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Prospective association between dietary pesticide exposure profiles and postmenopausal breast cancer risk in the NutriNet-Santé cohort

**Pauline Rebouillat<sup>1</sup>, Rodolphe Vidal<sup>2</sup>, Jean-Pierre Cravedi<sup>3</sup>, Bruno Taupier-Letage<sup>2</sup>, Laurent Debrauwer<sup>3</sup>, Laurence Gamet-Payraastre<sup>3</sup>, Mathilde Touvier<sup>1</sup>, Mélanie Deschasaux-Tanguy<sup>1</sup>, Paule Latino-Martel<sup>1</sup>, Serge Hercberg<sup>1,5</sup>, Denis Lairon<sup>4</sup>, Julia Baudry<sup>1</sup>, Emmanuelle Kesse-Guyot<sup>1</sup>.**

<sup>1</sup> Sorbonne Paris Nord University, Inserm, INRAE, Cnam, Nutritional Epidemiology Research Team (EREN), Epidemiology and Statistics Research Center – University of Paris (CRESS), 93017 Bobigny, France

<sup>2</sup> Institut de l’Agriculture et de l’Alimentation Biologiques (ITAB), 75595 Paris, France

<sup>3</sup> Toxalim (Research Centre in Food Toxicology), Université de Toulouse, INRAE, ENVT, INP-Purpan, UPS, 31027 Toulouse, France

<sup>4</sup> Aix Marseille Université, INSERM, INRAE, C2VN, 13005 Marseille, France

<sup>5</sup> Département de Santé Publique, Hôpital Avicenne, 93017 Bobigny, France

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**\*Corresponding author:**

Pauline REBOUILLAT, Equipe de Recherche en Epidémiologie Nutritionnelle (EREN)

SMBH Université Sorbonne Paris Nord, 74 rue Marcel Cachin, 93017 Bobigny, France.

p.rebouillat@eren.smbh.univ-paris13.fr

+33 1 48 38 89 79

**ORCID Identifiers:**

Pauline Rebouillat : 0000-0002-7270-6032

Mathilde Touvier : 0000-0002-8322-8857

Emmanuelle Kesse-Guyot : 0000-0002-9715-3534

Denis Lairon : 0000-0001-9941-3742

Short running head: Dietary pesticide exposure and post-menopausal breast cancer risk

**Abbreviations:**

ADI: Acceptable Daily Intake; AhR: Aromatic hydrocarbon Receptor; ANSES: Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail ; BMR:

Basal Metabolic Rate ; BC: Breast Cancer;  $\beta$ -HCH :  $\beta$ -Hexachlorocyclohexane ; BMI: Body Mass Index; CépiDC : French Centre for Epidemiology Medical Causes of Death database ;

CI: Confidence Interval ; CNIL: Commission Nationale de l'Informatique et des Libertés ;

CVUA: Chemisches und Veterinäruntersuchungsamt; DDE:

Dichlorodiphenyldichloroethylene ; DDT: Dichlorodiphenyltrichloroethane ; DNA:

Deoxyribonucleic acid ; EDI: Estimated Daily Intake; EFSA: European Food and Safety

Authority; ER-/PR-: Estrogen Receptor Negative/Progesterone Receptor Negative ; FFQ:

Food Frequency Questionnaire; HCB: Hexachlorobenzene ; HR: Hazard Ratio; ICD-10:

International Statistical Classification of Diseases and Related Health Problems 10th

Revision; IPAQ: International Physical Activity Questionnaire; IRB INSERM: Institutional

Review Board of the French Institute for Health and Medical Research; NMF: Non-negative

Matrix Factorization; ; OC: Organochlorine; OP: Organophosphorous;; PCTA:

Pentachlorothioanisole ; PNNS: Programme National Nutrition Santé; SD: Standard

Deviation; SNIIRAM: Système National d'Information Inter-Régimes de l'Assurance

Maladie; sPNNS-GS2: simplified Programme National Nutrition Santé Guideline Score 2;

WHO: World Health Organization.

Clinical Trial Registry: NCT03335644

URL for Trial Registration : <https://clinicaltrials.gov/ct2/show/NCT03335644>

Manuscript Word Count: 4318 words

Data Share Statement:

Data of the study are protected under the protection of health data regulation set by the French National Commission for Information Technology and Liberties (Commission Nationale de l'Informatique et des Libertés, CNIL). The data are available upon reasonable request to the study's operational manager, Nathalie Pecollo ([n.pecollo@eren.smbh.univ-paris13.fr](mailto:n.pecollo@eren.smbh.univ-paris13.fr)), for review by the steering committee of the NutriNet-Santé study.

1 **Abstract:**

2 **Background:**

3 Some pesticides, used in large quantities in current agricultural practices all over Europe, are  
4 suspected of adverse effects on human reproductive health (breast and prostate cancers),  
5 through mechanisms of endocrine disruption and possible carcinogenic properties, as  
6 observed in agricultural settings.

7 However, evidence on dietary pesticide exposure and breast cancer (BC) is lacking for  
8 general population. We aimed to assess the associations between dietary exposure to  
9 pesticides and BC risk among postmenopausal women of the NutriNet-Santé cohort.

10 **Methods:**

11 In 2014, participants completed a self-administered semi-quantitative Food Frequency  
12 Questionnaire, distinguishing conventional and organic foods. Exposures to 25 active  
13 substances used in EU plant protection products were estimated using a pesticide residue  
14 database accounting for farming practices, from Chemisches und Veterinäruntersuchungsamt  
15 Stuttgart, Germany.

16 Non-Negative Matrix Factorization (NMF), adapted for data with excess zeros, was used to  
17 establish exposure profiles. The four extracted NMF components' quintiles were introduced  
18 into Cox models estimating Hazard Ratio (HR) and 95% confidence interval (95% CI),  
19 adjusted for known confounding factors.

20 **Results :**

21 A total of 13,149 postmenopausal women were included in the analysis(169 BC cases,  
22 median follow-up=4.83 years). Negative associations between component 3, reflecting low  
23 exposure to synthetic pesticides, and post-menopausal BC risk were found (HR<sub>Q5</sub>=0.57;  
24 95%CI(0.34;0.93), p-trend=0.006). Positive association between component 1 score (highly  
25 correlated to chlorpyrifos, imazalil, malathion, thiabendazole) and postmenopausal BC risk

26 was found specifically among overweight and obese women ( $HR_{Q5}=4.13$ ; 95%CI(1.50;11.44),  
27 p-trend=0.006). No associations were detected for the other components.

28 **Conclusions:**

29 These associations suggest a potential role of dietary pesticide exposure on BC risk. Further  
30 research is needed to investigate mechanisms and confirm these results in other populations.

31 **Keywords:** dietary exposure; pesticides; organic farming; epidemiology; breast cancer;  
32 environmental health.

33

**Key Messages:**

- Diet is considered as the main exposure route for pesticide exposure in the general population. Dietary pesticide exposure has been rarely studied in relation with cancers.
- Non-Negative Matrix Factorization (NMF), a method adapted for data with excess zeros, was used to characterise dietary pesticide exposure profiles.
- We observed a reduction in the risk of postmenopausal breast cancer for NMF Component 3 (reflecting low exposure to several synthetic pesticides).
- A positive association between NMF component 1 score (highly correlated to chlorpyrifos, imazalil, malathion, thiabendazole) and postmenopausal breast cancer risk was observed specifically among overweight and obese women.
- For NMF Components 2 and 4, Hazard Ratios (HR) were HR<sub>Quintile 5 vs Quintile 1</sub> 0.96, 95% Confidence Interval (0.59; 1.56), p for trend : 0.30 and HR<sub>Quintile 5 vs Quintile 1</sub> 0.65, 95% Confidence Interval (0.38; 1.12), p for trend : 0.13.

35 **Introduction:**

36 Large quantities of plant protection products are used in current European agricultural  
37 practices <sup>1</sup>. In particular, France has high usage of pesticides, synthetic or natural, both in  
38 global tonnages (80 000 tons in 2018) and by surface area (4.45 kg/ha in 2018) <sup>2-5</sup>.  
39 Deleterious impacts of pesticides on human health have been evidenced. Various effects of  
40 pesticide active substances have been documented , including genetic material alteration,  
41 endocrine disrupting effects, cell apoptosis and cell signaling dysregulation, and oxidative  
42 stress induction <sup>4,6-8</sup>. These mechanisms have been shown to be involved in carcinogenesis <sup>9</sup>.  
43 Recently, IARC classified many pesticides as “probably carcinogenic to humans” (Group 2A)  
44 and “possibly carcinogenic to humans” (Group 2B) <sup>10</sup>. In addition, many pesticides exhibit  
45 endocrine disruptors properties <sup>7</sup>.  
46 Indeed, cancer is nowadays the first or second leading cause of premature death in many  
47 European countries. It is the first cause of mortality in France <sup>11-13</sup>, breast cancer being the  
48 most common and leading cause of cancer death for women in France. Associations between  
49 occupational pesticide exposure in agricultural settings (involving respiratory and cutaneous  
50 exposure routes) and the occurrence of some locations of cancers (myeloma, non-Hodgkin  
51 lymphoma, prostate) were found in several studies<sup>14-19</sup>. Associations in agricultural settings  
52 with other cancer locations have been reported (stomach, esophagus, liver, colorectal...), and  
53 especially reproductive system cancers (prostate, breast), potentially induced by endocrine  
54 disruption mechanisms <sup>4,7,20</sup>. Notably, associations between breast cancer risk and  
55 organophosphorus pesticide exposure were found for farmer’s wives in some studies <sup>21,22</sup>.  
56 However, in the general population, although food is considered as the first exposure  
57 pathway, data is lacking on associations between dietary exposure to pesticides and cancer  
58 <sup>23,24</sup>. This may be explained by three main challenges. Firstly, measuring pesticide residue  
59 concentrations in food is expensive and tedious. In addition, it is difficult to measure  
60 pesticides mixtures (opposed to compounds taken separately), but necessary, as it can



61 potentially lead to synergistic effects. Finally, data existing so far generally lacks of precision  
62 regarding the production system (conventional vs organic), limiting proper estimation of  
63 pesticide exposure.

64 Recently, a study conducted in the NutriNet-Santé cohort showed protective associations  
65 between the high proportion of organic food in the diet and different types of cancers,  
66 including postmenopausal breast cancer<sup>22</sup>. An hypothesis advanced to explain this association  
67 was the potentially lower concentrations of pesticides residues in plant organic foods <sup>25</sup>.

68 In that context, the purpose of this work was to study the associations between dietary  
69 pesticide exposure profiles and breast cancer risk among postmenopausal women included in  
70 the NutriNet-Santé cohort.

71

72 **Material and Methods:**

73 *Study population*

74 The NutriNet-Santé study is a web-based prospective cohort of adults launched in France in  
75 May 2009<sup>26</sup>. Inclusion criteria was to be aged 18 years old and over and to speak French. A  
76 set of self-administered validated questionnaires<sup>27–29</sup> was completed online by participants at  
77 baseline and repeated every year. Complementary questionnaires were regularly proposed  
78 concerning dietary behaviors and specific health issue during follow-up.

79 *Dietary intake assessment*

80 A 264-item web-based self-administered semi-quantitative food frequency questionnaire  
81 (Org-FFQ) distinguishing organic and conventional foods was sent to the participants  
82 between June and December 2014. The Org-FFQ has been extensively described elsewhere<sup>30</sup>.  
83 Briefly, it was elaborated on the basis of an existing validated FFQ<sup>31</sup> to which a 5-point  
84 ordinal scale was added to measure the frequency of organic food consumption. For each  
85 item, participants provided their frequency of consumption and the quantity consumed  
86 helping with photographs showing different portion sizes<sup>32</sup>. For food and beverages with an  
87 existing organic version (labelled), participants answered the question “How often was the  
88 product of organic origin?” by selecting 1 of the 5 following frequency modalities: never,  
89 rarely, half-of-time, often, or always. The organic food consumption was then obtained by  
90 attributing the respective percentages, 0, 25, 50, 75, and 100, to the modalities. Weighting and  
91 sensitivity analyses for the Org-FFQ have been published elsewhere<sup>30</sup>.

92 All food and beverage items were aggregated into 33 food groups. Nutritional values were  
93 obtained from a published food composition database<sup>33</sup>. A global proportion (as weight) of  
94 organic food in the diet was calculated as well as the proportion of organic food for each food  
95 group.

96

97 *Pesticide exposure assessment*

98 Dietary pesticide exposure was estimated by combining dietary intakes of each adult with  
 99 pesticide residue concentration values in foods using contamination data from Chemisches  
 100 und Veterinäruntersuchungsamt (CVUA) Stuttgart, a European Union reference laboratory for  
 101 pesticides<sup>34</sup>. The database comprised contamination data for conventional and organic food  
 102 products. Twenty-five commonly used pesticides were selected among components available  
 103 in this database, given both their frequency of detection above the Maximum Residue Levels  
 104 (MRL) when sufficient data were available, and their frequency above Acceptable Daily  
 105 Intake (ADI) otherwise, as detailed in Baudry et al. 2019 study<sup>35</sup>. Pesticides commonly used  
 106 in organic agricultural systems (e.g. natural pyrethrins, spinosad) were also selected. These  
 107 criteria made it possible to take into account a broad spectrum of classes of pesticides. The  
 108 264 Org-FFQ items were decomposed into 442 ingredients (comprising at least 5% of at least  
 109 one food item). Animal-based ingredients were excluded, as CVUA encompassed plant-based  
 110 ingredients only. Indeed, plant-based foods have markedly more frequent and higher  
 111 pesticides residues levels than foods of animal origin<sup>36</sup>. The resulting 180 plant ingredients  
 112 were matched to CVUA database and then were attributed a contamination value in organic  
 113 and conventional farming modes (as the mean of corresponding data point). A flowchart of  
 114 the different steps for the decomposition and matching is shown in **Supplementary Material**  
 115 **1**.

116 For each ingredient/pesticide pair in conventional and organic farming, a frequency of  
 117 detection and a frequency of quantification were determined using the formula as follows:

$$118 \quad \textit{Frequency of detection} = 100 \times \frac{\textit{Number of analyses} - \textit{Number of undetected}}{\textit{Number of analyses}}$$

$$119 \quad \textit{Frequency of quantification}$$

$$120 \quad = 100 \times \frac{\textit{Number of analyses} - \textit{Number of unquantified}}{\textit{Number of analyses}}$$

121 Treatment of data below detection limit has been extensively described elsewhere<sup>35</sup>.

122 As food consumption data from NutriNet-Santé referred to edible foods (bone-free, peeled or  
123 cooked products), edibility and cooking factors were allocated to each ingredient when  
124 necessary. The same conversion factors were used for both conventional and organic  
125 products. Cooking or peeling effects on pesticide residue levels were not accounted for as  
126 dilution factors are not available for all food/pesticide couples <sup>37</sup>. For each pesticide, the  
127 estimated daily intake (EDI) (in µg/kg of weight/day) under both lower- and upper-bound  
128 scenarios was calculated using methods recommended by EFSA and WHO <sup>38,39</sup>. Lower-bound  
129 (optimistic) scenario was used for this work, as more in line with available literature  
130 comparing both production systems <sup>35,40</sup>.

### 131 *Covariates*

132 Baseline and yearly questionnaires collected sociodemographic and lifestyle characteristics  
133 such as sex, date of birth, occupation, educational level, smoking status, number of children.  
134 Monthly income by household unit was obtained was obtained using both the household  
135 income and composition. Anthropometric measures (height, weight), physical activity (using  
136 the validated Physical Activity Questionnaire <sup>41</sup>) and health status (menopausal status, family  
137 history of cancer, treatments) were also collected.

138 A specific questionnaire on environmental exposure collected the type of environment in  
139 which participants lived: agricultural or urban area.

140 The simplified Programme National Nutrition Santé Guideline Score 2 (sPNNS-GS2), based  
141 on the level of adherence to 2017 French dietary guidelines proposed by the High Council of  
142 Public Health <sup>42,43</sup>, the provegetarian score <sup>44</sup> and the percentage of ultra-processed foods in  
143 the diet <sup>45</sup> were computed to be used as adjustment factors. Briefly, the sPNNS-GS2 includes  
144 13 components. One point was allocated for following the guideline (and 0 otherwise), and  
145 conversely for moderation components. Component with several subcomponents were  
146 standardized and a penalty for overconsumption was applied. The score ranged from  $-\infty$  to

147 14.25. Component, cut-off, scoring system and ponderation are presented in **Supplementary**  
148 **Material 2**.

149 The provegetarian score was computed as follows <sup>44</sup>: 7 vegetable food groups and 5 animal  
150 food groups were defined and sex-specific quintiles adjusted for total energy intake were  
151 calculated. For each plant component, 1 to 5 points were allocated to quintile 1 to 5 and for  
152 animal food groups the scoring was reversed. The provegetarian score was obtained by  
153 summing each quintile value of vegetable food group and each reverse quintile value of  
154 animal food group thus ranging from 12 (low plant food consumption) to 60 (high plant food  
155 consumption).

156 Percentage of ultra-processed foods consumed was computed after classification of foods  
157 using NOVA categories <sup>45</sup>, by a committee of dietitians and researchers <sup>46</sup>. NOVA  
158 classification is described in details in **Supplementary Material 3**. Data used to calculate the  
159 proportion of ultra-processed foods in the diet were the closest to the Org-FFQ completion  
160 date.

#### 161 *Cancer cases*

162 Health events were declared by participants through a yearly health status questionnaire and a  
163 dedicated web-interface at any time of the study. All medical records were collected and  
164 analyzed by dedicated physicians. Physicians of participants declaring major health events  
165 were contacted to collect additional information if necessary. Validation of these major health  
166 events was carried out by a medical expert committee.

167 Overall, medical records were obtained for more than 90% of self-reported cancer cases.

168 Moreover, we performed a linkage between our declared health data to medico-administrative  
169 registers of the national health insurance system (Système National d'Information Inter-  
170 Régimes de l'Assurance Maladie [SNIIRAM] databases). Mortality data were also used from  
171 the French Centre for Epidemiology Medical Causes of Death database (CépiDC). Cancer

172 cases were classified using the *International Statistical Classification of Diseases and Related*  
173 *Health Problems, 10th Revision, Clinical Modification*<sup>47</sup>. In this study, we considered all first  
174 primary breast cancers (ICD-10 C50) diagnosed between baseline (i.e. the date of completion  
175 of the Org-FFQ in 2014 or the menopause date, whichever occurred last) and 18 July 2019 to  
176 be cases.

#### 177 *Statistical analyses*

178 A flowchart for the study sample selection is presented in Figure 1.

179 For the present study, postmenopausal female participants who completed the Org-FFQ  
180 between June and December 2014 (N = 28,445), with no missing covariates for basal  
181 metabolic rate computation (N = 28,137), who were not detected as under- or over-reporters  
182 (N = 27,158), who were postmenopausal and free of breast cancer when they completed the  
183 Org-FFQ, were selected (N=13,149).

184 Regarding under or overreporters, only participants with a plausible energy intake were  
185 included in the analyses. The detection method for under and overreporters was based on the  
186 comparison between energy intake and energy requirement and is extensively described in a  
187 previous article by Baudry et al.<sup>30</sup>

188 Dietary pesticide exposure profiles were analyzed using Non-Negative Matrix factorization  
189 (NMF) (detailed in **Supplementary Material 4**), specially adapted for non-negative data with  
190 excess zeros, developed by Lee et al<sup>48</sup>. In total, four components were computed for the NMF  
191 procedure using 25 selected pesticide exposure values, reflecting various pesticide exposure  
192 patterns.

193 Sociodemographic and lifestyle characteristics were compared between cases and non-cases,  
194 and also across NMF-extracted component quintiles using Chi<sup>2</sup>, Mantel-Haenzel, Wilcoxon  
195 and Kruskal-Wallis tests, as appropriate.

196 Associations between dietary pesticide exposure, using NMF components divided into  
197 quintiles (first quintile used as reference) and breast cancer were assessed using Cox  
198 proportional hazards regression models. Participants contributed person time until the date of  
199 diagnosis of cancer, the date of last completed questionnaire, the date of death, or 18<sup>th</sup> July  
200 2019, whichever occurred first.

201 NMF component scores were divided into quintiles and introduced into separate models, with  
202 age as time scale, and first quintile as reference.

203 Cox models were adjusted for known confounders such as smoking status, alcohol intake,  
204 educational level, physical activity (measured with International Physical Activity  
205 Questionnaire), Body Mass Index (BMI), height, family history of cancer, menopausal  
206 treatment and parity and overall quality of the diet (measured by the PNNS-GS2 score <sup>43</sup>).

207 Interactions between potential modulating factors and components were tested by introducing  
208 the multiplicative interaction term into the models, namely body mass index, sPNNS-GS2  
209 (overall nutritional quality of the diet) and the level of plant-based consumption (using the  
210 provegetarian score). Interactions with  $p < 0.10$  were further investigated.

211 Schoenfeld residuals were used to test the proportional hazard assumption of the Cox model.  
212 Potential nonlinear effects of continuous exposure variables were evaluated using martingale  
213 residuals.

214 Tests for linear trend were performed using quintiles of the NMF components as ordinal  
215 variables.

216 Sensitivity analyses were carried out. A model was performed excluding early cases (1 year  
217 after baseline) and two other models were computed with additional adjustments for the level  
218 of ultra-processed foods in the diet, and the provegetarian score. Two-sided tests were used..

219 Data management and statistical analyses were performed using SAS (version 9.4; SAS  
220 Institute, Inc.). NMF was performed using R's NMF package <sup>49</sup>.

221 **Results:**

222 *Characteristics of the participants*

223 Sociodemographic characteristics of the studied participants are presented in **Table 1**. A total  
224 of 13,149 postmenopausal women were included in the analyses; 169 postmenopausal breast  
225 cancer were diagnosed during the follow-up (mean  $\pm$  SD: 4.35  $\pm$  1.06 years; median: 4.83  
226 years). Mean age at baseline was 60.5 years (SD=7.39). The majority of individuals had a  
227 graduate educational attainment, was retired and lived in more than 200,000 inhabitant urban  
228 units and were never smokers for 49% of them. One third of the sample was overweight  
229 (BMI>25 kg/m<sup>2</sup>). Most frequent physical activity levels were 'high' and 'moderate'. Overall,  
230 no significant differences on sociodemographic characteristics were found between cases and  
231 non-cases. The nutritional characteristics of the cases and non-cases are presented  
232 in **Supplementary Table S1**. Overall, no differences were observed between cases and non-  
233 cases except for organic food proportion in the diet.

234 The absolute estimated dietary pesticide exposure for cases and non-cases is presented  
235 in **Table 2**. Among others, the pesticide exhibiting the highest means for exposures in cases  
236 and non-cases were boscalid, iprodione, spinosad, thiabendazole, and imazalil.

237 The correlations between the 4 NMF-extracted components and pesticide exposure are shown  
238 in **Table 3**. Pesticides such as chlorpyrifos, imazalil, malathion, profenofos, thiabendazole  
239 were highly correlated with NMF Component 1. For NMF Component 2, highly correlated  
240 pesticides were azoxystrobin, boscalid, cyprodinil, difenoconazole, fenhexamid, iprodione,  
241 tebuconazole, lambda cyhalothrin.

242 NMF Component 3 was characterized by low correlations with synthetic pesticides and high  
243 correlation with organic pesticide spinosad. For NMF Component 4, high correlations with  
244 acetamiprid, carbendazim, chlorpyrifos, cypermethrin, dimethoate/omethoate were  
245 observed.

246 Each NMF Component exhibited specific correlates. For information, profiles and dietary



247 patterns are presented in **Supplementary Tables S2 to S9: Supplementary Tables S2-S3** for  
248 NMF Component 1, **S4-S5** for NMF Component 2, **S6-S7** for NMF Component 3, **S8-S9** for  
249 NMF Component 4. Main findings are the negative and positive linear associations between  
250 proportion of organic food and NMF components 1-2 and 3 respectively.  
251 The absolute estimated dietary pesticide exposures compared across components quintiles are  
252 presented in **Supplementary Table S10** and **Supplementary Table S11**.  
253 Correlations between dietary intakes for 33 food groups and NMF components are shown in  
254 **Supplementary Table S12**.

255 *Associations between pesticide dietary exposure and breast cancer risk*

256 **Table 4** presents Hazard Ratios (HR) for the associations between NMF components and the  
257 risk of postmenopausal breast cancer, with several levels of adjustments. Positive and  
258 significant association was found for the fifth quintile of NMF component 1, HR=1.73,  
259 95%CI(1.05;2.84). With regard to NMF component 3, participants in the fifth quintile had  
260 significantly lower risks (HR=0.57, 95%CI(0.34;0.93), p trend=0.006) of postmenopausal  
261 breast cancer than the first quintile (p<0.05). HR for the fifth quintiles of NMF Components 2  
262 and 4 were HR 0.96, 95% CI(0.59;1.56), p-trend : 0.30 and HR 0.65, 95% CI(0.38;1.12), p-  
263 trend : 0.13.

264 Further adjustments for the quality of the diet (with the sPNNS-GS2 score, Model 2), and  
265 residing in an agricultural area (Model 3) did not modify the findings (**Table 4**).

266 Several interactions between NMF components and other variables were tested in the models  
267 (provegetarian score, sPNNS-GS2, overweight vs non-overweight). A significant interaction  
268 was found between BMI and NMF component 1 (p for interaction with BMI in 2 categories =  
269 0.004) on the risk of postmenopausal breast cancer. Therefore, stratified analyses were  
270 performed, with a threshold of 25 kg/m<sup>2</sup>, and results are shown in **Table 5**. Associations  
271 between NMF Component 1 and post-menopausal breast cancer risk were significant among

272 individuals with a BMI>25 kg/m<sup>2</sup> only, with higher risk for the fifth quintile and fourth  
273 quintile compared to the first quintile, HR<sub>Quintile 5 vs Quintile 1</sub>: 4.13 (95%CI(1.50;11.44) and  
274 HR<sub>Quintile 4 vs Quintile 1</sub>: 3.02 (95%CI(1.08;8.47)), p trend=0.006 (**Table 5**).

275 *Sensitivity analyses*

276 After exclusion of cancer cases occurring less than 1 year after baseline, HR were similar but  
277 the loss of statistical power did not allow to reach significance (**Table 6**).

278 Further adjustments for the percentage of ultra-processed foods, or provegetarian score, did  
279 not modify the results substantially.

280 **Discussion:**

281 In this large population of French postmenopausal women, we found significant negative  
282 associations between NMF component 3 (reflecting low exposure to several synthetic  
283 pesticides) and post-menopausal breast cancer risk. When analyses were stratified on BMI  
284 (threshold 25 kg/m<sup>2</sup>), positive association between NMF Component 1 (reflecting exposure to  
285 chlorpyrifos, imazalil, malathion, thiabendazole) and postmenopausal breast cancer risk was  
286 found among overweight women. No significant associations were detected for the other  
287 components.

288 To our knowledge, the present study is the first to investigate various pesticide exposure  
289 patterns, accounting for farming practices in relation with breast cancer risk in the general  
290 population. Thus, our findings cannot be directly compared to previous scientific literature.

291 However, some studies have been conducted to investigate associations between  
292 occupational, residential or domestic pesticide exposure and breast cancer risks. Studies  
293 largely focused on organochlorine (OC) pesticides and related metabolites (for instance  
294 Dichlorodiphenyltrichloroethane (DDT), Dichlorodiphenyldichloroethylene (DDE),  $\beta$ -  
295 Hexachlorocyclohexane ( $\beta$ -HCH), Hexachlorobenzene (HCB), Pentachloroanisole  
296 (PCTA), now banned in European Union, reporting higher breast cancer risk for users  
297 (personal or occupational) <sup>50-52</sup>.

298 Breast cancer risks were found higher with exposure to OC (use vs never use) in a study  
299 published by Engel et al (2005) conducted in farmer's wives population <sup>21</sup>. In this study,  
300 breast cancer risks also appeared elevated regarding organophosphorus pesticide family (OP)  
301 as a whole. When analysis was performed on compounds taken separately, association was  
302 significant only for malathion. Stratification on menopausal status was performed and showed  
303 higher risks among postmenopausal women whose husbands used OC and also OP such as  
304 chlorpyrifos, diazinon and malathion. In our study, NMF component 1, positively correlated  
305 with malathion and chlorpyrifos (respective correlation coefficients 0.76 and 0.73), was

306 significantly associated with breast cancer risk for participants with a BMI > 25 kg/m<sup>2</sup>.  
307 Moreover, in analyses conducted in 2015 by Lerro *et al.* in the Agricultural Health Study <sup>22</sup>,  
308 spouses whose husband used OPs had higher breast cancer risk compared to spouses whose  
309 husbands never used OPs (RR= 1.20, 95%CI(1.01; 1.43)). However, in that study, when  
310 considering pesticides molecules separately (malathion, chlorpyrifos, terbufos), associations  
311 with breast cancer risk were no longer significant, except for chlorpyrifos, and especially for  
312 Estrogen Receptor Negative/Progesterone Receptor Negative (ER-/PR-) breast cancer risk.  
313 These observations could be interpreted in light of some kind of synergistic effects evidenced  
314 in toxicological studies when exposed to pesticide residue mixtures <sup>6,53,54</sup>. In the same study  
315 by Lerro *et al.*, after stratification on menopausal status, significant association between  
316 higher breast cancer risks and use of any OPs was observed among the postmenopausal  
317 women. Again, no significant associations between OP pesticides taken separately and breast  
318 cancer risk were found. Another recent study also found elevated risks in women exposed to  
319 chlorpyrifos compared with those not exposed (OR = 3.22; 95%CI(1.38,7.53) <sup>55</sup>. These results  
320 are consistent with our results suggesting an association between NMF component 1  
321 (reflecting exposure to chlorpyrifos, imazalil, malathion, thiabendazole) and  
322 postmenopausal breast cancer risk.

323 It is important to note that after exclusion of ‘early cases’ (<1 year after baseline), an  
324 important drop was observed in the HR<sub>Quintile 5 vs Quintile 1</sub> for Component 1 from 1.73 to 1.37. It  
325 is possible that excluded cases exhibited very specific nutritional and health characteristics  
326 linked to their imminent diagnosis and probable health deterioration linked to it. We should  
327 also note that Quintile 5 lost more cases than other quintiles (42 cases to 31) and this could  
328 somehow influence the analysis.

329 In our study, possible hypotheses to explain the negative associations between NMF  
330 Component 3 and postmenopausal breast cancer risk rely on the fact that besides being highly

331 correlated with some pesticides used in organic farming (i.e. natural pyrethrins, spinosad), this  
332 component is also negatively correlated with several synthetic pesticides (azoxystrobin,  
333 chlorpropham, methamidophos). Participants with high component 3 score, seemed generally  
334 less exposed to the synthetic studied pesticides but also less exposed to pesticides with high  
335 suspected toxicity such as chlorpyrifos, imazalil, malathion. These results are consistent  
336 with those of another study, conducted in the NutriNet-Santé cohort in 2018, that reported a  
337 negative association between high organic food score and postmenopausal breast cancer risk  
338 ( $HR_{\text{Quintile4}} = 0.66$ ; 95% CI(0.45-0.96))<sup>56</sup>. One formulated hypothesis for this association was  
339 that organic farming regulations lead to a lower frequency or an absence of pesticide residues  
340 in organic foods compared with conventional foods<sup>25</sup>. Thus, our present results are consistent  
341 with this hypothesis. Moreover, effects had comparable magnitude.

342 Mechanisms underlying these associations could be related to carcinogenic properties of some  
343 organophosphate pesticides provoking DNA damage, cell apoptosis dysregulation, epigenetic  
344 changes<sup>57</sup>, cell signaling disruption<sup>58</sup>, nuclear receptor binding (Aromatic hydrocarbon  
345 Receptor, AhR)<sup>59</sup> or oxidative stress induction<sup>4,8,9</sup>. It can be noted that IARC classified some  
346 organophosphate pesticides as “probably carcinogenic to humans” (Group 2A) and “possibly  
347 carcinogenic to humans” (Group 2B)<sup>10</sup>. Endocrine disruption potential of pesticides has also  
348 been described in toxicological studies and recently in a review by Yang et al.<sup>7,60</sup>, and could  
349 be particularly involved in hormone-dependent breast carcinogenesis, as some pesticides are  
350 known to mimic estrogen functions<sup>57,61</sup>. Indeed, azole fungicides, including imazalil, for  
351 which we found high correlations with NMF Component 1, have been related to inhibition of  
352 estrogen biosynthesis in some studies<sup>62</sup>. These pesticides are also known to affect  
353 mitochondrial activity and oxidoreduction status<sup>63</sup>.

354 When considering stratified analyses on BMI (threshold 25 kg/m<sup>2</sup>), a positive association  
355 between component 1 and post-menopausal breast cancer risk was observed in overweight

356 individuals.

357 Several studies have found positive associations between body fat and OC pesticide blood  
358 levels, overweight subjects having higher blood levels of these pesticides <sup>64,65</sup>. However, it is  
359 unlikely this would be the case for OPs, which are not accumulated in adipose tissue. It is  
360 possible that there is cumulative effect between obesity and pesticide exposure on cancer  
361 risks. The specific association in overweight women could also be explained by differences in  
362 paraoxonase 1 (PON1) activity, as this enzyme is involved in lipid metabolism, but also  
363 participates in hydrolysis of organophosphate compounds <sup>66</sup>. Indeed, some studies have  
364 shown lower levels of PON1 activity in overweight and obese patients <sup>67,68</sup>. In consequence,  
365 toxicity of these pesticides could be higher for this subgroup.

366 More data are needed on OP pesticides, in order to fully understand underlying mechanisms  
367 of this association and potential modifying effects of BMI on breast cancer.

368 It should be noted that associations between NMF Components 2 and 4 and postmenopausal  
369 breast cancer risk were not statistically significant in our study. Given the lack of evidence on  
370 specific pesticide mixtures in relation to human health, it is difficult to know whether this  
371 could be due to specific non-carcinogenic patterns of the studied pesticides or to the fact that  
372 the population may not be exposed enough to experience deleterious health effects.

### 373 *Limitations and strengths*

374 Some limitations of this study should be mentioned. Firstly, the NutriNet-Santé cohort is  
375 composed of volunteers, mostly highly educated, who can be more interested in their health  
376 and dietary intakes than the general French population <sup>69</sup>. This implies cautions when  
377 generalizing our results to other populations.

378 It is important to mention that dietary intakes were self-reported through a food frequency  
379 questionnaire (FFQ) and this may have caused overestimation of organic food consumption.

380 Other limitations come from the database used to estimate dietary pesticide exposures, since

381 data were not available for animal products and the database did not contain measures for  
382 copper or sulfur-based products, widely used in organic farming, but not known as  
383 carcinogenic compounds. Measures were performed in Germany, but products from all over  
384 European Union were tested.

385 Another limitation that should be mentioned was that the dietary pesticide exposure was  
386 estimated and is therefore not as accurate as measuring biomarkers. It is to note that  
387 biomarkers can rarely be measured on very large samples given feasibility and cost  
388 constraints. Another disadvantage of using biomarkers is that it would not give precision on  
389 the active substances to which individuals are exposed since biomarkers are not specific to  
390 one molecule.

391 We should acknowledge that pesticide exposure have probably been overestimated as  
392 potential concentration or dilution effects during washing, cooking or peeling on pesticide  
393 residue levels were not accounted for<sup>37</sup>. Finally, for this study, follow-up duration was short  
394 and the number of cases limited, given a high estimated latency period for this type of disease.  
395 This can be a limitation for causal inference and statistical power of the analyses. However,  
396 we hypothesize that dietary habits change marginally over time, therefore dietary habits four  
397 years before diagnosis were probably very similar to those 10 years before. In the same way,  
398 patterns of pesticide use in France were similar during this period, as there were changes in  
399 authorizations only for three selected pesticides (anthraquinone, methamidophos and  
400 profenofos)<sup>70</sup>. Nevertheless, it will be interesting to reassess cancer risks after several years,  
401 in order estimate long-term effects.

402 Some strengths of this study can also be put forward.

403 Cox regression models were adjusted for a wide range of covariates, including major  
404 confounders such as diet quality indicators. Despite a limited number of cases, the sample size

405 still allowed us to perform some stratification and sensitivity analyses in order to deepen the  
406 understanding of these results and reduce confounding bias.

407



408 **Conclusion**

409 We observed a negative association between low synthetic pesticide exposure profile (through  
410 NMF component 3) and post-menopausal breast cancer risk. Positive association between  
411 component 1 (highly correlated to chlorpyrifos, imazalil, malathion, thiabendazole) and  
412 postmenopausal breast cancer risk was also found specifically among overweight and obese  
413 women. If confirmed by other studies, some pesticides profiles may constitute risk factors  
414 among subgroups such as those with overweight. Observed associations should be  
415 investigated in other prospective studies, in different settings, coupled with experimental  
416 studies to complement these observational studies in order to validate estimated dietary  
417 pesticide exposure. A better understanding of the impact of dietary pesticides on human  
418 health could unlock prevention strategies for the whole population through regulation.

419

420 **Ethics approval :**

421 The NutriNet-Santé study is conducted in accordance with the Declaration of Helsinki, and all  
422 procedures were approved by the Institutional Review Board of the French Institute for  
423 Health and Medical Research (IRB Inserm 0000388FWA00005831) and the Commission  
424 Nationale de l'Informatique et des Libertés (CNIL 908,450 and 909,216). All participants  
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428

#### 429 **Data availability**

430 Data of the study are protected under the protection of health data regulation set by the French  
431 National Commission for Information Technology and Liberties (Commission Nationale de  
432 l'Informatique et des Libertés, CNIL). The data are available upon reasonable request to the  
433 study's operational manager, Nathalie Pecollo ([n.pecollo@eren.smbh.univ-paris13.fr](mailto:n.pecollo@eren.smbh.univ-paris13.fr)), for  
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#### 445 **Author contributions**

446 RV, DL, JB, SH and EK-G conducted the research.

447 PR performed statistical analyses and drafted the manuscript.

448 All authors critically helped in the interpretation of results, revised the manuscript and  
449 provided relevant intellectual input. They all read and approved the final manuscript. EK-G  
450 supervised the study, had primary responsibility for the final content, she is the guarantor.

451 **Conflict of Interest:**

452 None declared.

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**Table 1: Characteristics of the participants, NutriNet-Santé Study, 2014 (N=13,149)**

	All participants	Non-cases	Cases	P <sup>1</sup>
N	13,149	12,980	169	
<b>Age</b> , mean (SD)	60.49 (7.39)	60.48 (7.40)	61.15 (6.43)	0.24
<b>Monthly income per household unit</b> , %				0.27
<€1200	9.29	9.30	8.88	
€1200-1800	21.63	21.69	16.57	
€1800-2700	28.09	28.11	26.04	
>€2700	33.61	33.54	38.46	
Unwilling to answer	7.38	7.35	10.06	
<b>Educational level</b> , %				0.17
Less than high-school diploma	26.73	26.81	20.71	
High school diploma	17.58	17.53	20.71	
Post Graduate	55.69	55.65	58.58	
<b>Occupational status</b> , %				0.26
Employee, manual worker	12.29	12.36	7.10	
Intermediate profession	12.91	12.90	13.61	
Managerial staff, intellectual	14.15	14.18	11.83	
Retired	48.92	48.82	56.21	
Self-employed, farmer	1.59	1.59	1.18	
Unemployed or never employed	10.14	10.14	10.06	
<b>Place of residence</b> , %				0.85
Rural community	22.98	23.00	21.30	
Urban unit with a population <20,000 inhabitants	15.77	15.76	16.57	
Urban unit with a population between 20,000 and 200,000	19.45	19.48	17.75	
Urban unit with a population >200,000 inhabitants	41.80	41.76	44.38	
<b>Smoking habits</b> , %				0.20
current smoker	9.00	9.04	5.92	
former smoker	42.29	42.33	39.64	
never smoker	48.71	48.64	54.44	
<b>Body Mass Index</b> (kg/m <sup>2</sup> ), mean (SD)	24.22 (4.64)	24.22 (4.64)	24.57 (4.45)	0.16
<b>Body Mass Index</b> > 25kg/m <sup>2</sup> , %	34.19	34.17	35.50	0.72
<b>Physical activity</b> , %				0.12
High	35.49	35.57	29.59	
Moderate	36.06	36.05	37.28	
Low	17.07	17.08	16.57	
Missing data	11.37	11.30	16.57	
<b>Use of hormonal treatment for menopause</b> , %				0.04
Yes	10.92	10.87	14.20	
No	83.30	83.29	84.02	
Missing data	5.78	5.83	1.78	
<b>Parity</b> , %				0.33
No children	14.47	14.43	17.75	
One child	17.56	17.59	15.38	
2 children	40.12	40.18	35.50	
More than 2 children	27.84	27.80	31.36	
<b>Family history of cancer</b> , %	52.25	52.19	57.40	0.18

<sup>1</sup>P-values for comparisons between cases and non-cases using Chi-square tests or Wilcoxon tests, as appropriate.

**Table 2: Estimated pesticide exposure for cases and non-cases, lower-bound scenario, NutriNet-Santé Study, 2014 (N=13,149)**

Variable	Non-cases N=12,980		Cases N=169	
	Mean	SD	Mean	SD
Acetamiprid	0.0598	0.0778	0.0548	0.0966
Anthraquinone	0.0005	0.0015	0.0005	0.0010
Azadirachtin	0.0004	0.0005	0.0003	0.0004
Azoxystrobin	0.0451	0.0453	0.0457	0.0520
Boscalid	0.1312	0.1114	0.1218	0.1096
Carbendazim	0.0564	0.0581	0.0535	0.0708
Chlorpropham	0.0607	0.0616	0.0674	0.0632
Chlorpyrifos	0.0753	0.0663	0.0758	0.0751
Cypermethrin	0.0881	0.1107	0.0815	0.1370
Cyprodinil	0.0821	0.0892	0.0782	0.0790
Difenoconazole	0.0190	0.0177	0.0175	0.0157
Dimethoate Ometoate	0.0106	0.0134	0.0090	0.0138
Fenhexamid	0.1067	0.1455	0.0897	0.1060
Glyphosate	0.0035	0.0048	0.0040	0.0057
Lambda-Cyhalothrin	0.0116	0.0112	0.0117	0.0122
Imazalil	0.8459	1.0395	0.9367	1.1376
Imidacloprid	0.0791	0.0750	0.0831	0.0750
Iprodione	0.1591	0.1833	0.1552	0.1706
Malathion	0.0003	0.0004	0.0003	0.0003
Methamidophos	0.0002	0.0003	0.0003	0.0005
Profenofos	0.0000	0.0001	0.0000	0.0001
Pyrethrins	0.0020	0.0017	0.0018	0.0015
Spinosad	0.1717	0.1870	0.1447	0.1660
Tebuconazole	0.0385	0.0471	0.0373	0.0399
Thiabendazole	0.2882	0.3247	0.3239	0.3322

**Table 3: Spearman Correlations between 25 selected pesticides and NMF Components, NutriNet-Santé Study, 2014 (N=13,149)**

Compounds	NMF Component 1	NMF Component 2	NMF Component 3	NMF Component 4
Acetamiprid	0.34	0.41	0.26	<b>0.87</b>
Anthraquinone	0.17	0.19	-0.06	0.18
Azadirachtin	-0.09	*-0.01	0.53	*-0.01
Azoxystrobin	0.59	<b>0.71</b>	-0.18	0.16
Boscalid	0.51	<b>0.90</b>	-0.13	0.19
Carbendazim	0.31	0.38	0.31	<b>0.89</b>
Chlorpropham	0.35	0.53	-0.30	0.12
Chlorpyrifos	<b>0.73</b>	0.44	0.11	<b>0.60</b>
Cypermethrin	0.29	0.27	0.36	<b>0.93</b>
Cyprodinil	0.50	<b>0.91</b>	-0.12	0.16
Difenoconazole	0.52	<b>0.68</b>	*0.02	0.47
Dimethoate Ometoate	0.36	0.42	0.26	<b>0.79</b>
Fenhexamid	0.46	<b>0.79</b>	-0.11	0.12
Glyphosate	0.38	0.45	-0.12	0.17
Imazalil	<b>1.00</b>	0.37	-0.11	0.14
Imidacloprid	0.51	0.24	0.20	0.56
Iprodione	0.52	<b>0.91</b>	-0.10	0.15
Lambda-Cyhalothrin	0.56	<b>0.84</b>	-0.08	0.24
Malathion	<b>0.76</b>	0.49	-0.10	0.17
Methamidophos	0.32	0.35	-0.19	0.17
Profenofos	<b>0.95</b>	0.38	-0.12	0.17
Pyrethrins	0.04	0.02	0.30	0.03
Spinosad	-0.07	-0.09	<b>0.99</b>	0.35
Tebuconazole	0.55	<b>0.84</b>	-0.10	0.19
Thiabendazole	<b>0.98</b>	0.36	-0.11	0.16

\*p-value for Spearman correlation >0.05

NMF: Non-negative Matrix Factorization

Bold values denote correlation coefficients >0.60.

**Table 4: Cox models for associations between dietary pesticide exposure and postmenopausal breast cancer risk, NutriNet-Santé Study, 2014 (N=13,149)**

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	Total	P value for trend
<b>NMF Component 1</b>							
Number of participants	2629	2630	2630	2630	2630	13,149	
Incident Cases	27	36	34	30	42	169	
Person-years	11,385.52	11,507.50	11,566.09	11,477.81	11,266.78	57,203.70	
Model 1 <sup>1</sup> , HR (95% CI)	1	1.34 (0.81; 2.21)	1.24 (0.75; 2.06)	1.14 (0.68; 1.93)	1.73 (1.05; 2.84)		0.09
Model 2 <sup>2</sup> , HR (95% CI)	1	1.33 (0.80; 2.19)	1.25 (0.75; 2.07)	1.15 (0.68; 1.95)	1.78 (1.08; 2.93)		0.07
Model 3 <sup>3</sup> , HR (95% CI)	1	1.32 (0.80; 2.18)	1.24 (0.75; 2.06)	1.15 (0.68; 1.94)	1.77 (1.07; 2.91)		0.08
<b>NMF Component 2</b>							
Number of participants	2629	2630	2630	2630	2630	13,149	
Incident cases	38	43	28	26	34	169	
Person-years	11,504.90	11,453.11	11,459.27	11,499.86	11,286.57	57,203.70	
Model 1 <sup>1</sup> , HR (95% CI)	1	1.11 (0.72; 1.72)	0.72 (0.44; 1.17)	0.69 (0.42; 1.15)	0.96 (0.59; 1.56)		0.30
Model 2 <sup>2</sup> , HR (95% CI)	1	1.09 (0.70; 1.69)	0.71 (0.44; 1.16)	0.70 (0.42; 1.16)	1.00 (0.61; 1.63)		0.38
Model 3 <sup>3</sup> , HR (95% CI)	1	1.08 (0.70; 1.68)	0.71 (0.43; 1.16)	0.69 (0.42; 1.15)	0.99 (0.61; 1.62)		0.37
<b>NMF Component 3</b>							
Number of participants	2629	2630	2630	2630	2630	13,149	
Incident cases	47	42	23	31	26	169	
Person-years	11,304.65	11,374.78	11,437.14	11,558.22	11,528.91	57,203.70	
Model 1 <sup>1</sup> , HR (95% CI)	1	0.88 (0.58; 1.34)	0.47 (0.29; 0.78)	0.64 (0.40; 1.01)	0.57 (0.34; 0.93)		<b>0.006</b>
Model 2 <sup>2</sup> , HR (95% CI)	1	0.89 (0.59; 1.35)	0.48 (0.29; 0.80)	0.66 (0.41; 1.04)	0.59 (0.36; 0.97)		<b>0.01</b>
Model 3 <sup>3</sup> , HR (95% CI)	1	0.89 (0.59; 1.35)	0.48 (0.29; 0.80)	0.66 (0.41; 1.04)	0.59 (0.36; 0.98)		<b>0.01</b>
<b>NMF Component 4</b>							
Number of participants	2629	2630	2630	2630	2630	13,149	
Incident cases	36	41	33	36	23	169	
Person-years	11,294.95	11,425.20	11,459.16	11,442.46	11,581.94	57,203.70	
Model 1 <sup>1</sup> , HR (95% CI)	1	1.14 (0.72; 1.78)	0.93 (0.58; 1.50)	1.01 (0.64; 1.62)	0.65 (0.38; 1.12)		0.13
Model 2 <sup>2</sup> , HR (95% CI)	1	1.15 (0.73; 1.80)	0.95 (0.59; 1.53)	1.02 (0.64; 1.63)	0.66 (0.39; 1.12)		0.13
Model 3 <sup>3</sup> , HR (95% CI)	1	1.15 (0.73; 1.80)	0.95 (0.59; 1.53)	1.02 (0.64; 1.62)	0.66 (0.39; 1.12)		0.13

Abbreviations: NMF:Non-negative Matrix Factorization; HR: Hazard Ratio; 95% CI : 95% Confidence Interval; sPNNS-GS2: Simplified Programme National Nutrition Santé Guideline Score 2

<sup>1</sup>Adjusted for smoking practices, educational level, physical activity, alcohol intake, alcohol-free energy intake, Body Mass Index, height, family history of cancer, menopausal treatment, parity

<sup>2</sup>Adjusted for Model 1 + sPNNS-GS2 score

<sup>3</sup>Adjusted for Model 1 + sPNNS-GS2 score + residing currently in an agricultural area

**Table 5: Cox models for associations between dietary pesticide exposure and postmenopausal breast cancer risk, stratified analyses on BMI, NutriNet-Santé Study, 2014 (N=13,149)<sup>1</sup>**

	BMI <25kg/m <sup>2</sup> N=8654, 109 cases					BMI >25kg/m <sup>2</sup> N= 4495, 60 cases						
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5		
<b>N</b>	<b>1731</b>	<b>1732</b>	<b>1732</b>	<b>1732</b>	<b>1732</b>	<b>901</b>	<b>901</b>	<b>901</b>	<b>901</b>	<b>901</b>		
	<b>HR</b>	<b>HR (95% CI)</b>	<b>HR (95% CI)</b>	<b>HR (95% CI)</b>	<b>HR (95% CI)</b>	<b>P-value for trend</b>	<b>HR</b>	<b>HR (95% CI)</b>	<b>HR (95% CI)</b>	<b>HR (95% CI)</b>	<b>HR (95% CI)</b>	<b>P-value for trend</b>
<b>NMF</b>		1.05	0.65	1.02	0.98		2.83	2.58	3.02	4.13		
<b>Component 1</b>	1	(0.60; 1.85)	(0.34; 1.23)	(0.57; 1.81)	(0.53; 1.81)	0.88	1	(0.83; 6.87)	(0.90; 7.38)	(1.08; 8.47)	(1.50; 11.44)	<b>0.006</b>

Abbreviations: NMF: Non-negative Matrix Factorization; HR: Hazard Ratio; 95% CI: 95% Confidence Interval; BMI: Body Mass Index; sPNNS-GS2: Simplified Programme National Nutrition Santé Guideline Score 2

<sup>1</sup>All models adjusted for sPNNS-GS2 score, smoking practices, educational level, physical activity, alcohol intake, alcohol-free energy intake, BMI, height, family history of cancer, menopausal treatment, parity.

**Table 6: Sensitivity analyses for associations between dietary pesticide exposure and postmenopausal cancer risk, NutriNet-Santé Study, 2014 (N=13,149)**

Model excluding early cases (1 year)	Quintile 1	Quintile 2		Quintile 3		Quintile 4		Quintile 5		P-value for trend
N=13,120; 140 cases	HR	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	
<b>NMF Component 1</b>	1	1.11	(0.65; 1.90)	1.19	(0.70; 2.03)	1.02	(0.58; 1.78)	1.37	(0.80; 2.36)	0.38
<b>NMF Component 2</b>	1	0.96	(0.60; 1.55)	0.65	(0.38; 1.11)	0.66	(0.38; 1.14)	0.86	(0.50; 1.47)	0.23
<b>NMF Component 3</b>	1	0.96	(0.61; 1.50)	0.46	(0.26; 0.81)	0.62	(0.37; 1.04)	0.62	(0.36; 1.07)	<b>0.016</b>
<b>NMF Component 4</b>	1	1.22	(0.75; 2.01)	1.15	(0.69; 1.91)	1.00	(0.59; 1.69)	0.59	(0.32; 1.10)	0.10
Model with additional adjustment for ultra-processed foods <sup>2</sup>	Quintile 1 N=2629	Quintile 2 N=2630		Quintile 3 N=2630		Quintile 4 N=2630		Quintile 5 N=2630		P-value for trend
N=13,149; 169 cases	HR	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	
<b>NMF Component 1</b>	1	1.33	(0.80; 2.19)	1.24	(0.75; 2.07)	1.15	(0.68; 1.94)	1.77	(1.08; 2.92)	0.08
<b>NMF Component 2</b>	1	1.09	(0.70; 1.69)	0.71	(0.43; 1.16)	0.70	(0.42; 1.16)	0.99	(0.61; 1.62)	0.37
<b>NMF Component 3</b>	1	0.88	(0.58; 1.34)	0.47	(0.29; 0.79)	0.64	(0.40; 1.03)	0.58	(0.35; 0.96)	<b>0.009</b>
<b>NMF Component 4</b>	1	1.15	(0.73; 1.80)	0.94	(0.59; 1.52)	1.01	(0.64; 1.62)	0.65	(0.38; 1.11)	0.12
Model with additional adjustment for provegetarian Score <sup>3</sup>	Quintile 1 N=2629	Quintile 2 N=2630		Quintile 3 N=2630		Quintile 4 N=2630		Quintile 5 N=2630		P-value for trend
N=13,149; 169 cases	HR	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI	
<b>NMF Component 1</b>	1	1.33	(0.80; 2.19)	1.23	(0.74; 2.04)	1.13	(0.67; 1.91)	1.72	(1.04; 2.82)	<b>0.009</b>
<b>NMF Component 2</b>	1	1.09	(0.70; 1.70)	0.71	(0.43; 1.16)	0.69	(0.41; 1.14)	0.96	(0.59; 1.56)	0.30
<b>NMF Component 3</b>	1	0.88	(0.58; 1.34)	0.47	(0.29; 0.78)	0.64	(0.40; 1.02)	0.57	(0.34; 0.95)	<b>0.008</b>
<b>NMF Component 4</b>	1	1.14	(0.73; 1.79)	0.94	(0.58; 1.51)	1.01	(0.64; 1.62)	0.65	(0.38; 1.12)	0.12

Abbreviations: NMF: Non-negative Matrix Factorization; HR: Hazard Ratio; 95 % CI: 95% Confidence Interval; BMI: Body Mass Index; sPNNS-GS2: Simplified

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<sup>1</sup>Adjusted for sPNNS-GS2 score, smoking practices, educational level, physical activity, alcohol intake, alcohol-free energy intake, BMI, height, family history of cancer, menopausal treatment, parity

<sup>2</sup>Adjusted for sPNNS-GS2 score, smoking practices, educational level, physical activity, alcohol intake, alcohol-free energy intake, BMI, height, family history of cancer, menopausal treatment, parity and percentage of ultra-processed foods in the diet

<sup>3</sup>Adjusted for provegetarian score, smoking practices, educational level, physical activity, alcohol intake, alcohol-free energy intake, BMI, height, family history of cancer, menopausal treatment, parity