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Healthy eating index and diet diversity score as determinants of serum perfluoroalkyl acid (PFAA) concentrations in a national survey of Swedish adolescents☆

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ABSTRACT

Food is an important source of perfluoroalkyl acid (PFAA) exposure for the general adult population, but few data exist for adolescents. Healthy food habits established during adolescence may positively influence health later in life. Associations between serum PFAA concentrations and a healthy eating index (SHEIA15), as well as a diet diversity score (RADDS), were determined in a nationally representative adolescent population from Sweden (Riksmaten Adolescents 2016–2017, RMA). Using consumption data from food registrations and frequency questionnaires, we additionally analyzed associations with commonly consumed food groups. Associations were analyzed by fitting a cumulative probability model using ordinal regression. Among the seven PFAAs detected in ≥70% of the 1098 participants (age 10–21 years), median concentrations ranged from <1 ng/g serum of perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perflurorundecanoic acid (PFUnDA), linear (lin-) perfluorohexanesulfonic acid (PFHxS) and branched (br-) perfluorooctanesulfonic acid (PFOS) to 1–2 ng/g serum of lin-perfluorooctanoic acid (PFOA) and lin-PFOS. PFNA, PFDA, PFUnDA and lin-PFOS concentrations were positively associated with both SHEIA15 and RADDS, a finding most likely driven by higher consumption of seafood. PFDA, PFUnDA and lin-PFOS concentrations were positively related to commonly consumed fish/shellfish groups, such as lean marine fish and shellfish. Inverse associations between PFAA concentrations and dairy consumption suggest an underlying factor behind dairy consumption that similarly affects adolescent exposure to the different PFAAs. Isomeric differences in dietary exposure between lin-PFOS and br-PFOS were suggested, as br-PFOS concentrations, in contrast to lin-PFOS, were not associated with SHEIA15, RADDS and consumption of different food groups. We conclude that Swedish adolescents, adhering to a diverse and healthy diet, appears to be more highly exposed to legacy PFAAs than those eating less healthy. Additional research is necessary for a better understanding of the health implications of healthy eating from a PFAA exposure perspective.

1. Introduction

Per- and polyfluoroalkyl substances (PFAS) are a vast group of more than 4700 registered compounds (OECD, 2018). The stability and combined oil-/water repelling properties of perfluorinated carbon chains have led to wide-spread use of PFAS in both consumer and industrial applications since the 1950s (Glüge et al., 2020). This widespread use of PFAS in society has led to their global occurrence in biota and humans (Houde et al., 2011). Perfluoroalkyl acids (PFAAs), such as the well-studied perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS), have been intentionally produced, but they are also formed by degradation of certain of PFAA-precursors

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(Martin et al., 2010; D'eon and Mabury, 2011). PFAAs are very persistent in the environment, leading to contamination of food and drinking water (Dhore and Murthy, 2021; Kurwadkar et al., 2021). In addition to PFOA and PFOS, other long-chained PFAAs, such as perfluorononanoic acid (PFNA), perfluorodecanoic acid (PFDA), perfluoroundecanoic acid (PFUnDA), and perfluorohexanesulfonic acid (PFHxS), are considered bioaccumulative in humans (Conder et al., 2008; ITRC, 2020). Epidemiological studies have suggested that certain long-chain PFAAs alter lipid levels in children and adolescents (Geiger et al., 2014; Frisbee et al., 2010), impair the immune system in children (Grandjean et al., 2012; Abraham et al., 2020), and restrict fetal growth (Fei et al., 2007; Marks et al., 2019; Zhuang et al., 2021).

Prenatal PFAA exposure through the placenta and exposure via breast milk are major contributors to serum/plasma PFAA burdens in children, at least up to 12 years of age (Gyllenhammar et al., 2018; Balk et al., 2019). As the child ages through adolescence, exposure sources become more complex (Balk et al., 2019). Among adults, dietary exposure, predominantly from seafood and drinking water, contributes significantly to PFAA body burdens (Domingo and Nadal, 2017; Sunderland et al., 2019). However, associations between these body burdens and food consumption in the transition period between childhood and adulthood, in adolescence, have rarely been studied (Averina et al., 2018; Pitter et al., 2020; Duffek et al., 2020). Due to the large physiological/life-style changes that occur during adolescence, dietary habits of adolescents seem to differ from those of children and adults (von Post-Skagegård et al., 2002; Harris et al., 2015). Moreover, adolescence may be a sensitive PFAA exposure window due to the large physiological changes occurring. Considering the European Food Safety Authority's (EFSA) recent conclusion that the dietary intake of the sum of PFOA, PFNA, PFHxS and PFOS is a health concern in Europe (EFSA Contam Panel et al., 2020), a better understanding of dietary PFAA exposure pathways for adolescent populations is urgently needed.

A healthy diet, rich in vegetables, fruits, wholegrains, legumes, seafood and vegetable oils, provides an essential foundation for the prevention of cardiovascular disease, obesity and cancer (WHO, 2003). Recent research has reported elevated perfluoroundecanoic acid (PFUnDA) and PFOS concentrations in blood from 6 to 11 year-old children that consumed more than two servings of fish/seafood per week (Papadopoulou et al., 2019). Simultaneously, less healthy foods, such as snack foods (Susmann et al., 2019; Park et al., 2019) and fast food (Averina et al., 2018), have been proposed as exposure sources for certain PFAAs, at least partially due to the use of PFAS in paper-based food contact materials (Trier et al., 2011; Poothong et al., 2020; Seshasayee et al., 2021). Moreover, EFSA identified healthy food groups, including fish/shellfish, fruit and fruit products, and egg and egg products, as significant contributors to the overall exposure to PFOA, PFNA, PFHxS and PFOS in the general population (EFSA Contam Panel et al., 2020). There is therefore a need to capture the holistic influence of diet on PFAS exposure (Halldorsson et al., 2008; Liu et al., 2017a), since healthy dietary patterns are important determinants of positive health development. Improved knowledge on the relationship between a healthy diet and PFAS exposure is important when assessing the possible health effects of PFAS, and also for future health risk-benefit analyses of dietary patterns.

In the present study, we aimed to evaluate the association between PFAA serum concentrations and the overall adolescent diet, using a healthy food index and a healthy diet diversity score, in a nation-wide Swedish adolescent population. Individual associations between PFAA body burdens and commonly consumed food and seafood groups were also evaluated, in an effort to determine which food groups that may give a large contribution to adolescent PFAA exposure.

2. Methods

2.1. Study population

This study utilized a subsample of participants from the nationally representative school-based dietary survey Riksmaten Adolescents 2016–17 (RMA), conducted by the Swedish Food Agency (SFA). A detailed account of the population and study design is given in Moraeus et al. (2018), Lindroos et al. (2019) and Nyström et al. (2022).

In short, 3099 adolescents from grades 5 (on average ages 11–12 year), 8 (ages 14–15 year) and 11 (ages 17–18 years) were recruited via their schools between September 2016 and May 2017. Selection of schools was carried out by Statistics Sweden and was based on school type (public or charter), municipality classification and geographical spread (Moraeus et al., 2018). Most of the participants resided in southern Sweden or other densely populated areas, such as around the Swedish capital Stockholm, with fewer participants residing in the far north. Of the 2377 individuals invited to donate biological samples, 1098 had provided blood samples available for PFAS analysis (Nyström et al., 2022). The present study population consisted of a total of 482 male and 616 female participants, with an average age of 14.6 years for the population as a whole (Table 1). Participants exceeding the UN-defined adolescent upper age limit of 19 years of age ($n = 11$) were included in the study population, as it has previously been reported that their dietary and life-style most likely resembles that of their fellow classmates (Sawyer et al., 2018).

Written, informed consent was obtained from all participants or legal guardians for those below 16 years of age. The Regional Ethical Review Board in Uppsala granted ethical approval (No. 2015/190).

2.2. Personal characteristics and dietary assessment

Information on the personal characteristics and dietary habits of the participants were collected using the SFA-developed and validated web-based system RiksmatenFlex, which consisted of RiksmatenFlexDiet (RFD) and RiksmatenFlexQuestionnaire (RFQ) (Lindroos et al., 2019; Moraeus et al., 2018). Dietary registration in RFD was based on the repeated 24-h dietary recall method which allowed for retrospective registration of consumption of both food and beverages. The registration was carried out over two non-consecutive days; the first registration occurred during a weekday while the second registration was randomized to occur 2–7 days after the first registration. The second registration could consequently occur during the weekend as well, taking possible differences in dietary habits between weekdays and weekends days into account. Additional information on less frequently consumed foods was collected using a non-quantitative food propensity questionnaire (FPQ) in RFQ. The FPQ was designed to collect dietary data with a consumption frequency over the last 12-months. RFQ also contained additional questions concerning the participants' lifestyle, socio-economic factors, and other personal characteristics and demographics (Moraeus et al., 2018).

2.3. Sampling and chemical analysis of blood

Comprehensive accounts of the blood sampling and the method for chemical analysis are given in Moraeus et al. (2018) and Nyström et al. (2022), respectively.

In short, non-fasting venous blood was drawn in 10 ml tubes coated with coagulation activators. Once centrifuged on site, serum was stored and transported at -20°C until final storage at -80°C awaiting PFAS analysis (Moraeus et al., 2018).

Serum samples were extracted with acetonitrile followed by a dispersive clean-up using graphitized carbon (Powley et al., 2005) and analysis by ultra-performance liquid chromatography tandem mass spectrometry (UPLC-MS/MS). A detailed description of the serum PFAS analysis, including quality control, is provided in a companion article

Table 1
Demographical, lifestyle and physiological determinants of the RMA study population, included in the base model and secondary models, reproduced from Nyström et al., (2022).

	All *n (%)*
Categorical covariates	1098 *(100)*
Alcohol consumption during last 6 months	
Has never consumed alcohol (incl. 5th graders)[a]	759 *(69)*
Once	107 *(10)*
Several times	209 *(19)*
Missing	23 *(2)*
Birth country (participant/mother)	
Both high income countries	898 *(82)*
High income/upper-middle countries	79 *(7)*
Both upper-middle income countries	39 *(4)*
High and upper-middle/low and lower-middle income countries	29 *(3)*
Both low and lower-middle income countries	42 *(4)*
Missing	11 *(1)*
BMI status[b]	
Underweight	72 *(7)*
Normal weight	793 *(72)*
Overweight	190 *(17)*
Obese	43 *(4)*
Education level – father	
No formal education and primary education	111 *(10)*
Vocational education or equivalent	215 *(20)*
3–4 year upper secondary education or equivalent	280 *(26)*
University education or equivalent	411 *(37)*
Missing	81 *(7)*
Education level - mother	
No formal education and primary education	84 *(8)*
Vocational education or equivalent	162 *(15)*
3–4 year upper secondary education or equivalent	229 *(21)*
University education or equivalent	565 *(51)*
Missing	58 *(5)*
Exclusively breastfed	
Never breastfed and breastfed for <1 month	111 *(10)*
1 to 6 months	591 *(54)*
7 to >12 months	359 *(33)*
Missing	37 *(3)*
Gender	
Males	482 *(44)*
Females	616 *(56)*
Smoking habits	
Non-smoker (incl. 5th graders)[a]	955 *(87)*
Smoker	123 *(11)*
Missing	20 *(2)*
Snus use	
Does not use snus (incl. 5th graders)[a]	1016 *(93)*
Snus user	70 *(6)*
Missing	12 *(1)*
Continuous covariates	**Median** (min, max) *(% missing)*
Age (years)	14.6 (10.6, 21.1) *(0)*

Note: min, minimum; max, maximum; BMI, body mass index.
[a] 5th grade participants were not asked about alcohol and tobacco use due to their young age but they were assumed to be non-consumers of alcohol and non-smokers.
[b] For participants <18 years of age, BMI 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).

(Nyström et al., 2022). A total of 42 PFAS were included in the analysis but only linear (lin) PFOA, PFNA, PFDA, PFUnDA, lin-PFHxS and lin/-branched (br)-PFOS are included in the present study as they were the only PFAS detected at high enough frequency (≥70% of the RMA participants) to produce stable regression models. Furthermore, these PFAS are those that have been "priority" listed by EFSA (EFSA Contam Panel et al., 2020). The measured serum concentrations for all 42 PFAS are accounted for in Nyström et al. (2022).

2.4. Model selection and processing of determinants

Associations between serum PFAA concentrations and dietary determinants were evaluated using ordinal logistic regression (see section 2.5.). We built upon our previous work (Nyström et al., 2022), and created a base model encompassing possible determinants which could arguably explain some of the variation in serum PFAA concentrations. This included participant/maternal birth country (BC), maternal and paternal education level (MEL/PEL), body mass index cut-offs (BMI status), gender (male/female), age (years), months exclusively breastfed early in life, alcohol consumption, smoking habits, and snus use (Table 1) (Nyström et al., 2022). To investigate the association between serum PFAA and healthy and diverse food habits as a whole, a healthy food index (the Swedish Healthy Eating Index for Adolescents 2015, SHEIA15), and a diet diversity score index (Riksmaten Adolescent Diet Diversity Score, RADDS) (Moraeus et al., 2020), were separately explored. Moreover, in order to investigate associations between serum PFAA concentrations and consumption of important food groups, long-term (habitual) consumption of commonly consumed food, and seafood groups were added to the base model, in this case excluding SHEIA15 or RADDS (see section 2.4.1–2.4.4).

As roughly 40 of the RMA participants were residing in areas with PFAS-contaminated municipal drinking water remediated a few years before the blood sampling in RMA (Nyström et al., 2022), we performed a sensitivity analysis on the SHEIA15 and RADDS model adjusting categorically for those who were residing in previously highly contaminated areas (n = 42) and those who were not (n = 1056).

2.4.1. Healthy food index – SHEIA15

SHEIA15 was developed by the SFA and is an index that quantifies diet quality. Further details of SHEIA15 are described in Moraeus et al. (2020). Briefly, SHEIA15 is based on key dietary advice from the 2015 SFA dietary guidelines "Find your way" , i.e. eat more fruits and vegetables, switch to whole grain, eat more seafood, switch to healthy fats, switch to low fat dairy products, eat less sugar and less red and processed meats. The index is a ratio between the actual consumption of food or nutrient intake registered by the participants in RFD and the recommended consumption of each food and nutrient intake included in the 2012 Nordic Nutrition Recommendations (Nordic Council of Ministers, 2014; Moraeus et al., 2020). The scores were summed up (maximum score: 9), where a high score shows a stronger compliance to the recommendations and, as a result, a healthier diet (Moraeus et al., 2020). SHEIA15 was included as a continuous variable in the regression models (Table 2).

2.4.2. Healthy diet diversity score – RADDS

RADDS was also developed by the SFA and quantifies diet diversity. Additional details on RADDS is provided in Moraeus et al. (2020). A diverse and varied diet has been recognized to ensure nutritional adequacy preventing nutritional imbalances. RADDS was included in the base model with the aim to evaluate whether the adolescent serum PFAA concentrations were associated with a healthy diverse diet. RADDS was derived in relation the encouragement of a varied diet in the 2015 SFA dietary guidelines "Find your way", and is based on a variation between 17 food groups, such as cabbage, fruit, wholegrain products, vegetables, fish and milk, to name a few. The participants were given one point if they consumed more than 5 g per day of each subgroup based on the dietary registration in RFD. The points were then summed up, allowing for a maximum score of 17 (Moraeus et al., 2020). RADDS was included as a continuous covariate in the regression models (Table 2).

2.4.3. Habitual consumption of commonly consumed food groups

We also evaluated associations between serum PFAA concentrations and habitual consumption of individual food groups (g/day), i.e. eggs, dairy, meat, cereals, pastry, vegetables, potatoes, sweets, fruits and seafood (Table 2). These groups represent the major food groups

Table 2
Dietary determinants included in the base and secondary regression analysis.

Dietary determinants	All	n = 1098
	Median (min, max)	*% missing*
Dietary indices		
Swedish Healthy Eating Index for Adolescents 2015 (SHEIA15)	5.8 (3.4, 8.7)	*0*
Riksmaten Adolescent Diet Diversity Score (RADDS)	6 (1, 12)	*0*
Habitual consumption determinants[a]		
Habitual consumption of eggs (g/day)	19 (2.0, 95)	*0*
Habitual consumption of dairy (g/day)	410 (24, 1800)	*0*
Habitual consumption of meats (g/day)	120 (0, 380)	*0*
Habitual consumption of fruits (g/day)	69 (1.8, 350)	*0*
Habitual consumption of vegetables (g/day)	150 (19, 650)	*0*
Habitual consumption of potatoes (g/day)	250 (62, 930)	*0*
Habitual consumption of cereals (g/day)	80 (16, 300)	*0*
Habitual consumption of sweets (g/day)	31 (3.9, 220)	*0*
Habitual consumption of pastry (g/day)	13 (1.6, 110)	*0*
Habitual consumption of fish and seafood (g/day)	21 (0, 100)	*0*
Daily fish consumption determinants[b]		
Daily consumption of lean marine fish (g/day)	4.4 (0, 110)	*0.2*
Daily consumption of processed fish (g/day)	2.3 (0, 49)	*0.4*
Daily consumption of canned herring/mackerel (g/day)	0 (0, 49)	*0.5*
Daily consumption of salmonid fish (g/day)	4.4 (0, 49)	*0.5*
Daily consumption of canned tuna (g/day)	0 (0, 110)	*0.5*
Daily consumption of anchovies/sardines (g/day)	0 (0, 39)	*0.7*
Daily consumption of Baltic herring (g/day)	0 (0, 33)	*0.7*
Daily consumption of freshwater fish (g/day)	0 (0, 39)	*0.8*
Daily consumption of large marine fish (g/day)	0 (0, 26)	*0.7*
Daily consumption of crab (g/day)	0 (0, 12)	*1.0*
Daily consumption of shellfish (excluding crab) (g/day)	0.3 (0, 14)	*0.5*

Note: min, minimum; max, maximum.
[a] Based on dietary recall data in RFD.
[b] Based on data from the food propensity questionnaire in RFQ.

consumed by Swedish consumers according to the Swedish Market Basket Survey (SFA, 2017). The habitual food consumption variables were derived from the two independent days of dietary registration in RFD and were transformed to long-term consumption using the Multiple Source Method (MSM, Version 1.0.1). By using the two 24-h recall dietary registrations, the MSM computes long-term intake distributions by combining the probability and amount consumed (Harttig et al., 2011; Haubrock et al., 2011). In the MSM model, all participants were assumed consumers of all foods except fish and meat, where frequency of consumption was collected from the FPQ. Only 50 percent had consumed fish during the two registration days but 90% stated that they generally eat fish. The FPQ was thus used to identify true non-consumers. All 3099 participants with complete RFD registration were used in the calculations, and each school grade was considered to be an individual population.

2.4.4. Daily consumption of specific seafood groups

In order to evaluate if consumption of specific seafood groups contributed to the overall variation in the adolescent serum PFAA concentrations, habitual seafood consumption in the regression models was replaced by the daily intake (g/day) of 11 defined groups of seafood, i.e. lean marine fish, processed fish products, canned herring and mackerel, salmonid fish, anchovies and sardines, Baltic herring, freshwater fish, large marine fish, canned tuna, shellfish (excluding crab) and crab (Table 2). The daily consumption was estimated from the FPQ for consumption of the specific seafood categories consumed over the last 12-months and calculated to daily consumption (g/day) using the average seafood portions (g) by gender and grade derived from the food registration in RFD (Table S1).

2.5. Statistical analysis

Data processing and statistical analysis were carried out in R (version 3.6.3; R Development Core Team), with a statistical significance set at $p \leq 0.05$. A detailed description of data processing is found in Nyström et al. (2022). In brief, missing data of both the dependent and independent variables were imputed 5 times for each gender separately using multiple imputation by chained equations (van Buuren and Groothuis-Oudshoorn, 2011; Rubin, 1987), and joined by stacking prior to the regression analysis. For PFAA concentrations < LOQ, concentrations ≥ LOD were used when possible in the regression analysis, instead of being set to a fixed value (e.g. zero or LOQ/$\sqrt{2}$) (RSC, 2001; Bergstrand and Karlsson, 2009; Nyström et al., 2022).

Ordinal logistic regression (OLR) fitting the cumulative probability model (CMP) was used to evaluate the association between PFAA serum concentrations and the dietary determinants. The OLR can model

Table 3
Legacy serum PFAA concentrations in RMA participants, reproduced from Nyström et al., (2022).

PFAA	*n*	LOD-range *(% < LOD)*	Concentration(ng/g serum)[a] Median (min, max)
PFCA			
lin-PFOA	1095	0.287 *(0.1)*	1.20 (<LOD, 9.75)
PFNA	1098	0.103–0.176 *(4.9)*	0.382 (<LOD, 2.80)
PFDA	1098	0.028–0.099 *(19.7)*	0.162 (<LOD, 1.35)
PFUnDA	1098	0.020–0.119 *(30.6)*	0.097 (<LOD, 1.01)
PFSA			
lin-PFHxS	1098	0.017–0.216 *(0.7)*	0.399 (<LOD, 255)
br-PFOS	1098	0.031–0.257 *(0)*	0.925 (0.031, 110)
lin-PFOS	1098	0.056–0.562 *(0)*	1.995 (0.281, 127)
Σ_4PFAS[b]	1095		5.137 (0.477, 494)

Note: The limit of detection (LOD) varied between batches; Min, minimum; Max, maximum; PFCA, perfluoroalkylcarboxylic acids; PFSA, perfluoroalkylsulfonic acids.
[a] Median (min, max) concentrations contain serum PFAA samples which were both quantified (>LOQ) and detected (>LOD).
[b] Σ_4PFAS is the summation of serum lin-PFOA, PFNA, lin-PFHxS, br-PFOS and lin-PFOS concentration, i.e. the sum PFAS that EFSA has used to determine the tolerable intake (TWI) in their risk assessment (EFSA Contam Panel et al., 2020).

continuous data by only including the order information of the dependent variable making it a more robust alternative to ordinary least squares. An in depth description of the model and procedure is found in Liu et al. (2017b) and Nyström et al. (2022), respectively. PFAA data < LOD were replaced by 0.0001 ng/g serum (an arbitrary value lower than the lowest detectable concentration) in order to be included in the regression analysis. Using the ORL, the entire empirical cumulative distribution function conditional on the covariates is estimated from which conditional means, medians and exceedance probabilities along with confidence intervals for these quantities can be acquired. The effect of clustering due to sampling by school was accounted for using the Huber-White method (Nyström et al., 2022). Furthermore, we computed the relative contribution of the habitual food groups to the variation of serum PFAA concentrations by calculating χ^2 - degrees of freedom for each of the model determinants separately.

We additionally carried out a Spearman Rank Correlation analysis, examining the correlations between all the habitual dietary determinants and SHEIA15 and RADDS, separately, as well as the correlation between SHEIA15 and RADDS.

3. Results

Serum concentrations of lin-PFOA, PFNA, PFDA, PFUnDA, lin-PFHxS and lin/br-PFOS are found in Table 3. Lin-PFOS had the highest median concentration followed by lin-PFOA and br-PFOS, with br-PFOS median slightly less than 1 ng/g serum. The other PFAAs showed medians of <1 ng/g serum. Although the median lin-PFHxS concentration was similar to the median of PFNA, and only 2.7-fold higher than that of PFDA, the highest lin-PFHxS concentration (>200 ng/g serum) was approximately 2-3 orders of magnitude higher than the highest concentrations of PFNA, PFDA and PFUnDA (Table 3). A similarly large variation as for lin-PFHxS was observed for lin- and br-PFOS with maximum concentrations >100 ng/g serum. Furthermore, median serum concentration of the sum of lin-PFOA, PFNA, lin-PFHxS, br-PFOS and lin-PFOS (Σ_4PFAS) was approximately 5 ng/g serum (n = 1095) (Table 3). About 29% of the RMA adolescents (n = 315) had serum Σ_4PFAS concentrations exceeding the benchmark concentration level 6.9 ng/mL serum (Table 3), corresponding to the EFSA TWI of 4.4 ng/kg bw/week (EFSA Contam Panel et al., 2020).

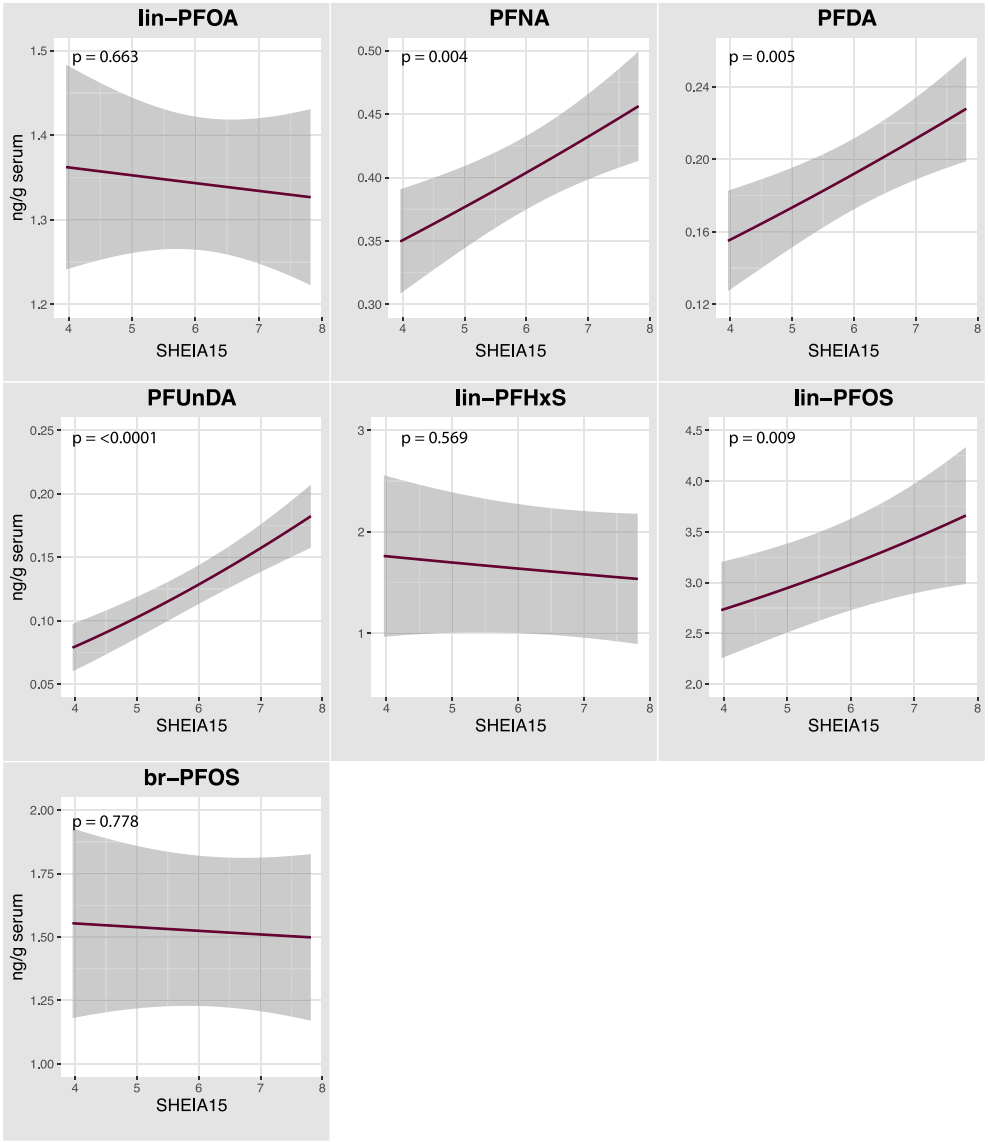

Fig. 1. Associations between adolescent serum PFAA concentrations and the Swedish Healthy Eating Index for Adolescents 2015 (SHEIA15) determined using ordinal logistic regression (OLR) and presented as estimated adjusted mean regression line with 95% confidence interval. The results were adjusted for age, BMI status, gender, maternal and paternal education level, participant/maternal birth country, months exclusively breastfed, snus and smoking habits and alcohol consumption.

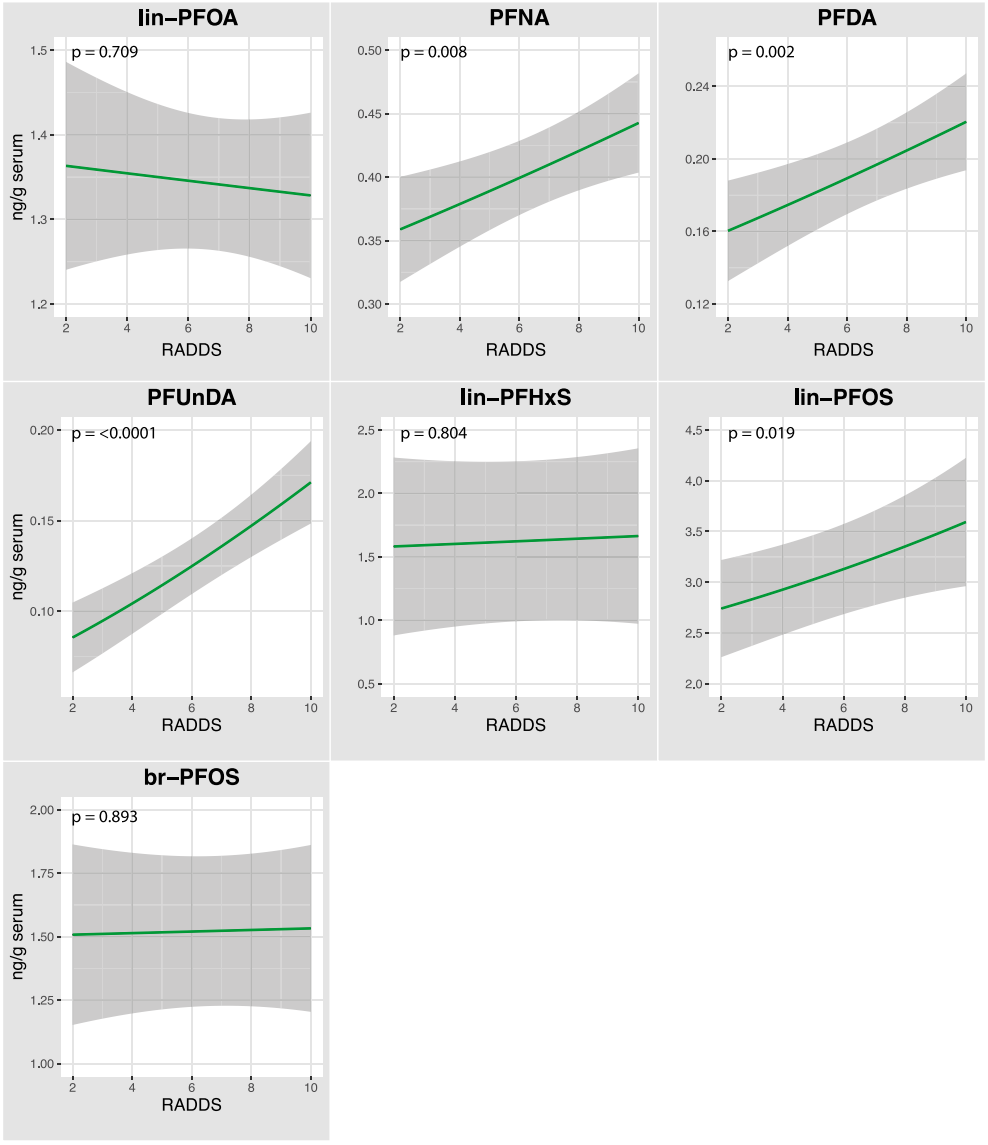

Fig. 2. Associations between adolescent serum PFAA concentrations and the Riksmaten Adolescent Diet Diversity Score (RADDS) determined using ordinal logistic regression (OLR) and presented as estimated adjusted mean regression line with 95% confidence interval. The results were adjusted for age, gender, BMI-status, participant/maternal birth country, maternal and paternal education level, months exclusively breastfed, snus and smoking habits and alcohol consumption.

Table 4
Spearman correlation coefficients for correlations between SHEIA15/RADDS as well as both indices and the habitual food consumption groups.

	SHEIA15		**RADDS**	
	ρ	p-value	ρ	p-value
Egg	0.02	0.493	0.13	<0.0001
Seafood	0.37	<0.0001	0.26	<0.0001
Meat	−0.40	<0.0001	−0.08	0.013
Dairy	−0.11	0.00035	0.24	<0.0001
Fruits	0.30	<0.0001	0.47	<0.0001
Vegetables	0.34	<0.0001	0.35	<0.0001
Potatoes	−0.03	0.347	−0.02	0.454
Cereals	0.08	0.0078	0.09	0.0454
Sweets	−0.16	<0.0001	0.07	0.020
Pastry	−0.03	0.391	0.07	0.016
SHEIA15			0.48	<0.0001

Note: SHEIA15, Swedish Healthy Eating Index for Adolescents 2015; RADDS, Riksmaten Diet Diversity Score. The p-value was determined using a two-tailed *t*-test.

3.1. Healthy eating index - SHEIA15

The scores of the healthy eating index, SHEIA15, ranged from approximately 3.5 to 8.5 (Table 2). PFNA, PFDA, PFUnDA and lin-PFOS serum concentrations were positively and significantly associated with SHEIA15 (Fig. 1; Table S2), with the highest average increase for PFUnDA (ca 2-fold) between the lowest and highest score. Average PFNA, PFDA and lin-PFOS concentrations increased approximately 1.3- to 1.4-fold. No statistically significant associations were observed for lin-PFOA, lin-PFHxS and br-PFOS. None of these associations changed in the sensitivity analysis (Fig. 2; Table S2). SHEIA15 was positively correlated with habitual consumption of seafood, fruits, vegetables and cereals and negatively correlated with consumption of meat, dairy and sweets (Table 4). Furthermore, a moderate positive correlation was found between the two dietary indices (Table 4).

3.2. Diet diversity score - RADDS

Serum PFNA, PFDA, PFUnDA and lin-PFOS concentrations were positively and significantly associated with RADDS scores, the latter of

Fig. 3. p-value heat map for the associations between serum legacy PFAA concentrations and habitual consumption of food groups (g/day) (A: green/yellow), and for the associations between PFAA concentrations and consumption of specific seafood groups (g/day) (B: purple/pink). + = positive association, - = negative association. A. was determined using ordinal logistic regression analysis (OLR), with all food groups included in the regression models and adjusted for snus use and smoking habits, alcohol consumption, gender, age, months exclusively breastfed, BMI, maternal and paternal education level, participant/maternal birth country. B. All seafood groups were included in the regression model A instead of habitual seafood consumption and adjusted for the same personal characteristics as in A, as well as habitual consumption of eggs/dairy/meat/fruits/vegetables/potatoes/cereals/sweets/pastry. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

which ranged from 1 to 12 (Table 2; Fig. 2; Table S2). The highest average increase between the lowest and the highest scores was observed for PFUnDA (ca 2-fold) and the lowest for PFNA (ca 1.2-fold). Lin-PFOA, lin-PFHxS and br-PFOS did not show significant associations with RADDS (Fig. 2; Table S2). None of the associations changed in the sensitivity analysis (Table S2). RADDS was negatively correlated with habitual meat consumption and positively correlated to habitual consumption of eggs, seafood, dairy, fruits, cereals, sweets and pastry (Table 4).

3.3. Habitual food consumption

The habitual consumption of the different food groups are given in Table 1. Significant inverse associations were observed between concentrations of all the legacy PFAA and dairy consumption, except for br-PFOS (Fig. 3; Table S3). Similarly, lin-PFOA and PFNA were inversely associated with cereal consumption, lin-PFOA with pastry, and PFNA and PFUnDA with sweets consumption (Fig. 3; Table S3). Significant positive associations were observed between PFNA and PFUnDA concentrations and vegetable consumption, and PFNA lin-PFHxS and meat consumption (Fig. 3; Table S3). Lin-PFHxS and lin-PFOS concentrations were positively associated with egg consumption, while PFNA, PFDA, PFUnDA and lin-PFOS were positively associated with seafood consumption (Fig. 3; Table S3). None of the legacy PFAAs were associated with habitual consumption of potatoes and fruits (Table S3).

Of the habitual food groups, seafood was the determinant explaining the largest part of the variation in serum concentrations of PFNA, PFDA and PFUnDA, while being the second most important determinant of lin-PFOS (Fig. 4). Habitual dairy consumption was the most important determinant of lin-PFOS and lin-PFOA, and the second most important in explaining the variation of PFNA, PFDA, lin-PFHxS and br-PFOS serum concentrations (Fig. 4). Meat consumption contributed most to the variation in br-PFOS, whilst egg consumption explained most of the variation for lin-PFHxS (Fig. 4). Meat consumption was the most important determinant of br-PFOS, but none of the relationships were statistically significant.

3.4. Consumption of specific seafood groups

Data on daily fish/seafood consumption based on the FPQ are given in Table 2. PFDA and lin-PFOS concentrations were positively associated with consumption of lean marine fish, while PFUnDA and lin-PFOS were inversely associated with consumption of processed fish (Fig. 3; Table S4). PFNA and lin-PFHxS were positively associated with consumption of canned tuna, as were PFUnDA, lin-PFHxS and lin-PFOS with shellfish consumption (Fig. 3; Table S4). PFUnDA was positively associated with pickled herring and mackerel consumption (Fig. 3; Table S4). Neither lin-PFOA nor br-PFOS were significantly associated with consumption of any of the individual seafood groups.

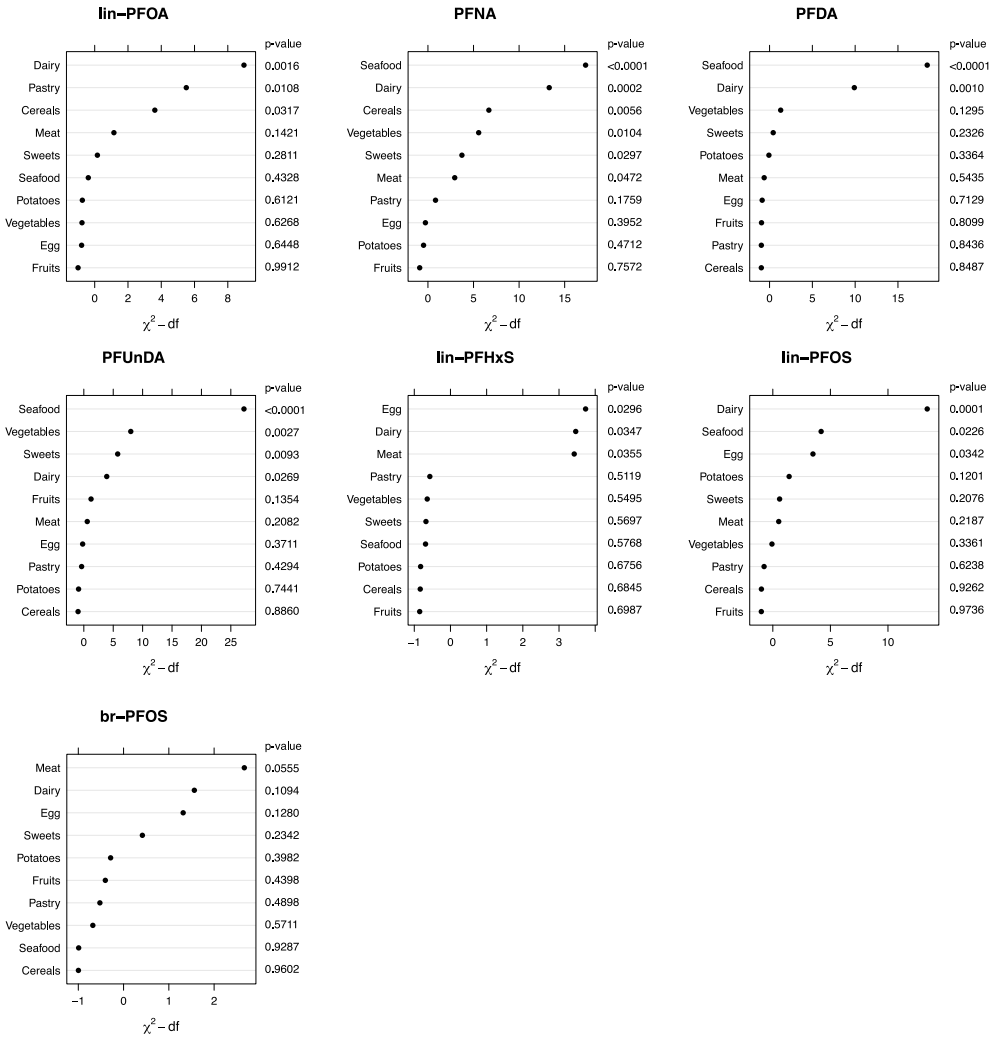

Fig. 4. The relative importance of the contribution for each habitual food group in explaining the variation in the RMA serum PFAA concentrations when included in the same regression model, adjusted for participant/maternal birth country, BMI-status, gender, age, maternal and paternal education level, snus use and smoking habits, alcohol habits and months exclusively breastfed. The relative importance is expressed as χ^2- df (x-axis), where a higher number indicates a higher relative importance. The relative importance of a determinant can only be compared within each PFAA model and not between models. Note that other base model determinants, not shown in this figure, could contribute more or less in explaining the variation in PFAA serum.

4. Discussion

Adolescence is a life stage of special interest, since health status at older ages is at least partially determined by habits established during adolescence (Kim et al., 2020; van Sluijs et al., 2021). Since dietary habits of adolescents may differ from that of adults due to the large physiological/life-style changes that occur during this time of life, it is important to gain knowledge about the relationships between PFAS exposure and dietary habits in adolescents. RMA participants who consumed an overall healthier diet, as suggested by a higher SHEIA15 score, had on average higher PFNA, PFDA, PFUnDA and lin-PFOS serum concentrations. Similar positive associations were found for the same PFAAs and consumption of a diverse diet, as determined by RADDS. Approximately one third of the RMA adolescents had Σ_4PFAS concentrations in serum that exceeded the 6.9 ng/ml serum benchmark concentration determined as no health concern by EFSA Contam Panel et al. (2020). Consequently, the relations between PFAA exposure and healthy diets may be regarded as problematic from a health development perspective. Although it is not possible from the present study to elucidate how much of the present serum Σ_4PFAS body burdens that are attributable to only dietary exposure sources, it is plausible that the RMA adolescent PFAA body burdens at least partially originate from dietary exposure. These findings highlight the problematic relationship between PFAA exposure and a healthy diet that is essential for a healthy human population.

To the best of our knowledge, associations between serum/plasma concentrations of PFAS and healthy diets have not been studied in adolescent populations, and scarcely among adults. Comparisons of results between dietary studies are made difficult due to differences in composition of diet scores and study populations (Lin et al., 2020). Nevertheless, in a U.S population of pre-diabetic adults, Lin et al. (2020) observed no statistically significant relations between plasma PFAS concentrations and Mediterranean-Like Diet Scores (MDS), and a positive association between plasma PFHxS and the Low-Carbohydrate and High-Protein (LCHP) diet. On the contrary, in an elderly Swedish cohort (PIVUS study), positive associations were observed between serum PFOA, PFNA, PFDA, PFUnDA and PFHxS, and MDS, and between serum PFNA, PFDA, PFUnDA and PFOS, and LCHP (Sjogren et al., 2016). In PIVUS, adherence to both MSD and LCHP was characterized by a higher seafood consumption (Sjogren et al., 2016), and much like PIVUS, seafood consumption in RMA correlated positively with both SHEIA15 and RADDS. Furthermore, habitual seafood consumption was one of the most important determinants in explaining the variation in PFAA concentrations in RMA, except for lin-PFOA,lin-PFHxS and br-PFOS. This corroborates with seafood consumption as a substantial contributor to the background PFNA, PFDA, PFUnDA and lin-PFOS exposure in adults in Sweden and other Nordic countries Haug et al. (2010a); Vestergren et al. (2012); (Bjermo et al., 2013; Papadopoulou et al., 2019). Several studies of health risk-benefits of fish consumption, including the toxic contaminants methyl-mercury and polychlorinated biphenyls and the health beneficial component long chain n-3 polyunsaturated fatty acids, have suggested that environmental pollution of fish may counteract the

positive health effects of fish consumption (Wennberg et al., 2012; Donat-Vargas et al. 2017, 2019; Noger-Huet et al., 2022). Hypothetically, PFAS in seafood may also to some degree counteract the beneficial health effects of seafood consumption, included in a healthy diet.

In Swedish market basket studies, seafood has been the dominating source of per capita intake of PFNA, PFDA, PFUnDA and PFOS, but not of PFOA and PFHxS (SFA, 2017; Vestergren et al., 2012). This could potentially explain the lack of associations between serum concentrations of these latter PFAAs and habitual seafood consumption, as well as with SHEIA15 and RADDS. Similarly as for PFOA and PFHxS, serum concentrations of br-PFOS, in contrast to lin-PFOS, was neither associated with SHEIA15 and RADDS nor seafood consumption, shows an isomer-specific difference in PFOS associations with seafood consumption. It has been reported that br-PFOS bioaccumulates to a lesser degree in fish than lin-PFOS, most probably resulting in enrichment of lin-PFOS in fish tissues (Sharpe et al., 2010; Greaves and Letcher, 2013; Beesoon and Martin, 2015; Shan et al., 2016).

The positive associations between body burdens of certain PFAAs and daily consumption of specific seafood groups in RMA further strengthens the role of seafood as a contributor to the PFAA body burdens among the adolescents. Similar to RMA, Duffek et al. (2020) reported lower plasma PFOA/PFHxS/PFOS concentrations in German children/adolescents (ages 3–17) who never consumed fish compared to those who do consumed fish. However, in contrast to RMA, a study on Norwegian adolescents aged 15–19 years (the Tromsø study) found that only serum PFUnDA concentrations were positively associated with consumption of lean marine fish (Averina et al., 2018). Moreover, serum concentrations of several PFAAs, including PFNA, PFDA, PFUnDA and PFOS, were positively associated to consumption of fatty fish, predominantly consisting of salmonids, mackerel and herring (Averina et al., 2018). Amongst the RMA participants, no associations were observed between PFAA body burdens and salmonid fish consumption, despite the fact that the average daily consumption of salmonids in RMA were at the same high level as consumption of lean marine fish, i.e. about 4 g/day. Due to the lack of comprehensive data on PFAS concentrations in seafood on the Swedish and Norwegian market it is not possible to determine if between-country variation in seafood PFAA concentrations may at least partly explain observed differences in PFAA associations with seafood consumption. This comparison is also made uncertain by differences in food groups included in the regression models and different composition of the included food groups. For instance, the fatty fish group in the Tromsø study consisted not only of salmonids but also of herring and mackerel (Averina et al., 2018). In RMA, serum concentrations of PFUnDA were positively associated with herring and mackerel consumption. Furthermore, given that the Tromsø study included a local population from an Arctic district of Norway (Averina et al., 2018), as opposed to the nation-wide study design of RMA, overall large differences in life-style and food habits further complicates comparisons of results. Albeit these differences in study populations and study design, both RMA and the Tromsø study contribute to the disconcerting evidence that seafood consumption, regarded as a healthy dietary component, is an important exposure source to some of the toxic legacy PFAA in adolescents.

Considering the lack of data on PFAA concentrations in seafood on the Swedish market, discussions about PFAA concentrations in seafood in relation to adolescent PFAA exposure can only be hypothetical. Even though daily consumption of shellfish was on average relatively low (median: 0.3 g/day), we could still see positive associations between PFUnDA, lin-PFHxS and lin-PFOS body burdens and shellfish consumption. It has previously been reported that crustaceans, such as shellfish, caught in Norwegian and Dutch waters have higher lin-PFOS and PFUnDA concentrations compared to white marine fish species (Carlsson et al., 2016; Zafeiraki et al., 2019). In RMA, inverse relations were observed between PFUnDA and PFOS serum concentrations and consumption of processed fish products, although this seafood type was one of the most frequently consumed (median: 2.3 g/day). This could be due to chance or possible residual confounding by other factors not studied by us. There are very limited information about PFAA concentrations in fish products, which in RMA mainly was composed of fish sticks and the seafood equivalent to meatballs, i.e. fish balls. In a total diet study from the US, only low concentrations of PFOS and PFNA was detected in fish sticks (Genualdi et al., 2021). Comparable observations have been made for fish sticks sampled in Norway (Haug et al., 2010b).

Even though higher PFAA concentrations have been reported in Swedish freshwater fish species, e.g. perch, burbot and freshwater salmon, compared to the same species caught in the Baltic Sea (Berger et al., 2009), no significant associations were found between serum PFAA and freshwater fish consumption in RMA. This is likely explained by the low median consumption of fresh water fish (0 g/day) among the adolescents. This explanation is also probable when pondering the lack of associations for the daily consumption of anchovies and sardines, large marine fish, Baltic herring and crab. However, even though the median daily consumption of canned tuna was 0 g/day, positive associations were still seen for serum PFNA and lin-PFHxS. This could suggestively be explained by a larger range of canned tuna consumption (0–110 g/day), as opposed to e.g. freshwater fish (0–33 g/day).

Significant associations between PFNA, PFDA, PFUnDA and lin-PFOS body burdens and seafood consumption were observed both in the food registration data (RFD) and in the data from the food frequency questionnaire (RFQ). The habitual seafood consumption variable, estimated from the 24-h recall method in RFD, takes the amount of seafood consumed during two independent days of food registration into account. The RFQ only account for the self-reported frequency of seafood consumption over the last year. However, the median daily consumption of all seafood groups together were only slightly lower in the RFQ data than in the habitual seafood consumption data; 17 g/day as opposed to 21 g/day. Nevertheless, a larger recall bias (Smith et al., 1991) when answering the RFQ than the RFD cannot be ruled out.

In RMA, serum concentrations increased with increasing habitual consumption of heńs eggs (lin-PFHxS and lin-PFOS) and meat (PFNA and lin-PFHxS). Egg consumption was not a component of the SHEIA15 index (Moraeus et al., 2020), which is corroborated by the finding of no relation between habitual egg consumption and the healthy food index in the present study. Consequently, egg consumption did most likely not contribute to a large extent to the observed positive associations between lin-PFOS body burdens and SHEIA15 scores. However, egg consumption could have contributed to the positive PFOS and RADDS association since habitual egg consumption increased with increasing RADDS. Positive associations between plasma PFOS concentrations and egg consumption have also been reported in a 3-17 year-old German population (Duffek et al., 2020). In Sweden, heńs egg and meat consumption have historically made a significant contribution to the average intake of PFHxS and PFOS from food, although decreasing in importance during the last decades (Vestergren et al., 2012; Johansson et al., 2014; SFA, 2017). Similar associations between PFOS body burdens and heńs egg consumption, as observed in RMA, have previously been reported for adults from other industrialized countries (Jain, 2018; Eriksen et al., 2011; Colles et al., 2020; Pitter et al., 2020). Positive associations between PFHxS body burdens and egg consumption are less frequently reported, though shown to be a determinant in pregnant Chinese women (Yang et al., 2019) and to contribute to roughly 20% of the PFHxS intake from food in an adult Spanish population (Arrebola et al., 2018). For heńs eggs, PFOS concentrations likely differ between production systems, since evidence, although limited, suggests much higher concentrations in home-produced compared to conventionally produced eggs (D'Hollander et al., 2011; Zafeiraki et al., 2016; Su et al., 2017; Fillol et al., 2021; Gazzotti et al., 2021). As with fish consumption, no association between br-PFOS and egg consumption was observed among the RMA participants, which might be attributable to lin-PFOS enrichment in heńs eggs compared to other PFOS isomers (Wang et al., 2019).

Inverse associations were found between serum concentrations of

almost all PFAAs and dairy consumption, and was also found to give a relatively large contribution to the variation of the serum PFAA concentrations in the RMA population. In the Tromsø study, no data on associations between PFAA concentrations and dairy consumption were reported (Averina et al., 2018). Similarly, Duffek et al. (2020) reported no significant associations with milk consumption in the child/-adolescent German population. However, similarly to RMA, inverse associations were observed between milk/dairy consumption and plasma PFOS concentrations in Danish middle-aged men (Eriksen et al., 2011), serum PFOA and PFOS concentrations in U.S. adolescents/adults (Jain, 2014) and serum PFOA, PFHxS and PFOS in an Italian adolescents/adult population (Pitter et al., 2020). Contrarily, studies from Spain and the Netherlands have suggested that dairy products may contribute to overall dietary PFAA exposure (Ericson et al., 2008; Noorlander et al., 2011). Apart from differences in study design and study populations, the diverging associations between studies could potentially be explained by regional differences in contamination of agricultural products, for instance due to variation in the use of biosolids and/or irrigation (Ghisi et al., 2019). From our results it is not possible to draw conclusions about the reasons behind the inverse association with dairy products. It could however be speculated that replacement of drinking water consumption, a suggested PFAS exposure source (Sims et al., 2021), with consumption of less PFAA-contaminated milk (Tao et al., 2008; Clarke et al., 2010) offered in school lunches (Patterson and Elinder, 2015) and at home in Sweden, may contribute to lower serum PFAA concentrations. However, this hypothesis fails to explain the negative association for PFDA and PFUnDA in RMA, which are infrequently detected in drinking water (Zafeiraki et al., 2015; Gobelius et al., 2018). In contrast to lin-PFOS, br-PFOS was not associated with dairy product consumption, further supporting the hypothesis of differences in exposure sources between linear and branched PFOS isomers.

It should be noted that some of the aforementioned relationships between serum PFAA concentrations and food habits may be coincidental, or at least partially confounded by life-style/dietary factors not studied in RMA. Apart from fish stick/balls and dairy consumption, this is likely also the reason behind inverse associations between legacy PFAA concentrations and consumption of cereals (lin-PFOA, PFNA), sweets (PFNA, PFUnDA), and pastry (lin-PFOA), and positive associations with vegetable consumption (PFNA, PFUnDA). For instance, vegetables are not an important source of dietary exposure to PFNA and PFUnDA in Sweden (Vestergren et al., 2012; SFA, 2017). Similar to RMA, no significant relationships were found between serum PFAA concentrations and consumption of fruits/vegetables amongst the Tromsø adolescents (Averina et al., 2018). In contrast to our results, a stronger adherence to a diet rich in vegetables was previously reported to be related to a decrease in PFAS exposure among adults, most probably caused by replacement of products of animal origin with higher PFAS contamination (Skuladottir et al., 2015; Tian et al., 2018; Yang et al., 2019; Lin et al., 2020; Menzel et al., 2021). Moreover, non-dietary exposure sources could at least partially be involved in the observed associations, due to the connection between a vegetable-rich diet and high socio-economic status (Lallukka et al., 2007; Hanson and Chen, 2007).

Considering that EFSA Contam Panel et al. (2020) highlighted fruit and fruit products as an important exposure source of PFOA, PFNA, PFHxS and PFOS, it is noteworthy that no significant associations were found between adolescent serum PFAA concentrations and habitual consumption of fruits in RMA. These results are further substantiated by habitual consumption of fruits being one of the dietary determinants that contributed the least in explaining the variation in serum PFAA concentrations. Amongst the many PFAS measured in a Swedish market-basket survey from 2015, PFHxA was the only PFAA with low but quantifiable concentrations in fruits (SFA, 2017) and in 1999, 2005 and 2010 only very low PFOA concentrations were reported (Vestergren et al., 2012). While PFAAs in fruits might be a significant exposure source in some European countries, this does not appear to be the case in Sweden.

The large number of participating adolescents is a strength of our study, including the population-based study design allowing us to generalize the findings for the school-attending adolescent population as a whole in Sweden (Lindroos et al., 2019). However, considering the school-based recruitment of participants, it should be highlighted that an additional dietary survey has been conducted including adolescents not attending upper-secondary school (SFA, 2018). Large discrepancies in socio-demographical factors and dietary habits were found between participants attending school and those not attending school (SFA, 2018). This suggests that the generalization of our results may not include adolescents not attending school. A strength of our study is that detailed food consumption data were collected by a validated recall method (Lindroos et al., 2019) and in agreement with the current European Food Safety Authority standard (Moraeus et al., 2018). However, it is always difficult for study participants to measure and report food consumption, which may add uncertainty to our results. It is also possible that the results were influenced by non-dietary sources of PFAA exposure not studied by us, or other unknown factors that may be associated with serum PFAA concentrations. A limitation of our study was that the regression models were not adjusted for caloric intake. However, several demographic/life-style factors that may explain some of the variation in consumption of different food groups, such as BMI, age, gender, participant and maternal birth country and parental education level (Nyström et al., 2022), were included in the regression models. To the best of our knowledge, associations between dietary determinants and serum concentrations of branched and linear isomers of PFOS have not previously been studied separately in adolescents, and our results showed isomer-related differences in associations with diet. It should however be highlighted that any isomer-related differences in associations between lin- and br-PFOS and food consumption could be confounded by discrepancies in human pharmacokinetic properties between branched and linear PFOS isomers (Benskin et al., 2010).

5. Conclusions

Swedish adolescents adhering to healthy and diverse diets had higher serum concentrations of the legacy PFAAs that have been reported as health concerns in Europe. The associations were most likely driven by a positive relation between seafood consumption and the healthy/diverse diet scores, including lean marine fish species and shellfish. Differences in relationships between br-PFOS and lin-PFOS serum concentrations and healthy and diverse diet scores was observed, showing the importance of analyzing different PFAS isomers separately. As a healthy diet during adolescence lays the foundation of a healthy adult life, more research is warranted on the health benefits of a healthy diet in relation to negative effects of PFAA exposure.

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Ethical approval

Participants ≥16 years, or legal guardians of participants <16 years of age, gave written informed consent for participation. Ethical approval was obtained from the Regional Ethical Review Board in Uppsala (No. 2015/190).

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.

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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.2022.113170.

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