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Demographic, life-style and physiological determinants of serum per- and polyfluoroalkyl substance (PFAS) concentrations in a national cross-sectional survey of Swedish adolescents

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ABSTRACT

Per: and polyfluoroalkyl substances (PFAS) may affect adolescent health, yet factors related to PFAS concentrations in serum are poorly understood. We studied demographic, life-style and physiological determinants of serum PFAS concentrations in Swedish adolescents from a nation-wide survey, Riksmaten Adolescents 2016–17 (RMA, age 10–21 years, n = 1098). Serum samples were analyzed for 42 PFAS, using liquid chromatography-tandem mass spectrometry. The cumulative probability model was used to estimate associations between serum PFAS and determinants, using ordinal logistic regression. Legacy linear (lin-) perfluorooctanoic acid (PFOA), perfluorononaoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), lin-perfluorohexanesulfonic acid (PFHxS) and lin-/branched (br-) perfluorooctanesulfonic acid (PFOS) were quantifiable in ≥70% of the samples. The emerging PFAS 9-chlorohexanedecafluoro-3-oxanone-1-sulfonic acid (9Cl-PF3ONS) was quantified in 5.4% of the samples, suggesting initiation of long-range transport far from production sites. Median concentrations of all legacy PFAS were <2 ng/g serum, with a few participants having very high (>100 ng/g serum) lin-PFHxS and lin-/br-PFOS concentrations due to previous high exposure from PFAS-contaminated drinking water. Legacy PFAS exposure was strongly associated with birth country of the participants and their mothers. 2-fold higher estimated adjusted mean (EAM) concentrations were seen among high income country participants with mothers from high income countries than among low/lower-middle income country participants with mothers from the same category. Menstruating females had lower br-PFOS EAM concentrations than those who were not. Iron status (plasma ferritin) among females may be a marker of intensity of menstrual bleeding, but it was not significantly associated with legacy PFAS concentrations among females. Further studies are needed to determine how physiological changes occurring around menstruation affect the toxicokinetics of PFAS in females. In conclusion, PFAS are pollutants of the industrialized world and some of the identified determinants may be overlooked confounders/effect modifiers that should be included in future PFAS/health studies among adolescents.

1. Introduction

Per- and polyfluoroalkyl substances (PFAS) are ubiquitously detected in biota and humans (Kelly et al., 2009; Ahrens and Bundschuh, 2014; DeWitt, 2015). A wide range of PFAS are linked with adverse health effects in animals, including endocrine disruption, offspring development, immunosuppression and liver toxicity (DeWitt, 2015; Lilienthal et al., 2017). Comparable results have been reported in epidemiological studies on children and adolescents, where PFAS exposure is associated with reduced antibody response post-vaccination (Grandjean et al., 2012; Granum et al., 2013; Abraham et al., 2020), dyslipidemia (Frisbee et al., 2010; Geiger et al., 2014), and reduced birth

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weights in infants (Fei et al., 2007; Darrow et al., 2013). For some of these end-points the literature is however not consistent (EFSA, 2020), and further studies are needed to elucidate the PFAS health risks for children/adolescents.

Of the approximately 5000 registered PFAS (OECD, 2018), the most studied are the persistent legacy chemicals perfluorooctanesulfonic acid (PFOS) and perfluorooctanoic acid (PFOA). However, due to a nearly complete global phase out of PFOS and PFOA, replacements such as hexafluoropropylene oxide dimer acid (HFPO-DA; GenX) and odecafluoro-3H-4,8-dioxanonanoate (ADONA) are already present in the environment in areas with high contamination due to industrial production (Gebbink et al., 2017; Wang et al., 2019a; Awad et al., 2020). Human biomonitoring of such emerging PFAS have been infrequently conducted due to the relative short production period as opposed to the half a century long production of legacy PFAS (Miaz et al., 2020; Brase et al., 2021). As a result, screening has predominantly been carried out for adults with occupational exposure and those residing within close proximity to fluorotelomer industries or in other highly contaminated areas (Brase et al., 2021; Miaz, 2020). Moreover, biomonitoring of emerging, but also legacy PFAS, has been primarily focused on adult and infant/child populations (Brase et al., 2021). There consequently exists a need to evaluate the prevalence of both emerging and legacy PFAS in a general adolescent population.

Furthermore, human exposure to PFAS is complex and varies both within and between populations. In the general adult population, drinking water from areas with high PFAS contamination of surface/groundwater and, in general, food have shown to contribute substantially to the total exposure (Domingo and Nadal, 2017; Sunderland et al., 2019). Inhalation and/or ingestion of indoor dust, as well as use of products containing PFAS, may also contribute significantly to exposure in some instances (DeLuca et al., 2021). Serum/plasma concentrations of PFAS are generally used as markers of PFAS body burdens in humans, as it reflects the long-term cumulative exposure to bioaccumulating PFAS. Understanding which life-style/demographic/physiological determinants that affects exposure and toxicokinetics of PFAS, such as excretion, is vital for identifying sensitive groups within a population. Identified determinants may also present valuable information on potential confounders in future health studies.

Recognized demographic/physiological determinants explaining some of the variation of serum/plasma PFAS concentrations in adult populations include age, gender (Calafat et al., 2007a; Kärrman et al., 2007), excretion of PFAS via menstruation among women (Wong et al., 2014; Park et al., 2019), ethnicity/race (Calafat et al., 2007b; Jain, 2014), and education level (Calafat et al., 2007b; Bjerregaard-Olesen et al., 2016). Intriguingly, the same determinants have not always been identified in children and adolescents, e.g. contradictory associations have been reported for both age (Ye et al., 2018; Kang et al., 2018; Daly et al., 2018) and gender (Toms et al., 2009; Schecter et al., 2012; Mondal et al., 2012; Ye et al., 2018). Additionally, biomonitoring studies in children and adolescents are often limited up to the age of 13 (Toms et al., 2009; Schecter et al., 2012; Winkens et al., 2017; Harris et al., 2017; Ye et al., 2018), and only a few studies include the entire WHO-defined adolescent period between 10 and 19 years (Zhou et al., 2016; Kang et al., 2018; Averina et al., 2018; Papadopoulou et al., 2019). Due to the large physiological and behavioral changes that occur with the onset of puberty, adolescents are potentially vulnerable to chemical insult (Wild and Kleinjans, 2003; Benedetti and Baltes, 2003). Consequently, more research is warranted on this age group, since determinants of PFAS body burdens in infant/child and adult populations may not be applicable for adolescent populations.

The objectives of the current nation-wide study of Swedish adolescents were two-fold: 1) screen and evaluate serum concentrations of legacy and emerging PFAS; and 2) assess life-style/demographic/physiological determinants that could explain the variation of PFAS concentrations in serum, i.e. variation in cumulative exposure and toxicokinetics. Among female participants, menstruation, an excretion route in adult women, yet rarely studied in adolescent females, was investigated. We additionally assessed the possibility of using plasma ferritin (biomarker of iron-status) as a proxy for menstrual blood loss (Wang et al., 2013).

2. Methods

2.1. Study population

The study population was a subsample of Riksmaten Adolescents 2016–17 (RMA), a nationally representative cross-sectional school-based dietary survey, conducted by the Swedish Food Agency and with approximately 3000 participants. A comprehensive description of the population and study design is given in Moraeus et al. (2018). In brief, students in school grades 5 (ages 11–12 years), 8 (ages 14–15 years) and 11 (ages 17–18 years) were invited to participate in the study between September 2016 and May 2017. Statistics Sweden selected schools based on geographical location, public or charter school, and municipality classification. Participant height and weight were measured by trained staff. A subsample of 2377 students were invited to donate biological samples, and 1176 (49%) completed this part of the study (Moraeus et al., 2018). 1098 participants completed the dietary assessment and donated a blood sample that was available for PFAS analysis. Ethical approval was granted by the Regional Ethical Review Board in Uppsala (No. 2015/190). All participants, or legal guardians of participants <16 years, gave written informed consent to participate in the study.

2.2. Assessment of diet and personal characteristics

A web-based system called RiksmatenFlex (RF), which consisted of the RiksmatenFlexDiet (RFD) and RiksmatenFlexQuestionnaire (RFQ) segments, was used for assessment of personal characteristics and diet. RFD is a validated (Lindroos et al., 2019) 24-h dietary recall method that allows participants to register their consumption of food and beverages on two non-consecutive days, retrospectively (Moraeus et al., 2018). The second day of dietary registration was randomized 2–7 days after the first day of registration. The RFQ covered participants' perceived health status and socio-economic and lifestyle factors. It additionally included food frequency questionnaires focusing on specific foods that are less likely to be consumed regularly and not captured in RFD (Moraeus et al., 2018).

2.3. Blood sampling and chemical analysis

Non-fasting venous blood was sampled in 10 ml tubes with coagulation activator and in 6 ml lithium heparin tubes. After centrifugation, serum and plasma were stored at −20 °C onsite and then transported and stored frozen at −80 °C until analysis (Moraeus et al., 2018).

Serum were analyzed for perfluorohexanoic acid (PFHxA), perfluoroheptanoic acid (PFHpA), linear and branched PFOA (lin- and br-), perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), perfluorododecanoic acid (PFDoDA), perfluorotridecanoic acid (PFTrDA), perfluorotetradecanoic acid (PFTeDA), perfluoropentadecanoic acid (PFPeDA), perfluorohexadecanoic acid (PFHxDA), perfluorooctadecanoic acid (PFOcDA), perfluoropentanesulfonic acid (PFPeS), lin/br-perfluorohexanesulfonic acid (PFHxS), perfluoroheptanesulfonic acid (PFHpS), lin/br-PFOS, perfluorononanesulfonic acid (PFNS), lin/br-perfluorodecanesulfonic acid (PFDS), perfluoroundecanesulfonic acid (PFUnDS), lin/br-perfluorooctansulfanomid (FOSA), lin/br-perfluorooctane sulfonamidoacetic acid (FOSAA), lin/br- N-methylperfluoro-1-octanesulfonamideoacetic acid (MeFOSAA), lin/br- N-ethylperfluoro-1-octanesulfonamidoacetic acid (EtFOSAA), 6:2 fluorotelomer phosphate diester (6:2 diPAP), 8:2 fluorotelomer phosphate diester (8:2 diPAP), 6:s/8:2 fluorotelomer phosphate diester (6:2/8:2 diPAP), 9-chlorohexadecafluoro-3-oxanone-1-sulfonic acid (9Cl-PF3ONS), 11-

Table 1
Categorical and continuous base model covariates.

	All *n (%)*	Males *n (%)*	Females *n (%)*
Categorical covariates	1098 (100)	482 *(44)*	616 (56)
BMI status[a]			
Underweight	72 *(7)*	31 *(6)*	41 *(7)*
Normal weight	793 *(72)*	349 *(72)*	444 *(72)*
Overweight	190 *(17)*	82 *(17)*	108 *(18)*
Obese	43 *(4)*	20 *(4)*	23 *(4)*
Birth country (participant/mother)			
Both high income countries	898 *(82)*	399 *(83)*	499 *(82)*
High income/upper-middle countries	79 *(7)*	31 *(6)*	48 *(8)*
Both upper-middle income countries	39 *(4)*	15 *(3)*	24 *(4)*
High and upper-middle/low and lower-middle income countries	29 *(3)*	13 *(3)*	16 *(3)*
Both low and lower-middle income countries	42 *(4)*	20 *(4)*	22 *(4)*
Missing	11 *(1)*	4 *(1)*	7 *(1)*
Education level - mother			
No formal education and primary education	84 *(8)*	34 *(7)*	50 *(8)*
Vocational education or equivalent	162 *(15)*	63 *(13)*	99 *(16)*
3–4 year upper secondary education or equivalent	229 *(21)*	99 *(21)*	130 *(21)*
University education or equivalent	565 *(51)*	256 *(53)*	309 *(50)*
Missing	58 *(5)*	30 *(6)*	28 *(5)*
Education level – father			
No formal education and primary education	111 *(10)*	43 *(9)*	68 *(11)*
Vocational education or equivalent	215 *(20)*	94 *(20)*	121 *(20)*
3–4 year upper secondary education or equivalent	280 *(26)*	132 *(27)*	148 *(24)*
University education or equivalent	411 *(37)*	179 *(37)*	232 *(38)*
Missing	81 *(7)*	34 *(7)*	47 *(8)*
Smoking habits			
Non-smoker (incl. 5th graders)[b]	955 *(87)*	430 *(89)*	525 *(85)*
Smoker	123 *(11)*	44 *(9)*	79 *(13)*
Missing	20 *(2)*	8 *(2)*	12 *(2)*
Snus use			
Does not use snus (incl. 5th graders)[b]	1016 *(93)*	441 *(86)*	575 *(93)*
Snus user	70 *(6)*	33 *(7)*	37 *(6)*
Missing	12 *(1)*	8 *(2)*	4 *(1)*
Alcohol consumption during last 6 months			
Has never consumed alcohol (incl. 5th graders)[b]	759 *(69)*	352 *(73)*	407 *(66)*
Once	107 *(10)*	48 *(10)*	59 *(10)*
Several times	209 *(19)*	75 *(16)*	134 *(22)*
Missing	23 *(2)*	7 *(2)*	16 *(3)*
Exclusively breastfed			
Never breastfed and breastfed for <1 month	111 *(10)*	47 *(10)*	64 *(10)*
1–6 months	591 *(54)*	260 *(54)*	331 *(54)*
7 to >12 months	359 *(33)*	156 *(33)*	203 *(33)*
Missing	37 *(3)*	19 *(4)*	18 *(3)*
Continuous covariates	**Median** (range) *(% missing)*	**Median** (range) *(% missing)*	**Median** (range) *(% missing)*
Age (years)	14.6 (10.6, 21.1) *(0)*	14.4 (10.6, 21.0) *(0)*	14.7 (10.8, 21.1) *(0)*
Swedish Healthy Eating Index for Adolescents 2015 (SHEIA15)	5.82 (3.37, 8.86) *(0)*	5.63 (3.76, 8.24) *(0)*	5.93 (3.37, 8.68) *(0)*

[a] For participants <18 years of age, BMI status was classified based on age- and sex dependent cut-offs (Cole and Lobstein, 2012), while for participants ≥18, the WHO cut-offs were used (WHO, 1999).
[b] 5th grade participants were not asked about alcohol and tobacco use due to their young age.

chloroeicosafluoro-3-oxanone-1-sulfonic acid (11Cl-PF3OUdS), ammonium 4,8-dioxa-3H-perfluorononnanoate (ADONA), 3:3 fluorotelomer carboxylic acid (3:3 FTCA), 5:3 fluorotelomer carboxylic acid (5:3 FTCA), 7:3 fluorotelomer carboxylic acid (7:3 FTCA), 4:2 fluorotelomer sulfonate (4:2 FTSA) and 8:2 fluorotelomer sulfonate (8:2 FTSA) by the Department of Environmental Science, Stockholm University. A detailed description of the serum PFAS analysis, including quality control, is provided in the Supplement in connection to Table S1. Briefly, sample extraction was carried out using a method adapted from Powley et al. (2005). The samples were analyzed using a Waters ultra-performance liquid chromatograph coupled to a Waters Xevo TQS triple quadrupole mass spectrometer operated in negative electrospray ionization, multiple reaction monitoring (MRM) mode. Quantification was based on isotope dilution. Targets and their corresponding isotopically labelled internal standards are provided in Table S1. Data for the PFAS were classified as either 'quantitative', 'semi-quantitative', or 'qualitative', based on either availability of authentic standards and/or performance of QC samples (Table S1). 'Quantitative' indicated that an exactly-matched authentic standard was available and that QC samples displayed reasonable accuracy and precision (25 targets). 'Semi--quantitative' targets were those quantified with exactly-matched authentic standards but displaying sub-optimal accuracy and/or precision for QC samples, including 6:2 and 8:2 diPAP, EtFOSAA, 7:3 FTCA, and 8:2 FTSA. 'Qualitative' targets included PFPeS, PFHpS, PFNS, PFUnDS, PFPeDA, PFHxDA, PFOcDA, 6:2/8:2 diPAP, FOSAA, 3:3 and 5:3 FTCA, due to poor accuracy and/or precision in QC samples or lack of authentic standards.

Ferritin and C-reactive protein (CRP) in plasma were analyzed on

Abbott Architect ci8200 analyzers (Abbott Laboratories, Abbott Park, IL, USA) at the accredited laboratory of Department of Clinical Chemistry and Pharmacology, University Hospital, Uppsala, Sweden.

2.4. Regression models

2.4.1. Base model

The associations between PFAS serum concentrations and possible determinants were investigated by ordinal regression analysis (see section 2.5.2.). For more detailed information about the determinants see Table 1. The base model included previously reported determinants of PFAS concentrations, i.e. parental education level, participant/maternal birth country (BC) (Glynn et al., 2020), tobacco use (Eriksen et al., 2011), alcohol consumption (Pitter et al., 2020), body mass index (BMI status) (Hölzer et al., 2008; Eriksen et al., 2011), gender (male or female), age (in years), and months exclusive breastfeeding early in life (Gyllenhammar et al., 2019). Participants (n = 11) exceeding the UN-defined age-span for adolescents (10–19) were included as recruitment was conducted through schools and the observed age range is most likely representative for grades 5, 8 and 11 (Saywer et al., 2018).

In order to account for possible differences in dietary PFAS exposure between different demographic groups, the Swedish Healthy Eating Index for Adolescents 2015 (SHEIA15) was included as a variable in the model. The results for this variable are presented in a separate companion paper investigating the importance of different dietary patterns on PFAS serum concentrations. SHEIA15 reflects healthy eating of RMA participants (Moraeus et al., 2020). In short, SHEIA15 was based on the key dietary advice from the 2012 Nordic Nutrition Recommendations (Nordic Nutrition Recommendations, 2014), calculated as the ratio between the actual consumption (as registered in RFD by participants) and the recommended consumption for each food or nutrient (fruits and vegetables, wholemeal, seafood, dietary fats, low fat dairy products, red and processed meat, added sugar), and summed up to a total continuous score of maximum 9 (Moraeus et al., 2020).

The participant and maternal birth countries were classified according to the World Bank Country Classification (World Bank Group, 2018), by per capita gross national income level with the following categories: high income-, upper-middle- and lower-middle/low income countries. To avoid issues with collinearity between the participant and the maternal birth country, a joint birth country covariate was created (BC) (Table 1).

2.4.2. Sensitivity analysis

A sensitivity analysis was conducted for the base model in order to evaluate potential bias of results due to some participants living in areas with a known history of PFAS-contaminated DW (Gyllenhammar et al., 2015; Li et al., 2018). Consequently, the categorical covariate containing the two categories 'schools in area with previous DW contamination' (i.e. Ronneby and Uppsala, n = 42) and 'schools elsewhere' was added to the base model (DW sensitivity analysis).

2.4.3. Secondary models

We created two separate secondary models with the aim of evaluating the association between menstrual blood loss and serum PFAS concentrations. Females registered in RFQ whether or not they had started menstruating and at what age menstruation began. Menstruation was assumed to have continued from onset to age at RMA participation. Onset of menstruation (yes or no) and years since onset of menstruation (continuous) were separately included in the base model for all females.

In two additional separate models, plasma ferritin (μg/L plasma) was included as a potential marker of long-term menstrual bleeding (Wang et al., 2013). Log-transformed C-reactive protein plasma levels (CRP, mg/L plasma), an infection marker, was included in the ferritin models to adjust for the increase in levels of ferritin during an infection (Khan et al., 2016). Additionally, an interaction term between CRP and ferritin was added to evaluate said relationship, and the significance of ferritin was consequently evaluated by forming contrasts for an inter quartile range increase in ferritin while holding CRP constant at the 10th, 50th and 90th percentiles. CRP < LOD was set to LOD/ $\sqrt{2}$. To ensure that a possible ferritin-PFAS association among the females was solely connected to blood loss, the same ferritin model was also fit for the males.

2.5. Statistical analysis

All data processing and statistical analyses were executed using R (version 3.6.3; R Development Core Team), and statistical significance was set at $p \leq 0.05$. ~18% of participants had single/a few missing data from RFQ or PFAS analyses. Missing data were imputed 5 times using multiple imputation by chained equations assuming data to be missing at random, conditional on the covariates. The imputation was carried out separately by gender as we wanted to ensure that our gender specific analysis (menstruation/ferritin) would not be influenced by any potential gender-dependent variability amongst the covariates. Coefficients and standard errors were estimated using Rubin's rules for pooling multiple imputed data (van Buuren and Groothuis-Oudshoorn, 2011; Rubin, 1987). When PFAS concentrations were <LOQ, reported concentrations ≥ LOD were used. Although these data are more uncertain compared to data ≥ LOQ, their use tends to reduce bias compared to if concentrations < LOQ are set to a fixed value, for instance zero, ½ LOQ or LOQ/$\sqrt{2}$. The latter replacements will add an undesirable systematic error if used in regression analyses (Bergstrand and Karlsson, 2009; RSC, 2001).

2.5.1. Principal component analysis

Principal component analysis (PCA) was used to visualize exposure patterns between legacy and emerging PFAS. The PCA used a singular value decomposition of the PFAS data matrix including PFAS with detectable concentrations for >2% of the study population. In an additional sensitivity analysis, participants residing in Uppsala and Ronneby were removed. Although analytical quality of PFPeS and PFHpS data was deemed qualitative (due to quantification using an authentic standard of PFHxS), these targets were nevertheless included in the PCA since they were detected in >2% of the participants as well as due to the high degree of confidence in their identification.

2.5.2. Ordinal logistic regression (OLR)

The cumulative probability model (CMP) was used, which fits the continuous response variable using ordinal logistic regression (OLR). Such models are invariant to monotonic transformations (e.g. log) of outcomes as only the order information of the outcome is incorporated. This successfully integrates PFAS concentrations below LOD without the need for prior estimation or imputations of undetectable concentrations. It also removes the need for transformation of the PFAS levels, which showed skewed distributions (Liu et al., 2017). All PFAS data < LOD were substituted with a value of 0.0001 ng/g in order to be included in the analyses. To account for the effect of clustering due to sampling by school, the Huber-White method was applied to the covariance matrices from the model fits. Model fit was evaluated using QQ-plots of the probability scale residuals (Liu et al., 2017). As data were imputed separately for gender, both imputed datasets were joined by stacking before fitting of the ordinal regression models. Being an ordinal logistic model, the OLR provides (log) odds ratios, but as it estimates the entire empirical cumulative distribution function it is possible to obtain conditional means, medians and exceedance probabilities (Liu et al., 2017). The covariate contribution to the variation of serum PFAS concentrations was evaluated by calculating χ^2 - degrees of freedom for each variable for each model separately. This levels the playing field between the variables in a particular model since the expected value of a χ^2 random variable with k degrees of freedom is k. However, this measure can only be compared within, and not across, models.

Table 2
PFAS serum concentrations in the study population, including the extra target analytes included in the PCA.

PFAS (ng/g serum)	*n*	LOD *(%<LOD)*	LOQ *(%<LOQ)*	Detected and quantified Median (range)	Quantified Median (range)
PFCA					
PFHpA	1098	0.020–0.103 *(88.6)*	0.058–0.288 *(92.2)*	<LOD (<LOD, 0.604)	<LOQ (<LOQ, 0.604)
lin-PFOA	1095	0.287 *(0.1)*	0.020–0.288 *(0.2)*	1.203 (<LOD, 9.75)	1.203 (<LOQ, 9.75)
PFNA	1098	0.103–0.176 *(4.9)*	0.058–0.288 *(7.3)*	0.382 (<LOD, 2.80)	0.382 (<LOQ, 2.80)
PFDA	1098	0.028–0.099 *(19.7)*	0.058–0.288 *(37.4)*	0.162 (<LOD, 1.35)	0.140 (<LOQ, 1.35)
PFUnDA	1098	0.020–0.119 *(30.6)*	0.058–0.288 *(52.9)*	0.097 (<LOD, 1.01)	0.097 (<LOQ, 1.01)
PFDoDA	1098	0.014–0.080 *(91.3)*	0.058–0.288 *(98.7)*	<LOD (<LOD, 0.182)	<LOQ (<LOQ, 0.182)
PFTrDA	1098	0.013–0.155 *(91.6)*	0.058–0.288 *(99.4)*	<LOD (<LOD, 0.168)	<LOQ (<LOQ, 0.113)
PFSA					
PFPeS[a]	830	0.044–0.195 *(97.2)*	0.078–3.30 *(99.3)*	<LOD (<LOD, 1.86)	<LOQ (<LOQ, 1.38)
br-PFHxS	1098	0.010–0.061 *(90.6)*	0.022–0.186 *(95.7)*	<LOD (<LOD, 3.74)	<LOQ (<LOQ, 3.74)
lin-PFHxS	1098	0.017–0.216 *(0.7)*	0.022–0.464 *(7.9)*	0.399 (<LOD, 255)	0.397 (<LOQ, 255)
PFHpS[a]	1098	0.021–0.102 *(90.5)*	0.022–3.34 *(97.6)*	<LOD (<LOD, 5.76)	<LOQ (<LOQ, 5.76)
br-PFOS	1098	0.031–0.257 *(0)*	0.056–0.562 *(2.0)*	0.925 (0.031, 110)	0.925 (<LOQ, 110)
lin-PFOS	1098	0.056–0.562 *(0)*	0.056–0.562 *(0)*	1.995 (0.281, 127)	1.995 (0.281, 127)
FASAA					
lin-MeFOSAA	1098	0.013–0.104 *(91.2)*	0.060–3.57 *(98.7)*	<LOD (<LOD, 6.04)	<LOQ (<LOQ, 6.04)
PFESA					
9Cl-PF3ONS	1098	0.005–0.067 *(94.6)*	0.024–3.50 *(99.8)*	<LOD (<LOD, 1.21)	<LOQ (<LOQ, 1.21)

Note: The limit of detection (LOD) and limit of quantification (LOQ) varied between batches; FASAA, perfluoroalkane sulfonamido acetic acid; PFESA, per- and polyfluoroalkyl ether sulfonic acids.
[a] Analytical quality: qualitative.

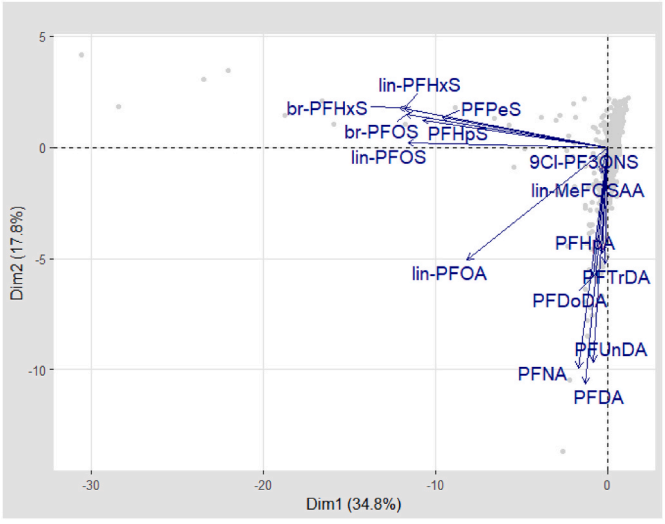

Fig. 1. Principal component analysis (PCA) biplot for PFAS detected in >2% of the adolescent participants, showing loading of each PFAS (arrows) and PC scores of samples (dots) (n = 827).

3. Results

3.1. Study population – PFAS concentrations and demographics

Table 1 presents the base model characteristics and demographics of the study population (n = 1098), while Table S2 presents the secondary and sensitivity analysis model covariates. The legacy PFAS lin-PFOA, PFNA, PFDA, PFUnDA, lin-PFHxS and lin/br-PFOS were detected in ≥70% of the samples and consequently included in the OLR (Table 2). lin-PFOS showed the highest median concentration, being roughly twenty-fold higher than medians of PFDA and PFUnDA. The highest individual concentrations were found among participants from Ronneby for lin-PFHxS, being approximately two-fold higher than the highest concentrations of lin/br-PFOS, and more than 100-fold higher than those of PFNA, PFDA and PFUnDA (Table 2 and S3). Median PFOA, PFHxS and PFOS concentrations were significantly higher in Uppsala and Ronneby participants than in the rest of the study group (Table S3). Lin-MeFOSAA and 9Cl-PF3ONS were detected in about 9% and 5% of the samples, respectively, and were included in the PCA, as were PFHpA, PFDoDA, PFTrDA, br-PFHxS (quantitative data), PFPeS and PFHpS (qualitative data) which were detected in 3–11% of all samples (Table 2). Serum PFAS concentrations not included in either OLRs or PCA, with <2% detected concentrations, are provided in Table S4. Among the PFAS with quantitative analytical quality, the emerging PFAS 11Cl-PF3OUdS and ADONA were detected and quantified in 0.6 and 0.1% of the participants, respectively.

The two first principal components (PCs) of the PCA explained roughly 53% of the total serum PFAS concentration variability (Fig. 1), with a total of eight PC's needed to explain a minimum of 90% of the variance. Based on the directions in the PC space, PFCA with a perfluorinated carbon chain length of ≥8 carbons clustered together and largely explained the variation of the second dimension, while PFSA with ≥5 carbons clustered together to explain a large amount of the variation in the first dimension (Fig. 1). Lin-PFOA did not cluster with any of the large clusters, while PFHpA, lin-MeFOSAA and 9Cl-PF3ONS (all displaying low detection frequency), clustered with the long-chained PFCA, but explained very little of the variation of PC2 (Fig. 1, Table S5). Removing participants from Uppsala and Ronneby reduced the explained total variability in PFAS serum concentrations to roughly 40% (Figure S1). Additionally, PFPeS and PFHpS were excluded from the PCA as they were only detected in a few samples outside of Uppsala/Ronneby. The orientation of the clusters in the PCA changed, with lin-PFOA moving closer to the long-chained PFCA and 9Cl-PF3ONS clustering with the PFSA instead of the PFCA (Figure S1).

3.2. Base model determinants

Birth country (BC) was significantly associated with concentrations of all studied legacy PFAS (Fig. 2, Table S6-S12), and participants whom, together with their mothers, were born in high income countries had the highest estimated adjusted mean (EAM) concentrations (Fig. 3). With the exception of PFDA and PFUnDA, participants whom, together with their mothers, originating from low and lower-middle income countries had the lowest EAM PFAS concentrations (Fig. 3). Moreover, the maternal contribution to the BC association is illustrated among participant born in high income countries, with mothers from upper-middle and lower-middle/low income countries, having lower EAMs than those with mothers from high income countries. BC was the

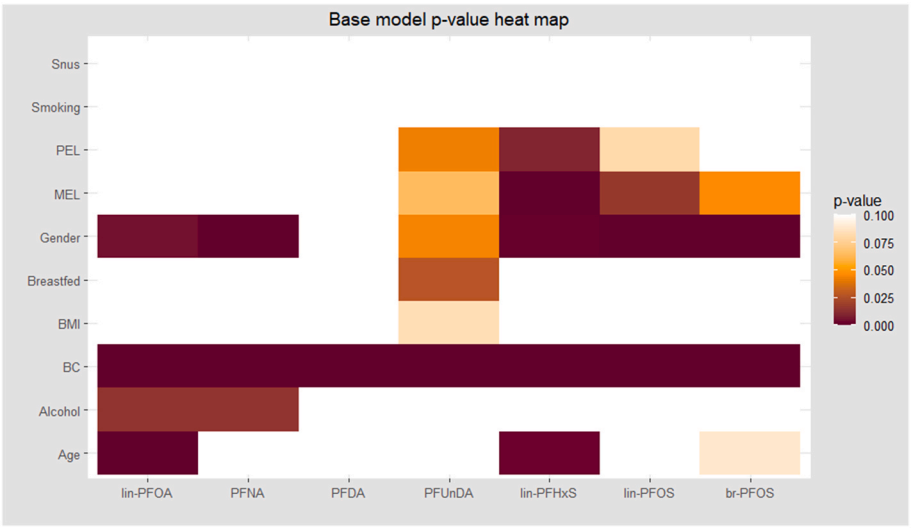

Fig. 2. Heat map of p-values for associations between potential determinants and serum legacy PFAS concentrations in adolescents, estimated in ordinal logistic regression (OLR) analyses (n = 1098). All determinants were included in the regression models and the results were also adjusted for the healthy diet index SHEIA15, Swedish Healthy Eating Index for Adolescents 2015; PEL, paternal education level; MEL, maternal education level; BMI status, body mass index cut-offs; BC, participant/maternal birth country.

strongest determinant of the serum legacy PFAS concentrations (Fig. 4). Females had significantly lower EAM concentrations compared to males, except in the case of PFDA (Fig. 2, Table S6-S12). Gender was the second strongest determinant of PFNA, lin-PFOS and br-PFOS, and third strongest for, lin-PFOS and br-PFOS and lin-PFHxS (Fig. 4). Age was inversely associated with lin-PFOA and lin-PFHxS concentrations

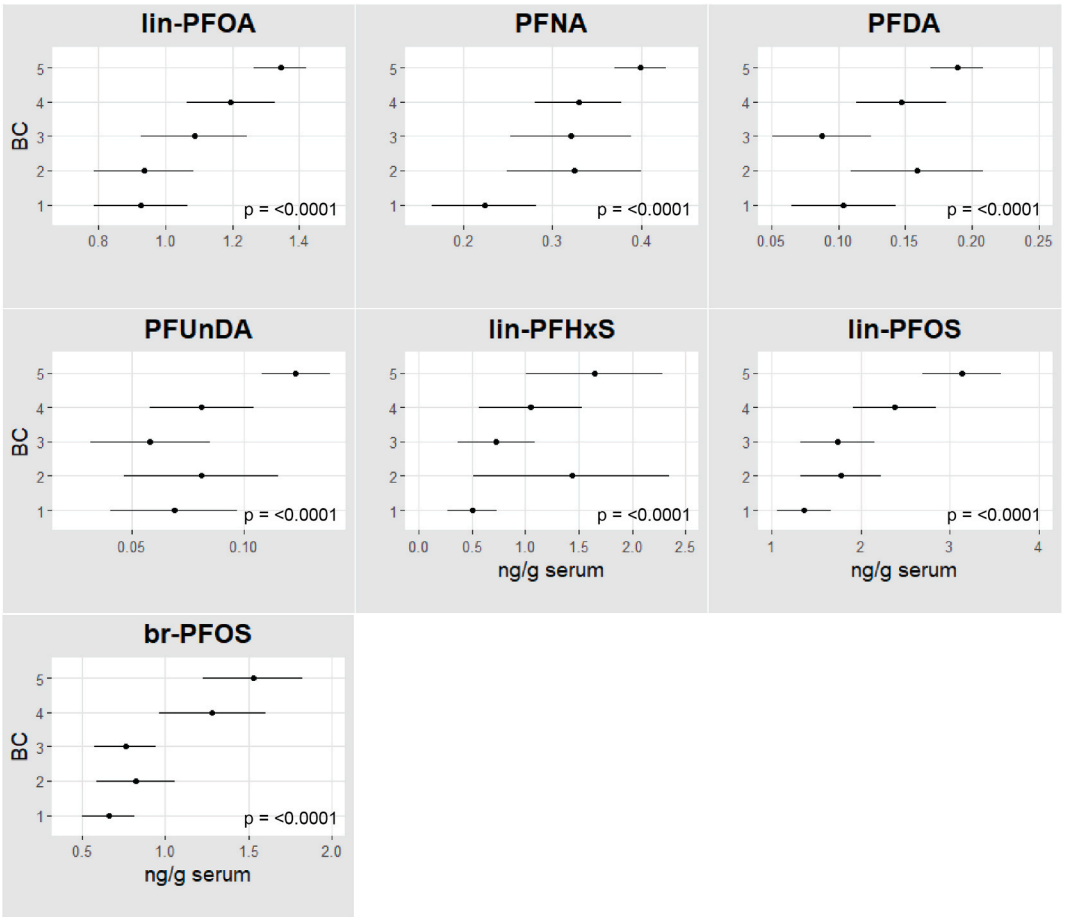

Fig. 3. Estimated adjusted mean serum PFAS concentrations and 95% confidence interval for different categories of birth country (BC) determined in the ordinal regression analysis (OLRs), and adjusted for the covariates age, gender, body mass index cut-offs, maternal and paternal education level (MEL/PEL), months exclusively breastfed, snus and smoking habits, alcohol consumption, and the healthy eating index (SHEIA15). BC; participant/maternal birth country, 5 = both from high income countries, 4 = high/upper-middle income countries, 3 = both upper-middle income countries, 2 = high and upper-middle/low and lower-middle income countries, 1 = both from low and lower-middle income countries. The p-value results from a global test of the variable where the null hypothesis is that all coefficients are equal to zero.

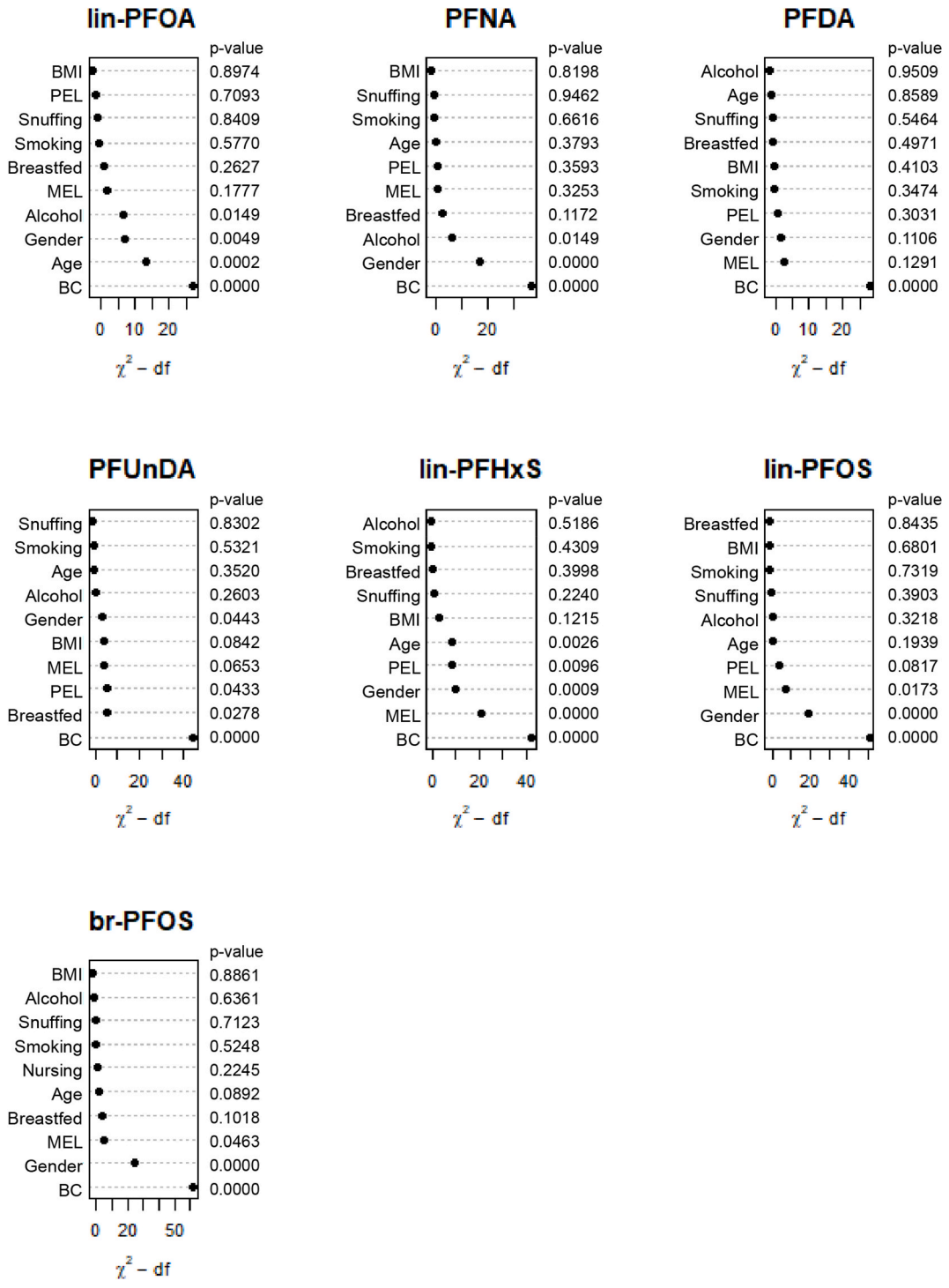

Fig. 4. The relative importance of base model covariates as determinants of PFAS concentrations estimated using ordinal logistic regression (n = 1098), expressed as the χ^2- df (x-axis). Covariates included in the regression models are given on the left y-axis and p-value for each covariate on the right y-axis. Note that the relative importance of a covariate can only be compared within each PFAS model, and not between different PFAS models. SHEIA15, Swedish Healthy Eating Index for Adolescents, was included in the regression model to adjust for differences in dietary patterns among the participants. BMI status, body mass index cut-offs; MEL, maternal education level; PEL, paternal education level; BC, participant/maternal birth country.

(Fig. 2, Table S6-S12), and was the second strongest determinant for lin-PFOA (Fig. 4). Participants who had consumed alcohol more than once in the last six months showed significantly higher EAM concentrations of lin-PFOA and PFNA compared to those not consuming alcohol (Fig. 2, Table S6-S12). EAMs of lin-PFHxS and lin-PFOS were highest among participants with mothers who had attended university/college (Fig. 2, Table S6-S12). Maternal education was the second strongest determinant of lin-PFHxS, and the third strongest for lin-PFOS (Fig. 4). Significant associations with paternal education were observed for PFUnDA and lin-PFHxS (Fig. 2, Table S6-S12), being the third and fourth strongest determinants, respectively (Fig. 4). Months of reported exclusive breastfeeding was significantly associated with PFUnDA (Fig. 2), with the highest EAM concentration found in participants who had the lowest degree of breastfeeding (Table S6-S12). No significant

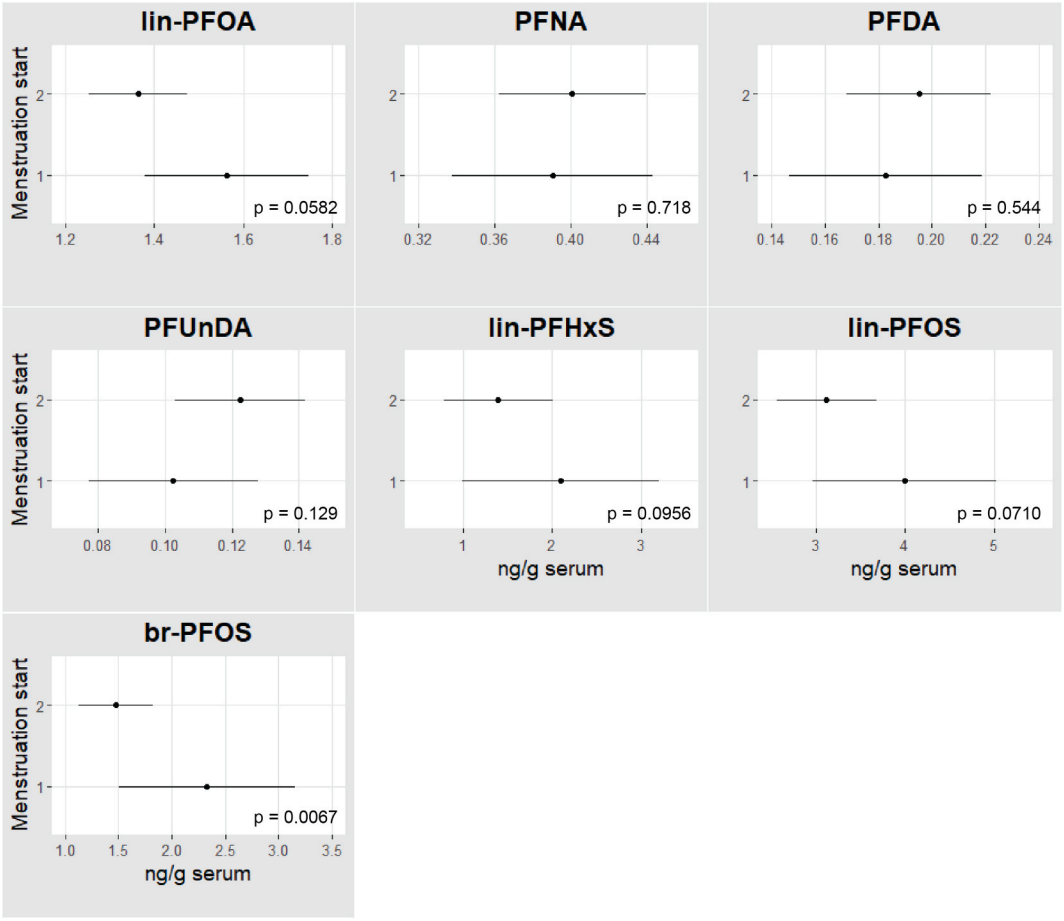

Fig. 5. Estimated adjusted mean serum PFAS concentration and 95% confidence interval for females who had not started menstruating (1) and females who had started menstruating (2) (n = 616). Adjusted for age, participant/maternal birth country (BC), maternal and paternal education level (MEL/PEL), smoking and snus habits, alcohol consumption, months exclusively breastfed, body mass index cut-offs and the healthy eating index SHEIA15. The p-value results from a global test of the variable where the null hypothesis is that all coefficients are equal to zero.

associations were found for BMI status, and smoking and snus (tobacco placed under upper lip) habits (Fig. 2, Table S6-S12).

3.3. Sensitivity analysis

The DW sensitivity analysis did not markedly influence the base model covariate association for lin-PFOA, PFNA, PFDA, PFUnDA, lin-PFHxS and br-PFOS (Table S6-S12). However, lin-PFOS and br-PFOS were no longer associated with maternal education.

3.4. Secondary models - menstruation

Females who had started menstruating had significantly lower adjusted br-PFOS serum concentrations compared to females who were yet to start menstruating (Fig. 5, Table S13) (n = 616). A similar tendency, although not statistically significant, was observed for lin-PFOA, lin-PFHxS and lin-PFOS (Fig. 5, Table S13). Number of years since onset of menstruation did not significantly influence PFAS serum concentrations (Table S13). No significant association was found between any of the PFAS and plasma ferritin levels among females at neither the 10th, 50th nor the 90th percentile of CRP (Table S13) (n = 616). However, among males (n = 482), the odds ratio for ferritin and serum PFNA, PFDA and PFUnDA increased significantly with increasing CRP level, a trend which also appeared for lin/br-PFOS (Table S13). Ferritin was also significantly associated with lin-PFOA and lin-PFHxS in males, though in this case the odds ratios appeared to decrease with increasing CRP levels (Table S13).

4. Discussion

The legacy PFAS lin-PFOA, PFNA, PFDA, PFUnDA, lin-PFHxS and lin/br-PFOS were detected in >70% of the serum samples from RMA participants, showing general long-term exposure to these PFAS among Swedish adolescents. The very high PFOS and PFHxS concentrations (>100 ng/ml) observed in some 5th graders from Ronneby were due to serious contamination of one of the two municipal waterworks in the area (Xu et al., 2020). These PFOS and PFHxS concentrations are amongst the highest reported for adolescents globally (Averina et al., 2018; Ramesh et al., 2019; Colles et al., 2020). This highlights the urgency of identifying and mitigating currently unknown hot-spots of PFAS contamination, which may be contributing to very high DW PFAS exposure in populations living in close proximity to the hot-spots. The contamination in Ronneby was discovered and remediated in 2013 (Xu et al., 2020), but the very long half-lives of PFHxS and PFOS (Li et al., 2018) will result in highly elevated body burdens in this exposed population for decades to come. Although production and use of some of the legacy PFAS already has been more or less banned or severely restricted in many countries of the world (Benskin et al., 2010; Stockholm Convention, 2019), the persistence of these PFAS in the environment makes it important to continue assessing human exposure by analyzing legacy PFAS in food and DW, as well as in human matrices.

Inter-study comparisons of PFAS concentrations in humans are

complicated by differences in analytical methods, non-matching age-span between studies, and temporal trends of human exposure (Nyberg et al., 2018). Nevertheless, average lin-PFOA, PFNA, PFDA, PFUnDA, lin-PFHxS and lin/br-PFOS concentrations were within the range of those observed in comparable adolescent populations from industrial countries such as the US, Taiwan, South Korea and Norway sampled in 2009–2011 (Schecter et al., 2012; Ji et al., 2012; Dong et al., 2013; Averina et al., 2018), but on average higher than those reported in a Canadian adolescent population in 2015 (Caron-Beaudoin et al., 2019). Although only quantified in ~5% of all participants, the quantification of 9Cl-PF3ONS in Swedish adolescents is especially disconcerting as this emerging PFAS exhibits a similar bioaccumulation potential as PFOS (Shi et al., 2015; Pan et al., 2021). Used in the Chinese metal electroplating industry as a PFOS replacement, 9Cl-PF3ONS (also known as 6:2 Cl-PFESA) has mostly been observed in human serum and breast milk samples in China (Awad et al., 2020; Brase et al., 2021). However, it was also detected recently in surface water throughout Europe (including Sweden) (Pan et al., 2018) and intermittently in primiparous Swedish women (Miaz et al., 2020). Our results strengthen the suspicion that this compound is becoming a globally dispersed environmental contaminant, with parts of the adolescent population in Sweden already exposed. The number of participants with 9Cl-PF3ONS concentrations in the same range as the legacy PFAS is, however, still low, suggesting that human exposure outside China may be in its initial phase. In addition to this substance, future biomonitoring studies should also include 11Cl-PF3OUdS and ADONA, both of which were detected in a small fraction of the adolescents in the present study. 11Cl-PF3OUdS has previously been observed in fish consumers from China (Shi et al., 2016), while ADONA was detected intermittently in blood donors from Southern Germany (Fromme et al., 2017).

Despite their low detection frequency in RMA, PCA clustering of PFPeS, PFHpS, and br-PFHxS together with lin-PFHxS and lin/br-PFOS suggests that DW was a source of exposure of the adolescents to these PFAS. The almost exclusive detection of PFPeS, PFHpS in Uppsala and Ronneby participants with a history of DW PFAS exposure explains this exposure pattern (Gyllenhammar et al., 2015; Li et al., 2018). While data quality for PFPeS and PFHpS is considered qualitative, we have considerable confidence in these assignments due to a) the presence of multiple product ions for both substances; b) alignment of retention times relative to other PFSA, and c) the observation of other PFSA, which are expected to co-occur with PFPeS and PFHpS. A study of Swedish airport employees exposed to PFAS-contaminated DW at work supports DW as a source of PFPeS and PFHpS exposure (Xu et al., 2020). While we were initially concerned that inclusion of participants from Uppsala and Ronneby might introduce bias in the statistical analyses of PFAS determinants, the DW sensitivity regression analysis showed that the elevated concentrations in Uppsala and Ronneby participants did not markedly affect the overall results for the other determinants studied.

Lower EAM concentrations of legacy PFAS in adolescents was related to a lower degree of industrialization of BC, as indicated by the per capita gross national income UN classification system. Consequently, BC may be an important confounder in population studies of health effects of legacy PFAS among children/adolescents, both influencing health outcomes and PFAS body burdens. The results are in line with studies from less industrialized countries (Hemat et al., 2010; Müller et al., 2019; Macheka et al., 2020; Timmermann et al., 2020) and studies of immigrant mothers from Sweden (Ode et al., 2013). A small study on Swedish 5th graders similarly observed higher average serum concentrations of legacy PFAS in participants born in high income countries than those born elsewhere (Glynn et al., 2020). These BC differences in exposure may be due to a combination of long half-lives of the PFAS (Olsen et al., 2007; Worley et al., 2017; Li et al., 2018) and general differences in PFAS contamination of human environment and food/DW between high income and low income countries. There are most likely differences in the establishment of PFAS-related industry, access and use of modern consumer/industrial products, and in housing and living standards between the different types of countries (Hanssen et al., 2010; Müller et al., 2019).

Placental transfer (Beesoon et al., 2011; Wang et al., 2019b) and breastfeeding (Fromme et al., 2010; Gyllenhammar et al., 2018) are major determinants of PFAS serum/plasma concentrations in infants, toddlers, and children up to 12 years of age in Sweden and elsewhere (Mogensen et al., 2015; Gyllenhammar et al., 2019). In the present study duration of breast-feeding of the participants early in life did not appear to be an important determinants of serum PFAS concentrations. However, the lower PFAS body burdens among mothers from less industrialized countries (Ode et al., 2013), may have resulted in lower early life maternal transfer of these PFAS to the RMA participants. This may have contributed to the BC differences observed among the RMA adolescents, as indicated by the influence of maternal BC on the results.

The observed BC-related differences in PFAS concentrations were not dependent on differences in parental education levels and healthy dietary patterns (SHEIA15) of the participants. BC relations to PFAS concentrations could nevertheless, in addition to differences in maternal PFAS transfer and other exposures of the participants early in life in their BC, reflect more current disparities in PFAS exposures due to BC-related dietary preferences and lifestyles of the adolescents now all living in Sweden (Säfsten et al., 2016). However, daycare and school lunches mitigate gender- and socio-economic differences in diet in Sweden (Eustachio Colombo et al., 2020), thus potentially diminishing dietary-related BC differences in PFAS exposure. The relations between serum concentrations of PFAS and dietary patterns in RMA will be explored in a separate study.

Similarly to RMA, positive associations were observed between PFOA and alcohol consumption in an Italian adolescent/adult population (14–39 years of age) (Pitter et al., 2020), as well as for PFNA in an adult US population (Jian et al., 2017). However, diverging results have been reported in middle-aged Danish men (Eriksen et al., 2011) and U.S. women (Park et al., 2019). Apart from the possibility that the observed associations are coincidental, it is conceivable that alcohol consumption is a direct exposure source if PFAS-contaminated DW is used in the production of alcoholic beverages, such as beer. Moreover, liver effects of alcohol consumption (Maher, 1997) may alter PFAS toxicokinetics, or alcohol consumption may be a marker for dissimilarities in life-style (Fored et al., 2003; Hanson and Chen, 2007), the latter indirectly affecting PFAS exposure.

Previous studies have reported higher serum/plasma PFAS concentrations among highly educated adults than among those with low education level (Bjermo et al., 2013; Brantsæter et al., 2013; Tsai et al., 2018). In RMA, most of the legacy PFAS were not associated with either maternal or paternal education level, suggesting that life-style connected to education level did not markedly affect PFAS exposure after adjustment for the other determinants and healthy eating habits in RMA. Parental education level was associated with a healthy dietary pattern (SHIEA15) of the RMA participants (Moraeus et al., 2020) and, hypothetically, inclusion of SHIEA15 in the regression models may have weakened potential relations between PFAS exposure and parental education level.

Inverse associations between lin-PFOA and lin-PFHxS concentrations and age agree with other studies of children/adolescents (Kato et al., 2009; Kang et al., 2018; Daly et al., 2018; Gyllenhammar et al., 2018), and could partially be due to growth dilution of PFAS accumulated early in life (Wu et al., 2015). However, PFAS and BMI status relations were not observed in RMA, at least partially arguing against a marked growth dilution effect. A higher consumption of food and DW per kilogram body weight at younger ages may also contribute to the inverse PFAS relation with age (Foster et al., 2010).

Gender was one of the strongest determinants of serum PFAS concentrations in RMA, with males generally having higher EAM serum PFAS concentrations than females. Although in line with previous research (Kang et al., 2018; Pitter et al., 2020; Duffek et al., 2020), the reasons behind these findings are not yet fully understood. Besides a

higher overall food consumption per kg body weight among males (Shomaker et al., 2010), menstrual blood loss among females have been suggested to at least partly account for gender differences among adults (Wong et al., 2014). This is supported in our study, as females who had started menstruating had lower EAM serum br-PFOS concentrations than those who had not, with a similar tendency for lin-PFOA, lin-PFHxS and lin-PFOS. Pharmacokinetic modeling has suggested that menstruation accounts for on average 30% of the shorter half-life of PFOS among adult women than among men (Wong et al., 2014), and an on average 22% reduction of PFOA serum concentrations in adult women (Lorber et al., 2015). Our results suggest that the effect of menstrual bleeding on PFAS toxicokinetics in adolescent females was mainly caused by onset of menstrual bleeding rather than years of menstrual bleeding after onset. The frequent irregularity of the menstrual cycle during adolescence may at least partially obscure associations between years of menstruation and PFAS serum concentrations in adolescence (American Academy of Pediatrics, 2006). It is plausible that pharmacokinetic alterations at menarche could potentially explain this association (Wu et al., 2015).

Serum/plasma ferritin may be a marker for degree of blood loss among women, where long-term blood loss due to menstruation could lead to decreasing iron status and consequently lower ferritin levels (Wang et al., 2013). We hypothesized that PFAS concentrations would increase with increased plasma ferritin among RMA females. However, no such associations were observed. Instead, increased lin-PFOA, PFNA, PFDA, PFUnDA and lin-PFHxS concentrations were related to increased ferritin in males. Positive associations between PFOS and serum ferritin have been noted in both male and female Taiwanese uremic patients prior to hemodialysis (Liu et al., 2018), an association which was not found in adults in a representative general U.S. population (Omoike et al., 2020). These diverging results cannot be explained by current knowledge. It has been suggested that ferritin in blood plays a role in PFAS blood transport (Liu et al., 2018), though further studies are needed in order to shed a light on possible gender-related PFAS-ferritin interactions.

A strength of our study is the population-based study design and the large number of participating adolescents. However, there was a slight overrepresentation of participants from densely populated municipalities among those donating blood, compared to those who declined to donate blood (Moraeus et al., 2018). It was nevertheless concluded by Moraeus et al. (2018), that no overall major skewness of distribution in regard to municipality could be seen. The most pronounced difference could be seen for gender, as females were overrepresented amongst those donating blood compared to those declining to donate blood (Moraeus et al., 2018). This should be taken into account in the interpretation of the representativeness of the results. An additional important limitation is that, except for BMI status, data was in most cases self-reported. As many studies predominantly focus on blood concentrations of legacy PFAS, having additional data on many different potentially emerging PFAS greatly adds to the knowledge about human PFAS exposure, especially among adolescents, which can be seen as a considerable strength.

5. Conclusions

Legacy PFAS were detected at high frequency in a nationally representative Swedish adolescent population. The occurrence of emerging PFAS, such as 9Cl-PF3ONS, highlights the importance of screening for PFAS replacements in future biomonitoring studies. Participant and maternal birth country was the most important determinant of legacy PFAS concentrations, which may at least partly be explained by relationships between PFAS environmental contamination and degree of industrialization of birth countries. Gender was an important determinant for adolescents, where females had lower serum PFAS levels as opposed to males. This association could partially be explained by higher excretion due to menstruation, as supported by our present study. However, other toxicokinetics alterations due to onset of puberty may contribute in explaining apparent difference in PFAS body burdens between genders. The determinants identified in this study may be important confounders in future health studies including adolescents.

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Ethical approval

Ethical approval was granted by the Regional Ethical Review Board in Uppsala (No. 2015/190), where participants or legal guardians of participants below 16 years of age, gave written informed consent to participate.

Declaration of competing interest

The authors declare that they have no or actual competing financial interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2022.112674.

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