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Perfluorinated substances in the Flemish population (Belgium): Levels and determinants of variability in exposure

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HIGHLIGHTS

- Flemish blood levels of five PFAS comparable to those in other Western countries.
- 77% of the adults exceeded HBM-I values for PFOS and PFOA in 2014
- Consumption of locally grown food is associated with higher PFAS blood levels.
- Use of cosmetics can be a possible route of exposure to PFASs.
- Menstruation can be a possible route of elimination of PFAS from the body.

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ABSTRACT

Because of their dirt-, water- and oil-repelling properties, per- and polyfluoroalkyl substances (PFASs) are frequently used in a broad variety of consumer products. They have been detected in human samples worldwide. In Flanders, Belgium, the Flemish Environment and Health Studies (FLEHS) measured the levels of five PFAS biomarkers in four different age groups of the Flemish population and identified determinants of variability in exposure.

Cord plasma or peripheric serum samples and questionnaire data were available for 220 mother-newborn pairs (2008–2009), 269 mother-newborn pairs (2013–2014), 199 adolescents (14–15 years old, 2010), 201 adults (20–40 years old, 2008–2009) and 205 adults (50–65 years old, 2014). Measured levels of perfluorooctane sulfonate (PFOS), perfluorooctanoic acid (PFOA), perfluorohexane sulfonic acid (PFHxS) and perfluorononanoic acid (PFNA) in Flanders are in the middle or low range compared to concentrations reported in other Western countries. Levels of perfluorobutanesulfonic acid (PFBS) were below the quantification limit in 98%–100% of the samples. Despite decreasing levels in time for PFOS and PFOA, 77% of the adults (2014) had serum levels exceeding HBM-I values of 5 μg/L for PFOS and 2 μg/L for PFOA. Beside age, sex, fish consumption, parity and breastfeeding, the multiple regression models identified additionally consumption of offal and locally grown food, and use of cosmetics as possible exposures and menstruation as a possible route of elimination. Better knowledge on determinants of exposure is essential to lower PFASs exposure.

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1. Introduction

Because of their dirt-, water- and oil-repelling properties, per- and polyfluoroalkyl substances (PFASs) are frequently used in industrial processes and in a broad variety of consumer products. PFASs are poorly biodegradable, can remain present in the environment for a long time (Ostertag et al., 2009) and have been detected in peripheral blood, cord blood and human milk samples from residents of different countries worldwide (Calafat et al., 2007; Lien et al., 2013; Cariou et al., 2015). There is also evidence that exposure to PFASs is associated with adverse health effects. Therefore, PFAS compounds such as perfluorooctane sulfonate (PFOS) and perfluorooctanoic acid (PFOA) were added to Annex B of the Stockholm convention, committing participating countries to reduce PFAS-levels in the environment and in humans. In Europe, the use of PFOS and PFOA has been phased-out since 2008 (European Directive, 2006/112/EC). Exposure routes have been identified, with dietary intake and inhalation and ingestion of house dust as exposure routes of main importance (Haug et al., 2011; Cornelis et al., 2012). Despite this knowledge and restrictions in production and use exposure continues as PFOS and PFOA are detected in newborns and, even more, many replacement PFASs have been developed and are now detected in human samples (Buck et al., 2011). To enhance further reduction of exposure, broadening the understanding of determinants of variability in exposure is needed.

With the successive human biomonitoring cycles, the Flemish Environment and Health Study (FLEHS) measures internal exposure to pollutants in the general population of Flanders (northern part of Belgium). One of the major aims is to gain insights in determinants that explain individual variability in exposure levels in four different age groups using multiple regression models. Along with confirming determinants that were already reported in other studies, we identified some additional determinants. We also compared the measured levels in the population with available health related HBM-I guidance values from the German HBM Commission. The HBM-I-value represents the concentration of a substance in human biological material below which no risk for adverse health effects over a life time is expected (HBM Commission, 2016; Umweltbundesamt, 2018). The respective HBM-I-values are 2 ng PFOA/mL and 5 ng PFOS/mL blood plasma. This study supports decision makers in developing science based policies and measures for better protection of the general population against exposure to hazardous chemicals.

2. Methods

2.1. Participants

The FLEHS studies were approved by the Ethics Committee of the University of Antwerp, studies on newborns were also approved by the Ethics Committees of the participating maternity units.

2.1.1. Flemish reference groups

In both FLEHS II (2007–2011) and FLEHS III (2012–2015) cycles, newborns, adolescents and adults were recruited in all five Flemish provinces to establish reference values for Flanders (Schoeters et al., 2012). PFASs were measured in the reference groups of 248 mother-newborn pairs sampled between August 2008 and July 2009, 281 mother-newborn pairs sampled between November 2013 and November 2014, 204 adults (20–40 years old) sampled between June 2008 and April 2009 and 209 adults (50–65 years old) sampled between May 2014 and November 2014.

A stratified clustered multi-stage design was used to select participants in primary sampling units (PSU) as a random sample of the Flemish population, proportionally to population density, sex, socioeconomic status and age (in the selected age range). These PSUs consisted of maternity units for newborns, provincial institutes for adults aged from 20 to 40 years (FLEHS II), and general practitioner offices for adults aged from 50 to 65 years (FLEHS III). Within each PSU, individuals were randomly selected. To account for seasonal variation, participants were recruited over one year in all studies, with the exception of the adults in FLEHS III (May–November 2014). The study design aimed to obtain representative study populations in terms of social class, an equal distribution of males and females and of participants over age classes.

Inclusion criteria were: 1) residing in Flanders for at least 10 years; 2) giving written informed consent; and 3) being able to complete an extensive Dutch questionnaire. For the adults, exclusion criteria were: severe kidney disease (glomerular filtration rate <60 ml/min) and active anti-cancer therapy (chemotherapy or radiotherapy).

More details about the study design and recruitment strategy of FLEHS II and the FLEHS III newborns study have been previously reported (Den Hond et al., 2009; Schoeters et al., 2012; Morrens et al., 2017).

2.1.2. The study population near to the industrial contaminated site (ICS)

PFASs were also measured in 199 adolescents aged 14–15 years, recruited in the municipalities Menen and Wevelgem near the “Grensland” industrial area and sampled from May 2010 to February 2011. The ICS has no specific records of PFAS production. It is home to an important recycling plant of ferrous and non-ferrous metals, timber industry, pigment industry, several incinerators and, until 2005, an important incinerator for municipal waste. The study area was delineated according to the predominant wind direction. More details about study design and recruitment can be found elsewhere (Den Hond et al., 2009; Schoeters et al., 2012; Schoeters, 2012a; Croes et al., 2014).

2.2. Measurement of perfluorinated compounds

On the day of the examination, the participants were examined by trained research nurses in rooms equipped for fieldwork. Peripheral blood from adults and adolescents and cord blood were aliquoted and peripheral serum and cord plasma was obtained after centrifugation. Plasma and serum were conserved at −80 °C. PFOS, perfluorohexane sulfonic acid (PFHxS), PFOA, perfluorononanoic acid (PFNA) and perfluorobutane sulfonate (PFBS) were determined in serum and cord plasma using procedures as described by (Kato et al., 2011). The analytical method consisted of an offline protein precipitation with acetonitrile, followed by separation by HPLC and a MS/MS detection (Applied Biosystems API3000 triple quadrupole mass spectrometer (Foster City, CA, USA)) in negative ionisation MS/MS mode with multiple reaction monitoring (MRM). Quality controls included reagent methods blanks comprised of bovine serum as well as calibration standards and quality control samples in bovine serum (ACILA AG, Weiterstadt, Germany). Reproducibility was checked by analysing spiked bovine serum and a native human plasma sample. Recovery rates were 102% for PFOS, 99% for PFOA, 104% for PFHxS, 95% for PFNA and 91% for PFBS. Detection limits (LOD) were calculated as three times the signal/noise ratio of the analytical background noise in the temporal vicinity of the analyte signal. The limit of quantification (LOQ) was determined as twice the LOD and was 0.3 μg/L for PFOS and PFOA in FLEHS II (2007–2011) and in FLEHS III (2012–2015) LOQ was 0.2 μg/L for PFOS, PFOA, PFHxS and PFBS, and 0.1 μg/L for PFNA. In terms of PFOS and PFOA, the only PFASs for which a round robin is currently available at G-EQUAS, participation in the German round robin G-

EQUAS (GERMAN EXTERNAL QUALITY ASSESSMENT SCHEME for Analyses in Biological Materials www.g-equas.de) was successful with deviation percentages ranging from −11.7% to +15.9% for PFOS and −0.6% to −8.2% for PFOA. To assess the comparability of measurements performed during FLEHS II (2007–2011) with those performed during FLEHS III (2012–2015), PFOS and PFOA levels were remeasured in 3 samples from the biobank of FLEHS II together with the samples of FLEHS III. Deviation percentages ranged from −7.8% to −29.4% for PFOS and +5.0% to +21.5% for PFOA.

2.3. Questionnaire data

Participants completed a self-reporting questionnaire on personal and lifestyle factors, including information on education and health status, housing, family composition, income, indoor use of pesticides, indoor exposures to pollutants and chemicals, sports, hobbies, smoking and consumption of alcohol. From the information provided regarding body length and weight, the body mass index (BMI) was calculated as BMI = body weight in kg/(body length in m)^2. Participants also completed food frequency questionnaires to assess the consumption of food items. Additionally, the consumption of locally produced food was recorded, defined as homegrown food or food produced in gardens of neighbors, family or friends. A score for Mediterranean diet was calculated as the sum of separate scores of weekly consumption of multiple food products (Ortega et al., 2013). Consumption of offal referred to animal products such as liver and kidneys. For adult women and mothers of newborns, parity was defined as the number of children born after a pregnancy of 22 weeks or more. To assess socioeconomic status (SES), two different variables were evaluated separately: equivalised household income (total monthly household income standardised according to the number of household members) and highest educational attainment of the mothers in the case of newborns, of parents in the case of the adolescents and the household in the case of the adults. Country of birth was also used to assess migrant background. Place of residence in urban or non-urban areas was categorised using a population density of more than 600 inhabitants per square kilometer on a community level as urban areas. Due to differences in the applied questionnaires in FLEHS II and FLEHS III, the available determinants or response categories of some determinants were not always identical. For this reason, it was not possible to test associations with consumption of shellfish, offal and potatoes and a tendency to adhere to a Mediterranean diet for FLEHS II. For the newborn study population of FLEHS III only the highest education of the mother and country of birth of the baby's parents were used to test for socioeconomic differentiation.

2.4. Statistical analysis

Statistical analysis was carried out when at least 70% of the samples had exposure values above LOQ, values below LOQ were replaced by half the LOQ (Lubin et al., 2004). Linear regression was used to identify those variables that significantly ($p < 0.05$) explained individual variability in exposure levels. Dependent variables are biomarker PFAS levels, transformed by the natural logarithm. Information on the independent variables (determinants) were derived from questionnaire data. Continuous variables were categorised in frequently used categories such as for BMI underweight (<18.5 kg/m^2), normal weight (18.5–25 kg/m^2), overweight (25–30 kg/m^2), obesity (≥30 kg/m^2), or in categories based on the distribution of values, e.g. age.

Multiple linear regression was used to evaluate the effect of different variables on the biomarker level in the same model. Variables were included in the statistical models using a stepwise procedure. Well-known determinants for persistent compounds (age, BMI and sex) were always included in the models. As perfluorinated compounds are mainly transported bound to blood proteins (Han et al., 2003; Luo et al., 2012), lipid concentration in blood was not included as a covariate in the statistical analysis. Other variables were included if the p-value in univariate regression was <0.25 and if the direction of the association was consistent with mechanistic or epidemiological insights. Variables were retained in final multiple regression models at $p < 0.05$. Season of sampling and variables reflecting socioeconomic differences can be proxies for other, underlying, determinants of exposure and are added to the models as final steps. Separate models were applied for adult women to test associations with typical female variables such as duration of breastfeeding their children, menopause and years since menstrual periods have stopped. The overall R-square of each model is given, reflecting the percentage of variability in exposure explained by the variables in the model. The coefficient of partial determination was calculated as the percentage remaining variability in the dependent variable additionally explained by a specific independent variable, given the other independent variables in the model.

An overview of the variables available in the different FLEHS studies, the variables tested in the univariate regression analyses and the variables included in the multiple regression models are shown in Table S1 of the supplementary material.

3. Results

The characteristics of the study populations are shown in Table S2 of supplementary material (Suppl.).

3.1. Internal exposure levels

The uncorrected PFAS plasma and serum concentrations for newborns and adults in Flanders are summarised in Table 1. For PFBS the limit of quantification was not attained in newborns and only in 6 of 209 adults. No further data are presented on PFBS. Meaningful time trends could only be assessed for newborns and are already reported and discussed elsewhere (Schoeters et al., 2017).

The levels of PFOS and PFOA were also compared with the HBM-I values for PFOS and PFOA in blood plasma of 5 μg/L and 2 μg/L respectively. In the population aged from 20 to 40 years old in FLEHS II (2008–2009), exceedances of these values for PFOS and PFOA were observed for 95% and 85% of the participants, respectively. In FLEHS III (2014), 77% of the participants (50–65 years old) exceeded the HBM I values for both PFOS and PFOA.

The uncorrected PFAS serum concentrations for 199 adolescents residing near to the ICS are presented in Table 1. The HBM-I value was exceeded in 62% and 81% of the participants for PFOS and PFOA, respectively.

3.2. Determinants of variability in exposure

The results of the multiple regression analysis can be found in Suppl. Table S3 (mothers of newborns), Suppl. Table S4 (adolescents ICS), Suppl. Table S5 (adults) and Suppl. Table S6 (adult women).

The adjusted R^2 values indicate the percentage of variance in measured PFAS levels that can be explained by all the determinants in the models. For mothers of newborns and adults, the explained variance ranges between 20% and 30% for all biomarkers, except for PFOA in the FLEHS III adult population (11%). When only adult women were included, the models explained between 12% and 36% of the measured variability in PFAS levels. For adolescents from the

Table 1
PFAS concentrations (μg/L) in cord plasma of newborns in Flanders and in serum of adolescents in the industrial area and adults in Flanders.

Substance	Population	Period	n	LOQ	% above LOQ	Geometric mean	95% CI	Median	Range (min/max)	P25/P75	P90
PFOS	Newborns	2008–2009	220	0.3	100	2.64	2.46–2.84	2.70	0.80/17.30	1.80/3.80	5.15
PFOS	Newborns	2013–2014	269	0.2	99.6	1.12	1.04–1.21	1.11	<LOQ/8.37	0.73/1.68	2.56
PFOS	Adolescents aged 14-15	2010–2011	199	0.3	100	5.83	5.41–6.29	5.70	1.50/74.70	4.00/7.80	10.80
PFOS	Adults aged 20-40	2008–2009	201	0.3	100	12.54	11.57 –13.59	12.60	1.70/71.50	9.10/17.00	25.20
PFOS	Adults aged 50-65	2014	205	0.2	100	7.53	6.92–8.20	7.58	1.54/45.84	5.22/11.15	16.30
PFBS	Newborns	2013–2014	269	0.2	0	<LOQ	/	<LOQ	<LOQ/ <LOQ	<LOQ	<LOQ
PFBS	Adults aged 50-65	2014	205	0.2	2.9	<LOQ	/	<LOQ	<LOQ/0.29	<LOQ/ <LOQ	<LOQ
PFHxS	Newborns	2013–2014	269	0.2	84.0	0.34	0.31–0.36	0.37	<LOQ/1.33	0.25/0.53	0.74
PFHxS	Adults aged 50-65	2014	205	0.2	99.5	1.57	1.43–1.73	1.61	0.10/12.43	1.02/2.36	3.61
PFOA	Newborns	2008–2009	220	0.3	100	1.51	1.43–1.59	1.50	0.50/4.30	1.10/2.00	2.50
PFOA	Newborns	2013–2014	269	0.2	100	1.19	1.12–1.26	1.27	0.26/5.87	0.89/1.57	2.14
PFOA	Adolescents aged 14-15	2010–2011	199	0.3	100	2.55	2.44–2.65	2.60	1.16/7.08	2.13/3.00	3.62
PFOA	Adults aged 20-40	2008–2009	201	0.3	100	3.23	3.02–3.46	3.50	0.60/9.10	2.50/4.50	5.80
PFOA	Adults aged 50-65	2014	205	0.2	100	2.82	2.62–3.02	2.94	0.24/25.20	2.13/3.69	4.93
PFNA	Newborns	2013–2014	269	0.1	89.6	0.20	0.18–0.22	0.21	<LOQ/1.39	0.14/0.31	0.44
PFNA	Adults aged 50-65	2014	205	0.1	100	0.86	0.80–0.93	0.87	0.18/7.70	0.60/1.18	1.64

P25/P75: 25th and 75th percentile; P90: 90th percentile; 95%CI: 95% confidence interval.

ICS, the models explained 23% of the observed variance in PFOS and only 3.5% of the variance in PFOA. The PFOA model of these adolescents only includes age, BMI and sex as determinants, which were forced into the model. No additional determinants that could explain part of the variance in PFAS exposure were retained at $p < 0.05$.

In the following paragraphs, the influence of the different determinants is described, after adjustment for all other determinants included in the models.

3.2.1. Personal characteristics

Regarding age, significant ($p < 0.05$) higher concentrations were observed with increasing age of FLEHS III adults. Cord samples of newborns showed higher levels for all PFASs in FLEHS III, and for PFOA in FLEHS II with increasing age of their mothers (Suppl., Tables S3, S4, S5). Levels of PFOS, PFOA and PFHxS were higher in men versus women. After adjustment for other determinants included in the models (Suppl. Tables 3–5), BMI did not show a significant association with cord plasma and serum PFAS concentrations, with the exception of PFOS measured in the FLEHS III adults, although no linear trend was observed.

Our results also indicate that some PFAS levels were associated with female characteristics such as the number of children a woman gave birth to (parity), the duration of the lactation periods, menopause and the number of years since menstrual periods have stopped. In the group of 20–40 year-old women (Suppl. Table S5), a history of breastfeeding for over six months was associated with 31% (95% CI: 18%–43%) lower PFOA serum levels compared to no history of breastfeeding. Women between 50 and 65 years of age with three or more children had, on average, lower serum levels for PFOA (35%, 95% CI: 9%–54%) and PFHxS (39%, 95% CI: 9%–59%) compared to women without children. Compared to mothers of newborns without a history of breastfeeding, mothers with a previous lactation period longer than six months had lower cord plasma levels of PFOS (33% (95% CI: 16%–46%) in FLEHS II), PFOA (29%, 95% CI: 14%–41%) in FLEHS II and 33% (95% CI: 20%–43%) in FLEHS III), and PFHxS and PFNA in FLEHS III (40%, 95% CI: 26%–52%) and 36% (95% CI: 20%–49%) respectively) (Suppl. Table S3). Mothers with three or more children had 21% (95% CI: 8%–32%) lower cord plasma levels of PFOA in FLEHS II and 27% (95% CI: 7%–43%) lower cord plasma levels of PFOS in FLEHS III than mothers who had given birth to their first child (Suppl. Table S3). Even when adjusted for age, within the age group of 50–65 years (Suppl. Table S5), women who had already undergone the menopause had 61% (95% CI: 2%–154%) higher PFHxS serum levels compared to women who had not yet undergone the menopause (Fig. 1). The same trend could be observed for PFOS (+53%, $p = 0.102$), PFOA (+47%, $p = 0.078$) and PFNA (+50%, $p = 0.103$), but since the p-values were above 0.05, this determinant was not retained in the reported models. The length of time for which menstrual periods had stopped (still menstrual periods, menstrual periods stopped $\leq$5 years ago, menstrual periods stopped > 5 years ago) also showed a tendency towards higher serum levels of PFOS, PFOA, PFHxS and PFNA at p-values > 0.05, and was therefore not retained in the reported models. These results are not statistically significant at $p < 0.05$, probably because of a lack of statistical power due to the limited sample size ($n = 108$).

3.2.2. Dietary factors

Our data confirmed that internal PFAS concentrations are associated with food consumption characteristics. FLEHS III mothers who reported consumption of offal had, on average, 60% (95% CI: 21%–113%) higher levels of PFOS, 71% (95% CI: 37%–113%) higher levels of PFOA and 129% (95% CI: 71%–208%) higher levels of PFNA in their cord plasma samples (Fig. 2, Suppl. Table S3). In the same study population, increasing PFHxS cord plasma levels were observed with a higher consumption of potatoes; however, the trend was not linear. In the adult population of FLEHS III (Suppl. Table S4), PFNA serum levels were significantly associated with consumption of eggs (more than on a weekly basis +41% (95% CI: 10%–79%)) and crustaceans (+20%, 95% CI: 1%–42%). A significant association was observed with a Mediterranean diet on PFHxS serum levels in the FLEHS III adults, although no clear trend could be observed. For adult women, consumption of cheese was associated with higher serum levels of PFNA (Suppl. Table S5) although the trend was not linear. Compared to cheese consumption of once a week or less, PFNA levels increased on average 60% (95% CI: 14%–124%) for a consumption frequency of 2–3 times a week, 52% (95% CI: 3%–124%) for 4 to 6 times a week and 34% (95% CI: −2%-84%) for once a day or more.

Associations with consumption of locally produced food were observed in all studied age groups (Fig. 3). Consumption of locally

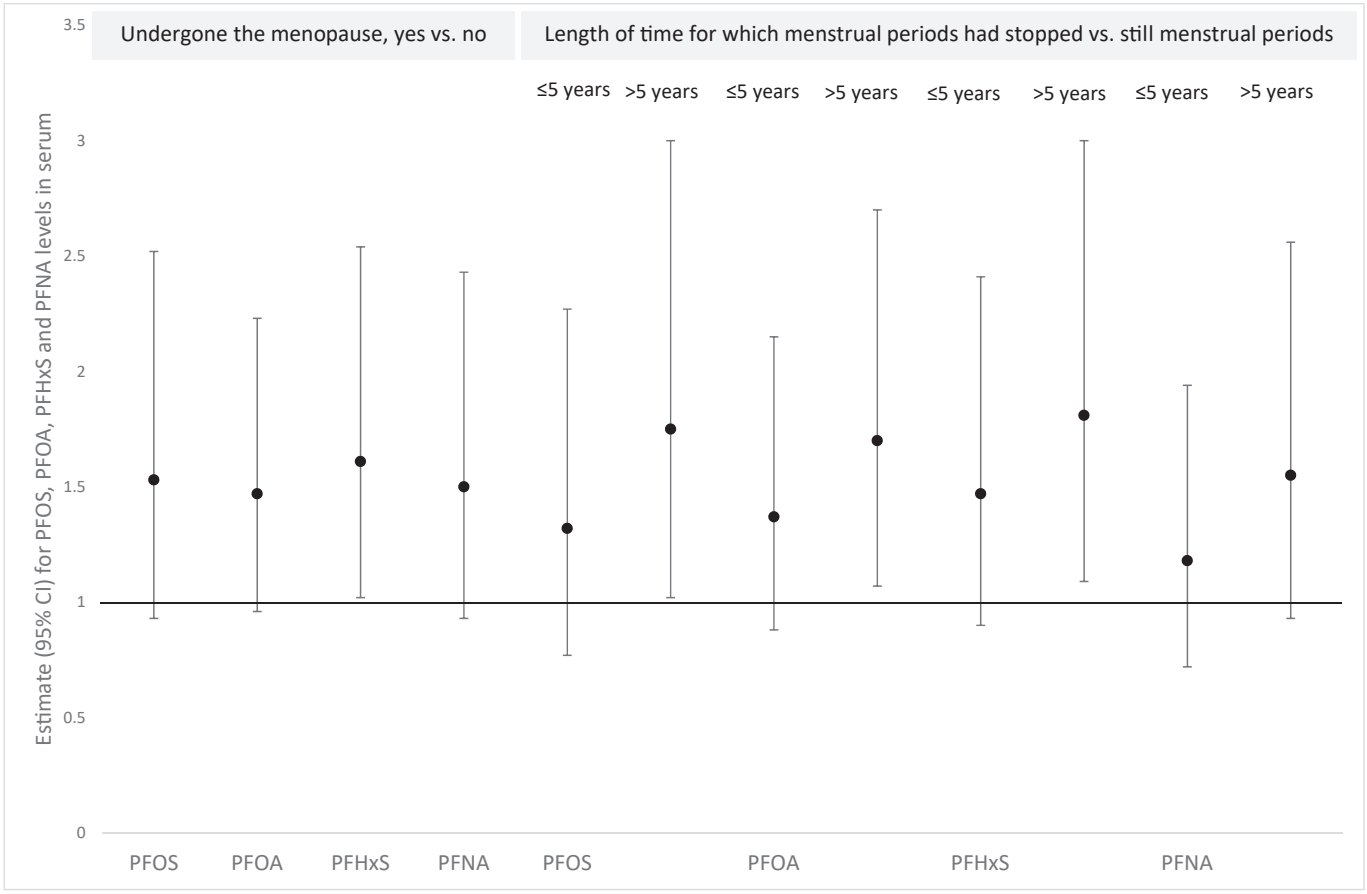

Fig. 1. Adjusted estimates (95% CI) for PFOS, PFOA, PFHxS and PFNA in serum of FLEHS III adult women (50–65 years) with menopause and length of time for which menstrual periods had stopped. Models adjusted for age, BMI, and additionally for: Menopause model: PFOS: equivalent household income, consumption of locally produced eggs, PFOA: level of education, parity, consumption of potatoes, PFHxS: parity, PFNA: equivalent household income, Model for time since menstrual periods stopped: PFOS: equivalent household income, consumption of locally produced eggs, PFOA: consumption of alcohol before pregnancy, level of education, parity, PFHxS: parity, PFNA: equivalent household income, consumption of cheese. The estimates are multiplicative factors, reference category is no menopause/still menstrual periods (estimate = 1), the vertical lines denote the 95% CIs, significance (at the 5% level) is demonstrated when the 95% CI does not include "1".

produced eggs was associated with increased levels of PFOS in FLEHS II cord plasma samples (Suppl. Table S3) by 34% (95% CI: 17%–54%), in serum levels of adolescents from the ICS (Suppl. Table S4) by 43% (95% CI: 19%–74%) and in serum levels of FLEHS II adults (Suppl. Table S4) by 43% (95% CI: 24%–65%). FLEHS III adults (Suppl. Table S4) who reported a moderate (less than weekly) or high (weekly or more) consumption of locally produced eggs had 34% (95% CI: 8%–66%) and 76% (95% CI: 43%–116%) higher PFOS serum levels respectively compared to participants who never consumed locally produced eggs. In cord plasma of mothers (Suppl. Table S3) reporting consumption of locally produced leafy vegetables (FLEHS II) or consumption of locally produced vegetables five times a week or less (FLEHS III), 25% (95% CI: 6%–48%) and 24% (95% CI: 5%–46%) higher PFOS levels were observed, respectively, compared to mothers who did not consume locally produced vegetables. Consumption of locally produced vegetables was also associated with increased PFOS serum levels in adolescents from the ICS (Suppl. Table S4) of, on average, 23% (95% CI: 3%–48%).

In the FLEHS III mothers, alcohol consumption before pregnancy was associated with increased levels of all four PFASs studied (Suppl. Table S3). For example, compared to mothers who did not drink alcohol before pregnancy, mothers with a weekly consumption of alcohol before pregnancy had, on average, higher cord plasma levels: 61% (95% CI: 28%–101%) for PFOS, 41% (95% CI: 19%–66%) for PFOA, 60% (95% CI: 30%–97%) for PFHxS and 39% (95% CI: 12%–74%) for PFNA.

3.2.3. Life style factors

PFNA serum levels in the FLEHS III adults were associated with the use of personal care products (Suppl. Table S5). However, there was no clear linear trend observed. Significantly higher levels of PFNA were found for adults using at least 7 care products 3 days before examination (+32%, 95%CI: 13%–46%) compared to adults using between 5 and 6 products (results not shown).

3.2.4. Determinants representing other influencing factors

Significant associations with socioeconomic factors and PFAS serum levels were observed in the adult study population of FLEHS III (Suppl. Table S4). The highest education category (college or university degree) had 21% (95% CI: 1%–45%) higher PFOA serum levels compared to the lowest education category (lower secondary degree). Compared to participants with an equivalent monthly income lower or equal to 1250 Euro, participants with an equivalent income between 1600 and 2000 Euro had, on average, 34% (95% CI: 5%–70%) higher serum levels of PFOS and 38% (95% CI: 9%–74%) higher PFNA levels and participants with equivalent income higher than 2000 Euro had on average 29% (95% CI: 2%–63%) higher PFOS serum levels.

A significant seasonal trend was observed in FLEHS II adults and adolescents from the ICS, (Suppl., Tables S4 and S3). Compared to

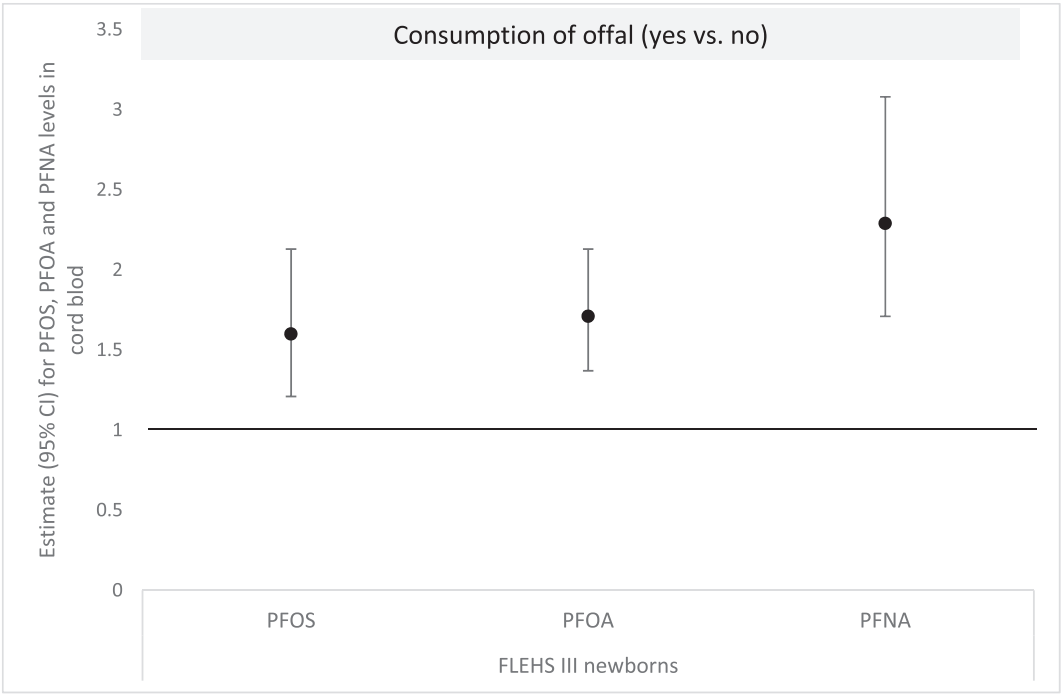

Fig. 2. Adjusted estimates (95% CI) for PFOS, PFOA and PFNA levels in cord plasma of FLEHS III newborns with consumption of offal. Models adjusted for age, BMI and additionally for PFOS: parity, alcohol consumption before pregnancy, consumption of locally grown vegetables, PFOA: duration of lactation, alcohol consumption before pregnancy, PFNA: duration of lactation, alcohol consumption before pregnancy, sex of the baby. The estimates are multiplicative factors, reference category is no consumption of offal (estimate = 1), the vertical lines denote the 95% CIs, significance (at the 5% level) is demonstrated when the 95% CI does not include "1".

participants sampled in winter, higher (+32%, 95% CI: 31%–55%) PFOS serum levels were observed in adolescents and higher PFOS (+39%, 95% CI: 16%–67%) and PFOA (+36%, 95% CI: 16%–60%) serum levels in FLEHS II adults sampled in spring. Participants sampled in spring also had significantly higher PFOS (adolescents and adults) and PFOA (adults) serum levels compared to participants sampled in summer (results not shown).

4. Discussion

4.1. Internal exposure: differences in function of geographical area

The internal exposure levels described in this paper are quite similar to the values found in other recent studies in Flanders. In a case-control fertility study, men from the control group with a mean age of 34.1 years (n = 80) had geometric mean serum concentrations of 10.4 μg/L for PFOS and 2.8 μg/L for PFOA (Den Hond et al., 2015). In the Walloon part of Belgium, PFAS levels measured in 281 cord blood samples collected in 2013–2016 were slightly lower compared to our results, with median concentrations of 0.73 μg/L for PFOS, 0.68 μg/L for PFOA, 0.16 μg/L for PFHxS, and 0.12 μg/L for PFNA (Dufour et al., 2018).

Internal exposure to PFASs in Flanders appears to be in the middle or low range compared to concentrations observed in other western countries (Suppl. Table S7). When comparing data from different regions or countries, attention should be paid to the time of sampling, since there is substantial evidence that internal exposure to PFASs has changed over time (Calafat et al., 2007; Olsen et al., 2008; Spliethoff et al., 2008; Haug et al., 2009). As reported earlier our dataset has shown decreasing levels in PFOS and PFOA in cord blood samples collected in 2008–2009 and in 2013–2014 (Schoeters et al., 2017). Still, exceedances of the HBM-I values were observed in peripheric serum samples of adolescents (14–15 years) and adults (20–40 years and 50–65 years).

4.2. Determinants of variability in exposure

The explained variability in exposure to PFAS of the multiple regression models is overall modest. This could mean that important sources of variability in exposure are still missing. Having limited gradients in determinants categories could be another explanation. The explanatory power could also increase when measurements of PFAS levels in exposure pathway media (air, dust, diet) would be available at individual level.

4.2.1. Personal characteristics

In literature several personal characteristics are well-described determinants of variability in exposure to PFASs, such as increasing serum or cord plasma concentrations of PFASs with increasing age (Rylander et al., 2009; Berg et al., 2014; Jain, 2014; Jensen et al., 2015; Bjerregaard-Olesen et al., 2016), and lower levels in women (Rylander et al., 2009; Jain, 2014) which can partly be explained by transplacental transfer to the children and excretion through breastfeeding (Brantsaeter et al., 2013; Lien et al., 2013; Berg et al., 2014; Cariou et al., 2015; Bjerregaard-Olesen et al., 2016). All these can be confirmed in our study.

In our datasets, BMI showed no significant association with cord plasma or serum levels of most PFASs (with exception of PFOS in adults of FLEHS III). Results reported in literature are inconclusive, both positive and negative associations between BMI and serum levels of PFASs were reported, but no clear general trend could be observed (Eriksen et al., 2011; Brantsaeter et al., 2013; Berg et al., 2014; Jain, 2014; Cariou et al., 2015; Jensen et al., 2015).

In addition, our results showed association between menopause and higher internal levels of PFHxS, which is less frequently reported in literature. This finding suggests menstruation as a route of elimination of PFASs, due to their affinity for blood proteins such as albumine (Han et al., 2003). This is consistent with the model-derived results of American researchers (Wong et al., 2014). The

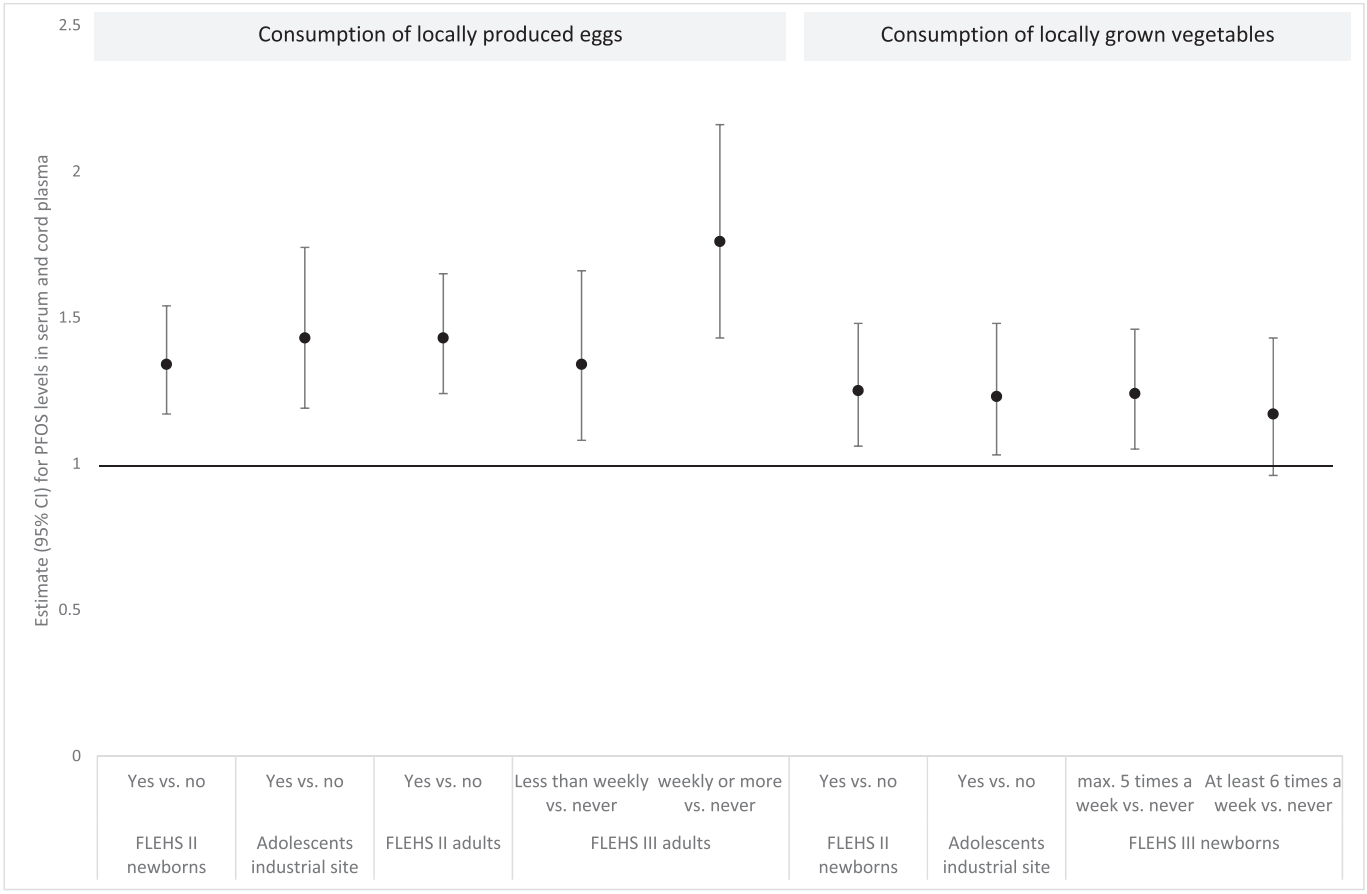

Fig. 3. Adjusted estimates (95% CI) for PFOS in serum and cord plasma of FLEHS II and FLEHS III participants with consumption of locally produced eggs and vegetables. Models adjusted for age, BMI and additionally for: FLEHS II newborns: duration of lactation, FLEHS III newborns: parity, alcohol consumption before pregnancy, consumption of offal, adolescents of the industrial area: sex, season, FLEHS II adults: season, FLEHS III adults: sex, equivalent household income. The estimates are multiplicative factors, reference category is no/never consumption of locally produced eggs (estimate = 1), the vertical lines denote the 95% CIs, significance (at the 5% level) is demonstrated when the 95% CI does not include "1".

association between PFASs levels and menopause can also be interpreted as an indication for the endocrine-disrupting activity of PFASs (Knox et al., 2011; Konkel, 2014; Taylor et al., 2014).

4.2.2. Dietary factors

Diet has already been identified as an important source of PFAS exposure (Trudel et al., 2008; Haug et al., 2011; Cornelis et al., 2012; Domingo, 2012). In this study several well-described determinants in literature could be confirmed, such as consumption of fish and seafood associated with higher internal levels of PFASs (Rylander et al., 2010; Tyrrell et al., 2013; Berg et al., 2014; Jain, 2014; Yamada et al., 2014; Bartolome et al., 2017). Additionally, the study identified several less common reported determinants of variability in PFAS exposure. Our study observed associations between higher internal exposure to the measured PFASs and consumption of offal and potatoes. Literature data on associations of internal PFAS levels with consumption of offal and potatoes are scarce (Cariou et al., 2015). Yet, PFASs have been detected in organ meat and foie gras (Domingo, 2012; European Food Safety Authority, 2012). In soil contaminated with PFASs through the utilisation of contaminated sludge, PFASs can end up in potatoes (Lechner and Knapp, 2011). In several European countries, PFASs have been detected in potatoes (Haug et al., 2010; Cornelis et al., 2012; European Food Safety Authority, 2012; Vestergren et al., 2012; Herzke et al., 2013). Dietary intake calculations (Cornelis et al., 2012) showed that the consumption of potatoes was the most important source of PFOS for children, and the second most important source for adults (after (lean) fish and shellfish). Our results showed alcohol consumption before pregnancy was associated with higher levels of PFASs in cord blood. This association was only observed in the FLEHS III newborns study population, but was consistent for all four PFASs (PFOS, PFHxS, PFOA and PFNA). A few other studies report associations between alcohol consumption and internal PFAS levels (Jain, 2014; Bjerregaard-Olesen et al., 2016). Furthermore, our study also identified the consumption of locally grown food as a source of exposure to PFASs. Very consistent results were obtained for associations between consumption of locally produced chicken eggs and higher internal PFOS levels, which were observed in all age groups studied and in both FLEHS II and FLEHS III cycles. A few other studies report similar results in Germany (Holzer et al., 2008) and in the United States of America (Christensen et al., 2016). Associations with locally produced food could be very region-specific. However, since participants in the newborn and adult study populations were recruited all over Flanders it is very unlikely that local sources are at the basis of this association. It could be possible that PFAS contamination of the environment, more specifically the soil compartment, is more wide spread. This could make consumption of locally grown food a pathway of concern in European regions other than Flanders.

4.2.3. Life style factors

To our knowledge, this study describes for the first time an

association between use of personal care products and internal exposure to PFNA. This supports the use of personal care products as a possible route of exposure to PFNA in adults. The presence of PFASs in consumer-ready personal care products has been observed. In foundation, nail polish and sunscreens available on the Japanese market (Fujii et al., 2013) nine different PFASs could be detected, including PFOA and PFNA. In foundation and cosmetic powder products purchased on the Swedish market (Schultes et al., 2018) 25 PFASs were present, with the highest detection frequency for short-chain perfluoroalkyl carboxylic acids or PFCAs (perfluoroheptanoate (PFHpA), PFBA, perfluorohexanoate (PFHxA), perfluoropentanoate (PFPeA)), but also levels above LOD for six long-chain PFCAs (among which PFOA and PFNA).

4.2.4. Determinants representing other influencing factors

Some of the multiple regression models also include determinants often considered as a proxy for other factors of influence. For that reason, these variables were added last to the models. Obtaining significant results for these variables means relevant information on underlying pathways and sources is still missing in our dataset. In our data internal exposure to PFOS and PFOA is higher in spring than in other seasons. A Spanish study (Bartolome et al., 2017) produced similar findings. Season can reflect other factors that might affect exposure to PFASs, e.g. changes in diet or in time spent outdoors or gardening.

Concerning parameters reflecting socioeconomic status, our study suggests an association between higher income and education levels and higher internal exposure to PFASs. Data consistent with such social inequalities have been published (Melzer et al., 2010; Belova et al., 2013; Tyrrell et al., 2013; Buekers et al., 2018). It is unlikely that income and education themselves are directly related to PFAS exposure in a general population. Instead, these parameters can reflect certain lifestyle factors and living or working conditions that are related to PFAS exposure.

4.3. Strenghts and limitations of the study

No measurements of PFAS levels in exposure pathway media were available at individual level. In stead questionnaire data on habits and life style factors were used. Therefore, the statistical models are restricted in offering relevant determinants of observed variation in exposure to PFASs and are not able to predict the main contributors to the exposure itself. The variability in exposure explained by the models is rather low. This could be improved by having available PFASs levels in e.g. soil and home-produced eggs at the individual locations of the participants. The study population was sampled from the general population and adolescents living in an industrialised region with no recods of PFASs production. The presented models are not applicable to occupationally exposed populations, nor to people living near PFASs production sites. However Flemish data were used in this study, some of the determinants of relevance identified in the multiple regression models are subjected to European legislation and guidelines, e.g. contaminant levels in food products, available personal care products on the European market. Locally grown food could reflect a specific regional situation, but since PFAS are wide-spread in the environment, contribution of locally grown food could also be of relevance in other parts of Europe. The availablilty of individual PFASs measurements in human samples and detailed questionnaire data gained insights in actual internal exposure levels for four age groups and at different points in time. Moreover, several additional determinants of variability in individual exposure levels could be identified. These offer new opportunities for additional research, for policy instruments and for informing the general public.

5. Conclusion

Levels of PFOS, PFOA, PFHxS and PFNA in cord plasma of newborns and serum of adolescents (14–15 years) and adults of two different age groups (20–40 years and 50–65 years) in Flanders, Belgium, were in the middle or low range compared to reported levels in other Western countries. Nevertheless, HBM I values for PFOA and PFOS were exceeded in 62%–81% of the participants, depending on the compound, the timing of sampling and on the study population considered. Higher internal levels of PFASs were observed with increasing age, indicating cumulative exposure over time. Consumption of crustaceans, consumption of offal, potatoes, alcohol, locally produced vegetables and eggs were identified as significant determinants of exposure. Sex differences could also be observed, with higher levels of PFOS, PFOA and PFHxS in men than in women. PFAS body burden of women can be lowered by transplacental transport and breastfeeding and probably also by menstruation, although it cannot be excluded that higher internal exposure leads to early menopause. Our study indicates an association between higher income and level of education and higher internal exposure to PFNA and PFOA, respectively, probably in relation with lifestyle factors related to PFAS exposure or socioeconomic differences in exposure pathways. Our results illustrate that further research is needed on the use of personal care products containing PFASs as a possible route of exposure. Our models could explain between 3.5% and 36% of the observed variance in exposure, so other relevant determinants are probably still lacking in our data.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.chemosphere.2019.125250.

References

Bartolome, M., Gallego-Pico, A., Cutanda, F., Huetos, O., Esteban, M., Perez-Gomez, B., Bioambient, es, Castano, A., 2017. Perfluorinated alkyl substances in Spanish adults: geographical distribution and determinants of exposure. Sci. Total Environ. 603–604, 352–360. https://doi.org/10.1016/j.scitotenv.2017.06.031.

Belova, A., Greco, S.L., Riederer, A.M., Olsho, L.E., Corrales, M.A., 2013. A method to screen U.S. environmental biomonitoring data for race/ethnicity and income-related disparity. Environ. Health 12, 114–1476. https://doi.org/10.1186/1476-069X-12-114, 069X-12-114 [pii].

Berg, V., Nost, T.H., Huber, S., Rylander, C., Hansen, S., Veyhe, A.S., Fuskevag, O.M., Odland, J.O., Sandanger, T.M., 2014. Maternal serum concentrations of per- and polyfluoroalkyl substances and their predictors in years with reduced production and use. Environ. Int. 69, 58–66. https://doi.org/10.1016/j.envint.2014.04.010.

Bjerregaard-Olesen, C., Bach, C.C., Long, M., Ghisari, M., Bech, B.H., Nohr, E.A., Henriksen, T.B., Olsen, J., Bonefeld-Jorgensen, E.C., 2016. Determinants of serum levels of perfluorinated alkyl acids in Danish pregnant women. Int. J. Hyg Environ. Health 219, 867–875. https://doi.org/10.1016/j.ijheh.2016.07.008.

Brantsaeter, A.L., Whitworth, K.W., Ydersbond, T.A., Haug, L.S., Haugen, M., Knutsen, H.K., Thomsen, C., Meltzer, H.M., Becher, G., Sabaredzovic, A., Hoppin, J.A., Eggesbo, M., Longnecker, M.P., 2013. Determinants of plasma concentrations of perfluoroalkyl substances in pregnant Norwegian women. Environ. Int. 54, 74–84. https://doi.org/10.1016/j.envint.2012.12.014.

Buck, R.C., Franklin, J., Berger, U., Conder, J.M., Cousins, I.T., de Voogt, P., Jensen, A.A.,

Kannan, K., Mabury, S.A., van Leeuwen, S.P., 2011. Perfluoroalkyl and polyfluoroalkyl substances in the environment: terminology, classification, and origins. Integr. Environ. Assess. Manag. 7, 513–541. https://doi.org/10.1002/ieam.258.

Buekers, J., Colles, A., Cornelis, C., Morrens, B., Govarts, E., Schoeters, G., 2018. Socio-economic status and health: evaluation of human biomonitored chemical exposure to per- and polyfluorinated substances across status. Int. J. Environ. Res. Public Health 15. https://doi.org/10.3390/ijerph15122818.

Calafat, A.M., Wong, L.Y., Kuklenyik, Z., Reidy, J.A., Needham, L.L., 2007. Polyfluoroalkyl chemicals in the U.S. Population: data from the national health and nutrition examination survey (NHANES) 2003-2004 and comparisons with NHANES 1999-2000. Environ. Health Perspect. 115, 1596–1602. https://doi.org/10.1289/ehp.10598.

Cariou, R., Veyrand, B., Yamada, A., Berrebi, A., Zalko, D., Durand, S., Pollono, C., Marchand, P., Leblanc, J.C., Antignac, J.P., Le Bizec, B., 2015. Perfluoroalkyl acid (PFAA) levels and profiles in breast milk, maternal and cord serum of French women and their newborns. Environ. Int. 84, 71–81. https://doi.org/10.1016/j.envint.2015.07.014.

Christensen, K.Y., Thompson, B.A., Werner, M., Malecki, K., Imm, P., Anderson, H.A., 2016. Levels of persistent contaminants in relation to fish consumption among older male anglers in Wisconsin. Int. J. Hyg Environ. Health 219, 184–194. https://doi.org/10.1016/j.ijheh.2015.11.001.

Cornelis, C., D'Hollander, W., Roosens, L., Covaci, A., Smolders, R., Van Den Heuvel, R., Govarts, E., Van Campenhout, K., Reynders, H., Bervoets, L., 2012. First assessment of population exposure to perfluorinated compounds in Flanders, Belgium. Chemosphere 86, 308–314. https://doi.org/10.1016/j.chemosphere.2011.10.034.

Croes, K., Den, H.E., Bruckers, L., Loots, I., Morrens, B., Nelen, V., Colles, A., Schoeters, G., Sioen, I., Covaci, A., Vandermarken, T., Van, L.N., Baeyens, W., 2014. Monitoring chlorinated persistent organic pollutants in adolescents in Flanders (Belgium): concentrations, trends and dose-effect relationships (FLEHS II). Environ. Int. 71, 20–28. https://doi.org/10.1016/j.envint.2014.05.022. S0160-4120(14)00172-X [pii].

Den Hond, E., Chovanova, H., Dumez, B., Keune, H., Schoeters, G., Teughels, C., Van Campenhout, K., 2009. Human Biomonitoring in Flanders: Some Aspects Related to Study Design, Future, Communication and Ethics. Bulletin épidémiologique hebdomadaire Special edition, pp. 9–13.

Den Hond, E., Tournaye, H., De Sutter, P., Ombelet, W., Baeyens, W., Covaci, A., Cox, B., Nawrot, T.S., Van Larebeke, N., D'Hooghe, T., 2015. Human exposure to endocrine disrupting chemicals and fertility: a case-control study in male subfertility patients. Environ. Int. 84, 154–160. https://doi.org/10.1016/j.envint.2015.07.017.

Domingo, J.L., 2012. Health risks of dietary exposure to perfluorinated compounds. Environ. Int. 40, 187–195. https://doi.org/10.1016/j.envint.2011.08.001. S0160-4120(11)00215-7 [pii].

Dufour, P., Pirard, C., Seghaye, M.C., Charlier, C., 2018. Association between organohalogenated pollutants in cord blood and thyroid function in newborns and mothers from Belgian population. Environ. Pollut. 238, 389–396. https://doi.org/10.1016/j.envpol.2018.03.058.

Eriksen, K.T., S+©rensen, M., Mclaughlin, J.K., Tj+©nneland, A., Overvad, K., Raaschou-Nielsen, O., 2011. Determinants of Plasma PFOA and PFOS Levels Among 652 Danish Men. Environmental Science & Technology. American Chemical Society, pp. 8137–8143. https://doi.org/10.1021/es100626h.

European Food Safety Authority, E., 2012. Scientific Report of EFSA: pefluorinated substances in food: occurrence and dietary exposure. EFSA Journal 10, 2743.

Fujii, Y., Harada, K.H., Koizumi, A., 2013. Occurrence of perfluorinated carboxylic acids (PFCAs) in personal care products and compounding agents. Chemosphere 93, 538–544.

Han, X., Snow, T.A., Kemper, R.A., Jepson, G.W., 2003. Binding of perfluorooctanoic acid to rat and human plasma proteins. Chem. Res. Toxicol. 16, 775–781. https://doi.org/10.1021/tx034005w.

Haug, L.S., Huber, S., Becher, G., Thomsen, C., 2011. Characterisation of human exposure pathways to perfluorinated compounds–comparing exposure estimates with biomarkers of exposure. Environ. Int. 37, 687–693. https://doi.org/10.1016/j.envint.2011.01.011. S0160-4120(11)00013-4 [pii].

Haug, L.S., Salihovic, S., Jogsten, I.E., Thomsen, C., van, B.B., Lindstrom, G., Becher, G., 2010. Levels in food and beverages and daily intake of perfluorinated compounds in Norway. Chemosphere 80, 1137–1143. https://doi.org/10.1016/j.chemosphere.2010.06.023. S0045-6535(10)00697-1 [pii].

Haug, L.S., Thomsen, C., Becher, G., 2009. Time trends and the influence of age and gender on serum concentrations of perfluorinated compounds in archived human samples. Environ. Sci. Technol. 43, 2131–2136.

HBM Commission, G.H.B.C., 2016. HBM I values for perfluorooactanoic acid (PFOA) and perfluorooactanesulfonic acid (PFOS) in blood plasma. Statement of the German human biomonitoring commission (HBM commission). Bundesgesundheitsblatt 59, 1364.

Herzke, D., Huber, S., Bervoets, L., D'Hollander, W., Hajslova, J., Pulkrabova, J., Brambilla, G., De Filippis, S.P., Klenow, S., Heinemeyer, G., de Voogt, P., 2013. Perfluorinated alkylated substances in vegetables collected in four European countries; occurrence and human exposure estimations. Environ. Sci. Pollut. Res. Int. 20, 7930–7939. https://doi.org/10.1007/s11356-013-1777-8.

Holzer, J., Midasch, O., Rauchfuss, K., Kraft, M., Reupert, R., Angerer, J., Kleeschulte, P., Marschall, N., Wilhelm, M., 2008. Biomonitoring of perfluorinated compounds in children and adults exposed to perfluorooctanoate-contaminated drinking water. Environ. Health Perspect. 116, 651–657. https://doi.org/10.1289/ehp.11064 ([doi]).

Jain, R.B., 2014. Contribution of diet and other factors to the levels of selected polyfluorinated compounds: data from NHANES 2003-2008. Int. J. Hyg Environ. Health 217, 52–61. https://doi.org/10.1016/j.ijheh.2013.03.008. S1438-4639(13)00046-1 [pii].

Jensen, T.K., Andersen, L.B., Kyhl, H.B., Nielsen, F., Christesen, H.T., Grandjean, P., 2015. Association between perfluorinated compound exposure and miscarriage in Danish pregnant women. PLoS One 10, e0123496. https://doi.org/10.1371/journal.pone.0123496.

Kato, K., Wong, L.Y., Jia, L.T., Kuklenyik, Z., Calafat, A.M., 2011. Trends in exposure to polyfluoroalkyl chemicals in the U.S. Population: 1999-2008. Environ. Sci. Technol. 45, 8037–8045. https://doi.org/10.1021/es1043613.

Knox, S.S., Jackson, T., Javins, B., Frisbee, S.J., Shankar, A., Ducatman, A.M., 2011. Implications of early menopause in women exposed to perfluorocarbons. J. Clin. Endocrinol. Metab. 96, 1747–1753. https://doi.org/10.1210/jc.2010-2401.

Konkel, L., 2014. PFCs and early menopause: association raises questions about causality. Environ. Health Perspect. 122, A59. https://doi.org/10.1289/ehp.122-A59.

Lechner, M., Knapp, H., 2011. Carryover of perfluorooctanoic acid (PFOA) and perfluorooctane sulfonate (PFOS) from soil to plant and distribution to the different plant compartments studied in cultures of carrots (Daucus carota ssp. Sativus), potatoes (Solanum tuberosum), and cucumbers (Cucumis Sativus). J. Agric. Food Chem. 59, 11011–11018. https://doi.org/10.1021/jf201355y.

Lien, G.W., Huang, C.C., Wu, K.Y., Chen, M.H., Lin, C.Y., Chen, C.Y., Hsieh, W.S., Chen, P.C., 2013. Neonatal-maternal factors and perfluoroalkyl substances in cord blood. Chemosphere 92, 843–850. https://doi.org/10.1016/j.chemosphere.2013.04.038. S0045-6535(13)00636-X [pii].

Lubin, J.H., Colt, J.S., Camann, D., Davis, S., Cerhan, J.R., Severson, R.K., Bernstein, L., Hartge, P., 2004. Epidemiologic evaluation of measurement data in the presence of detection limits. Environ. Health Perspect. 112, 1691–1696.

Luo, Z., Shi, X., Hu, Q., Zhao, B., Huang, M., 2012. Structural evidence of perfluorooctane sulfonate transport by human serum albumin. Chem. Res. Toxicol. 25, 990–992. https://doi.org/10.1021/tx300112p.

Melzer, D., Rice, N., Depledge, M.H., Henley, W.E., Galloway, T.S., 2010. Association between serum perfluorooctanoic acid (PFOA) and thyroid disease in the U.S. National Health and Nutrition Examination Survey. Environ. Health Perspect. 118, 686–692. https://doi.org/10.1289/ehp.0901584.

Morrens, B., Den Hond, E., Schoeters, G., Coertjens, D., Colles, A., Nawrot, T.S., Baeyens, W., De Henauw, S., Nelen, V., Loots, I., 2017. Human biomonitoring from an environmental justice perspective: supporting study participation of women of Turkish and Moroccan descent. Environ. Health 16, 48. https://doi.org/10.1186/s12940-017-0260-2.

Olsen, G.W., Mair, D.C., Church, T.R., Ellefson, M.E., Reagen, W.K., Boyd, T.M., Herron, R.M., Medhdizadehkashi, Z., Nobiletti, J.B., Rios, J.A., Butenhoff, J.L., Zobel, L.R., 2008. Decline in perfluorooctanesulfonate and other polyfluoroalkyl chemicals in American Red Cross adult blood donors, 2000-2006. Environ. Sci. Technol. 42, 4989–4995.

Ortega, E., Franch, J., Castell, C., Goday, A., Ribas-Barba, L., Soriguer, F., Vendrell, J., Casamitjana, R., Bosch-Comas, A., Bordiu, E., Calle-Pascual, A., Carmena, R., Castano, L., Catala, M., Delgado, E., Gaztambide, S., Girbes, J., Lopez-Alba, A., Martinez-Larrad, M.T., Menendez, E., Mora-Peces, I., Pascual-Manich, G., Rojo-Martinez, G., Serrano-Rios, M., Urrutia, I., Valdes, S., Vazquez, J.A., Gomis, R., 2013. Mediterranean diet adherence in individuals with prediabetes and unknown diabetes: the Di@bet.es Study. Ann. Nutr. Metab. 62, 339–346. https://doi.org/10.1159/000346553.

Ostertag, S.K., Tague, B.A., Humphries, M.M., Tittlemier, S.A., Chan, H.M., 2009. Estimated dietary exposure to fluorinated compounds from traditional foods among Inuit in Nunavut, Canada. Chemosphere 75, 1165–1172.

Rylander, C., Brustad, M., Falk, H., Sandanger, T.M., 2009. Dietary predictors and plasma concentrations of perfluorinated compounds in a coastal population from northern Norway. J. Environ. Public Health 268219. https://doi.org/10.1155/2009/268219, 2009.

Rylander, C., Sandanger, T.M., Froyland, L., Lund, E., 2010. Dietary patterns and plasma concentrations of perfluorinated compounds in 315 Norwegian women: the NOWAC Postgenome Study. Environ. Sci. Technol. 44, 5225–5232. https://doi.org/10.1021/es100224q.

Schoeters, G., Colles, A., Den Hond, E., Croes, K., Vrijens, J., Baeyens, W., nelen, V., van de Mieroop, E., Covaci, A., Bruckers, L., Van Larebeke, N., Sioens, I., Morrens, B., Loots, I., 2012a. The Flemish Environment and Health Study (FLEHS) : Second Survey(2007-2011) : Establishing Reference Values for Biomarkers of Exposure in the Flemish Population. Biomarkers and Human Biomonitoring, vol. 1. Ongoing programs and exposures, pp. 135–165.

Schoeters, G., Den Hond, E., Colles, A., Loots, I., Morrens, B., Keune, H., Bruckers, L., Nawrot, T., Sioen, I., De Coster, S., Van Larebeke, N., Nelen, V., Van de Mieroop, E., Vrijens, J., Croes, K., Goeyens, K., Baeyens, W., 2012. Concept of the Flemish human biomonitoring programme. Int. J. Hyg Environ. Health 215, 102–108. https://doi.org/10.1016/j.ijheh.2011.11.006.

Schoeters, G., Govarts, E., Bruckers, L., Den Hond, E., Nelen, V., De Henauw, S., Sioen, I., Nawrot, T.S., Plusquin, M., Vriens, A., Covaci, A., Loots, I., Morrens, B., Coertjens, D., Van Larebeke, N., De Craemer, S., Croes, K., Lambrechts, N., Colles, A., Baeyens, W., 2017. Three cycles of human biomonitoring in Flanders - time trends observed in the Flemish environment and health study. Int. J. Hyg Environ. Health 220, 36–45. https://doi.org/10.1016/j.ijheh.2016.11.006.

Schultes, L., Vestergren, R., Volkova, K., Westberg, E., Jacobson, T., Benskin, J.P., 2018. Per- and polyfluoroalkyl substances and fluorine mass balance in cosmetic

products from the Swedish market: implications for environmental emissions and human exposure. Environ Sci Process Impacts 20, 1680–1690. https://doi.org/10.1039/c8em00368h.

Spliethoff, H.M., Tao, L., Shaver, S.M., Aldous, K.M., Pass, K.A., Kannan, K., Eadon, G.A., 2008. Use of newborn screening program blood spots for exposure assessment: declining levels of perluorinated compounds in New York State infants. Environ. Sci. Technol. 42, 5361–5367.

Taylor, K.W., Hoffman, K., Thayer, K.A., Daniels, J.L., 2014. Polyfluoroalkyl chemicals and menopause among women 20-65 years of age (NHANES). Environ. Health Perspect. 122, 145–150. https://doi.org/10.1289/ehp.1306707.

Trudel, D., Horowitz, L., Wormuth, M., Scheringer, M., Cousins, I.T., Hungerbuhler, K., 2008. Estimating consumer exposure to PFOS and PFOA. Risk Anal. 28, 251–269. https://doi.org/10.1111/j.1539-6924.2008.01017.x.

Tyrrell, J., Melzer, D., Henley, W., Galloway, T.S., Osborne, N.J., 2013. Associations between socioeconomic status and environmental toxicant concentrations in adults in the USA: NHANES 2001-2010. Environ. Int. 59, 328–335. https://doi.org/10.1016/j.envint.2013.06.017. S0160-4120(13)00135-9 [pii].

Umweltbundesamt, 2018. [HBM-I values for perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS) in blood plasma - statement of the German human biomonitoring commission (HBM commission)]. Bundesgesundheitsblatt - Gesundheitsforsch. - Gesundheitsschutz 61, 474–487. https://doi.org/10.1007/s00103-018-2709-z.

Vestergren, R., Berger, U., Glynn, A., Cousins, I.T., 2012. Dietary exposure to perfluoroalkyl acids for the Swedish population in 1999, 2005 and 2010. Environ. Int. 49, 120–127. https://doi.org/10.1016/j.envint.2012.08.016. S0160-4120(12)00190-0 [pii].

Wong, F., MacLeod, M., Mueller, J.F., Cousins, I.T., 2014. Enhanced elimination of perfluorooctane sulfonic acid by menstruating women: evidence from population-based pharmacokinetic modeling. Environ. Sci. Technol. 48, 8807–8814. https://doi.org/10.1021/es500796y.

Yamada, A., Bemrah, N., Veyrand, B., Pollono, C., Merlo, M., Desvignes, V., Sirot, V., Marchand, P., Berrebi, A., Cariou, R., Antignac, J.P., Le Bizec, B., Leblanc, J.C., 2014. Dietary Exposure to Perfluoroalkyl Acids of Specific French Adult Subpopulations: High Seafood Consumers, High Freshwater Fish Consumers and Pregnant Women. Science of The Total Environment Halogenated Persistent Organic Pollutants (Dioxin2013, Daegu/Korea), pp. 170-175.