Environmental Research 284 (2025) 122229

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Urinary parabens, advanced glycation end products and blood pressure in children: a longitudinal cohort study

Brigitte Reimann [a,*], Hanne Sleurs [a], Rossella Alfano [a], Eleni Renaers [a], Hanne Croons [a], Thessa van Pee [a], Lore Verheyen [a], Nick Giesberts [a], Anna E. Soerensen [a], Catherine Pirard [b,c], Corinne Charlier [b,c], Tim S. Nawrot [a,d], Michelle Plusquin [a]

[a] Centre for Environmental Sciences, Hasselt University, Hasselt, Belgium
[b] Laboratory of Clinical, Forensic and Environmental Toxicology, CHU of Liege, B35, 4000, Liege, Belgium
[c] Center for Interdisciplinary Research on Medicines (CIRM), University of Liege (ULg), CHU (B35), 4000, Liege, Belgium
[d] Department of Public Health, Environment & Health Unit, Leuven University (KU Leuven), 3000, Leuven, Belgium

ARTICLE INFO

Keywords:
Parabens
Advanced glycation end products
Blood pressure
Child health

ABSTRACT

Background: Paraben exposure and advanced glycation end products (AGEs) have both been linked to cardiovascular conditions, including hypertension. However, the association between parabens and AGEs has not been studied yet. Parabens could affect blood pressure (BP) via AGEs.

Methods: In this longitudinal study, urinary paraben concentrations [methyl (MeP), ethyl (EtP), propyl (PrP), butyl (BuP)] were measured in preschool children from the ENVIRONAGE birth cohort using ultra-performance liquid chromatography/tandem mass spectrometry. BP and AGEs, assessed with skin-autofluorescence (SAF) z-scores, were measured at baseline (4 years) and six years later in 83 children (166 observations). First, generalized linear mixed models and quantile g-computation were applied to assess associations and mixture effects of parabens with AGEs and with BP. Next, structural equation modeling (SEM) was employed to disentangle time-specific effects in these associations and explore the role of AGEs as mediators in the relationship between parabens and BP.

Results: We observed an inverse association between the paraben mixture and AGEs ($\beta = -0.30$ per quantile increase; 95 % CI: −0.55, −0.042), driven by PrP with the strongest negative weight. Single-pollutant models confirmed this association for PrP ($\beta = -0.15$; 95 % CI: −2.51, −0.049). SEM revealed direct effects of parabens on systolic blood pressure at 4 years (est.std. = 0.50; 95 % Boot CI: 0.10, 0.82). AGEs mediated an inverse indirect effect of parabens on DBP at 10 years ($\beta = -0.21$; 95 % Boot CI: −0.41, −0.05).

Conclusions: Early-life paraben exposure, particularly PrP, is associated with AGEs and blood pressure, warranting further investigation into long-term consequences.

1. Introduction

Parabens, low-cost, broad-spectrum antimicrobial agents in personal care products, food, and pharmaceuticals (Ana and Paula, 2016; Elder, 1984) are restricted in Europe due to concerns about their endocrine-disrupting properties (Azeredo et al., 2023; Commission Regulation (EU) no. 1004/2014; Liang et al., 2022; Nowak et al., 2018). As parabens are readily metabolized, with a half-life of less than 24h after dermal application in humans (Shin et al., 2023), the use of short-chained parabens like MeP and EtP in personal care products is deemed safe under certain concentration limits in the EU, and unrestricted in the U.S. and most parts of the world. In epidemiological studies, associations between paraben exposure and cardiovascular disease have been reported in adult populations (Yin et al., 2021; Zhang et al., 2023). Studies on associations with subclinical markers of cardiovascular risk in children and adolescents are scarce and inconsistent. While one study reported no statistically significant associations between prenatal paraben exposure and systolic or diastolic BP in early adolescence (Montazeri et al., 2022), another, cross-sectional study from our group showed inverse effects of EtP on mean arterial pressure (MAP) in preschool children (Reimann et al., 2023). However, investigating this relationship in children is vital because early development is highly

* Corresponding author. Hasselt University, Agoralaan Gebouw D, 3590, Diepenbeek, Belgium.
E-mail address: brigitte.reimann@uhasselt.be (B. Reimann).

https://doi.org/10.1016/j.envres.2025.122229
Received 19 March 2025; Received in revised form 3 June 2025; Accepted 23 June 2025
Available online 27 June 2025

sensitive even to low-dose endocrine disruptors (Di Pietro et al., 2023; Heindel and Vandenberg, 2015), the worldwide prevalence of pediatric hypertension is rising sharply (Robinson and Chanchlani, 2022; Song et al., 2019), and elevated childhood blood pressure is associated with adult hypertension (Cook et al., 1997; Liao et al., 2020; Urbina et al., 2019).

Also advanced glycation end products (AGEs) have been associated with cardiovascular disease (Hegab et al., 2012; Lamprea-Montealegre et al., 2022) and cardiovascular risk factors (C. Y. Chen et al., 2022; Robles-Rivera et al., 2023). These sugar-modified adducts arise during non-enzymatic glycoxidative stress in the classical Maillard reaction (Maillard, 1912) either endogenously as part of normal metabolic function or exogenously by consuming heated animal-derived foods that are high in fat and protein (Uribarri et al., 2010). They can have adverse effects on the endothelium causing vascular dysfunction by cross-linking of extracellular matrix proteins like elastin and collagen (Hegab et al., 2012).

Little is known about the potential effects of environmental chemical exposures on AGE levels, with only very few exposures, including cigarette smoke, air pollution, nickel and polycyclic aromatic hydrocarbons being investigated so far (Cerami et al., 1997; Gursinsky et al., 2006; Lai et al., 2020). Parabens are associated with increased levels of oxidative stress (Wei et al., 2022; Zhao et al., 2021), while AGEs not only elicit oxidative stress, but can also be generated under conditions of oxidative stress (Miyata et al., 1997; Moldogazieva et al., 2019; Nowotny et al., 2015). Paraben exposure may therefore be linked with cardiometabolic changes by altering skin AGE levels. Furthermore, an unbiased evaluation of dose-response associations requires the consideration of mixture effects. In real-life exposure scenarios, correlated chemical exposures can reinforce or cancel each other's impact contributing to a greater or smaller overall effect than estimated in single pollutant models (Robinson et al., 2015; Rosofsky et al., 2017). The aim of this study is to contribute to filling the knowledge gap about i) potential associations between parabens, individually or as a mixture, and AGEs, ii) the effect of early life paraben and AGEs exposure on childhood BP in a longitudinal setting, and iii) the role of AGEs as a potential mediator in the association between parabens and BP assessed through Structural Equation Modelling (SEM). Awareness about potential links between the wide-spread exposure to parabens in childhood and AGEs as an early preclinical marker of cardiovascular risk is important in the context of public health recommendations. This study may provide information about underlying mechanisms explaining the observed effects between parabens and cardiovascular health outcomes in previous epidemiological studies at a very early stage, when preventive actions yield the most health advantage.

2. Material and methods

2.1. Study population

Within the framework of the ongoing birth cohort Environmental Influence on Early Aging (ENVIRONAGE) (Janssen et al., 2017), mothers who did not have planned caesareans and could complete questionnaires in Dutch were enrolled upon arrival at the delivery ward at the East-Limburg Hospital in Genk, Belgium. Recruitment was conducted after providing written consent and according to procedures approved by the ethical committees of Hasselt University and the East-Limburg Hospital (EudraCT B37120107805), conform to the principles outlined in the Helsinki Declaration.

The parents were invited to fill in an online questionnaire when the child was between four and six years old and again at 9–10 years, and invited for a follow-up examination (FU1 and FU2 respectively). At 9–10 years old, additionally also the child filled in an online questionnaire. Prior to participating in the follow-ups, mothers renewed their written consent each time, and the children gave oral consent for the measurements.

Recruitment at birth started from February 2010 onwards, and is still ongoing. FU1 examinations included in this study occurred between August 2015 and April 2018, and FU2 examinations between July 2021 and April 2023. For this study we used urinary paraben data collected during FU1 examinations until June 2021. From the pool of 1978 children who had participated until June 2021, 538 had attended the FU1 examination by then. From these, 452 children supplied a sufficient amount of urine during the follow-up examination and had a complete set of key-covariates. From this subset, 300 samples were randomly selected for urinary paraben analysis. For our longitudinal study, we then excluded 148 children who had not attended the second follow-up examination at 10 years by April 2023, the time-point of study set-up. From the remaining 152 children with paraben measurements and follow-up visits at 4 and 10 years, 87 were excluded because of missing skin autofluorescence (SAF) measurements, and two more due to a non-European ancestry as a proxy of skin pigmentation, resulting in a final sample size of n = 83 (Supplementary Fig. S1). As the study end-points of SAF measurements and blood pressure were assessed at both time-points (4 years and 10 years) the number of observations used in this study was 166.

2.2. Data collection

At birth, medical information on newborns' sex, delivery date, and maternal parity from medical hospital records was retrieved. Parity was divided into three categories: mothers having their first, second, or third child or more. Additional information was obtained through a questionnaire during the mothers' stay at the delivery ward. The child's ethnicity was considered European when two or more grandparents of the newborn were European; otherwise, it was coded as non-European. From the online questionnaires at FU1 and FU2, household smoking was categorized with yes and no, depending on whether one or both parents were currently smoking. Maternal educational level was coded as "low" for mothers who did not obtain any diploma, "middle" when they obtained a high school diploma, and "high" when they obtained a college or university degree. The child's exact age at FU1 and FU2 was calculated as the difference between the numerical values of the date of FU participation and date of delivery and expressed with decimal precision as age in years. The child's height was measured by trained examiners with a fixed stadiometer with an accuracy of 0.5 cm and the weight with a digital scale to the nearest 0.1 kg. From the height and weight measurements, BMI z-scores were calculated according to the World Health Organization's (WHO) Child Growth Standards (World Health Organization (WHO), 2006), with the CRAN package zscorer (Myatt and Ernest Guevarra, 2019) taking into account the age and sex of the child.

2.3. Urinary paraben concentrations

During the FU examination, spot-urine samples were collected in metal-free polypropylene containers (Yvsolab, Turnhout, Belgium) and temporarily stored on ice until the end of the examination. Then the samples were aliquoted into metal-free 50 ml Falcon tubes (VWR, Haasrode, Belgium) and stored at −20 °C until further processing.

For the mass spectrometric analysis, the samples were thawed, aliquoted into 15 ml tubes, and shipped on dry ice to the Laboratory of Clinical, Forensic and Environmental Toxicology, University of Liege, Belgium, where they were processed according to a previously described protocol (Dewalque et al., 2014) (Supplementary Text 1), using a Quattro Premier XE mass spectrometer coupled to an Acquity UPLC system (Waters, Milford, MA, USA). The levels of quantitation (LOQ) were 0.79 μg/L for MeP, 0.30 μg/L for EtP, 0.36 μg/L for PrP and 1.00 for BuP. For further analysis, MeP, EtP and PrP exposure values below the LOQ were imputed via a truncated lognormal distribution using the R package "lnormimp" (Herbers et al., 2021). In detail, a truncated lognormal distribution was first fitted for the values above the LOQ, resulting in the mean and standard deviation of the lognormal

distribution. Random values between 0 and the LOQ were then imputed using the estimated lognormal distribution's mean and standard deviation. The paraben values were corrected for osmolality of the urine sample measured by freezing point determination with a Knauer Semi-Micro Osmometer (K-7400S).

2.4. Blood pressure measurements

BP was measured during the follow-up examinations at 4 and 10 years with an automated upper-arm blood pressure monitor (Omron 705IT; Omron Corporation, Gent, Belgium), with a specially accustomed cuff fitting the arm size of children. Measurements were performed in a standardized way, as described previously (Flynn et al., 2017). In detail, after resting 5 min in a supine position, a trained field worker obtained five consecutive readings of the systolic BP (SBP) and diastolic BP (DBP) at 1-min intervals, according to the guidelines of the European Society of Hypertension (Stergiou et al., 2021).

2.5. Advanced glycation end product measurement

AGE accumulation was estimated by skin autofluorescence (SAF) using the AGE Reader mu (Diagnoptics BV, Groningen, Netherlands). With this device, skin fluorescence, emitted by different AGEs, can be measured non-invasively as a proxy of dermal AGE levels, which makes it suitable as a biomarker in AGE-related conditions (Da Moura Semedo et al., 2017). During the FU examinations at ages 4 and 10, the child was seated, and the volar side of the forearm of the dominant limb was placed on the base of the device for measurement. Because body lotion and sunscreen were found previously to increase SAF significantly (Noordzij et al., 2011), we asked the participants about their use of these products in the days before the examination. If the participant indicated that sunscreen or body lotion had been applied earlier that day, the forearm was wiped off with alcohol prior to examination to at least partially remove the product. Whenever the forearm of the dominant limb showed dermatological diseases or normal skin variations such as birthmarks, the measurement was performed on the other forearm. The ratio of the intensity of the emitted light (420–600 nm) to the excitation intensity (300–420 nm) multiplied by 100 was calculated by the device and provided in arbitrary units (AU). To exclude unmeasured confounding due to differences in staff, location, and time-varying effects for FU1 and FU2, we transformed the SAF measurements into z-scores calculated separately for FU1 and FU2 and used the z-scores for further analyses.

2.6. Statistics

To explore the correlation structure between the two time points of AGEs measurement, Spearman Rank correlation coefficients between the FU1 and FU2 measurements of the same individual were calculated for the imputed and natural log-transformed values. A Wilcoxon Paired Test was performed to compare the medians at both time points.

For the statistical analysis of the associations between parabens and cardiovascular outcomes we applied different steps to investigate the combined and individual effects in a longitudinal setting. For both, the mixture models and the single pollutant models several *a priori* selected variables described in the literature to be associated with the outcomes were added as covariates to the models. For the models investigating the association of parabens with SAF z-scores, child's sex, age at FU examination, BMI z-score, parity, maternal education, current household smoking, the season of the examination and osmolality of the child's urine were considered. The models analyzing the relation with BP were additionally adjusted for the hour of the investigation, as BP follows a diurnal rhythm (Staessen et al., 1992).

Because in the follow-up at age 10 (FU2), 13 BP measurements were randomly missing, these values were imputed with the R package "mice" (Multivariate Imputation by Chained Equations) (van Buuren and Groothuis-Oudshoorn, 2011). Specifically, we generated 20 imputed datasets using the 2l.norm method in the mice package, which employs a two-level normal model to account for the clustered nature of repeated measurements within individuals (Audigier et al., 2017; van Buuren and Groothuis-Oudshoorn, 2011). Each of the 20 imputed datasets was then analyzed separately, and the results were combined using Rubin's rules (Rubin, 2004) to obtain pooled estimates and standard errors.

For the mixture analysis, we first applied quantile g-computation with the qgcomp package (Keil et al., 2020) to determine the combined effects of natural log transformed MeP, EtP, and PrP levels in association with SAF z-scores. Quantile g-computation estimates the effect of a simultaneous increase of all constituents of a mixture by one quantile while allowing for heterogeneity in the directions of the individual exposure-outcome associations (Keil et al., 2020). Each exposure is given a positive or negative weight. When both directions occur within a mixture-effect relation, the weights for each direction sum up to one and have to be interpreted as the proportion of the partial effect. This allows for relatively unbiased estimates also in smaller sample sizes (Keil et al., 2020). If all effects are linear and in the same direction, quantile g-computation is equivalent to weighted quantile sum (WQS) regression in large samples. To accommodate the longitudinal character of the study design, an extension to the qgcomp package was used as described previously by Welch et al. (2021). This method accounts for the clustering of repeated measures by participant, considering dependent effects over time within an individual via bootstrapping as proposed by Cheng et al. (2013).

The exposure-response relationship across quantiles of the paraben mixture was assumed to be linear and additive based on the Akaike information criteria (AIC) after applying a stepwise procedure to explore nonlinearity. For the quantile g-computation, we performed 500 bootstrap iterations with 2500 MC simulation iterations for each model to estimate the 95 % confidence intervals (CI).

Second, the individual effects of the different chemicals were evaluated with a single pollutant approach for comparability with other studies using mixed models with the participants as random effect variables. The restricted cubic spline (RCS) model in the R package "rcssci" (Nie, 2023) was further used to investigate possible non-linear relationships between urinary paraben concentrations and cardiovascular outcomes. The number of knots was chosen between 3 and 7 by minimizing the AIC. The collinearity of variables was examined by calculating the variance inflation factor with the R package *'car'* (Fox and Weisberg, 2019).

In a third step, we applied SEM in order to disentangle the associations between parabens, AGEs and BP separately for the different timepoints and especially explore the role of AGEs in the association between paraben exposure at 4 years and different BP measures at 10 years in a longitudinal design (Supplementary Fig. S2). SEM in this context offers the advantage of testing multiple dependent relationships and indirect effects within a single model, ensuring more accurate estimates by including multiple independent and dependent variables accounting for their interdependencies and reducing bias compared to separate regression analyses (Hayes, 2018). Furthermore, by using standardized estimates which are unitless and interpretable as changes in standard deviations of the outcome per standard deviation change in the predictor, a more intuitive comparability between the different paths is generated. In a first model we included all parabens to correct the associations for the effects of the respective other parabens, additionally we then explored the role of the individual parabens in the observed associations in SEM models with only one paraben at a time. The models furthermore included the AGEs and BP measurements at both time-points to correct for the effects of i) AGEs levels at 10 years, and ii) BP measurements at 4 years, in the association between AGEs levels at 4 years and BP at 10 years, and additionally the same covariate sets from the linear mixed models (child's sex, age at FU examination, BMI z-score, parity, maternal education, current household smoking, season and hour of examination and urinary osmolality). We fitted the models

with the lavaan R package (Rosseel, 2011) using the default maximum likelihood estimator and computed the bootstrap percentile confidence intervals with the "standardizedSolution_boot_ci()" function from the semhelpinghands package (Cheung S, 2023) with 1000 replications. Because SEM does not support multiple imputation within the modeling process, we performed multiple imputation using the "mice" function to create 20 imputed datasets. The imputed values were then combined using the "complete" function in mice to generate a single dataset for SEM analysis. In order to test the robustness of our results regarding the imputation of missing BP measurements, we performed complete-case analyses for the mixture and individual effects and for the SEM. Additionally we also performed the main SEM analysis for the statistically significant outcomes in the linear mixed models again with un-standardized estimates to allow comparability between both approaches. Statistical significance was defined as $p < 0.05$ in all analyses. Data analysis was performed in RStudio (RStudio Team, 2020) using R 4.1.2.

3. Results

3.1. Demographics

In this study there was a slightly lower number of girls than boys (42.2 %) (Table 1). The mean age at the first follow-up (FU1) was 4.6 (±0.4) years, and at FU2, 10.3 (±0.7) years. The mean BMI at FU1 was 16.2 (±1.5) and 18.8 (±3.3) kg/m^2 at FU2. Most mothers had achieved a higher education level (81.9 %), which did not change between FU1 and FU2, and gave birth to their first child (55.4 %). In 27.7 % of the children's households, at least one of the parents was smoking at the time of the FU1 examination and 21.7 % at the time of the FU2 examination (Table 1).

Table 1
Population characteristics of n = 83 participants for the first examination at age 4 and the second examination at age 10.

Characteristics	Mean (SD) or n (%)	
	4 years	10 years
Child		
Girls, n	35 (42.2 %)	/
Age, years	4.6 (±0.4)	10.3 (±0.7)
BMI, kg/m^2	16.2 (±1.5)	18.8 (±3.3)
AGEs, SAF AU[a]	1.2 (±0.2)	1.0 (±0.2)
Season Follow-Up, (warm)[b], n	36 (43.4 %)	40 (48.2 %)
Urinary osmolality, mOsm/kg	709.0 (±260.2)	/
Systolic blood pressure, mm/Hg[c]	98.5 (±7.4)	107.9 (±10.8)
Diastolic blood pressure, mm/Hg[c]	55.6 (±6.8)	66.1 (±7.0)
Mother		
Education level, n		
Low	3 (3.6 %)	3 (3.6 %)
Middle	12 (14.5 %)	12 (14.5 %)
High	68 (81.9 %)	68 (81.9 %)
Household smoking, n	23 (27.7 %)	18 (21.7 %)
Parity index child, n		
1	46 (55.4 %)	/
2	26 (31.3 %)	/
≥3	11 (13.3 %)	/

The numbers represent counts (percentages) for categorical and mean ± standard deviation (SD) for continuous variables. Skin autofluorescence values are reported as geometric mean with its geometric standard deviation. FU1 = follow-up examination at 4 years; FU2 = follow-up examination at 10 years.

[a] Advanced glycation end products measured by skin autofluorescence (SAF) and calculated as the ratio of skin fluorescence and reflectance given in arbitrary units (AU).

[b] Warm season = April 1st – September 30th.

[c] Average blood pressure at 10 years was calculated form measurements in 70 children.

3.2. Urinary paraben measurements

The geometric means and additional descriptive statistics of all 300 paraben measurements have been described previously (Reimann et al., 2023). For the 83 participants included in the longitudinal analysis, all BuP measurements were below the LOQ except for one. Therefore, only the values of MeP (100 % > LOQ), EtP (60 % > LOQ), and PrP (89 % > LOQ) were used for further statistical analysis. For the 83 participants in this study, the geometric means (geometric SD) before imputation and log-transformation were 30.86 (±4.75), 1.34 (±2.64), 6.21 (±3.40) μg/L for MeP, EtP, and PrP, respectively.

MeP was significantly correlated with EtP (Spearman rank r = 0.23) and PrP (Spearman rank r = 0.56) (Supplementary Figure S3 A). The paired samples of SAF z-score values for both time points were moderately correlated (r = 0.30, p = 0.0053) and the difference in median between both time points was not significant (Wilcoxon Signed Rank Test: p = 0.77) (Supplementary Figure S3 B).

3.3. Mixture effects of parabens on cardiovascular risk measures

A one-quantile increase in the mixture of natural log-transformed paraben values was associated with a 0.30-point decrease in the SAF z-score (p = 0.024). The association with AGEs was driven by PrP, which was assigned the largest negative weight in the mixture analysis (Table 2, Fig. 1). In the mixture models, none of the BP associations reached statistical significance, and individual parabens exhibited different directions of weights (Table 2 Fig. 2). These findings were consistent with those from the complete-case analysis (Supplementary Table S1).

3.4. Single pollutant effects of parabens on cardiovascular risk measures

Log transformed PrP values were inversely associated with AGEs in a linear mixed model, adjusted for the child's sex, age at FU examination, BMI z-score, urinary osmolality, parity, maternal education, current household smoking and season of the examination as fixed effects variables and participant as random effects variable (β −0.15, p = 7.2e-03) (Table 3). When stratified for both time-points we observed that the association was stronger at 4 years (β −0.29, p < 0.001) (Supplementary Table S2). The RCS model provided no evidence for a non-linear relationship between PrP and AGEs (p for non-linear = 0.29) when applying 3 knots which resulted in the lowest AIC. None of the other associations between individual parabens and BP measures was statistically significant. The complete-case analysis provided comparable results (Supplementary Table S3).

Table 2
Quantile g-computation estimates, 95 % confidence intervals, and p-value for the combined effect of a one-quantile increase in natural log-transformed paraben values (mixture of methyl, ethyl and propyl-paraben) measured at 4 years on changes in blood pressure measured at 4 and 10 years in a longitudinal setting. Obs = number of observations in the longitudinal design.

Cardiovascular outcome	Obs.	β	95 % CI	P
Advanced glycation end products[a]	166	−0.30	−0.55, −0.042	0.024*
Systolic plood pressure[b]	166	1.11	−1.21, 3.43	0.35
Diastolic blood pressure[b]	166	−0.33	−2.21, 1.56	0.73

Significance levels *< 0.05, **< 0.01 and ***<0.001 and ***<0.001.

[a] Adjusted for the child's sex, age at FU examination, BMI z-score, and urinary osmolality, maternal parity, education, current household smoking and season of the examination as fixed effect variables and participant as random effects variable.

[b] Adjusted as in [a] and additionally for hour of examination.

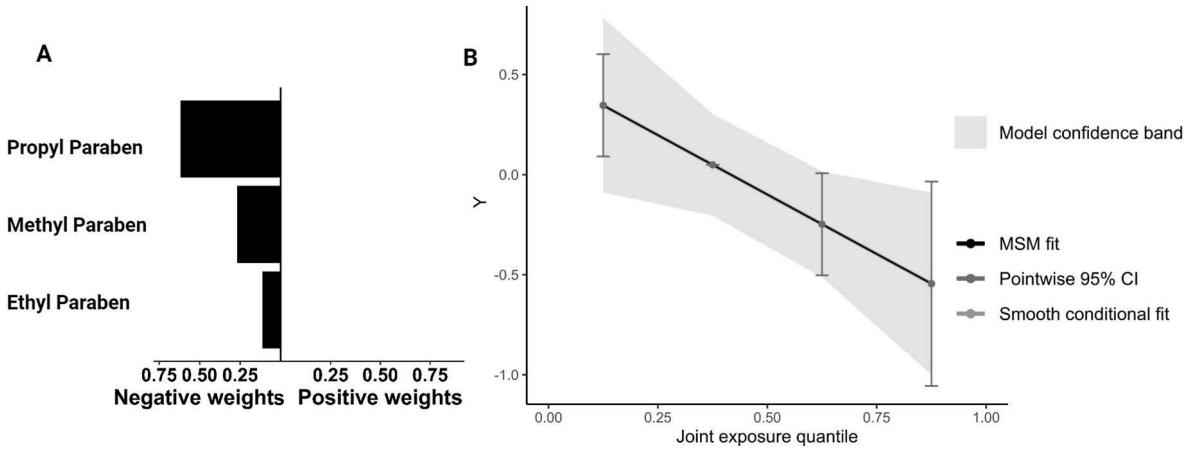

Fig. 1. **A** Butterfly plot of relative weights representing the effect proportion for the individual parabens in the mixture for the association with skin autofluorescence z-scores using quantile g-computation. The weights are considered fixed for the overall exposure effect and therefore do not have confidence intervals or p-values. **B** Box plot with smoothed line overlaying that represents a non-parametric fit of a model to the expected outcomes in the population at each quantile of the joint exposures. The quantile g-computation model is applied on a longitudinal data set with outcome measurements at 4 and 10 years, adjusted for the child's sex, age at follow-up examinations, BMI z-score, maternal parity, education, current household smoking, season of examination and osmolality of the child's urine as fixed effect variables and time point of measurement (child ID) as random effects variable.

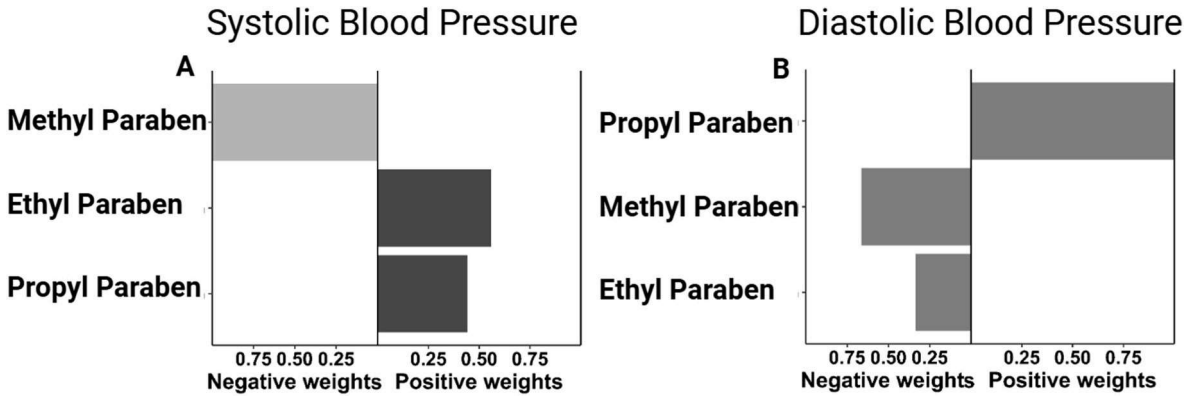

Fig. 2. Relative weights representing the effect proportion for the individual paraben in the mixture for the association with different measures of blood pressure using quantile g-computation. The weights are considered fixed for the overall exposure effect and therefore do not have confidence intervals or p-values. The models A and B, analyzing the mixture effect of parabens on respectively systolic and diastolic blood pressure were adjusted for the child's sex, age at follow-up examinations, BMI z-score, maternal parity, education, current household smoking, season and hour of examination and osmolality of the child's urine as fixed effect variables and time point of measurement (child ID) as random effects variable.

3.5. Time-specific associations between parabens, and repeated measures of AGEs and BP at ages 4 and 10 years

In the SEM models including the AGEs and BP measurements at 4 and 10 years and various covariates, the paraben mixture had a direct effect on SBP at 4 years (standardized estimate (est.std) = 0.50, 95 % Boot CI: 0.10, 0.82) and PrP alone on DBP at ages 4 and 10 combined (est.std = 0.55, 95 % Boot CI: 0.08, 0.92) (Supplementary Table S4). We observed a statistically significant indirect effect of parabens on DBP at 10 years and at 4 and 10 years combined via AGEs in the SEM model containing all parabens, showing an inverse direction (est.std = −0.21, 95 % Boot.CI: −0.41, −0.05 and est.std = −0.20, 95 % Boot.CI: −0.44, −0.03 respectively) (Supplementary Table S4). Because the direct effect was positive, the indirect effect via AGEs partially cancelled out the direct effect.

In the models containing only one paraben ester, we also found for PrP significant inverse indirect effects via AGEs on DBP at 10 years and at 4 and 10 years combined (est.std = −0.16, 95 % Boot.CI: −0.32, −0.04 and est.std = −0.15, 95 % Boot.CI: −0.33, −0.02 respectively) (Supplementary Table S4). When performing the complete-case analysis, standardized estimates and corresponding 95 % bootstrapped confidence intervals were comparable to those of the main analysis (Supplementary Table S5).

Furthermore, the association between AGEs measured at 4 years and at 10 years with DBP measured at 10 years was statistically significant (est.std = 0.34, 95 % Boot.CI: 0.10, 0.54 and est.std = 0.26, 95 % Boot. CI: 0.04, 0.51 respectively) (Supplementary Table S6).

In the additional SEM analysis for the statistically significant results in the linear mixed models, the unstandardized estimate for the association between PrP and AGEs at 4 years (β = −0.17, 95 % CI: −0.30, −0.02) (Supplementary Fig. S4) was comparable with the estimate in the linear mixed model.

4. Discussion

The primary discovery from our research highlights a link between paraben exposure and lower AGE levels in children in a longitudinal setting, driven by PrP.

4.1. Parabens and AGEs

The observed inverse association between parabens and AGEs has not been described in literature before. Other environmental exposures including cigarette smoke (Cerami et al., 1997; Nicholl and Bucala, 1998), air pollution (Gursinsky et al., 2006), and nickel (Lai et al.,

Table 3
Linear regression coefficients, 95 % confidence intervals and p value for the change in advanced glycation end products and blood pressure measured longitudinally at 4 and 10 years for a one-unit increase in the natural log-transformed values of the individual urinary parabens in linear mixed models adjusted for potential confounders (166 observations for all analyses).

	β	95 % CI	P
Advanced glycation end products[a]			
Methyl Paraben	−0.098	−0.21, 0.012	0.10
Ethyl Paraben	−0.013	−0.13, 0.10	0.83
Propyl Paraben	−0.15	−2.51, −0.049	0.0072**
Systolic blood pressure[b]			
Methyl Paraben	−0.41	−1.61, 0.80	0.50
Ethyl Paraben	0.63	−0.64, 1.91	0.33
Propyl Paraben	0.27	−0.89, 1.43	0.64
Diastolic blood pressure[b]			
Methyl Paraben	−0.21	−1.11, 0.70	0.65
Ethyl Paraben	−0.44	−1.44, 0.57	0.39
Propyl Paraben	0.47	−0.46, 1.41	0.31

Significance levels *< 0.05, **< 0.01 and ***<0.001.
[a] Adjusted for the child's sex, age at FU examination, BMI z-score, and urinary osmolality, parity, maternal education, current household smoking and season of the examination as fixed effects variables and participant as random effects variable.
[b] Adjusted as in [a] and additionally for hour of examination.

2020), but not benzene (Costa et al., 2016; Spatari et al., 2012), have been reported to increase AGEs in epidemiological and in *in vitro* studies. Oxidative stress may contribute to higher levels of AGEs in the skin due to both the body's natural aging and pathological processes (Q. Chen et al., 2022), which could be further exacerbated by parabens that have been reported to increase oxidative stress and reactive oxygen species (ROS) production in animal studies (Nagar et al., 2020; Shah and Verma, 2011), *in vitro* (Martín et al., 2010) and in epidemiological studies (Wei et al., 2022; Zhao et al., 2021). Conversely, we found an inverse association between the paraben mixture and PrP individually with skin AGEs. The underlying mechanism for the observed direction of association may be found in a lowering of endogenous glucose levels by parabens. Glucose levels were not available for the children in this study, but previously our group and others have demonstrated an inverse association between glucose levels and EtP (Reimann et al., 2021) in newborns, for PrP in pregnant women (Bellavia et al., 2019), and in the general U.S. public for different parabens including PrP (Ward et al., 2020). In addition, other compounds have been described to possess AGEs lowering properties, for example aminoguanidine derivatives, which inhibit the formation of AGEs by reacting with reactive carbonyl species (Hou et al., 1998). These compounds often possess functional groups capable of nucleophilic addition to carbonyl groups. Phenolic compounds such as polyphenols from natural sources have also been described to inhibit endogenous AGE formation through their antioxidant properties. These antioxidant properties stem from a hydroxyl group (-OH) attached directly to an aromatic ring (Kumar and Goel, 2019). Parabens also have a hydroxyl group, not attached directly to the aromatic ring, but to a carboxylic acid moiety via ester linkage (Palacios Colón et al., 2023). Despite the different position of the hydroxyl group, parabens may still exert antioxidant effects through other mechanisms, albeit different from those of phenolic compounds. However, their antioxidant properties generally have been described as less potent than those of true phenolic compounds (Velika and Kron, 2012).

When investigating potential indirect effects of parabens via AGEs in the longitudinal association with BP at 10 years by SEM, we observed that the lowering of AGEs also ameliorated the adverse direct effect of PrP on DBP measured six years later. The SEM with integration of both time-points of AGEs and BP measurements might represent a more realistic assessment of the longitudinal effects.

4.2. Parabens and BP

In the linear mixed models with repeated measures we did not observe a significant association between the combined or individual parabens and BP parameters. Parabens have previously been found to increase BP, but also studies reporting no significant, or inverse associations exist. In a cross-sectional study in 1405 individuals of the general Chinese population a 2.10-fold (95 % CI: 1.40, 3.00), 1.83-fold (95 % CI: 1.27, 2.62) and 1.84-fold (95 % CI: 1.27, 2.65) increased risk of hypertension was found by comparing the first exposure with the fourth quartile group participants using Bayesian kernel machine regression (BKMR) models (Zhang et al., 2023). Furthermore, in the same study, higher urinary EtP, PrP, and ∑PBs levels were found to increase the levels of systolic and diastolic BP (Zhang et al., 2023). A study in 73 Mexican women found the odds of hypertension to be 3.77 (95 % CI: 0.76, 18.62, $p < 0.10$) times higher for every IQR increase in PrP (Zamora et al., 2021), while a study performed with 9756 participants (31.1 % with high BP) from NHANES found no association between different parabens and hypertension (Shiue, 2014). Another study in 152 pregnant women from Spain, France and Norway found a decrease in systolic BP for increased levels of MeP ($\beta = -0.75$ mmHg; 95 % CI: −1.44, −0.07 per doubling of MeP concentrations), and decreases in systolic BP in association with higher concentrations of EtP in the second semester only (Warembourg et al., 2019). The only study to our knowledge investigating the effect of parabens on BP in children did not observe a statistically significant association between paraben concentrations in maternal pregnancy spot-urine samples and macrovascular health in 416 Spanish 11-year olds (Montazeri et al., 2022).

Interestingly, we did find statistically significant direct and total effects for the combined parabens and SBP in the cross-sectional assessment at 4 years using SEM, indicating adverse effects even when accounting for the inverse indirect effects via AGEs.

4.3. The role of AGEs in the association between parabens and BP

Applying SEM, we found evidence of an increased DBP at 10 years in the cross-sectional and longitudinal assessment with AGEs.

In literature, AGEs have been associated with increased arterial stiffness (Birukov et al., 2021; McNulty et al., 2007). As AGEs increase the expression and release of inflammatory cytokines and generation of ROS, via their interaction with the receptor for advanced glycation end products (RAGE), they potentially affect the structures of arterial walls or produce contraction of the arterial wall, both resulting in increased arterial stiffness and changes in cell function (Prasad and Mishra, 2017; Schmidt et al., 1999). Arterial stiffness increases systolic BP as shown in a study that found higher plasma levels of AGEs in untreated hypertensive patients than in normotensive subjects (7.84 ± 0.94 vs. 2.97 ± 0.94 μg/mL) (McNulty et al., 2007). For diastolic BP on the other hand, plasma levels of carboxymethyl-lysine, a marker of circulating AGEs, were inversely related to the diastolic pressure in a study of normotensive non-diabetic individuals (Sourris et al., 2014), and in type-1- diabetics circulating levels of two different plasma AGEs (Nε-(carboxymethyl)lysine and Nε-(carboxyethyl)lysine) were positively associated with systolic pressure but inversely associated with diastolic pressure (Schram et al., 2005). One possible explanation for the discrepancy between our finding of positive associations between AGEs and DBP instead of SBP could be that these studies assessed circulating plasma AGEs and not dermal AGEs assessed by skin autofluorescence. In a study comparing skin and plasma AGEs and their association with different cardio-metabolic outcomes, it was demonstrated that even though skin and plasma AGEs showed similar associations with gender and diabetes or prediabetes, they may reflect distinct underlying processes and hold different clinical significance, particularly in relation to arterial stiffness (Liu et al., 2017).

To summarize our finding: for the first time, we investigated the association between parabens, widely used biocides in personal care

products, and AGEs, biomarkers of cardiometabolic risk, and found a statistically significant inverse association for PrP. Furthermore, we confirmed with a SEM approach prior evidence of adverse effects of parabens and AGEs on BP. When decomposing the chronological sequence of direct effects, We observed that parabens showed a cross-sectional association with AGEs and BP, while AGEs predominantly influenced BP at a later time point in longitudinal analyses, in line with the understanding that AGEs exert adverse effects on the endothelium via long-term cross-linking of extracellular matrix proteins (Hegab et al., 2012).

Moreover, we observed inverse indirect effects of parabens via AGEs on DBP, driven primarily by PrP, which reduced the total effect and thus partially ameliorated their adverse impact on BP. In the analysis with SEM using unstandardized estimates we observed comparable results for the association between PrP and AGEs corroborating our results from the linear mixed model.

The associations we observed are based on snapshots of the child's life, allowing us to hypothesize about potential effects. These effects in early life might not only indicate negative impacts but also reflect compensatory mechanisms. The inverse indirect effect of the paraben mixture and PrP alone on DBP via AGEs needs further investigation by mechanistic studies, however it might indicate that by decreasing AGE levels the adverse effect of PrP on diastolic BP could be decreased.

We acknowledge particular strengths and limitations of our present study. We are the first to investigate the association between urinary paraben levels and AGEs, a cardiometabolic biomarker with prognostic significance (Hegab et al., 2012; Lamprea-Montealegre et al., 2022). We were also able to investigate the associations for repeated outcome measures of AGE levels at 4 and 10 years of age. This longitudinal design strengthens conclusions about the causal relationships found in the analyses. Furthermore, a strength of this study is the additional use of SEM to decompensate the direct and indirect effects for the different time points. This enabled us to assess the effects for each time point also separately and draw conclusions about the causal sequence of effects. Nevertheless, we also have to recognize potential limitations. The sample size was relatively small, which might have resulted in limited power and prevented associations from reaching statistical significance. Furthermore, the reported p-values were not adjusted for multiple testing. Even though we cleaned the skin of participants who used body lotion or sunscreen products before the examination with alcohol, this procedure does not completely ameliorate their influence on the SAF values (Noordzij et al., 2011). If participants who used paraben containing body lotion or sunscreen before the examination would be more likely to have higher paraben as well as higher SAF values the association might be biased. In this case the estimated association would be biased towards a stronger positive effect for children using these products before the examination. As we observed here an inverse effect between urinary PrP concentration and SAF levels there is no indication of a bias in our analysis. Another limitation is the fact that we did not have questionnaire information about certain lifestyle characteristics like the use of personal care products, nutrition and exercise which may influence AGEs and/or BP. Furthermore, we utilized spot-urine samples to evaluate the levels of parabens in urine. The fluctuation over time in the concentration of nonpersistent chemicals such as parabens might lead to misclassification of exposure and bias in exposure-response relationships (Casas et al., 2018). Nonetheless, the likelihood of measurement errors is potentially restricted, given the relatively high and consistent intraclass correlation coefficients reported for urinary parabens (with a median of 0.52) (Roggeman et al., 2022). This consistency is likely attributed to the gradual and consistent absorption of personal care products through the skin (Roggeman et al., 2022).

5. Conclusions

With this study we found inverse associations between urinary parabens and AGEs measured by skin-autofluorescence, which might indicate still unknown properties of parabens in decreasing the adverse impact of AGEs on cardiovascular health. While the association of PrP with AGEs and BP may suggest protective effects, these findings must be approached with caution as they represent only one potential mode of action of parabens. Considering the growing body of evidence in the literature regarding the adverse cardiometabolic effects of parabens, our results contribute to the understanding of the complex relationships underlying paraben exposure, cardiometabolic health, and associated molecular mechanisms, and offer a basis for future mechanistic studies.

CRediT authorship contribution statement

Brigitte Reimann: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis. **Hanne Sleurs:** Writing – review & editing, Investigation. **Rossella Alfano:** Writing – review & editing, Data curation. **Eleni Renaers:** Writing – review & editing, Investigation. **Hanne Croons:** Writing – review & editing, Investigation. **Thessa van Pee:** Writing – review & editing, Investigation. **Lore Verheyen:** Writing – review & editing, Investigation. **Nick Giesberts:** Writing – review & editing, Investigation. **Anna E. Soerensen:** Writing – review & editing, Investigation. **Catherine Pirard:** Writing – review & editing, Resources, Investigation. **Corinne Charlier:** Writing – review & editing, Resources, Investigation. **Tim S. Nawrot:** Writing – review & editing, Supervision, Funding acquisition, Project administration. **Michelle Plusquin:** Writing – review & editing, Supervision, Conceptualization.

Data sharing

The data used in this study are not publicly available because they contain information that could compromise research participant privacy but are available within General Data Protection Regulation restrictions from the corresponding author upon reasonable request.

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

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

Declaration of competing interest

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

Acknowledgments

The ENVIRONAGE birth cohort is supported by the Methusalem Fund of the Flemish Government, Belgium, the Research Foundation Flanders, Belgium (FWO, grant numbers 1516112N, G.0873.11.N.10, G026222N), the Horizon 2020 research and innovation programme, European Union, for the STOP project (Grant No. 774548H2020), and Kom op Tegen Kanker, Belgium.the Research Foundation Flanders, Belgium financially supported RA (FWO grant number 1296523N). MP has received funding from the Bijzonder Onderzoeksfonds (BOF) of Hasselt University, Belgium.

The authors are very grateful to the participating parents and children, as well as the staff of the maternity ward, midwives, and the staff of the clinical laboratory of East-Limburg Hospital in Genk.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2025.122229.

Data availability

Data will be made available on request.

References

Ana, F., Paula, F.A., 2016. Parabens paradoxes in cosmetic formulations: a review. Int J Med Res Pharm Sci 8, 3.

Audigier, V., White, I., Jolani, S., Debray, T., Quartagno, M., Carpenter, J., Buuren, S., Resche-Rigon, M., 2017. Multiple imputation for multilevel data with continuous and binary variables. Stat. Sci. 33. https://doi.org/10.1214/18-STS646.

Azeredo, D.B.C., de Sousa Anselmo, D., Soares, P., Graceli, J.B., Magliano, D.C., Miranda-Alves, L., 2023. Environmental endocrinology: Parabens hazardous effects on hypothalamic-pituitary-thyroid axis. Int. J. Mol. Sci. 24 (20). https://doi.org/10.3390/ijms242015246.

Bellavia, A., Chiu, Y.H., Brown, F.M., Minguez-Alarcon, L., Ford, J.B., Keller, M., Petrozza, J., Williams, P.L., Ye, X., Calafat, A.M., Hauser, R., James-Todd, T., 2019. Urinary concentrations of parabens mixture and pregnancy glucose levels among women from a fertility clinic. Environ. Res. 168, 389–396. https://doi.org/10.1016/j.envres.2018.10.009.

Birukov, A., Cuadrat, R., Polemiti, E., Eichelmann, F., Schulze, M.B., 2021. Advanced glycation end-products, measured as skin autofluorescence, associate with vascular stiffness in diabetic, pre-diabetic and normoglycemic individuals: a cross-sectional study. Cardiovasc. Diabetol. 20 (1), 110. https://doi.org/10.1186/s12933-021-01296-5.

Casas, M., Basagaña, X., Sakhi, A.K., Haug, L.S., Philippat, C., Granum, B., Manzano-Salgado, C.B., Brochot, C., Zeman, F., de Bont, J., Andrusaityte, S., Chatzi, L., Donaire-Gonzalez, D., Giorgis-Allemand, L., Gonzalez, J.R., Gracia-Lavedan, E., Grazuleviciene, R., Kampouri, M., Lyon-Caen, S., Vrijheid, M., 2018. Variability of urinary concentrations of non-persistent chemicals in pregnant women and school-aged children. Environ. Int. 121, 561–573. https://doi.org/10.1016/j.envint.2018.09.046.

Cerami, C., Founds, H., Nicholl, I., Mitsuhashi, T., Giordano, D., Vanpatten, S., Lee, A., Al-Abed, Y., Vlassara, H., Bucala, R., Cerami, A., 1997. Tobacco smoke is a source of toxic reactive glycation products. Proc. Natl. Acad. Sci. USA 94 (25), 13915–13920. https://doi.org/10.1073/pnas.94.25.13915.

Chen, C.Y., Zhang, J.Q., Li, L., Guo, M.M., He, Y.F., Dong, Y.M., Meng, H., Yi, F., 2022. Advanced glycation end products in the skin: molecular mechanisms, methods of measurement, and inhibitory pathways. Front. Med. 9, 837222. https://doi.org/10.3389/fmed.2022.837222.

Chen, Q., Huang, Q., Liu, W., Zhou, X., 2022. Advanced glycation end products via skin autofluorescence as a new biomarker for major adverse cardiovascular events: a meta-analysis of prospective studies. Nutr. Metabol. Cardiovasc. Dis. 32 (5), 1083–1092. https://doi.org/10.1016/j.numecd.2022.01.032.

Cheng, G., Yu, Z., Huang, J.Z., 2013. The cluster bootstrap consistency in generalized estimating equations. J. Multivariate Anal. 115, 33–47.

Cheung, S., 2023. semhelpinghands: Helper Functions for Structural Equation Modeling. R package version 0.1.9.10 sfcheung.github.io/semhelpinghands.

Commission Regulation (EU). No 1004/2014 of 18 September 2014 amending annex V to regulation (EC) no 1223/2009 of the European Parliament and of the council on cosmetic products, 5-8 282. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32014R1004.

Cook, N.R., Gillman, M.W., Rosner, B.A., Taylor, J.O., Hennekens, C.H., 1997. Prediction of young adult blood pressure from childhood blood pressure, height, and weight. J. Clin. Epidemiol. 50 (5), 571–579. https://doi.org/10.1016/S0895-4356(97)00046-2.

Costa, C., Ozcagli, E., Gangemi, S., Schembri, F., Giambò, F., Androutsopoulos, V., Tsatsakis, A., Fenga, C., 2016. Molecular biomarkers of oxidative stress and role of dietary factors in gasoline station attendants. Food Chem. Toxicol. 90, 30–35. https://doi.org/10.1016/j.fct.2016.01.017.

Da Moura Semedo, C., Webb, M., Waller, H., Khunti, K., Davies, M., 2017. Skin autofluorescence, a non-invasive marker of advanced glycation end products: clinical relevance and limitations. Postgrad. Med. J. 93 (1099), 289–294. https://doi.org/10.1136/postgradmedj-2016-134579.

Dewalque, L., Pirard, C., Dubois, N., Charlier, C., 2014. Simultaneous determination of some phthalate metabolites, parabens and benzophenone-3 in urine by ultra high pressure liquid chromatography tandem mass spectrometry. J. Chromatogr. B 949–950, 37–47. https://doi.org/10.1016/j.jchromb.2014.01.002.

Di Pietro, G., Forcucci, F., Chiarelli, F., 2023. Endocrine disruptor chemicals and children's health. Int. J. Mol. Sci. 24 (3). https://doi.org/10.3390/ijms24032671.

Elder, R., 1984. 3 final report on the safety assessment of methylparaben, ethylparaben, propylparaben, and butylparaben. J. Am. Coll. Toxicol. 3 (5), 147–209. https://doi.org/10.3109/10915818409021274.

Flynn, J.T., Kaelber, D.C., Baker-Smith, C.M., Blowey, D., Carroll, A.E., Daniels, S.R., de Ferranti, S.D., Dionne, J.M., Falkner, B., Flinn, S.K., Gidding, S.S., Goodwin, C., Leu, M.G., Powers, M.E., Rea, C., Samuels, J., Simasek, M., Thaker, V.V., Urbina, E.M., 2017. Clinical practice guideline for screening and management of high blood pressure in children and adolescents. Pediatrics 140 (3). https://doi.org/10.1542/peds.2017-1904.

Fox, J., Weisberg, S., 2019. An R Companion to Applied Regression/John Fox, McMaster University, Sanford Weisberg, University of Minnesota, third ed. SAGE Publications, Inc.

Gursinsky, T., Ruhs, S., Friess, U., Diabaté, S., Krug, H.F., Silber, R.E., Simm, A., 2006. Air pollution-associated fly ash particles induce fibrotic mechanisms in primary fibroblasts. Biol. Chem. 387 (10–11), 1411–1420. https://doi.org/10.1515/bc.2006.177.

Hayes, A.F., 2018. Introduction to Mediation, Moderation, and Conditional Process Analysis : a Regression-based Approach, second ed. Guilford press, New York (N.Y. http://lib.ugent.be/catalog/rug01:002386794

Hegab, Z., Gibbons, S., Neyses, L., Mamas, M.A., 2012. Role of advanced glycation end products in cardiovascular disease. World J. Cardiol. 4 (4), 90–102. https://doi.org/10.4330/wjc.v4.i4.90.

Heindel, J.J., Vandenberg, L.N., 2015. Developmental origins of health and disease: a paradigm for understanding disease cause and prevention. Curr. Opin. Pediatr. 27 (2), 248–253. https://doi.org/10.1097/mop.0000000000000191.

Herbers, J., Miller, R., Walther, A., Schindler, L., Schmidt, K., Gao, W., Rupprecht, F., 2021. How to deal with non-detectable and outlying values in biomarker research: best practices and recommendations for univariate imputation approaches. Compr. Psychoneuroendocrinol. 7, 100052. https://doi.org/10.1016/j.cpnec.2021.100052.

Hou, F.F., Boyce, J., Chertow, G.M., Kay, J., Owen Jr., W.F., 1998. Aminoguanidine inhibits advanced glycation end products formation on beta2-microglobulin. J. Am. Soc. Nephrol. 9 (2), 277–283. https://doi.org/10.1681/asn.V92277.

Janssen, B.G., Madlhoum, N., Gyselaers, W., Bijnens, E., Clemente, D.B., Cox, B., Hogervorst, J., Luyten, L., Martens, D.S., Peusens, M., Plusquin, M., Provost, E.B., Roels, H.A., Saenen, N.D., Tsamou, M., Vriens, A., Winckelmans, E., Vrijens, K., Nawrot, T.S., 2017. Cohort profile: the ENVIRonmental influence ON early AGEing (ENVIRONAGE): a birth cohort study. Int. J. Epidemiol. https://doi.org/10.1093/ije/dyw269.

Keil, A.P., Buckley, J.P., O'Brien, K.M., Ferguson, K.K., Zhao, S., White, A.J., 2020. A quantile-based g-Computation approach to addressing the effects of exposure mixtures. Environ. Health Perspect. 128 (4), 047004, 10.1289/EHP5838.

Kumar, N., Goel, N., 2019. Phenolic acids: natural versatile molecules with promising therapeutic applications. Biotechnol Rep (Amst) 24, e00370. https://doi.org/10.1016/j.btre.2019.e00370.

Lai, C.-H., Chou, C.-C., Chuang, H.-C., Lin, G.-J., Pan, C.-H., Chen, W.-L., 2020. Receptor for advanced glycation end products in relation to exposure to metal fumes and polycyclic aromatic hydrocarbon in shipyard welders. Ecotoxicol. Environ. Saf. 202, 110920. https://doi.org/10.1016/j.ecoenv.2020.110920.

Lamprea-Montealegre, J.A., Arnold, A.M., McCLelland, R.L., Mukamal, K.J., Djousse, L., Biggs, M.L., Siscovick, D.S., Tracy, R.P., Beisswenger, P.J., Psaty, B.M., Ix, J.H., Kizer, J.R., 2022. Plasma levels of advanced glycation endproducts and risk of cardiovascular events: findings from 2 prospective cohorts. J. Am. Heart Assoc. 11 (15), e024012. https://doi.org/10.1161/JAHA.121.024012.

Liang, J., Yang, X., Liu, Q.S., Sun, Z., Ren, Z., Wang, X., Zhang, Q., Ren, X., Liu, X., Zhou, Q., Jiang, G., 2022. Assessment of thyroid endocrine disruption effects of parabens using in vivo, in vitro, and in silico approaches. Environ. Sci. Technol. 56 (1), 460–469. https://doi.org/10.1021/acs.est.1c06562.

Liao, Y.-Y., Ma, Q., Chu, C., Wang, Y., Zheng, W.-L., Hu, J.-W., Yan, Y., Wang, K.-K., Yuan, Y., Chen, C., Mu, J.-J., 2020. The predictive value of repeated blood pressure measurements in childhood for cardiovascular risk in adults: the Hanzhong adolescent hypertension study. Hypertens. Res. 43 (9), 969–978. https://doi.org/10.1038/s41440-020-0480-7.

Liu, C.Y., Huang, Q.F., Cheng, Y.B., Guo, Q.H., Chen, Q., Li, Y., Wang, J.G., 2017. A comparative study on skin and plasma advanced glycation end products and their associations with arterial stiffness. Pulse 4 (4), 208–218. https://doi.org/10.1159/000453581.

Maillard, L., 1912. Action des acides amines sur les sucres : Formation des melanoidines par voie methodique.

Martín, J.M.P., Peropadre, A., Herrero, Ó., Freire, P.F., Labrador, V., Hazen, M.J., 2010. Oxidative DNA damage contributes to the toxic activity of propylparaben in mammalian cells. Mutat. Res. Genet. Toxicol. Environ. Mutagen 702 (1), 86–91.

McNulty, M., Mahmud, A., Feely, J., 2007. Advanced glycation end-products and arterial stiffness in hypertension. Am. J. Hypertens. 20 (3), 242–247. https://doi.org/10.1016/j.amjhyper.2006.08.009.

Miyata, T., Wada, Y., Cai, Z., Iida, Y., Horie, K., Yasuda, Y., Maeda, K., Kurokawa, K., van Ypersele de Strihou, C., 1997. Implication of an increased oxidative stress in the formation of advanced glycation end products in patients with end-stage renal failure. Kidney Int. 51 (4), 1170–1181. https://doi.org/10.1038/ki.1997.160.

Moldogazieva, N.T., Mokhosoev, I.M., Mel'nikova, T.I., Porozov, Y.B., Terentiev, A.A., 2019. Oxidative stress and advanced lipoxidation and glycation end products (ALEs and AGEs) in aging and age-related diseases. Oxid. Med. Cell. Longev. 2019, 3085756. https://doi.org/10.1155/2019/3085756.

Montazeri, P., Fossati, S., Warembourg, C., Casas, M., Clemente, D.B.P., Garcia-Esteban, R., Nawrot, T.S., Vrijheid, M., 2022. Prenatal exposure to phthalates and phenols and preclinical vascular health during early adolescence. Int. J. Hyg Environ. Health 240, 113909. https://doi.org/10.1016/j.ijheh.2021.113909.

Nagar, Y., Thakur, R.S., Parveen, T., Patel, D.K., Ram, K.R., Satish, A., 2020. Toxicity assessment of parabens in Caenorhabditis elegans. Chemosphere 246, 125730. https://doi.org/10.1016/j.chemosphere.2019.125730.

Nicholl, I.D., Bucala, R., 1998. Advanced glycation endproducts and cigarette smoking. Cell. Mol. Biol. (Noisy-Le-Grand) 44 (7), 1025–1033.
Nie, Z., 2023. rcssci: Visualization of Restricted Cubic Splines *[(accessed on April 05, 2024)]. Available online:*. https://cran.r-project.org/web/packages/rcssci/index.html.
Noordzij, M., Lefrandt, J., Graaff, R., Smit, A., 2011. Dermal factors influencing measurement of skin autofluorescence. Diabetes Technol. Therapeut. 13, 165–170. https://doi.org/10.1089/dia.2010.0123.
Nowak, K., Ratajczak-Wrona, W., Gorska, M., Jablonska, E., 2018. Parabens and their effects on the endocrine system. Mol. Cell. Endocrinol. 474, 238–251. https://doi.org/10.1016/j.mce.2018.03.014.
Nowotny, K., Jung, T., Höhn, A., Weber, D., Grune, T., 2015. Advanced glycation end products and oxidative stress in type 2 diabetes mellitus. Biomolecules 5 (1), 194–222. https://doi.org/10.3390/biom5010194.
Palacios Colón, L., Rascón, A.J., Ballesteros, E., 2023. Determination of parabens and phenolic compounds in dairy products through the use of a two-step continuous SPE system including an enhanced matrix removal sorbent in combination with UHPLC–MS/MS. Foods 12 (15), 2909. https://www.mdpi.com/2304-8158/12/15/2909.
Prasad, K., Mishra, M., 2017. Do advanced glycation end products and its receptor play a role in pathophysiology of hypertension? Int. J. Angiol. 26 (1), 1–11. https://doi.org/10.1055/s-0037-1598183.
Reimann, B., Sleurs, H., Dockx, Y., Rasking, L., De Boever, P., Pirard, C., Charlier, C., Nawrot, T.S., Plusquin, M., 2023. Exposure to endocrine disrupters and cardiometabolic health effects in preschool children: urinary parabens are associated with wider retinal venular vessels. Chemosphere 328, 138570. https://doi.org/10.1016/j.chemosphere.2023.138570.
Reimann, B., Vrijens, K., Roels, H.A., Wang, C., Cosemans, C., Van Overmeire, I., Nawrot, T.S., Plusquin, M., 2021. In utero exposure to parabens and early childhood BMI z-scores - associations between placental ethyl paraben, longitudinal BMI trajectories and cord blood metabolic biomarkers. Environ. Int. 157, 106845. https://doi.org/10.1016/j.envint.2021.106845, 106845.
Robinson, C.H., Chanchlani, R., 2022. High blood pressure in children and adolescents: current perspectives and strategies to improve future kidney and cardiovascular health. Kidney Int Rep 7 (5), 954–970. https://doi.org/10.1016/j.ekir.2022.02.018.
Robinson, O., Basagaña, X., Agier, L., de Castro, M., Hernandez-Ferrer, C., Gonzalez, J.R., Grimalt, J.O., Nieuwenhuijsen, M., Sunyer, J., Slama, R., Vrijheid, M., 2015. The pregnancy exposome: multiple environmental exposures in the INMA-sabadell birth cohort. Environ. Sci. Technol. 49 (17), 10632–10641. https://doi.org/10.1021/acs.est.5b01782.
Robles-Rivera, K., Rivera-Paredez, B., Quezada-Sanchéz, A.D., Velázquez-Cruz, R., Salmerón, J., 2023. Advanced glycation end products are associated with cardiovascular risk in the Mexican population. Nutr. Metabol. Cardiovasc. Dis. 33 (4), 826–834. https://doi.org/10.1016/j.numecd.2022.12.028.
Roggeman, M., Gys, C., Klimowska, A., Bastiaensen, M., Wielgomas, B., Ait Bamai, Y., Covaci, A., 2022. Reviewing the variability in urinary concentrations of non-persistent organic chemicals: evaluation across classes, sampling strategies and dilution corrections. Environ. Res. 215, 114332. https://doi.org/10.1016/j.envres.2022.114332.
Rosofsky, A., Janulewicz, P., Thayer, K.A., McClean, M., Wise, L.A., Calafat, A.M., Mikkelsen, E.M., Taylor, K.W., Hatch, E.E., 2017. Exposure to multiple chemicals in a cohort of reproductive-aged Danish women. Environ. Res. 154, 73–85. https://doi.org/10.1016/j.envres.2016.12.011.
Rosseel, Y., 2011. lavaan: an R package for structural equation modeling. J. Stat. Software 48. https://doi.org/10.18637/jss.v048.i02.
RStudio Team, 2020. RStudio. Integrated Development for R. RStudio, PBC, Boston, MA. http://www.rstudio.com/.
Rubin, D.B., 2004. Multiple Imputation for Nonresponse in Surveys, 2, 2004. Wiley-Interscience. 1. https://go.exlibris.link/XVFwMYgy.
Schmidt, A.M., Yan, S.D., Wautier, J.L., Stern, D., 1999. Activation of receptor for advanced glycation end products: a mechanism for chronic vascular dysfunction in diabetic vasculopathy and atherosclerosis. Circ. Res. 84 (5), 489–497. https://doi.org/10.1161/01.res.84.5.489.
Schram, M.T., Schalkwijk, C.G., Bootsma, A.H., Fuller, J.H., Chaturvedi, N., Stehouwer, C.D., 2005. Advanced glycation end products are associated with pulse pressure in type 1 diabetes: the EURODIAB prospective complications study. Hypertension 46 (1), 232–237. https://doi.org/10.1161/01.HYP.0000164574.60279.ba.
Shah, K.H., Verma, R.J., 2011. Butyl p-hydroxybenzoic acid induces oxidative stress in mice liver–an in vivo study. Acta Pol. Pharm. 68 (6), 875–879.
Shin, M.-Y., Choi, J.W., Lee, S., Kim, S., Kho, Y., Choi, K., Kim, S., 2023. Pharmacokinetics of transdermal methyl-, ethyl-, and propylparaben in humans following single dermal administration. Chemosphere 310, 136689. https://doi.org/10.1016/j.chemosphere.2022.136689.
Shiue, I., 2014. Higher urinary heavy metal, phthalate, and arsenic but not parabens concentrations in people with high blood pressure, U.S. NHANES, 2011-2012. Int. J. Environ. Res. Publ. Health 11 (6), 5989–5999. https://doi.org/10.3390/ijerph110605989.
Song, P., Zhang, Y., Yu, J., Zha, M., Zhu, Y., Rahimi, K., Rudan, I., 2019. Global prevalence of hypertension in children: a systematic review and meta-analysis. JAMA Pediatr. 173 (12), 1154–1163. https://doi.org/10.1001/jamapediatrics.2019.3310.
Sourris, K.C., Lyons, J.G., Dougherty, S.L., Chand, V., Straznicky, N.E., Schlaich, M.P., Grima, M.T., Cooper, M.E., Kingwell, B.A., de Courten, M.P., Forbes, J.M., de Courten, B., 2014. Plasma advanced glycation end products (AGEs) and NF-κB activity are independent determinants of diastolic and pulse pressure. Clin. Chem. Lab. Med. 52 (1), 129–138. https://doi.org/10.1515/cclm-2012-0850.
Spatari, G., Saitta, S., Cimino, F., Sapienza, D., Quattrocchi, P., Carrieri, M., Barbaro, M., Saija, A., Gangemi, S., 2012. Increased serum levels of advanced oxidation protein products and glycation end products in subjects exposed to low-dose benzene. Int. J. Hyg Environ. Health 215 (3), 389–392. https://doi.org/10.1016/j.ijheh.2011.11.001.
Staessen, J., Bulpitt, C.J., O'Brien, E., Cox, J., Fagard, R., Stanton, A., Thijs, L., Van Hulle, S., Vyncke, G., Amery, A., 1992. The diurnal blood pressure profile. A population study. Am. J. Hypertens. 5 (6 Pt 1), 386–392. https://doi.org/10.1093/ajh/5.6.386.
Stergiou, G.S., Palatini, P., Parati, G., O'Brien, E., Januszewicz, A., Lurbe, E., Persu, A., Mancia, G., Kreutz, R., 2021. 2021 European Society of hypertension practice guidelines for office and out-of-office blood pressure measurement. J. Hypertens. 39 (7), 1293–1302. https://doi.org/10.1097/hjh.0000000000002843.
Urbina, E.M., Khoury, P.R., Bazzano, L., Burns, T.L., Daniels, S., Dwyer, T., Hu, T., Jacobs Jr., D.R., Juonala, M., Prineas, R., Raitakari, O., Steinberger, J., Venn, A., Woo, J.G., Sinaiko, A., 2019. Relation of blood pressure in childhood to self-reported hypertension in adulthood. Hypertension 73 (6), 1224–1230. https://doi.org/10.1161/hypertensionaha.118.12334.
Uribarri, J., Woodruff, S., Goodman, S., Cai, W., Chen, X., Pyzik, R., Yong, A., Striker, G.E., Vlassara, H., 2010. Advanced glycation end products in foods and a practical guide to their reduction in the diet. J. Am. Diet. Assoc. 110 (6), 911–916.e912. https://doi.org/10.1016/j.jada.2010.03.018.
van Buuren, S., Groothuis-Oudshoorn, K., 2011. Mice: multivariate imputation by chained equations in R. J. Stat. Software 45 (3), 1–67. https://doi.org/10.18637/jss.v045.i03.
Velika, B., Kron, I., 2012. Antioxidant properties of benzoic acid derivatives against superoxide radical. Free Radic. Antioxid. 2 (4), 62–67. https://doi.org/10.5530/ax.2012.4.11.
Ward, J.B., Casagrande, S.S., Cowie, C.C., 2020. Urinary phenols and parabens and diabetes among US adults, NHANES 2005-2014. Nutr. Metabol. Cardiovasc. Dis. 30 (5), 768–776. https://doi.org/10.1016/j.numecd.2020.01.005.
Warembourg, C., Maitre, L., Tamayo-Uria, I., Fossati, S., Roumeliotaki, T., Aasvang, G.M., Andrusaityte, S., Casas, M., Cequier, E., Chatzi, L., Dedele, A., Gonzalez, J.-R., Gražulevičienė, R., Haug, L.S., Hernandez-Ferrer, C., Heude, B., Karachaliou, M., Krog, N.H., McEachan, R., Basagaña, X., 2019. Early-life environmental exposures and blood pressure in children. J. Am. Coll. Cardiol. 74 (10), 1317–1328. https://doi.org/10.1016/j.jacc.2019.06.069.
Wei, M., Wang, P., Wan, Y., Jiang, Y., Song, W., He, Z., Wang, Q., 2022. Urinary parabens and their derivatives associated with oxidative stress biomarkers in children from South and Central China: repeated measures. Sci. Total Environ. 817, 152639. https://doi.org/10.1016/j.scitotenv.2021.152639.
Welch, B.M., Keil, A.P., Bommarito, P.A., van T' Erve, T.J., Deterding, L.J., Williams, J.G., Lih, F.B., Cantonwine, D.E., McElrath, T.F., Ferguson, K.K., 2021. Longitudinal exposure to consumer product chemicals and changes in plasma oxylipins in pregnant women. Environ. Int. 157, 106787. https://doi.org/10.1016/j.envint.2021.106787.
Yin, T., Zhu, X., Cheang, I., Zhou, Y., Liao, S., Lu, X., Zhou, Y., Yao, W., Li, X., Zhang, H., 2021. Urinary phenols and parabens metabolites associated with cardiovascular disease among adults in the United States. Environ. Sci. Pollut. Res. Int. https://doi.org/10.1007/s11356-021-15589-5.
Zamora, A.N., Jansen, E.C., Tamayo-Ortiz, M., Goodrich, J.M., Sánchez, B.N., Watkins, D.J., Tamayo-Orozco, J.A., Téllez-Rojo, M.M., Mercado-García, A., Baylin, A., Meeker, J.D., Peterson, K.E., 2021. Exposure to Phenols, Phthalates, and Parabens and Development of Metabolic Syndrome Among Mexican Women in Midlife [Brief Research Report]. Front. Public Health 9. https://doi.org/10.3389/fpubh.2021.620769.
Zhang, X., Zhang, Y., Lu, H., Yu, F., Shi, X., Ma, B., Zhou, S., Wang, L., Lu, Q., 2023. Environmental exposure to paraben and its association with blood pressure: a cross-sectional study in China. Chemosphere 339, 139656. https://doi.org/10.1016/j.chemosphere.2023.139656.
Zhao, Y., Liu, Y., Chen, Y., Wu, X., Xiao, Q., Li, C., Li, M., Hu, W., Gu, H., Lu, S., 2021. Exposure to parabens and associations with oxidative stress in adults from South China. Sci. Total Environ. 774, 144917. https://doi.org/10.1016/j.scitotenv.2020.144917.
Mark Myatt and Ernest Guevarra (2019). zscorer: An Anthropometric z-score Calculator. R package version 0.3.1. URL https://nutriverse.io/zscorer/.