Environmental Research 296 (2026) 124068

Contents lists available at ScienceDirect

Environmental Research

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

Serum PCBs, OCPs, PBDEs and PCAs: Associations with metabolic syndrome risk factors in the Flemish Gut Flora Project cohort

Adam Cseresznye [a,b], Fatima den Ouden [a,c], Yu Ait Bamai [a,d], Liesa Engelen [a,c], Elias Maris [e,f], Ellen De Paepe [b], Giulia Poma [a], Muriel Derrien [f], Arnau Vich Vila [f], Sebastian Proost [f], Lindsey de Commer [f], Chloe Verspecht [f], Lindsay Devolder [f], Sara Vieira-Silva [f], Gwen Falony [f], Lieselot Y. Hemeryck [b], Shanshan Yin [a,g], Thomas J. McGrath [a,h], Roger Pero-Gascon [e,i], Alexander van Nuijs [a], Sarah De Saeger [e], Tim Nawrot [c], Lynn Vanhaecke [b], Jeroen Raes [f,*], Adrian Covaci [a,**]

[a] Toxicological Centre, Department of Pharmaceutical Sciences, University of Antwerp, Antwerpen, Belgium
[b] Laboratory of Integrative Metabolomics, Faculty of Veterinary Medicine, Ghent University, Ghent, Belgium
[c] Centre for Environmental Sciences, Hasselt University, Hasselt, Belgium
[d] Center for Environmental and Health Sciences, Hokkaido University, Sapporo, Japan
[e] Centre of Excellence in Mycotoxicology and Public Health, Faculty of Pharmaceutical Sciences, Ghent University, Ghent, Belgium
[f] Laboratory of Molecular Bacteriology, Department of Microbiology and Immunology, Rega Institute, Leuven, Belgium
[g] Department of Clinical Laboratory Technology, Shulan International Medical College, Zhejiang Shuren University, Hangzhou, China
[h] Institute of Health and Environment, Graduate School of Public Health, Seoul National University, Seoul, Republic of Korea
[i] Department of Chemical Engineering and Analytical Chemistry, Institute for Research on Nutrition and Food Safety (INSA-UB), University of Barcelona, Barcelona, Spain

ARTICLE INFO

Keywords:
metabolic syndrome
biomonitoring
exposomics
persistent organic pollutants
general population

ABSTRACT

Metabolic syndrome (MetS) is a complex, multifactorial disorder mainly linked to lifestyle factors. However, emerging evidence suggests that environmental exposures, such as persistent organic pollutants (POPs), may also contribute to its development. This study investigated serum POP levels and their associations with MetS and related cardiometabolic outcomes in Belgian adults.

The study included 403 adults from the Flemish Gut Flora Project (FGFP), a Belgian population-based cohort. Serum concentrations of polychlorinated biphenyls (PCBs), organochlorine pesticides (OCPs) and polybrominated diphenyl ethers (PBDEs) were measured using GC-ECNI/MS, while polychlorinated alkanes (PCAs) were quantified using LC/MS. MetS and its components (central obesity, hypertriglyceridemia, low HDL cholesterol, hypertension, impaired fasting glucose) were defined by the International Diabetes Federation criteria. The overall prevalence of MetS was 16.5 % (n = 23) for males and 8.0% (n = 21) for females.

Detection frequencies (DFs) were generally high: 13 of the 21 POPs, including PCBs and OCPs were present in 40% of the samples. In pooled serum extracts, DFs for PCAs were 44% for $\Sigma PCA(C_{10}\text{-}C_{13})$, 68% for $\Sigma PCA(C_{14}\text{-}C_{17})$ and 5% for $\Sigma PCA(C_{18}\text{-}C_{20})$. Multi-pollutant models revealed significant associations between POPs and several MetS indicators stratified by sex. Notably, females exhibited significantly increased odds of elevated blood pressure (OR: 2.29, FDR <0.05).

This study provides evidence of ongoing exposure to POPs in Belgium, linking these mixtures to cardiometabolic alterations. These findings emphasize a potential differential susceptibility in females and underscore the need for targeted public health considerations.

* Corresponding author.
** Corresponding author.
E-mail addresses: jeroen.raes@kuleuven.be (J. Raes), adrian.covaci@uantwerpen.be (A. Covaci).

https://doi.org/10.1016/j.envres.2026.124068
Received 21 June 2025; Received in revised form 16 February 2026; Accepted 18 February 2026
Available online 18 February 2026

1. Introduction

Metabolic syndrome (MetS) is a complex disorder characterized by a cluster of interrelated metabolic dysregulations, including central obesity, elevated blood pressure, dyslipidemia and dysglycemia, which occur simultaneously and thereby increase the risk of developing type 2 diabetes (T2D) and cardiovascular disease (Alberti et al., 2005). MetS is also commonly associated with a state of chronic low-grade inflammation (Devaraj et al., 2009; Reddy et al., 2019).

The rising prevalence of MetS is a trend that is widely recognized across various organizations and research groups globally (Jamali et al., 2024; Noubiap et al., 2022; O'Neill and O'Driscoll, 2015). According to estimates by the International Diabetes Federation (IDF), approximately 20% of adults in Western countries are affected by MetS (O'Neill and O'Driscoll, 2015). A recent meta-analysis of 28 million individuals reported that global MetS prevalence varies from 12.5% to 31.4% depending on the definition used (Noubiap et al., 2022). Regarding individual components, central obesity (45.1%) and raised blood pressure (42.6%) are the most prevalent risk factors globally, followed by low HDL cholesterol (40.2%) and hypertriglyceridemia (28.9%) (Noubiap et al., 2022). In Belgium, the Metabolic syndrome and Arteries REsearch (MARE) Consortium reported that the prevalence of MetS in 2015, as defined by the ATP III criteria, was approximately 20% regardless of sex (Scuteri et al., 2015).

Polychlorinated biphenyls (PCBs) and certain organochlorine pesticides (OCPs), such as hexachlorobenzene (HCB) and dichlorodiphenyltrichloroethane (DDT) were among the first substances listed under the Stockholm Convention on Persistent Organic Pollutants (POPs), due to their high toxicity and environmental persistence (Lallas, 2001). In a subsequent development, short-chain ($C_{10\text{-}13}$) polychlorinated alkenes (PCAs) with a chlorine content exceeding 48% by weight were also added to the list of POPs under Annex A in May 2017 (Guida et al., 2020). Despite being largely restricted or banned, PCBs and OCPs continue to be frequently detected in soil (Devendrapandi et al., 2024; Nigar et al., 2024; Pănescu et al., 2024), water bodies (Piscia et al., 2024; Polasko et al., 2024) and food (Becerra-Tomás et al., 2024; Larebeke et al., 2002; McGrath et al., 2021) as a result of their persistence, bioaccumulation and migratory properties. Dietary intake is an important route of human exposure, leading to elevated POP concentrations in serum and other biological compartments, which reflects the overall body burden (Aerts et al., 2019; Dirtu and Covaci, 2010; Roosens et al., 2010). Following ingestion, POPs accumulate in adipose tissue, leading to prolonged *in vivo* exposure (Mustieles et al., 2017).

A substantial body of evidence from both experimental and epidemiological studies links POPs and MetS (Gray et al., 2013; Ruzzin et al., 2010; Taylor et al., 2013). For instance, chronic exposure to a mixture of POPs commonly found in the food chain has been shown to induce insulin resistance and abdominal obesity in rats (Ruzzin et al., 2010). Furthermore, *in vitro* treatment of adipocytes with a POP mixture mimicking the relative abundance of organic contaminants found in crude salmon oil, inhibited insulin-dependent glucose uptake, highlighting a direct effect of POPs on insulin sensitivity (Ruzzin et al., 2010). Additionally, chronic exposure to the PCB mixture Aroclor 1254 has been found to exacerbate obesity-induced insulin resistance and hyperinsulinemia in mice, suggesting that PCBs may worsen the negative metabolic consequences of obesity (Gray et al., 2013). Several epidemiological studies have investigated the association between POPs and various components of MetS (Taylor et al., 2013). A comprehensive review of 72 epidemiological studies conducted by the National Toxicology Program (USA) in 2013 found consistent positive associations between several organochlorine POPs, such as *trans*-nonachlor (TN), dichlorodiphenyldichloroethylene (DDE) and dioxin-like PCBs and T2D (Taylor et al., 2013).

While numerous studies have reported levels of legacy POPs in various human matrices in Belgium, including serum (Covaci et al., 2006; Cseresznye et al., 2024; Malarvannan et al., 2018), breast milk (Aerts et al., 2019; Andjelkovic et al., 2024; Croes et al., 2012), adipose tissue (Pauwels et al., 2000) and hair (Król et al., 2013; Pauwels et al., 2000), the extent of human PCA exposure in the European context remains largely unknown. However, assessing human exposure to PCAs is particularly relevant due to their recent listing under the Stockholm Convention (Guida et al., 2020) and suspected potential metabolic effects. Characterization of PCA exposure in European populations remains limited, with data primarily available from Norway, Sweden and Czechia. (Tomasko et al., 2021; Xu et al., 2022; Yuan et al., 2024). The present study helps addressing this knowledge gap by providing the first measurements of PCAs in serum from a Belgian cohort. The relevance of these PCA measurements is underscored by previously identified potential exposure pathways, including dietary intake (McGrath et al., 2021) and household dust (McGrath et al., 2022a) in Belgium.

While individual POPs have been positively associated with components of MetS in global studies (Taylor et al., 2013), the health effects of exposure to complex POP mixtures are less understood, particularly within the Belgian population. Such mixtures are important to study as they may better reflect real-world environmental exposures. In addition, given established sex-specific differences in POP toxicokinetics, adipose tissue distribution and hormonal regulation of metabolism, examining potential differential susceptibilities between males and females is critical (Eti et al., 2022; Han et al., 2020; Warner et al., 2014).

Therefore, this study aimed to: (1) determine the serum concentrations of various classes of POPs, including PCBs, OCPs, PBDEs and PCAs, in Belgian adults recruited as part of the Flemish Gut Flora Project (FGFP), a population-based cross-sectional cohort in Flanders, and (2) examine sex-specific associations between POP serum concentrations and cardiometabolic parameters, as well as the individual components defining MetS (i.e., central obesity, hypertriglyceridemia, low HDL cholesterol, hypertension and impaired fasting glucose) and MetS itself.

2. Methods

2.1. Study population

All procedures and protocols described in this study were approved by the Ethics Committee Research of University Hospitals Leuven (Belgium) (study ID S60030) and aligned with the Declaration of Helsinki and Belgian privacy laws. Participants were recruited through repeated announcements in print, audiovisual and social media, as well as through the FGFP website (Falony et al., 2016). Registration required an informal consent based on a short description of the study protocol, followed by the completion of online questionnaires. All participants were over 18 years old, resided in Belgium at the time of recruitment and provided informed consent. For the present study, a subset of 403 participants was randomly selected from the biobank to undergo POP quantification, ensuring a representative sample of the larger cohort.

2.2. Outcome assessment

A comprehensive description of the outcome assessment is provided in the study by Falony et al. (Falony et al., 2016). In short, each participant completed a detailed medical questionnaire designed to obtain information regarding their medical history and current health status. Furthermore, general practitioners conducted anthropometric assessments measuring height, weight, abdominal and hip circumference and recorded blood pressure readings.

Participants were instructed to avoid calorie intake for 8 h prior to blood sample collection. Each blood sample consisted of a total volume of 20.5 mL, including one serum tube of 8 mL, two EDTA tubes of 4 mL, one fluoride tube of 2 mL and one PAXgene Blood RNA tube of 2.5 mL. Blood analyses were conducted at The Centrum voor Medische Analyse (Herentals, Belgium). A range of parameters was assessed including hematological, metabolic and inflammatory markers as well as lipid levels (Table SI-1).

Indicators of MetS variables were derived based on the IDF definition (Qiao and The DECODE Study Group, 2006), which provides a standardized framework for identifying individuals with MetS. Specifically, central obesity was defined as waist circumference ≥94 cm for males and ≥80 cm for females. Hypertriglyceridemia was defined as serum triglyceride (TG) levels ≥150 mg/dL or receipt of specific treatment for dyslipidemia. Low high-density lipoprotein (HDL) cholesterol was defined as HDL levels <40 mg/dL for males and <50 mg/dL for females or receipt of specific treatment for dyslipidemia. Hypertension was defined as systolic blood pressure ≥130 mmHg or diastolic blood pressure ≥85 mmHg or receipt of specific treatment for hypertension. Additionally, impaired fasting glucose was defined as fasting plasma glucose levels ≥100 mg/dL or previously diagnosed T2D. MetS was subsequently assigned to individuals who met the criteria for central obesity and any two of the four additional factors listed above, in accordance with the IDF definition. The assessment of medication usage, including lipid-lowering medications, antihypertensive medications and previous diagnosis of T2D, was based on self-reported information obtained from the study participants.

2.3. Exposure assessment

2.3.1. Sample preparation

Targeted analytes included 11 polychlorinated biphenyls (PCB 101, 99, 118, 153, 138, 187, 183, 156, 180, 170, 194), 6 polybrominated diphenyl ethers (PBDE 28, 47, 99, 100, 153, 154), and 3 organochlorine pesticides (p,p'-DDE, oxychlordane (OxC) and TN). Extraction of these compounds from serum was performed according to a validated protocol (Dirtu et al., 2013). Briefly, serum samples were spiked with internal standards (13C-HCB, PCB 143 and PBDE 103), followed by liquid-liquid extraction using n-hexane/dichloromethane/toluene (8:8:1, v/v). Sample clean-up was performed using acidified silica solid-phase extraction (SPE) cartridges. Detailed extraction procedures, including volumes and reagent specifications are provided in the Supplementary Information (Text SI-1).

The extraction of PCAs was conducted concurrently. Chlorinated paraffins were quantified as short-chain (C_{10} - C_{13}), medium-chain (C_{14} - C_{17}) and long-chain (C_{18} - C_{20}) based on chlorine-content calibration using technical mixtures (Yin et al., 2023). Given the anticipated low concentrations of PCAs in human serum, extracts were pooled in groups of ten to enhance the signal-to-noise ratio. The pooling sequence followed the extraction order without specific selection criteria. Samples were analyzed using an additional SPE clean-up step to minimize matrix effects. Full details on the PCA extraction and pooling strategy are available in Text SI-1.

2.3.2. Instrumental analysis

Target analysis of PCBs, PBDEs and OCPs in serum was performed using an Agilent 6890 Gas Chromatograph (GC) (Palo Alto, CA, USA) equipped with an Agilent J&W DB-5ms column (30 m, 0.25 mm I.D., 0.25 μm film thickness) and coupled to an Agilent 5973 Series Mass Selective Detector (MSD) operated in electron capture negative ionization (ECNI) mode with methane as reagent gas and helium as carrier gas (Ali et al., 2012). Standard calibration curves were included in each batch and comprised of five concentration levels. For PCBs, the calibration ranged from 16.8 to 1200 pg of analyte on the column, with the exception of PCB 105, which ranged from 4.2 to 300 pg. For OCPs and PBDEs, the calibration range was 25 to 5250 pg and 25 to 2000 pg, respectively. Calibration standards were injected at the end of each analytical sequence, following sample injections. The corresponding GC-ECNI/MS parameters are detailed in Table SI-2 and Text SI-1.

PCA analysis was performed using an Agilent 1290 Infinity II liquid chromatograph coupled to an Agilent 6560 quadrupole time-of-flight mass spectrometer (QTOF-MS) equipped with an electrospray ionization source operating in negative ionization mode, following a methodology previously described (McGrath et al., 2022a; Yin et al., 2023).

Quantification of PCAs was performed by chlorine-content-based calibration using technical mixtures of short-chain (SCCPs, $C_{10\text{-}13}$), medium-chain (MCCPs, $C_{14\text{-}17}$) and long-chain CPs (LCCPs, $C_{18\text{-}20}$). Response factors were calculated relative to the IS abundance in each sample. Calibration was established using normalized cumulative isotopomeric peak areas using ^{13}C-α-HBCD as the IS. Calibration standards were prepared at 2.5 ng/μL for each class, including the following chlorine content ranges: SCCPs: 51.5%, 53.5%, 55.5%, 59.3% and 63% Cl; MCCPs: 42%, 47%, 52%, 54.5% and 57% Cl and LCCPs: 36%, 39.3%, 42.5%, 45.8% and 49% Cl. The detailed methodology is available in the Supplementary Information (Text SI-1).

2.3.3. Quality assurance (QA) and quality control (QC)

For the analysis of serum PCBs, PBDEs and OCPs, internal QA and QC procedures were implemented, which included the routine analysis of procedural blanks and QCs provided by the Arctic Monitoring and Assessment Programme (AMAP) for persistent organic pollutants in human serum (AMAP, 2024). Each analytical batch of 20 samples included at least one procedural blank and one QC. Solvent blanks and QC samples were systematically injected throughout the instrumental runs to monitor analytical performance. Concentrations measured in procedural blanks were assessed to identify background contamination originating from the laboratory environment. These blank values were subtracted from the corresponding analyte concentrations in the samples. The limits of quantification (LOQs) were calculated as three times the standard deviation of the blank measurements (Table 1). Furthermore, the quality and accuracy of the analytical methods were ensured via participation in AMAP inter-laboratory comparison exercises for the determination of POPs in human serum (Table SI-3).

QA and QC procedures for the analysis of serum PCAs were implemented through the extraction and analysis of procedural blanks and horse serum (Sigma Aldrich) spiked with 100 μL 0.2 μg/mL individual CP technical mixtures (SCCP 55.5% Cl, MCCP 52% Cl and LCCP 49% Cl standards, LGC) (Table SI-3). This served as a QC, with a minimum of one QC included in each batch. Additionally, procedural blank concentrations were subtracted from the analyte concentrations in the samples to correct for any potential background contamination and to ensure accurate quantification of the targeted compounds. LOQs were determined according to the method described by McGrath et al. (McGrath et al., 2022b).

2.4. Statistical analysis

2.4.1. Data pre-processing

Analytes with concentrations below their corresponding LOQs were replaced with LOQ/2 (Aerts et al., 2019). Only POPs with DF ≥ 40% were included in subsequent statistical analysis. PCAs were excluded from statistical tests due to the pooling strategy used during sample preparation. To enhance analytical sensitivity, ten PCA extracts were combined to create composite samples. While this approach improved detection frequency, it prevented the use of individual sample concentrations of ΣPCA ($C_{10\text{-}13}$), ΣPCA ($C_{14\text{-}17}$) and ΣPCA ($C_{18\text{-}20}$) in subsequent statistical analysis. The normality of the concentration distributions in serum and cardiometabolic parameters was evaluated using multiple methods, including visual inspection of histograms, numerical assessment of skewness and kurtosis, and Shapiro-Wilk tests. The results indicated positively skewed distributions for all analytes, as well as triglyceride and insulin. Hence, the concentrations of POPs, triglyceride and insulin were natural log-transformed to approximate a normal distribution. The number of available observations (N) for each variable is reported in Table SI-1. Missing data for primary covariates (age, weight) were minimal (<5%) and were not imputed. Spearman's rank correlation coefficient was employed to assess the strength and direction of associations among continuous variables. For associations between continuous and dichotomous qualitative variables, Point-Biserial correlation analysis was applied. To assess sex-stratified differences among

Table 1
Exposure to environmental chemicals.

	Total							Stratified by sex			
	LOQ	DF%	Min	25%	50%	75%	Max	Median, male	Median, female	*p*-value	FDR
PBDE 100	6.6	16	3.3			<LOQ	248.4				
PBDE 153	14.0	12	7.0			<LOQ	66				
PBDE 154	8.9	16	4.4			<LOQ	34.6				
PBDE 28	4.3	1	2.2			<LOQ	8.8				
PBDE 47	4.0	14	2.0			<LOQ	69.5				
PBDE 99	7.5	9	3.8			<LOQ	133.1				
PCB 101	9.6	3	4.8			<LOQ	51.1				
PCB 118	48.6	58	24.3	<LOQ	54.6	70.8	197.1	54.0	55.0	0.995	0.995
PCB 138	5.7	100	6.1	42.6	74.8	150	965	90.0	68.6	**<0.05**	0.051
PCB 153	9.0	100	9.8	77	158.4	359.5	2569.5	215.5	146.2	**<0.01**	**<0.05**
PCB 156	1.2	99	0.6	3.8	7.1	14.6	80.9	9.0	6.5	**<0.01**	**<0.01**
PCB 170	6.0	98	3.0	29.6	61.4	140.7	878.6	85.1	53.2	**<0.01**	**<0.01**
PCB 180	8.6	99	4.3	56.6	124.7	295.2	2388.9	204.5	99.7	**<0.01**	**<0.01**
PCB 183	1.8	95	0.9	6	12.9	25.1	160.4	14.4	12.3	**<0.05**	0.051
PCB 187	3.2	97	1.6	14.8	32.2	74.2	588.9	43.5	27.0	**<0.01**	**<0.01**
PCB 194	2.2	83	1.1	3.2	6.7	13.9	93.5	10.3	5.7	**<0.01**	**<0.01**
PCB 99	13.3	7	6.6			<LOQ	72.6				
HCB	36.4	49	18.2		<LOQ	50.4	278.6	18.2	18.2	0.937	0.995
OxC	10.7	52	5.3	<LOQ	11.2	22.5	176.2	12.3	5.4	0.052	0.067
TN	1.8	93	0.9	4.7	9.1	16.2	163.9	11.8	7.6	**<0.01**	**<0.01**
p,p'-DDE	24.0	99	12.0	179.6	353.2	679.3	13656.1	369.9	343.4	0.325	0.385
ΣPCA(C_{10}-C_{13})	1.2	44	0.6		<LOQ	2.0	38.6				
ΣPCA(C_{14}-C_{17})	1.2	68	0.6	<LOQ	11.7	26.8	174.6				
ΣPCA(C_{18}-C_{20})	1.2	5	0.6			<LOQ	3.0				

Concentrations of PBDEs, PCBs and OCPs are expressed in pg/mL, while PCAs are in ng/mL. To compare levels of pollutants between males and females, Mann–Whitney *U* test was used. Only compounds with DF ≥40% were compared.

selected continuous variables, Mann-Whitney *U* test was employed, while qualitative variables were compared using the Chi-square test. All data processing and statistical analyses were conducted with Python 3.11 (Python Software Foundation), using the following packages: statsmodels (v0.14), SciPy (v1.8), pandas (v2.2), Matplotlib (v3.10) and seaborn (v0.13). A significance level of $p < 0.05$ and FDR-adjusted $p < 0.05$ was applied for all statistical tests.

2.4.2. Covariates

The *a priori* selection of covariates for model adjustment was informed through relevant literature (Reina-Pérez et al., 2023; Sergeev and Carpenter, 2011). The following variables were identified as potential covariates and were included in the analysis: age (in years) and weight (in kilograms). These covariates were considered relevant for adjustment in the single and multi-pollutant models. A Directed Acyclic Graph (DAG) illustrating the assumed causal relationships, including confounders and outcomes, is provided in Figure SI-3. Age was collected through an online questionnaire that assessed the background of the participants, self-reported general health, childhood and current life habits. Additionally, general practitioners measured the weight of the participants.

2.4.3. Single-pollutant models

Outcomes were analyzed at three levels: (1) continuous cardiometabolic biomarkers, (2) binary individual MetS components to assess clinically relevant disease endpoints and (3) the composite MetS diagnosis to assess clustering of risk factors. Each MetS component and cardiometabolic parameter was modeled as a separate outcome in independent regression models, without adjustment for other outcome variables to avoid over-adjustment (Figure SI-3). Associations were estimated using multivariable linear regression for continuous outcomes (triglycerides, glucose, insulin, total cholesterol, HDL, systolic blood pressure, diastolic blood pressure) and multivariable logistic regression for binary outcomes (central obesity, raised triglycerides, reduced HDL, raised blood pressure, raised glucose, MetS diagnosis). To account for physiological variations in serum lipid levels which influence the partitioning of lipophilic POPs, exposure metrics were selected based on the nature of the outcome variable. For non-lipid outcomes (e.g., abdominal circumference, blood pressure, glucose, insulin and composite MetS diagnosis), lipid-standardized concentrations (ng/g lipid) were used as the primary exposure metric.

Total serum lipid concentrations were calculated using the formula based on total cholesterol (TC) and triglyceride (TG) levels: $TL=2.27 \times TC + TG+62.3$ (mg/dL) (Phillips et al., 1989). Lipid-standardized POP concentrations were subsequently calculated by dividing the wet-weight concentration by the total lipid content. Conversely, for lipid-related outcomes (triglycerides, total cholesterol and HDL cholesterol), wet-weight concentrations (pg/mL) were retained to avoid the bias introduced by mathematical coupling (Schisterman et al., 2005). All models were adjusted for age and weight. Medication use and dietary intake were not included as a covariate in the primary analysis. For dietary adjustment, we included total fish consumption and total meat consumption as continuous covariates, calculated from calorie-adjusted portion sizes. However, sensitivity analyses performed for both continuous and binary outcomes confirmed that adjusting for medication use (specifically antihypertensive and dyslipidemia medications) and diet did not confound the observed associations (see Table SI-9). We also conducted sensitivity analyses excluding participants with raised fasting plasma glucose or diagnosed type 2 diabetes (N=38) to assess potential reverse causality bias.

Given established biological differences in POP toxicokinetics and metabolic regulation between sexes, all regression models were stratified by sex *a priori* to examine sex-specific associations. This stratification approach characterizes distinct metabolic responses in each sex rather than testing for statistical sex-by-pollutant interactions. The performance of these models was evaluated both with and without covariate adjustments. The assumptions of normality, independence and linearity were evaluated using a combination of statistical tests and informal diagnostic plots, including Q-Q plots, residuals versus fitted values plots, scale-location plots and influence plots. Potential outliers and influential data points were identified using Cook's distance (Cook's D), with samples exhibiting a Cook's D value exceeding 0.5 regarded as influential. To examine the robustness of the findings, regression models were fitted both with and without these influential outliers. As the exclusion of these points did not substantively alter the main associations, the final reported models included all participants. To address

multicollinearity, continuous variables were centered by subtracting their respective column-wise mean. Variance inflation factor was used to assess multicollinearity, with a threshold value of 5. To account for multiple comparisons, false discovery rate (FDR) correction was applied using the Benjamini-Hochberg (BH) procedure with a significance threshold set at $\alpha = 0.05$ for all statistical tests.

2.4.4. Multi-pollutant models

To estimate the cumulative effect of POPs on MetS outcomes, weighted quantile sum (WQS) regression models were employed. This approach is particularly useful for evaluating highly correlated exposures, as it addresses multicollinearity by constructing a weighted index in which the weights denote the relative contribution of each individual chemical. WQS regression has been applied in environmental epidemiology to assess the effects of chemical mixtures on MetS (Arrebola et al., 2019; Güil-Oumrait et al., 2024; Wen et al., 2024). The WQS index was generated by categorizing exposure concentrations into quartiles (q = 4) and employing 100 bootstrap samples (b = 100) for parameter estimation examining bidirectional associations through the assessment of both positive (pwqs) and negative (nwqs) indices. Consistent with the single-pollutant models, the WQS indices were constructed using lipid-standardized concentrations for non-lipid outcomes and wet-weight concentrations for lipid outcomes. The distributional assumptions for the outcome variables were specified as Gaussian for continuous outcomes and binomial for binary outcomes. Consistent with the single-pollutant models, continuous variables were centered prior to model fitting and covariates employed in single-pollutant models were incorporated into the WQS models. Following model convergence, empirical weights were calculated by averaging the ω_i values for each chemical. All data processing and analysis were conducted in R 4.4 (R Core Team) using the gWQS package (version 3.0.5). Statistical significance was evaluated using bootstrap-derived confidence intervals, generated from the distribution of regression coefficients. An FDR corrected *p*-value threshold of <0.05 was employed to determine statistical significance.

3. Results

3.1. Description of the study population

The study population included 403 individuals, consisting of 139 males and 262 females, with two participants excluded from the statistical analysis due to missing information regarding sex (Table SI-1). The majority of participants (n = 365, 91%) reported being born in Belgium, while a smaller proportion (n = 6, 1.4%) was born in the Netherlands. Additionally, eight participants (2.0%) were born in other countries. Information on the place of birth was missing for 21 individuals (5.2%).

Comparing demographic characteristics between sexes, the mean age of male participants was 49.3 years (STD = 13.9 years), compared to 42.8 years (STD = 12.2 years) for female participants. The average BMI values for males and females were 26.9 (STD = 13.2) and 25.1 (STD = 5.2), respectively. Regarding the prevalence of individual MetS factors, central obesity was present in 198 (49.4%) participants, 75 (18.7%) had elevated triglycerides, 72 (17.9%) had reduced HDL cholesterol, 98 (24.4%) had elevated blood pressure and 38 (9.5%) had elevated fasting plasma glucose. In accordance with the IDF criteria (requiring central obesity plus at least two of the other four listed factors), the overall prevalence of MetS was 16.5 % (n = 23) for males and 8.0% (n = 21) for females. When considering the number of MetS factors excluding central obesity, more than half of the participants (222, 55.3%) had none of the MetS factors. A smaller proportion of participants presented with one factor (109, 27.1%), while 11.0% (44) presented with two factors. A smaller proportion of participants (18, 4.5%) had three factors and 8 (2.0%) participants exhibited all four.

Based on self-reported medication use, a total of 58 participants (14.5%) reported current medication use. When screened against a predefined list of 76 relevant medications, comprising 18 lipid-lowering and 58 antihypertensive agents, 30 (7.5%) individuals reported taking medication for dyslipidemia and 16 (4.0%) for hypertension.

3.2. Serum POP levels

A total of 21 POPs including PCBs (n = 11), PBDEs (n = 6) and OCPs (n = 4) were quantified using a targeted analytical approach (Table 1). The detection frequencies of these analytes ranged from 1 (PBDE 28) to 100% (PCB 138 and PCB 153). Notably, 9 PCBs and 4 OCPs exhibited DF > 40%. The median concentrations of POPs (DF > 50%) ranged between 7.1 (PCB 156) and 353 pg/mL (*p,p'*-DDE). The Mann-Whitney *U* test revealed statistically significant sex-specific differences in the concentrations of most analytes, with male participants generally exhibiting higher median serum levels compared to females. Spearman correlation analysis showed positive correlations among most pollutants (Figure SI-1). The strongest correlations were noted among PCB congeners, with correlation coefficients ranging from 0.19 to 0.99 ($p < 0.05$). Regarding PCAs, short-chain PCAs (C_{10}-C_{13}) were detectable in 44% (n = 18), medium-chain PCAs (C_{14}-C_{17}) in 68% (n = 28), and long-chain PCAs (C_{18}-C_{20}) in 5% (n = 2) of the pooled composite sample extracts (Table 1). The median values for PCAs ranged between < LOQ (ΣPCA (C_{10}-C_{13}) and ΣPCA(C_{14}-C_{17})) to 11.7 ng/mL, with the maximum level contributed by medium-length PCAs at 175 ng/mL.

3.3. Associations between POP levels and MetS risk factors

3.3.1. Single pollutant models

Sex-stratified single-pollutant models, adjusted for age and body weight, identified multiple significant associations between serum POP concentrations and cardiometabolic parameters (Table SI-4, SI-5). Notably, in males, several PCB congeners, such as PCB 180 (β = -2.28; 95% CI: -3.64, -0.92; FDR <0.01) and TN (β = -2.29; 95% CI: -3.75, -0.83; FDR <0.05) were inversely associated with abdominal circumference. Additionally, PCBs demonstrated a negative association with insulin levels in males only. In contrast, OCPs, including HCB (β = 11.59; 95% CI: 4.59, 18.59; FDR <0.05) and TN (β = 7.80; 95% CI: 2.77, 12.84; FDR <0.05), were positively associated with total cholesterol concentrations in females, but not in males.

When evaluating the relationship between MetS indicators and serum POPs, some analytes showed associations that approached, but did not consistently achieve statistical significance after FDR correction (Table SI-6). Notably, OCPs such as HCB (OR = 2.85; 95% CI: 1.19, 6.82; $p < 0.05$) and *p,p'*-DDE (OR = 2.09; 95% CI: 1.18, 3.69; $p < 0.05$) were associated with increased odds of MetS assignment for females. However, these associations were only borderline significant following FDR correction (FDR = 0.120 for both).

3.3.2. Multi-pollutant models

The multi-pollutant analysis using WQS regression identified several significant associations between the POP mixture and various cardiometabolic parameters (Table SI-7). In females, the mixture was positively associated with triglyceride (β = 0.26; 95% CI: 0.12, 0.40; FDR <0.01) and total cholesterol levels (β = 17.72; 95% CI: 9.27, 26.16; FDR <0.01). Conversely, in males, while positive trends were observed for triglycerides (β = 0.17, $p = 0.037$) and total cholesterol (β = 12.47, $p = 0.010$), these associations did not remain statistically significant after FDR adjustment (FDR = 0.185 and FDR = 0.100, respectively).

Furthermore, among males, abdominal circumference (β = -2.90; 95% CI: -4.65, -1.16; FDR <0.01) and insulin levels (β = -0.33; 95% CI: -0.51, -0.15; FDR <0.01) exhibited significant negative associations with the POP mixture. In contrast, among females, systolic blood pressure (β = 1.27; 95% CI: 0.21, 2.75; FDR <0.01) was positively and significantly associated with the POP mixture. Based on the estimated chemical weights, OCPs, including TN, OxC as well as PCB 118, were identified as main contributors to these observed significant associations

(Figure SI-2).

Evaluating the relationship between serum POPs and MetS indicators using sex-stratified multi-pollutant models yielded different findings for males and females (Figure 1A and Table SI-8). Females exhibited a significant association between increased POP exposure and increased odds of elevated blood pressure (OR = 2.29; 95% CI: 1.32, 4.07; FDR <0.05). While females exhibited a borderline trend toward increased MetS risk (OR = 1.91; p = 0.086), this signal was attenuated after adjusting for multiple comparisons (FDR = 0.172). No significant association was found in males (OR = 1.78; FDR = 0.472). Consistent with the contributors identified in relation to cardiometabolic parameters, OCPs such as TN and *p,p'*-DDE, along with PCB 118 and PCB 194 were the most significant contributors within the evaluated mixture (Figure 1B).

4. Discussion

This study examined exposure to POPs, including PCBs, PBDEs, OCPs and PCAs in a Belgian population, exploring potential associations between these exposures and cardiometabolic parameters as well as markers of MetS. Our findings indicate continued exposure to POPs within the Belgian population, as evidenced by the detection frequency of several PCBs exceeding 90%. This study also presents, for the first time, the levels of PCAs in Belgium, using pooled serum extracts.

Our sex-stratified analyses also suggested differing phenotypic responses to POP exposure regarding certain cardiometabolic parameters between males and females. For instance, while an inverse association with insulin levels was observed in males (FDR <0.01), no significant association was found in females. Regarding MetS indicators, multi-pollutant models revealed that females exhibited greater susceptibility to raised blood pressure (FDR <0.01) in association with exposure to PCBs and OCPs. This contrasts with males, where comparable associations did not achieve statistical significance, thus further highlighting sex-divergent patterns in metabolic response.

4.1. Serum levels of PCBs, OCPs and PCAs in a Belgian population

In comparison to recent European studies reporting non-lipid-standardized POP concentrations, the median PCBs and OCP levels measured in our study (ΣPCBs = 533 pg/mL, ΣOCPs = 374 pg/mL) generally fell within the range of previously reported values (Cseresznye et al., 2024; Junqué et al., 2020; Pineda et al., 2024; Porta et al., 2021; Simeone et al., 2022). Regarding PCBs, concentrations in the FGFP cohort were lower than those reported in some regions, such as Slovakia (ΣPCBs = 1820 pg/mL, 2002-2004 recruitment period) and Spain (ΣPCBs = 1000 pg/mL, 2006 and 2016 recruitment) (Porta et al., 2021; Simeone et al., 2022). In contrast, levels in this current study were higher than those from Sweden (ΣPCBs = 118 pg/mL, 2016-2017 recruitment period) and Spain (ΣPCBs = 195 pg/mL, 2016-2017 recruitment period) (Junqué et al., 2020; Pineda et al., 2024). The variation in PCB levels between these two Spanish studies may reflect differences in their cohort characteristics. The study reporting lower PCBs (Pineda et al., 2024) comprised of younger participants (mean age 34 years) with a lower mean BMI (25 kg/m^2) compared to the cohort with higher PCB levels (Porta et al., 2021) (mean age ~50 years, mean BMI ~26 kg/m^2), factors known to influence POP concentrations. However, the elevated levels in our cohort compared to the Swedish and Spanish populations likely reflects the historical industrial density of the Flanders region (Croes et al., 2014) and underscores the necessity for region-specific biomonitoring.

Notably, a study comparing POP levels in occupationally exposed e-waste recycling workers and non-industrial controls in six European

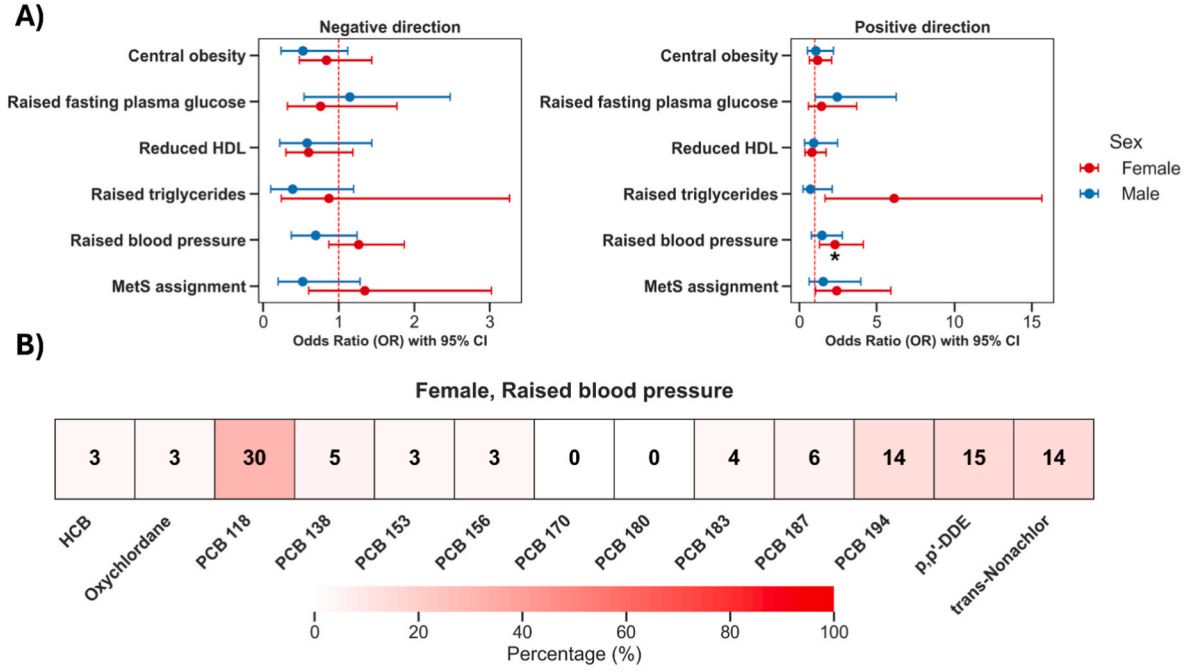

Figure 1. WQS analysis assessing the association between the combined effects of blood POP concentrations on indicators of MetS. (A) Forest plots displaying Odds Ratios (ORs) with 95% confidence intervals from WQS regression models. These models assess the association between the serum POP mixture and indicators of MetS, examining overall mixture effects in both the negative (left panel) and positive (right panel) directions. The ORs represent the estimated effect on MetS indicators for a one-unit increase in the WQS index. The models are adjusted for age and weight, both of which were centered prior to model fitting, in addition to the pollutants. Analyses are based on lipid-standardized POP concentrations (ng/g lipid), with the exception of lipid outcomes (raised triglyceride and reduced HDL) where wet-weight concentrations (pg/mL) were applied. The corresponding data can be found in Table SI-8. Red points indicate females, blue points indicate males. (B) Estimated chemical weights (%) for the multi-pollutant regression analysis between serum POP levels and indicators of MetS where associations reached statistical significance (FDR-adjusted p-value <0.05). The p-values were adjusted for multiple comparisons using the FDR procedure. Statistical significance was determined at an FDR-adjusted p-value <0.05.*: p< 0.05, **: p< 0.01.

countries found lower levels in non-industrial controls (ΣPCBs = 195 pg/mL) compared to our study (Cseresznye et al., 2024). This may indicate a temporal decline in POP concentrations, as the previous study was conducted in 2021, whereas our sampling rounds took place in 2014. Similarly, for OCPs, the levels in this study were generally lower than the median levels reported in Germany (ΣOCPs = 550 pg/mL, recruitment in 2016) and France (ΣOCPs = 429 pg/mL, 1994-1999 recruitment period) (Deering et al., 2020; Frenoy et al., 2024; Jang et al., 2022).

To our knowledge, this study is the first to report levels of PCAs in human serum in Belgium. PCAs are of particular interest due to emerging evidence linking them to metabolic disruptions, in e.g. lipid metabolism and thyroid function, which may contribute to T2D and gestational diabetes (Cheng et al., 2024; Hallgren and Darnerud, 2002; Yang et al., 2024; Zhang et al., 2024). For instance, a nested case-control study in Eastern China has shown that exposure to both PCA(C_{10}-C_{13}) and PCA(C_{14}-C_{17}) can disrupt maternal glucose homeostasis (Yang et al., 2024). PCA(C_{10}-C_{13}) exposure has been positively associated with levels of total cholesterol, low-density lipoprotein-cholesterol, total lipids and increased risk of T2D (Zhang et al., 2024). However, due to the pooling of serum extracts for PCA analysis to enhance detection sensitivity, we were unable to statistically evaluate the relationship between serum PCAs and cardiometabolic parameters within the FGFP cohort based on individual-level exposure data. Nevertheless, exploratory correlations between pooled PCA concentrations and averaged metabolic parameters showed no significant associations (Table SI-10). However, these pool-level analyses have limited statistical power and should be interpreted with caution.

Despite this limitation, characterizing exposure levels is important, since data on PCA levels in European populations remain limited. Although recent studies have reported concentrations in human serum in Norway (Xu et al., 2022) (sum ΣPCA(C_{10}-C_{13}) 0.14 μg/L wet weight, sum ΣPCA(C_{14}-C_{17}) 0.36 μg/L wet weight), Sweden (Yuan et al., 2024) (median ΣPCA(C_{10}-C_{13}) 785 ng/g lipid weight, median ΣPCA(C_{14}-C_{17}) 519 ng/g lipid weight) and Czechia (Tomasko et al., 2021) (median ΣPCA(C_{10}-C_{13}) 370 ng/g lipid weight, median ΣPCA(C_{14}-C_{17}) 360 ng/g lipid weight). However, direct comparison of absolute concentrations between these studies and ours is challenging due to differences in reporting units.

Nevertheless, when comparing our findings to regions with typically higher exposures, such as China, the median ΣPCA(C_{10}-C_{13}) and ΣPCA (C_{14}-C_{17}) values observed in the Belgian population were lower (Aamir et al., 2019; Liu et al., 2020; Yang et al., 2024; Zhou et al., 2019). This difference is likely attributable to China's status as the world's largest producer and consumer of PCAs (Aamir et al., 2019). Specifically, the median ΣPCA(C_{10}-C_{13}) concentration in the current study was below the LOQ, while the median ΣPCA(C_{14}-C_{17}) concentration was 11.7 ng/mL. In contrast, studies in China reported median short-chain ΣPCA concentrations ranging from 1.73 to 127 ng/mL and median medium-chain ΣPCA concentrations ranging from 1.59 to 114 ng/mL (Yang et al., 2024; Zhou et al., 2019).

4.2. Serum POP concentrations linked to increased lipids and blood pressure

Our study explored POP associations with health outcomes using sex-stratified analyses. We observed a higher baseline prevalence of MetS in males (16.5%) compared to females (8.0%) in our FGFP cohort. This difference may be attributable to males being older (mean age 49.3 and 42.8 years) and having a higher mean BMI (26.9 and 25.1 kg/m^2), both of which are established MetS risk factors (Alberti et al., 2005). While our sex-stratified analysis identifies associations specific to each group, it does not statistically evaluate whether the effect estimates differ significantly between males and females as we did not formally test for sex-by-pollutant interactions. Differences in observed significance could, in part, be influenced by varying statistical power between the groups due to sample size.

Nevertheless, our multi-pollutant model analysis identified a positive association between serum POPs and elevated levels of triglycerides as well as total cholesterol in females (FDR <0.01 for both) with OCPs playing a significant role among the measured pollutants. While similar positive trends were observed in males for triglycerides ($p = 0.037$, FDR = 0.185) and total cholesterol ($p = 0.010$, FDR = 0.100), these associations did not maintain statistical significance after FDR adjustment.

These findings align with multiple studies indicating a potential positive association between POP exposure and elevated triglycerides as well as cholesterol levels (Al-Othman et al., 2014, 2015; Aminian et al., 2020; Mohd Efendy Goon et al., 2024). For example, a 2024 meta-analysis of epidemiological studies on MetS risk factors reported a weak association between PCB exposure and hypertriglyceridemia (OR = 1.6, 95% CI 0.9-2.6) (Mohd Efendy Goon et al., 2024). Similarly, research conducted in Iran and Saudi Arabia demonstrated that even at concentrations considered within the normal range, PCB exposure was associated with elevated triglyceride levels, after adjusting for covariates such as age, sex and diet (Al-Othman et al., 2014, 2015; Aminian et al., 2020). Moreover, exposure to HCH and *p,p'*-DDE has been shown to disrupt lipid metabolism and glucose homeostasis, thereby contributing to an increased risk of cardiometabolic disorders (Al-Othman et al., 2014, 2015). As for total cholesterol, one study found that higher levels of β-HCH and *p,p'*-DDE in adipose tissue were associated with increased expression of hepatic cholesterol transporters ABCG5 and G8, potentially resulting in enhanced hepatic secretion of cholesterol into gallbladder bile (Ji et al., 2016).

Our findings also indicated that exposure to POP mixture was associated with elevated systolic blood pressure (FDR <0.01) and a trend towards elevated diastolic blood pressure (FDR = 0.186) among females, with OCPs and dioxin-like PCBs shown to be the most significant contributors within the evaluated mixture. These observations were further supported by increased odds ratios for elevated blood pressure in females, a key component of MetS. Epidemiological studies have consistently reported significant associations between exposure to POPs and elevated blood pressure (Arrebola et al., 2015; Donat-Vargas et al., 2018; Park et al., 2016; Pavuk et al., 2019). Moreover, research has demonstrated that POPs are implicated in atherosclerosis and contribute to endothelial cell dysfunction. These findings align with data from other European cohorts, including the Swedish PIVUS and VIP studies (Donat-Vargas et al., 2018; Lee et al., 2011), as well as research from Spain reporting associations between PCB exposure and metabolic syndrome components (Arrebola et al., 2015). Similarly, a study examining residents near a former PCB production plant in Alabama concluded that multiple pathways, including those related to the estrogenic and thyroid-disrupting effects of dioxin-like PCBs, may contribute to the development of hypertension (Pavuk et al., 2019).

4.2. Sex-stratified associations between POPs and anthropometric measures

Our sex-stratified single and multi-pollutant models indicated differences in the strengths of associations between males and females, particularly concerning the metabolic impacts of POPs. With respect to anthropometric measures, both single and multi-pollutant models demonstrated a negative association between non-dioxin-like PCBs and abdominal circumference in males (FDR <0.05), while females only showed a similar inverse trend that did not reach statistical significance. The interpretation of the negative association, particularly in males may involve several factors. One plausible consideration is the dilution effect, given the lipophilic nature of PCBs, which are preferentially stored in subcutaneous adipose tissue (Dirinck et al., 2011). Consequently, in individuals with greater adiposity, lower serum PCB concentrations might reflect these distribution dynamics rather than a direct protective effect (Dirinck et al., 2011). This interpretation is supported by Dirinck et al., who found a significant inverse relationship between serum levels of PCB 153, 180 and 170, as well as the sum of PCBs ($\rho = -0.228$, $p <$ 0.01) and waist circumference in a cohort of obese and lean adult men

and women (Dirinck et al., 2011).

In contrast to these inverse associations with PCBs, other research has reported positive associations between OCPs and markers of visceral obesity (Lee et al., 2007). For example, one study analyzing data from the National Health and Nutrition Examination Survey (NHANES, USA) found that some OCPs (e.g. OxC, TN, *p,p'*-DDE and β-HCH) were positively associated with four out of five MetS components, including presence of central obesity (Lee et al., 2007). These findings suggest that different POP classes may exert distinct effects on central obesity, which should be considered in risk assessments.

4.3. Sex-stratified effects of POP mixtures on insulin regulation

Our sex-stratified analyses also highlighted differing associations between POP mixture exposure and insulin levels for males and females. In males, insulin levels showed a negative association with POP exposure (FDR <0.01), where PCBs were identified as the primary contributors within the assessed mixture. Conversely, no significant association between POP exposure and insulin levels was observed in females.

The observation of such sex-related differences in response to POP exposure is consistent with previous studies, although the direct effects are not yet well understood. For instance, a recent study comparing the effect of PCB 126 on aryl hydrocarbon receptor knockout (AhR-KO) and wild-type (WT) male and female Holtzman Sprague Dawley rats found that following PCB 126 exposure, the expression of genes encoding enzymes related to xenobiotic metabolism, gluconeogenesis, glycogenolysis and fatty acid oxidation were unaffected in the AhR-KO rats, as opposed to WT rats (Eti et al., 2022). Interestingly, while several genes were affected in both sexes, the gluconeogenesis and glucose transporter genes Pck1, Glut2, Sds and Crem were only affected in male WT-PCB rats, suggesting that males are more susceptible to perturbed glucose homeostasis. Conversely, alterations related to fatty acid and lipid homeostasis, such as changes in the peroxisome proliferator-activated receptor alpha (PPARα) expression and serum cholesterol, were more prominent in females.

Consistent with these toxicological findings, a case-control study conducted in Shandong Province, China involving 158 participants between the ages of 20 and 79 years showed that POPs had stronger associations with diabetes in males than in females after adjusting for age, sex, BMI, triglycerides and total cholesterol (Han et al., 2020). The same phenomenon was noted in younger populations as well. The CHAMACOS Study, a longitudinal birth cohort conducted in California, found that prenatal exposure to DDT and DDE was associated with several measures of obesity in 9-year-old boys but not in girls (Warner et al., 2014). The potential mechanisms explaining the male-specific reduction in insulin levels observed here could include endocrine disruption leading to impaired insulin secretion, possible cytotoxicity towards beta-cells and downregulation of insulin-responsive genes involved in lipid homeostasis (Ruzzin et al., 2010; Tyagi et al., 2021).

4.4. Molecular pathways linking POP exposure to MetS

The mechanisms by which POPs affect MetS are complex and may vary depending on their chemical structure and interactions with various molecular targets (Kim et al., 2019; Taylor et al., 2013). In general, it is assumed that dioxin-like PCBs exert their effects through the activation of the AhR (Safe et al., 1985), which in turn has been shown to trigger a cascade of events that may contribute to the development of MetS. Specifically, AhR activation has been linked to impaired glucose uptake in insulin-sensitive tissues, which can lead to insulin resistance and hyperglycemia (Kim et al., 2019). Furthermore, the upregulation of CD36 and fatty acid-binding protein 1 (FABP1) in response to AhR activation can increase the uptake of non-esterified fatty acids, leading to the development of hepatic steatosis (Boucher et al., 2015; Wahlang et al., 2014). Additionally, the downregulation of PPARα and its target genes in the liver can result in decreased fatty acid oxidation and increased lipid accumulation, further exacerbating insulin resistance (Shan et al., 2020). AhR activation can also promote the formation of lipid droplets, potentially disrupting insulin signaling (Kim et al., 2019). On the other hand, non-dioxin-like PCBs primarily act as ligands for other nuclear receptors, such as PXR and CAR (Shan et al., 2020). These receptors play roles in regulating lipid and glucose metabolism and their dysregulation by non-dioxin-like PCBs can contribute to lipid accumulation and insulin resistance (Xiao et al., 2010; Xu et al., 2018). Overall, there is substantial evidence that POPs can disrupt metabolic processes through multiple pathways, contributing to an increased risk of MetS and its associated markers (Lind and Lind, 2018; Taylor et al., 2013). These pathways involve the disruption of insulin signaling (Lind and Lind, 2018), the promotion of lipotoxicity and inflammation (Bessone et al., 2019; Kawano and Cohen, 2013), as well as the induction of mitochondrial dysfunction (Shan et al., 2020). However, it is also important to consider that exposure to POPs mostly occurs via mixtures rather than individual compounds, underscoring the need for further research to understand the combined effects of these mixtures on metabolic health.

4.5. Strengths and limitations

The present study benefits from several methodological advantages. Notably, the composition of the cohort, initially established to examine microbiota variation in Flanders, Belgium, provided a unique opportunity to assess the effects of POPs on MetS markers in a generally healthy demographic. Furthermore, the application of advanced analytical biomonitoring techniques, such as GC-ECNI/MS and LC/QTOF-MS, ensured sensitive and specific quantification of a wide range of POPs, including the first reported measurements of PCAs in pooled Belgian human serum. Additionally, we also employed advanced statistical methods to assess POP exposure as a mixture. Several potential covariates, such as age and weight, were also included in our models. The lack of significance observed for the single pollutant models underscores the limitations of examining environmental exposures in isolation, as human populations are typically exposed to complex chemical mixtures. It is possible that the individual effects of these pollutants, when analyzed separately, were too weak to be distinguished from the inherent variability in the data (Pan et al., 2024). In contrast, the significance observed in the WQS analysis suggests that combined effects of these pollutants enhance their impact on health outcomes.

Despite these strengths, our study is not without limitations. Our study did not account for the potential influence of other environmental pollutants, which could leave potential confounding by unmeasured exposures. Similarly, data on socioeconomic factors were not available for this analysis. As socioeconomic status can influence both environmental exposure and metabolic health, we cannot rule out residual confounding. However, sensitivity analyses adjusting for available covariates, such as medication use and dietary intake (Table SI-9), demonstrated that our primary findings remained robust, suggesting limited confounding by these factors. Regarding exposure metrics, we employed lipid-standardized concentrations to account for lipid partitioning. A comparison with wet-weight models (Table SI-9) indicated that associations with MetS in females and glucose in males were attenuated after standardization, suggesting that these were likely confounded by lipid variation. In contrast, most of our primary findings remained robust across both models. This confirms that our main reported findings represent stable biological signals independent of lipid variation. The cross-sectional design of the study prevents a definitive determination of the relationships between exposure and outcome. Additionally, the relatively homogeneous nature of the study population could also restrict the generalizability of the findings to different populations. Lastly, the relatively small sample size and low incidence of MetS and related factors resulted in limited statistical power.

Post-hoc power calculations for the binary MetS outcome, based on the observed effect estimates in the wet-weight analysis, indicated a

power of 31% for males (OR = 2.66; 95% CI: 0.72, 9.94) and 79% for females (OR = 6.06; 95% CI: 1.77, 22.62). While these calculations suggest adequate power to detect large effect sizes in females, the lower power in males suggests that the absence of statistically significant associations in this group should be interpreted with caution. Importantly, analyses of the continuous cardiometabolic parameters included the full study population (N=403), which provided greater precision and narrower confidence intervals for these outcomes (Table SI-7). The lower incidence of MetS, when compared to the general Belgian population estimates, likely reflects the FGFP's recruitment strategy, which was designed to examine microbiota variation within a population not specifically selected for metabolic disorders. In addition, the volunteer-based nature of participant recruitment could have introduced a self-selection bias, as individuals who choose to participate in the study often tend to be more health-conscious than the general population, thereby potentially contributing to the lower observed MetS prevalence. Increasing the sample size, potentially from populations with a higher baseline MetS prevalence, may uncover more pronounced associations, and future research should prioritize this to enhance the generalizability of findings.

5. Conclusions

This study provides novel insights into the impact of POPs on cardiometabolic health within a Belgian population, moreover reporting PCA concentrations in Belgian pooled serum samples for the first time. By using multi-pollutant models to assess POP mixtures, our study offers a detailed analysis of the associations between POP exposures and cardiometabolic parameters within the Flemish Gut Flora Project cohort. Our findings demonstrate that ambient-level exposure to POPs, particularly PCBs and OCPs, is positively associated with various cardiometabolic parameters. Additionally, our sex-stratified analyses revealed different patterns concerning various MetS indicators for males versus females, suggesting potential differences in susceptibility. Additionally, females demonstrated increased odds of elevated blood pressure linked to the POP mixture, with OCPs and PCBs identified as the predominant contributors to these adverse outcomes among the measured pollutants. Conversely, no statistically significant associations were observed between the pollutant mixture and MetS indicators in males after FDR correction. Collectively, our findings indicate that exposure to POP mixtures, including OCPs and PCBs, significantly contributes to cardiometabolic risk, with females appearing disproportionately predisposed. These results underscore the importance of considering sex in POP-related health risk assessments and highlight the need for further investigation into the specific mechanisms, including inflammatory pathways that may drive these differential cardiometabolic risks.

CRediT authorship contribution statement

Adam Cseresznye: Writing – review & editing, Writing – original draft, Visualization, Investigation, Formal analysis. **Fatima den Ouden:** Writing – review & editing. **Yu Ait Bamai:** Writing – review & editing, Visualization. **Liesa Engelen:** Writing – review & editing. **Elias Maris:** Writing – review & editing. **Ellen De Paepe:** Writing – review & editing. **Giulia Poma:** Writing – review & editing. **Muriel Derrien:** Writing – review & editing, Data curation. **Arnau Vich Vila:** Writing – review & editing, Data curation. **Sebastian Proost:** Data curation. **Lindsey de Commer:** Data curation. **Chloe Verspecht:** Data curation. **Lindsay Devolder:** Data curation. **Sara Vieira-Silva:** Data curation. **Gwen Falony:** Data curation. **Lieselot Y. Hemeryck:** Writing – review & editing. **Shanshan Yin:** Writing – review & editing, Data curation. **Thomas J. McGrath:** Writing – review & editing, Data curation. **Roger Pero-Gascon:** Writing – review & editing, Project administration. **Alexander van Nuijs:** Writing – review & editing, Supervision. **Sarah De Saeger:** Writing – review & editing, Funding acquisition, Conceptualization. **Tim Nawrot:** Writing – review & editing, Funding acquisition, Conceptualization. **Lynn Vanhaecke:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Jeroen Raes:** Writing – review & editing, Funding acquisition, Conceptualization. **Adrian Covaci:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

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

ACs, FdO, LE, EM, RPG and EDP acknowledge the support of the Interuniversity Special Research Fund from Flanders (GISMO 01IB1320, Flexigut project). GP is supported by the Exposome Centre of Excellence of the University of Antwerp (BOF grant, Antigoon database n. 41222). LYH is supported by Research Foundation Flanders (1297623N, FWO). RPG is supported by Research Foundation Flanders (12D4423N, FWO). TJM acknowledges the Brain Pool program funded by the Ministry of Science and ICT through the National Research Foundation of Korea (RS-2023-00281992).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2026.124068.

Data availability

Data will be made available on request.

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