Prenatal and childhood exposure to per-/polyfluoroalkyl substances (PFASs) and its associations with childhood overweight and/or obesity: a systematic review with meta- analyses

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Systematic Review

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Posted Date: January 5th, 2023

DOI: https://doi.org/10.21203/rs.3.rs-2431622/v1

Additional Declarations: No competing interests reported.

Prenatal and childhood exposure to per-/polyfluoroalkyl substances (PFASs) and its associations with childhood overweight and/or obesity: a systematic review with meta-analyses

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Abstract

Background. Per-/polyfluoroalkyl substances (PFASs) are persistent organic pollutants and suspected endocrine disrupters.

Objective. The aim of this work was to conduct a systematic review with meta-analysis to summarise the associations between prenatal or childhood exposure to PFASs and childhood overweight/obesity.

Methods. The search was performed on the bibliographic databases PubMed and Embase with text strings containing terms related to prenatal, childhood, overweight, obesity, and PFASs. Only papers describing a biomonitoring study in pregnant women or in children up to 18 years that assessed body mass index (BMI), waist circumference (WC), or fat mass in children were included. When the estimates of the association between a PFAS and an outcome were reported from at least 3 studies, a meta-analysis was conducted; moreover, to correctly compare the studies, we developed a method to convert the different effect estimates and made them comparable each other.

Results. In total, 354 and 565 articles were retrieved from PubMed and Embase, respectively, resulting in a total of 613 articles after merging duplicates. The papers included in this systematic review were 31: 18 evaluating prenatal exposure to PFASs, 11 childhood exposure, and 2 both. Overall, results were conflicting, with positive, negative, and null associations. 17 papers were included in meta-analyses (12 prenatal, 3 children, and 2 both). The method implemented for data conversion allowed a suitable comparison of different effect estimates. Meta-analyses evaluating the associations between prenatal exposure to PFOA, PFOS, PFNA, PFHxS, and the outcomes BMI, WC, and Dual-Energy X-ray Absorptiometry (DXA) showed no significant results. Meta-analyses for the associations between childhood exposure to PFASs and the outcomes BMI showed no significant results except for a negative association between PFNA and BMI (pooled estimate from a random effect model: -0.045; 95%CI: -0.087, -0.002), however, more studies are required to confirm the strength of this association.

Conclusion. To increase the reliability of meta-analyses in environmental epidemiology we suggest the conversion of effect estimates to compare different studies. The pooled evidence of the meta-analyses of the present study suggests that there is no overall association between exposure to PFASs and childhood overweight/obesity.

Keywords

Persistent environmental pollutants; fetal exposure; early life exposure; paediatric exposure; childhood adiposity; effect estimate conversion.

List of abbreviations

6:2 diPAP: 6:2 polyfluoroalkyl phosphoric acid diesters; 8:2 diPAP: 8:2 polyfluoroalkyl phosphoric acid diesters; 95% CI: 95% confidence interval; ALSPAC: Avon Longitudinal Study of Parents and Children; BCERP: Breast Cancer and Environment Research Program; BFP: body fat percentage; BMI: Body mass idex; CI: confidence interval; CLEAR: Climate change, environmental contaminants and reproductive health; DXA: Dual-Energy X-ray Absorptiometry; EDCs: endocrine disrupters compounds; EYHS: European Youth Heart Study; FM: fat mass; HOME: Health Outcomes and Measures of the Environment; INMA: INfancia y Medio Ambiente, Environment and Childhood; INUENDO: Biopersistent organochlorines in diet and human fertility; LL: lower limit of the 95% confidence interval; LOD/LOQ: limits of determination or quantitation (LOD/LOQ); N-EtFOSAA: N-Ethylperfluorooctane sulfonamidoacetic acid; NHANES: National Health and Nutrition Examination Survey; NICHD-SGA: U.S. National Institute of Child Health and Human Development Scandinavian Successive Small-for-Gestational Age births study; N-MeFOSAA: N-Methylperfluorooctane sulfonamidoacetic acid; n-PFOA: linear perfluorooctanoic acid; n-PFOS: linear perfluorooctanesulfonic acid; OCC: Odense Child Cohort; PFASs: per-/polyfluoroalkyl substances; PFBA: Perfluorobutanoic acid; PFBS: Perfluorobutanesulfonic acid; PFDA: Perfluorodecanoid acid; PFDoDA: Perfluorododecanoic acid; PFDS: Perfluorodecane sulfonic acid; PFHpA: Perfluoroheptanoic acid; PFHpS: Perfluoroheptanesulfonic acid; PFHxA: Perfluorohexanoic acid; PFHxS: Perfluorohexanesulfonic acid; PFNA: Perfluorononanoic acid; PFOA: Perfluorooctanoic acid; PFOS: perfluorooctanesulfonic acid; PFOSA: Perfluorooctanesulfonamide; PFPeA: Perfluoropentanoic acid; PFTeDA: Perfluorotetradecanoic acid; PFTrDA: Perfluorotridecanoic acid; PFUnDA: Perfluoroundecanoic acid; POPUP: Persistent Organic Pollutants in Uppsala Primiparas; REML: restricted maximum-likelihood estimator; Sb-PFOA: sum of branched isomers of perfluorooctanoic acid; Sm-PFOS: sum of perfluoromethylheptane sulfonate isomers; STROBE-ME: STrengthening Reporting of Observational studies in Epidemiology-Molecular Epidemiology; UL:

upper limit of the 95% confidence interval; WC: waist circumference; WHO: World Health Organization; WtHe: waist to height ratio; WtHi: waist to hip ratio.

1. Background

Childhood overweight and obesity are recognised worldwide issues. Under 5 years, children are considered affected by overweight if their weight-for-height is greater than 2 standard deviations above WHO Child Growth Standards median; or affected by obesity if their weight-for-height is greater than 3 standard deviations. Between 5 and 19 years, overweight and obesity are defined by a BMI-for-age greater than 1 and 2 standard deviations above the WHO Growth Reference median, respectively [1]. According to the World Health Organisation, 39 million children under 5 years were affected by overweight or obesity in 2020 and over 340 million aged 5-19 years were affected by overweight or obesity in 2016 [1]. The high prevalence of overweight and obesity is caused by a complex interaction between predisposing genetic factors and environmental factors [2, 3]. Unhealthy diet and physical inactivity are well-known causes leading to these problematic conditions [4]. However, other environmental factors that may contribute to the development of these conditions include exposure to endocrine disrupter chemicals [5, 6]. Furthermore, the exposure to environmental pollutants may be critical, especially if it occurs in susceptible period of life, such as the prenatal period or infancy [7].

Per- and polyfluoroalkyl substances (PFASs) are a group of artificial compounds. Thanks to their surfactant, greaseproof, stain-proof, water repellent, and fire repellent properties, PFASs are used widely, including in food processing, medical articles, apparel, household products, electronics, and firefighting [8, 9]. PFAS pollution has been reported at global level since the beginning of this millennium, especially perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS) [10–12]. In 2009, PFOS, its precursor, and its related salts, were included in the Annex B (restriction) of the Stockholm Convention; in 2019, PFOA, its salts and PFOA-related compounds were added in

Annex A (elimination); recently (2022) also perfluorohexanesulfonic acid (PFHxS), its salts, and PFHxS-related compounds have been included in the Annex A; and long-chain PFASs, their salts and related compounds, are currently reviewed by the Commitee for their possible inclusion in Annexes A [13]. Despite the restrictions, these persistent compounds are still widespread in the environment and in living organisms [14–16].

PFASs are often classified as endocrine disrupters compounds (EDCs), i.e., they can potentially interfere with the endocrine system [17–19]. Some *in-vitro* studies showed that PFASs can disrupt some hormone functions [20, 21], and adipocyte differentiation [22]; moreover, effects on body weight and adipogenesis were observed in animals [23, 24], highlighting the importance of investigating these compounds in human epidemiological studies.

Several observational studies in humans were conducted to assess the effects of PFASs, and many studied their effect on prenatal growth: indeed, previous systematic reviews evidenced that a prenatal exposure to PFOA and PFOS is associated with a lower birth weight [25–27]. Several epidemiological studies also investigated the adverse effects of the exposure to PFASs on childhood overweight and obesity, and the evidence deriving from these studies were partially summarised in some narrative reviews [6, 28, 29]. Vrijheid et al., in their narrative review, classified the evidence of the effects of PFASs on childhood growth and obesity as “insufficient”, due to the low number of studies and the inconsistent findings [30]. Conversely, according to the narrative review conducted by Braun, a prenatal exposure to PFASs may be related to increased adiposity and risk of childhood overweight or obesity [17]. Szilagyi at al., in their narrative review, stated that in utero exposure to PFAS is associated with increased incidence of childhood obesity [31]. Rappazzo and co-workers carried out a systematic review of the epidemiologic literature evaluating the exposure to PFASs and different health outcomes, among which outcomes of overweight and obesity were described within the cardio-metabolic category [32]. Lee and co-workers wrote a systematic review summarising the evidence of early-life exposure to several PFASs and different outcomes in children, including adiposity, and concluded that, although

131 the evidence was inconsistent, prenatal PFASs mostly have negative associations with BMI in the first
132 2 years of life and positive associations with adiposity in childhood and adolescence, the latter
133 observation is true for PFOA in particular [33]. Ribeiro and co-workers conducted a systematic review
134 with meta-analysis considering the exposure to different EDCs after the age of 2 years and their
135 association with anthropometric measures of obesity or body fat, but only one study assessing PFASs
136 was included [34]. Liu and co-workers published a systematic review with meta-analysed focused
137 exclusively to early life exposure to PFOA, in which they pooled the evidence from 10 prospective
138 cohort studies and found a positive association with an increased risk for childhood adiposity [35].
139 Finally, a recent comprehensive systematic review with meta-analysis conducted by Stratakis and co-
140 workers summarised the evidence of prenatal exposure to persistent organic pollutants and childhood
141 obesity considering different outcomes such as childhood BMI-z, waist circumference, and overweight
142 risk; for PFOS and PFOA, they found no overall significant associations for most of the considered
143 outcomes [36]. However, in those previous meta-analyses, effect estimates were extracted from the
144 studies and compared irrespectively from their differences: indeed, comparisons between continuous
145 data and categorical data were found, as well as comparisons between data obtained from different log-
146 transformations. Considering the importance of assessing both prenatal and childhood exposure to
147 PFASs and to include a higher number of PFASs, the aim of this work was to conduct a systematic
148 review of the literature to critically summarise the existing evidence of the effect of a prenatal and
149 childhood exposure to as many PFASs as possible on childhood overweight and obesity, with also an
150 effort to develop a methodology to convert data from different studies to make effect estimates
151 comparable each other before conducting the meta-analysis.
152 The PECO statement [37] for the present study is the following: (P) in children, what is the effect of
153 (E) higher PFASs exposure during pregnancy or during childhood versus (C) lowest PFASs exposure
154 during pregnancy or during childhood on (O) childhood overweight and obesity.
155

2. Materials and methods

2.1. Search strategy and inclusion criteria

This review and its protocol were registered on PROSPERO, the International prospective register of systematic reviews [38, 39].

The papers were searched in the PubMed and Embase bibliographic databases. Search terms included: prenatal, children, adolescents, and synonyms; overweight, obesity, BMI, waist circumference, fat mass, and similar; perfluorates and related terms. The PFASs considered for the research terms were the most spread and the most interesting PFASs on our knowledge, including both legacy and emerging compounds, and have been described on our previous work [40]. The complete text strings are reported in supplementary material (supplementary text), and they were elaborated thanks to the help of the library system staff of the University of Milan. Only articles published from 1st January 2000 to 31st December 2020 and in English language were considered. Articles retrieved were collected in electronic databases (Table S01 and Table S02). Duplicates of papers were identified using the DOI number and merged in a single line using the R software [41] with the "tidyverse" package [42], and then exported to an Excel database (Table S03). The script developed to carry out this merge is reported in the supplementary material (supplementary text, R script, section 1).

Two reviewers (G.F. and C.M.F.) independently read the titles and abstracts to select suitable papers for inclusion, while blinded to each other's decisions. At the end of the process, discrepancies were discussed and evaluated with the final decision made by a third person acting as a supervisor (S.F.). To be eligible for inclusion, a human biomonitoring study quantifying one or more PFASs in biological samples of pregnant women or in children/adolescent up to 18 years old had to be conducted. Furthermore, the measured outcomes had to include a measure of overweight/obesity in children (up to 18 years old) such as BMI, waist circumference (WC), or fat mass/body fat percentage (BFP), which can be obtained with different approaches such as Dual-Energy X-ray Absorptiometry (DXA)

(considered the gold standard) or skinfold thickness [43, 44]. The measurement of weight alone was not considered an outcome suitable for inclusion; likewise, birthweight and any other parameters measured right after delivery were not considered suitable for inclusion, as they are indicator of prenatal growth, which is not the purpose of this review. Non-original works (such reviews), non-full articles (such as conference abstracts or letters to editor), and studies considering only non-pregnant adults were excluded.

Afterwards, papers judged suitable after reading their title and abstract were further inspected in their entirety. Finally, included papers were grouped in three categories: studies considering only prenatal exposure to PFASs, studies considering only exposure in children/adolescents, and studies considering both prenatal and children exposure.

2.2. Data elaboration

Information from included papers were collected in the Excel database (Table S03). As for the paper selection, this elaboration was performed independently by G.F. and C.M.F. and discussed with S.F.. Information collected from the papers included: type of study, number of subjects, country or region, years of the first enrolment, measured PFASs and blood sampling period(s), outcome measured and period(s) of measurements, and if they were statistically positively or negatively associated with the considered outcomes.

Furthermore, each article was evaluated for the quality of its reporting: a list of 28 items was established, most of which following the STrengthening Reporting of Observational studies in Epidemiology-Molecular Epidemiology (STROBE-ME) [45], while others were created to specifically match the considered studies. The complete list of items is reported in the supplementary material (Table S03). For each item, either a 0 (not reported or not fulfilled), 0.5 (partially fulfilled) or 1

(fulfilled) was assigned. For each paper, the scores assigned to all the items were summed to evaluate the quality of reporting.

2.3. Meta-analyses

2.3.1 Inclusion criteria

Aside from the extraction of the information reported in the previous section and the qualitative evaluation of studies, meta-analyses were performed among a subset of the included papers. Studies were eligible for inclusion in meta-analyses if they reported the estimated beta coefficient of the association between PFAS concentrations and the considered outcomes, along with confidence intervals (CI). If the same cohort of subjects was considered in more than one paper, only the most recent one was included in the meta-analyses. For each PFAS and each outcome, a meta-analysis was performed only if at least three studies reported suitable estimates.

2.3.2 Data extraction

The slopes of the continuous associations were considered; when only slopes from categories (such as percentiles) were reported, we considered the highest estimate reported (worst-case scenario) [46]. If multiple models were reported, we considered the adjusted estimates from the model with the highest number of considered confounding factors. When the slopes were reported for outcomes measured at different time periods during infancy, the one related to the latest measurement was considered. For each study, estimates from subgroups (e.g., sex of subjects or region of the study) were considered only if there were not overall estimates reported. If necessary, corresponding author of the paper was contacted.

2.3.3 Data conversion of the effect estimates

A specific methodology was developed to ensure that the beta coefficients and the confidence intervals included for meta-analysis were comparable each other. The conversions were performed to have, for all the included studies, beta estimates and coefficient intervals that represent the mean increase of z-scores of the outcome for each unit increase in the PFAS.

Firstly, the standard error was calculated from the 95% CI as follow:

$$se(\beta) = (\mathrm{UL} - \mathrm{LL})/3.92$$

Where $se(\beta)$ is the calculated standard error, UL is the upper limit, and LL is the lower limit of the 95% coefficient interval.

Then, four different steps of conversion were performed:

1) If the concentrations of PFASs were log-transformed before performing the linear models, the beta was changed according to the following formula elaborated by Rodríguez-Barranco and co-workers [47].

$$\beta_f = \log_b\left(1 + \frac{1}{E[X]}\right) * \beta_i$$

While 95% CI was calculated as follows:

$$95\%\mathrm{CI}_f = \log_b\left(1 + \frac{1}{E[X]}\right) * (\beta_i \pm 1.96 * se(\beta_i))$$

Where β_f and $95\%\mathrm{CI}_f$ are the converted beta and coefficient intervals, b is the base of the logarithm used, $E[X]$ is the mean (if not available, the median) of the PFAS concentration, β_i is the slope reported by the study and $se(\beta_i)$ is the standard error of the beta calculated as reported above.

2) If also the outcome variable were log-transformed and the effect estimates were reported as percent change; first, the beta was calculated from the variation percentage (var%) with the following formula:

$$\beta_i = \ln((\text{var}\%/100) + 1)$$

and the standard error was calculated from the 95% CI of the var% as follow:

$$se(\beta_i) = \ln(((\text{UL} - \text{LL})/3.92/100) + 1)$$

then, beta and 95% CI were calculated with the following equation elaborated by Rodríguez-Barranco et. al [47].

$$\beta_f = \left(a^{\log_b\left(1+\frac{1}{E[X]}\right)*\beta_i} - 1\right) * E[Y]$$

While 95% coefficients intervals were calculated as follows:

$$95\%\text{CI}_f = \left(a^{\log_b\left(1+\frac{1}{E[X]}\right)*(\beta_i \pm 1.96 * se(\beta_i))} - 1\right) * E[Y]$$

Where β_f and $95\%\text{CI}_f$ are the converted beta and coefficient intervals, a is the base of the logarithm used for outcome data, b is the base of the logarithm used for PFASs, $E[X]$ is the mean (or median, if mean was not reported) of the PFAS concentration, $E[Y]$ is the mean (or median, if mean was not reported) of the outcome measure, β_i is the slope reported by the study and $se(\beta_i)$ is the standard error of the beta.

3) If the effect estimate was reported by change in interquartile range, the slope was divided by the interquartile range in order to have a plausible beta for unit increase. Analogously, if it was reported by change of a specific tercile versus the reference tercile, it was divided by the difference of means of tercile. The standard error was also divided accordingly, and the coefficient intervals calculated again.

4) Finally, a further correction was carried out considering the type of data outcome used in each study. For BMI data, no change was made if the effect estimate was calculated from BMI z-

score or BMI SDS, while if calculated from BMI expressed as kg/m^2 the reported BMI mean (or median) was converted into BMI z-score using the Word Health Organization (WHO) references [48, 49], implementing the "anthro" R package for calculation [50], which uses the following formula [51]:

$$Z = \left[\left(\frac{X}{M}\right)^{L} - 1\right] / LS$$

Where Z is the calculated z-score, X is the mean (or median) of the BMI (in kg/m^2) reported by the study; while the value used for L, M, and S were chosen considering the overall age of children in each study and the sex of subjects: if the effect estimate of a study reported separately girls or boys, only one z-score was calculated, while if the study included both males and females, two different z-scores were calculated, and then the mean of the two was considered. Then, the beta estimates and 95%CI were calculated with a proportion:

$$\beta_f = (Z * \beta_i)/M$$

$$se(\beta_f) = |(Z * se(\beta_i))/M|$$

$$95\%\mathrm{CI}_f = \beta_f \pm 1.96 * se(\beta_f)$$

Where β_f, $se(\beta_f)$, and $95\%\mathrm{CI}_f$ are the final beta, standard error, and coefficient intervals, respectively; Z is the z-score calculated as reported above, β_i and $se(\beta_i)$ are the beta and standard error as converted so far, M is the reported mean (or median) of the BMI (in kg/m^2) Analogously, estimates obtained from waist circumference (in cm) were transformed using the tables reported by Sharma et al. [52]. For body fat, if expressed as body fat percentage, the mean (or median) was firstly converted as total fat index (kg/m^2) by dividing the percentage per 100 and multiplying by mean (or median) BMI, then as fat mass index z-score using tables from Weber et al. [53].

All these elaborations were carried out by developing a specific R-script, which is reported in the supplementary material (supplementary text, R script, section 2).

2.3.4 Performing the meta-analyses

The generic inverse variance method was used, both fixed and random pooled estimates were calculated, heterogeneity was measured with the I^2 statistics [54] and the between-study variance was calculated using the restricted maximum-likelihood estimator (REML) (τ^2) [55]. To assess for the possible publication bias, a funnel plot was plotted [56] and an Egger's test was carried out [57]. All these functions were conducted in the R environment, using the R package "meta" [58]. Forest plots and funnel plots were created using functions from the "meta" package (supplementary text, R script, section 3). Furthermore, sensitivity analyses were performed by repeating the meta-analyses by excluding one study at a time; when a study reported separated data for sub-population (e.g.: boys and girls or different countries), both the single sub-population and the entire study was excluded at a time (supplementary text, R script, section 4).

Finally, innovative superimposed forest plots were ideated and set up by developing an R script, implementing functions from the packages "tidyverse" and "cowplot" [42, 59], which is reported in the supplementary material (supplementary text, R script, section 5).

3. Results

3.1. Search results

A total of 354 papers were retrieved from PubMed (Table S01) and 565 from Embase (Table S02), for a total of 919 entries. Papers derived from both databases were 306, while 48 were uniquely retrieved from PubMed and 259 were unique from Embase; thus, after merging the duplicates, the papers considered for inclusion were 613. Titles and abstracts were evaluated and, eventually, the papers were inspected in their full text. Several articles were not eligible for inclusion: 207 were not pertinent, 53 did not report original findings (such as reviews or project presentations), 15 were not full articles (such

as letters or conference abstracts), and 1 was a retracted article. Furthermore, several studies did not meet the inclusion criteria for one or more reasons of the following: no humans involved (103); the outcomes were measured in human adults (48 of the remaining); while considering children, the outcomes of interest were not measured (143 of the remaining); a biomonitoring study to measured exposure to PFASs was not performed (12). Hence, the total number of included papers were 31. Among included studies, 18 evaluated the prenatal exposure, 11 considered the exposure in children, and 2 both. A summary of the literature search results is given in Figure 1, while the complete database is reported in the supplementary material (Table S03).

3.2. Studies included in this review

A summary of the included papers is reported in Table 1 and 2. Overall, the enrolment periods ranged from 1986 to 2012. Several studies were conducted in Europe (15), among which most in Northern Europe (12) (Norway, Sweden, Denmark, Greenland, and Finland). Other studies were conducted in the United States (13), and a few in Asia (3). The number of subjects considered for the analyses varied greatly among studies, from only 54 to 2920 subjects. Among considered PFASs, PFOA and PFOS were monitored in all studies; PFNA and PFHxS were measured in 20 and 21 studies, respectively. For studies evaluating the prenatal exposure to PFASs, they were quantified in the blood of mothers at different periods during gestation, at birth, or a couple of weeks after birth; only one study evaluated the prenatal exposure in blood samples of children at birth. For studies assessing PFASs during childhood, they were quantified in children blood across various ages: from 1 to 18 years. BMI was measured in almost all studies, while WC and FT/BFP were measured in less than half of the studies. Outcomes were measured at different ages, from few weeks after birth to 18 years old.

Each study was evaluated for the quality of reporting, considering the guidelines of the STROBE-ME [45]. Most studies were judged of high quality: information needed were clearly reported, including selection criteria, possible follow-up, sample-size, collection of biological samples, methods and tools implemented for data collection and outcome measurements, demographic and clinical characteristics

of subjects. Furthermore, most studies took into consideration several potential confounding factors in the statistical analysis. No particular bias was noted in the selection of study individuals. Even if it was not clearly stated in most studies, it is reasonable to assume that analytical measurements were blinded, in order to counter this possible bias. Moreover, no conflicts of interests were reported. Considering the score of reporting, all the articles had score equal to or higher than 22/28, with a mean of 26.8 (Table S03), thus all of them were judged of high quality and suitable for being considered.

3.2.1. Studies evaluating the effect of prenatal exposure

Lauritzen et al. analysed PFOA and PFOS in 412 pregnant women from Norway and Sweden at 17–20 weeks of gestation and measured BMI and skinfold thickness in children at 5 years. In the total population, increased maternal PFOS levels determined an increment of adjusted BMI for-age-and-sex z-score, of adjusted triceps skinfold z-score, and of adjusted odds ratio for childhood overweight/obesity; while for PFOA, non-significant associations for the same outcomes were observed. When considering only Norwegian (254) or Swedish (158) subjects, the significant positive associations both PFOS and PFOA and all outcomes between was observed in Norwegian, while no significant associations were found for Swedish participants [60].

In a prospective birth cohort, PFOA, PFOS, PFHxS, and PFNA were measured in mothers, while BMI, WC, and FM/BFP were measured in 359 nine-years-old girls. Overall, PFOS was inversely associated with BMI and WC, and PFOA was inversely associated with WC, while no overall associations were found for BFP. Some associations between PFOA/PFOS and BPB were found within some strata of maternal education status [61].

PFOA and PFOS were measured in blood samples obtained from women of the Danish National Birth Cohort, while BMI was first measured at 5 months and at 12 months of age in 1010 children [62]; afterwards, later BMI (811) and WC (804) were assessed at seven years of age [63]. There was not a

363 strong association between prenatal exposure to PFASs and the outcomes, and only slight non-
364 significant inverse associations were observed.

365 Gyllenhammar and co-workers measured 7 PFASs 3 weeks after delivery in mothers and found PFOA,
366 PFNA, PFHxS, and PFOS positively associated with the BMI of their children at 3, 4 and 5 years (200
367 subjects). In particular, the association was significant at 3 and 4 years, but not at 5 years for PFOA,
368 PFNA, PFHxS, thus becoming less strong over age; conversely, it was significant at 4 and 5 years for
369 PFOS, becoming stronger at increasing age over the time span considered [64].

370 Mora and co-workers analysed PFOA, PFOS, PFHxS, and PFNA in 1645 pregnant women and
371 measured BMI, WC, and FM/BFP (skinfold thickness and DXA total fat mass index) in their children
372 during early childhood (2.9–6.1 years, for 1006 children) and during mid-childhood (6.6-10.9 years,
373 for 876 children). They did not find strong associations of measured outcomes with prenatal PFASs,
374 but a modest association only in mid-childhood and in girls [65].

375 Alkhalawi and co-workers measured PFOA, PFOS, PFHxS in mothers of the Duisburg Birth Cohort
376 Study and found that PFHxS was positively associated with the ponderal index of their children (156
377 subjects). This association was particularly significant in children of 3-4 months of age [66].

378 Høyer and co-workers measured PFOA and PFOS in sera from 1022 pregnant women, including 531
379 from Greenland and 491 from Ukraine. BMI and WC were measured in the offspring between 5 and 9
380 years old. When considering overall data (both countries and both boys and girls), no significant
381 association was found between PFASs and risk of overweight, while the risk of having WHtR > 0.5 in
382 relation to PFOS concentrations was increased. A few significant results were found when considering
383 only girls or only Ukraine or Greenland populations. In this regard, the authors concluded that females
384 could be more sensitive to exposure than males [67].

385 Four papers referred to the HOME study, which was conducted in Cincinnati, Ohio. PFOA, PFOS,
386 PFNA, and PFHxS were quantified in more than three hundred mothers, while BMI, WC, and BFP

were measured in several follow-up studies. Braun et al. reported that no association was found with prenatal exposure to PFOS, PFNA, and PFHxS; while PFOA was positively associated with WC in 8 years old children, BMI gains from 2 to 8 years, and body fat percent, although these associations were non-linear [68]. Shoaff et al., analysing data at 4 weeks, 1 and 2 years, reported a negative association between all the four measured PFASs and BMI, although it was statistically significant only for PFOA and PFOS [69]. Adiposity was assessed also at 12 years by Liu et al. and the results showed that prenatal PFOA and PFHxS were associated with modest increases in measures of central body fat, although some of these associations for PFOA were non-linear. Moreover, the evidence for both PFOA and PFHxS were stronger in girls than in boys [70]. Braun and co-workers, considering various time points until 12 years, reported that PFOA varied non-monotonically with BMI: compared to the 1st tercile, the 2nd tercile of PFOA exposure showed an earlier BMI nadir and a more rapid increase in BMI from 8 to 12 years, while the 3rd tercile of PFOA exposure had lower magnitude of BMI zenith and lower magnitude and earlier of BMI nadir. PFOS and PFHxS were associated with reduced BMI from 4 weeks to 12 years of age, including lower magnitude of BMI zenith and BMI nadir. No associations were found for PFNA [71].

Martisson and co-workers conducted a case-control study on a total of 1048 children, in which PFOS, PFOA, PFHxS and PFNA were measured in their mothers around gestational week 14. The age and sex adjusted body mass index (ISO-BMI) was calculated at 4 years of age. The case group (354) was defined as children with an ISO-BMI $\geq$ 18 kg/m^2, while the control group (694) included children with ISO-BMI $\leq$ 17 kg/m^2. No significant association was found, except for some significant odds ratios (OR) with some quartiles of PFOS (positive association: OR>1), PFHxS (negative association: OR<1), and PFNA (negative association: OR<1), but with no consistent patterns over quartiles, so findings were regarded as spurious. Also, the stratified analyses showed that prenatal PFASs exposure had no effect over risk strata [72].

411 In a birth cohort in Spain, PFHxS, PFOS, PFOA, and PFNA were measured in the first trimester of
412 pregnancy in 1243 women. Anthropometric measures were measured form their children at 6 months
413 (n=1154), and BMI was assessed at 4 years (n=1230) and 7 years (n=1086); furthermore, WC were
414 available at 4 years of age for children from a subcohort (n=839). A positive association was found
415 between PFOA and weight gain from birth to 6 months. However, most of the other associations were
416 not significant [73].

417 In a study conducted in Taiwan, PFOA and PFOS were measured at birth in 429 mothers, while weight
418 and height were collected at different times up to 9 years of age in their children. While no evidence
419 was found for PFOA, BMI was negatively associated with PFOS at birth, but only in the unadjusted
420 model. When stratifying per sex, a negative association was found in girls between PFOS and BMI in
421 the time span from 6 to 12 months and from 12 to 24 months. This effect diminished as children grew
422 up, and a positive association was found from 60 to 108 months [74].

423 Karlsen and co-workers conducted a study in mother-child pairs of the Faroe Islands. PFOS, PFOA,
424 PFHxS, PFNA, and PFDA were measured in mothers 2 weeks after delivery, while BMI of offspring
425 was measured at 18 months (for 444 children) and 5 years (371 children). The main statistically
426 significant results are a positive association between PFOS and BMI z-score and the risk of being
427 overweight at 18 months, and a positive association between PFOA and overweight risk at 5 years.
428 Interestingly, some non-linear inverse associations were found between maternal exposure to PFNA
429 and PFDA and the overweight risk [75].

430 PFOA and PFOS were quantified at birth in the dried blood spot of 2920 infants, of which 1954
431 singletons and 966 were twins, while BMI was reported by mothers over 3 years, for an average of
432 seven measurements at different times. Both PFOA and PFOS were negatively associated with BMI in
433 overall singletons and in singleton females. In singleton males a non-linear negative association was
434 found between PFOA and BMI (second and third quartiles, compared to the first), while, conversely,

435 in twins a non-linear positive association between PFOA and BMI was found (second and third
436 quartiles, compared to the first) [76].

437 Starling et al. measured several PFASs in mothers during pregnancy, while BMI and fat mass was
438 measured in children at 5 months, for a total of 415 mother-infant pairs. Some positive associations
439 were found when considering adiposity (fat mass as a percentage of total body mass), particularly for
440 PFOA and PFNA. PFOS was negatively associated with weight for age and weight for length z-score
441 in females, N-MeFOSAA was positively associated with weight for age and in rapid growth in weight
442 for ages and with rapid growth in weight for age and weight for length z-score; while PFHxS was both
443 positively associated with rapid growth in weight-for-length z-score and negatively associated with
444 weight for ages z-score in females, although a multipollutant model attenuated this last association to
445 the null, suggesting it may have been confounded by PFOS [77].

446 In a study performed by Jensen and co-workers, PFOA, PFOS, PFHxS, PFNA, and PFDA were
447 analysed in pregnant women; while outcomes, among which BMI, waist circumference and BF% sex-
448 specific standard deviations, were measured in 602 and 530 children, at 3 and 18 months, respectively.
449 For prenatal PFNA and PFDA, significant associations with BMI were found both at 3 and 18 months,
450 and in particular for girls. Prenatal PFNA and PFDA were also significantly associated with BFP at 3
451 months [78].

452 Several PFASs were analysed at birth in cord plasma in a study conducted in China, while BMI, WC,
453 WtHr, and FM/BFP (measured with a bioelectrical impedance method) were measured at 5 years, for
454 a total of 404 measurements. Associations were studied by dividing children by sex. In girls, an increase
455 in PFBS was positively associated with WC, FM, BFP, and WtHr; and these continuous associations
456 were also confirmed comparing the third tercile with the first one. In girls, PFDoA concentrations were
457 inversely associated with WC, FM, and BFP while comparing the second tercile with the first
458 (conversely, no significant association with the third tercile were found, nor it was significant in the

459 continuous). In boys, comparing the highest tercile of PFNA concentrations with the first, positive
460 association was found for BPP [79].

461

462 ### *3.2.2. Studies evaluating the effect of childhood exposure*

463 In the frame of the European Youth Heart Study (EYHS), conducted on about 500 children, PFOA and
464 PFOS were measured at 9, 15 and 21 years (the latter time point was not considered for the purpose of
465 this review); at those time points, also BMI, WC, and skinfold thickness were measured. The main
466 result was the positive association of PFOS measured at 9 years with with BMI, WC and skinfold
467 thickness measured at 15 years old [80, 81]. In a sub-study of the EYHS, Domazt et al. evaluated the
468 exposure to PFAS in relation to fitness, physical activity, and adipokine levels, and the levels of PFOS,
469 PFOA, PFNA, PFDA and PFHxS were also compared to BMI and fat mass. Among the 242 children
470 considered, PFNA and PFDA were higher in underweight children; also, in the multiple linear models,
471 PFNA, PFDA, and PFHxS were inversely associated with fat mass [82].

472 Within the Project Viva study, conducted in the Eastern Massachusetts, several PFASs were measured
473 in 653 children aged 6-10 years. PFOA and PFDeA levels were inversely associated with children
474 BMI. Those data were also corrected for PFAS concentrations measured in pregnancy [83].

475 In the NHANES data of 1999-2000 and 2003-2012 surveys, PFOA and PFOS were measured in a
476 sample of 2473 children aged 12-18 years old. A pattern of positive associations was found with odds
477 of being affected with overweight/obesity and odds of abdominal obesity, although, for PFOA only a
478 marginally significant association with odds of overweight/obesity was found, and for PFOA the
479 significant associations were only found in the unadjusted models [84].

480 In a follow-up of the HOME study, no significant associations were observed for BMI, WC, and
481 FM/BFB (DXA scan) measured at 12 years and PFOA, PFOS, PFNA, and PFHxS measured at 3, 8,
482 and 12 [70].

In 704 girls from the San Francisco Bay Area and from Cincinnati (U.S.), PFOA was inversely associated with BMI and with waist to height ratio, but not with waist to hip ratio. The study found that the strength of the relationship decreased with age. Interestingly, the effect of PFOA on those outcomes was greater in girls from Cincinnati than from San Francisco, as for the latter the associations were not statistically significant [85]. In a separate paper, with data from the Cincinnati cohort only (353 girls), PFOA, Me-PFOSA-AcOH, PFDeA, and PFOS were negatively associated with BMIz and waist-to-height ratio, and also PFOA was inversely associated with fat mass and fat mass percent [86].

In a small subset of the birth cohort study LUKAS2, in the Eastern Finland, no association was found between BMI and a total of 20 different PFASs measured at 1, 6 and 10.5 years of age in 54 children [87].

Between 2007 and 2009, Karlsen et al. conduct a study in the Faroe Islands which included 444 children. Several PFAS were measured in child's serum at 5 years old, as well as the outcomes, and an inverse association was found between PFNA, PFDA, PFOA, and PFOS measured in children serum and BMI z-scores or overweight risk [75].

In a study conducted in 120 children aged 5-13 years in South Korea, PFOA, PFHxS, and the sum of all the 16 analysed PFASs were significantly negatively associated with BMI [88].

Among a subset of NHANES 2013-2014, 14 PFASs were measured in 639 children aged 3-11 years, and a marginally significant difference in the geometric mean of ΣPFOA and n-PFOA was found for BMI, in particular children with underweight/normalweight had higher geometric means than those with overweight/obesity [89].

Again, the NHANES data collected in 2013–2014 cycle, quantifying PFOA, PFNA, PFHxS, and PFOS in 600 children aged 3-11 years, showed that higher levels of PFASs were inversely associated with BMI z-score, although this association was significant only in boys for PFOA and PFHxS [90].

3.2.3. Meta-analyses

After collecting the estimates from all the studies included in this systematic review, we calculated the pooled estimates for the overall association between prenatal concentrations of PFOA, PFOS, PFNA, PFHxS and childhood BMI, WC, and DXA. Furthermore, suitable data were available for calculating pooled estimates of the association between childhood concentrations of PFOA, PFOS, PFNA, PFHxS and childhood BMI. When more studies describing the same cohort were reported, only the most recent one was included in the meta-analysis, in particular: for prenatal PFOA, PFOS and childhood BMI, considering the Danish National Birth Cohort, the paper from Andersen et al. (2010) [62] was excluded and only the paper Andersen et al., (2013) [63] was included; for prenatal PFOA, PFOS, PFNA, PFHxS and childhood BMI, considering the HOME study, three studies (Braun et al. 2016, Shoaff et al. 2018, and Liu et al. 2020) [68–70] were excluded and only Braun et. al. (2021) [71] was included; for prenatal PFOA, PFOS, PFNA, PFHxS and childhood WC, Braun et al. (2016) [68] were excluded while Liu et al. (2020) [70] was included. Moreover, Gyllenhammar was contacted to ask for numeric data as the data of interest were reported as figures in her study [64].

Altogether, out of the 20 studies evaluating prenatal exposure to PFASs, 14 could be included for the meta-analyses, in particular: 13 studies for the meta-analysis evaluating the associations between PFOA, PFOS and BMI; 8 for PFNA, PFHxS and BMI; 7 for PFOA, PFOS and WC, 6 for PFNA, PFHxS and WC; 3 for PFOA, PFOS, PFNA, PFHxS and DXA. Moreover, out of the 13 papers evaluating childhood exposure to PFASs, 5 were included for the meta-analyses, in particular: 5 for PFOA and BMI; 4 for PFOS and BMI; 3 for PFNA, PFHxS and BMI; 3 for PFOA, PFOS and fat mass (Table S04).

Overall, considering all the 17 studies included in the meta-analyses, the effect estimates were calculated with different log-transformations of PFASs: in particular, 6 were reported as unit (non log-transformed), 5 as natural logarithm, 4 as base-10 logarithm and 2 as base-2 logarithm. Moreover, one study also natural log-transformed the outcome variable and reported the result as percentage change

532 in the outcome. Among all the 17 studies, 12 reported calculated the estimates out of continuous data,
533 3 reported mean changes for interquartile range increase, 1 reported differences between terciles, and
534 1 reported mean differences for each standard deviation increase. Among the 16 studies considering
535 BMI, 12 calculated the beta estimate from BMI z-scores or BMI SDS, while 4 from BMI as kg/m^2.
536 Among the 7 studies considering WC, 3 calculated the beta estimate from WC z-scores or WC SDS,
537 while 4 from WC as cm. Among the 3 studies considering DXA, one calculated the beta estimate from
538 fat mass index z-score, one from total fat mass index as kg/m^2, and one from total body fat percentage.
539 Thus, the data conversions described in the section "2.3.3" were useful to properly include all these
540 studies in the meta-analyses ensuring that the effects estimates were comparable each other (Table
541 S05).

542 The results of all the meta-analyses performed are summarised in Table 3 and graphical representations
543 are given in Figure 2. The forest plots and funnel plots for each meta-analysis are reported in the
544 supplementary material (Supplementary Figures).

545 Overall, when considering prenatal exposure to PFASs and childhood BMI, WC, and DXA, the results
546 were non-significant (Table 3). Heterogeneity across studies was present for some meta-analyses, in
547 particular for prenatal PFOA, PFOS and BMI ($I^2 = 0.64$) and for prenatal PFOA and DXA ($I^2 = 0.60$).
548 For some meta-analyses, a predominant weight was attributed to a single study (e.g.: 94.7% to Chen et
549 al., 2019 - girls [79] for prenatal PFOA and BMI), however, in the sensitivity analyses, where studies
550 where meta-analyses were repeated by excluding studies one per time, the overall pooled estimates
551 were still non-significant (Table S06 and Supplementary Figures).

552 Considering the childhood exposure to PFASs and childhood BMI, results were non-significant, with
553 the exception of a significant negative association for PFNA (pooled estimate from random effects
554 model: -0.045; 95%CI: -0.087, -0.002); however, among the 3 studies included in this meta-analyses,
555 the data from Karlsen et al. (2017) [75] weigher predominantly (93.7%) and in the sensitivity analyses,
556 when the meta-analyses was repeated by excluding this study, the pooled estimate was no longer

557 significative (0.026; 95%CI: -0.144, 0.196). Interestingly, for childhood exposure to PFOA and BMI,
558 while data where non-significative (-0.024; 95%CI: -0.051, 0.003), heterogeneous (I^2 = 0.80), and
559 possibly affected by publication bias (Egger's test *p*-value: 0.029), in the sensitivity analysis, when
560 excluding the study by Timmermann et al., (2014) [80], the pooled estimate was significant (-0.035;
561 95%CI: -0.052, -0.018), and data were non-heterogeneous (I^2 = 0.00), even though Eggs t-test was still
562 significative (*p*-value: 0.018). Similarly, for childhood exposure to PFOS and BMI, data were
563 significant only when excluding the study by Timmermann et al., (2014) [80] (-0.019; 95%CI: -0.037,
564 -0.001; I^2 = 0.00; Egger's test *p*-value: 0.29).

565

566 # 4. Discussion

567 We conducted a systematic review aimed to summarise the available evidence about an early-life
568 exposure to PFASs and the association with childhood overweight and obesity. Thirty-one different
569 papers were included, among which 18 assessing prenatal exposure to PFASs, 11 childhood exposure,
570 and 2 both. Overall, most associations were conflicting and there was no clear pattern of unequivocal
571 evidence. We developed a methodology to convert the effect estimates from the different studies to
572 make them comparable each other, and when data were available and suitable from at least three
573 studies, we conducted meta-analyses to pool the estimates. In particular, meta-analyses were performed
574 with 17 studies (12 evaluating prenatal exposure, 3 evaluating childhood exposure, and 2 both). No
575 overall strongly significant association was observed between prenatal exposure to PFASs and the
576 outcomes, while a significantly negative association was found only for childhood concentrations of
577 PFNA and BMI in children, and a significant negative association between PFOA and BMI, and
578 between PFOS and BMI, in a sensitivity analysis after excluding a study.

579 Concerning the PFASs measured in the included studies, PFOA and PFOS were always quantified and
580 PFHxS and PFNA were measured in several studies. These are legacy compounds, whose presence is

very persistent and ubiquitous in the environments despite having been restricted. Moreover, in the last years, other emerging PFASs have been introduced in the market; they include molecules with a shorter carbon chain such as PFBA and PFBS [9, 91, 92]. Only 3 studies quantified PFBS, one of which found positive associations between prenatal levels of PFBS and adiposity in girls [79], and only one study quantified PFBA. Other emerging PFASs, such as the fluorotelomers and per-/polyfluoroalkyl ether acids [92], were not quantified in any studies. Furthermore, most studies did not report information about the chain branching of PFASs; indeed, both linear and branched isomers can be found in the environment, with potentially different implication for human health [93], and they can be separately quantified, as performed in Ye et al. [89].

Concerning the analytical assay, PFASs were quantified using liquid chromatography coupled with tandem mass spectrometry, with isotopic dilution; this can be considered the gold standard approach to quantify PFASs in biological samples [94, 95]. Moreover, some studies also reported validation data, in particular the limits of determination or quantitation (LOD/LOQ). A further support to the validity of the analytical measures would be the participation in interlaboratory quality assessment studies, such as the German External Quality Assessment Scheme (G -EQUAS) [96], which would certify a better reproducibility of the data among laboratories. Moreover, PFASs were measured in both serum and plasma; this is not regarded as a source of bias as no difference in the quantitation of PFASs was reported [97]. According to the new definition by Organisation for Economic Co-operation and Development (OECD), more than 6 million molecules in PubChem can be defined as PFASs [98, 99], thus suggesting that, although targeted biomarker investigations remain the gold standard in terms of accuracy and precision, also non-targeted and suspect screening investigations are required to have a better picture of the exposure to this vast class of compounds [100–103].

The outcomes considered for this review were measures of overweight, obesity, or adiposity. Almost all studies measured BMI in children, and some of them also WC and/or FM/BFP. A possible source of bias is represented by how the anthropometric measures were collected: they were measured by

606 experts in most studies (21), while in few studies they were only reported by questionnaires or in other
607 indirect ways (5), while the information about the collection of anthropometric measures was not clear
608 in a few other studies (5) (Table S03). Although the measurements of height and weight performed by
609 experts can reduce the bias of measurements, previous investigations reported that there is a good
610 correlation between measured and self-reported measures [104, 105]. Furthermore, the evaluation of
611 FM/BFP (12) was performed with different approaches including skinfold thickness (6), bioelectrical
612 impedance analysis (BIA) (3), dual-energy x-ray absorptiometry (DXA) (2), air displacement
613 plethysmography (ADP) (1). While DXA can be considered the gold standard, other approaches such
614 as skinfold thickness, are generally considered a good proxy for measuring adiposity [43]; however,
615 some limitations in their use have been pointed out, especially in children and adolescents of particular
616 population [106, 107].

617 Although the reporting of the studies was judged of good quality, some limitations in the study design
618 can be pointed out. Studies evaluating the prenatal exposure to PFASs were longitudinal studies (i.e.,
619 PFASs were measured during pregnancy or at birth and the outcomes were measured later in the
620 childhood), while mostly of those assessing the exposure to PFASs in children are cross-sectional
621 studies. The latter approach limits the evidence for a causal effect. Only 3 studies quantifying PFASs
622 in children were conducted measuring outcomes some years later [70, 81, 85]. Finally, while several
623 confounders were taken into account in the considered studies, the concomitant exposure to other
624 persistent organic pollutants may also play a role [36] but it was not considered in most studies.

625 The meta-analyses allowed to perform a quantitative evaluation of the association between PFASs
626 exposure and the considered outcome for 17 of the studies included in the systematic review. In order
627 to include in the systematic review as many studies as possible, while also ensuring the data
628 compatibility, a specific methodology was developed to convert the effect estimates from different
629 studies, considering the different log-transformations, if the estimates were calculated from continuous
630 data or from differences from terciles, interquartile ranges, or standard deviations, and whether the

631 outcomes were reported as raw measurements or as z-score or SDS (section "2.3.3 Data conversion of
632 the effect estimates"). The method here developed combines the formula reported by Rodríguez-
633 Barranco and co-workers [47], proposes a way to divide the slopes for combining continuous with
634 percentile differences, and converts data from raw BMI, WC, and fat mass to z-score using the LMS
635 method and reference tables [48, 49, 51–53]. Overall, this methodology for conversion of estimates is
636 a novelty that can be applied to other similar future meta-analyses. The two previous meta-analyses
637 that evaluated the association of prenatal exposure of PFOA [35], and of PFOS or PFOA [36] and
638 outcome of overweight or obesity in children, considered the effect estimates from the different studies
639 regardless of whether the data used to calculate the estimates were log-transformed, without performing
640 any conversion. Likewise, estimates obtained from continuous associations or from differences of
641 percentiles were combined as such. Furthermore, these other two meta-analyses considered only
642 studies that expressed BMI as z-scores, thus missing the information from those studies that reported
643 the data as kg/m^2; while this was taken into consideration in the present work thanks to the conversions
644 carried out; similarly in the meta-analyses of Stratakis and co-workers [36] only studies reporting WC
645 as cm were included, not considering not calculating the WC z-scores, while in the present work the
646 estimates were converted and meta-analyses were performed on WC z-scores. Indeed, the method used
647 for data conversion developed for the present meta-analysis allowed the inclusion of a greater number
648 of studies, while suitably taking into account the different ways data were reported from the included
649 works. A possible limitation of the present methodology applied to the studies included in this
650 systematic review, is that the conversions carried out to estimate z-scores, instead of raw
651 measurements, gave very low standard errors of the slopes, that led to some meta-analyses where a
652 single study had a predominant weight (e.g.: 94.7% to Chen et al., 2019 - girls [79] for prenatal PFOA
653 and BMI). Also, for this purpose, sensitivity analyses were carried out by repeating the meta-analyses
654 excluding one study at a time.

655 Comparing the results of the present work with the two previously published meta-analyses, our results
656 were not in agreement with the one performed by Liu and co-workers, as they found a positive

association between early life exposure to PFOA and childhood BMI z-score [35], while we found no significant associations. The reason for this contrasting result is explained by differences in the included studies, in fact, we included some recent studies not previously available [69–71, 76, 78, 79], thus increasing the strength of the pooled evidence of the present work; moreover, we performed the conversion of estimates prior the meta-analyses that allowed a more suitable comparability of the data. Recently, a systematic review with meta-analysis conducted by Stratakis and co-workers investigated the association between prenatal exposure to persistent organic pollutants and childhood obesity [36]. Although some differences between that and our work, among which grouping the studies by children age in the meta-analyses from Stratakis et al., some additional studies included in the present work, and the conversion of estimates that we carried out prior the meta-analyses, the overall conclusion about the absence of a significant association between prenatal exposure to PFAS and childhood BMI was the same. Furthermore, both this review and the one conducted by Stratakis et al. considered waist circumference as an outcome and we both found no considerable significant associations. Other differences between our work and the one from Stratakis and co-workers include: other persistent organic pollutants considered by Stratakis, more PFASs assessed in our work (in particular, meta-analyses also for PFHxS and PFNA), the also inclusion of fat mass as an outcome (calculated with DXA) in our work, further meta-analyses evaluating childhood exposure to PFASs performed in our work, and the methodology for data conversion of estimates. Finally, we set up additional innovative graphs with the superimposed forest plots related to the meta-analyses from different PFASs and outcomes (Figure 2); the R script developed to produce these graphs are available to the whole scientific community and reported in the supplementary material of the present work (supplementary text, R script, section 5).

There are also some limitations in performing the meta-analyses, due to differences in the designs of the studies, in particular for the various times, or range of times, the PFASs were quantified during gestation, as well as the different ages, or range of ages, the PFASs were measured in children. Likewise, the outcomes were measured at several different ages, or range of ages, among the studies.

Moreover, for some of the studies, the measures of outcomes suitable for this review were the result of a secondary analysis. Finally, since only studies published in indexed journals were considered, there is the possibility that other unpublished studies were missed, in particular studies reporting no statistically significant associations [108]. We tried to assess this source of bias with the funnel plots and the Egger's test (Supplementary Figures). Moreover, the low number of studies available for some associations does not allow a firm conclusion with the performed meta-analysis.

To our knowledge, this is the first systematic review conducting meta-analyses evaluating the exposure to PFASs in children and their associations with childhood overweight and obesity, although this evidence comes from cross sectional studies, thus limiting the causal relationship.

The developed methodology for the conversion of effect estimates before performing the meta-analyses can be implemented in future meta-analyses in environmental epidemiology to ensure a better comparability of data among studies.

In conclusion, the evidence summarised in this systematic review with meta-analyses confirms that there are no overall significant associations between prenatal exposure to PFASs and outcomes of childhood overweight, obesity, or adiposity; while the significant negative association found between childhood exposure to PFASs, in particular PFNA, has to be confirmed by more studies.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All the data are reported in the supplementary material of the present article, including all the R-scripts developed for this work.

Competing interests

The authors declare that they have no competing interests.

Funding

G.F. is currently supported by the Luxembourg National Research Fund (FNR) for project A18/BM/12341006.

Authors' contributions

S.F. and G.F. conceived the work; C.M.F. and G.F. conducted the literature search, the evaluation, and the collection of information from studies, with S.F. acting as supervisor; G.F. curated the database, extracted the estimates from the articles, developed the methodology for conversion of the estimates, performed the meta-analyses, designed the graphs, and wrote the paper; C.M.F. contributed to the paper preparation and revision; S.F. carried out major paper curation and revision.

Acknowledgements

We thank the library system staff of the University of Milan, in particular Flavia Rampichini, for the valuable help in developing the text strings used for the literature search. We also thank Dr. Laura Campo for providing an initial Excel table for the quality of reporting. Moreover, we thank Ana Leticia Antonio Vital, University of Bayreuth, for the initial suggestions for the development of our graphs reported in Figure 2. Finally, we thank Prof. Dr. Emma Schymanski for the helpful comments provided for improving the manuscript.

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Tables

Table 1 – Summary of the studies included in this review considering a prenatal exposure to PFASs. For each study, information about the name of the study, country or region, year of the first enrolment, and number of subjects included in the statistical analyses were reported. Moreover, the information about PFASs (which ones monitored, when the samples were collected, and measured concentrations) is reported, as well as which outcomes were measured and when. Finally, the main associations found are also reported; in particular, each line represents a positive or a negative association between a compound and an outcome: an up arrow before the compound and an up arrow before the outcome indicates a positive association, while an up arrow before the compound and a downward arrow before the outcome indicates a negative association. Marginally significant associations are also reported (^{m}).

Reference	**Name of the study**	**Country or region**	**Years of first enrolment**	**Number of subjects**	**Exposure assessment in mothers**			**Outcomes measured in children**		**Significant or marginally significant associations between exposure and outcomes**
					PFASs measured in blood	**Sampling time**	**PFAS concentrations (ng/mL)**	**Type**	**Time**	
[60] (Lauritzen et al., 2018)	NICHD-SGA	Norway and Sweden	1986–88	412 (254 Norway, 158 Sweden)	PFOA, PFOS	17–20 weeks of gestation	Median: PFOA: 1.64 (Norwegian), 2.33 (Swedish) PFOS: 9.62 (Norwegian), 16.3 (Swedish)	BMI FM/BFP	5 years	↑ PFOA - ↑ BMI-for-age-and-sex z-score (only in Norway) ↑ PFOA - ↑ FM Triceps skinfold z-score (only in Norway) ↑ PFOA - ↑ OR Overweight (only in Norway) ↑ PFOS - ↑ BMI BMI-for-age-and-sex z-score (all) ↑ PFOS - ↑ FM Triceps skinfold z-score (all) ↑ PFOS - ↑ OR Overweight (all)
[61]	ALSPAC	Avon, U.K.	1991-1992	359 girls	PFOA, PFOS, PFHxS, PFNA	15 weeks of gestation (median;	Median: PFOA: 3.7 PFOS: 19.7	BMI WC FM/BFP	9 years	↑ PFOS - ↓ BMI ↑ PFOS - ↓ WC ↑ PFOA - ↓ WC

(Hartman et al. 2017)						interquartile range: 10 and 28 weeks)	PFHxS: 1.6 PFNA: 0.5			↑ PFOA - ↑ BFP (girls with mothers in the middle education group) ↑ PFOA - ↓ BFP (girls with mothers in the highest education group) ↑ PFOS - ↓ BFP(girls with mothers in the highest education group)
[62] (Andersen et al., 2010)	Danish National Birth Cohort	Denmark	1996–2002	1010	PFOS, PFOA	1st and 2nd trimesters of gestation, and at delivery	Median: PFOS 33.4 PFOA 5.21	BMI	5 months 12 months	↑ PFOS - ↓ BMI [m] (5 months) ↑ PFOS - ↓ BMI (12 months) ↑ PFOA - ↓ BMI [m] (5 months) ↑ PFOA - ↓ BMI [m] (12 months) ↑ PFOS - ↓ BMI [m] (5 months, boys) ↑ PFOS - ↓ BMI (12 months, boys) ↑ PFOA - ↓ BMI (5 months, boys) ↑ PFOA - ↓ BMI (12 months, boys)
[63] (Andersen et al., 2013)	Danish National Birth Cohort	Denmark	1996–2002	811 (BMI) 804 (WC)	PFOA, PFOS	1st and 2nd trimesters of gestation, and at delivery	Median: PFOS: 33.8 PFOA: 5.25	BMI WC	7 years	↑ PFOA - ↓ BMI [m] ↑ PFOA - ↓ WC [m] (in boys) ↑ PFOS - ↓ BMI [m] ↑ PFOS - ↓ WC [m] (in boys)
[64] (Gyllenhammar et al., 2018)	POPUP study	Uppsala County, Sweden	1996–2011	182–193	PFOA, PFNA, PFDA, PFUnDA, PFBS, PFHxS, and PFOS	3 weeks after delivery	Mean: PFOA 2.4 PFNA 0.46 PFDA 0.23 PFUnDA 0.19 PFBS 0.03 PFHxS 3.6 PFOS 14	BMI	at 3, 4, and 5 years	↑ PFOA - ↑ BMI (3 and 4 years) ↑ PFNA - ↑ BMI (3 and 4 years) ↑ PFHxS - ↑ BMI (3 and 4 years) ↑ PFOS - ↑ BMI (4 and 5 years)
[65] (Mora et al., 2017)	Project Viva	Greater Boston, (U.S)	1999-2002	1645	PFOA, PFOS, PFHxS, PFNA	9.6 weeks of gestation (median)	Median: Children with early-childhood data PFOS: 24.8 PFOA: 5.6 PFHxS: 2.4 PFNA: 0.6 Median: Children with mid-childhood data PFOS: 24.7 PFOA: 5.6 PFHxS: 2.3 PFNA: 0.6	BMI WC FM/BFP	3.2 years (median; range: 2.9-6.1) for 1006 children (61%). 7.7 years (median; range: 6.6-10.9) for 876 children (53%).	↑ PFOS - ↑ BMI (early childhood) ↑ PFHxS - ↑ BFP (early childhood) ↑ PFOA - ↑ WC (early childhood) ↑ PFOA - ↑ WC (early childhood, boys) ↑ PFOS - ↑ BMI (mid-childhood, girls) ↑ PFNA - ↑ BMI (mid-childhood, girls) ↑ PFHxS - ↑ BFP (mid-childhood, girls) ↑ PFNA - ↑ BFP (mid-childhood) ↑ PFNA - ↑ BFP (mid-childhood, girls)
[66] (Alkhalawi et al., 2018)	Duisburg Birth Cohort Study	North Rhine–Westphalia State (Germany)	2000-2002	156	PFOA, PFOS, PFHxS	32 weeks of gestation and at delivery	Geometric mean: PFOA: 2.43 PFOS: 9.04 PFHxS: 0.62	Ponderal index	4-5 weeks, 3-4 months, 6-7 months, and 12 months	↑ PFHxS - ↑ Ponderal index (at 3-4 months)
[67]	CLEAR and INUENDO studies	Greenland and Kharkiv (Ukraine)	2002-2004	1022	PFOA, PFOS	24 ± 10 weeks of gestation (mean ± SD)	Median PFOA: 1.3 PFOS: 10.8	BM WC	between 5 and 9 years old	↑ PFOA - ↑ WtHe [m] ↑ PFOS - ↑ WtHe

(Høyer et al., 2015)							Greenland: PFOA: 1.8 PFOS: 20.2 Ukraine: PFOA 1.0 PFOS 5.0			↑ PFOA - ↑ overweight (girls, Greenland) ↑ PFOS - ↑ WtHe (girls, ↑ PFOA - ↑ BMI (Ukraine) ↑ PFOA - ↑ WtHr (girls, Greenland)
[68] (Braun et al., 2016)	HOME Study	Cincinnati, Ohio (U.S)	2003-2006	204	PFOA, PFOS, PFNA, PFHxS	16 (n=173, 87%) and 26 weeks of gestation (n=19, 9%) and at delivery (n=8, 4%)	Median: PFOA: 5.3 PFOS: 13 PFNA 0.9 PFHxS 1.4	BMI WC BFP	at 8 years and at 2, 3, 4, 5 years of age	↑ PFOA - ↑ WC at 8 years (non-linear) ↑ PFOA - ↑ BMI at 8 years (non-linear) ↑ PFOA - ↑ BFP at 8 years (non-linear) ↑ PFOA - ↑ BMI gains from 2 to 8 years
[69] (Shoaff et al., 2018)	HOME study	Cincinnati, Ohio (U.S)	2003-2006	334	PFOA, PFOS, PFNA, PHFxS	16 (86%) and 26 weeks gestation (9%), or within 48 hours from delivery (5%).	Median: PFOA: 5.5 PFOS: 14 PFNA: 0.9 PFHxS: 1.5	BMI	4 weeks, 1 and 2 years old.	↑ PFOA - ↓ BMI ↑ PFOS - ↓ BMI ↑ PFNA - ↓ BMI [m] ↑ PFHxS - ↓ BMI [m]
[70] (Liu et al., 2020)	HOME study	Cincinnati, Ohio (U.S)	2003-2006	212	PFOA, PFOS, PFNA, PFHxS	16 or 26 weeks of gestation or within 48 h from delivery	Median (during pregnancy): PFOA: 5.3 PFOS: 13.3 PFNA: 0.9 PFHxS: 1.3	BMI WC FM/BFP	12 years	↑ PFOA - ↑ WtHr ↑ PFOA - ↑ WC [m] (non-linear) ↑ PFOA - ↑ visceral fat area [m] (non-linear) ↑ PFOA - ↑ trunk fat percent [m] ↑ PFOA - ↑ android fat percent [m] ↑ PFOA - ↓ gynoid fat percent [m] ↑ PFOA - ↑ WC in girls ↑ PFOA - ↑ WtHr in girls ↑ PFOA - ↑ BFP in girls ↑ PFHxS - ↑ WtHr [m] ↑ PFHxS - ↑ WC [m] ↑ PFHxS - ↑ visceral fat area [m] ↑ PFHxS - ↑ trunk fat percent [m] ↑ PFHxS - ↑ android fat percent [m] ↑ PFHxS - ↓ gynoid fat percent [m] ↑ PFHxS - ↑ WtHr in girls ↑ PFHxS - ↑ android/gynoid fat percent ratio in girls ↑ PFHxS - ↑ risk of overweight/obesity
[71] (Braun et al., 2021)	HOME study	Cincinnati, Ohio (U.S)	2003-2006	345	PFOA, PFOS, PFNA, PFHxS	16 weeks of gestation (n=294, 85.2%), 26 weeks of	Median PFOA: 5.5 PFOS: 13.8 PFNA: 0.9	BMI	at 4 weeks and 1, 2, 3, 4, 5, 8, and 12 years	↑ PFOA - ↓ BMI (infancy and early childhood) (non-monotonic)

						gestation (n=34, 9.9%), or within 24 hours of delivery (n=17, 4.2%)	PFHxS: 1.5			↑ PFOA - ↑ BMI (mid-childhood and adolescence) (non-monotonic) ↑ PFOS - ↓ BMI (infancy, childhood, adolescence) ↑ PFHxS - ↓ BMI (infancy, childhood, adolescence)
[72] (Martinsson et al., 2020)	Southern Sweden Maternity Cohort	Malmö, Sweden	2003–2008	1048	PFOS, PFOA, PFHxS, PFNA	14 weeks of gestation	Median PFOS: 16.6 PFOA: 3.1 PFHxS: 0.7 PFNA: 0.4	BMI	4 years	No associations
[73] (Manzano-Salgado et al., 2017)	INMA birth cohort study	three Spanish regions: Gipuzkoa, Sabadell, and Valencia	2003–2008	1154 (6 months) 1230 (4 years) 1086 (7 years)	PFHxS, PFOS, PFOA, PFNA	1st trimester of gestation	Geometric mean: PFHxS: 0.61 PFOS: 5.80 PFOA: 2.32 PFNA: 0.66	Weight gain from birth to 6 months BMI WC (only at 4 years for the Valencia and Sabadell subcohorts (n=839, 68%))	6 months, 4, and 7 years	↑ PFOA - ↑ weight gain to 6 months (boys) ↑ PFHxS - ↓ weight gain to 6 months [m] ↑ PFHxS - ↓ BMI [m] (overall and boys) (at 4 and 7 years) ↑ PFHxS - ↓ WC [m] (overall and boys) (at 4 and 7 years) ↑ PFHxS - ↑ BMI [m] (girls) (at 4 and 7 years) ↑ PFHxS - ↑ WC [m] (girls) (at 4 and 7 years) ↑ PFOS - ↑ BMI [m] (overall and boys) (at 4 and 7 years) ↑ PFOA - ↑ BMI [m] (overall and boys) (at 4 and 7 years) ↑ PFNA - ↑ BMI [m] (overall and boys) (at 4 and 7 years) ↑ PFOS - ↑ WC [m] (at 7 years) ↑ PFNA - ↑ BMI [m] (at 7 years) ↑ PFNA - ↑ WC [m] (at 7 years)
[74] (Chen et al., 2017)	Taiwan Birth Panel Study	Taipei and New Taipei, Taiwan	2004-2005	429	PFOA, PFOS	At birth	Median PFOA: 2.6 PFOS: 7.6	BMI	at 4, 6, 12, 24, 60, 84 and 108 months	↑ PFOS - ↓ BMI (for girls, time span from 6 to 12 months) ↑ PFOS - ↓ BMI (for girls, time span from 12 to 24 months) ↑ PFOS - ↑ BMI (for girls, time span from 60 to 108 months)
[75] (Karlsen et al., 2017)	Not specified	Faroe Islands, Denmark	2007-2009	444 (at 18 months) 371 (at 5 years)	PFOS, PFOA, PFHxS, PFNA, PFDA	2 weeks after delivery	Median PFOS: 8.25 PFOA: 1.40 PFHxS: 0.20 PFNA: 0.66	BMI	at 18 months and 5 years	↑ PFOS - ↑ BMI (18 months) ↑ PFOS - ↑ RR overweight (18 months)

							PFDA: 0.26			↑ PFOA - ↑ overweight risk (5 years) ↑ PFOA - ↑ BMI [m] (18 months) ↑ PFHxS - ↑ BMI [m] (18 months) ↑ PFDA - ↓ overweight risk (5 years) (non-linear) ↑ PFNA - ↓ overweight risk [m] (18 months and 5 years) (non-linear
[76] (Yeung et al., 2019)	Upstate KIDS Study	New York State (excluding New York City), (U.S)	2008-2010	2920 (1,954 singletons and 966 twins)	PFOA, PFOS	at birth in children (dried blood spot)	Mean PFOS 1.7 PFOA 1.1	BMI	4, 8, 12, 18, 24, 30, and 36 months	↑ PFOA - ↓ BMI (in singletons) ↑ PFOS - ↓ BMI (in singletons) ↑ PFOA - ↓ BMI (in singleton girls) ↑ PFOS - ↓ BMI (in singleton girls) ↑ PFOA - ↓ BMI (in singleton boys, non-linearly) ↑ PFOA - ↑ BMI (in twins, non-linearly)
[77] (Starling et al., 2019)	Healthy Start Study	Colorado, (U.S)	2009-2014	415	PFOSA, N-EtFOSAA, N-MeFOSAA, PFHxS, PFOA, PFOS, PFNA	27 weeks of gestation, (median, range 20–34 weeks)	Median PFOA: 1.0 PFOS: 2.2 PFNA: 0.4 PFDA: 0.1 PFHxS: 0.7 MeFOSAA: 0.1	weight-for-length weight-for-age FM/BFP	5 months of age (average: 5.1 months, range: 2.8 - 9.4 months)	↑ PFOA - ↑ FM/BFP (males) ↑ PFNA - ↑ FM/BFP (males) ↑ PFOS - ↓ FM/BFP [m] (females) ↑ PFOS - ↓ weight-for-age (females)↑ PFOS - ↓ weight-for-length (females) ↑ PFHxS - ↓ weight-for-age (females) ↑ PFHxS - ↑ rapid growth in weight-for-length ↑ N-MeFOSAA - ↑ weight-for-age (both sexes combined and females) ↑ N-MeFOSAA - ↑ rapid growth in weight-for-age ↑ N-MeFOSAA - ↑ rapid growth in weight-for-length
[78] (Jensen et al., 2020)	OCC	Odense, Southern Denmark	2010-2012	602 (3 months) 530 (18 months)	PFOA, PFOS, PFHxS, PFNA, PFDA	before 16 weeks of gestation: median GA (IQR): 11.3 (9.9, 14.3) weeks	Median PFHxS: 0.30 PFOS: 8.04 PFOA: 1.62 PFNA: 0.66 PFDA: 0.26	BMI WC FM/BFP	3, and 18 months	↑ PFNA - ↑ BMI (3 and 18 months) ↑ PFNA - ↑ BMI (in girls, 3 and 18 months) ↑ PFNA - ↑ BFP (3 months) ↑ PFDA - ↑ BMI (3 and 18 months) ↑ PFDA - ↑ BMI [m] (in girls, 3 and 18 months) ↑ PFDA - ↑ BFP (3 months) ↑ PFOS - ↑ BMI [m] (3 and 18 months)

[79] (Chen et al., 2019)	Shanghai Prenatal Cohort	Shanghai, China	2012-2017	404	PFOA, PFOS, PFNA, PFDA, PFUnDA, PFHxS, PFOSA, PFDoA, PFBS, PFHpA	at birth	Median PFOS: 2.44 PFOA: 6.74 PFNA: 0.64 PFDA: 0.36 PFUA: 0.40 PFDoA: 0.09 PFHxS: 0.16 PFBS: 0.05	BMI WC WtHr FM/BFP	5 years	↑ PFBS - ↑ WC (girls) ↑ PFBS - ↑ WtHe (girls) ↑ PFBS - ↑ FM (girls) ↑ PFBS - ↑ BFP (girls) ↑PFDoA - ↓ WC (girls) ↑PFDoA - ↓ FM (girls) ↑PFDoA - ↓ BFP (girls) ↑ PFNA - ↑ BFP (boys)

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Table 2 – Summary of the studies included in this review considering a childhood exposure to PFASs. For each study, information about the name of the study, country, year of the first enrolment, and number of subjects included in the statistical analyses were reported. Moreover, the information about PFASs (which ones monitored, when the samples were collected, and measured concentrations) is reported, as well as which outcomes were measured and when. Finally, the main associations found are also reported; in particular, each line represents a positive or a negative association between a compound and an outcome: an up arrow before the compound and an up arrow before the outcome indicates a positive association, while an up arrow before the compound and a downward arrow before the outcome indicates a negative association. Marginally significant associations are also reported ([m]).

Reference	**Name of study**	**Country and region**	**Years of first enrolment**	**Number of subjects**	**Exposure assessment in children**			**Outcomes measured in children**		**Significant or marginally significant associations between exposure and outcomes**
					PFASs measured in blood	**Sampling time**	**PFASs concentrations (ng/mL)**	**Type**	**Time**	
[80] (Timmermann et al., 2014)	EYHS	Odense, Denmark	1997	499	PFOA, PFOS	8-10-year-old children (third-grade students)	Median PFOS: 41.5 PFOA: 9.3	BMI WC FM/BFP	8-10-year-old children (third-grade students)	↑ PFOS - ↓ FM/BFP in girls [m] ↑ PFOS - ↓ FM/BFP in boys [m]
[81] (Domazet et al., 2016)	EYHS	Odense, Denmark	1997 and 2003	501	PFOA, PFOS	9 yeas 15 years	Medians PFOS: from 20.8 to 44.5 PFOA: from 3.4 to 9.7	BMI WC FM/BFP	9 yeas 15 years	↑ PFOS (at 9 y) - ↑ BMI (at 15y) ↑ PFOS (at 9 y) - ↑ WC (at 15 y) ↑ PFOS (at 9 y) - ↑ FM/BFP (at 15 y)
[82]	Danish sub-study	Odense, Denmark	1997	242	PFOS, PFOA,	9 years	Median PFOS: 42.0 - 42.9	BMI FM/BFP	9 years	↑ PFNA - ↓ BMI ↑ PFDA - ↓ BMI

(Domazet et al., 2020)	of the EYHS				PFNA, PFDA, PFHxS		PFOA: 9.5 PFNA: 0.41 - 0.44 PFDA: 0.11 PFHxS 0.89 - 0.95			↑ PFNA - ↓ FM ↑ PFDA - ↓ FM ↑ PFHxS - ↓ FM
[83] (Harris et al., 2017)	Project Viva	Boston - urban and suburban Eastern Massachusetts (U.S)	2007-2010	653	PFOS, PFOA, PFHxS PFNA, N-EtFOSAA N-MeFOSAA, PFDA, PFOSA	7.7 years (median; range: 6.6−10.6)	Median PFOS: 6.2 PFOA: 4.4 PFHxS: 1.9 PFNA: 1.5 Et-PFOSA-AcOH:LOD Me-PFOSA-AcOH: 0.3 PFDeA: 0.3 FOSA: <LOD	BMI	7.7 years (median; range: 6.6−10.6)	↑ PFOA - ↓ BMI ↑ PFDeA - ↓BMI
[84] (Geiger et l., 2021)	NHANES	U.S.	1999-2000, 2003-2012	2473	PFOA, PFOS	12-18 years	Mean PFOA 3.79 PFOS 15.66	BMI WC	12-18 years	↑ PFOA - ↑ BMI [m] ↑ PFOS - ↑ BMI (significant in the unadjusted model) ↑ PFOS - ↑ WC (significant in the unadjusted model)
[70] (Liu et al., 2020)	HOME Study	Cincinnati, Ohio (U.S)	2003-2006	212	PFOA, PFOS, PFNA, PFHxS	at birth and ages 3, 8 and 12 years.	Median PFOA: 5.4 (3 y), 2.5 (8 y), 1.3 (12 y) PFOS: 6.2 (3 y), 3.6 (8 y), 2.4 (12 y) PFNA: 1.3 (3 y), 0.7 (8 y), 0.3 (12 y) PFHxS: 1.9 (3 y), 1.2 (8 y), 0.7 (12 y)	BMI WC FM/BFP	12 years	No associations
[85] (Pinney et al., 2019)	the female puberty cohort of the BCERP	San Francisco Bay Area and Cincinnati (U.S.)	2004–2007	704 (only girls)	PFOA	6–8 years at first enrolments	Median: 6.4	BMI WtHe WtHi	6–8 years at first enrolments. Repeated measures up to 18 years.	↑ PFOA - ↓ BMI ↑ PFOA - ↓ WtHe

[86] (Fassler et al., 2019)	BCERP	Cincinnati (U.S)	2004-2006	353 (only girls)	N-MeFOSAA, PFDA, PFNA, PFOA, PFOS, PFHxS.	6-8 years	Median Me-PFOSA-AcOH: 0.8 PFDeA: 0.30 PFHxS: 5.20 PFNA: 1.40 PFOA: 7.30 PFOS: 13.60	BMI WtHe WtHi FM	6-8 years	↑ PFOA - ↓ BMI ↑ N-MeFOSAA - ↓ BMI ↑ PFDeA - ↓ BMI ↑ PFOS - ↓ BMI ↑ PFOA - ↓ WtHe ↑ N-MeFOSAA - ↓ WtHe ↑ PFDeA - ↓ WtHe ↑ PFOS - ↓ WtHe ↑ PFOA - ↓ FM
[87] (Koponen et al., 2018)	birth cohort study LUKAS2	Eastern Finland	2005–2015	54	PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFTrDA, PFTeDA, PFHxS, PFHpS, PFDS; N-MeFOSAA, N-EtFOSAA, 6:2 diPAP, 8:2 diPAP	1, 6 and 10.5 years	Median PFOS: 1.5 - 6.3 PFOA: 1.4 - 7.1 PFNA: 0.35 - 0.84 PFHxS: 0.20 - 0.49	BMI	1, 6, and 10.5 years	No association
[75] (Karlsen et al., 2017)	Not specified	Faroe Islands, Denmark	2007-2009	444	PFOS, PFOA, PFHxS, PFNA, PFDA	5 years	Median PFOS: 4.70 PFOA: 2.20 PFHxS: 0.33 PFNA: 1.13 PFDA: 0.34	BMI	5 years	↑ PFNA - ↓ BMI ↑ PFDA - ↓ BMI ↑ PFOA - ↓ BMI ↑ PFOS - ↓ BMI

[88] (Kim et al., 2014)	Not specified	Dae-gu City, South Korea	2012	120	PFBA, PFPeA, PFHxA, PFHpA, PFOA, PFNA, PFDA, PFUnDA, PFDoDA, PFTrDA, PFTeDA, PFBS, PFHxS, PFHpS, PFOS, PFDS	5 - 13 years	Mean PFBA: 0.346 PFPeA: 0.497 PFHxA: 0.353 PFHpA: 0.312 PFOA: 5.15 PFNA: 1.72 PFDA: 0.604 PFUnDA: 0.748 PFDoDA: - PFTrDA: 0.306 PFTeDA: - PFBS: 0.105 PFHxS: 1.13 PFHpS: 0.203 PFOS: 6.58 PFDS: -	BMI	5 - 13 years	↑ PFOA - ↓ BMI ↑ PFHxS - ↓ BMI ↑ total PFASs - ↓ BMI
[89] (Ye et al. ; 2018)	NHANES	U.S.	2013–2014	639	PFOSA, N-MeFOSAA, N-EtFOSAA, PFBS, PFHxS, PFHpA, PFNA, PFDA, PFUnDA, PFDoDA, n-PFOA, Sb-PFOA, n-PFOS, Sm-PFOS.	3–11 years	Median ΣPFOS: 3.75 ΣPFOA: 1.94 PFHxS: 0.810 PFNA: 0.700 n-PFOS: 2.47 Sm-PFOS: 1.28 n-PFOA: 1.82 Sb-PFOA: < LOD PFBS: < LOD PFOSA: < LOD N-MeFOSAA: 0.110 N-EtFOSAA: < LOD PFHpA: < LOD PFDA: < LOD PFUnDA: < LOD PFDoDA: < LOD	BMI	3–11 years	↑ ΣPFOA - ↓ BMI [m] ↑ n-PFOA - ↓ BMI [m]

[90] (Scinicariello et al., 2020)	NHANES	U.S.	2013–2014	600	PFOA, PFNA, PFHxS, PFOS	3–11 years	Geometric mean PFOA: 1.92 PFNA: 0.80 PFHxS: 0.85 PFOS: 3.90	BMI	3–11 years	↑ PFOA - ↓ BMI [m] ↑ PFHxS - ↓ BMI [m] ↑ PFOS - ↓ BMI [m] ↑ PFOA - ↓ BMI (boys) ↑ PFHxS - ↓ BMI (boys)

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Table 3 – Results of the meta-analyses performed on a subset of the studies included in the systematic review. For each combination of exposure and outcome, a meta-analysis was performed only if suitable information was reported from at least 3 studies. In this table, the pooled estimated of the random effects models (with the 95% confidence interval), the I^2 of the heterogeneity test, and *p*-value Egger's test are reported. The complete forest and funnel plots are reported in the supplementary material.

Conditions assessed	Studies included	Random effects model [95% CI]	Heterogeneity (I^2)	Egger's test *p*-value
Prenatal PFOA and childhood BMI	[60, 61, 63–65, 67, 71, 73–76, 78, 79]	$3.51*10^{-5}$ [$-1.38*10^{-4}$; $2.08*10^{-4}$]	0.64	0.473
Prenatal PFOS and childhood BMI	[60, 61, 63–65, 67, 71, 73–76, 78, 79]	$-1.07*10^{-3}$ [$-4.84*10^{-3}$; $2.70*10^{-3}$]	0.64	0.746
Prenatal PFNA and childhood BMI	[61, 64, 65, 71, 73, 75, 78, 79]	$3.60*10^{-4}$ [$-3.02*10^{-3}$; $3.74*10^{-3}$]	0.34	0.008
Prenatal PFHxS and childhood BMI	[61, 64, 65, 71, 73, 75, 78, 79]	$-1.33*10^{-3}$ [$-3.45*10^{-3}$; $7.93*10^{-4}$]	0.00	0.449
Prenatal PFOA and childhood WC	[61, 63, 65, 70, 73, 78, 79]	$-5.49*10^{-6}$ [$-5.61*10^{-5}$; $4.51*10^{-5}$]	0.20	0.552
Prenatal PFOS and childhood WC	[61, 63, 65, 70, 73, 78, 79]	$-5.22*10^{-5}$ [$-3.32*10^{-4}$; $2.27*10^{-4}$]	0.35	0.886
Prenatal PFNA and childhood WC	[61, 65, 70, 73, 78, 79]	$1.53*10^{-4}$ [$-4.08*10^{-4}$; $7.15*10^{-4}$]	0.00	0.095
Prenatal PFHxS and childhood WC	[61, 65, 70, 73, 78, 79]	$-6.20*10^{-5}$ [$-5.02*10^{-4}$; $3.78*10^{-4}$]	0.19	0.615
Prenatal PFOA and childhood DXA	[61, 65, 70]	$2.56*10^{-3}$ [$-2.51*10^{-2}$; $3.03*10^{-2}$]	0.60	0.669
Prenatal PFOS and childhood DXA	[61, 65, 70]	$1.19*10^{-3}$ [$-9.67*10^{-3}$; $1.21*10^{-2}$]	0.42	0.569
Prenatal PFNA and childhood DXA	[61, 65, 70]	$-1.59*10^{-2}$ [$-4.23*10^{-2}$; $1.06*10^{-2}$]	0.00	0.995
Prenatal PFHxS and childhood DXA	[61, 65, 70]	$2.53*10^{-4}$ [$-9.70*10^{-3}$; $1.02*10^{-2}$]	0.48	0.626
Childhood PFOA and childhood BMI	[70, 75, 80, 85, 90]	$-2.43*10^{-2}$ [$-5.13*10^{-2}$; $2.64*10^{-3}$]	0.80	0.029
Childhood PFOS and childhood BMI	[70, 75, 80, 90]	$-8.00*10^{-3}$ [$-2.32*10^{-2}$; $7.24*10^{-3}$]	0.38	0.058
Childhood PFNA and childhood BMI	[70, 75, 90]	$-4.48*10^{-2}$ [$-8.74*10^{-2}$; $-2.16*10^{-3}$]	0.00	0.366
Childhood PFHxS and childhood BMI	[70, 75, 90]	$-7.01*10^{-2}$ [$-1.45*10^{-1}$; $5.34*10^{-3}$]	0.00	0.292

Figure legends

Figure 1 – Summary of the literature search performed in this review.

Figure 2 – Superimposed forest plots of the meta-analyses performed to evaluate associations between prenatal (A) or childhood (B) exposure to PFASs and outcomes in children. The squares are proportional to the weight assigned to each study in the random effects models, while horizontal lines represent the 95% confidence intervals reported. The diamonds at the bottom represent the pooled estimated of the random effects models (with the 95% confidence interval).

Figures

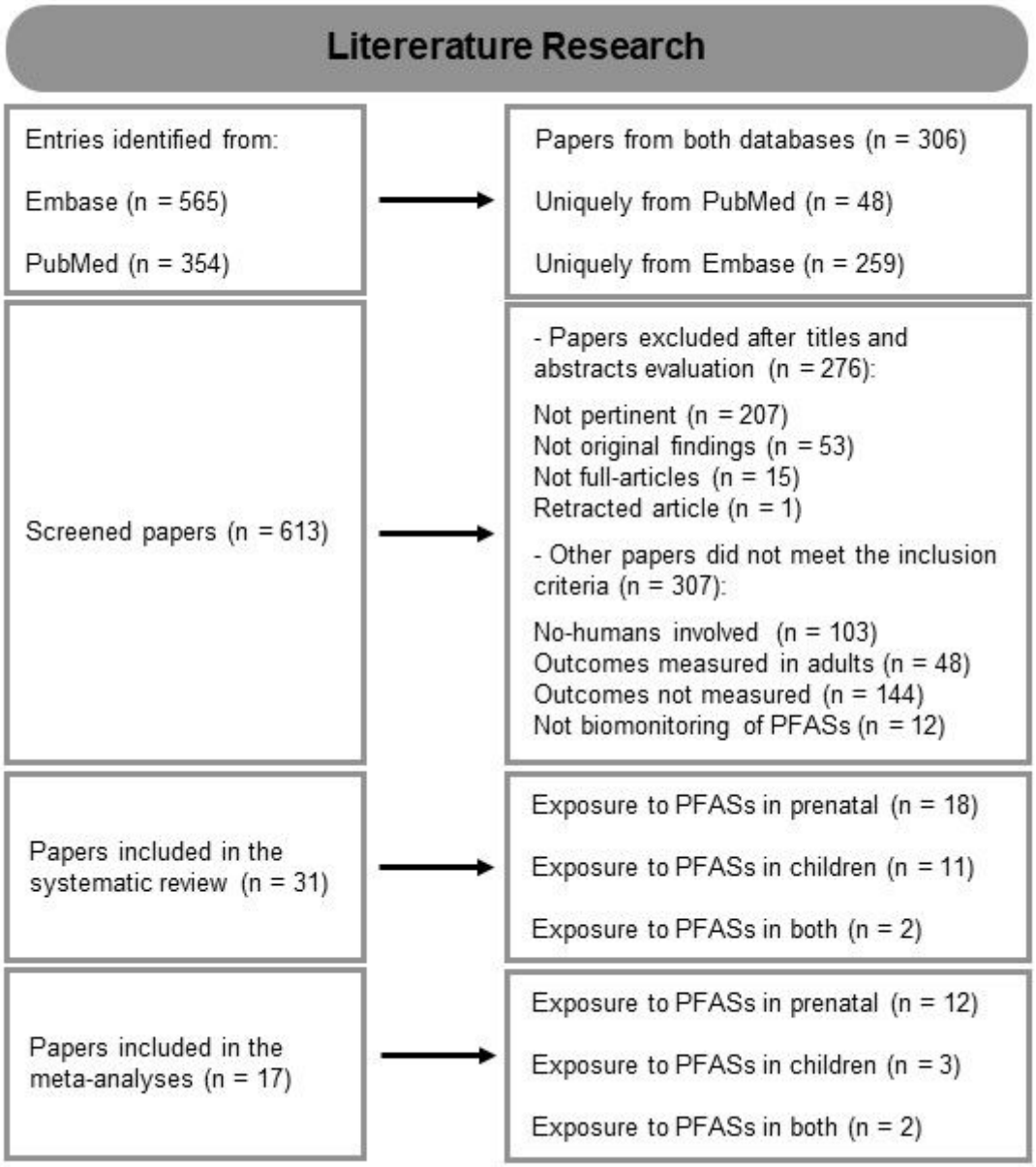

Figure 1

Summary of the literature search performed in this review.

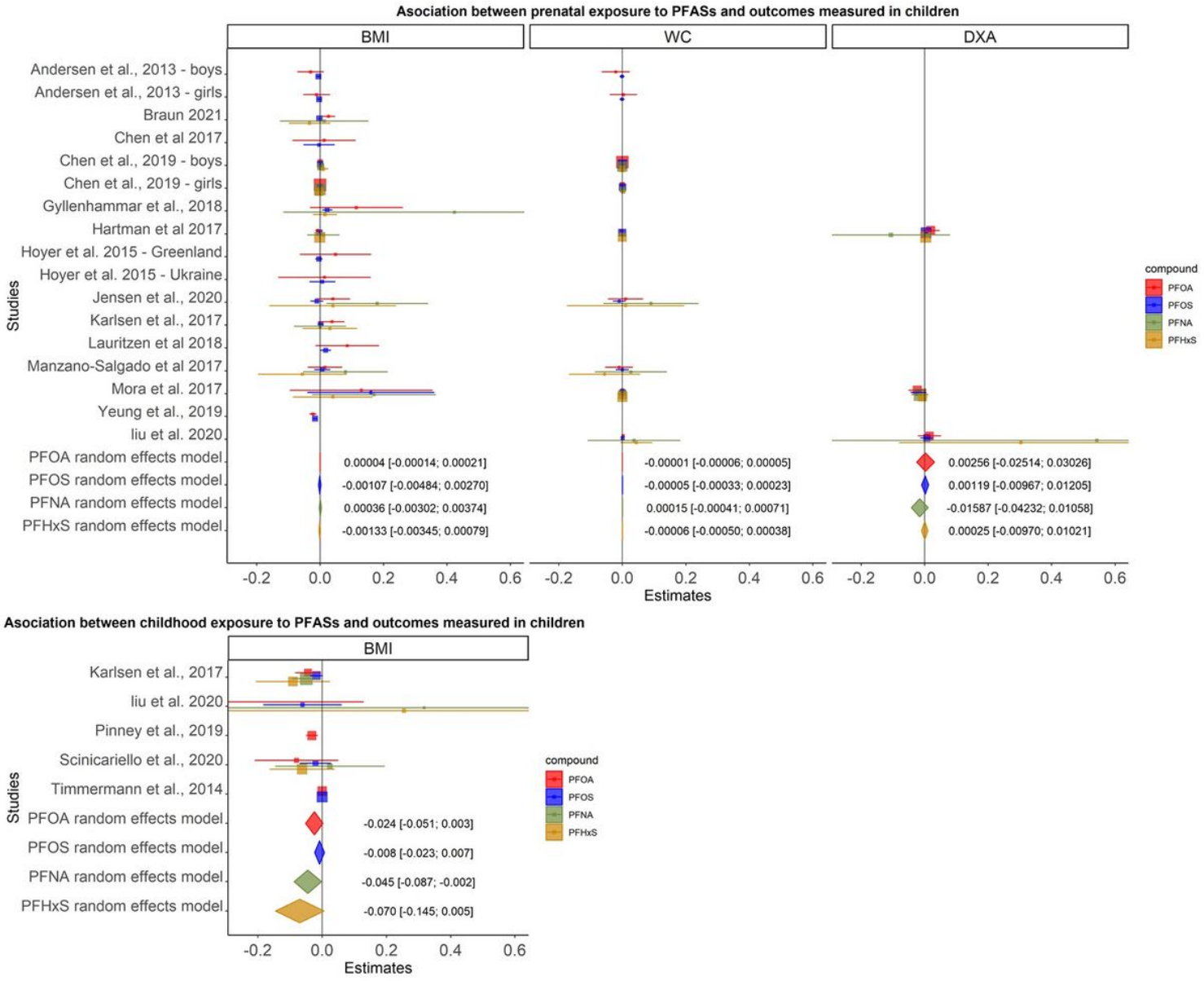

Figure 2

Superimposed forest plots of the meta-analyses performed to evaluate associations between prenatal (A) or childhood (B) exposure to PFASs and outcomes in children. The squares are proportional to the weight assigned to each study in the random effects models, while horizontal lines represent the 95% confidence intervals reported. The diamonds at the bottom represent the pooled estimated of the random effects models (with the 95% confidence interval).

Supplementary Files

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- FrigerioPFASsrevsupplTableS01Pmtot.csv
- FrigerioPFASsrevsupplTableS02EMtot.csv

- FrigerioPFASsrevsupplTableS03studies.xlsx
- FrigerioPFASsrevsupplTableS04.txt
- FrigerioPFASsrevsupplTableS05.xlsx
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