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Full length article



Association between dietary pesticide exposure profiles and body weight change in French adults: Results from the NutriNet-Santé cohort

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ABSTRACT

Background: Pesticides cause a wide range of deleterious health effects, including metabolic disorders. Little is known about the effects of dietary pesticide exposure on body weight (BW) change in the general population. We aimed to investigate the role of dietary pesticide exposure in BW change among NutriNet-Santé participants, focusing on potential sexual dimorphism.

Methods: Participants completed a Food Frequency Questionnaire (2014), assessing conventional and organic food consumption. Dietary exposure from plant foods of 25 commonly used pesticides was estimated using a residue database, accounting for agricultural practices (conventional and organic).

Exposure profiles based on dietary patterns were computed using Non-negative Matrix Factorization (NMF). Mixed models were used to estimate the associations between BW change and exposure to pesticide mixtures, overall and after stratification by sex and menopausal status.

Results: The final sample included 32,062 participants (8,211 men, 10,637 premenopausal, and 13,214 postmenopausal women). The median (IQR) follow-up was 7.0 (4.4; 8.0) years. Four pesticide profiles were inferred. Overall, men and postmenopausal women lost BW during follow-up, whereas premenopausal women gained BW. Higher exposure to NMF3, reflecting a lower exposure to synthetic pesticides, was associated with a lower BW gain, especially in premenopausal women ($\beta(95\%CI) = -0.04 (-0.07; 0)$ kg/year, $p = 0.04$).

Higher exposure to NMF2, highly positively correlated with a mixture of synthetic pesticides (azoxystrobin, boscalid, chlorpropham, cyprodinil, difenoconazole, fenhexamid, iprodione, tebuconazole, and lambda-cyhalothrin), was associated with a higher BW loss in men ($\beta(95\%CI) = -0.05 (-0.08; -0.03)$ kg/year, $p < 0.0001$). No associations were observed for NMF1 and 4.

Conclusions: This study suggests a role of pesticide exposure, inferred from dietary patterns, on BW change, with sexually dimorphic actions, including a potential role of a lower exposure to synthetic pesticides on BW change in

Abbreviations: EDC, Endocrine-Disrupting Chemicals; T2D, Type 2 Diabetes; BW, Body Weight; Org-FFQ, Organic Food Frequency Questionnaire; UPF, Ultra-Processed Food; CVUAS, Chemisches und Veterinäruntersuchungsamt Stuttgart; EFSA, European Food Safety Authority; y.o, years old; MET, Metabolic Equivalent of Task; PNNS, Programme National Nutrition Santé; NMF, Non-negative Matrix Factorization.

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women. In men, exposure to a specific pesticide mixture was associated with higher BW loss. The underlying mechanisms need further elucidation.

1. Introduction

Prevalence of overweight and obesity has been dramatically increasing for the past three decades, reaching epidemic proportions, thus becoming one of the major public health challenges worldwide. If current trends persist, it is estimated that, by the year 2030, 38 % of the world's population will be overweight and another 20 % will be obese (Smith and Smith, 2016). These conditions are known to enhance the incidence of a broad spectrum of comorbidities including insulin resistance, metabolic syndrome, type 2 diabetes (T2D), cardiovascular diseases, some cancers and infertility (Belladelli et al., 2022; Petrakis et al., 2017).

Body weight (BW) gain, leading to obesity is the result of an imbalance between energy expenditure and food intake. It can arise from multiple causes, and, beyond genetic and lifestyle factors, environmental factors have been increasingly pointed out (Heindel et al., 2022). Among environmental factors, synthetic pesticides are molecules of interest because they are used on very large scale in conventional agricultural practices to ensure the quantity of food production, representing a large economic market worldwide. However, given their absence of specificity, they contaminate the whole environment (*i.e.*, soil, water, air,...) (Tudi et al., 2021).

The deleterious effects of pesticides on both human health and ecosystems are more and more documented (Blair et al., 2015). In particular, more than 100 pesticide substances have been suspected or confirmed as endocrine disruptors (EDCs) (Mnif et al., 2011). By mimicking hormonal actions, EDCs exhibit a wide range of deleterious effects, including potential metabolic dysregulation, reprotoxicity, as well as thyroid dysregulation, neurodevelopmental and neuroendocrine impairments, which could be gender-dependent. These perturbations could lead to the development of diabetes, obesity, and hormone-dependent cancers (Gore et al., 2015). Organochlorine pesticides, which are persistent pollutants in the environment have been shown to increase the risk of T2D (Evangelou et al., 2016). Although these substances have been banned in many European countries since the Stockholm Convention in 2001, they still persist in the environment. They have been gradually replaced by other families of pesticide substances which can also play a role in the development of obesity (organophosphorus, neonicotinoids, pyrethroids, etc.). Some epidemiological studies qualify these classes of compounds as "obesogenic factors", due to their ability to increase adipocyte commitment, differentiation and size, to alter metabolic setpoints or affect the hormonal regulation of appetite and satiety (Heindel and Blumberg, 2019). Given the sex differences on metabolic regulation, it is relevant to focus on the potential sexual dimorphism of the associations (Tramunt et al., 2020).

However, studies investigating the effects of pesticides on BW change and metabolic dysregulation are scarce and mostly conducted in occupational settings. Among farmers, occupational chronic pesticide exposure have been associated with higher odds of overweight in Brazil, and higher odds of obesity in Thailand (Araújo et al., 2022; Noppakun and Juntarawijit, 2021).

The main source of pesticide exposure in the general population is through the diet (Nougadère et al., 2012) and consumers are chronically exposed to low doses of residues of contaminants mixtures. However, studies investigating the effects of pesticides at relevant doses for the general adult population are lacking. Indeed, most of the studies reported in reviews have been conducted in laboratory animals, and have generally considered the association between prenatal or postnatal exposure to different categories of pesticides and BW (Pinos et al., 2021). A study has identified a sexual dimorphism in mice exposed to a

low-dose pesticide mixture (Lukowicz et al., 2018). The few works in humans have been also conducted during childhood and results remain inconsistent (Pinos et al., 2021).

Additional studies focusing on the role of chronic pesticide mixtures exposure are therefore needed to account for potential synergism or potentiation effects in humans, considering men and women separately.

Therefore, the aim of our study was to assess whether distinct dietary pesticide exposure profiles were differentially associated with BW change in both adult men and women over time. We hypothesized, based on the literature, that higher dietary exposure to pesticide would be associated with higher weight gain. We used a prospective design and selected 25 pesticides commonly used in Europe, 3 of them being authorized in organic farming.

2. Materials and methods

2.1. Study population

In 2009, the NutriNet-Santé study (NCT03335644), an ongoing web-based prospective cohort of French volunteers, was launched. This study was conducted in accordance with the Helsinki Declaration and all procedures were approved by the Institutional Review Board of the French Institute for Health and Medical Research (IRB Inserm 94 0000388FWA00005831).

2.2. Dietary intake assessment

Dietary data were derived from a sub-sample of adults who completed a validated semi-quantitative food frequency questionnaire about organic and conventional food consumption between June and December 2014 (Org-FFQ).

For each of the 264 items (food and beverages) of the Org-FFQ, participants answered the question «How often was the product of organic origin?» by choosing one of the following answers: never, rarely, half-of-the-time, often, always. Then, organic food consumption was estimated by applying weights of 0, 0.25, 0.5, 0.75 and 1 to the 5 categories of frequency, in ascending order, for each item. All items were combined into 33 food groups (*e.g.* fruits, vegetables, cereals, meat, etc.), and the share (as weight, *i.e.* g/day) of organic food consumption was calculated as the proportion of organic food for each group. The sensitivity analyses regarding the weighting of the modalities have been published elsewhere (Baudry et al., 2015).

We also calculated the amount of food from plant origin consumed by each participant (in g/day), and we estimated the degree of processing of each food item according to the NOVA classification (Srouf et al., 2020), so as to estimate the amount of ultra-processed food (UPF, as % of weight of the total diet) using repeated 24 h-records around the Org-FFQ.

2.3. Pesticide exposure assessment

Plant-based food contamination data came from the European Union reference laboratory for plant pesticide analyses, the Chemisches und Veterinäruntersuchungsamt Stuttgart (CVUAS) ("Untersuchungssämter Baden-Württemberg. Chemisches und Veterinäruntersuchungsamt Stuttgart (Startseite) [internet]," 2023). Only plant-derived foods were considered in this study to estimate pesticide exposure, as much higher levels of pesticide contamination have been observed in plant food than animal food (European Food Safety Authority (EFSA), 2018a). The computation methods for pesticide data, pesticide selection, and calculation of dietary pesticide exposure are described in details in

Supplemental Method 1.

2.4. Body weight data assessment

Participants were invited to complete anthropometric questionnaires on the NutriNet-Santé website to report their BW on a half-yearly basis, from 2014 to June 2021. Anthropometric measurements were assessed by a healthcare professional or self-declared according to a standardized procedure. A validation study showed high adequacy between self-reported weight and height data and data collected during a face-to-face interview (Lassale et al., 2015). We included participants who have completed an anthropometric questionnaire during the 6 months preceding the completion of the Org-FFQ, and the BW closest to the filling-in of the Org-FFQ was considered as the baseline BW.

2.5. Covariates

We collected sociodemographic and lifestyle characteristics at baseline, including sex, age (>18 y. o., continuous), height (in cm, continuous), occupation (categorized into: employee and manual worker, intermediate profession, managerial staff and intellectual, retired, self-employed and farmer, student, unemployed or never employed), educational level (trichotomized as less than high-school diploma, high-school diploma, and post-graduate), smoking status (current, former or never smoker) and alcohol consumption (in g/day, continuous). Monthly income was calculated per unit of consumption, and categorized into four classes: less than 1200€, 1200-1800€, 1800-2700€, and more than 2700€. Physical activity level was evaluated using the validated International Physical Activity Questionnaire and trichotomized as low, moderate, and high level (Craig et al., 2003). We did not account for ethnicity in this study since the French legislation does not allow to collect this type of data, except upon special request for specific research.

For adjustment purposes, we computed the simplified PNNS (Programme National Nutrition Santé) guidelines score 2, expressing the level of adherence to French dietary guidelines proposed by the High Council of Public Health. The scoring system is described elsewhere (Kesse-Guyot et al., 2021) and details are provided in Supplemental Method 2.

Furthermore, participants were asked if they were on a weight-loss diet, during the whole follow-up, or particularly during the year of completion of the Org-FFQ, since experiencing a weight-loss diet modifies one's usual eating behavior. Participants were also asked if they suffered from diseases or encountered an event which may play a role on BW change (i.e. cancers, eating disorders, Cushing syndrome, or bariatric surgery). We also identified participants who used drugs (during at least 3 months) that could interfere in BW change (e.g. steroids, antidepressants, ...), based on a list established by a medical practitioner.

The adjustment variables are interlinked, therefore, we constructed a Directed Acyclic Graph to scheme their possible relation with pesticide exposure and/or BW change (Supplemental Fig. 1).

2.6. Statistical analysis

Among the 37,685 participants who filled in the Org-FFQ, we were able to calculate the basal metabolic rate for 37,305 participants (n = 380 exclusions). We excluded those who were detected as under- or over- reporters, on the basis of the ratio of their energy intake to their energy requirement (n = 2109 exclusions) (Schofield, 1985). Cut-offs corresponded to the 1st and the 99th percentile of the ratio distribution in the sample of the Org-FFQ (Baudry et al., 2015). We also excluded those not living in mainland France with missing data to assess the PNNS guidelines score 2 (n = 754 exclusions), and those with no BW data during the 6 months before or after the Org-FFQ (n = 323 exclusions). We excluded volunteers with only one BW measurement during the follow-up (n = 461 exclusions), and also all pregnant women during

the follow-up (n = 1,596 exclusions), yielding a final sample of 32,062 participants. A flowchart for the study sample selection is presented in Fig. 1.

Pesticide exposure profiles related to diet were inferred from dietary patterns using Non-negative Matrix Factorization (NMF), a non-supervised data decomposition method, relevant for the analysis of high dimensional data with excess zeros such as exposure to chemicals constrained by the detection limits of assay techniques. Pesticides profiles have been set up on the basis of Lee's decision rules (Lee and Seung, 2000). Details about the implementation of this technique in the

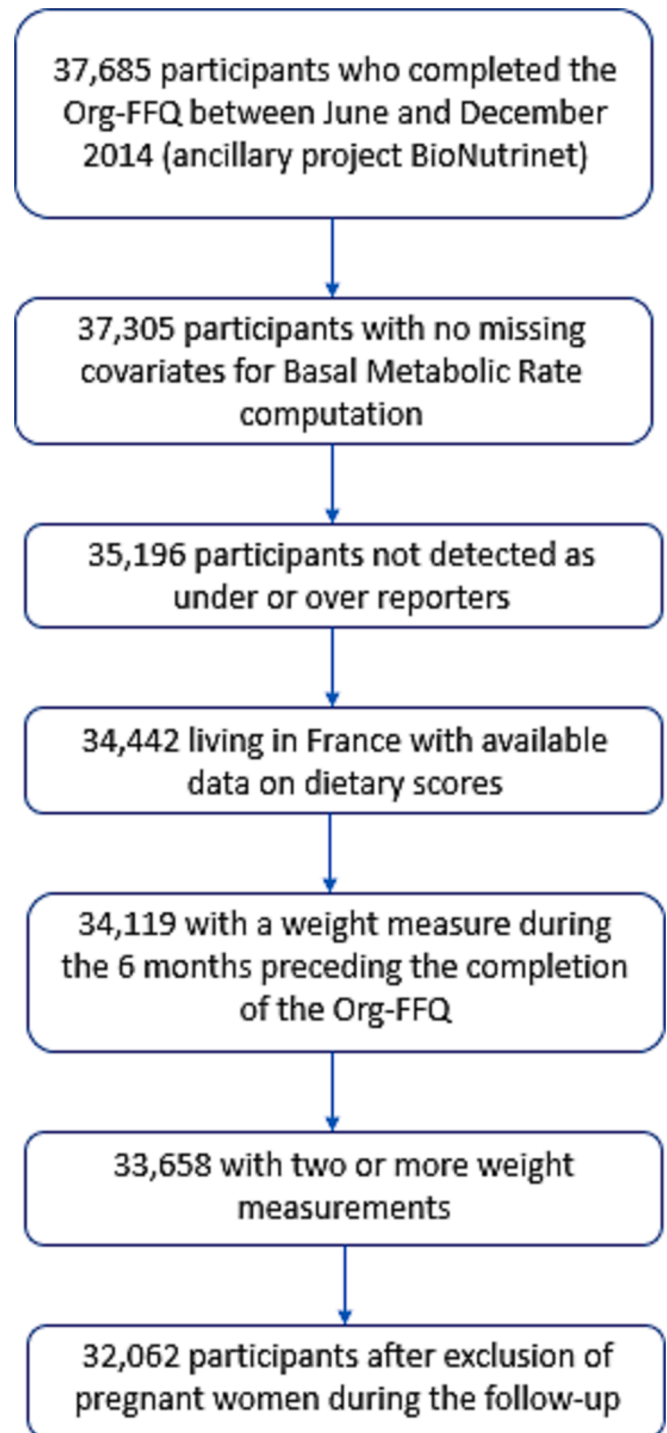


Fig. 1. Flow-chart for the study sample selection, NutriNet-Santé study, 2014–2021.

Table 1
Characteristics of the study sample, NutriNet-Santé study (N = 32,062).

	Women (N = 23,851 74.4 %)	Men (N = 8,211,26.6 %)
Age, mean (SD)	52.9 (13.1)	58.5 (13.1)
Monthly income per household unit		
< €1200	3023 (12.7 %)	661 (8.1 %)
€ 1200 – 1800	5671 (23.8 %)	1723 (21.0 %)
€ 1800 – 2700	6409 (26.9 %)	2247 (27.4 %)
> € 2700	6993 (29.3 %)	3313 (40.4 %)
Unwilling to answer	1755 (7.4 %)	267 (3.3 %)
Educational level		
Less than high-school diploma	4814 (20.2 %)	2132 (26.0 %)
High-school diploma	3810 (16.0 %)	1010 (12.3 %)
Post-graduate	15,227 (63.8 %)	5069 (61.7 %)
Occupational status		
Employee, manual worker	3934 (16.5 %)	608 (7.4 %)
Intermediate profession	3931 (16.5 %)	798 (9.7 %)
Managerial staff, intellectual	4673 (19.6 %)	1866 (22.7 %)
Retired	7778 (32.6 %)	4357 (53.1 %)
Self-employed, farmer	424 (1.8 %)	180 (2.2 %)
Student	515 (2.2 %)	70 (0.9 %)
Unemployed or never employed	3051 (10.9 %)	332 (4.0 %)
Marital status		
Single	3280 (13.8 %)	757 (9.2 %)
Divorced or separated	2682 (11.2 %)	552 (6.7 %)
Cohabiting	3970 (16.7 %)	1203 (14.7 %)
Married	13,000 (54.5 %)	5524 (67.3 %)
Widowed	919 (3.9 %)	175 (2.1 %)
Level of physical activity*		
High (>1500 MET-min/week)	3420 (41.7 %)	7425 (31.1 %)
Moderate (600–1500 MET-min/week)	2668 (32.5 %)	9029 (37.9 %)
Low (<600 MET-min/week)	1368 (16.7 %)	4702 (19.7 %)
Missing data	755 (9.2 %)	2695 (11.3 %)
Place of residence		
Rural community	5396 (22.6 %)	1831 (22.3 %)
Urban unit with less than 20,000 inhabitants	3654 (15.3 %)	1345 (16.4 %)
Urban unit with between 20,000 and 200,000 inhabitants	4403 (18.5 %)	1544 (18.8 %)
Urban unit with more than 200,000 inhabitants	10,398 (43.6 %)	3491 (42.5 %)
Smoking habits		
Current smoker	2652 (11.1 %)	76 (9.31 %)
Former smoker	8969 (37.6 %)	4248 (51.7 %)
Never smoker	12,230 (51.3 %)	3199 (39.0 %)
Body Mass Index at baseline (kg/m ²)		
< 18.5	1417 (5.9 %)	69 (0.8 %)
18.5–25	15,040 (63.9 %)	4322 (52.6 %)
25–30	4987 (20.9 %)	3008 (36.6 %)
> 30	2407 (10.1 %)	812 (9.9 %)

SD: standard deviation, MET: Metabolic Equivalent of Task.

* Missing data are due to optional questions.

NutriNet-Santé cohort have been previously published (Rebouillat et al., 2021). An individual score for each profile was extracted.

General linear mixed models were used (combining the characteristics of general linear models and mixed models), with a random effect on intercept and time and a repeated effect on individuals, to estimate the association between each pesticide exposure profiles inferred from dietary patterns and repeated measurements of BW. Scores were standardized, so that the parameters associated to time were numerically comparable for each NMF profile.

The first model was adjusted for height (cm), age (>18 y. o.) and sex (when appropriate, minimally adjusted model), and the second (main model) was further adjusted for occupational status, educational level, physical activity level, smoking practices, alcohol consumption, menopausal status for women, energy intake without alcohol, PNNS guidelines score 2, and weight-loss diet practice during the year covering the FFQ window. Models were implemented for the total sample, by sex, and by menopausal status for women, given the hypothesis of a sexually dimorphic response led by estrogen metabolism.

Several sensitivity analyses were performed. Models with additional adjustments, for the amount of fruits and vegetables (without fruit juices and soups) in the diet (g/day), for the amount of plant-based foods in the diet (g/day), for the quantity of UPF (% of weight of the total diet), or for

the intake of some nutrients (carbohydrates, saturated fatty acids, sodium and fibers, g/day) were implemented. The share of UPF in the diet was estimated by multiple imputations to handle missing data (n = 12,601 missing data among participants who did not provide a sufficient number of 24 h-records). We also built an adjusted model taking account of participants who declared a weight-loss diet practice during the whole follow-up. In another analysis, we excluded participants who declared being on a weight-loss diet during the year covering the FFQ window. Then, we excluded participants who declared a disease or health event which could impact their BW during the follow-up (cancers, eating disorders, Cushing syndrome or bariatric surgery), or those who declared using drugs that could lead to BW change for more than 3 months. Analyses were all stratified by sex. In addition, we also performed a set of stratification analyses for the whole sample and in men and women separately: i) by overall dietary quality (using the PNNS guidelines score 2), ii) by median-age, and considering menopausal status for women (as BW change dynamics could vary during lifetime), and iii) by baseline BMI.

The analyses were computed with R software V4.0.3® (for the extraction of the NMF profiles) and SAS software V9.4® (for descriptive analyses and mixed models).

Table 2
Association between NMF pesticide exposure profiles and BW change, adjusted for the principal sociodemographic and lifestyle characteristics, 2014–2021, France¹.

	Total (N = 32,062)		Men (N = 8,211)		Women (N = 23,851)		Pre-menopausal women (N = 10,637)		Post-menopausal women (N = 13,214)	
	Weight change (kg/year)	P ¹	Weight change (kg/year)	P ¹	Weight change (kg/year)	P ¹	Weight change (kg/year)	P ¹	Weight change (kg/year)	P ¹
Weight change / year	0.08 (0.06; 0.09)	< 0.0001	-0.05 (-0.07; -0.03)	< 0.0001	0.12 (0.10; 0.14)	< 0.0001	0.32 (0.29; 0.35)	< 0.0001	-0.03 (-0.05; -0.01)	0.01
Weight at baseline										
NMF: 1	0.45 (0.27; 0.62)	< 0.0001	0.44 (0.17; 0.70)	0.001	0.43 (0.22; 0.64)	< 0.0001	0.48 (0.13; 0.83)	0.007	0.39 (0.12; 0.65)	0.005
NMF: 2	0.84 (0.65; 1.02)	< 0.0001	0.98 (0.68; 1.28)	< 0.0001	0.78 (0.56; 1.01)	< 0.0001	0.79 (0.40; 1.18)	< 0.0001	0.76 (-0.49; 1.03)	< 0.0001
NMF: 3	-0.64 (-0.82; -0.46)	< 0.0001	-0.43 (-0.71; -0.15)	0.003	-0.68 (-0.89; -0.46)	< 0.0001	-0.87 (-1.23; -0.50)	< 0.0001	-0.65 (-0.92; -0.39)	< 0.0001
NMF: 4	-0.43 (-0.60; -0.25)	< 0.0001	-0.11 (-0.44; 0.22)	0.50	-0.48 (-0.68; -0.28)	< 0.0001	-0.56 (-0.89; -0.23)	0.0009	-0.44 (-0.69; -0.18)	0.0008
Additional weight change / year										
NMF: 1 x t	0 (-0.02; 0.01)	0.64	0 (-0.02; 0.02)	0.86	0 (-0.02; 0.02)	0.92	0.02 (-0.0; 0.06)	0.18	0.01 (-0.01; 0.03)	0.51
NMF: 2 x t	-0.03 (-0.04; -0.01)	0.0003	-0.05 (-0.08; -0.03)	< 0.0001	-0.02 (-0.03; 0)	0.08	0.02 (-0.01; 0.05)	0.20	0 (-0.02; 0.02)	0.84
NMF: 3 x t	-0.02 (-0.03; -0.01)	0.006	-0.01 (-0.04; 0.01)	0.30	-0.03 (-0.05; -0.01)	0.0008	-0.04 (-0.07; 0)	0.04	0 (-0.02; 0.02)	0.75
NMF: 4 x t	0.01 (-0.01; 0.02)	0.42	-0.01 (-0.04; 0.02)	0.45	0 (-0.02; 0.01)	0.84	0.02 (-0.01; 0.04)	0.31	-0.01 (-0.03; 0.01)	0.32

BW: body weight, t: time.

¹ P: p-value of β coefficient. Pint refers to the interaction between NMF component and population subgroups (by sex and menopausal status) on the BW change. The β -coefficient associated to time indicates the BW change over time. The β associated to NMF component gives the direction of variation of BW change given the level of exposure to the pesticide profile considered. The β -coefficient for interaction provides the additional BW change over time. The main model is adjusted for age, sex (when appropriate), height, occupational status, educational level, physical activity, smoking practices, alcohol consumption, menopausal status (for women), energy intake without alcohol, PNNS guidelines score 2, weight-loss diet status during the year covering the FFQ window.

3. Results

The median (P25; P75) follow-up time was 7.0 (4.4; 8.0) years.

Table 1 describes the baseline characteristics of the sample by sex. The sample was composed of 74 % women. Men were older (mean = 58.5 y. o., SD 13.1) than women (mean = 52.9 y. o., SD 13.1). Most participants earned more than 2700€ monthly (per household unit), had post-graduate education, and 32.6 % of women and 53.1 % of men were retired. Most of them lived in an urban unit with more than 200,000 inhabitants.

3.1. NMF profiles

NMF computation led to the inference of four pesticide exposure profiles based on dietary patterns. Spearman's correlations between selected pesticides and NMF components were presented in Table S1. Highly positive correlations (>0.60) were observed between NMF component 1 (referred to as NMF1 hereafter) and chlorpyrifos, imazalil, malathion, profenofos and thiabendazole. NMF2 positively correlated with azoxystrobin, boscalid, cyprodinil, chlorpropham, difenoconazole, fenhexamid, iprodione, tebuconazole, and lambda-cyhalothrin. NMF3 was characterized by highly positive correlations with spinosad and azadirachtin (authorized in organic farming). Strong positive correlations for NMF4 were found with acetamiprid, carbendazim, cypermethrin and dimethoate/omethoate.

We provided a detailed description of the characteristics of the sample across the NMF component quintiles in Supplemental Tables S2-S5.

3.2. Association between NMF profiles and BW change

The minimally adjusted model is presented in Supplemental Table S6.

In the main model, participants globally gained BW over time (Table 2). Significant interactions were observed between NMF components, time and sex for NMF2 and 3 (Table 2), and after stratification on sex, results differed.

Among men, baseline BW was positively associated with NMF1 and 2: participants more exposed to NMF1 and 2 (correlated with some synthetic pesticides) had a higher BW at baseline than less exposed participants. An inverse association was observed for NMF3, and no association with NMF4 was observed (Table 2). Among women, participants more exposed to NMF1 and NMF2 had a higher BW at baseline than the ones who were less exposed, whereas the participants more exposed to NMF3 and 4 had a lower baseline BW than others. Findings were similar for premenopausal and postmenopausal women, separately.

In men and women, mean BMI at baseline was 23.9 kg/m² (SD = 4.7) and 25.5 kg/m² (SD = 3.8), respectively. Overall, women gained BW ($\beta = 0.12$ (95 %CI = 0.10; 0.14) kg/year) while men lost BW over time ($\beta = -0.05$ (95 %CI = -0.07; -0.03) kg/year) (Table 2). When stratifying by menopausal status, only premenopausal women gained BW over time, whereas postmenopausal women lost weight, like men.

Regarding the interaction between dietary pesticide exposure and time, which reflects BW change over time associated with the level of NMF profiles, higher exposure to NMF2 was related to higher BW loss in men ($\beta_{\text{time}} < 0$ and $\beta_{\text{interaction}} < 0$). Women, and particularly premenopausal women more exposed to NMF3 gained less BW than women less exposed to NMF3 ($\beta_{\text{time}} > 0$ and $\beta_{\text{interaction}} < 0$). This trend was not observed for postmenopausal women. No associations were observed between BW change and NMF1 and 4, for men and women, separately.

Further adjustments for consumption of fruits and vegetables in the diet (excluding fruit juices and soups), consumption of plant-based products, % UPF in the diet, and daily intake of saturated fatty acids, carbohydrates, sodium and fibers did not substantially modify the

findings (Supplemental Tables S7 - S10). In addition, adjustment for weight-loss diet practice during the whole follow-up did not change the conclusions (Table S11).

In further analyses, we excluded participants who declared a weight-loss diet during the year covering the FFQ window ($n = 7814$ exclusions). As in the main model, the interaction between sex, time and dietary pesticide exposure was significant for NMF2 and NMF3 ($p = 0.001$ and 0.0005 , respectively) (Table S12). Men more exposed to NMF2 lost more BW than others, and women more exposed to NMF3 gained less BW than less exposed women; but the association between BW and dietary pesticide exposure did not remain significant for premenopausal women ($p = 0.08$), probably due to a lack of power. Finally, similar associations to those of the main model were observed among participants free of diseases or health events that could have altered their BW status. Additionally, in this final model, the premenopausal women who were more exposed to NMF2 gained less BW than the ones who were less exposed (Table S13). This association among women was also observed when only excluding participants who declared having an eating disorder during the follow-up (data not shown).

We also performed an analysis excluding participants who were medicated for at least three months by drugs that could lead to BW change (including steroids, antidepressants, oral contraceptives ...). Results did not substantially change as regards both men and women. The association between NMF3 and lower weight gain was not significant anymore for premenopausal women ($p = 0.08$), probably due to a lack of statistical power, given that this subsample of women was reduced after the exclusion of women using oral contraceptives (Table S14).

We also made stratified analyses by sex and overall dietary quality (Table S15). In men, a higher weight loss associated with NMF2 was observed, regardless of the dietary quality. However, the association appeared to be stronger among men with high adherence to French nutritional recommendations.

When stratifying analyses by age, considering the sex-specific median age as the cut-off (55 y.o. for women, and 63 y.o. for men), the association between NMF3 and lower weight gain was maintained among the younger group of women only. For older women, an overall weight loss over time was observed, not associated with any pesticide profile exposure. We made further stratified analyses by both age and menopausal status. The association observed between NMF3 and lower weight gain in women was not detected after stratification. These additional stratifications lowered the statistical power and did not allow us to disentangle the role of age and menopausal status, as these factors are highly correlated. Among men, the overall association between NMF2 and higher weight loss did not persist, neither among the younger, nor the older, but the model's convergence was questionable for the older group, and results should be considered cautiously as statistical power was lowered (Table S16). Finally, when stratifying by sex (2 strata) and baseline BMI (3 strata), we also encountered convergence issues, and results were robust only among women with a BMI lower than 25. In this subsample of women, we observed a lower weight gain associated with NMF3 exposure profile, as in the main analysis. In this subgroup, we also noticed a lower weight gain associated with NMF2 exposure profile (Table S17).

4. Discussion

4.1. Main findings

To our knowledge, this longitudinal study is the first to evaluate the association between pesticide exposure from food intakes, inferred from dietary patterns, and BW change over time in a large population-based sample, with a special focus on a potential sexual dimorphic response.

Overall, in this large sample of French adults, premenopausal women gained BW over time, whereas postmenopausal women and men lost BW over time. This overall BW variation (decrease) in men could be

specifically driven by the subsample of the older men (age > 62 y.o.). However, additional stratification led to lower statistical power and convergence issues, making difficult to draw firm conclusions.

On the one hand, women (especially premenopausal women) more exposed to pesticides highly correlated with the third NMF profile gained less BW than the ones who were less exposed. NMF3 was positively correlated to spinosad, azadirachtin, and pyrethrins, and negatively correlated with most of the studied synthetic pesticides. These results were consistent with previous conclusions from our cohort (Kesse-Guyot et al., 2017) and reviews (Jiang et al., 2023), which showed that a higher consumption of organic food could provide health benefits, including reduction of overweight and obesity (Bhagavathula et al., 2022; Vigar et al., 2019). In a recent review, the authors suggested that the benefits of organic food consumption could be associated with the lower contamination in pesticide residues (Glibowski, 2020).

Furthermore, a negative association between NMF2 mixture and BW gain was observed among women with BMI lower than 25, and also after excluding diseased participants.

On the other hand, in men, an increased weight loss associated with NMF2 was observed. This association was robust even after a large set of additional adjustments (for the consumption of fruits and vegetables, for the amount of plant-based food in the diet, for the share of UPF in the diet, or for the amount of carbohydrates, saturated fatty acids, sodium and fibers in the diet) or after excluding participants who could have specific BW variation due to a prompt change of dietary habits or health condition (e.g. weight-loss diet, diseases/health events), confirming the robustness of the findings. Besides, the association was observed whatever the level of dietary quality. The relationship seemed however slightly more pronounced among participants with the highest adherence to the French dietary guidelines.

In men, the association pertaining to higher weight loss and NMF2 (highly positively correlated with azoxystrobin, boscalid, cyprodinil, chlorpropham, difenoconazole, fenhexamid, iprodione, tebuconazole, and lambda-cyhalothrin) was somewhat unexpected. Although none of the 9 main active substances considered have shown "obesogenic" properties, most experimental studies provided mechanistic evidence for a role of pesticides in the onset and development of obesity and related metabolic diseases. At the cellular level, some pesticides were reported to act on metabolic homeostasis and its endocrine control (Gutgesell et al., 2020). Azoxystrobin (EL-Hak et al., 2022), lambda-cyhalothrin and boscalid (Al-Amoudi, 2018; Martínez et al., 2018; Qian et al., 2019; Wang et al., 2020), have previously been reported to induce oxidative stress or disturb mitochondria activity, two pathways that may influence obesity. Besides, other compounds of this mixture (cyprodinil, iprodione, fenhexamid, chlorpropham) are endocrine-disruptors and act as anti-androgenic or anti-estrogenic compounds (Blystone et al., 2007; Go et al., 2022; Hassan et al., 2021; Jeong et al., 2023; Kugathas et al., 2016; Orton et al., 2009; Scholze et al., 2020; Tang et al., 2022). Moreover, one might consider that consumers are exposed through food intake to pesticide mixtures and that, when combined, these compounds may interact in a synergistic manner (Rizzati et al., 2016). Pesticide effects may also result from interactions occurring at the organism level and affecting distinct organs (adipocytes, microbiota, endocrine system) involved in metabolic homeostasis.

To date, without previous epidemiological and experimental studies, we cannot exclude the involvement of this mixture in other adverse health effects associated to weight loss.

The relatively advanced mean age of the sample could partly explain the weight loss in men, in particular among the older. However, it is hard to conclude since methodological limitations (such as convergence issues due to double stratification) prevent us from confirming this assumption.

We observed herein divergent results among men and women as regards NMF2 and NMF3. Few experimental (Lukowicz et al., 2018) and epidemiological (Araki et al., 2018) studies have reported a sexually dimorphic impact of pesticides, which could be due to distinct

biotransformation processes, distinct effects on gut microbiota between males and females, and/or to the endocrine disruptive properties of pesticides. However, the underlying mechanisms need clarification.

The association between lower BW gain in premenopausal women and NMF3, negatively correlated with most of the synthetic pesticides, suggests a role of a lower exposure to these compounds on human health. Despite the fact that studies regarding the role of lower pesticide exposure in the general population are scarce, a reduction of mortality and some diseases (cardiovascular diseases, respiratory diseases and cancers) was associated with consumption of low-pesticide-residue fruits and vegetables in three large American cohorts (Sandoval-Insauti et al., 2022). A lower risk of coronary heart disease was also observed among high consumers of low-pesticide-residue fruits and vegetables (Chiu et al., 2019). High dietary pesticide exposure was linked to the risk of glioma and postmenopausal breast cancer (Cote et al., 2022; Rebouillat et al., 2021). Finally, our previous study focusing on T2D risk also highlighted an association with dietary exposure to some of the synthetic pesticides studied in the present work (Rebouillat et al., 2021).

4.2. Limitations of the study

This study has some limitations. This large cohort was composed of volunteers, with a majority of women, older people, also with higher education and higher incomes, and probably more interested in health and dietary intakes than the general French population.

Although we controlled for many lifestyle- and dietary-associated factors, we cannot conclude on the causality of the associations, since the design of the study was observational and residual confounding can never entirely be excluded.

Dietary intakes were self-reported through only one Org-FFQ completed at baseline. Dietary habits change marginally over time, but the gradual expansion of the supply of products from organic farming on the food market might have changed the consumption practices. Consequently, exposure patterns may have changed over time. Besides, the self-reporting of dietary habits could lead to overestimation of organic food consumption.

Pesticides data were not available for animal products, but they generally contain low levels of pesticides residues, and we did not have information about copper and sulphur-based products, widely used in organic agricultural practices, but to date no convincing adverse effect for the general population was reported for these substances (European Food Safety Authority (EFSA), 2018b).

Measures were performed in the German market, but products from all over the European Union were tested. Pesticide exposure was estimated based on dietary intakes, since the financial burden limited biomarker monitoring in large cohorts. However, biomarkers would not have allowed to identify specific chemicals, since they are generally not specific to one molecule. Pesticide exposure might have been misestimated, as potential concentration or dilution effects during washing, peeling or cooking on pesticide-residues levels were not taken into account (Yigit and Velioglu, 2020) or due to overestimation of consumption. Lastly, the associations found might be due to a not measured correlated substance rather than to the effect of one or several of the 25 selected pesticides.

4.3. Strengths of the study

This study exhibits some strengths. The very large sample size enabled us to conduct stratified analyses by sex and menopausal status, but also by baseline BMI, and age, with relatively high statistical power. The median follow-up was considered long enough to capture BW changes. The large number of available variables allowed us to control for confounding effects. Statistical models were adjusted for a wide range of covariates including major potential confounders and sensitivity analyses showed the robustness of the results, improving causal

inference. Besides, we undertook a “multi-pollutant” approach, accounting for possible synergism and potentiation effects in pesticide mixtures (Rizzati et al., 2016), which probably better reflects the real-life exposure through the diet.

5. Conclusion

We observed that, when more exposed to a specific dietary pesticide exposure profile, negatively correlated with dietary exposure to the studied synthetic pesticides, women gained less BW over time. In contrast, men more exposed to a specific mixture of pesticides lost more BW. Other studies are needed to replicate and confirm the associations and decipher the possible underlying biological mechanisms. Nonetheless, it remains that given the already known deleterious effects of pesticides on human health and ecosystems, as part of a “one health” approach, the use of synthetic pesticides should be reduced.

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CRediT authorship contribution statement

Justine Berlivet: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation. **Laurence Payraastre:** Writing – review & editing, Writing – original draft, Project administration, Funding acquisition. **Pauline Rebouillat:** Writing – review & editing, Formal analysis. **Anne Fougerat:** Writing – review & editing, Writing – original draft, Project administration, Funding acquisition. **Mathilde Touvier:** Writing – review & editing, Investigation, Funding acquisition, Conceptualization. **Denis Lairon:** Writing – review & editing, Conceptualization. **Philippe Pointereau:** Writing – review & editing, Conceptualization. **Hervé Guillou:** Writing – review & editing, Writing – original draft, Project administration, Funding acquisition. **Rodolphe Vidal:** Writing – review & editing, Data curation. **Julia Baudry:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology. **Emmanuelle Kesse-Guyot:** Writing – review & editing, Validation, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization.

Rodolphe Vidal, Denis Lairon, Serge Hercberg, Mathilde Touvier, Léopold Fezeu, Julia Baudry and Emmanuelle Kesse-Guyot conducted the research. Justine Berlivet performed statistical analyses and drafted the manuscript. All authors critically helped in the interpretation of results, revised the manuscript and provided relevant intellectual input. They all read and approved the final manuscript. Emmanuelle Kesse-Guyot and Julia Baudry supervised the study, had primary responsibility for the final content, they are the guarantors.

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

Researchers from public institutions can submit a collaboration request including information on the institution and a brief description of the project. A financial contribution may be requested.

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Availability of data and material

Researchers from public institutions can submit a collaboration request including information on the institution and a brief description of the project to collaboration@etude-nutrinet-sante.fr. All requests will be reviewed by the steering committee of the NutriNet-Santé study. A financial contribution may be requested. If the collaboration is accepted, a data access agreement will be necessary and appropriate authorizations from the competent administrative authorities may be needed. In accordance with existing regulations, no personal data will be accessible.

Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2024.108485>.

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