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Socio-demographic inequalities influence differences in the chemical exposome among Swedish adolescents

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ABSTRACT

Relatively little is known about the relationship between socio-demographic factors and the chemical exposome in adolescent populations. This knowledge gap hampers global efforts to meet certain UN sustainability goals. The present work addresses this problem in Swedish adolescents by discerning patterns within the chemical exposome and identify demographic groups susceptible to heightened exposures.

Enlisting the Riksmaten Adolescents 2016–17 (RMA) study population (N = 1082) in human-biomonitoring, and using proportional odds ordinal logistic regression models, we examined the associations between concentrations of a diverse array of substances (N = 63) with the determinants: gender, age, participant/maternal birth country income per capita level, parental education levels, and geographic place of living (longitude/latitude).

Participant/maternal birth country exhibited a significant association with the concentrations of 46 substances, followed by gender (N = 41), and longitude (N = 37). Notably, individuals born in high-income countries by high-income country mothers demonstrated substantially higher estimated adjusted means (EAM) concentrations of polychlorinated biphenyls (PCBs), brominated flame retardants (BFRs) and per- and polyfluoroalkyl substances (PFASs) compared to those born in low-income countries by low-income country mothers. A reverse trend was observed for cobalt (Co), cadmium (Cd), lead (Pb), aluminium (Al), chlorinated pesticides, and phthalate metabolites. Males exhibited higher EAM concentrations of chromium (Cr), mercury (Hg), Pb, PCBs, chlorinated pesticides, BFRs and PFASs than females. In contrast, females displayed higher EAM concentrations of Mn, Co, Cd and metabolites of phthalates and phosphorous flame retardants, and phenolic substances. Geographical disparities, indicative of north-to-south or west-to-east substance concentrations gradients, were identified in Sweden. Only a limited number of lifestyle, physiological and dietary factors were identified as possible drivers of demographic inequalities for specific substances.

This research underscores birth country, gender, and geographical disparities as contributors to exposure differences among Swedish adolescents. Identifying underlying drivers is crucial to addressing societal inequalities associated with chemical exposure and aligning with UN sustainability goals.

1. Introduction

In 2015, the United Nations (UN) established a set of 17 sustainable development goals to be achieved by 2030 (U.N., 2015). Several of these goals are particularly relevant to the issue of chemical pollution, notably Goal 3: "Ensure healthy lives and promote well-being", Goal 5: "Gender equality" and Goal 10: "Reduce inequality within and among countries". According to the Lancet Commission (Collaborators, 2017), the

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Table 1
Demographic characteristics of the participants in Riksmaten Adolescents 2016–2017.

	5th Grade (N = 329)	8th Grade (N = 405)	11th Grade (N = 348)	Total (N = 1082)
Gender				
Female	164 (49.8 %)	226 (55.8 %)	216 (62.1 %)	606 (56.0 %)
Male	165 (50.2 %)	179 (44.2 %)	132 (37.9 %)	476 (44.0 %)
Age (years)				
Mean ± (SD)	11.6 (0.4)	14.5 (0.4)	17.8 (0.7)	14.7 (2.5)
Median	11.5	14.5	17.7	14.6
Range	10.6–13.1	11.6–15.7	16.8–21.1	10.6–21.1
Participant | Maternal birth country per capita income				
N-missing	4	2	0	6
Low | Low	15 (4.6 %)	10 (2.5 %)	20 (5.7 %)	45 (4.2 %)
High | Low	7 (2.2 %)	15 (3.7 %)	4 (1.1 %)	26 (2.4 %)
Upper-middle |Upper-middle	6 (1.8 %)	10 (2.5 %)	21 (6.0 %)	37 (3.4 %)
High | Upper-middle	37 (11.4 %)	25 (6.2 %)	15 (4.3 %)	77 (7.2 %)
High | High	260 (80.0 %)	343 (85.1 %)	288 (82.8 %)	891 (82.8 %)
Maternal education level				
N-missing	13	20	25	58
Elementary or None	27 (8.5 %)	28 (7.3 %)	27 (8.4 %)	82 (8.0 %)
≤2 years Secondary	43 (13.6 %)	49 (12.7 %)	69 (21.4 %)	161 (15.7 %)
≥3 years Secondary	79 (25.0 %)	77 (20.0 %)	71 (22.0 %)	227 (22.2 %)
Higher Education	167 (52.8 %)	231 (60.0 %)	156 (48.3 %)	554 (54.1 %)
Paternal education level				
N-missing	17	26	38	81
Elementary or None	29 (9.3 %)	39 (10.3 %)	41 (13.2 %)	109 (10.9 %)
≤ 2 years Secondary	59 (18.9 %)	72 (19.0 %)	82 (26.5 %)	213 (21.3 %)
≥ 3 years Secondary	105 (33.7 %)	87 (23.0 %)	85 (27.4 %)	277 (27.7 %)
Higher Education	119 (38.1 %)	181 (47.8 %)	102 (32.9 %)	402 (40.2 %)

sustainable global management and reduction of chemicals is a critical factor in attaining Goal 3. Indirect benefits of pollution mitigation include enhancing gender equity (Goal 5) (Collaborators, 2017), due to gender-related differences in lifestyle that affect chemical exposure and biological disparities in chemical toxico-kinetics and toxico-dynamics (Liang et al., 2018; Sakali et al., 2021). Furthermore, regional and country disparities in the development of industrial and agricultural/forestry sectors contribute to inequalities in chemical pollution exposure (Berg et al., 2017). To address these challenges, it is imperative to gain a better understanding of socio-demographic differences in the body burdens of chemicals in humans. Such knowledge is essential for identifying populations at risk of high chemical exposure, ultimately improving our capacity to manage chemicals effectively and support sustainable global development.

Regrettably, there is a lack of population-based studies that have examined the connections between socio-demographic factors and exposure to a diverse spectrum of toxic substances in adolescents. Although there has been an uptick in public health attention and scientific interest in understanding the exposome at large, that being all internal and external stressors on the body, little is still known specifically about the chemical component of the exposome (i.e., the 'chemical exposome'). Previous investigations have predominantly focused on associations with individual chemical compounds or chemical categories. In contrast to adulthood, adolescence may represent a critical period of heightened vulnerability to the adverse effects of chemical exposure, primarily due to the profound physiological changes that transpire during this developmental phase (Abreu and Kaiser, 2016). Adolescence is also characterised by rapid and substantial shifts in behaviour, which may exert a pronounced influence on patterns of chemical exposure. Recent national and regional, population-based studies on adolescents in Germany (GerES V 2014–17), the United States (NHANES, 2011–16) and Belgium (FLEHS IV 2016–2020) have published data pertaining to the body burden of numerous chemical groups measured in whole blood, serum and urine (Bandow et al., 2020; Fillol et al., 2021; Murawski et al., 2020; NHANES, 2022; Schoeters et al., 2022; Schulz et al., 2021; Schwedler et al., 2020b; Tschersich et al., 2021). Some of these investigations have reported chemical body burdens in relation to age, sex, socioeconomic status, and immigration status. However, to the best of our knowledge, only the FLEHS IV study has disseminated its findings in a single publication, employing a more holistic approach in exploring the interplay between gender, age, and sociodemographic variables in relation to the chemical exposome (Schoeters et al., 2022). Moreover, studies investigating the association between country of birth and chemical body burdens in adolescents have remained notably scarce.

In Sweden, the recent nation-wide survey of adolescents, Riksmaten Adolescents 2016–17 (RMA), showed that Swedish adolescents were exposed to a variety of toxic substances, including elements, halogenated persistent organic pollutants (POPs), phthalates, phosphorous flame retardants (PFRs), pesticides and bisphenols and other potentially toxic phenolic substances (Pineda et al., 2023). Parts of the study population had concentrations of some elements, POPs and pesticides that exceeded the most conservative human biomonitoring guidance values (HBM-GVs) or other proposed health-based guidance values (Pineda et al., 2023).

In a recently published paper based on the RMA study, concentrations of per- and polyfluoroalkyl substances (PFASs) in serum were strongly associated with gender and immigration status, but less so with age and maternal/paternal education level (Nyström et al., 2022). In the present study we expanded the previous investigations on RMA to explore potential socio-demographic disparities in body burdens of elements, chlorinated, brominated and fluorinated persistent organic pollutants (POPs), phthalates, phthalate alternatives, phosphorous flame retardants, bisphenols, and other phenolic substances among the RMA participants, by determining the relationship between measured substance concentrations with age, gender, birth country income per capita, parental education levels, and latitude/longitude of residence in Sweden. Furthermore, in instances where significant associations emerged with demographic factors, we investigated if some previously reported determinants of body burdens of the studied substances in Sweden, such as diet, smoking, and body mass index (BMI), could at least partially explain some of the observed demography-related associations.

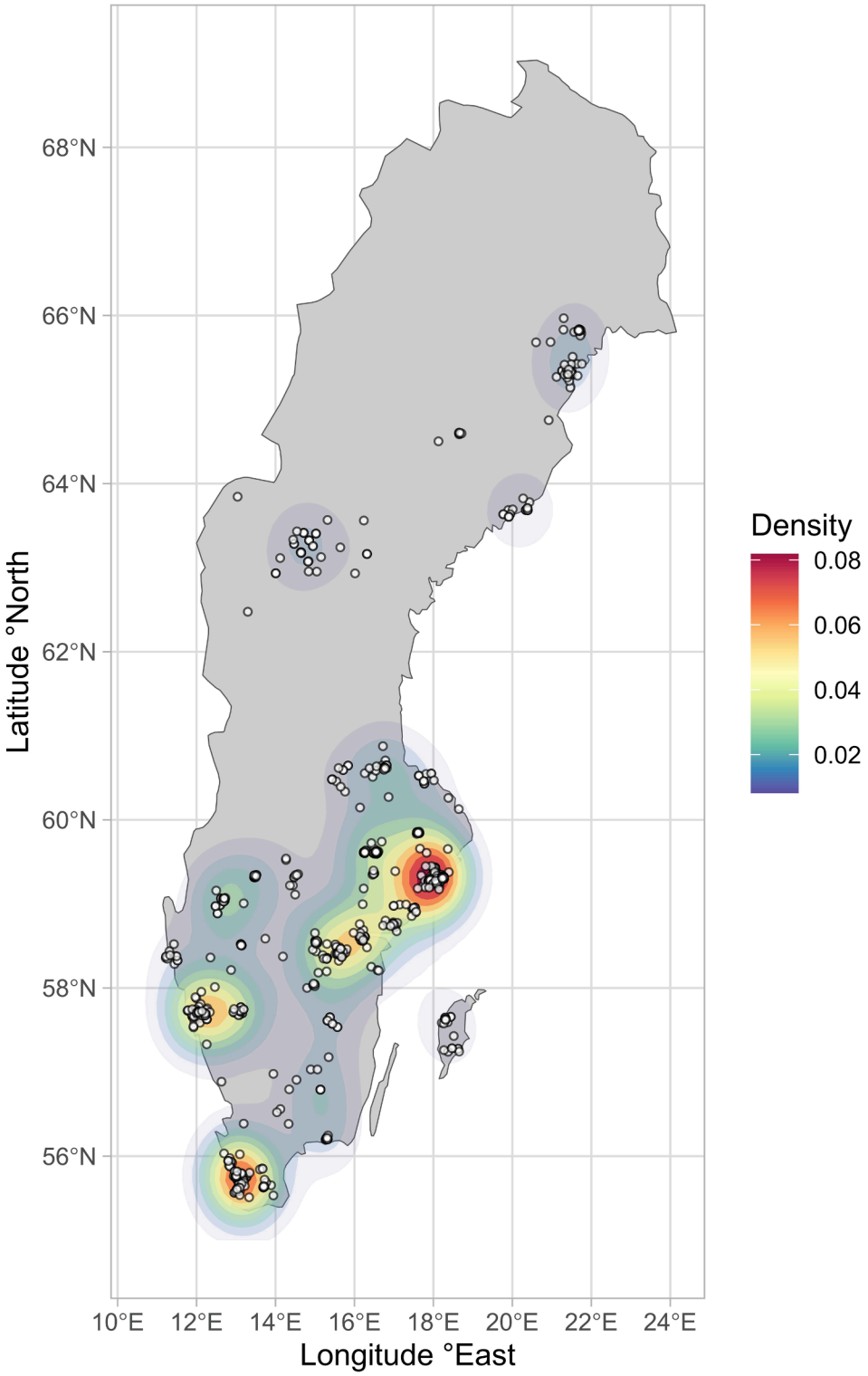

Fig. 1. Map of Sweden demonstrating the coordinates of all 1082 participants zip code of home address (white dots) included in this study. Coloured contours represent the spatial density relative to the study populations coordinates. Sweden encompasses latitudes ~ 55° to ~ 69° north, and longitudes ~ 11° to ~ 24° east, with the largest urban areas in the south-west being Malmö (55.6°N, 13°E) at the south Baltic Sea coast, and Gothenburg (57.7°N, 11.9°E) at the Atlantic Ocean coast, along with Stockholm (59.3°N, 18°E) in the east at the central Baltic Sea coast.

2. Methods

2.1. Study group and design

The study population was a sub-sample of RMA 2016–17, a nationally representative cross-sectional school-based dietary survey of Swedish adolescents in school grades 5 (average 12-year-olds), 8 (15-year-olds) and 11 (18-year-olds) conducted by the Swedish Food Agency (Table 1 and Fig. 1). Details about the recruitment process and study design are described in Pineda et al. (2023) and Moraeus et al. (2018). In short, a web-based dietary assessment method (RiksmatenFlexDiet), and four online-based questionnaires (RiksmatenFlexQ) were used to collect

Table 2
Concentrations of substances included in this study (N = 1082). Substances concentrations in urine adjusted for density.

Substances[1]	Median (Range)[2]	N < LOQ or LOD	N = 0[3]
Chromium (Cr)	0.58 (<0.2, 2.95)	3	0
Manganese (Mn)	10.5 (<0.16, 32.6)	1	0
Cobalt (Co)	0.12 (<0.05, 0.73)	22	1
Nickel (Ni)	0.62 (<0.21, 3.62)	1	1
Selenium (Se)	95.1 (<5, 198)	1	0
Cadmium (Cd)	0.12 (<0.05, 3.9)	30	0
Mercury (Hg)	0.72 (<0.05, 14.5)	8	1
Lead (Pb)	7.15 (<0.07, 139)	1	0
Aluminium (Al)	<5 (<5, 94.8)	571	0
Pentachlorobenzene (PeCB)	<10 (<10, 15.2)	1080	192
Hexachlorbenzene (HCB)	42.5 (11.7, 7420)	0	0
alpha-Hexachlorocyclohexane (α–HCH)	<20 (<20, <20)	1082	731
beta-Hexachlorocyclohexane (β–HCH)	<15 (<15, 528)	1025	9
gamma-Hexachlorocyclohexane (γ–HCH)	<20 (<20, 93,8)	1077	708
Oxychlordane	<25 (<25, 29.2)	1081	588
trans-Nonachlor	<5 (<5, 64)	836	0
1,1-bis-(4-chlorophenyl)-2,2,2-trichlorethane (p,p'-DDT)	<15 (<15, 404)	1048	524
1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene (p,p'-DDE)	92.6 (<40, 6130)	78	0
2,4,4′,5-Tetrachlorobiphenyl (PCB-74)	<5 (<5, 1050)	817	0
2,2′,4,4′,5-Pentachlorobiphenyl (PCB-99)	<5 (<5, 145)	733	0
2,3′,4,4′,5-Pentachlorobiphenyl (PCB-118)	6.43 (<5, 94.5)	328	0
2,2′,3,4,4′,5′-Hexachlorobiphenyl (PCB-138)	26.7 (<5, 255)	9	0
2,2′,4,4′,5,5′-Hexachlorobiphenyl (PCB-153)	43.3 (<5, 298)	1	0
2,3,3′,4,4′,5-Hexachlorobiphenyl (PCB-156)	<5 (<5, 65.1)	653	1
2,2′,3,3′,4,4′,5-Heptachlorobiphenyl (PCB-170)	11.9 (<5, 141)	178	0
2,2′,3,4,4′,5,5′-Heptachlorobiphenyl (PCB-180)	23.7 (<5, 402)	42	0
2,2′,3,4,4′,5′,6-Heptachlorobiphenyl (PCB-183)	<5 (<5, 46.7)	988	1
2,2′,3,4′,5,5′,6-Heptachlorobiphenyl (PCB-187)	5.48 (<5, 148)	497	0
2,2′,4,4′-Tetrabromodiphenyl ether (BDE-47)	<15 (<15, 232)	1060	137
2,2′,4,4′,5-Pentabromodiphenyl ether (BDE-99)	<15 (<15, 170)	1074	262
2,2′,4,4′,5,5′-Hexabromodiphenyl ether (BDE-153)	<15 (<15, 158)	1076	87
Linear-Perfluorooctanoic acid (L-PFOA)	1.2 (<LOQ, 9.75)	2	1
Perfluorononanoic acid (PFNA)	0.38 (<LOQ, 2.79)	78	53
Perfluorodecanoic acid (PFDA)	<LOQ (<LOQ, 1.35)	409	216
Perfluoroundecanoic acid (PFUnDA)	<LOQ (<LOQ, 1.01)	574	332
Linear Perfluorohexanesulfonic acid (L-PFHxS)	<LOQ (<LOQ, 255)	86	7
Linear Perfluorooctanesulfonic acid (L-PFOS)	1.99 (<LOQ, 127)	0	0
Branched Perfluorooctanesulfonic acid (br-PFOS)	0.92 (<LOQ, 110)	22	0
Monoethyl phthalate (MEP)	32.8 (3.43, 8300)	0	0
Mono-butyl phthalate (MBP)	40.1 (3.76, 916)	0	0
Monobenzyl phthalate (MBzP)	6.48 (0.35, 231)	0	0
Mono-(2-ethylhexyl) phthalate (MEHP)	1.61 (<0.3, 290)	1	0
Mono-(2-ethyl-5-hydroxyhexyl) phthalate (5OH-MEHP)	7.69 (<0.1, 1140)	2	0
Mono-(2-ethyl-5-oxohexyl) phthalate (5oxo-MEHP)	6.01 (0.27, 1060)	0	0
Mono-(2-ethyl-5-carboxypentyl) phthalate (5cx-MEPP)	6.91 (0.86, 912)	0	0
Mono(2-(carboxymethyl)hexyl) phthalate (2cx-MEHP)	2.03 (0.21, 90.9)	0	0
Mono-(4-methyl-7-hydroxyoctyl) phthalate (OH-MiNP)	3.68 (0.46, 635)	0	0
Mono-(4-methyl-7-oxooctyl) phthalate (oxo-MiNP)	1.8 (0.09, 228)	0	0
Mono-(4-methyl-7-carboxyheptyl) phthalate (cx-MiNP)	5.85 (0.55, 1130)	0	0
Monocarboxyisononyl phthalate (cx-MiDP)	0.4 (<0.1, 20)	36	0
6-Hydroxy monopropylheptyl phthalate (OH-MPHP)	1.01 (<0.08, 92.1)	1	0
Cyclohexane-1,2-dicarboxylate-mono(oxo-isononyl) ester (oxo-MINCH)	1.01 (<0.08, 1100)	1	0
1,2-Cyclohexanedicarboxylic Acid Mono 4-Methyl-7-carboxy-heptyl Ester (cx-MINCH)	0.79 (<0.1, 391)	10	1
2-(((Hydroxy-4-methyloctyl)oxy)carbonyl)cyclohexanecarboxylic acid (OH-MINCH)	0.76 (<0.1, 672)	4	0
Diphenyl phosphate (DPP)	1.89 (0.29, 45.4)	0	0
Dibutyl phosphate (DBP)	0.15 (<0.05, 11.7)	116	1
Bis(2-butoxyethyl) phosphate (BBOEP)	<0.05 (<0.05, 2.14)	564	0
Bisphenol A (BPA)	0.9 (<0.2, 49.4)	48	5
Bisphenol S (BPS)	0.13 (<0.03, 49.4)	33	0
4,4-Bisphenol F (4,4BPF)	0.1 (<0.03, 207)	204	22
2-hydroxy-phenanthrene (2-OH-PH)	0.15 (<0.1, 7.09)	308	0
1-Hydroxypyrene (1-HP)	<0.1 (<0.1, 4.12)	692	14
Trichloropyridinol (TCP)	1.19 (0.15, 50.6)	0	0
3-Phenoxybenzoic acid (3-PBA)	0.26 (<0.05, 11.7)	12	0
Triclosan (TCS)	0.28 (<0.1, 1130)	181	6
3-*tert*-Butyl-4-hydroxyanisole (BHA)	0.9 (<0.02, 494)	137	28
Benzophenone-3 (BP3)	0.76 (<0.2, 1250)	145	0

[1] Elements: μg/L whole blood, except Aluminium: μg/L serum; Chlorinated and brominated substances: pg/ml serum; Fluorinated substances: ng/g serum; Urine substances (phthalate metabolites, etc.): μg/L urine (density adjusted).

[2] LODs given for elements and substances measured in urine. LOQs given for chlorinated pesticides, PCBs, BFRs and PFASs. PFASs have range of LOQs depending on analysis batch; L-PFOA: 0.02–0.288, PFNA: 0.058–0.288, PFDA: 0.058–0.288, PFUnDA: 0.058–0.288, L-PFHxS: 0.022–0.463, L-PFOS: 0.056–0.562, br-PFOS: 0.056–0.562.

[3] Statistical analyses included concentrations below LOQ/LOD that were reported being above background noise (i.e. machine reads) as estimated in the analytical run. Concentrations were set to 0.0001 in cases when machine reads were below the background noise (see article section 2.5 Substance concentrations). N = 0: number of samples with concentrations below the background noise in the analyses.

data about demographic factors, lifestyle habits and food consumption (Moraeus et al., 2018; Nyström-Kandola et al., 2023). Participants retrospectively registered their food intake (24-h recall) on 2 non-consecutive days and filled in the questionnaires at home with the aid of parents if required (Moraeus et al., 2018). Of the 1305 students who accepted to donate blood and urine, 1111 participants had all three biomonitoring matrices (i.e., whole blood, blood serum and urine) analysed for substance concentrations. Of these participants, 28 participants were manually removed as large sections of data were incomplete, resulting in 1083 participants. Due to an inability to impute missing substance concentrations for a single participant (see article section 2.8 Imputation), the final number of participants included in the analysis became 1082.

Ethical approval was obtained from the Regional Ethical Review Board in Uppsala (No 2015/190). Written informed consent was obtained from all participants and from their legal guardians if younger than 16 years.

2.2. Sample collection

Non-fasting serum, plasma and whole blood samples were collected by trained staff from the regional divisions of Occupational and Environmental Medicine in Sweden during school visits as previously described in Pineda et al. (2023). Single-spot urine samples were collected by the individual participants during the same school visits. All samples were frozen at the sampling site and stored at −20 °C before transportation to the Swedish Food Agency, where they were stored at −80 °C before analysis.

2.3. Sample analysis

All of the analysed substances included in this study, along with full names and abbreviations are given in Table 2. Details on the analytical methods are provided in Pineda et al. (2023). Briefly, elements in whole blood and serum were analysed by the Department of Laboratory Medicine, Lund University, Lund, Sweden, using inductively coupled plasma mass spectrometry (ICP-MS; iCAP Q, Thermo Fisher Scientific, Bremen, GmbH). Polychlorinated biphenyls (PCBs), chlorinated pesticides/metabolites and polybrominated diphenyl ethers (PBDEs) in serum (Table 2) were analysed at the Department of Health Security, National Institute for Health and Welfare, Kuopio, Finland, using gas chromatography - triple quadrupole mass spectrometry (GC–MS/MS, Agilent 7010 GC–MS/MS system, Wilmington, DE, U.S.). Per- and polyfluoroalkyl substances (PFASs) in serum (Table 2) were analysed by the Department of Environmental Science, Stockholm University, Stockholm, Sweden, using a Waters ACQUITY ultra performance liquid chromatograph (UPLC) coupled to a Waters Xevo TQS triple quadrupole mass spectrometer.

In urine, utilising a Shimadzu UFLC system (Shimadzu Corporation, Kyoto, Japan) coupled to a QTRAP5500 triple quadrupole linear ion trap mass spectrometer (LC-MS/MS; AB Sciex, Foster City, CA, U.S.), metabolites of phthalates, phthalate alternatives, phosphorous flame retardants (PFRs), pesticides and polycyclic aromatic hydrocarbons (PAHs) were measured (Table 2). In addition, the plastics chemicals bisphenols, the biocide triclosan (TCS), the preservative/antioxidant 3-*tert*-butyl-4-hydroxyanisole (BHA), and the UV filter benzophenone-3 (BP-3) were analysed (Table 2). Analyses were performed at the Department of Laboratory Medicine, Lund University, Lund, Sweden.

Ferritin was analysed in plasma samples by the accredited laboratory of the Department of Clinical Chemistry and Pharmacology, University Hospital in Uppsala, Sweden, using Abbott Architect ci8200 analysers (Abbott Laboratories, Abbott Park, IL, USA).

2.4. Data processing

All data processing, statistical analyses and figures were produced using R version 4.0.2 (22–06-2020). The cut-off significance level in the statistical analyses was set to $p \leq 0.05$.

2.5. Substance concentrations

As described in Pineda et al. (2023), measurable concentrations which were below limits of quantification or detection (LOQ and LOD, respectively), were used when reported by the laboratories to keep as low of a bias as possible within the statistical analyses (AMC, 2001; Bergstrand and Karlsson, 2009). However, when interpreting the results, it is important to consider that measured concentrations below LOD or LOQ are more uncertain than concentrations above these limits. Concentrations reported by the laboratories to be at or below 0 were converted to 0.0001 independent of unit of concentration, a number selected as it is lower than any value reported by the laboratories. This value would represent the assumption that although a substance had been reported at or below 0 within a sample, it is highly unlikely that there was absolutely no trace of the substance at all in the sample. For the PFASs, concentrations < LOD were deemed too uncertain by the analytical laboratory, thus in the statistical analyses PFASs concentrations < LOD were set to 0.0001. Only substances with < 30 % of the concentrations set to 0.0001 (Table 2), and/or with models demonstrating goodness of fit (Fig. S.1) were included in the final statistical analyses.

2.6. Demographic determinants

Characteristics of the socio-demographics of the studied population are presented in Table 1. The 'Participant | Maternal birth country income per capita level' variable was combined from two individual variables: 'Participant birth-country income per capita level' and 'Maternal birth-country income per capita level'. The combination of the participant/maternal birth country was done to avoid multicollinearity bias within the model as the variables were highly correlated to each other. The reasoning behind including maternal birth country in the exposome analyses was that exposure to some chlorinated POPs early in foetal life and during breast-feeding, are detectable in humans for decades after cessation of these exposures (Glynn et al., 2007; Lignell et al., 2011; Wesselink et al., 2019). Moreover, after the move to Sweden there may be birth country differences in sources of exposure affected by housing conditions, and the participant use of products and dietary habits. A maternal influence on lifestyle and diet of the adolescents is also possible, thus potentially affecting more recent exposure to the toxic substances in Sweden. Birth country reported by the RMA participants and their biological mothers was classified according to the World Bank Country Classification (WBG, 2018), based on each countrýs gross national income per capita. The combined participant/maternal birth country variable was primary ordered based on the maternal birth country in the order; low, lower-middle, upper-middle, high-income country. Secondary the variable was ordered according to the participants birth country generating the order for participant/maternal birth country; 'Low | Low', 'High | Low', 'Upper-middle | Upper-middle',

'High | Upper-middle, 'High | High' birth country (Table 1). Maternal and Paternal Education variables were both ordered as: Elementary school or none (ES), < 2 years of upper-secondary or vocational (2-Us), 3 Years or more of upper-secondary or vocational (3 + Us), and Higher education (HE) (Table 2). Latitude and longitude coordinates were derived from the ZIP codes of the participants home address using the Google Maps Platform API. In the case of 20 participants which had missing ZIP codes, the latitude and longitude coordinates of their corresponding school address were used instead as an approximation. Spearman's rank correlation coefficients were calculated for all demographical determinants in the base model except for gender due it being a dichotomous variable with no inherent order (Fig. S.3).

2.7. Additional determinants in secondary models

Some additional determinants were explored as possible explanatory determinants of observed demographic differences in substance concentrations. These determinants were chosen based on statistically significant relationships with body burdens of the studied substances reported from other studies of Swedish populations, or in some cases in other populations, and the availability of data in RMA (Table S.1). For example, BMI, smoking, consumption of alcohol, eggs and seafood have been shown to be significantly related to PCBs body burdens in different populations in Sweden and were therefore added as additional determinants in the PCBs regression models (Table S.1 and S.40-S.77). Season of sampling was included in all secondary models, since previous studies have reported seasonal variation of blood levels of some of the elements, POPs, and substances in urine included in this study (Table S.1) (Bastiaensen et al., 2021a; Geller et al., 2023; Koppen et al., 2009; Makey et al., 2014).

It was assumed that all 5th graders were non-smokers and non-consumers of alcohol, as no data were collected from these participants. For other participants, the variable 'current smoking habits' was ordered as follows: 'No', 'Quit', 'Yes'. For 'alcohol consumption the last 6 months', the variable was ordered as: 'No', 'Yes, once', 'Yes, several times'. Food consumption variables (Table S.1); game meat products, chocolate, ice cream and tube packaged foods were based on participant answers given for frequency questions about consumption the prior year and were recoded, condensed and ordered as follows: 'Never' = 'Never', '< 1 per month' = 'Seldom', 'Once per month' = 'Irregularly monthly', '2–3 times per month' = 'Often monthly', 'Once per week' = 'Irregularly weekly, '2–3 times a week' = 'Often weekly', '4–6 times a week' = 'Often weekly', 'Every day' = 'Often weekly'. Canned fish were summed from three separate yearly consumption variables; canned herring/mackerel, canned tuna, and canned anchovies/sardines, where their original frequencies were translated to numeric integers as follows: 'Never' = 0, '1–3 times a year' = 2, '4–8 times a year' = 6, '9–11 times a year' = 24, 'Once per week' = 52, 'Twice a week' = 104, '×3 times a week' = 156, 'Once a day or more' = 365.

To estimate consumption of seafood, meat and eggs (g/day) over a longer time period (Table S.1), data from the two days of 24-h dietary recall were transformed to habitual (long-term) intake using the Multiple Source Method (Harttig et al., 2011). These calculations were based on the total participating population of the RMA study (Nyström-Kandola et al., 2023). Habitual egg consumption was calculated with the assumption that all individuals consumed it to some extent, therefore meaning that all individuals were regarded as consumers. This was not the case for habitual meat and seafood consumption where individuals could be identified and represented as non-consumers. BMI classification was based on the IOTF cut-offs dependent on age and sex for those under 18 (Cole and Lobstein, 2012). For participants 18 and older, standard IOTF BMI definitions for adults were applied (Cole and Lobstein, 2012). BMI was divided into four groups: Underweight, Normal weight, Overweight and Obese (Table S.1).

2.8. Imputation

From the remaining data set of 1083 participants, there were 605 participants with complete data across all variables, with the remaining 478 participants having at least 1 or more missing values in any of the dependent or explanatory variables (Table 1). Among the substances analysed; L-PFOA, BPS, 3-PBA, BHA and BP3 had 1 missing value each; TCP 2 values; DPP, DBP and BBOEP 3 values each; Al and MBP 6 values each; cx-MiNCH and OH-MiNCH 7 values each. Missing values were imputed using MICE package version 3.10.0 for R (13–07-2020) using Rubin's rules across 16 multiple imputations and 5 iterations. All missing values were successfully imputed apart from a single participant who was manually removed from the analysis with a missing value of L-PFOA which could not be successfully imputed from the other variables, bringing the final number of included participants to 1082.

2.9. Ordinal regression models

All associations between substance concentrations and possible determinants were analysed using Ordinal Regression Models (ORM), also known as 'proportional odds ordinal logistic regression'. Bias and increased variation due to the multiple imputation were accounted for within the models by using the 'fit.mult.impute' function from the Hmisc package (ver. 4.4–0) with an ORM fitter from the 'rms' package (ver. 6.0–0) for R. Additionally, the model fits were adjusted for clustering of the schools using the 'robcov' function from the Hmisc package utilising the Huber-White method to adjust the variance–covariance matrix correctly for heteroscedasticity. The same base model was applied to all contaminants which included the covariates; age, gender, participant/maternal birth country income per capita, maternal and paternal education, latitude, longitude and the combined effect of latitude * longitude. This can be expressed in the formal equation:

$$logit(\Pr(y \leq C_k|X)) = a_k - X_b$$

Where $X_b = b_{Age} + b_{Gender} + b_{Participant/maternal\ birth\ country\ income\ per\ capita} + b_{Maternal\ education} + b_{Paternal\ education} + b_{Latitude} + b_{Longitude} + b_{(Latitude\ *\ Longitude)}$ and C_k is the k^{th} ordered outcome value.

Summary tables for each substance base model were created demonstrating the odds ratios for each variable as well as ANOVA tables calculated for each substance model providing the chi-square, degrees of freedom, and p-value for each variable (see Supplement, Tables S.2 – S.167). Estimated adjusted means (EAM) of substance concentrations for each determinant were computed from the ordinal regression models using the smearing estimation nonparametric method (Duan, 1983). Values from the ANOVA result tables were used to create a p-value heatmap and chi-square proportion heat map (Figs. 2 and S.2). In the chi-square heatmap (Fig. S.2) each covariates contribution to the variation of substance concentrations in each separate model was evaluated by dividing the chi-square of each variable by the total sum of all chi-squares for any given model.

3. Results and Discussion

In our study on the associations between concentrations of 63 toxic substances and demographic determinants in Swedish adolescents, the ORMs uniformly incorporated seven demographic determinants for all substances. As a result, any statistically significant relationship between a determinant and substance concentrations has been adjusted for the effects of the remaining six determinants.

Spearman's rank correlation coefficients showed that most social-demographic determinants were not correlated to each other with some minor exceptions (Fig. S.3). Maternal and paternal education levels were as expected significantly and moderately correlated (r = 0.46) to each other, and so was latitude to longitude (r = 0.62) (Fig. S.3). The positive correlation between latitude and longitude was likely a

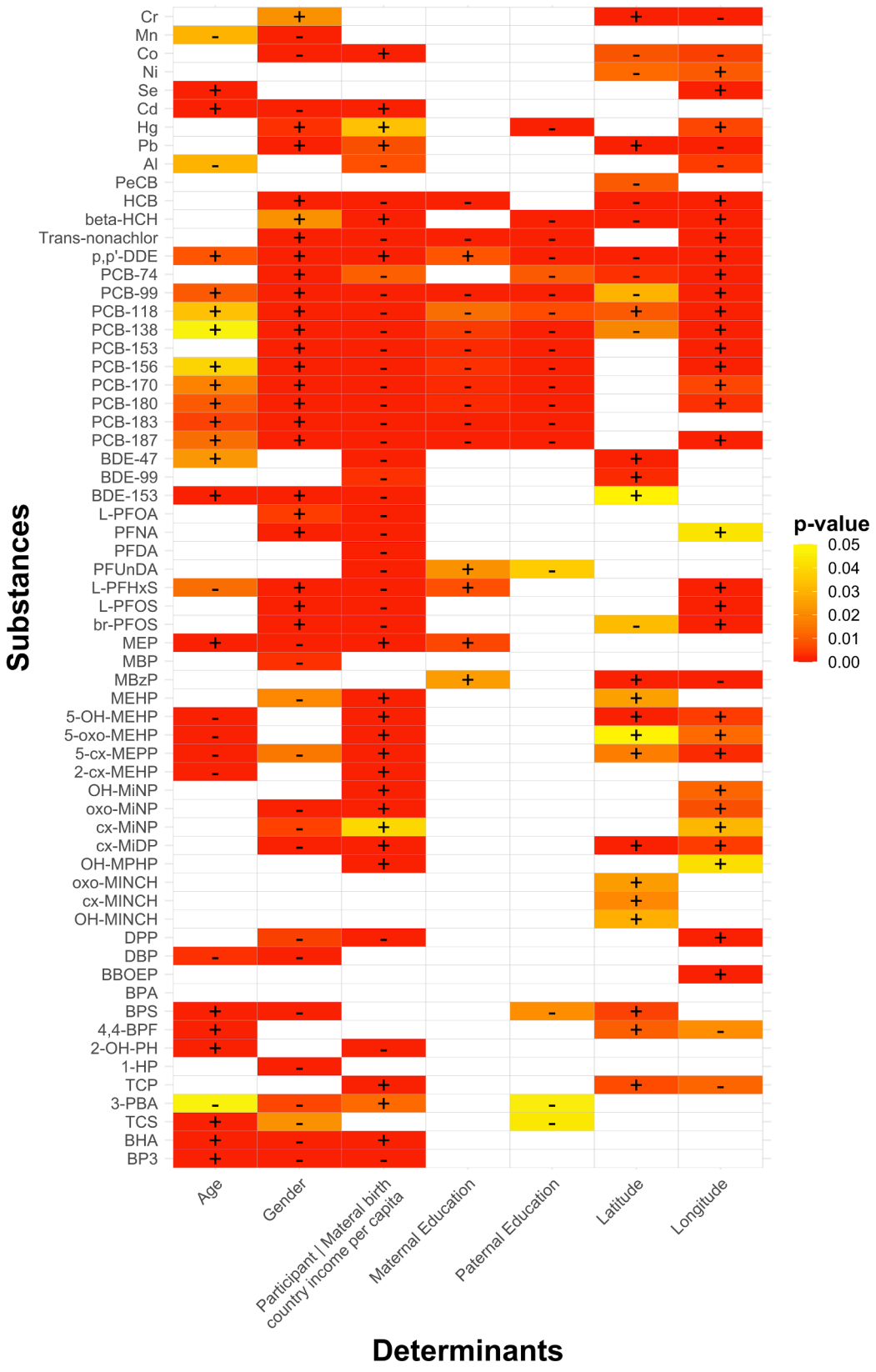

Fig. 2. Heat map demonstrating an overview of p-values for associations between substance concentrations and the demographic determinants obtained from the base ordinal regression models. The symbol within each cell indicates the direction of the association; if positive (+) with odds-ratio > 1 or negative (-) with odds-ratio < 1 (Tables S.2 - S.167). In the case of categorical variables, (i.e., gender, P|M birth country and parental education) the association direction is calculated from the odds-ratio comparing the lowest level (low|low per capita income; elementary school or none) with the highest level (high|high, higher education) or with female as the reference category (See 'Demographic determinants').

consequence of having two major metropolitan areas in Sweden (i.e., Malmö/Gothenburg) located in the south-west of the country whilst the other major population centres (e.g., Stockholm and Umeå) are generally located towards the east coast as you progress north through the country, as indicated by the distribution of the participants (Fig. 1). Participant/maternal birth country income per capita was weakly correlated with maternal education (r = 0.22) (Fig. S.3).

Participant/maternal birth country income per capita had the largest number of significant associations across all substances (N = 46), followed by gender (N = 41), longitude (N = 37), age (N = 29), latitude (N = 28), paternal education (N = 18), and maternal education (N = 16) (Fig. 2). Participant/maternal birth country income per capita in many cases tended to explain the largest part of the variation in substance concentrations compared to other covariates (Fig. S.2), suggesting that there are birth country-related inequities in exposures of Swedish adolescents.

The elements had varied combinations of significant determinants (Fig. 2). This is in concordance with the generally negligible-weak

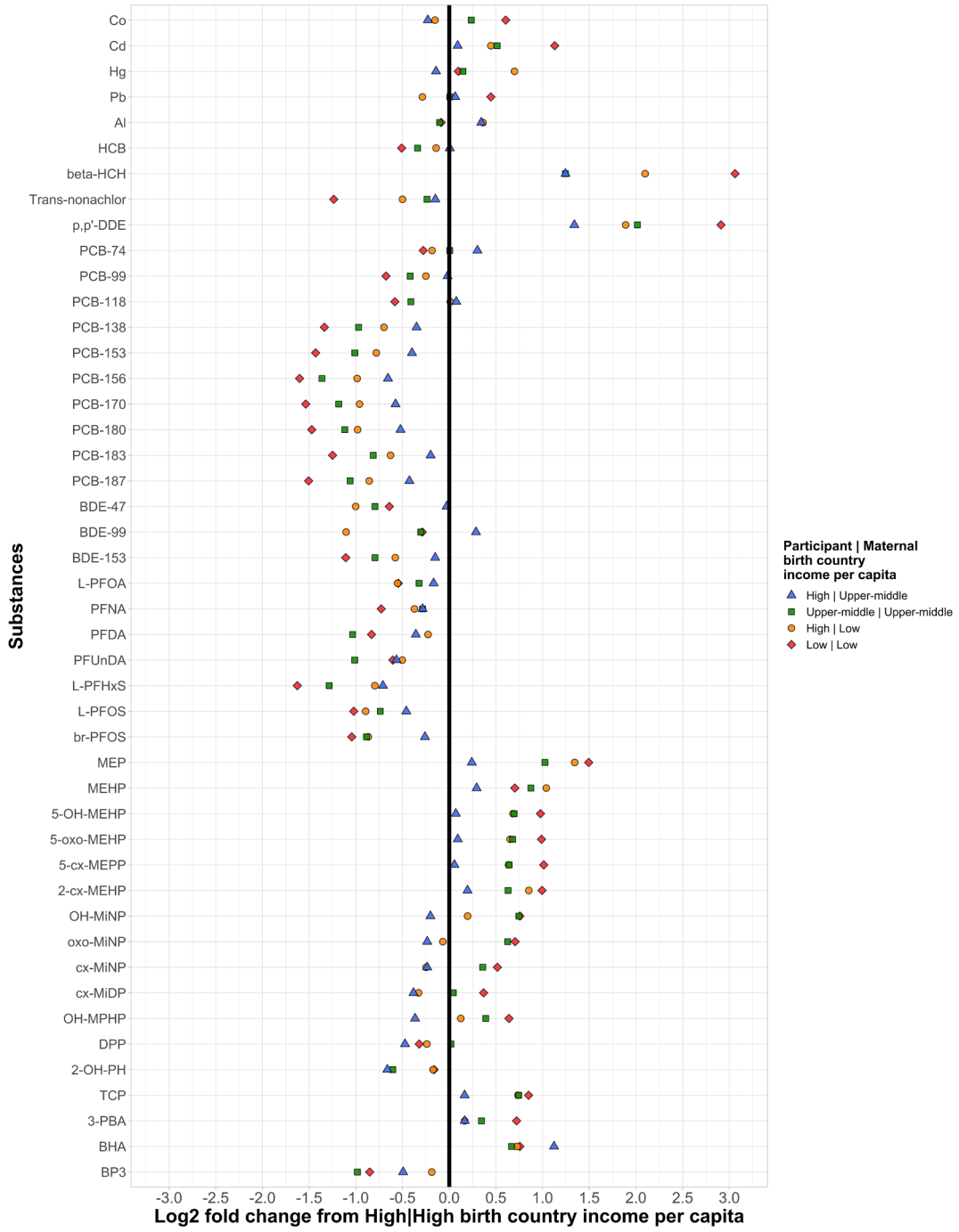

Fig. 3. Graph demonstrating the $\log_2$ converted fold-change of the estimated adjusted mean (EAM) substance concentrations for the different Participant/Maternal birth-country income per capita groups in comparison to the EAM concentration of the reference group: 'High | High income' (black line set at 0). Points to the left of the reference indicates negative fold-change whilst points to the right of the reference indicates positive fold-change. Adjusted for participant age, gender, maternal and paternal education level, and place of living (latitude and longitude). Only substances with significant association (p-values $\leq$ 0.05) with the Participant/Maternal birth-country income variable were included. Log_2 −0.5/0.5 corresponds to a fold-change of 1.4, −1/1 a 2-fold change, −2/2 a 4-fold change and −3/3 an 8-fold change.

correlations between element concentrations observed in RMA (Pineda et al., 2023). Chlorinated POPs showed a high degree of similarity of significant determinants, mainly; age, gender, participant/maternal birth country income per capita, parental education, and longitude (Fig. 2), in line with the moderate to very strong correlations between serum concentrations of the chlorinated POPs (Pineda et al., 2023). In contrast, the brominated POPs (PBDEs) and the fluorinated POPs (PFASs) showed a larger variation in significant determinants, which is most probably a reflection of differences in physicochemical properties, production, and use of these substances (Sharkey et al., 2020; Weber et al., 2011).

Our results suggests that at least some of the exposures of the adolescents to phthalates/phthalate alternatives, PFRs, pesticides, bisphenols and other rapidly metabolised/excreted substances on an individual basis occurred consistently over time, enough to be detected in single spot urine samples from all participants. This 'persistent' exposure made it possible to observe demography-dependent variation in urinary concentrations. As expected by the strong relationship between concentrations of urine metabolites with the same "mother substance" in RMA (Pineda et al., 2023), metabolites of the phthalates DEHP and DiNP, and phthalate alternative DiNCH, to a large degree shared significant determinants (Fig. 2). However, there were phthalate substance-dependent differences in determinants, suggesting differences in exposure sources among these plasticisers. As with the phthalates, metabolites of PFRs and PAHs, as well as the bisphenols, did not show consistent in-substance group determinant patterns (Fig. 2).

3.1. Participant/maternal birth country income per capita level

We found birth country disparities in adolescent body burdens for many of the substances (Fig. 3 and S.16). To the best of our knowledge, previous human adolescent biomonitoring studies have generally not considered the birth country of both the participant and the mother in their exposome analyses. Moreover, classification of birth countries according to national gross income per capita has rarely been used. Taken together the results strongly suggest that participant/maternal birth country income per capita level should be considered in future populations studies looking at the human chemical exposome and possible health effect outcomes (Figs. 3, S.2 and S.16).

Compared to the reference High | High group, EAM concentrations of Co, Pb, and Al among the different participant/maternal birth country groups were never more than 1.5-fold ($\log_2$ 0.6) higher or lower (Figs. 3 and S.16). The largest difference was observed for Cd with the 'Low | Low' group having a more than 2-fold higher EAM concentration than the 'High | High' group (Fig. 3). Cd has a very long half-life in the body (Nordberg et al., 2015), and therefore exposure of participants in their birth countries before moving to Sweden most probably contributed to the observed birth country relationships. A 'maternal effect' was, however, suggested since the EAM of Cd among high-income country participants became 1.4-fold higher ($\log_2$ 0.5) going from a high maternal birth country income to a low maternal birth country income (Fig. 3). Maternal transfer of Cd during foetal life and breast-feeding period is low (Vahter et al., 2002), suggesting that maternal birth country affected exposure after these periods. In German children/adolescents (GerES V), the geometric mean of Cd in urine was higher among 3–17 years old participants with two-sided immigration background (both participant and parents) than among those with no immigration background (Vogel et al., 2021). Direct comparisons between RMA and GerES results however remain uncertain as results in GerES were not adjusted for other demographic determinants. For Cd, Pb and Al the additional determinants included in the secondary regression models (Table S.1) did not markedly change the significance level of the birth country associations (Fig. S.9).

Due to the long half-lives of many of the halogenated POPs (Grandjean et al., 2008; Li et al., 2022; Ritter et al., 2009; Sjödin et al., 2020; Xu et al., 2020), exposure of participants in their birth countries is expected to be detectable for a long time after moving to Sweden. The PCB, PBDE and PFAS EAM concentrations in serum of 'High | High' participants were at most about 3-fold ($\log_2$ 1.6) higher than the 'Low | Low' group (Figs. 3 and S.16). In contrast, beta-HCH and p,p'-DDE (Fig. 4) showed a staggering 8-fold ($\log_2$ 3) higher EAM concentration among the 'Low | Low group compared to the 'High | High' group (Fig. 3). Similarly, GerES V participants with no immigration background had lower p,p'-DDE concentrations and higher PCB concentrations in plasma than those with a two-sided immigration background (Bandow et al., 2020). Higher DDT and HCH exposures have been reported in tropical and lower-income countries than in many industrialised high-income countries, whereas the reverse has been observed for PCBs (Berg et al., 2017; Haraguchi et al., 2009). Shorter half-lives of the lower-chlorinated PCBs and PBDEs (EFSA, 2005; Sjödin et al., 2020), resulting in a higher contribution of more recent exposure sources such as indoor environments (Johansson et al., 2003; Meyer et al., 2013; Wingfors et al., 2006) may at least partially explain the less obvious birth country relationships for these substances (Fig. 3).

Additionally, EAM PCB concentrations among high income-country participants decreased with decreasing maternal birth country income levels, suggesting a maternal effect, whilst the reverse was observed for beta-HCH and p,p'-DDE (Figs. 3 and S.16). Our results fit well with the observations that early life exposures to many lipid-soluble chlorinated POPs occurs via the placenta to the foetus and to infants via breast-feeding (Karmaus et al., 2001; Lignell et al., 2011), that persist as body burdens well into adult life (Gallo et al., 2011; Glynn et al., 2007; Lignell et al., 2011; Wesselink et al., 2019). The lower-chlorinated PCBs, PBDEs and PFASs with less pronounced adolescent participant/maternal birth country effects also showed less obvious maternal effects (Figs. 3 and S.16). The additional determinants in the secondary models (Table S.1) did not markedly affect the significance levels of the birth country relations of POPs (Fig. S.9).

The relationships between PFAS concentrations and birth country were similar as those reported by Nyström et al. (2023), generally with the highest EAM concentrations found in the 'High | High' group (Figs. 3 and S.16). Similarly, GerES V participants with no immigration background had higher PFOA concentrations in plasma than those with two-sided immigration background, whereas PFHxS and PFOS showed no associations (Duffek et al., 2020).

There were birth country-dependent disparities also in adolescent exposure to some metabolites of phthalates, PFRs, PAHs and the pesticides chlorpyrifos and pyrethroids, and the antioxidant BHA and the UV filter BP-3 (Figs. 3 and S.16). In the case of theses rapidly excreted/metabolised substances, it is likely that the participant/maternal birth country variable was a proxy for birth country-related household habits and living conditions in Sweden, including: diet, product usage, and housing, significantly affecting recurrent exposure among the adolescents. Metabolites of the phthalates DEP and DEHP all followed similar patterns in which the 'Low | Low' group had 2 to 3-fold ($\log_2$ 1–1.5) higher EAM concentrations compared to the 'High | High' group (Fig. 3). Results were more varied for the other phthalate metabolites but in general the 'Low | Low' group had the highest EAM concentrations. Similarly, GerES V participants with two-sided immigration background had higher DEP, DEHP, DiNP and DiDP metabolite concentrations in urine than those born in Germany with German born parents (Schwedler et al., 2020b). Although direct comparisons between RMA and GerES remain uncertain due to the non-adjusted immigration results in GerES, there appears to be similar exposure pathways involved in birth country inequalities of phthalate exposure of adolescents in Sweden and Germany. Moreover, in both RMA (Fig. 2) and GerES V, no birth country-related differences were observed in urine concentrations of BPA, and phthalate metabolites MBzP and MBP, and the metabolites of the phthalate alternative DiNCH (Schwedler et al., 2020a; Tschersich et al., 2021). The phosphorous flame-retardant metabolite DPP, PAH metabolite 2-OH-PH and the UV-filter BP3 generally showed a trend of highest EAM concentrations in the 'High | High' group, whereas the reverse was

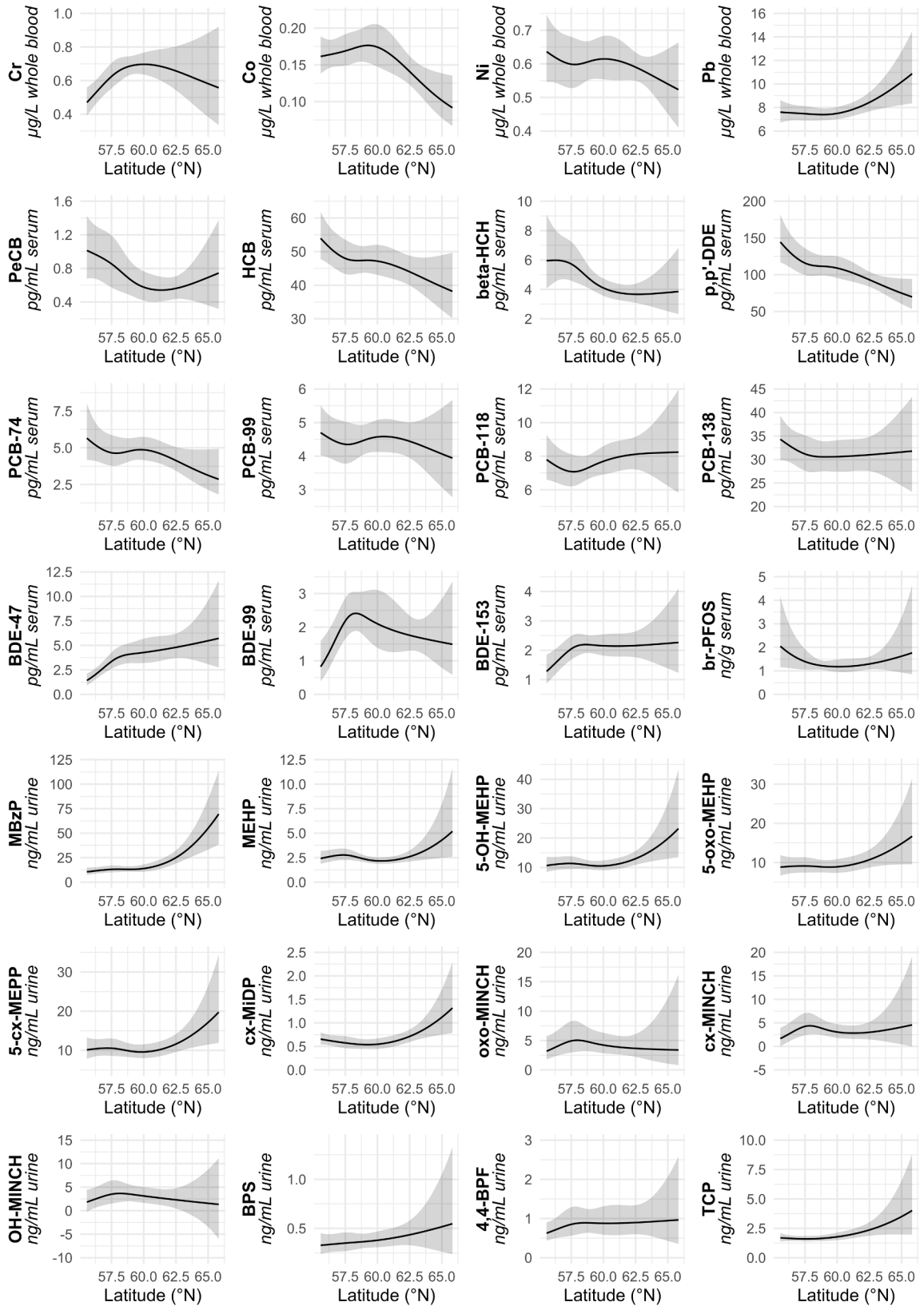

Fig. 4. Associations between concentrations of substances given at the normal scale and latitude of the home address. The solid line represents the estimated regression line whilst the shaded area represents the 95 % confidence interval. Determined in ordinal regression analyses with participant age, gender, maternal and paternal education level, place of living (longitude) and participant/maternal birth country per capita income as covariates in the regression models. Only substances with statistically significant associations with latitude ($p \leq 0.05$) are included in this figure.

evident for the pesticide metabolites TCP and 3-BPA and for the preservative BHA (Fig. 3). In GerES V no immigration status relationships were observed for 2-OH-PH and BP3. In RMA, inclusion of the additional determinants in the secondary models (Table S.1) did not markedly alter the significance levels of the birth country associations for phthalate and PAH metabolites, with the exception of cx-MiNP (Fig. S.9). The addition of ice cream consumption and season of sampling to the secondary model made the association non-significant, with ice cream consumption showing a significant association with cx-MiNP and greater share of the variance in the secondary model (Table S.127).

3.2. Gender, age and parental education

Many of the measured substances showed significant relations with gender, age and parental education (proxy of socioeconomic status) (Fig. 2) after adjustment of the associations with the other demographic variables. The differences in EAM concentrations between males and females were less than 1.5-fold ($\log_2$ 0.6) for many of the substances (Figs. S.4 and S.15). The largest gender inequality in EAM concentrations were observed for L-PFHxS (≈1.7-fold higher in males), br-PFOS (≈1.5-fold higher in males), the DEP metabolite MEP (≈1.7-fold higher in females), BHA (≈2-fold higher in females) and BP3 (≈2.3-fold higher in females) (Figs. S.4 and S.15). Food is a major source of exposure to some of the elements and POPs in Sweden (Livsmedelsverkets, 2017). Male adolescents having generally higher food consumption (Shomaker et al., 2010), may at least partially explain the higher concentrations of Hg, Pb, and halogenated POPs in RMA males compared to the female participants (Figs. S.4 and S.15). Due to these gender differences, a higher proportion of RMA males exceeded human biomonitoring guideline values (HBGVs) of Pb, HCB and PFOS compared to females (Pineda et al., 2023).

Direct comparisons of the RMA gender results with those from other studies are somewhat hampered by differences in adjustment for other demographic/life-style covariates. Nevertheless, Pb, chlorinated POPs and some PFASs were higher in males than females among the Flemish adolescents in FLEHS IV (Schoeters et al., 2022), as also reported for PFASs in a HBM4EU study with multiple EU countries included (also a subsample of RMA) (Richterová et al., 2023). This difference may in part be due to elimination of PFAS among females because of menstrual bleeding (Upson et al., 2022), although it has been speculated that other mechanistic differences in toxico-kinetics between males and females may be involved and initiated during puberty (Wu et al., 2015). Moreover, as in RMA, FLEHS IV females also had higher body burdens of Cd than males (Schoeters et al., 2022). PBDE concentrations in FLEHS were to a large degree non-detectable (Schoeters et al., 2022), whereas the use of estimated concentrations in the statistically analyses of RMA results suggested higher BDE-153 concentrations among males (Figs. 2 and S.15). In RMA, further adjustment for additional determinants in the secondary regression models (Table S.1) did not influence the p-values of the significant gender relations, except for Cd. The gender relation of Cd became non-significant, which appeared to be explained by gender differences in smoking (source of Cd exposure) and iron status (affects Cd toxicokinetics) (Bárány et al., 2005) (Fig. S.8; Table S.14).

Female participants had higher EAM concentrations of many substances measured in urine compared to males (Figs. 2, S.4 and S.15), suggesting day-to-day gender inequality in exposure. This could for instance entail higher use of cosmetics/hygiene products among female participants (Harley et al., 2016; Schoeters et al., 2022; Thakore, 2014; Wnuk et al., 2022), leading to the observed higher average female exposures to the phthalate DEP, the preservative BHA and the UV-filter BP3 (Fig. S.4). Similarly as in RMA, FLEHS IV females had higher concentrations of the phthalate metabolites MEP, MBP, and DEHP metabolites, and no gender association with MBzP (Fig. 2) (Schoeters et al., 2022). In contrast, FLEHS IV reported higher BPA concentrations among female participants whereas no gender relation of BPA was observed in RMA (Fig. 2). BPS concentrations were to a large degree not detectable in FLEHS IV, whilst in RMA, females had higher concentrations than males (Fig. S.4). Differences regarding associations between gender and PAH, PFR and pesticide metabolites were also observed between RMA (Fig. S.4) and FLEHS IV (Schoeters et al., 2022). Further adjustment for the additional determinants in the secondary regression models (Table S.1) did not markedly change the significance levels of the gender relations of the urine substances (Fig. S.8).

RMA participants had an age difference of on average 6 years and a maximum difference of 11 years. This may be considered as too small of an age difference for detection of significant relationships between substance concentrations and age. Nonetheless, a significant age-dependent increase in concentrations were observed for Se, Cd, p,p'-DDE, PCBs, BDE-47, BDE-153, the DEP metabolite MEP, BPS, 4,4-BPF, 2-OH-PH, TCS, BHA and BP3, whereas concentrations of Mn, Al, PFHxS, DEHP metabolites, the PFR metabolite DBP, and the pyrethroid metabolite 3-PBA decreased with increasing age (Fig. S.14). Among the elements, increases/decreases in EAM concentrations over the 11 years ranged from 1.1-fold to about 1.4-fold for Mn (decrease), Se (increase) and Al (decrease), whereas EAM concentrations of Cd increased ≈2-fold (Fig. S.14). The chlorinated and brominated POP EAM concentrations increased 1.2 to 1.9-fold, with BDE-153 showing the largest increase with age (Fig. S.14). Positive age associations of Cd and some chlorinated and brominated POPs could in part be due to the long half-lives of these substances in the human body, causing bioaccumulation with increasing age (Nordberg et al., 2022; Sjödin et al., 2020; Verner et al., 2009).

PFASs displayed an absence of significant trends with age (Fig. 2), despite having half-lives of several years (Li et al., 2022). The only exception was for PFHxS (Fig. S.14), which decreased with increasing age. In the context of RMA, the observed inverse relation with age is presumably influenced by the youngest participants (5th-graders) hailing from two schools situated in regions with elevated historical exposure to PFHxS through drinking water, specifically in Uppsala and Ronneby (Nyström et al., 2022). Consequently, 5th graders to a larger degree exceeded HBGVs of PFAS (Pineda et al., 2023).

When including the additional determinants in the secondary regression models (Table S.1), the positive age associations of PCBs became non-significant (Fig. S.7), suggesting that the additional significantly associated determinants; alcohol consumption (PCB-99, -118, -138, -183), BMI (PCB-99, -118, -138, -156, -170, -180, -183, -187), seafood consumption (PCB-99, -187), breastfeeding early in life (PCB-138, -156, -170, -180, -183, -187), and season of sampling (PCB-99, -118) to a large degree explained the age relations (Tables S.40-S.67). Additionally, the inverse age association of Al also became non-significant with the inclusion of ferritin levels and sampling season as additional variables (Fig S.7 & Table S.23).

The varying age relationships among substances measured in urine, even within chemical groups of similar substances, such as phthalates, (Fig. S.14) most probably reflect age-dependent differences in use of consumer products, dietary habits and living conditions affecting exposure (Bastiaensen et al., 2021b; Schwedler et al., 2020b; Tschersich et al., 2021). The largest increase in EAM concentrations during the 11-year age span was observed for BP-3 (≈4-fold), 4,4-BPF (≈4-fold) and MEP (≈3.5-fold) whilst the largest decrease was observed for the DEHP metabolites (≈1.4 – 1.8-fold) (Fig. S.14).

Unlike participant/maternal birth country income per capita level, we decided to keep the parental education determinants separated even though it could be argued that the maternal and paternal education levels are similar enough to potentially cause multicollinearity issues within the models. We justify the separation mainly due to there being only moderate correlation (Fig. S.3) and previous evidence indicating that there may be perceivable maternal and paternal relation differences at least within PFASs substances (Glynn et al., 2020), and therefore potentially other substance groups. The differences in EAM concentrations between parental 'higher education' and the other educational groups were not more than 1.5-fold (Figs. S.5, S.6, S.17 and S.18).

Participants with the highest maternal/paternal education levels generally had the highest EAM concentrations of chlorinated POPs (Figs. S.5 and S.6), similar to results observed in FLEHS IV when comparing to household education levels (Schoeters et al., 2022). In RMA, none of the elements and PBDEs showed relationships with parental education level, except Hg (paternal education) (Fig. S.5). Among PFASs and substances measured in urine, only PFUnDA, PFHxS, MEP, MBzP, BPS, 3-PBA and TCS were associated with maternal and/or paternal education levels (Fig. 2). In a HBM4EU study, adolescents with the highest household education level generally had the highest concentrations of PFOA, PFNA, PFHxS and PFOS (Richterová et al., 2023), which was not observed in the present study. As in the case of parental education levels, participant/maternal birth country income level is most probably a proxy for socio/economic status that could influence chemical exposure. In RMA, maternal education levels showed a weak positive correlation with participant/maternal birth country income levels, which may in part influence the mutually adjusted birth country and education level results. (Fig. S.3). In the HBM4EU the household education PFAS results were not adjusted for birth country income levels (Richterová et al., 2023).

Similar to RMA, Flemish adolescents with a high household education level had the lowest concentrations of MEP and the highest of PBA-3 (Schoeters et al., 2022). In RMA, HCB, L-PFHxS, MEP and MBzP were only related to maternal education and Hg, β-HCH, PCB-74, BPS, 3-PBA and TCS with paternal education (Figs. S.5 and S.6), suggesting diverging paternal and maternal influence on exposures to these substances. Similarly as for maternal education level in RMA, urinary concentrations of MEP and MBzP were lowest among the HBM4EU adolescents with high household education level (Govarts et al., 2023). However, in contrast to RMA, this was also reported for the other phthalate metabolites included (Govarts et al., 2023).

The additional determinants included in the secondary regression models (Table S.1), made the association between maternal education and PCB-118 non-significant, including the significant additional variables alcohol consumption, BMI, and season of sampling (Table S.46). Paternal education level associations with PCB-74, PCB-118 and PFUnDA turned non-significant (Fig. S.11). In these cases, the significant additional variables were alcohol consumption (PCB-74, -118), seafood consumption (PFUnDA), BMI (PCB-74, -118), being nursed early in life (PCB-74), and season of sampling (PCB-74, -118) (Tables S.40, S.46, S.87).

3.3. Latitude and longitude

The latitudinal trends were longitude-adjusted to 15.4 °East (Fig. 1), traversing Sweden through the regions Götaland, Svealand and Norrland from south to north with a trend of colder climate going north (Pettersson et al., 2020). Moreover, most arable land is found within Götaland and Svealand, declining in Norrland from around 60°N with forest land dominating the landscape going further north (Lindblom, 2008). The regions south of Norrland exhibit higher population density and industrial activity (Bustos et al., 2020; IF-Metall, 2014; OECD, 2020). This is reflected in the RMA study population, where a greater proportion resides below latitude 60°N (Fig. 1). Consequently, in some cases the latitudinal trend becomes increasingly uncertain as one moves further north in Sweden, as evidenced by inflated confidence intervals extending into Norrland (Fig. 4). Nevertheless, when looking at Fig. 4; Co, Ni, PeCB, HCB, β-HCH, p,p'-DDE, PCB-74 and PCB-99 showed a general trend of higher concentrations in southern Sweden compared to the north (Fig. 4). The reverse was indicated for Pb, BDE-47/-99/-153, MBzP, the DEHP metabolites, cx-MiDP, BPS and TCP (Fig. 4).

The longitudinal models were latitude-adjusted to 59°N (approximate to Stockholm) with the longitudinal *trans*-section of Sweden crossing from the Atlantic west coast to the Baltic Sea east coast of Sweden (Fig. 1). The longitudinal trends were most likely driven to an extent by the larger number of RMA participants living in the south of Sweden, with the urban Malmö and Göteborg regions in the southwest at the Atlantic coast, and the Stockholm region on the east coast of Sweden at the Baltic Sea (Fig. 1). Estimated longitudinal trends extending past ~18°E at the Baltic Sea coast are in some cases uncertain as noted by the inflated confidence intervals (Fig. S.19). A tendency of higher concentrations in the west than the east of Sweden was indicated for Cr, Pb and Al (Fig. S.19). The reverse was indicated for HCB, β-HCH, p,p'-DDE, some of the PCBs, L-PFHxS (to ~18°E), L- and br-PFOS, some DEHP metabolites, cx-MiDP, OH– MPHP, DPP and BBOEP (to ~18°E) (Fig. S.19).

Among the elements the largest contrast in EAM concentrations along the latitudinal gradient was observed for Co (≈2-fold) (Fig. 4). Plant-based foods is a major source of element exposure of the Swedish population (Livsmedelsverket, 2017) and the varying latitudinal trends for the elements (Fig. 4) may be due to regional differences in food consumption patterns of both domestically produced and imported foods, and/or regional differences in element concentrations in domestically produced food. Agricultural use of the fungicide HCB and insecticides HCH and DDT could contribute to the decreasing south-north trend of HCB, β-HCH, p,p'-DDE (Fig. 4), and for HCB also industrial/combustion pollution in the south (Chen et al., 2019). Among the chlorinated POPs, p,p'-DDE showed the most obvious difference in EAM concentrations decreasing ≈2.5-fold going south-to-north (Fig. 4). Similar gradients were observed in adipose tissue of food-producing bovines and pigs farmed within Sweden for HCB, p,p'-DDE and PCBs (Glynn et al., 2009). BDE-47 showed the largest difference between the lowest and highest latitudinal EAM concentration at ≈3.5-fold from south to north (Fig. 4). This corroborates the findings of a previous small study focusing on nursing women in Sweden which showed higher PBDEs concentrations in breast milk among women living in a northern Norrland municipality than in urban areas in southern/central Sweden (Glynn et al., 2011). The south to north trends of increasing concentrations observed for MBzP, DEHP metabolites and cx-MiDP (Fig. 4), may be due to a climate-dependent influence of exposure from the indoor environment (Bastiaensen et al., 2021a; Schwedler et al., 2020b). Moreover, a contributing factor could be the higher degree of urbanisation of Götaland and Svealand compared to Norrland affecting the type of housing in the regions. The largest difference in EAM concentration was observed for MBzP, being ≈5.5-fold lower in southern Sweden than in the north (Fig. 4).

As in the case of the south-north trends, elements showed diverging west-east gradients, further emphasising dissimilar exposure sources (Fig. S.19). Cr showed the largest west-east variation in EAM concentration, being ≈3-fold higher in the west (Fig. S.19). Almost all chlorinated POPs showed a tendency of lower concentrations in the western than in the eastern part of Sweden, in some cases with lowest concentrations in-between (Fig. S.19). The largest difference in EAM concentrations from west to east was observed for PCB-74 (≈8-fold), with a large uncertainty in the estimate for the eastern part of Sweden. The eastern Baltic Sea coast of Sweden is more highly contaminated with chlorinated POPs than the Atlantic west coast (Nyberg et al., 2015). Among the PFASs, west-east gradients varied somewhat, with the largest difference in EAM concentrations between west and east observed for br-PFOS (≈4-fold) with large estimate uncertainties in the east (Fig. S.19). In urine, MBzP, metabolites of DEHP and DiNP, cx-MiDP and OH-MPHP showed significant but varying mother substance group longitudinal trends (Fig. S.19). The differences in EAM concentrations going west to east ranged from ≈1.6-fold (some DEHP and DiNP metabolites) to ≈3.3-fold (OH-MPHP). As in the case of the latitudinal trends, the indoor environment may have influenced exposure to some phthalates. Unlike the latitudinal trends, climate-driven factors are less likely to be important for the longitudinal trends.

The additional determinants included in the secondary regression models (Table S.1) resulted in a non-significant latitudinal trend of Pb, PCB-99, PCB-118, and PCB-138 (Fig. S.12), including the significant determinants smoking (Pb), season of sampling (PCB-99, -118), alcohol

(PCB-99, -118, -138), seafood consumption (Pb, PCB-99), and BMI (PCB-99, -118, -138) within the models (Table S.20, S.43, S.46 and S.49), as well as breastfeeding early in life in the case of PCB-138 (Table S.49). Moreover, the longitudinal trend of PFNA and cx-MiNP became non-significant (Fig. S.13), with seafood consumption significantly associated with PFNA concentrations and ice cream consumption to cx-MiNP (Table S.81 and S.127).

4. Strengths and limitations

A major strength of the study is the RMA study population itself, with a population-based design encompassing the whole of Sweden (Fig. 1). The recruited population could be regarded as representative for the adolescent population in Sweden when looking at school type and size, education level and income of the parents, and with all types of municipalities represented (Moraeus et al., 2018). Moreover, the distribution of household incomes, parental education levels and country of birth of the adolescents (Sweden/outside Sweden) were similar when comparing RMA participants and the total population of school-attending adolescents in Sweden (Moraeus et al., 2018). However, limitations of representativeness include slightly more females than males among the participants, and lack of adolescents not attending school; mostly in the same age group as the 11th graders (Moraeus et al., 2018).

In addition to the targeted chemical analysis of a multitude of toxic substances from various chemical groups, the RMA survey also collected data on lifestyle and dietary habits. While self-reporting contributed to uncertainty in the statistical analyses, the collected data allowed for a comprehensive, representative and holistic analysis of the associations between toxic substance mixture burden within Swedish adolescents and socio-demographic factors. The use of ORMs enabled us to deal with the natural skewness of the substance concentration data and still incorporate outliers with extreme substance concentrations, without requiring transformation of the data.

Although the schools were selected to include a sample of adolescents representative of the Swedish population, due to the demographic distribution of Sweden, a larger proportion of the schools were located in the southern part of the country (Fig. 1). Moreover, RMA did not include data on the duration participants had lived in the study area and ultimately this factor could not be controlled for within the models. Regardless, we could predict latitudinal and longitudinal concentration patterns with a reasonable degree of confidence, suggesting this approach to be promising for studies of regional differences in human exposure to toxic substances outside of Sweden. Furthermore, we acknowledge there are some potential issues in using birth country income per capita as a determinant for exposure. Countries belonging to any given national income per capita bracket can be geographically distant from each other and also be in different stages of industrialisation despite having the same national income per capita classification. Additionally, we did not have data available on the time the participants and their mothers spent in their reported birth countries and are therefore unable to control for time not living in Sweden within the models.

There are some inherent issues with the analysis of substances in single spot urine samples. Namely, the substantially short half-lives of substances found in urine cause large day to day variation in concentrations (Philippat and Calafat, 2021). Nevertheless, in many cases we observed clear associations between substances measured in single spot urine samples and demographic determinants, suggesting that some exposure sources are likely to be consistent from day-to-day.

5. Conclusions

Our study offers unique insight into the chemical exposome, including various types of toxic substances, in a population undergoing a sensitive window of development (puberty). Our results show that there are gender, age, socio-economical (parental education), birth country and regional inequalities in toxic substance exposure among adolescents living in Sweden that should be considered in future risk management decisions aiming to reduce exposure. Further, the results show that UN sustainable development goal 10, “Reduce inequality within and among countries”, was highly relevant for the RMA adolescents in Sweden, since we identified participant/maternal birth country income as the most impactful determinant. The use of birth country income per capita level as a base for grouping of birth countries showed to be a promising path for future studies of this important factor in exposure assessment and relations to health outcomes. The UN goal 5, Gender equality, was also highlighted by our results since gender disparities in concentrations of substances varied between substances/substance groups, most likely due to gender differences in exposure, but in some cases likely also due to sex differences in toxicokinetics. The within-country aspect of Goal 10 is also an important goal to consider in Sweden since we observed latitudinal and longitudinal patterns for some substances/substance groups, which can aid in identification of regional populations at risk of elevated exposure. Additional studies are needed to better characterise the underlying factors which drive associations between contaminant exposure and socio-demographic status.

CRediT authorship contribution statement

Sebastian Pineda: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Sanna Lignell:** Writing – review & editing, Writing – original draft, Supervision, Resources, Data curation, Conceptualization. **Irina Gyllenhammar:** Writing – review & editing, Writing – original draft, Supervision, Resources, Data curation, Conceptualization. **Erik Lampa:** Writing – review & editing, Writing – original draft, Supervision, Software, Methodology. **Jonathan P. Benskin:** Writing – review & editing, Writing – original draft, Validation, Resources, Methodology, Data curation. **Thomas Lundh:** Writing – review & editing, Writing – original draft, Validation, Resources, Methodology, Data curation. **Christian Lindh:** Writing – review & editing, Writing – original draft, Validation, Resources, Methodology, Data curation. **Hannu Kiviranta:** Writing – review & editing, Writing – original draft, Validation, Resources, Methodology, Data curation. **Anders Glynn:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Investigation, Funding acquisition, Formal analysis, Conceptualization.

Declaration of competing interest

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

Data availability

The authors do not have permission to share data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2024.108618.

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