Review Article

Maternal Serum Concentrations of Per- and Polyfluoroalkyl Substances and Gestational Weight Gain: A Systematic Review and Meta-analysis

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Abstract

Background: Humans are exposed everywhere to per- and polyfluoroalkyl substances (PFASs) through water, food, and air. PFASs can alter cellular signals involved in weight homeostasis, particularly those related to peroxisome proliferator-activated receptors involved in abiogenesis. Some studies have shown a positive correlation between PFASs and gestational weight gain (GWG), but others have found no correlation. Therefore, the association between PFASs and weight gain in pregnancy was reviewed and meta-analyzed. **Methods:** This meta-analysis was approved by the PROSPERO team (CRD42023466602) and presented with a prospective protocol in accordance with the PRISMA guidelines. Google Scholar and databases such as the Cochrane Library, Web of Science, Scopus, Medline, Science Direct, and ProQuest were searched for English language findings from October 2023 to March 2024. **Results:** According to pooled regression coefficients, no significant relationship was observed between GWG values and the levels of all four PFASs, including perfluorooctanoic acid (PFOA) (β =0.01 [95% CI = -0.38, -0.36] I^2 = 71.75%, P = 0.03), perfluorooctane sulfonic acid (PFOS) (β = -0.18 [95% CI = -0.55, -0.19] I^2 = 36.65%, P = 0.21), perfluorononanoic acid (PFNA) (β =0.07 [95% CI = -0.27, -0.41] I^2 = 0.0%, P = 0.74), and perfluorohexane-1-sulphonic acid (PFHxS), (β = -0.10 [95% CI = -0.34, -14] I^2 = 18.54%, P = 0.293). The results of subgroup analysis based on pre-pregnancy body mass index (BMI) ≤25 showed only a significant relationship between PFNA plasma level and GWG (β =0.03 [95% CI =0.00, -0.05] I^2 = 64.96%, P = 0.04). The findings from the subgroup analysis, which was conducted based on a pre-pregnancy body BMI of ≤25, revealed a significant correlation solely between PFNA plasma levels and GWG (β =0.03 [95% CI =0.00, -0.05] I2 = 64.96%, P = 0.04). **Conclusions:** Consequently, according to the estimated general regression coefficient, a doubling of the blood PFNA level is associated with an increase in the average GWG by 30 grams. In women with pre-pregnancy BMI >25 kg, no significant relationship between different levels of exposure and GWG was observed. No significant association was observed between major PFASs and weight gain during pregnancy, which may be because the exposure period (gestational length) was not sufficient. Especially as most of the influencing factors were adjusted in majority of the studies included in the meta-analysis. However, further cohort studies with larger sample sizes are needed.

Keywords: *Gestational weight gain, perfluorohexanesulfonic acid, perfluorooctane sulfonic acid, perfluorononanoic acid, perfluorooctanoic acid*

Introduction

Per- and polyfluoroalkyl substances (PFASs) are a group of chemicals that have been used to prepare fluoropolymer coatings and products that resist heat, oil, stains, grease, and water. Humans are exposed to these substances through water, food, and air inside the house and everywhere.[1] PFASs are harmful to human and animal health. For example, studies have shown that branched-chain perfluorooctane sulfonic acid (PFOS) accumulates more in humans, while perfluorooctanoic acid (PFOA) and PFOS accumulate more in animals owing to their greater binding strength to serum albumin.[2] Researchers have investigated the potential health effects of these substances, including the possibility of disrupting the endocrine and metabolic systems. During pregnancy, exposure to PFASs may also affect the health of the mother and fetus in the short or long term due to its effects on the endocrine glands and other systems.[3] In this context, determining weight gain during pregnancy is very important. In this context, determining weight gain during pregnancy is of great significance. The weight that falls below or exceeds the range established

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by the Institute of Medicine (IOM) in the United States can lead to complications and issues for both the mother and the child.[4] Considering that the aim is to investigate the relationship between PFASs and weight gain, some studies have shown a positive correlation between PFASs and GWG.[5] Indeed, PFASs can disrupt endocrine system signaling,[6] alter adipocyte profiles,[7] and affect adipocyte gene expression.[8] Furthermore, PFASs have the potential to alter cellular signaling pathways that are crucial for maintaining weight homeostasis, especially those associated with peroxisome proliferator-activated receptors that play a role in abiogenesis.[9] Nevertheless, other studies have failed to establish a connection,[10] and body mass index (BMI) significantly affects the correlation between weight gain during pregnancy and exposure to chemicals.[11,12] This discrepancy is also observed in non-pregnant populations when examining the relationship between exposure to POPs and obesity.[13] Therefore, we decided to systematically review and meta-analyze the association between PFASs and GWG.

Materials and Methods

Search strategy

This meta-analysis was approved by the PROSPERO team (CRD42023466602) and presented with a prospective protocol in accordance with the PRISMA[1] guidelines and PECO[2]. We searched Google Scholar and the Cochrane Library, Web of Science, Scopus, Medline, Science Direct, and ProQuest databases using the following search lines in titles, abstracts, or keywords:

For Medline, also Google scholar, the search line was [("gestational weight gain" OR "GWG" OR "excessive gestational weight gain" OR "EGWG" OR "maternal obesity" OR "maternal overweight" OR "postpartum Weight Retention")] AND [("PFAS" OR "Per- and Polyfluoroalkyl Substances" OR "Per and Polyfluoroalkyl Substances" OR "Fluorocarbon" OR "Perfluorinated Chemicals, PFC" OR "Polyfluorocarbons" OR "Fluorocarbon Emulsions" OR "Fluorocarbons, Telomer" OR "Perfluoropolyether Carboxylic Acids" OR "N-Alkyl Perfluoroalkyl Sulfonamido Carboxylates" OR "Ether Carboxylates, Perfluoroalkyl" OR "Fluorotelomer Phosphate Esters" OR "Phosphate Esters, Fluorotelomer" OR "Polyether Carboxylates, Perfluoroalkyl" OR "Perfluoroalkane Sulfonamides" OR "Alcohols, Fluorinated Telomer" OR "PFECAs Perfluoropolyether Carboxylic Acids" OR "Perfluoroalkane Sulfonamides")].

For Science direct and Scopus, we used this search line: [("gestational weight gain" OR "GWG" OR "maternal obesity" OR "maternal overweight" OR "postpartum Weight Retention")] AND [("PFAS" OR "Per- and Polyfluoroalkyl Substances")].

We searched for cohort, cross-sectional, case-control, and possibly meta-analyses that examined the relationship between PFASs and GWG. Then, we checked the references of selected articles and relevant meta-analyses to make the search more comprehensive. In the next step, the obtained articles were reviewed to determine whether they included the desired variables. We did not review animal studies. The mentioned procedures were performed by one of the authors and confirmed by the other. Endnote software [20.2.19 (Bld 15749)] was used to perform the search process.

Ethical considerations

Ethical Committee of Research and Technology Vice-Chancellor of Isfahan University of Medical Sciences has issued the code of ethics for this project (IR.ARI.MUI.REC.1402.322).

Review question

PECO criteria were used to focus on the research question(s) and the inclusion/exclusion criteria in the present meta-analysis. Pregnant women with a live fetus were included in this study if they had been referred in the first or second trimester, gave birth at or after 37 weeks, were 18 years of age or older, and chosen to continue their prenatal care and delivery in the study settings. Exclusion criteria were the lack of measured serum PFAS levels, pregnancy-related hypertension, type 1 or 2 diabetes before pregnancy, endocrine disorders, epilepsy, history of HIV infection, and exposure to radiotherapy or chemotherapy. The comparison was to evaluate the desired outcomes at varying concentrations of PFASs (for instance, the lowest levels in contrast to the highest levels). Exposure included serum levels of PFASs determined primarily using online solid phase coupled to high performance liquid chromatography isotope dilution tandem mass spectrometry. The outcomes (of interest) were mean GWG or percent weight gained according to the IOM classification. GWG is the sum of the weights obtained, which are recorded at different prenatal visits. In certain studies, total GWG was categorized according to the percentage of subjects falling within the normal range, as well as those below or exceeding the Institute of Medicine (IOM) limit.[14]

Inclusion criteria

Observational studies that assessed the association of PFASs with GWG and/or categorized GWG in healthy pregnant women. Animal studies were excluded.

Study selection

Data extraction: The first author name, publication year, country, study design, name of the study, study period, sample size, age, race, pre-pregnancy BMI, gestational

1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)

2 Population, Exposure, comparator, outcomes.

age at PFASs measurement (wks)], measured PFASs, exposure scale, outcome [GWG (kg), categorized GWG], results, adjusted factors [age, pre-pregnancy BMI, marital status, education, race/ethnicity, prenatal smoking, parity, household income, alcohol use during pregnancy, log10 serum cotinine levels in pregnancy, gestational age at delivery, gestational age at sampling], prenatal smoking, parity were extracted by first author (M G-KH), and confirmed by the other author (A H) [Table 1]

Quality assessment: The National Institutes of Health (NIH) quality assessment tool for Cohort and Cross-Sectional studies and NIH quality assessment tool for case-control study were used to inspect the study quality and risk of bias of selected studies [Table 2].

Statistical analysis

The desired effect size was considered a regression coefficient with a 95% confidence interval (β, 95% CI). It should be noted that owing to the linear correlation between logarithmic transformations and the linear relationship between pounds and kilograms, the necessary linear transformations were performed so that each regression coefficient shows the average changes of GWG (in kilograms) per doubling of the desired PFAS level. The fixed effect model with the inverse variance method was used to estimate the overall effect and 95% confidence interval of each of the 4 measured PFASs (PFOA, PFOS, PFNA, PFHxS) on GWG. Cochran's Q and inconsistency index (I^2) were used to check the heterogeneity of the included articles. Considering the proposed association between pre-pregnancy BMI index and maternal GWG, subgroup analyses were also performed in two groups (BMI ≤ 25 and BMI >25) to identify any relationship between blood serum PFAS levels and GWG considering pre-pregnancy BMI. In addition, the effect of each study on pooled β was assessed using sensitivity analysis. Begg's funnel plots and Begg's and Egger's tests were performed to investigate publication bias. A P value < 0.05 from both tests indicated significant publication bias. All analyses were performed in Stata version 17.

Results

Study selection process

Among the 786 included studies, 250 were excluded owing to duplication; 356 were removed after reviewing the titles and abstracts of the articles. In the next step, the full text of the screened articles was studied, and 175 articles were excluded owing to insufficient information and inclusion criteria. Finally, five studies (six hypotheses) were selected for systematic review and meta-analyses.

Description of included trials

Mitro *et al*.[5] studied 1614 pregnant women in the Project Viva cohort and investigated the associations between PFOS, PFOA, PFHxS, EtFOSAA, and MeFOSAA and GWG. For each doubling of EtFOSAA, women gained 0.37 kg (95%CI: 0.11, 0.62). Romano *et al*.[10] in the HOME cohort measured PFOA, PFOS, PFHxS, and PFNA in 277 pregnant women. They observed that for a doubling of PFOA, PFOS, and PFNA, there was a slight increase in GWG and GWG rate. The relationship between weight gain and PFNA was greater in women with BMI ≥25 than in women with BMI <25. Ashley-Martin *et al*.[11] determined the association between plasma levels of PFOA, PFOS, and PFHxS and GWG in 1723 participants in the MIREC study. They concluded that PFOS levels were positively associated with GWG (b = 0.39, 95% CI: 0.02, 0.75) among women with BMI ≤ 25. No statistically significant association was observed between GWG and PFHxS. Marks *et al*.[12] analyzed associations between PFOS, PFOA, and PFHxS and GWG in 905 women (448 mothers of daughters and 457 mothers of sons) in a subsample of the ALSPAC study. They reported no significant association, except for a weak association between PFNA and GWG, and a slight inverse association between PFOS and GWG among under-/normal weight women. Kinkade *et al*.[15] enrolled 243 women in UPSIDE MOMS study and examined the serum levels of PFOS, PFOA, PFNA, PFHxS, and PFDA in relation to GWG. They reported that PFHxS (ß = - 1.59 kg, 95% CI: -3.39, 0.21) and PFOA (ß = - 1.54 kg, 95% CI: -2.79, -0.30), were inversely associated with total GWG.

Quality of the included studies

Study quality and risk of bias were evaluated by the NIH quality assessment tool for cohort studies. Such a way that first author (A H) assessed the quality, and the corresponding author (M G-KH) confirmed it [Table 2]. The absence of the desired item in the study was indicated as "not written" (NR) or "not available" (NA). The quality of cohort studies was evaluated using a scoring system where a score of 0–4 is classified as poor, a score of 5–10 is deemed favorable, and a score of 11–14 is considered good. This scoring system is grounded in methodological characteristics. Most of the tool items were considered in the selected studies, and four hypotheses received a good score. Participation rate and blinding of the outcome assessor to the exposure status of the participants were not mentioned in all the studies. Additionally, the sample size formula and its components were not mentioned in most of the studies.

Meta-analysis results

A forest plot for the relationship between serum levels of PFASs and GWG among pregnant women is shown in Figure 1. Pooled regression coefficients showed no significant relationship between GWG values and the levels of all four PFASs including PFOA (β =.01 [95% CI = -0.38, -0.36] I^2 = 71.75%, P = 0.03), PFOS (β = - 0.18 [95% CI = -0.55, -0.19] I^2 = 36.65%, P = 0.21), PFNA (β =0.07 [95% CI = -0.27, -0.41] I^2 = 0.0%,

Table 1: Participants' characteristics

Author name, publication year, country	Study design	Sample size	Age (years)	Race	Pre-pregnancy BMI (kg/m²)	Gestational age at PFAS measurement (wks)	Measured PFASs	Exposure scale	Outcome		Results	Adjusted factors	Prenatal smoking	Parity
									GWG (kg)	Categorized GWG				
Marks KJ,2019[12] (Mothers of daughters), Great Britain	Prospective birth cohort	448	<25 92 (20.7) 25–29 164 (36.9) ≥30 189 (42.5)	Predominantly white (98.7%)	<18.5 43 (10.7) 18.5–24.99 268 (66.8) 29.99-25 63 (15.7) ≥30 27 (6.7)	At median 18 weeks gestation (interquartile range (IQR: 11, 32).	PFOA, PFOS, PFHxS, PFNA	log-transformed		Below 120 (31.7) Within 141 (37.2) Above 118 (31.3)	Not significant (Ten percent greater PFOS was related with−0.03 kg of GWG in under/ normal weight participants. Ten percent higher PFNA was correlated with a greater GWG of 0.09 kg in under/normal pre-pregnancy BMI)	Maternal education, prenatal smoking, maternal age at delivery, parity, pre-pregnancy BMI, gestational age at delivery, and gestational age at sample	Any 79 (18.5) None 348 (81.5)	Nulliparous 208 (49.6) Parous 211 (50.4)
Marks KJ, 2019[12] (Mothers of sons), Great Britain	Prospective birth cohort	457	<25 54 (11.9) 25–29 188 (41.5) ≥30 211 (46.6)	Predominantly white (98.7%)	<18.5 46 (11.1) 18.5–24.99 282 (68.3) 25–29.99 63 (15.3) ≥30 22 (5.3)	At median 18 weeks gestation (interquartile range (IQR: 11, 32).	PFOA, PFOS, PFHxS, PFNA	log-transformed		Below 115 (29.4) Within 171 (43.7) Above1 05 (26.9)	Not significant	Maternal education, prenatal smoking, maternal age at delivery, parity, pre-pregnancy BMI, gestational age at delivery, and gestational age at sample	Any 44 (10.0) None 397 (90.0)	Nulliparous 213 (48.2) Parous 229 (51.8)
Kinkade CW, 2023,[15] USA	Cohort	243	29.3±4.4 years	Non-Hispanic White 151 (62.1) Non-Hispanic Black 51 (21.0) Other 41 (16.9)	27.9 (7.2)	At the 2nd trimester: 21.1 (1.8)	PFOA, PFOS, PFHxS, PFNA, PFDA	log-transformed	12.22 (6.27)	Below 50 (20.6) Within 97 (39.9) Above 96 (39.5)	PFHxS and PFOA concentrations were inversely associated with mid-to-late pregnancy GWG and total GWG.	Maternal race/ ethnicity, education, parity, age, early pregnancy BMI, and smoking, PFAS serum weeks, mid-late pregnancy kcal/day and METs/week, gestational age at delivery	Any 15 (6.2)	Nulliparous 81 (33.3) 45 (32.4) Parous 162 (66.7)

Contd...

Table 1: Contd...

Author name, publication year, country	Study design	Sample size	Age (years)	Race	Pre-pregnancy BMI (kg/m²)	Gestational age at PFAS measurement (wks)	Measured PFASs	Exposure scale	Outcome		Results	Adjusted factors	Prenatal smoking	Parity
									GWG (kg)	Categorized GWG				
Miro, SD, 2020,[5] USA	Prospective pre-birth cohort	1614	31.8 (5.2)	White 1104 (68.4) Black 254 (15.7) Other 256 (15.8)	Median (IQR) BMI (kg/m²) 23.6 (21.2-27.5) <25.0 993 (61.5) 25.0 - <30.0 359 (22.3) ≥ 30.0 262 (16.2)	In early pregnancy (median 9.7 weeks; range 4.8-21.4 weeks)	PFOA, PFOS, PFNA, PFOSA, Me-PFOSA-AcOH, Et-PFOSA-AcOH	log2-transformed	15.7 (5.7)	Above (60%)	Women gained 0.37 kg more weight per doubling of EtFOSAA.	Age, pre-pregnancy BMI, marital status, race ethnicity, education, income smoking, and parity	Smoked during pregnancy 212 (13.2) Former 300 (18.6) Never 1101 (68.2)	Nulliparous 794 (49.2) Parous 820 (50.8)
Ashley-Martin J, 2016,[11] Canada	A trans-Canada cohort	1036	Median (IQR) 33.0 (18.0, 49.0)	White (>90%),	<18.5 44 (2.7) 18.5–24.9 9993 (61.6) 25–29.0 99 348 (21.6) ≥30 228 (14.1)	1st trimester	PFOA, PFOS, PFHxS	log2- transformed	Median (IQR) 15.2 (-3.8, 44.5)	Below 278 (17.8) Within 403 (25.8) Above 883 (56.5)	A doubling of PFOS level was associated with modest, statistically significant increases in GWG among women in the underweight or normal pre-pregnancy BMI category	Age, income, and parity	Never or quit before pregnancy 1517 (88.0) Quit during pregnancy 119 (6.9) Current 87 (5.1)	Nulliparous 742 (43.1) Parous 979 (56.8)
Romano ME, 2021,[10] USA	Prospective pregnancy and birth cohort	277	18–25 years 55 (19.9) 25–35 years 176 (63.5) >35 years 46 (16.6)	Non-Hispanic White 183 (66.1) Black 79 (28.5) Other 15 (5.4)	<25 150 (54.2) 25–30 74 (26.7) >30 53 (19.1)	Pregnant (16±3 weeks gestation) The majority of samples analyzed were from the 16-week visit (85%), but in instances where women had insufficient serum volume at that visit, we analyzed samples from the 26-week visit (10%) or at delivery (5%) (mean±standard	PFOA , PFOS, PFHxS, PFNA	log2- transformed		<25 23.4 (9.0) 25–30 21.9 (9.4) >30 17.4 (13.3)	Not significant	Maternal education, age at delivery, race, pre-pregnancy BMI, household income, log10-serum cotinine from pregnancy, alcohol use during pregnancy, gestational week of blood draw, parity and gestational age at delivery	Unexposed 108 (39.0) Secondhand) 141 (50.9) Active 28 (10.1)	Nulliparous 124 (44.8) Parous 153 (55.2)

Contd...

Table 1: Contd...

Author name, publication year, country	Study design	Sample size	Age (years)	Race	Pre-pregnancy BMI (kg/m^2)	Gestational age at PFAS measurement (wks)	Measured PFASs	Exposure scale	Outcome		Results	Adjusted factors	Prenatal smoking	Parity
									GWG (kg)	Categorized GWG				
						deviation (std) 18±5 weeks' gestation).								

ALSPAC=AVON longitudinal study of parents and children, BMI=body mass index, GNRI=geriatric nutritional risk index, GWG=gestational weight gain, HOME=health outcomes and measures of the environment, IQR=interquartile range, MIREC=maternal-infant research on environmental chemicals, METs=metabolic equivalents, ME-PFOSA-AcOH=methyl perfluorooctane sulfonamidoacetic acid, PFAS=per- and polyfluoroalkyl substances, PFDA=perfluorodecanoic acid, PFHxS=perfluorohexane sulfonate, PFNA=perfluorononanoic acid, PFOA=perfluorooctanoic acid, PFOS=perfluorooctane sulfonate, PFOSA=perfluorooctane sulfonamide, PSM=propensity score matching, RCS=restricted cubic spline, RA=rheumatoid arthritis, UPSIDE=understanding pregnancy signals and infant development

P = 0.74), and PFHxS (β = -0.10 [95% CI = -0.34, -14] I^2 = 18.54%, P = 0.293). There was no evidence of significant heterogeneity among studies based on I^2, P values, and publication bias (with respect to PFOA, there was little heterogeneity between studies). For all PFASs, Egger's P value and Begg's P value were greater than 0.05 [Table 3]; no serious asymmetry was observed in the Begg's funnel plot [Figure 2].

The results of the subgroup analyses based on pre-pregnancy BMI (≤25 and >25) have been shown in Supplementary Figures 1 and 2, respectively. In women with pre-pregnancy BMI ≤ 25 kg, there was a significant relationship between the plasma level of PFNA and GWG (β = 0.03 [95% CI = 0.00, -0.05] I^2 = 64.96%, P = 0.04). Consequently, according to the estimated general regression coefficient, a doubling of the blood PFNA level is associated with an increase in the average GWG by 30 grams. The relationship between serum levels of other PFASs and GWG was not significant in this subgroup either (Supplementary Figure 1). In women with pre-pregnancy BMI >25 kg, no significant association was observed between different exposure levels and GWG (Supplementary Figure 2).

Begg's funnel plots were drawn to assess publication bias in both subgroups. Begg's rank correlation test and Egger's regression test were also used to evaluate publication bias. There was no evidence of diffusion bias (or asymmetry) in the funnel plots (Supplementary Figures 3 and 4), and none of the aforementioned statistical tests led to significant results [Table 3].

Sensitivity analysis

The results of the sensitivity analysis showed that after removing each of the studies, no significant changes were observed in the estimated overall effect sizes of the studied exposures. Accordingly, none of the included studies had a significant and different effect on the estimated regression coefficients.

However, in women with pre-pregnancy BMI ≤ 25, the results of sensitivity analysis showed that after removing Marks' hypothesis including mothers of daughters, the relationship between PFNA and GWG changed from a significant relationship (in the presence of this study) to a non-significant relationship (β = 0.001 [95% CI = -0.031, -0.032] P = 0.956).

In women with a pre-pregnancy BMI >25, after excluding the Marks' hypothesis including mothers of sons (β = -0.089 [95% CI = -0.174, -0.003] P = 0.043) and deleting the Romano›s study (β = -0.067 [95% CI = -0.132, -0.001] P = 0.046), the association between PFOA levels and GWG was inversely significant.

Discussion

Our meta-analysis showed no significant association between

Table 2: NIH quality assessment tool for observational cohort and cross-sectional studies

Studies	Was the research question or objective in this paper clearly stated?	Was the study population clearly specified and defined?	Was the participation rate of eligible persons at least 50%?	Were all the subjects selected or recruited from the same or similar populations? (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	Was a sample size justification, power description, or variance and effect estimates provided?	For the analyses in this paper, were the exposure (s) of interest measured prior to the outcome (s) being measured?	Was the time frame sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	For exposures that can vary in amount or level, did the study examine different levels of the exposure? as related to the outcome (e.g., categories of exposure or exposure measured as continuous variable)?	Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Was the exposure (s) assessed more than once over time?	Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	Were the outcome assessors blinded to the exposure status of participants?	Was loss to follow-up after baseline 20% or less?	Were key potential confounding variables measured and adjusted statistically for their impact on the relationship? between exposure (s), and outcome (s)?	Summary Quality
Marks KJ, 2019[12] (Mothers of daughters)	1	1	NR	1	1	1	1	1	1	NA	1	NR	1	1	11
Marks KJ, 2019[12] (Mothers of sons)	1	1	NR	1	1	1	1	1	1	NA	1	NR	1	1	11
Kinkade CW, 2023[15]	1	1	1	1	NR	1	1	1	1	NA	1	NR	1	1	11
Mitro SD, 2020[5]	1	1	NR	1	NR	1	1	1	1	1	1	NR	1	1	11
Ashley-Martin J,2016[11]	1	1	NR	1	NR	1	1	NA	1	NA	1	NR	1	1	9
Romano M E.2021[10]	1	1	NR	1	NR	1	1	1	1	NA	1	NR	1	1	10

NIH=National Institutes of Health, NR, not written, NA, not available

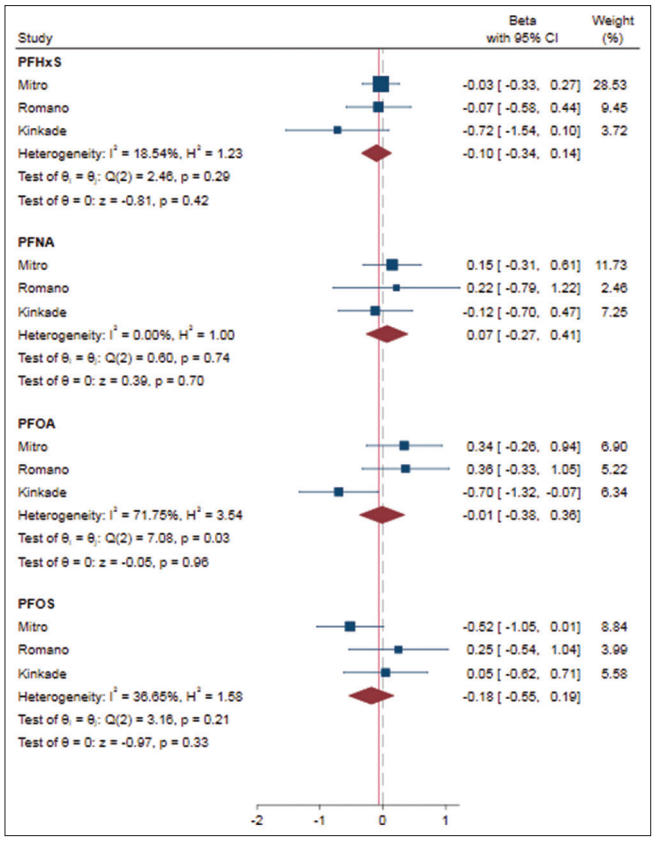

Figure 1: Correlation between serum levels of all four PFASs and GWG in all participants

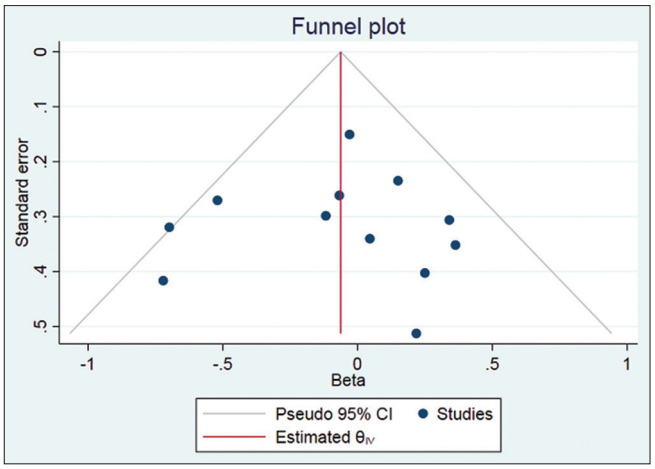

Figure 2: Funnel diagram (all participants)

Table 3: Begg's and Egger's tests

PFAAs	Total		BMI ≤25		BMI >25	
	Begg's p	Eggers's p	Begg's p	Eggers's p	Begg's p	Eggers's p
PFOA	>0.99	0.623	0.462	0.589	0.734	0.818
PFOS	0.296	0.083	0.806	0.535	0.308	0.185
PFNA	>0.99	0.957	0.734	0.051	0.089	0.070
PFHxS	0.296	0.172	0.221	0.283	0.734	0.563

serum levels of any PFASs and GWG. We found no other meta-analysis on this topic. However, consistent with our findings, the European Food Safety Authority stated that there is still insufficient information on the association between PFASs and obesity and further studies are needed.[16] Similarly, a cross-sectional study in Canada also showed no significant association between PFOA and PFOS and serum cholesterol indices (LDL, TC, NON-HDL, TC/HDL ratio), but PFHxS was significantly associated with these indices.[17] In addition, although there are some reports of a significant association between some types of PFASs in the serum of pregnant women and their child's obesity during the fetal period up to 20 years of age, these results are also contradictory.[18,19] Furthermore, the association of PFASs with resting metabolic rate or thyroid hormones, which are important determinants of energy expenditure, is largely unknown.[20–22] In support of the findings of this meta-analysis, it can be stated that the majority of the studies were carried out during years when the overall concentration of total PFAS except PFNA, declined as a result of the gradual cessation of PFOS and PFOA production in the United States. Furthermore, research involving women has indicated that the levels of PFOS, PFHxS, and PFNA are lower compared to those in men.[27] However, new large cohort studies in pregnant women are needed. In the continuation of the discussion, some other reasons for the lack of correlation between PFAS and weighing are mentioned.

In non-pregnant women, a cohort of 957 overweight and obese adults at risk for type 2 diabetes concluded that PFASs caused weight gain in the presence of other obesity risk factors. In women who are not pregnant, a study involving 957 overweight and obese adults at risk for type 2 diabetes found that PFASs contributed to weight gain when other obesity risk factors were present. This conclusion was drawn from the observation that elevated serum PFAS levels correlated with signs of weight gain in the placebo group, whereas this correlation was absent in the experimental group that adopted a lifestyle intervention aimed at mitigating risk factors.[23,16] Similarly, a Japanese study showed that vitamin C supplementation for 4 weeks and reduction of oxidative stress significantly reduced the association between PFOS and perfluorododecanoic acid and indices of insulin resistance and oxidative stress.[24] Another explanation for the non-significant association of PFASs with weight gain is the presence of confounding factors. For example, if physical activity in the intervention group of a study can reduce the obesogenic effect of PFASs, exposure to PFASs through sports and outdoor garments as confounding variables could decrease the protective role of physical activity.[23] Similarly, diets containing fast food and fish, which are good sources of PFASs, can have a confounding effect and impair the protective effect of lifestyle interventions.[25,26]

An important point is that the gestational period may be too short for exposure effects, and further studies with large sample sizes on the association of weight gain and duration of PFAS exposure in the non-pregnant state are recommended.

In contrast to our findings, in a weight loss trial in overweight and obese subjects aged 30–70 years, higher PFAS concentrations were associated with weight regain, which was particularly observed in women, where the regression of resting metabolic rate was slower.[20] Additionally, results obtained from a review in the general population showed that at least one type of PFAS is associated with weight gain, increased BMI, and waist circumference.[27] This review concluded that higher serum levels of PFOS were associated with higher markers of obesity. In the next ranks, blood levels of PFOA and PFNA were also positively correlated with weight gain markers, respectively. Nonetheless, PFHxS was not related with obesity indices,[27] except in one study.[20]

One of the strengths of our meta-analysis is that it provided clarity on the connection between PFASs and GWG, highlighting that weight gain during pregnancy leads to complications for both the mother and the child. Moreover, a meta-analysis was performed on prospective cohort studies in which other influential factors such as maternal age, number of deliveries, pre-pregnancy BMI, race, gestational age at delivery, and time of blood sampling (duration of exposure) were adjusted. However, the number of included studies was small.

Conclusions

No significant association was observed between major PFASs and weight gain during pregnancy, possibly due to the inadequacy of the exposure duration (gestational length). Especially as most of the influencing factors were adjusted in majority of the studies included in the meta-analysis. However, further cohort studies with larger sample sizes are needed.

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Conflicts of interest

There are no conflicts of interest.

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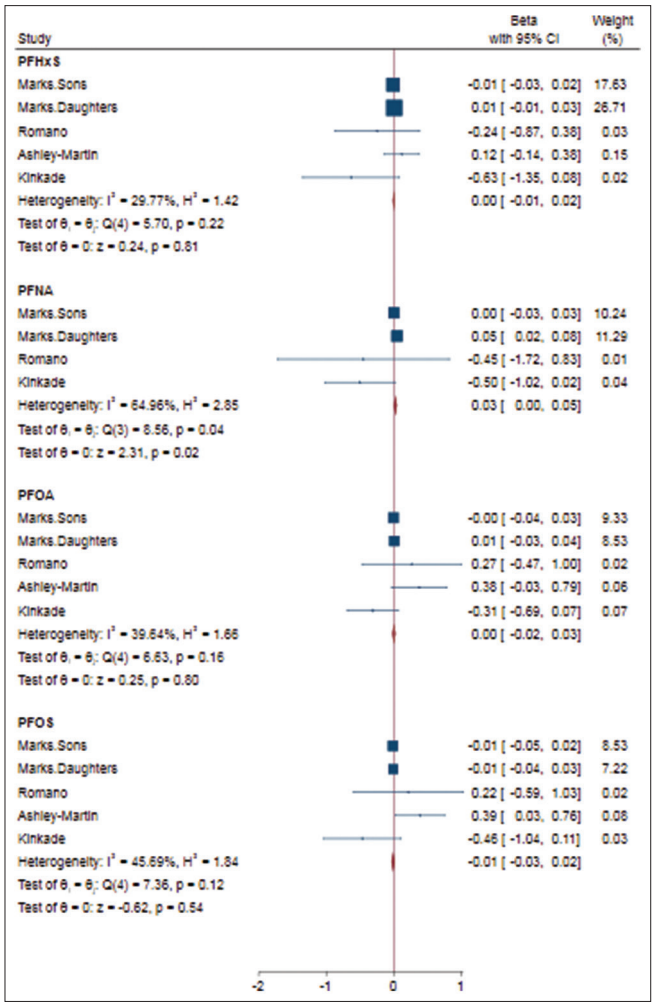
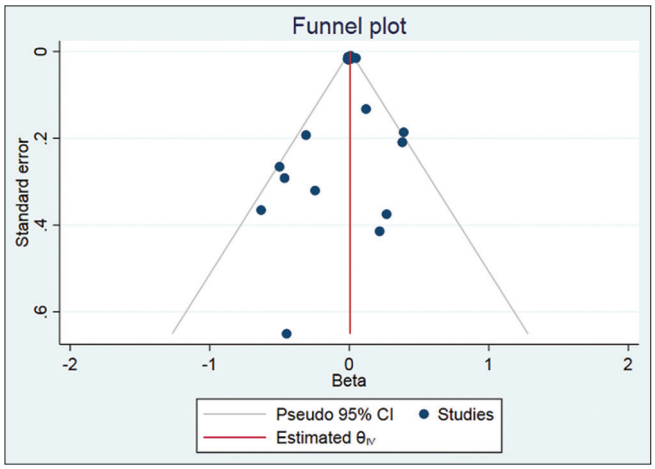
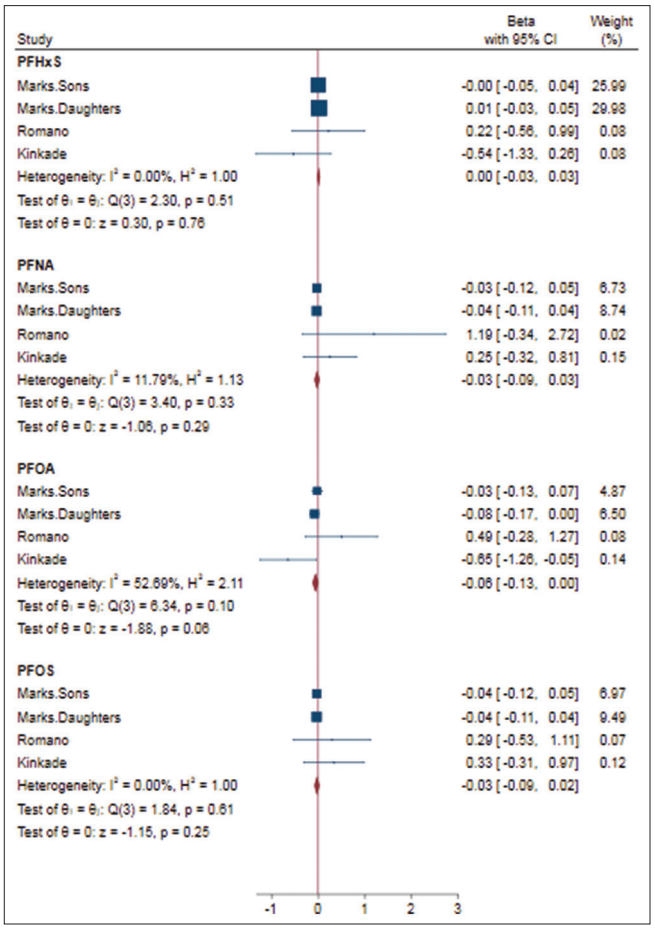
Supplementary file



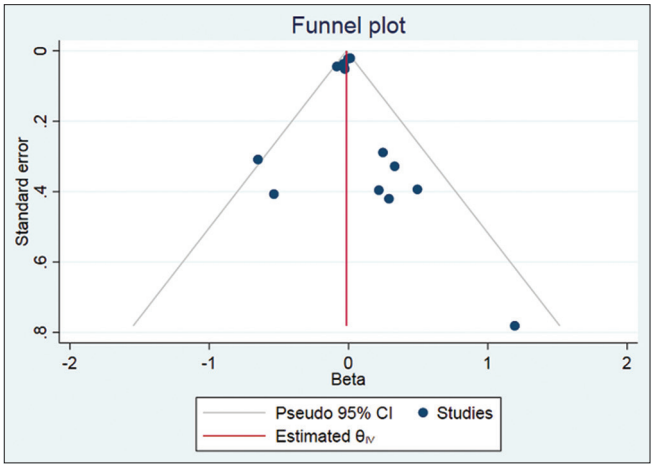
Supplementary Figure 1: Relationship between serum levels of PFASs and GWG in women with pre-pregnancy BMI ≤ 25



Supplementary Figure 3: Funnel chart (women with pre-pregnancy BMI ≤ 25)



Supplementary Figure 2: Association between blood levels of PFASs and GWG in group with pre-pregnancy BMI > 25



Supplementary Figure 4: Funnel chart (women with pre-pregnancy BMI > 25)