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Cross-sectional associations between exposure to per- and polyfluoroalkyl substances and body mass index among European teenagers in the HBM4EU aligned studies☆

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ABSTRACT

Per- and polyfluoroalkyl substances (PFAS) are widespread pollutants that may impact youth adiposity patterns. We investigated cross-sectional associations between PFAS and body mass index (BMI) in teenagers/adolescents across nine European countries within the Human Biomonitoring for Europe (HBM4EU) initiative. We used data from 1957 teenagers (12–18 yrs) that were part of the HBM4EU aligned studies, consisting of nine HBM studies (NEBII, Norway; Riksmaten Adolescents 2016–17, Sweden; PCB cohort (follow-up), Slovakia; SLO CRP, Slovenia; CROME, Greece; BEA, Spain; ESTEBAN, France; FLEHS IV, Belgium; GerES V-sub, Germany). Twelve PFAS were measured in blood, whilst weight and height were measured by field nurse/physician or self-reported in questionnaires. We assessed associations between PFAS and age- and sex-adjusted BMI z-scores using linear and logistic regression adjusted for potential confounders. Random-effects meta-analysis and mixed effects models were used to pool studies. We assessed mixture effects using molar sums of exposure biomarkers with

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toxicological/structural similarities and quantile g-computation. In all studies, the highest concentrations of PFAS were PFOS (medians ranging from 1.34 to 2.79 μg/L). There was a tendency for negative associations with BMI z-scores for all PFAS (except for PFHxS and PFHpS), which was borderline significant for the molar sum of [PFOA and PFNA] and significant for single PFOA [β-coefficient (95% CI) per interquartile range fold change = −0.06 (−0.17, 0.00) and −0.08 (−0.15, −0.01), respectively]. Mixture assessment indicated similar negative associations of the total mixture of [PFOA, PFNA, PFHxS and PFOS] with BMI z-score, but not all compounds showed associations in the same direction: whilst [PFOA, PFNA and PFOS] were negatively associated, [PFHxS] associated positively with BMI z-score. Our results indicated a tendency for associations of relatively low PFAS concentrations with lower BMI in European teenagers. More prospective research is needed to investigate this potential relationship and its implications for health later in life.

1. Introduction

Childhood and adolescent adiposity patterns are risk factors for obesity, hypertension, type 2 diabetes, atherosclerosis and cardiovascular disease in adulthood (Reilly and Kelly, 2011). The prevalence of obesity worldwide in children, adolescents and adults has increased over the past decades and this trend will likely continue (Ng et al., 2014), painting a dangerous picture for future population health. Youth adiposity patterns may be impacted by exposure to obesogenic chemicals (Grün and Blumberg, 2009), e.g. per- and polyfluoroalkyl substances (PFAS). PFAS are a human-made group of chemicals that are extremely widespread, environmentally persistent and almost omnipresent in humans with generally long half-lives of 3–5 years (Lau et al., 2007) (2–5 years for PFOS and PFOA and 4–5 years for shorter chain PFHxS and PFHpS (Li et al., 2022)). Generally, long-chain, sulfonated and linear isomer PFAS have slower excretion rates than shorter-chain, carboxylated and major branched isomer PFAS (Zhang et al., 2013).

Experimental studies indicate that PFAS induces perturbations in pathways relevant to metabolism, e.g. peroxisome proliferator activated receptor (PPAR) activation (Bijland et al., 2011; Vanden Heuvel et al., 2006). In addition, PFAS exposure associates with unfavorable lipid profile changes as reviewed by the European Food Safety Agency (EFSA et al., 2018) as well as with metabolic dysfunction (Margolis and Sant, 2021). Other potential mechanisms for an obesogenic effect of PFAS exposure in youth include endocrine disruption (Du et al., 2013), dyslipidemia (Bijland et al., 2011) and inflammation (Takacs and Abbott, 2007). However, epidemiological studies investigating associations between prenatal PFAS exposures and youth adiposity patterns are inconclusive, reporting positive (Braun et al., 2016; Chen et al., 2019; Lauritzen et al., 2018; Liu et al., 2020; Mora et al., 2017), negative (Braun et al., 2021; Hartman et al., 2017; Starling et al., 2019; Starling et al., 2017) and null (Bloom et al., 2021; Manzano-Salgado et al., 2017; Martinsson et al., 2020) associations. Similarly, cross-sectional studies with postnatal PFAS exposure during childhood or adolescence are equivocal, reporting positive (Averina et al., 2021; Geiger et al., 2021), negative (Fassler et al., 2019; Thomsen et al., 2021) and null (Averina et al., 2021; Thomsen et al., 2021) associations. One longitudinal study indicated childhood perfluorooctane sulfonic acid (PFOS) exposure associated with higher adolescent body mass index (BMI), but adolescent PFOS exposure did not associate with higher BMI in adulthood (Domazet et al., 2016). In addition to these inconsistent findings, only few studies have looked at the effect of mixtures (Janis et al., 2021; Vrijheid et al., 2020), whilst these findings could shed light on previous inconsistent findings and provide more insight in specific compound effects.

Improved knowledge of preventable risk factors, including obesogenic chemicals, is imperative to improve population health and reduce disease risk later in life. Therefore, within the Horizon 2020 project 'HBM4EU', the Human Biomonitoring for Europe initiative (see www.hbm4eu.eu for details (Ganzleben et al., 2017)), we aimed to investigate associations of single PFAS exposures and PFAS mixtures with BMI in teenagers/adolescents (12–18 yrs old; hereafter referred to as teenagers). We used data from nine studies from different countries in Europe, resulting in a large study population (n = 1957) with quality assured PFAS measurements.

2. Methods

2.1. Study population

The study population was drawn from the 'HBM4EU aligned studies' (Gilles et al., 2021; Gilles et al., 2022). The HBM4EU aligned studies are a survey aimed at collecting HBM samples and data from European HBM studies to derive current internal exposure data for the European population across a wide geographic spread. For the present study, nine studies targeting teenagers (12–18 years) had available blood samples used for PFAS measurement: NEBII (Norwegian Environmental Biobank II; a sub study of The Norwegian Mother, Father and Child Cohort Study (MoBa) (Magnus et al., 2016); Norway), Riksmaten adolescents 2016–17 (Sweden), PCB cohort (follow-up) (Endocrine disruptors and health in children and teenagers in Slovakia; Slovakia), SLO CRP (Exposure of children and adolescents to selected chemicals through their habitat environment; Slovenia), CROME (Cross-Mediterranean Environment and Health Network; Greece), BEA (Biomonitorización en Adolescentes; Spain), ESTEBAN (Étude de santé sur l'environnement, la biosurveillance, l'activité physique et la nutrition; France), FLEHS IV (Flemish Environment and Health Study IV; Belgium), GerES V-sub (German Environmental Survey, 2014–2017 unweighted subsample; Germany). All studies were national or regional cross-sectional population-based studies, except the longitudinal NEBII and PCB cohort (follow-up). In all studies, parents (and for some studies additionally the teenagers) have signed informed consent.

Detailed information about each study, the study selection process and data homogenization within the HBM4EU has been described previously (Gilles et al., 2021; Gilles et al., 2022). In brief, recommendations for selecting participants were: 1) to have lived at least 5 years in the catchment area of the data collection, not be hospitalized or institutionalized and be between 12 and 19 years of age; 2) to have completed a questionnaire and have available serum or plasma samples with appropriate sample matrix and volume. Stratification of the participants into mutually exclusive subgroups was applied in chronological order and with a specified proportion: sex (50% ± 2% of each sex), degree of urbanization according to Eurostat categorization into cities, towns/suburbs, rural area (at least 10% of each of the three levels); household educational level based on the International Standard Classification of Education (ISCED, 2011) [low (ISCED 0–2), medium (ISCED 3–4) and high (ISCED 5–8)] (at least 10% of each of the three levels); sampling season (approximately equal distribution over all seasons); age (all ages from the original data collection were present in the selection). Subsequently, if applicable, participants were randomly selected while adhering to the subgroup population proportions. This selection process resulted in a final study population of 1957 teenagers with PFAS measurements.

2.2. Chemical analysis of PFAS

The harmonization of chemical analysis has also been outlined by Gilles et al. (2021). In brief, analyses of six studies were performed in

laboratories that successfully passed the HBM4EU quality assurance quality control (QA/QC) programme (Esteban López et al., 2021; Nübler et al., 2022). Data for two studies, ESTEBAN and GerES V-sub, were generated before HBM4EU QA/QC programme, but were deemed comparable in quality (as determined by evaluation of analytical methods and proficiency tests) and were approved *posterior*. Data for Riksmaten Adolescents 2016-17 has been generated outside of the HBM4EU and the laboratory presented PFAS in ng/g (μg/kg), which was reported to HBM4EU in μg/L assuming that 1 ml blood serum equals 1 g blood serum. PFAS concentrations (linear form or sum of all isomers including linear and branched forms) were measured in serum in all studies, except for NEBII and GerES V-sub, which were measured in plasma. Liquid chromatography-tandem mass spectrometry was used in all studies, except in NEBII and Riksmaten Adolescents 2016–17 where ultraperformance liquid chromatography-tandem mass spectrometry was used (Supplemental Table 1). Twelve PFAS were assessed: perfluoropentanoic acid (PFPeA), perfluorohexanoic acid (PFHxA), perfluoroheptanoic acid (PFHpA), perfluorooctanoate (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), perfluorododecanoic acid (PFDoDA), perfluorobutane sulfonic acid (PFBS), perfluorohexane sulfonic acid (PFHxS), perfluoroheptanane sulfonic acid (PFHpS) and PFOS.

PFAS values below the limit of quantification (LOQ) were imputed using single random imputation from a truncated lognormal distribution. We included PFAS measurements within a study if at least 70% of the values for a single PFAS were ≥LOQ, to be able to accurately assess tertiles and continuous. PFDoDA and PFBS were below this threshold in all studies and not used for further analysis. Supplemental Table 1 provides details of the PFAS measurements for the individual studies, including number of observations with PFAS measurements, LOQs, and % <LOQ for each PFAS.

2.3. Assessment of outcome and covariates

Height and weight were either measured by field nurse/physician and/or self-reported (in 3 studies: CROME, BEA and NEBII), 45 participants were excluded from the analyses due to missing values (from NEBII, PCB cohort follow-up and BEA). A BMI z-score was calculated standardized for age and sex according to growth charts from the World Health Organization and categorized according to the International Obesity Task Force classification, using the 'zanthro' package in Stata (Vidmar et al., 2013). Self-reported co-variates included highest educational level of the household (ISCED scale: low/medium vs high education), consumption of several dietary components (fish, meat, milk, egg and fastfood; frequency of consumption: <1/week vs 1/week vs > 1/week), breastfeeding (in months, available in NEBII, Riksmaten Adolescents 2016–17, PCB cohort (follow-up), CROME, FLEHS IV and GerES V-sub) and birthweight (in grams, available in NEBII, PCB cohort (follow-up), FLEHS IV and GerES V-sub). Missing information on covariates (<20% within each study) was imputed using multiple imputation chained equations (20 imputations).

2.4. Statistical analyses

For the exposure, the individual PFAS concentrations or molar sums were assessed as a continuous variable per interquartile range (IQR) increment in log transformed PFAS, as well as categorized into PFAS tertiles (all according to the study-specific distribution) to relax the linearity assumption. Molar sums were created for *i)* the most abundant PFAS (as also assessed together by EFSA due to similarities in animal effects, toxicokinetics and human blood concentrations (EFSA et al., 2020)) [PFHxS, PFOS, PFOA and PFNA], *ii)* those with sulfonate functional group [PFHxS and PFOS] and *iii)* those with carboxyl functional group [PFOA and PFNA].

Pairwise Spearman rank correlation coefficients were calculated to describe correlations between PFAS. Cross-sectional associations between PFAS concentrations and continuous BMI z-scores were assessed using linear regression models, adjusted for potential confounders. Pooled results from all studies, using linear mixed effects models, are presented as β-coefficients with corresponding 95% confidence intervals (CI). Random-effects meta-analysis was used to visualize individual study results contributing to the overall result and potential heterogeneity between studies for IQR increment in log transformed PFAS. Additionally, pooled results from all studies, using logistic mixed effects models with categorized BMI (binary: normal *versus* overweight including obese or normal *versus* obese, cutoff points are equivalent to adult BMI of <25, 25–29.99, ≥30 kg/m^2) (Cole et al., 2000; Vidmar et al., 2013) are presented as odds ratios (OR) with corresponding 95% CI.

Potential confounders were selected based on directed acyclic graphs (DAGs), and availability of data in the studies (Supplemental Fig. 1) (Textor et al., 2017). Model 1 was unadjusted whilst Model 2 was adjusted for highest level of education in the household (2 categories) and fish consumption (3 categories). Other dietary components such as meat (missing in Riksmaten Adolescents, 2016–17), milk (missing in Riksmaten Adolescents, 2016–17), egg (missing in Riksmaten Adolescents, 2016–17 and BEA) and fastfood (missing in Riksmaten Adolescents, 2016–17 and FLEHS IV) consumption were tested, but these did not impact the estimates and were removed from the final models. Other potential confounders of degree of urbanization and sampling season also did not impact estimates and were not considered further. We explored potential confounding by breastfeeding or birthweight, by additionally including these variables in sensitivity analyses for the studies that had these data available (six or four, respectively). Studies with self-reported BMI were excluded in sensitivity analyses and this did not impact the estimates. Furthermore, potential modification by sex using stratified analysis for males and females was also explored.

Quantile G-computation was used for mixture assessment using the 'qgcomp' package in R (version 3.6.1), this is a relatively new method to estimate the effect of an exposure mixture without assuming directional homogeneity of the individual compounds (Keil et al., 2020). It transforms exposures into quantized versions and fits a linear model which estimates the change in the outcome expected for a one-unit change in all exposures (corresponding to the sum of all regression coefficients of the exposures). The weights of each exposure are calculated by dividing the coefficient for each exposure by the sum of all exposure coefficients. We used data from 7 studies with [PFHxS, PFOS, PFOA and PFNA] available (PFHxS and PFNA were excluded in BEA and GerES V-sub, respectively, due to ≤70% ≥LOQ), with 500 bootstraps. For the mixture assessment, the 7 studies were pooled and 'study centre' was used as a covariate in the model. As the multiple imputation method was not compatible with the quantile G-computation, we used a missing indicator category for missing values. Both the use of simple pooling instead of mixed effects models and the use of missing indicator category instead of multiple imputation did not impact the estimates in the main analysis. All other statistical analyses were performed using the statistical software STATA (version 15.1) (Stata Corp LP, College Station, TX, USA) and using the 'metan' package for the meta-analysis (Harris et al., 2008). P-values were calculated based on 2-sided tests and the cut-off for statistical significance was set at 0.05.

3. Results

3.1. Population description

Population characteristics are described in Table 1 according to the distributions within each study. SLO CRP and CROME are the smallest studies with <100 observations. All studies were sampled between 2014 and 2021, had approximately equal numbers of males and females and participants between 12 and 18 years old. BMI was the lowest for participants of the NEBII study, which also had participants with the lowest ages (Table 1). The highest educational level of the household was

Table 1
Population characteristics (sampling years 2014–2021) for each of the nine HBM4EU aligned studies in teenagers (12–18 years).

	NEBII	Riksmaten adolescents 2016-17	PCB cohort follow-up	SLO CRP	CROME	BEA	ESTEBAN	FLEHS IV	GerES V-sub	Pooled cohorts
Characteristics										
Country (Region)	Norway (North)	Sweden (North)	Slovakia (East)	SIovenia (South)	Greece (South)	Spain (South)	France (West)	Belgium (West)	Germany (West)	NA
n obs	177	300	292	94	52	299	143	300	300	1957
Sampling Year, range	2016–2017	2016–2017	2019–2020	2018	2020–2021	2017–2018	2014–2016	2018	2014–2017	2014–2021
Sex, % female	57	50	57	45	44	52	57	50	50	52
Age (yrs), mean (SD)	12.3 (0.5)	14.8 (1.6)	15.7 (0.6)	13.8 (0.8)	14.4 (1.8)	14.8 (0.8)[a]	14.2 (1.6)	14.5 (0.6)	14.5 (1.7)	14.5 (1.5)
BMI, mean (SD)	18.5 (2.5)[b]	21.3 (3.5)	22.3 (4.7)[b]	21.2 (4.8)	21.8 (3.8)	21.2 (3.2)[b]	20.2 (4.1)	21.0 (3.6)	20.7 (3.7)	21.0 (3.9)
ISCED house., %										
Low/medium	6	42	80	57	33	43	53	39	43	46
High	85	58	14	43	67	52	47	61	57	52
Missing	8	0	6	0	0	5	0	0	0	2
Fish cons., %										
<1/wk	3	2	98	32	12	4	24	0	24	23
1/wk	12	51	2	61	44	12	64	71	72	42
>=1/wk	69	37	0	7	44	84	5	10	3	29
Missing	16	10	0	0	0	0	8	19	0	7
Breastfed (mths), mean (SD)	11.6 (4.7)	6.4 (3.7)	7.1 (8.3)		6.9 (5.5)			3.4 (5.0)	7.8 (6.2)	NA
Missing, %	0.2	4	4	100	10	100	100	4	16	
Birthweight (gr), mean (SD)	3631 (501)		3368 (520)					3377 (568)	3394 (556)	NA
Missing, %	0.01	100	1	100	100	100	100	4	3	

Abbreviations: International Standard Classifiction of Education (ISCED) of the household.
[a] There were 4 participants with missing age values within the BEA study.
[b] There were 31, 1 and 13 participants with missing BMI values within the NEBII, PCB cohort follow-up and BEA studies, respectively.

relatively equally distributed in each study except for NEBII, which had mainly participants from highly educated households, and PCB cohort (follow-up), which had mainly participants from low/medium educated households (Table 1). Fish consumption differed amongst studies, with a low consumption in the PCB cohort (follow-up) from Slovakia, whereas a more modest consumption was seen in the Western studies and a

Table 2
PFAS concentrations (sampling years 2014–2021) for each of the nine HBM4EU aligned studies in teenagers (12–18 years).

	NEBII	Riksmaten adolescents 2016–17	PCB cohort follow-up	SLO CRP	CROME	BEA	ESTEBAN	FLEHS IV	GerES V-sub
PFAS in µg/L[a] [median (25–75th percentiles)]									
PFPeA	NA	NA	47% <LOQ	0.10 (0.07–0.12)	≥70% <LOQ	≥70% <LOQ	≥70% <LOQ	≥70% <LOQ	≥70% <LOQ
PFHxA	NA	≥70% <LOQ	0.07 (0.06–0.10)	≥70% <LOQ	0.14 (0.11–0.16)	≥70% <LOQ	≥70% <LOQ	≥70% <LOQ	≥70% <LOQ
PFHpA	0.07 (0.05–0.10)	≥70% <LOQ	0.03 (0.02–0.05)	48% <LOQ	≥70% <LOQ	≥70% <LOQ	≥70% <LOQ	≥70% <LOQ	≥70% <LOQ
PFOA	1.28 (1.05–1.57)	1.15 (0.89–1.51)	0.71 (0.48–0.96)	0.86 (0.74–1.06)	0.88 (0.74–1.25)	0.66 (0.52–0.80)	1.47 (1.22–1.80)	1.10 (0.88–1.40)	1.25 (0.81–1.80)
PFNA	0.44 (0.32–0.62)	0.38 (0.27–0.51)	0.17 (0.09–0.26)	0.25 (0.19–0.31)	0.41 (0.30–0.56)	0.28 (0.21–0.38)	0.54 (0.43–0.71)	0.32 (0.23–0.44)	≥70% <LOQ
PFDA	0.13 (0.10–0.18)	41% <LOQ	32% <LOQ	0.14 (0.10–0.19)	0.17 (0.14–0.26)	≥70% <LOQ	39% <LOQ	52% <LOQ	≥70% <LOQ
PFUnDA	0.09 (0.06–0.15)	53% <LOQ	58% <LOQ	0.06 (0.04–0.08)	0.04 (0.01–0.08)	≥70% <LOQ	0.11 (0.07–0.15)	≥70% <LOQ	≥70% <LOQ
PFHxS	0.48 (0.37–0.62)	0.39 (0.26–0.58)	0.29 (0.21–0.44)	0.23 (0.19–0.30)	0.28 (0.21–0.40)	≥70% <LOQ	0.68 (0.53–1.03)	0.49 (0.37–0.66)	0.39 (0.24–0.53)
PFHpS	59% <LOQ	NA	0.03 (0.02–0.05)	0.03 (0.02–0.05)	0.05 (0.04–0.07)	≥70% <LOQ	≥70% <LOQ	≥70% <LOQ	NA
PFOS	2.79 (2.18–3.68)	2.68 (1.97–4.08)	1.37 (0.84–2.47)	1.65 (1.16–2.71)	2.11 (1.57–3.31)	1.34 (0.93–1.84)	2.01 (1.51–3.18)	2.20 (1.55–3.40)	2.60 (1.95–3.48)

Note: Some studies did not assess specific PFAS compounds (indicated as NA) or had >30% <LOQ in which case it was not included in the analyses.
Abbreviations: perfluoropentanoic acid (PFPeA), perfluorohexanoic acid (PFHxA), perfluoroheptanoic acid (PFHpA), perfluorooctanoate (PFOA), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), perfluorododecanoic acid (PFDoDA), perfluorobutane sulfonic acid (PFBS), perfluorohexane sulfonic acid (PFHxS), perfluoroheptanane sulfonic acid (PFHpS) and perfluorooctane sulfonic acid (PFOS).
[a] In Riksmaten adolescents 2016–17 the laboratory presented PFAS in ng/g (µg/kg), which was reported to HBM4EU in µg/L assuming that 1 ml blood serum equals 1 g blood serum.

higher consumption in the Northern and Southern studies (particularly the studies from Norway and Spain) (Table 1).

LOQs differed between studies and not all studies could be used for all PFAS analyses: on average five PFAS could be included per study. PFOA, PFNA, PFHxS and PFOS were ≥70% ≥LOQ in almost all or all studies, but for the other PFAS less studies could be included (PFPeA, PFHxA and PFHpA were ≥70% ≥LOQ in only one or two studies and PFDA, PFUnDA and PFHpS in only three or four studies) (Table 2 and Supplemental Table 1). We observed generally higher PFAS concentrations in the North and West regions of Europe. The highest median concentrations were 1.47, 0.54, 2.79 and 0.68 μg/L for the most prevalent PFAS (PFOA, PFNA, PFOS and PFHxS, respectively) (Table 2). The strongest correlations were seen for PFOA, PFNA, PFHxS, PFHpS and PFOS ($0.4 < r < 0.9$) (Supplemental Table 2).

3.2. Associations of individual PFAS compounds and molar sums with BMI

Significant negative associations were found in the pooled analyses: the molar sums of [PFHxS, PFOS, PFOA and PFNA], [PFHxS and PFOS] and [PFOA and PFNA], as well as individual compounds of PFPeA, PFHpA, PFOA, PFNA and PFOS associated with lower BMI z-scores (Table 3). Only PFHxS and PFHpS showed non-significant opposite results with a tendency for positive associations (Table 3, Fig. 1, Supplemental Fig. 2). The pooled results from the meta-analyses were similar, indicating a significant 0.08 (−0.15, −0.01) lower BMI z-score per interquartile range increase in PFOA (Figs. 1 and 2, Supplemental Fig. 2). Except for CROME and PCB cohort (follow-up), there were either null- or negative associations in the individual studies. Additional adjustment for breastfeeding or birthweight did not materially impact the estimates for PFAS and BMI associations within individual studies (Supplemental Table 3). We did find stronger negative associations with BMI for males for most of the PFAS in the pooled analyses (with estimates of −0.12 (−0.22, −0.03) for males and 0.02 (−0.06, 0.11) for females for the molar sum of [PFHxS, PFOS, PFOA and PFNA]; Supplemental Table 4). Although the same inverse tendency was observed in the pooled logistic regression models between the PFAS and overweight/obese (~20% were overweight or obese), the association was only significant for PFpeA and PFHpA (Table 4). Similar associations were seen for PFAS and obesity (~5% were obese) (data not shown).

Table 3
Associations of tertiles and interquartile range-increment of log transformed PFAS with BMI z-score (age and sex standardized) in the pooled HBM4EU aligned studies (sampling years 2014–2021).

PFAS (n studies)	n observations			Median (25-75th percentiles, nmol/L or μg/L)				Model 1 – β (95% CI)			Model 2 – β (95% CI)		
	T1	T2	T3	T1	T2	T3	Total	T2	T3	IQR (25th −75th)	T2	T3	IQR (25th – 75th)
ΣPFAS (7)	446	444	436	6.14 (4.27–7.50)	9.58 (7.17–10.93)	14.90 (12.51–19.24)	9.24 (6.49–12.9)	**−0.19 (-0.33, -0.04)**	**−0.19 (-0.33, -0.04)**	**−0.07 (-0.13, -0.01)**	**−0.17 (-0.31, -0.02)**	**−0.16 (-0.31, -0.02)**	−0.03 (−0.10, 0.03)
ΣsPFAS (8)	545	545	536	3.57 (2.53–4.45)	5.92 (4.83–6.70)	9.88 (8.27–13.53)	5.78 (4.00–8.28)	**−0.19 (-0.32, -0.06)**	**−0.19 (-0.32, -0.06)**	**−0.08 (-0.13, -0.03)**	**−0.16 (-0.29, -0.03)**	**−0.16 (-0.29, -0.03)**	−0.05 (−0.11, 0.01)
ΣcPFAS (8)	539	540	533	2.11 (1.50–2.70)	3.17 (2.33–3.72)	4.47 (3.29–5.67)	3.04 (2.24–4.14)	−0.11 (−0.24, 0.02)	**−0.18 (-0.31, -0.05)**	**−0.09 (-0.14, -0.04)**	−0.09 (−0.22, 0.04)	**−0.15 (-0.28, -0.02)**	**−0.07 (-0.13, -0.01)**
PFPeA (1)	35	30	29	0.05 (0.01–0.07)	0.10 (0.09–0.11)	0.14 (0.13–0.17)	0.10 (0.07–0.12)	−0.15 (−0.74, 0.44)	**−0.64 (-1.24, -0.05)**	−0.05 (−0.20, 0.11)	−0.15 (−0.73, 0.42)	**−0.67 (-1.25, -0.10)**	−0.05 (−0.20, 0.11)
PFHxA (2)	129	108	106	0.05 (0.04–0.06)	0.08 (0.07–0.09)	0.12 (0.10–0.15)	0.09 (0.06–0.11)	−0.20 (−0.50, 0.10)	−0.08 (−0.39, 0.22)	−0.08 (−0.21, 0.06)	−0.19 (−0.49, 0.11)	−0.08 (−0.38, 0.22)	−0.07 (−0.20, 0.07)
PFHpA (2)	147	168	122	0.02 (0.02–0.04)	0.04 (0.03–0.06)	0.10 (0.07–0.12)	0.05 (0.03–0.08)	**−0.36 (-0.61, -0.11)**	**−0.54 (-0.81, -0.27)**	**−0.19 (-0.30, -0.07)**	**−0.36 (-0.60, -0.11)**	**−0.51 (-0.78, -0.24)**	**−0.19 (-0.30, -0.07)**
PFOA (9)	646	639	627	0.65 (0.46–0.86)	1.08 (0.77–1.24)	1.55 (1.13–1.96)	0.99 (0.71–1.38)	**−0.15 (-0.26, -0.03)**	**−0.20 (-0.32, -0.08)**	**−0.09 (-0.15, -0.04)**	**−0.13 (-0.24, -0.01)**	**−0.18 (-0.29, -0.06)**	**−0.08 (-0.13, -0.02)**
PFNA (8)	549	542	521	0.19 (0.12–0.26)	0.32 (0.26–0.39)	0.53 (0.41–0.71)	0.32 (0.22–0.47)	**−0.15 (-0.28, -0.02)**	**−0.18 (-0.31, -0.04)**	**−0.09 (-0.15, -0.03)**	**−0.13 (-0.26, -0.00)**	**−0.14 (-0.27, -0.00)**	**−0.07 (-0.13, -0.01)**
PFDA (3)	111	88	93	0.09 (0.08–0.11)	0.15 (0.13–0.16)	0.23 (0.19–0.30)	0.14 (0.10–0.20)	−0.12 (−0.42, 0.17)	−0.16 (−0.45, 0.14)	−0.03 (−0.19, 0.14)	−0.07 (−0.37, 0.23)	−0.13 (−0.42, 0.17)	−0.02 (−0.19, 0.14)
PFUnDA (4)	155	144	136	0.04 (0.03–0.06)	0.09 (0.07–0.11)	0.15 (0.13–0.21)	0.08 (0.05–0.13)	−0.25 (−0.50, 0.01)	−0.25 (−0.51, 0.01)	−0.12 (−0.25, 0.00)	−0.21 (−0.47, 0.05)	−0.19 (−0.46, 0.08)	−0.09 (−0.22, 0.04)
PFHxS (8)	558	540	528	0.23 (0.17–0.31)	0.41 (0.32–0.48)	0.71 (0.56–1.01)	0.4 (0.26–0.59)	−0.01 (−0.14, 0.12)	0.01 (−0.12, 0.14)	0.00 (−0.05, 0.06)	0.00 (−0.13, 0.13)	0.02 (−0.11, 0.15)	0.01 (−0.04, 0.07)
PFHpS (3)	203	100	134	0.02 (0.00–0.02)	0.04 (0.03–0.04)	0.08 (0.06–0.12)	0.03 (0.02–0.06)	0.11 (−0.17, 0.40)	0.17 (−0.10, 0.43)	0.03 (−0.06, 0.11)	0.10 (−0.18, 0.38)	0.17 (−0.09, 0.43)	0.04 (−0.04, 0.13)
PFOS (9)	652	629	631	1.25 (0.85–1.70)	2.22 (1.55–2.63)	3.84 (3.03–5.39)	2.1 (1.39–3.13)	**−0.18 (-0.30, -0.06)**	**−0.19 (-0.31, -0.07)**	**−0.07 (-0.12, -0.01)**	**−0.15 (-0.27, -0.03)**	**−0.15 (-0.27, -0.03)**	−0.04 (−0.10, 0.02)

Note: Beta1 coefficients from linear regression mixed effects models (fitted with a random intercept for study) per study specific IQR increase (difference between 25th to 75th percentile) in log transformed PFAS or per tertile (T1 reference). Model 1 was unadjusted and model 2 was adjusted for highest educational level in the household and fish consumption. Significant results are indicated in bold. **Abbreviations**: ΣPFAS, molar weight sum including PFHxS, PFOS, PFOA and PFNA; ΣsPFAS, molar weight sum including PFHxS and PFOS; ΣcPFAS, molar weight sum including PFOA and PFNA; IQR, interquartile range; T, tertile.

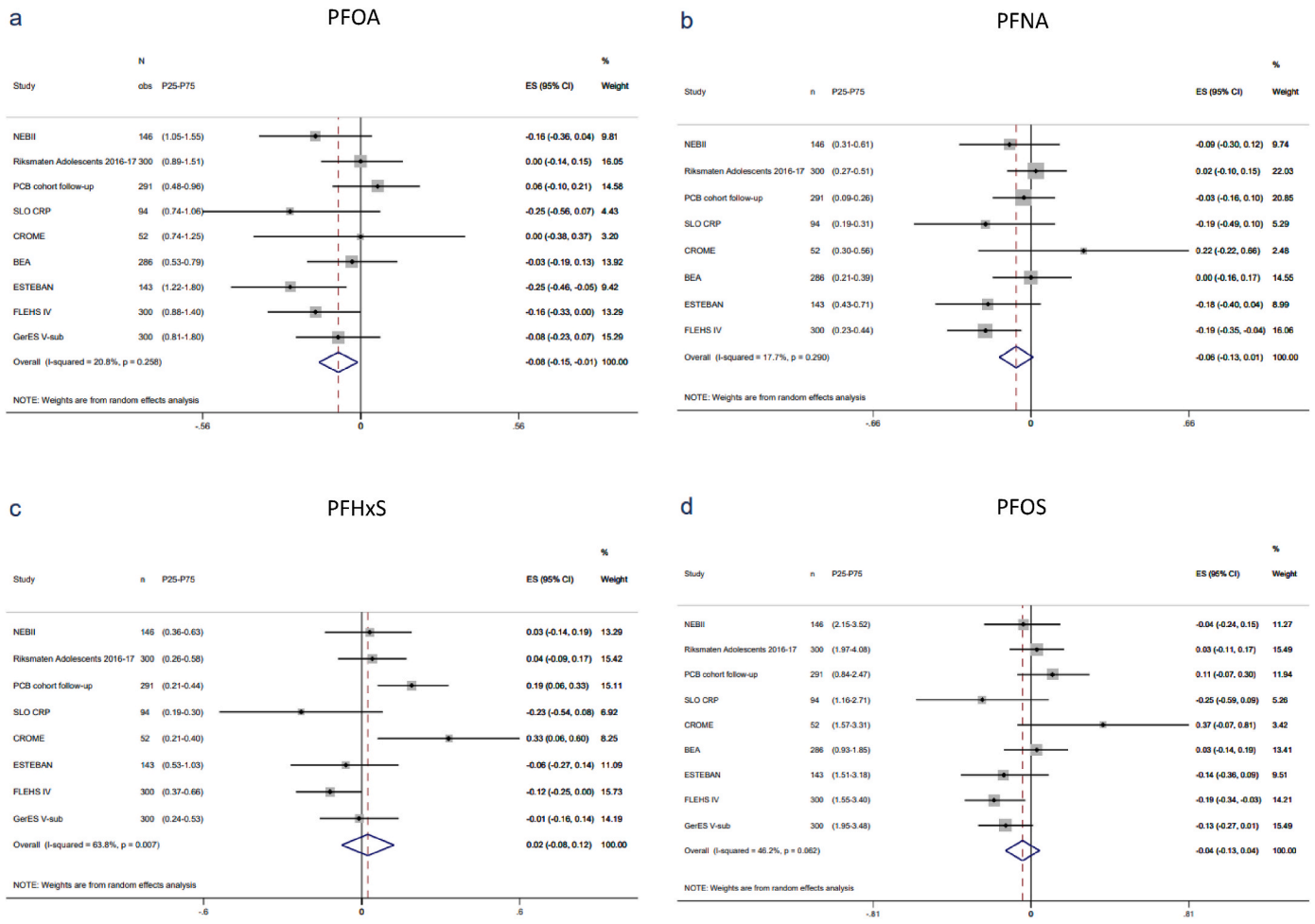

Fig. 1. Associations between PFAS and BMI z-score (age and sex standardized) using linear regression meta-analysis models combining the HBM4EU aligned studies in teenagers. Associations are shown per study specific IQR increase (difference between 25th to 75th percentile) in log transformed PFAS and are adjusted according to model 2 (highest level of household education and fish consumption). a) PFOA, b) PFNA, c) PFHxS and d) PFOS.

3.3. Associations of PFAS mixture with BMI

Mixture assessment using g-computation indicated the same tendency for negative associations, although not significant, of the mixture of the most abundant PFAS [PFHxS, PFOS, PFOA and PFNA] with BMI z-score with estimates of −0.05 (−0.13, 0.03) per one quartile increase in mixture (Fig. 3a and c). In line with the individual exposure linear regression models, PFHxS showed opposite associations with BMI z-scores as compared to PFOS, PFOA and PFNA (Figs. 1c and 3b). Thus, to separate these associations, we included in the same linear regression model a molar sum of [PFOS, PFOA and PFNA] adjusting for PFHxS. In agreement with the previous results, we observed significant negative and positive associations, respectively (Fig. 3c).

4. Discussion

In the present cross-sectional study, we found overall negative associations between relatively low PFAS (PFPeA, PFHpA, PFOA, PFNA and PFOS) blood concentrations and BMI z-scores in teenagers in nine studies across Europe (the HBM4EU aligned studies). The same inverse tendency was observed for PFAS concentrations with risk of overweight/obesity. Mixture assessment indicated similar negative associations for PFOS, PFOA and PFNA, but a positive association for PFHxS.

4.1. Epidemiological evidence

Although the PFAS levels observed in the present study are considerably lower, our findings are in line with another recent cross-sectional study among highly exposed Italian adolescents and children (Canova et al., 2021), and another among young US girls (Fassler et al., 2019); both showing negative associations between single PFAS and BMI. Negative associations between PFOS and body fat have also been described in Danish boys (Thomsen et al., 2021). Our findings are similar to those of others using mixture approaches: a longitudinal study indicated a negative association of PFAS mixture exposure during childhood with less accrual of lean mass in early adolescence, mainly driven by PFOA (Janis et al., 2021) and an exposome-wide study in children placed PFOA among the chemicals associated with lower BMI (Vrijheid et al., 2020).

However, there are also cross-sectional studies during adolescence that found a positive association between PFOA and overweight/obesity in US teenagers (Geiger et al., 2021) and between PFHpS and PFHxS and obesity in Norwegian teenagers (Averina et al., 2021), which was not the case for the Norwegian teenagers in this study. Although, PFHpS and PFHxS both had positive estimates in the present study as well and for PFHxS this association became significant when adjusting for the sum of PFOA, PFNA and PFOS. Meanwhile, others mostly reported null associations between PFAS and BMI or body fat measures (Averina et al., 2021; Thomsen et al., 2021). Similarly, we found null associations for PFHxA, PFDA, PFUnDA, PFHxS and PFHpS potentially due to high

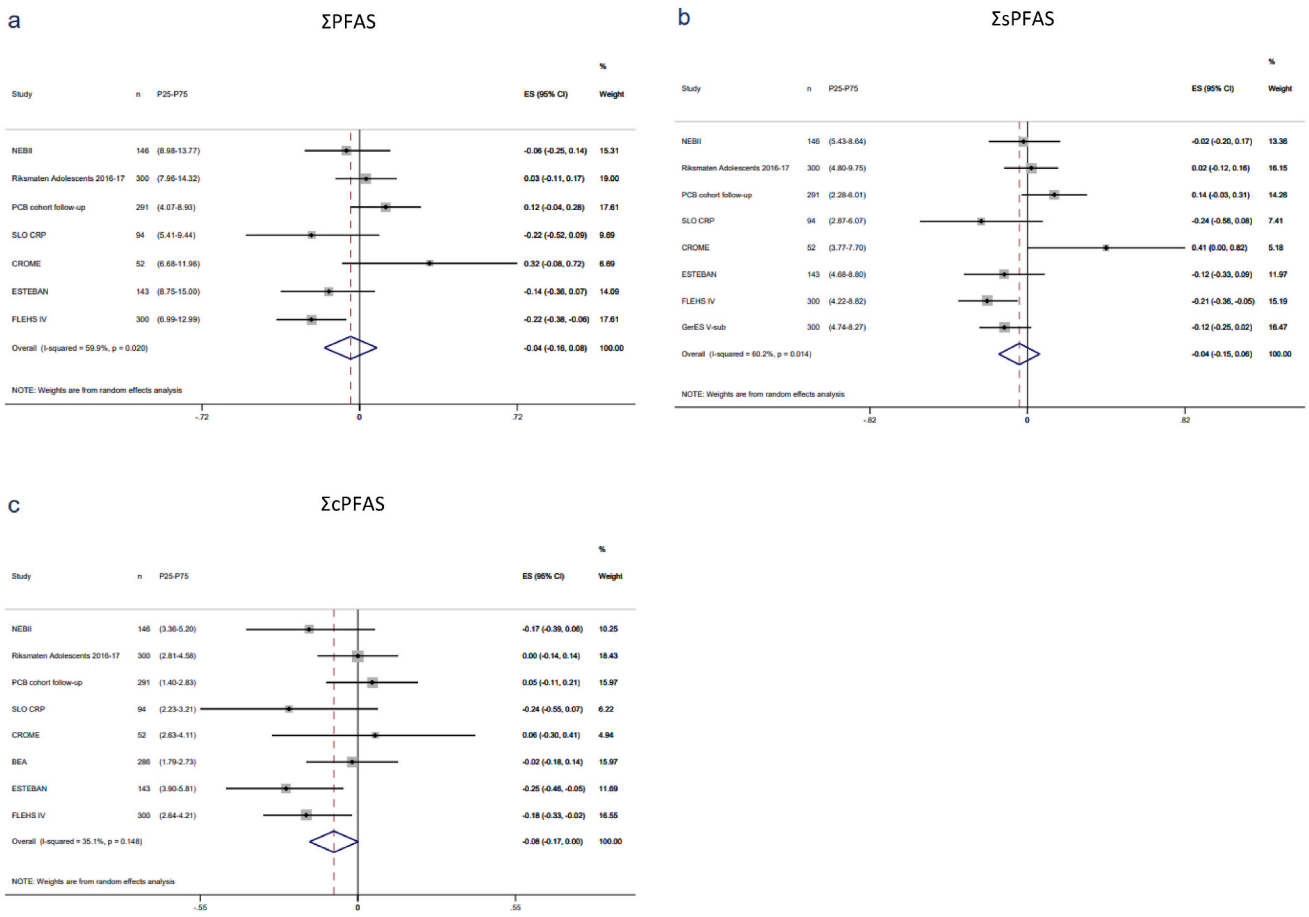

Fig. 2. Associations between PFAS and BMI z-score (age and sex standardized) using linear regression meta-analysis models combining the HBM4EU aligned studies. Associations are shown per study specific IQR increase (difference between 25th to 75th percentile) in log transformed PFAS and are adjusted according to model 2 (highest level of household education and fish consumption). a) ΣPFAS [molar weight sum including PFHxS, PFOS, PFOA and PFNA] b) ΣsPFAS [molar weight sum including PFHxS and PFOS] c) ΣcPFAS [molar weight sum including PFOA and PFNA].

correlations between PFAS with opposite effects (as indicated by our mixture analysis results: PFHxS *versus* PFOA, PFNA and PFOS). There are only a few prospective studies, one European multicenter study indicated that childhood PFOS exposure was associated with higher BMI during adolescence, while adolescent PFOS exposure did not associate with higher BMI during young adulthood (Domazet et al., 2016).

Prenatal exposures are also considered important for adiposity in children and teenagers and the evidence for PFAS exposures is similarly inconsistent, as recently reviewed by Lee et al. (2021). In general, studies investigating prenatal PFAS exposure and associations with childhood adiposity indicate more of a negative association with BMI during the first years of life (Starling et al., 2019; Starling et al., 2017) and a positive association with BMI during childhood (Braun et al., 2016; Chen et al., 2019; Lauritzen et al., 2018; Mora et al., 2017) and adolescence (Liu et al., 2020). However, negative associations between prenatal PFAS and childhood and adolescent adiposity (Braun et al., 2021; Hartman et al., 2017) and overall null associations were also found (Andersen et al., 2013; Bloom et al., 2021; Manzano-Salgado et al., 2017; Martinsson et al., 2020). A recent systematic review and meta-analysis indicated null-associations between prenatal PFOS and PFOA with childhood BMI (Stratakis et al., 2022).

Potential modifications by sex, race-ethnicity, maternal BMI (Bloom et al., 2021) and education (Hartman et al., 2017) as well as other obesogenic and PFAS chemicals (Starling et al., 2019; Starling et al., 2017) may explain these divergent results. Furthermore, age and puberty status may impact PFAS' effects on BMI, potentially as a confounder (menarche both affects PFAS levels and BMI) or as mediator (PFAS may impact hormone levels and thereby affect puberty status and BMI).

4.2. Molecular evidence

We found that higher PFAS levels associated with lower BMI. However, PFAS has been consistently shown to associate with higher cholesterol in adults (EFSA et al., 2020) and in adolescents (Averina et al., 2021; Canova et al., 2021). Experimental studies indicate that PFAS-induced PPARα or PPARγ activation may induce toxicological changes in metabolism (Takacs and Abbott, 2007), which could decrease BMI (Xie et al., 2002). PPARs are linked to modulating glucose and lipid metabolism, adipogenesis, adipocyte differentiation and inflammation. Other nuclear receptors relevant for lipid homeostasis may also be involved, such as constitutive androstane receptor (CAR) (Rosen et al., 2017), estrogen receptor (ER) (Rosen et al., 2017), pregnane X receptor (PXR) (Bijland et al., 2011), liver X receptor (LXR) (Bijland et al., 2011), farsenoid X receptor (FXR) (Bijland et al., 2011) and hepatocyte nuclear factor (HNF4α) (Beggs et al., 2016). Other pathways potentially relevant for metabolic disruptions include PFAS-related disruptions in the enterohepatic circulation and hepatic injury (Roth et al., 2021) and PFAS-related changes in hormone levels and sexual maturation via alterations of thyroid and/or steroid hormone synthesis and metabolism (Lee and Choi, 2017; Zhao et al., 2011). We found stronger negative associations between PFAS and BMI z-score in males, potentially related to endocrine disruption (Du et al., 2013; Zhou et al., 2017). PFAS has been shown to inhibit 11-β hydroxysteroid dehydrogenase 2 which

Table 4
Associations of tertiles and interquartile range-increment of log transformed PFAS with overweight (age and sex standardized) in the pooled HBM4EU aligned studies (sampling years 2014–2021).

PFAS (n studies)	n observations (overweight/normal)			Model 1 – OR (95% CI)				Model 2 – OR (95% CI)			
	T1	T2	T3	T1 (ref)	T2	T3	IQR (25th −75th)	T1 (ref)	T2	T3	IQR (25th −75th)
ΣPFAS (7)	109/308	86/317	91/312		0.76 (0.55, 1.06)	0.82 (0.59, 1.13)	0.84 (0.76, 0.94)		0.79 (0.57, 1.10)	0.86 (0.62, 1.19)	0.95 (0.83, 1.08)
ΣsPFAS (8)	128/375	105/397	107/387		0.78 (0.58, 1.04)	0.81 (0.60, 1.08)	0.82 (0.74, 0.92)		0.81 (0.60, 1.09)	0.86 (0.63, 1.15)	0.91 (0.80, 1.03)
ΣcPFAS (8)	129/377	116/375	105/386		0.90 (0.68, 1.21)	0.79 (0.59, 1.06)	0.85 (0.77, 0.94)		0.96 (0.72, 1.29)	0.84 (0.62, 1.13)	0.92 (0.83, 1.04)
PFPeA (1)	14/19	8/21	2/27		0.52 (0.18, 1.50)	0.10 (0.02, 0.49)	0.86 (0.65, 1.12)		0.51 (0.16, 1.58)	0.08 (0.01, 0.43)	0.85 (0.64, 1.13)
PFHxA (2)	36/84	24/75	32/62		0.75 (0.41, 1.36)	1.20 (0.68, 2.15)	1.01 (0.78, 1.31)		0.75 (0.41, 1.38)	1.20 (0.67, 2.15)	1.02 (0.78, 1.32)
PFHpA (2)	48/92	32/118	15/92		0.49 (0.29, 0.84)	0.34 (0.17, 0.65)	0.73 (0.58, 0.93)		0.50 (0.29, 0.86)	0.35 (0.18, 0.67)	0.74 (0.58, 0.94)
PFOA (9)	157/449	128/451	119/460		0.81 (0.62, 1.06)	0.74 (0.56, 0.97)	0.87 (0.77, 0.98)		0.85 (0.65, 1.11)	0.77 (0.58, 1.01)	0.91 (0.81, 1.02)
PFNA (8)	131/384	115/378	104/376		0.89 (0.67, 1.19)	0.81 (0.61, 1.09)	0.87 (0.77, 0.99)		0.94 (0.70, 1.26)	0.89 (0.66, 1.20)	0.90 (0.80, 1.02)
PFDA (3)	22/84	14/67	17/69		0.83 (0.39, 1.76)	0.95 (0.46, 1.94)	1.19 (0.78, 1.81)		0.93 (0.43, 2.01)	1.01 (0.48, 2.10)	1.24 (0.82, 1.87)
PFUnDA (4)	32/115	24/101	22/100		0.87 (0.48, 1.57)	0.79 (0.43, 1.46)	0.83 (0.64, 1.07)		0.93 (0.50, 1.75)	0.88 (0.46, 1.71)	0.85 (0.62, 1.15)
PFHxS (8)	110/406	122/370	108/383		1.22 (0.91, 1.64)	1.04 (0.77, 1.41)	1.02 (0.91, 1.16)		1.24 (0.92, 1.67)	1.07 (0.79, 1.45)	1.03 (0.92, 1.15)
PFHpS (3)	51/135	22/70	43/83		0.83 (0.47, 1.48)	1.37 (0.84, 2.24)	1.08 (0.92, 1.27)		0.81 (0.45, 1.45)	1.39 (0.85, 2.28)	1.10 (0.93, 1.29)
PFOS (9)	155/446	129/450	120/464		0.83 (0.63, 1.08)	0.74 (0.57, 0.98)	0.83 (0.72, 0.96)		0.87 (0.66, 1.14)	0.80 (0.61, 1.06)	0.91 (0.81, 1.03)

Note: Odds ratios (±95% confidence intervals) from logistic regression mixed effects models (fitted with a random intercept for study) per study specific IQR increase (difference between 25th to 75th percentile) in log transformed PFAS or per tertile (T1 reference). Model 1 was unadjusted and model 2 was adjusted for highest level of education in the household and fish consumption. **Abbreviations**: ΣPFAS, molar weight sum including PFHxS, PFOS, PFOA and PFNA; ΣsPFAS, molar weight sum including PFHxS and PFOS; ΣcPFAS, molar weight sum including PFOA and PFNA; IQR, interquartile range; T, tertile.

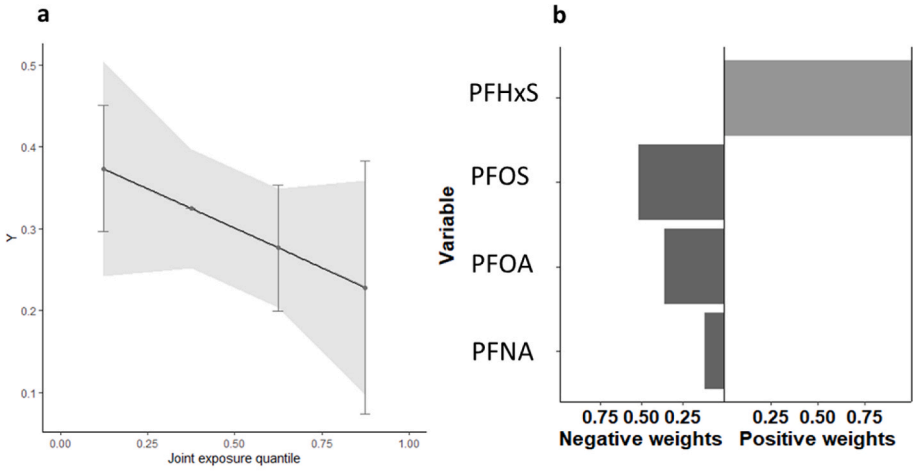

Fig. 3. Associations between PFAS and BMI z-score (age and sex standardized) using quantile G-computation using data from seven HBM4EU aligned studies (n = 1326). Associations are shown per 1-quartile increase in mixture PFAS (PFOA, PFNA, PFHxS, PFOS) and are adjusted according to model 2 (highest level of household education, fish consumption). Panel a) shows the association between PFAS mixture and BMI z-score, b) shows the weights of each individual PFAS contributing to the mixture and c) shows the estimates for the G-computation and for the linear regression mixed effects model including ΣgPFAS [molar weight sum of PFOS, PFOA and PFNA] and PFHxS (both mutually adjusted and separated). **Abbreviations**: ΣgPFAS [molar weight sum including PFOS, PFOA and PFNA].

c

G computation - Adjusted model - B(95% CI)

	1 quartile increase in mixture
Mixture	-0.05 (-0.13,0.03)

Linear mixed effects - Adjusted model - B(95% CI)

	T1 (ref)	T2	T3	IQR (25th-75th)
Mutually adjusted				
ΣgPFAS		-0.19 (-0.34, -0.04)	-0.26 (-0.44, -0.09)	-0.11 (-0.26, 0.03)
PFHxS		0.04 (-0.12, 0.19)	0.19 (0.01, 0.36)	0.06 (-0.02, 0.14)
Seperate				
ΣgPFAS		-0.13 (-0.26, 0.00)	-0.13 (-0.26, 0.00)	-0.04 (-0.14, 0.07)
PFHxS		0.00 (-0.13, 0.13)	0.02 (-0.11, 0.15)	0.01 (-0.38, 0.07)

could lead to the suppression of testosterone production in Leydig cells (Zhao et al., 2011). Negative associations between PFAS and testosterone in adolescent males have been found before (Zhou et al., 2016) and low testosterone could decrease lean mass (Kelly and Jones, 2015).

4.3. Strengths and limitations

The present study has several strengths and limitations. Pooling the studies gave a large sample size and a wider range of PFAS concentrations. The harmonization of the sampling protocol and the participation in the QA/QC programme for PFAS measurements reduced the potential for bias from exposure misclassification. However, studies had different procedures (different questionnaires, measured *versus* self-reported BMI, serum *versus* plasma, linear *versus* linear and branched PFAS and different LOQs for PFAS), which complicated comparisons of PFAS levels between data collections. The measurement of multiple PFAS allowed us to consider PFAS mixtures. However, for PFAS sums we assumed equipotency of the included compounds and this might not reflect the reality, thus we also included another mixture approach (g-computation) that allowed the weights of each compound to differ. Additionally, BMI is vulnerable to outcome misclassification as it cannot differentiate between lean and fat body mass and was self-reported for some participants. There was some heterogeneity between studies, which could potentially be explained by differences in age (puberty could impact associations), bias resulting from differences in outcome measurements (e.g. self-reported in CROME), residual or unmeasured confounding (e.g. fish consumption was lower in PCB cohort-follow up) or differences in PFAS levels (e.g. PFHxS is lower in SLO CRP). However, exclusions of studies with self-reported BMI and adjustments for main potential confounders (according to our DAG; socio-economic status, diet, breastfeeding and birthweight) only impact results marginally.

Although PFAS have long half-lives and thus we assess cumulative exposure over the last years, we are still unable to infer causality due to the cross-sectional nature of this study. Reverse causality is theoretically possible as PFAS is excreted in the bile and urine (EFSA et al., 2018) and higher BMI has been associated with enterohepatic circulation (Haeusler et al., 2016) and with reduced eGFR (Gunta and Mak, 2013). Higher BMI is associated with increased bile acid synthesis so potentially higher BMI causes increased PFAS excretion. However, PFAS affecting bile acid synthesis is also plausible via decreasing CYP7A1 (Behr et al., 2020). Higher BMI associations with reduced eGFR would not explain the negative associations found in this study, as higher BMI would then give higher PFAS levels. As PFAS is not lipid-soluble, reverse causality due to PFAS storage in fat is not likely (Forsthuber et al., 2020). Furthermore, we were not able to investigate the potential effects of prenatal PFAS exposures and these have been proposed to be more relevant than postnatal PFAS exposures for adiposity in childhood (Papadopoulou et al., 2021). Additionally, we cannot yet study the potential long-term consequences of the association between PFAS and lower BMI in teenagers in this population.

5. Conclusions

We found evidence for negative cross-sectional associations with age- and sex-standardized BMI for 5 of the 10 PFAS compounds (PFPeA, PFHpA, PFOA, PFNA and PFOS) in teenagers from nine studies across Europe. This indicates that these exposures may impact pathways relevant to metabolism in teenagers. Our results furthermore suggest opposite associations for PFOS, PFOA and PFNA versus PFHxS on BMI z-scores in teenagers. Although effect estimates were only minor, this could still be relevant for population health considering that such a large part of the population is exposed to these compounds. Further research is needed both on epidemiological and molecular level to understand these associations and their implications in teenagers as well as subsequently during adulthood.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2022.120566.

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