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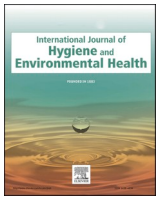

Exposure to the pesticide DDT and risk of diabetes and hypertension: Systematic review and meta-analysis of prospective studies

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ABSTRACT

Background: Experimental evidence suggests that *p,p'*-DDE might be involved in the development of diabetes and hypertension (HTN); however, the evidence in humans is inconclusive.
Objective: To summarize the epidemiological evidence for the association of *p,p'*-DDT exposure and its breakdown products with the risk of diabetes and HTN from prospective studies.
Methods: We performed a systematic review and meta-analysis based on the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement. Eligible studies (prospective) were search in PubMed, Web of Science, EBSCO, and SciELO databases (July 11, 2020). Different search algorithms were used for diabetes and HTN. Pooled odds ratios (ORs) were estimated from meta-analysis with random effects for each exposure and outcome.
Results: A total of 23 prospective studies were included in this review, 16 assessed diabetes and seven HTN; very few measured *p,p'*-DDT. Exposure to *p,p'*-DDE was associated with a slightly increased risk of type 2 diabetes (T2D) (pooled OR = 1.44; 95%CI: 1.00, 2.07; $p = 0.049$) and HTN (pooled OR = 1.21; 95%CI: 1.07, 1.38). Dose-response meta-analysis suggested a non-linear relation between *p,p'*-DDE and T2D. Exposure to *p,p'*-DDE was not associated with gestational diabetes (pooled OR = 1.01; 95%CI: 0.94, 1.09); similarly, *p,p'*-DDT was not associated with T2D (pooled OR = 1.03; 95%CI: 0.79, 1.35).
Conclusions: Evidence from prospective studies suggests that exposure to *p,p'*-DDE, the main breakdown product of *p,p'*-DDT, might increase the risk of developing T2D; such increase may be apparent only at low levels. Exposure to *p,p'*-DDE may also increase the risk of having HTN; however, further evidence is required.

1. Introduction

In the last three decades, the number of people with type 2 diabetes (T2D) and hypertension (HTN) worldwide has increased substantially (Mills et al., 2016; Saeedi et al., 2019); both diseases are major risk factors for cardiovascular disease, representing an important burden on public health globally. Risk factors of T2D and HTN such as family history, ethnicity, obesity, unhealthy diet, lack of physical activity, tobacco, and alcohol consumption are well documented (Bellou et al., 2018; Oparil et al., 2018). Nonetheless, emerging evidence suggests that exposure to persistent organic pollutants (POPs) such as polychlorinated biphenyls and *p,p'*-DDT (1,1,1-trichloro-2,2-bis (4-chlorophenyl) ethane), may play a role in the etiology of cardiometabolic disorders including T2D and HTN (Andersson et al., 2011; Heindel et al., 2017; Thayer et al., 2012).

P,p'-DDT is an organochlorine pesticide widely used worldwide since the 1940s, mainly to exterminate pests in crops and for the control of vector-borne diseases such as malaria and typhus. The toxicity of *p,p'*-DDT on the wildlife lead to its generalized banning since the 1970s and 1980s (ATSDR, 2019). However, its use continues nowadays under close surveillance for malaria control and some regions of the world such as Latin America still have reserves of *p,p'*-DDT stored (van den Berg, 2009). The half-life of *p,p'*-DDT and *p,p'*-DDE in human serum is approximately 7 and (Woodruff et al., 1994) 10 years, respectively (Hunter et al., 1997). Therefore, it is still possible to detect residues of these compounds among people whom experienced some degree of exposure in the past (Turusov et al., 2002).

The underlying mechanisms associating *p,p'*-DDT exposure with the

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risk of developing T2D and HTN are not fully elucidated yet. Studies using animal models suggest that exposure to *p,p'*-DDT might decrease pancreatic secretory activity leading to impaired insulin secretion (Yau and Mennear, 1977); *in vitro* evidence also suggest that *p,p'*-DDT and *p,p'*-DDE might impair glucose metabolism and induce insulin resistance possibly due to disruptions in lipid homeostasis (Ruzzin et al., 2010). Additionally, perinatal exposure to *p,p'*-DDT might disturb the regulation of thermogenesis, lipids, and glucose, which could lead to insulin resistance and metabolic alterations (La Merrill et al., 2014). The main mechanism from experimental data linking prenatal exposure to *p.p'-DDT* with hypertension is the reported over-activation of the renin angiotensin system (La Merrill et al., 2016).

Regardless of the experimental evidence, epidemiological data continues to be inconclusive. Some of the prior studies in humans have reported positive associations between exposure to *p,p'*-DDE and the risk of T2D and HTN (La Merrill et al., 2013; Rylander et al., 2015; Singh and Chan, 2017; Turyk et al., 2009; Van Larebeke et al., 2015; Zong et al., 2018), whereas others have reported null associations (Arrebola et al., 2015; Donat-Vargas et al., 2018; Jaacks et al., 2019; Rahman et al., 2019; Rignell-Hydbom et al., 2010; Smarr et al., 2016). Discrepancies between these findings could be accounted by different study designs, methods to determine the exposure (*e.g.,* directly with biomarkers or indirectly through questionnaires), and the availability of data to control for confounding factors, among others.

Meta-analysis summarizing previous studies have assessed the association between the exposure to POPs and the risk of T2D and HTN regardless of the study design, rather than focusing on the effect of *p,p'*-DDT and its breakdown products in prospective studies (Evangelou et al., 2016; Park et al., 2016; Tang et al., 2014). A prior meta-analysis from prospective studies estimated a non-statistically significant association between *p,p'*-DDE exposure and T2D based on five available studies almost a decade ago (Wu et al., 2013). Hence, integrating the recent evidence from observational prospective studies assessing the potential adverse effects of the pesticide DDT on metabolic-related outcomes through a systematic review and meta-analysis using standard guidelines, would provide useful evidence for decision making process in public health. Therefore, our objective was to systematically review and integrate the epidemiologic evidence regarding the association of *p,p'*-DDT exposure and its breakdown products with the risk of diabetes and HTN from prospective studies and to summarize the evidence quantitatively by conducting a meta-analysis.

2. Materials and methods

2.1. Data source and searching algorithms

The systematic review and meta-analysis was based on the *Preferred Reporting Items for Systematic Reviews and Meta-analyses* (PRISMA) statement (Liberati et al., 2009). Epidemiological evidence on the association of *p,p'*-DDT exposure with the risk of diabetes and HTN was identified by conducting electronic searches on PubMed, Web of Science, EBSCO, and SciELO databases. We constructed and performed independent searching algorithms for each health outcome (Supplemental Table 1); the search was limited to human studies published in English and Spanish up to July 11, 2020. The titles and abstracts of the retrieved documents were independently screened by two authors to assess their relevance to our research objective. Subsequently, authors examined the full text of all potentially relevant studies applying the eligibility criteria to select the studies for the qualitative data synthesis (*i.e.,* prospective studies with exposure measured in biological samples). All discrepancies between the authors who examined the full texts were resolved by consensus.

2.2. Study question and eligibility criteria

The eligibility criteria for the studies were formulated based on the components of the *PECOS* statement (population, exposure, comparators, outcome, and study design) (Morgan et al., 2018) to answer the following research question: "*Does exposure to p,p'-DDT and its breakdown products increases the risk diabetes and HTN in humans?*" (Table 1). Therefore, we included all studies that investigated any potential association of exposure to *p,p'*-DDT and its breakdown products with the risk of diabetes and hypertension without restrictions on the type of diabetes or HTN. Cross-sectional studies were excluded from the systematic review in order to avoid potential reverse causality when interpreting the results. When two or more eligible articles reported results from the same study cohort, same isomers of *p,p'*-DDT, and same exposure period, the most recent study was included.

2.3. Data extraction and quality assessment

The data from the eligible studies were extracted independently in Excel spreadsheet forms. We extracted the following information from each study: first author, year of publication and country where the study was conducted; study design and name of the cohort; sample size and sex of the participants; ages of the participants; health outcome and how it was ascertained; type of exposure (prenatal or postnatal) and biospecimen; median levels of exposure (as reported: wet weight or lipid adjusted); estimated effect and its confidence intervals; risk and reference categories of the exposure; covariates used for adjustment; and the length of the follow-up.

The risk of bias (RoB) of each study was examined using a modified version of the ROBINS-I (*Risk Of Bias In Non-randomised Studies - of Interventions*) instrument, proposed for non-randomized studies that assess the effects of environmental exposures on health outcomes (Morgan et al., 2019; Sterne et al., 2016). The RoB instrument has seven items that assess the strengths and limitations of each study: 1) bias due to confounding, 2) bias in selecting participants in the study, 3) bias in exposures classification, 4) bias due to departures from intended exposures, 5) bias due to missing data, 6) bias in measurement of outcomes, and 7) bias in selection of reported results. Each item and study is rated as: low RoB, moderate RoB, serious RoB, or critical RoB (Morgan et al., 2019); the criteria for the risk of bias evaluation is reported in Supplemental Table 2. These results were then integrated in the GRADE framework *(Grading of Recommendations Assessment, Development, and Evaluation*) (Guyatt et al., 2011) to assess the certainty of the evidence.

We also assessed the quality of the studies included in the systematic review using the *Newcastle-Ottawa Scale* (NOS) for observational studies (Wells et al., 2009). The NOS has eight items grouped in three domains: I) selection of study groups; II) comparability of the groups; and III) exposure or outcomes of interest. Each domain is scored with a maximum of four, two, and three stars, respectively; thus, the total score for the scale sums up to nine stars. Based on this scale, the studies were classified as high quality ($\geq$7 stars), moderate (4–6 stars), and low quality ($\leq$3 stars) (Xing et al., 2016). The discrepancies when rating the quality of the studies were resolved by consensus.

2.4. Statistical analysis

We conducted meta-analysis with random effects to consider both within-and-between study variations (DerSimonian and Laird, 1986). Pooled odds ratios (ORs) were estimated from the published ORs and its 95% confidence intervals (95%CI); there were not enough coefficients from linear regressions to combine in a meta-analysis. Few studies (n = 3) reported only risk ratios (RRs) with its corresponding 95%CI, these were combined with the ORs assuming that the latter is a valid estimator of the RR in nested case-control studies (Szklo and Nieto, 2007). For the studies with three or more exposure categories, we used the reported OR from the highest exposure category relative to the reference to estimate the pooled OR. We conducted separate meta-analysis for each exposure (*p,p'*-DDT and *p,p'*-DDE) and outcome (T2D, gestational diabetes [GDM] and HTN) when there were at least three available studies; very few

Table 1
PECO statement.

Population	Exposure	Comparators	Outcomes	Study type
Humans without any restriction on race, sex, spoken language, geographic region, or religion. Exposure and outcomes measured at all life-stages, except newborns.	Prenatal and/or postnatal exposure to *p,p'*-DDT and its isomers. Exposure measured directly by standardized methods in biological samples (*i.e.,* blood serum, adipose tissue, etc.). Exclusions: determinations by environmental data or other indirect methods (*i.e.,* self-administered questionnaires of lifestyles or dietary intake).	Subsets/categories or groups used as reference in the publications with the lowest levels of exposure to *p,p'*-DDT and its isomers, compared to those with the highest levels of exposure.	Diabetes: Glycated hemoglobin levels (glycosylated hemoglobin); plasma glucose levels; type 1 diabetes; type 2 diabetes; gestational diabetes; or any type of diabetes. Hypertension: Systolic and diastolic blood pressure in mmHg, hypertension, and gestational hypertension.	Prospective epidemiological studies (*i.e.,* cohort, nested case-control or case-cohort). Exclusions: reviews, commentaries, conference abstracts, books, letters to the Editor, and meta-analyses.

studies assessed *p,p'*-DDT, thus we only estimated a pooled ORs for this isomer with T2D. Most of the studies reported associations with the outcomes using different exposure scales for *p,p'*-DDE such as categories based on quantiles, log-transformed (*ln* or log10), per interquartile range (IQR) increase, and a standard deviation (SD) increase of the *ln*-transformed exposure. Therefore, for T2D we conducted separate meta-analysis for the studies that modeled *ln*-transformed and for those modeling categories based on quantiles of *p,p'-DDE* in order to have consistent estimates. Most of the studies categorized *p,p'-DDE* in quartiles (one used tertiles and another quintiles), these were pooled together because their estimates were consistently obtained for the population in the top percentiles of exposure compared to those in the lowest percentiles; thus, the main results are based on this meta-analysis. Such approach was not feasible for the other outcomes due to the limited number of studies. The presence of statistical heterogeneity among the selected studies was assessed using the *Q*-test and the I^2 statistic (range 0–100%) (Higgins et al., 2019). Based on the Cochrane's criteria, an I^2 <30% is not relevant, an I^2 between 30 and 60% indicates moderate heterogeneity, while an $I^2 \geq 75\%$ indicates considerable heterogeneity (Higgins et al., 2019). Therefore, we conducted subgroup meta-analysis in the presence of moderate heterogeneity to identify the potential sources of heterogeneity such as exposure units (lipid standardized or not), outcome definition (self-reported or not), length of follow-up, participant's age, sex (only women or both), and geographic region where the study was conducted.

Two-stage random-effect dose-response meta-analysis with weighted linear mixed models were conducted to assess the shape of the relation between *p,p'*-DDE exposure and T2D (Crippa et al., 2019; Orsini, 2021; Orsini et al., 2006) across studies with at least three exposure categories. We extracted the ORs and medians (or means) of each exposure category from the publications; for the studies without medians (or means) we assigned the midpoint of each exposure category and for the open categories we used half the width of the adjacent category. The potential non-linear dose-response relation was assessed using restricted cubic splines with three knots located at fixed percentiles of the overall distribution according to Harrell's method (Harrell, 2001); these spline terms were then included in the dose-response meta-analysis (using Stata algorithms: *drmeta, drmeta_graph, drmeta_gof*) (Orsini, 2021). The estimated dose-response model was plotted using as reference the lowest level of exposure from the studies included in this meta-analysis (*p,p'*-DDE = 2.5 ng/g lipids).

The small-study effect as an indicator of publication bias was assessed by visual inspection of the funnel plots to identify asymmetric patterns and was complemented with the Egger's test (*p-value* <0.05) (Harbord et al., 2006). Additionally, as sensitivity analysis, we explored the effect of a single study on the overall pooled OR (from the top vs lowest quantiles) by excluding one study at the time to re-estimate the pooled OR. For the association between *p,p'*-DDE and T2D, we also applied the methodology described by Chêne and Thompson (1996) to rescale the study-specific *ln*(ORs) in order to have consistent estimates to pool in a meta-analysis (Chêne and Thompson, 1996). Thus, using the available information extracted, the study-specific *ln*(ORs) were rescaled to estimate the risk associated to an interquartile range (IQR) increase in *p,p'*-DDE; additionally, the study-specific estimates were also rescaled using the IQR (1147.9 ng/g lipids) from one of the study populations reported by Wu et al. (2013). All analyses were conducted using Stata (version 15.1, release 2020; StataCorp, College Station, TX, USA).

3. Results

3.1. Meta-analysis for diabetes

We identified a total 1569 (Fig. 1) potentially relevant references from the search in all databases (PubMed, Web of Science, EBSCO, and SciELO); after removing 522 duplicated references, 1047 were left to screen the titles and abstracts for relevance. With the screening process, 21 references were selected for full-text review, of these, five were excluded after full-text review (four of them were cross-sectional), leaving 16 articles for data extraction.

The information extracted from these 16 studies is summarized in Table 2. Nine were nested case-control studies (Grice et al., 2017; Jaacks et al., 2019; Lee et al., 2010; Rignell-Hydbom et al., 2009, 2010; Rylander et al., 2015; Wolf et al., 2019; Wu et al., 2013; Zong et al., 2018) and seven were cohort studies (Lee et al., 2011; Rahman et al., 2019; Shapiro et al., 2016; Smarr et al., 2016; Turyk et al., 2015; Vafeiadi et al., 2017; Van Larebeke et al., 2015). Seven were conducted in Europe, eight in North America (Grice et al., 2017; Lee et al., 2010; Rahman et al., 2019; Shapiro et al., 2016; Smarr et al., 2016; Turyk et al., 2015; Wu et al., 2013; Zong et al., 2018), and one in Asia (Jaacks et al., 2019). The length of follow-up ranged from four (Wolf et al., 2019) to 27 (Rignell-Hydbom et al., 2010) years, four had a follow-up of 5 years or less (Grice et al., 2017; Jaacks et al., 2019; Lee et al., 2011; Rylander et al., 2015; Wolf et al., 2019) and five had more than 15 years of follow-up (Lee et al., 2010; Rignell-Hydbom et al., 2010; Turyk et al., 2015; Wu et al., 2013); for the studies that assessed GDM the length of follow-up ranged from 13 to 24 weeks (Rahman et al., 2019; Shapiro et al., 2016; Smarr et al., 2016; Vafeiadi et al., 2017). The sample size of each study ranged from 212 (Rylander et al., 2015) to 2294 (Rahman et al., 2019); the ages of the participants ranged from >18 to 80 years, seven assessing T2D as an outcome included participants ≥60 years old (Jaacks et al., 2019; Lee et al., 2011; Rylander et al., 2015; Turyk et al., 2015; Van Larebeke et al., 2015; Wolf et al., 2019); half of the studies included only women and the other half included men and women. All the studies determined the exposure postnatally, with the exception of one that reported prenatal exposure (Rignell-Hydbom et al., 2010). Levels of *p,p'*-DDE were measured in all studies, five also determined concentrations of *p,p*-DDT (Grice et al., 2017; Lee et al., 2010; Rahman et al., 2019; Smarr et al., 2016; Wu et al., 2013), only two studies measured *o,p'*-DDT (Grice et al., 2017) and *p,p'*-DDD (Rahman et al., 2019). Concentrations of DDT and its congeners were reported on a wet basis in eight studies (Grice et al., 2017; Lee et al., 2011; Rignell-Hydbom et al., 2009, 2010; Shapiro et al., 2016; Turyk et al., 2015; Vafeiadi et al., 2017; Wolf et al., 2019). Nine studies added serum lipids as adjusting variables into their models (*i.e.,* serum total lipids, total

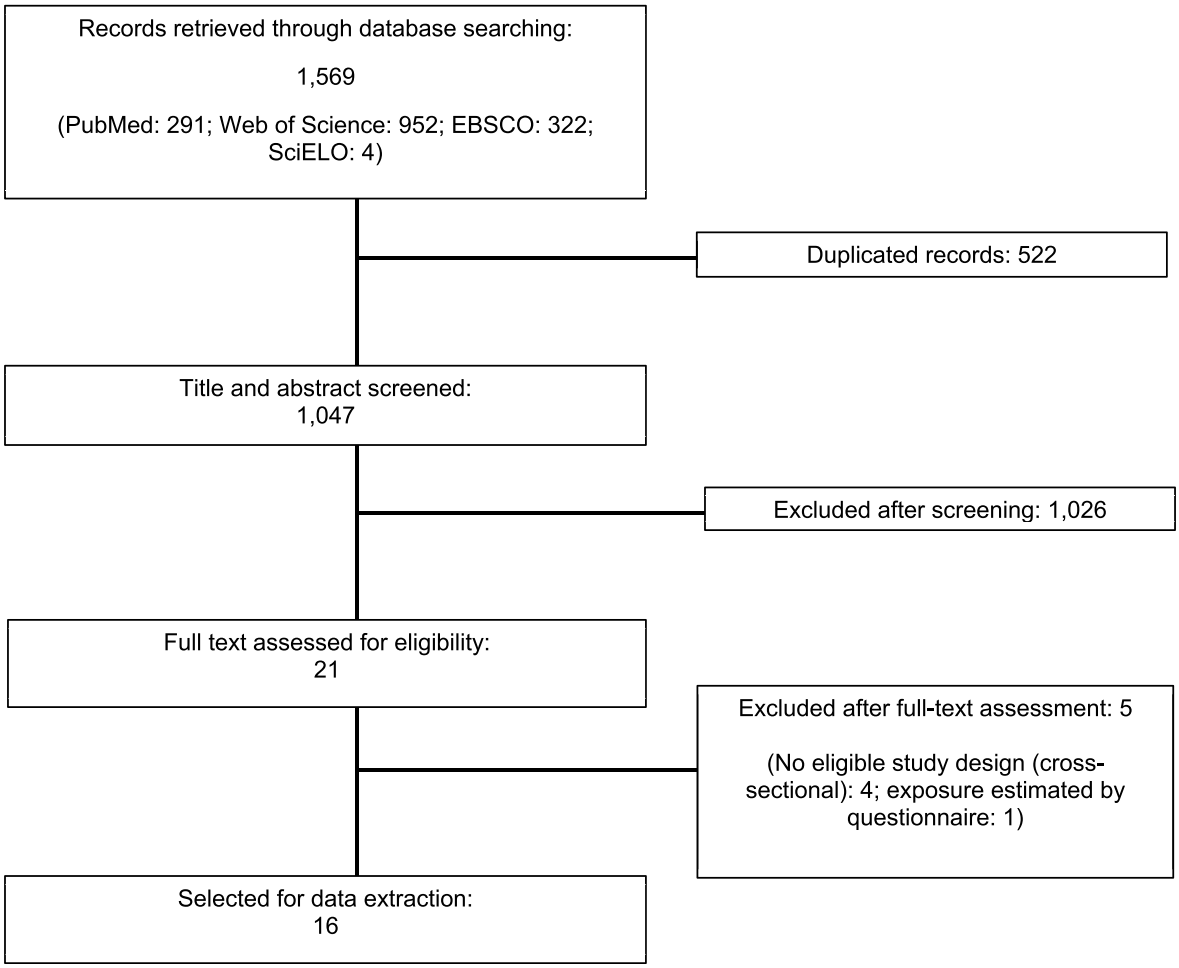

Fig. 1. Flow chart of the selection process of the studies assessing the association between *p,p'-DDT* exposure and risk of diabetes.

cholesterol, or triglycerides and cholesterol) (Grice et al., 2017; Jaacks et al., 2019; Lee et al., 2011; Rahman et al., 2019; Shapiro et al., 2016; Smarr et al., 2016; Turyk et al., 2015; Vafeiadi et al., 2017; Wolf et al., 2019); seven assessed the effect of lipid-standardized concentrations of DDT and its compounds; and two did not account for lipids at all (Rignell-Hydbom et al., 2009, 2010). Five studies log-transformed the exposure to estimate the ORs (Grice et al., 2017; Rahman et al., 2019; Turyk et al., 2015; Van Larebeke et al., 2015) and 11 categorized the exposure in quantiles. The type of diabetes was not clearly defined in two studies (Turyk et al., 2015; Van Larebeke et al., 2015), four assessed gestational diabetes as their main health outcome (Rahman et al., 2019; Shapiro et al., 2016; Smarr et al., 2016; Vafeiadi et al., 2017), one focused on type 1 diabetes (T1D) only (Rignell-Hydbom et al., 2010), and the remain focused on T2D as their main outcome. Two publications, Wolf et al. (2019) and Wu et al. (2013), reported ORs from two independent cohort studies. Potentially confounding factors considered in most studies included age, sex, education, body mass index (BMI), smoking, and alcohol consumption; studies that modeled non lipid-standardized concentrations of DDT and its compounds also adjusted for serum lipids, except two of them (Rignell-Hydbom et al., 2009, 2010); only one reported an OR adjusted for other POPs (*i.e.,* hexachlorobenzene, trans-Nonachlor & oxychlordane) (Smarr et al., 2016). Overall, based on the NOS quality assessment, all the studies included in this review have moderate to high quality (Supplemental Table 3).

A total of seven studies examined the association between *p,p'*-DDE (top vs lowest quantile) and T2D, one of them was multicenter, therefore it contributed with two ORs in the meta-analysis. We observed a slight increased risk of T2D (pooled OR = 1.44; 95%CI: 1.00, 2.07; $p = 0.049$) among those with the highest concentrations of *p,p'*-DDE relative to the lowest; there was evidence of moderate heterogeneity ($I^2 = 44.4\%$) (Fig. 3A). The meta-analysis based on the studies that modeled *ln*-transformed *p,p'*-DDE, showed results in the same direction (pooled OR = 1.28; 95%CI: 0.92, 1.78), but the observed heterogeneity ($I^2 = 67.8\%$) between-studies was higher (Fig. 3B). Because *p,p'*-DDE is a lipophilic pollutant, we conducted a meta-analysis (from Fig. 3A) limited to the studies that considered the effect of lipids (lipid standardization or adding lipids as a covariate in the regression models); only one study did not account for lipids (Rignell-Hydbom et al., 2009). The pooled OR from the studies that considered the effect of lipids was 1.60 (95%CI: 1.00, 2.55; $p = 0.049$; n = 6 studies) with moderate heterogeneity ($I^2 = 41.1\%$) (Supplemental Fig. 1). There were not enough studies to stratify by the approach used to take into account the effect of lipids, only two included serum lipids as a covariate in their regression models (Lee et al., 2010, 2011).

Stratified meta-analysis (Supplemental Table 4) showed stronger associations than those from Fig. 3A among studies that relied mostly on self-reported diagnosis of T2D (pooled OR = 2.12; 95%CI: 1.05, 4.26; n = 3 studies) and those conducted only among women (pooled OR = 1.62; 95%CI: 1.02, 2.58; n = 4 studies). The magnitude of the effect were similar for the studies with longer follow-up (≥10 years, pooled OR = 1.49; 95%CI: 1.12, 1.97; n = 3 studies) and those conducted in the American continent (pooled OR = 1.49; n = 3 studies) as these were estimated from the same three studies. Although the association between *p,p'*-DDE and T2D seem stronger among studies that included participants ≥60 years of age (pooled OR = 2.52), the estimate was

Table 2
Characteristics of the studies evaluating the association of *p,p'*-DDT and its breakdown products with diabetes.

First author, year & country	Study design (Cohort's name)	n (sex)	Age in years	Outcome & ascertainment	Type of exposure (sample)	Median of measured compounds	OR (95% IC)	Risk category	Adjusting variables	Follow-up time
Wolf et al. (2019). Germany	Nested case-control (CARLA)	231 (♂138; ♀93	45–83	T2D. Self-reported diabetes or HbA1c ≥ 6.5% or newly prescribed glucose-lowering medication.	Postnatal (serum)	*p,p'*-DDE: 838 ng/g[a] (IQR = 1169)	1.39 (1.01, 1.89)	Per interquartile range increase in exposure (IQR = 8.9 ng/mL).	BMI, alcohol, smoking, physical activity, parental diabetes, & total cholesterol.	~4 years
Wolf et al. 2019. Germany	Nested case-control (KORA).	165 (♂ 99; ♀ 66)	25–74	T2D. Self-reported diabetes & HbA1c ≥ 6.3%, or HbA1c >6.5% & OGTT; diagnosed diabetes.	Postnatal (serum)	*p,p'*-DDE: 337 ng/g[a] (IQR = 254)	1.28 (0.95, 1.72)	Per interquartile range increase in exposure (IQR = 2.5 ng/mL).	BMI, alcohol, smoking, physical activity, parental diabetes, & total cholesterol.	~7 years
Rahman et al. 2019. USA	Cohort (NICHD Fetal Grow Study).	2294 (♀)	18–44	GD. Test at 23–31 weeks: 100-g 3-hr OGTT or 75 g 2-h OGTT. At least 2-diagnostic plasma glucose measurements of: fasting ≥5.3 mmol/L; 1-hr, ≥10.0 mmol/L; 2-h, ≥8.6 mmol/L; 3-h, ≥7.8 mmol/L. The same thresholds for fasting, 1-h and 2-h glucose measurements were applied.	Postnatal (serum)	*p,p'*-DDE: 103 (99.2, 107.5) ng/g[b] *p,p'*-DDD: 1.2 ng/g[b] *p,p'*-DDT: 2.77 ng/g[b]	1.01 (0.94, 1.09)[c] 0.99 (0.89, 1.09)[c] 0.95 (0.79, 1.13)[c]	Per SD increase in exposure.	Age, BMI at enrollment, education, parity, race/ethnicity, history of T2D, & serum total lipids.	~14 weeks
Jaacks et al. 2019. India	Nested case-control (CARRS)	516 (♂ 222; ♀ 294)	≥20	T2D. Fasting plasma glucose ≥126 mg/dl, HbA1c ≥ 6.5%, or self-reported physician-diagnosed diabetes.	Postnatal (serum)	p,p'-DDE: 454.9 ± 665.3 ng/g[a,d]	0.87 (0.30, 2.55) 0.99 (0.83, 1.18)	Fourth *vs.* first quartile. Per one increase in the *ln*-transformed exposure.	Age, occupation, household income, ever use tobacco products, waist circumference, & fasting plasma glucose.	~5 years
Zong et al. 2018. USA	Nested case-control (NHSII)	1586 (♀)	32–55	T2D. Self-reported physician-diagnosed diabetes plus treatment with insulin or oral hypoglycemic medication or measurement of glucose concentration.	Postnatal (serum)	*p,p'*-DDE: 272 ng/g[a] (IQR = 331)	1.56 (1.14, 2.13)	Third *vs.* first tertile.	Age, ethnicity, time of sample collection, fasting status, menopausal status, post-menopausal hormone use, history of diabetes, oral contraceptive, lifetime breastfeeding, parity, state of residence, smoking, alcohol, & physical activity.	~11 years
Grice et al. 2017. USA	Nested case-control (NAGRIC)	300 (♂ 100; ♀ 200)	18–40	T2D. Plasma glucose concentration 2-hr post-load (2hrPG) ≥200 mg/dl; by clinical diagnosis between examinations.	Postnatal (serum)	*o,p'*-DDT: 126.3 ng/g[b] *p,p'*-DDT: 1949.7 ng/g[b] *p,p'*-DDE: 7417.2 (6998.36, 7861.07) ng/g[b]	1.12 (0.83, 1.50) 1.04 (0.78, 1.40) 0.92 (0.65, 1.30)	Per SD increase in the *ln*-transformed exposures.	Age, sex, BMI, sample water loss after thawing, serum storage time, cholesterol, & triglycerides.	~23 years
Vafeiadi et al. 2017. Greece	Cohort (Rhea)	939 (♀)	>16	GD. 100-g, 3-hr OGTT at 24–28 weeks: fasting ≥95 mg/dl; 1hr of ≥180 mg/dl; 2 h of ≥155 mg/dl; and 3 h ≥ 140 mg/dl.	Postnatal (serum)	*p,p'*-DDE: 2.03 ng/mL[a] (IQR = 2.4661)	0.65 (0.28, 1.47) 0.59 (0.23, 1.51)	Third vs. first tertile. Per $\log_{10}$ increase	Gestational age at sample collection, age, pre-pregnancy BMI, parity, education, smoking during pregnancy, gestational weight gain, serum triglycerides & cholesterol.	~ 13 weeks
Smarr et al. 2016. USA	Cohort (LIFE)	258 (♀)	18–40	GD. Physician report of high blood sugar at ≥24 weeks of gestation.	Postnatal (serum)	*p,p'*-DDE: 0.56 ng/g[a] (IQR = 0.39) *p,p'*-DDT: <LOD	1.20 (0.72, 2.02)	Per SD increase in the *ln*-transformed exposure.	Age, BMI, non-white race, smoking, sum of log-transformed and rescaled POPs (HCB, trans-Nonachlor & oxychlordane), & serum lipids.	~24 weeks

(*continued on next page*)

Table 2 (*continued*)

First author, year & country	Study design (Cohort's name)	n (sex)	Age in years	Outcome & ascertainment	Type of exposure (sample)	Median of measured compounds	OR (95% IC)	Risk category	Adjusting variables	Follow-up time
							1.01 (0.55, 1.85)			
Shapiro et al. 2016. Canada	Cohort (MIREC)	1274 (♀)	>18	GD. Test at 24–28 weeks: 100-g 3-hr OGTT. At least 2-plasma glucose measurements of: fasting, ≥5.3 mmol/L; 1-hr, ≥10.0 mmol/L; 2-h, ≥8.6 mmol/L; 3-h, ≥7.8 mmol/L.	Postnatal (serum)	*p,p′*-DDE: 0.32 ng/mL (IQR = 0.29)	1.1 (0.4, 2.9)	Fourth *vs.* first quartile.	Age, race, pre-pregnancy BMI, education, & total lipids.	~14 weeks
Rylander et al. 2015. Norway	Nested case-control (NOWAC)	212 (♀)	30–70	T2D. Self-reported diabetes diagnosis.	Posnatal (serum)	*p,p′*-DDE: 125 ng/g[a] (Range: 10.9–895)	11.3 (2.55, 49.9)	Fourth *vs.* first quartile.	BMI, breastfeeding, hypertension, & smoking.	~5 years
Turyk et al. 2015. USA	Cohort (GLCHAGL)	413 (♂ 313; ♀ 100)	25–76	Unspecified diabetes. Self-reported diabetes diagnosis & date of diagnosis.	Posnatal (serum)	*p,p′*-DDE: 2.0 (1.8, 2.1) ng/g[b]	2.63 (1.17, 5.89)	Per one increment in the *ln*-transformed exposure.	Age, BMI, gender, calcium channel blockers use, & serum lipids.	~16 years
Van Larebeke et al. 2015. Belgium	Cohort (FLEHS)	1583 (♂ 313; ♀ 100)	50–65	Unspecified diabetes. Self-reported diabetes.	Postnatal (serum)	*p,p'*-DDE: 486 ng/g (percentiles 10th = 147 & 90th = 1575)	1.72 (1.21, 2.42)	Per one increment in *ln*-transformed exposure.	BMI, exercise (min/week), education, alcohol (glass/week).	~7 years
Wu et al. 2013. USA	Nested case-control (Breast cancer study)	981 (♀)	30–55	T2D. Self-reported physician-diagnosis of diabetes plus treatment with insulin or oral hypoglycemic medication or measurement of glucose concentration.	Postnatal (serum)	*p,p'*-DDT: 53.5 ng/g[a] *p,p'*-DDE: 773 ng/g[a] (IQR = 762.3)	1.11 (0.38, 3.27) 1.59 (0.50, 5.03) 0.94 (0.57, 1.61)	Fourth *vs.* first quartile. Fourth *vs.* first quartile Per one increment *ln*-transformed exposure.	Age, baseline BMI in 1990, smoking, alcohol intake, physical activity, & history of diabetes.	~18 years
Wu et al. 2013. USA	Nested case-control (NHL study)	422 (♀)	30–55	T2D. Self-reported physician-diagnosis of diabetes plus treatment with insulin or oral hypoglycemic medication or measurement of glucose concentration.	Postnatal (serum)	*p,p'*-DDT: 43.5 ng/g[a] *p,p'*-DDE: 973.8 ng/g[a] (IQR = 1147.9)	1.01 (0.34, 3.02) 1.57 (0.49, 5.07) 1.15 (0.65, 2.01)	Fourth *vs.* first quartile. Fourth *vs.* first quartile. Per one increment *ln*-transformed exposure.	Age, baseline BMI in 1990, smoking, alcohol intake, physical activity, & history of diabetes.	~18 years
Lee et al. 2011. Sweden	Cohort (PIVUS)	725 (♂ 350; ♀ 375)	>70	T2D. Fasting glucose ≥6.2 mmol/L or use of insulin or oral hypoglycemic agents.	Postnatal (serum)	*p,p'-DDE*: NR (Range 0.011–23.271 ng/g (IQR = 3.58)	2.1 (0.7, 6.3)	Fifth *vs.* first quintile.	Sex, BMI, smoking, physical activity, alcohol, triglycerides, & total cholesterol.	~5 years
Rignell et al. 2010. Sweden	Nested case-control (Malmö)	300 (♂ 150; ♀ 150)	<27	T1D. Based on the diabetes incidence study from the Swedish registry.	Prenatal (maternal serum)	*p,p'*-DDE: 9.60 ng/mL[a] (IQR = 11.0)	0.64 (0.28, 1.46)	Fourth *vs.* first quartile.	Age, sex, preterm, high birth weight; maternal age & smoking in early pregnancy.	~27 years
Lee et al. 2010. USA	Nested case-control (CARDIA)	180 (♂ 72; ♀ 108)	18–30	Fasting glucose ≥126 mg/dL at 2+ examinations or use of antidiabetic drugs.	Postnatal (serum)	*p,p'*-DDE: 3.3130 ng/g *p,p′*-DDT: NR	0.70 (0.2, 1.9)	Fourth *vs.* first quartile.	Age, sex, race, & BMI.	~18 years

(*continued on next page*)

Table 2 (*continued*)

First author, year & country	Study design (Cohort's name)	n (sex)	Age in years	Outcome & ascertainment	Type of exposure (sample)	Median of measured compounds	OR (95% IC)	Risk category	Adjusting variables	Follow-up time
							0.90 (0.31, 2.65)			
Rignell et al. 2009. Sweden	Nested case-control (WHILA)	742 (♀)	50–59	T2D. Fasting glucose >6.1 mmol/l or 2-hr post challenge venous blood glucose level >10.0 mmol/l.	Postnatal (serum)	*p,p'*-DDE: 2.89 ng/mL[a] (Range: 0.063–34.86)	1.1 (0.76, 1.5)	Fourth vs. first quartile.	Age, calendar year, BMI, heredity, birth country, education, smoking, alcohol, hormone replacement therapy & physical activity.	~6 years

Symbols: ♂, males; ♀, females.

Abbreviations: CARDIA, Coronary Artery Risk Development in Young Adults; CARLA, Cardiovascular Disease, Living and Ageing in Halle. CARRS, Centre for Cardiometabolic Risk Reduction in South-Asia; FLEHS, Flemish Environment and Health Survey; IQR, interquartile range; GD, gestational diabetes; GLCHAGL, The Great Lakes Consortium for the Health Assessment of Great Lakes Sport Fish; HbA1c, glycosylated hemoglobin; hr, hours; KORA, Cooperative Health Research in the Region of Augsburg; LIFE, Investigation of Fertility and the Environment; LOD, limit of detection; *ln*, natural logarithm; MIREC, Maternal Infant Research on Environmental Chemicals; NAGRIC, Native American from the Gila River Indian Community; NHL, Non-Hodgkin lymphoma; NHSII, Nurses' Health Study II; NICHD, National Institute of Child Health and Human Development; NOWAC, Norwegian Women and Cancer study; ng/g, nanograms/gram of lipids; ng/mL, nanograms/milliliter; NR, Not reported; OGTT, oral glucose tolerance test; OR, odds ratio; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors study; Rhea, The Mother-Child Cohort in Crete, Greece; SD, standard deviation; T1D, type 1 diabetes; T2D, type 2 diabetes; WHILA. Women's Health in the Lund Area.

[a] From the controls.

[b] Geometric mean (95%CI).

[c] Relative risks.

[d] Mean ± standard deviation.

imprecise with substantial heterogeneity (I^2 = 73.4%); however, the association remain among studies that included participants <60 years (OR = 1.32; 95%CI: 1.06, 1.65; n = 4 studies). The greatest attenuations were observed for the strata of studies that used fasting glucose or glycosylated hemoglobin as part of their outcome definition (pooled OR = 1.01; 95%CI: 0.80, 1.50; n = 4 studies) and for those that included both men and women (pooled OR = 1.09; 95%CI: 0.57, 2.09: n = 3 studies). However, some of these strata showed moderate to considerable heterogeneity, suggesting unaccounted sources of heterogeneity.

The two-stage random-effects dose-response meta-analysis included five studies with available data (Supplemental Table 5). Except for one study, none of the individual studies showed a linear relation between *p,p'*-DDE and T2D. According to the Akaike Information Criterion (AIC) and deviance, the shape of the dose-response relationship was not linear (Supplemental Table 6 and Supplemental Fig. 2). However, a 500 ng/g increase in *p,p'*-DDE exposure was associated with a slight increased risk of T2D (OR = 1.20; 95%CI: 1.04, 1.39; *p-linear trend* = 0.01). The dose-response meta-analysis using cubic splines suggests a non-linear relationship. The overall risk of T2D tended to increase with increasing levels of *p,p'*-DDE up to ~1100 ng/g of lipids (Fig. 4), whereas at higher levels of exposure the risk increase little and the estimates become imprecise as showed by the wide confidence intervals. The strongest association is observed with *p,p'*-DDE levels of ~950 ng/g (OR = 1.65; 95%CI: 1.07, 2.53).

Our results from the sensitivity analysis after omitting one study at the time, showed associations in the same direction and of similar magnitude as what we observed in Fig. 3A (Supplemental Table 7). The pooled OR ranged from 1.33 to 1.60, the greatest attenuation occurred after excluding the study by Rylander et al. (pooled OR = 1.33; 95%CI; 1.07, 1.64) and the greatest increase after excluding the study by Rignel-Hydbom et al. (pooled OR = 1.60; 95%CI; 1.00, 2.55); these exclusions changed the pooled ORs by 7.6% and 11.1%, respectively. As expected, the greatest attenuation was caused when excluding the study with the strongest association (OR = 11.3; 95%CI: 2.55, 49.99); interestingly, such exclusion practically eliminated the observed heterogeneity, suggesting that this single study was the main source of heterogeneity in our meta-analysis.

The results from the sensitivity analysis rescaling the *ln*(OR) of T2D in order to have consistent estimates for the exposure across studies, showed results in the same direction as those observed in Fig. 3A, but the magnitude of the associations observed were lessened. The risk of T2D increased little with an IQR increase in *p,p'*-DDE (pooled OR = 1.13; 95%CI: 1.05, 1.23; n = 5 studies) with no heterogeneity (Supplemental Fig. 3). When we rescaled the study-specific estimates using the IQR (1147.9 ng/g lipids) reported by Wu et al. (2013), the effect was similar to that observed in Fig. 3A (pooled OR = 1.41; 95%CI: 1.16, 1.71: n = 4 studies) with no heterogeneity (Supplemental Fig. 4). Overall, these results were also consistent with those from the dose-response meta-analysis.

We did not observe a statistically significant risk of GDM in relation to *p,p'*-DDE exposure, the estimated pooled ORs from four studies was 1.01 (95%CI: 0.94, 1.09) and there was no evidence of heterogeneity (I^2 = 0%) (Supplemental Fig. 5). No high risk of T2D with *p,p'*-DDT exposure (pooled OR = 1.03; 95%CI: 0.79, 1.35) was observed in a meta-analysis with four studies, and again, there was no evidence of heterogeneity (I^2 = 0%) (Supplemental Fig. 6).

3.2. Meta-analysis for hypertension

A total of 980 references (Fig. 2) were retrieve by the search in all databases (PubMed, Web of Science, EBSCO, and SciELO); of these, 427 duplicated references were removed leaving 533 to screen. With the screening of titles and abstracts, 15 references were selected for full-text review; of these, eight did not meet the inclusion criteria (six of them were cross-sectional) and were excluded after full-text review leaving seven relevant references for data extraction.

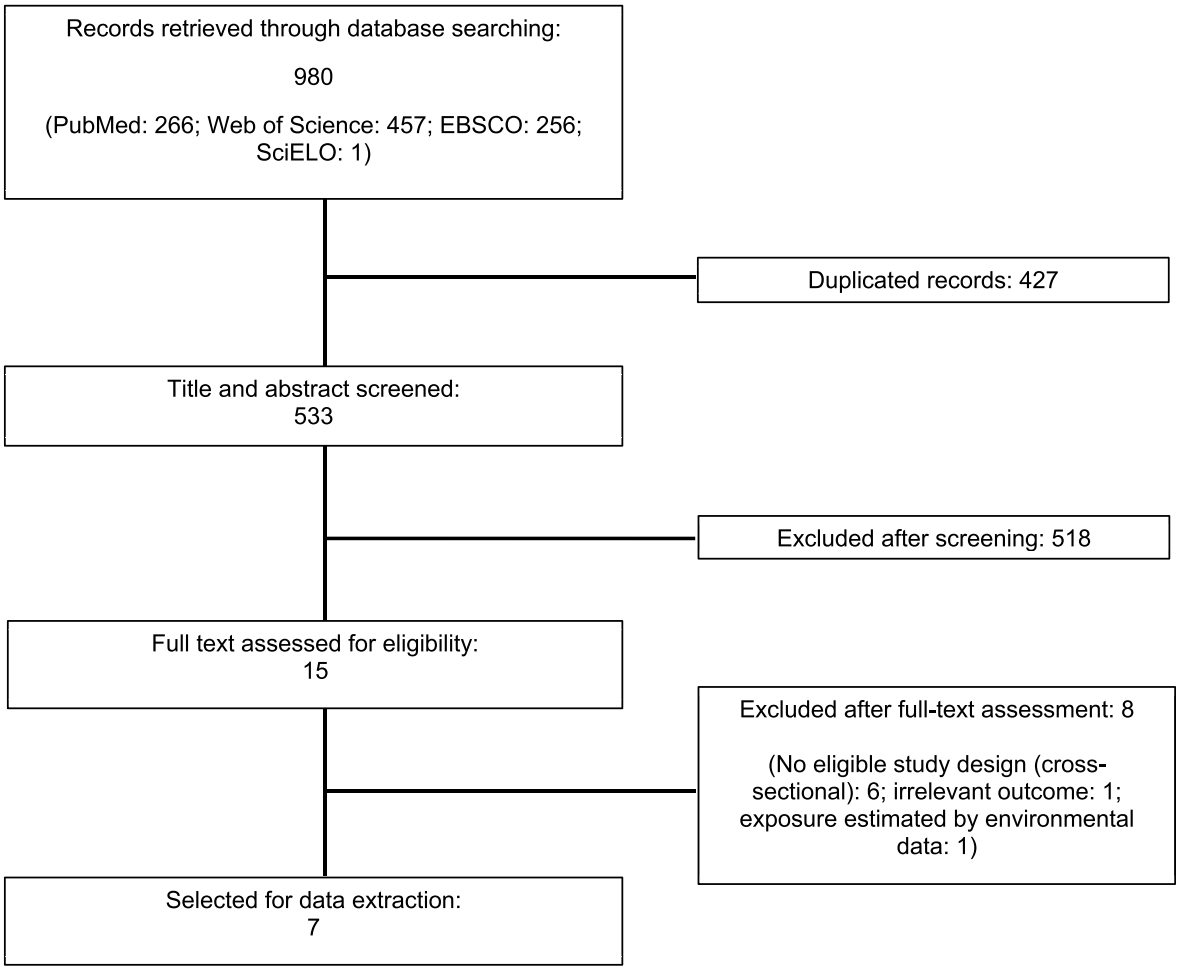

Fig. 2. Flow chart of the selection process of the studies assessing the association between *p,p'-DDT* exposure and risk of hypertension.

Data extracted from the selected studies is summarized in Table 3. All studies were cohorts, except for a nested case-control study; four were conducted in Europe (Arrebola et al., 2015; Donat-Vargas et al., 2018; Vafeiadi et al., 2015; Van Larebeke et al., 2015), two in North America (La Merrill et al., 2013; Smarr et al., 2016), and one in Asia (Lee et al., 2016). The sample sizes of the studies ranged from 214 (Lee et al., 2016) to 1583 (Van Larebeke et al., 2015); the length of follow-up ranged from one (Lee et al., 2016) to 47 years (La Merrill et al., 2013); the study that assessed gestational hypertension had a follow-up of ~24 weeks (Smarr et al., 2016). The ages of the participants ranged from 4 to 80 years, only two studies included participants older than 60 years of age (Arrebola et al., 2015; Van Larebeke et al., 2015); and most of the studies included men and women. As expected, all studies determined concentrations of *p,p'*-DDE in biological samples, three studies also measured *p,p*-DDT (La Merrill et al., 2013; Lee et al., 2016; Smarr et al., 2016) and one o,*p'*-DDT (La Merrill et al., 2013). Two studies assessed the exposure prenatally (La Merrill et al., 2013; Vafeiadi et al., 2015); four modeled lipid-standardized concentrations of DDT and its compounds (Arrebola et al., 2015; Donat-Vargas et al., 2018; Lee et al., 2016; Van Larebeke et al., 2015), two added serum lipids as adjusting variables into their models (*i.e.,* serum total lipids or triglycerides and cholesterol) (Smarr et al., 2016; Vafeiadi et al., 2015) and one did not considered lipids at all (La Merrill et al., 2013). Five studies log-transformed the exposure to estimate the ORs and two categorized the exposure in quantiles (Donat-Vargas et al., 2018; La Merrill et al., 2013). The outcome of interest in most studies was chronic hypertension (Arrebola et al., 2015, 2015, 2015; Donat-Vargas et al., 2018; La Merrill et al., 2013; Van Larebeke et al., 2015), one was focused on gestational hypertension (Smarr et al., 2016), and two studies conducted among children assessed the average change of systolic and diastolic blood pressure (mmHg) as their outcome (Lee et al., 2016; Vafeiadi et al., 2015). Similar to what we observed with T2D, potentially confounding factors considered varied by study, but most of them adjusted for age, sex, smoking, and BMI; one study also adjusted for other POPs (i.e., hexachlorobenzene, trans-Nonachlor & oxychlordane) (Smarr et al., 2016). Based on the NOS quality assessment, all the studies included in the review were scored with moderate to high quality (Supplemental Table 8).

Overall, we observed that the studies reporting higher risks of HTN or increased blood pressure also reported higher levels of exposure compared to the others with null findings (La Merrill et al., 2013; Vafeiadi et al., 2015; Van Larebeke et al., 2015) (Table 3). The number of studies with similar data to combine in meta-analysis were very few and limited to chronic hypertension in relation to *p,p'*-DDE exposure. We observed a slight increased risk of chronic HTN with increasing concentrations of *p,p'*-DDE (pooled OR = 1.21; 95%CI: 1.07, 1.38); there was no evidence of heterogeneity (I^2 = 9.3%), however, this meta-analysis included only four studies with different exposure scales (two categorized by tertiles and two *ln*-transformed *p,p'*-DDE) (Fig. 5). Due to the limited number of studies, were unable con conduct stratified analysis and dose-response meta-analysis. Results from the sensitivity analysis consisting in omitting one study at the time (Supplemental Table 9), showed results comparable to those from Fig. 5, the pooled OR ranged from 1.19 to 1.30. The greatest attenuation (1.7%) was observed when omitting the study by La Merrill et al. (2013) and the greatest increase (by 7.4%) when omitting the study by Van Larebeke et al. (2015).

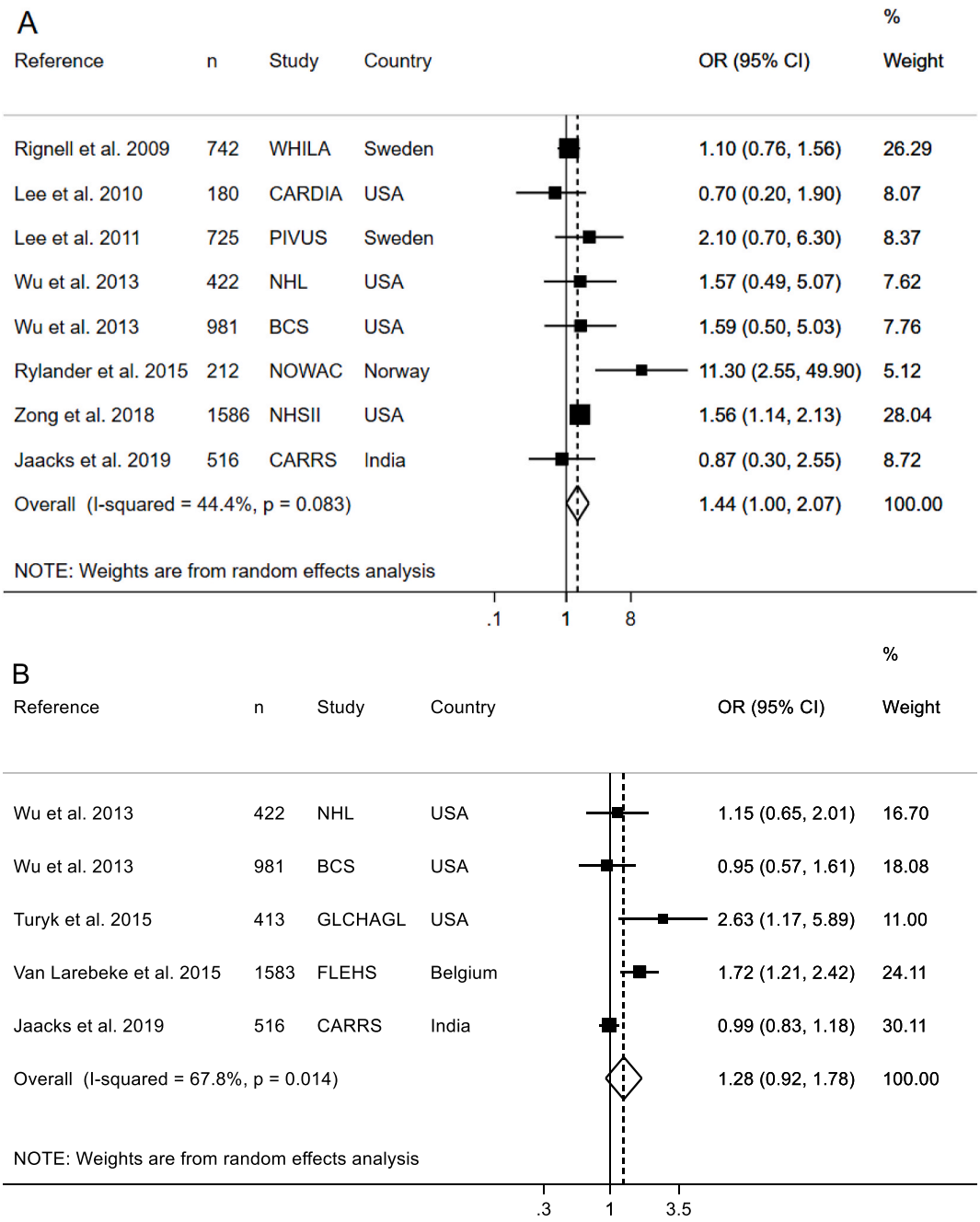

Fig. 3. Meta-analysis of studies assessing *p,p'*-DDE exposure and type 2 diabetes risk. ***A)*** Pooled OR from all studies estimating ORs for the top quantile compared to the lowest quantile. ***B)*** Pooled OR from all studies that reported *ln*-transformed *p,p'*-DDE.
All studies from panel A categorized the exposure into quartiles except the studies by Lee et al. (2011) and Zong et al. (2018) that used quintiles and the tertiles, respectively.

3.3. Assessment of publication bias

As mentioned before, evidence of publication bias was assessed using the funnel plots. No marked asymmetry (Supplemental Figs. 7–10) was observed for the meta-analysis that assessed the relationship between *p, p'*-DDE (top vs lowest quantiles, *ln*-transformed, rescaled estimators) and TD2 risk; moreover, the *Egger's* tests did not show statistically significant small-study effects ($p \geq 0.19$). As expected, the *Egger's* test was not statistically significant in the meta-analysis with non-statistically significant results (data not shown). Similarly, no marked asymmetry emerged in the meta-analysis of *p,p'*-DDE and risk of chronic HTN (Supplemental Fig. 11); the *Egger's* test did not show statistically significant small-study effects ($p = 0.14$).

Most of the studies included in the meta-analysis of T2D were rated with low to moderate risk of bias according to the RoB instrument (Supplemental Tables 10 and 11). The GRADE assessment also suggests high-certainty of the evidence for an increased risk of T2D associated to *p,p'*-DDE exposure (top vs lowest quantiles). The estimated effect for T2D had somewhat good precision as shown by the width of confidence interval; a non-linear dose response relationship was also evaluated. Exposure to *p,p'*-DDE was determined using standardized methods in biological samples, hence, indirectness was apparently not of concern. The risk of bias was not serious and no publication bias was detected (Supplemental Table 12). Similarly, the results from the RoB instrument rated the studies included in the meta-analysis of HTN with low to moderate risk of bias (Supplemental Tables 13 and 14). According to the

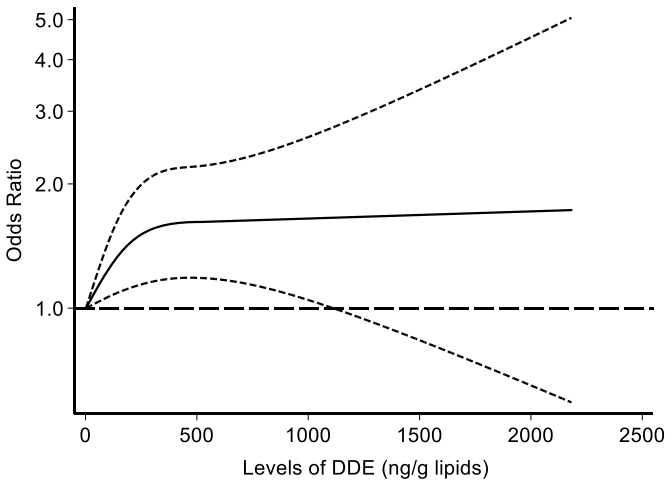

Fig. 4. Dose-response meta-analysis between *p,p'*-DDE exposure and type 2 diabetes: modeling the exposure using restricted cubic splines.
Perphaps it is unnecessary to add "Fig. 4 legend" if the legend will follow the title in the final version of the manuscript. OR's were estimated using as reference the lowest exposure level from one the studies included in the dose-response meta-analysis (2.15 ng/g lipids).

GRADE assessment, there is moderate certainty of the evidence for an association between *p,p'*-DDE exposure and hypertension (Supplemental Table 15). The risk of bias was not serious, inconsistency and indirectness were not of concern apparently, however, prospective studies were scarce, therefore potential publication bias cannot be disregarded; and we were unable to assess a dose-response gradient.

4. Discussion

Results from the present meta-analysis limited to prospective studies, suggest that exposure to *p,p'*-DDE, the main breakdown product of *p,p'*-DDT, might increase the risk of T2D; yet, the size of the effect remains uncertain and may be as little as 13%. Exposure to *p,p'*-DDE may also increase the risk of having chronic HTN, however, this result was based on few studies, thus more studies are warranted to confirm such association.

Most of the studies included in this review assessed the risk of developing T2D and chronic HTN in relation to postnatal exposure to *p,p'*-DDE, only three evaluated prenatal exposure. Our meta-analysis of chronic HTN included a study assessing prenatal exposure (La Merrill et al., 2013) to *p,p'*-DDE (on a wet-weight basis, Table 3) that reported a stronger association than the observed with postnatal exposure. However, the estimate obtained after excluding such study (pooled OR = 1.19; 95%CI: 1.06, 1.34) did not change our main conclusions. Further epidemiological studies are required before dismissing the potential adverse effect of prenatal exposure to *p,p'*-DDT and its breakdown products on the risk of T2D and HTN. Fetal development as a stage of greatest cellular plasticity, represents a vulnerable window for chemical exposure that can lead to epigenetic reprogramming that might influence the susceptibility of the exposed individual to develop metabolic disorders in later life (Barker et al., 2002; Wadhwa et al., 2009). Experimental evidence from animal studies suggests that prenatal exposure to *p,p'*-DDT and its breakdown products are capable to induce alterations in the programming of the offspring, which might lead to disease in adulthood (Bommarito et al., 2017; La Merrill et al., 2014; Schug et al., 2011).

As shown with the present review, few studies have focused on evaluating the effect of the *p,p'*-DDT isomer; only the study by La Merrill et al. (2013) reported a statistically significant association of this isomer with HTN (RR = 2.5; 95%CI: 1.2, 5.3) among adults. Detectable levels of *p,p'*-DDT represents ongoing exposure, whereas *p,p'*-DDE is an indicator of past exposure (Jaga and Dharmani, 2003) and therefore the most commonly measured across studies. Nevertheless, this review shows the importance to distinguish the effect between both compounds as well as to generate evidence related to active exposure to *p,p'*-DDT, especially in countries with ongoing use or manufacture.

Our results are consistent with a prior meta-analysis performed almost a decade ago (2012) limited to prospective studies as the present, though such study reported a non-statistically significant association between *p,p'*-DDE exposure and T2D (pooled OR = 1.25; 95%CI: 0.94, 1.66) based on five studies (Wu et al., 2013). The present meta-analysis based on seven studies (with eight ORs) showed a marginally significant association (*p-value* = 0.049). In agreement with our findings, no significant association between *p,p'*-DDT exposure and T2D risk was observed in the same review (pooled OR = 1.00; 95%CI: 0.54, 1.87) based on three studies (Wu et al., 2013). Also consistent with our findings, a previous meta-analysis of nine studies with various designs reported a somewhat stronger pooled OR between *p,p'*-DDE exposure and T2D (pooled OR = 1.65; 95%CI; 1.15, 2.37) than the estimated in the present (pooled OR = 1.44). However, associations of similar magnitude were observed from studies that accounted for lipids (pooled OR = 1.60; Supplemental Fig. 1) and those limited to women (pooled OR = 1.62; Supplemental Table 4). The main differences with this prior meta-analysis, besides the inclusion of cross-sectional and studies with indirect assessment of exposure, was the evidence of small-study effect as shown by their *Egger's* test (*p-value* <0.05) (Evangelou et al., 2016). A larger meta-analysis of 18 studies with various designs estimated a risk of T2D in relation to *p,p'*-DDE exposure (pooled OR = 1.33; 95%CI: 1.15, 1.54) that is comparable our estimate (Tang et al., 2014). However, the reported heterogeneity although moderate (I^2 = 56%) (Tang et al., 2014), was slightly higher than the observed in the present. The inclusion of cross-sectional studies in these previous meta-analyses is an important limitation when trying to establish a temporal association between the exposure and outcome of interest in order to avoid reverse causality.

Our stratified meta-analysis limited to studies that considered the effect of lipids (lipid-standardized *p,p'*-DDE or added total lipids as a covariate into their models) improve little the heterogeneity and showed stronger associations that were also marginally significant (Supplemental Fig. 1). Previous literature have showed that modeling *p,p'*-DDT and its compounds on a lipids-basis leads to more biased results than adding lipids as a covariate in the regression models (Schisterman et al., 2005). We were unable to conduct stratified analyses based on the approach used to take into account the effect of lipids due to the limited number of studies that adjusted for lipids, most studies modeled lipid-standardized *p,p'*-DDE concentrations. Nonetheless, one of the two studies that adjusted for lipids (as a covariate) reported a stronger association between *p,p'*-DDE and T2D (Lee et al., 2011) than the overall estimate (Fig. 3A). Because lipid concentrations (in serum or plasma) could be an intermediate variable in the association under study (Lee et al., 2007), this results suggest a direct effect of *p,p'*-DDE on T2D that is not explained by lipids.

We could not compare directly our results from the dose-response meta-analysis, to our knowledge this is the first attempt to assess the shape of the relation between *p,p'*-DDE exposure and T2D risk in a meta-analysis. Although based on five studies, our dose-response meta-analysis suggest a non-linear relationship between *p,p'*-DDE exposure and T2D; the confidence intervals at higher levels of exposure showed some degree of imprecision in the estimates. Nonetheless, this result is consistent with the hypothesis that exposure to persistent organic pollutant acting as endocrine disrupters show adverse effects at low-doses but not at higher doses (Lee et al., 2010; Vandenberg et al., 2012; Welshons et al., 2003).

In agreement with our findings, a previous meta-analysis of six studies reported a slight increased risk of hypertension with *p,p'*-DDE exposure (pooled OR = 1.10; 95%CI: 1.03, 1.18); no data on heterogeneity was reported (Park et al., 2016). However, a relevant limitations of

Table 3
Characteristics of the studies evaluating the association of *p,p'*-DDT and its breakdown products with hypertension.

First author, year & country	Study design (Cohort's name)	n (sex)	Age in years	Outcome & ascertainment	Type of exposure (sample)	Median of measured compounds	OR (95%IC)	Risk category	Adjusting variables	Follow-up time
Donat-Vargas et al. 2018. Sweden	Nested case-control (VIP)	427 (♂; ♀)	40–60	Hypertension. SBP>140 or DBP >90 mmHg or use of antihypertensive drugs or self-reported diagnosis of hypertension.	Postnatal (serum).	*p,p'*-DDE: 241 ± 198 ng/g[a,b]	1.59 (0.91, 2.82)	Third *vs.* first tertile.	Gender, age, year of sample collection, & pre-diabetic status.	~13 years
Van Larebeke et al. 2015. Belgium	Cohort (FLEHS)	1583 (♂ 77; ♀ 808)	50–65	Hypertension. Self-reported diagnosis of hypertension in last year.	Postnatal (serum).	*p,p'*-DDE: 486 ng/g (percentiles 10th = 147 & 90th = 1575)	1.23 (1.04, 1.45)	Per one increment in the *ln*-transformed exposure.	Gender, age, smoking, BMI, physical activity, education, & alcohol.	~7 years
Lee et al. 2016. South Korea	Cohort (EB&GC)	214 (♂ 106; ♀ 108)	8–10	DBP & SBP (relative change from baseline to follow-up). DBP & SBP in mmHg: average of 2 measurements.	Postnatal (serum).	*p,p'*-DDT: 3.03 ng/g *p,p'*-DDE: 43.46 ng/g	0.15 (−2.72, 241)[c] 1.70 (−1.89, 5.28)[d] 0.30 (−1.31, 1.92)[c] 1.61 (−0.64, 3.87)[d]	Per one increment in the *ln*-transformed exposure.	Sex, age, household income, & BMI change.	~1 year
Smarr et al. 2016. USA	Cohort (LIFE)	258 (♀)	18–40	Gestational hypertension. Physician report of gestational hypertension at ≥24 weeks of gestation.	Postnatal (serum).	*p,p'*-DDE: 0.56 ng/g[a] (IQR = 0.39) *p,p'*-DDT: <LOD	0.68 (0.33, 1.40) 0.27 (0.04, 1.73)	Per SD increase in the *ln*-transformed exposure.	Age, BMI, non-white race, smoking, sum of log-transformed and rescaled POPs (HCB, trans-Nonachlor & oxychlordane), & serum lipids.	NR
Vafeiadi et al. 2015. Greece	Cohort (Rhea)	689 (♂ 358; ♀ 331)	4	DBP & SBP. DBP & SBP in mmHg: average of 5 measurements.	Prenatal (maternal serum).	*p,p'*-DDE: 1.981 ng/mL (IQR = 2.24)	2.31 (−0.07, 4.69)[c] 1.79 (0.13, 3.46)[d]	Per log-10 increase in exposure.	Maternal: age, pre-pregnant BMI, parity, education, smoking during pregnancy, breastfeeding, triglycerides & cholesterol. Child: sex, birth weight, gestational age, & age at examination.	4 years
Arrebola et al. 2015. Spain	Cohort (Granada-Motril)	297 (♂ 131; ♀ 166)	>16	Hypertension. SBP>140 or DBP >90 mmHg or receipt of anti-hypertensive medication.	Postnatal (adipose tissue).	*p,p'*-DDE: 77.3 ng/g (IQR = 161.3)	1.11 (0.93, 1.33)[e]	Per one increment in the *ln*-transformed exposure.	Age, BMI, smoking, & alcohol.	~10 years
La Merril et al. 2013. USA	Cohort (CHDS)	527 (♀)	39–47	Hypertension. Self-reported physician-diagnosis of hypertension & use of antihypertensive medication.	Prenatal (maternal serum).	*p,p'*-DDT: NR 11.90 ng/mL[f] *o,p'*-DDT: NR 0.51 ng/mL[f] *p,p'*-DDE: NR 54.0 ng/mL[f]	2.5 (1.2, 5.3)[e] 1.2 (0.6, 2.2)[e] 1.7 (1.0, 3.0)[e]	Third *vs.* first tertile.	BMI, diabetes, menopausal status, race, & mother's race.	~39–47 years

Symbols: ♂, males; ♀, females.
Abbreviations: BMI, body mass index; CHDS, Child Health and Development Studies; DBP, diastolic blood pressure; EB&GC, the Ewha Birth & Growth cohort study; FLEHS, Flemish Environment and Health Survey; IQR, interquartile range; LIFE, Investigation of Fertility and the Environment; *ln*, natural logarithm; LOD, limit of detection; ng/g, nanograms/gram of lipids; ng/mL, nanograms/milliliter; NR, Not reported; OR, Odds ratio; PIVUS, Prospective Investigation of the Vasculature in Uppsala Seniors; Rhea, The Mother-Child Cohort in Crete, Greece; SBP, systolic blood pressure; SD, standard deviation; VIP, Ästerbotten Intervention Programme.
[a] From the controls.
[b] Values are means ± standard deviation.
[c] Beta coefficient for SBP (mmHg).
[d] Beta coefficient for DBP (mmHg).
[e] Relative risks.
[f] Levels from the upper tertiles.

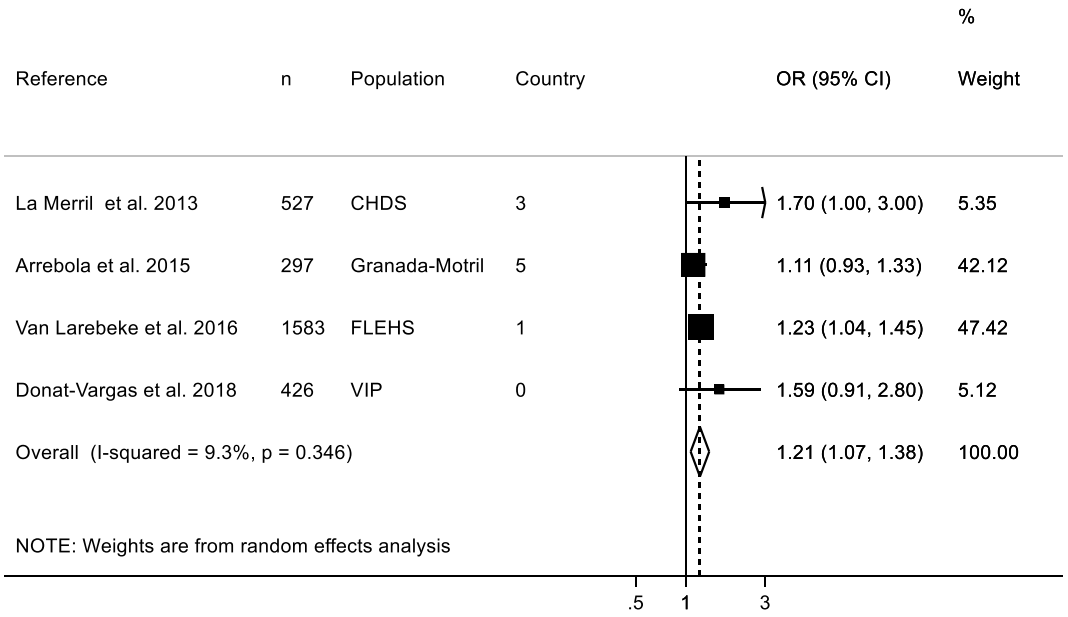

Fig. 5. Meta-analysis of studies assessing *p,p'*-DDE exposure and risk of hypertension.

such meta-analysis was the inclusion of cross-sectional studies (Park et al., 2016) unlike the present meta-analysis limited to prospective studies.

The biological mechanisms underlying the association of *p,p'*-DDT exposure with T2D and HTN risk have not been clearly elucidated yet. However, experimental evidence suggests that *p,p'*-DDT could inhibit the expression of glucose transporter proteins in the beta cells, decreasing the absorption of glucose in adipose tissue, liver, and pancreas, therefore limiting the access of glucose to glucokinase, which can prevent an adequate insulin secretion (Yau and Mennear, 1977). Additionally, *in vitro* evidence have showed the ability of *p,p'*-DDT and *p,p'*-DDE to impair glucose metabolism and induce insulin resistance, a plausible consequence of disrupted lipid homeostasis (Ruzzin et al., 2010). Results from animal models also suggests that perinatal exposure might disrupt the regulation of thermogenesis, lipids, and glucose, which could result in insulin resistance and metabolic alterations (La Merrill et al., 2014). Regarding hypertension, experimental evidence suggests that exposure to *p,p'*-DDT might cause an over-activation of the renin angiotensin system, which might produce a rise in blood pressure (La Merrill et al., 2016).

Some limitations of the present review include the scarcity of prospective epidemiological studies evaluating the associations of interest, which limited our ability to conduct meta-analysis for each metabolite of *p,p'*-DDT with each type of diabetes and hypertension. The effect of the exposure was not consistently assessed across all studies and not all studies had enough data to harmonize the scale of the exposure; therefore, we did attempt to rescale the estimates (ORs) using standard statistical methods (Chêne and Thompson, 1996) in order to have a consistent assessment of the exposure. Yet, we were unable to include all the selected studies in a single meta-analysis; but the overall results from our different meta-analyses were consistently in the same direction. Due to the limited number of studies, publication bias cannot be disregarded. We were unable to assess small-study effects in the meta-analysis of *p,p'*-DDE and HTN due to the limited number of studies, a preference to publish studies with positive results cannot be disregarded. The confounding factors selected to adjust the ORs varied among studies, therefore our pooled OR might be affected by residual confounding. Moreover, human populations are generally exposed to a mixture of chemicals including persistent organic pollutants highly correlated with *p,p'*-DDT, therefore our estimates might not reflect the effect of DDE alone but a mixture of chemicals. We were unable to conduct a dose-response meta-analysis for hypertension due to the limited number of studies.

Despite these limitations, important strengths of the present review includes the use of independent search algorithms for each outcome (diabetes and hypertension), therefore it is unlikely the exclusion of relevant publications as would have occur with a single search strategy for both outcomes. We only included prospective studies with the exposures determined in biospecimens, which contributed to the low risk of bias shown in the meta-analysis of DDE and T2D. Additionally, reverse causality is of little concern in the present review because only prospective studies were included. There is evidence that some metabolic disorders like diabetes might alter the metabolism of POPs in the body, such disorders may increase the chemicals' release from the adipose tissue or may slow its excretion from the body (Porta, 2006). Through this mechanism, diabetes may increase circulating levels of *p,p'*-DDT leading to a spurious association between higher levels of *p,p'*-DDT and higher risk of T2D in cross-sectional studies; nonetheless, this might be an unlikely explanation in the present study.

This revision reveals the need of more prospective evidence, especially considering other outcomes such as hypertension, GDM, and gestational hypertension. Future studies should also focused on the shape of the relationship, prenatal exposure, and mixtures of exposures. Prospective studies assessing the potential adverse effects of the *p,p'*-DDT isomer are scarce, but necessary when reconsidering the use of this pesticide.

4.1. Conclusion

The present meta-analysis limited to prospective studies in humans, provides evidence of the potential adverse effect of *p,p'*-DDE exposure, the main breakdown product of the pesticide *p,p'*-DDT. A slight increased risk of developing type 2 diabetes with *p,p'*-DDE exposure was consistently observed; the dose-response meta-analysis was suggestive of a non-linear relationship and the association with T2D was apparent at lower concentrations of *p,p'*-DDE. Despite a similar increased risk of developing hypertension was apparent, such result was based on very few studies that did not assessed *p,p'*-DDE exposure consistently, therefore confirmation is required before disregarding an adverse effect.

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Declaration of competing interest

None.

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Appendix A. Supplementary data

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References

Andersson, H., Garscha, U., Brittebo, E., 2011. Effects of PCB126 and 17β-oestradiol on endothelium-derived vasoactive factors in human endothelial cells. Toxicology 285, 46–56. https://doi.org/10.1016/j.tox.2011.04.003.

Arrebola, J.P., Fernández, M.F., Martin-Olmedo, P., Bonde, J.P., Martín-Rodriguez, J.L., Expósito, J., Rubio-Domínguez, A., Olea, N., 2015. Historical exposure to persistent organic pollutants and risk of incident hypertension. Environ. Res. 138, 217–223. https://doi.org/10.1016/j.envres.2015.02.018.

ATSDR, 2019. Agency for toxic substances and disease Registry, US Department of health and human Services, Atlanta, GA. https://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=81&tid=20. (Accessed 17 September 2020).

Barker, D.J.P., Eriksson, J.G., Forsén, T., Osmond, C., 2002. Fetal origins of adult disease: strength of effects and biological basis. Int. J. Epidemiol. 31, 1235–1239. https://doi.org/10.1093/ije/31.6.1235.

Bellou, V., Belbasis, L., Tzoulaki, I., Evangelou, E., 2018. Risk factors for type 2 diabetes mellitus: an exposure-wide umbrella review of meta-analyses. PLoS One 13. https://doi.org/10.1371/journal.pone.0194127.

Bommarito, P.A., Martin, E., Fry, R.C., 2017. Effects of prenatal exposure to endocrine disruptors and toxic metals on the fetal epigenome. Epigenomics 9, 333–350. https://doi.org/10.2217/epi-2016-0112.

Chêne, G., Thompson, S.G., 1996. Methods for summarizing the risk associations of quantitative variables in epidemiologic studies in a consistent form. Am. J. Epidemiol. 144, 610–621. https://doi.org/10.1093/oxfordjournals.aje.a008971.

Crippa, A., Discacciati, A., Bottai, M., Spiegelman, D., Orsini, N., 2019. One-stage dose–response meta-analysis for aggregated data. Stat. Methods Med. Res. 28, 1579–1596. https://doi.org/10.1177/0962280218773122.

DerSimonian, R., Laird, N., 1986. Meta-analysis in clinical trials. Control. Clin. Trials 7, 177–188. https://doi.org/10.1016/0197-2456(86)90046-2.

Donat-Vargas, C., Åkesson, A., Tornevi, A., Wennberg, M., Sommar, J., Kiviranta, H., Rantakokko, P., Bergdahl, I.A., 2018. Persistent organochlorine pollutants in plasma, blood pressure, and hypertension in a longitudinal study. Hypertens. Dallas Tex 71, 1258–1268. https://doi.org/10.1161/HYPERTENSIONAHA.117.10691, 1979.

Evangelou, E., Ntritsos, G., Chondrogiorgi, M., Kavvoura, F.K., Hernández, A.F., Ntzani, E.E., Tzoulaki, I., 2016. Exposure to pesticides and diabetes: a systematic review and meta-analysis. Environ. Int. 91, 60–68. https://doi.org/10.1016/j.envint.2016.02.013.

Grice, B.A., Nelson, R.G., Williams, D.E., Knowler, W.C., Mason, C.C., Hanson, R.L., Bullard, K.M., Pavkov, M.E., 2017. Associations between persistent organic pollutants, type 2 diabetes, diabetic nephropathy, and mortality. Occup. Environ. Med. 74, 521–527. https://doi.org/10.1136/oemed-2016-103948.

Guyatt, G.H., Oxman, A.D., Vist, G., Kunz, R., Brozek, J., Alonso-Coello, P., Montori, V., Akl, E.A., Djulbegovic, B., Falck-Ytter, Y., Norris, S.L., Williams, J.W., Atkins, D., Meerpohl, J., Schünemann, H.J., 2011. GRADE guidelines: 4. Rating the quality of evidence–study limitations (risk of bias). J. Clin. Epidemiol. 64, 407–415. https://doi.org/10.1016/j.jclinepi.2010.07.017.

Harbord, R.M., Egger, M., Sterne, J.A.C., 2006. A modified test for small-study effects in meta-analyses of controlled trials with binary endpoints. Stat. Med. 25, 3443–3457. https://doi.org/10.1002/sim.2380.

Harrell, F., 2001. Regression modeling Strategies-with applications to linear models, logistic regression, and Survival analysis: Springer Series in statistics. Springer. https://doi.org/10.1007/978-1-4757-3462-1.

Heindel, J.J., Blumberg, B., Cave, M., Machtinger, R., Mantovani, A., Mendez, M.A., Nadal, A., Palanza, P., Panzica, G., Sargis, R., Vandenberg, L.N., Saal, F. vom, 2017. Metabolism disrupting chemicals and metabolic disorders. Reprod. Toxicol. Elmsford N 68, 3–33. https://doi.org/10.1016/j.reprotox.2016.10.001.

Higgins, J., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M., Welch, V. (Eds.), 2019. Cochrane Handbook for Systematic Reviews of Interventions, second ed. John Wiley & Sons, Chichester (UK).

Hunter, D.J., Hankinson, S.E., Laden, F., Colditz, G.A., Manson, J.E., Willett, W.C., Speizer, F.E., Wolff, M.S., 1997. Plasma organochlorine levels and the risk of breast cancer. N. Engl. J. Med. 337, 1253–1258. https://doi.org/10.1056/NEJM199710303371801.

Jaacks, L.M., Yadav, S., Panuwet, P., Kumar, S., Rajacharya, G.H., Johnson, C., Rawal, I., Mohan, D., Mohan, V., Tandon, N., Barr, D.B., Narayan, K.M.V., Prabhakaran, D., 2019. Metabolite of the pesticide DDT and incident type 2 diabetes in urban India. Environ. Int. 133, 105089. https://doi.org/10.1016/j.envint.2019.105089.

Jaga, K., Dharmani, C., 2003. Global surveillance of DDT and DDE levels in human tissues. Int. J. Occup. Med. Environ. Health 16, 7–20.

La Merrill, M., Cirillo, P.M., Terry, M.B., Krigbaum, N.Y., Flom, J.D., Cohn, B.A., 2013. Prenatal exposure to the pesticide DDT and hypertension diagnosed in women before age 50: a longitudinal Birth cohort study. Environ. Health Perspect. 121, 594–599. https://doi.org/10.1289/ehp.1205921.

La Merrill, M., Karey, E., Moshier, E., Lindtner, C., La Frano, M.R., Newman, J.W., Buettner, C., 2014. Perinatal exposure of mice to the pesticide DDT impairs energy expenditure and metabolism in adult female offspring. PLoS One 9, e103337. https://doi.org/10.1371/journal.pone.0103337.

La Merrill, M.A., Sethi, S., Benard, L., Moshier, E., Haraldsson, B., Buettner, C., 2016. Perinatal DDT exposure induces hypertension and cardiac hypertrophy in adult mice. Environ. Health Perspect. 124, 1722–1727. https://doi.org/10.1289/EHP164.

Lee, D.-H., Lee, I.-K., Porta, M., Steffes, M., Jacobs, D.R., 2007. Relationship between serum concentrations of persistent organic pollutants and the prevalence of metabolic syndrome among non-diabetic adults: results from the National Health and Nutrition Examination Survey 1999-2002. Diabetologia 50, 1841–1851. https://doi.org/10.1007/s00125-007-0755-4.

Lee, D.-H., Lind, P.M., Jacobs, D.R., Salihovic, S., van Bavel, B., Lind, L., 2011. Polychlorinated biphenyls and organochlorine pesticides in plasma predict development of type 2 diabetes in the elderly. Diabetes Care 34, 1778–1784. https://doi.org/10.2337/dc10-2116.

Lee, D.-H., Steffes, M.W., Sjödin, A., Jones, R.S., Needham, L.L., Jacobs, D.R., 2010. Low dose of some persistent organic pollutants predicts type 2 diabetes: a nested case–control study. Environ. Health Perspect. 118, 1235–1242. https://doi.org/10.1289/ehp.0901480.

Lee, H.A., Park, S.H., Hong, Y.S., Ha, E.H., Park, H., 2016. The effect of exposure to persistent organic pollutants on metabolic health among Korean children during a 1-year follow-up. Int. J. Environ. Res. Publ. Health 13. https://doi.org/10.3390/ijerph13030270.

Liberati, A., Altman, D.G., Tetzlaff, J., Mulrow, C., Gøtzsche, P.C., Ioannidis, J.P.A., Clarke, M., Devereaux, P.J., Kleijnen, J., Moher, D., 2009. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med. 6, e1000100 https://doi.org/10.1371/journal.pmed.1000100.

Mills, K.T., Bundy, J.D., Kelly, T.N., Reed, J.E., Kearney, P.M., Reynolds, K., Chen, J., He, J., 2016. Global Disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. Circulation 134, 441–450. https://doi.org/10.1161/CIRCULATIONAHA.115.018912.

Morgan, R.L., Thayer, K.A., Santesso, N., Holloway, A.C., Blain, R., Eftim, S.E., Goldstone, A.E., Ross, P., Ansari, M., Akl, E.A., Filippini, T., Hansell, A., Meerpohl, J. J., Mustafa, R.A., Verbeek, J., Vinceti, M., Whaley, P., Schünemann, H.J., GRADE Working Group, 2019. A risk of bias instrument for non-randomized studies of exposures: a users' guide to its application in the context of GRADE. Environ. Int. 122, 168–184. https://doi.org/10.1016/j.envint.2018.11.004.

Morgan, R.L., Whaley, P., Thayer, K.A., Schünemann, H.J., 2018. Identifying the PECO: a framework for formulating good questions to explore the association of environmental and other exposures with health outcomes. Environ. Int. 121, 1027–1031. https://doi.org/10.1016/j.envint.2018.07.015.

Oparil, S., Acelajado, M.C., Bakris, G.L., Berlowitz, D.R., Cífková, R., Dominiczak, A.F., Grassi, G., Jordan, J., Poulter, N.R., Rodgers, A., Whelton, P.K., 2018. Hypertension. Nat. Rev. Dis. Primer 4, 18014. https://doi.org/10.1038/nrdp.2018.14.

Orsini, N., 2021. Weighted mixed-effects dose–response models for tables of correlated contrasts. STATA J. 21, 320–347. https://doi.org/10.1177/1536867X211025798.

Orsini, N., Bellocco, R., Greenland, S., 2006. Generalized least squares for trend estimation of summarized dose–response data. STATA J. 6, 40. https://doi.org/10.1177/1536867X0600600103.

Park, S.H., Lim, J.-E., Park, H., Jee, S.H., 2016. Body burden of persistent organic pollutants on hypertension: a meta-analysis. Environ. Sci. Pollut. Res. Int. 23, 14284–14293. https://doi.org/10.1007/s11356-016-6568-6.

Porta, M., 2006. Persistent organic pollutants and the burden of diabetes. Lancet Lond. Engl. 368, 558–559. https://doi.org/10.1016/S0140-6736(06)69174-5.

Rahman, M.L., Zhang, C., Smarr, M.M., Lee, S., Honda, M., Kannan, K., Tekola-Ayele, F., Buck Louis, G.M., 2019. Persistent organic pollutants and gestational diabetes: a multi-center prospective cohort study of healthy US women. Environ. Int. 124, 249–258. https://doi.org/10.1016/j.envint.2019.01.027.

Rignell-Hydbom, A., Elfving, M., Ivarsson, S.A., Lindh, C., Jönsson, B.A.G., Olofsson, P., Rylander, L., 2010. A nested case-control study of intrauterine exposure to persistent organochlorine pollutants in relation to risk of type 1 diabetes. PLoS One 5. https://doi.org/10.1371/journal.pone.0011281.

Rignell-Hydbom, A., Lidfeldt, J., Kiviranta, H., Rantakokko, P., Samsioe, G., Agardh, C.-D., Rylander, L., 2009. Exposure to p,p′-DDE: a risk factor for type 2 diabetes. PLoS One 4. https://doi.org/10.1371/journal.pone.0007503.

Ruzzin, J., Petersen, R., Meugnier, E., Madsen, L., Lock, E.-J., Lillefosse, H., Ma, T., Pesenti, S., Sonne, S.B., Marstrand, T.T., Malde, M.K., Du, Z.-Y., Chavey, C., Fajas, L., Lundebye, A.-K., Brand, C.L., Vidal, H., Kristiansen, K., Frøyland, L., 2010. Persistent organic pollutant exposure leads to insulin resistance syndrome. Environ. Health Perspect. 118, 465–471. https://doi.org/10.1289/ehp.0901321.

Rylander, C., Sandanger, T.M., Nøst, T.H., Breivik, K., Lund, E., 2015. Combining plasma measurements and mechanistic modeling to explore the effect of POPs on type 2

diabetes mellitus in Norwegian women. Environ. Res. 142, 365–373. https://doi.org/10.1016/j.envres.2015.07.002.

Saeedi, P., Petersohn, I., Salpea, P., Malanda, B., Karuranga, S., Unwin, N., Colagiuri, S., Guariguata, L., Motala, A.A., Ogurtsova, K., Shaw, J.E., Bright, D., Williams, R., 2019. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the international diabetes federation diabetes atlas. Diabetes Res. Clin. Pract. 157 https://doi.org/10.1016/j.diabres.2019.107843 ninth ed.

Schisterman, E.F., Whitcomb, B.W., Louis, G.M.B., Louis, T.A., 2005. Lipid adjustment in the analysis of environmental contaminants and human health risks. Environ. Health Perspect. 113, 853–857. https://doi.org/10.1289/ehp.7640.

Schug, T.T., Janesick, A., Blumberg, B., Heindel, J.J., 2011. Endocrine disrupting chemicals and disease susceptibility. J. Steroid Biochem. Mol. Biol. 127, 204–215. https://doi.org/10.1016/j.jsbmb.2011.08.007.

Shapiro, G.D., Dodds, L., Arbuckle, T.E., Ashley-Martin, J., Ettinger, A.S., Fisher, M., Taback, S., Bouchard, M.F., Monnier, P., Dallaire, R., Morisset, A.-S., Fraser, W., 2016. Exposure to organophosphorus and organochlorine pesticides, perfluoroalkyl substances, and polychlorinated biphenyls in pregnancy and the association with impaired glucose tolerance and gestational diabetes mellitus: the MIREC Study. Environ. Res. 147, 71–81. https://doi.org/10.1016/j.envres.2016.01.040.

Singh, K., Chan, H.M., 2017. Persistent organic pollutants and diabetes among Inuit in the Canadian Arctic. Environ. Int. 101, 183–189. https://doi.org/10.1016/j.envint.2017.02.002.

Smarr, M.M., Grantz, K.L., Zhang, C., Sundaram, R., Maisog, J.M., Barr, D.B., Louis, G.M.B., 2016. Persistent organic pollutants and pregnancy complications. Sci. Total Environ. 551 (552), 285–291. https://doi.org/10.1016/j.scitotenv.2016.02.030.

Sterne, J.A., Hernán, M.A., Reeves, B.C., Savović, J., Berkman, N.D., Viswanathan, M., Henry, D., Altman, D.G., Ansari, M.T., Boutron, I., Carpenter, J.R., Chan, A.-W., Churchill, R., Deeks, J.J., Hróbjartsson, A., Kirkham, J., Jüni, P., Loke, Y.K., Pigott, T.D., Ramsay, C.R., Regidor, D., Rothstein, H.R., Sandhu, L., Santaguida, P.L., Schünemann, H.J., Shea, B., Shrier, I., Tugwell, P., Turner, L., Valentine, J.C., Waddington, H., Waters, E., Wells, G.A., Whiting, P.F., Higgins, J.P., 2016. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ 355, i4919. https://doi.org/10.1136/bmj.i4919.

Szklo, M., Nieto, J., 2007. Epidemiology : beyond the Basics, second ed. Jones and Bartlett Publishers, Sudbury, Mass.

Tang, M., Chen, K., Yang, F., Liu, W., 2014. Exposure to organochlorine pollutants and type 2 diabetes: a systematic review and meta-analysis. PLoS One 9. https://doi.org/10.1371/journal.pone.0085556.

Thayer, K.A., Heindel, J.J., Bucher, J.R., Gallo, M.A., 2012. Role of environmental chemicals in diabetes and obesity: a National Toxicology Program workshop review. Environ. Health Perspect. 120, 779–789. https://doi.org/10.1289/ehp.1104597.

Turusov, V., Rakitsky, V., Tomatis, L., 2002. Dichlorodiphenyltrichloroethane (DDT): ubiquity, persistence, and risks. Environ. Health Perspect. 110, 125–128.

Turyk, M., Anderson, H., Knobeloch, L., Imm, P., Persky, V., 2009. Organochlorine exposure and incidence of diabetes in a cohort of Great Lakes Sport fish consumers. Environ. Health Perspect. 117, 1076–1082. https://doi.org/10.1289/ehp.0800281.

Turyk, M., Fantuzzi, G., Persky, V., Freels, S., Lambertino, A., Pini, M., Rhodes, D.H., Anderson, H.A., 2015. Persistent organic pollutants and biomarkers of diabetes risk in a cohort of Great Lakes Sport caught fish consumers. Environ. Res. 140, 335–344. https://doi.org/10.1016/j.envres.2015.03.037.

Vafeiadi, M., Georgiou, V., Chalkiadaki, G., Rantakokko, P., Kiviranta, H., Karachaliou, M., Fthenou, E., Venihaki, M., Sarri, K., Vassilaki, M., Kyrtopoulos, S. A., Oken, E., Kogevinas, M., Chatzi, L., 2015. Association of prenatal exposure to persistent organic pollutants with obesity and cardiometabolic traits in early childhood: the Rhea Mother–child cohort (Crete, Greece). Environ. Health Perspect. 123, 1015–1021. https://doi.org/10.1289/ehp.1409062.

Vafeiadi, M., Roumeliotaki, T., Chalkiadaki, G., Rantakokko, P., Kiviranta, H., Fthenou, E., Kyrtopoulos, S.A., Kogevinas, M., Chatzi, L., 2017. Persistent organic pollutants in early pregnancy and risk of gestational diabetes mellitus. Environ. Int. 98, 89–95. https://doi.org/10.1016/j.envint.2016.10.005.

van den Berg, H., 2009. Global status of DDT and its alternatives for Use in vector control to prevent disease. Environ. Health Perspect. 117, 1656–1663. https://doi.org/10.1289/ehp.0900785.

Van Larebeke, N., Sioen, I., Hond, E.D., Nelen, V., Van de Mieroop, E., Nawrot, T., Bruckers, L., Schoeters, G., Baeyens, W., 2015. Internal exposure to organochlorine pollutants and cadmium and self-reported health status: a prospective study. Int. J. Hyg Environ. Health 218, 232–245. https://doi.org/10.1016/j.ijheh.2014.11.002.

Vandenberg, L.N., Colborn, T., Hayes, T.B., Heindel, J.J., Jacobs, D.R., Lee, D.-H., Shioda, T., Soto, A.M., vom Saal, F.S., Welshons, W.V., Zoeller, R.T., Myers, J.P., 2012. Hormones and endocrine-disrupting chemicals: low-dose effects and Nonmonotonic dose responses. Endocr. Rev. 33, 378–455. https://doi.org/10.1210/er.2011-1050.

Wadhwa, P.D., Buss, C., Entringer, S., Swanson, J.M., 2009. Developmental origins of health and disease: brief history of the approach and current focus on epigenetic mechanisms. Semin. Reprod. Med. 27, 358–368. https://doi.org/10.1055/s-0029-1237424.

Wells, G., Shea, B., O'Connell, D., Peterson, J., Welch, v, Losos, M., Tugwell, P., 2009. The Newcastle–Ottawa Scale (NOS) for assessing the quality if nonrandomized studies in meta-analyses. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. (Accessed 17 September 2020).

Welshons, W.V., Thayer, K.A., Judy, B.M., Taylor, J.A., Curran, E.M., vom Saal, F.S., 2003. Large effects from small exposures. I. Mechanisms for endocrine-disrupting chemicals with estrogenic activity. Environ. Health Perspect. 111, 994–1006. https://doi.org/10.1289/ehp.5494.

Wolf, K., Bongaerts, B.W.C., Schneider, Alexandra, Huth, C., Meisinger, C., Peters, A., Schneider, Andrea, Wittsiepe, J., Schramm, K.-W., Greiser, K.H., Hartwig, S., Kluttig, A., Rathmann, W., 2019. Persistent organic pollutants and the incidence of type 2 diabetes in the CARLA and KORA cohort studies. Environ. Int. 129, 221–228. https://doi.org/10.1016/j.envint.2019.05.030.

Woodruff, T., Wolff, M.S., Davis, D.L., Hayward, D., 1994. Organochlorine exposure estimation in the study of cancer etiology. Environ. Res. 65, 132–144. https://doi.org/10.1006/enrs.1994.1026.

Wu, H., Bertrand, K.A., Choi, A.L., Hu, F.B., Laden, F., Grandjean, P., Sun, Q., 2013. Persistent organic pollutants and type 2 diabetes: a prospective analysis in the Nurses' health study and meta-analysis. Environ. Health Perspect. 121, 153–161. https://doi.org/10.1289/ehp.1205248.

Xing, D., Xu, Y., Liu, Q., Ke, Y., Wang, B., Li, Z., Lin, J., 2016. Osteoarthritis and all-cause mortality in worldwide populations: grading the evidence from a meta-analysis. Sci. Rep. 6 https://doi.org/10.1038/srep24393.

Yau, D.T., Mennear, J.H., 1977. The inhibitory effect of DDT on insulin secretion in mice. Toxicol. Appl. Pharmacol. 39, 81–88. https://doi.org/10.1016/0041-008x(77)90179-x.

Zong, G., Valvi, D., Coull, B., Göen, T., Hu, F.B., Grandjean, P., Sun, Q., 2018. Persistent organic pollutants and risk of type 2 diabetes: a prospective investigation among Middle-aged women in Nurses' health study II. Environ. Int. 114, 334–342. https://doi.org/10.1016/j.envint.2017.12.010.