Blood Concentrations of Persistent Organic Pollutants and Unhealthy Metabolic Phenotypes in Normal-weight, Overweight and Obese Individuals

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Abbreviations: ATPIII, National Cholesterol Education Program - Third Adult Treatment Panel; BMI, body mass index; CI, confidence interval; DDE, dichlorodiphenyldichloroethene; DDT, dichlorodiphenyltrichloroethane; HCB, hexachlorobenzene; HCH, hexachlorocyclohexane; HOMA-IR, homeostatic model assessment-insulin resistance; hsCRP, high-sensitivity C-reactive protein; IDF, International Diabetes Federation; MetS, Metabolic Syndrome; MHO, metabolically healthy obese; MONO, metabolically obese non-obese; PR, prevalence ratio; PCBs, polychlorinated biphenyls; POPs, persistent organic pollutants.

A B S T R A C T

Factors underlying metabolic phenotypes, such as the metabolically healthy but obese phenotype, remain unclear. Differences in metabolic phenotypes –particularly, among individuals with a similar body mass index– could be related to concentrations of persistent organic pollutants (POPs). No studies have analyzed POPs and metabolic phenotypes in normal-weight persons. The authors investigated the relationships between serum concentrations of POPs and metabolic phenotypes in 860 normal-weight, overweight, and obese participants in the 2002 Catalan Health Interview Survey (Spain). POP concentrations were significantly higher in metabolically unhealthy than in metabolically healthy individuals. In models adjusted for body mass index and other confounders, hexachlorobenzene, beta-hexachlorocyclohexane and polychlorinated biphenyls were associated with the unhealthy metabolic phenotype and the metabolic syndrome. Among normal-weight individuals, the adjusted prevalence ratio of having an unhealthy phenotype for the upper category of the sum of orders of the mentioned POPs was 4.1 (95% confidence interval: 1.7, 10.0). Among overweight and obese individuals, the corresponding prevalence ratio for the sum of polychlorinated biphenyls was 1.4 (95% confidence interval: 1.0, 1.8). Findings support the hypothesis that POP concentrations are associated with unhealthy metabolic phenotypes, and not only in obese and overweight individuals but also (and probably more strongly) in normal-weight individuals.

Key words: Environmental exposure / adverse effects; environmental pollutants / toxicity; health survey; human biomonitoring; metabolically healthy obese; metabolic phenotype; metabolic syndrome; persistent organic pollutants (POPs).

Recent studies have unveiled factors that appear to protect obese individuals from cardiometabolic disturbances (1, 2). Such studies used body-size metabolic phenotypes to classify individuals according to body mass index (BMI) and the presence or absence of cardiometabolic complications –including hypertension, dyslipidemia, or insulin resistance. One of such phenotypes, the metabolically healthy obese (MHO), consists of individuals who remain free of metabolic abnormalities despite being obese. Another metabolic phenotype comprises normal-weight but metabolically unhealthy individuals; i.e., individuals who present cardiometabolic abnormalities despite having a normal BMI, also called metabolically obese non-obese (MONO) (3). Some studies found factors such as visceral fat accumulation, adipose cell size, and behavioral characteristics as physical activity and alcohol intake to be related to metabolic phenotypes (1, 4-6). However, the underlying factors and mechanisms that could explain the normal metabolic profile of MHO individuals remain unclear (1, 2).

Similar to MHO, the understanding of the MONO individual is important because an abnormal metabolic profile, rather than adiposity itself, is associated with a higher risk for cardiovascular diseases (7). While regional fat distribution and body composition could partly explain differences in the metabolic profile among non-obese individuals (8), some environmental contaminants, such as persistent organic pollutants (POPs), may also play a role, like they probably do in obese individuals (9, 10).

POPs are synthetic chemicals highly lipophilic and resistant to degradation; virtually all humans accumulate POP mixtures throughout the life course, with wide inter-individual differences in concentrations (10-12). Most POPs are endocrine-disruptors (13), and several prospective studies reported positive relationships between POP concentrations and type 2 diabetes, insulin resistance, hypertension, and other cardiometabolic disorders (9, 10, 12, 14-17). Additionally, other studies reported positive associations between POPs and metabolic

syndrome (MetS) (18-21). Therefore, differences among metabolic phenotypes –which not only take into account the components of the metabolic syndrome, but also other factors as insulin resistance and biomarkers of inflammation– could be related to differences in POP concentrations.

Only two previous studies have analyzed the association between POPs and metabolic phenotypes. One study was performed in 76 non-diabetic obese postmenopausal women (22), whilst the other selected 184 overweight and obese patients visiting a weight-management clinic (23). Thus, no studies have analyzed POPs and unhealthy metabolic phenotypes in normal-weight persons. By contrast, the present study is the first to analyze the relationship between body POP concentrations and metabolic phenotypes in a moderately large sample of the general population (N = 860). It includes: *a)* men and women; *b)* a wide range of ages (18 to 74 years); *c)* normal-weight, overweight and obese individuals; and *d)* diabetic and non-diabetic individuals. Of potential importance, Catalonia (Spain) is a Mediterranean region with dietary patterns generally protective against several cardiometabolic risk factors (24).

Thus, the aim of the present study was to analyze the relationship between POP serum concentrations and metabolic phenotypes in normal-weight, overweight and obese individuals in the general adult population of Catalonia (Spain). Additionally, we analyzed the relationship between POPs and MetS.

METHODS

Study population

The study population has been described in detail elsewhere (25, 26). Briefly, participants in the Catalan Health Interview Survey aged 18-74 years were offered to take part in a health examination, which included a physical exam, a supplementary interview, and the collection of urine and blood samples. A total of 1,374 individuals –who gave specific written informed consent– participated during 2002 in the health examination (27).

Trained nurses recorded the weight and height; the corresponding BMI was computed (measured weight [kg] divided by measured height squared [m^2]), and grouped into four categories: underweight (<18.50 kg/m^2), normal-weight (18.50 - 24.99 kg/m^2), overweight (25.00 - 29.99 kg/m^2), and obese (≥30.00 kg/m^2). Waist circumference was measured at the level of the umbilicus. Systolic and diastolic blood pressures were measured twice, and the average was used in the statistical analyses. Blood samples were drawn after twelve hours of fasting (27). A capillary blood sample was also obtained during the health examination and used to determine glucose concentration in whole blood (26). Information on blood concentrations of lipids and at least 1 mL of serum (for POP analyses) was available from 919 participants.

Ten underweight participants were excluded from the statistical analyses. In the present report, analyses on metabolic phenotypes were based on 860 participants with data available on POP serum concentrations and on metabolic phenotype (see below). There were no statistically significant differences between the 860 individuals and the remaining participants in the health examination with respect to age, sex, BMI, educational level and occupational social class. Analyses on the metabolic syndrome were based on 858 and 881 participants with information on metabolic syndrome status according to the definitions of the

International Diabetes Federation (IDF) (28) and the National Cholesterol Education Program - Third Adult Treatment Panel (ATPIII) (29), respectively.

Body-size metabolic phenotypes

Body-size metabolic phenotypes were defined using criteria previously described by Wildman and colleagues (6). An individual was classified as having an unhealthy metabolic phenotype if he/she had 2 or more of the following cardiometabolic abnormalities: hypertension (systolic blood pressure ≥130 mmHg, diastolic blood pressure ≥85 mmHg, or current use of antihypertensive medication); hypertriglyceridemia (fasting triglyceride level ≥150 mg/dL, no information on triglyceride-lowering medication was available); low HDL-cholesterol (<40 mg/dL in men, <50 mg/dL in women, or current use of cholesterol-lowering medication); hyperglycemia (fasting glucose level ≥100mg/dL, current use of insulin or oral antidiabetic medication, or previous diagnosis of diabetes); insulin resistance (homeostatic model assessment-insulin resistance (HOMA-IR) > 4.66, the 90th percentile); and systemic inflammation (high-sensitivity C-reactive protein (hsCRP) level > 7.35 mg/L, the 90th percentile) (Table 1).

Metabolic syndrome (MetS) status

MetS status was assigned to participants following the IDF and ATPIII definitions. According to IDF (28), participants were considered to have MetS if they had *a)* abdominal obesity (waist circumference ≥ 94 cm in men or ≥ 80 cm in women), and also *b)* two or more of the following cardiometabolic abnormalities (as previously defined): hypertriglyceridemia, low HDL-cholesterol, hypertension, and hyperglycemia. According to the ATPIII definition (29), participants were considered to have MetS if they had three or more of these five components: abdominal obesity (waist circumference ≥ 102 cm in men or ≥ 88 cm in women),

hypertriglyceridemia, low HDL-cholesterol, hypertension, and hyperglycemia (fasting glucose level ≥100mg/dL, or current use of insulin or oral antidiabetic medication).

Analytical chemical methods

Serum POP concentrations assays

A detailed account of laboratory methods has previously been published (25) (details are also provided in the Web Appendix). Serum concentrations of 19 POPs were analyzed by gas chromatography with electron-capture detection. Main statistical analyses were limited to the 8 compounds that were above the detection limit in > 85% of participants: p,p'-dichlorodiphenyltrichloroethane (DDT), p,p'-dichlorodiphenyldichloroethene (DDE), polychlorinated biphenyl (PCB) congeners 118, 138, 153 and 180, hexachlorobenzene (HCB) and β-hexachlorocyclohexane (HCH) (25). Lipid correction (division of individual crude serum POP concentrations by total lipids) is not appropriate when studying metabolic phenotypes (10, 30, 31) and, thus, in the present study POP concentrations are expressed in nanograms per milliliter (ng/mL).

Clinical bioassays

Cholesterol and triglycerides were determined enzymatically (Txad-Pap and CIN-UV methods, respectively) in serum obtained in the health examination (25, 27). Serum concentrations of hsCRP were measured with a high-sensitivity turbidimetric assay (Quantex CRP ultra-sensitive, Biokit SA, Barcelona, Spain) (32). Fasting insulin was determined by radioimmunoassay, using commercial kits (Amersham, Little Chalfont, UK), and the homeostasis model assessment was used to calculate insulin resistance (HOMA-IR) applying the following formula: (fasting insulin (mU/L) x fasting glucose (mg/dL) x 0.0555) / 22.5 (33).

Statistical analyses

Univariate statistics were computed as customary (34). Fisher's exact test for homogeneity was applied to assess the relationship between two categorical variables. To assess differences on age, BMI and POP concentrations by metabolic phenotype and MetS status, Student's *t*-test and Mann–Whitney's *U*-test were used.

To estimate the magnitude of the associations between POPs and an unhealthy metabolic phenotype (≥2 cardiometabolic abnormalities), prevalence ratios (PRs) and their 95% confidence intervals (CIs) were computed by Poisson regression models with robust variance (35). Statistically significant interactions were found between BMI and POP concentrations (all *P* for interaction terms ≤ 0.005); thus, analyses were stratified by BMI (dichotomized as normal-weight and overweight/obese). PRs were also estimated from logistic models as the ratio of the predicted probabilities for each outcome comparing the 3 highest quartiles with the lowest one, and 95% CIs were generated by the bootstrap percentile method using 1,000 resamples (36). PRs were also computed by Poisson regression to estimate the magnitude of the associations between POPs and the MetS.

POP concentrations were entered in the models as quartile categories. To assess exposure to multiple compounds, we computed the sum of PCBs, the sum of orders of the 8 most prevalent POPs mentioned, and the sum of orders of the 6 POPs individually associated with metabolic phenotypes (11, 26) (see Web Appendix).

In adjusted models, the following potential confounders were included: age, sex, BMI, cigarette smoking, alcohol consumption, physical activity, occupational social class and educational level. We assessed linear dose-response relations through the multivariate analogue of Mantel's extension test for linear trend; when a linear trend was not apparent, the probability test was used.

General linear regression models were used to assess the relationship between number of cardiometabolic abnormalities (as a continuous variable, instead of the binary outcome 'healthy / unhealthy metabolic phenotype', Table 1) and concentrations of POPs. Results are expressed as adjusted geometric means with their corresponding 95% CIs (34).

The level of statistical significance was set at 0.05 and all tests were two tailed. Analyses were conducted using SPSS version 22.0.0 (SPSS, Chicago, IL, USA, 2013) and R version 3.1.3 (R Core Team, Vienna, Austria, 2015).

RESULTS

The prevalence of the metabolically healthy phenotype in the study population was 56.2% (Table 1). Of the 860 participants, 39 (4.5%) were obese yet metabolically healthy (i.e., MHO), 151 (17.6%) were overweight yet metabolically healthy, and 71 (8.3%) had normal-weight but were metabolically unhealthy (≥2 cardiometabolic abnormalities) (i.e., MONO). The percentages of individuals with a healthy metabolic phenotype among overweight and obese participants were 46.5 and 22.8, respectively, whereas 19.5% of the normal-weight participants were metabolically unhealthy (Table 1).

Both among normal-weight participants, and among overweight and obese participants, individuals with an unhealthy metabolic phenotype were older, had a higher BMI, and a higher waist circumference than individuals with a healthy metabolic phenotype (Table 2). Concentrations of all POPs were significantly higher in metabolically unhealthy individuals than in metabolically healthy subjects (Figure 1 and Web Table 1). For instance, among normal-weight individuals, the median concentration of HCB and PCB 118 was 2 times higher in metabolically unhealthy individuals than in metabolically healthy subjects. The

corresponding values among overweight and obese individuals were 1.8 and 1.7 for HCB and PCB 118, respectively (*P* values < 0.001). The differences in POP concentrations between metabolically healthy and unhealthy individuals (Figure 1) show patterns strikingly similar among normal-weight and overweight/obese participants.

Among normal-weight individuals, multivariate analyses showed that concentrations of all four PCBs were positively associated with having an unhealthy (vs. healthy) metabolic phenotype –the so called MONO–, after adjusting for age, sex, BMI, cigarette smoking, alcohol consumption, and physical activity, in a non-linear dose-response manner. PRs for the upper quartile of PCBs ranged between 1.1 and 1.9, whereas PRs for the third quartile ranged between 2.5 and 3.2 (*P* values<0.01) (Table 3, model 1). When the sum of PCBs was considered, normal-weight individuals in the third quartile had 3.0-times the risk of having an unhealthy metabolic phenotype than individuals in the lowest quartile of the sum of PCBs (95% CI: 1.4, 6.3) (*P* = <0.001). HCB and β-HCH were also significantly associated with having an unhealthy metabolic phenotype, in this case in a linear dose-response manner; PRs for the upper quartile of HCB and β-HCH were 2.0 (95% CI: 0.8, 4.9) and 2.4 (95% CI: 1.0, 5.9), respectively (*P* values for linear trend <0.1) (Table 3, model 1). Among normal-weight individuals, the unhealthy metabolic phenotype was also associated with mixtures of POPs: individuals in the upper category of the sum of orders of the 6 mentioned POPs had 3.7-times the risk of having an unhealthy metabolic phenotype than subjects in the lowest category. The PRs for the second and third categories were 2.6 and 3.0, respectively (*P* trend = 0.003). Associations were also found between the sum of orders of all 8 POPs and the unhealthy phenotype (PRs for the second, third and fourth categories = 2.4, 2.9 and 3.0, respectively; *P* trend = 0.008). When model 1 was further adjusted for occupational social class (Table 3, model 2), all above-mentioned associations remained statistically significant and the magnitude of the PRs increased slightly; e.g., the PR for the third quartile of PCB 180 became

3.6 (95% CI: 1.6, 7.9). Further adjusting model 1 for education did not materially change the estimates.

Among overweight and obese individuals, adjusted models showed that individuals with concentrations of PCBs in the upper quartile were more likely to have an unhealthy metabolic phenotype than individuals in the lower quartile. PRs for individuals in the upper quartile of PCBs ranged between 1.2 and 1.4 (all *P* trend < 0.005) (Table 4, model 1). For HCB this PR was also 1.4 (95% CI: 1.0, 1.9) (*P* = 0.023). The unhealthy metabolic phenotype was also associated with the sum of orders of the 6 mentioned POPs and with the sum of orders of all 8 POPs: the PR of having an unhealthy phenotype for individuals in the each upper category was 1.2 (95% CI: 0.9, 1.7 and P ≤ 0.020 in both cases) (Table 4, model 1). Further adjusting for occupational social class (Table 4, model 2) or for education did not materially change the estimates. No significant interactions were observed between POP concentrations and sex or age in overweight/obese individuals, neither in normal-weight subjects. As compared to previously shown PRs (computed by Poisson regression), PRs estimated from logistic models were slightly larger (Web Table 2).

The sum of concentrations of the 6 POPs tended to increase as the number of cardiometabolic abnormalities increased (*P* trend = 0.001) (Web Figure 1). The association was similarly observed among normal-weight and overweight/obese individuals.

The prevalence of MetS was 25.2% (216 of 858 participants) and 23.0% (203 of 881) when using IDF and ATPIII definitions, respectively (Web Table 3). Adjusted PRs of having MetS by POP concentrations are shown in Figure 2 and Web Tables 4 and 5. Similar to what was observed for metabolic phenotypes, no associations with MetS were observed for DDT and DDE. By contrast, HCB was positively associated with MetS using either definition. The risk of having MetS (IDF and ATPIII definitions, respectively) was 2.7 and 2.8-times higher for

individuals with HCB concentrations in the top quartile than in the lower quartile. β-HCH and all four PCBs were also associated with at least one definition of the MetS (Figure 2 and Web Tables 4 and 5). Sensitivity analyses excluding participants with type 2 diabetes yielded similar results.

DISCUSSION

Metabolically healthy individuals –obese, overweight, or normal-weight– had significantly lower serum concentrations of POPs than individuals with 2 or more cardiometabolic abnormalities. In obese/overweight individuals and normal-weight individuals, lower concentrations of HCB, β-HCH and PCBs were also generally associated with a healthy metabolic phenotype even when age, sex, BMI, cigarette smoking, alcohol consumption, physical activity, occupational social class, and education were adjusted for. The magnitude of the associations was stronger in normal-weight individuals than in the obese/overweight. The sum of orders of the 6 POPs individually associated with metabolic phenotypes and the sum of orders of all 8 POPs showed linear dose-response relationships among normal-weight individuals and were also associated with the metabolic phenotype in obese/overweight individuals.

Similarly, a positive linear association was observed between the sum of POP concentrations and the number of cardiometabolic abnormalities. Thus, the observed POP-metabolic phenotype relationship appears to be independent of the cutoff number of abnormalities used to classify the unhealthy phenotype. Multiple criteria have been applied to define metabolic phenotypes (1, 2, 37); we used not just information on the components of the metabolic syndrome, but also on HOMA measured insulin resistance and inflammation, which are some of the possible mechanisms of action or effects of POPs along with endocrine disruption (9, 13, 16). POPs may also increase the risk of obesity (38), the main risk factor of unhealthy

metabolic phenotypes, and have also been associated to an increased risk for some of the cardiometabolic abnormalities considered when defining the unhealthy phenotype, such as hyperglycemia or hypertension (9, 14, 17).

Only two studies have analyzed associations between POP concentrations and metabolic phenotypes, and such studies did not include normal-weight individuals. Our results agree with Gauthier et al. (22), and Dirinck et al. (23), who reported positive associations between PCB concentrations and unhealthy metabolic phenotypes in overweight and obese individuals. Remarkably, we also observed the association in normal-weight individuals. The lack of association that we noted between DDE concentrations and metabolic phenotypes is also consistent with results reported by Gauthier et al. (22); Dirinck et al., only studied PCBs. Ours is the first study to analyze associations between DDT, HCB and β-HCH and metabolic phenotypes (including CRP and HOMA). It is also the first report on the relationship between POP concentrations and metabolic phenotypes in a sample of the general population. Also by contrast with previous studies, ours included diabetic and non-diabetic individuals, the two genders, a wide age range, and a much larger number of individuals.

Our observation that in normal-weight participants the association with the unhealthy metabolic phenotype was stronger with PCB concentrations in the third quartile than in the fourth quartile is coherent with evidence that endocrine-disrupting chemicals as POPs can have non-monotonic effects (10, 39). Some previous studies on POPs also reported non-monotonic associations with outcomes as type 2 diabetes and metabolic syndrome (9, 10, 14, 19, 39, 40). However, confirmation of the non-linear dose-responses in larger populations is needed.

In accordance with our results, some previous studies also reported positive associations between PCBs and some organochlorine pesticides as β-HCH, and MetS (18-21), but not with

DDT and DDE (20). In one prospective nested case-control study based on the Korean general population (with 64 cases of MetS and 182 controls followed during 4 years), serum concentrations of PCBs and organochlorine pesticides at baseline were associated with an increased risk for MetS (19). Although random sampling variation cannot be discarded, the different results for specific POPs might reflect different mechanisms of action or different target organs.

The main study limitation is its cross-sectional design, which prevents inferring causal relationships: theoretically, individuals who developed an unhealthy metabolic phenotype might have accumulated POPs at a higher rate than individuals who retained a healthy phenotype. However, empirical evidence in support of such possibility is scant, and the putative mechanisms have not been elucidated; e.g., few if any human studies have shown that the underlying pathophysiological processes that eventually lead to clinical type 2 diabetes or other metabolic disorders also induce a higher accumulation of POPs (10). Furthermore, the study findings are in accordance with results of experimental animal studies (10, 13, 16) and human prospective studies (9, 10, 14, 15, 19), which were able to rule out 'reverse causation' and disease progression bias. Also because of its cross-sectional design, and because dyslipidemia was one of the abnormalities considered when defining phenotypes, lipid correction of POP concentrations would entail an overadjustment (31). A relatively high number of comparisons were made; hence, false positives may have occurred. Nonetheless, the associations with the unhealthy phenotype were largely consistent for normal-weight and overweight/obese individuals and for groups of compounds highly correlated (for example, among PCBs). Study limitations also include lack of information on changes in body weight (23), and use of capillary blood instead of venous blood to define hyperglycemia (26).

Findings support the hypothesis that exposure to POPs is associated with unhealthy metabolic phenotypes, and not only in obese and overweight individuals, but also in normal-weight

individuals. POPs may also contribute to increase the risk of the metabolic syndrome. The results should be refuted or confirmed by prospective longitudinal studies assessing a larger number of potentially obesogenic environmental and individual factors. Nevertheless, findings add to the existing evidence supporting policies to decrease human exposure to POPs (12, 41, 42). Considering that in the majority of the general population POP exposure occurs largely through the ingestion of fatty parts of animal foods (43-45), results may also support existing dietary guidelines to prevent cardiometabolic disorders.

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FIGURE LEGENDS

Figure 1. Serum concentrations of persistent organic pollutants by metabolic phenotypes among normal-weight participants (A), and among overweight and obese participants (B), Catalan Health Interview Survey, 2002.

Footnote: Differences between pairs of medians were all statistically significant (all $P < 0.001$, except for p,p'-DDT: $P = 0.013$ and 0.027 for normal-weight and overweight/obese participants, respectively) (Mann-Whitney's U-test, two-tail).

Figure 2. The association between metabolic syndrome (by IDF and ATPIII definitions) and concentrations of persistent organic pollutants (POPs). Catalan Health Interview Survey, 2002.

Footnote: Prevalence ratio (PR) and 95% confidence interval (CIs) of metabolic syndrome for the upper quartile (vs. lower quartile) of POP concentrations, adjusted for age, body mass index, sex, cigarette smoking, alcohol consumption, and physical activity.

Abbreviations: ATPIII, National Cholesterol Education Program - Third Adult Treatment Panel; IDF, International Diabetes Federation.

Table 1. Metabolic Phenotype and its Component Cardiometabolic Abnormalities in Participants by Body Mass Index, Catalan Health Interview Survey, 2002.

			Normal-weight		Overweight		Obese		
Component	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	***P*** [a]
Number of subjects (%)	860	100	364	42.3	325	37.8	171	19.9	
Metabolic phenotype									<0.001
Healthy (≤1 abnormalities)	483	56.2	293	80.5	151	46.5	39	22.8	
Unhealthy (≥2 abnormalities)	377	43.8	71	19.5	174	53.5	132	77.2	
Hypertension[b]	393	45.8	89	24.5	176	54.2	128	75.3	<0.001
Hypertriglyceridemia[c]	115	13.5	13	3.6	58	18.0	44	26.2	<0.001
Low HDL cholesterol[d]	300	34.9	89	24.5	128	39.4	83	48.5	<0.001
Hyperglycemia[e]	315	37.2	69	19.1	138	43.4	108	64.7	<0.001
HOMA-IR [f]	81	10.2	6	1.7	29	9.6	46	31.5	<0.001
hsCRP [g]	82	10.0	24	6.8	24	7.8	34	21.7	<0.001

Abbreviations: HOMA-IR, homeostatic model assessment-insulin resistance; hsCRP, high-sensitivity C-reactive protein.
[a] Fisher's exact test.
[b] ≥130/85 mmHg and/or medication use.
[c] ≥150 mg/dL; 14 non-fasting subjects with triglyceride levels ≥150 mg / dL were excluded.
[d] <40 mg/dL in men, <50 mg/dL in women and /or medication use.
[e] ≥100 mg/dL and/or medications use; 7 subjects missing blood glucose concentrations, 6 subjects with blood glucose concentration ≤60 mg/dL, 16 non-fasting subjects with blood glucose concentration ≥100 mg/dL and no medication use, and 4 pregnant women, were excluded.
[f] >P90 (4.66); 43 subjects reporting a current use of insulin or oral antidiabetic medication, 32 non-fasting subjects, 7 subjects missing blood glucose concentrations, 5 subjects with blood glucose concentration ≤60 mg/dL, and 4 pregnant women, were excluded.
[g] >P90 (7.35 mg/L).

Table 2. Characteristics of Study Participants by Body Mass Index and Metabolic Phenotype, Catalan Health Interview Survey, 2002.

			Normal-weight			Overweight and Obese		
	Total		Metabolically Healthy	Metabolically Unhealthy		Metabolically Healthy	Metabolically Unhealthy	
Characteristics	N	%	N %	N %	*P* [a]	N %	N %	*P* [a]
Number of subjects	860	100	293 80.5	71 19.5		190 38.3	306 61.7	
Sex					0.024[b]			0.053[b]
Men	375	43.6	88 30.0	32 45.1		87 45.8	168 54.9	
Women	485	56.4	205 70.0	39 54.9		103 54.2	138 45.1	
Age (years) [c]	45.3 (15.2)		35.7 (12.3)	49.4 (14.9)	<0.001	44.2 (12.9)	54.3 (13.2)	<0.001
Body mass index [c, d]	26.5 (4.6)		22.4 (1.7)	23.0 (1.6)	0.003	28.2 (3.1)	30.1 (4.0)	<0.001
Waist circumference (cm) [c]	87.0 (12.8)		75.9 (7.9)	82.0 (9.1)	<0.001	90.0 (9.2)	96.7 (10.3)	<0.001
Occupational social class [e]					0.008[b]			0.161[b]
V (less affluent)	54	6.4	15 5.2	6 8.5		9 4.8	24 8.1	
IV	358	42.5	101 35.1	39 54.9		80 42.8	138 46.5	
III	238	28.2	79 27.4	15 21.1		54 28.9	90 30.3	
II	115	13.6	54 18.8	5 7.0		28 15.0	28 9.4	
I (most affluent)	78	9.3	39 13.5	6 8.5		16 8.6	17 5.7	
Educational level [e]					0.001[b]			<0.001[b]
Without formal education	136	15.9	15 5.2	12 16.9		29 15.3	80 26.6	
Primary schooling (1st stage)	219	25.7	50 17.2	21 29.6		48 25.3	100 33.2	
Primary schooling (2nd stage)	216	25.3	91 31.3	16 22.5		55 28.9	54 17.9	
Secondary schooling	179	21.0	85 29.2	16 22.5		32 16.8	46 15.3	
University	103	12.1	50 17.2	6 8.5		26 13.7	21 7.0	
Smoking status [e]					0.153[b]			0.635[b]
Never	421	49.6	135 46.7	30 42.9		92 49.2	164 54.1	
Other (past-occasionally)	56	6.6	18 6.2	2 2.9		13 7.0	23 7.6	
Past	117	13.8	24 8.3	12 17.1		32 17.1	49 16.2	
Current	255	30.0	112 38.8	26 37.1		50 26.7	67 22.1	
Alcohol drinking [e]					0.056[b]			0.472[b]
Non-drinker	391	45.7	120 41.2	39 55.7		89 47.1	143 46.7	
Regular drinker	421	49.2	154 52.9	26 37.1		89 47.1	152 49.7	
Heavy drinker	44	5.1	17 5.8	5 7.1		11 5.8	11 3.6	
Physical activity [e]					0.855[b]			0.293[b]
Very active	32	3.9	14 4.9	2 2.9		7 3.8	9 3.1	
Active	72	8.7	24 8.5	7 10.3		22 12.1	19 6.5	
Moderately active	411	49.8	142 50.2	37 54.4		87 47.8	145 49.5	
Moderately inactive	149	18.0	53 18.7	13 19.1		29 15.9	54 18.4	
Inactive	162	19.6	50 17.7	9 13.2		37 20.3	66 22.5	

[a] Unless otherwise specified, *P* derived from Student's *t*-test. [b] Fisher's exact test. [c] Values are expressed as mean (standard deviation). [d] Weight (kg) / height (m)^2.
[e] 17, 7, 11, 4, and 34 participants with missing values for occupational social class, educational level, smoking status, alcohol drinking, and physical activity, respectively.

Table 3. Association Between Serum Concentrations of Persistent Organic Pollutants and the Unhealthy Metabolic Phenotype (≥2 Cardiometabolic Abnormalities) Among Normal-Weight Participants, Catalan Health Interview Survey, 2002.

	Crude model (N=364)			Model 1 [a] (N=349)			Model 2 [b] (N=344)		
Compounds (ng/mL)	**PR**	**95% CI**	***P*** [c]	**PR**	**95% CI**	***P*** [c]	**PR**	**95% CI**	***P*** [c]
p,p'-DDT			0.043			0.469			0.443
≤ 0.086	1.0	Referent		1.0	Referent		1.0	Referent	
0.087-0.178	1.2	0.6, 2.1		1.1	0.6, 1.9		1.0	0.6, 1.8	
0.179-0.349	1.6	0.9, 2.8		1.3	0.7, 2.2		1.2	0.7, 2.1	
> 0.349	1.7	0.9, 3.1		1.2	0.6, 2.1		1.2	0.6, 2.2	
p,p'-DDE			<0.001			0.181			0.194
≤ 1.24	1.0	Referent		1.0	Referent		1.0	Referent	
1.25-2.63	1.5	0.8, 2.9		1.3	0.7, 2.3		1.3	0.7, 2.4	
2.64-5.56	2.4	1.3, 4.5		1.6	0.9, 3.2		1.7	0.9, 3.4	
> 5.56	3.2	1.8, 5.8		1.5	0.8, 2.9		1.5	0.8, 2.8	
HCB			<0.001			0.082			0.118
≤ 0.509	1.0	Referent		1.0	Referent		1.0	Referent	
0.510-1.193	1.7	0.9, 3.3		1.6	0.9, 3.1		1.8	0.9, 3.4	
1.194-2.610	2.5	1.4, 4.7		2.0	1.0, 3.9		2.1	1.0, 4.3	
> 2.610	4.0	2.2, 7.3		2.0	0.8, 4.9		2.0	0.8, 5.1	
β-HCH			<0.001			0.047			0.031
≤ 0.288	1.0	Referent		1.0	Referent		1.0	Referent	
0.289-0.670	1.8	0.9, 3.6		1.6	0.8, 3.3		1.7	0.9, 3.4	
0.671-1.547	3.7	2.0, 6.9		1.9	0.9, 4.1		1.9	0.9, 4.2	
> 1.547	4.9	2.6, 9.4		2.4	1.0, 5.9		2.8	1.1, 6.7	
PCB 118			<0.001[d]			0.001[d]			0.001[d]
≤ 0.060	1.0	Referent		1.0	Referent		1.0	Referent	
0.061-0.135	1.2	0.6, 2.6		1.6	0.9, 3.1		1.2	0.6, 2.3	
0.135-0.242	3.7	2.0, 6.7		2.5	1.5, 4.3		2.6	1.5, 4.5	
> 0.242	3.0	1.5, 6.0		1.1	0.6, 2.2		1.6	0.8, 3.0	
PCB 138			<0.001[d]			0.001[d]			<0.001[d]
≤ 0.258	1.0	Referent		1.0	Referent		1.0	Referent	
0.259-0.451	1.6	0.7, 3.7		1.2	0.5, 2.7		1.2	0.5, 2.8	
0.452-0.722	5.6	2.8, 11.3		2.9	1.4, 6.1		3.3	1.6, 7.0	
> 0.722	5.2	2.6, 10.7		1.9	0.9, 4.3		1.9	0.8, 4.4	
PCB 153			<0.001[d]			0.003[d]			0.001[d]
≤ 0.361	1.0	Referent		1.0	Referent		1.0	Referent	
0.362-0.626	1.9	0.8, 4.4		1.3	0.6, 3.1		1.3	0.6, 3.2	
0.627-0.978	5.9	2.8, 12.2		3.0	1.3, 6.8		3.3	1.5, 7.5	
> 0.978	5.6	2.6, 11.8		1.9	0.8, 4.3		2.0	0.8, 4.6	
PCB 180			<0.001[d]			<0.001[d]			<0.001[d]
≤ 0.314	1.0	Referent		1.0	Referent		1.0	Referent	
0.315-0.503	1.2	0.5, 3.2		0.8	0.3, 2.0		0.8	0.3, 2.1	
0.504-0.783	5.9	2.9, 12.3		3.2	1.4, 7.0		3.6	1.6, 7.9	
> 0.783	6.3	3.0, 13.1		2.0	0.9, 4.7		2.3	1.0, 5.4	
Sum of PCBs			<0.001[d]			<0.001[d]			<0.001[d]
≤ 1.03	1.0	Referent		1.0	Referent		1.0	Referent	
1.04-1.76	1.4	0.6, 3.3		0.9	0.4, 2.2		1.0	0.4, 2.4	
1.76-2.72	5.6	2.8, 11.1		3.0	1.4, 6.3		3.3	1.6, 7.1	
> 2.73	5.8	2.9, 11.8		1.9	0.9, 4.1		2.0	0.9, 4.6	
Sum of orders 6 POPs[e]			<0.001			0.003			0.003
6-10	1.0	Referent		1.0	Referent		1.0	Referent	
11-15	3.3	1.5, 7.2		2.6	1.1, 5.9		3.0	1.3, 6.8	
16-19	5.4	2.5, 11.7		3.0	1.2, 7.2		3.5	1.4, 8.7	
20-24	8.6	4.1, 17.8		3.7	1.5, 9.1		4.1	1.7, 10.0	
Sum of orders all POPs			<0.001			0.008			0.034[d]
8-14	1.0	Referent		1.0	Referent		1.0	Referent	
15-20	3.8	1.9, 7.9		2.4	1.1, 5.2		2.6	1.2, 5.5	
21-26	5.0	2.4, 10.3		2.9	1.3, 6.5		3.4	1.5, 7.8	
27-32	7.7	3.7, 15.9		3.0	1.3, 6.8		3.1	1.3, 7.3	

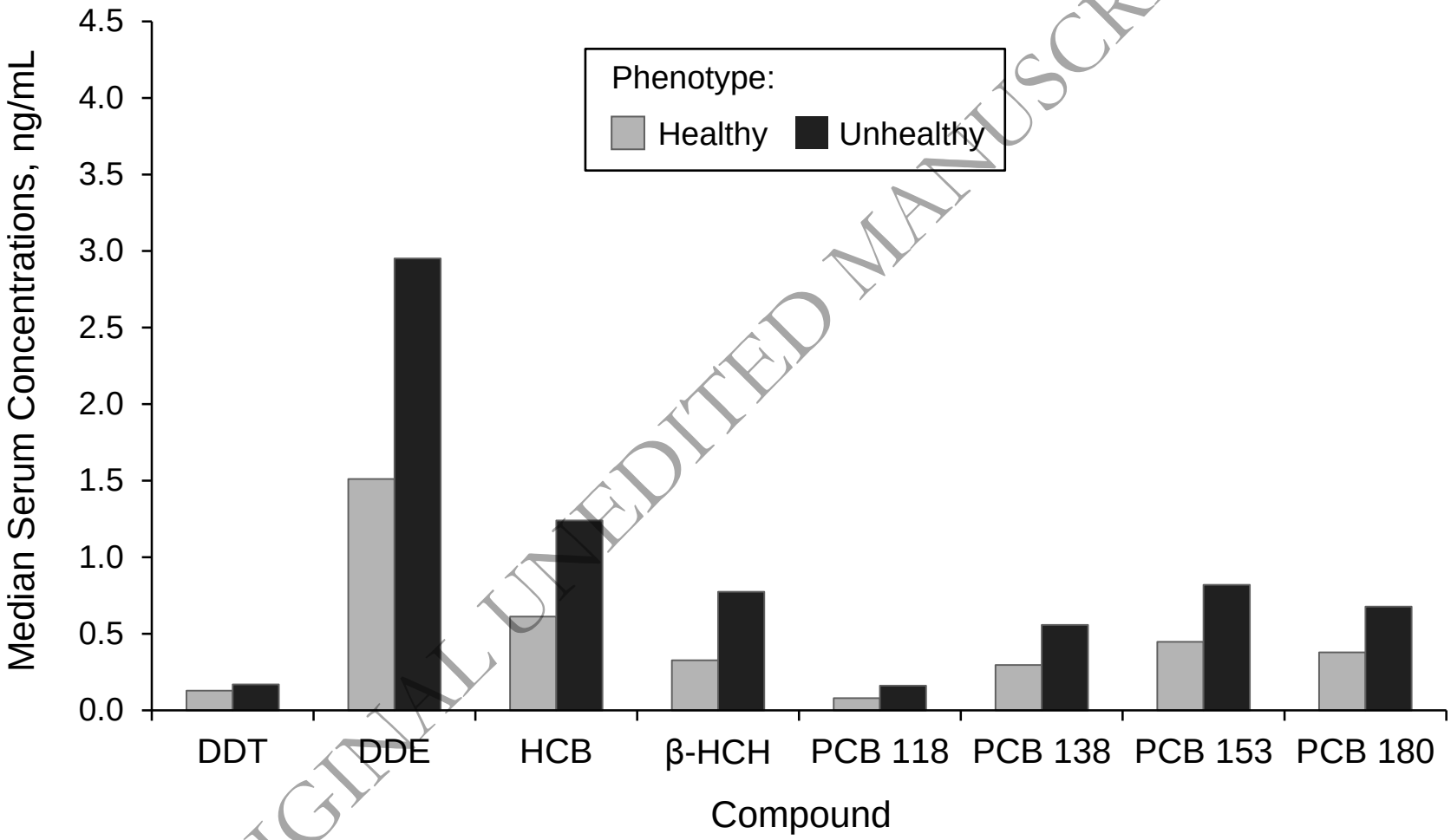
Abbreviations: CI, confidence interval; PR, prevalence ratio; POP: persistent organic pollutant.
[a] Model 1: adjusted for age, sex, body mass index, cigarette smoking, alcohol consumption, and physical activity.
[b] Model 2: adjusted for age, sex, body mass index, cigarette smoking, alcohol consumption, physical activity and occupational social class.
[c] Unless otherwise specified, *P* derived from the multivariate analogue of Mantel's extension test for linear trend.
[d] Wald test. [e] HCB, β-HCH, and PCB congeners 118, 138, 153, and 180.

Table 4. Association Between Serum Concentrations of Persistent Organic Pollutants and the Unhealthy Metabolic Phenotype (≥2 Cardiometabolic Abnormalities) Among Overweight and Obese Participants, Catalan Health Interview Survey, 2002.

	Crude model (N=496)			Model 1 [a] (N=472)			Model 2 [b] (N=462)		
Compounds (ng/mL)	**PR**	**95% CI**	***P*** [c]	**PR**	**95% CI**	***P*** [c]	**PR**	**95% CI**	***P*** [c]
p,p'-DDT			0.101			0.454[d]			0.333[d]
≤ 0.086	1.0	Referent		1.0	Referent		1.0	Referent	
0.087-0.178	1.2	0.9, 1.5		1.1	0.9, 1.4		1.1	0.9, 1.4	
0.179-0.349	1.1	0.9, 1.4		1.0	0.8, 1.2		0.9	0.7, 1.2	
> 0.349	1.3	1.0, 1.6		1.0	0.8, 1.3		1.0	0.8, 1.3	
p,p'-DDE			<0.001			0.624[d]			0.710[d]
≤ 1.24	1.0	Referent		1.0	Referent		1.0	Referent	
1.25-2.63	1.4	1.0, 1.9		1.1	0.8, 1.5		1.1	0.8, 1.4	
2.64-5.56	1.4	1.0, 1.8		1.0	0.8, 1.3		1.0	0.7, 1.3	
> 5.56	1.8	1.3, 2.3		1.1	0.8, 1.4		1.1	0.8, 1.4	
HCB			<0.001			0.023[d]			0.028[d]
≤ 0.509	1.0	Referent		1.0	Referent		1.0	Referent	
0.510-1.193	1.4	1.0, 2.0		1.1	0.8, 1.5		1.1	0.8, 1.5	
1.194-2.610	1.4	1.0, 2.0		1.1	0.8, 1.5		1.1	0.8, 1.5	
> 2.610	2.0	1.5, 2.8		1.4	1.0, 1.9		1.4	1.0, 1.9	
β-HCH			<0.001			0.030[d]			0.031[d]
≤ 0.288	1.0	Referent		1.0	Referent		1.0	Referent	
0.289-0.670	0.9	0.6, 1.2		0.7	0.5, 1.0		0.7	0.5, 1.0	
0.671-1.547	1.4	1.1, 1.9		1.0	0.7, 1.3		1.0	0.7, 1.3	
> 1.547	1.7	1.3, 2.2		1.0	0.8, 1.4		1.0	0.8, 1.4	
PCB 118			<0.001			0.046			0.074
≤ 0.060	1.0	Referent		1.0	Referent		1.0	Referent	
0.061-0.135	1.0	0.8, 1.4		1.0	0.8, 1.3		1.0	0.8, 1.3	
0.135-0.242	1.2	0.9, 1.6		1.0	0.8, 1.3		1.0	0.8, 1.3	
> 0.242	1.6	1.3, 2.0		1.2	1.0, 1.6		1.2	0.9, 1.5	
PCB 138			<0.001			0.045			0.040
≤ 0.258	1.0	Referent		1.0	Referent		1.0	Referent	
0.259-0.451	1.2	0.9, 1.6		1.0	0.7, 1.3		1.0	0.7, 1.3	
0.452-0.722	1.5	1.1, 2.0		1.1	0.8, 1.4		1.1	0.8, 1.4	
> 0.722	1.8	1.4, 2.3		1.2	0.9, 1.6		1.2	0.9, 1.6	
PCB 153			<0.001			0.027			0.026
≤ 0.361	1.0	Referent		1.0	Referent		1.0	Referent	
0.362-0.626	1.4	1.0, 1.9		1.2	0.9, 1.7		1.2	0.9, 1.6	
0.627-0.978	1.7	1.3, 2.2		1.2	0.9, 1.7		1.2	0.9, 1.7	
> 0.978	1.9	1.5, 2.5		1.4	1.0, 1.9		1.4	1.0, 1.8	
PCB 180			<0.001			0.029			0.027
≤ 0.314	1.0	Referent		1.0	Referent		1.0	Referent	
0.315-0.503	1.4	1.0, 1.8		1.1	0.8, 1.4		1.0	0.8, 1.4	
0.504-0.783	1.7	1.3, 2.2		1.3	1.0, 1.7		1.3	1.0, 1.7	
> 0.783	1.8	1.4, 2.4		1.3	1.0, 1.7		1.3	1.0, 1.7	
Sum of PCBs			<0.001			0.007			0.007
≤ 1.03	1.0	Referent		1.0	Referent		1.0	Referent	
1.04-1.76	1.4	1.0, 1.9		1.1	0.8, 1.5		1.1	0.8, 1.4	
1.76-2.72	1.7	1.3, 2.3		1.2	0.9, 1.6		1.2	0.9, 1.6	
> 2.73	2.0	1.5, 2.6		1.4	1.0, 1.8		1.4	1.0, 1.8	
Sum of orders 6 POPs[e]			<0.001			0.020[d]			0.028[d]
6-10	1.0	Referent		1.0	Referent		1.0	Referent	
11-15	1.3	0.9, 1.7		1.0	0.7, 1.4		1.0	0.7, 1.4	
16-19	1.4	1.0, 1.9		0.9	0.7, 1.3		1.0	0.7, 1.3	
20-24	1.9	1.5, 2.5		1.2	0.9, 1.7		1.2	0.9, 1.7	
Sum of orders all POPs			<0.001			0.009[d]			0.012[d]
8-14	1.0	Referent		1.0	Referent		1.0	Referent	
15-20	1.4	1.0, 1.9		1.1	0.8, 1.5		1.0	0.8, 1.4	
21-26	1.3	1.0, 1.8		0.9	0.7, 1.3		0.9	0.7, 1.3	
27-32	2.0	1.5, 2.6		1.2	0.9, 1.7		1.2	0.9, 1.7	

Abbreviations: CI, confidence interval; PR, prevalence ratio; POP: persistent organic pollutant.
[a] Model 1: adjusted for age, sex, body mass index, cigarette smoking, alcohol consumption, and physical activity.
[b] Model 2: adjusted for age, sex, body mass index, cigarette smoking, alcohol consumption, physical activity and occupational social class.
[c] Unless otherwise specified, *P* derived from the multivariate analogue of Mantel's extension test for linear trend.
[d] Wald test. [e] HCB, β-HCH, and PCB congeners 118, 138, 153, and 180.

A)



B)