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► To cite this version:

Chloé Marques, Thibault Fiolet, Pauline Frenoy, Gianluca Severi, Francesca Romana Mancini. Association between polycyclic aromatic hydrocarbons (PAH) dietary exposure and mortality risk in the E3N cohort. *Science of the Total Environment*, 2022, 840, pp.156626. 10.1016/j.scitotenv.2022.156626 . hal-03918032

HAL Id: hal-03918032

<https://hal.science/hal-03918032>

Submitted on 2 Jan 2023

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Association between polycyclic aromatic hydrocarbons (PAH) dietary exposure and mortality risk in the E3N cohort

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Abstract

Most studies have explored the adverse health effects of polycyclic aromatic hydrocarbons (PAH) occupational exposure. However, the general population is also exposed to PAH, mainly through the diet. The goal of the present study is thus to investigate the association between PAH dietary exposure and mortality risk in middle-aged women of the E3N (Étude Épidémiologique auprès de femmes de la mutuelle générale de l'Éducation Nationale) French prospective cohort.

The study included 72 513 women, whom completed a validated semi-quantitative food frequency questionnaire on 208 food items in 1993. Food contamination levels were assessed using data provided by the Anses (French Agency for Food, Environmental and Occupational Health & Safety) in the framework of the French second total diet study. PAH dietary exposure was studied as the sum of four PAH (PAH4), namely benzo[a]pyrene (BaP), chrysene (CHR), benzo[a]anthracene (BaA) and benzo[b]fluoranthene (BbF). Cox proportional hazard models were used to estimate hazard ratios (HR) and their 95% confidence intervals (CI) for the risk of all-cause mortality as well as all-cancer, specific cancer (separately from breast, lung/tracheal, and colorectal cancer), cardiovascular disease (CVD), and specific CVD (including only stroke and coronary heart disease) mortality.

During follow-up (1993-2011), 4 620 validated deaths were reported, of which 2 726 due to cancer and 584 to CVD. The median PAH4 dietary intake was 66.1 ng/day. There was no significant association between PAH4 dietary intake and the risk of all-cause, all-cancer, breast cancer, colorectal cancer, all-CVD and stroke and coronary heart disease mortality. On the contrary, we observed a positive and statistically significant association between PAH4 dietary intake and lung/tracheal cancer mortality risk, with a stronger association among current smokers than among former smokers and never smokers.

In this study, we observed an association between PAH dietary exposure and lung/tracheal cancer mortality risk, especially among current smokers.

Keywords: polycyclic aromatic hydrocarbon; dietary exposure; mortality; cohort study

1. Introduction

Polycyclic aromatic hydrocarbons (PAH) are a group of more than 100 chemical substances composed only of carbon and hydrogen and organised in two or more aromatic rings. These organic compounds are formed during incomplete combustion or pyrolysis of coal, oil, gas, waste, or other organic substances from natural or anthropic origins such as wood fires, motor vehicle exhausts, or home heating [1]. PAH are classified as persistent organic pollutants (POPs) [2], which are persistent, toxic and ubiquitous compounds that can move over long distances and bio-accumulate in the food chain as lipophilic compounds. PAH are also considered to act as endocrine-disrupting chemicals [3,4], affecting foetal viability, inducing troubles in female fertility, and cancer of reproductive organs [4]. Moreover, PAH can be genotoxic and/or carcinogenic. Indeed, the International Agency for Research on Cancer (IARC) classified benzo[a]pyrene (BaP) as carcinogenic to humans (i.e. group 1), and chrysene (CHR), benzo[a]anthracene (BaA) or benzo[b]fluoranthene (BbF) as possibly carcinogenic to humans (i.e. group 2B) [5].

The general population may be exposed to PAH through inhalation (atmospheric pollution, smoking, etc.), contact (occupational application), and ingestion (food consumption). For the general population in developing countries, inhalation and ingestion are equally important routes of exposure to PAH. In contrast, in industrialised countries, diet is the major source of exposure to PAH [6,7], accounting for more than 90% of the total PAH exposure [8], except for smokers, for which tobacco smoke can lead to the same level of exposure as food consumption [1]. PAH contaminate food in the environment through air, soil, and water, or PAH can be formed during industrial or home cooking processes such as heating, drying, smoking, grilling or roasting, especially over an open flame [7].

Most studies have investigated the health effect of PAH due to occupational exposure, so mainly at high doses. This exposure can result in acute effects in the short term like irritation, nausea, vomiting or diarrhoea, or to medium to long term health issues as increased risk of lung, skin, bladder or gastrointestinal cancers [9], respiratory and urinary tracts cancers [10], larynx cancer [11], decreased lung function [12] or higher levels of markers of cardiovascular disease (CVD) [13].

In the general population, contrary to occupational exposure, PAH exposure is rather observed at low doses that may potentially lead to long term health effects, including effects across generations [14]. Previous studies have highlighted an association between exposure to PAH and cancer mortality, notably lung cancer mortality [15], as well as breast cancer [16], CVD, obesity, elevated blood pressure [17,18], and diabetes risk [19]. In some of these studies, a combination of different routes of exposure to PAH (via inhalation and ingestion) was considered [15,16]. PAH exposure was estimated through various ways, for example, via urinary biomarkers [18,19], questionnaires or

35 historical geographic models [16], or by combining sample analyses (of air, soil, drinking water and
36 food) and urinary biomarkers [15]. Furthermore, some studies have focused explicitly on PAH
37 dietary exposure, but they studied only the incremental lifetime cancer risk (ILCR), which is the
38 increased probability of developing cancer for an exposed population compared to a non-exposed
39 population. These studies highlighted a slight to high potential cancer risk depending on the level of
40 dietary exposure to PAH [20–23].

41 Up to date, little information is available on the association between PAH dietary exposure and
42 health in the general population. Then, the goal of the present study is to describe PAH dietary
43 exposure of women within the E3N French prospective cohort and investigate the association
44 between dietary exposure to PAH and all-cause or cause-specific mortality risk.

45 **2. Material and methods**

46 *2.1. The E3N study*

47 The E3N study is an ongoing prospective cohort initiated in 1990 in metropolitan France with the
48 inclusion of 98 995 women aged between 40 and 65 years old at recruitment and insured by the
49 MGEN (Mutuelle Générale de l'Éducation Nationale), a national health insurance plan primarily
50 covering people working for the French national education system. The follow-up consists of self-
51 administered questionnaires sent every 2-3 years including questions on lifestyle and medical
52 events. The participation rate has remained good and stable through the years, approximately
53 around 83%, and only 3% of women have been lost to follow-up since 1990. The main goal of this
54 prospective cohort study is to investigate the association between risk factors and cancer and other
55 non-communicable diseases [24,25].

56 All participants signed informed consent in agreement with the rules of the French National
57 Commission for Data Protection and Privacy (CNIL, in French "Commission Nationale de
58 l'Informatique et des Libertés"), from which the study was approved.

59 *2.2. Dietary questionnaire*

60 In the E3N cohort, dietary data were collected through the dietary questionnaire sent in June 1993,
61 including 208 food items. This questionnaire was composed of two parts: the first part inquired on
62 the frequency and quantity of food groups' consumption, while the second part provided more
63 details on food items within each food group. Through this self-administered questionnaire that
64 included questions for eight meal occasions based on French meal patterns, including snacks and
65 aperitifs occasions, information concerning dietary consumption of foods and drinks during the
66 previous year was collected. The dietary questionnaire's validity and reproducibility were previously
67 tested [26].

68 Individual mean daily nutrient intakes were estimated using a food composition table derived from
69 the French food composition table of the French Information Centre on Food Quality (CIQUAL).

70 2.3. Assessment of PAH dietary intake

71 PAH contamination levels in food were derived from the second French total diet study (TDS2)
72 conducted by the Anses, the French Agency for Food, Environmental and Occupational Health &
73 Safety [27]. Briefly, 20 280 food items were purchased between June 2007 and January 2009 in
74 eight great regions of French metropole, leading to the preparation of 1 352 composite samples
75 prepared "as consumed" according to the French population cooking habits (to take into account the
76 effect of cooking, washing, peeling, etc.) to measure 445 chemical substances [28]. In particular,
77 PAH were analysed in 725 samples, i.e. including known or potential contributors to the dietary
78 exposure to PAH [29]. Food contamination levels for 20 PAH were available for the present study.
79 More information on sampling or analytical methodology, especially for PAH, is detailed elsewhere
80 [28,29].

81 Two scenarios were built to assess PAH dietary intake: the lower bound (LB) and the middle bound
82 (MB) scenario. In the LB scenario, values below the limit of detection (LOD) were replaced by zero,
83 while they were replaced by half of the LOD in the MB scenario. In our study, the LB scenario was
84 used in principal analyses, and the MB scenario was used in a sensitivity analysis.

85 The E3N database on food consumption and the Anses database on food contaminants were
86 merged to obtain the E3N-TDS2 database, as described in detail elsewhere [30]. Briefly, the E3N-
87 TDS2 database was created by giving a common code to the food items of the TDS2 and the E3N
88 databases. From the 238 food items of the E3N database, 146 had a direct correspondence with
89 TDS2 food items. When there was not a direct correspondence, the most similar food item available
90 in the TDS2 was identified and matched (n=56). Finally, 36 food items of the E3N database were
91 excluded for lack of possible matching with the TDS2. For each participant of the E3N prospective
92 cohort, the PAH dietary intake (ng/day) was calculated as follows:

$$i_a = \sum_{each\ f} q_{af} \times c_f$$

93 where i_a is the PAH dietary intake of the individual a (ng/day), q_{af} is the quantity of food f consumed
94 by the individual a (g of food/day), c_f is the PAH contamination level in the food f (ng/g of food).

95 With the term "PAH20" we refer to the sum of the 20 PAH measured in the TDS2 (as presented in
96 **Supplementary table 1**). Nevertheless, in the present study, the main exposure variable
97 corresponded to the sum of four PAH (namely BaP, CHR, BaA, and BbF), which we will name
98 "PAH4" from now on. Indeed, according to EFSA, PAH4, together with PAH8 (corresponding to
99 PAH4 plus benzo[k]fluoranthene (BkF), benzo[g,h,i]perylene (BghiP), dibenzo[a,h]anthracene

100 (DBahA), indeno[1,2,3-cd]pyrene (IP)) are the best indicators of PAH total levels of contamination in
101 food. Nevertheless, it has also been highlighted that PAH8 does not provide much additional
102 information compared to PAH4, mainly due to their high correlation [1].

103 2.4. *Ascertainment of mortality cases*

104 Information on vital status and death dates was obtained from the health insurance database, postal
105 service, municipal registries, physicians or next of kin. Inserm-CépiDc (Centre d'épidémiologie sur
106 les causes médicales de Décès), the French centre of epidemiology on medical causes of death,
107 provided detailed information on causes of death, which was coded according to the 9th (ICD-9, for
108 deaths before 2000) and the 10th (ICD-10, for deaths since 2000) revisions of the International
109 Classification of Diseases (ICD). Cause-specific mortality was defined as follows: 140-210 and C00-
110 C99 for cancers; 174 and C50 for breast cancers; 153, 1540, 1541 and C18-C20 for colorectal
111 cancers; 162 and C33-C34 for lung/tracheal cancers; 390-459 and I00-I99 for CVD; 430-434 and
112 I60-I64 for stroke; 410-414 and I20-I25 for coronary heart disease, respectively for ICD-9 and ICD-
113 10.

114 2.5. *Study population*

115 In the present study, we included 74 522 women who answered the dietary questionnaire, which is
116 the third questionnaire (Q3) sent since the initial recruitment.

117 To avoid under or over declarations of dietary intakes, we excluded women with extreme values of
118 energy intake, i.e. individuals in the top and bottom 1% of the ratio of energy intake to estimated
119 energy requirements (n=1 491). The basal metabolic rate, calculated with Schofield equations
120 based on age, sex and weight, was multiplied by 1.55 (for lightly active people) to estimate each
121 woman's estimated energy requirements [31]. We also excluded women who did not complete any
122 questionnaire after the dietary questionnaire (n=518).

123 Finally, our study population for all-cause mortality analyses was composed of 72 513 women. For
124 all-cancer and CVD mortality, we further excluded women with unknown causes of death (n=62),
125 and we thus studied 72 451 women. For specific cancer mortality, we also excluded women who
126 died of cancer with an unknown primary location (n=142), which led us to study a population of
127 72 309 women.

128 The flow chart is presented in **Supplementary figure 1**.

129 2.6. *Statistical analyses*

130 We first performed descriptive analyses on the causes of death reported for the study population.
131 Baseline characteristics (mean and standard deviation (STD) for continuous variables, N and

132 proportions for categorical variables) of the women included and excluded of the study were
133 compared. Baseline characteristics of the study population were then described in the overall
134 population and separately among cases and non-cases or among each quartile group of PAH4
135 dietary intake. We also analysed characteristics of PAH4 dietary intake by studying food groups that
136 most contribute to the intake, and the proportion of each PAH (BaP, CHR, BaA and BbF) in PAH4
137 dietary intake. Correlations between PAH dietary intake variables (the four PAH of PAH4, but also
138 PAH4, PAH8 and PAH20) were estimated using Spearman rank correlation coefficients.

139 Cox proportional hazard models, with age as time-scale, were used to estimate hazard ratios (HR)
140 and their 95% confidence intervals (CI) for the risk of all-cause mortality, all-cancer mortality,
141 specific cancer mortality (separately for breast, lung/tracheal and colorectal primary location of
142 cancer), all-CVD mortality, and specific CVD mortality (including only stroke and coronary heart
143 disease). Age at entry was the age of answer to the dietary questionnaire and exit time was the age
144 at the first event observed between the date of death (for cases), the date of return of the last
145 completed questionnaire (for lost to follow-up) or the date of the end of follow-up (corresponding to
146 the date of the last mailed questionnaire, Q10, sent the 7th of December 2011, for a complete follow-
147 up), whichever occurred first. For cancer or CVD mortality analyses, deaths respectively due to
148 cancer or CVD were assigned as cases, and other causes of death were censored at the date of
149 death. Similarly, for specific cancer or CVD mortality, deaths due to each cancer or CVD were
150 assigned as cases, and other causes of death, including those from other types of cancer or CVD,
151 were censored at the date of death, respectively.

152 In Cox models, we analysed PAH4 dietary intake as a continuous variable and as a categorical
153 variable (in quartile groups based on the distribution in all the study population), taking the lowest
154 quartile group as reference. The continuous PAH4 dietary intake was divided by its STD to estimate
155 HR per standard deviation increment. Linear trends across PAH4 dietary intake categories were
156 tested by assigning the median value for each category and by modelling it as a continuous
157 variable.

158 Adjustment variables were selected using a directed acyclic graph (DAG) to estimate the total effect
159 derived from available knowledge (**Supplementary figure 2**). In order to respect temporality,
160 adjustment covariates were selected in questionnaire 2 (Q2, sent in January 1992), when available,
161 to precede the dietary questionnaire (Q3, sent in June 1993) which collected information on food
162 consumption over the previous year.

163 2.6.1. All-cause mortality

164 First, we ran three successive models to study the risk of all-cause mortality. Model 1 was only
165 adjusted on age as the time-scale (continuous, years). Model 2 was further adjusted on body mass
166 index (BMI) at Q2 (continuous, kg/m²), birth generation (<=1930,]1930 – 1935],]1935 – 1940],
167]1940 – 1945], >1945), education level (<12 years, 12 to 14 years, >14 years), smoking status at Q2
168 (never smoker, former smoker, current smoker), physical activity at Q3 (continuous, MET-
169 hours/week), and menopausal status and recent use of menopausal hormone therapy (MHT) at Q2
170 (premenopausal, menopausal and recent MHT use, menopausal and no recent MHT use,
171 menopausal but we don't know if and when the MHT was used). Model 3, our main model, was
172 additionally adjusted on total energy intake estimated excluding energy from alcohol and lipids
173 (continuous, kcal/day), alcohol consumption (continuous, g of ethanol/day), and lipids consumption
174 (continuous, g/day), all measured at Q3, the dietary questionnaire. Two additional models were
175 tested: Model 4 further adjusted on the calculated adherence to a healthy dietary pattern at Q3
176 (continuous) derived from principal component analysis (PCA), as previously described [32], and
177 Model 5 adjusted on bread and salty cereal products consumption at Q3 (the food group that most
178 contributes to PAH4 dietary intake, continuous, g/day).

179 We additionally performed sensitivity analyses on the main model for all-cause mortality. We applied
180 the energy adjustment residual method [33], where the residual estimates PAH dietary intake
181 uncorrelated with total energy intake, and is used as the main exposure variable in the model. We
182 used PAH4 dietary intake estimated according to the MB scenario because the LB scenario may
183 underestimate the dietary intake. We excluded cases that occurred during the first five years of
184 follow-up to investigate potential reverse causation bias. We performed two distinct analyses
185 according to the median follow-up duration of cases in order to separate early and late cases: in the
186 first analysis, we stopped the follow-up at the median (12.0 years), thus censoring at this time point
187 all participants followed longer, and in the second analysis, we excluded the ones with a follow-up
188 time shorter than the median. We excluded women with missing values for at least one variable of
189 Model 3 to perform a complete case analysis. To produce results comparable with the risk
190 assessment outputs, we used as main exposure variable PAH4 expressed as dietary exposure,
191 meaning dietary intake divided by body weight (ng/kg bw/day). We also tested the interaction
192 between continuous PAH4 dietary intake and BMI and stratified the main model on BMI at Q2 (≤ 25
193 kg/m², > 25 kg/m²) to investigate the potential different association between PAH4 intake and
194 mortality risk among normal or underweight and overweight women.

195 2.6.2. Cancer mortality

196 For all-cancer, breast cancer, lung/tracheal cancer, and colorectal cancer mortality, our principal
197 analyses consisted in studying Model 3. For all-cancer mortality, the sensibility analyses excluded
198 prevalent cancer cases or adjusted the main model on a diagnosis of cancer or diabetes before
199 inclusion (yes, no, the diagnosis occurring at least one year before the answer to the dietary
200 questionnaire). For breast cancer mortality, we additionally adjusted the main model on current or
201 past use of contraceptive pill at Q2 (never, ever) and on age at menarche (continuous, years). For
202 lung/tracheal cancer mortality, we performed Model 3' which corresponds to Model 3 with an
203 additional treatment of smoking status as a time-varying covariate, and Model 3'' equivalent to
204 Model 3 without the smoking status to compare the effect with or without this covariate. We also
205 tested the interaction between continuous PAH4 dietary intake and smoking status, and we stratified
206 the main model on smoking status.

207 2.6.3. CVD mortality

208 For all-CVD and stroke and coronary heart disease mortality, we studied Model 3 as the principal
209 analysis. In sensibility analyses, we additionally adjusted Model 3 on a diagnosis of diabetes (yes,
210 no), hypertension (yes, no) and high cholesterol occurring before inclusion (yes, no).

211 The proportional hazard assumption was verified using Schoenfeld residuals, and restricted cubic
212 splines [34] with 3 knots (at the 10th, 50th and 90th percentiles) [35] were used to verify the log-
213 linearity assumption. For covariates with missing values <5%, we substituted them with the modal
214 category for categorical variables and with the median for continuous variables. We created an
215 unknown values category above 5% (only for menopausal status and recent MHT use). We
216 considered a p-value <0.05 as statistically significant. Data were analysed with the Statistical
217 Analysis Systems software package, version 9.4 (SAS Institute, Cary, North California).

218 **3. Results**

219 3.1. *Study population characteristics*

220 Our study population of 72 513 women included 4 620 deaths, among which 2 726 were due to
221 cancer and 584 were due to CVD. More specifically, there were 790 deaths from breast cancer, 277
222 from lung/tracheal cancer, 243 from colorectal cancer, 1 478 from cancer in other localisations, and
223 287 from stroke and coronary heart disease mortality during an average follow-up of 16.5 years
224 (16.9±2.9 for non-cases and 11.1±4.9 for cases) or 1 199 233 person-years. Causes of death, types
225 of cancer leading to death and type of CVD leading to death are listed in **Supplementary table 2**,
226 **Supplementary table 3**, and **Supplementary table 4**, respectively.

227 The baseline characteristics of participants among each quartile group of PAH4 dietary intake are
228 presented in **Table 1**. At inclusion, the women had an average of 52.9 years and a BMI of 22.7
229 kg/m². The majority (52.9%) presented a level of school education from 12 to 14 years, 55.5% had
230 never smoked, and 51.4% were not menopausal. Their mean energy intake (excluding energy from
231 alcohol and lipids) was 1 329 kcal/day. The baseline characteristics comparing included and
232 excluded women and those among cases and non-cases are presented in **Supplementary table 5**
233 and **Supplementary table 6**, respectively.

234 **Supplementary figure 3** presents the proportion of each PAH to PAH4 dietary intake. CHR was the
235 PAH contributing the most to PAH4 dietary intake (45.0%), while BaA and BbF represented 22.3%
236 and 21.0%, respectively, and BaP only 11.7%. Correlation among PAH included in PAH4 varied
237 between 0.68 and 0.94. Moreover, as previously suggested by others [1], PAH4 was highly
238 correlated with PAH8 ($\rho=0.98$), and to a lower extent also to PAH20 ($\rho=0.82$) (**Supplementary**
239 **table 1**). The median estimated PAH4 dietary intake for all women included in the study was 66.1
240 ng/day (interquartile range: 49.9-88.5), as presented in **Supplementary table 7**. Food groups that
241 contributed the most to PAH4 dietary intake were bread and salty cereal products (22.3%), followed
242 by fat food (mainly butter, margarine and oil) and sea products (seafood and fish), which both
243 contributed to 14.9% of the total PAH4 dietary intake (**Supplementary figure 4**).

244 3.2. PAH dietary intake and mortality risk

245 There was no statistically significant association between PAH4 dietary intake as a continuous
246 variable (HR 1.00, 95%CI 0.97-1.04) and in quartile groups (p-trend 0.429) and the risk of all-cause
247 mortality, independently of the model used (**Table 2**). We observed the same results when we
248 further adjusted for the most contributing food group to PAH4 dietary intake (bread and salty cereal
249 products) or for a healthy dietary pattern (**Supplementary table 8**).

250 When studying cancer mortality, the association remained not statistically significant for the risks of
251 all-cancer (HR 1.02, 95%CI 0.97-1.06, p-trend 0.445), breast cancer (HR 0.99, 95%CI 0.91-1.08, p-
252 trend 0.192), or colorectal cancer (HR 0.99, 95%CI 0.85-1.15, p-trend 0.816). Conversely, we
253 observed a positive and statistically significant association between continuous PAH4 dietary intake
254 and lung/tracheal cancer mortality risk with an HR of 1.15 (95%CI 1.02-1.29). However, this
255 association was not statistically significant when analysing PAH4 dietary intake expressed as
256 quartile groups (p-trend 0.160) (**Table 3**). We didn't identify a significant interaction between PAH4
257 dietary intake and smoking status ($P_{\text{interaction}}=0.54$). However, when stratifying the main model on
258 smoking status (never smoker, former smoker, current smoker), measured at the time of answer to
259 the second questionnaire sent in 1992, we found a stronger association between PAH4 dietary
260 intake and the risk of lung/tracheal cancer mortality among current smokers (HR 1.21, 95%CI 1.01-

261 1.44, p-trend 0.121) than among former smokers (HR 1.14, 95%CI 0.92-1.42, p-trend 0.429) and
262 never smokers (HR 1.09, 95%CI 0.87-1.37, p-trend 0.782). This association was only statistically
263 significant for current smokers (**Table 4**).

264 In our CVD mortality analyses, the association was not significant for the risk of all-CVD mortality
265 (HR 1.03, 95%CI 0.94-1.14, p-trend 0.959) and for the risk of stroke and coronary heart disease
266 mortality (HR 1.00, 95%CI 0.87-1.15, p-trend 0.599) (**Table 3**).

267 3.3. Sensitivity analyses

268 Results remain unchanged in terms of statistical significance and of HR values in all sensitivity
269 analyses, stratified or additionally adjusted models (**Supplementary table 9 to Supplementary**
270 **table 20**). The interaction between continuous PAH4 dietary intake and BMI was significant
271 ($P_{\text{interaction}}=0.03$), but stratifying the analysis on BMI also conducted to not significant results
272 (**Supplementary table 11**). A minor difference was observed when the main exposure variable was
273 used in ng/kg bw/day: results remained globally similar to principal analyses, although a significant
274 inverse association was observed between the third quartile group of PAH4 dietary exposure and
275 the risk of mortality, compared to the first quartile group (HR 0.89, 95%CI 0.82-0.98)
276 (**Supplementary table 21**). Finally, removing the smoking status covariate from Model 3 or adding it
277 as a time-varying covariate did not impact the results in comparison with Model 3 (**Supplementary**
278 **table 22**).

279 4. Discussion

280 In the E3N French prospective cohort of middle-aged women, no statistically significant association
281 between PAH4 dietary intake and the risk of all-cause, all-cancer, breast cancer, colorectal cancer,
282 all-CVD, stroke and coronary heart disease mortality was highlighted in the present study. On the
283 contrary, a positive association was found between continuous dietary intake of PAH4 and
284 lung/tracheal cancer mortality. Moreover, when stratifying the model for lung/tracheal cancer
285 mortality on smoking status, a gradient association was observed when passing from never
286 smokers to former smokers and current smokers. A statistically significant positive association was
287 found only for current smokers.

288 The toxicity of PAH, mainly demonstrated in humans through occupational exposure studies, can be
289 explained by some mechanisms identified in experimental in-vivo studies. Low molecular mass PAH
290 (2 to 4 rings) are more absorbed than high molecular mass PAH (>4 rings). After absorption, PAH
291 are distributed to all organs and are highly metabolised [1]. Indeed, some PAH are converted into
292 reactive intermediates (namely diol-epoxides, radical cations or o-quinones) that can covalently bind
293 with DNA and thus form DNA adducts, which can result in mutations, modification of expression,
294 immunosuppressive and teratogenic damage, or carcinogenesis in some cases [36–39]. Moorthy et

295 al. describe different mechanisms induced by PAH and leading to lung cancer, like mutations of p53
296 gene-specific sequences associated with lung cancer [38]. An animal study on mice compared the
297 tumours induced by the PAH dietary exposure through BaP only or coal tar mixtures. More
298 adenomas or carcinomas of alveoli/bronchioles were detected among mice exposed to a mixture of
299 PAH, with a dose-response effect, than among mice exposed to BaP only, supporting the
300 hypothesis that other PAH than BaP were responsible for this association and thus suggesting that
301 BaP only is not the more suitable indicator for PAH dietary exposure effects [40].

302 4.1. PAH dietary exposure estimates

303 Previous studies on PAH dietary exposure estimates reported similar results. As expected, our
304 results were of the same magnitude as those reported by Anses. Indeed, Anses found a mean
305 PAH4 dietary exposure estimated according to the MB scenario of 1.5 ng/kg bw/day [29], very
306 comparable with our result (1.3 ng/kg bw/day). Food contamination levels used by Anses were also
307 those obtained with the TDS2, but the food consumption data used to estimate dietary exposure to
308 PAH were those obtained with the INCA2 (Etude Individuelle Nationale des Consommations
309 Alimentaires) French study, a study including 1 918 adults from 18 to 79 years conducted in 2006-
310 2007. Similarly, the mean BaP dietary exposure estimated according to the LB scenario in our study
311 was 0.1 ng/kg bw/day, not very different from the Australian mean dietary exposure estimates
312 according to the same scenario for adult women (0.2 ng/kg bw/day) [41]. On the contrary, the PAH4
313 median dietary intake estimated according to the upper bound (UB) scenario (by using the LOD
314 directly when a value is not detected) was 1 168 ng/day in the EFSA report, so 16 times greater
315 than our estimate based on the MB scenario (71.9 ng/day) [1]. This difference could be explained by
316 the different scenarios used (MB vs UB) and by improved analytical methods (more precision, lower
317 limit of detection). Indeed food contamination data obtained by the Anses are more recent than
318 those used by EFSA (2007-2009 for the Anses against 2000-2007 for EFSA) [1,29], and it could be
319 suggested that the measurements conducted by the Anses are more accurate so that the proportion
320 of the left-censored data is lower. This implies a reduced impact of the choice of the scenario on the
321 final estimates. Furthermore, some foods analysed in the EFSA report contained particularly high
322 levels of PAH, grilled foods for example, whereas in the E3N study, there isn't the same level of
323 detail in terms of food consumption or contamination data (because the French TDS2 represents
324 the common French dietary pattern, not taking into account barbecue for example [27]). In the same
325 way, an American study also found a higher median BaP intake (73 ng/day) in comparison with our
326 results (7 to 11 ng/day under the LB and MB scenario, respectively) [42]. This difference can be
327 partly explained by the difference of food analysed (for example, in contrast to our study, different
328 meat cooking methods and doneness were taken into account in the American study) and by
329 different food habits and levels of food contamination. Finally, the comparison with the American

330 study has to be interpreted with caution since the authors did not specify how left censored data
331 were handled.

332 As in our results, cereals and cereal products were the most contributing food group to PAH dietary
333 exposure in several studies, frequently followed by fats and/or seafood products [1,7,20,23,41,43].
334 In the Anses study, the three main food groups were the same as in our analysis, but not in the
335 same order, with first fats (23.5%), contributing almost twice as much as crustaceans and molluscs
336 (13.1%) and bread and dry bakery products (12.6%) [29].

337 4.2. PAH dietary exposure and mortality risk

338 To our knowledge, no previous study on PAH dietary exposure and mortality risk is available, and
339 only one study focused on the association between internal levels of PAH and mortality risk in the
340 general population. This prospective cohort study on 1 409 American participants revealed that
341 some PAH urinary metabolites were positively associated with all-cause or cardiovascular mortality,
342 particularly for women, but not cancer mortality. Moreover, the authors claimed that the association
343 was not significant for cancer mortality, maybe because of the short follow-up time (only five years),
344 which didn't allow for observing potential long-term adverse effects of PAH exposure [44]. The
345 difference between this study and our results may be explained by different food consumption and
346 contamination profiles and thus different exposure patterns between the French and the Americans.
347 Moreover, this study has estimated the exposure using internal biomarkers, which are the result of
348 PAH exposure from several sources, not only from food consumption.

349 We also reported a positive association between PAH dietary exposure and lung/tracheal cancer
350 mortality. Similarly, a study on 300 Chinese adults with a low, medium or high PAH exposure and
351 living in a high cancer mortality area highlighted an association between exposure to 16 PAH in air,
352 soil, drinking water and food samples (and thus through dermal contact, inhalation and ingestion)
353 and lung cancer mortality [15]. The link between PAH exposure and lung cancer was also previously
354 explored. In this way, a review reminded the association between PAH exposure through inhalation
355 and an increased risk of lung cancer [38].

356 Concerning the positive association between PAH dietary exposure and lung/tracheal cancer
357 mortality in our study, we observed a stronger association in current smokers. It can be noted that
358 according to the descriptive analyses on excluded women (**Supplementary table 5**), a large
359 number (17 915) of never smokers were excluded from analyses, but it should not impact the
360 interpretation of our results as we have performed stratified analyses on smoking status. Moreover,
361 it is possible that there is residual confusion from smoking. However, our results suggest that in
362 current smokers, a higher PAH dietary intake is associated with a higher mortality risk from
363 lung/tracheal cancer. This might be due to a cumulative effect between dietary PAH and PAH in

364 tobacco. Indeed, smoking is a known source of PAH exposure as some PAH are present in tobacco
365 [1]. Alexandrov et al. observed a mutational signature associated with lung cancer among smokers
366 very similar to that *in vitro* cells treated with BaP. These results suggest that BaP may be involved in
367 inducing lung cancer in smokers [37].

368 4.3. *Strengths and limitations*

369 This study presents some limitations. First, our population only consisted of women. Nevertheless,
370 studying the PAH dietary exposure of a population of only women is relevant because differences in
371 the exposure and health effects compared to men were previously observed [44,45] and because of
372 the importance of taking into account gender differences when studying endocrine-disrupting
373 chemicals. Moreover, we studied middle-aged women who are leaner and with a higher level of
374 education [24] compared to middle-aged women of the French population, which does not allow us
375 to generalise the results. On top of that, women in the cohort are quite homogeneous regarding
376 PAH dietary intake. In that way, it should be noted that there are no unexposed women since PAH
377 are ubiquitously found in food. However, we can still classify them in higher and lower exposure
378 groups and compare the association between different levels of PAH dietary intake and the risk of
379 mortality.

380 There is also a limitation because the dietary questionnaire was completed in 1993, whereas the
381 contamination levels were assessed from 2007 to 2009. This could have resulted in variations of
382 food habits of women. However, Thorpe et al. suggest that dietary pattern of middle-aged women
383 remains stable overtime [46]. This could also have conducted to variations of food contamination
384 levels. However, we had no other alternatives because, on the one hand, the only currently
385 available consumption data in the E3N cohort is from the third questionnaire of 1993, and on the
386 other hand, the TDS2 is the most accurate, recent and complete database on French food
387 contamination levels. Moreover, PAH are POPs and thus are persistent in the environment with a
388 long half-life, therefore their concentrations change slowly overtime [47]. Furthermore, even if a
389 decrease in contamination levels may have occurred, we can assume that this diminution is the
390 same in all food groups as environmental contamination is ubiquitous. Consequentially, the error in
391 the estimation of the PAH dietary exposure of the participants may have been homogeneous among
392 them, and thus we can assume that the participants have been correctly classified between them in
393 the four quartile groups of exposure. Finally, the potential classification error is expected to be non-
394 differential and to lead to the attenuation of the real association.

395 Furthermore, even if the TDS2 analysed samples prepared “as consumed” according to the French
396 cooking habits, individual food preparation methods of the E3N women are not known. In particular,
397 some practices known to increase PAH contamination levels of food, like barbecue, were not
398 considered in our study because of a lack of data. This could have led to an underestimation of the

399 PAH exposure. Nevertheless, Veyrand et al. claimed that French consumption of barbecued food is
400 low and seasonal and thus may impact PAH acute exposure but not the chronic one [29].

401 Furthermore, although PAH exposure from other sources and co-exposure to other chemicals could
402 also contribute to the overall mortality risk, this information could not yet be integrated in the present
403 study.

404 Moreover, we only studied the sum of four PAH, which does not enable possible non-additive
405 effects (such as interactions between substances) to be taken into account. We can also underline
406 the complexity of separating the effect of PAH from the effect of food, despite adjustments on
407 possible residual confounders. Finally, due to the observational design, potential residual
408 confounding cannot be ruled out.

409 Despite some limitations, our study also has several strengths. Indeed, with more than 70 000
410 women followed during an average of 16.5 years and with a good participation rate over time, this
411 study allows us to explore long term health effects associated with PAH dietary exposure among a
412 large study population. We could perform several sensitivity analyses and investigate the
413 association between PAH dietary intake and cause-specific mortality thanks to the high-quality data
414 concerning mortality as well as to the large study population that ensured a good statistical power.
415 Investigating the mortality risk as the main outcome allows, on the one hand, including in the study
416 many cases, and on the other hand, it represents an interesting outcome given the wide variety of
417 health issues associated with PAH exposure. Dietary exposure to PAH was estimated at baseline,
418 before the outcome occurrence, thus respecting temporality between the events and limiting recall
419 bias on food consumption. Moreover, the food frequency questionnaire and the mortality cases were
420 previously validated. These validations reduce the risk of misclassification of participants according
421 to their exposure or their vital status. More generally, the information collected is of good quality, as
422 demonstrated by the low proportion of missing data (data not shown). The data availability also
423 allowed taking into account many adjustment variables, selected with a DAG. Finally, the results are
424 robust, as illustrated by the different scenarios tested (LB or MB, dietary intake or exposure, etc.).

425 **5. Conclusion**

426 In conclusion, this is the first observational study to investigate the association between dietary
427 exposure to PAH and mortality. This study suggests a lack of association between dietary exposure
428 to PAH and the risk of all-cause, all-cancer, breast cancer, colorectal cancer, all-CVD, stroke and
429 coronary heart disease mortality. On the contrary, the present study highlights an association
430 between PAH dietary exposure and lung/tracheal cancer mortality risk, especially among current
431 smokers. These results need to be further investigated in other studies.

432 From a public health perspective, there is a real need for large observational studies focusing on the
433 adverse effects of PAH dietary exposure, notably the lung/tracheal cancer, in non-occupationally

434 and more dietary exposed population. Analytical methods also need to be improved to better detect
435 PAH, even at low doses, in order to provide more accurate PAH dietary exposure estimates.

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446 **Statements & Declarations**

447 *Acknowledgments*

448 The authors of this study thank all the women in the E3N cohort. They also thank the members of
449 the "Exposome and Heredity" team.

450 *Funding*

451 This work was realized with the data of the E3N cohort of the Inserm and supported by the Mutuelle
452 Générale de l'Education Nationale (MGEN), the Gustave Roussy Institute, and the French League
453 against Cancer for the constitution and maintenance of the cohort. This work has benefited from
454 State aid managed by the National Research Agency under the program "Investment in the future"
455 bearing the reference ANR-10-COHO-0006 as well as subsidy from the Ministry of Higher
456 Education, Research and Innovation for public service charges bearing the reference
457 n°2103586016. The work was also supported by the grant EQ9-C17014LS from the Cancer ITMO of
458 the French National Alliance for Life and Health Sciences (AVIESAN), in collaboration with the
459 Institut National du Cancer (French National Cancer Institute) and Inserm. This work was also
460 supported by a doctoral funding from the University Paris-Saclay Doctoral School of Public Health
461 EDSP.

462 *Competing Interests*

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

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