICE: a CALIBER study. *Am J Epidemiol* 2014; **179:** 764–74.
27 Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. *Epidemiology* 2010; **21:** 383–88.
28 Mansournia MA, Altman DG. Population attributable fraction. *BMJ* 2018; **360:** k757.
29 Zhang Y, Mustieles V, Wang Y-X, et al. Red blood cell folate modifies the association between serum per- and polyfluoroalkyl substances and antibody concentrations in US adolescents. *Environ Sci Technol* 2023; **57:** 2445–56.

30 Zhang Y, Mustieles V, Sun Q, et al. Association of early pregnancy perfluoroalkyl and polyfluoroalkyl substance exposure with birth outcomes. *JAMA Netw Open* 2023; **6:** e2314934.

31 Mangione CM, Barry MJ, Nicholson WK, et al. Vitamin, mineral, and multivitamin supplementation to prevent cardiovascular disease and cancer: US preventive services task force recommendation statement. *JAMA* 2022; **327:** 2326–33.

32 Schwingshackl L, Boeing H, Stelmach-Mardas M, et al. Dietary supplements and risk of cause-specific death, cardiovascular disease, and cancer: a systematic review and meta-analysis of primary prevention trials. *Adv Nutr* 2017; **8:** 27–39.

33 Ebbing M, Bønaa KH, Nygård O, et al. Cancer incidence and mortality after treatment with folic acid and vitamin B12. *JAMA* 2009; **302:** 2119–26.

34 Beyer A, Schorgg P, Karavasiloglou N, et al. Urinary phthalate concentrations and mortality risk: a population-based study. *Environ Res* 2022; **214:** 113927.

35 Fan Y, Tao C, Li Z, et al. Association of endocrine-disrupting chemicals with all-cause and cause-specific mortality in the US: a prospective cohort study. *Environ Sci Technol* 2023; **57:** 2877–86.

36 Di D, Zhang R, Zhou H, et al. Exposure to phenols, chlorophenol pesticides, phthalate and PAHs and mortality risk: a prospective study based on 6 rounds of NHANES. *Chemosphere* 2023; **329:** 138650.

37 Zeng G, Zhang Q, Wang X, Wu K-H. Low-level plasticizer exposure and all-cause and cardiovascular disease mortality in the general population. *Environ Health* 2022; **21:** 32.

38 Giovannucci E, Liu Y, Rimm EB, et al. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. *J Natl Cancer Inst* 2006; **98:** 451–59.

39 Zhang Y, Fang F, Tang J, et al. Association between vitamin D supplementation and mortality: systematic review and meta-analysis. *BMJ* 2019; **366:** l4673.

40 Loftfield E, O'Connell CP, Abnet CC, et al. Multivitamin use and mortality risk in 3 prospective US cohorts. *JAMA Netw Open* 2024; **7:** e2418729.

41 Melamed ML, Michos ED, Post W, Astor B. 25-hydroxyvitamin D levels and the risk of mortality in the general population. *Arch Intern Med* 2008; **168:** 1629–37.

42 Vollset SE, Clarke R, Lewington S, et al. Effects of folic acid supplementation on overall and site-specific cancer incidence during the randomised trials: meta-analyses of data on 50 000 individuals. *Lancet* 2013; **381:** 1029–36.

43 Johns LE, Ferguson KK, Meeker JD. Relationships between urinary phthalate metabolite and bisphenol A concentrations and vitamin D levels in US adults: National Health and Nutrition Examination Survey (NHANES), 2005–2010. *J Clin Endocrinol Metab* 2016; **101:** 4062–69.

44 He X, Xue Q, Li D, et al. Association between biomarkers of phthalate exposure and serum folate concentrations in children: a population-based cross-sectional study of the NHANES from 2011 to 2016. *J Nutr* 2024; **154:** 1596–603.

45 Mínguez-Alarcón L, Gaskins AJ, Chiu YH, et al. Dietary folate intake and modification of the association of urinary bisphenol A concentrations with in vitro fertilization outcomes among women from a fertility clinic. *Reprod Toxicol* 2016; **65:** 104–12.

46 Oulhote Y, Lanphear B, Braun JM, et al. Gestational exposures to phthalates and folic acid, and autistic traits in Canadian children. *Environ Health Perspect* 2020; **128:** 27004.

47 India-Aldana S, Midya V, Betanzos-Robledo L, et al. Impact of metabolism-disrupting chemicals and folic acid supplementation on liver injury and steatosis in mother–child pairs. *J Hepatol* 2025; **82:** 956–66.

48 Flores-Guerrero JL, Minović I, Groothof D, et al. Association of plasma concentration of vitamin B12 with all-cause mortality in the general population in the Netherlands. *JAMA Netw Open* 2020; **3:** e1919274.

49 Liu K, Yang Z, Lu X, et al. The origin of vitamin B12 levels and risk of all-cause, cardiovascular and cancer specific mortality: a systematic review and dose-response meta-analysis. *Arch Gerontol Geriatr* 2024; **117:** 105230.

50 Chen Y-M, Liu Z-Y, Chen S, et al. Mitigating the impact of bisphenol A exposure on mortality: is diet the key? A cohort study based on NHANES. *Ecotoxicol Environ Saf* 2023; **267:** 115629.

51 Liu Z-Y, Wang C, Huang S-Y, et al. Does anti-inflammatory diet mitigate the deleterious effect of bisphenol A on mortality in US adults? Results from NHANES 2003–2016. *Ecotoxicol Environ Saf* 2023; **253:** 114706.

52 Yang TC, Jovanovic N, Chong F, et al. Interventions to reduce exposure to synthetic phenols and phthalates from dietary intake and personal care products: a scoping review. *Curr Environ Health Rep* 2023; **10:** 184–214.

53 Martin L, Zhang Y, First O, et al. Lifestyle interventions to reduce endocrine-disrupting phthalate and phenol exposures among reproductive age men and women: a review and future steps. *Environ Int* 2022; **170:** 107576.

54 Mustieles V, Fernández MF, Messerlian C. In utero metabolic disruption—a preventable antecedent of adult disease? *JAMA Netw Open* 2024; **7:** e2412022.

55 Wang D, Jiang SY, Fan C, Fu L, Ruan HD. Occurrence and correlation of microplastics and dibutyl phthalate in rivers from Pearl River Delta, China. *Mar Pollut Bull* 2023; **197:** 115759.

56 Landrigan P, Symeonides C, Raps H, Dunlop S. The global plastics treaty: why is it needed? *Lancet* 2023; **402:** 2274–76.

57 Landrigan PJ, Dunlop S, Treskova M, et al. The *Lancet* Countdown on health and plastics. *Lancet* 2025; **406:** 1044–62.

58 Perrier F, Giorgis-Allemand L, Slama R, Philippat C. Within-subject pooling of biological samples to reduce exposure misclassification in biomarker-based studies. *Epidemiology* 2016; **27:** 378–88.