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Historical exposure to persistent organic pollutants and cardiovascular disease: A 15-year longitudinal analysis focused on pharmaceutical consumption in primary care

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ABSTRACT

Background: Despite restrictions on their production and use, most of the population is still exposed to Persistent Organic Pollutants (POPs), including organochlorine pesticides (OCPs) and polychlorinated biphenyls (PCBs). These chemicals are thought to contribute to the aetiology of highly prevalent chronic conditions, such as cardiovascular diseases (CVDs), although current evidences are still controversial.

Objectives: To explore the potential contribution of historical POP exposure to 15-year pharmaceutical consumption in relation to CVD.

Methods: This study is framed within GraMo adult cohort. Participants (n = 387) were recruited in two hospitals in Granada province, Southern Spain (2003–2004). Historical exposure to 5 OCPs and 3 non-dioxine-like PCBs was estimated by analysing adipose tissue concentrations at recruitment. Pharmaceutical consumption from recruitment until year 2017 was quantified by reviewing dispensation databases. Average consumption increase (ACI) in CVD medication was calculated by subtracting average consumption in 2002 to the average yearly consumption during follow-up. ACI was expressed as Defined Daily Dose (DDD)/year units. Data analyses were carried out using a multivariable multinomial logistic regression and weighted quantile sum regression (WQS), with ACI categorized in quartiles (Q) as the dependent variable.

Results: Concentrations of most pollutants showed a positive trend with the quartiles of ACI. Particularly, PCB-153 showed increasing and statistically significant odds ratios (ORs) for Q2 (OR: 1.27, 95% confidence interval (CI): 1.07–1.52), Q3 (OR: 1.49, 95 %CI: 1.17–1.88) and Q4 (OR: 1.42, 95 %CI: 1.13–1.78) vs Q1. Similarly, beta-hexachlorocyclohexane (β-HCH) also showed increasing ORs, that reached statistical significance in Q4 (OR: 1.36, 95 %CI: 1.06–1.74) vs Q1. These findings were corroborated by WQS analyses, that revealed a significant mixture effect, predominantly accounted for by PCB-153 and β-HCH.

Discussion: Our results suggest that long-term POP exposure might represent a modifiable risk factor for CVD. These findings are relevant for public health campaigns and management, since pharmaceutical consumption is considered an indicator of both morbidity and health expenditure.

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1. Introduction

According to the World Health Organization (WHO), 12.6 million of annual deaths are attributable to preventable environmental causes, accounting for 22% of the global burden of disease (life years lost) and 23% of total premature deaths (Prüss-Üstün et al., 2016).

Persistent Organic Pollutants (POPs) represent a relevant health concern (World Bank and CIDA, 2001). POPs are characterized by a great resistance to chemical degradation, lipophilicity and, thus, a high biomagnification and bioaccumulation potential in living organisms (Ritter et al., 1995). In addition, POPs are semi-volatile so that they can be transported over long distances in successive cycles of deposit and re-emission, consequently, can be found in regions far from their sources (Porta et al., 2003, 2002).

POPs include polychlorinated biphenyls (PCBs), used in industrial processes as refrigerants, lubricants, hydraulic fluids, among other commercial applications (WHO, 2014); and organochlorine pesticides (OCPs), used in agricultural activities as insecticides and as vector control (Porta et al., 2002). The production of PCBs and OCPs begun in the 1920s, and were extensively used worldwide from 1940s until 1970s–1980s, when their use and production were severely restricted on the basis of their persistence and suspected health effects. However, they are still present in old equipment and/or used for public health campaigns, as well as in virtually all the ecosystems as a consequence of their high persistence (El-Shahawi et al. 2010; Markowitz, 2018). Consequently, the general population is exposed to relatively low but frequent doses of OCPs and PCBs, with diet being considered the main source of exposure (Darnerud et al., 2006; Pandelova et al., 2011; Arrebola et al., 2012; Bräuner et al., 2012).

Despite the impossibility to completely avoid exposure, certain dietary strategies have shown to decrease exposure levels (Arguin et al., 2010; Guo et al., 2016; Lignell et al., 2016; Perkins et al., 2016; Gupta et al., 2018). Therefore, chronic exposure to OCPs and PCBs could be considered, to some extent, as potentially modifiable.

Low-dose OCP and PCB exposure is suspected to cause endocrine/metabolic disruption and, has been linked to a number of highly-prevalent chronic conditions related to the Metabolic Syndrome (Mustieles et al., 2017; Raffetti et al., 2018). Although with not entirely congruent results, a number of epidemiological studies have evidenced associations of OCP/PCB exposure with several cardiovascular risk factors/conditions, including hypertensive disorders (Henríquez-Hernández et al., 2014; Lind et al., 2014; Arrebola et al., 2015; Park et al., 2016; Donat-Vargas et al., 2018), stroke risk (Lim et al., 2018), altered serum lipids and obesity/adiposity (Arrebola et al., 2014b; La Merrill et al., 2019; J et al., 2020), left ventricular mass (La Merrill et al., 2018), carotid intima-media thickness (cIMT) (Liberda et al., 2019), homocysteine levels (Yin et al., 2020) or myocardial infarction incidence (Mills et al., 2009), among others. The abovementioned conditions are closely inter-related, which hamper the establishment of causal relationships between OCP/PCB exposure and CVD risk. Interestingly, the use of health resources (e.g., pharmaceutical consumption) in relation to CVD might be considered as an adequate proxy of the total burden of disease (Chini et al., 2011; Slobbe et al., 2019). It is noteworthy that CVDs represent the major cause of morbidity and mortality worldwide, with substantial health resource consumption, representing an estimated yearly cost of 110,000 million for the European Union (EU) health systems (Wilkins et al., 2017)

The Spanish Healthcare System follows the so-called Beveridge model of high coverage, based on universality and free access to health services, and covers virtually 100% of the population with legal residence in the country (Ministerio de Sanidad, 2019). Despite the coverage of private health care cannot be dismissed, 70% of Spanish hospital beds belong to the public health system (García-Armesto, 2010). 70.5% of total healthcare expenditure in Spain (77,404 M€) corresponds to public administrations, versus 29.5% (32,451 M€) by the private sector. Both sectors have a positive compound annual growth rate (CAGR), 2.63% in the private sector in comparison with 1% in the public sector, however, the economic impact of the public sector is substantially greater than the private sector (idisalud, 2020).

In order to shed light on the possible contribution of historical POP exposure to CVD burden, the present study aims to longitudinally assess the associations of adipose tissue POP concentrations with the average pharmaceutical consumption over 15 years.

2. Materials and methods

2.1. Design and study population

This study is framed within GraMo adult cohort, focused on the characterization of environmental factors potentially affecting the development of chronic health conditions. The characteristics of the cohort, including study design, recruitment and methods have been extensively described elsewhere (Arrebola et al., 2013, 2014a, 2015). In brief, the study population was recruited during 2003–2004 in two public hospitals from Granada province, Santa Ana Hospital in Motril and San Cecilio University Hospital in the city of Granada. Participants were recruited from patients undergoing different types of surgery (47% inguinal hernia or abdominal surgery, 17% biliary surgery, 12% varicose vein surgery, and 24% other surgeries). Out of 409 patients contacted, 387 agreed to participate (Table 1). All participants signed an informed consent to participate in the cohort, and the present study protocol was approved by the Clinical Research Ethics Committee of Granada (7/2019).

2.2. Exposure assessment

Long-term exposure to POPs was estimated by analysing POP concentrations in adipose tissue. Samples of 5–10 g adipose tissue was intraoperatively collected and immediately coded and stored at −80 °C until chemical analysis. A chemical extraction procedure was performed on the adipose tissue samples to isolate the analytes, as previously described (Botella et al., 2004). Briefly, 200 mg of adipose tissue were extracted using n-hexane and the solution was then purified through

Table 1
Baseline characteristics of the study population and adipose tissue POP concentrations (ng/g lipid).

	n (%)
Sex = male	197 (50.9)
Education	
Primary uncompleted	111 (28.7)
Primary	172 (44.4)
Secondary or higher	104 (26.9)
Residence	
Urban	186 (48.1)
Semi-rural	201 (51.9)
Alcohol consumer (=yes)	200 (51.7)
Smoker (=yes)	126 (32.6)
Deceased during follow-up	61 (15.8)
	Median (P25, P75)
Age (years)	52.0 (37.0–63.0)
BMI (kg/m^2)	26.6 (23.9–29.5)
ACI (DDDs/year)	2.1(0.0–22.2)
Adipose tissue POP concentrations (%>LOD)	**Median (P25 - P75 - Maximum)**
β-HCH (84.0)	10.6 (3.7–21.4–211.9)
***p,p'*-DDE (100.0)**	93.0 (32.9–210.2–2331.4)
HCB (90.7)	14.5 (5.0–39.6–395.4)
PCB-138 (86.0)	82.7 (31.1–136.0–564.1)
PCB-153 (92.0)	223.2 (136.0–361.5–1519.5)
PCB-180 (90.0)	179.6 (104.0–290.2–1363.2)
Dicofol (19.6)	< LOD (<LOD -<LOD − 240)
α-HCH (21.7)	< LOD (<LOD - <LOD − 14)

LOD: Limit of detection. POP concentrations are expressed as ng/g lipid.

200 mg alumina in a glass column and kept in test tubes at − 80 °C. The samples were analysed in Laboratorio Analitico Bioclinico (LAB, SL., Almería, Spain), by means of gas chromatography coupled to mass spectrometry in tandem mode following previously-validated protocols (Rivas et al., 2001; Moreno Frías et al., 2004). The analyses were performed between 2004 and 2005. Residues of *p,p'*-dichlorodiphenyldichloroethylene (*p,p'*-DDE, the main metabolite of the pesticide dichlorodiphenyltrichloroethane [DDT]), hexachlorobenzene (HCB), β-hexachlorocyclohexane (β-HCH), α-hexachlorocyclohexane (α-HCH), dicofol, as well as non-dioxin-like PCB congeners -138, -153, and -180 were quantified. Chromatographic concentrations under the limit of detection (LOD) were assigned a random value between 0 and LOD.

Lipid content of adipose tissue samples was quantified by gravimetry (Rivas et al., 2001), and POP concentrations were expressed on a lipid basis (ng/g lipid).

2.3. Dependent variable

The quantification of pharmaceutical consumption over follow-up was performed by reviewing the participants clinical records in the Andalusian Health System databases. First, all previous CVD episodes were extracted from Diraya Primary Care database (Protti 2007). Pharmaceutical consumption was gathered from MicroStrategy® dispensation database (Microstrategy Healthcare Services, 2021). Pharmaceutical consumption was registered as Defined Daily Dose (DDD) units, defined as the average daily maintenance dose of a drug, in adults, when used routinely in its main indication (Blundell, 2001). The use of DDD units is routinely used both in clinical and research contexts, and help to standardize the consumption of pharmaceuticals with different prices, pharmaceutical forms, therapeutic groups, active ingredients, and package contents, among others (Peretta, 2005).

Pharmaceutical prescriptions related to CVD were selected based on Anatomical, Therapeutic, Chemical classification system (ATC) (WHO, 2020), which classifies pharmacological substances and drugs according to their target system, therapeutic indications and chemical composition. For the purposes of the present study, pharmacological dispensation was classified by using the ATC 4th level, eventually resulting in 44 CVD-related ATC groups in the study population (Supplementary Table 1).

The dependant variable was defined as the average consumption increase (ACI), i.e., the difference between the average annual consumption over follow-up (from recruitment until 31st December 2017 or death) and the average consumption during the year prior to recruitment, expressed as DDDs/year units, as detailed in the formula:

We chose to focus on relative figures instead of using absolute consumption as the dependent variable, since absolute measures would penalize the consumption of those participants prematurely deceased during follow-up, regardless if they had a high average consumption. In addition, the use of differences pre-post recruitment would better account for potential changes/no changes in pharmaceutical consumption over follow-up. As an example, if a participant had been taking a large number of medications before recruitment, he/she will be likely to have an increased consumption during follow- up. However, we also performed additional sensitivity analyses by using the difference between the total pharmaceutical consumption (DDDs) during the last follow-up year and the year prior recruitment (DDDs) as the dependent variable (Supplementary Material Table 2).

$$ACI\left(\frac{DDDs}{year}\right) = \left(\frac{\sum total\ DDDs\ during\ each\ follow\ up\ month}{Number\ of\ follow\ up\ months} - \frac{\sum total\ DDDs\ during\ year\ prior\ recruitment}{12}\right)*12$$

2.4. Covariates

Validated questionnaires were performed by trained staff at recruitment, when sociodemographic, lifestyle, and health characteristics were gathered. The body mass index (BMI) was expressed as weight/height squared (Kg/m^2). Alcohol consumption was considered at $\geq$ 1 drink/week, and smokers were defined as $\geq$ 1 cig. /day. Residence at the time of recruitment in Granada and metropolitan area (529.678 habitants) was considered urban while residence in the area of Motril and surroundings (58.020 habitants) was considered semi-rural. We also registered if patients deceased during the follow-up as well as the date of death.

2.5. Statistical analyses

Descriptive analyses included calculating medians and the 25th and 75th percentiles for continuous variables and percentages for categorical variables. Dicofol and α-HCH concentrations were considered as dichotomous variables (>LOD/<LOD) because of their relatively low number of samples with concentrations > LOD.

The associations between adipose tissue POP concentrations and the pharmaceutical consumption were explored by using multinomial logistic regression, considering ACI as the dependent variable. For this, ACI was categorized into quartiles, with the reference quartile (Q1) represented by those with ACI $\leq$ 0. Thus, for each POP, three odds ratios (ORs) were calculated (Q2 vs Q1, Q3 vs Q1, and Q4 vs Q1). Multinomial logistic regression was used instead of ordinal logistic regression on the basis of the asymmetric distribution of ACI quartiles, with the 4th quartile representing disproportionately higher ACI levels that the others (Fig. 1). POP concentrations were natural log-transformed in order to minimize their skewed distribution. Models were adjusted for sex, age, body mass index, deceased during follow-up, education, residence, smoking habit, and alcohol consumption.

The potential mixture effect of the selected POPs on ACI was estimated by means of 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 its corresponding outcome were further studied by using multinomial logistic regression. Therefore, three WQS indices were calculated (i.e., Q2 vs Q1, Q3 vs Q1, and Q4 vs Q1). WQS model was adjusted for the same covariates included in the individual models. The WQS analysis was performed with 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 500 bootstrap steps. Only POP concentrations that were treated as continuous variables were included in the WQS analyses (i.e., *p,p'*-DDE, HCB, β-HCH, and PCB congeners −138, −153 and −180).

Statistical analyses were performed by using R statistical computing environment v4.0.3 (R Development Core Team, 2019), ggplot2 (Wickham, 2009), and gWQS v3.0.1 (Renzetti et al., 2021) packages.

3. Results

3.1. Study population

Main characteristics of the study population, adipose tissue POP concentrations and detection levels are summarized in Table 1, and have

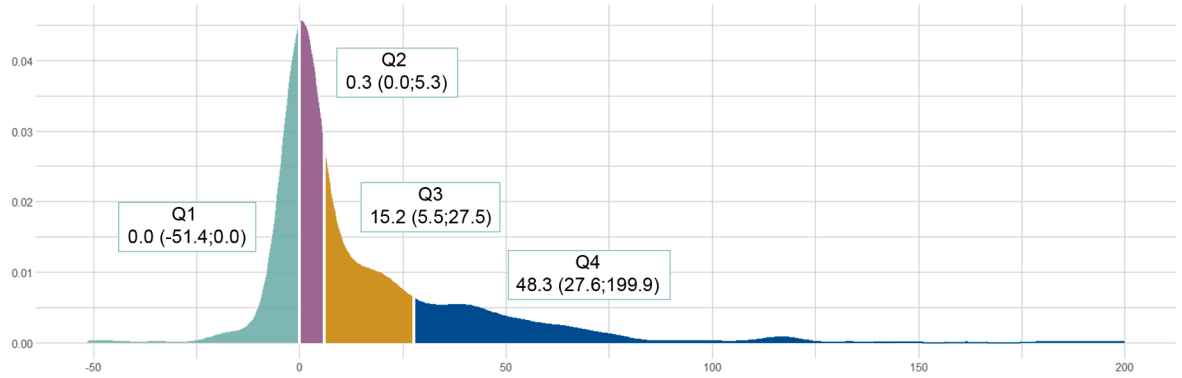


Fig. 1. Distribution of ACI levels in the study population. Density plot. *Below each ACI quartile (Q1-Q4), median (range) ACI values are displayed.*

been discussed elsewhere (Arrebola et al., 2009, 2010; Arrebola, 2013). As reported elsewhere, moderate-to-high Spearman correlations were found for both the three PCB congeners ($0.86 \leq \rho \leq 0.95$) the group of OCPs ($0.69 \leq \rho \leq 0.84$) (Echeverría et al., 2020). The distribution of ACI values in the study population is described in Table 1 and Fig. 1.

3.2. Associations of adipose tissue POP concentrations and ACI

In multinomial logistic regression models, the concentrations of most POPs showed a positive trend with the quartiles of ACI (Table 2). Particularly, PCB-153 showed increasing and statistically significant ORs for Q2, Q3 and Q4 vs Q1. Similarly, β-HCH also showed increasing ORs, that reached statistical significance in Q4 vs Q1 (Table 2). In general, we also observed positive associations in the models using the difference between the total consumption over the last follow-up year and the year before recruitment, although the highest ORs were observed in Q3 instead of Q4 (Supplementary Table 2).

Taking Q1 as the reference quartile in multinomial logistic regression analyses, WQS index showed significant and positive ORs for Q2 (OR:1.09, 95 %CI: 0.84,1.42), Q3 (OR:1.75, 95 %CI: 1.18,2.60), and Q4 (OR: 1.59, 95 %CI: 1.12,2.26). PCB-153 was the main contributor to these indices, as shown in Fig. 2.

Supplementary Table 1 displays a detailed description of all ATC groups representing each ACI quartile. Briefly, Q4 mainly included medication related to hypertension (e.g., C09AA: ACE inhibitors, plain; C09CA: Angiotensin II receptor blockers [ARBs], plain), hypercholesterolemia (C10AA: HMG CoA reductase inhibitors) and antithrombotic agents (B01AC: Platelet aggregation inhibitors excl. Heparin) . The same pharmaceuticals accounted for the majority of total ACI in Q3, in addition to the use of combinations of antihypertensive drugs with diuretics (C09DA: Angiotensin II antagonists and diuretics) (Supplementary Table 1).

4. Discussion

To the best of our knowledge, our study represents the first individual epidemiological study exploring the impact of long-term POP exposure on CVD pharmaceutical prescriptions.

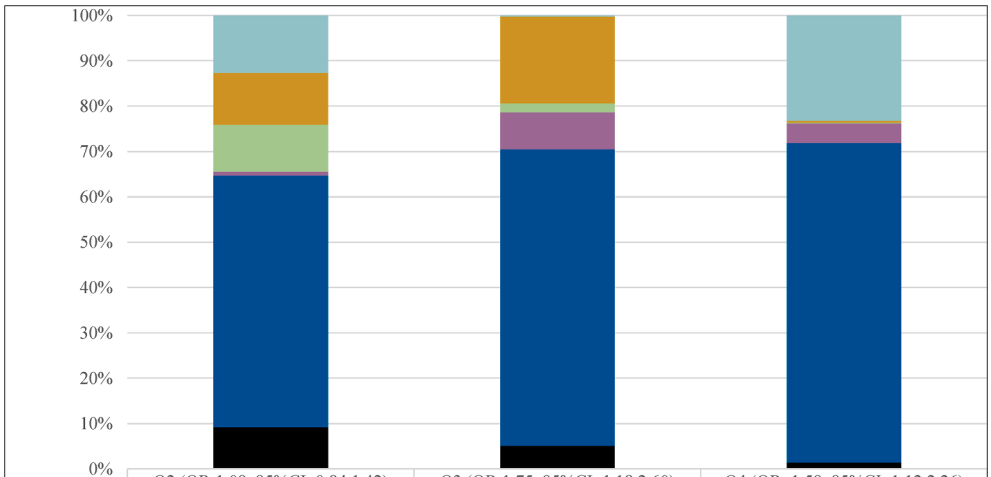
Our results complement previously-described associations of accumulated adipose tissue POP concentrations with CVD risk factors within GraMo cohort, such as hypertension (Arrebola et al., 2015), increased serum lipids and obesity (Arrebola et al., 2014b), and metabolic syndrome (Mustieles et al., 2017). Previous studies on different populations also reported positive associations between internal POP levels and cardiovascular conditions, such as multiple PCB congeners and *p,p'*-DDE with elevated blood pressure (Donat-Vargas et al., 2018; Goncharov et al., 2011), *p,p'*-DDE with increased serum lipoproteins (Jugan et al., 2020), dioxins, PCBs and perfluoroalkyl substances (PFASs) with atherosclerosis (Lind and Lind, 2020), and PCBs with mortality risk (Lind et al., 2019). However, current evidence is still conflicting (Encarnação et al., 2019; Lee et al., 2016; Valera et al., 2013) or inconclusive (Raffetti et al., 2018), Therefore, it is important that future research studies continue to deepen into these relationships. (Perkins et al., 2016)

It is noteworthy that CVD represents a highly heterogeneous and overlapped cluster of conditions (Murakami et al., 2013), which might hamper the elucidation of associations when specific CVDs are considered as individual outcomes. The use of prescription data may compensate this issue, since it is considered an adequate indicator of the total burden of CVD and other chronic diseases (Chini et al., 2011; Slobbe et al., 2019). Indeed, it is highly frequent that CVD patients receive common medication for different conditions, e.g., angiotensin converting enzyme inhibitors (ACE inhibitors) as antihypertensives and/or in secondary prevention of acute coronary syndrome. In addition, drug dispensing databases may complement information gathered

Table 2
Individual associations of adipose tissue POP concentrations with ACI in CVD. Multivariable multinomial logistic regression models.

	ACI Quartiles (n)(range)											
	Q2 (n = 87)(0.01; 5.31)				**Q3 (n = 87)**(5.53; 27.49)				**Q4 (n = 87)**(27.63; 199.89)			
	OR	95% CI		p-value	OR	95 %CI		p-value	OR	95 %CI		p-value
		lower	upper			lower	upper			lower	upper	
β-HCH (ng/g lipid)	1.03	0.87	1.22	0.714	1.12	0.91	1.36	0.282	1.36	1.06	1.74	0.018
p,p'-DDE (ng/g lipid)	0.93	0.71	1.21	0.596	1.21	0.91	1.60	0.196	1.04	0.78	1.38	0.811
HCB (ng/g lipid)	1.04	0.87	1.24	0.690	1.09	0.88	1.36	0.436	1.23	0.96	1.57	0.110
PCB-138 (ng/g lipid)	0.97	0.85	1.10	0.598	1.09	0.90	1.32	0.378	1.02	0.84	1.24	0.873
PCB-153 (ng/g lipid)	1.27	1.07	1.52	0.008	1.49	1.17	1.88	0.001	1.42	1.13	1.78	0.003
PCB-180 (ng/g lipid)	1.01	0.87	1.18	0.855	1.15	0.91	1.44	0.243	1.07	0.85	1.35	0.547
Dicofol (>LOD vs < LOD)	1.16	0.56	2.41	0.685	0.99	0.46	2.14	0.976	0.73	0.31	1.73	0.479
α-HCH (>LOD vs < LOD)	2.31	0.90	5.91	0.081	1.27	0.51	3.17	0.613	1.56	0.61	3.95	0.353

CVD: Cardiovascular disease; OR: Odds Ratio; 95% CI: Confidence Interval; Q: Quartile; Reference quartile: Q1 (n = 126).
Model adjusted for sex, age, body mass index, deceased during follow-up, education, residence, smoking habit, alcohol consumption.



	Q2 (OR:1.09, 95%CI: 0.84,1.42)	Q3 (OR:1.75, 95%CI: 1.18,2.60)	Q4 (OR: 1.59, 95%CI: 1.12,2.26)
β-HCH	12.7%	0.3%	23.2%
p,p'-DDE	11.4%	19.1%	0.4%
HCB	10.3%	2.0%	0.2%
PCB-138	0.9%	8.1%	4.3%
PCB-153	55.4%	65.5%	70.5%
PCB-180	9.2%	5.0%	1.4%

Fig. 2. Estimated mixture effect of POPs and individual contributions on ACI quartiles. WQS Multinomial Logistic Regression Analyses. *Q: ACI quartiles. Q1 was used as the reference quartile.*

from clinical records with more objective data, since the latter are frequently filled in by different professionals with not always similar criteria.

In our study, we evidenced significantly increased odds for belonging to higher quartiles of ACI with higher levels of adipose tissue PCB-153 concentrations, although positive trends were also observed for the majority of POPs. The strong correlations among adipose tissue OCP and PCB concentrations hamper ascertainment of individual effects, which represents a current issue for environmental epidemiology (Mustieles and Arrebola, 2020). Moreover, a mixture effect caused by exposure to a myriad of chemicals with similar structures and mechanisms of action cannot be rule out (Braun et al. 2016). Indeed, WQS regression showed a significant combined effect of POPs, mainly explained by PCB-153 and β-HCH, indicating a potential mixture effect on the disease development.

It is worth to mention that the associations found between POPs and ACI are mainly explained by medication for highly relevant cardiovascular conditions, such as antihypertensive, lipid-lowering, and antithrombotic treatments (Supplementary Table 1). Indeed, these drugs are considered among the 15 pharmaceuticals most widely dispensed in Spain (MSCBS 2018), with lipid-lowering prescriptions accounting for 6.2% of total dispensations.

Our study population was entirely covered by the Andalusian Health Service during the follow-up. However, we cannot exclude that a number of participants were underdiagnosed, i.e., not detected at a clinical setting. This fact has been highlighted in previous epidemiological research estimating a prevalence of underdiagnosed ischemic heart disease and hypertension of, respectively, 35–50% and 30–40% (Falagas et al., 2007). Another source of misclassification bias might relate to the potential low adherence to the treatment of certain individuals. Furthermore, in the present study we did not account for changes in exposure and covariates over follow-up, e.g., BMI or smoking habit, which might modify the disease risk. Indeed, substantial weight changes could induce the release of POPs from adipose tissue and, therefore, alter POP bioavailability (Chevrier et al., 2000). The above-mentioned non-differential biases would likely attenuate the associations found.

Lastly, and despite using one single measurement at recruitment, POP exposure was estimated by analyzing adipose tissue concentrations, which are considered the most accurate estimator of long-term exposure to persistent organic pollutants (Jackson et al., 2017). Furthermore, adipose tissue dysfunction has been acknowledged to play a critical role in the development of a number of cardiometabolic conditions and, therefore, might also be considered a target site for the effect of POPs (Rolle-Kampczyk et al., 2020), that would trigger subclinical processes related to the future onset of diseases, e.g., oxidative stress or inflammation (Artacho-Cordón et al., 2016; Ferro et al., 2019).

5. Conclusions

This is the first study using the healthcare expenditure approach to explore associations between human exposure to environmental pollutants and disease development. Historical POP exposure was associated with increased pharmaceutical consumption for the treatment of CVD. We are highly confident on the relevance of our findings, since OCP and PCB exposure is still highly ubiquitous – but potentially modifiable - in the general population (Kahleova et al., 2016), and CVD represents a major public health concern with substantial implications for health economy (Leal et al., 2006). Confirmation in further multidisciplinary studies is required in order to ascertain the overall implications of POP exposure for the health systems.

CRediT authorship contribution statement

Francisco Miguel Pérez-Carrascosa: Data curation, Software, Formal analysis, Investigation, Visualization, Writing - original draft, Writing - review & editing. **Celia Gómez-Peña:** Data curation, Software, Formal analysis, Investigation, Visualization, Writing - original draft, Writing - review & editing. **Ruth Echeverría:** Visualization, Writing - review & editing. **José Juan Jiménez Moleón:** Writing - review & editing. **Juan Manuel Melchor:** Formal analysis, Software, Writing - review & editing. **Antonio García-Ruiz:** Writing - review & editing. **José Luis Navarro-Espigares:** Writing - review & editing. **José Cabeza-Barrera:** Writing - review & editing. **Piedad Martin-Olmedo:** Writing - review & editing. **Juan Carlos Ortigosa-García:** Data curation, Software. **Juan Pedro Arrebola:** Conceptualization, Methodology, Investigation, Supervision, Project administration, Funding acquisition.

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2021.106734.

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