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## SYSTEMATIC REVIEW

# Persistent organic pollutant exposure as a risk factor of gestational diabetes mellitus: A systematic review and meta-analysis

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**Abstract**

**Background:** Findings related to the association between persistent organic pollutants (POPs) and gestational diabetes mellitus (GDM) are inconclusive.

**Objectives:** To estimate the strength of the association between POP exposure and GDM in a systematic review with meta-analysis.

**Search strategy:** MEDLINE, Scopus and Web of Science were searched until July 2023.

**Selection criteria:** Cohort and case-control studies analysing the association between POPs and GDM.

**Data collection and analysis:** We assessed the risk of bias using the Quality in Prognosis Studies scale (QUIPS). Standardised mean differences were pooled using random-effect models.

**Main results:** Sixteen articles including 12 216 participants were selected. The risk of bias was high in four articles (25%), moderate in 11 (68.75%) and low in one (6.25%). Small mean difference between GDM cases and controls was observed for PFHpA (0.26, 95% confidence interval [CI] 0.1–0.35,  $I^2 = 0.0\%$ ), PCB180 (0.37, 95% CI 0.19–0.56;  $I^2 = 25.3\%$ ), BDE47 (0.23, 95% CI 0.0–0.45,  $I^2 = 0\%$ ), BDE99 (0.36, 95% CI 0.14–0.59;  $I^2 = 0\%$ ), BDE100 (0.42, 95% CI 0.19–0.64;  $I^2 = 0\%$ ) and HCB (0.22, 95% CI 0.01–0.42,  $I^2 = 39.6\%$ ). No considerable difference was observed for the rest of POPs.

**Conclusion:** Small mean differences between GDM cases and controls were observed for some POPs. However, evidence shows mostly moderate quality and results were heterogeneous. Improved research methodology is needed to assess POPs and GDM risk.

**KEY WORDS**

exposure, gestational diabetes mellitus, meta-analysis, persistent organic pollutants, risk factor, systematic review

## 1 | INTRODUCTION

Persistent organic pollutants (POPs), such as Per- and polyfluoroalkyl substances (PFAS), polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs) and

organochlorine pesticides (OCPs) are highly lipophilic compounds and are peculiarly persistent and resistant to biodegradation. Due to their long half-life, POPs have the ability to bioaccumulate in the environment, food and organisms.<sup>1</sup> The principal pathway for human exposure to

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most POPs is through dietary intake. However, occupational exposure, indoor inhalation and inadvertent ingestion of dust are important sources of exposure for some POPs.<sup>2–4</sup> Chronic exposure to POPs can be related to ill health, even in low doses.<sup>5</sup> In adults, high specimen POPs levels were associated with a high risk of carcinogenic, neurological, endocrine and metabolic conditions.<sup>6–9</sup> Several POPs, such as **hexachlorobenzene** (HCB), dichlorodiphenyldichloroethylene (p,p'-DDE) and PCBs have been described as potential risk factors for diabetes mellitus type 2.<sup>10,11</sup>

During pregnancy, POPs exposure increases the risk of several outcomes such as miscarriage, preterm birth and low birthweight.<sup>12–14</sup> However, findings related to gestational diabetes mellitus (GDM) tend to show more discrepancies.<sup>12,15,16</sup> Zhang et al.<sup>17</sup> describe a positive association between PCB 52 and GDM, and no association for PCB 138, 153 and 180. However, Jaack et al.'s<sup>18</sup> cohort study shows a negative association between PCB 138, 15, and 180 with GDM. Regarding PFAS, Yan et al.'s<sup>19</sup> systematic review supports that PFAS increase the risk for GDM; in contrast, no association was affirmed by Gao et al.<sup>12</sup> This disparity may be caused by population characteristics and selection biases, small sample sizes, lipid adjustment, POPs measurement procedures, the use of different definitions for GDM, and methodological issues related to the adjustment for confounding factors. Furthermore, it would be necessary to ensure that exposure assessment precedes the outcome's occurrence to reduce possible bias, especially as blood concentrations of POPs may change throughout pregnancy.<sup>20,21</sup> We found one systematic review based on follow-up studies, but this review focused only on the relation between DDT and GDM.<sup>15</sup>

Therefore, we aimed to explore comprehensively the association between POPs and GDM using a systematic review with a meta-analysis of cohort and case-control studies.

## 2 | METHODS

This systematic review and meta-analysis protocol has been registered previously in PROSPERO ([www.crd.york.ac.uk/PROSPERO](http://www.crd.york.ac.uk/PROSPERO), CRD42022303450). It was reported according to the 2020 update of Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) statement.<sup>22</sup> Patients were not involved in the development of the research and ethical approval was not required due to the study design.

### 2.1 | Eligibility criteria

Eligibility criteria were defined a priori according to the PECOS statement (P: population, E: exposure, C: comparators, O: outcome, S: study design). More information about these criteria are provided in [Table S1](#). The selection criteria were: (1) cohort, case-control studies and hybrid studies

(nested case-control studies and case-cohort studies); (2) studies based on women of childbearing age; (3) studies analysing the relation between the individual contamination levels of POPs and the incidence of GDM; (4) published studies from the inception of the database used for the search until July 2023. All cross-sectional studies, book chapters and conference communications were excluded.

### 2.2 | Information source and research strategy

A systematic search was conducted in March 2022, and then updated every 6 months. The last update was realised on July 2023, and two additional records were included in our systematic review.<sup>23,24</sup> Terms were searched on PubMed Central, Web of Science via Clarivate, and Scopus via Elsevier. The updated version of each platform was used. Free keywords were combined on a search equation according to each database's recommendations ([Appendix S1](#)).

The following terms were used for the searches: organochlorinate, organochlorine, chlorinated, persistent organic pollutant, POP, persistent pesticides, persistent toxic substances, per- and polyfluoroalkyl substances, PFAs, polybrominated diphenyl ethers, PBDEs, polychlorinated biphenyls, PCBs, hexachlorobenzene, HCB, dichlorodiphenyltrichloroethane, DDT, p,p'-DDT, dichlorodiphenyldichloroethylene, DDE, p,p'-DDE, dichlorodiphenyldichloroethane, DDD, p,p'-DDD, gestational diabetes mellitus, gestational diabetes, GDM.

Additionally, the reference lists of selected reviews were hand-searched. Details of search results are provided for each data resource in [Appendix S1](#). Two investigators (MK and MACH) independently conducted the search and identified the eligible articles. After duplicated articles were removed, a first screening by title and abstract was done. Articles that met inclusion criteria were assessed by reading the full text. Disagreement or uncertainties in the selection of studies was resolved through discussion with senior reviewers (JJJM and JZ).

### 2.3 | Data extraction and quality assessment

Selected articles were reviewed by MK and MACH independently. From each article the following information was extracted in a standardised form:

*Basic data:* authors, publication year, study period, country and research funding.

*Study characteristics:* type of study design, sample method, sample size, selection criteria, characteristics of the participants and compliance with ethical principles.

*Exposure data:* type of examined POPs, biomarkers used to assess contamination level, gestational age for the sample collection, analytic methodology, limit of detection (LOD) or limit of quantification (LOQ), unit of measurement for POPs and lipid adjustment for the final determinations.

**Outcome data:** criteria used for the diagnosis of GDM were collected from the National Diabetes Data Group criteria, Carpenter–Coustan criteria, International Association of Diabetes and Pregnancy Study Groups criteria, World Health Organization criteria, Canadian Diabetes Association and the Society of Obstetricians and Gynaecologists of Canada).

**Descriptive measurements of POPs by comparison groups and analytic results:** mean and standard deviation (SD), median and interquartile range (IQR) or geometric mean (GSD) to describe the levels of POPs; and relative risk (RR), odds ratio (OR) and their 95% confidence interval (CI) as association measures. Confounding factors used for adjustment analyses were also collected. The authors were contacted by email in the case of missing information.

Risk of bias and methodological quality of each included study in the systematic review were evaluated independently by two researchers (MK and MACH) using the Quality in Prognosis Studies scale (QUIPS).<sup>25</sup> The following describes the six domains with their respective issues and cut-off points to consider for judging the risk of bias in QUIPS:

**Study participation,** including factors such as the source of the target population, method/s used to identify the population, recruitment period, inclusion and exclusion criteria, adequate study participation and baseline characteristics. The risk of bias was classified as low (5–7 items), moderate (3, 4) and high (1, 2).

**Study attribution,** related to strategies to avoid losses, the reasons for the losses, and the potential impact of subjects lost to follow-up on the results based on outcome and prognostic factor/s information on those lost to follow-up. The risk of bias was categorised as low (met 5 items), moderate (3, 4) and high (1, 2).

**Appropriate definition** of the following: the exposure and measurement methods, the same method and setting for all study participants, exposure measurement available for adequate sample proportion, and appropriate methods of imputation. The cut-off points for the risk of bias were: low (met 5 items), moderate (3, 4) and high (1, 2).

**Outcomes:** outcome measurement collection, definition of the outcome (gestational diabetes or not), valid and reliable measurement of outcome, method and setting of outcome measurement were assessed. These were classified as low (met 3 items), moderate (2) and high (1) risk of bias.

**Collection of confounding factors and their characteristics:** definition of confounding factor, methods, setting, validity and reliability of the measurements, methods used for missing data, and appropriate strategies to avoid the effect of confounding factors. The risk of bias was classified as low (met 5–7 items), moderate (3, 4) and high (1, 2) risk of bias.

**Statistical analysis and reporting:** the analytical strategy, models of development strategy, and reporting of results were assessed. The risk of bias was classified as low (met 4 items), moderate (2, 3) and high (1).

In addition to the guidelines provided by the QUIPS scale to judge the risk of bias in each item, supplementary comments were developed to facilitate the consensus. Studies were classified as follows:

- low risk of bias, requires at least five domains judged as low risk of bias and none classified as high risk of bias;
- moderate risk of bias for those cases with (1) five items classified as low risk of bias and one item judged as high risk of bias, or (2) two items evaluated as moderate risk of bias;
- high risk of bias for those cases with at least two items judged as high risk of bias or at least three items evaluated as moderate risk of bias.

The weighted kappa coefficient (Kw) for the six domains was measured to assess inter-rater reliability.<sup>26</sup> Disagreements and uncertainties were solved through discussion with senior reviewers (JJJM and JZ).

## 2.4 | Data synthesis and meta-analysis

To determine the method to combine individual studies data in the meta-analysis, the characteristics and the results of each included study were assessed. To combine the information from every study, the exposed levels of POPs expressed as continuous data in groups of GDM and non-GDM pregnant women was used. Studies that only showed association measurements (e.g. OR, log OR, ln-OR per-unit increment, RR per unit of increase of SD, terciles, quartiles and quintiles) were excluded from meta-analyses. Mean values and standard deviations were used when provided. If not provided, the median as a mean approximation was used, and SD was estimated using the IQR according to the formula:  $(SD = IQR/1.35)$ . The standardised mean difference was interpreted according to the following cut-off point: 'Small standardised mean difference: 0.2–0.5, medium 0.5–0.8 and large >0.8'.<sup>27</sup> A random-effects meta-analysis was conducted separately for each exposure according to POP type. Heterogeneity was assessed using the  $I^2$  test. Publication bias was evaluated using a funnel plot and Egger's lineal regression asymmetry tests. Significance was considered at a  $P$ -value <0.05. Analyses were conducted using STATA software version 14.0.

## 3 | RESULTS

### 3.1 | Literature search and study characteristic

From 161 identified studies, 78 duplicated records were removed, and 83 screened by title and abstract. Accordingly, 19 studies were selected for full-text screening after our initial search for studies, and 13 records met the selection criteria (Figure 1). One additional article was identified by hand searching references<sup>28</sup> and two records were added after the last update using alerts for the identification of new studies.<sup>23,24</sup> Excluded records are provided in Table S2.

Of the 16 articles finally included in our systematic review, 75% ( $n = 12$ ) were cohort studies, 18.75% ( $n = 3$ ) nested

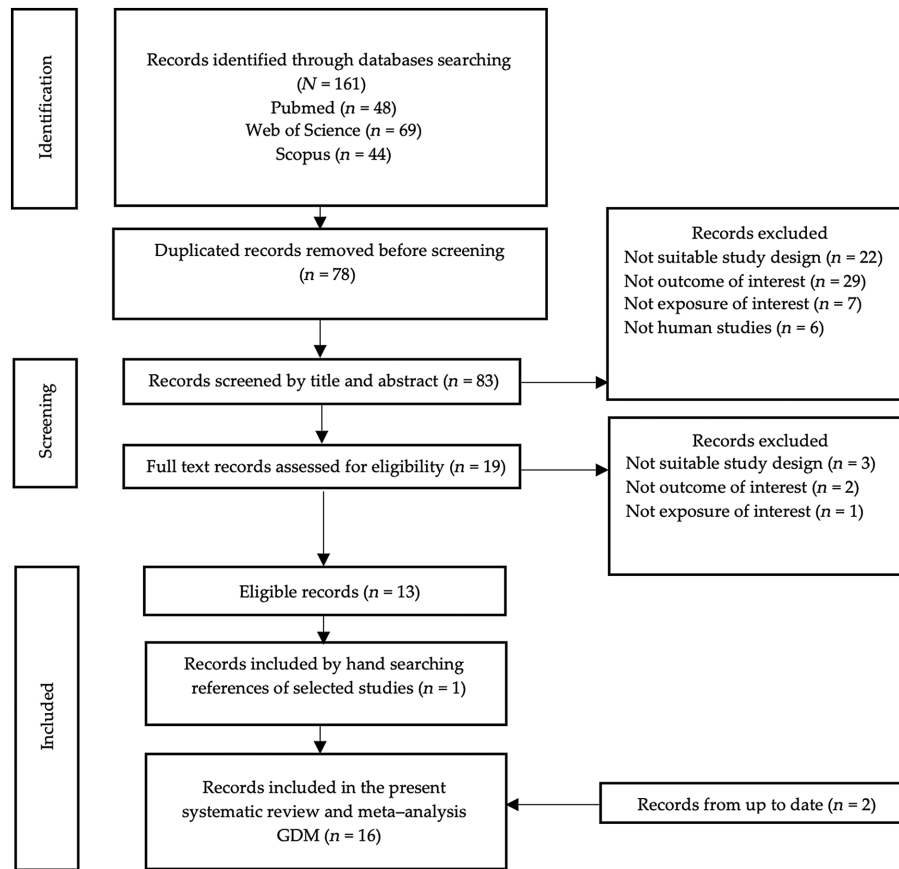


FIGURE 1 Flow chart diagram: study selection process.

case-control studies and 6.25% ( $n = 1$ ) a case-control study. Eight studies were conducted in China, five in the USA, and one each of the following countries: Spain, Greece and Canada. Four studies were derived from the Xicheng hospital cohort<sup>17,29–31</sup> and three from the Life cohort.<sup>28,32,33</sup> Total sample size ranged from 154 to 2747 pregnant women;<sup>34</sup> sample size median (IQR) of the cases and controls was 77 (53–135) and 258 (154–1161), respectively. In most of the studies included in the systematic review, women were aged  $\geq 18$  years, except for two studies which included women aged  $\geq 16$  years.<sup>35,36</sup>

Serum was used as a biological sample in most studies 68.75% ( $n = 11$ ),<sup>17,23,24,28–33,36,37</sup> plasma was used in 25% ( $n = 4$ )<sup>16,34,35,38</sup> and only one study also combined two types of biological sample (urine and plasma).<sup>39</sup> GDM was screened using the International Association of Diabetes and Pregnancy Study Groups criteria in eight studies<sup>17,23,24,29–31,34,37</sup> and the Carpenter–Coustan criteria in three studies.<sup>16,36,38</sup> The National Diabetes Data Group criteria were used only once.<sup>35</sup> One study screened GDM using two criteria: Canadian Diabetes Association and Society of Obstetricians and Gynaecologists of Canada.<sup>39</sup> GDM diagnosis was self-reported in the three studies from the Life cohort<sup>18,28,33</sup> (Table S3). In all studies, regression analysis was adjusted by at least maternal age and body mass index (BMI), except for Xicheng hospital cohort studies, where age was used for a paired matched design.<sup>17,29–31</sup> Exposure contrast

was provided in different scales, and some studies supply two different measures.<sup>31,35–37,40</sup> Three studies log-transformed the exposure level to estimate odds ratios,<sup>31,34,37</sup> two studies presented log<sub>10</sub>-unit change OR,<sup>35,36</sup> one study provided ln-unit change OR<sup>30</sup> and one study provided risk ratio per each unit of increase of SD.<sup>16</sup> Exposure levels were categorised as quartiles in five studies<sup>24,35,37–39</sup> and terciles in three.<sup>23,30,36</sup>

## 3.2 | Study quality assessment

Risk of bias was moderate in most of studies 68.75% ( $n = 11$ ), high in 25% ( $n = 4$ ) and low in one study. Weaknesses were related to limited reporting of study attrition details in 81.25% ( $n = 13$ ), exposure factor measurement in 31.25% ( $n = 5$ ), outcome measurement in 25% ( $n = 4$ ) and study confounding in 12% ( $n = 3$ ) (Appendix S2). A weighted Kappa was calculated of the six domains and agreement was substantial between raters (weighted Kappa = 0.75).

## 3.3 | Data synthesis

### 3.3.1 | PFAS exposure and GDM risk

Findings regarding 10 PFAS were reported in eight studies.<sup>16,23,24,28,30,34,35,37–39</sup> Results are summarised in

**Table S4.** The approaches to measure the exposure to PFAS were very variable and were reported as per unit of increase of SD, per unit of increase according to a log scale or categorised from the original data. The Liu et al.<sup>29</sup> study estimated the association between dioxin-like compounds using total toxic equivalent (TEQ); this was estimated only in this study. Their results showed a TEQ of 0.025 versus 0.015 ng/ml in cases and controls, respectively ( $P=0.020$ ).<sup>29</sup> For most PFAS, such as PFBS, PFDoA and PFHpA, the association was isolated and reported in a specific study with moderate risk of bias (Table S4).<sup>34,37</sup> Our meta-analysis based on continuous data shows a small mean difference on the PFHpA exposure between GDM cases and controls (SMD = 0.26, 95% CI 0.17–0.35,  $I^2=0.0\%$ ) and no considerable mean difference was observed for the rest of the PFAS (Figure 2).

### 3.3.2 | PCB exposure and GDM risk

Five studies<sup>16,17,32,36,39</sup> analysed the association between 16 PCBs and risk of GDM (Table S5). Only two studies with low and moderate risk of bias<sup>16,17</sup> reported a positive association between some PCBs, such as PCB18 and PCB101, and GDM (Table S5). Additionally, TEQs of PCB101 were 1.40 versus 0.99 pg/g in cases and controls respectively ( $P=0.005$ ).<sup>29</sup> Although Jaack et al.<sup>32</sup> stressed an inverse association between PCB (#138–153, 156, 167, 170, 180, 194) and GDM (Table S5), the risk of bias in their results was classified as high. The pooled standardised mean difference for three PCBs (PCB138, PCB153 and PCB180) was estimated. Our results show a small mean difference on the PCB180 exposure between GDM cases and controls (SMD = 0.37, 95% CI 0.19–0.56,  $I^2=25.3\%$ ). High heterogeneity was observed for PCB 138 and PCB 153 (Figure 3).

### 3.3.3 | PBDE exposure and GDM risk

Results related to seven PBDE were summarised from three studies (Table S6).<sup>16,31,33</sup> The association between PBDE and GDM was positive or negative, depending on the type of PBDE. Two studies, with moderate quality, describe a higher risk of GDM for BDE47, 54 and 183.<sup>29,31</sup> In contrast, our meta-analysis show a small mean difference for BDE47, BDE99 and BDE100 exposure between GDM cases and control: respectively 0.23, 95% CI 0.00–0.45,  $I^2=0\%$ ; 0.36, 95% CI 0.14–0.59,  $I^2=0\%$ ; and 0.42 (95% CI 0.19–0.64,  $I^2=0\%$ ) (Figure 3).

### 3.3.4 | OCP exposure and GDM risk

Findings related to three OCPs were reported in four studies (Table S7).<sup>16,33,36,39</sup> Meta-analysis results between HCB and GDM show a small mean difference on the standardised

mean difference between cases and controls (0.22, 95% CI 0.01–0.42,  $I^2=39.6\%$ ). No considerable difference was observed for p,p'DDE (Figure 4).

Publication bias results are reported in Appendix S3.

## 4 | DISCUSSION

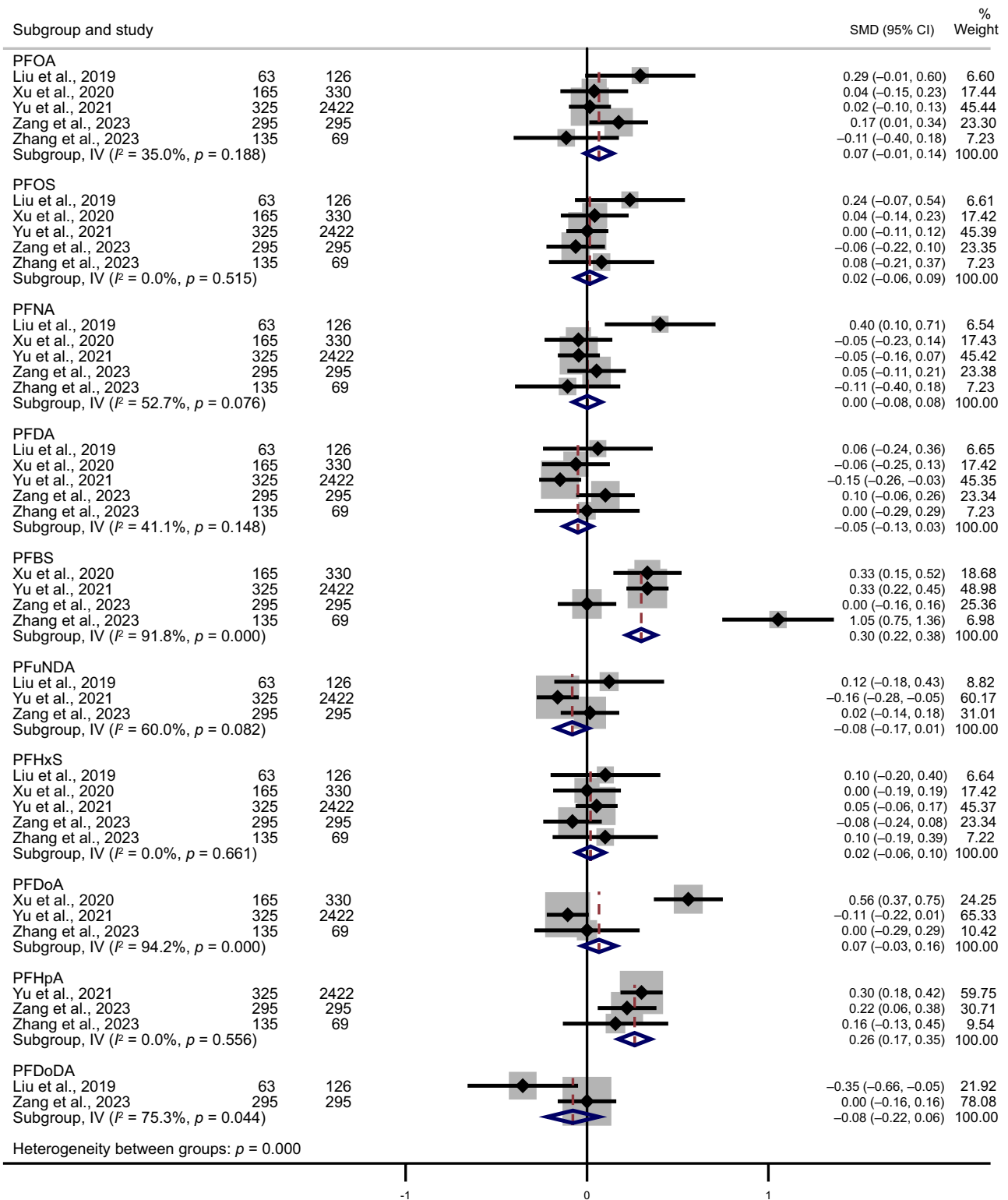
### 4.1 | Main findings

In this systematic review and meta-analysis, the pooled effect of the standardised mean difference between GDM cases and controls of 20 POPs was estimated. Generally, the associations found were for isolated POPs subtypes and were based on a small number of studies. Small mean differences were observed for PFHpA, PCB 180, BDE 47, BDE99, BDE100 and HCB. No considerable difference was observed for the rest of POPs.

### 4.2 | Strengths and limitations

Our systematic review and meta-analysis have several strengths. First, to our knowledge this is the first systematic review with meta-analysis including exclusively prospective studies assessing the association of several POPs and risk of GDM (prospective studies based on the measurement of the level of POPs exposure prior to the diagnosis of GDM). Secondly, we used a strengths algorithm for research that included the different possible names of included POPs. Moreover, only exposures measured in biospecimens were included. Thirdly, to reduce possible bias due to the design of studies and estimate a possible causal effect association between the exposure and the outcome, only prospective cohort and case–control studies where the exposure was measured at the beginning of or before pregnancy were included. However, we cannot be sure that no cases of gestational diabetes appeared at the beginning of pregnancy, even if diagnosed later. And finally, this systematic review was conducted according to the protocol previously registered in PROSPERO and was reported according to PRISMA recommendations.

Our findings may be limited by the quality of included studies and therefore should be interpreted with caution. Furthermore, owing to the limited data combinable for each exposure, we were unable to conduct a dose–response analysis, assess the sources of heterogeneity by subgroup analysis, or analyse the publication of bias. However, the risk of bias of each study was assessed by two authors independently using an adapted and strong instrument (QUIPS). Another limitation may be related to residual confounders. Information related to diet and physical activity, factors closely associated with GDM, and the possible effect of not measured contaminants, such as metals and non-organic pollutants, was missed in most studies.



**FIGURE 2** Pooled estimate of SMD with 95% CI of PFAS and gestational diabetes mellitus cases versus controls.

### 4.3 | Interpretation

POPs have been defined as endocrine disruptors; they affect glucose metabolism by reducing insulin secretion and disrupting glucose homeostasis,<sup>41,42</sup> and have been associated in

several studies with a high risk of diabetes mellitus type 2 and other metabolic diseases. On this basis, we hypothesised the existence of an association between POPs and GDM.<sup>10</sup>

The systematic review by Wang et al.<sup>43</sup> suggested a significant association between PFOA and GDM, while no

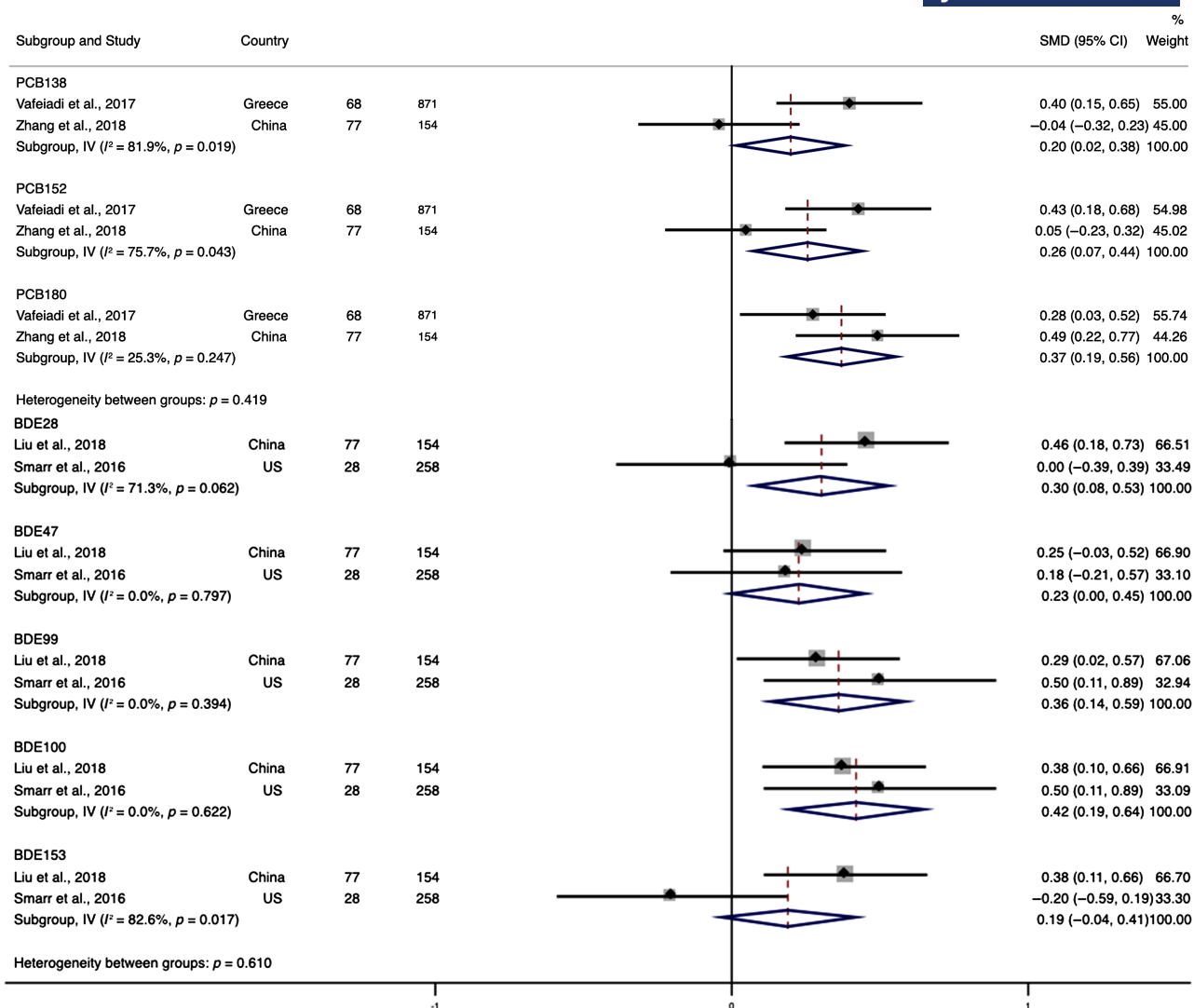


FIGURE 3 Pooled estimate of SMD with 95% CI of PCBs and PBDE with gestational diabetes mellitus cases versus controls.

OCPs

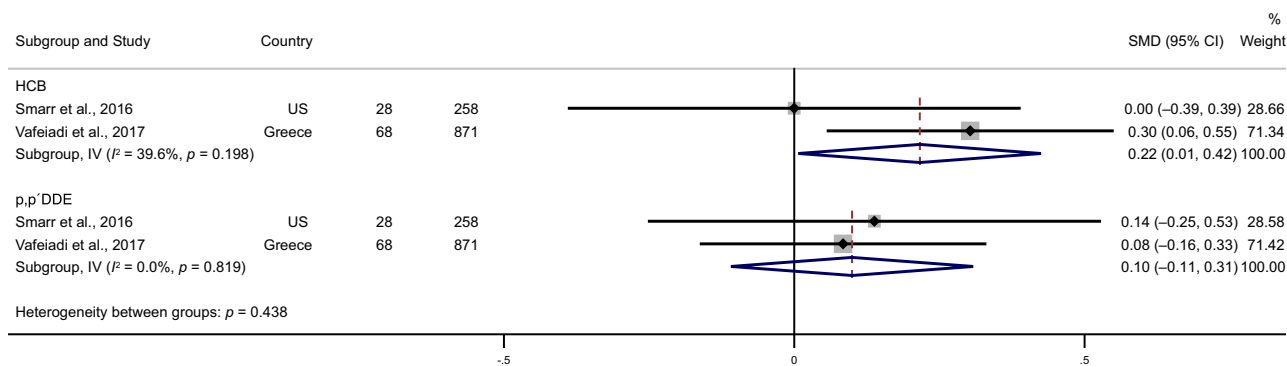


FIGURE 4 Pooled estimate of SMD with 95% CI of OCPs and gestational diabetes mellitus cases versus controls.

association was observed for the rest of PFAS. A recent systematic review found a significant association with GDM estimated for the sum of subgroups POPs; ΣPCB congeners, ΣPBDE compounds and ΣPFAS chemicals, and when most

of these exposures were analysed separately. Meanwhile, high heterogeneity was observed in all meta-analyses, including the sum for each POP categories, and in most meta-analyses analysing POPs separately.<sup>19</sup> Discrepancies between



systematic reviews can be explained by the differences in the way the individual studies were combined. These systematic reviews combined different scales of measurement of association in the same meta-analysis. Another factor influencing the results could be the selection criteria established in each systematic review.

Although several studies consider that the sum of POPs may increase the risk of GDM, interpreting these results is challenging, as the correlation between the different compounds is unclear, and different congeners can have opposite effects.<sup>17,30</sup> For example, when the association between a PFAS exposure and GDM was controlled by other PFAS, it appears that the PFOS, PFNA and PFHpA are the main contributors to this association.<sup>34</sup> This is why the results of the overall effect for  $\Sigma$ PFAS,  $\Sigma$ PCBs,  $\Sigma$ PBDE and  $\Sigma$ OCPs are not provided in our meta-analysis.

When exposure was measured after the occurrence of the outcome, the association was less clear. A cohort analysing placental samples of 86 participants showed a negative association between PCBs and PBDE and GDM.<sup>44</sup> A case-control study of 86 participants showed an inverse association between PCBs and PBDE with GDM.<sup>44</sup> Another case-control study of 140 participants, showed a positive association between Ln PCB 187, 118 and Ln PBDE99 with GDM, and an inverse association with Ln PCB28.<sup>45</sup> Results from Valvi et al., 2017 suggest a significant association between DDE and GDM, while the association with PCBs congeners and PFAS was not significant.<sup>46</sup> Several factors closely associated with GDM, such as gestational weight gain, diabetes mellitus and GDM history, may be responsible for these differences.

Our results suggest a possible association between some types of POPs and GDM. Data with better quality and homogeneity are required to carry out stronger reviews and more consistent and concise conclusions. In this systematic review, we join other authors in stressing the need for a standardised approach to studying and analysing POPs and the creation of a consortium with individual data.<sup>15,47</sup>

## 5 | CONCLUSION

This systematic review and meta-analysis of prospective studies provides a synthesis of the possible effect of POPs exposure in increasing the risk of GDM. There are insufficient data to analyse each exposure with more consistency and conduct a dose-response analysis. To confirm our results and draw stronger conclusions, further research is needed to ensure that the effects measured are due to a specific pollutant or the entire sub-category. In particular, a standardised method of studying POPs is required to make combining results more consistent.

### AUTHOR CONTRIBUTIONS

This work was conceptualised and supervised by J.J.J.-M., J.Z., R.O.-R. and M.K. The methodology was developed by J.J.J.-M., J.Z., M.K., M.A.C.-H., I.Y.-M. and R.O.-R. All

analyses and data curation were performed by M.K. and M.A.C.-H., and supervised by J.Z., J.J.J.-M., R.O.-R. and I.Y.-M. The interpretation of data was realised by all authors. The original draft was written by M.K. and J.J.J.-M. Critical review and editing of the article was provided by J.J.J.-M., M.K., J.Z., I.Y.-M., S.T., K.S.K., M.A.C.-H. and R.O.-R. All other authors provided final approval of this manuscript. K.S.K. is a distinguished investigator at the University of Granada funded by the Beatriz Galindo (senior modality) programme of the Spanish Ministry of Education.

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### CONFLICT OF INTEREST STATEMENT

None declared.

### DATA AVAILABILITY STATEMENT

All necessary data to replicate the analysis can be found in this article.

### ETHICS APPROVAL

This study involved only literature review of previously published studies and the contained data. It involved no primary research on human or animal subjects, or medical records. As such, this work was considered exempt from ethical review.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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