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Characterizing the adult exposome in men and women from the general population: Results from the EHES-LUX study

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ABSTRACT

Throughout life individuals are exposed to a large array of diverse environmental exposures (exposome). Hair analyses can assess chronic exposure to a large number of chemicals with less intra-variability than urine and blood. This is essential for studies that aim to achieve a global vision of the exposome. We aimed at characterizing the adult exposome by describing 175 environmental exposures and correlation patterns between and within exposure groups. A subsample of participants of the European Health Examination Survey, covering information on exposure to chemical pollutants in hair samples, were included in the present analysis (N = 442). Concentrations of micronutrients, lifestyle, home environment and socioeconomic information completed the exposome description and were obtained through blood analyses and questionnaires. We detected 29 persistent and non-persistent chemical pollutants in more than 70% of hair samples. Compared to women, men had higher concentrations of pesticides, lower concentrations of micronutrients (with the exception of vitamin A), and presented higher alcohol consumption. Across all exposures, a low median absolute correlation was found, 0.05 (5th − 95th centiles = 0.10, 0.20). We observed higher correlations and median correlations within exposure groups than between groups of exposure. The highest median correlation was observed between plasticizers (bisphenol A and S) in both men (0.50) and women (0.31). A 70% and 95% of cumulative variance was explained by 37 and 73 principal components respectively. We found a wide range of chemical exposures in hair samples of men and women. The adult exposome was complex and multidimensional. Future exposome studies should include hair as a matrix for characterizing exposure to multiple environmental chemicals.

Abbreviations: PBDE, Polybrominated flame retardants; PCBs, Polychlorinated biphenyls; OCs, Organochlorine compounds; OP, Organophosphate; BDE47, 2,2′,4,4′-tetrabromodiphenyl ether; PCB153, 2,2′,4,4′,5,5′-Hexachlorobiphenyl; PCB138, 2,2′,3,4,4′,5′-Hexachlorobiphenyl; PCB180, 2,2′,3,4,4′,5,5′-Heptachlorobiphenyl; β-HCH, β-Hexachlorocyclohexane; γ-HCH, γ-Hexachlorocyclohexane; p,p`-DDE, 1,1-dichloro-2,2-bis(4-chlorophenyl)ethane; PCP, Pentachlorophenol; 2-ClBA, 2-(4-chlorophenyl)-3-methylbutyric acid; Br2CA, Cis-3-(2,2dibromovinyl)-2,2-dimethylcyclopropane-carboxylic acid; Cl2CA, Cis-3-(2,2dichlorovinyl)-2,2-dimethylcyclopropane-carboxylic acid; ClCF3CA, 3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylic acid; 4F3PBA, 4-fluoro-3-phenoxybenzoic acid; 3-PBA, 3-phenoxybenzoic acid; IMPy, 2-isopropyl-4-methyl-6-hydroxypyrimidine; DMP, Di-methyl-phosphate; DMTP, Di-methyl-thiophosphate; DMDTP, Di-methyl-di-thiophosphate; DEP, Di-ethylphosphate; DETP, Di-ethyl-thiophosphate; DEDTP, Di-ethyl-di-thiophosphate; TCPy, 3,5,6-trichloro-2-pyridinol; PNP, P-Nitrophenol; 3Me4NP, 3-methyl-4-nitrophenol; MCPA, 4-chloro-2-methylphenoxyacetic acid; 2,4-D, 2,4-dichlorophenoxyacetic acid; MCPB, 4-(4chloro-2-methylphenoxy) butyric acid; 2,4-DB, 2,4-dichlorophenoxybutyric acid; HCB, Hexachlorobenzene; DMST, Dimethylsulftoluidide; BPA, Bisphenol A; BPS, Bisphenol S; GC–MS/MS, Gas chromatography-tandem mass spectrometry; HLCP, High Performance Liquid Chromatography.

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1. Introduction

Throughout life, individuals are exposed to a high number of environmental exposures such as environmental chemical, lifestyles, psychosocial, and physical factors. Grouped under the umbrella term exposome, these exposures are dynamic as they can occur and change over an individual's lifetime and places and, when interacted with genetic factors, can generate biological responses and contribute to the development of chronic diseases (Wild, 2005). A good characterization of the exposome at various stages of life (prenatal period, childhood, adolescence and adulthood) and among different population groups and places is necessary in order to better understand the health of the population and to identify possible at-risk groups with simultaneous exposure to multiple environmental factors. This approach has its limitations, however, since it is impossible to obtain a complete measure of all exposures. In Europe, it is estimated that more than 350,000 chemical entities (including complex chemical mixtures) are being used or produced (a number that keeps increasing), yet their harmful effects on health and the environment remains to be fully assessed (Wang et al., 2020). Moreover, the population is exposed to chemicals that are not produced anymore, but due to their high persistence in the environment, residues can still be found, e.g. registered banned pesticides found in food products and drinking water (Authority et al., 2021). Although the general population is usually exposed to low concentrations of persistent and non-persistent chemical pollutants, there is increasing evidence of their possible adverse effects on health (Palaniswamy et al., 2021; Seo et al., 2022).

Most studies to date have focused on the health risks of single chemicals and a reduced number of environmental exposures. In recent years, studies have started to assess a wider range of exposures by including a greater number of chemical pollutants (Iglesias-González et al., 2021; Peng et al., 2021) or multiple chemical and non-chemical environmental exposures (Chung et al., 2018; Patel and Manrai, 2015; Potera, 2014; Robinson et al., 2015; Tamayo-Uria et al., 2019; Vineis et al., 2017). This is because reducing environmental exposure to only a few exposure components offers a limited view, since it does not account for the possible combined effects that multiple exposures can have and therefore does not account for the complexity of the exposome and its possible health effects.

Unlike the genome, the whole exposome is difficult to characterize. This is not only because we do not know all of an individual's exposures, but also because the exposome can change throughout life, adding to the complexity of measuring it. As such, even partial descriptions of the exposome are useful and more studies now focus on describing parts of the exposome and prioritizing a multi-exposure approach that allows a better understanding of the relation to disease (Patel and Manrai, 2015; Potera, 2014; Robinson et al., 2015; Tamayo-Uria et al., 2019). Examples of studies following a multi-exposure approach include those focusing on early life periods such as the *Human Early-Life Exposome* project (HELIX) (Potera, 2014; Tamayo-Uria et al., 2019), the *Longitudinal Investigation of Fertility and the Environment* study (LIFE) (Chung et al., 2018), the *Infancia y Medio Ambiente* study (INMA) (Robinson et al., 2015), or throughout different life stages combining different cohorts, such as the *National Health and Nutrition Examination Survey* (NHANES) in the US (Patel and Manrai, 2015), or the EXPOsOMICS study in Europe (Vineis et al., 2017). In most cases, these studies have used biological fluids (urine and blood) for assessing chemical exposure. Urine and blood provide information for a short period after exposure and concentrations of biomarkers measured can be highly variable, depending on the moment at which the sample is collected (Casas et al., 2018; Li et al., 2019; Fäys et al., 2021). An effective alternative matrix to assess chemical exposure increasingly used in recent years is hair. Hair analyses, in addition to being a non-invasive method, can provide information on chronic exposure (e.g. up to several months depending on samples length). Moreover, contrary to fluids, chemicals' concentrations in hair are not affected regardless the moment when the sample was collected (Fäys et al., 2021). Moreover, compared to urine, hair analyses can provide a more complete information on exposure, as both hydrophobic (parent pesticides) and hydrophilic compounds (metabolites) can be detected in hair, while mainly hydrophilic metabolites are detected in urine (Hardy et al., 2021). This was particularly well illustrated in studies applying multiresidue methods (simultaneously targeting compounds from several chemical classes), in which the number of chemicals detected in hair was much higher than in urine, both in humans and in animals (Hardy et al., 2021; Appenzeller et al., 2017). Studies conducted on animal models also demonstrated significant relationship between the intake dose of chemicals and their concentration in hair, and strongly suggest that concentration of chemicals in hair is representative of the internal dose (Fäys et al., 2021; Appenzeller et al., 2017). Recent studies reported that a large number of chemicals were detected in hair samples from the general population such as pesticides, polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDEs), plasticizers, metals and polycyclic aromatic hydrocarbons in both adults and children (Iglesias-González et al., 2021; Peng et al., 2021; Iglesias-Gonzalez et al., 2020; Béranger et al., 2018). These studies demonstrated that hair could be a relevant matrix for analysing chronic and multiple chemical exposure, and hence a suitable tool for studying health effects of chemicals in the general population.

Since many of the measured exposures can be highly correlated, a first step is to describe them together and determine correlation patterns between and within exposure groups [Chung et al., 2018; Robinson et al., 2015; Tamayo-Uria et al., 2019; Patel and Ioannidis, 2014). This approach provides a more accurate understanding of the exposome, allowing to identify the optimal method and interpret more accurately the analysis of the association of the exposome with health outcomes (Patel and Manrai, 2015). As observed in different studies, the high dimensionality and complexity of the exposome makes it necessary to analyze and describe all components measured (instead of a reduced number of exposures) to better interpret the role that the exposome plays on health (Robinson et al., 2015; Tamayo-Uria et al., 2019; Patel and Ioannidis, 2014).

Our study aims at describing the exposome of a subsample of the Luxembourgish population that participated in the European Health Examination Survey (EHES-LUX), a population-based survey of adults aged 25–64 years (Bocquet et al., 2018). We analyzed 175 environmental exposures (152 persistent and non-persistent organic pollutants, lifestyles and socioeconomic characteristics) and described correlations and patterns of selected exposures in order to better understand the adult exposome structure, describe its multi-dimensionality and present possible differences between men and women.

2. Materials and methods

2.1. Study population and design

We analyzed data from EHES-LUX, a cross-sectional population-based survey that aims to characterize the general health status of the Luxembourg adult population aged 25–64 years. Institutionalized individuals were excluded. EHES-LUX was conducted between 2013 and 2015 and participants' health information was obtained from medical examinations, health questionnaires and biological samples (hair and blood). Details about the study population and design have been published elsewhere (Bocquet et al., 2018). In the present study, blood samples and questionnaires provided information about each participant's lifestyle, concentration of micronutrients from their diet, along with the home environment and socioeconomic information. Moreover, hair analyses provided information about chemical exposure. From the 1529 adults that participated in EHES-LUX, 21 pregnant women were excluded from the present analysis. From the 1508 participants, 1290 had available hair samples (reasons for not having hair samples included no hair or shaved (44%), refusal to provide a hair sample (15%), and other reasons such as hair too short (41%). From the 1290 participants with hair samples, 442 participants had enough hair mass for chemical exposure analysis and were included in the present study. Compared to the population of EHES-LUX, participants were older, had attained a higher level of education, and had a greater diversity in terms of their place of origin (**Table A1**). All participants signed an informed consent form. EHES-LUX was approved by the National Research Ethics Committee (1st CNER's notice N° 201205/07 Version 1.0, amended by CNER's notice N°201205/07 version 1.4) and notified to the National Commission for Data Protection (CNPD, date: 14/05/2012).

2.2. Exposome assessment

Overall, we analyzed 175 environmental exposures (152 persistent and non-persistent organic pollutants, diet, lifestyles, home environment and socioeconomic characteristics) through biomonitoring and questionnaires as described below. Exposure variables were selected based on preexisting data from EHES-LUX. Chemical pollutants analysed in the present study were defined by Beranger et al. (2018) and selected based on i) sales information (French Ministry of Agriculture, 2012), ii) the priority list of pesticides with potential risk to consumers (Nougadère et al., 2014), iii) information from the summary and recommendations of the national observatory of pesticide residues (Anses, 2010); and iv) the list of molecules of concern established in the context of the French biomonitoring strategy (Fillol et al., 2014). Moreover, in our study we also analyzed PCBs, PBDEs and Bisphenols due to the exposure relevance (Iglesias-González et al., 2021; Iglesias-Gonzalez et al., 2020; Peng et al., 2020).

2.2.1. Chemical exposure analyses in hair

A description of all chemical exposure variables measured is presented in **Table A2**. The list of persistent and non-persistent chemical pollutants included: 27 organochlorines, 12 organophosphates, 13 pyrethroids, 6 acid herbicides, 2 anilino-pyrimidines, 15 azoles, 2 benzamides, 9 carbamates, 2 carboxamides, 6 neonicotinoids, 2 oxadiazins, 2 phenylhydrazones, 4 strobilurins, 11 triazines, 13 ureas, 2 dinitroanilines and 12 miscelaneous pesticides. In addition, we also analysed 4 representative polychlorobiphenyls (PCBs), 6 polybrominated flame retardants (PBDEs) and 2 bisphenols (bisphenol A and S). We selected for further analyses 76 chemical pollutants with at least 30 quantifiable observations (values above the limit of detection (LOD). Moreover, two exposures had more than 40% of missing information and were not included in the analysis (e.g. acetamiprid and thiacloprid). For these reasons, of the total chemical pollutants measured (152), 74 were selected and included for analysis.

2.2.1.1. Hair collection and sample preparation. Trained nurses collected hair samples by cutting a hair-lock from each participant and then placing it in aluminum foil. For long hair, locks were cut and 8 cm starting from the root/scalp were extracted for analysis. In order to remove remaining sweat and hair care products that could interfere with the analysis, as well as any contaminants (organic impurities) externally deposited from the environment, it is essential to perform a washing step (Appenzeller, 2015). Hair samples were decontaminated using a validated protocol (Duca et al., 2014) of three successive washings: a first wash with SDS 5% (Sodium dodecyl sulphate from Sigma-Aldrich – ReagentPlus*L4509) for 5 min, followed by a second wash with ultrapure water (Millipore-AFS-8 system) for 1 min and a third and last wash using Methanol 100% (Biosolve-Analytical grade) for 5 min. During these washing steps, samples were agitated using a New Brunswick-G25 incubator shaker. After decontamination, hair strands were placed on soft paper wipes (Kimtech), gently dabbed and let to dry. Dried hair were pulverized for approximately 5 min (depending on the amount) with a ball mill (Retsch MM200) at 25 Hz.

2.2.1.2. Extraction and chemical analysis procedure. For each sample, 50 mg of hair powder were weighed in a 4 ml screw neck glass vial (La-Pha-Pack). Following the validated protocol of Hardy et al. (2015), 10 µl of internal standard (IS) solution (stable isotope labelled analogues) were added into each sample. IS solution concentrations, as well as their preparation, can be found in the corresponding publication of Hardy et al. (2015). Internal standards were purchased from Dr. Ehrenstorfer, Sigma-Aldrich, Toronto Research Chemicals (Toronto, ON, Canada), Cambridge Isotope laboratories (Tewksbury, MA, USA) and US Biological (Swampscott, MA, USA). The extraction was finally performed with the addition of 1 ml of an acetonitrile/water (Biosolve, ULC/MS grade) mixture, and with an overnight agitation at 350 rpm in a New Brunswick-G25 incubator shaker. The morning after, the samples were vortexed for 2 sec and centrifuged (Sigma 4–16 KS) for 10 min at 2800 × g. The supernatant was recovered and split into three parts for different analyses: i) 300 µl of the extract were transferred into a 10 ml screw neck glass vial (Supelco) suitable for solid-phase microextraction (SPME) analysis, targeting parent pesticides and other persistent organic pollutants. 7.6 ml of phosphate buffer 1 M were then added in each vial and the samples were placed for analysis by GC–MS/MS (gas chromatography-tandem mass spectrometry, Agilent Technologies). ii) 300 µl of the extract were transferred in a 5 ml screw neck vial (Supelco) for derivatization, targeting metabolite compounds. The extract was evaporated to dryness under a gentle nitrogen stream at 37 °C, followed by an addition of 100 µl of a PFBBr (2, 3, 4, 5, 6-pentafluorobenzyl bromide, Sigma Aldrich-101052)/acetonitrile (Biosolve-ULC/MS grade) mixture at a ratio 1:3, v/v. The derivatization process was, thereafter, performed in a heating chamber (Binder-FD53) for 30 min at 80 °C. After the derivatization step, the extract was evaporated to dryness following the above-mentioned conditions. The residue was reconstituted in 200 µl ethyl acetate (Biosolve-Analytical grade), and the final extract was placed for analysis by GC–MS/MS with a liquid injection of 2 µl. iii) 200 µl of the extract were transferred into a 2 ml screw neck vial (La-Pha-Pack) and evaporated to dryness, as described earlier. The residue was reconstituted in 50 µl of an ammonium acetate (Biosolve-ULC/MS grade) buffer /acetonitrile (Biosolve-ULC/MS grade) mixture at a ratio 3:1, v/v and transferred into a new micro-insert, placed in a 2 ml screw neck vial and set for analysis by liquid chromatography coupled with tandem mass spectrometry, LC-MS/MS (Waters Corporation) with an injection volume of 10 µl.

2.2.1.3. Instrumentation and conditions. The gas chromatograph (GC) system used (Agilent Technologies, 7890) was equipped with a HP-5MS capillary column (30 m, 0.25 mm I.D., 0.25 µm film thickness), a split/splitless injector, an oven (Agilent Technologies, 7890), an autosampler (Agilent Technologies, CTC Pal) and a shaker-incubator suitable for SPME. The GC system was coupled to a triple quadrupole mass spectrometer (Agilent Technologies, 7000A) in negative chemical ionization mode (NCI). The liquid chromatograph (LC) system (Waters Corporation) was equipped with a quaternary solvent manager, a sample manager and an ACQUITY system combined with a 15 cm T3 (silica-based, reversed-phase C18) column (Atlantis, Waters). A pre-column with a 0.2 µm filter (Waters) was also installed in order to remove any particulates and contamination present in the mobile-phase stream which was an ammonium acetate (Biosolve-ULC/MS grade) buffer (10 mM). The LC system was coupled to a triple quadrupole mass spectrometer Xevo TQS (Waters Corporation) in electrospray ionization mode (ESI).

2.2.2. Diet, lifestyle, home environment and socioeconomic variables

We included information on the following concentration of circulating micronutrients: vitamins A, D (as 25 hydroxyvitamin D) and E, folic acid, total carotenoids, and total phenolics. Details on the analysis procedure in serum and plasma samples are described in Ruiz-Castell et al. (2020). Daily fruit/vegetable consumption (number of portions per day) were also included in the present analyses. Information on home environment, lifestyle and socioeconomic characteristics were obtained from health questionnaires. Home environment included use of pesticides at home or in the garden, living at proximity to a heavy road (<100 m, 100–500 m, greater than500 m) and having pets. Lifestyle characteristics included passive/active tobacco smoking (no exposure, passive, active), aerobic physical activity (minutes per week), alcohol consumption (non-alcohol consumption, ≤ 6 drinks/week, greater than 6 drinks/week) and sleep duration (hours per night). Socioeconomic characteristics included education (primary, secondary tertiary), job status (working, not working), social support (low, moderate and good), immigration status (Luxembourg as country of birth, country of birth different from Luxembourg) and household crowding (number of people in the household). The variable social support was created using two questions: 1) "how much concern do people show in what you are doing?" 2) "how easy is it to get practical help from neighbors if you should need it?".

2.3. Statistical data analysis

Concentrations of chemical exposures with values below the LOD were considered left-censored and described using non-parametric methods (Kaplan-Meier) based on ranks, using the NADA package in R. Chemical exposures with values below the LOD were imputed using the Quantile Regression Imputation of Left-Censored data (QRILC) method (Wei et al., 2018a, b). The QRILC method drew at random one observation within a truncated distribution estimated by a quantile regression. To ensure that data would be positive, the data were log-transformed before imputation and transformed back after. After the imputation of values below the LOD, we imputed the rest of the missing values (without any value or information) using the chained equations method with the MICE package in R (Van Buuren, 2018). Data were assumed to be missing at random and the predictive mean matching was applied to perform imputations. For our analysis we used the first dataset imputed (Donders et al., 2006). Missing values of exposures ranged from 0.23% (e.g. PCB 153) to 5.4% (e.g. total phenolics) and 88.0% of participants had complete data on all exposure variables. We compared the original and imputed data sets (imputation of limits of detection and missing data) and observed similar descriptive values for selected variables (**Table A3**). For a better interpretation, we classified chemical pollutants into different groups related to their use: flame-retardants and industrial wastes, insecticides, herbicides, fungicides and plasticizers. We calculated spearman correlations (for continuous variables), polyserial correlations (for categorical and continuous variables), and polychoric correlations (for categorical variables) between exposures in the overall sample and separately by men and women. In addition, to summarize correlation strengths we calculated the median absolute correlation by group of exposures and between groups of exposure. Both correlation matrices and median absolute correlation distributions were calculated for men and women. Median absolute correlations were presented using heat maps (median absolute correlation by group of exposures in diagonal values and between groups of exposure in values off the diagonal) and boxplots. Using Gephi software (Bastian et al., 2009), we performed network analysis separately on men and women to visualize the correlations between exposures. Exposures that were more correlated were closer in the network and node's size increased with number of correlations (e.g. the higher the number of correlations of one exposure with other exposures, the bigger the node). We presented all correlations higher than 0.2. Socioeconomic, lifestyle, diet, home environment and health differences between men and women were analysed using a Chi-square test (for categorical variables) or Spearman's test (to avoid assuming normality). We used the Wilcoxon test to compare chemical concentrations between men and women. All p-values were FDR (false discovery rate) corrected through Benjamini Hochberg procedure. An alpha < 0.05 was considered as statistical significance. Finally, we used principal component analysis (PCA) to i) compare groups' exposure levels and reduce data dimensionality and ii) to quantify data dimensionality. We did both PCA analyses in the overall sample and separately for men and women. For the first PCA, we calculated principal component scores for each exposure group. For the second PCA, we included exposures from all groups and presented the number of components needed to explain different percentages of cumulative variance (50%, 70%, 90% and 99.5%). All analyses were performed using the R statistical software.

3. Results

3.1. Characteristics of the study population and exposure values

Our study finally included 94 exposure variables measured in 442 individuals, including 74 chemical pollutants in hair; 3 exposures on the home environment; 8 diet related variables; 4 exposures on lifestyle; and 5 socioeconomic exposure variables (Table 1).

Distributions of the selected variables are presented in **Fig A1**. Nearly half of participants were women (49%). Participants' median age was 46 years old for both men and women. Women reported consuming less alcohol and more fruits and vegetables per day and, compared to men, presented higher concentrations of vitamin D, folic acid and total carotenoids. Men presented higher values of cardiometabolic risk factors (Table 2) and higher concentrations of vitamin A.

3.2. Both currently used and banned pesticides were detected in our study samples (***Table A2***)

Of the 152 chemical pollutants measured in hair, 40 chemicals were detected in more than 50% of the samples. Bisphenol A and S, DETP, TCPy, PNP, 3-PBA, HCB, 2,4-D, carbendazim, 1-(3,4-dichlorophenyl) urea and prosulfocarb were detected in 100% of the samples. We observed that bisphenols presented the highest concentration levels. We also observed differences in hair concentrations of chemical pollutants between men and women (**Table A4**). In most cases, men presented higher concentrations of insecticides, herbicides, fungicides and plasticizers. *Correlations within and between exposure groups (median correlations)*.

In the overall sample, we observed higher correlations between exposures from the same group than between exposures from different groups (**Table A5**). Nearly 70% of all correlations above 0.4 were within groups of exposure (vs 30% between groups of exposures) and only those within groups of exposures were statistically significant. We observed higher values of median correlation within an exposure group (Fig. 1, diagonal values) than between groups of exposure in both men and women (Fig. 1, all other values off the diagonal). Within most exposure groups, median correlation values were below 0.2 in both men and women. In men, the highest median correlation was observed between plasticizers (r = 0.5) and the lowest between banned herbicides (r = 0.03). In women, we observed the highest median correlation between bisphenols (r = 0.31) and the lowest between banned insecticides (r = 0.06) (Fig. 1 **and** Fig. 2). The median absolute correlation of all exposure variables for men was 0.07 (5th − 95th centiles, 0.00–0.77), and for women was 0.06 (5th − 95th centiles, 0.00–0.74) (**Table A6**).

3.3. Network visualization

We observed some differences between men and women when performing a separate visualization through correlation networks between exposures (Fig. 3). Although in both men and women the network was quite compact within a one big cluster composed of links between chemical pollutants, in women we observed a second cluster formed mainly by dietary variables, lifestyle and socioeconomic variables. Three currently used fungicides (difenoconazole, pyrimethanil and propiconazole) also formed a small separated cluster. In men, we observed that the main cluster composed by chemical pollutants included also socioeconomic variables such as education, job status and social support and dietary variables such fruit and vegetable

Table 1
Selected exposome variables description.

Exposure group		Exposure variables		Matrix	Method	Number of variables
Flame retardants and industrial wastes		**PBDE**	BDE47	Hair	GC–MS/MS	4
		PCBs	PCB (153, 138, 180)			
Insecticides	**Banned**	**OCs**	β-HCH, γ-HCH, p,p'-DDE, α-endosulfan, β-endosulfan, *trans*-chlordane, PCP	Hair	GC–MS/MS	7
	Currently used	**Pyrethrinoides**	Permethrin, Cyfluthrin, Cypermethrin, Deltamethrin	Hair	GC–MS/MS	25
		Pyrethrinoides metabolites	2-ClBA, Br_2CA, Cl_2CA, $ClCF_3CA$, 4F3PBA, 3-PBA			
		OP metabolites	IMPy, DMP, DMTP, DMDTP, DEP, DETP, DEDTP, TCPy, PNP, 3Me4NP			
		Phenylpyrazoles	Fipronil, Fipronil sulfone			
		Carbamates	Propoxur			
		Neonicotinoids	Imidacloprid			
		Other	Spinosyn A			
Herbicides	**Banned**	**OCs**	Metazachlor, Metolachlor	Hair	GC–MS/MS	3
		Dinitroanilines	Trifluraline			
	Currently used	**Herbicides acides**	Mecoprop, MCPA, Dichlorprop, 2,4-D, MCPB, 2,4-DB	Hair	GC–MS/MS	18
		Carboxamides	Diflufenican			
		Oxadiazines	Oxadiazon			
		Triazines	Prometryn, Terbutryn,			
		Ureas	Diuron, Fenuron, Isoproturon, 1-(3,4-dichlorophenyl)-3-methylurea, 1-(3,4-dichlorophenyl)urea,			
		Other	Dimethachlor, Prosulfocarb, Lenacil			
Fungicides	**Banned**	**OCs**	HCB	Hair	GC–MS/MS	2
		Other	DMST			
	Currently used	**Anilinopyrimidine**	Pyrimethanil	Hair	GC–MS/MS	13
		Azoles	Difenoconazole, Imazalil, Myclobutanil, Prochloraz, Propiconazole, Tebuconazole, Thiabendazole			
		Carbamates	Carbendazim,			
		Carboxamides	Boscalid			
		Strobilurins	Azoxystrobin, Pyraclostrobin, Trifloxystrobin			
Plasticizers			BPA, BPS	Hair	GC–MS/MS	2
Home environment			Use of pesticide (at home or in the garden)	Questionnaire	Interview	3
			Proximity to heavy road			
			Pets (allergens)			
Diet			Daily fruit consumption	Questionnaire	Interview	8
			Daily vegetable consumption			
			Vitamin A	Serum	HPLC combined with	
			Vitamin E		UV–Vis detection	
			Vitamin D		Chemiluminescent	
			Folic acid		enzymatic antibody-based method	
			Total carotenoids		Micro-extraction procedure with heptane	
			Total phenolics		Folin Ciocalteu assay	
Lifestyle			Passive/active tobacco	Questionnaire	Interview	4
			Aerobic physical activity			
			Alcohol consumption			
			Sleep duration			
Socioeconomic			Education	Questionnaire	Interview	5
			Job status			
			Social Support			
			Immigration Status			
			House Crowding			

Abbreviations: **PBDE**: Polybrominated flame retardants; **PCBs:** Polychlorinated biphenyls; **OCs:** Organochlorine compounds; **OP:** Organophosphate; **BDE47:** 2,2′,4,4′-tetrabromodiphenyl ether; **PCB153**: 2,2′,4,4′,5,5′-Hexachlorobiphenyl; **PCB138**: 2,2′,3,4,4′,5′-Hexachlorobiphenyl; **PCB180**: 2,2′,3,4,4′,5,5′-Heptachlorobiphenyl; **β-HCH**: β-Hexachlorocyclohexane; **γ-HCH**: γ-Hexachlorocyclohexane**; p,p'-DDE**: 1,1-dichloro-2,2-bis(4-chlorophenyl)ethane; **PCP**: Pentachlorophenol; **2-ClBA**: 2-(4-chlorophenyl)-3-methylbutyric acid**; Br2CA**: Cis-3-(2,2dibromovinyl)-2,2-dimethylcyclopropane-carboxylic acid**; Cl2CA**: Cis-3-(2,2dichlorovinyl)-2,2-dimethylcyclopropane-carboxylic acid**; ClCF3CA**: 3-(2-chloro-3,3,3-trifluoro-1-propenyl)-2,2-dimethylcyclopropanecarboxylic acid**; 4F3PBA**: 4-fluoro-3-phenoxy-benzoic acid**; 3-PBA**: 3-phenoxybenzoic acid**; IMPy**: 2-isopropyl-4-methyl-6-hydroxypyrimidine**; DMP**: Di-methyl-phosphate**; DMTP**: Di-methyl-thiophosphate**; DMDTP**: Di-methyl-di-thiophosphate**; DEP**: Di-ethylphosphate**; DETP**: Di-ethyl-thiophosphate**; DEDTP**: Di-ethyl-di-thiophosphate**; TCPy:** 3,5,6-trichloro-2-pyridinol**; PNP**: P-Nitrophenol**; 3Me4NP**: 3-methyl-4-nitrophenol**; MCPA**: 4-chloro-2-methylphenoxyacetic acid**; 2,4-D**: 2,4-dichlorophenoxyacetic acid**; MCPB**: 4-(4chloro-2-methylphenoxy) butyric acid**; 2,4-DB**: 2,4-dichlorophenoxybutyric acid**; HCB**: Hexachlorobenzene**; DMST**: Dimethylsulftoluidide**; BPA**: Bisphenol A**; BPS**: Bisphenol S; **GC–MS/MS**: Gas chromatography-tandem mass spectrometry; **HLCP**: High Performance Liquid Chromatography.

Table 2
Socioeconomic, lifestyle, diet, home environment and health characteristics stratified by sex (N = 442).

Exposure variables	Men (N = 226) Median (P25, P75), N (%)	Women (N = 216) Median (P25, P75), N (%)	P-value [a] Exposure variables
Age, *years*	46.76 (37.23, 55.85)	46.48 (38.00, 55.35)	0.87
Socioeconomic			
Education			0.35
Primary	61 (26.99)	58 (26.85)	
Secondary	64 (28.32)	77 (35.65)	
Tertiary	101 (44.69)	81 (37.50)	
Job status			0.07
Not working	43 (19.03)	60 (27.78)	
Working	183 (80.97)	156 (72.22)	
Social Support			0.07
Low	8 (3.54)	1 (0.46)	
Moderate	100 (44.25)	86 (39.81)	
Good	118 (52.21)	129 (59.72)	
Immigration Status	132 (58.41)	132 (61.11)	0.70
Crowding, *num people in the household*	3.00 (2.00, 4.00)	3.00 (2.00, 4.00)	0.28
Lifestyle			
Passive/active tobacco			0.17
No exposure	135 (59.73)	150 (69.44)	
Passive	31 (13.72)	21 (9.72)	
Active	60 (26.55)	45 (20.83)	
Aerobic physical activity, min/*week*	70.00 (0.00, 240.00)	60.00 (0.00, 180.00)	0.28
Alcohol consumption			<0.001
Non-alcohol consumptiom	52 (23.01)	119 (55.09)	
≤ 6 drinks/week	71 (31.42)	65 (30.09)	
greater than 6 drinks/week	103 (45.58)	32 (14.81)	
Sleep duration, *hours/night*	7.29 (6.57, 8.00)	7.29 (6.57, 8.00)	0.15
Diet			
Daily fruit consumption, *portions/day*	1.00 (0.00, 2.00)	2.00 (0.00, 3.00)	<0.001
Daily vegetable consumption, *portions/day*	1.00 (0.00, 2.00)	1.50 (0.00, 2.00)	<0.0001
Vitamin A, *μg/dL*	71.45 (62.00, 82.00)	63.00 (52.00, 74.00)	<0.0001
Vitamin E, *μg/dL*	1195 (1010, 1427)	1189 (999.0, 1358)	0.58
Vitamin D, *ng/mL*	18.50 (13.00, 25.78)	23.50 (16.18, 31.25)	<0.0001
Folic acid, *nmol/L*	11.35 (8.10, 15.48)	14.10 (10.55, 20.65)	<0.0001
Total carotenois, *μmol/L*	1.13 (0.84, 1.60)	1.37 (0.88, 1.89)	0.07
Total phenolics [b], *mg/L*	2585 (2427, 2746)	2585 (2459, 2766)	0.87
Home environment			
Use of pesticide (home or garden)	59 (26.11)	57 (26.39)	0.95
Proximity to heavy road			0.95
<100 *m*	120 (53.10)	115 (53.24)	
100 m-500 *m*	77 (34.07)	76 (35.19)	
greater than500 *m*	29 (12.83)	25 (11.57)	
Pets (allergens)	92 (40.71)	82 (37.96)	0.70
Cardiometabolic conditions			
Abdominal obesity [c]	123 (54.42)	136 (62.96)	0.14
Hypertension [d]	78 (34.51)	45 (20.83)	<0.01
Prediabetes and diabetes [e]	96 (42.48)	52 (24.07)	<0.001
Hypertriglyceridemia [f]	91 (40.27)	48 (22.22)	<0.001
Low HDL-C [g]	103 (45.58)	90 (41.67)	0.77

[a] Chi-square test (for categorical variables) or Wilcoxon test (for continuous variables) with the Benjamini-Hochberg correction. [b] Folin Ciocalteuassay. [c] Waist circumference ≥ 94 cm for men and ≥ 80 cm for women. [d] Systolic/diastolic blood pressure of ≥ 140/90 mm Hg, self-report of a physician diagnosis, or on antihypertensive medication. [e] Fasting glucose of ≥ 100 mg/dL, self-report of physician diagnosis, or on antidiabetic medication. [f] Triglycerides ≥ 150 mg/dL or on medication. [g] High-density lipoprotein cholesterol < 40 mg/dL for men and < 50 mg/dL for women or being on related medication.

consumption. Unlike women, in men we did not observe a lifestyle cluster. Moreover, variables such as physical activity were not in contact with other exposures. In men, we observed two small cluster composed with i) three dietary variables (vitamin A, vitamin E and total carotenoids) connected to the main cluster of chemical pollutants through fipronil and ii) vitamin D, folic acid and alcohol consumption connected to the main cluster of chemical pollutants through bisphenol S and carbendazim.

3.4. Adult exposome dimensionality

Table A7 shows results from PCA (first principal component) obtained for each exposure group in order to compare patterns of groups of exposures between men and women in a reduced dimensionality form. Flame-retardants and industrial wastes were highly loaded with PCB138, PCB 153 and PCB180 in both men (-0.57, −0.59 and −0.56 respectively) and women (-0.61, −0.60 and −0.52, respectively). Exposure to banned insecticides were mainly explained by γ-HCH, α-endosulfan and PCP in men (loadings 0.56, 0.45 and 0.57 respectively) and women (loadings 0.64, 0.42 and 0.60 respectively). Exposure to banned herbicides was highly loaded in men with metolachlor and trifluraline in both men and women. The home environment exposure was highly loaded in men with pesticide use (0.68) and pets (0.64) and with pesticide use (0.48), proximity to heavy road (-0.69) and pets (0.54) in women. All four lifestyle exposures were highly loaded in men (0.53 for aerobic physical activity, −0.42 for alcohol consumption, 0.70 for sleep and 0.24 for tobacco exposure) and women (0.55 for aerobic physical activity, −0.60 for alcohol consumption, −0.36 for sleep, -and 0.45 for tobacco exposure). The socioeconomic environment exposure was highly loaded in men with immigration status (-0.62), education (-0.64), and job status (-0.39). In women, socioeconomic exposures were mainly explained by immigration status (-0.63), education (-0.54) and social support (0.46). Table 3 presents results from a PCA with all exposure groups to reduce the dimensionality of the exposome. We did not observe differences between men and women. In both men and women, 32 and 65 principal components (34% and 68% of the original exposome) explained respectively 70% and 95% of cumulative variance of all data set.

4. Discussion

In our study, we measured a significant number of environmental exposures in the general adult population, including a detailed and exhaustive list of chemical pollutants detectable in hair. Moreover, we presented correlations and patterns of a large number of exposures between and within exposure groups as a first step to understand and describe differences in the adult exposome between women and men. Correlations and median correlations were higher within exposure groups than between groups of exposure. Correlations were similar in both men and women, although with some slightly different patterns. Of the 94 variables that we included in our analysis of the exposome, 79 were required in men and 80 in women to explain 99.5% of the accumulated variance, indicating the complexity of the exposome and the difficulty of reducing its components.

Compared with a previous study measuring concentrations of pollutants in hair in the general population of Luxemburg in 2007–2008 (Peng et al., 2021) (7 years difference with the present study), detection rates were generally higher in our study and some chemical pollutants not detected in 2007 were now detected (e.g. DMDTP and DEDTP). For example, in our study, detection rates of PCB reached more than 90% for PCB180 (compared to 44% 7 years earlier) and OPs such as DETP and DMP detection rates reached more than 90% (compared to < 30% 7 years earlier). This could be explained by a better detection sensitivity in our study compared to 2007–2008 data. When compared to previous studies using the same analytical method for measuring concentration of pollutants in hair, detection rates of bisphenols were similar to those

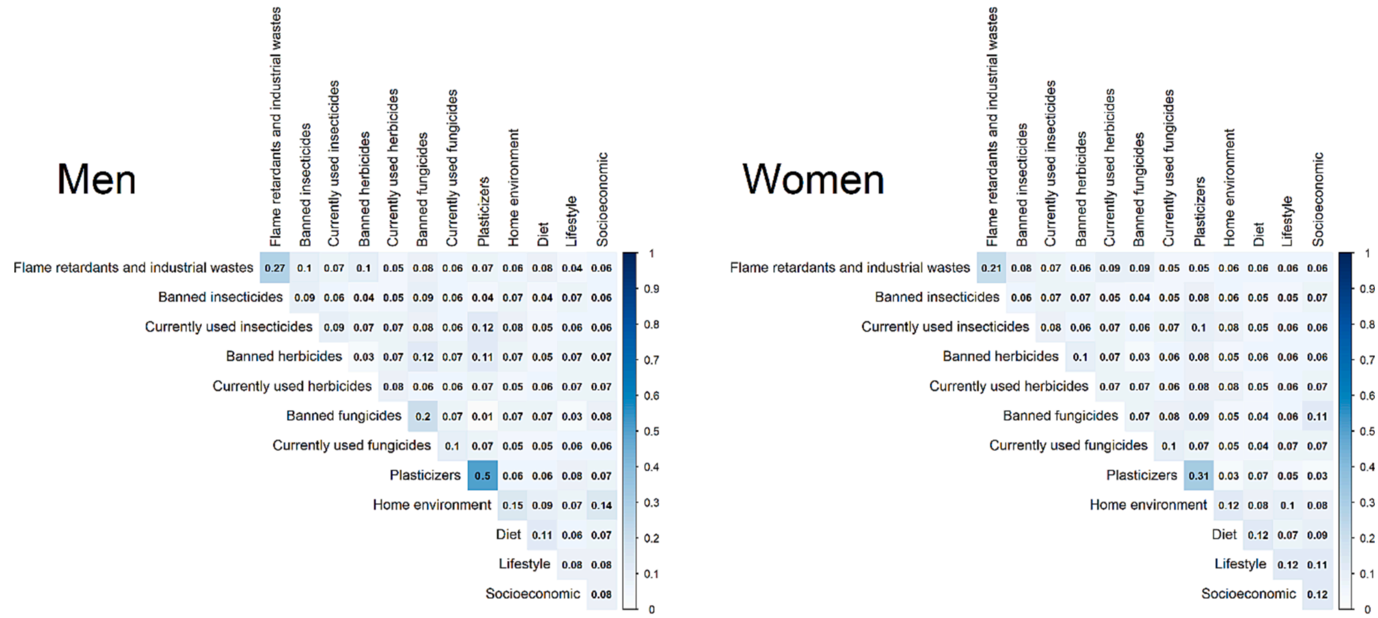

Fig 1. Median absolute correlations by group of exposure (in diagonal) and between groups of exposure (off the diagonal) in men and women.

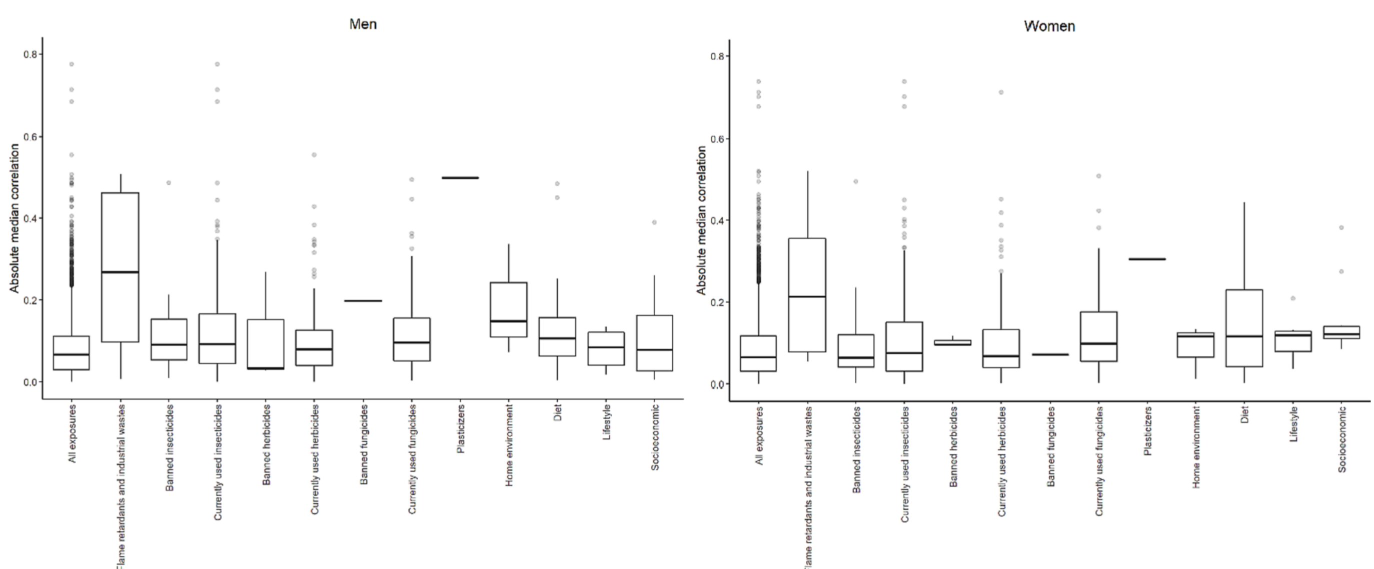

Fig 2. Absolute median correlations by group of exposure in men and women.

observed by Peng et al. (2021) in French volunteers (nearly 100%) (Iglesias-González et al., 2021) and OPs had detection rates similar to those observed by (Peng et al., 2020) in a sample of women in China (Peng et al., 2020).

Among those detected, we found pesticides that were banned in Europe before 2008 due to their negative health/environmental effects (Commission, 2022). In some cases, banned pesticides were detected in almost all samples, which requires particular attention. For example, HCB, trifluraline and γ-HCH were detected in more than 95% of samples in our study as also observed in Luxembourg in 2007 (Peng et al., 2021), in France in 2011 and 2017 (Iglesias-González et al., 2021; Béranger et al., 2018) and in China in 2016 (Peng et al., 2020). Moreover, in the present study, the number of chemical pollutants detected in each participant ranged from 27 to 61. This indicated that the general population was exposed simultaneously to multiple chemical pollutants, and the need to control possible cumulative effects as well as continue controlling not only those currently being in use, but also those that are banned. Although detection rates were different when compared with previous studies on hair analyses, with some exceptions, concentrations in hair were similar to those measured in a recent study in a sample of 134 adults in France (Iglesias-González et al., 2021) and in the population of Luxembourg in 2007 (Peng et al., 2021), although lower than those reported in 2011 in pregnant women in France (Béranger et al., 2018).

We observed differences in exposure variables between men and women, mainly in hair concentrations of chemical pollutants, circulating micronutrients and alcohol consumption. Chemical concentrations were mostly higher in men than in women, as observed in previous studies (Salihovic et al., 2012; Hardell et al., 2010; Porta et al., 2010). This may be due to different factors such as occupation, diet or physiological differences. Alcohol consumption was lower in women and fruit and vegetable consumption, as well as concentrations of micronutrients were higher in women compared to men (with the exception of vitamin A), suggesting different lifestyle behaviours. Indeed, several studies

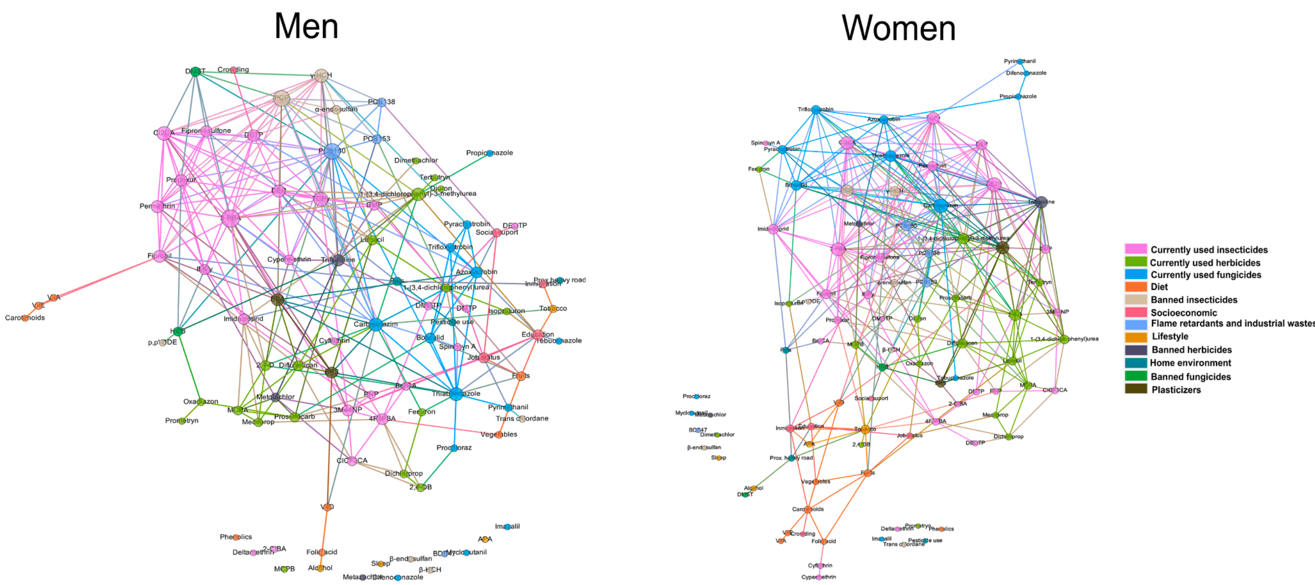

Fig 3. Exposome network visualization separately on men and women. Exposures that were more correlated were closer in the network and node's size increased with number of correlations. Correlations presented were higher than 0.2.

Table 3
Principal Component Analysis by exposure groups and across exposures (N = 442).

Exposure group	N° of variables	Total N° of PCs required to explain % of cumulative variance				Men N° of PCs required to explain % of cumulative variance				Women N° of PCs required to explain % of cumulative variance			
		50	70	95	99.5	50	70	95	99.5	50	70	95	99.5
All exposure variables	94	21	37	73	88	18	32	65	79	18	32	65	80
Flame retardants and industrial wastes	4	2	2	4	4	2	2	4	4	2	2	4	4
Banned insecticides	7	3	4	6	7	3	4	6	7	3	5	7	7
Currently used insecticides	25	7	12	19	21	7	12	21	25	7	12	21	25
Banned herbicides	3	2	2	3	3	2	2	3	3	2	2	3	3
Currently used herbicides	18	6	10	16	18	6	9	16	18	6	9	16	18
Banned fungicides	2	1	2	2	2	1	2	2	2	1	2	2	2
Currently used fungicides	13	5	7	11	12	5	7	12	13	5	7	12	13
Plasticizers	2	1	1	2	2	1	1	2	2	1	2	2	2
Home environment	3	2	2	3	3	2	2	3	3	2	2	3	3
Diet	8	3	5	7	8	3	5	8	8	3	5	8	8
Lifestyle	4	2	3	4	4	2	3	4	4	2	3	4	4
Socioeconomic	5	2	3	5	5	2	3	5	5	2	3	5	5

have reported a higher consumption of fruits/vegetables in women compared to men, which is reflected by higher concentrations of circulating carotenoids and vitamin E as markers of a plant-rich diet (Bohn et al., 2017; Lee-Kwan et al., 2017).

Exposures were low to moderately correlated, though in some cases correlations between exposures were high, especially between exposures of the same group. This result is similar to what was observed in previous studies using the same analytical methodology for chemical exposure analysis in the general population (Iglesias-González et al., 2021; Béranger et al., 2018; Peng et al., 2020). Although our study presented a higher number of chemical exposures compared to Peng et al. (2021), the observation of similar concentrations and correlations of chemical exposures in both studies at different periods in the same country, shown reproducibility. When focusing on home environment, as expected fipronil (and its metabolite fipronil sulfone) was positively correlated with having pets since fipronil is used against ticks, fleas and ear mites in pets (e.g. dogs and cats) (Page, 2008). Country of birth other than Luxembourg was positively correlated with tobacco exposure and negatively correlated with physical activity, suggesting less healthy lifestyle habits in the immigrant population. Results from the population based survey EHIS in 2014 shown that participants whose country of birth was different from Luxembourg reported higher percentages of tobacco consumption and lower percentages of aerobic physical activity (European Commission. Eurostat, 2022), which was in line with our results. Positive correlations observed between diet variables were also expected, as healthier diets with an increased consumption of fruits and vegetables will result in higher concentrations of circulating micronutrients (Fulton et al., 2016).

Values of correlations and median correlations within exposure groups were higher than between groups of exposure, as also previously reported (Robinson et al., 2015; Tamayo-Uria et al., 2019; Vineis et al., 2017). Nevertheless, in our study, median correlations within exposure groups were generally lower than those observed in other populations using other matrices for analyses, but correlation values were similar between exposure groups (Robinson et al., 2015; Tamayo-Uria et al., 2019). This was observed even when grouping chemical pollutants differently (e.g. by chemical composition). This result is important since we presented correlations in different populations and used different analytical methodologies as previously reported. This means that in our study, for example, a possible negative health effect of banned fungicides would probably not be affected/strongly influenced by banned herbicides in women or with plasticizers in men (no confounded effect), and thus it would not be necessary to adjust for them. However, here we only presented a small part of possible exposures, which does not mean that if we include others such as traffic, noise, light or green spaces (not available in EHES-LUX), that they would not be highly correlated with each other.

To reduce the dimensionality of the exposome, we calculated the number of components needed to explain 95% and 99.5% of its cumulative variance. We observed that from the 94 variables measured, 65 (in both men and women) and 79 (men)/80 (women) variables explained respectively 95% and 99.5% of the total variance. This is in line with previous results that described a highly complex exposome with little redundancy (Robinson et al., 2015; Tamayo-Uria et al., 2019; Patel and Ioannidis, 2014). This indicated that each exposure had a unique contribution and possibly an independent effect from the rest of the exposures. This supports what other authors suggested that when studying the effect of the exposome on health outcomes, reducing the number of components, is not the right approach (Robinson et al., 2015; Tamayo-Uria et al., 2019).

A limitation of the present study was the cross-sectional design of the study that did not allow causal inference nor described changes in the exposome through different life periods (only at one point in time). Another limitation was the sample size of individuals with chemical exposure measurement. Only 34% of the total number of participants with hair samples had enough material to analyze chemical exposure. Although health and exposure information came from a population-based survey, only 29% of participants had information on chemical exposure and therefore results must be considered with caution, as they were not representative of the population of Luxembourg. Nevertheless, the present study included a high number of chemical pollutants analyzed simultaneously, which allowed us to have a more complete overview of the exposure to chemicals than previous studies. We used hair samples instead of blood or urine, and while some chemicals detected in blood/urine are less detectable in hair, this is also the case the other way around. This matrix specificity of some chemicals seems to be due to physicochemical properties and pharmacokinetics of the target biomarkers. Nevertheless, although this “matrix-specific-chemical” effect concerns all types of matrices including hair, studies conducted with multi-residue methods simultaneously targeting chemicals from several classes in paired samples (hair vs urine vs blood) reported a significant higher number of chemicals detected in hair (Hardy et al., 2021; Appenzeller et al., 2017). Moreover, the use of hair samples helped us to remove the short-term variability of chemicals present in other matrices used (Casas et al., 2018; Fäys et al., 2021). The choice of hair as matrix remains promising to investigate chemical exposome, although more validation is needed in the future. We did not compare between groups at risk, such as immigrants, especially important in a population like Luxembourg, in which half of the population is of foreign origin. Finally, there was a lack of other exposome characteristics such as built environment, air pollution or noise as well as the internal exposome, which was not available in EHES-LUX. However, we were able to complete the exposome description with information from the home environment, diet, lifestyle and socioeconomic characteristics.

5. Conclusion

We found a wide range of chemical exposures in hair samples of men and women. In our study, exposures (chemical pollutants, micronutrients, lifestyle, home environment and socioeconomic information) were low to moderately correlated and correlations within exposure groups were higher than between groups of exposure. The adult exposome was complex and multidimensional with many components, which means that reducing environmental exposure to a few exposure components only may thus offer a too limited view. This overview is a first report of the correlation profile of the exposome in the adult population of Luxembourg, which can be used to better interpret future analyses on exposure effects. Future exposome studies should include hair as a matrix for characterizing exposure to multiple environmental chemicals….

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CRediT authorship contribution statement

Maria Ruiz-Castell: Conceptualization, Investigation, Resources, Writing – original draft, Writing – review & editing, Visualization, Project administration, Funding acquisition. **Gwenaëlle Le Coroller:** Conceptualization, Methodology, Software, Formal analysis, Data curation, Writing – review & editing. **Achilleas Pexaras:** Validation, Methodology, Writing – review & editing. **Giovana M. Ciprián:** Methodology, Software, Formal analysis. **Guy Fagherazzi:** Writing – review & editing. **Torsten Bohn:** Validation, Methodology, Writing – review & editing. **Léa Maitre:** Writing – review & editing. **Jordi Sunyer:** Writing – review & editing, Supervision. **Brice M.R. Appenzeller:** Conceptualization, Methodology, Writing – review & editing, Supervision.

Declaration of Competing Interest

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

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Appendix A. Supplementary data

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References

ANSES (Agence française de sécurité sanitaire de l’environnement et du travail)., Exposition de la population générale aux résidus de pesticides en France: Synthèse et recommandations du comité d’orientation et de prospective scientifique de l’observatoire des résidus de pesticides, ORP **2010**. (Available: https://www.ecophytopro.fr/data/exposition_population_generale_pesticides_2010_vdef.pdf. Last access: 13 May 2022).

Appenzeller, B.M., 2015. Hair analysis for the biomonitoring of human exposure to organic pollutants. In *Hair analysis in clinical and forensic toxicology*. Elsevier 179–196.

Appenzeller, B.M.R., Hardy, E.M., Grova, N., Chata, C., Faÿs, F., Briand, O., Schroeder, H., Duca, R.C., 2017. Hair analysis for the biomonitoring of pesticide exposure: comparison with blood and urine in a rat model. Arch Toxicol 91 (8), 2813–2825.

Authority, E. F. S.; Carrasco Cabrera, L.; Medina Pastor, P., The 2019 European Union report on pesticide residues in food. *EFSA Journal* **2021,** *19*, (4), e06491.

Bastian, M.; Heymann, S.; Jacomy, M. In Gephi: an open source software for exploring and manipulating networks, Proceedings of the international AAAI conference on web and social media, **2009**, pp 361-362.

Béranger, R., Hardy, E.M., Dexet, C., Guldner, L., Zaros, C., Nougadère, A., Metten, M.A., Chevrier, C., Appenzeller, B.M.R., 2018. Multiple pesticide analysis in hair samples of pregnant French women: Results from the ELFE national birth cohort. Environ Int 120, 43–53.

Bocquet, V., Barre, J., Couffignal, S., d’Incau, M., Delagardelle, C., Michel, G., Schlesser, M., Stranges, S., Kuemmerle, A., Ruiz-Castell, M., 2018. Study design and characteristics of the Luxembourg European Health Examination Survey (EHES-LUX). BMC Public Health 18 (1), 1169.

Bohn, T., Desmarchelier, C., Dragsted, L.O., Nielsen, C.S., Stahl, W., Rühl, R., Keijer, J., Borel, P., 2017. Host-related factors explaining interindividual variability of carotenoid bioavailability and tissue concentrations in humans. Mol Nutr Food Res 61, (6).

Casas, M., Basagaña, X., Sakhi, A.K., Haug, L.S., Philippat, C., Granum, B., Manzano-Salgado, C.B., Brochot, C., Zeman, F., de Bont, J., Andrusaityte, S., Chatzi, L., Donaire-Gonzalez, D., Giorgis-Allemand, L., Gonzalez, J.R., Gracia-Lavedan, E., Grazuleviciene, R., Kampouri, M., Lyon-Caen, S., Pañella, P., Petraviciene, I., Robinson, O., Urquiza, J., Vafeiadi, M., Vernet, C., Waiblinger, D., Wright, J., Thomsen, C., Slama, R., Vrijheid, M., 2018. Variability of urinary concentrations of non-persistent chemicals in pregnant women and school-aged children. Environ Int 121 (Pt 1), 561–573.

Chung, M.K., Kannan, K., Louis, G.M., Patel, C.J., 2018. Toward Capturing the Exposome: Exposure Biomarker Variability and Coexposure Patterns in the Shared Environment. Environ Sci Technol 52 (15), 8801–8810.

European Commission. Directorate-General for Health and Food Safety., EU Pesticide Database. (Available: https://ec.europa.eu/food/plants/pesticides/eu-pesticides-database_en. Last access 12 April 2022).

Donders, A.R.T., Van Der Heijden, G.J., Stijnen, T., Moons, K.G., 2006. A gentle introduction to imputation of missing values. J Clin Epidemiol 59 (10), 1087–1091.

Duca, R.C., Hardy, E., Salquèbre, G., Appenzeller, B.M., 2014. Hair decontamination procedure prior to multi-class pesticide analysis. Drug Test Anal 6 (S1), 55–66.

European Commission. Eurostat., Health Database **2014**. (Available: https://ec.europa.eu/eurostat/web/health/data/database?node_code=hlth_det. Last access 16 May 2022).

Fäys, F., Hardy, E.M., Palazzi, P., Haan, S., Beausoleil, C., Appenzeller, B.M.R., 2021. Biomonitoring of fast-elimination endocrine disruptors - Results from a 6-month follow up on human volunteers with repeated urine and hair collection. Sci Total Environ 778, 146330.

Fillol, C., Garnier, R., Mullot, J.-U., Boudet, C., Momas, I., Salmi, L.R., Vandentorren, S., 2014. Prioritization of the biomarkers to be analyzed in the French biomonitoring program. Biomonitoring 1 (1).

French Ministry of Agriculture ., Qu'est-ce que la Banque National des Ventes distributeurs(BNV-d) ? **2012**. (Available: http://agriculture.gouv.fr/sites/minagri/files/documents/La_BNV-d_cle8978db.pdf. Last access: 13 May 2022).

Fulton, S.L., McKinley, M.C., Young, I.S., Cardwell, C.R., Woodside, J.V., 2016. The Effect of Increasing Fruit and Vegetable Consumption on Overall Diet: A Systematic Review and Meta-analysis. Crit Rev Food Sci Nutr 56 (5), 802–816.

Hardell, E., Carlberg, M., Nordström, M., van Bavel, B., 2010. Time trends of persistent organic pollutants in Sweden during 1993–2007 and relation to age, gender, body mass index, breast-feeding and parity. Sci Total Environ 408 (20), 4412–4419.

Hardy, E.M., Duca, R.C., Salquebre, G., Appenzeller, B.M., 2015. Multi-residue analysis of organic pollutants in hair and urine for matrices comparison. Forensic Sci Int 249, 6–19.

Hardy, E.M., Dereumeaux, C., Guldner, L., Briand, O., Vandentorren, S., Oleko, A., Zaros, C., Appenzeller, B.M.R., 2021. Hair versus urine for the biomonitoring of pesticide exposure: Results from a pilot cohort study on pregnant women. Environ Int 152, 106481.

Iglesias-Gonzalez, A., Hardy, E.M., Appenzeller, B.M., 2020. Cumulative exposure to organic pollutants of French children assessed by hair analysis. Environ Int 134, 105332.

Iglesias-González, A., Schaeffer, C., Dahm, G., Hardy, E.M., Pexaras, A., Palazzi, P., Appenzeller, B.M.R., 2021. Comprehensive Assessment of Local Population Chemical Exposome by Combination of Organic Pollutant- and Metal-Multi-Residue Analysis in Hair. *Expo*. Health.

Lee-Kwan, S.H., Moore, L.V., Blanck, H.M., Harris, D.M., Galuska, D., 2017. Disparities in State-Specific Adult Fruit and Vegetable Consumption - United States, 2015. MMWR Morb Mortal Wkly Rep 66 (45), 1241–1247.

Li, A.J., Martinez-Moral, M.P., Kannan, K., 2019. Temporal variability in urinary pesticide concentrations in repeated-spot and first-morning-void samples and its association with oxidative stress in healthy individuals. Environ Int 130, 104904.

Nougadère, A., Merlo, M., Héraud, F., Réty, J., Truchot, E., Vial, G., Cravedi, J.-P., Leblanc, J.-C., 2014. How dietary risk assessment can guide risk management and food monitoring programmes: The approach and results of the French Observatory on Pesticide Residues (ANSES/ORP). Food Control 41, 32–48.

Page, S.W., 2008. Antiparasitic drugs. Small animal clinical pharmacology 2, 198–260.

Palaniswamy, S., Abass, K., Rysä, J., Odland, J., Grimalt, J.O., Rautio, A., Järvelin, M.R., 2021. Non-occupational exposure to pesticides and health markers in general population in Northern Finland: Differences between sexes. Environ Int 156, 106766.

Patel, C.J., Ioannidis, J.P., 2014. Placing epidemiological results in the context of multiplicity and typical correlations of exposures. J Epidemiol Community Health 68 (11), 1096–1100.

Patel, C.J., Manrai, A.K., 2015. Development of exposome correlation globes to map out environment-wide associations. Pac Symp Biocomput 20, 231–242.

Peng, F.J., Hardy, E.M., Mezzache, S., Bourokba, N., Palazzi, P., Stojiljkovic, N., Bastien, P., Li, J., Soeur, J., Appenzeller, B.M.R., 2020. Exposure to multiclass pesticides among female adult population in two Chinese cities revealed by hair analysis. Environ Int 138, 105633.

Peng, F.J., Emond, C., Hardy, E.M., Sauvageot, N., Alkerwi, A., Lair, M.L., Appenzeller, B.M.R., 2021. Population-based biomonitoring of exposure to persistent and non-persistent organic pollutants in the Grand Duchy of Luxembourg: Results from hair analysis. Enviro Int 153, 106526.

Porta, M., Gasull, M., Puigdomènech, E., Garí, M., Bosch de Basea, M., Guillén, M., López, T., Bigas, E., Pumarega, J., Llebaria, X., Grimalt, J.O., Tresserras, R., 2010. Distribution of blood concentrations of persistent organic pollutants in a representative sample of the population of Catalonia. Environ Int 36 (7), 655–664.

Potera, C., 2014. The HELIX Project: tracking the exposome in real time. Environ Health Perspect 122, (6), A169.

Robinson, O., Basagaña, X., Agier, L., de Castro, M., Hernandez-Ferrer, C., Gonzalez, J.R., Grimalt, J.O., Nieuwenhuijsen, M., Sunyer, J., Slama, R., Vrijheid, M., 2015. The Pregnancy Exposome: Multiple Environmental Exposures in the INMA-Sabadell Birth Cohort. Environ Sci Technol 49 (17), 10632–10641.

Ruiz-Castell, M., Le Coroller, G., Landrier, J.F., Kerkour, D., Weber, B., Fagherazzi, G., Appenzeller, B.M.R., Vaillant, M., Bohn, T., 2020. Micronutrients and Markers of Oxidative Stress and Inflammation Related to Cardiometabolic Health: Results from the EHES-LUX Study. Nutrients 13, (1).

Salihovic, S., Lampa, E., Lindström, G., Lind, L., Lind, P.M., van Bavel, B., 2012. Circulating levels of persistent organic pollutants (POPs) among elderly men and women from Sweden: results from the Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS). Environ Int 44, 59–67.

Seo, S. H.; Choi, S. D.; Batterman, S.; Chang, Y. S., Health risk assessment of exposure to organochlorine pesticides in the general population in Seoul, Korea over 12 years: A cross-sectional epidemiological study. *J Hazard Mater* **2022,** *424*, (Pt B), 127381.

Tamayo-Uria, I., Maitre, L., Thomsen, C., Nieuwenhuijsen, M.J., Chatzi, L., Siroux, V., Aasvang, G.M., Agier, L., Andrusaityte, S., Casas, M., de Castro, M., Dedele, A., Haug, L.S., Heude, B., Grazuleviciene, R., Gutzkow, K.B., Krog, N.H., Mason, D., McEachan, R.R.C., Meltzer, H.M., Petraviciene, I., Robinson, O., Roumeliotaki, T., Sakhi, A.K., Urquiza, J., Vafeiadi, M., Waiblinger, D., Warembourg, C., Wright, J., Slama, R., Vrijheid, M., Basagaña, X., 2019. The early-life exposome: Description and patterns in six European countries. Environ Int 123, 189–200.

Van Buuren, S., 2018. Flexible imputation of missing data. CRC Press.

Vineis, P., Chadeau-Hyam, M., Gmuender, H., Gulliver, J., Herceg, Z., Kleinjans, J., Kogevinas, M., Kyrtopoulos, S., Nieuwenhuijsen, M., Phillips, D.H., 2017. The exposome in practice: design of the EXPOsOMICS project. Int J Hyg Environ Health 220 (2), 142–151.

Wang, Z., Walker, G.W., Muir, D.C.G., Nagatani-Yoshida, K., 2020. Toward a Global Understanding of Chemical Pollution: A First Comprehensive Analysis of National and Regional Chemical Inventories. Environ Sci Technol 54 (5), 2575–2584.

Wei, R., Wang, J., Jia, E., Chen, T., Ni, Y., Jia, W., 2018. GSimp: A Gibbs sampler based left-censored missing value imputation approach for metabolomics studies. PLoS Comp Biol 14 (1), e1005973.

Wei, R., Wang, J., Su, M., Jia, E., Chen, S., Chen, T., Ni, Y., 2018. Missing value imputation approach for mass spectrometry-based metabolomics data. Sci Rep 8 (1), 1–10.

Wild, C.P., 2005. Complementing the genome with an "exposome": the outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiol Biomarkers Prev 14 (8), 1847–1850.