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Historical exposure to persistent organic pollutants and risk of incident hypertension

Juan P. Arrebola [a,b,c,*], Mariana F. Fernández [b,c], Piedad Martin-Olmedo [d], Jens Peter Bonde [e], José L. Martín-Rodriguez [f], José Expósito [a], Antonio Rubio-Domínguez [g], Nicolás Olea [a,b]

[a] Oncology Unit, Virgen de las Nieves University Hospital, Granada, Spain
[b] Instituto de Investigación Biosanitaria ibs.Granada, University of Granada, San Cecilio University Hospital, Granada, Spain
[c] CIBER en Epidemiología y Salud Pública (CIBERESP), Spain
[d] Escuela Andaluza de Salud Pública, Instituto de Investigación Biosanitaria ibs.Granada, Granada, Spain
[e] Department of Occupational and Environmental Medicine, Bispebjerg University Hospital, University of Copenhagen, Denmark
[f] Department of Radiology, San Cecilio University Hospital, Granada, Spain
[g] Gran Capitán Center for Primary Care, Virgen de las Nieves University Hospital, Granada, Spain

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ABSTRACT

The aim of this study was to assess the influence of adipose tissue concentrations of a group of persistent organic pollutants (POPs) on the risk of hypertension in an adult cohort of residents of Granada (Southern Spain) over a 10-year follow-up. No chemical was significantly associated with the risk of hypertension in the overall population or when models were stratified by sex or median age. However, we found positive associations between log-transformed POP concentrations and hypertension risk in participants with body mass index (BMI) above the median value of 26.3 kg/m^2, which were statistically significant for hexachlorobenzene (HR=1.26, 95% CI=1.03–1.56), β-hexachlorocyclohexane (HR=1.25, 95% CI=1.03–1.51), and polychlorinated biphenyl congeners -138 (HR=1.32, 95% CI=1.04–1.69) and -153 (HR=1.36, 95% CI=1.00–1.84). Inverse associations were observed in the subgroup with BMI ≤ 26.3 kg/m^2, but none was statistically significant. More research and a longer follow-up period are warranted to verify these associations and elucidate the role of obesity as a potential effect modifier. Given the elevated worldwide frequency of POP exposure and hypertension, the public health impact of this relationship may be substantial.

1. Introduction

There is increasing evidence of potential adverse health outcomes derived from exposure of the general population to certain environmental pollutants at levels traditionally considered “safe” (United Nations Environment Programme and World Health Organization, 2013). In this regard, it is suspected that long-term human exposure to low doses of persistent organic pollutants (POPs) may have a relevant impact in relatively frequent chronic diseases, including diabetes mellitus (Taylor et al., 2013), cancer (Soto and Sonnenschein, 2010), dyslipidemia (Aminov et al., 2013), cardiovascular disease (Lind and Lind, 2012), obesity (Sharpe and Drake, 2013), and hypertension (Lind et al., 2014).

POPs are highly lipophilic and resistant to degradation and therefore tend to accumulate and biomagnify in food chains, resulting in the considerable exposure of living organisms (UNEP, 2003). POPs include organochlorine pesticides (OCPs), which have long been used in many agricultural activities and as vector control (Porta et al., 2002), as well as polychlorinated biphenyls, employed as dielectric and heat exchange fluids among other commercial applications (WHO, 2014). Although the production and handling of POPs are in decline worldwide, human exposure to these chemicals remains of relevance to public health. This is because they can persist in living organisms, even for decades (Yu et al., 2011), so that current generations might suffer the effects of exposure accumulated throughout their lives. In addition, these chemicals are present in several food items (Darnerud et al., 2006; Pandelova et al., 2011), and fatty food is considered as the main source of exposure in the general population (Arrebola et al., 2012b; Brauner et al., 2012).

The prevalence of hypertension has been estimated to be 30–45% of the general population (Mancia et al., 2013) and 35% of Spanish adults (Banegas, 2005). Additionally, hypertension is considered the most prevalent treatable risk factor for stroke,

* Correspondence to: Instituto de Investigación Biosanitaria de Granada, 18071 Granada, Spain. Phone: Tel.: +34 958 240758; fax: +34 958 249953.
E-mail address: jparrebola@ugr.es (J.P. Arrebola).

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coronary artery disease, and renal disease (August, 2004), as well as a direct cause of 7.6 million deaths worldwide (Lawes et al., 2008). It is also believed to be related to certain cancers, premature death, and cardiovascular disease (Joffres et al., 2013; World Health Organization, 2014). Traditional risk factors for hypertensive disease include age, sex, race, social class, obesity, starting level of blood pressure, smoking habit, early life experiences, diet, alcohol consumption, physical inactivity, and exposure to certain environmental agents (Joffres et al., 2013; Whelton, 1994). The first observations of a potential relationship between POP exposure and hypertension were in occupationally/accidentally exposed populations (Morgan et al., 1980; Sandifer et al., 1972; Wassermann et al., 1980). The few available studies on non-occupationally-exposed subgroups have published inconsistent results, both in the associations found and in the chemicals responsible for the effects observed (Everett et al., 2008; Goncharov et al., 2010, 2011; Ha et al., 2009; Henriquez-Hernandez et al., 2014; Pestana et al., 2014; Savitz et al., 2014; Valera et al., 2013a, 2013b), and there has been a call for further prospective studies to elucidate the effects of these pollutants.

The mechanisms of action by which POPs may cause hypertensive disorders are poorly understood (Ha et al., 2009). It has been suggested that POPs may cause hypertension through a mechanism involving the androgen receptor, given that many OCPs have been shown to act as anti-androgens (Freire et al., 2014). Thus, high OCP concentrations have been found to be inversely correlated to testosterone levels (Blanco-Munoz et al., 2012), which are associated with hypertension (Akishita et al., 2010). Furthermore, it is believed that female sex hormones may confer protection against cardiovascular disease. In fact, 2-hydroxyestradiol, a hydroxylated metabolite of estradiol, is considered a potent inhibitor of vascular smooth muscle cell proliferation (Masi et al., 2006), and chemicals with (anti-) estrogenic potential (such as certain organochlorine pesticides and PCBs) may interact with this mechanism. In vitro research has also suggested that PCB-126 can stimulate the production of vasoconstriction factors and reactive oxygen species, as well as inhibiting the release of nitric oxide (Andersson et al., 2011).

Furthermore, a number of potential effect modifiers have been described in the literature, although the results are controversial. These include: sex, probably due to POP interaction with sex hormone nuclear receptors and differences in the metabolism rate between men and women (Arrebola et al., 2013a; Ha et al., 2009; Robledo et al., 2014); age, given that both POP exposure and the prevalence of many chronic diseases are usually higher in older individuals (Valera et al., 2013b); and BMI, which is usually correlated with adipose tissue concentrations of POPs (Arrebola et al., 2013b), which have a longer half-life in obese subjects (Wolff et al., 2007).

Our aim in this study was to assess the influence of historical exposure to a group of POPs on the risk of hypertension in an adult cohort of residents in Granada (Southern Spain) over a 10-year follow-up.

2. Material and methods

2.1. Study cohort

This research is part of a wider hospital-based study that aims to characterize the exposure to POPs of an adult cohort from Southern Spain and to assess potential health outcomes. The study design, recruitment, and methods have been extensively described elsewhere (Arrebola et al., 2012a, 2013a, 2010, 2009). In brief, study subjects were recruited in two public hospitals from Granada province: San Cecilio University Hospital in the city of Granada (240,000 inhabitants) and Santa Ana Hospital in the town of Motril (50,000 inhabitants). The study cohort was recruited between July 2003 and June 2004 among patients undergoing non-cancer-related surgery (47% inguinal hernia or abdominal surgery, 17% gall bladder surgery, 12% varicose vein surgery, and 24% other surgery). Inclusion criteria were: age over 16 years, absence of cancer, non-receipt of hormone therapy, and residence in one of the study areas for ≥ 10 years. All subjects signed their informed consent to participate in the study, which was approved by the ethics committees of both hospitals. Out of 409 subjects who were contacted, 387 agreed to participate. Among these 387 participants, 42 were excluded because of a previous diagnosis of hypertension (systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg) or receipt of antihypertensive therapy at the time of their recruitment, and 48 were excluded due to discrepancies between the information collected at recruitment and the data in their clinical records, leaving a final cohort of 297 participants. All of the participants were users of the public health system. No statistically significant differences in sex distribution or age were found between participants and non-participants (data not shown in tables).

2.2. Exposure assessment

Samples of 5–10 g adipose tissue were intraoperatively collected, immediately coded, and stored at -80 °C until chemical analyses. Sample extraction and purification procedures were previously described by Rivas et al. (2001). In brief, 200 mg of adipose tissue was extracted using *n*-hexane, and the solution was then purified through 2 g alumina in a glass column. All extracts were stored in glass tubes at -80 °C.

POPs were quantified by high-resolution gas chromatography with a mass spectrometry detector in tandem mode, using a system Saturn 2000 ion trap (Varian, Walnut Creek, CA). We used a 2 m × 0.25 mm silica capillary column (Bellefonte, PA) coupled with a 30 m × 0.25 mm analytical column (Factor FOUR VF-5MS, Varian Inc., Walnut Creek, CA). The limit of detection was set at 0.01 μg/L for all POPs under study. Chromatographic concentrations below the limit of detection were assigned a random value between 0 and the limit of detection. Residues of *p,p*′-dichlorodiphenyldichloroethylene (*p,p*′-DDE, the main metabolite of the pesticide dichlorodiphenyltrichloroethane [DDT]), hexachlorobenzene (HCB), β-hexachlorocyclohexane (β-HCH), and PCB congeners -138, -153 and -180 were quantified. ∑PCBs was computed as the sum of individual PCB concentrations. Recovery of the POPs from adipose tissue was studied to assess the extraction efficiency of the method and ranged from 90–98%.

Lipid content in adipose tissue samples was quantified gravimetrically as reported by Rivas et al. (2001), including a homogenization step of 100 mg adipose tissue with 5 mL of chloroform: methanol:hydrochloric acid (20:10:0.1) and acidification with hydrochloric acid 0.1 N before collection and weighing of the organic phase. Lipid-basis POP concentrations were calculated as suggested by Phillips et al. (1989) and expressed in nanograms per gram lipid (ng/g lipid).

2.3. Outcome assessment

Between January and February 2014, data from new cases of hypertension were retrieved from the DIRAYA clinical records database. DIRAYA, developed in 1997 and implemented in 2003, was designed to facilitate clinical procedures and also to assist clinical and epidemiological research. The system integrates all clinical information for each user of the public health system, including primary and specialized care, with data on all diagnostic tests performed and pharmaceutical treatments received. Each