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Cross-sectional associations of persistent organic pollutants measured in adipose tissue and metabolic syndrome in clinically diagnosed middle-aged adults☆

Iris Reina-Pérez [a,b,1], Francisco Artacho-Cordón [a,b,c,1], Vicente Mustieles [a,b,c], Daniel Castellano-Castillo [d], Fernando Cardona [e,f], Inmaculada Jiménez-Díaz [b], Jose A. López-Medina [g], Juan Alcaide [g], Luis Ocaña-Wilhelmi [h], Luz M. Iribarne-Durán [b], Juan P. Arrebola [b,c,i], Nicolás Olea [a,b,c], Francisco J. Tinahones [f,j,**], Mariana F. Fernández [a,b,c,*]

[a] Centro de Investigación Biomédica y Departamento de Radiología y Medicina Física, Facultad de Medicina, Universidad de Granada, E-18016 Granada, Spain
[b] Instituto de Investigación Biosanitaria (ibs.GRANADA), E-18012 Granada, Spain
[c] Centro de Investigación Biomédica en Red de Epidemiología y Salud Pública (CIBEResp), E-28029 Madrid, Spain
[d] Unidad de Gestión Clínica Intercentro de Oncología Médica, Hospitales Universitarios Regional y Virgen de la Victoria, Instituto de Investigación Biomédica de Málaga (IBIMA)-CIMES-UMA-29010 Málaga, Spain
[e] Department of Surgical Specialties, Biochemistry and Immunology School of Medicine, University of Malaga, 29010 Málaga, Spain
[f] Unidad de Gestión Clínica de Pediatría, Hospital Universitario Regional de Málaga, Instituto de Investigación Biomédica de Málaga (IBIMA), 29010 Málaga, Spain
[g] Unidad de Gestión Clínica de Endocrinología, Hospital Universitario Virgen de la Victoria. Instituto de Investigación Biomédica de Málaga (IBIMA), E-29010 Málaga, Spain
[h] Unidad de Cirugía Metabólica, Hospital Clínico Universitario Virgen de la Victoria, 29010 Málaga, Spain
[i] Departmento de Medicina Preventiva y Salud Pública, Facultad de Medicina Universidad de Granada, E-18016 Granada, Spain
[j] Centro de Investigación Biomédica en Red de Fisiopatología de la Obesidad y la Nutrición, (CIBERobn), E-28029 Madrid, Spain

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ABSTRACT

Introduction: Although often overlooked in clinical settings, accumulation of persistent organic pollutants (POPs) in visceral adipose tissue (VAT) is thought to be a relevant risk factor for metabolic syndrome (MetS).
Methods: One hundred and seventeen patients undergoing non-oncological surgery were randomly recruited and classified as MetS + if presented 3 out of the 5 MetS components: waist circumference (WC), systolic and diastolic blood pressure (SBP and DBP, respectively), serum glucose, insulin, triglycerides (TG) and high-density lipoprotein (HDL) cholesterol levels, according International Diabetes Federation (IDF) criteria. Seventeen organochlorine pesticides (OCPs) and polychlorinated biphenyls (PCBs) were measured in adipose tissue samples. Linear, logistic and weighted quantile sum (WQS) regression models, adjusted for age and sex, were performed.
Results: One third of the participants were males (36.8%) with a median age of 44 years, showing clinical evidences of MetS (35.0%). Adjusted linear regression models showed that WC correlated positively with all OCP concentrations. Higher fasting serum glucose levels were related to higher HCB and γ-HCH concentrations. The

Abbreviations: Adipose tissue, (AT); Adult Treatment Panel III, (ATPIII); American Association of Clinical Endocrinologists, (AACE); Body mass index, (BMI); Diastolic blood pressure, (DBP); Dichlorodiphenyltrichloroethane, (DDT); Gas chromatography and mass spectrometry, (GC-MS/MS); Hexachlorobenzene, (HCB); Hexachlorohexane, (HCH); High-density lipoprotein, (HDL); High-performance liquid chromatography, (HPLC); International Diabetes Federation, (IDF); Limit of detection, (LOD); Metabolic syndrome, (MetS); Metabolism-disrupting chemicals, (MDCs); Organochlorine pesticides, (OCPs); *o,p*'-dichlorodiphenyltrichloroethane, (*o,p*'-DDT); Systolic blood pressure, (SBP); Triglycerides, (TG); Type-2 diabetes, (T2D); Waist circumference, (WC); Weight/height squared, (kg/m^2); World Health Organization, (WHO).

☆ Clinical associations between adipose tissue concentrations of persistent organic pollutants and metabolic syndrome.

* Corresponding author.Centro de Investigación Biomédica y Departamento de Radiología y Medicina Física, Facultad de Medicina, Universidad de Granada, E-18016 Granada, Spain

** Corresponding author.Unidad de Gestión Clínica de Pediatría, Hospital Universitario Regional de Málaga, Instituto de Investigación Biomédica de Málaga (IBIMA), 29010 Málaga, Spain

E-mail addresses: fjtinahones@uma.es (F.J. Tinahones), marieta@ugr.es (M.F. Fernández).

[1] These authors contributed equally to this work and share first authorship.

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remaining OCPs and PCBs were not associated with this MetS component. HCB was inversely associated with HDL cholesterol levels, while PCB-180 was positively associated. HCB and γ-HCH concentrations were also positively correlated with DBP and SBP levels. PCB-138 was also positively associated with SBP. Adjusted logistic models revealed that exposure to HCB and γ-HCH were associated with increased odds of MetS [ORs (95%CI) 1.53 (1.22–1.92) and 1.39 (1.10–1.76) respectively; $p < 0.01$]. No associations were observed for the remaining POPs. WQS models showed a positive and significant mixture effect of POPs on the odds of MetS (exp [beta] = 2.34; $p < 0.001$), with γ-HCH (52.9%), *o,p'*-DDT (26.9%) and HCB (19.7%) driving the association.
Conclusions: Our findings support that POPs accumulated in VAT, specifically HCB and (gamma)-HCH, are associated with both isolated components and clinically diagnosed SMT.

1. Introduction

Metabolic syndrome (MetS) describes a complex cluster of adverse health conditions (also named 'MetS components') that substantially increases the risk of other chronic diseases such as heart failure, type-2 diabetes (T2D) or non-alcoholic fatty liver disease (Mustieles and Arrebola, 2020). In spite of several subsets of criteria proposed by different international organizations [Cholesterol Education Program's Adult Treatment Panel III (ATPIII), World Health Organization (WHO), and American Association of Clinical Endocrinologists (AACE)], the working definition for MetS classification used worldwide was proposed in 2009 by the International Diabetes Federation (IDF). It included 5 MetS components: fasting glucose, triglycerides (TG) and high-density lipoprotein (HDL) cholesterol, as well as blood pressure and waist circumference (WC), considering that the presence of any 3 out 5 MetS components constitutes a clinical diagnosis of MetS (Alberti et al., 2009). Although the trends of elevated TG and blood pressure have decreased in the last decade, mainly due to increased prescription of anti-hypertensives and lipid modifying agents (Shin et al., 2018), some reports that have assessed the prevalence of MetS, for example in the United States, have found an increase over the years (from 25.3% in 1988–1994 to 36.9% in 2015–2016) (Hirode and Wong, 2020; Moore et al., 2017). This is particularly relevant given the enormous economic costs derived from MetS patients as well as the healthcare expenditure associated to POP exposure (Pérez-Carrascosa et al., 2022, Pérez-Carrascosa et al., 2021).

It remains unclear which factors trigger the development of MetS, although all indicates that MetS has a multifactorial origin (Fahed et al., 2022; Lam and LeRoith., 2019). In this regard, it has been suggested that, in addition to unhealthy lifestyle factors (excessive calorie intake and sedentary lifestyle), body fat distribution, birth weight, smoking habits during pregnancy and maternal weight would be important determinants (Fahed et al., 2022; González-Jiménez et al., 2015; Müller et al., 2012). Also, human exposure to some environmental chemicals has been linked to the development of some metabolic disorders such as obesity and T2D, those classified as 'metabolism-disrupting chemicals' (MDCs) (Heindel et al., 2015; Nadal et al., 2017; Sun et al., 2022). These MDCs include persistent organic pollutants (POPs), a wide group of synthetic chemicals [including organochlorine pesticides (OCPs) such as dichlorodiphenyltrichloroethane (DDT) and its metabolite *p,p'*-dichlorodiphenyldichloroethylene (*p,p'*-DDE), hexachlorobenzene (HCB), hexachlorohexane (HCH), and polychlorinated biphenyls (PCBs)], with a tendency to bioaccumulate in fat compartments, given their lipophilicity and high environmental persistence (Bokobza et al., 2021; La Merrill et al., 2013). Adipose tissue (AT) is therefore regarded as the main reservoir of these compounds, accounting for all routes and sources of exposure and representing a stable and long-term reservoir of these chemicals (Artacho-Cordón et al., 2015b; Bokobza et al., 2021; Jackson et al., 2017; Kohlmeier and Kohlmeier, 1995; La Merrill et al., 2013). Despite the fact that the production, handling and disposal of POPs was banned or severely restricted in most countries, starting in the early 1970s, levels of POPs are currently still detected in biological samples of most humans, worldwide (Artacho-Cordón et al., 2015a; Bergonzi et al., 2011; Bjerregaard-Olesen et al., 2017; Björvang et al., 2021; Centers for Disease Control and Prevention, 2017; Fernández-Rodríguez et al., 2015).

Contrary to the traditional consideration of AT as a simple energy store depot, its relevant immunological and endocrine roles have been acknowledged during the last decades (Kershaw and Flier, 2004). In fact, AT dysfunction has been demonstrated to be the main precursor of MetS (Fahed et al., 2022, van Greevenbroek et al., 2016). Although the exact mechanisms of action for the development of MetS are not fully understood, hormonal imbalance (Banos et al., 2011), chronic low-grade inflammation (Esser et al., 2014), altered redox status (Höhn et al., 2016; Seillier et al., 2015; Spanidis et al., 2016) and mitochondrial dysfunction in AT (Fahed et al., 2022; Grundy, 2016; Kim and Lee, 2014), may play a crucial role. In this regards, exposure to POPs might interfere with the endocrine system (Grünfeld and Bonefeld-Jorgensen, 2004) and it has been also related to inflammatory responses (Pandolfi et al., 2016; Rolle-Kampczyk et al., 2020), macromolecule oxidation (Artacho-Cordón et al., 2016), and mitochondrial dysfunction (Kim et al., 2019). Although mounting research suggests a relevant role of POP exposure in the development of MetS, the relationship between POPs exposure and MetS has not been fully elucidated. Many of the epidemiological studies that assessed POPs exposure did so in serum samples (Lee et al., 2007, 2011, 2014; Tomar et al., 2013), which may be influenced by point exposures or altered by AT dynamics (Mustieles and Arrebola, 2020). Furthermore, most of the investigations that have observed relationships between AT POP concentrations and risk of MetS components (Arrebola et al., 2015, 2014; Mustieles et al., 2017; Pestana et al., 2014; Tawar et al., 2022; Valvi et al., 2020), often did not include clinical diagnoses of MetS as an outcome (Mustieles et al., 2017). The recent systematic review by Lamat et al. (2022) indicates that the occurrence of MetS would be linked to visceral adiposity, supporting that the influence of adiposity may be a very important factor for the influence of POP exposure on MetS (Mustieles et al., 2017).

Therefore, given the relevance of visceral adiposity disruption of AT physiology in the development of MetS, the aim of this study was to evaluate the relationship between cumulative POP concentrations in VAT and the presence of individual MetS components, as well as to assess the risk of clinically diagnosis of MetS in a hospitalized adult population from Southern Spain.

2. Material and methods

2.1. Study population and sample collection

The population of this cross-sectional clinical study consisted of 117 middle-aged adults selected from among patients undergoing non-oncologic surgery (mostly hiatal hernia, umbilical hernia, inguinal hernia, para-oesophageal hernia, achalasia and cholecystectomy), in both the Endocrinology and Nutrition Unit and the Surgery Unit at the Virgen de la Victoria University Hospital (Málaga, Spain).

The recruitment took place between 2013 and 2015. Exclusion criteria included patients receiving blood glucose-lowering treatment, major cardiovascular disease in the last 6 months before recruitment, evidence of acute/chronic inflammatory disease (such us chronic inflammatory bowel diseases, ulcerative colitis and Crohn's disease),

cancer patients and infectious diseases, as well as those who did not signed the informed consent to participate in this study. Sociodemographic data was recorded during recruitment. The height and weight of the participants were recorded, and body mass index (BMI) as weight/height squared (kg/m^2), was calculated. All participant data were extracted from medical records.

Approximately 300 mg of visceral adipose tissue (VAT) and 10 mL of blood were collected under fasting conditions during surgery. Blood samples were immediately centrifuged for 5 min at 2500 rpm and 4 °C to separate the serum. Both serum and VAT samples were immediately coded and stored at −80 °C until chemical analysis. Blood samples were used to determine clinical biomarkers of MetS.

The study was approved by the Ethics Committee of Virgen de la Victoria Hospital before all participants were informed of the objective and characteristics of the study and gave their signed consent. The study was conducted in accordance with the Declaration of Helsinki, and all the information collected was anonymized. Once all the fat samples had been collected, they were sent to the chemistry laboratories of the ibs. GRANADA/University of Granada (Spain) for analysis.

2.2. Adipose tissue sample extraction and chemical analyses

Concentrations of 17 POPs were determined in 150 mg of VAT, as previously described (Martínez Vidal et al., 2002; Moreno Frías et al., 2004). VAT samples were spiked with p-chlorobenzophenone as internal standard, and extracted following a two-step methodology, consisting on a mechanical homogenization in n-hexane followed by a filtration through a glass column with 200 mg of alumina. Extracts were dried under a continuous nitrogen stream and fractionated in duplicate by high-performance liquid chromatography (HPLC). Residues of *o,p'*-DDT, *p,p'*-DDE, HCB, α-HCH, β-HCH γ-HCH, aldrin, isodrin, endrin, dieldrin, heptachlor, vinclozolin, endosulfan I and II and PCBs (congeners −138, −153, and −180) were quantified by gas chromatography and mass spectrometry (GC-MS/MS) with an Agilent 7890 A system and MS Agilent 7000 GC/MS (triple quadrupole) mass spectrometer (Agilent Tehcnologies, Santa Clara, CA) after reconstitution in 200 μL *n*-hexane (Arrebola et al., 2014; Moreno Frías et al., 2004). Procedural laboratory blanks with solvents alone were tested and always yielded a negative result. Laboratory fortified matrix samples at different concentrations were used for quality control procedures. Inter- and intra-day variabilities were calculated by analyzing fortified samples within the same day (repeatability) and on different days (intermediate precision), always yielding values < 20%, respectively. The limit of detection (LOD) was determined as the smallest amount of the analyte that gave a signal-to-noise ratio ≥3 and was set at 4 ng/mL for *o,p'*-DDT and *p,p'*-DDE, and 2 ng/mL for the rest of POPs. Concentrations below the LOD were assigned half of the LOD.

2.3. Assessment of MetS components and clinical diagnosis of MetS

Waist circumference (WC) was measured at the nearest 0.1 cm using an inelastic tape (in a standing position and after a gentle exhalation by trained clinicians using standardized protocols. Fasting glucose, TG and HDL cholesterol levels were quantified in serum samples by using a Dimension autoanalyzer, Dade Behring Inc. (Deerfield, IL) in the analytical unit of Virgen de la Victoria Hospital. Diastolic and systolic blood pressures were also measured. Blood pressure was measured twice in a sitting position after a 5-min rest at 5-min intervals, and the mean of both measurements used.

Following the IDF working group criteria, the following 5 MetS components were considered and their respective cut-off points: fasting glucose (≥100 mg/dL), TG (≥150 mg/dL), HDL cholesterol (<40 mg/dL in males and <50 mg/dL in females), blood pressure [SBP ≥130 mmHg and/or DBP ≥85 mmHg], and WC (≥94 cm for males and ≥80 cm for females from European population). In addition, participants were classified as MetS + when the simultaneous presence of 3 of the above 5 MetS components was detected. Those participants with less than 3 MetS components were included in the MetS- group (Alberti et al., 2009).

2.4. Statistical analyses

Description of continuous variables was performed using arithmetic mean ± standard deviation (SD), median and 25th-75th percentiles, while categorical variables were expressed as percentages.

Individual MetS components were considered as continuous, but also as categorical variables considering the cut-off points established in the IDF working definition for the clinical diagnosis of MetS (MetS +/−) (Alberti et al., 2009). POP concentrations were natural-log transformed to reduce the skewness of the distributions and the influence of extreme values, especially in the context of a modest sample size. Spearman's correlation test was used to assess relationships between POPs concentrations (Fig. 1). Continuous outcomes were also log-transformed. The linearity of the relationship between POP exposure and MetS components was examined using generalized additive models (GAMs), supporting the modelling of POP concentrations as continuous variables (Fig. S1). Thus, associations between concentrations of selected POPs (HCB, *o,p'*-DDT, *p,p'*-DDE, γ-HCH, PCB-138, PCB-153 and PCB-180) and MetS components were examined using both multivariable linear and logistic regression analyses when outcomes were coded as continuous or categorical variables, respectively. Linear regression models were also performed using dichotomized exposure variables (exposed *vs*. not exposed) for those POPs with ~50% below LOD (HCB, *o,p'*-DDT, γ-HCH) in the adipose samples. Furthermore, logistic regression analyses were performed to explore the influence of VAT levels of selected POPs on the risk of clinically-diagnosed MetS. All models were adjusted for age (years) and sex (male/female) as potential confounders. In addition, a sensitivity analysis was performed further adjusting models by BMI.

The potential POP mixture effect on MetS was assessed using Weighted Quantile Sum Regression (WQS) (Carrico et al., 2015), which combines the individual associations into a weighted index, and estimates the specific weight of each chemical on the mixture. Associations between each WQS index and the outcome were further studied by using multivariable logistic regression adjusting for age, sex and BMI. The WQS analyses were performed with log-transformed continuous pollutant concentrations, using a training set defined as a 40% random sample of the dataset, being the remaining 60% used for model validation. The final weights were calculated using a total of 1000 bootstrap steps. On the basis of our hypothesis and the associations found in the models for individual chemicals, the WQS index was calculated for a priori assumed positive associations.

The results were interpreted taking into their internal validity, consistency and coherence, the existing epidemiological and toxicological evidence, and not exclusively considering the statistical significance (Amrhein et al., 2019). Given the hypothesis investigated in this work, and the moderate number of comparisons tested, we did not perform a post-hoc correction for multiple comparisons to avoid a disproportionate increase in the frequency of type II errors (Rothman, 2014). Diagnosis of the models was performed in order to ensure the goodness of fit and the fulfilment of implementation conditions. The significance level was set at 0.05 (two-sided), and data were stored and processed using SPSS 20.0 (IBM, Chicago, IL).

3. Results

3.1. Characteristics of the study population and adipose tissue concentrations of selected POPs

Table 1 summarizes the characteristics of the study population. A total of 41 participants (35.0%) had a clinical diagnosis of MetS (i.e., showed at least 3 components of MetS established by the IDF classification). More than one third of the sample population was male (36.8%) and the median age across the entire study population was 44 years,

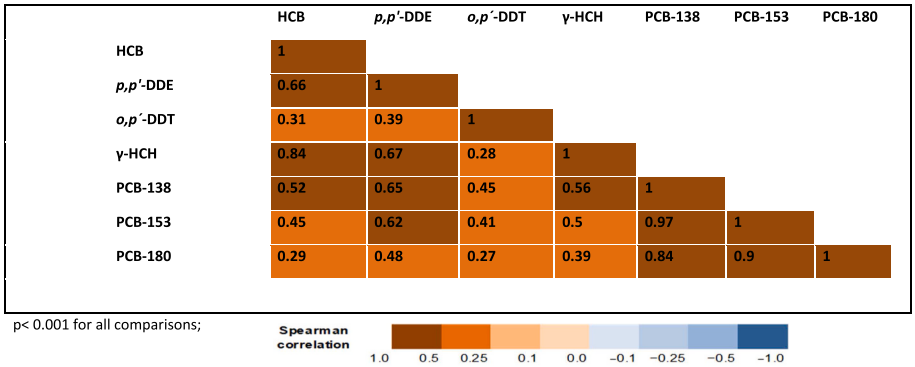

Fig. 1. Correlation heatmap for POP concentrations in adipose tissue samples.

with older individuals in the MetS + group relative to the MetS- group (50 *vs.* 42 years, p = 0.04). As expected, compared with the MetS- group, participants in the MetS + group showed higher BMI (34.2 kg/m^2 *vs.* 30.5 kg/m^2, respectively; p < 0.01) and WC (121.0 cm *vs.* 95 cm, respectively; p < 0.01). Median TG and HDL cholesterol concentrations were 160.0 mg/dL and 44.0 mg/dL in the MetS + group, respectively, whereas lower median concentrations of 92.5 mg/dL and 53.0 mg/dL for TG and HDL cholesterol, respectively, were detected in the MetS- group (p < 0.01 in both cases). As for blood pressure, median DBP and SBP were 85.0 mmHg and 140.0 mmHg in the MetS + group and 76.0 mmHg and 119.0 mmHg in the MetS- group, respectively (p < 0.01 in both cases). Considering the IDF cut-off points, 84 out of the 117 participants (68.3%) showed elevated WC, 56 (45.5%) elevated blood pressure, 37 (30.1%) reduced HDL cholesterol, 45 (36.6%) elevated serum TG levels and 17 (13.8%) had elevated fasting blood glucose (data not shown in the tables).

Detection levels and concentrations of OCPs and PCBs in VAT are also shown in Table 1. Median concentrations of HCB and γ-HCH were 4.5 ng/g tissue and 11.4 ng/g tissue, respectively, showing significantly higher concentrations in the MetS+ group (28.6 ng/g tissue and 34.4 ng/g tissue, respectively) than in the MetS- group (median concentrations of both chemicals were below the LOD). Median concentration of *o,p'*-DDT and *p,p'*-DDE were 6.6 ng/g tissue and 49.9 ng/g tissue, showing non-significant differences between MetS groups. Finally, levels of PCBs were 21.2 ng/g tissue, 26.8 ng/g tissue and 10.0 ng/g tissue for PCB-138, PCB-153 and PCB-180, respectively, with similar median levels in both groups.

3.2. Associations between adipose tissue levels of POPs and MetS components

Table S2 and Table 2 shows unadjusted and adjusted (sex and age) linear regression analyses assessing the influence of POP burden on each individual MetS component (considered as continuous variables), respectively. WC was positively correlated with concentrations of all OCPs, either in the unadjusted analysis or in the multivariate models adjusted. None of the PCB congeners were associated with WC. Higher fasting blood glucose levels were associated with higher HCB and γ-HCH concentrations, while the rest of OCPs and PCBs were not associated with this MetS component. Exposure to HCB was inversely associated with HDL cholesterol levels after adjusting, while PCB-180 and HDL cholesterol were positively associated. Concentrations of HCB and γ-HCH in VAT were positively correlated with TG in the unadjusted analyses and borderline associated in the adjusted models [exp(β) (95% CI) 1.04 (1.00–1.09), p = 0.07 for HCB and 1.04 (0.99–1.10) p = 0.09 for γ-HCH]. DBP and SBP levels were positively associated with exposure to HCB and γ-HCH, both in the unadjusted and in the multivariate analysis. PCB-138 was also positively associated with SBP after adjusting. Similar results were found for HCB, *o,p'*-DDT, and γ-HCH (POPs around 50% detection) when the assessment was performed between exposed *vs.* not exposed subjects (Table S3).

Additionally, unadjusted (Table S4) and adjusted logistic regression analyses were performed to explore the role of the cumulative POP concentrations in the VAT on the odds of each individual MetS component (considered as categorical variables) (Table 3). Exposure to HCB and γ-HCH consistently showed a positive association for elevated WC and blood pressure, while the association with elevated TG was only detected in the unadjusted analysis. HCB exposure was also associated with higher odds of reduced HDL and borderline associated with elevated blood glucose [OR (95%CI) 1.22 (0.98–1.53), p = 0.08]. Intriguingly, an inverse relationship was found between exposure to *p, p'*-DDE and the odds of elevated TG in the adjusted models.

3.3. Associations between chronic adipose tissue POPs concentrations and MetS risk

The risk for MetS according to VAT concentrations of each POP is shown in Table 4. Both unadjusted (Table S5) and adjusted logistic models for age and sex revealed that the exposure to HCB and γ-HCH were associated with an increased odds of MetS [ORs (95%CI) 1.53 (1.22–1.92) and 1.39 (1.10–1.76) respectively; p < 0.01]. No associations with MetS were observed for the remaining contaminants analyzed in VAT samples. When BMI was included as an additional variable, the previously found associations were attenuated in all models (Tables 2–4), probably because BMI is in the causal pathway between POPs and MetS.

3.4. Mixture associations between chronic adipose tissue POPs concentrations and MetS risk

The combined effect of POPs on MetS, assessed using WQS, showed that WQS index for the seven POPs was positively and significantly associated with MetS, in both the adjusted model for age and sex [(exp [beta] = 2.34; p < 0.001)], as well as in the model adjusted for age, sex and BMI [(exp [beta] = 2.44; p = 0.016)] (Table 5). Concentrations of γ-HCH (52.9%), *o,p'*-DDT (26.9%) and HCB (19.7%) drove the mixture effect in the model adjusted for age and sex; while γ-HCH (47.6%), PCB-180 (26.2%), *o,p'*-DDT (21.7%) and PCB-153 (4.5%) drove the mixture effect in the model adjusted for age, sex and BMI.

4. Discussion

This cross-sectional epidemiological study shows that VAT concentrations of HCB and γ-HCH, are associated with a greater risk of clinically-diagnosed MetS in an adult hospital population. Participants with higher VAT concentrations of these two chemical compounds also showed higher risk for several MetS components when considered individually. Hence, considering IDF cut-off points, HCB and γ-HCH AT

Table 1
Characteristics of the study population (N = 117).

	Total (N = 117)						MetS + (N = 41)					MetS - (N = 76)					
	DF (%)	Mean / N (%)	SD	Percentiles			Mean / N (%)	SD	Percentiles			Mean	SD	Percentiles			p-value
				25	50	75			25	50	75			25	50	75	
Age (yr)		47.14	14.37	38.00	44.00	58.75	50.83	15.22	38.00	50.00	65.00	45.12	13.56	36.00	42.00	53.00	***0.040***
Sex[a]																	0.217
Male		43 (36.8%)	-	-	-	-	12 (29.3%)	-	-	-	-	31 (40.8%)	-	-	-	-	
Female		74 (63.2%)	-	-	-	-	29 (70.7%)	-	-	-	-	45 (59.2%)	-	-	-	-	
BMI (kg/m^2)		35.25	12.96	24.11	32.05	44.27	39.76	11.56	31.14	34.22	50.81	32.82	13.09	23.15	30.45	38.73	***0.005***
Fasting blood glucose (mg/dL)		100.76	24.09	89.00	94.00	102.00	114.98	32.24	92.50	104.00	133.00	92.88	12.68	87.00	92.00	96.25	***<0.001***
Triglycerides (mg/dL)		130.75	65.04	83.00	115.00	156.00	180.52	59.45	132.90	160.00	214.50	103.18	50.06	71.25	92.50	126.25	***<0.001***
HDL cholesterol (mg/dL)		50.44	12.57	41.00	50.00	58.25	45.44	11.13	37.50	44.00	52.50	53.25	12.52	45.00	53.00	61.00	***0.001***
Diastolic blood pressure (mmHg)		79.59	11.50	70.00	80.00	87.00	85.33	10.58	80.00	85.00	90.00	76.25	10.73	70.00	76.00	83.00	***<0.001***
Systolic blood pressure (mmHg)		128.70	21.50	112.75	125.00	146.00	140.97	21.01	125.00	140.00	153.00	121.55	18.44	110.00	119.00	134.00	***<0.001***
Waist circumference (cm)		106.60	25.73	88.00	102.00	123.00	127.60	23.64	109.00	121.00	151.00	100.28	24.98	82.25	95.00	109.00	***<0.001***
Adipose tissue concentration of POPs (ng/g tissue)																	
Organochlorine pesticides (OCPs)																	
HCB	49.6	36.52	65.31	<LOD	4.47	46.05	65.94	87.14	2.55	28.55	85.85	20.64	42.66	<LOD	<LOD	17.84	***<0.001***
p,p'-DDE	62.6	228.93	672.67	<LOD	49.89	211.39	337.25	1085.22	<LOD	54.83	257.13	170.50	248.72	<LOD	49.66	235.82	0.202
o,p'-DDT	56.1	15.88	36.46	<LOD	6.59	12.25	21.81	49.56	<LOD	7.33	16.05	12.67	26.76	<LOD	6.42	11.44	0.197
γ-HCH	54.5	41.62	80.50	<LOD	11.44	40.94	68.99	113.24	5.83	34.42	70.29	26.85	50.53	<LOD	<LOD	31.46	***0.006***
Polychlorinated biphenyls (PCBs)																	
PCB-138	78.0	50.77	137.73	5.77	21.18	50.29	79.07	222.82	9.92	28.63	58.97	35.51	46.75	4.42	18.86	46.24	0.103
PCB-153	79.7	61.17	161.72	6.02	26.79	59.09	92.29	260.59	10.24	31.45	84.88	44.38	58.46	5.56	22.94	59.06	0.127
PCB-180	62.6	35.98	107.15	<LOD	9.95	40.93	52.57	173.03	<LOD	12.05	45.07	27.03	39.47	<LOD	7.99	40.04	0.220

[a] DF (%): detection frequency of the investigated chemicals; BMI: body mass index; HDL: high density lipoprotein; mean: arithmetic mean; SD: standard deviation; MetS: metabolic syndrome; POPs: Persistent Organic Pollutants. Patients were classified as **MetS+** if they presented 3 out of the 5 MetS components: waist circumference, systolic and diastolic blood pressure, serum glucose, insulin, triglycerides and high-density lipoprotein (HDL) cholesterol levels, according to the International Diabetes Federation criteria.

Table 2
Multivariate linear regression analyses between MetS components and log-transformed adipose tissue POPs concentration (ng/g tissue).

	Adjusted Model [a]					Adjusted Model [b]				
	β	exp(β)	95% CI		p-value	β	exp(β)	95% CI		p-value
Waist circumference (cm)										
HCB	**0.08**	**1.08**	**1.06**	**1.10**	**<0.001**	0.06	1.06	1.00	1.02	0.236
p,p'-DDE	**0.03**	**1.03**	**1.01**	**1.05**	**0.003**	−0.07	0.94	0.99	1.00	0.112
o,p'-DDT	**0.06**	**1.06**	**1.02**	**1.10**	**0.002**	−0.02	0.98	0.98	1.01	0.635
γ-HCH	**0.07**	**1.07**	**1.05**	**1.10**	**<0.001**	0.07	1.07	1.00	1.02	0.172
PCB-138	0.03	1.03	1.00	1.06	0.074	−0.06	0.94	0.98	1.00	0.143
PCB-153	0.01	1.01	0.98	1.04	0.609	−0.07	0.93	0.98	1.00	0.077
PCB-180	−0.02	0.98	0.96	1.01	0.233	−0.05	0.95	0.98	1.00	0.213
Fasting blood glucose (mg/dL)										
HCB	**0.02**	**1.02**	**1.00**	**1.04**	**0.020**	0.06	1.06	0.98	1.03	0.611
p,p'-DDE	0.00	1.00	0.99	1.02	0.660	−0.06	0.94	0.98	1.01	0.523
o,p'-DDT	0.02	1.02	0.99	1.05	0.308	0.01	1.01	0.97	1.03	0.888
γ-HCH	**0.02**	**1.02**	**1.00**	**1.04**	**0.028**	0.08	1.08	0.99	1.03	0.487
PCB-138	0.01	1.01	0.99	1.04	0.418	0.03	1.03	0.98	1.03	0.772
PCB-153	0.01	1.01	0.98	1.03	0.556	0.05	1.05	0.98	1.03	0.640
PCB-180	0.01	1.01	0.98	1.03	0.573	0.12	1.12	0.99	1.04	0.261
Triglycerides (mg/dL)										
HCB	0.04	1.04	1.00	1.09	0.072	0.05	1.05	0.96	1.07	0.641
p,p'-DDE	−0.03	0.97	0.94	1.02	0.223	**−0.22**	**0.80**	**0.92**	**1.00**	**0.030**
o,p'-DDT	−0.02	0.98	0.91	1.05	0.545	−0.13	0.88	0.88	1.02	0.166
γ-HCH	0.04	1.04	0.99	1.10	0.089	0.07	1.07	0.96	1.08	0.556
PCB-138	−0.04	0.96	0.90	1.02	0.189	−0.19	0.83	0.89	1.00	0.067
PCB-153	−0.05	0.95	0.89	1.01	0.080	**−0.20**	**0.82**	**0.89**	**1.00**	**0.049**
PCB-180	−0.05	0.96	0.90	1.01	0.112	−0.14	0.87	0.91	1.02	0.194
HDL cholesterol (mg/dL)										
HCB	**−0.03**	**0.97**	**0.95**	**0.99**	**0.012**	−0.05	0.96	0.97	1.02	0.689
p,p'-DDE	0.00	1.00	0.98	1.02	0.986	0.14	1.16	0.99	1.04	0.149
o,p'-DDT	0.00	1.00	0.96	1.04	0.842	0.10	1.10	0.98	1.06	0.289
γ-HCH	−0.02	0.98	0.96	1.01	0.142	0.05	1.05	0.98	1.03	0.663
PCB-138	0.02	1.02	0.99	1.06	0.133	**0.25**	**1.29**	**1.01**	**1.07**	**0.011**
PCB-153	0.03	1.03	1.00	1.06	0.087	**0.22**	**1.25**	**1.00**	**1.06**	**0.027**
PCB-180	**0.03**	**1.03**	**1.00**	**1.06**	**0.046**	0.17	1.19	1.00	1.05	0.096
Diastolic Blood Pressure (mmHg)										
HCB	**0.02**	**1.02**	**1.00**	**1.03**	**0.028**	0.05	1.05	0.99	1.02	0.677
p,p'-DDE	0.00	1.00	0.98	1.01	0.881	−0.11	0.90	0.98	1.01	0.297
o,p'-DDT	0.01	1.01	0.99	1.04	0.277	0.03	1.03	0.98	1.03	0.772
γ-HCH	**0.02**	**1.02**	**1.00**	**1.04**	**0.033**	0.10	1.10	0.99	1.03	0.421
PCB-138	0.02	1.02	1.00	1.04	0.077	0.15	1.16	0.99	1.03	0.157
PCB-153	0.02	1.02	1.00	1.04	0.099	0.19	1.21	1.00	1.04	0.077
PCB-180	0.01	1.01	0.99	1.03	0.469	0.19	1.21	1.00	1.04	0.089
Systolic Blood Pressure (mmHg)										
HCB	**0.02**	**1.02**	**1.00**	**1.03**	**0.044**	−0.05	0.95	0.98	1.01	0.668
p,p'-DDE	0.00	1.00	0.99	1.02	0.575	−0.05	0.95	0.98	1.01	0.604
o,p'-DDT	0.02	1.02	1.00	1.05	0.077	0.07	1.08	0.99	1.04	0.409
γ-HCH	**0.02**	**1.02**	**1.01**	**1.04**	**0.014**	0.09	1.09	0.99	1.03	0.440
PCB-138	**0.02**	**1.02**	**1.00**	**1.05**	**0.032**	0.17	1.19	1.00	1.04	0.078
PCB-153	0.02	1.02	0.99	1.04	0.172	0.15	1.16	1.00	1.04	0.123
PCB-180	0.00	1.00	0.98	1.02	0.731	0.17	1.18	1.00	1.03	0.112

[a] Adjusted for age (yr) and sex (male/female).
[b] Adjusted for age (yr), sex (male/female) and BMI (body mass index); MetS: metabolic syndrome; POPs: Persistent Organic Pollutants.

concentrations were associated with elevated WC and blood pressure. Moreover, HCB concentrations were also related to lower HDL cholesterol levels. Consistently, linear positive associations were further detected between both HCB and γ-HCH levels in VAT and WC, fasting blood glucose, DBP, SBP and TG, while HCB was inversely associated with HDL cholesterol levels. PCBs in VAT were not associated with greater risk of MetS or any MetS component in our study, except for PCB-138 whose concentration was positively associated with SBP levels. WQS models further showed a positive and significant mixture effect of POPs on MetS, with γ-HCH (52.9%), and HCB (19.7%) being two of the main drivers of the association, in line which what was reported in the systematic review and meta-analysis of Lamat et al. (2022).

Our data show that VAT levels of both HCB and γ-HCH were positively associated with the prevalence of MetS. These results confirm previous articles published by our team in a prospective study in the Granada province (Southern Spain). For example, Mustieles et al. (2017) investigated AT concentrations of OCPs and PCBs in 387 hospitalized adults in relation to the prevalence of being "metabolically compromised" (defined as having ≥1 diagnosis of the following diagnosis: T2D, hypertension, hypertriglyceridemia or low HDL cholesterol), identifying HCB and β-HCH as the main contributors in the cross-sectional analyses. Interestingly, those participants without any MetS component at baseline were followed during 10 years on average, and again AT HCB and β-HCH levels at baseline were found to be longitudinally associated with the risk of being metabolically compromised (Mustieles et al., 2017). Our current study, performed in a similar population in the neighbouring province of Málaga, complements these results showing that VAT concentrations of HCB and γ-HCH are not only associated with single MetS components, but with the risk of clinically-diagnosed MetS, strengthening the weight of evidence. In other words, this study reinforces the clinical relevance of POP-metabolism associations found in population studies. In line with our results, it has been interestingly reported that living in close proximity to environmental sources of POPs is associated with a statistically significant 39.2% increase in MetS-related hospitalizations in a population-based semi-ecological study based on zip codes of residence

Table 3
ORs (95%CI) of the risk of MetS components according to adipose tissue POP concentration (ng/g tissue).

	Adjusted Model [a]				Adjusted Model [b]			
	OR	95% CI		p-value	OR	95% CI		p-value
Elevated waist circumference (≥ 94 cm men or ≥ 80 cm women)								
HCB	**1.92**	**1.35**	**2.73**	**<0.001**	0.63	0.31	1.29	0.207
p,p'-DDE	1.06	0.85	1.31	0.625	**0.42**	**0.21**	**0.83**	**0.012**
o,p'-DDT	1.45	0.94	2.22	0.092	0.74	0.33	1.66	0.461
γ-HCH	**1.78**	**1.28**	**2.48**	**0.001**	0.90	0.50	1.64	0.730
PCB-138	1.17	0.86	1.59	0.322	0.81	0.46	1.43	0.473
PCB-153	1.02	0.75	1.39	0.896	0.82	0.46	1.46	0.506
PCB-180	0.85	0.63	1.15	0.294	0.97	0.58	1.64	0.912
Elevated fasting blood glucose (≥100 mg/dL)								
HCB	1.22	0.98	1.53	0.081	1.05	0.81	1.37	0.701
p,p'-DDE	0.99	0.81	1.21	0.921	0.90	0.72	1.12	0.332
o,p'-DDT	1.01	0.70	1.47	0.947	0.87	0.59	1.30	0.500
γ-HCH	1.20	0.93	1.53	0.159	1.03	0.78	1.36	0.829
PCB-138	0.93	0.68	1.27	0.637	0.84	0.61	1.17	0.315
PCB-153	0.92	0.68	1.25	0.584	0.88	0.64	1.22	0.450
PCB-180	0.96	0.72	1.28	0.784	1.01	0.75	1.36	0.951
Elevated triglycerides (≥ 150 mg/dL)								
HCB	1.17	0.95	1.45	0.137	1.22	0.94	1.58	0.135
p,p'-DDE	**0.77**	**0.62**	**0.95**	**0.014**	**0.73**	**0.58**	**0.92**	**0.007**
o,p'-DDT	0.76	0.52	1.10	0.145	0.72	0.49	1.07	0.105
γ-HCH	1.19	0.95	1.51	0.136	1.22	0.93	1.60	0.145
PCB-138	0.77	0.57	1.04	0.086	0.75	0.56	1.02	0.069
PCB-153	0.77	0.57	1.03	0.082	0.77	0.57	1.03	0.076
PCB-180	0.87	0.66	1.15	0.336	0.88	0.67	1.16	0.358
Reduced HDL cholesterol (<40 mg/dL in men or < 50 mg/dL in women)								
HCB	**1.28**	**1.04**	**1.57**	**0.022**	1.06	0.83	1.37	0.629
p,p'-DDE	1.07	0.89	1.28	0.497	0.95	0.77	1.16	0.617
o,p'-DDT	1.24	0.89	1.72	0.197	1.06	0.74	1.52	0.760
γ-HCH	1.15	0.92	1.43	0.221	0.94	0.73	1.22	0.636
PCB-138	0.86	0.65	1.12	0.264	**0.73**	**0.54**	**1.00**	**0.049**
PCB-153	0.87	0.67	1.13	0.301	0.81	0.61	1.08	0.154
PCB-180	0.81	0.63	1.05	0.112	0.83	0.63	1.10	0.196
Elevated blood pressure (SBP ≥ 130 mmHg and/or DBP ≥ 85 mmHg)								
HCB	**1.27**	**1.02**	**1.59**	**0.034**	0.95	0.71	1.27	0.726
p,p'-DDE	1.01	0.84	1.22	0.924	0.89	0.71	1.10	0.284
o,p'-DDT	1.20	0.85	1.70	0.295	0.99	0.66	1.48	0.959
γ-HCH	**1.39**	**1.09**	**1.79**	**0.009**	1.16	0.87	1.54	0.315
PCB-138	1.24	0.94	1.64	0.128	1.19	0.87	1.62	0.268
PCB-153	1.11	0.85	1.45	0.450	1.15	0.85	1.55	0.374
PCB-180	1.03	0.80	1.33	0.826	1.24	0.92	1.66	0.152

[a] Adjusted for age (yr) and sex (male/female).
[b] Adjusted for age (yr), sex (male/female) and BMI (body mass index); MetS: metabolic syndrome; POPs: Persistent Organic Pollutants. SBP, DBP: systolic and diastolic blood pressure, respectively.

Table 4
ORs (95%CI) of the risk of MetS according to adipose tissue POP concentration (ng/g tissue).

	Adjusted Model [a]				Adjusted Model [b]			
	OR	95% CI		p-value	OR	95% CI		p-value
HCB	**1.53**	**1.22**	**1.92**	**<0.001**	**1.36**	**1.05**	**1.76**	**0.021**
p,p'-DDE	0.98	0.82	1.18	0.849	0.86	0.70	1.06	0.163
o,p'-DDT	1.25	0.89	1.75	0.199	1.07	0.74	1.53	0.736
γ-HCH	**1.39**	**1.10**	**1.76**	**0.006**	1.20	0.92	1.56	0.174
PCB-138	1.15	0.87	1.52	0.316	1.06	0.78	1.43	0.716
PCB-153	1.15	0.87	1.51	0.323	1.12	0.84	1.50	0.449
PCB-180	1.06	0.82	1.37	0.676	1.13	0.86	1.50	0.377

[a] Adjusted for age (yr) and sex (male/female).
[b] Adjusted for age (yr), sex (male/female) and BMI; MetS: metabolic syndrome; POPs: Persistent Organic Pollutants.

(Sergeev and Carpenter, 2011).

Few previous investigations have investigated the relationship between POP AT concentrations and risk of MetS components using either cross-sectional, longitudinal (Arrebola et al., 2015, 2014; Dirinck et al., 2015, 2016; Lee et al., 2012, 2014; Mustieles et al., 2017; Penell et al., 2014), or combined designs (Dirinck et al., 2014; Mustieles et al., 2017). Thus, some studies using cross-sectional design reported increased risk for MetS related to serum POP exposure (Aminov and Carpenter, 2020; Gasull et al., 2018; Lee et al., 2014; Park et al., 2010; Rosenbaum et al., 2017), yielding similar conclusions. Tomar et al. (2013) and Kim et al. (2018) detected increased serum levels of β-HCH among those MetS patients. Lee et al. (2007) also revealed that patients with detectable serum levels of β-HCH had higher risk for MetS compared with patients with β-HCH levels below LOD. However, Pestana et al. (2014) found no statistically significant differences between AT γ-HCH levels and MetS prevalence, although they did detect a positive association when POP exposure was considered as the sum of single chemicals. Regarding PCBs, we observed non-significant higher concentrations of PCBs in patients with MetS. Similarly, Dirinck et al. (2016) found that MetS+ patients had significantly higher serum concentrations of PCB-153, -138 and -180, and the sum of these PCBs (ΣPCBs) than MetS- patients.

We also explored the influence of POP exposure in the prevalence of individual MetS components. It was observed that HCB and γ-HCH levels in VAT was related to higher blood pressure and/or hypertension risk, in line with previous findings (Arrebola et al., 2015; Lee et al., 2007; Park et al., 2010). Similarly, other authors have also found positive associations between any POP and hypertension. For instance, Henríquez-Hernández et al. (2014) found positive associations between serum *p,p'*-DDE and hypertension, and between *p,p'*-DDE and blood pressure (systolic and diastolic) in subjects not taking anti-hypertensive drugs. However, other studies have reported inverse associations between hypertension and exposure to HCH congeners (Pestana et al., 2014; Valera et al., 2013). Regarding HDL cholesterol, we also detected an inverse relationship between HCB concentrations and HDL cholesterol, either when HDL cholesterol was considered as a continuous variable and after using IDF cut-off point. Similarly, another study found inverse associations between HDL cholesterol levels and concentrations of HCB, in both Caucasian and African American residents of Alabama (Aminov et al., 2014), although a study carried out in northern Europe reported no association between HCB and changes in HDL cholesterol over a 5-year follow-up (Penell et al., 2014). Inversely, significant quadratic association between HDL cholesterol and HCB was found by Arrebola et al. (2014). Concerning the elevated serum TG, other MetS component, we found no statistically significant associations between the studied POPs and TG, unlike Arrebola et al. (2014) that found quadratic associations between TG and PCB-138 and -180. Increased WC comprises another MetS component with different cut-off point depending on the sex and population/country. Following above definition, we observed elevated WC among those participants with higher HCB and γ-HCH levels. Consistently, positive associations were found for WC and HCB and γ-HCH levels, as well as *p,p'*-DDE and *o,p'*-DDT, which is in line with previous findings (Lee et al., 2012, 2007; Tawar et al., 2022). We did not observe statistically significant risk with the exposure to POPs for increased fasting plasma glucose, another MetS component. Nevertheless, other groups have reported positive associations between fasting plasma glucose and some POPs. For instance, Tawar et al. (2022) found the VAT levels of δ-HCH, *p,p'*-DDT, heptachlor and endrin, were positively and significantly correlated with fasting plasma glucose. In this line, other groups also observed positive associations between fasting plasma glucose and serum levels of different PCB congeners [PCB-153, -138 and −180, and the sum of PCBs (ΣPCBs = PCB-153 + PCB-138 + PCB-180)] (Dirinck et al., 2014; Mehta et al., 2021), as well for DDE, HCB and various PCBs (Aminov and Carpenter, 2020). Overall, while the associations between different POPs and specific single MetS components are rather heterogenous in the scientific literature, the associations between these chemical pollutants and the risk of MetS are more consistent. This may be explained by the fact that POPs seem to show a complex interplay with different metabolic organs including AT, the liver, the pancreas and other critical organs (Heindel et al., 2015). Thus, clinically-diagnosed MetS may better reflect the final expected outcome of POPs exposure compared to isolated components.

Table 5
Estimation of the mixture effect of POPs on the risk of MetS using WQS.

Adjusted for age (yr) and sex (male/female)			Adjusted for age (yr), sex (male/female) and BMI		
exp (Beta)	Standard Error	p-value	exp (Beta)	Standard Error	p-value
2.34	0.25	<0.001	2.44	0.37	0.016
	%			%	
γ-HCH	52.90		γ-HCH	47.60	
o,p'-DDT	26.90		*o,p'*-DDT	21.70	
HCB	19.70		PCB-180	26.20	
p,p'-DDE	0.33		PCB-153	4.53	

% shows individual contributions to the WQS index. POPs: Persistent Organic Pollutants; MetS: metabolic syndrome.
WQS: Weighted Quantile Sum; BMI: body mass index.

POPs may contribute to MetS by: 1) promoting obesity through different mechanisms including increased fat accumulation, decreased thermogenesis and disruption of satiety signals; and 2) by altering metabolic signalling in AT and other crucial metabolic organs (e.g., liver, pancreas) and not necessarily mediated through an increase in fat increase (Aaseth et al., 2022; Mustieles and Arrebola, 2020). At a molecular level, POPs may interact with different nuclear receptors involved in adipogenesis and metabolism such as peroxisome-proliferator activated receptors (PPARs) and estrogenic receptors (ERs) among others (Heindel et al., 2015; Mrema et al., 2013; Pereira-Fernandes et al., 2014), as well as with the protein and gene expressions of endoplasmatic stress and pro-inflammatory markers (Tawar et al., 2022). The best-known mechanism of action of some obesogenic POPs is the alteration of PPAR-γ, considered the main regulator of adipogenesis and lipid homeostasis (Gore et al., 2015). Zhang et al. (2015) also reported a POP-induced modification of gut microbiota-host metabolic homeostasis via activation of the AhR.

The mechanisms of action linking POP exposure to MetS are not fully elucidated, but probably involve endocrine disruption, oxidative stress/inflammation and epigenetic mechanisms, which can lead to insulin resistance, as well as the secretion of adipokines and inflammatory cytokines (Artacho-Cordón et al., 2016; Desai et al., 2015; Grünfeld and Bonefeld-Jorgensen, 2004; Mrema et al., 2013; Mustieles et al., 2021; Pandolfi et al., 2016), recently reviewed by Aaseth et al. (2022). In the last decade, additional pathways have been identified, which might also lead to MetS thorough mitochondrial dysfunction (Kim and Lee, 2014), among other mechanisms. All of them contribute to a greater or lesser extent to dysfunctional AT due to POPs exposure. In addition to these typical changes, exposure to POPs has been linked to altered lipid metabolism (lipolytic and lipogenic processes) and altered adipokines involved in energy balance (e.g., leptin and adiponectin) (Bays et al., 2013; Cano-Sancho et al., 2017). Recently, Valvi et al. (2020) analyzed the levels of 18 POPs in abdominal AT from 11 obese adolescents, in addition to potentially altered biological pathways, by untargeted plasma metabolomics assessment. The results found showed high correlations between POPs and metabolic alterations in the pathways of amino acid, lipid and fatty acid metabolism, and carbohydrate metabolism (Valvi et al., 2020). A recent meta-analysis by Lamat et al. (2022) has also reported that HCH would be involved in oxidative dysregulation, altering cytochrome P450, glutathione-S-transferase and glucose-6-phosphate dehydrogenase activities, increasing the risk of MetS compared to other POPs. Previous studies of our team also support the involvement of γ-HCH in the oxidative microenvironment of AT (Artacho-Cordón et al., 2016; Mustieles et al., 2021). Future studies should explore potential modes of action linking POP exposure to MetS, especially using multidisciplinary approaches including combined *in vitro, in vivo* and observational designs.

Several limitations should be acknowledged in this study. Firstly, the sample size was limited, although it was sufficient to yield statistically significant associations. Moreover, our hospital-based population might not be entirely representative of the general population. It is also important to note the cross-sectional design of this study, which only allow us to highlight potential associations, and reverse causality cannot be ruled out, since it was not possible to explore the temporal link between exposure and outcome. Another shortcoming of this study was the limited adjustment for potential confounders (mainly age and sex). Other known potential confounders, such as food intake, physical activity, smoking or alcohol, were not available in the clinical database, nor was the fat content of biopsies determined. Furthermore, mechanisms of action were not addressed in this study. Nevertheless, several mechanistic studies conducted in animals support our findings (Hong et al., 2015; Howell and Mangum, 2011; Mulligan et al., 2017; Ruzzin et al., 2010). Among the strengths of this study was the examination of the associations between exposure and clinically diagnosed MetS. Additionally, we evaluated the influence of POPs on each related MetS components, considering them as continuous and clinical diagnostic components (according to IDF cut-off points). Although the continuous outcomes allowed to increase the statistical power to detect associations, the binary results facilitated the clinical interpretation of the magnitude of the associations found. In addition, the coherence between both types of modelling (continuous *vs*. binary) could be interpreted as a greater degree of confidence in the associations described.

In contrast to previous studies addressing the influence of circulating POP levels in MetS, we have analyzed the contribution of visceral adipose POP levels on the development of MetS. Ample research points to AT being a central factor in POP toxicity (Barrett, 2013; La Merrill et al., 2013), and the recent systematic review of Lamat et al. (2022) supports that the onset of MetS would be linked to visceral adiposity. Moreover, by using AT samples, we were able to partially counteract the possibility of reverse causality, more plausible by measuring POPs in serum samples, due to the so-called disease progression bias (Porta, 2014). AT is also the preferred reservoir for POP accumulation, and concentrations in this matrix can be considered indicative of long-term exposure (Crinnion WJ, 2009; Kohlmeier and Kohlmeier, 1995; Mustieles and Arrebola, 2020).

Although the results found in this study may only indicate an association between POP exposure and MetS risk, and not causation, it is of interest to highlight that a previous study by our team also identified HCB and γ-HCH levels in AT as predictors of MetS components, both in the cross-sectional and longitudinal designs of that study (Mustieles et al., 2017). Moreover, even using different approaches (clinical *vs.* population-based population), different analytical laboratories, and different study areas [the province of Málaga in the current study *vs*. the province of Granada in Mustieles et al. (2017)], similar conclusions have been obtained, supporting the epidemiological literature with this hypothesis.

Our findings shed light on the potential of POPs accumulated in the AT to trigger the risk of MetS, as well as most of the MetS components. It is necessary to recognize the increasing prevalence of the MetS in the world, and therefore, the need to identify preventable risk factors and establish intervention measures to halt and potentially reverse the progression of this syndrome (Saklayen, 2018).

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Credit author statement

Iris Reina-Pérez: Writing - original draft, Data curation, Formal analysis, Writing - review & editing, Visualization, Supervision. Francisco Artacho-Cordón: Methodology, Validation, Data curation, Formal analysis, Investigation, Software, Writing - original draft, Writing - review & editing, Supervision. Vicente Mustieles: Writing - original draft, Data curation, Investigation, Writing - review & editing, Supervision. Daniel Castellano-Castillo: Writing - review & editing, Supervision. Fernando Cardona: Investigation Writing - review & editing, Supervision, Resources. Inmaculada Jiménez-Díaz: Methodology, Validation. Jose A. López-Medina: Investigation Writing - review & editing, Supervision. Juan Alcaide: Data curation, Writing - review & editing, Supervision. Luis Ocaña-Wilhelmi: Writing - review & editing, Supervision. Luz M. Iribarne-Durán: Methodology, Validation. Juan P. Arrebola: Writing - review & editing, Supervision. Nicolás Olea: Writing - review & editing, Supervision, Resources. Francisco J. Tinahones: Investigation, Writing - review & editing, Supervision, Resources. Mariana F. Fernández: Conceptualization, Resources, Funding acquisition, Project administration, Resources. Writing - review & editing, Supervision.

Ethics

This paper includes human samples for the investigation. The study was approved by the Ethics Committee of Virgen de la Victoria Hospital and conducted in accordance with the Declaration of Helsinki. All participants gave their signed consent after being fully informed of the goal and characteristics of the study at recruitment.

Declaration of competing interest

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

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

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