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Public healthcare costs associated with long-term exposure to mixtures of persistent organic pollutants in two areas of Southern Spain: A longitudinal analysis.

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ABSTRACT

Background: Polychlorinated biphenyls and organochlorine pesticides are persistent organic pollutants (POPs) that had been banned or restricted in many countries, including Spain. However, their ubiquity still poses environmental and human health threats.
Objective: To longitudinally explore public healthcare costs associated with long-term exposure to a mixture of 8 POPs in a cohort of residents of two areas of Granada Province, Southern Spain.
Methods: Longitudinal study in a subsample ($n = 385$) of GraMo adult cohort. Exposure assessment was performed by analyzing adipose tissue POP concentrations at recruitment. Average primary care (APC) and average hospital care (AHC) expenditures of each participant over 14 years were estimated using the data from their medical records. Data analyses were performed by robust MM regression, weighted quantile sum regression (WQS) and G-computation analysis.
Results: In the adjusted robust MM models for APC, most POPs showed positive beta coefficients, being Hexachlorobenzene (HCB) significantly associated (β: 1.87; 95% Confidence interval (95%CI): 0.17, 3.57). The magnitude of this association increased (β: 3.72; 95%CI: 0.80, 6.64) when the analyses were restricted to semi-rural residents, where β-HCH was also marginally-significantly associated to APC (β: 3.40; 95%CI: −0.10, 6.90). WQS revealed a positive but non-significant mixture association with APC (β: 0.14; 95%CI: −0.06, 0.34), mainly accounted for by β-HCH (54%) and HCB (43%), that was borderline-significant in the semi-rural residents (β: 0.23; 95%CI: −0.01, 0.48). No significant results were observed in G-Computation analyses.
Conclusion: Long-term exposure to POP mixtures might represent a modifiable factor increasing healthcare costs, thus affecting the efficiency of the healthcare systems. However, and owing the complexity of the potential causal pathways and the limitations of the present study, further research is warranted to fully elucidate ascertain whether interventions to reduce human exposure should be considered in healthcare policies.

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1. Introduction

Persistent organic pollutants (POPs) are chemical pollutants that have long been a matter of public health concern because of their potential toxicity to humans and environment, high resistance to degradation and high bioaccumulation potential in living organisms, especially in fatty compartments (Idowu et al., 2013; Pacyna-Kuchta et al., 2020). POPs include polychlorinated biphenyls (PCBs) as well as organochlorine pesticides (OCPs). PCBs are characterized by high thermal stability and high resistance to flammability. PCBs were used as lubricating oils, dielectrics, hydraulic fluids, insulating resins, paints, waxes, or concrete joint sealants. Despite their worldwide banning and severe restrictions on their use, PCBs can still be found in old equipment (Wexler et al., 2011). OCPs were first used to control vector-borne diseases such as malaria as well as agricultural plagues, and for seed preservation, and were also gradually banned in most countries worldwide (Awasthi and Awasthi, 2019). Both OCPs and PCBs can be found in lipid-rich foodstuff, such as red meat, eggs, milk and fish. Indeed, the diet is considered the main source for POP exposure in the general population (Harmouche-Karaki et al., 2019). Despite mentioned restrictions, POPs can be detected in virtually all human populations (Arrebola et al., 2013a; Mercado et al., 2013; Centers for Disease Control and Prevention, 2021). A number of studies have linked PCB and OCP human exposure with an increased risk of a variety of chronic diseases, such as diabetes, cardiovascular disease and cancer (Airaksinen et al., 2011; Arrebola et al., 2015; Barrios-Rodríguez et al., 2021; Magliano et al., 2021; Mustieles et al., 2021). However, the results in the literature are still controversial. This poses a potential relevant problem for public health, since these chronic conditions are considered relevant causes of morbidity and mortality (WHO, 2021), thus, being major determinants of healthcare costs for healthcare systems (Duff-Brown, 2017). Indeed, in the United States, total direct healthcare costs over 2016 related to chronic conditions reached 1.1 trillion USD, equivalent to 5.8% of the national gross domestic product (GDP). Particularly, cardiovascular disease and diabetes are those with the highest direct costs associated (Waters H, 2020). Likewise, the Organisation for Economic Co-operation and Development (OECD) estimated that chronicity accounted for 550, 000 deaths in the European Union (38,000 in Spain), representing 115 billion € per year for the EU, equivalent to 0.8% of Europe's annual GDP. Noteworthy, cardiovascular disease, cancer, respiratory disease and diabetes account for 60% of hospitalizations, 85% of admissions to internal medicine wards and 80% of primary care consultations in the Spanish Healthcare System, resulting in 80% of total healthcare costs (Estévez and Guerrero, 2015).

Our study aims to longitudinally explore public healthcare costs associated with long-term exposure to a mixture of 8 Persistent Organic Pollutants (POPs) in a cohort of residents of two areas of Granada Province (Southern Spain).

2. Materials and methods

2.1. Design and study population

This study was performed within the GraMo cohort, which has been extensively described elsewhere (Arrebola et al., 2013a, 2014a, 2015). The study population was intraoperatively recruited in 2003 and 2004, in two public hospitals of the province of Granada (Spain): Santa Ana Hospital in the Southern coastal town of Motril, and San Cecilio University Hospital in the inland city of Granada. Reasons for surgery were a total of 70 different health issues, including hernias, gallbladder diseases, varicose veins and others (Mustieles et al., 2017). From the 409 patients initially invited, 387 agreed to participate and signed the informed consent. Two participants who died 1 and 9 months after recruitment, respectively, were not included in the analyses. We considered that these data might distort the results since the extremely short follow-up do not allow to ascertain long-term health expenditure in relation to POP exposure. Thus, 385 participants constituted the final study population.

2.2. Exposure assessment

Historical POP exposure was estimated by analysing their concentrations in adipose tissue samples collected at recruitment. An adipose tissue sample of 5–10 g was obtained of each participant and immediately stored at −80 °C. Analytical protocols and quality control have been previously described in detail, including the calculation of linearity, limits of detection, recovery, precision, specificity, and uncertainty (Rivas et al., 2001; Moreno Frías et al., 2004; Arrebola et al., 2013a; Artacho-Cordón et al., 2016a). After undergoing a chemical extraction process, the samples were analysed in Laboratorio Analítico Bioclínico (LAB, SL., Almería, Spain), by means of gas chromatography coupled to mass spectrometry in tandem mode. Residues of the following POPs were quantified: *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, and non-dioxin-like PCB congeners −138, −153 and −180. Chromatographic concentrations under the limit of detection (LOD) were assigned a random value between 0 and the LOD. LODs for target analytes have been reported in previous publications (Arrebola et al., 2016; Artacho-Cordón et al., 2016a; Mustieles et al., 2017b).

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

2.3. Dependent variables

Dependent variables were calculated following the so-called partial economic evaluation in health economics, specifically, a cost description or cost of illness study (Drummond et al., 2015). The main study outcomes were the direct healthcare costs of each participant from recruitment until December 31, 2017. The information on individual healthcare events was gathered by reviewing primary and hospital care electronic records in the Andalusian Health System - so-called DIRAYA database - (Protti, 2007), with the exception of pharmaceutical expenditure, obtained from MicroStrategy® database dispensation software for primary care and Farmatools Dominion software for hospital dispensations. Monetization of the events was performed by using the public price catalog of the Andalusian Health Service (Servicio Andaluz de Salud, 2019). For each participant, the total cost of his/her specific events was calculated by multiplying the event's price by the times it occurred. Total costs were expressed in Euros (€) and standardized by considering the 2003–2017 series of the Consumer Price Index (CPI) of Andalusia (INE, 2021).

Finally, standardized costs were expressed for each patient as average yearly costs, applying the following formula:

$$Average\ healthcare\ cost(€ / year) = \frac{\sum total\ patient\acute{s}\ costs - \sum patient\acute{s}\ cost\ at\ year\ of\ recruitment}{Follow-up\ years\ after\ the\ year\ of\ recruitment}$$

Healthcare average costs were calculated both for hospital healthcare and primary healthcare, i.e., Average Hospital Care Costs (AHC) and Average Primary Care Costs (APC), respectively.

2.4. Covariates

Sociodemographic, lifestyle and clinical data were collected by trained staff at recruitment using pre-validated questionnaires (Buckland et al., 2009; Gonzalez and Riboli, 2010). Residence in Granada and metropolitan area (529,678 inhabitants at recruitment) was considered as urban area, while residence in Motril and surroundings (58,020 inhabitants at recruitment) was considered as semi-rural area. Alcohol consumption was considered at ≥1 drinks/week, and smoking habit was defined as ≥1 cig./day. Body mass index (BMI) was calculated from participant's weight and height at recruitment, and expressed as Kg/m^2.

2.5. Statistical analyses

Descriptive analyses included the calculation of means, medians, 25th and 75th percentiles, minimum and maximum 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.

We evidenced a total of 10 outliers in AHC and 6 in APC, defined as those with z-scores significantly higher/lower than 1.96 ($p < 0.05$). No independent nor dependent variable showed a normal distribution according to Kolmogorov-Smirnov's normality test with Lilliefors' correction. Considering the abovementioned, the associations of POP concentrations with healthcare costs were explored by means of robust regression based on MM-estimators (Wilcox, 2017). Models were a priori adjusted for the following covariates: age at recruitment (years), sex (male/female), BMI (Kg/m^2), residence area (urban/semi-rural), follow-up period (years), smoking habit (smoker/former smoker/non-smoker), and alcohol consumption (consumer/no consumer). In order to improve model comparability, we adjusted for dietary variables whose inclusion produced a change in any POP coefficient of >10%), i.e., consumption of chicken (consumer/no consumer), fruit (≤1/week, ≥2/week), vegetables (<2/week, ≥2/week), dairy products (never, ≤2/week, >2/week, every day) and fish (never, <1/week, 1/week, 2/week, >2/week). Multicollinearity was assessed by calculating variance inflation factors (VIFs), that were all <2.

The potential mixture associations of selected POPs on AHC and APC were estimated by Weighted Quantile Sum (WQS) regression (Carrico et al., 2015) and Quantile G-Computation (Nguyen et al., 2021). Both methods combine the individual associations into a weighted index, and estimate the specific weight for each chemical in the mixture. We excluded dicofol and α-HCH of the analysis due to their low level of detection. Both WQS and Quantile G-Computation analyses were performed by generating 1000 bootstrap samples and were adjusted for the same covariates included in the single-chemical models. In addition, WQS analyses were performed using continuous pollutant concentrations, with a training set defined as a random sample of 40% of the data set, with the remaining 60% being used for model validation, in order to maximize the variability and representativeness of our relatively limited population. Beta values for WQS index show the increase in the dependent variable per 1-unit increase in the WQS index. On the other hand, beta values for Quantile G-Computation index show the increase in the dependent variable corresponding to an increase of one quartile in all the exposures included in the analysis. While WQS requires to specify a priori the expected direction of all the individual associations within the mixture (positive or negative), individual contributions to the mixture associations in Quantile G-Computation can have opposite directions (Keil et al., 2020). Considering that virtually all the associations in the individual models yielded positive coefficients, WQS analyses were performed assuming positive associations. Dependent variables were log2-transformed in order to improve data normality minimize the effect of outliers in the WQS and Quantile G-Computation analyses (Lee, 2020).

Statistical analyses were performed using R statistical computing environment v4.1.1 (R Core Team, 2021), and packages robustbase v0.93–9 (Maechler et al., 2021), rrcov v3.0.1 (Todorov, 2021), MASS v7.3-54 (Venables and Ripley, 2002), gWQS v3.0.1 (Renzetti et al., 2021) and qgcomp v2.8.0 (Keil et al., 2020). Our findings were interpreted in a global context, including statistical significance but also the magnitude of the associations, consistency, plausibility and coherence with the literature (Amrhein et al., 2019).

3. Results

3.1. Study population

The number of participants in our study population is similar in both areas of residence. While in the urban area there was a slightly higher proportion of males (56%), females were predominant in the semi-rural (55%). In comparison to the semi-rural area, urban residents showed a higher percentage of individuals with ≥secondary studies (31% *vs* 24%). Both APC and AHC expenditure, as well as adipose tissue concentrations of PCB-153, PCB-180, and HCB were higher in the urban area. While semi-rural residents showed increased median concentrations of β-HCH, *p,p'*-DDE and PCB-138 (Table 1). A summary of the dietary variables is displayed as Supplementary Material (Supplementary Table S1).

The main groups of healthcare items contributing to the overall healthcare costs in the GraMo cohort are summarized in Table 2. Hospitalization events (including surgery) and pharmaceutical dispensation accounted for 74% of total AHC in the cohort. While in APC pharmaceutical dispensations were similar in both areas, most pharmaceutical expenses in AHC were performed in the urban area (95%). Our finding in AHC is probably since more complex treatments are frequently derived to the main hospital in the urban area. In APC, the expenses were mainly accounted for (98%) by nursing, medical consultations events, and pharmaceutical dispensation. Total healthcare costs over follow-up for the 385 participants were 9.64 million €, with AHC (54.6% of the total) being slightly higher than APC (45.4% of the total) (Table 2). The urban area accounted for the majority (66%) of AHC, while primary healthcare costs are similar in both areas. Median (percentiles 25th-75th) healthcare cost per patient was 14,130.49 € (4848.01–30,309.01) (data not shown).

At the end of the follow-up (December 31, 2017), 76% of the participants had had at least one event related to chronic diseases, as

Table 1
Description of study population, POP concentrations and healthcare costs by residence area in the study population (n = 385).

	n (%)		
	Urban 185 (48.1)	**Semi-rural 200 (51.9)**	**Total 385 (100)**
Sex			
Male	104 (56.2)	91 (45.5)	195 (50.6)
Female	81 (43.8)	109 (54.5)	190 (49.4)
Education			
Primary uncompleted	45 (24.3)	65 (32.5)	110 (28.6)
Primary	83 (44.9)	88 (44.0)	171 (44.4)
Secondary or higher	57 (30.8)	47 (23.5)	104 (27.0)
Alcohol consumer (= yes)	102 (55.1)	97 (48.5)	199 (51.7)
Smoker (= yes)	62 (33.5)	63 (31.5)	125 (32.5)
Social Class			
Non-manual worker	35 (18.9)	36 (18.0)	71 (18.4)
Manual worker	130 (70.3)	163 (81.5)	293 (76.1)
Retired	20 (10.8)	1 (0.5)	21 (5.5)
Deceased over follow-up	31 (16.8)	27 (13.5)	58 (15.1)
Chronic disease at the end of follow-up(= yes)	142 (76.8)	150 (75.0)	292 (75.8)
	Urban	**Semi-rural**	**Total**
	Median (IQR)	**Median (IQR)**	**Median (IQR)**
Age at recruitment (years)	54 (25.5)	48 (27)	52 (26.0)
Age at the end of follow-up (years)	67 (24.5)	61 (27.5)	64 (27.0)
Follow-up time (years)	12.9 (0.0)	13.9 (0.0)	12.9 (1.0)
Time to death (years, n = 58)	14 (1.0)	13 (1.0)	8.2 (5.8)
BMI (kg/m^2)	26.5 (3.0)	26.7 (5.6)	26.6 (5.6)
APC (Euros)	649.4 (1278.6)	548.0 (1030.7)	572.7 (1172.5)
AHC (Euros)	528.7 (1394.6)	266.9 (654.8)	378.3 (852.7)
	Urban	**Semi-rural**	**Total**
Adipose tissue POP concentrations (% > LOD) (ng/g lipid)	**Median (IQR)**	**Median (IQR)**	**Median (IQR)**
HCB (90.7)	19.7 (42.3)	11.3 (29.4)	14.6 (34.6)
β-HCH (84.0)	10.3 (18.0)	10.6 (16.8)	10.6 (17.7)
***p.p'*-DDE (100.0)**	89.9 (180.3)	93.1 (176.2)	90.6 (176.6)
PCB-138 (86.0)	76.4 (77.8)	93.6 (125.4)	82.6 (105.2)
PCB-153 (92.0)	238.3 (203.1)	209.8 (259.2)	221.9 (225)
PCB-180 (90.0)	183.8 (187.2)	176.6 (190.4)	179.2 (185)
Dicofol (19.7)	<LOD (<LOD)	<LOD (1.0)	<LOD (<LOD)
α-HCH (21.6)	<LOD (<LOD)	<LOD (1.0)	<LOD (<LOD)

LOD: Limit of detection; BMI: Body Mass Index at recruitment; APC: Average Primary Care Costs during follow-up; AHC: Average Hospital Care Costs during follow-up; HCB: Hexachlorobenzene; β-HCH: β-Hexachlorocyclohexane; p,p'-DDE: p-p'-Dichlorodiphenyldichloroethylene; PCB-138, -153, −180: Polychlorinated Biphenyls −138, −153 and −180; α-HCH: α- Hexachlorocyclohexane; IQR: Interquartile Range.

defined by the WHO (2021). Most frequent incident diseases in our cohort were the following: cardiovascular disease (n = 241; 62%), total cancer (n = 78, 20%), diabetes (n = 57; 15%), and chronic respiratory diseases (n = 51; 13%). The magnitude of these data are similar to those published for the region of Andalucía (OPIMEC).

3.2. Adipose tissue POP concentrations and healthcare costs: single-chemical models

A description of healthcare expenditure by adipose tissue POP concentration quartiles is shown as Supplementary material (Supplementary figure S1). In general, we observed higher APC and AHC with increasing POP quartiles.

In the adjusted robust MM single-chemical models for APC, most POPs showed positive beta coefficients, being Hexachlorobenzene (HCB) significantly associated (β: 1.87; 95% Confidence interval (95% CI): 0.17–3.57) (Table 3). In this regard, an increase in one interquartile range (IQR) of HCB concentrations was associated with an increase of 64.7 € in APC over follow-up (Table 3). The results were congruent when considering POP concentrations categorized in quartiles as independent variable, since an apparently positive dose-response association was observed for HCB with APC, although the limited sample size in each quartile hampered statistical significance (Supplementary material, Table S2). No association was observed between POP concentrations and AHC in the overall population (Table 3).

Given that we previously observed different OCP levels in the two study areas (Arrebola et al., 2009, 2013a; Echeverría et al., 2020), and considering that health expenditure might be influenced by the reference hospital as well as specific sociodemographic characteristics of the populations, we performed sensitivity analyses stratified by residence (Urban/Semi-rural) (Supplementary table S3). In the semi-rural area, HCB and β-HCH were positively associated with increased APC (Fig. 1, Supplementary table S3), while no association was observed in the urban area. No significant associations were found with AHC in the stratified models (Supplementary table S3).

3.3. Associations of adipose tissue POP concentrations with healthcare costs: multi-pollutant models

WQS analysis revealed a positive but non-significant POP mixture association with APC (β: 0.14, 95% CI: −0.06, 0.34) (Fig. 2), as well as a negative and non-significant association with AHC (β: −0.09, 95% CI: −0.32, 0.15) (Supplementary figure S2). After stratification by residence, multi-pollutant associations were only evident in the semi-rural area (β: 0.23; 95%CI: −0.01, 0.48) (Fig. 2, Supplementary figure S2). The mixture associations observed with APC in the semi-rural area was mainly accounted for by β-HCH (55%) and HCB (19%) (Fig. 2).

On the other hand, G-Computation analyses showed positive but non-significant coefficients for the POP mixture association with APC in the whole population (β: −0.01; 95% CI: −0.18, 0.15) as well as in the semi-rural (β: 0.01; 95% CI: −0.21, 0.22) and urban areas (β: −0.01; 95% CI: −0.28, 0.27) (Fig. 3). Lastly, we did not find any mixture association with AHC in the G-Computation analyses (Supplementary figure S3).

4. Discussion

In the present novel study, we have evidenced the potential economic implications of chronic exposure to selected POPs for health systems. Indeed, our results are in line with previously reported associations in the GraMo cohort of POP exposure with highly prevalent chronic conditions, i.e., such as type 2 diabetes, hypertension and other cardiovascular risk factors, and cancer (Arrebola et al., 2013c, 2014a, 2014b, 2015; Barrios-Rodríguez et al., 2021; Pérez-Carrascosa FM et al., 2021; Mustieles et al., 2021). Interestingly, previous research using aggregated data reported increased healthcare costs associated with environmental pollutant exposure in the European Union, (Trasande et al., 2015, 2016, 2017; Attina et al., 2016). Interestingly, the high variability of potential health outcomes linked to the exposure is in agreement with previously described unspecific mechanisms of action, such as oxidative stress, inflammation, or activation of cell growth pathway (Kumar et al., 2014; Artacho-Cordón et al., 2016b; Klaunig et al., 2020).

Interestingly, associations between OCPs and primary healthcare cost were mainly observed in semi-rural residents. Primary healthcare is the first level of ordinary access to the Spanish Public Healthcare System, providing, among others, therapy and follow-up of most frequent

Table 2
Main items contributing to healthcare costs in GraMo cohort by residence area.

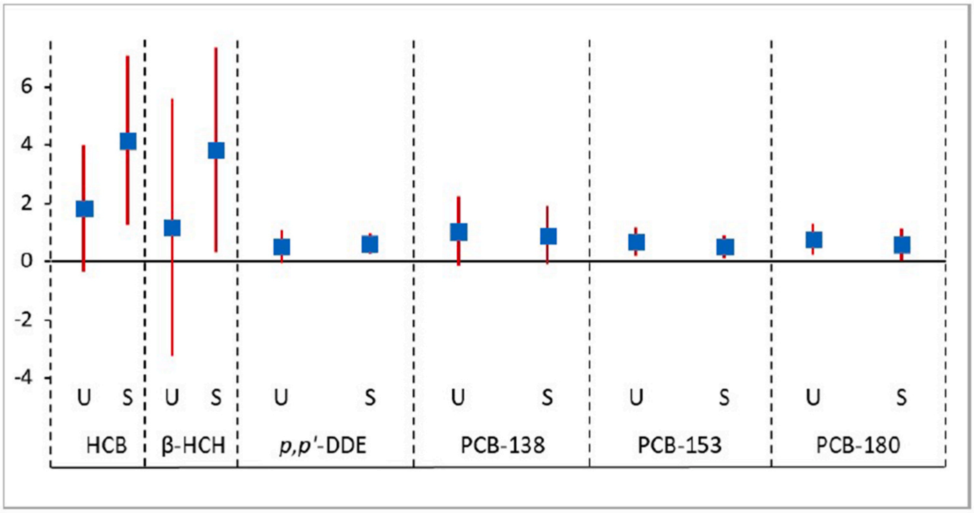
	AHC (54.6%)			APC (45.4%)		
	Laboratory test			Minor Surgery		
	Semi-rural	Urban	Total	Semi-rural	Urban	Total
Total cost (€)	81,638.00	75,514.65	157,152.65	1986.16	1555.93	3542.09
%	51.9%	48.1%	100.0%	56.1%	43.9%	100.0%
Number of events	6326	5609	11,935	18	14	32
	Diagnostisc test			**Other consultations**		
	Semi-rural	**Urban**	**Total**	**Semi-rural**	**Urban**	**Total**
Total cost (€)	209,467.13	344,658.11	554,125.24	11,497.20	25,281.39	36,778.59
%	37.8%	62.2%	100.0%	31.3%	68.7%	100.0%
Number of events	1591	3585	5176	471	614	1085
	Outpatients and emergency consultations			**Diagnostisc test**		
	Semi-rural	**Urban**	**Total**	**Semi-rural**	**Urban**	**Total**
Total cost (€)	179,008.20	468,474.95	647,483.15	21,152.36	17,042.91	38,195.27
%	27.6%	72.4%	100.0%	55.4%	44.6%	100.0%
Number of events	3013	6998	10,011	356	375	731
	Pharmaceutical dispensation			**Nursing consultations (Cures, emergency and follow-up)**		
	Semi-rural	**Urban**	**Total**	**Semi-rural**	**Urban**	**Total**
Total cost (€)	49,684.89	872,795.27	922,480.16	200,517.59	225,259.91	425,777.50
%	5.4%	94.6%	100.0%	47.1%	52.9%	100.0%
Number of events	66,102	434,573	500,675	7986	7584	15,570
	Hospitalization events			**Medical consultations (Scheduled, urgent and home)**		
	Semi-rural	**Urban**	**Total**	**Semi-rural**	**Urban**	**Total**
Total cost (€)	1,276,166.38	1,710,792.22	2,986,958.60	801,325.61	752,439.14	1,553,764.75
%	42.7%	57.3%	100.0%	51.6%	48.4%	100.0%
Number of events	862	592	1454	14,332	13,446	27,778
				Pharmaceutical dispensation		
				Semi-rural	**Urban**	**Total**
Total cost (€)				1,123,840.73	1,190,704.10	2,314,544.83
%				48.6%	51.4%	100.0%
Number of events				450,746	425,435	876,181
	Total AHC			**Total APC**		
	Semi-rural	**Urban**	**Total**	**Semi-rural**	**Urban**	**Total**
	1,795,964.60	3,472,235.20	5,268,199.80	2,160,319.65	2,212,283.38	4,372,603.03
Total AHC and APC	**Total Semi-rural (AHC + APC)**		**Total Urban (AHC + APC)**		**Total (AHC + APC)**	
	3,956,284.25		5,684,518.58		9,640,802.83	

AHC: Average Hospital Care Costs during follow-up; APC: Average Primary Care Costs during follow-up; 1: Including odontology, social work and physiotherapy; ** Percentage over total healthcare costs.

Table 3
Associations of adipose tissue POP concentrations (ng/g lipid) with healthcare costs (€). Robust MM regression.

POPs (ng/g lip)	Dependent Variable (€)	β	Standard error	p-value	95% CI		Change in average cost associated to one IQR change in POP concentrations (€)	R^2
					Lower	Upper		
HCB	**AHC**	1.021	0.685	0.137	−0.322	2.364	35.33	0.197
	APC	1.870	0.866	0.031	0.173	3.566	64.70	0.374
β-HCH	**AHC**	−0.319	1.094	0.771	−2.463	1.826	−5.64	0.188
	APC	1.695	1.470	0.249	−1.186	4.576	30.00	0.362
***p,p'*-DDE**	**AHC**	−0.048	0.110	0.664	−0.262	0.167	−8.41	0.189
	APC	0.049	0.135	0.713	−0.214	0.313	8.74	0.374
PCB-138	**AHC**	0.138	0.308	0.655	−0.467	0.742	14.49	0.191
	APC	0.384	0.395	0.333	−0.391	1.159	40.35	0.368
PCB-153	**AHC**	0.055	0.126	0.665	−0.192	0.301	12.27	0.190
	APC	0.049	0.158	0.756	−0.261	0.359	11.05	0.377
PCB-180	**AHC**	0.195	0.158	0.216	−0.114	0.504	36.09	0.174
	APC	0.197	0.191	0.305	−0.178	0.572	36.41	0.379
Dicofol	**AHC**	62.572	60.498	0.302	−56.004	181.148	Not calculated*	0.195
	APC	−43.234	79.212	0.586	−198.490	112.022		0.375
α-HCH	**AHC**	5.483	70.171	0.938	−132.052	143.018		0.190
	APC	5.736	89.909	0.949	−170.486	181.958		0.372

POP: Pollutant Organic Persistent; IQR: Interquartile Range; CI: Confidence Interval; *Not possible to calculate since these pollutants have >25% of concentrations < Limit of Detection; AHC: Average Hospital Care Costs during follow-up; APC: Average Primary Care Costs during follow-up; HCB: Hexachlorobenzene; β-HCH: β-Hexachlorocyclohexane; p,p'-DDE: p-p'-Dichlorodiphenyldichloroethylene; PCB: Polychlorinated Biphenyl; α-HCH: α- Hexachlorocyclohexane. Robust MM regression was adjusted for residence area, follow-up years, age at recruitment, educational level, alcohol consumption, sex, smoking, consumption of chicken, fruit, vegetables, dairy products, and fish.



U: Urban, S: Semi-rural. Figure shows beta coefficients with 95% confidence intervals for each model. HCB: Hexachlorobenzene; β-HCH: β-Hexachlorocyclohexane; p,p'-DDE: p-p'-Dichlorodiphenyldichloroethylene; PCB: Polychlorinated Biphenyl; α-HCH: α- Hexachlorocyclohexane Models adjusted for residence area, follow-up years, age at recruitment, educational level, alcohol consumption, sex, smoking, consumption of chicken, fruit, vegetables, dairy products and fish.

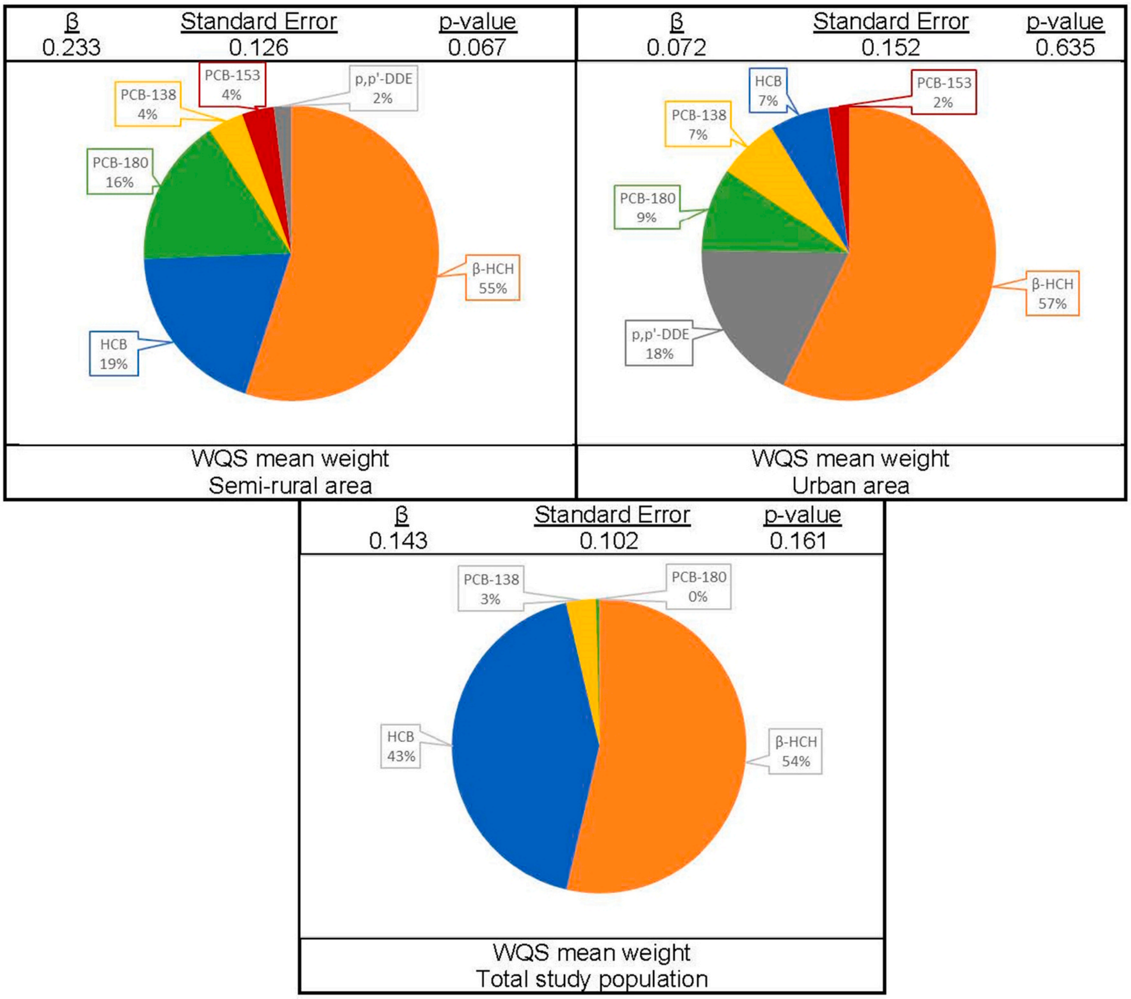
Fig. 1. Associations of adipose tissue POP concentrations with APC. Robust MM regression by residence.

chronic conditions (Ministerio de Sanidad, 2018). Therefore, primary healthcare costs are more likely to might more accurately reflect the burden of chronic diseases potentially associated with OCP and PCB exposure, such as cardiometabolic disorders (indeed, the most frequent in the GraMo cohort). The only exception would be cancer patients, whose follow-up is frequently shared between primary and hospital care. Indeed, chronic non-communicable diseases account for an estimated 80% of visits to Spanish primary healthcare centres (Ambrosio et al., 2020) and two-thirds of premature deaths worldwide (Duff-Brown, 2017). In fact, our results are in line with previous findings of associations of OCP exposure with highly prevalent conditions, such as metabolic syndrome, type 2 diabetes or cardiovascular disease (Rosenbaum et al., 2017; Zong et al., 2018; Kaur et al., 2020). On the contrary, hospital healthcare costs are highly influenced by acute episodes that are not likely related to POP exposure, that can even reach >50% of total healthcare expenses (Ministerio de Sanidad, 2018). Lastly, in comparison to primary healthcare costs, estimation of hospital healthcare costs in the Andalusian Healthcare System is a more complex process, since it is hampered by the large number of different databases in the DIRAYA system, which are more prone to errors in health events registration (Defensor del pueblo Andaluz, 2018).

In spite of the abovementioned, individual associations might be biased by mixture associations, given that these chemicals frequently have converging mechanisms of action (Latchney and Majewska, 2021; Ruiz et al., 2016). In our population, we observed dissimilar results using two multipollutant approaches that have been recently proposed as relevant strategies for assessing multiple effects. While WQS revealed a marginally significant positive mixture association (particularly in the semi-rural area), G-computation did not evidence any significant mixture association. WQS analyses need to a priori specify the expected direction of the associations, while G-Comp estimates an overall mixture effect, to which some chemicals may contribute positively and others negatively. Therefore, the influence of those chemicals contributing negatively to the mixture may be minimized in the WQS analyses, while they would maintain a negative effect in the G-Computation models, therefore counteracting the positive effect of the others (Keil et al., 2020). Therefore, the results of both approaches might be complementary. However, more efforts are needed for the standardization of multi-pollutant statistical approaches. Despite the difficulties for interpreting the magnitude of overall mixture associations with these multi-pollutant approaches, it is crucial to take them into consideration, since individual associations might over-estimate the effect of highly correlated chemicals (Carrico et al., 2015; Wheeler et al., 2021). In addition, overall mixture effects might considerably differ from those evidenced when considering individual chemicals because of their potential biological interactions (Braun Joseph M. et al., 2016; Altenburger et al., 2018).

Interestingly, the coefficients of both the associations of HCB and β-HCH with APC (including WQS analyses) were markedly increased in the subsample of residents of the semi-rural area (i.e., those recruited in the Santa Ana Hospital). Sociodemographic and economic disparities in these areas might influence factors contributing to both health status and the extent of different environmental exposures, including chemical pollutants (Eurostat, 2016). Indeed, residents in rural areas frequently show specific characteristics that can increase their vulnerability to certain environmental factors, such as higher population ageing, hampered access to health care facilities (that may result in delayed diagnosis and treatment), higher gender-related inequalities, increased occupational risks, and lower medication adherence (Asociación para la Defensa de la Sanidad Pública de Andalucía, 2008; Murphy et al., 2014). Although some of these disparities might be difficult to identify in the present study, it is noteworthy that the sample recruited in the semi-rural area showed an increased proportion of females, individuals without studies, and manual workers. On the other hand, the semi-rural was slightly younger and had a lower proportion of alcohol consumers. Interestingly, we previously reported markedly increased *p,p'*-DDE concentrations in rural women *vs* rural men, but this was not observed in residents of more urban areas (Arrebola et al., 2013a). The relatively limited sample size hampers conclusions from stratified models and, therefore, our findings point to the need for further research on potential disparities in (semi)-rural *vs* urban areas.

Among the main strengths of our study, it is the universal coverage provided by the Public Healthcare System, which is based on the Beveridge model and reaches 98% of the Andalusian population (SSPA, 2017; World Health Organization, 2010). In addition, the longitudinal design supports the causality assumption. Furthermore, adipose tissue is considered the most accurate estimator of long-term exposure to POPs (Jackson et al., 2017; La Merrill Michele et al., 2013; Mustieles and



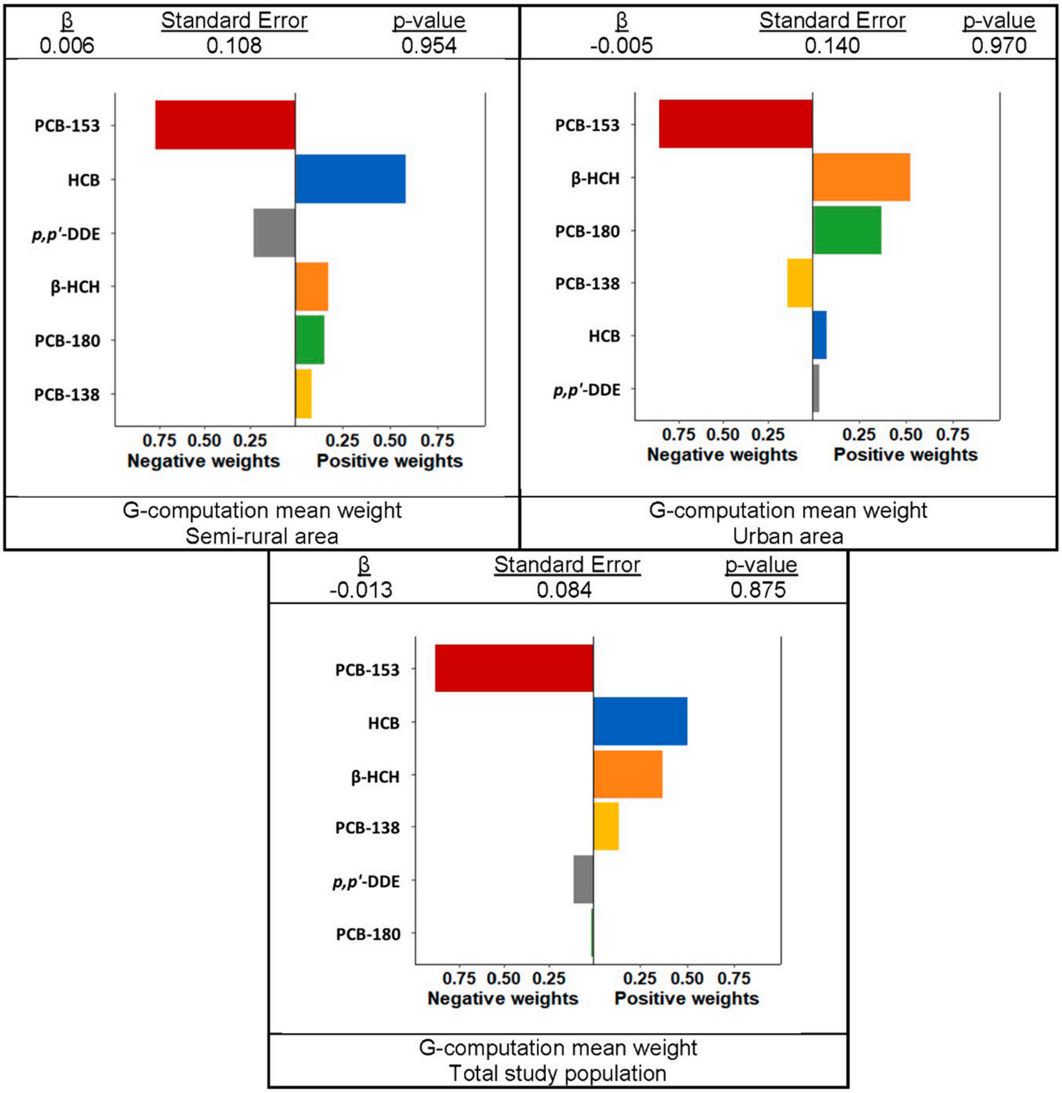
APC: Average Primary Care Costs during follow-up; HCB: Hexachlorobenzene; β-HCH: β-Hexachlorocyclohexane; p,p'-DDE: p-p'-Dichlorodiphenyldichloroethylene; PCB-138, -153, -180: Polychlorinated Biphenyls; α-HCH: α-Hexachlorocyclohexane; Models adjusted for residence area, follow-up years, age at recruitment, educational level, alcohol consumption, sex, smoking, consumption of chicken, fruit, vegetables, dairy products and fish.

Fig. 2. POP mixture associations with APC. Weighted Quantile Sum Regression (WQS) by residence.

Arrebola, 2020). Lastly, it is remarkable that the two multi-pollutant approaches showed differences in terms of statistical significance, although were in general congruent in the direction of the associations, as well as in the chemicals mainly accounting for the mixture associations.

The sample size in the present exploratory study was relatively limited and, therefore, our results warrant further research in other populations. In addition, and despite the extensive questionnaires performed, we cannot exclude the presence of unmeasured confounding variables, and even residual confounding, since many variables, such as BMI or lifestyle habits might have changed over follow-up. In addition, it was not possible to ascertain if all the events considered were related to the chronic diseases related to POPs. This would result in an attenuation of the real associations. Furthermore, even though the study population had a wide age range at recruitment (18–90 years), 50% of them were 37–63 years. Thus, our results might be more representative of middle-aged adults and certainly not of population <18 years. In addition, our hospital-based study might hamper the representativeness of our results. However, our population characteristics does not substantially differ to those of the general adult population of Granada province (Instituto de Estadística y Cartografía de Andalucía, 2005; Ministerio de Sanidad, 2006; OPIMEC) (Supplementary table S4).

To best of our knowledge, our study represents one of the very first attempts to monetise the global health implications of POP exposure based on biomonitoring data. Our results also highlight the need to include economic evaluation in health outcome assessment. In a context of limited resources, their proper assignation is essential for the sustainability of any healthcare system. Therefore, any intervention focused on reducing POP exposure would likely reduce the disease burden and, consequently, associated healthcare costs. Despite the expected change in cost associated to an IQR in our population may not seem very large at an individual level, we believe that it could have important economic implications at a global level since: 1) virtually 100% of the population shows detectable levels of these chemicals (United States Environmental Protection Agency, 2014), and 2) mixture effects cannot be disregarded, including interactions with other chemicals not included in the present study. Consequently, further research on a wider range of pollutants is warranted.



APC: Average Primary Care Costs during follow-up; HCB: Hexachlorobenzene; β-HCH: β-Hexachlorocyclohexane; p,p'-DDE: p-p'-Dichlorodiphenyldichloroethylene; PCB-138, -153, -180: Polychlorinated Biphenyls; α-HCH: α-Hexachlorocyclohexane; Models adjusted for residence area, follow-up years, age at recruitment, educational level, alcohol consumption, sex, smoking, consumption of chicken, fruit, vegetables, dairy products and fish.

Fig. 3. POP mixture associations with APC. G-Computation analyses by residence.

5. Conclusion

Our findings suggest that long-term exposure to mixtures of POPs might unspecifically affect human health at different levels, thus increasing healthcare expenditure, which would be more evident at a primary care level and in rural areas. Thus, our study offers a novel approach using public healthcare records for estimating the global implications of human exposure to environmental pollutants. The impact of environmental exposure on the efficiency of the health systemswarrant further research.

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Ethics committee

The study protocol was approved by the Clinical Research Ethics Committee of Granada (7/2019).

Role of the funder/sponsor

The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of this manuscript.

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.envres.2022.113609.

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