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Evidence of a positive association between dietary exposure to polychlorinated biphenyl (PCB) and weight gain among women in the E3N prospective cohort

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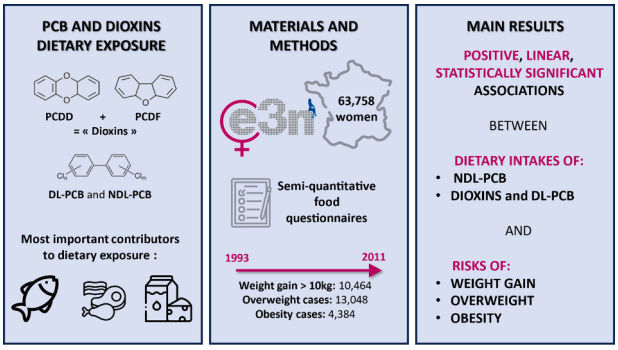
HIGHLIGHTS

- PCBs and dioxins may play a role in the weight change.
- We studied the association between intakes of dioxins and PCB in relation to overweight, obesity and weight gain in women.
- Positive and linear associations were observed between NDL-PCBs intake and risk of overweight, obesity and weight gain.
- These associations remain stable in all sensitivity analyses.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Polychlorinated biphenyls (PCB) and dioxins are persistent organic pollutants found in food and known for their ability to bioaccumulate. Various animal studies have highlighted obesogenic effects related to the exposure to PCB and dioxins, nevertheless human studies have led to inconsistent results. The present study aims to investigate the associations between dietary intakes of PCB and dioxins and the risk of weight gain,

Abbreviations: Afssa, Agence française de sécurité sanitaire des aliments; Anses, Agence nationale de sécurité sanitaire de l'alimentation, de l'environnement et du travail; BMI, body mass index; CESP, Centre de Recherche en Epidémiologie et Santé des Populations; CIQUAL, Centre d'Information sur la Qualité des Aliments; CNIL, Commission nationale de l'informatique et des libertés; DAG, directed acyclic graph; E3N, Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale; TDS, total dietary study; EFSA, European Food Safety Authority; HR, hazard ratio; CI, confidence intervals; INCA2, Enquête individuelle de consommation alimentaire 2; LB, lower bound [scenario]; LOD, limit of detection; MB, Middle Bound [scenario]; MGEN, Mutuelle Générale de l'Education Nationale; WHO, World Health Organization; PCB, polychlorobiphenyls; DL-PCB, non-dioxin-like polychlorobiphenyls; NDL-PCB, dioxin-like polychlorobiphenyls; PCDD, polychlorodibenzodioxins; PCDF, polychlorodibenzofurans; POP, persistant organic pollutants; Q1 to Q11, Questionnaires 1 to 11; TEQ, toxic equivalent quantity; TWI, tolerable weekly intake.

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Polychlorobiphenyls
Diet

overweight and obesity in the French E3N cohort (*Étude Épidémiologique auprès de femmes de la mutuelle générale de l'Éducation Nationale*).
Methods: The present study included 63,758 women with a mean age of 52.9 years, who completed a food frequency questionnaire in 1993 and were followed for 23 years. Dietary intakes to the sum of dioxins and dioxin-like PCB (DL-PCB) and to non-dioxin-like PCB (NDL-PCB) were estimated using food consumption data combined with food contamination levels from the French Agency for Food, Environmental and Occupational Health and Safety (ANSES). Adjusted Cox proportional hazard models were used to estimate hazard ratios (HR) and their 95 % confidence intervals for the risk of obesity, overweight and weight gain >10 kg during follow-up.
Results: Our results suggest a positive and linear association between dietary intakes of dioxins + DL-PCB and intakes of NDL-PCB and the risk of weight gain ($HR_{dioxins+DL\text{-}PCB}$ = 1.07 (1.05–1.1), $HR_{NDL\text{-}PCB}$ = 1.08 (1.06–1.1)), overweight ($HR_{dioxins+DL\text{-}PCB}$ = 1.03 (1.01–1.05), $HR_{NDL\text{-}PCB}$ = 1.05 (1.03–1.06)), and obesity ($HR_{dioxins+DL\text{-}PCB}$ = 1.08 (1.04–1.12), $HR_{NDL\text{-}PCB}$ = 1.09 (1.06–1.12)). In sensitivity analyses adjusting for diet, the association between dioxins + DL-PCB dietary intake and obesity was no longer observed. Results remained unchanged or were attenuated but still significant regarding the association between dietary intake of NDL-PCB and obesity risk in all sensitivity analyses. Similar results were observed for the risks of weight gain and overweight.
Discussion: This study suggests a positive and linear association between dietary intakes of NDL-PCB and the risk of obesity, a major risk factor for most non communicable diseases. Further studies are needed to confirm these results in other populations and to better understand the biological mechanisms underlying this association.

1. Introduction

In 2016, the World Health Organization (WHO) reported that 39 % of adults aged 18 years and above were overweight, and 13 % were obese and the rate of obesity worldwide has nearly tripled since 1975 (WHO, 2024). WHO has identified obesity as a major risk factor for various chronic diseases, including diabetes and cardiovascular disorders. Obesity can be prevented and managed mainly by a healthy diet and regular physical activity, nevertheless a wide variety of other causes are suspected to influence weight gain, including exposure to food contaminants (Aaseth et al., 2022).

Dioxins and polychlorinated biphenyls (PCB) are chlorinated polycyclic aromatic hydrocarbons (PAH) classified as persistent organic pollutants (POPs) by the Stockholm Convention due to their toxicity, persistence in the environment, ability to migrate over long distances and bioaccumulation in food chains (ANSES, 2013). The term "dioxin" covers two types of PAH: polychlorinated dibenzodioxins (PCDD) and polychlorinated dibenzofurans (PCDF). Dioxins were mainly produced by household waste incinerators, industrial processes, and fires. Of the 210 congeners, 17 are considered toxic and very (EFSA, 2018). PCB comprise 209 congeners. PCB were once widely used as non-flammable electrical insulators. They were banned in the late 1970s and 1980s in several countries, but they persist in the environment (EFSA, 2018). PCB can be classified in two groups: dioxin-like (DL) and non-dioxin-like (NDL). Dioxins and DL-PCB bind to the same cellular receptor, the AhR (aryl hydrocarbon receptor). Their toxicity is therefore based on the same mechanisms. NDL-PCB have a different, less well-known mechanism of action (EFSA, 2018).

Food is the main route of exposure to dioxins and PCB for the general population, accounting for over 90 % of total exposure. Estimates of the half-lives of PCB and dioxins in the human body vary from one study to another, and from one substance to another, but they are generally estimated to range from a few years to several decades (Idowu et al., 2023).

A literature review published in 2022 examined the obesogenic role of POPs (Aaseth et al., 2022). PCB are thought to play a role in modulating some of the main regulators of adipogenesis (PPARγ and C/EPB), and thus in phenomena such as obesity, dyslipidemia, and atherosclerosis. In addition, certain POPs, including PCB, are thought to influence adipogenesis through their action on estrogen receptors. The effect of dioxins and DL-PCB on adipogenesis is thought to be linked to the Ah receptor. In vitro studies indicate an inhibition of adipogenesis, while in vivo studies show that exposure to PCB and dioxins may promote excessive adiposity and obesity in animals (Aaseth et al., 2022). Several studies on human populations have investigated the association between internal exposure to PCB and dioxins (serum levels) and obesity risk. The results are highly variable. Some studies suggest a positive association (Tang-Péronard et al., 2011; Valvi et al., 2012) while others suggest a negative association (Dirinck et al., 2011; Wang et al., 2019). However, due to PCB and dioxins fat-soluble and bio-accumulative properties, internal exposure measures can be influenced by individual fat tissue distribution and metabolic differences. In comparison, dietary exposure estimates are repose on a more cost-effective methods, suitable for large populations, and produce results that easier for policymakers to interpret. Only two human population studies explored estimated dietary intake of PCB and dioxins (external exposure estimates) and obesity risk. The first is a prospective study involving over 12,000 participants followed for 8 years (Donat-Vargas et al., 2014). This study suggests a positive association between DL-PCB dietary intake and obesity. The second article is a cross-sectional and longitudinal study including almost 5900 adults (Khoury et al., 2023). The authors observed higher BMI and waist circumference, as well as a higher prevalence of obesity in the third tertile group of dioxins dietary intake. In the prospective part, participants with higher dioxins dietary intake showed an increase in waist circumference after 1 year of follow-up. No significant associations were observed for BMI, obesity, or abdominal obesity.

In conclusion, very few studies in human populations have investigated the association between dioxin and PCB dietary intake and obesity risk leading to inconsistent findings. Considering the above, the main objective of the present study was therefore to investigate potential associations between dietary intake of dioxins, DL-PCB and NDL-PCB and risk of weight gain, overweight and obesity in the E3N prospective cohort.

2. Materials and methods

2.1. The E3N study

The E3N cohort (Etude Epidémiologique auprès de femmes de la Mutuelle Générale de l'Education Nationale) was created in 1990 to study risk factors associated with cancer and other chronic diseases in adult women (Clavel-Chapelon and E3N Study Group, 2015).

This ongoing prospective cohort includes 98,995 women aged 40 to 65, resident in France and affiliated to MGEN (Mutuelle Générale de l'Education Nationale), a health insurance for workers of the French national education system, at baseline. Follow-up is based on self-administrated questionnaires sent every 2 or 3 years, including questions on lifestyle and medical events. Cohort data are enriched by MGEN medical treatment reimbursement data. Self-reported pathologies are validated and detailed thanks to the collaboration of attending

physicians, pathology laboratories and hospitals. At the same time, information from the questionnaires was supplemented by biological data: 25,000 E3N volunteers donated a blood sample and 47,000 provided a saliva sample.

Since the start of the follow-up program, the participation rate has remained stable and satisfactory, around 83 %. All participants signed an informed consent form in compliance with CNIL (*Commission Nationale de l'Informatique et des Libertés*) regulations.

2.2. Assessment of food consumption

A semi-quantitative food frequency questionnaire was sent to the study participants in Questionnaire 3 (Q3), in 1993. This questionnaire, comprising 208 food items, was divided into two parts: the first part dealt with the frequency and quantity of consumption of different food groups, while the second part provided details of the items included within each food group identified in the first part. The questions related to food and beverages consumed in the year prior to completing the questionnaire, and were constructed considering French dietary habits, with questions for eight types of daily meal, including snacks and aperitifs. A booklet of photographs was used to estimate portions. The validity and reproducibility of the food questionnaire were previously tested (van Liere et al., 1997). The women in the cohort completed the food questionnaire between June 1993 and July 1995.

Daily macro- and micro-nutrient intakes for each woman responding to the E3N food questionnaire were estimated using a table derived from the French food composition table of the *Centre d'Information sur la Qualité des Aliments* (CIQUAL).

2.3. Assessment of PCB and dioxin intakes

Food contamination levels were measured by Anses in the second French Total Diet Study (TDS 2). Between 2007 and 2009, 20,280 food products were collected in eight regions of France and transformed into 1352 samples corresponding to 186 types of food, prepared as consumed. In these prepared samples, 445 chemical contaminants were measured (Sirot et al., 2012). A total of 583 food samples combining 19 food groups were analysed for PCB and dioxins, including fish, meat, and dairy products, all known to be contaminated with PCB and dioxins (Sirot et al., 2012).

In the present study, values below the limit of detection (LOD) were replaced by 0 (lower-bound scenario). For dioxins, 17.1 % of values were below the LOD, 16.0 % for DL-PCB and 0.1 % for NDL-PCB.

Food consumption data from the E3N food questionnaire and the Anses TDS2 database were then combined (Mancini et al., 2020). For each participant, the daily mean dietary intake of each contaminant was obtained by multiplying the mean daily quantities consumed of each food component by the levels of contamination of this specific food component. The total dioxin and DL-PCB dietary intake (in pg TEQ/day) was obtained by summing the estimated intakes of each dioxin (TCDD 2378, PCDD 12378, HCDD 123478, HCDD 123678, HCDD 123789, HCDD 1234678, OCDD, TCDF 2378, PCDF 12378, PCDF 23478, HCDF 123478, HCDF 123678, HCDF 234678, HCDF 123789, HCDF 1234678, HCDF 1234789, OCDF) and DL-PCB (PCB 77, PCB 81, PCB 126, PCB 169, PCB 105, PCB 114, PCB 118, PCB 123, PCB 156, PCB 157, PCB 167, PCB 189). The toxic equivalent (TEQ) is the product of a dioxin-like contaminant quantity and a toxic equivalence factor. Each congener has its own toxic equivalence factor, expressing its relative toxicity compared to the most toxic dioxin, 2,3,7,8-tetrachlorodibenzo-p-dioxin (Van den Berg et al., 2006). The total NDL-PCB dietary intake (in ng/day) was obtained by summing the estimated intakes of each NDL-PCB (PCB 28, PCB 52, PCB 101, PCB 138, PCB 153, PCB 180).

2.4. Ascertainment of cases

In this specific analysis, the follow-up duration is 23 years (1993–2016). Height and body weight data were self-reported at each E3N questionnaire. The BMI (body mass index) is defined as the body mass divided by the square of the body height (kg/m^2). Repeated weight data made it possible to define weight gain in three complementary ways:

- Overweight defined as a BMI $>$ 25 kg/m^2, as defined by the WHO (WHO, 2024).
- Obesity defined as a BMI $>$ 30 kg/m^2, again according to the WHO.
- Weight gain defined as weight gain of $>$10 kg compared with the body weight reported at baseline (Q3 in 1993).

2.5. Study populations

Among the 74,522 women who responded to the dietary questionnaire, participants whose follow-up stopped at Q3 were excluded from the study. Participants who had not entered their height or weight at baseline (Q3) were also excluded.

When the body weight was not reported in the follow-up questionnaires, the missing value was replaced by the average of the body weight at the previous questionnaire and the body weight at the following questionnaire. If body weight values were missing for consecutive questionnaires, the participant was excluded.

To avoid under- or over-reporting of dietary intakes, we excluded women with extreme values of energy intake, i.e. individuals in the top and bottom 1 % of the ratio of energy intake to estimated energy requirements. Basal metabolic rate, calculated using Schofield equations for age, sex and weight, was multiplied by 1.55 (for slightly active individuals) to estimate energy requirements for each woman (Schofield, 1985).

Finally, to study obesity and overweight risk, prevalent cases, i.e., individuals already obese or overweight at baseline (Q3), were excluded. This resulted in three different study populations, depending on the outcome considered. These steps are summarized in a flow-chart in Supplementary Fig. 1.

2.6. Statistical analysis

2.6.1. Descriptive analyses

First, we described the characteristics of the population at baseline. We calculated means and standard deviations for continuous variables and distributions for categorical variables. Population baseline characteristics were also described within the different quartiles of dietary intake of NDL-PCB and quartiles of dietary intake of DL-PCB and dioxins, as well as among cases and non-cases separately.

Correlations between dietary intake of dioxins, DL-PCB and NDL-PCB, and correlations between food groups consumption and dietary intake of dioxins and DL-PCB or NDL-PCB were estimated using Spearman's rank correlation coefficients.

2.7. Main analyses

Cox proportional hazards models were adjusted on age as time scale. We estimated hazard ratios (HRs) and their 95 % confidence intervals (95 % CIs) for the risk of gaining $>$10 kg since the baseline, for the risk of becoming overweight, and finally for the risk of becoming obese. The two exposure variables were tested separately for each of the three outcomes.

Continuous dietary NDL-PCB intakes as well as continuous DL-PCB and dioxin intakes were divided by their standard deviation to estimate hazard ratios for a one standard deviation increase in dietary intake. The models were also run using a categorical exposure variable: the population was divided into four groups using the 25th, 50th and 75th percentiles of distribution. The first group was used as a reference. Linear trends between exposure quartile groups were tested by creating a continuous variable taking the median within each exposure quartile

as its value.

The beginning of the follow-up corresponds to the age when the participant responded to Q3. The end of the follow-up corresponds to the age at the time of the first event observed among: weight gain/overweight/obesity according to the study definition, date of response to the last completed questionnaire or date of end of the study follow-up (2014), whichever occurred first.

The adjustment variables were first selected using a directed acyclic graph (Supplementary Fig. 2). To respect temporality, when possible, the adjustment variables were extracted at the 2nd questionnaire (Q2) sent in 1992. If not collected at Q2, adjustment variables were extracted from Q3. We ran 5 successive models. Model 0 was only adjusted for age as time scale. Model 1 was also adjusted on physical activity (MET-hours/week) at Q3, smoking status (smoker, non-smoker, former smoker) at Q2, birth generation (≤1930, (1930–1935], (1935–1940], (1940–1945], >1945), education level (<12 years, 12 to 14 years, >14 years), silhouette at puberty (very thin, thin, medium, wide, very wide). Model 2 was further adjusted on daily fat and alcohol intake (g/day), daily calorie intake not including fat and alcohol intake (kcal/day) collected at Q3. Model 3, also included BMI at Q3. The last model (Model 4, main model) was further adjusted on hormonal variables: contraceptive pill use (never, already), parity (nulliparous, 1 to 2 children and first full-term pregnancy before age 30, 1 to 2 children and first full-term pregnancy after age 30, >2 children), breastfeeding (never, <6 months, >6 months), menopausal status (pre-menopause, menopause and use of menopausal hormone therapy, menopause without menopausal hormone therapy, menopause without information on menopausal hormone therapy) collected at Q2.

We also tested interactions between exposure variables and BMI at Q3 and body shape at puberty. Weight history can influence adult weight. In addition, because of their hydrophobic properties, PCBs and dioxins accumulate in fatty tissue. Changes in weight can therefore influence the storage and elimination of these substances.

The Cox proportional hazards assumption was verified using the Schoenfeld residuals method (statistical test on residuals and graphical verification), and the log-linearity assumption was verified with a linearity deviation test using restricted cubic splines with four nodes placed at different distribution quantiles of the variable of interest (0.05, 0.35, 0.65 and 0.95) (Harrell, 2015). In the main model (model 3), variables for which the test for deviation from linearity was significant were modelled with spline functions (namely physical activity, fat, and alcohol intake) to compensate for their non-log-linearity. As BMI at baseline did not satisfy either the log-linearity or proportionality of risk hypotheses, we decided to include it in the model by stratifying the baseline hazard function by quintiles of baseline BMI. This made it possible to include BMI at baseline without making any assumptions about its link with the outcome.

2.7.1. Sensitivity analysis

Additional analyses were carried out on the main model (model 3). A first sensitivity analysis aimed to identify a possible reverse causality bias by excluding people censored or who became cases during the first 5 years of follow-up.

As the estimation of dietary intake is based on one estimate at baseline, it is assumed that dietary habits remain constant throughout the follow-up period. Indeed, this assumption is more likely to be respected at the beginning of the follow-up, whereas the longer the follow-up, the greater the probability that dietary habits may change, thus inducing a higher probability of exposure classification bias. To assess the stability of associations over time, a second sensitivity analysis was conducted separating the study population based on the median follow-up of cases. In a first analysis, people censored before 11.5 years (half of maximum follow-up) were excluded, whether they were cases or non-cases. In a second analysis, the follow-up was stopped at 11.5 years (people still uncensored after 11.5 years were marked as non-cases and their follow-up stopped at 11.5 years).

A third sensitivity analysis involved adjusting the main model simultaneously on the two groups of contaminants (NDL-PCB/DL-PCB and dioxins) within the same model, to consider potential confusion between one exposure and another, and vice versa.

The final sensitivity analysis was aimed at adjusting for other dietary variables to consider a possible diet-related confounding bias. The model was adjusted on the PNNS (Programme national de nutrition santé) adequacy score. The PNNS is a French national program revised in 2017 with the aim of improving the health status of the French population and providing dietary recommendations. Adherence to the PNNS score of women in the E3N cohort had been calculated upstream of this project based on the sPNNS-GS2 score, described and validated in the literature (Chaltiel et al., 2019). The PNNS contains 13 dietary recommendations. Finally, the main model was adjusted for fish consumption (g/day), which is one of the main contributors to dietary intake of PCB and dioxins, and which may be contaminated by other potentially obesogenic pollutants.

For co-variables with <5 % missing values, the missing values were substituted by the most frequent modality in the population for categorical variables, and by the median for continuous variables. Above 5 %, a "missing values" category was created, the proportions of missing values for each variable are presented in Supplementary Table 1. p-Values < 0.05 were considered statistically significant, and analyses were carried out using SAS version 9.4 (SAS Institute, Cary, North California) and R version 4.3.1.

3. Results

3.1. Descriptive analysis

Our total study population of 63,758 women included 10,464 cases of weight gain (>10 kg compared to inclusion). Our population excluding prevalent cases of overweight included 51,087 women of whom 13,948 became overweight during follow-up. Our population excluding prevalent cases of obesity included 61,648 women of whom 4384 became obese during follow-up.

The baseline characteristics of all participants and among quartiles of dietary NDL-PCB intakes are presented in Table 1. Inclusion characteristics according to quartiles of dietary intake of dioxins and DL-PCB are presented in Supplementary Table 2. The baseline characteristics of the populations among non-cases and cases are presented in Supplementary Tables 3a to 3c.

In the total population (N = 63,758), the average follow-up duration was 17.7 years, i.e. 1,128,517 person-years of observation. Participants had a mean age of 52.9 years and a BMI of 22.9 kg/m^2 at baseline. The majority (53.4 %) had a high level of education, from 12 to 14 years, 55.5 % had never smoked and 52.7 % were not yet menopausal at baseline.

The estimated average dietary intake of NDL-PCB in the full study population (N = 63,758) was 151.3 ± 70.1 ng/day. For dioxins and DL-PCB, the estimated mean dietary intake was 30.8 ± 12.0 pg TEQ/day (see Supplementary Tables 4 and 5a to 5c).

Dietary intakes of NDL-PCB, DL-PCB and dioxins were strongly correlated ($\rho = 0.94$ between NDL-PCB and dioxins + DL-PCB) (see Supplementary Table 6). The correlations between food groups consumption and dietary intake of dioxins and DL-PCB or NDL-PCB are presented in Supplementary Table 7. The contributions of different food groups to dietary intakes of NDL-PCB or dioxins and DL-PCB are presented in Supplementary Table 8.

3.2. Main analysis

3.2.1. Dioxins and DL-PCB

All adjustment models showed positive and statistically significant associations between dietary intake of dioxins and DL-PCB and the risk of weight gain, overweight and obesity in the E3N cohort (Table 2).

Table 1
Baseline characteristics of the total population (N = 63,758) according to quartiles of NDL-PCB dietary intakes.

	All	NDL-PCB daily dietary intake (ng/day)			
		Q1 (N = 15,939) Min–Max	Q2 (N = 15,940)	Q3 (N = 15,940)	Q4 (N = 15,939)
	(N = 63,758)	2.9–103.6	103.6–138.5	138.5–183.9	183.9–798.1
Dietary intake of NDL-PCB	151.3 (70.1)	78.0 (17.5)	121.0 (10.1)	159.2 (12.9)	245.3 (63.1)
Age (years)	52.9 (6.7)	53.6 (6.9)	52.8 (6.7)	52.5 (6.5)	52.9 (6.5)
Follow-up duration (years)	17.7 (5.5)	17.7 (5.4)	17.9 (5.3)	17.7 (5.5)	17.4 (5.6)
BMI (kg/m^2)	22.9 (3.2)	22.5 (3)	22.7 (3.1)	22.9 (3.1)	23.3 (3.4)
<18.5	51,089 (80.13)	13,203 (82.83)	12,962 (81.32)	12,786 (80.21)	12,138 (76.15)
[18.5–25]	10,559 (16.56)	2356 (14.78)	2522 (15.82)	2631 (16.51)	3050 (19.14)
>25	2110 (3.31)	380 (2.38)	456 (2.86)	523 (3.28)	751 (4.71)
Silhouette at puberty					
Very thin	13,587 (21.31)	3516 (22.06)	3501 (21.96)	3325 (20.86)	3245 (20.36)
Thin	22,168 (34.77)	5553 (34.84)	5522 (34.64)	5542 (34.77)	5551 (34.83)
Medium	14,815 (23.24)	3634 (22.8)	3720 (23.34)	3758 (23.58)	3703 (23.23)
Large	9822 (15.41)	2429 (15.24)	2350 (14.74)	2472 (15.51)	2571 (16.13)
Very large	3366 (5.28)	807 (5.06)	847 (5.31)	843 (5.29)	869 (5.45)
Birth generation					
≤1930	6353 (9.96)	1966 (12.33)	1521 (9.54)	1438 (9.02)	1428 (8.96)
(1930–1935]	8861 (13.9)	2514 (15.77)	2233 (14.01)	1982 (12.43)	2132 (13.38)
(1935–1940]	13,028 (20.43)	3215 (20.17)	3178 (19.94)	3208 (20.13)	3427 (21.5)
(1940–1945]	15,688 (24.61)	3698 (23.2)	3867 (24.26)	4034 (25.31)	4089 (25.65)
>1945	19,828 (31.1)	4546 (28.52)	5141 (32.25)	5278 (33.11)	4863 (30.51)
Education level					
<12 years	6894 (10.81)	2162 (13.56)	1697 (10.65)	1543 (9.68)	1492 (9.36)
12 to 14 years	34,039 (53.39)	8719 (54.7)	8764 (54.98)	8447 (52.99)	8109 (50.88)
>14 years	22,825 (35.8)	5058 (31.73)	5479 (34.37)	5950 (37.33)	6338 (39.76)
Smoking status					
Smoker	7872 (12.35)	1914 (12.01)	1952 (12.25)	2005 (12.58)	2001 (12.55)
Former smoker	20,499 (32.15)	4657 (29.22)	5115 (32.09)	5276 (33.1)	5451 (34.2)
Non-smoker	35,387 (55.5)	9368 (58.77)	8873 (55.66)	8659 (54.32)	8487 (53.25)
Physical activity (MET-hours/day)	49.2 (45.8)	46.6 (45.5)	47.8 (44.9)	49.3 (43.7)	52.9 (48.6)
Contraceptive pill use					
Never	24,432 (38.32)	6903 (43.31)	6026 (37.8)	5889 (36.94)	5614 (35.22)
Ever	39,326 (61.68)	9036 (56.69)	9914 (62.2)	10,051 (63.06)	10,325 (64.78)
Menopausal status and recent use of menopausal hormone therapy (MHT)					
Premenopausal	33,570 (52.65)	7821 (49.07)	8495 (53.29)	8805 (55.24)	8449 (53.01)
Menopausal and recent MHT use	9076 (14.24)	2140 (13.43)	2309 (14.49)	2243 (14.07)	2384 (14.96)
Menopausal and no recent use of MHT	19,060 (29.89)	5424 (34.03)	4654 (29.2)	4429 (27.79)	4553 (28.57)
Menopausal and no information on recent use of MHT	2052 (3.22)	554 (3.48)	482 (3.02)	463 (2.9)	553 (3.47)
Parity					
Nulliparous	7585 (11.9)	2084 (13.07)	1852 (11.62)	1776 (11.14)	1873 (11.75)
1 or 2 children and age at first full-term pregnancy <30 years old	31,468 (49.36)	7726 (48.47)	7882 (49.45)	7931 (49.76)	7929 (49.75)
>2 children and age at first full-term pregnancy <30 years old	18,012 (28.25)	4469 (28.04)	4492 (28.18)	4487 (28.15)	4564 (28.63)
Age at first full-term pregnancy >30 years old	6693 (10.5)	1660 (10.41)	1714 (10.75)	1746 (10.95)	1573 (9.87)
Breastfeeding					
Never	24,301 (38.11)	6344 (39.8)	6078 (38.13)	5926 (37.18)	5953 (37.35)
Duration <6 months	27,804 (43.61)	6713 (42.12)	6998 (43.9)	7090 (44.48)	7003 (43.94)
Duration ≥6 months	11,653 (18.28)	2882 (18.08)	2864 (17.97)	2924 (18.34)	2983 (18.72)
Daily calory intake (excluding lipid and alcohol intakes, kcal/day)	1330.3 (353.7)	1169.8 (311.6)	1303.8 (316.7)	1386.5 (340.1)	1461.3 (374.9)
Alcohol consumption (g/day)	11.6 (13.8)	9.1 (12.4)	10.8 (13.0)	12.2 (13.7)	14.2 (15.6)
Total lipid intake (g/day)	89 (26.9)	70 (17.9)	85.1 (20.2)	95.4 (23.9)	105.4 (30)

Model 3 was chosen as the main model for the rest of the analysis. Further adjustment only slightly modifies the results, so they have not been included in the main model for the sake of parsimony.

The main model showed a positive, linear, and statistically significant association between dietary intake of dioxins and DL-PCB and the risk of weight gain in the E3N cohort (Fig. 1 and Supp Table 10). In other words, for a one standard deviation increase in dietary intake of dioxins and DL-PCB (i.e. 12.0 pg TEQ/day), the risk of weight gain of over 10 kg during follow-up increases by 7 %. Women in the most exposed quartile group had a 22 % higher risk of gaining >10 kg than women in the least exposed quartile group.

A positive, linear, and statistically significant association between dietary intake of dioxins and DL-PCB and the risk of overweight was also found (Fig. 1 and Supp Table 10). For a one-standard-deviation increase in dietary intake of dioxins and DL-PCB (11.7 pg TEQ/day), the risk of being overweight increases by 3 %. Women in the most exposed quartile group had a 9 % higher risk of becoming overweight than women in the least exposed quartile group.

Finally, the association between dietary intake of dioxins and DL-PCB and obesity was also positive, linear, and statistically significant, with an 8 % increase in the risk of obesity for a one standard deviation increase (11.9 pg TEQ/day) (Fig. 1 and Supp Table 10). Women in the most exposed quartile group had a 21 % higher risk of obesity than women in the least exposed quartile group.

No significant interaction was observed between dietary intake of dioxins and DL-PCB and BMI at baseline or body shape at puberty (details in Supplementary table 8) regarding the three outcomes of interest.

Table 2
Hazard ratios of successive adjustment models estimated by multivariable Cox regressions for the risks of weight gain, overweight and obesity as a function of dietary intake of dioxins and DL-PCB estimated according to the "lower-bound scenario" in the E3N cohort.

	Non-cases/cases	Model 0	Model 1	Model 2	Model 3	Model 4
Weight gain HR (CI 95 %)	53,294/10464	1.11 (1.09–1.13)	1.1 (1.08–1.12)	1.08 (1.05–1.11)	1.07 (1.05–1.10)	1.07 (1.05–1.10)
p-Value		***<0.001***	***<0.001***	***<0.001***	***<0.001***	***<0.001***
Overweight HR (CI 95 %)	37,141/13946	1.07 (1.05–1.09)	1.08 (1.07–1.1)	1.04 (1.01–1.06)	1.03 (1.01–1.05)	1.03 (1.01–1.05)
p-Value		***<0.001***	***<0.001***	***<0.001***	***<0.001***	***<0.001***
Obesity HR (CI 95 %)	57,264/4384	1.14 (1.11–1.18)	1.16 (1.13–1.19)	1.10 (1.06–1.14)	1.08 (1.04–1.12)	1.08 (1.04–1.12)
p-Value		***<0.001***	***<0.001***	***<0.001***	***<0.001***	***<0.001***

M0: Age as time scale.
M1: M0 + physical activity (MET-hours/week) measured at Q3, smoking status (smoker, non-smoker, former smoker), birth generation (≤1930,]1930–1935],]1935–1940],]1940–1945], >1945), education level (<12 years, 12 to 14 years, >14 years), silhouette at puberty (very thin, thin, medium, wide, very wide), all measured at Q2.
M2: M1 + daily fat and alcohol intake (g/day), daily calorie intake not including fat and alcohol intake (kcal/day) measured at Q3.
M3: M2 + stratification into BMI quintiles at baseline categorized into quintiles (cut-off: 18.8 kg/m^2; 21.3 kg/m^2; 23.2 kg/m^2; 25.0 kg/m^2) measured at Q3 (cut-off for the weight gain: 18.8 kg/m^2; 21.3 kg/m^2; 23.5 kg/m^2; 29.0 kg/m^2; cut-off for the overweight: 18.7 kg/m^2; 20.9 kg/m^2; 22.5 kg/m^2; 24.5 kg/m^2; cut-off for the obesity: 18.8 kg/m^2; 21.3 kg/m^2; 23.3 kg/m^2; 27.4 kg/m^2).
M4: M3 + contraceptive pill use (never, already), parity (nulliparous, 1 to 2 children and first full-term pregnancy before age 30, 1 to 2 children and first full-term pregnancy after age 30, >2 children), breastfeeding (never, <6 months, >6 months), menopausal status (pre-menopause, menopause and use of menopausal hormone therapy, menopause without menopausal hormone therapy, menopause without information on menopausal hormone therapy) measured at Q2.
Statistically significant p-values are reported in ***bold italic***.

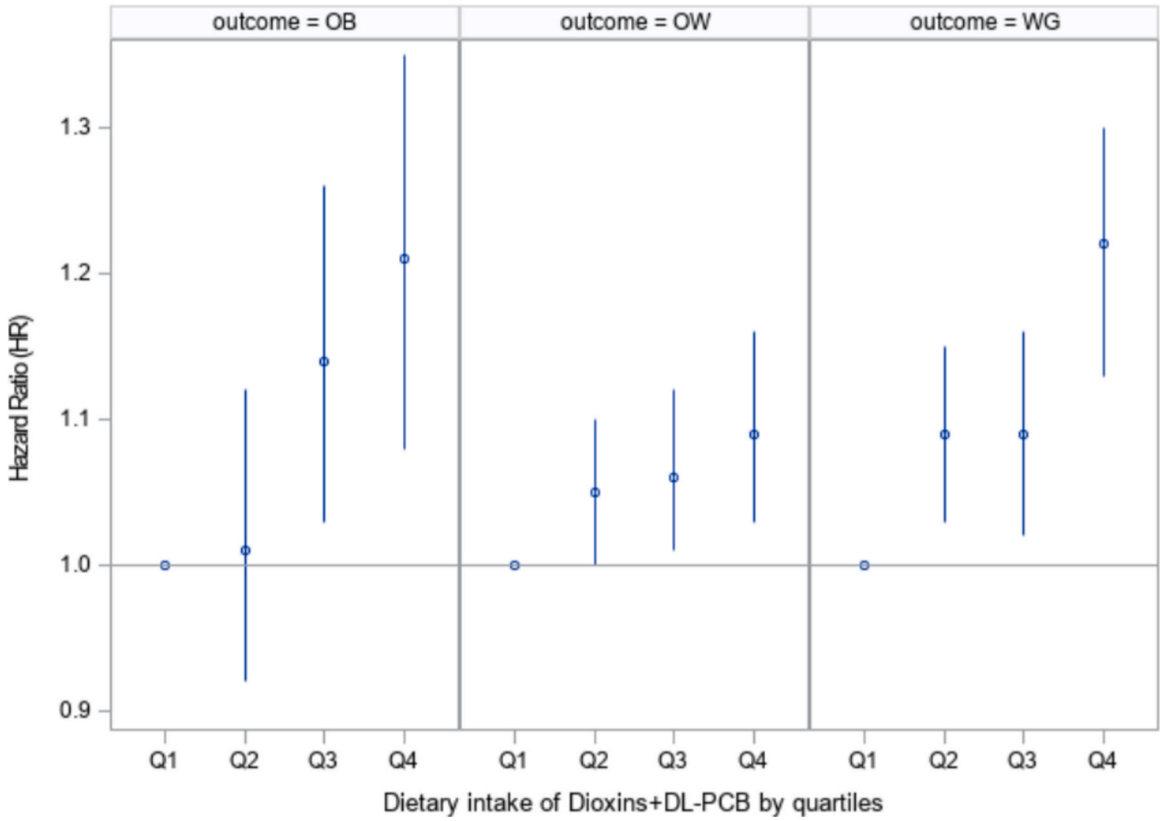

Fig. 1. Forest plot showing the hazard ratio and 95 % confidence intervals for the risks of obesity, overweight and weight gain as a function of dietary dioxin and DL-PCB intake estimated according to the "lower-bound scenario" in the E3N cohort. (Abbreviations: OB = obesity; OW = overweight; WG = weight gain).

3.2.2. NDL-PCB

All tested models showed positive and statistically significant associations between dietary intake of NDL-PCB and the risk of weight gain, overweight and obesity in the E3N cohort (3). Model 3 is once again chosen as the main model for all the following analyses.

The main model showed a positive, linear, and statistically significant association between dietary intake of NDL-PCB and the risk of gaining over 10 kg of body weight during follow-up in the E3N cohort (Fig. 2 and Supp Table 10). For a one standard deviation increase in dietary intake of NDL-PCB (i.e., 69.7 ng/day), the risk of weight gain of over 10 kg increases by 8 %. Women in the most exposed quartile group have a 22 % higher risk of gaining >10 kg than women in the least exposed quartile group.

This positive, linear, and statistically significant association between dietary intake of NDL-PCB and the risk of overweight was also observed (Fig. 2 and Supp Table 10). For a one-standard-deviation increase in dietary intake of NDL-PCB (67.7 ng/day), the risk of overweight increases by 4 %. Women in the most exposed quartile group had a 13 % higher risk of becoming overweight than women in the least exposed quartile group.

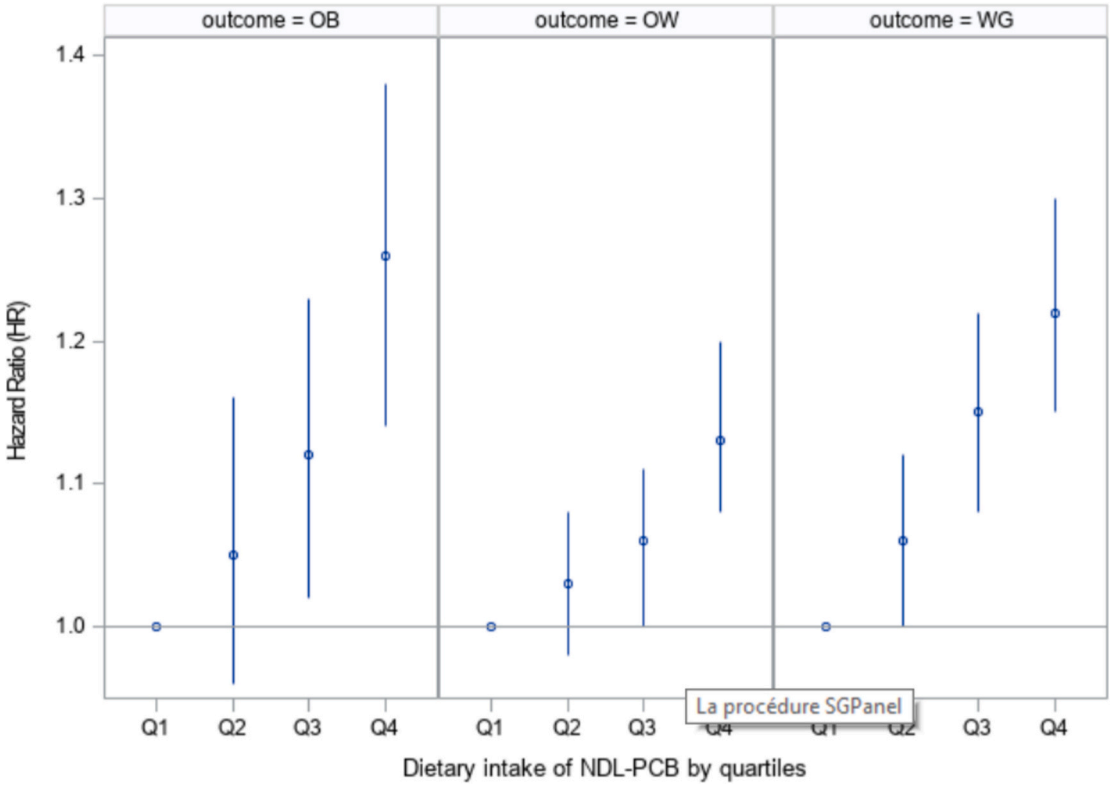

Fig. 2. Forest plot showing the hazard ratio and 95 % confidence intervals for the risks of obesity, overweight and weight gain as a function of dietary NDL-PCB intake estimated according to the "lower-bound scenario" in the E3N cohort. (Abbreviations: OB = obesity; OW = overweight; WG = weight gain).

Finally, the association between dietary intake of NDL-PCB and obesity was also positive, linear and statistically significant, with a 9 % increase in the risk of obesity for an increase of one standard deviation (69.1 ng/day) (Fig. 2 and Supp Table 10). Women in the most exposed quartile group have a 26 % higher risk of becoming obese than women in the least exposed quartile group.

No statistically significant interaction was found between dietary intake of NDL-PCB and BMI at baseline or body shape at puberty regarding the three outcomes of interest (details in Supplementary Table 9).

3.3. Sensitivity analysis

The first sensitivity analysis was designed to investigate a possible reverse causality bias. When excluding people followed for <5 years (whether cases or non-cases), the same positive, linear, and statistically significant associations were found (Supplementary Tables 10a to 10f).

The second analysis involved dividing the study population in two groups according to the duration of the follow-up. The results showed the same trend when including in the model only women with a follow-up longer than 11.5 years, as well as when the follow-up was truncated at 11.5 years. Nevertheless, we observed a loss of significance that can be explained by the reduced number of cases. The results are detailed in Supplementary Tables 9a to 9f. These results demonstrate the stability of the model over time.

A third sensitivity analysis involved adjusting the main model simultaneously for the two exposure variables of interest (dietary intake of NDL-PCB and dietary intake of DL-PCB and dioxins) to adjust the effect of one intake on another. This model confirms the positive and statistically significant association between dietary intake of NDL-PCB and the risk of obesity (HR_{1sd} 1.15 (IC95% 1.08–1.23)). However, the association between dietary intake of dioxins and DL-PCB and the risk of obesity was no longer observed (HR_{1sd} 0.92 (IC95% 0.85–1.01)) (Supplementary Table 11a). Similar results were found for the risk of overweight and for the risk of weight gain >10 kg compared with inclusion regarding NDL-PCB while the inverse trend observed with dioxins + DL-PCB became statistically significant (Supplementary Tables 11b and 11c).

The last sensitivity analysis examined the effect of other dietary variables on the main model. After adjusting the main model for PNNS adequacy score, the association between dioxins and DL-PCB dietary intake and obesity was no longer appreciable, while results remained unchanged with regard to the association between dietary intake of NDL-PCB and obesity risk (Table 3).

When adjusted for fish consumption (g/day), the association between dietary intake of NDL-PCB and obesity risk is attenuated but can still be observed, and the association between dietary intake of dioxins and DL-PCB and obesity risk is no longer present (Table 4). Similar trends were observed for the risks of weight gain and overweight (Supplementary Tables 12a and 12b).

4. Discussion

This study suggests positive, linear, and statistically significant associations between dietary intake of NDL-PCB and the risk of weight gain of over 10 kg, overweight and obesity. These results were overall consistent when performing sensitivity analyses.

4.1. Association between NDL-PCB or dioxin and DL-PCB dietary intake and the risk of obesity

Obesity is an important public health issue and is a well-known risk factor for several non-communicable diseases such as type 2 diabetes. Nevertheless, while diet is the most important source of exposure to PCB and dioxins in the general population, only two published studies have examined the association between dietary PCB and dioxins intake and the risk of obesity in human populations. The first one is a Spanish prospective study involving 12,313 participants, followed for a median

Table 3
Hazard ratios of successive adjustment models estimated by multivariable Cox regressions for the risks of weight gain, overweight and obesity as a function of dietary intake of NDL-PCB estimated according to the "lower-bound scenario" in the E3N cohort.

	Non-cases/cases	Model 0	Model 1	Model 2	Model 3	Model 4
Weight gain HR (CI 95 %)	53,294/10464	1.11 (1.09–1.13)	1.12 (1.1–1.14)	1.11 (1.08–1.13)	1.08 (1.06–1.10)	1.08 (1.06–1.10)
p-Value		***<0.001***	***<0.001***	***<0.001***	***<0.001***	***<0.001***
Overweight HR CI 95 %)	37,141/13946	1.1 (1.08–1.12)	1.11 (1.1–1.13)	1.09 (1.07–1.11)	1.05 (1.03–1.06)	1.04 (1.03–1.06)
p-Value		***<0.001***	***<0.001***	***<0.001***	***<0.001***	***<0.001***
Obesity HR (CI 95 %)	57,264/4384	1.17 (1.14–1.21)	1.19 (1.16–1.22)	1.16 (1.12–1.19)	1.09 (1.06–1.12)	1.09 (1.06–1.12)
p-Value		***<0.001***	***<0.001***	***<0.001***	***<0.001***	***<0.001***

M0: age as timescale.
M1: M0 + physical activity (MET-hours/week) measured at Q3, smoking status (smoker, non-smoker, former smoker), birth generation (≤1930,]1930;1935],] 1935,1940],]1940–1945], >1945), education level (<12 years, 12 to 14 years, >14 years), silhouette at puberty (very thin, thin, medium, wide, very wide), all measured at Q2.
M2: M1 + daily fat and alcohol intake (g/day), daily calorie intake not including fat and alcohol intake (kcal/day) measured at Q3.
M3: M2 + stratification into BMI quintiles at baseline categorized into quintiles, measured at Q3.
M4: M3 + contraceptive pill use (never, already), parity (nulliparous, 1 to 2 children and first full-term pregnancy before age 30, 1 to 2 children and first full-term pregnancy after age 30, >2 children), breastfeeding (never, <6 months, >6 months), menopausal status (pre-menopause, menopause and use of menopausal hormone therapy, menopause without hormone therapy, menopause without information on hormone therapy) measured at Q2.
Statistically significant p-values are reported in ***bold italic***.

of 8.1 years, which led to results overall consistent with those of our study (Donat-Vargas et al., 2014). However, the effect sizes reported differ from those in the present study, possibly due to differences in the populations included. Indeed, the Spanish study examined both men and women, and overall the population was younger and with higher dietary intake levels of DL-PCBs. The second study explores the associations between dietary dioxins intake and the risk of obesity (Khoury et al., 2023). It was carried out in Spain including 5899 adults aged 55 to 75 years at baseline with both cross-sectional and longitudinal analyses. The cross-sectional analysis revealed a higher BMI, a higher waist circumference, as well as a higher prevalence of obesity in the third tertile group of dietary exposure to dioxins compared to the first tertile group. In the prospective analysis, participants in the third tertile group showed a linear increase in waist circumference after 1 year of follow-up, but no statistically significant association was observed for BMI, obesity, or incidence of abdominal obesity, although the direction of these associations remained the same as that observed in the cross-sectional analysis. However, in this study, only dietary intake of PCDD/F were investigated.

By including NDL-PCB in the study, and thanks to the size of the E3N cohort, the long follow-up duration, and the definition of three complementary outcomes (e.g., weight gain of over 10 kg, overweight and obesity), our study complements and reinforces the interpretations of these two previous publications. It should be noted that, in our study, when simultaneously adjusting for NDL-PCB dietary intake and for dioxins and DL-PCB dietary intake, only the positive association with NDL-PCB remained appreciable. These results suggest that NDL-PCB could act as a main confounder in the association between dioxins and DL-PCB and obesity risk although the presence of collinearity between the two variables of exposure may affect the interpretability of the results.

Fish is one of the main contributors to exposure to PCB and dioxins, but also to other pollutants. Adjusting for fish consumption attenuated the results observed in our main analyses. Nevertheless, the strong correlation between fish consumption and PCB and dioxins intake may affect the interpretability of these results. Thus, the presence of residual confounding by the diet and/or by other food chemical contaminants cannot be completely ruled out in our study.

4.2. Strengths and limitations of the study

This study has certain limitations. Firstly, our study population is composed of middle-aged women with a higher level of education in comparison to the general French population. Consequently, these results must be generalized with great caution. On the other hand, the food contamination data come from samples collected from 2007 to 2009, whereas our food consumption data were collected in 1993. This may have led to inaccurate estimates of dietary intake of PCB and dioxins. However, these substances are ubiquitous and very persistent in the environment. The estimation error is therefore assumed to be relatively low and homogeneous across the study population, potentially leading to a non-differential exposure misclassification. In addition, the use of food frequency questionnaires to estimate dietary consumptions may lead to an imprecise estimation of the diet. However, the dietary questionnaire has been filed in at baseline, and the potential errors are likely to be non-differential among cases and non-cases. Moreover, PCB and dioxins have been summed (NDL-PCB on the one hand, dioxins, and DL-PCB on the other) on the assumption that the congeners included in the two groups present the same toxic mechanisms and that their effects are additive. Inaccuracies may also arise from dietary and weight data, as these are derived from self-administered questionnaires. Indeed, the questionnaires may be subject to memory or social desirability bias, leading more probably to an attenuation of the real association. In addition, we cannot exclude residual confounding by diet or other factors. Also, the definitions of the three outcomes (weight gain, overweight, obesity) are based on arbitrary conventions in the literature, but their complementarity aims to compensate for these choices. Finally, our study examined changes in body weight or BMI as categorical variables, which may limit our ability to comprehensively capture longitudinal weight fluctuations, such as shifts between categories (e.g., from obese to overweight) at different points in time. Weight loss is often closely associated with dietary changes (energy restrictions) or lifestyle modifications. However, dietary data were only collected at baseline, we do not have the necessary information to assess how changes in the diet may impact the association between PCBs dietary exposure and body weight transitions. Future studies could address this issue by using repeated estimates of dietary exposure as well as longitudinal measures of BMI.

This study also has several strengths. It is the first epidemiological study to examine the association between dietary intakes of NDL-PCB and the risk of weight gain, overweight and obesity. Although dietary intakes may be considered as imperfect estimates of exposure, they are complementary to blood measurements more often used in the literature (Dirinck et al., 2011; Lee et al., 2014). Firstly, the use of dietary intakes is interesting for formulating public health recommendations. In addition, plasma measurements are costly and more invasive, limiting the size of study populations. Moreover, these substances are stored in adipose tissue, circulating levels are only partially representative of the individual internal exposure levels. Finally, PCB and dioxins blood levels may vary in time depending on changes in body weight and fat tissue volume, potentially inducing reverse causation bias when investigating

Table 4
Hazard ratios estimated by multivariable Cox regression models adjusted for fish consumption and PNNS adequacy score for obesity risk as a function of dietary intakes of dioxins, DL-PCB and NDL-PCB estimated according to the "lower-bound scenario" in the E3N cohort (N = 61,648).

	N non-cases/N cases	Model 3	Model 3.1	Model 3.2
		HR (CI 95 %)	HR (CI 95 %)	HR (CI 95 %)
Daily dietary NDL-PCB intake for an increase of one standard deviation (69.1 ng/day)	57,264/4384	1.09 (1.06–1.12)	1.09 (1.05–1.12)	1.05 (1.00−1.11)
p-Value		***<0.001***	***<0.001***	0.056
Dietary intake quartiles (min–max, ng/day)				
Q1 (2.9–103.3)	14,485/927	Ref	Ref	Ref
Q2 (103.3–138.0)	14,420/992	1.05 (0.96–1.16)	1.06 (0.96–1.16)	1.03 (0.94–1.13)
Q3 (138.0–182.9)	14,302/1110	1.12 (1.02–1.23)	1.13 (1.02–1.24)	1.07 (0.97–1.19)
Q4 (182.9–798.1)	14,057/1355	1.26 (1.14–1.38)	1.26 (1.14–1.39)	1.14 (1–1.29)
p-Trend		***<0.001***	***<0.001***	***0.04***
Daily dietary DL-PCB and dioxin intake for an increase of one standard deviation (11.9 pg TEQ/day)	57,264/4384	1.08 (1.04–1.12)	1.01 (0.97–1.05)	1.02 (0.97–1.07)
p-Value		***<0.001***	0.582	0.371
Dietary intake quartiles (min-max, pg TEQ/day)				
Q1 (0.8–22.4)	14,471/941	Ref	Ref	Ref
Q2 (22.4–29.1)	14,401/1011	1.01 (0.92–1.12)	0.99 (0.9–1.08)	0.98 (0.89–1.08)
Q3 (29.1–37.1)	14,292/1120	1.14 (1.03–1.26)	1.08 (0.97–1.19)	1.07 (0.96–1.19)
Q4 (37.1–130)	14,100/1312	1.21 (1.08–1.35)	1.06 (0.94–1.18)	1.07 (0.94–1.21)
p-Trend		***<0.001***	0.212	0.171

Model 3: adjusted for age (years) as time scale, physical activity (MET-hours/week), smoking (smoker, former smoker, non-smoker), generation of birth (≤1930,]1930; 1935],]1935,1940],]1940–1945], >1945), level of education (<12 years, 12 to 14 years, >14 years), body shape at puberty (very thin, thin, medium, wide, very wide), calorie intake excluding fat and alcohol (kcal/day), fat intake (g/day) and alcohol intake (g ethanol/day) and stratification into BMI quintiles at baseline (kg/m^2).
Model 3.1: Model 3 + adjustment on the PNNS adequacy score.
Model 3.2: Model 3 + adjustment on the daily fish consumption (g/day).
Statistically significant p-values are reported in ***bold italic***.

the relationship with obesity. In the present study, the inclusion of many participants (>60,000 in this study), the long follow-up period (>20 years), and therefore the observation of many cases, ensure a strong statistical power and enable us to perform several sensitivity analyses. The availability of body weight data collected repeatedly during follow-up enabled to study different outcomes, namely weight gain, overweight and obesity, which are complementary and ensure a better interpretation our findings from a public health perspective. Finally, the richness of the E3N data enabled us to adjust for many potential confounders, selected with the help of a DAG.

5. Conclusion and perspectives

This study, including over 60,000 participants followed for over 20 years, suggests a positive, linear, and statistically significant association between dietary intakes of NDL-PCB and the risk of weight gain, overweight and obesity in adult women. Further studies are needed to confirm these results in other populations and to better understand the biological mechanisms underlying this association.

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CRediT authorship contribution statement

Luna Chetrit: Writing – original draft. **Pauline Frenoy:** Writing – review & editing. **Fanny Artaud:** Writing – review & editing. **Chloé Marques:** Writing – review & editing. **Xuan Ren:** Writing – review & editing. **Gianluca Severi:** Writing – review & editing, Supervision. **Francesca Romana Mancini:** Writing – review & editing, Supervision.

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.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2024.177587.

Data availability

Data will be made available on request.

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