Association Between Dietary Intake of Polychlorinated Biphenyls and the Incidence of Hypertension in a Spanish Cohort

The Seguimiento Universidad de Navarra Project

Carolina Donat-Vargas, Alfredo Gea, Carmen Sayon-Orea, Carmen de la Fuente-Arrillaga, Miguel Angel Martinez-Gonzalez, Maira Bes-Rastrollo

Abstract—Polychlorinated biphenyls are persistent organic pollutants that are consumed because of their bioaccumulation through the food chain. Evidence from different sources suggests a positive association between polychlorinated biphenyls exposure and the incidence of hypertension. However, no previous prospective study has investigated this potential relationship in adults. We prospectively assessed the association between dietary intake of polychlorinated biphenyls and the incidence of hypertension in a large cohort. The Seguimiento Universidad de Navarra project is a Spanish cohort of university graduates, most of them health professionals. We included 14521 participants, initially free of hypertension, who were followed-up for a median of 8.3 years. Dietary intake of polychlorinated biphenyls was assessed at baseline through a previously validated 136-item semiquantitative food frequency questionnaire. The published concentration levels of polychlorinated biphenyls measured in samples of food consumed in Spain were used to estimate dietary intake. Multivariable Cox regression models were fitted to estimate hazard ratios and 95% confidence interval for incident hypertension. During follow-up, 1497 incident cases of medically diagnosed hypertension were identified. After adjusting for total energy intake and for potential confounders, participants in the fifth quintile of total polychlorinated biphenyls intake were at higher risk of developing hypertension (adjusted hazard ratio, 1.43 [95% confidence interval, 1.09–1.88; P for trend 0.017]) compared with those in the first quintile. In this Mediterranean cohort, dietary intake of polychlorinated biphenyls, estimated using a food frequency questionnaire, was associated with a higher risk of developing hypertension during follow-up. Nevertheless, further longitudinal studies are needed to confirm our results. (Hypertension. 2015;65:714-721. DOI: 10.1161/HYPERTENSIONAHA.114.04435.)

Key Words: cohort studies ■ endocrine disrupting chemicals ■ hypertension ■ prospective studies

Hypertension, which affects one billion people worldwide, is the most important and well-known risk factor for cardiovascular disease (CVD), the leading cause of death in the world.1 It is estimated that in 2013 hypertension was responsible for ≥45% of mortality caused by heart disease, 51% of mortality caused by stroke, and it contributed to 12.8% of deaths worldwide.2 Hypertension is often considered a lifestyle disease, and its prevention has been focused entirely on the change in behavioral factors, such as diet, high alcohol consumption, smoking, stress, and physical inactivity.3

However, these lifestyle changes alone fail to completely justify the current magnitude and disease burden of hypertension in most countries. Consequently, more attention has been given to the growing body of evidence linking the risk of CVD and hypertension with additional exogenous factors, such as persistent organic pollutants (POPs).4-8

The term POPs refers to a number of highly divergent chemicals with the common characteristics of toxicity and resistance to degradation. Polychlorinated biphenyls (PCBs) are included among the best-known POPs. They are synthetic chlorinated aromatic compounds that have been used on a large scale in a wide variety of industrial and commercial applications.9

Owing to their lipophilicity, stability, and resistance to degradation, they are still widespread in the environment and bioaccumulated up the food chain over time and, once ingested, persist for a long time in the body.10,11 Consequently, even having been banned in most European countries during the 1980s, including Spain in 1989, they continue to be measured in environmental samples, as well as in the bodies of human and animals.12,13 In fact, human biomonitoring studies in Europe, North America, Australia, and elsewhere have
repeatedly detected POPs in the blood of the majority of citizens around the world.14–19

Food intake is the major route of PCB exposure in the general population (>90%), especially from fatty foods and products of animal origin, mainly in fish (contributing to >80% of total PCB intake).20

The first human evidence to PCBs and cardiovascular toxic effects was focused on the high exposure of PCBs in workers or residents near accidental spills.21–23 Likewise, a growing number of epidemiological studies have reported an elevated incidence of hypertension in populations highly exposed to PCBs.24–27 Furthermore, a study using the 1999 to 2004 National Health and Nutrition Examination Survey (NHANES) found an odds ratio for hypertension of 1.38 (95% confidence interval [CI], 1.02–1.87) among those in the highest compared with the lowest quartile of serum concentration of total PCBs.28

In addition, PCBs are presently considered major potential endocrine disrupting chemical, for their ability to modulate endogenous hormonal signaling pathways.29,30 and, there is new substantial evidence that low but chronic doses of endocrine disrupting chemicals, similar to current exposure levels in postindustrial population, have adverse effects on human health.31–33

To date, a particularly strong evidence has been accumulated supporting POPs as a risk factor for type 2 diabetes mellitus, insulin resistance, and obesity.32–36 However, prospective population-based studies linking current exposures to different POPs and hypertension are still lacking. Further evidence on the role of certain POP, such as PCB, exposures on the risk of hypertension and CVD is needed.37

Hence, to test the hypothesis that PCB exposure through the diet may increase the risk of hypertension in free-living populations, we prospectively assessed the association between dietary PCB intake and the risk of hypertension in a Spanish cohort of university graduates.

Methods

Study Population

The Seguimiento Universidad de Navarra (SUN) Project is a Spanish multipurpose, dynamic, and prospective cohort study that was designed to establish associations between the diet and the occurrence of several diseases and chronic conditions, including hypertension. Participants were recruited through collaborations with alumni and professional associations throughout the country. University graduate status is a requirement for inclusion. This cohort has a permanently open recruitment. On completion of the first questionnaire (the most detailed questionnaire used to collect baseline information), the participant becomes a member of the cohort. Additional questionnaires are mailed every 2 years to follow-up the participant and to track any changes in food habits, diagnoses of new diseases, and overall well-being. In the year between each 2 follow-up questionnaires, participants are sent a card to remind them of the study, to thank them for their involvement in the project, and also to verify any changes in mailing addresses.

The recruitment of participants, all of them university graduates and >50% of them health professionals, started in December 1999 and it is permanently open. More details on the study design, recruitment strategy, and follow-up methods have been published elsewhere.34

Up to March 2011, 20580 subjects were recruited. Among them, we excluded 2296 participants with prevalent hypertension at baseline; 1365 participants who reported values for total energy intake at baseline of predefined limits (<800 or >4000 kcal/d and ≤500 or >3500 kcal/d in men and women, respectively); 1119 participants with chronic disease at baseline (diabetes mellitus, CVD, and cancer); and 1279 participants without any follow-up who were considered lost to follow-up, obtaining a retention rate of 92.1% and leaving a total of 14521 participants available for the final analyses (Figure S1 in the online-only Data Supplement).

The Institutional Review Board of the University of Navarra approved the study. Informed consent was implied by the voluntary completion of the baseline questionnaire.

Dietary Exposure Assessment

The baseline questionnaire included a semiquantitative food frequency questionnaire with 136-food items, previously validated in Spain and recently re-evaluated.40,41

The estimations of dietary intake of total PCBs were based on individual concentrations of 18 PCB congeners in samples of food items, obtained by an earlier study performed in Spain,42 in combination with the information from the food frequency questionnaire. The 12 dioxin-like PCB (DL-PCB) congeners determined in the samples were 81, 77, 126, 169, 105, 114, 118, 123, 156, 157, 167, and 189; and the nondioxin-like PCB (NDL-PCB) congeners were 28, 52, 101, 138, 153, and 180.

The total PCB levels (DL-PCBs and NDL-PCBs together) in food samples were estimated in picograms (pg)/grams (g) of food. The estimation of exclusively DL-PCB levels was also expressed as toxic equivalents. They were calculated by multiplying the individual congeners concentrations by their respective toxic equivalency factor and were subsequently summed up to give the total concentrations as toxic equivalents.43

Based on these data, we obtained the total amount of PCBs (pg) per serving of each food item by multiplying the concentration of PCBs (pg/g of food) by the serving size. Then, we multiplied the amount of PCBs by the frequency of consumption of each food item, and finally, we summed up all the food items to obtain the amount of PCBs (pg/d) ingested by the participants at baseline. Total PCB intake was adjusted for total energy intake through the residual method.39

Outcome Assessment

The end point of the study was incident hypertension. Participants were asked whether they had received a medical diagnosis of hypertension at baseline and during follow-up, and also, we inquired about the date of diagnosis.

For the present analyses, participants were considered to have prevalent hypertension at baseline if they reported a medical diagnosis of hypertension, a systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, or any use of antihypertensive medication. New cases of hypertension were defined as those participants who did not have hypertension at baseline and reported a new medical diagnosis of hypertension during follow-up. The validity of self-reported hypertension diagnosis was assessed in a subsample of the cohort.44 This validation study showed an adequate validity of the self-reported diagnosis of hypertension: among those participants who reported a diagnosis of hypertension, 82.3% (95% CI, 72.8–92.8) were confirmed through a conventional measurement of blood pressure, and among those who did not report a diagnosis of hypertension, 85.4% (95% CI, 72.4–89.1) were confirmed as normotensive.

Moreover, in a more recent study, we have validated each component of the metabolic syndrome (including high blood pressure). We found adequate intraclass correlation coefficients for high systolic blood pressure (0.47 [0.36–0.57]) and high diastolic blood pressure (0.46 [0.34–0.56]), using as gold standard direct assessments by an experienced physician.45

Assessment of Other Variables

The baseline questionnaire also included other questions (46 items for men and 54 for women) that assessed the participants’ medical history (prevalence of chronic diseases, such as cancer, diabetes mellitus, and CVD, and habitual use of medication), health-related habits (smoking status, physical activity during leisure time), lifestyle, and...
sociodemographic variables (sex, age, marital status, and employment), as well as anthropometric data (weight and height) previously validated in the cohort. Body mass index was calculated as the self-reported weight in kilograms divided by the square of the self-reported height in meters. To quantify the amount of physical activity, we inquired about 17 activities, and a metabolic equivalent index (hour/wk) was computed. In a previous validation, conducted in a subsample of the cohort, weekly metabolic equivalent index hours shown to adequately correlate with the objectively measured energy expenditure (Spearman $p=0.51$; 95% CI, 0.232–0.707).

Statistical Analyses

Person-time of follow-up was calculated for each participant from the date of completion of the baseline questionnaire until the date of completion of the last follow-up questionnaire, the date of diagnosis of hypertension, or date of death, whichever occurred first. We used Cox regression models to assess the relationship between the energy-adjusted quintiles of dietary intake of total PCBs and the subsequent risk of developing hypertension during follow-up. Linear trend tests were calculated using the median in total dietary intake of PCBs of each quintile and by introducing this new variable as a continuous variable in the models.

We fitted a crude univariate model (without any adjustment), an age- and sex-adjusted model and a multivariate model after adjustment for the following potential confounders: age, sex, smoking habit (current, never, former), physical activity (metabolic equivalent index [h/wk]), total energy intake (kcal/d), fast-food consumption (g/d), sitting hours (h/d), sugar soft drink consumption (mL/d), following special diet (yes/no), hypercholesterolemia (yes/no), family history of hypertension (yes/no), fried food consumption (g/d), alcohol intake (g/d), use of aspirin and nonaspirin analgesics (yes/no), caffeine intake (g/d), cereal fiber intake (g/d), low-fat dairy consumption (g/d), olive oil consumption (g/d), fruit and vegetables consumption (g/d), energy-adjusted fatty fish intake (serving/wk), and energy-adjusted sodium (g/d) and potassium intake (g/d).

To test the proportional hazard assumption, we calculated a Cox regression with the exposure as a continuous time-varying covariate to check that the hazard ratio (HR) did not vary over time, obtaining a nonsignificant result ($P=0.49$). A different approach was also used, the Schoenfeld residual method, and likewise, a nonsignificant result was found ($P=0.83$), suggesting that the proportionality assumption was met.

Taking into account the incidence and HR for the comparison between extreme quintiles observed in our study and the number of participants in each quintile, the expected power was 94.5%, with a bilateral alpha error of 0.05. Furthermore, sensitivity analyses were conducted, and all the models were repeated in different scenarios: (1) after additional adjustment for baseline body mass index and weight gain during follow-up; (2) after additional adjustment for incident obesity (excluding obese participants and pregnant women at baseline); (3) excluding those participants who were under the 5th percentile and over the 95th percentile of total energy intake; (4) excluding late cases of hypertension (reported after 10 years of follow-up); (5) excluding very late incident cases of hypertension (reported after 12 years of follow-up); (6) excluding participants with incident chronic diseases; (7) excluding early incident cases of hypertension (reported within the first 2 years of follow-up); (8) including also participants with antihypertensive drug treatment as incident cases of hypertension; (9) only assessing NDLCB intake; (10) only assessing DL-PCB intake; and (11) only assessing DL-PCB intake measured in toxic equivalents.

All $P$ values presented were 2-tailed, and $P<0.05$ was considered statistically significant. Analyses were performed using STATA/SE version 12.0 (StataCorp, College Station, TX).

Results

A total of 5317 men and 9204 women were included for the analysis. The main baseline characteristics of participants according to their total PCB intake are presented in Table 1. The mean age of participants was 36.6 years (SD, 10.7), and the mean body mass index was 23.2 kg/m$^2$ (SD, 3.3). Participants in the fifth quintile of PCB intake compared with those in the first quintile were more likely to be women and to have a history of hypertension, their total energy intake was lower, they were more physically active, and they were more prone to be former smokers and to use analgesics. Moreover, on average, they consumed less fast food, sugar soft drinks, alcohol, fried foods, and caffeine. In contrast, they had higher intake of fatty fish, olive oil, fruits and vegetables, low-fat dairy, and cereal fiber; also, they were more likely to follow special diets. Regarding micronutrients, participants in the fifth quintile, on average had less sodium and more potassium intake compared with those in the first quintile. There was a statistically significant trend across the quintiles for all the characteristics ($P$ for trend $<0.05$) except for total energy intake, weight gain during follow-up, alcohol consumption, and dietary cereal fiber intake.

During follow-up (median, 8.3 years), we observed 1497 incident cases of hypertension. In multivariate models, when we assessed the risk of hypertension according to levels of PCB intake, we found a significant direct association (Table 2). Those participants with the highest baseline dietary total PCB intake (DL-PCBs and NDLCBs together) presented a 43% higher risk of developing hypertension in comparison with those in the lowest quintile (adjusted HR, 1.43 [95% CI, 1.09–1.88]). The estimate showed a statistically significant linear trend ($P$ for trend $=0.017$). Incident cases of hypertension occurring over time were described using Nelson–Aalen curves. To adjust these curves for age and sex, we used inverse probability weighting (Figure S2).

We conducted multiple sensitivity analyses to account for potential uncertainties in our assumptions regarding the induction period and also for possible sources of bias including measurement errors (Table S1). Results hardly changed in any of these scenarios. Also, when we only assessed NDLCBs, participants in the fifth quintile of NDLCB intake presented an adjusted HR (95% CI) of 1.39 (1.06–1.82) and a statistically significant linear trend ($P$ for trend $=0.032$) compared with those in the first quintile. Similarly, when we only assessed the DL-PCBs, participants in the fifth quintile of DL-PCB intake presented an adjusted HR (95% CI) of 1.43 (1.09–1.88) and a statistically significant linear trend ($P$ for trend $=0.030$) compared with those in the first quintile.

The self-reported diagnosis of hypertension was validated in a subsample of the cohort as mentioned above. When we used directly measured blood pressure in this small validation subset of the cohort to categorize participants as new cases of hypertension instead of using a self-reported diagnosis of hypertension as the outcome, we also found a significantly higher risk of hypertension in the fifth quintile than that in the first quintile of PCB intake, after adjusting for age and sex. Nevertheless, in this ancillary analysis, because of the small sample size, the CI was wide (odds ratio, 17.2 [95% CI, 1.1–271.6]; $P$ for trend $=0.015$).

Discussion

To date, most of the previous studies have evaluated the risk of hypertension in individuals exposed to large concentrations of PCBs after industrial accidents or via occupational...
applications, and they were entirely based on cross-sectional data, making it difficult to draw conclusions on causality.\textsuperscript{21–28} Hence, this is the first longitudinal study showing that higher dietary PCB intake was associated with a greater incidence of hypertension, 43% (95% CI, 9–88%) relatively increased risk, in a middle-aged general adult population.

Table 1. Distribution of the Main Baseline Characteristics of Participants and Potential Confounding Variables Across Quintiles of Total PCBs—Energy-Adjusted Intake

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Quintiles of Total PCBs—Energy-Adjusted Intake</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Q1</td>
<td>Q2</td>
</tr>
<tr>
<td>n</td>
<td>2905</td>
<td>2904</td>
</tr>
<tr>
<td>Total PCB intake, ng/d\textsuperscript{*}</td>
<td>393.5</td>
<td>664.2</td>
</tr>
<tr>
<td>Sex, % women</td>
<td>58.9</td>
<td>62.8</td>
</tr>
<tr>
<td>Age, y</td>
<td>35.0</td>
<td>35.7</td>
</tr>
<tr>
<td>Body mass index, kg/m\textsuperscript{2}</td>
<td>23.0</td>
<td>23.0</td>
</tr>
<tr>
<td>Analgesic consumption, %</td>
<td>2.7</td>
<td>2.7</td>
</tr>
<tr>
<td>Family history of hypertension, %</td>
<td>36.9</td>
<td>39.2</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>23.9</td>
<td>22.8</td>
</tr>
<tr>
<td>Former smoker, %</td>
<td>24.3</td>
<td>25.6</td>
</tr>
<tr>
<td>Physical activity, MET-h/wk</td>
<td>20.8</td>
<td>20.1</td>
</tr>
<tr>
<td>Sitting hours, h/d</td>
<td>5.5</td>
<td>5.4</td>
</tr>
<tr>
<td>Total energy intake, kcal/d</td>
<td>2475</td>
<td>2321</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>10.2</td>
<td>12.9</td>
</tr>
<tr>
<td>Weight gain during the follow-up, kg/y</td>
<td>0.2</td>
<td>0.2</td>
</tr>
<tr>
<td>Fatty fish consumption;\textsuperscript{†} serving/wk</td>
<td>0.4</td>
<td>0.8</td>
</tr>
<tr>
<td>Olive oil intake, g/d</td>
<td>19.8</td>
<td>18.7</td>
</tr>
<tr>
<td>Fruits and vegetables intake, g/d</td>
<td>778</td>
<td>807</td>
</tr>
<tr>
<td>Fast-food consumption,\textsuperscript{‡} g/d</td>
<td>27.3</td>
<td>24.5</td>
</tr>
<tr>
<td>Sugared soft drinks consumption, mL/d</td>
<td>82.2</td>
<td>65.9</td>
</tr>
<tr>
<td>Caffeine intake, mg/d</td>
<td>47.4</td>
<td>43.1</td>
</tr>
<tr>
<td>Alcohol consumption, g/d</td>
<td>6.4</td>
<td>6.3</td>
</tr>
<tr>
<td>Fried food consumption, serving/wk</td>
<td>4.4</td>
<td>4.0</td>
</tr>
<tr>
<td>Low-fat dairy consumption, g/d</td>
<td>196</td>
<td>206</td>
</tr>
<tr>
<td>Following special diet, %</td>
<td>5.1</td>
<td>5.0</td>
</tr>
<tr>
<td>Dietary cereal fiber intake, g/d</td>
<td>4.5</td>
<td>4.0</td>
</tr>
<tr>
<td>Sodium intake,\textsuperscript{†} g/d</td>
<td>3.5</td>
<td>3.4</td>
</tr>
<tr>
<td>Potassium intake,\textsuperscript{‡} g/d</td>
<td>4.3</td>
<td>4.5</td>
</tr>
</tbody>
</table>

Values are mean (SD) or percentages (%). The Seguimiento Universidad de Navarra (SUN) Project 1999 to 2013. MET indicates metabolic equivalent index; and PCB, polychlorinated biphenyl.

\textsuperscript{*}Total PCBs (median) include both dioxin-like and nondioxin-like PCBs (ng/d).

\textsuperscript{†}Energy-adjusted.

\textsuperscript{‡}Fast food is the sum of hamburgers, sausages, and pizza consumption.

Table 2. Hazard Ratios (95% Confidence Intervals) for Incident Hypertension According to Energy-Adjusted Quintiles of Total PCB Intake

<table>
<thead>
<tr>
<th>Quintiles of Total PCBs—Energy Adjusted Intake\textsuperscript{*}</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>P for Trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases/person-years</td>
<td>262/24107</td>
<td>281/24038</td>
<td>288/22966</td>
<td>310/22593</td>
<td>356/22454</td>
<td></td>
</tr>
<tr>
<td>Crude model</td>
<td>1 (Ref.)</td>
<td>1.03 (0.87–1.22)</td>
<td>1.07 (0.90–1.26)</td>
<td>1.07 (0.91–1.26)</td>
<td>1.12 (0.95–1.31)</td>
<td>0.172</td>
</tr>
<tr>
<td>Age- and sex-adjusted model</td>
<td>1 (Ref.)</td>
<td>1.06 (0.90–1.26)</td>
<td>1.10 (0.93–1.30)</td>
<td>1.16 (0.98–1.36)</td>
<td>1.22 (1.04–1.43)</td>
<td>0.013</td>
</tr>
<tr>
<td>Multiple-adjusted model\textsuperscript{†}</td>
<td>1 (Ref.)</td>
<td>1.08 (0.90–1.31)</td>
<td>1.18 (0.96–1.44)</td>
<td>1.26 (1.01–1.58)</td>
<td>1.43 (1.09–1.88)</td>
<td>0.017</td>
</tr>
</tbody>
</table>

The Seguimiento Universidad de Navarra (SUN) Project 1999 to 2013. PCB indicates polychlorinated biphenyl.

\textsuperscript{*}Total PCBs include dioxin-like and nondioxin-like PCBs (pg/d).

\textsuperscript{†}Adjusted for age, sex, smoking habit, physical activity, total energy intake, fast-food consumption, sitting hours, sugar soft drinks consumption, following special diet, hypercholesterolemia, family history of hypertension, fried food consumption, alcohol consumption, use of aspirin and nonaspirin analgesics, caffeine intake, cereal fiber intake, low-fat dairy intake, olive oil intake, fruit and vegetables intake, energy-adjusted fatty fish consumption, and energy-adjusted sodium and potassium intake.
As we mentioned earlier, many food chains worldwide, as well as many people, are contaminated by PCBs generally at low concentrations\textsuperscript{14–19}, and there is emerging evidence that the background exposure to low but chronic levels of these persistent pollutants may not be safe in humans.\textsuperscript{31}

PCBs cover a group of 209 different PCB congeners. They can be divided into 2 groups based on their differing structural properties and biological activities: the non-/mono-ortho and ortho-substituted congeners. The non-ortho substituted (coplanar) congeners, also including some mono-ortho substituted congeners, are known as DL-PCBs (dioxin like-PCBs), because their highly toxic effect seems to be mediated by the activation of the aryl hydrocarbon receptor (AhR), such as dioxins. DL-PCBs include 12 congeners. This is the basis for the toxic equivalents concept, and it uses the relative potencies of individual congeners according to their ability to bind to the AhR.\textsuperscript{43} However, the ortho-substituted congeners (noncoplanar PCBs) do not bind to the AhR; subsequently, sometimes they are termed NDL-PCBs, and the link with specific toxic end points is less known.

Although NDL-PCBs are the most frequently detected PCBs and they can be found in high concentrations both in human tissues and in the environment, the majority of functional and mechanistic studies have been focused on DL-PCBs and the AhR. Most experimental evidence supports that chronic inflammation and dysfunction of the vascular endothelium, through an increasing cellular oxidative stress and AhR-mediated mechanisms, are critical events in the toxicity of DL-PCBs on hypertension.\textsuperscript{49–51} In addition, experimental studies found that DL-PCBs have the ability to reduce the synthesis of physiologically essential long-chain unsaturated fatty acids\textsuperscript{52} and, consequently, to alter the endothelial cell lipid and metabolism.

There is also some evidence suggesting specific toxic effects of NDL-PCBs. A recent study showed that PCB 153 and 180 induced the increase in interleukin-6 and tumor necrosis factor-\(\alpha\).\textsuperscript{53} The elevation of these 2 proinflammatory cytokines plays a role in metabolic dysfunction related to type 2 diabetes mellitus, metabolic syndrome, and possibly in the hypertension pathogenesis.\textsuperscript{54–56} Likewise, it seems that NDL-PCBs also have the ability to downregulate the AMP-activated protein kinase activation\textsuperscript{55}; and the AMP-activated protein kinase inhibits the synthesis of proinflammatory cytokines.\textsuperscript{55,56}

In addition, endocrine disrupting chemicals may affect the mechanism involved in the risk of hypertension through several different ways. One important pathway is through their direct interaction with the nuclear receptors family. The nuclear receptors are structurally related transcription factors involved in virtually all vital functions, such as homeostasis, reproduction, metabolism, and response to xenobiotic substances. Hence, in addition to AhR-mediated mechanism, some endocrine disrupting chemical can bind directly to these nuclear receptors either as agonists or as antagonists, thus enhancing or inhibiting the effect of a hormone, respectively.\textsuperscript{10,57}

Regarding the epidemiological evidence on general populations, a study using the 1999 to 2004 NHANES\textsuperscript{28} found a significant 38\% increased risk of hypertension among those participants in the highest compared with those in the lowest quartile of serum concentration of total PCBs (odds ratio, 1.38 [95\% CI, 1.02–1.87]). Moreover, the congeners identified were not only DL-PCBs (PCB 66 and 118), but also NDL-PCBs (PCB 101, 128, and 187). Each of these congeners was also associated with the risk of hypertension in individual congener-specific models. Likewise, a 2008 study conducted by Everett et al\textsuperscript{41} found that 7 of the 11 PCB congeners assessed were significantly associated with hypertension. However, the strongest association with hypertension was found for the DL-PCB congeners 118 and 126.

In a cross-sectional study conducted among nondiabetic adults participating in the NHANES 1999 to 2002,\textsuperscript{28} when the sum of DL-PCBs and NDL-PCBs were evaluated, no significant association was found. However, when congeners of PCBs were assessed separately, only the 118 and 126 DL-PCB congeners showed a positive and significant association. Moreover, Uemura et al\textsuperscript{6} who evaluated only the DL-PCBs among general Japanese population, observed an adjusted odds ratio for hypertension of 1.9 (95\% CI, 1.1–3.1) and \(P\) for trend <0.01 for the highest quartile of DL-PCBs versus the first quartile.

However, Goncharov et al\textsuperscript{25,26} found that both total PCBs and grouped into di-ortho, tri-ortho, and tetra-ortho (NDL-PCBs) were all associated with high blood pressure among Alabama residents living near a PCB production facility.

Based on these preceding findings, it seems that the biological mechanisms by which PCBs affect blood pressure are not entirely clear. Congeners with similar structure or biological activity do not show similar associations with hypertension. Some authors hypothesize that the specific arrangement of chlorine atoms may explain differences in the observed associations even among congeners similar in structure or activity.\textsuperscript{5} Nevertheless, DL-PCB congeners do not seem to be the only ones responsible for the blood pressure increase, neither the interaction with the AhR is the exclusively pathway through which PCBs may affect blood pressure.

Although previous studies have demonstrated differential associations with different congeners of PCBs, our aim was not to evaluate each of the individual PCB congeners but to assess the association between total PCB intake, as well as total concentration of exclusively DL-PCBs and NDL-PCBs, and hypertension. The fact that we used the sum of all PCBs and not only those congeners with a stronger known toxicity may have led to some degree of underestimation in our results. However, according to the database we used, there are no food products with only DL-PCBs or only NDL-PCBs (we found correlation coefficients >0.99 between DL-PCBs and NDL-PCBs), and consequently, it is difficult to independently assess the differential effects of DL-PCBs and NDL-PCBs on hypertension (Table S1).

The main source of variability in PCB intake in our sample was fatty fish, as was previously reported.\textsuperscript{24} Moreover, fatty fish intake is the main exposure to heavy metals, and there is evidence that lead, arsenic, and mercury exposures may also increase the risk of hypertension. On the contrary, it is well established that n-3 fatty acids from fatty fish may lower blood pressure.\textsuperscript{59} With the goal of having all these aspects into account, we adjusted for fatty fish consumption.

Also, we adjusted for obesity and after rerunning the analyses excluding incident cases of obesity, we found that the
assumption also remained present (Table S1). Hence, it seems that the association between dietary PCB intake and hypertension is independent of obesity, and therefore, the mechanisms of action by PCBs increase the risk of both diseases are different.

Some limitations should be noted. The present study only assessed PCB exposure through dietary sources but not from other sources. Nevertheless, in the majority of the general population, exposure occurs almost exclusively through the diet.40 Another limitation of our study is that food preparation and cooking methods could have altered PCB levels in the final food products, and we had no data on these aspects. However, this may have resulted in an underestimation of PCB intake, and consequently in an underestimation of the absolute amount of PCBs related to a higher hypertension risk.

The aforementioned previous study reported PCBs from food sources in samples collected from different regions of Spain in year 2006 but not from each of the regions that compose Spain.42 Moreover, in recent years, atmospheric concentrations of PCBs have shown a continuous decline. However, all the participants’ dietary intake estimations of PCBs were calculated between 1999 and 2011, being the year 2003 the average, not so far from the data collected in the abovementioned study. Furthermore, levels of PCBs for each food item were similar to those reported in other Spanish studies conducted in different years and whose samples were collected in several different regions.51,62

As in any study in nutritional epidemiology, an inherent information bias would be expected. However, the possible measurement error in the assessment of diet would be most likely nondifferential, and therefore, it would bias our results toward the null value.

It might be thought that a potential limitation of our study was the inclusion of only university graduates because they are not a representative sample. This issue may have affected the external validity of our findings; therefore, caution is needed before extrapolating these results to the general population. In any case, the generalizability of our results should be based on biological mechanisms and not in the representativeness of our sample in the strict statistical sense of the term. In addition, our procedure of selection enhanced the internal validity of our study because the high level of education and homogeneity of our cohort and the high proportion of participants who were health professionals reduced the potential confounding related to socioeconomic status and educational level and increased the validity of their self-reported data.

Last, the present study did not take into account the pharmacokinetics and bioavailability of different PCB congeners. All these factors may influence the PCB levels on adipose tissue and blood, and therefore, their activity. If we had measured directly the levels of PCBs in blood, it might be thought that a better and more accurate estimation of PCB exposure would have been obtained. However, it is known that PCBs are accumulated largely in adipose tissue during 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 bioactive PCBs.

Major advantages of our study are its prospective design, that avoids reverse causation bias and allows us to take into account long-term exposures, the use of a wide range of scoring for each food portion (9 categories), the previous validation of the methods used to assess the main variables, the use of a large sample of participants, and their high educational level, which allows for a better understanding of the questionnaire, a higher accuracy in their self-reported information, and also preserves the homogeneity of this large sample with respect to many sociodemographic characteristics and, thus, reduces the potential for confounding. In addition, we were able to control for multiple potential confounding variables and to perform a wide variety of sensitivity analyses.

Perspectives
These findings support the hypothesis that PCBs may be an important factor in the development of hypertension. Nevertheless, further longitudinal studies assessing a link between exposure to dietary PCB intake and the development of hypertension are needed to confirm our findings and provide additional evidence for this hypothesis. Besides, a better understanding of the biological properties of PCB congeners and more experimental models elucidating the mechanisms by which PCBs may contribute to hypertension are required.

Acknowledgments
We thank participants of the Seguimiento Universidad de Navarra (SUN) Project for their continued cooperation and participation. We thank all the members of the SUN project for administrative, technical and material support.

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Disclosures
None.

References


What Is New?

- To date, most of the studies evaluating the risk of hypertension have been focused on individuals exposed to large concentrations of polychlorinated biphenyls (PCBs) after industrial accidents or via occupational applications, and they were mainly based on cross-sectional data. Therefore, this is the first longitudinal study showing that higher dietary PCB intake is associated with a greater incidence of hypertension in a middle-aged general adult population.

What Is Relevant?

- The major strengths of the study are the prospective design, which avoids reverse causation bias, and the assessment of the common exposure to PCBs in the general population and, not only, the accidental, occupational, or residential exposure. Consequently, these findings provide evidence supporting the PCB effects even in low doses, being that PCBs are present in low concentrations in general population tissues and fluids, as well as in environmental samples. Furthermore, these findings suggest that the association between dietary PCB intake and hypertension found is independent of obesity.

Summary

This study provides evidence on the positive association between higher concentrations of dietary PCB intake and the incidence of hypertension. Hence, our findings support the hypothesis that dietary exposure to PCBs may be a relevant factor in the development of hypertension.
Association Between Dietary Intake of Polychlorinated Biphenyls and the Incidence of Hypertension in a Spanish Cohort: The Seguimiento Universidad de Navarra Project
Carolina Donat-Vargas, Alfredo Gea, Carmen Sayon-Orea, Carmen de la Fuente-Arrillaga, Miguel Angel Martinez-Gonzalez and Maira Bes-Rastrollo

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ASSOCIATION BETWEEN DIETARY INTAKE OF POLYCHLORINATED BIPHENYLS AND THE INCIDENCE OF HYPERTENSION IN A SPANISH COHORT: THE SUN PROJECT

Carolina Donat-Vargas\textsuperscript{a}, Alfredo Gea\textsuperscript{a}, Carmen Sayon-Orea\textsuperscript{a}, Carmen de la Fuente-Arrillaga\textsuperscript{a,b}, Miguel Angel Martinez-Gonzalez \textsuperscript{a,b}, Maira Bes-Rastrollo\textsuperscript{a,b}

\textsuperscript{a} Dept. of Preventive Medicine and Public Health, University of Navarra, Pamplona, Spain.

\textsuperscript{b} CIBER Fisiopatología de la Obesidad y Nutrición (CIBERobn), Instituto de Salud Carlos III, Spain.

Short title

Dietary intake of PCBs and hypertension

Corresponding author:

Maira Bes-Rastrollo
Universidad de Navarra. Ed. Investigación. C/ Irunlarrea, 1 31008 Pamplona, Navarra
Tel: +34 948 425600 ext. 806602
Fax: +34 948 455649
Email: mbes@unav.es

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Manuscript:
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- References: 63
- Appendix: 2 figures and 1 table
Table S1. Sensitivity analyses. Hazard Ratios (95% Confidence Intervals) for incident hypertension according to energy-adjusted quintiles of PCBs intake. The SUN Project 1999-2013.

<table>
<thead>
<tr>
<th>Sensitivity analyses</th>
<th>Cases/Person-yr</th>
<th>Q1</th>
<th>Q3</th>
<th>Q5</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall*</td>
<td>1,497/116,160</td>
<td>1 (Ref.)</td>
<td>1.18 (0.96-1.44)</td>
<td>1.43 (1.09-1.88)</td>
<td>0.017</td>
</tr>
<tr>
<td>Additionally adjusted for baseline BMI and weight gain during the follow up</td>
<td>1,497/116,160</td>
<td>1 (Ref.)</td>
<td>1.09 (0.92-1.30)</td>
<td>1.20 (1.01-1.42)</td>
<td>0.034</td>
</tr>
<tr>
<td>Additionally adjusted for obesity incidence</td>
<td>1,247/88,812</td>
<td>1 (Ref.)</td>
<td>1.15 (0.93-1.44)</td>
<td>1.51 (1.12-2.04)</td>
<td>0.007</td>
</tr>
<tr>
<td>Energy limits: percentiles 5 to 95</td>
<td>1,421/113,425</td>
<td>1 (Ref.)</td>
<td>1.22 (0.99-1.49)</td>
<td>1.35 (1.02-1.78)</td>
<td>0.084</td>
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<tr>
<td>Excluding late incident cases of hypertension (reported after 10 years of follow-up)</td>
<td>1,043/112,369</td>
<td>1 (Ref.)</td>
<td>1.17 (0.92-1.49)</td>
<td>1.38 (1.00-1.91)</td>
<td>0.053</td>
</tr>
<tr>
<td>Excluding late incident cases of hypertension (reported after 12 years of follow-up)</td>
<td>1,317/114,541</td>
<td>1 (Ref.)</td>
<td>1.18 (0.96-1.46)</td>
<td>1.40 (1.05-1.87)</td>
<td>0.039</td>
</tr>
<tr>
<td>Excluding participants with incident chronic diseases</td>
<td>1,286/108,934</td>
<td>1 (Ref.)</td>
<td>1.22 (0.99-1.51)</td>
<td>1.40 (1.05-1.88)</td>
<td>0.054</td>
</tr>
<tr>
<td>Excluding early incident cases of hypertension (reported within the first 2 years of follow-up)</td>
<td>1059/115,096</td>
<td>1 (Ref.)</td>
<td>1.12 (0.88-1.42)</td>
<td>1.50 (1.09-2.08)</td>
<td>0.013</td>
</tr>
<tr>
<td>Including also participants with antihypertensive drug treatment as incident cases of hypertension</td>
<td>1709/115,072</td>
<td>1 (Ref.)</td>
<td>1.14 (0.94-1.37)</td>
<td>1.39 (1.08-1.80)</td>
<td>0.017</td>
</tr>
<tr>
<td>Only assessing non dioxin like-PCBs intake</td>
<td>1,497/116,160</td>
<td>1 (Ref.)</td>
<td>1.19 (0.98-1.45)</td>
<td>1.39 (1.06-1.82)</td>
<td>0.032</td>
</tr>
<tr>
<td>Only assessing dioxin like-PCBs intake</td>
<td>1,497/116,160</td>
<td>1 (Ref.)</td>
<td>1.25 (1.03-1.53)</td>
<td>1.43 (1.09-1.88)</td>
<td>0.030</td>
</tr>
<tr>
<td>Only assessing dioxin like-PCBs intake measured in TEQ†</td>
<td>1,497/116,160</td>
<td>1 (Ref.)</td>
<td>1.07 (0.87-1.31)</td>
<td>1.35 (1.02-1.78)</td>
<td>0.040</td>
</tr>
</tbody>
</table>
* Adjusted for age, sex, smoking habit, physical activity, total energy intake, fast-food consumption, sitting hours, sugar soft drinks consumption, following special diet, hypercholesterolemia, family history of hypertension, fried food consumption, alcohol consumption, use of aspirin and non-aspirin analgesics, caffeine intake, cereal fiber intake, low-fat dairy intake, olive oil intake, fruit and vegetables intake, energy-adjusted fatty fish consumption and energy-adjusted sodium and potassium intake.

† Toxic Equivalents (TEQ).

#
Figure S1: Flow chart of participants: The SUN Project 1999-2013.

N= 20,580 participants recruited before March 2011

N= 18,284 participants

N= 16,919 participants

N= 15,800 participants

Retention rate=92%
Final sample
N=14,521 participants
1,497 Incident cases

N=2,296 with prevalent hypertension

N= 1,365 with total energy intake out of predefined values

N= 1,119 with cancer, diabetes or cardiovascular disease at baseline

N= 1,279 without any follow-up
Figure S2: Nelson-Aalen estimates of the incidence of hypertension according to energy-adjusted quintiles of total PCBs intake. The SUN Project 1999-2013.