Science of the Total Environment 1003 (2025) 180691

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

Chemical pollutant mixtures associated with metabolic health: Results from the European Health Examination Survey in Luxembourg

Jesús Martínez-Gómez[a,b,1], Giovana M. Ciprián[a,1], Gwenaëlle Le Coroller[c], Achilleas Pexaras[d], Rodrigo Fernández-Jiménez[b,e,f], Brice M.R. Appenzeller[g], Maria Ruiz-Castell[a,*]

[a] Department of Precision Health, Socio-economic, Environmental Health and Health Services Research Unit, Luxembourg Institute of Health, 1A-B, rue Thomas Edison, L-1445, Strassen, Luxembourg

[b] Cardiovascular and Health Imaging Laboratory, Centro Nacional de Investigaciones Cardiovasculares (CNIC), C. de Melchor Fernández Almagro, 3, 28029, Madrid, Spain

[c] Department of Medical Informatics, Competence Center for Methodology and Statistics, Luxembourg Institute of Health, 1A-B, rue Thomas Edison, L-1445, Strassen, Luxembourg

[d] Translational Medicine Operations Hub, Clinical Project Management Office, Luxembourg Institute of Health, 1A-B, rue Thomas Edison, L-1445, Strassen, Luxembourg

[e] Department of Cardiology, Hospital Universitario Clínico San Carlos, IdISSC, C. del Prof Martín Lagos, S/N, 28040, Madrid, Spain

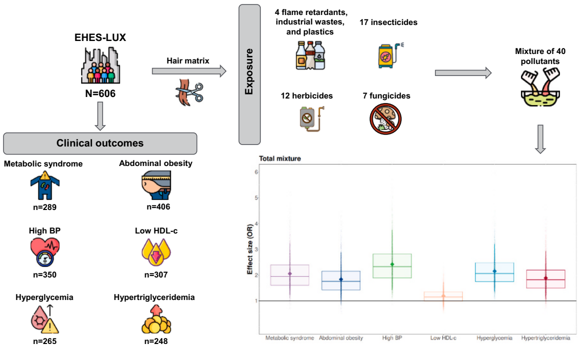
[f] Centro de Investigación Biomédica En Red en enfermedades CardioVasculares (CIBERCV), Av. Monforte de Lemos, 3-5. Pabellón 11. Planta 0, 28029, Madrid, Spain

[g] Department of Precision Health, Human Biomonitoring Research Unit, Luxembourg Institute of Health, 1A-B, rue Thomas Edison, L-1445, Strassen, Luxembourg

HIGHLIGHTS

- Exposure to pollutant mixtures was associated to different metabolic outcomes.
- Key contributors within these mixtures were identified using weighted quantile sum regression.
- Prosulfocarb, $ClCF_3CA$, and PNP were important contributors to the mixture effects.
- Considering chemical mixtures into health policy and regulatory frameworks is needed.

GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:
Metabolic health
Hair analysis
Chemical mixtures
Pesticides

ABSTRACT

Metabolic syndrome (MetS) and its components –central obesity, hypertriglyceridemia, reduced levels of serum high-density cholesterol (HDL-c), high blood pressure (BP), and hyperglycemia– are highly prevalent worldwide. Classical modifiable risk factors and environmental ones, such as exposure to pollutants can contribute to these high prevalence rates. We assessed whether exposure to pollutant mixtures was associated with MetS and its components, identifying key contributing pollutants. We analyzed data from 606 adults aged 25–64 from the European Health Examination Survey (2013–2015). Among 152 analyzed chemicals, 40 were present in over 50

---

* Corresponding author at: Luxembourg Institute of Health, 1A-B, rue Thomas Edison, L-1445, Strassen, Luxembourg.

E-mail addresses: jesus.martinez@cnic.es (J. Martínez-Gómez), giovana.ciprian@gmail.com (G.M. Ciprián), Gwenaelle.LeCoroller@lih.lu (G. Le Coroller), Achilleas.Pexaras@lih.lu (A. Pexaras), rodrigo.fernandez@cnic.es (R. Fernández-Jiménez), Brice.Appenzeller@lih.lu (B.M.R. Appenzeller), Maria.Ruiz@lih.lu (M. Ruiz-Castell).

[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.scitotenv.2025.180691
Received 22 May 2025; Received in revised form 22 August 2025; Accepted 7 October 2025

Exposome
WQS regression

% of the samples and classified as flame retardants, industrial wastes, and plastics (4), insecticides (17), herbicides (12), and fungicides (7). Using weighted quantile sum regressions, we estimated associations of groups of pollutants and the total mixture with metabolic outcomes. Exposure to insecticides was associated with high BP, hyperglycemia, and hypertriglyceridemia; herbicides with abdominal obesity; and fungicides with MetS, hyperglycemia, and hypertriglyceridemia. The total mixture increased the odds of all outcomes, except low HDL-c [average $OR_{MetS} = 2.06$ (5th PCT = 1.23); average $OR_{Abdominal\ obesity} = 1.83$ (5th PCT = 1.03); average $OR_{High\ BP} = 2.42$ (5th PCT = 1.42); average $OR_{Low\ HDL\text{-}c} = 1.19$ (5th PCT = 0.77); average $OR_{Hyperglycemia} = 2.15$ (5th PCT = 1.37); average $OR_{Hypertriglyceridemia} = 1.89$ (5th PCT = 1.10)]. Prosulfocarb was a probable contributor to the mixture effect on MetS and abdominal obesity, $ClCF_3CA$ on hypertriglyceridemia, and PNP on high BP. In conclusion, chemical pollutants are more present in individuals with metabolic derangements, with potentially stronger effects when combined. Reducing pesticide use, promoting safer alternatives, and creating protocols/regulatory standards for multiple-exposure scenarios are crucial for public health.

1. Introduction

Metabolic syndrome (MetS) and its components – central obesity, increased blood levels of triglycerides, reduced levels of blood high-density lipoprotein cholesterol (HDL-c), high blood pressure (BP), and hyperglycemia – are highly prevalent worldwide (Noubiap et al., 2022). Over the past three decades, countries have experienced a sharp rise in obesity, diabetes and hypertension rates (Phelps et al., 2024; WHO, 2018; Zhou et al., 2021). These factors increase the risk of cardiovascular and neurodegenerative diseases, cancer, or premature death (de A Boleti et al., 2021; Fahed et al., 2022; Gami et al., 2007; Karra et al., 2022).

Metabolic derangements can be partially explained by the influence of classical modifiable risk factors like physical inactivity, unhealthy diet or insufficient sleep, which are increasingly common worldwide (López-Bueno et al., 2024). To date, public health strategies have mainly focused on addressing these classical factors. However, the contribution of environmental factors, including exposure to chemical pollutants, often remains overlooked, indicating room for improvement (Wang et al., 2024).

Anthropogenic pollutants such as pesticides are examples of substances with potential health effects, given their widespread use in domestic and agricultural practices (Le Magueresse-Battistoni et al., 2018). These include insecticides, herbicides, fungicides and other chemicals used to prevent, destroy, repel or control pests (*U.S. Code*, n.d.). In recent decades, the presence and use of new chemical compounds, including pesticides and other substances, have increased. Growing trends have raised concerns about their persistence, bioaccumulation, and potential or unknown health effects (Iglesias-Gonzalez and Appenzeller, 2025; Pathak et al., 2022; Sharma et al., 2023). The magnitude of this public health problem has led to regulations such as the Stockholm Convention, ratified by Luxembourg and other 151 countries, and the regulation on the registration, evaluation, authorisation and restriction of chemicals (REACH) (Bergkamp, 2013; Lallas, 2001). Biomonitoring studies have confirmed the widespread presence of chemical compounds in the general population, reinforcing the scenario of multiple exposures (Lallmahomed et al., 2024; Peng et al., 2021). These exposures can lead to additive or synergistic “cocktail effects”, even at low concentrations, when chemicals share similar mechanisms of action or targets (Barouki et al., 2022; Christou et al., 2021; Hernandez et al., 2019; Martin et al., 2021).

Despite increasing awareness of mixtures' health effects, current risk assessments typically evaluate chemicals individually, failing to account for real-world scenarios and underestimating their potential health impact. Although experimental studies link pollutants to hormonal disruption and inflammation, epidemiological findings are less consistent, often focusing on individual or limited number of chemicals, non-metabolic outcomes, or specific occupational settings (Barbey et al., 2024; Evangelou et al., 2016; Lamat et al., 2022; Mérida et al., 2023; Petit and Vuillerme, 2025; Shoshtari-Yeganeh et al., 2019; Vuong et al., 2022; Xiao et al., 2024; Zhang et al., 2024). The effects of complex chemical mixtures and their key drivers on cardiometabolic health remain understudied, highlighting the need for more comprehensive research.

Our study aimed to address this gap by assessing whether exposure to a mixture of 40 different chemical compounds, measured in hair samples, was associated with metabolic outcomes (MetS and its components). This study also aimed to identify key pollutants that mainly drive these associations, offering insights into potential metabolic risks by environmental mixtures.

2. Methods

2.1. Study population and design

This study used data collected from 635 randomly selected participants (with and without MetS) out of the 1529 included in the European Health Examination Survey (EHES-LUX) (Bocquet et al., 2018). The sample was stratified by MetS status to increase exposure variability and the ability to detect associations between chemical mixtures and MetS and its components. Participants without information for clinical outcomes ($n = 22$) and pregnant women ($n = 7$) were excluded. Finally, 606 individuals were included in the subsequent analyses. The EHES-LUX, a cross-sectional population-based survey conducted between 2013 and 2015, aimed to evaluate the general health status of adults aged 25 to 64 in the Grand-Duchy of Luxembourg (Bocquet et al., 2018). The EHES-LUX included a self-administered questionnaire, clinical and anthropometric measurements and biological samples (e.g. blood and hair). Self-administered questionnaires gathered information on demographic details, medication use, and lifestyle variables. All participants provided written informed consent before inclusion. The project 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). A proof/certificate of approval can be provided upon request.

2.2. Chemical assessment of exposure in hair

A total of 152 exposure biomarkers to persistent and non-persistent pollutants were selected for analysis in hair samples as previously described (Ruiz-Castell et al., 2023). These 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 miscellaneous pesticides. In addition, 4 polychlorobiphenyls (PCBs), 6 polybrominated flame retardants (PBDEs) and 2 bisphenols (bisphenol A and S) were also analyzed. Specific information regarding the materials and analytical methods has been published elsewhere (Ruiz-Castell et al., 2023). Briefly, 50 mg of hair powder samples were decontaminated following a validated protocol (Hardy et al., 2015), involving washes with sodium dodecyl sulfate solution, ultrapure water, and methanol. After drying, hair samples were pulverized and extracted using acetonitrile/water solution under continuous agitation overnight. Chemical concentrations were quantified using gas chromatography-tandem mass spectrometry (GC–MS/MS). Out of the 152 pollutants analyzed, we focused on 40 chemicals, each with over 50 % of their detected values above the limit of detection (LOD) (Supplementary Table 1). These were grouped into four categories based on their usage: flame retardants, industrial wastes, and plastics ($n = 4$); insecticides ($n = 17$); herbicides ($n = 12$); and fungicides ($n = 7$).

Compared to other matrices such as blood, hair analysis is a non-invasive method that captures chronic exposure to both hydrophobic and hydrophilic compounds (Hardy et al., 2021). Moreover, the concentration of pesticides and their metabolites in hair is representative of their levels in blood (Junaid et al., 2024). Additionally, unlike biological fluids, the timing of sample collection does not influence chemical concentrations in hair (Fäys et al., 2021). These characteristics make hair a relevant and robust matrix for assessing long-term, multi-chemical exposure, making it a suitable tool for investigating chronic environmental exposures in population studies.

2.3. *Outcomes*

Waist circumference (WC) was measured using a measuring tape (cm). Systolic blood and diastolic BP (mm Hg) were measured at least 3 times on the right arm while seated (Ruiz-Castell et al., 2016). The reported values represent the average of the second and third measurements (Ruiz-Castell et al., 2016; Streel et al., 2015). Biochemical parameters, fasting plasma glucose (FPG, mg/dL), serum triglycerides (mg/dL), low-density lipoprotein cholesterol (LDL-c, mg/dL), and HDL-c (mg/dL) were analyzed in a national laboratory.

Clinical outcomes examined in the present study included MetS and its components: abdominal obesity, hypertriglyceridemia, low HDL-c, high BP, and hyperglycemia. MetS was considered based on the criteria set by the International Diabetes Federation (Alberti et al., 2006): WC $\geq$ 94 cm for men and $\geq$80 cm for women and the presence of at least two of the following factors: (1) total triglycerides $\geq$150 mg/dL irrespective of sex or taking related medication; (2) HDL-c $<$ 40 mg/dL for men and $<$50 mg/dL for women or being on related medication; (3) systolic BP $\geq$ 130 or diastolic BP $\geq$ 85 mm Hg irrespective of sex or using anti-hypertensive medications; and (4) FPG $\geq$ 100 mg/dL or previous diagnosis of diabetes for both men and women. MetS individual components were defined with the thresholds for each condition.

2.4. *Covariates*

Demographic, socioeconomic, and lifestyle information was obtained from health questionnaires. We included age, sex (male/female), country of birth (Luxembourg, Portugal, other EU countries, other non-EU countries), education level (primary, secondary, tertiary education), job status (working/not working), physical activity (aerobic physical activity $\geq$150 min/$<$150 min per week), and organic food consumption (always, from time to time, and never).

2.5. *Statistical analyses*

Descriptive data for continuous variables are presented as medians with 25th and 75th percentiles (25thPCT, 75thPCT), while categorical variables are presented as frequencies and percentages.

Out of the 40 selected pollutants, chemical exposures with values below the LOD were imputed using the Quantile Regression Imputation of Left-Censored data (QRILC) method (Wei et al., 2018a, 2018b). The subsequent missing values were imputed using the chained equations method with the MICE package in R (van Buuren, 2012). The original data set ($N = 417$) and the imputed data set ($N = 606$) were compared, observing similar descriptive values for the selected variables (Supplementary Tables 2 and 3). Imputation was performed across 30 cycles with 5 iterations, generating 30 imputed datasets.

Two regression approaches were employed to assess the relationship between the chemicals of interest and the clinical outcomes (Supplementary Fig. 1): single chemical and mixture models.

Single chemical logistic regression models were applied to each of the 40 chemical compounds. The Benjamini and Hochberg correction was applied to control the False Discovery Rate (FDR).

Mixture models were performed using weighted quantile sum (WQS) regression, which evaluates the association between highly correlated co-exposures and health outcomes (Carrico et al., 2015). These models were applied in two ways: first, by combining individual compounds within the four categories of chemicals, i.e. i) flame retardants, industrial wastes, and plastics, ii) insecticides, iii) herbicides, and iv) fungicides, and analyzing each category separately; second, by combining compounds from the four categories into a global mixture model.

Exposures were divided into quantiles and combined into a weighted index, reducing dimensionality and multicollinearity. WQS estimates the mixture's overall effect and ranks individual chemicals by their estimated weights. Chemicals with higher weights contribute more to the weighted index. Analyses were conducted using one sided confidence limits, focusing the inference on a positive direction (i.e., increased risk). 5thPCT was used to establish the lower limit. All models were adjusted by age, sex, country of birth, education level, job status, physical activity, and organic food consumption. We conducted a sensitivity analysis using only chemical values without imputation ($N = 417$). To improve stability, we applied repeated holdout validation combining cross-validation and bootstrap resampling (Tanner et al., 2019). The data were randomly split (40/60 %) with replacement 100 times, running a WQS regression on each split to generate distributions of estimates and weights. This process was repeated across 30 imputed datasets, having a total of 3000 WQS estimates. Chemicals with weights above 1/c (c = total chemicals) in $\geq$90 % of holdouts were classified as 'probable' contributors (Bennett et al., 2022; Busgang et al., 2022). We used the R package "gWQS: generalized weighted quantile sum regression" version 3.0.4 to perform these models.

All statistical analyses were performed using R statistical software, and the result presented was validated by an independent programmer.

3. Results

Out of the 606 individuals included in the study, 47.69 % presented with MetS, 67.00 % had abdominal obesity, 40.92 % had hypertriglyceridemia, 50.66 % had low HDL-c, 57.76 % had high BP, and 43.73 % had hyperglycemia (Table 1). A total of 91 individuals presented all four individual MetS components, whereas 80 individuals did not present any of these components (Fig. 1). Individuals with MetS or at least one of its components were generally older, more likely to be men, had a lower education level, were not employed, reported lower levels of physical activity, and consumed fewer organic foods than the overall sample (Table 1); and generally presented with higher concentrations of chemical pollutants in their hair (Supplementary Table 4).

3.1. *Flame retardants, industrial wastes and plasticizers*

The repeated holdout WQS showed no significant mixture effect for flame retardants, industrial wastes and plasticizers on any of the metabolic outcomes (Table 2). On average, all effect point estimates were positive with at least 75 % of repetitions exceeding 1 for MetS, low HDL-c, high BP and hyperglycemia. However, the estimates exhibited substantial dispersion, limiting the confidence for a significant association (Supplementary Fig. 2). Single chemical regressions indicated higher concentrations of PCB 180 in hair associated with reduced odds of abdominal obesity [OR = 0.66 (95 % CI, 0.52; 0.84)] (Supplementary Table 5). A similar trend was found in the single quartile regression [OR = 0.75 (95 % CI, 0.60; 0.93)]; however, the association was not significant after FDR correction (Supplementary Table 6).

Table 1
Characteristics of the participants included in the analysis in the overall sample and by metabolic outcome.

	Overall	Metabolic syndrome	Abdominal obesity	High BP	Low HDL-c	Hyperglycemia	Hypertriglyceridemia
Number of participants, n (%)	606 (100.00)	289 (47.69)	406 (67.00)	350 (57.76)	307 (50.66)	265 (43.73)	248 (40.92)
Sociodemographic characteristics							
Age in years, median (25th PCT, 75th PCT)	47.11 (38.87, 55.85)	51.80 (43.50, 57.47)	50.21 (42.03, 56.94)	51.58 (42.96, 57.63)	48.16 (40.50, 56.31)	51.78 (42.33, 57.74)	51.84 (43.13, 57.27)
Sex, n (%)							
Female	277 (45.71)	116 (40.14)	194 (47.78)	125 (35.71)	136 (44.30)	90 (33.96)	78 (31.45)
Male	329 (54.29)	173 (59.86)	212 (52.22)	225 (64.29)	171 (55.70)	175 (66.04)	170 (68.55)
Birth country, n (%)							
Luxembourg	269 (44.39)	134 (46.37)	176 (43.35)	166 (47.43)	124 (40.39)	120 (45.28)	117 (47.18)
Portugal	115 (18.97)	64 (22.14)	86 (21.18)	67 (19.14)	73 (23.78)	59 (22.26)	56 (22.58)
Other EU countries	157 (25.91)	66 (22.84)	105 (25.86)	85 (24.29)	75 (24.43)	64 (24.15)	54 (21.77)
Other non-EU countries	65 (10.73)	25 (8.65)	39 (9.61)	32 (9.14)	35 (11.40)	22 (8.30)	21 (8.47)
Education level, n (%)							
Primary	171 (28.22)	105 (36.33)	134 (33.00)	118 (33.71)	98 (31.92)	90 (33.96)	90 (36.29)
Secondary	214 (35.31)	104 (35.99)	142 (34.98)	127 (36.29)	108 (35.18)	99 (37.36)	86 (34.68)
Tertiary	221 (36.47)	80 (27.68)	130 (32.02)	105 (30.00)	101 (32.90)	76 (28.68)	72 (29.03)
Job status, n (%)							
Not working	157 (25.91)	90 (31.14)	122 (30.05)	108 (30.86)	90 (29.32)	79 (29.81)	82 (33.06)
Working	449 (74.09)	199 (68.86)	284 (69.95)	242 (69.14)	217 (70.68)	186 (70.19)	166 (66.94)
Lifestyle characteristics							
Physical activity per week, n (%)							
Aerobic physical activity <150 min	417 (68.81)	229 (79.24)	303 (74.63)	262 (74.86)	233 (75.90)	199 (75.09)	186 (75.00)
Aerobic physical activity ≥150 min	189 (31.19)	60 (20.76)	103 (25.37)	88 (25.14)	74 (24.10)	66 (24.91)	62 (25.00)
Organic food consumption, n (%)							
Never	207 (34.16)	101 (34.95)	141 (34.73)	121 (34.57)	110 (35.83)	87 (32.83)	95 (38.31)
Time to time	348 (57.42)	174 (60.21)	240 (59.11)	203 (58.00)	180 (58.63)	161 (60.75)	142 (57.26)
Always	51 (8.42)	14 (4.84)	25 (6.16)	26 (7.43)	17 (5.54)	17 (6.42)	11 (4.43)

Descriptives were obtained using the fifth imputed dataset. BP: blood pressure; HDL-c: high-density lipoprotein cholesterol; PCT: percentile; n: number.

3.2. Insecticides

The WQS analysis revealed a significant association between the insecticides index and high BP [average OR = 1.95, (5^{th}PCT = 1.35)], hyperglycemia [average OR = 1.49, (5^{th}PCT = 1.09)], and hypertriglyceridemia [average OR = 1.35, (5^{th}PCT = 1.05)] (Table 2; Supplementary Fig. 2). Moreover, P-Nitrophenol (PNP) was a probable contributor to the mixture effect for the association between the insecticides and high BP (Fig. 2). In the single chemical model, PNP remained significant [OR = 1.60 (95 % CI, 1.12; 2.29)], as did fipronil sulfone [OR = 1.15 (95 % CI, 1.02; 1.30)]. However, these associations were not significant after FDR correction (Supplementary Table 5). Similar trends were observed in the single chemical analysis with quartiles (Supplementary Table 6).

3.3. Herbicides

The herbicide mixture was significantly associated with increased odds of abdominal obesity [average OR = 1.71, (5^{th}PCT = 1.18)] (Table 2; Supplementary Fig. 2). Prosulfocarb was a probable contributor to the mixture effect on abdominal obesity (Fig. 2). Additionally, single chemical regressions, either considering exposure in continuous or categorized in exposure quartiles, showed that higher concentrations of prosulfocarb in hair were associated with increased odds of abdominal obesity [OR = 1.82, (95 % CI, 1.32; 2.51) and OR = 1.40, (95 % CI, 1.16; 1.69), respectively] (Supplementary Tables 5 and 6). These associations remained significant after correcting for FDR (FDR-corrected *p*-value <0.001).

3.4. Fungicides

No fungicide showed strong evidence of contributing to MetS, hyperglycemia, nor hypertriglyceridemia (Fig. 2). However, the combined effect of different fungicides was associated with changes in these outcomes [average OR_{MetS} = 1.38, (5^{th}PCT = 1.07); average $OR_{Hyperglycemia}$ = 1.68, (5^{th}PCT = 1.27); average $OR_{Hypertriglyceridemia}$ = 1.35, (5^{th}PCT = 1.05)] (Table 2; Supplementary Fig. 2). Trifloxystrobin was associated with increased odds of MetS. In contrast, boscalid was associated with increased odds of hyperglycemia and hypertriglyceridemia in single chemical regression models, although these associations were not significant after FDR correction (Supplementary Tables 5 and 6).

3.5. Total mixture

A total mixture effect, combining all hair pollutants ($n = 40$ chemical pollutants) was analyzed for each outcome separately. The mixture effect was associated with all clinical outcomes, except for low HDL-c, and especially with high BP and hyperglycemia (Fig. 3). Fig. 4 presents chemical contributions for each outcome categorized by color according to their chemical category. Prosulfocarb was a probable contributor to the total mixture effect on MetS (92.2 % holdouts) and abdominal obesity (99.9 % holdouts). Moreover, $ClCF_3CA$ and PNP were also probable contributors to the total mixture effect on hypertriglyceridemia (91.1 % holdouts) and high BP (94.9 % holdouts), respectively. These pollutants were indicated as potentially important contributors, either because they were identified in the single category mixtures or showed significance in the single chemical analysis.

4. Discussion

The present cross-sectional analysis of 606 individuals from the EHES-LUX study found associations between exposure to pollutant mixtures and different metabolic outcomes in adults residing in the Grand-Duchy of Luxembourg. Exposure to insecticides was associated with high BP, hyperglycemia, and hypertriglyceridemia, to herbicides with abdominal obesity, and to fungicides with MetS, hyperglycemia,

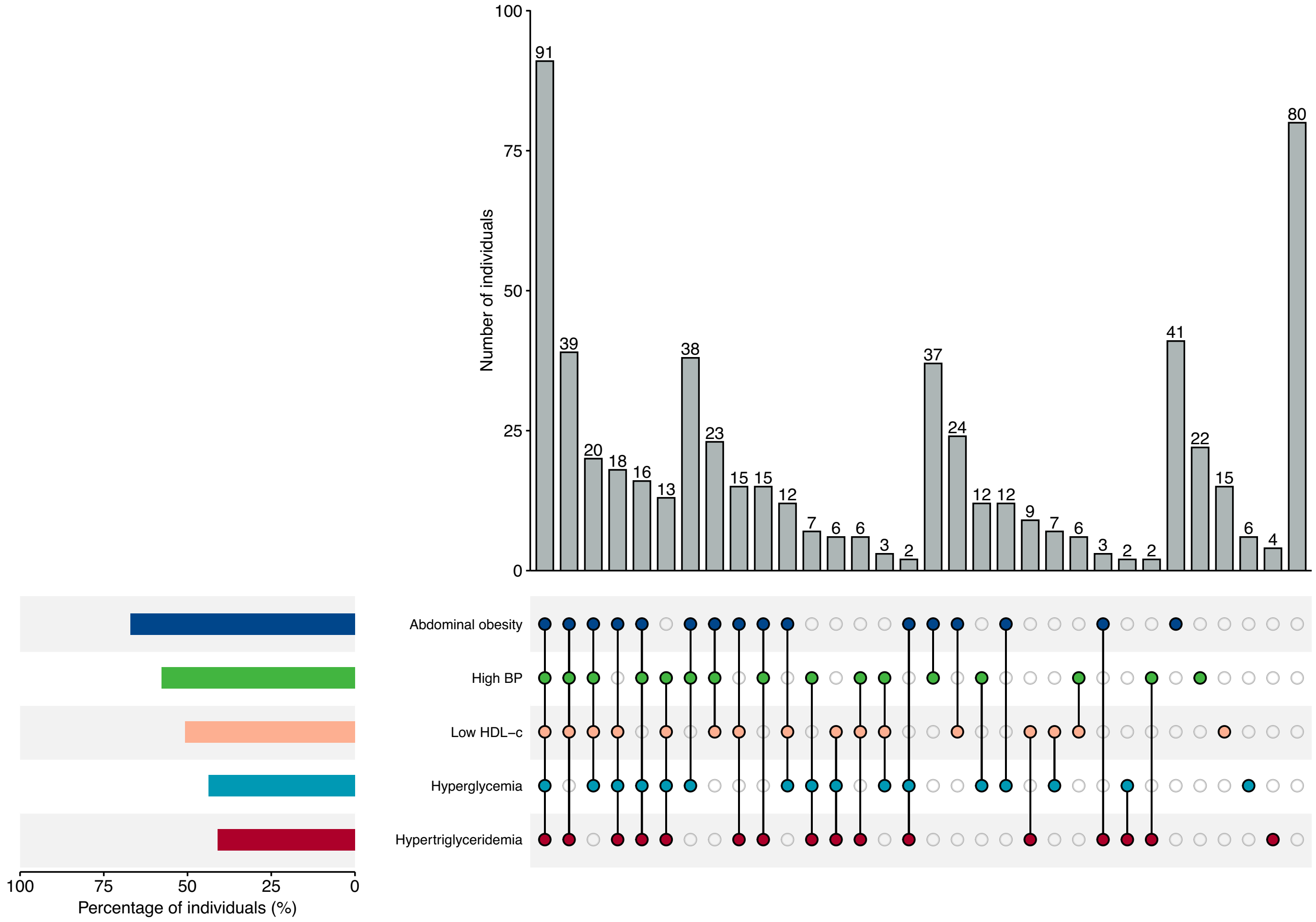


Fig. 1. Metabolic syndrome distribution and its individual components in the selected participants of the EHES-LUX study (N = 606).

and hypertriglyceridemia. When all 40 individual pollutants were combined and analyzed, the total mixture was associated with higher odds of all clinical outcomes, except for low HDL-c, and especially with high BP and hyperglycemia. Our study showed that environmental pollutants were more present when metabolic derangements occurred, and their effects were higher when they were combined. To the best of our knowledge, this is one of the first studies analyzing the association between metabolic outcomes and an exposure to a complex mixture of pollutants.

Previous research suggests that exposure to pollutants during the first stages of life may have harmful effects (Waalen, 2014). While evidence in adult populations remains limited and scarce (Peng et al., 2024a), our findings showed that pollutants measured in adulthood (25–64 years) were also linked to metabolic health. Longitudinal studies are needed to determine when in lifespan the cocktail effect is more relevant and how impacts older adults, who are more prone to metabolic derangements.

Regarding each chemical category, we found a positive association between exposure to herbicides and abdominal obesity. Some chemicals can act as endocrine disruptors, interfering with lipid homeostasis and promoting lipid accumulation (Muscogiuri et al., 2017). Moreover, they can also modify the gut microbiota and alter the hormonal control of appetite and satiety (Lagisz et al., 2015; Snedeker and Hay, 2012). Among herbicides, prosulfocarb was the most probable contributor to the association between this chemical category and abdominal obesity. Prosulfocarb is a pre-emergent herbicide rapidly gaining use in many countries due to the increasing bioresistance and the restrictions or bans on other pesticides (Devault et al., 2022). Although it has a low toxicological effect in vitro and in animal models, its use is recent, and there are limited studies characterizing its effects on human health. However, two recent studies by Peng et al. have highlighted potential impacts of prosulfocarb on thyroid and sex steroid hormones (Peng et al., 2023, 2024b). These findings suggest that prosulfocarb may have endocrine-disrupting effects, with possible implications for metabolism. Our results point toward the need to further investigate the potential health impacts of prosulfocarb and the necessity to update its consideration in future regulations.

We also observed a positive association between exposure to insecticides and hypertriglyceridemia, high BP, and hyperglycemia, in line with previous studies (Dong et al., 2024; Evangelou et al., 2016; Samsuddin et al., 2016; Wei et al., 2023). Organophosphates (OPs) and their metabolites, like PNP, a major contributor in our analyses to high BP, can induce plasma hypertriglyceridemia and impair the renin-angiotensin system, producing an increase in BP (Rajak et al., 2022; Suzuki et al., 2014). Moreover, organophosphorus and carbamate compounds are cholinesterase inhibitors, which can further raise BP by stimulating the sympathetic nervous system (Zago et al., 2022). Other possible mechanisms include effects on miRNA-dependent pathways and the induction of oxidative stress in various organ systems (Glover et al., 2022a, 2022b). Recently, serum albumin and aspartate transaminase/alanine transaminase (AST/ALT) ratio have been identified as potential mediators in these associations (Dong et al., 2024). In the case of blood glucose alterations, exposure to certain insecticides can enhance the activity of enzymes involved in hepatic gluconeogenesis and glycogenolysis, produce acute pancreatitis influencing insulin secretion, or cause dysregulations of other hormones such as

Table 2

Results from the logistic WQS for each of the categories of chemical exposures and the total mixture of pollutants.

	Chemical class mixture		Mean	Median	5th PCT	95th PCT
Metabolic syndrome	FRIWP	OR	1.12	1.11	0.88	1.37
	Insecticides	OR	1.42	1.39	1.00	1.90
	Herbicides	OR	1.26	1.22	0.80	1.83
	Fungicides	OR	1.38	1.37	1.07	1.73
	Mixture of pollutants	OR	2.06	1.95	1.23	3.23
Abdominal obesity	FRIWP	OR	0.98	0.97	0.77	1.18
	Insecticides	OR	1.09	1.07	0.77	1.46
	Herbicides	OR	1.71	1.67	1.18	2.37
	Fungicides	OR	1.02	1.01	0.79	1.26
	Mixture of pollutants	OR	1.83	1.76	1.03	2.88
High BP	FRIWP	OR	1.12	1.11	0.89	1.40
	Insecticides	OR	1.95	1.91	1.35	2.73
	Herbicides	OR	1.22	1.18	0.82	1.73
	Fungicides	OR	1.21	1.20	0.93	1.56
	Mixture of pollutants	OR	2.42	2.33	1.42	3.75
Low HDL-c	FRIWP	OR	1.08	1.07	0.88	1.31
	Insecticides	OR	1.13	1.11	0.84	1.47
	Herbicides	OR	1.00	0.99	0.69	1.34
	Fungicides	OR	1.11	1.09	0.87	1.37
	Mixture of pollutants	OR	1.19	1.15	0.77	1.72
Hyperglycemia	FRIWP	OR	1.16	1.15	0.93	1.42
	Insecticides	OR	1.49	1.47	1.09	1.95
	Herbicides	OR	1.11	1.09	0.72	1.60
	Fungicides	OR	1.68	1.65	1.27	2.18
	Mixture of pollutants	OR	2.15	2.06	1.37	3.21
Hypertriglyceridemia	FRIWP	OR	1.03	1.03	0.82	1.25
	Insecticides	OR	1.51	1.48	1.05	2.11
	Herbicides	OR	1.12	1.10	0.72	1.59
	Fungicides	OR	1.35	1.34	1.05	1.70
	Mixture of pollutants	OR	1.89	1.82	1.10	2.92

Models were adjusted by age, sex, country of birth, education level, job status, physical activity, and organic food consumption. WQS: weighted quantile sum. FRIWP: flame retardants, industrial wastes, and plastics; BP: blood pressure; HDL-c: high-density lipoprotein cholesterol; OR: odds ratio; PCT: percentile.

catecholamines, progesterone, or testosterone, among others (Dong et al., 2024; Xiao et al., 2017). Moreover, exposure to insecticides is linked with the disruption of hepatic lipid and glucose metabolism, potentially contributing to non-alcoholic fatty liver disease (Yang and Park, 2018). While previous studies have primarily focused on organochlorine and organophosphorus insecticides, our findings suggest that other insecticides such as imidacloprid, a neonicotinoid that is part of a family of insecticides increasingly used worldwide, should also be targeted for future studies on metabolic health.

Exposure to fungicides was associated with MetS, hyperglycemia, and hypertriglyceridemia (Langer et al., 2009; Lee et al., 2011; Wu et al., 2013a; Xiao et al., 2017). However, evidence on fungicides is scarce, with most studies focusing on in vitro or animal models. In mice, exposure to carbenzamid caused damage to the intestinal mucosa, which was associated with increased levels of blood glucose, TNF-α and IL-1β, a reduced *Bacteroides* abundance, and lower fecal acetate (one of SCFAs) concentrations (Jin et al., 2018). In pancreatic β-cells (RIN-m5F), exposure to a pesticide mixture, including HCB, increased ROS production and suppressed insulin secretion (Park et al., 2020). HCB is often used as a fungicide, but it can also be released from industrial and other processes (Bailey, 2001). Additionally, a similar mixture inhibited basal glucose uptake in L6 myotubes by downregulating Glut4 expression (Park et al., 2021). Wild-type male mice fed pesticide chow (a mixture of 6 pollutants including boscalid) developed characteristics of hepatic steatosis and glucose intolerance, while females developed fasting hyperglycemia, higher reduced glutathione (GSH): oxidized glutathione (GSSG) liver ratio, and alterations in gut microbiota-related urinary metabolites compared to controls (Lukowicz et al., 2018). Mice fed with fish oil contaminated with a pesticide-mixture containing HCB gained more weight, had higher muscle triacylglyceride levels and lower AKT activity (Ibrahim et al., 2011). A Swedish population-based prospective study found that most metabolites associated with HCB exposure originated from fatty acids and phosphoethanolamine metabolism, both of which are crucial components of plasma lipoproteins and have signaling functions (Salihovic et al., 2016). Moreover, fungicides such as pyraclostrobin or tebuconazole produce lipid accumulation and oxidative stress in cells (Kwon et al., 2021; Luz et al., 2018). To our knowledge, no studies before have directly linked fungicides with hypertriglyceridemia as detected in this work, highlighting the need for further research to validate our findings.

Even if some chemical categories were not associated with clinical outcomes, the general population is exposed to multiple pollutants simultaneously, which can have a cumulative and interacting effects. Therefore, it is crucial to consider the overall exposure rather than individual chemicals in isolation. The exposome is complex, making it crucial to assess all these exposures together (Ruiz-Castell et al., 2023). While some studies in other populations have examined chemical mixtures and cardiometabolic health outcomes, they have mainly focused on a limited number of pollutants, used different biological matrices or employed alternative analytical methods (Donat-Vargas et al., 2018; Nguyen et al., 2022; Reina-Pérez et al., 2023; Wu et al., 2013b; Zhang et al., 2019). We did not find associations for most pollutants in single-chemical analysis. However, this finding aligns with the hypothesis that low-dose exposure to mixtures may affect metabolic health (Le Magueresse-Battistoni et al., 2018). This is relevant as toxicity is usually assessed for individual pollutants (*EU Pesticides Database*, n.d.; Van Ael et al., 2013), without considering potential synergic effects. In our sample, five detected pollutants were banned before our study (*Delegated Regulation - 2022/2291 - EN - EUR-Lex*, n.d.), yet they were probable contributors to the observed metabolic derangements.

Our findings highlight the need to guide regulatory bodies and promote cleaner, sustainable industrial practices (Kurul et al., 2025).

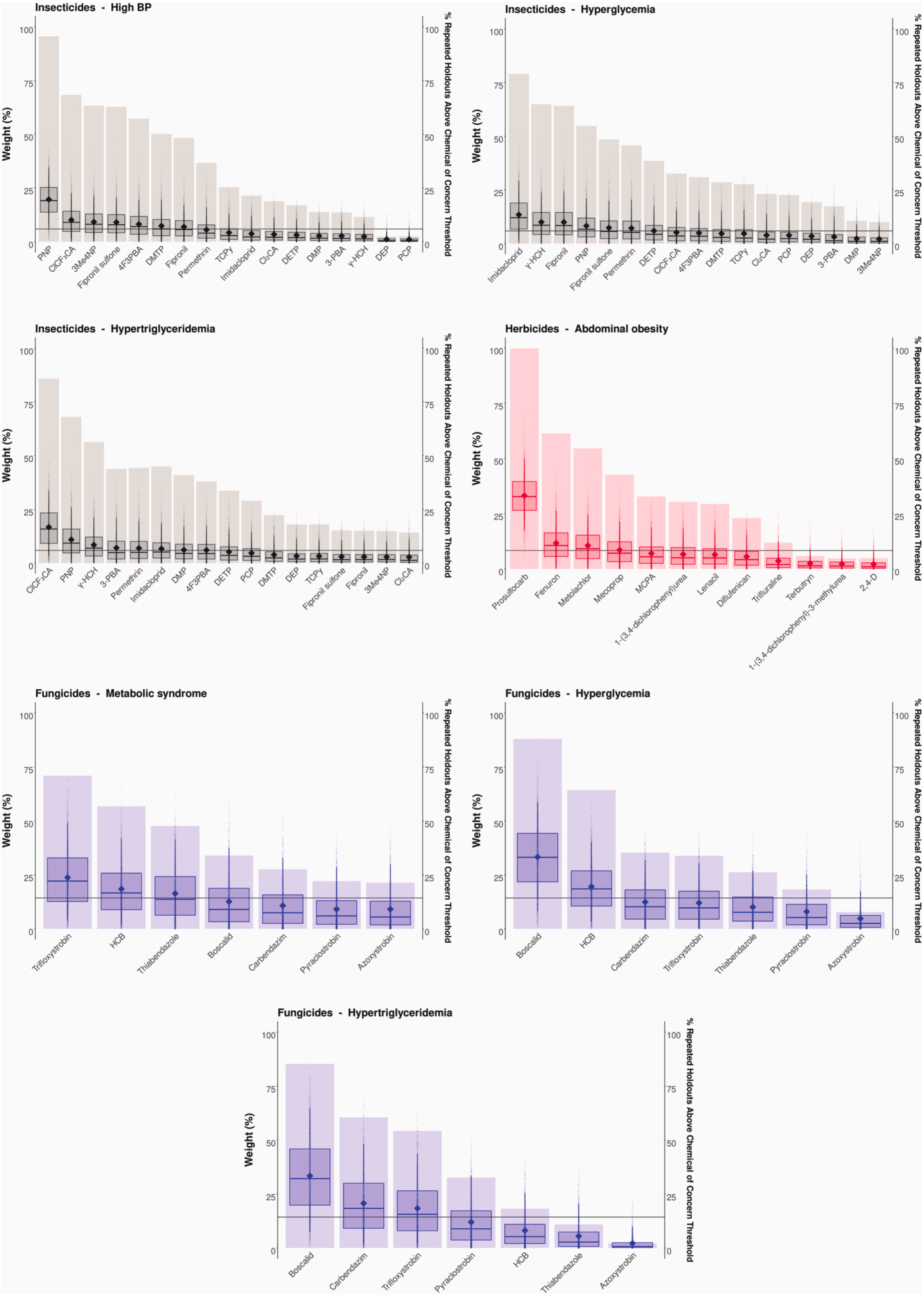


Fig. 2. Weight distributions of each chemical pollutant (left axis) and the number of repetitions in which the pollutant exceeded the 1/c threshold contribution of concern (right axis) for categories of mixtures logistic WQS models with more than 95 % repetitions above the null ($N = 606$). Models were adjusted by age, sex, country of birth, education level, job status, physical activity, and organic food consumption.

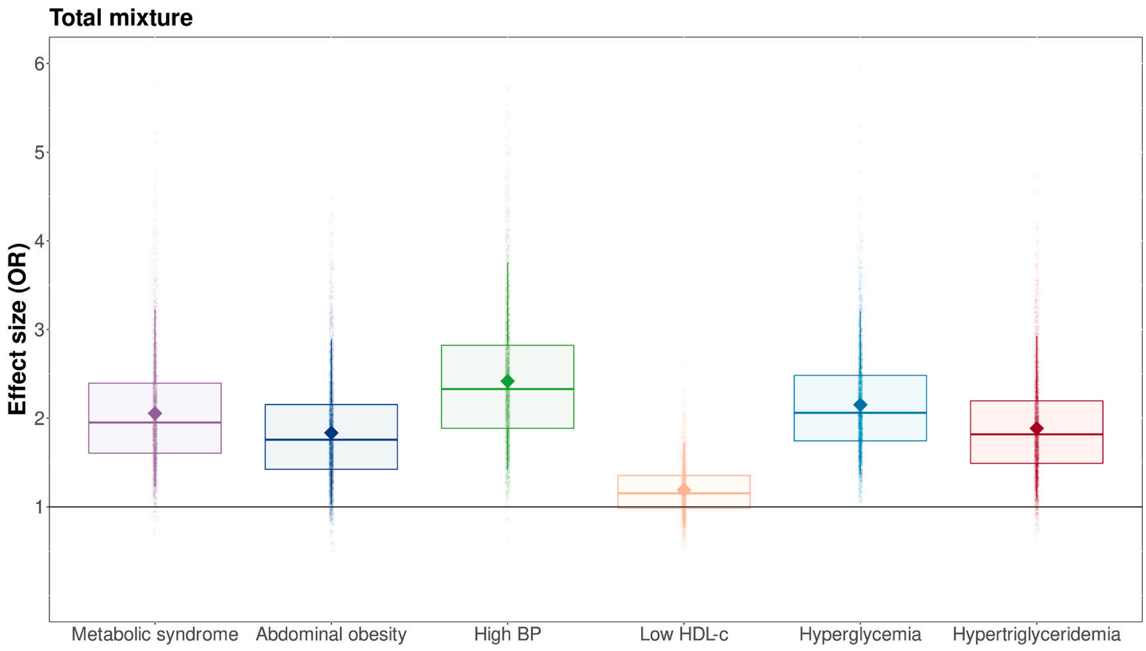


Fig. 3. Visual representation of OR distributions from the logistic WQS with the mixture of all chemical categories combined (N = 606). Models were adjusted by age, sex, country of birth, education level, job status, physical activity, and organic food consumption. The box represents the 25th and 75th percentiles, the line represents the median, the closed diamond represents the mean, and the whiskers show the 5th and 95th percentiles.

Industries can support this by investing in green chemistry, improving supply chain traceability, adopting cleaner production processes, and phasing out hazardous substances. However, regulatory bans do not necessarily eliminate persistent pollutants from the environment, which continue to affect human health (Van Ael et al., 2013). Our study supports the urgent need to transition toward safer chemical alternatives.

For society, our findings call for stronger public health protection through enforcement of international agreements, greater transparency in chemical substitutions, and increased public awareness. Addressing these challenges requires collaboration among governments, industries, and individuals. The 2030 Agenda for Sustainable Development provides a roadmap to protect both human and planetary health while promoting environmental justice and sustainability.

Some limitations need to be considered. Due to the study's observational and cross-sectional design, residual confounding cannot be ruled out, and causal inference cannot be established. Nearly 50 % measurements for some pollutants fell below the LOD, likely reflecting low exposure levels. Nonetheless, even low dose exposures could contribute to metabolic alterations in susceptible individuals. Despite these limitations, the present study assessed the association between a mixture of 40 chemical pollutants and metabolic outcomes, representing the highest number of pollutants examined in relation to these outcomes to date. The main analysis using imputed data was supplemented by a complete case sensitivity analysis, which yielded similar results (Supplementary Figs. 3 and 4). Moreover, the use of hair samples reflects average exposure over the four months preceding sample collection and allows for the detection of both hydrophilic and hydrophobic compounds, providing a more complete picture of exposure. Another strength of our study is the use of WQS regression to assess the associations between chemical pollutants and metabolic health outcomes. This approach overcomes limitations of traditional regression models related to multicollinearity and allows identification of the most influential components in the mixture. Moreover, to enhance stability and generalizability, we applied repeated holdout validation with bootstrap resampling.

5. Conclusion

This study found associations between exposure to certain classes of pesticides (insecticides, herbicides and fungicides) and several metabolic health outcomes, including high BP, hyperglycemia, hypertriglyceridemia, abdominal obesity and MetS. No clear associations were observed for exposure to flame-retardants, industrial wastes, or plasticizers. The chemical mixture was associated with MetS and its components, except for low HDL-c cholesterol, although the cross-sectional nature of the study limits causal interpretation. Prosulfocarb, $ClCF_3CA$, and PNP emerged as potential contributors to these associations; however, further longitudinal studies are warranted to clarify their role and assess possible long-term health effects. These findings underscore the importance of supporting initiatives aimed at reducing pesticide overuse, promoting the development of safer alternatives, and exploring alternative pest control strategies. Furthermore, enhanced safety protocols and regulatory standards that address multiple exposures that we face nowadays may be crucial for protecting both those who handle pesticides directly and, indirectly, to the general population.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2025.180691.

CRediT authorship contribution statement

Jesús Martínez-Gómez: Writing – original draft, Visualization, Investigation, Formal analysis, Data curation. **Giovana M. Ciprián:** Writing – review & editing, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Gwenaëlle Le Coroller:** Writing – review & editing, Methodology, Data curation. **Achilleas Pexaras:** Writing – review & editing, Methodology. **Rodrigo Fernández-Jiménez:** Writing – review & editing, Supervision. **Brice M.R. Appenzeller:** Writing – review & editing, Resources. **Maria Ruiz-Castell:** Writing – review & editing, Writing – original draft, Validation, Supervision, Resources, Investigation, Funding acquisition, Conceptualization.

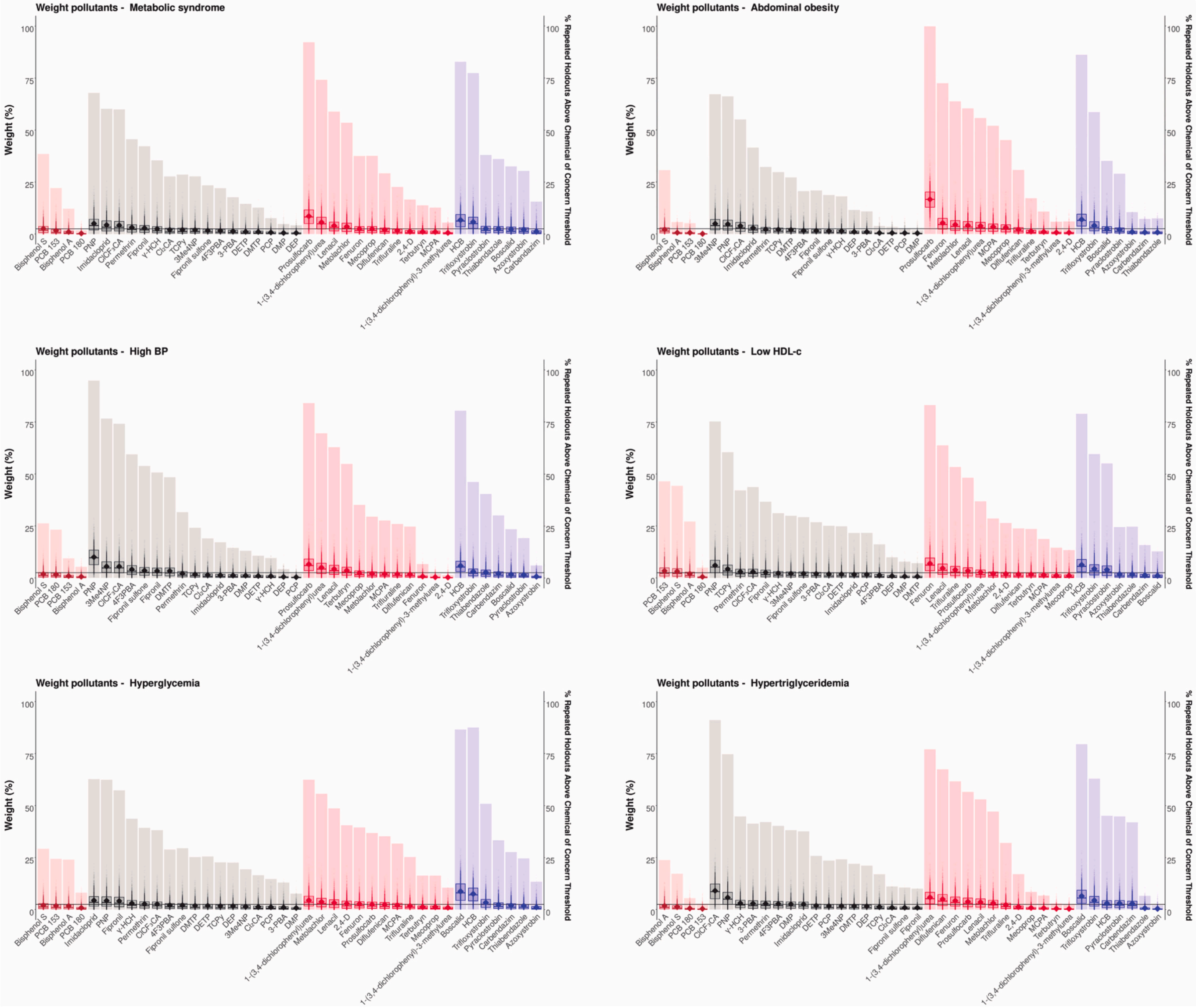


Fig. 4. Weight distributions of each chemical pollutant (left axis) and the number of repetitions in which the pollutant exceeded the 1/c threshold contribution of concern (right axis) for total mixture logistic WQS models (N = 606). Models were adjusted by age, sex, country of birth, education level, job status, physical activity, and organic food consumption.

Funding

This research was funded by the National Research Fund (FNR), Luxembourg (C17/BM/11653863/iMPACT.lu to MRC), the Ministry of Higher Education and Research (MESR), Luxembourg. J.M-G is a recipient of grant FPU21/04891 (*Ayudas para la formación de profesorado universitario*, FPU-2021) from the *Ministerio de Educación, Cultura y Deporte* and this work was possible thanks to the short-stay program within the framework of the FPU grants (EST24/00675). RF-J is supported by the ISCIII (Project "PI22/01560"), funded by ISCIII and co-funded by the European Union. The CNIC is supported by the *Instituto de Salud Carlos III* (ISCIII), the *Ministerio de Ciencia, Innovación y Universidades* (MCIUN) and the Pro CNIC Foundation and is a Severo Ochoa Center of Excellence (grant CEX2020-001041-S funded by MICIN/AEI/10.13039/501100011033).

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

Data availability to external researchers is restricted to related project proposals upon request to the corresponding author.

Acknowledgements

The authors thank the population of Luxembourg and to all of the EHES-LUX team who have contributed to this study. J.M-G would like to dedicate his four paper as first (co-)author and thank to all the Department of Precision Health for all the professional and personal help, especially to Lisa, Mauro, Dr. Babul Hossain, Dr. Alejandra Loyola Leyva, Dr. Elena Lacomba Arnau, Dr. Valérie Moran, Dr. Gloria Aguayo, Dr. Sophie Pilleron, and Dr. Magali Perquin.

References

Alberti, K.G.M.M., Zimmet, P., Shaw, J., 2006. Metabolic syndrome—a new world-wide definition. A consensus statement from the International Diabetes Federation. Diabet. Med. 23 (5), 469–480. https://doi.org/10.1111/j.1464-5491.2006.01858.x.

Bailey, R.E., 2001. Global hexachlorobenzene emissions. Chemosphere 43 (2), 167–182. https://doi.org/10.1016/S0045-6535(00)00186-7.

Barbey, C., Bonvallot, N., Clerc, F., 2024. Health outcomes related to multiple exposures in occupational settings: a review. Saf. Health Work 15 (4), 382–395. https://doi.org/10.1016/j.shaw.2024.10.004.

Barouki, R., Audouze, K., Becker, C., Blaha, L., Coumoul, X., Karakitsios, S., Klanova, J., Miller, G.W., Price, E.J., Sarigiannis, D., 2022. The exposome and toxicology: a win–win collaboration. Toxicol. Sci. 186 (1), 1–11. https://doi.org/10.1093/toxsci/kfab149.

Bennett, D.H., Busgang, S.A., Kannan, K., Parsons, P.J., Takazawa, M., Palmer, C.D., Schmidt, R.J., Doucette, J.T., Schweitzer, J.B., Gennings, C., Hertz-Picciotto, I., 2022. Environmental exposures to pesticides, phthalates, phenols and trace elements are associated with neurodevelopment in the CHARGE study. Environ. Int. 161, 107075. https://doi.org/10.1016/j.envint.2021.107075.

Bergkamp, L., 2013. The European Union REACH Regulation for Chemicals: Law and Practice. OUP Oxford.

Bocquet, V., Barré, 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. https://doi.org/10.1186/s12889-018-6087-0.

Busgang, S.A., Spear, E.A., Andra, S.S., Narasimhan, S., Bragg, J.B., Renzetti, S., Curtin, P., Bates, M., Arora, M., Gennings, C., Stroustrup, A., 2022. Application of growth modeling to assess the impact of hospital-based phthalate exposure on preterm infant growth parameters during the neonatal intensive care unit hospitalization. Sci. Total Environ. 850, 157830. https://doi.org/10.1016/j.scitotenv.2022.157830.

Carrico, C., Gennings, C., Wheeler, D.C., Factor-Litvak, P., 2015. Characterization of weighted quantile sum regression for highly correlated data in a risk analysis setting. J. Agric. Biol. Environ. Stat. 20 (1), 100–120. https://doi.org/10.1007/s13253-014-0180-3.

Christou, M., Ropstad, E., Brown, S., Kamstra, J.H., Fraser, T.W.K., 2021. Developmental exposure to a POPs mixture or PFOS increased body weight and reduced swimming ability but had no effect on reproduction or behavior in zebrafish adults. Aquat. Toxicol. 237, 105882. https://doi.org/10.1016/j.aquatox.2021.105882.

de A Boleti, A.P., Almeida, J.A., Migliolo, L., 2021. Impact of the metabolic syndrome on the evolution of neurodegenerative diseases. Neural Regen. Res. 16 (4), 688–689. https://doi.org/10.4103/1673-5374.295329.

Devault, D.A., Guillemin, J.-P., Millet, M., Eymery, F., Hulin, M., Merlo, M., 2022. Prosulfocarb at center stage! Environ. Sci. Pollut. Res. Int. 29 (1), 61–67. https://doi.org/10.1007/s11356-019-06928-8.

Donat-Vargas, C., Åkesson, A., Tornevi, A., Wennberg, M., Sommar, J., Kiviranta, H., Rantakokko, P., Bergdahl, I.A., 2018. Persistent organochlorine pollutants in plasma, blood pressure, and hypertension in a longitudinal study. Hypertension 71 (6), 1258–1268. https://doi.org/10.1161/hypertensionaha.117.10691.

Dong, Y., Xu, W., Liu, S., Xu, Z., Qiao, S., Cai, Y., 2024. Serum albumin and liver dysfunction mediate the associations between organophosphorus pesticide exposure and hypertension among US adults. Sci. Total Environ. 948, 174748. https://doi.org/10.1016/j.scitotenv.2024.174748.

Delegated regulation—2022/2291—EN, EUR-Lex. . Retrieved 7 November 2024, from. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=uriserv%3AOJ.L_.2022.303.01.0019.01.ENG&toc=OJ%3AL%3A2022%3A303%3ATOC (n.d.).

Evangelou, E., Ntritsos, G., Chondrogiorgi, M., Kavvoura, F.K., Hernández, A.F., Ntzani, E.E., Tzoulaki, I., 2016. Exposure to pesticides and diabetes: a systematic review and meta-analysis. Environ. Int. 91, 60–68. https://doi.org/10.1016/j.envint.2016.02.013.

Fahed, G., Aoun, L., Bou Zerdan, M., Allam, S., Bou Zerdan, M., Bouferraa, Y., Assi, H.I., 2022. Metabolic syndrome: updates on pathophysiology and management in 2021. Int. J. Mol. Sci. 23 (2). https://doi.org/10.3390/ijms23020786.

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. https://doi.org/10.1016/j.scitotenv.2021.146330.

Gami, A.S., Witt, B.J., Howard, D.E., Erwin, P.J., Gami, L.A., Somers, V.K., Montori, V.M., 2007. Metabolic syndrome and risk of incident cardiovascular events and death: a systematic review and meta-analysis of longitudinal studies. J. Am. Coll. Cardiol. 49 (4), 403–414. https://doi.org/10.1016/j.jacc.2006.09.032.

Glover, F., Eisenberg, M.L., Belladelli, F., Del Giudice, F., Chen, T., Mulloy, E., Caudle, W.M., 2022a. The association between organophosphate insecticides and blood pressure dysregulation: NHANES 2013-2014. Environ. Health 21 (1), 74. https://doi.org/10.1186/s12940-022-00887-3.

Glover, F., Steenland, K., Eisenberg, M.L., Belladelli, F., Mulloy, E., Del Giudice, F., Caudle, W.M., 2022b. The association between organophosphate insecticides, blood pressure dysregulation, and metabolic syndrome among U.S. adults: NHANES 2015-2016. Hyg. Environ. Health Adv. 4, 100035. https://doi.org/10.1016/j.heha.2022.100035.

Hardy, E.M., Duca, R.C., Salquebre, G., Appenzeller, B.M.R., 2015. Multi-residue analysis of organic pollutants in hair and urine for matrices comparison. Forensic Sci. Int. 249, 6–19. https://doi.org/10.1016/j.forsciint.2014.12.003.

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. https://doi.org/10.1016/j.envint.2021.106481.

Hernandez, A.F., Buha, A., Constantin, C., Wallace, D.R., Sarigiannis, D., Neagu, M., Antonijevic, B., Hayes, A.W., Wilks, M.F., Tsatsakis, A., 2019. Critical assessment and integration of separate lines of evidence for risk assessment of chemical mixtures. Arch. Toxicol. 93 (10), 2741–2757. https://doi.org/10.1007/s00204-019-02547-x.

EU Pesticides Database. Retrieved 7 November 2024, from. https://food.ec.europa.eu/plants/pesticides/eu-pesticides-database_en (n.d.).

U.S. Code. Retrieved 21 August 2025, from. https://www.epa.gov/minimum-risk-pesticides/what-pesticide (n.d.).

Ibrahim, M.M., Fjære, E., Lock, E.-J., Naville, D., Amlund, H., Meugnier, E., Le Magueresse Battistoni, B., Frøyland, L., Madsen, L., Jessen, N., Lund, S., Vidal, H., Ruzzin, J., 2011. Chronic consumption of farmed salmon containing persistent organic pollutants causes insulin resistance and obesity in mice. PLoS One 6 (9), e25170. https://doi.org/10.1371/journal.pone.0025170.

Iglesias-Gonzalez, A., Appenzeller, B.M.R., 2025. Comprehensive analysis, comprehensive understanding: the benefit of widening the scope to uncover the complexity of human chemical exposome and tailor personalized risk assessment. Sci. Total Environ. 958, 178111. https://doi.org/10.1016/j.scitotenv.2024.178111.

Jin, C., Zeng, Z., Wang, C., Luo, T., Wang, S., Zhou, J., Ni, Y., Fu, Z., Jin, Y., 2018. Insights into a possible mechanism underlying the connection of carbendazim-induced lipid metabolism disorder and gut microbiota dysbiosis in mice. Toxicol. Sci. 166 (2), 382–393. https://doi.org/10.1093/toxsci/kfy205.

Junaid, M., Sultan, M., Liu, S., Hamid, N., Yue, Q., Pei, D.-S., Wang, J., Appenzeller, B.M.R., 2024. A meta-analysis highlighting the increasing relevance of the hair matrix in exposure assessment to organic pollutants. Sci. Total Environ. 917, 170535. https://doi.org/10.1016/j.scitotenv.2024.170535.

Karra, P., Winn, M., Pauleck, S., Bulsiewicz-Jacobsen, A., Peterson, L., Coletta, A., Doherty, J., Ulrich, C.M., Summers, S.A., Gunter, M., Hardikar, S., Playdon, M.C., 2022. Metabolic dysfunction and obesity-related cancer: beyond obesity and metabolic syndrome. Obesity (Silver Spring) 30 (7), 1323–1334. https://doi.org/10.1002/oby.23444.

Kurul, F., Doruk, B., Topkaya, S.N., 2025. Principles of green chemistry: building a sustainable future. Discov. Chem. 2 (1). https://doi.org/10.1007/s44371-025-00152-9.

Kwon, H.-C., Kim, D.-H., Jeong, C.-H., Kim, Y.-J., Han, J.-H., Lim, S.-J., Shin, D.-M., Kim, D.-W., Han, S.-G., 2021. Tebuconazole fungicide induces lipid accumulation and oxidative stress in HepG2 cells. Foods 10 (10). https://doi.org/10.3390/foods10102242.

Lagisz, M., Blair, H., Kenyon, P., Uller, T., Raubenheimer, D., Nakagawa, S., 2015. Little appetite for obesity: meta-analysis of the effects of maternal obesogenic diets on offspring food intake and body mass in rodents. Int. J. Obes. 39 (12), 1669–1678. https://doi.org/10.1038/ijo.2015.160.

Lallas, P.L., 2001. The Stockholm Convention on persistent organic pollutants. Am. J. Int. Law 95 (3), 692–708. https://doi.org/10.2307/2668517.

Lallmahomed, A., Mercier, F., Costet, N., Fillol, C., Bonvallot, N., Le Bot, B., 2024. Characterization of organic contaminants in hair for biomonitoring purposes. Environ. Int. 183, 108419. https://doi.org/10.1016/j.envint.2024.108419.

Lamat, H., Sauvant-Rochat, M.-P., Tauveron, I., Bagheri, R., Ugbolue, U.C., Maqdasi, S., Navel, V., Dutheil, F., 2022. Metabolic syndrome and pesticides: a systematic review and meta-analysis. Environ. Pollut. 305, 119288. https://doi.org/10.1016/j.envpol.2022.119288.

Langer, P., Kocan, A., Tajtáková, M., Susienková, K., Rádiková, Z., Koska, J., Ksinantová, L., Imrich, R., Hucková, M., Drobná, B., Gasperíková, D., Trnovec, T., Klimes, I., 2009. Multiple adverse thyroid and metabolic health signs in the population from the area heavily polluted by organochlorine cocktail (PCB, DDE, HCB, dioxin). Thyroid. Res. 2 (1), 3. https://doi.org/10.1186/1756-6614-2-3.

Le Magueresse-Battistoni, B., Vidal, H., Naville, D., 2018. Environmental pollutants and metabolic disorders: the multi-exposure scenario of life. Front. Endocrinol. (Lausanne) 9, 582. https://doi.org/10.3389/fendo.2018.00582.

Lee, D.-H., Steffes, M.W., Sjödin, A., Jones, R.S., Needham, L.L., Jacobs Jr., D.R., 2011. Low dose organochlorine pesticides and polychlorinated biphenyls predict obesity, dyslipidemia, and insulin resistance among people free of diabetes. PLoS One 6 (1), e15977. https://doi.org/10.1371/journal.pone.0015977.

López-Bueno, R., Núñez-Cortés, R., Calatayud, J., Salazar-Méndez, J., Petermann-Rocha, F., López-Gil, J.F., Del Pozo Cruz, B., 2024. Global prevalence of cardiovascular risk factors based on the Life's Essential 8 score: an overview of systematic reviews and meta-analysis. Cardiovasc. Res. 120 (1), 13–33. https://doi.org/10.1093/cvr/cvad176.

Lukowicz, C., Ellero-Simatos, S., Régnier, M., Polizzi, A., Lasserre, F., Montagner, A., Lippi, Y., Jamin, E.L., Martin, J.-F., Naylies, C., Canlet, C., Debrauwer, L., Bertrand-Michel, J., Al Saati, T., Théodorou, V., Loiseau, N., Mselli-Lakhal, L., Guillou, H., Gamet-Payrastre, L., 2018. Metabolic effects of a chronic dietary exposure to a low-dose pesticide cocktail in mice: sexual dimorphism and role of the constitutive androstane receptor. Environ. Health Perspect. 126 (6), 067007. https://doi.org/10.1289/EHP2877.

Luz, A.L., Kassotis, C.D., Stapleton, H.M., Meyer, J.N., 2018. The high-production volume fungicide pyraclostrobin induces triglyceride accumulation associated with mitochondrial dysfunction, and promotes adipocyte differentiation independent of PPARγ activation, in 3T3-L1 cells. Toxicology 393, 150–159. https://doi.org/10.1016/j.tox.2017.11.010.

Martin, O., Scholze, M., Ermler, S., McPhie, J., Bopp, S.K., Kienzler, A., Parissis, N., Kortenkamp, A., 2021. Ten years of research on synergisms and antagonisms in chemical mixtures: a systematic review and quantitative reappraisal of mixture studies. Environ. Int. 146, 106206. https://doi.org/10.1016/j.envint.2020.106206.

Mérida, D.M., Moreno-Franco, B., Marquès, M., León-Latre, M., Laclaustra, M., Guallar-Castillón, P., 2023. Phthalate exposure and the metabolic syndrome: a systematic review and meta-analysis. Environ. Pollut. 333, 121957. https://doi.org/10.1016/j.envpol.2023.121957.

Muscogiuri, G., Barrea, L., Laudisio, D., Savastano, S., Colao, A., 2017. Obesogenic endocrine disruptors and obesity: myths and truths. Arch. Toxicol. 91 (11), 3469–3475. https://doi.org/10.1007/s00204-017-2071-1.

Nguyen, H.D., Oh, H., Kim, M.-S., 2022. The effects of chemical mixtures on lipid profiles in the Korean adult population: threshold and molecular mechanisms for dyslipidemia involved. Environ. Sci. Pollut. Res. 29 (26), 39182–39208. https://doi.org/10.1007/s11356-022-18871-2.

Noubiap, J.J., Nansseu, J.R., Lontchi-Yimagou, E., Nkeck, J.R., Nyaga, U.F., Ngouo, A.T., Tounouga, D.N., Tianyi, F.-L., Foka, A.J., Ndoadoumgue, A.L., Bigna, J.J., 2022. Geographic distribution of metabolic syndrome and its components in the general adult population: a meta-analysis of global data from 28 million individuals. Diabetes Res. Clin. Pract. 188, 109924. https://doi.org/10.1016/j.diabres.2022.109924.

Park, C.M., Kim, K.-T., Rhyu, D.Y., 2020. Low-concentration exposure to organochlorine pesticides (OCPs) in L6 myotubes and RIN-m5F pancreatic beta cells induces disorders of glucose metabolism. Toxicol. in Vitro 65 (104767), 104767. https://doi.org/10.1016/j.tiv.2020.104767.

Park, C.-M., Kim, K.-T., Rhyu, D.-Y., 2021. Exposure to a low concentration of mixed organochlorine pesticides impairs glucose metabolism and mitochondrial function in L6 myotubes and zebrafish. J. Hazard. Mater. 414, 125437. https://doi.org/10.1016/j.jhazmat.2021.125437.

Pathak, V.M., Verma, V.K., Rawat, B.S., Kaur, B., Babu, N., Sharma, A., Dewali, S., Yadav, M., Kumari, R., Singh, S., Mohapatra, A., Pandey, V., Rana, N., Cunill, J.M., 2022. Current status of pesticide effects on environment, human health and it's eco-friendly management as bioremediation: a comprehensive review. Front. Microbiol. 13, 962619. https://doi.org/10.3389/fmicb.2022.962619.

Peng, F.-J., Emond, C., Hardy, E.M., Sauvageot, N., Alkerwi, A., Lair, M.-L., Appenzeller, B.M.R., NESCAV project group for the Grand Duchy of Luxembourg, 2021. Population-based biomonitoring of exposure to persistent and non-persistent organic pollutants in the Grand Duchy of Luxembourg: results from hair analysis. Environ. Int. 153, 106526. https://doi.org/10.1016/j.envint.2021.106526.

Peng, F.-J., Palazzi, P., Mezzache, S., Adelin, E., Bourokba, N., Bastien, P., Appenzeller, B.M.R., 2023. Association between environmental exposure to multiclass organic pollutants and sex steroid hormone levels in women of reproductive age. Environ. Sci. Technol. https://doi.org/10.1021/acs.est.3c06095.

Peng, F.-J., Lin, C.-A., Wada, R., Bodinier, B., Iglesias-González, A., Palazzi, P., Streel, S., Guillaume, M., Vuckovic, D., Chadeau-Hyam, M., Appenzeller, B.M.R., NESCAV project group, 2024a. Association of hair polychlorinated biphenyls and multiclass pesticides with obesity, diabetes, hypertension and dyslipidemia in NESCAV study. J. Hazard. Mater. 461, 132637. https://doi.org/10.1016/j.jhazmat.2023.132637.

Peng, F.-J., Palazzi, P., Mezzache, S., Adelin, E., Bourokba, N., Bastien, P., Appenzeller, B.M.R., 2024b. Cross-sectional examination of thyroid hormones and environmental exposure to multiclass pesticides in women of reproductive age in China. Environ. Health Perspect. https://doi.org/10.1289/EHP14378.

Petit, P., Vuillerme, N., 2025. Global research trends on the human exposome: a bibliometric analysis (2005–2024). Environ. Sci. Pollut. Res. 32 (13), 7808–7833. https://doi.org/10.1007/s11356-025-36197-7.

Phelps, N.H., Singleton, R.K., Zhou, B., Heap, R.A., Mishra, A., Bennett, J.E., Paciorek, C.J., Lhoste, V.P., Carrillo-Larco, R.M., Stevens, G.A., Rodriguez-Martinez, A., Bixby, H., Bentham, J., Di Cesare, M., Danaei, G., Rayner, A.W., Barradas-Pires, A., Cowan, M.J., Savin, S., Ezzati, M., 2024. Worldwide trends in underweight and obesity from 1990 to 2022: a pooled analysis of 3663 population-representative studies with 222 million children, adolescents, and adults. Lancet 403 (10431), 1027–1050. https://doi.org/10.1016/s0140-6736(23)02750-2.

Rajak, P., Roy, S., Podder, S., Dutta, M., Sarkar, S., Ganguly, A., Mandi, M., Dutta, A., Nanda, S., Khatun, S., 2022. Synergistic action of organophosphates and COVID-19 on inflammation, oxidative stress, and renin-angiotensin system can amplify the risk of cardiovascular maladies. Toxicol. Appl. Pharmacol. 456, 116267. https://doi.org/10.1016/j.taap.2022.116267.

Reina-Pérez, I., Artacho-Cordón, F., Mustieles, V., Castellano-Castillo, D., Cardona, F., Jiménez-Díaz, I., López-Medina, J.A., Alcaide, J., Ocaña-Wilhelmi, L., Iribarne-Durán, L.M., Arrebola, J.P., Olea, N., Tinahones, F.J., Fernández, M.F., 2023. Cross-sectional associations of persistent organic pollutants measured in adipose tissue and metabolic syndrome in clinically diagnosed middle-aged adults. Environ. Res. 222, 115350. https://doi.org/10.1016/j.envres.2023.115350.

Ruiz-Castell, M., Kandala, N.-B., Kuemmerle, A., Schritz, A., Barré, J., Delagardelle, C., Krippler, S., Schmit, J.-C., Stranges, S., 2016. Hypertension burden in Luxembourg: individual risk factors and geographic variations, 2013 to 2015 European Health Examination Survey. Medicine (Baltimore) 95 (36), e4758. https://doi.org/10.1097/MD.0000000000004758.

Ruiz-Castell, M., Le Coroller, G., Pexaras, A., Ciprián, G.M., Fagherazzi, G., Bohn, T., Maitre, L., Sunyer, J., Appenzeller, B.M.R., 2023. Characterizing the adult exposome in men and women from the general population: results from the EHES-LUX study. Environ. Int. 173, 107780. https://doi.org/10.1016/j.envint.2023.107780.

Salihovic, S., Ganna, A., Fall, T., Broeckling, C.D., Prenni, J.E., van Bavel, B., Lind, P.M., Ingelsson, E., Lind, L., 2016. The metabolic fingerprint of p,p'-DDE and HCB exposure in humans. Environ. Int. 88, 60–66. https://doi.org/10.1016/j.envint.2015.12.015.

Samsuddin, N., Rampal, K.G., Ismail, N.H., Abdullah, N.Z., Nasreen, H.E., 2016. Pesticides exposure and cardiovascular hemodynamic parameters among male workers involved in mosquito control in east coast of Malaysia. Am. J. Hypertens. 29 (2), 226–233. https://doi.org/10.1093/ajh/hpv093.

Sharma, S., Kumar, S., Kumar, V., Sharma, R., 2023. Pesticides and vegetables: ecological and metabolic fate with their field and food significance. Int. J. Environ. Sci. Technol. (Tehran) 20 (2), 2267–2292. https://doi.org/10.1007/s13762-021-03716-1.

Shoshtari-Yeganeh, B., Zarean, M., Mansourian, M., Riahi, R., Poursafa, P., Teiri, H., Rafiei, N., Dehdashti, B., Kelishadi, R., 2019. Systematic review and meta-analysis on the association between phthalates exposure and insulin resistance. Environ. Sci. Pollut. Res. Int. 26 (10), 9435–9442. https://doi.org/10.1007/s11356-019-04373-1.

Snedeker, S.M., Hay, A.G., 2012. Do interactions between gut ecology and environmental chemicals contribute to obesity and diabetes? Environ. Health Perspect. 120 (3), 332–339. https://doi.org/10.1289/ehp.1104204.

Streel, S., Donneau, A.-F., Hoge, A., Majerus, S., Kolh, P., Chapelle, J.-P., Albert, A., Guillaume, M., 2015. Socioeconomic impact on the prevalence of cardiovascular risk factors in Wallonia, Belgium: a population-based study. Biomed. Res. Int. 2015, 580849. https://doi.org/10.1155/2015/580849.

Suzuki, H., Ito, Y., Noro, Y., Koketsu, M., Kamijima, M., Tomizawa, M., 2014. Organophosphate agents induce plasma hypertriglyceridemia in mouse via single or dual inhibition of the endocannabinoid hydrolyzing enzyme(s). Toxicol. Lett. 225 (1), 153–157. https://doi.org/10.1016/j.toxlet.2013.12.004.

Tanner, E.M., Bornehag, C.-G., Gennings, C., 2019. Repeated holdout validation for weighted quantile sum regression. MethodsX 6, 2855–2860. https://doi.org/10.1016/j.mex.2019.11.008.

Van Ael, E., Covaci, A., Das, K., Lepoint, G., Blust, R., Bervoets, L., 2013. Factors influencing the bioaccumulation of persistent organic pollutants in food webs of the scheldt estuary. Environ. Sci. Technol. 47 (19), 11221–11231. https://doi.org/10.1021/es400307s.

van Buuren, S., 2012. Flexible Imputation of Missing Data. CRC Press. https://books.google.com/books/about/Flexible_Imputation_of_Missing_Data.html?hl=&id=M89TDSml-FoC.

Vuong, A.M., Zhang, C., Chen, A., 2022. Associations of neonicotinoids with insulin and glucose homeostasis parameters in US adults: NHANES 2015-2016. Chemosphere 286 (Pt 1), 131642. https://doi.org/10.1016/j.chemosphere.2021.131642.

Waalen, J., 2014. The genetics of human obesity. Transl. Res. 164 (4), 293–301. https://doi.org/10.1016/j.trsl.2014.05.010.

Wang, F., Xiang, L., Sze-Yin Leung, K., Elsner, M., Zhang, Y., Guo, Y., Pan, B., Sun, H., An, T., Ying, G., Brooks, B.W., Hou, D., Helbling, D.E., Sun, J., Qiu, H., Vogel, T.M., Zhang, W., Gao, Y., Simpson, M.J., Tiedje, J.M., 2024. Emerging contaminants: a one health perspective. Innovation (Camb.) 5 (4), 100612. https://doi.org/10.1016/j.xinn.2024.100612.

Wei, R., Wang, J., Jia, E., Chen, T., Ni, Y., Jia, W., 2018a. GSimp: a Gibbs sampler based left-censored missing value imputation approach for metabolomics studies. PLoS Comput. Biol. 14 (1), e1005973. https://doi.org/10.1371/journal.pcbi.1005973.

Wei, R., Wang, J., Su, M., Jia, E., Chen, S., Chen, T., Ni, Y., 2018b. Missing value imputation approach for mass spectrometry-based metabolomics data. Sci. Rep. 8 (1), 663. https://doi.org/10.1038/s41598-017-19120-0.

Wei, Y., Wang, L., Liu, J., 2023. The diabetogenic effects of pesticides: evidence based on epidemiological and toxicological studies. Environ. Pollut. 331 (Pt 2), 121927. https://doi.org/10.1016/j.envpol.2023.121927.

WHO, 2018. Diabetes. https://www.who.int/news-room/fact-sheets/detail/diabetes.

Wu, H., Bertrand, K.A., Choi, A.L., Hu, F.B., Laden, F., Grandjean, P., Sun, Q., 2013. Persistent organic pollutants and type 2 diabetes: a prospective analysis in the nurses' health study and meta-analysis. Environ. Health Perspect. 121 (2), 153–161. https://doi.org/10.1289/ehp.1205248.

Xiao, X., Clark, J.M., Park, Y., 2017. Potential contribution of insecticide exposure and development of obesity and type 2 diabetes. Food Chem. Toxicol. 105, 456–474. https://doi.org/10.1016/j.fct.2017.05.003.

Xiao, T., Huang, Z., Zheng, C., Quach, B., Zhu, Y., Li, F., Liang, W., Baker, J., Reichetzeder, C., Hocher, B., Yang, Y., 2024. Associations of bisphenol A exposure with metabolic syndrome and its components: a systematic review and meta-analysis. Obes. Rev. 25 (6), e13738. https://doi.org/10.1111/obr.13738.

Yang, J.S., Park, Y., 2018. Insecticide exposure and development of nonalcoholic fatty liver disease. J. Agric. Food Chem. 66 (39), 10132–10138. https://doi.org/10.1021/acs.jafc.8b03177.

Zago, A.M., Faria, N.M.X., Fávero, J.L., Meucci, R.D., Woskie, S., Fassa, A.G., 2022. Pesticide exposure and risk of cardiovascular disease: a systematic review. Glob. Public Health 17 (12), 3944–3966. https://doi.org/10.1080/17441692.2020.1808693.

Zhang, Y., Dong, T., Hu, W., Wang, X., Xu, B., Lin, Z., Hofer, T., Stefanoff, P., Chen, Y., Wang, X., Xia, Y., 2019. Association between exposure to a mixture of phenols, pesticides, and phthalates and obesity: comparison of three statistical models. Environ. Int. 123, 325–336. https://doi.org/10.1016/j.envint.2018.11.076.

Zhang, M., Zhu, J., Zheng, P., Wei, C., Li, D., Wang, Q., Zhang, H., 2024. Neonicotinoid insecticides and their characteristic metabolites may induce high fasting blood glucose and obesity in human. Expo. Health. https://doi.org/10.1007/s12403-024-00633-9.

Zhou, B., Carrillo-Larco, R.M., Danaei, G., Riley, L.M., Paciorek, C.J., Stevens, G.A., Gregg, E.W., Bennett, J.E., Solomon, B., Singleton, R.K., Sophiea, M.K., Iurilli, M.L., Lhoste, V.P., Cowan, M.J., Savin, S., Woodward, M., Balanova, Y., Cifkova, R., Damasceno, A., Ezzati, M., 2021. Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. Lancet 398 (10304), 957–980. https://doi.org/10.1016/s0140-6736(21)01330-1.

Glossary

BP: Blood pressure
FDR: False discovery rate
FPG: Fasting plasma glucose
EHES-LUX: European Health Examination Survey in Luxembourg
GC–MS/MS: Gas chromatography-tandem mass spectrometry
HDL-c: High density cholesterol
LDL-C: Low-density lipoprotein cholesterol
LOD: Limit of detection
MetS: Metabolic syndrome
NAFLD: Non-alcoholic fatty liver disease
OCs: Organochlorines
OPs: Organophosphates
PBDEs: Polybrominated flame retardants
PCT: Percentile
PCBs: Polychlorobiphenyls
PNP: P-Nitrophenol
QRILC: Quantile Regression Imputation of Left-Censored data
T4: Tetraiodothyronine
WC: Waist circumference
WQS: Weighted quantile sum