Persistent Organic Pollutant exposure as a risk factor of Gestational Diabetes Mellitus: A systematic review and meta-analysis.

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Abstract

Background: The findings of individual epidemiological studies that suggest an association between some Persistent Organic Pollutants (POPs) and Gestational Diabetes Mellitus (GDM) are inconclusive. **Objectives:** To estimate the strength of the association between POPs exposure and GDM in a systematic review with meta-analysis. **Search strategy:** MEDLINE, Scopus, and Web of Science were searched until 2022. **Selection criteria:** Cohort and case-control studies analyzing the association between POPs and GDM in healthy pregnant women. **Data collection and analysis:** Quality was assessed using QUIPS scale and standardized mean differences (SMD) and 95% confidence intervals (CI) was pooled using random-effect model. **Main results:** Fourteen articles including 11,422 participants were selected. The risk of bias of included studies was high in 4 (28.6%), moderate in 9 (64.3%) and low in 1 (7.14%). Only six POPs showed a significative SMD between GDM cases and controls: Perfluorobutanesulfonic acid (PFBS) 0.33 (95% CI 0.23, 0.43; I2=0%); Perfluorodecanoic acid (PFDA) -0.11 (95% CI -0.20, -0.01, I2 = 0.0%); 2,2',3,4,4',5,5'-Heptachlorobiphenyl (PCB 180) 0.37 (95% CI 0.19, 0.56; I2=25.3%); 2,2',4,4',5-Decabromodiphenyl ether (BDE 99) 0.36 (95% CI 0.14, 0.59; I2=0%); 2,2',4,4',6-Decabromodiphenyl ether (BDE 100) 0.42 (95% CI 0.19, 0.38; I2=0%); and, Hexachlorobenzene (HCB) 0.22 (95% CI 0.01, 0.42, I2=39.6%). For other POPs, no statistically significant association was observed. **Conclusion:** The available evidence is variable on quality and results were heterogeneous making impossible to establish a clear association between POPs exposure and risk of GDM. Improve the methodology of epidemiological studies assessing the association of POPs and risk of adverse clinical outcomes are needed.

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jjmoleon@ugr.es.[+]These authors contributed equally to this work.**Running title:** Persistent Organic Pollutant and Gestational Diabetes Mellitus. **Word account: 3210****ABSTRACTBackground:** The findings of individual epidemiological studies that suggest an association between some Persistent Organic Pollutants (POPs) and Gestational Diabetes Mellitus (GDM) are inconclusive.**Objectives:** To estimate the strength of the association between POPs exposure and GDM in a systematic review with meta-analysis.**Search strategy:** MEDLINE, Scopus, and Web of Science were searched until 2022.**Selection criteria:** Cohort and case-control studies analyzing the association between POPs and GDM in healthy pregnant women.**Data collection and analysis:** Quality was assessed using QUIPS scale and standardized mean differences (SMD) and 95% confidence intervals (CI) was pooled using random-effect model.**Main results:** Fourteen articles including 11,422 participants were selected. The risk of bias of included studies was high in 4 (28.6%), moderate in 9 (64.3%) and low in 1 (7.14%). Only six POPs showed a significative SMD between GDM cases and controls: Perfluorobutanesulfonic acid (PFBS) 0.33 (95% CI 0.23, 0.43; I2=0%); Perfluorodecanoic acid (PFDA) -0.11 (95% CI -0.20, -0.01, I2 = 0.0%); 2,2',3,4,4',5,5'-Heptachlorobiphenyl (PCB 180) 0.37 (95% CI 0.19, 0.56; I2=25.3%); 2,2',4,4',5-Decabromodiphenyl ether (BDE 99) 0.36 (95% CI 0.14, 0.59; I2=0%); 2,2',4,4',6-Decabromodiphenyl ether (BDE 100) 0.42 (95% CI 0.19, 0.38; I2=0%); and, Hexachlorobenzene (HCB) 0.22 (95% CI 0.01, 0.42, I2=39.6%). For other POPs, no statistically significant association was observed.**Conclusion:** The available evidence is variable on quality and results were heterogeneous making impossible to establish a clear association between POPs exposure and risk of GDM. Improve the methodology of epidemiological studies assessing the association of POPs and risk of adverse clinical outcomes are needed.**Funding:**This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.**Keywords:** persistent organic pollutants, exposure, risk factor, gestational diabetes mellitus, systematic review, meta-analysis. Introduction Persistent Organic Pollutants (POPs), such as Organochlorine Pesticides (OCPs) and Polychlorinated Biphenyls (PCBs), are highly lipophilic compounds and peculiarly persistent and resistant to biodegradation. Due to their long half-life, POPs have the ability to bioaccumulate in the environment, food, and organisms. The principal pathway for human exposure is through dietary intake. However, occupational exposure and indoor inhalation can also be alternative pathways. Chronic exposure to POPs can be related to ill health, even in low doses. In adults, high specimen POPs level was associated with a high risk of carcinogenic, neurological, endocrine, and metabolic conditions. Several POPs, such as hexachlorobenzene (HCB), dichlorodiphenyl-dichloroethylene (p,p'-DDE), and PCBs have been described as potential risk factors for diabetes mellitus type 2. During pregnancy, POPs exposure increases the risk of several outcomes such as miscarriage, preterm birth, and low birth weight. However, findings related to Gestational Diabetes Mellitus (GDM) tend to show more discrepancies. Zhang et al describe a positive association between PCB 52 and GDM, and no association for PCB 138, 153 and 180. However, Jaack et al cohort study show a negative association between PCB 138, 153 and 180 with GDM. Regarding PFAS, Yan et al systematic review support that PFAS increase the risk for GDM, while no association was affirmed by Gao et al. 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. Our search for systematic reviews including prospective studies found only one that was restricted to DDTs, and no relationship was found between exposure and GDM. Other POPs were not explored in this review. Therefore, we aimed to comprehensively explore the association between POPs and GDM using a systematic review with meta-analysis of cohort and case-control studies. Methods This systematic review and meta-analysis protocol was previously registered in PROSPERO (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. Ethical approval was not required due to the study design. Eligibility criteria Eligibility criteria was defined a priori according to the PECOS statement (P: population, E: exposure, C: comparators, O: outcome and S: study design). More information about these criteria is shown in Table S1. The selection criteria were: (1) Cohort, case-control studies, and hybrid studies (nested case-control studies and case-cohort studies); (2) Based on women of childbearing age; (3) Analyzing the relationship between the individual contamination levels of

POPs and the incidence of GDM; (4) Published from the inception of the database used for the search until June 2022. All cross-sectional studies, book chapters, and conference communications were excluded. Information source and research strategy A systematic search was conducted in the major biomedical databases: MEDLINE, Scopus, and Web of Science. MeSH terms and/or free keywords were combined according to the used source. The following MeSH terms were used for the research: 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 S2). 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 doubt in the selection of studies was resolved through discussion with senior reviewers (JJJM and JZ). Data extraction and quality assessment Selected articles were reviewed by MK and MACH independently. From each article the following information was extracted in a standardized form: 1) Basic data: authors, publication year, study period, country, and research funding. 2) Study characteristics: type of study design, sample method, sample size, selection criteria, characteristics of the participants, and compliance with ethical principles. 3) 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. 4) Outcome data: The criteria used for the diagnosis of GDM were collected (National Diabetes Data Group criteria, Carpenter-Coustan criteria, International Association of Diabetes and Pregnancy Study Groups criteria, and World Health Organization criteria). 5) 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 as association measures. Confusion factors used for adjustment analyses were also collected. The authors have been contacted by e-mail in 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). The following describe the six domains with their respective issues to consider for judging the risk of bias in QUIPS: 1) Study participation: factors such as the source of target population, method/s used to identify the population, recruitment period, inclusion and exclusion criteria, adequate study participation, and baseline characteristics were evaluated. 2) Study attribution related to strategies to avoid losses. For example, the number of attempts to collect information on participants who dropped out, 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. 3) Information about prognostic factors was collected. 4) Outcome measurement collection: definition of the outcome (gestational diabetes or not), valid and reliable measurement of outcome, method and setting of outcome measurement. 5) Collection of confounding factors and their characteristics, such as definition used for the confounding factor, methods and setting of confounding measurement, validity and reliability of the measurements, methods used for working with missing data, and appropriate strategies to avoid or eliminate the effect of confounding factors. 6) Finally, information about statistical analysis and reporting, including the presentation of the analytical strategy, models of development strategy, and reporting of results. In addition to the guidelines provided by QUIPS scale, to judge the risk of bias in each item, supplementary comments were developed to facilitate the consensus. Studies were classified as follow: a) Low risk of bias. Requires at least five domains judged as low risk of bias and none classified as high risk of bias; b) Moderate risk of bias for those cases with: i) five items classified as low risk of bias and one item judged as high risk of bias, or ii) two items evaluated as moderate risk of bias; c) High risk of bias for those cases with [?] 2 items judged as high risk of bias or [?] 3 items evaluated as moderate risk of bias. Weighted kappa coefficient (Kw) for the six domains was measured to assess inter-rater reliability. Disagreement and doubt were solved through discussion with senior reviewers (JJJM and JZ). 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 was 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 (i.e. OR, logOR, 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 (SD) was used when provided. If not provided the median as a mean approximation was used, and standard deviation (SD) was estimated using the Interquartile Range (IQR) according to the formula: (SD = IQR/1.35). A random-effects meta-analysis was conducted separately for each exposure according to POP types. Heterogeneity was assessed using the I^2test. Publication bias was evaluated using a funnel plot and Egger's lineal regression asymmetry tests. Significance was considered at$p\ value < 0.05$. Analyses were conducted using STATA software version 14.0. Results 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, and 13 records met the selection criteria (Figure 1). One additional article was identified by hand searching references. Excluded records are reported in Table S2. Of the 14 articles finally included in our systematic review, 64.3% (n=9) were cohort studies, and 35.7% (n=5) were nested case-control studies. Six studies were conducted in China, five in the United States, and one for each of the following countries: Spain, Greece, and Canada. Four studies were derived from the Xicheng hospital cohort and three from the Life cohort. Total sample size ranged from 154 to 2747 pregnant women, cases and controls sample size median (IQR) were 68 (53-77) and 230 (154-871), respectively. Most of the studies included in the systematic review collected women aged [?] 18 years, except two studies included women aged [?] 16 years. Serum was used as a biological sample in most studies 64.29% (n=9), plasma in 28.57% (n=4), and only one study also combined two types of biological sample (urine and plasma). GDM was screened using International Association of Diabetes and Pregnancy Study Groups criteria in five studies. Each of the following criteria; American College of Obstetrics and Gynecologists, National Diabetes Data Group, Carpenter and Coustan was used only one time. One study screened GDM using two criteria; Canadian Diabetes Association and Society of Obstetricians and Gynecologists of Canada. Whereas, GDM diagnostic was self-reported in the three studies from Life cohort (Table 3). In all studies, regression analysis was used to adjust for maternal age and Body Mass Index (BMI), at least, except for Xicheng hospital cohort studies where age was used for a paired matched design. Exposure contrast was provided in different scales, and some studies supply two different measures. Three studies log-transformed the exposure level to estimate odds ratios, Two studies presented $\log_{10}$-unit change OR, one study provided ln-unit change OR and one study provided risk ratio per each unit of increase of SD. Exposure levels were categorized as quartiles in four studies, terciles in two. Study quality assessment Risk of bias related to study participation, study attrition, exposure measurement, outcomes measurement, study confounding, and statistical analysis reporting was assessed using QUIPS scale. Most studies 64.3% (n=9) had a moderate risk of bias, 28.6% (n=4) a high risk of bias, and only one study a low risk of bias. Weaknesses were related to limited reporting of study attrition details in 78.6% (n=11), exposure factor measurement in 35.7% (n=5), outcome measurement in 28.6% (n=4), and study confounding in 21.4% (n=3) (Figure S1). A weighted Kappa was calculated of the six domains and agreement was substantial between raters (Weighted Kappa=0.75). Data synthesis Results were summarized for ten PFAS, sixteen PCBs, seven PBDE, and three OCPs (Table 3-6).*PFAS exposure and GDM risk*Findings regarding 10 PFAS were reported in eight studies. Results are summarized 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 categorized from the original data. The concentration of PFAS seems to be higher in women with gestational diabetes as compared to control group. Total Toxic Equivalents (TEQ) were 0.025 vs. 0.015 ng/ml in cases and controls respectively (P = 0.020). However, for most PFAS, such as PFBS, PFDoA, and PFHpA, the association was isolated and reported in a specific studies with moderate risk of bias (Table S4). The exposure analysed more frequently was PFHpA. However, the results were very heterogeneous to estimate a pooled effect. Our meta-analysis based on continuous data show an association between PFBS and GDM with standardized mean difference between cases and controls of 0.33 (95% CI 0.23 to 0.43, $I^2 = 0.0\%$). On the other hand, a possible inverse association was observed for PFDA with GDM, standardized mean difference between cases and controls was -0.11 (95%

CI -0.20 to -0.01, I^2 = 0.0%).*PCBs exposure and GDM risk* Five studies analyzed the association between 16 PCBs and risk of GDM (Table S5). Only two studies with low and moderate risk of bias reported a positive association between some PCBs, such as PCB18 and PCB101, and GDM (Table S5). Additionally, Total Toxic Equivalents TEQ of PCB101 were 1.40 vs. 0.99 pg/g in cases and controls respectively P=0.005. Although Jaack et al. results stressed an inverse association between PCB (#138-153, 156, 167, 170, 180, 194) and GDM (Table S5), the risk of bias was classified as high. The pooled standardized mean difference for three PCBs (PCB138, PCB153 and PCB180) was estimated. Our results showed a significant association between PCB180 and GDM with a standardized mean difference between cases and controls of 0.37 (95% CI 0.19 to 0.56, I^2=25.3%). PCB 138 and PCB 153 meta-analysis show a high heterogeneity (Figure 3).*PBDE exposure and GDM risk*Results related to seven PBDE were summarized from three studies (Table S6). 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. On the other hand, our meta-analysis showed a possible association between BDE99 and BDE100 and GDM (Figure 3).*OCPs exposure and GDM risk*Findings related to three OCPs were reported in four studies (Table S7). Meta-analysis results between HCB and GDM show a standardized mean difference of 0.22 (95% CI 0.01 to 0.42, I^2=39.6%) between cases and controls. p,p'DDE show a standardized mean difference of 0.10 (95% CI -0.11 to 0.31, I^2 = 0.0%) between GDM cases and controls (Figure 4). Unfortunately, we could not assess publication bias because the low number of studies included in each meta-analysis. Discussion*Main findings*This systematic review summarizes findings about the exposure to 36 POPs and risk of GDM. We included 16 POPs in the meta-analysis, however only 6 show an association with GDM (PFDA, PFBS, PCB180, BDE99, BDE100 and HCB). The direction of the association varied, PFDA compound seems decreasing this risk of GDM, while PFBS, PCB 180, BDE99, BDE100, HCB increasing the risk of GDM. Generally, the associations founded were sporadic and concerned individual studies or specific pollutants. Unfortunately, available information about POPs and the way in which are analyzed do not allow for more insightful analyses.*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. Second, a strengths algorithm for research that included the different possible nominations of included POPs was used. Moreover, only exposures measured in biospecimens were included. Third, 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-controls studies where the exposure was measured at the beginning of pregnancy was 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 finding can be limited by the quality relatively low 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, subgroups analysis, or publication of bias assessment. However, the risk of bias of each study was assessed using an adapted and strong instrument (QUIPS) by two authors independently. Another limitation can 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.*Interpretation*The systematic review by Wang et al. suggested a significant association between PFOA and GDM, while no 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; [?]PCBs congeners, [?]PBDEs compounds, [?]PFASs chemicals, and also when most of these exposures were analyzed separately. Meanwhile, high heterogeneity was observed in all meta-analyses, including the sum for each POPs categories, and in most meta-analyses analyzing POPs separately. 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.

For example, when association between a PFAS exposure and GDM was controlled by the others PFAS, it appears the PFOS, PFNA and PFHpA are the main contributors to this association. This is the reason why results of the overall effect for [?]PFAS, [?]PCBs, [?]PBDE, [?]OCPs were not provided in our meta-analysis. When exposure was measured after the occurrence of the outcome, the association was less clear. A cohort analyzing placental samples of 86 participants showed an negative association between PCBs and PBDE and GDM. A case-control study of 140 participants, whose serum samples were collected in the third semester of pregnancy, showed a positive association between Ln PCB 187, 118 and Ln PBDE99, 28 and GDM; the association with Ln PCB28 was negative. Findings from another retrospective study showed a significative association between DDE and GDM, while the association with PCBs congeners and PFAS was not significant. 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 a requires a standardized method to create a consortium with individual data to be able for adjustment and establish a standardized approach to studying and analyzing POPs. 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. Therefore, there are insufficient data to analyze each exposure with more consistency and conduct a dose-response analysis. Ensure that the effect is due to a specific pollutant or the entire sub-category, confirm our results and draw stronger conclusions requires a standardized method of studying POPs to make combining results more consistent. Author contributions This work was conceptualized 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 realized by all authors. The original manuscript draft was written by M.K. and J.J.J.M. Critical review and editing of the manuscript 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) program of the Spanish Ministry of Education. Acknowledgments The results of this study are part of the doctoral thesis of Malak Kouiti.**Funding information**This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. Conflict of interest The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. 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.

References

Table/Figure Caption List Figure 1. Flow chart diagram: Study selection process. Figure 2. Pooled estimate of SMD with 95% CI of PFAS and gestational diabetes mellitus cases versus controls Figure 3. Pooled estimate of SMD with 95% CI of PCBs and PBDE with gestational diabetes mellitus cases versus controls. Figure 4. Pooled estimate of SMD with 95% CI of OCPs and gestational diabetes mellitus cases versus controls.

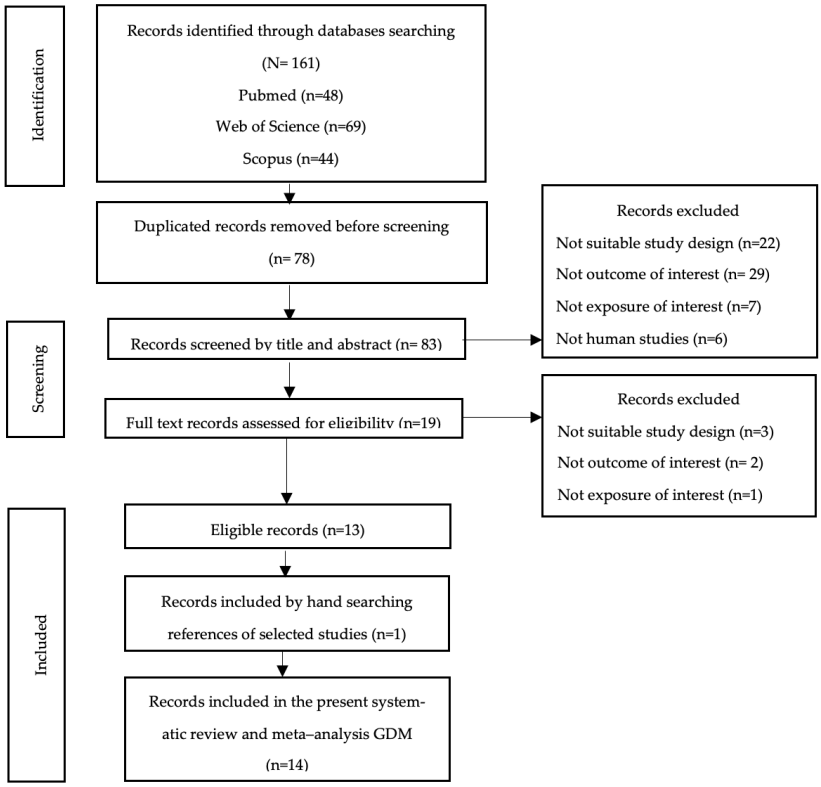
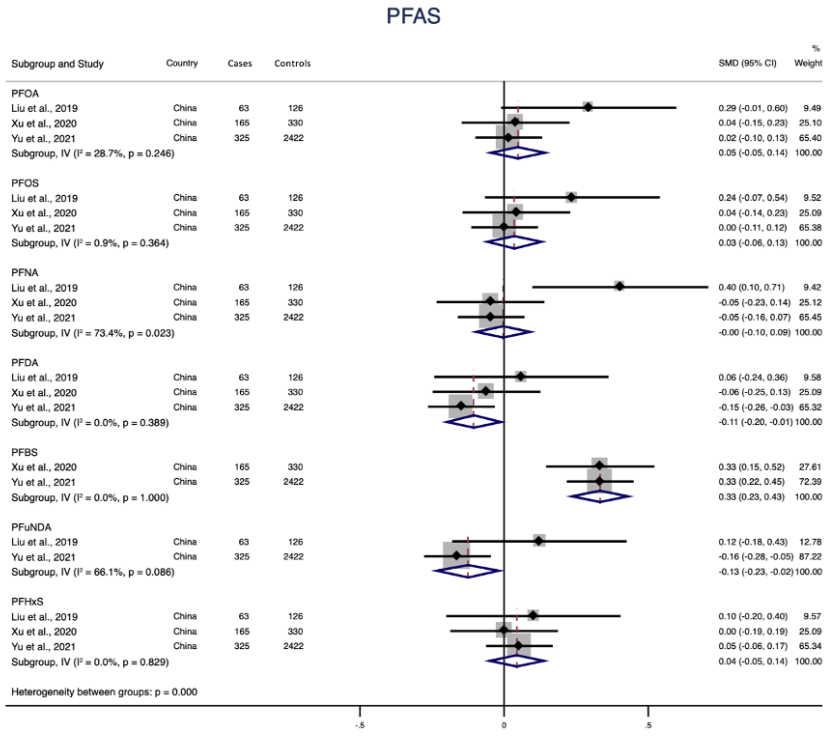
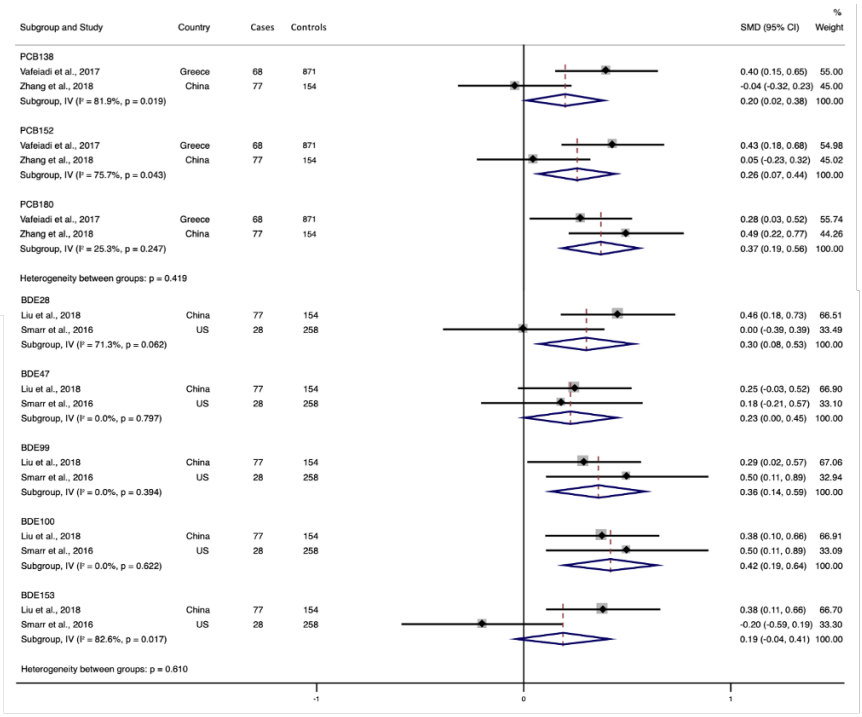
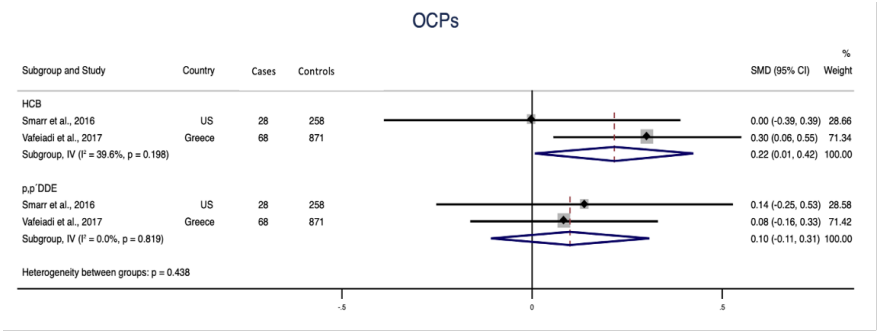


Figure 1. Flow chart diagram: Study selection process.







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