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Exposure to dietary polychlorinated biphenyls and dioxins, and its relationship with subclinical coronary atherosclerosis: The Aragon Workers' Health Study

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ABSTRACT

Background: Experimental evidence has revealed that exposure to polychlorinated biphenyls (PCBs) and dioxins directly impairs endothelial function and induces atherosclerosis progression. In the general population, despite a small number of recent studies finding a link between PCBs, and stroke and myocardial infraction, the association with early coronary atherosclerosis has not been examined yet.

Objective: To examine whether dietary exposure to PCBs and dioxins is associated with subclinical coronary atherosclerosis in a middle-aged men.

Design: Cross-sectional analysis comprising 1844 men in their 50 s and free of cardiovascular disease, who participated in the Aragon Workers' Health Study (AWHS). Individual dietary exposures to PCBs and dioxins were estimated by the contaminant's concentration in food coupled with the corresponding consumption and then participants were classified into quartiles of consumption. Coronary artery calcium score (CACS) was assessed by computerized tomography. We conducted ordered logistic regressions to estimate the odds ratio (OR) and 95% confidence intervals (CIs) for progression to the categories of more coronary artery calcium, adjusting for potential confounders.

Results: Among the participants, coronary calcium was not shown in 60.1% (n = 1108), 29.8% had a CACS > 0 and < 100 (n = 550), and the remaining 10.1% (n = 186) had a CACS ≥ 100. Compared with those in the first quartile of PCBs exposure, those in the fourth one had an increased odds for having coronary calcium (OR 2.02, 95% CI [1.18, 3.47], *p* trend 0.019) and for having progressed to categories of more intense calcification (OR 2.03, 95% CI [1.21, 3.40], *p* trend 0.012). However, no association was found between dietary dioxins exposure and prevalent coronary artery calcium.

Conclusions: In this general male population, dietary exposure to PCBs, but not to dioxins, was associated with a higher prevalence of coronary calcium and to more intense subclinical coronary atherosclerosis. PCBs exposure seems to increase the risk of coronary disease in men from the very early stages.

Abbreviations: PCBs, Dietary polychlorinated biphenyls; CVD, Cardiovascular disease; CACS, Coronary artery calcium score; OR, Odds ratio; CI, Confidence interval; MI, Myocardial infarction; BMI, body mass index; FFQ, Food frequency questionnaire

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1. Introduction

Polychlorinated biphenyls (PCBs) and dioxins are persistent organic pollutants (POPs), a group of toxic chemicals with high lipophilic and bioaccumulative potential. PCBs have been widely employed in industry as heat exchange fluids, in electric transformers and capacitors (ATSDR, 2008). Contamination was produced by direct discharge from industries that use them or by combustion and discharge into rivers and marine waters of contaminated waste. Despite the long-term ban because of their association with cancer (Unep, 2008), PCBs are today widely disseminated in the environment. In turn, dioxins, which are grouped into the categories polychlorinated dibenzo-p-dioxins (PCDDs) and dibenzofurans (PCDFs), are produced unintentionally due to incomplete combustion, as well as, during the manufacturing of certain pesticides and other chemicals (Fiedler, 2007).

Thus, while historically the exposure to POPs was either occupational or accidental; nowadays, the most relevant source of POPs worldwide is through ingestion of contaminated food (Bergkvist et al., 2012; Efsa, 2012; Llobet et al., 2008). Moreover, once ingested, POPs are slowly eliminated, resulting in an age-dependent body burden in humans (Gao et al., 2019). POPs exposure remains of concern to the international community since they still accumulate in the food chain resulting in low but continuous human exposure.

Increasing evidence is placing environmental contaminants as potential preventable cardiovascular risk factors in the general population. In particular, PCBs have been associated with myocardial infarction (MI) (Bergkvist et al., 2016; Bergkvist et al., 2015), stroke (Bergkvist et al., 2014; Lee et al., 2012) and more extensively with hypertension (Donat-Vargas et al., 2018; Donat-Vargas et al., 2015; Park et al., 2016). In the same vein, extensive evidence from experimental studies is demonstrating that exposure to PCBs and dioxins directly impairs endothelial function and induces atherosclerosis progression via inflammation, oxidative stress, endocrine disruption, and immunotoxicity-related mechanisms (Hennig et al., 2007; Petriello et al., 2018), as well as, by altering gene expression patterns in vascular cells (Puga et al., 2004).

Atherosclerosis, the process underlying cardiovascular disease (CVD), is a complex disease in which fatty deposits, cell inflammation, and scar tissue build up within the walls of the arteries. While the aforementioned experimental data suggests a direct effect of PCBs and dioxins in the development of atherosclerosis, together with observational population evidence shows that PCBs are associated with an increase in atherosclerosis final expression; to our knowledge, no previous epidemiological studies have assessed the early damaging impact of PCBs and dioxins in the walls of coronary arteries. So far, there is only one cross-sectional study of 70-year-old men and women from Uppsala (Sweden), where levels of PCBs in the blood were associated with the presence of carotid artery plaques (Lind et al., 2012), suggesting PCBs' have an influence in subclinical atherosclerosis, but late in life and outside of the coronary territory.

The aim of this study was to examine whether dietary exposure to PCBs and dioxins was associated with coronary artery calcium — a well-established measure of the burden of subclinical atherosclerosis in the coronary arteries (Budoff et al., 2009; Budoff et al., 2009) — in an apparently healthy middle-aged sample with low prevalence of clinical comorbidities.

2. Participants and methods

2.1. Study design and population

The present study included a sample of participants belonging to The Aragon Workers' Health Study (AWHS), an ongoing prospective longitudinal cohort study designed to characterize the association of traditional and emergent cardiovascular risk factors with the prevalence and progression of subclinical atherosclerosis. Study participants are workers of Opel Spaiń s automobile assembly plant located in Figueruelas (Zaragoza, Spain) that were recruited during a standardized clinical exam in 2009–2010 (participation rate 95.6%). In addition, between January 2011 and December 2014, all participants aged 40–60 years old were invited to undergo a noninvasive imaging exploration of subclinical atherosclerosis and provided blood and urine samples for the studý s biobank, as well as, to answer a comprehensive questionnaires on cardiovascular and lifestyle factors, including diet.

A total of 2091 workers (all Caucasians) were recruited into the AWHS imaging study and completed the dietary questionnaire. Due to the small number of women (n = 95), the present report was restricted to men (n = 1996). Likewise, after exclusion of participants with prevalent CVD (n = 27) and/or implausible dietary energy intake (n = 125), the final sample consisted of 1844 participants. Since the study design has been described in detail elsewhere (Casasnovas et al., 2012; Laclaustra et al., 2016), only a brief description has been provided. The study was approved by the central Institutional Review Board of Aragón (CEICA). All participants gave informed consent prior to the inclusion in the study and the investigation conformed to all principles outlined in the Declaration of Helsinki.

2.2. Data collection

Demographic information from questionnaires included age, sex, marital status, education level, sleeping duration (both on weekdays and weekends), smoking habits, medication and diagnosed diseases. Information on diet and physical activity was obtained using standardized questionnaires administered by trained interviewers. Usual diet over the preceding year was assessed using a 136-item semi-quantitative food frequency questionnaire (FFQ) previously validated in Spain (de la Fuente-Arrillaga et al., 2010), considering seasonal variations and differences between weekday and weekend patterns. Intakes of total calories, fats (saturated, monounsaturated, polyunsaturated, and trans), alcohol, cholesterol and fiber were measured by using standard Spanish food composition tables. Leisure-time physical activity and time spent in sedentary activities was assessed using the Health Professionals' Follow-up physical activity questionnaires (Martinez-Gonzalez et al., 2005). Participants were asked about the time devoted to 17 different activities during the preceding year, and leisure-time physical activity was expressed in metabolic equivalents (METs)-h/week.

Serum samples were obtained and total, as well as, HDL-cholesterol were measured. Study participants went through a standardized clinical exam with blood pressure (BP) and heart rate measurements. BP was measured three consecutive times using an automatic oscillometric sphygmomanometer with the participant sitting after a 5-min rest. Anthropometric, including height, weight, and waist circumference were also measured following standardized procedures, and body mass index (BMI, in kg/m^2) was calculated.

Physicians and nurses collecting the data previously underwent training and standardization programs organized by the study investigators. Compliance with study procedures was routinely monitored and deviations were corrected. The study conforms to the ISO9001-2008 quality standard.

2.3. Estimations of dietary exposure of PCBs and dioxins

Daily dietary exposure to total PCBs (ng/day) and total dioxins (pg/day) was estimated by multiplying the average concentration in various foods, obtained from a previous study performed in Spain (Llobet et al., 2008), with the respective frequency of consumption and serving size, adjusting afterwards for total dietary energy intake (mean of 2825 kcal per day, for the cohort) using the residual-regression method (Willett and Stampfer, 1986)

2.4. Coronary artery calcium

The amount of coronary artery calcium is associated with the overall burden of coronary atherosclerosis and is a marker of coronary damage. Coronary calcium scoring was performed using noncontrast ECG gated prospective acquisition by a 16 multidetector computed tomography scanner (Philips).

Agatston's method uses multiplication of calcified plaque density and area, and results are a strong indicator of extensive disease as well as significant involvement of vessels with calcification. Agatston's score (CACS) remains the standard reference and the most commonly used coronary artery calcium score in clinical practice (Agatston et al., 1990).

Hence, for the present assessment, coronary artery calcium Agatston score (CACS) was divided into three consecutive categories: 0, > 0 and < 100, and ≥100, thus reflecting calcium presence (> 0) and surpassing a threshold (≥100) associated with mild increases in coronary heart disease event rates (Erbel et al., 2010).

2.5. Statistical analysis

Participants were categorized into quartiles of dietary exposures of total PCBs and total dioxins (each quartile n = 461). Due to the ordinal nature of the response variable (CACS in three categories: 0, > 0 and < 100, and ≥100), we confirmed in the first place that data complied with the proportional odds assumption (a requirement for conducting ordered logistic regression) by using the Wald test and the likelihood-ratio test for proportionality of odds across response categories.

We estimated the odds ratio (OR) and corresponding 95% confidence intervals (CI) for having progressed to categories of more coronary artery calcium using ordered logistic regressions (ologit/parallel-lines odds model), which assume, in our 3-category case, that the OR that describes the relationship between, the lowest versus all higher categories of the response variable (CACS) is similar enough to be considered the same as the one that describes the relationship between the lower categories versus the highest one. Because in this approach the relationship between all collapsed pairs of CACS category is assumed to be the same, only one OR is estimated for each explanatory condition.

Additionally, we conducted generalized ordered logistic models (gologit/partial proportional odds model), which are less restrictive than the proportional-odds/parallel-lines models and do not assume the equality of slopes among categories (Williams, 2016). We also performed the standard binary logistic regression for the collapsed categories to estimate the OR for CACS > 0 (compared with CACS = 0) and for CACS ≥ 100 (compared with CACS < 1 0 0), to provide estimations whose meaning can be easily be understood as they are widely used, although they do not provide an integral unique descriptive model as the previous regressions.

To test for linear trends (*P* trend) across increasing categories of dietary exposure to PCBs and dioxins, the median concentration within each quartile was included and treated as a continuous variable in the model.

For all the analyses, we used three models with progressive adjustment for covariates that may possibly confound the association (Ahmed et al., 2013; Lee et al., 2009). **Model 1**, adjusted for demographic and lifestyle factors: age (continuous, yrs.), marital status (married, not married), education (middle school, high school, professional training, and college), time spent sleeping during the week (number of hours of sleep, continuous), time spent sleeping during the weekend (number of hours of sleep, continuous), smoking status (never, former, and current smoker), and physical activity (total MET-h/wk). **Model 2**, further adjusted for dietary components: alcohol consumption (g/d), total fiber (g/d), saturated fats (g/d), trans fats (g/d), cholesterol (mg/d) and long-chain ω-3 polyunsaturated fatty acids (ω-3 PUFAs) (g/d). **Model 3**, further adjusted for cardiometabolic risk conditions: total cholesterol (mg/dL), HDL cholesterol (mg/dL), systolic and diastolic blood pressure (mmHg), BMI (< 25, 25- < 30, ≥30 kg/m^2), and self-reported diabetes (yes, no).

Multivariable-adjusted models were fitted including the missing values in a separate category for education (< 1%), smoking (< 1%) and prevalent diabetes (3%). Although POP values are already calculated taking into account energy intake, we performed a sensitivity analysis further adjusting for the latter in which association estimations remained substantially unchanged with only a slight increase of their standard errors (results not shown).

As a sensitivity analysis, we additionally (**i**) re-ran the analysis excluding those participants with prevalent hypertension, high cholesterol, diabetes and obesity (n = 1054); (**ii**) tested for potential effect modification by omega-3 fatty acids, adherence to Mediterranean diet and BMI, on the PCBs-coronary calcium relationship.

All analyses were run in Stata version 15.0 (StataCorp LP), with statistical significance set at the two-sided 0.05 level.

3. Results

The mean (SD) age of participants was 51 (3.7) years. Compared to participants with less dietary exposure to PCBs (mean 449 ± 139 ng/day), those most exposed (mean 1641 ± 379 ng/day) were, on average, more educated, slightly more physically active, and had consumed more fiber, fish and marine omega-3 fatty acids. In turn, compared to participants with less dietary exposure to dioxins (mean 519 ± 114 pg/day), those most exposed (mean 809 ± 146 ng/day) were, on average, more educated, were more frequently current smokers, had a higher intake of fruits, vegetables and fiber, and consumed remarkably less alcohol (Table 1**, Online** Table 1**, Online** Table 2).

Participants in the highest quartile had three times higher dietary PCBs exposure than those in the lowest quartile (Table 1**, Online** Table 1**, and Online** Table 2). In this cohort, the leading food group responsible for dietary PCBs exposure was fish and related products (e.g., seafood and fish preserves); in particular, fatty fish contributed to 33.5% of the total dietary exposure to PCBs (Table 2). Overall and considering the main food groups, the PCB congeners in higher concentrations, by far, were PCB-153 and PCB-138 followed by PCB-180, all of them high chlorinated. The exception were eggs and vegetables, where PCB-28 was the congener found in higher concentrations (**Online** Table 3**)**

On the contrary, differences among extreme quartiles for dietary dioxin exposure were smaller, more spread across different foods, and headed by other food groups than fish or seafood, e.g. the highest contribution was from lettuce, which was responsible for only 12% of the total dietary exposure to dioxins.

Regarding the outcome of interest, coronary calcium was not shown in 60.1% of the participants (n = 1108), 28.8% had a CACS > 0 and < 100 (n = 550), and the remaining 10.1% (n = 186) had a CACS ≥ 100.

Once verified that data complied with the required assumptions, the fully adjusted ordered logistic model revealed that, those in the fourth quartile of PCBs exposure, compared to those in the first quartile, had a statistically significant 2-fold increased odds (OR 2.03, 95%CI [1.21, 3.40], *P* trend across quartiles 0.012, for the adjusted model 3) for progression to categories of more coronary artery calcium — i.e., from the lowest category (CACS = 0) to the higher categories (CACS > 0 and < 100, together with CACS ≥ 100), as well as, from the lower categories (CACS = 0, together with CACS > 0 and < 100) to the highest category (CACS ≥ 100) (**Model 2;** Table 3). PCBs therefore seem to be associated with higher coronary calcium independently of cholesterol, systolic and diastolic blood pressure, BMI and prevalent diabetes. This association did not differ from the resulted by lower level of adjustment (**Model 2;** Table 3), suggesting that metabolic diseases/conditions have no impact on PCBs − coronary calcium association.

Table 1
Descriptive characteristics of study participants by extreme categories of dietary PCBs and dioxins exposures (N = 1844).

	Dietary PCBs exposure					
	1st quartile	4th quartile	*P*-value*	1st quartile	4th quartile	*P*-value*
N	461	461		461	461	
Dietary PCBs exposure (ng/day)	**449** (139)	**1641** (379)	< 0.01	**833** (447)	**1088** (535)	< 0.01
Dietary dioxins exposure (pg/day)	**620** (175)	**689** (160)	< 0.01	**519** (114)	**809** (146)	< 0.01
Age (years)	50.9 (3.8)	51.3 (3.7)	0.39	51.3 (3.6)	51.1 (3.8)	0.47
Married (%)	83.7	87.0	0.49	83.9	86.6	0.59
Education (%)			0.01			< 0.01
Middle school	58.5	46.3		59.6	46.2	
High school	10.9	12.1		8.6	10.5	
Professional training	27.7	34.9		28.7	38.3	
College	2.8	6.8		3.1	5.0	
Sleep duration (hours)						
On weekdays	6.36 (1.02)	6.24 (0.94)	0.24	6.23 (1.0)	6.32 (0.99)	0.47
On weekends	7.31 (1.24)	7.33 (1.06)	0.66	7.23 (1.23)	7.32 (1.16)	0.53
Smoking habits (%)			< 0.01			< 0.01
Never	21.8	25.2		20.3	23.8	
Former	35.1	29.2		37.3	22.5	
Current	43.1	45.6		42.5	53.7	
Physical activity (MET-h/week)	30.2 (21.8)	35.8 (23.4)	< 0.01	32.4 (20.7)	35.5 (25.7)	< 0.01
Total cholesterol in blood (mg/dL)	221 (35)	225 (38)	0.29	223 (36)	220 (34)	0.05
HDL cholesterol in blood (mg/dL)	51.1 (10.7)	54.7 (11.5)	< 0.01	53.0 (11.8)	53.2 (10.7)	0.66
Blood pressure (mmHg)						
Systolic	126 (15)	126 (15)	0.51	127 (14)	125 (14)	0.25
Diastolic	83.4 (9.9)	83.1 (10.0)	0.79	83.1 (9.1)	82.8 (9.6)	0.78
Body mass index (%)			0.82			0.24
$< 25\ kg/m^2$	21.0	18.0		22.6	16.1	
$25– < 30\ kg/m^2$	56.6	57.5		54.0	60.3	
$\geq 30\ kg/m^2$	22.3	24.5		23.4	23.6	
Prevalent diabetes (%)	5.0	4.0	0.69	3.6	4.9	0.55
Alcohol consumption (g/day)	21.5 (21.9)	20.1 (18.3)	0.66	31.0 (24.8)	15.1 (14.5)	< 0.01
Total fiber (g/day)	23.1 (6.8)	26.9 (8.2)	< 0.01	22.6 (7.1)	28.4 (7.7)	< 0.01
Saturated fat intake (g/day)	31.6 (9.8)	31.8 (9.5)	0.14	30.7 (9.1)	33.1 (9.0)	< 0.01
Trans fat intake (g/day)	0.88 (0.45)	0.77 (0.43)	< 0.01	0.74 (0.39)	0.92 (0.47)	< 0.01
Cholesterol intake (mg/day)	420 (136)	505 (137)	< 0.01	445 (145)	474 (129)	< 0.01
ω-3 PUFAs intake (g/day)	0.27 (0.12)	1.25 (0.38)	< 0.01	0.59 (0.39)	0.78 (0.46)	< 0.01
Total energy intake (Kcal)	2841 (659)	2857 (604)	0.08	2971 (616)	2818 (575)	< 0.01
Mediterranean Diet†	3.3 (1.5)	3.9 (1.6)	< 0.01	3.3 (1.5)	3.8 (1.6)	< 0.01
Individual food groups intake (g/day)						
Fish	39.0 (17)	142.0 (33.6)	< 0.01	74.0 (40)	96.5 (46)	< 0.01
Meat products	179.1 (67)	181.2 (74.5)	0.01	192.0 (71)	176.5 (66)	< 0.01
Dairy products	323.9 (206)	332.9 (208)	0.54	309.6 (237)	347.1 (184)	< 0.01
Vegetables	274.9 (118)	371.8 (130)	< 0.01	228.0 (90)	421.2 (154)	< 0.01
Fruit	267.8 (177)	297 (165)	< 0.01	258 (167)	362.8 (176)	< 0.01
Legumes	16.04 (6)	16.7 (6)	0.02	15.9 (6)	16 (6)	0.51
Cereals	328.9 (136)	300.8 (129)	< 0.01	350.7 (144)	286.8 (116)	< 0.01
Olive oil	26.9 (12)	29.5 (12)	0.02	27.3 (13)	28.2 (12)	0.06

NOTE: Continuous variables are shown as mean (standard deviation) and categorical variables are shown as percentage (%).
ω-3 PUFAs: long-chain ω-3 polyunsaturated fatty acids.
† A score indicating compliance to the Mediterranean diet but excluding fish intake. A high intake of the Mediterranean foods: cereals, legumes, fruits, vegetables and olive oil were scored positive (1) and a high intake of the non-Mediterranean foods: dairy, meat and ratio monounsaturated/saturated fatty acids negative (0). The score ranged from 0 to 8 and the higher the score the better the compliance to a traditional Mediterranean diet.
* *P*-value estimates are based on one-way ANOVA for variables expressed as mean (standard deviation) or Pearson χ^2 test for variables expressed as percentages.

Table 2
Main food groups responsible for dietary exposure to PCBs and dioxins in AWHS (N = 1844).

PCBs			Dioxins		
		Contribution (%)			Contribution (%)
1	Fatty fish	33,5	1	Lettuce	12,1
2	White fish	26,9	2	Bread	8,3
3	Octopus, squid	13,0	3	Cheese	6,2
4	Canned fish and seafood in oil	10,6	4	Cookies	5,6
5	Naturally canned fish and seafood	3,2	5	Potatoes	5,3
6	Bread	1,8	6	Olive oil	3,2

The numbers denote the contribution (in percentage) of the food to the total exposure of PCBs and dioxins in this sample.

In contrast, there was no indication found of an association between dietary exposure to dioxins and coronary artery calcium (Table 3). When using the less restrictive and more flexible generalized ordered logit models (with no restriction to estimate one single common OR across progression) (**Online Table 4**), the OR for each CACS progression across categories provided a similar result for both, consistent with describing it with a single OR (Table 3). Likewise, analogous results were obtained by performing the standard binary logistic regression to estimate OR for CACS > 0 (with CACS = 0 as ref.) and for CACS ≥ 100 (with CACS < 100 as ref.) (**Online Table 5**). Compared with those in the first quartile of PCBs exposure, those in the fourth one had an OR 2.02 (95%CI [1.18, 3.47], *P* trend across quartiles 0.019) for having coronary calcium. While dietary PCBs exposure was consistently associated with coronary artery calcium through the different approaches, dioxins exposure was not.

When as a sensitivity analysis we re-ran the analysis excluding those

Table 3
Odds ratios (95% CI) for progression to higher coronary artery calcium score (CACS) categories by PCBs and dioxin exposure quartiles, using ordered logistic models (N = 1844).

OR for progression to higher CACS categories*	PCBs					Dioxins				
	Q1	Q2	Q3	Q4	*P* trend	Q1	Q2	Q3	Q4	*P* trend
Model 1	1 (ref.)	1.03 (0.79, 1.34)	0.94 (0.72, 1.23)	0.89 (0.68, 1.17)	0.308	1 (ref.)	0.74 (0.57, 0.97)	0.91 (0.70, 1.19)	0.92 (0.71, 1.20)	0.827
Model 2	1 (ref.)	1.26 (0.94, 1.68)	1.30 (0.94, 1.81)	1.96 (1.17, 3.26)	0.014	1 (ref.)	0.81 (0.61, 1.06)	1.03 (0.78, 1.36)	1.10 (0.81, 1.49)	0.305
Model 3	1 (ref.)	1.31 (0.98, 1.75)	1.32 (0.94, 1.83)	2.03 (1.21, 3.40)	0.012	1 (ref.)	0.80 (0.60, 1.05)	0.97 (0.73, 1.29)	1.07 (0.79, 1.46)	0.438

NOTE: The ordered logistic model (parallel-lines model) assume the equality of slopes among categories, i.e. the relationship between all pairs of categories is the same, and consequently, there is only one set of coefficients. The no violation of the proportional odds/parallel-lines assumption was verified by the Wald test (for PCBs model 3: p = 0.8149 and for dioxins model 3 p = 0.8083) and likelihood-ratio test (for PCBs model 3: p = 0.1253 and for dioxins model 3 p = 0.1390) for proportionality of odds across response categories.
Model 1: Adjusted for age, marital status, education, sleeping duration (both on weekdays and weekends), smoking habits, physical activity.
Model 2: Further adjusted for energy-adjusted fiber intake, saturated fats intake, trans fats intake, n-3 long chain polyunsaturated fatty acids intake, cholesterol intake, and alcohol consumption.
Model 3: Further adjusted for cardiometabolic risk conditions: total and HDL cholesterol, systolic and diastolic blood pressure, body mass index and prevalent diabetes.
* Progression from the lowest category (CACS = 0) to the higher categories (CACS > 0 and < 100, together with CACS ≥ 100), as well as, from the lower categories (CACS = 0, together with CACS > 0 and < 100) to the highest category (CACS ≥ 100).

participants with prevalent hypertension, high cholesterol, diabetes and obesity (n = 1054), consistent results were obtained despite the resulting limited sample size. Finally, there was no evidence of any interaction between PCBs and omega-3 fatty acids, adherence to Mediterranean diet and BMI, on the PCBs-coronary calcium relationship; although we acknowledge our limited sample size.

4. Discussion

In this large sample of middle-aged men, a higher dietary exposure to PCBs was associated with a higher prevalence of subclinical coronary atherosclerosis independently of cardiometabolic risk factors (i.e., cholesterol level, blood pressure, BMI and diabetes), as well as, other diet and lifestyle cardiovascular risk factors. In addition, a dose-response association was observed between dietary exposure to PCBs and atherosclerosis. In contrast, the results for dietary exposure to dioxins did not show an association with coronary artery calcium.

The most important route for human exposure to PCBs and dioxins is food consumption contributing to over 90% of total exposure (Liem et al., 2000). According to the studies already reported (Arrebola et al., 2018), we observed that fish was the main food group contributor to PCB exposure in this cohort of male workers. Thus, fish consumption becomes controversial, as it is the main source of omega-3 fatty acids but also of PCBs (together with mercury). In a recent published paper (Donat-Vargas et al., 2019), we observed that PCBs were associated with higher cardiovascular mortality, and, at the same time, omega-3 fatty acids were associated with lower cardiovascular mortality. These effects were only observed when regression models were mutually adjusted for omega-3 fatty acids and PCBs, respectively. We concluded that optimal fish consumption will depend on the concentrations in fish of both components (Donat-Vargas et al., 2019). In the present study we found a similar scenario. Omega-3 fatty acids and PCBs, with opposite effects are very correlated, and, the effect of PCBs on coronary calcium is only clear when adjusting for omega-3 fatty acids. However, there was no evidence of interaction between PCBs and omega 3 acids, although we acknowledge our limited sample size.

Dioxin food sources were more variable, and in this study, vegetables and fruits were the main contributors to dioxin exposure. At the same time, the Mediterranean diet, rich in omega-3 fatty acids, fruits, vegetables and whole grains, is indicated to provide protection against adverse cardiovascular events (Estruch et al., 2018). This protective potential is mainly attributed to its rich content of antioxidant and anti-inflammatory compounds (e.g., phytochemicals and polyphenols), which, in turn, seem to be capable of blunting the toxic and inflammatory effects of POPs (Hennig et al., 2007). To take this into account, but avoiding over-adjusting, instead of directly adjusting for fish, fruit and vegetables, which are the sources of the exposures of interest, we adjusted for omega-3 fatty acids and fiber.

Likewise, nutrition and POPs may interact and alter similar mechanistic pathways and even, some nutritional components may be able to bind and increase POPs excretion and ultimately reduce the body burden of certain pollutants. For instance, it was observed that consumption of green tea can reduce oxidative and inflammatory responses associated with PCB-126 exposure through upregulation of antioxidant enzymes (Newsome et al., 2014). It was also observed that dietary fat may interact with PCBs and induce changes in lipid metabolism in mice. Interestingly, this finding was observed in corn oil–fed mice but not in olive oil fed mice, indicating the selective interaction of specific dietary fats with PCB inflammatory processes (Hennig et al., 2005). Also, the overconsumption of processed and refined foods showed to exacerbate the pollutant-associated inflammatory processes. (Hennig et al., 2012). In the current work, we were not able to capture a significant interaction between POPs and diet. In addition, due to the small sample size and few cases with CAC > 0. This possibility needs to be properly studied with studies already designed for this purpose (Hennig et al., 2012). Besides, in the light of our findings regarding PCBs, if the presence of PCBs in fish could mitigate the beneficial cardiovascular effects attributed to fish, mostly due to its content in omega-3 fatty acids needs further research. (Rimm et al., 2018)

The amount of coronary artery calcium is associated with the overall burden of coronary atherosclerosis, resulting in coronary heart disease (CHD) while also happening in association with cerebrovascular disease, which are the leading causes of death worldwide (Who, 2014). More specifically, a high CACS have reliably been associated with overall CHD (Detrano et al., 2008), stroke (Hermann et al., 2013) and myocardial infraction (MI) (Leening et al., 2012). Likewise, in the Multi-Ethnic Study of Atherosclerosis, coronary artery calcium was noted to be highly predictive of CHD risk across all ages (Tota-Maharaj et al., 2014), and an absence of coronary artery calcium meant very low risk for future CVD (Budoff et al., 2009; Sarwar et al., 2009).

Estimates of dietary exposure to PCBs have also been assessed in the Swedish mammography cohort (SMC) and the Cohort of Swedish Men (COSM) - two population-based prospective cohorts including > 70,000 women and men. In these cohorts, dietary exposure to PCBs was

associated with a 60–70% higher risk of MI (Bergkvist et al., 2016; Bergkvist et al., 2015) in both genders, and with a 61% higher risk of ischemic stroke in women (Bergkvist et al., 2014). In line with these findings, a prospective study performed with the elderly participants from the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS), showed that after a 5-year follow-up, those in the fourth quartile of plasma PCBs levels (compared with the first quartile) had an adjusted OR of 2.1 (CI 95%: 0.7, 6.2) for hospital-treated stroke; and the corresponding ORs among participants ≥ 90th percentile of PCBs was 5.5 (CI 95%: 1.7, 18.1) (Lee et al., 2012). Also, in a cross-sectional assessment of these same participants, PCBs, but not dioxins, were associated with the presence of carotid artery plaques and echogenicity of the carotid artery intima-media complex (Lind et al., 2012). No other previous studies conducted in the general population have addressed the exposure to POPs in relation to atherosclerosis.

Activation, dysfunction of the vascular endothelium, and chronic vascular inflammation are critical events in the initiation and progression of the atherosclerotic lesion. Rodent studies have reported PCBs- and dioxins-induced vascular injury, inflammation, and endothelial apoptosis, leading to endothelial dysfunction and atherosclerosis (Petriello et al., 2018; Arsenescu et al., 2011; Dalton et al., 2001; Kopf et al., 2008; Lind et al., 2004; Tang et al., 2017). This is also supported by in vitro findings, revealing that PCBs and dioxins may induce inflammation (Eske et al., 2014; Hennig et al., 2002), oxidative stress (Kopf et al., 2008; Tang et al., 2017), and dysfunction of the vascular endothelium (Andersson et al., 2011; Helyar et al., 2009; Lim et al., 2007; Majkova et al., 2009; Yu et al., 2017), ultimately causing the formation of atherosclerotic plaques (Hennig et al., 2002).

The different PCBs congeners have been traditionally classified into two large groups based on their molecular structure. While coplanar dioxin-like (DL)-PCBs elicit their toxicity partly through the aryl hydrocarbon receptor (AhR) activation – a mechanism that is shared with dioxins –, non-dioxin-like (NDL)-PCBs, that cannot adopt a coplanar structure, activate other xenobiotic receptors such as androgen, estrogen and transthyretin receptors (Hamers et al., 2011), the pregnane-xenobiotic receptor (PXR), and the constitutive androstane receptor (CAR) (Wahlang et al., 2014). Most of the vascular effect of PCBs and dioxins, however, have evidenced to occur through AhR-mediated pathways, such as via expression of several inflammatory markers (Eske et al., 2014; Liu et al., 2015) and increasing cellular oxidative stress (Kopf et al., 2008; Tang et al., 2017). The DL-PCB congener 126 have shown to stimulate the production of vasoconstriction factors, including cyclooxygenase (COX-2), prostaglandins, and reactive oxygen species (ROS), as well as, to inhibit the release of the vasodilator nitric oxide (NO) (Andersson et al., 2011; Helyar et al., 2009). Furthermore, there is also evidence that dioxin-like pollutant exposure (PCB-126) can result in upregulation of the enzyme flavin-containing monooxygenase 3 (FMO3) and subsequently increase circulating levels of trimethylamine-N-oxide (TMAO), a biomarker strongly associated with cardiovascular disease (Petriello et al., 2016).

Nonetheless, as there are high intra-individual correlations among both classes of PCBs (DL and NDL) in food sources (Llobet et al., 2008), as well as, in human tissue (Donat-Vargas et al., 2018), trying to isolate the effect of one class of PCBs independently of the other is very challenging for the analytical tools that we currently have in epidemiology. At any rate, since PCBs occur as mixtures of PCBs congener – and consequently the general population is exposed through diet to a PCBs mixtures (Ibrahim et al., 2011; Ruzzin et al., 2010) –, what is interesting from the public health point of view, risk assessment, and prevention, is to try to evaluate the overall effect of the exposure to total PCBs (Wahlang et al., 2014).

Lastly, reference must be made to the differences between the amounts of PCBs vs. dioxins ingested through the diet. Dietary exposure to PCBs was several thousand times higher than dietary exposure to dioxins. This might be one reason for not finding a positive association between dioxins and atherosclerosis in this study. Certainly, the latest EFSA report (Efsa, 2018) concluded that the strongest support for increased risk of CVD following exposure to dioxins was from studies of occupational high exposure to dioxins (Flesch-Janys et al., 1995; Steenland et al., 1999). By contrast, results from studies conducted in the general population with lower exposure to dioxins in relation to CVD risk, were considered inconsistent (Efsa, 2018). This consistent association between high exposure to dioxins and cardiovascular mortality (Flesch-Janys et al., 1995; Steenland et al., 1999), along with animal testing results and mechanistic findings (Hennig et al., 2002), make plausible an association between dioxin and atherosclerosis. However, in the general population with constant but low dietary exposure to dioxins, such hazard may not arise.

Some limitations of the study should be acknowledged, especially those that may result in certain degree of measurement error potentially diluting the associations. (**i**) Although the FFQ provides an appropriate assessment of the habitual dietary exposure of an individual (Fernandez-Ballart et al., 2010), because of the own nature of the methodology (e.g., self-reporting), inaccuracies cannot be ruled out. This non-differential misclassification draws association estimates to the null. (**ii**) PCBs and dioxins were measured in food samples collected in the year 2006 (Llobet et al., 2008), while participants' FFQs were completed between 2011 and 14. Although environmental levels of PCBs and dioxins have shown a progressive decline since the end of production (Perello et al., 2012), PCBs and dioxins, once ingested, accumulate in the adipose tissue and are difficult to eliminate, resulting in an age-dependent body burden in humans (Gao et al., 2019). Thus, it is unlikely that this lack of temporal consistency affects the classification of participants. (**iii**) The present study only assessed the exposure to PCBs and dioxins through dietary sources. Although inhalation exposure has been pointed out as a source worth considering (Ampleman et al., 2015), food consumption remains the main and crucial source of exposure (Liem et al., 2000; Arrebola et al., 2018). (**iv**) Data on food preparation nor cooking methods was considered. Nonetheless, FFQ-based dietary estimate of PCBs exposure has been extensively validated against serum PCBs congeners (Bergkvist et al., 2012), and it is deemed that, regardless of the above-mentioned limitations which prevent obtaining a precise measure of the real exposure (and the absolute PCBs and dioxins dietary exposure intake is only estimated approximately), a satisfactorily ranking of an individual's exposure is achieved using these methodology. (**v**) As it is not possible to discriminate between PCBs and other contaminants present in the same foods, we cannot dismiss the possibility that the co-exposure to other chemicals, such as heavy metals, would result in residual confounding.

On a side note, had we directly measured the levels of PCBs and dioxins in blood, it might have been considered a more accurate estimation of PCBs exposure. However, it is known that PCBs are accumulated largely in adipose tissue throughout our life and become a source of chronic internal exposure because they are continuously released from adipose tissue to the circulation and vital organs with lipid content. Consequently, blood concentrations may not represent adequately the total bioactive PCBs and dioxins in the body either (Lee et al., 2018).

Finally, with our cross-sectional design we cannot establish a firm causal link between PCBs and subclinical coronary atherosclerosis, regardless of the implausibility of reverse causality due to changes in habits because of the patients' knowledge of the disease —since the coronary artery calcium is subclinical—, nor due to mechanisms like "disease progression bias" (Porta, 2014). However, a further assessment of the association of PCBs with atherosclerosis requires evidence from longitudinal epidemiological data.

The major strengths of our study were the use of high quality data collection methods to obtain information on subclinical coronary atherosclerosis and potential confounders, the use of a population free of CVD, as well as, the performance of multiple statistical approaches that gave all congruent results.

In conclusion, this is the first study to address the association

between dietary exposure to PCBs and dioxins, and subclinical coronary atherosclerosis. We found that in this general male population, independently of well-known risk factors and other dietary factors, dietary exposure to PCBs, but not to dioxins, was associated with a higher prevalence of subclinical coronary atherosclerosis. These findings support the growing epidemiological data linking the current exposure to PCBs with an increased risk of CVD, coupled with experimental data elucidating the potential biological mechanisms behind this association. This association becomes remarkably relevant given that fatty fish constitutes the major source of PCBs, being able to counterbalance the beneficial effects of fish intake. Thus, despite production having stopped in the 80s, PCBs continue to pose a serious health risk, raising worries about high exposure to PCBs and an increased risk of CVD since the very early stages of the disease. Confirmatory independent and long-term studies including women would further strengthen our findings.

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 material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.105433.

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