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Association between dietary exposure to chemical contaminants and risk of dementia in older persons

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ABSTRACT

Background: Diet is a major route of exposure to potentially neurotoxic chemicals, yet the epidemiological association of diet contaminants with dementia is unknown. We studied the link between dietary exposure to multiple chemicals and dementia risk in older persons, considering interaction with dietary fat content, which may modify the bioavailability and toxicity of (lipophilic) chemicals.

Methods: We included 1,288 non-demented participants from the French Three-City cohort who answered a food frequency questionnaire and 24-hour recall at baseline and were followed for incident dementia. Dietary exposure to 167 contaminants was assessed by combining food intakes with food chemical content from the French second Total Diet Study. We assessed the relation of each individual contaminant with dementia risk using multivariable-adjusted Cox models, exploring effect modification by high-fat diet (>35 % energy from fat). Among high-fat diet consumers, we looked for a signature of contaminants associated with dementia using elastic-net penalization and assess their joint effect.

Results: Participants were 76 years-old on average at baseline and 62 % were women. In total, 314 individuals developed dementia over a median 10 years. No contaminant was associated with dementia in the whole population. However, having a high-fat diet was a strong effect modifier for 85 contaminants (FDR-corrected $p < 0.05$ for interactions) in single-chemical analyses, so that higher intakes were significantly associated with higher dementia risk among high-fat consumers only ($n = 386$). Among them, a multi-chemical approach revealed a signature of 9 contaminants related to dementia, including 4 perfluoroalkyl substances, 2 flame retardants hexabromocyclododecane (HBCDD) congeners, 2 mycotoxins, and nitrites. This selection included two top hits from the single-chemical analyses (α-HBCDD and perfluorooctanesulfonic acid [PFOS]), and was mainly provided by delicatessen meat, seafood and bread/crispbread.

Conclusion: In this large population-based study, dietary exposure to several chemicals was associated with higher dementia risk among older persons consuming > 35 % energy from fat in diet.

1. Introduction

With the aging of the population, dementia and its main cause, Alzheimer's disease (AD), are rapidly increasing worldwide. Although multiple genetic, cardiometabolic and lifestyle risk factors are known to contribute to AD, much of the environmental etiology of the disease, in particular concerning the chemical exposome, remains unknown (Livingston et al., 2020; Lefèvre-Arbogast et al., 2024).

Diet is a primary source of exposure to chemicals in the general population (Papadopoulou et al., 2019). These dietary contaminants may originate from food production and processing (e.g. pesticides, additives, polyaromatic hydrocarbons [PAH]) and/or from environmental contamination by industrial (e.g. PAH, dioxins, polychlorinated bisphenyls [PCB], brominated flame retardants [BFR], per- and polyfluoroalkyl substances [PFAS]) or naturally-occurring substances (e.g. metals found in soils, mycotoxins produced by fungi) (Second French

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Total Diet Study (TDS 2), 2011; Second French Total Diet Study (TDS 2), 2011). For instance, fish may be contaminated by a variety of lipophilic chemicals that bioaccumulate in fatty tissues along the food chain, including methylmercury, organochlorine pesticides, PCB and certain BFR and PFAS (Second French Total Diet Study (TDS 2), 2011). Most of them have been detected in almost 100 % of human biofluid samples in several large-scale biomonitoring programs, suggesting widespread exposure of the general population (Govarts et al., 2023; Woodruff et al., 2011; Haines et al., 2017). In addition, many of these chemicals (e.g. certain metals, organochlorine pesticides, PCB, BFR, PFAS) can reach the human brain (Mitchell et al., 2012; Richardson et al., 2014; Hatcher-Martin et al., 2012; Morris et al., 2016; Pérez et al., 2013), and have documented neurotoxic effects in experimental studies, including oxidative stress, calcium dyshomeostasis, excitotoxicity, neuronal apoptosis, neurotransmitter dysregulation and amyloid accumulation (a neuropathological hallmark of AD) (Long et al., 2013; Reffatto et al., 2018; Basaly et al., 2021; Li et al., 2015; Wallin et al., 2017).

Growing evidence, especially from studies of occupationally exposed populations (e.g. agricultural workers), indicates that some chemicals such as pesticides may increase the risk to develop AD (Lefèvre-Arbogast et al., 2024; Expertise collective, ed. Effects of Pesticides on Health – New Data, 2022). However, little is known regarding the influence of chemical exposures at lower doses within the general population. In the context of high food contamination following industrial accidents, epidemiological studies have reported associations between higher blood levels of PCB or dioxins (from consumption of contaminated cooking oil, Great Lakes fish, or food produced in polluted area), and lower learning and memory abilities in older adults and higher risk of dementia (Lin et al., 2008; Schantz et al., 2001; Raffetti et al., 2020). However, very few cohort studies have investigated prospective associations with dementia risk, especially at low background exposure levels (Raffetti et al., 2020; Medehouenou et al., 2019; Tanner et al., 2020). Moreover, most studies have focused on single substances belonging to one or two chemical families, while individuals are simultaneously exposed to multiple chemicals. In addition, the impact on toxicity of various aspects relative to the route of exposure, such as the composition of the food matrix, has been overlooked, although dietary contaminants, most of which lipophilic, co-occur with nutrients in diet and may share common mechanisms of absorption, transport, storage or excretion as well as molecular signaling pathways (Cano-Sancho and Casas, 2021). Hence, several experimental studies have reported that multiple chemical-induced metabolic dysfunctions were exacerbated by a high-fat diet (Tan et al., 2013; Chen et al., 2022; Wahlang et al., 2013; Yanagisawa et al., 2014; de la Monte et al., 2009). A high-fat content may increase the bioaccessibility of lipophilic contaminants (Yu et al., 2010), as observed with other lipophilic substances (e.g. drugs, nutrients) (Koch et al., 2009; Moran et al., 2018), by promoting the formation of mixed bile salt micelles and the secretion of chylomicrons by enterocytes (Charman et al., 1997). A high-fat diet may also decrease the xenobiotic metabolism activity, thereby impairing the body's ability to detoxify and increasing its susceptibility to adverse effects upon xenobiotic exposure (Sadler et al., 2018). Furthermore, sex-specific vulnerabilities may arise due to variations in metabolism between men and women, which can influence their response to contaminants, as well as differences in disease susceptibility (D'Archivio et al., 2024; Aggarwal and Mielke, 2023). In this context, the objective of this exploratory study was to investigate the link between dietary exposure to a broad spectrum of food contaminants, considered individually or jointly, and the incidence of dementia in a large prospective French cohort of older persons, considering potential effect modification by dietary fat or sex.

2. Methods

2.1. Study population

The Three-City (3C) study is a French population-based cohort on dementia that enrolled 9,294 community dwellers aged 65 years or older in Bordeaux (n = 2,104), Dijon (n = 4,931), and Montpellier (n = 2,259) in years 1999–2000 (3C Study Group, 2003). At recruitment, sociodemographic and lifestyle characteristics, medical data, neuropsychological testing and blood sampling were collected during in-person interviews. Follow-up examinations were performed every 2–3 years until 2012 in Dijon, 2016 in Montpellier and 2018 in Bordeaux center. An additional follow-up was performed in Bordeaux in 2020, though the results have not yet been released. All examinations included neuropsychological testing for dementia screening. In 2001–2002, in the Bordeaux center, a comprehensive in-person dietary interview was conducted at home by trained dieticians. The present study was based on participants from the Bordeaux 3C sample who participated in both the dietary survey and the screening procedure for dementia (n = 1,595) (see flow chart in **Supplementary Fig. 1**). Among them, we excluded 73 prevalent dementia cases at the time of the dietary survey, 98 participants who were not evaluated for cognition thereafter (including 53 deceased before next follow-up) and 136 participants with missing data for genotyping of the apolipoprotein E (carrying the ApoE-ε4 allele being the main genetic risk factor for dementia). Our study sample thus included 1,288 participants followed for up to 16 years after dietary assessment. Among them, the cumulative number of deaths over follow-up was 674, and 154 were lost to follow-up while 460 (75 % of the surviving participants) were examined at the last visit. The Consultative Committee for the Protection of Persons participating in Biomedical Research of the Kremlin-Bicêtre University Hospital (Paris, France) and Sud-Mediterranée III approved the 3C study protocol, and written informed consent was obtained from each participant.

2.2. Assessment of incident dementia

At each visit, participants were administered a battery of neuropsychological tests at home by a trained psychologist. Participants suspected of dementia based on their cognitive performances were then examined by a neurologist to establish a clinical diagnosis, which was further reviewed and validated by an independent committee of neurologists according to the Diagnostic and Statistical Manual of Mental Disorders, fourth edition (American Psychiatric Association, 1994). Dementia cases were classified as probable or possible AD on the basis of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association Alzheimer criteria.

2.3. Assessment of dietary exposure to chemical contaminants

Detailed dietary data were collected using two complementary questionnaires: a food frequency questionnaire (FFQ) and a 24 h-dietary recall (24HDR). For each participant, the habitual daily intake in 55 foods and drinks was estimated (in g/d) by multiplying, for each food/beverage item, the average number of eating occasions per week as assessed by the FFQ, with the average portion size reported in the 24HDR (see detailed procedure in **Supplementary Methods**). Dietary exposure to major chemical contaminants was then assessed by multiplying these food intakes with food chemical contamination estimates from the French Agency for Food Safety in the second Total Diet Study (TDS2) (Second French Total Diet Study (TDS 2), 2011; Second French Total Diet Study (TDS 2), 2011; Sirot et al., 2009) The TDS2 provided real measures, in year 2006, of contamination levels in 445 substances of composite samples of 212 core foods representative of French national and regional dietary habits, prepared "as consumed" (e.g., fruit and vegetables were washed) (**Supplementary Methods**).

Because measurement instruments have detection limits, TDS2 contamination data included concentrations below the analytical limits of detection (LD) or quantification (LQ) (i.e., concentrations that could not be detected and/or accurately quantified), at various extent depending on the substance, the food and the method. These left-censored contamination values may be imputed according to different scenario. In our study, we used the optimistic "lower-bound scenario". Following this scenario, non-detected values (i.e. < LD) were imputed to zero, while values detected but non-quantified (i.e. [LD; LQ]) were assigned the LD. From the 445 chemicals measured in the TDS2, we excluded 33 substances which were not food contaminants (11 phytoestrogens and 12 minerals). Among the remaining 412 chemical contaminants, 247 were not considered in our study because no participant was exposed (4 PFAS, 7 mycotoxins, and 236 pesticides). After further grouping of the food additives E249-250 (nitrites) and E220-228 (sulphites), the final analytical database contained 167 chemical contaminants including 4 food additives, 47 pesticides, 18 mycotoxins, 16 metal trace elements, 17 dioxins/furans, 18 PCBs, 14 brominated flame retardants, 21 PAHs, 12 PFAS. Due to the exploratory nature of our study, no further selection of contaminants was performed. Chemical intakes were standardized to mean 0 and standard deviation (SD) of 1.

2.4. Assessment of covariates

Covariates were collected at inclusion (a mean 1.9 years before dietary assessment), except age and dietary factors that were ascertained at the time of the dietary survey. All potential confounders were selected a priori. Sociodemographic information included age, sex, the level of education (considered dichotomously as attaining at least secondary school) and the monthly income (considered dichotomously, as earning at least 1500€/month or less). ApoE-ε4 genotype was defined as carrying at least one ε4 allele vs. none. Cardiometabolic risk factors included the history of cardiovascular diseases (considered dichotomously if any of the following self-reported conditions: myocardial infarction, angina, heart rhythm disorders and heart failure, arteritis of the lower limbs disease, stroke or cardiac/vascular surgery), the body mass index (in 3 categories < 25, [25–30[, ≥30 kg/m^2 based on measured height and weight), hypertension (systolic to diastolic blood pressure ≥ 140/90 mm Hg or treatment), hypercholesterolemia (plasma total cholesterol ≥ 6.2 mmol/L, or treatment), and diabetes mellitus (fasting blood glucose ≥ 7.0 mmol/L, or treatment). Lifestyle factors included self-reported alcohol consumption (in 4 categories 0, ≤12,]12–24] or > 24 g/d), tobacco consumption (in 3 categories, 0, <20 or ≥ 20 pack-year), and engagement in regular physical activity (defined dichotomously as practicing a sport or an intensive leisure activity [e.g., hiking] ≥ 1h/wk or engaging in a more moderate activity [e.g., walking or household] ≥ 1h/d. Dietary factors included total energy intake (in kcal) and a high-fat diet (defined dichotomously as having > 35 % of energy provided by fat in the diet(Vannice and Rasmussen, 2014), both assessed by the 24HDR. The adherence to the Mediterranean Diet was assessed by a 9-component score based on the number of serving/weeks of 8 food groups assessed by the FFQ (vegetables, fruit, legumes, cereals, fish, meat, dairy products, alcohol) and the monounsaturated-to-saturated fatty acids ratio assessed by the 24HDR. Each of the 9 components was dichotomized based on sex-specific medians of the population, assigning 1 to beneficial behaviors (e.g. consumption of fish higher than the median) and 0 otherwise, except alcohol for which the second quartile was assigned 1 (i.e., a moderate consumption was considered beneficial) and 0 otherwise. The total score ranged from 0 to 9, with higher scores indicating greater adherence (Féart et al., 2009).

2.5. Statistical analyses

Two complementary approaches were used to examine associations between dietary exposure to chemical contaminants and the risk of dementia. In a first stage, we studied the relation of each individual contaminant with dementia risk, using Cox proportional hazard regression models adjusted for age (as a spline function), sex, level of education, ApoE-ε4 carrier status (the main genetic risk for dementia being directly involved in lipid metabolism), and adherence to the Mediterranean diet (a model of healthy diet pattern (Féart et al., 2009), controlling for multiple testing using Benjamini-Hochberg false discovery rate (FDR) (with $P_{FDR} = 0.05$, i.e., tolerating 5 % of false discoveries among significant tests). We primarily modeled linear associations using contaminant intakes as continuous variables, and secondarily assessed non-linear associations using quartiles of contaminants and penalized splines. We explored systematically potential effect modification by sex and high-fat diet (>35 % of energy from fat (Vannice and Rasmussen, 2014), as assessed by the 24HDR). In case of significant interactions tests ($P_{FDR} < 0.05$), we conducted stratified analyses.

Single-chemical analyses are prone to residual confounding by other chemical substances provided by the same food source(s). In a second stage of analysis, we therefore considered all contaminants jointly, searching for a signature of food contaminants associated with dementia risk. We applied Elastic-Net penalized regression, which allows variable selection in high dimensional sets of correlated variables (as the food contaminants analyzed here). With Elastic-Net, strongly correlated predictors tend to be selected together (see **Supplementary Methods** for details on implementation). We preselected for entry in the Elastic-Net procedure the contaminants associated with dementia risk in single-chemical analyses at p ≤ 0.10 (uncorrected, to avoid overly conservative filtering and favor discovery while reducing noise and computational burden). The model was adjusted for the same potential confounders as in the single-chemical approach (considered as unpenalized covariates) and we applied bootstrap resampling (500 random resampling with replacement from the initial sample) to enhance the robustness and reliability of variable selection. The final selection included the chemical contaminants selected over > 50 % of bootstraps. From these selected contaminants, we computed a food contaminant signature score associated with dementia risk as the sum of individual intakes of each contaminant weighted by coefficient estimates from an unpenalized Cox model. In case of major effect modification by sex or high-fat diet, as evidenced in single-chemical analysis, we performed Elastic-Net regression exclusively within subgroups.

We run several additional analyses. We adjusted the single-chemical analyses for a larger set of confounders selected a priori, including total energy intake, monthly income, as well as cardiometabolic and lifestyle factors, to examine potential residual confounding. For this analysis, missing data for covariates (which were missing for 11.6 % for physical activity, 5.7 % for income, 1.5 % for smoking, and ≤ 1.0 % for alcohol, diabetes and hypercholesterolemia) were imputed by multiple imputation. We also conducted sensitivity analyses evaluating the robustness of findings to variations in the imputation scenario for imputing left-censored food chemical contamination estimates. Instead of the "lower-bound" scenario as used in the main analysis (where values < LD were imputed to zero and values [LD; LQ] were assigned the LD) we applied the "medium-bound" scenario, where values < LD are imputed to 1/2LD and values [LD; LQ] are imputed to 1/2(LQ-LD). In addition, since chemical toxicity may vary according to body weight (e.g., underweight individuals may experience toxicity effects at lower levels of contaminant intake than overweight individuals), we considered normalization of intakes by body weight as complementary analyses. Finally, given that a high-fat diet can induce obesity and share common metabolic disruptions, we examined effect modification by obesity (BMI ≥ 30 kg/m^2) instead of dietary fat content.

Statistical analyses were performed using R software version 4.3.1 (survival 3.4–0, glmnet 4.1–4 and mice 3.14.0 packages).

3. Results

The study participants were 75.8 years old on average at the time of

the dietary survey and 62 % were women (Table 1). Compared to the 234 participants excluded because of no follow up for cognition or missing genetic data, the 1,288 included participants were slightly younger on average, more adherent to the Mediterranean diet and had generally a better cardiovascular health (less hypertension, and history of cardiovascular diseases) but higher BMI (**Supplementary Table 1**). Dietary contaminants intakes were broadly similar between groups (except nitrites provided by delicatessen meat to which included participants were slightly less exposed). A total of 314 individuals (24 %) developed dementia over a median follow-up of 10 years (range 1–16 years), of which 246 (78 %) were Alzheimer's Disease cases. Compared to participants who remained free of dementia over follow-up, those who developed dementia were older, more often carrier of the ε4 allele of the APOE gene and more often diabetics. They also consumed less frequently a high-fat diet.

The distributions of the 167 chemical contaminants and pairwise correlations are presented in **Supplementary Figs. 2-3**. Distributions were gaussian-like for many contaminants, although there were also a substantial proportion of contaminants with log-normal (e.g. PCBs), bimodal (e.g. some pesticides) or zero-inflated (e.g. some PFAS) distributions. As expected, correlations were generally strong within contaminant families, especially dioxins, PCB, BFR and pesticides, as well as between contaminants of different families likely originating from the same foods, especially between PCB and BFR provided by fish/seafood.

Table 1
Baseline characteristics of participants by the percentage of total energy intake provided by fats in the diet and incident all-cause dementia over 16 years, the Three-City Study (N = 1,288).

	Overall sample			Normal-fat diet (≤35 % of energy from fat)			High-fat diet (>35 % of energy from fat)		
	Overall N = 1,288	Incident dementia N = 314	No dementia N = 974	Overall N = 902	Incident dementia N = 232	No dementia N = 670	Overall N = 386	Incident dementia N = 82	No dementia N = 304
Age, years, mean (SD)	75.8 (4.8)	77.5 (4.6)	75.2 (4.7)	75.6 (4.8)	77.6 (4.6)	75.0 (4.6)	76.1 (4.9)	77.2 (4.6)	75.8 (4.9)
Sex, female	62	69	60	61	69	59	65	72	62
Education, ≥ secondary school	68	61	70	68	60	70	68	66	69
Income, ≥ 1500€/ month	57	52	58	57	51	60	56	57	55
APOEε4 carrier	18	21	17	19	22	18	16	16	15
Smoking									
0 pack-year	65	69	63	65	69	63	64	67	64
<20 pack-year	18	16	18	17	15	18	20	21	20
≥ 20 pack-year	18	15	18	18	16	19	16	12	17
Daily alcohol intake									
0 g/d	19	17	20	18	17	19	21	16	22
≤12 g/d	45	51	43	44	52	42	45	49	44
12–24 g/d	19	19	19	19	19	19	19	21	19
>24 g/d	17	13	19	18	13	21	15	14	16
Mediterranean diet adherence, mean (SD)[1]	4.0 (1.6)	3.9 (1.6)	4.1 (1.6)	4.0 (1.6)	3.8 (1.6)	4.1 (1.6)	4.0 (1.5)	4.4 (1.5)	4.0 (1.6)
Body mass index									
Normal < 25 kg/m²	37	36	38	38	40	37	37	26	40
Overweight [25–30[kg/m²	45	48	44	45	47	45	43	54	40
Obesity ≥ 30 kg/m²	18	15	19	17	13	18	20	21	19
Regular physical activity[2]	28	27	29	30	28	31	23	25	23
Diabetes mellitus[3]	10	13	9	9	12	8	13	18	11
Hypercholesterolemia[4]	39	39	38	39	40	38	39	38	39
Hypertension[5]	77	81	76	77	79	76	79	87	77
History of cardiovascular diseases[6]	30	31	30	31	31	30	29	30	29
Total energy intake, kcal/d, median [IQR]	1660 [1310–2070]	1610 [1330–2050]	1670 [1300–2080]	1630 [1290–2000]	1580 [1300–1970]	1650 [1290–2030]	1730 [1370–2170]	1690 [1420–2200]	1750 [1320–2170]

Abbreviations: APOE ε4, allele ε4 for the apolipoprotein E gene.
Figures are percentages of non-missing values unless otherwise stated. Values are missing for 11.6 % for physical activity, 5.7 % for income, 1.5 % for smoking, and ≤ 1.0 % for alcohol, diabetes and hypercholesterolemia.

[1] 9-component score based on the number of servings/weeks of 8 food groups assessed by a food frequency questionnaire (vegetables, fruit, legumes, cereals, fish, meat, dairy products, alcohol) and the monounsaturated-to-saturated fatty acids ratio assessed by a 24 h-dietary recall. Each of the 9 components was dichotomized based on sex-specific medians of the population, assigning 1 to beneficial behaviors (e.g. consumption of fish higher than the median) and 0 otherwise, except for alcohol for which the second quartile was assigned 1 and 0 otherwise. The total score ranges from 0 to 9, with higher scores indicating greater adherence.(Féart et al., 2009)

[2] practicing a sport or an intensive leisure activity (e.g., hiking) ≥ 1h/wk or engaging in a more moderate activity (e.g., walking or household) ≥ 1h/d.

[3] fasting glucose ≥ 7.2 mmol/L or treated.

[4] total cholesterol ≥ 6.2 mmol/L or treated.

[5] systolic to diastolic blood pressure ≥ 140/90 mm Hg or treated.

[6] self-reported history of myocardial infarction, angina, heart rhythm disorders and heart failure, arteritis of the lower limbs disease, stroke or cardiac/vascular surgery.

3.1. Single-chemical approach

In analyses of each contaminant considered individually, no chemical was linearly associated with dementia risk in the whole population (Supplementary Table 2). There was suggestion of non-linear inverse U-shaped associations for 9 contaminants (some PCB and dioxins, p for non-linearity < 0.05), although none survived multiple testing correction (see Supplementary Figure 4 for risk associated with quantiles of contaminant intake). We found no evidence of effect modification by sex. However, consuming a diet with higher fat content was a strong

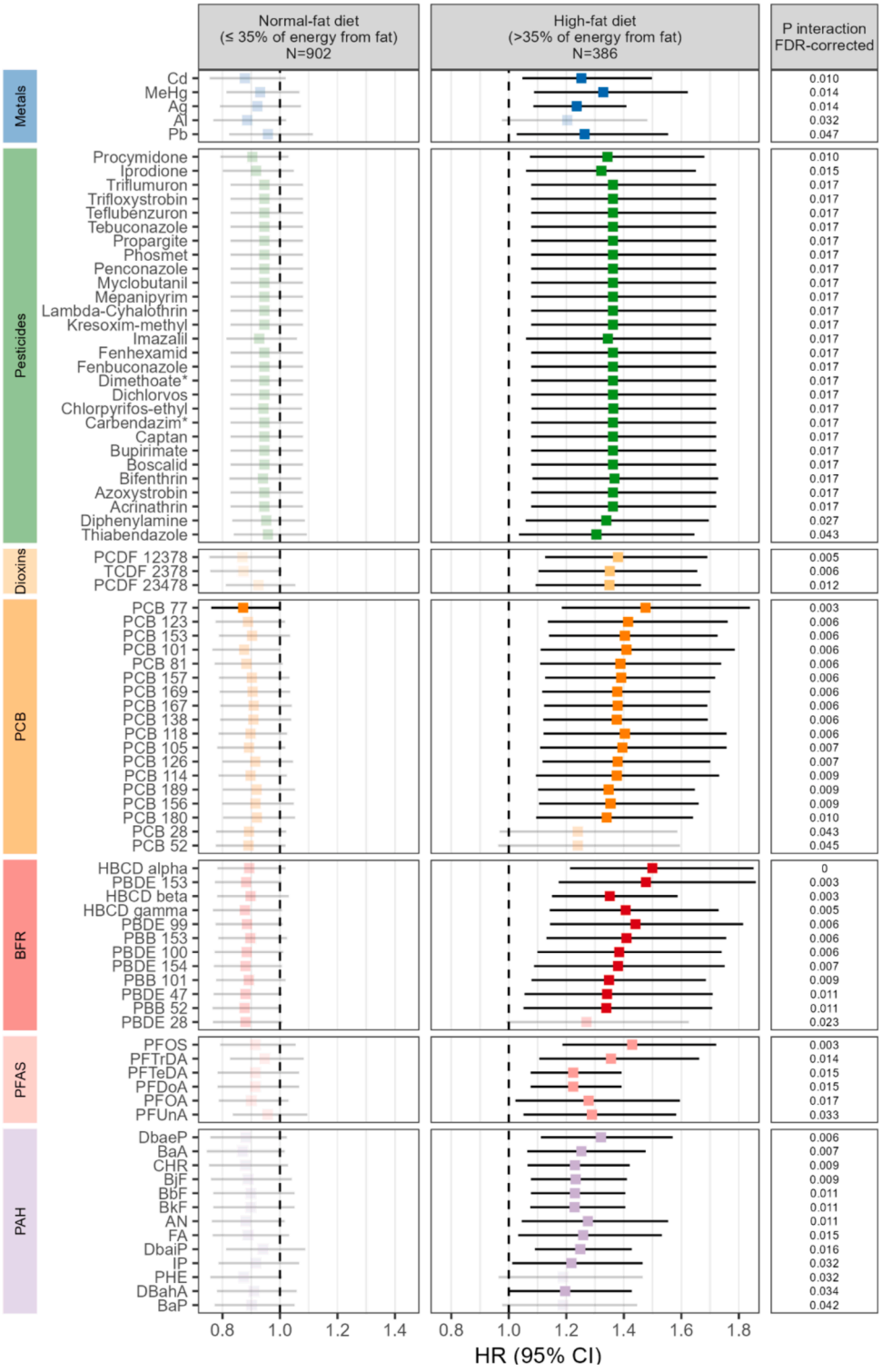

Fig. 1. Associations between the 85 dietary contaminants of which intake interacted with fat content in the diet in relation to dementia risk, the Three-City Study (N = 1,288) Hazard Ratio (HR) and 95 % Confidence Intervals (CI) are for one SD-increase in dietary contaminant intake estimated using Cox proportional hazard models adjusted for age (spline function), sex, level of education, ApoE-ε4 genotype, and adherence to the Mediterranean Diet. Bold lines indicate significant associations, while light grey lines indicate non-significant associations. Only the 85 chemicals with a FDR-corrected p < 0.05 for interaction test with fat content in the diet in relation with dementia risk are displayed (see Supplementary Fig. 3 for remaining contaminants).

effect modifier for 85 contaminants out of the 167 studied (i.e., all studied PCB, 12/14 BFR congeners, 28/47 pesticides, 13/21 PAH, 6/12 PFAS, some metals and dioxins; $P_{FDR} < 0.05$ for interaction tests). For these contaminants, higher intakes were significantly associated to higher risk of dementia among consumers of a high-fat diet only (n = 386 participants [30 % of the population], see Table 1 for their main characteristics and **Supplementary Results and Supplementary Table 3** for details on food and contaminant intakes), while there was broadly no significant relationship among consumers of a normal-fat diet (Fig. 1; **Supplementary Figure 5**).

The strongest and most significant hazard ratios (HR) for dementia risk were observed for the BFR α-hexabromocyclododecane (α-HBCDD) and the PFAS perfluorooctanesulfonic acid (PFOS) (HR = 1.50 and 1.43 respectively, for one SD increase in intake among consumers of high-fat diet, uncorrected $p < 0.001$; Fig. 1). For a number of contaminants, and specifically those most strongly associated with increased dementia risk in the high-fat group such as α-HBCDD or PFOS, interactions with dietary fat content were robust to variations in methodological choices (**Supplementary Results and Supplementary Figure 6**). Supplementary analyses exploring effect modification by obesity found that 35 substances also interacted with obesity on dementia risk, including mostly PCB and BFR, four dioxins-furans, three PFAS, methyl-mercury, the ochratoxin B, the PAH anthracene, and the food additive nitrites, such that higher intakes were associated with higher dementia risk among obese participants only (**Supplementary Figure 7**).

3.2. Multi-chemical approach

Given the extended interactions evidenced by single-chemical analyses in first stage, suggesting strong effects limited to persons having a high-fat diet, for the multi-chemical approach in second stage we restricted analyses to the group of 386 participants reporting a high-fat diet. The Elastic-Net model retained 9 contaminants in > 50 % of bootstrap samples: 4 PFAS (PFOS, perfluorododecanoate [PFDoA], perfluorotetradecanoate [PFTeDA] and perfluorooctanoate [PFOA]), 2 BFR (HBCDD α- and β-congeners), 2 mycotoxins (monoacetoxyscirpenol [MAS] and ochratoxin B [OTB]), and nitrites (Fig. 2). The signature included two top hits from the single-chemical analysis (α-HBCDD and PFOS).

By construction, the food contaminant signature score reflected moderate-to-high intakes of all 9 contaminants (correlations with signature between 0.39 and 0.69, Fig. 3A) and was associated with a higher risk of dementia among high-fat diet consumers (see Fig. 3B for cumulative risk of dementia by tertiles of score). Participants with high fat diet and scoring higher to the food contaminant signature were more often male, adhered more to a Mediterranean diet and had lower prevalence of cardiovascular diseases; but they consumed more alcohol and had more often diabetes (**Supplementary Table 4**). In multivariable-adjusted analyses, compared to individuals in the first tertile of the food contaminant signature score, HR for dementia (95 % confidence intervals) for individuals in the second and third tertiles were 1.9 (1.0–3.5), and 3.5 (1.9–6.5) (p for trend across tertiles < 0.001). In supplementary analyses, HR for AD were 2.1 (0.9–4.7) and 5.0 (2.4–10.6) for the second and third tertiles compared to the first one.

In the high-fat diet group, the top dietary sources of the food contaminant signature were delicatessen meat (which contributed primarily to the intake of nitrites and to a lower extent OTB and HBCDD congeners, **Figure C left-panel**; correlation with the signature score r = 0.63, **Figure C, right-panel**), seafood (with fish/crustacean contributing 40–100 % of most PFAS and 20–40 % of HBCDD congeners) and crispbread/bread (the main source of the mycotoxins MAS and OTB). Other foods representative of the pattern included sandwich/pizza, meat, wine and viennoiserie (correlations with the signature score 0.20–0.25, **Figure C right-panel**).

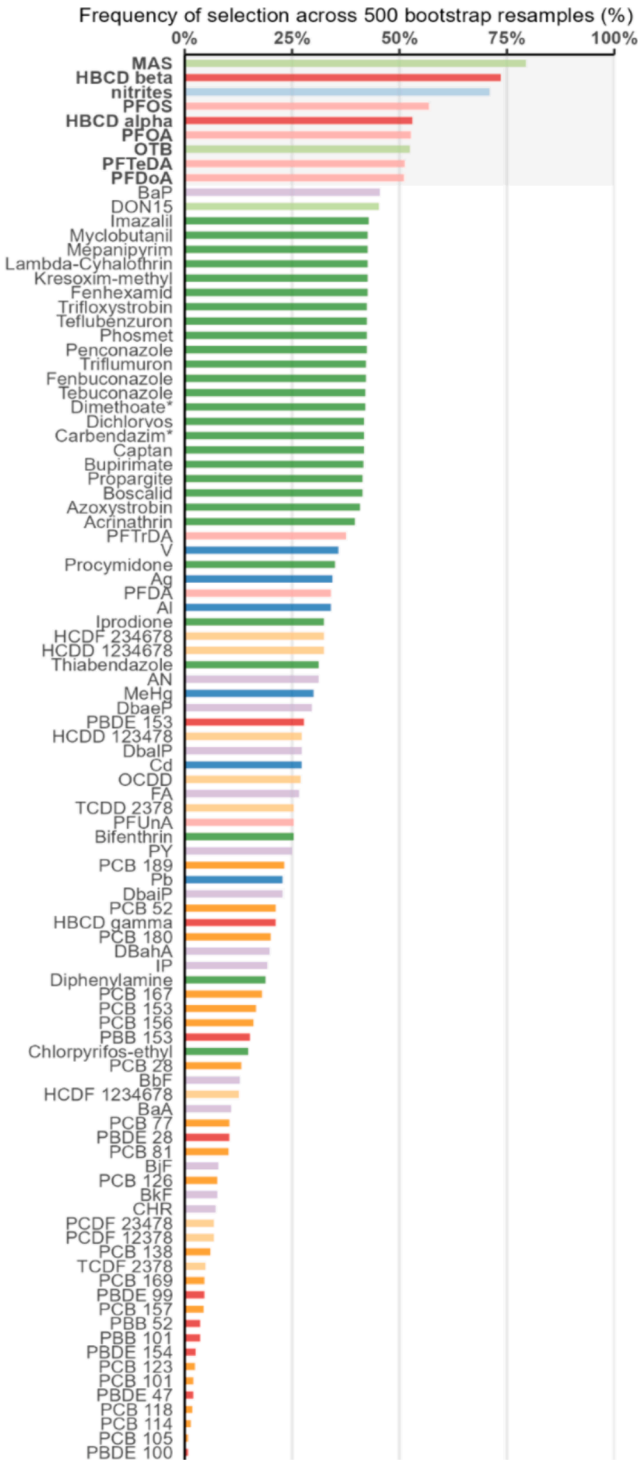

Fig. 2. Food contaminant signature associated with dementia risk in 386 participants having a high-fat diet, as defined by contaminants most selected by elastic-net penalized regression across 500 bootstrap resamples.

4. Discussion

In this large cohort of older adults, we found that when consuming a high-fat diet, increased intake in various food contaminants was strongly associated with a higher risk to develop dementia over the following 16 years. Using a multi-chemical analysis strategy taking into account potential confounding by co-exposed chemicals, we identified a food contaminant signature composed of four PFAS, two BFR HBCDD congeners, the mycotoxins monoacetoxyscirpenol and ochratoxin B, and

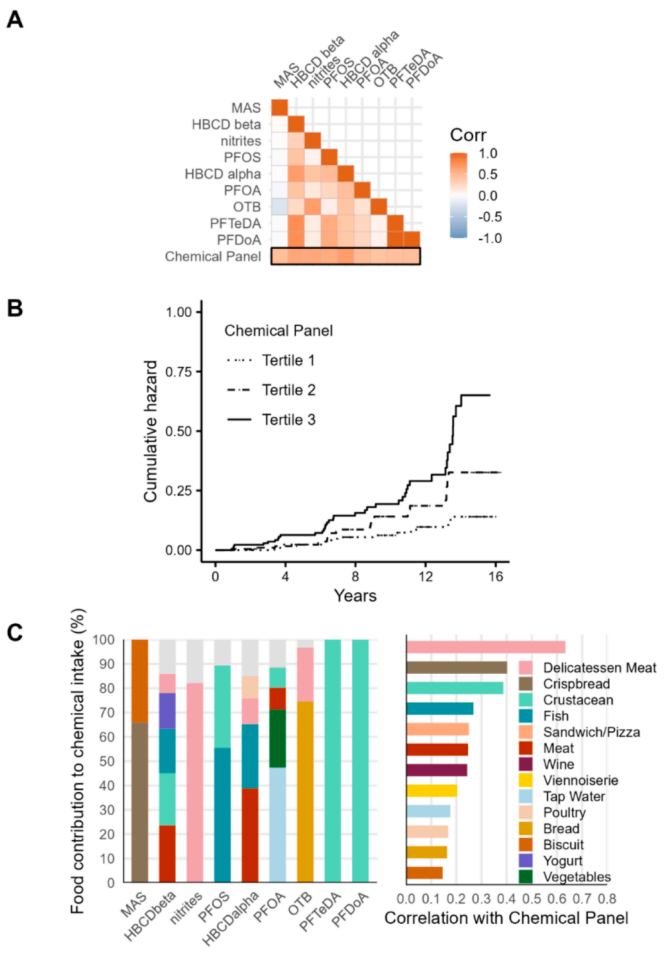

Fig. 3. Characterization of the food contaminant signature score in terms of (A) correlations with contaminants, (B) associated cumulative risk of dementia, and (C) top food contributions/correlations among the 386 participants having a high-fat diet Cumulative hazard in panel B was estimated using Cox proportional hazard models adjusted for age (spline function), sex, level of education, ApoE-ε4 genotype, and adherence to the Mediterranean Diet.

nitrites, associated with higher risk of dementia among individuals having a high-fat diet. This chemical contaminant signature was provided by a diet rich in delicatessen meat, seafood, bread/crispbread, sandwich/pizza, wine, meat and viennoiserie. Individuals in the highest tertile of score had more than three-times greater risk to develop dementia compared to those in the lowest tertile – an association larger than that found with APOE4 allele, the strongest genetic risk for dementia.

Our results suggest a potential role of Persistent Organic Pollutants (POP) in dementia. Hence, PFOS, PFOA and HBCDD were added in the early 2010′s to the Stockholm Convention list on POP initially focused on organochlorine chemicals (PCB, pesticides, dioxins) with the aim to eliminate or restrict their use due to their recognized persistence in the environment, bioaccumulation along the food chain and toxicity even at low dose. Although previous epidemiological studies did not focus specifically on dietary POP exposures, there is existing literature on POP biomarkers and cognitive outcomes in the general older population, albeit limited and inconsistent so far. Most cross-sectional and prospective analyses have examined original POP such as PCB and suggested adverse relationships with the executive function of older persons and the risk of dementia, though with inconsistencies (Raffetti et al., 2020; Medehouenou et al., 2019; Tanner et al., 2020; Bouchard et al., 2014; Kim et al., 2015; Przybyla et al., 2017). For example in prospective cohort studies, higher serum levels of PCB were associated with higher risk of dementia in a highly-polluted region of Italy (Raffetti et al., 2020), while no association was found in a Canadian cohort (Medehouenou et al., 2019). However, these previous studies were not performed by multi-chemical signature so it is difficult to infer from them independent associations of specific pollutants – and to compare those results with our study (which handled co-exposures by design). In particular, although associated with dementia in high-fat diet consumers in single-chemical analyses, PCB intake was not selected in our food contaminantsignature, suggesting PCB may not be the sole driver of the association with dementia risk, but possibly co-occur with other neurotoxic POP in foods, such as PFAS and BFR (from seafood) found in our signature. Less work has focused on these newly listed POP included in our food contaminant signature. An ecological mortality study in Italy suggested higher AD-related mortality in municipalities contaminated by PFAS in drinking water compared to uncontaminated ones (Mastrantonio et al., 2018). However, cross-sectional studies reported mixed findings, with higher circulating PFAS levels associated with both poorer and better cognitive function in older adults (Park et al., 2021; Weng et al., 2022; Shrestha et al., 2017), and we are aware of no large prospective study so far. Regarding BFR, while no study specifically focused on HBCDD exposure, interestingly, higher bromine levels in the brain was associated with AD neuropathology and clinical dementia in the Memory and Aging Project cohort (Agarwal et al., 2020). Similarly, mycotoxins and nitrites have been little studied thus far in epidemiological studies on dementia. A previous study in patients with a confirmed mold-exposure history reported impaired neuropsychological function and hypoactivation in the frontal cortex, as compared to normative data (Crago et al., 2003).

Besides, nitrites are used as food additives primarily in delicatessen meat, and our findings are at least consistent with recent cohort studies relating higher intake of ultra-processed meat with greater cognitive decline and increased risk of dementia (Weinstein et al., 2022; Zhang et al., 2021). Other foods representative of the chemical pattern have a more complex risk/benefit balance, especially seafood, which was a primary contaminant source (of PFAS, HBCDD as well as PCB and heavy metals evidenced in single-chemical analyses) in our study, but at the same time, higher seafood consumption has generally been associated with a decreased risk of dementia owing to its content in omega-3 fatty acids (Scarmeas et al., 2018). We found adverse associations of fish-derived contaminants on dementia only when consumed in a context of high-fat diet and interestingly, in a small clinical trial of men at risk of cardiovascular disease, fish had greater favorable effects on cardiovascular risk factors when part of a low-fat rather than a high-fat diet (Mori et al., 1997; Mori et al., 1994). This supports the importance of considering the global dietary pattern when studying effects of specific food components, as suggested by fish-rich healthy dietary pattern, such as the Mediterranean diet, being more consistently related to dementia risk than the individual fish component (Scarmeas et al., 2006; Scarmeas et al., 2018).

Multiple biological mechanisms may underline the effect modification we found between dietary chemicals and dementia risk by dietary fat composition. A first explanation relates to toxicokinetics, as several incriminated chemicals are hydrophobic (=lipophilic) and their bioavailability may thus be enhanced by a high-fat diet, which promotes the formation of mixed bile salt micelles and the secretion of chylomicrons by enterocytes, both necessary for the absorption of hydrophobic substances in the systematic circulation (Charman et al., 1997). For example, using an in-vitro digestion model, previous research suggested that fat was the most important dietary component affecting the bioaccessibility and absorption of certain BFR (polybrominated diphenyl ethers) (Yu et al., 2010; Li et al., 2021). Another possible explanation for the reported interaction might be that a high-fat diet could decrease the xenobiotic metabolism activity, thereby impairing the body's ability to detoxify and increasing its susceptibility to adverse effects upon xenobiotic exposure (Sadler et al., 2018). Hence, a recent experimental study

reported higher heavy metals accumulation in the liver and kidney along with more severe functional damage in mice fed a high-fat diet compared to a normal diet, possibly due to differences in gut microbiota and associated detoxification abilities (Liu et al., 2020). In addition, several experimental studies have reported that multiple chemical-induced metabolic dysfunctions were exacerbated by a high-fat diet (Tan et al., 2013; Chen et al., 2022; Wahlang et al., 2013; Yanagisawa et al., 2014; de la Monte et al., 2009). In particular, HBCDD exposure of mice fed a high-fat diet led to body weight gain, hyperglycemia, hyperinsulinemia, hepatic steatosis and macrophage accumulation in adipose tissue, while no effect was observed in mice fed a normal diet (Yanagisawa et al., 2014). Since metabolic disorders are closely related to AD (de la Monte et al., 2009), these observations may have implications for brain outcomes. One epidemiological study also reported similar interaction between dietary exposure to certain BFR and vegetable oil intake on breast cancer risk, whereby adverse effects were only observed among higher oil consumers (Frenoy et al., 2022), although another study found no effect modification by lipid intake when investigating dietary HBCDD exposure in relation with the risk of type 2 diabetes (Ongono et al., 2019). Mediation of the associations of dietary pollutants with dementia risk by metabolic parameters in the context of high fat diets could be investigated in future work.

Some of the contaminants from our signature have documented neurotoxic effects in experimental studies. PFAS cause cerebellar and hippocampal cell death *in vitro* and *in vivo*, possibly mediated by the overactivation of the N-methyl-D-aspartate-receptor; induce oxidative stress; disrupt glutamate and dopamine levels; and impair spatial learning and memory in mice (Long et al., 2013; Berntsen et al., 2021). PFOS also modulates the amyloid and tau pathways *in vitro* (Basaly et al., 2021), two neuropathological hallmark of AD. HBCDD has been implicated in dysregulation of intracellular calcium and zinc signaling pathways, disruption of glutamatergic neuron activity, apoptosis and oxidative stress in mouse hippocampal neurons (Reffatto et al., 2018). Nitrites may form N-nitroso compounds, including nitrosamine, which may result in oxidative stress, lipid peroxidation, activation of pro-inflammatory cytokines and cell death (de la Monte et al., 2009). There is little literature on MAS and OTB mycotoxins. However, type A trichothecenes (the mycotoxin family of MAS) and ochratoxin A can cross the blood brain barrier, and may induce neurotoxicity by causing neuronal apoptosis, glial cell dysfunction, oxidative stress, and mitochondrial dysfunction (Pei et al., 2021). Furthermore, it is plausible that the combination of chemicals within foods may have additive or synergistic effects on brain health. Chemical mixture has been little studied so far in experimental studies, but an *in vitro* study reported greater toxicity on rat cerebellar neurons when exposed to a mixture of PFAS with PCB or BFR rather than PFAS alone (Berntsen et al., 2021). Since populations are mostly exposed to contaminants as mixture, it is possible that the contaminants included in our signature may act as surrogate markers for an overall contaminant mixture rather than being solely responsible for the associations observed.

The strengths of our study include a prospective design with a long follow-up of 16 years for dementia and a clinical diagnosis for dementia and its subtypes adjudicated by an expert committee. Main limitations include potential measurement errors in the dietary (3C) and/or food contamination (TDS2) surveys, a lag of 4 years between the 3C dietary survey and the TDS2, and the combination of these two databases with different items (a complex process involving numerous assumptions); all of these aspects may lead to misclassification of chemical exposures in our cohort participants. We developed a methodology combining 24HDR and FFQ data to limit misclassification due to the 3C dietary survey, and the estimates we obtained were close to others reported in similar populations. For example, in our sample, the estimated average intake of PFOS was very similar to the one reported in another large French study of middle-aged women based on a 208-item semi quantitative FFQ (0.49 in our study vs 0.50 ng/kg bw/d) (Mancini et al., 2018), while average intakes of HBCDD were slightly higher in our study (0.32 vs 0.22 ng/kg bw/d under the medium-bound scenario) (Ongono et al., 2019). In addition, the TDS2 food sampling was initially built to cover food habits of the French adult population (based on the national survey of food consumption INCA2), and may not be totally adapted for those of older adults. As another limitation, for several chemicals (most pesticides, mycotoxins, and PFAS), data were strongly left-censored in TDS2 (likely due to sensitivity limits of measurement instruments available at that time in year 2006, although true null contamination cannot be excluded, especially for pesticides and mycotoxins), and our complementary analyses suggested that for these chemicals, results were little robust to different scenarios of imputation of censored data. Finally, although we controlled analyses for several potential confounders, we cannot exclude that residual confounding persist in our observational study. In particular, adjustment for the socio-economic status through education level and income, as well as for diet patterns by adherence to the Mediterranean diet, may not be sufficient to disentangle whether the observed associations are driven by lower socio-economic status, unhealthy dietary patterns (for which socioeconomic status is a strong determinant) or a combination of both.

In conclusion, in this large population-based cohort of older persons, dietary exposure to several contaminants, including PFOS, HBCDD, nitrites and mycotoxins, was associated to a higher risk of dementia, but only among individuals having a high-fat diet. Additional epidemiological studies are needed to confirm the role of dietary chemical exposure in dementia and the influence of dietary components such as fat content in diet.

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CRediT authorship contribution statement

Sophie Lefèvre-Arbogast: Conceptualization, Formal analysis, Writing - Original Draft. **Pauline Duquenne:** Data curation, Writing - Review & Editing. **Catherine Helmer:** Investigation, Resources, Writing - Review & Editing. **Sophie Auriacombe:** Investigation, Writing - Review & Editing. **Véronique Sirot:** Resources, Writing - Review & Editing. **Cécilia Samieri:** Conceptualization, Supervision, Writing - Original Draft.

Declaration of competing interest

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

Data availability

Anonymized data described in the current study will be shared by the 3C scientific committee upon reasonable request from any qualified investigator.

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SLA, PD, CH, SA, VS, CS have no conflicts of interest to declare.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2024.109033.

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