

## Original article

# Associations between dietary exposure to dioxins and polychlorinated biphenyls (PCBs) and Longitudinal changes in weight and waist circumference– an EPIC study

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## SUMMARY

**Background:** Obesity is a growing global health concern. Some evidence suggests that exposure to polychlorinated biphenyls (PCBs) and dioxins, may play a role in weight gain, but human prospective data are limited and have shown inconsistent results. Therefore, this study investigate the association between dietary exposure to dioxins and PCBs and changes in weight and in waist circumference after 5 years of follow-up in a large prospective cohort.

**Method:** We included 215,556 participants recruited between 1992 and 2000; of whom 99,046 provided data on waist circumference. Body weight or waist circumference were measured at recruitment and self-reported at follow-up. Intakes of dioxins and PCBs were estimated using country-specific dietary

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Dioxin-like PCBs (DL-PCBs)  
 Non-dioxin-like PCBs (NDL-PCBs)  
 Polychlorinated biphenyls (PCBs)

questionnaires collected at baseline, and food contamination concentrations based on a European Food Safety Authority database. Associations were estimated using multilevel mixed linear regression models.

**Results:** Higher intake of both dioxins and dioxin-like PCBs (dioxins + DL-PCBs) (Q4vsQ1 = 0.07kg/5-years (95%CI 0.01, 0.13)), and non-dioxin like PCBs (NDL-PCBs) (Q4vsQ1 = 0.27kg/5-years (95%CI 0.20, 0.35), p-trend<0.001) were associated with weight gain. Inverse associations were observed between dietary intake of dioxins + DL-PCBs and NDL-PCBs and waist circumference change (Q4vsQ1 = -0.44cm/5-years (95%CI -0.56, -0.31), p-trend<0.001 and Q4vsQ1 = -0.21cm/5-years (95%CI -0.34, -0.07), p-trend<0.001, respectively). These inverse associations were primarily caused by a subset of participants from one country who provided most of the waist circumference data. Results were consistent across stratified and sensitivity analyses.

**Conclusion:** Results obtained in this large prospective study show a positive association between dietary intake of both dioxins + DL-PCBs and NDL-PCBs and weight gain. Although the observed associations were small and there may be measurement errors, the consistency of these associations across multiple stratified analyses and sensitivity analyses strengthens the validity of the findings. The findings suggest that the effect of dioxins and PCBs are still present in the food chain despite regulatory bans. Efforts should be strengthened to reduce the exposure levels in the general population not only to lower the risk of obesity, but also to prevent various chronic conditions.

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## 1. Introduction

The increasing prevalence of obesity worldwide is a critical health problem, as it is associated with an increased risk of numerous chronic conditions, including cardiovascular diseases and various types of cancer. The World Health Organization (WHO) indicates that 43 % of the global population aged 18 years and over is currently classified as either overweight or obese [1]. In addition, more than 2.8 million deaths are attributed to overweight or obesity each year [1]. The importance of addressing obesity through effective prevention and treatment strategies has been widely recognized and highlighted.

In recent years, research on the environmental causes of obesity has increased, with growing attention to the role of dioxins and polychlorinated biphenyls (PCBs), two groups of persistent organic pollutants (POPs). Both dioxins and PCBs can travel long distances from the source of emission, and bio-accumulate along the food chain. Dioxins and PCBs represent archetypal endocrine-disrupting chemicals with distinct yet overlapping mechanisms of metabolic disruption. Dioxins comprise 75 types of polychlorinated dibenzo-p-dioxins (PCDDs) and 135 types of polychlorinated dibenzofurans (PCDFs), primarily byproducts of industrial processes and combustion. PCBs, historically used in electrical applications, include 209 congeners. Dioxin-like PCBs (DL-PCBs) activate the aryl hydrocarbon receptor (AhR), similar to 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD), while, non-dioxin-like PCBs (NDL-PCBs) have two or more chlorine atoms in orthogonal positions, primarily target alternative pathways including the constitutive androstane receptor (CAR) [2].

At the molecular level, dioxins and PCBs disrupt adipogenesis and energy homeostasis through multiple pathways. Through AhR activation, DL-PCBs and dioxins inhibit adipocyte differentiation and promote ectopic lipid accumulation [3]. NDL-PCBs impair leptin signaling and reduce AMP-activated protein kinase activity, further compromising metabolic regulation [4]. Despite bans and restrictions since the 1970s, dioxins and PCBs remain widespread in food, soil, and water [5,6]. Over 90 % of human exposure occurs through the diet, particularly meat, dairy products, fish, and shellfish [7]. These substances are highly persistent, TCDD, the most toxic dioxin, has a half-life of 7–11 years in the human body, while PCB congeners can persist in plasma for less than a year to nearly three decades [7,8].

Despite biological plausibility, evidence linking dioxins or PCBs exposure with changes in body weight or waist circumference in humans remains limited and inconsistent. Our previous study found positive associations between NDL-PCBs intake and the risk of obesity, and weight gain among French women [9] consistent with findings from other prospective studies [10,11]. Studies assessing the blood concentrations of PCBs and dioxins have shown conflicting results; while cross-sectional studies reported positive associations [12,13], one prospective study [14], and a meta-analysis based on three other studies [15], found no association between exposure and obesity. Since previous studies focused on specified congeners [16,17] or population groups with high environmental contamination [12,17], their relevance to general dietary exposure is limited; moreover, small sample size [13] reduced statistical power and the ability to detect associations. Indeed, large prospective studies with longer follow-up are still needed to clarify the effects of differing levels of dietary exposure to dioxins and PCBs on weight or waist circumference [10,15].

Therefore, we investigated the association between dietary exposure to dioxins and PCBs and subsequent changes in weight and waist circumference over a 5-year period among 215,556 adults from seven European countries, with particular attention to geographic heterogeneity in these relationships.

## 2. Materials and methods

### 2.1. Study population

The European Prospective Investigation into Cancer and Nutrition (EPIC) cohort is an ongoing multi-centre prospective cohort study comprising about 520,000 healthy adults aged 35–69 years recruited from 23 centres across 10 European countries between 1992 and 2000: Denmark (Aarhus and Copenhagen), all over France and Greece, Germany (Heidelberg and Potsdam), Italy (Florence, Varese, Ragusa, Turin, and Naples), Norway, Spain (Asturias, Granada, Murcia, Navarra, and Guipuzcoa), Sweden (Malmö and Umeå), the Netherlands (Bilthoven and Utrecht), and the United Kingdom (Cambridge and Oxford). Dietary and lifestyle information was collected at baseline using validated questionnaires. A more detailed description of the EPIC cohort has been provided elsewhere [18,19].

Due to data unavailability, participants from Greece, Sweden, and Norway were not included in the present analysis. This study initially included 276,630 participants with follow-up records and reported weight information. A total of 36,448 individuals in the top or bottom 1 % of the energy intake-to-energy requirement ratio and 24,626 individuals without follow-up weight data were excluded. Consequently, 215,556 participants (77,958 men and 137,598 women) were included (Fig. 1). Among them, 99,046 participants also provided waist circumference data at baseline and follow-up.

Baseline information on medical history, education level, smoking status, and physical activity was collected through self-administered questionnaires [19]. All participants provided written informed consent to participate in the EPIC cohort. The study protocol was approved by the ethics committee of the International Agency for Research on Cancer (IARC) and the ethics committees of all participating research centres.

### 2.2. Food consumption data

Dietary intake data were collected using country or centre specific validated dietary questionnaires at the recruitment in the

average daily intake  $\left(\frac{pg}{day}\right)$

$$= \sum_{each\ food} (average\ food\ daily\ consumption\ in\ g\ of\ food / day) \times \left( median\ of\ contamination\ level\ for\ food\ in\ \frac{pg}{g\ of\ food}\ food \right)$$

1990s. The methods varied among study centres and included self-administered or interviewer-administered semi-quantitative food frequency questionnaires (FFQs), dietary history questionnaires, or a combination of FFQs with 7-day dietary records. The recipes from the questionnaires were broken down into ingredients by local dietitians in order to fit the EPIC food classification system. The initial list of 43,954 food and ingredient items, varying from 146 in Umeå to 23,655 in Malmö, was aggregated into a harmonized list of 11,858 items [20]. Dietary questionnaire items were classified according to the FoodEx classification system as explained in Huybrechts et al., 2025 [20].

### 2.3. Food contaminant database and dietary intake of dioxins and PCBs

The European Food Safety Authority (EFSA) collects annual data on the occurrence of chemical contaminations in food products, including dioxins and PCBs, from national authorities, research institutions, academia, food business operators, and other stakeholders [20]. For this study, EFSA provided a food contamination database containing food samples of dioxins and PCBs collected between 2000 and 2018. These samples were categorized using EFSA's FoodEx classification system [21]. Data analysed by different European countries was combined and a series of exclusions of samples was performed as explained in Fiolet et al. [18]. Two scenarios were used to handling left-censored values. In the present study, to minimizing the risk of overestimating exposures, only the lower bound (LB) scenario, where a null value was assigned to values below the limit of detection was applied [18]. Dietary intake of dioxins and PCBs was calculated by combining EPIC food consumption data with EFSA occurrence data for each congener of each food item. The dietary intake of the substance was estimated by the following formula:

The concentrations of each congener was multiplied by their toxic equivalency factor (TEF) [18]. Toxic equivalent values (TEQ) were calculated for each dioxin and DL-PCB congener to assess their relative toxicity compared to the most toxic dioxins (TCDD). In the present study, four indicators were calculated based on their toxicological properties: the sum of 17 dioxins (pg TEQ/day); sum of 12 DL-PCBs (pg TEQ/day); sum of 29 dioxins + DL-PCBs (pg TEQ/day) and 6 NDL-PCBs (ng/day). The NDL-PCBs include PCB 28, 52, 101, 138, 153, and 180, which are considered indicators for maximum residue limits in food. The sum of these six NDL-PCBs accounts for 50 % of the total NDL-PCBs in food [22].

### 2.4. Anthropometric measures

Body weight and height were measured without shoes by trained personnel, except in the French and Oxford centres where this information was self-reported. Baseline waist circumference (cm) was measured at either the narrowest part of the torso or midway between the lower ribs and the iliac crest. Anthropometric data were adjusted for protocol differences in clothing during measurements [23]. Briefly, in some centres, weight was measured in light underwear, while in others, participants wore normal clothing and no shoes. Correction factors from a prior study were applied: -1.5 kg for weight and -2.0 cm for waist circumference for participants fully dressed, and -1.0 kg for those in light indoor clothing [23,24].

In the EPIC cohort, each participant had two anthropometric assessments: at baseline and at one follow-up. At follow-up, weight and waist circumference were self-reported across all centres, except in Cambridge (UK) and Doetinchem (The Netherlands, part of the Bilthoven centre), where measurements

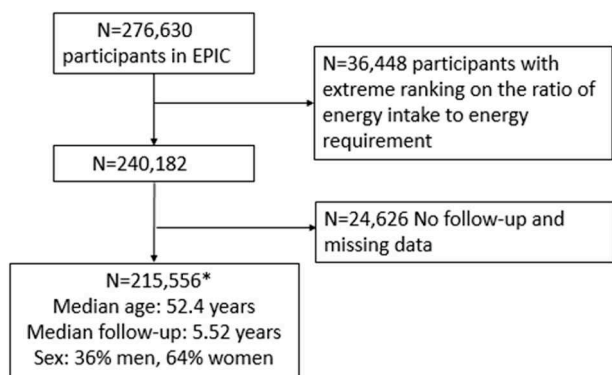


Fig. 1. Flow chart of study population  
\*99,046 participants provided information on waist circumference.

were taken according to the baseline protocol. The accuracy of self-reported anthropometric measures was improved using correction equations derived from participants with both measured and self-reported data [25]. BMI was calculated as body weight (kg)/height squared ( $m^2$ ) [24].

In this study, the follow-up periods between the two anthropometric assessments varied by research centre, ranging from 3 to 12 years. Consequently, the main outcome was the weight and waist circumference change estimated for 5 years. These changes were calculated by taking the difference between follow-up and baseline values, dividing by the duration of follow-up in years, and multiplying by 5, as follows:

$$\text{Change per 5 years} = \left( \frac{\text{Measurement at followup} - \text{Measurement at baseline}}{\text{followup time in years}} \right) * 5$$

## 2.5. Statistical analyses

The baseline characteristics of participants were described according to quartile groups of NDL-PCBs and dioxins + DL-PCBs. In the present study, we assume that the missing data are missing at random, covariates with <5 % missing values were imputed by single imputation; the modal value was used for categorical variables or the median for continuous variables. Missing data for education level (2.41 %) were imputed by the category “primary school completion”, and missing data for physical activity level (1.13 %) were imputed by the category “moderate inactive”.

The associations between dietary intakes of dioxins + DL-PCBs and NDL-PCBs and changes in body weight change (kg/5y) or waist circumference (cm/5y) were estimated using multi-level mixed linear regression models with centre as a random effect. The first model was adjusted for age and BMI at baseline and sex; the second model was further adjusted for alcohol consumption, total energy intake without alcohol, follow-up duration, smoking status, education level and physical activity [9,16]; the third model is further adjusted for the Relative Mediterranean Diet Score (rMED), which has been described in detail elsewhere [26].

In the linear models, dietary intake of dioxins + DL-PCBs and NDL-PCBs was analysed as both continuous variables and as categorical variables divided into quartiles, with the lowest quartile serving as the reference group. Continuous exposure variables were normalized by dividing each by their respective standard deviation (SD), allowing for interpretation of weight changes per one SD increment. Linear trends across quartiles of dioxins + DL-PCBs and NDL-PCBs dietary intake were assessed by assigning median values to each quartile and modelling these as continuous variables. To explore potential non-linear relationships, restricted cubic splines were applied. The number of knots was selected based on the Akaike Information Criterion (AIC), chosen among models with 3–5 candidate knots. To address potential concerns about model assumptions, we assessed the distribution of residuals and observed deviations from normality primarily in the upper tail; therefore, for the spline models only, we exclude participants with dioxins + DL-PCBs or NDL-PCBs intake values above the 99th percentile as outliers. Primary analyses used food contamination data for dioxins + DL-PCBs and NDL-PCBs collected between 2000 and 2018.

Several sensitivity analyses were performed. First, because polyunsaturated fatty acid (PUFA) shares the same food sources with dioxins and PCBs [27], model 2 was further adjusted separately for total fat intake and PUFA intake in order to distinguish the effects of food contaminant exposure from those of fat intake, as this may influence weight change. An energy-adjusted contaminant residual model was applied to account for variation attributed to total energy intake [28]. In a previous study [16], we found that fish and seafood were the primary sources of NDL-PCBs, contributing 74 % of total intake, while for dioxins + DL-PCBs, dairy products contributed the most (35 %). To distinguish the effects of food contaminant from those related to the consumption of the

main food groups, model 3 was further adjusted for the consumptions of the food groups that mainly contributed to dioxins and/or PCBs intake (“dairy products” and “fish and shell seafood”). Further analyses were conducted using food contamination data from two different time periods (2005–2018 and 2010–2018), to assess the impacts of potentially improved quality of the food contamination data.

To evaluate possible geographic variations, country-specific analyses were performed using generalized linear models, and the results were pooled using random-effects meta-analysis. Heterogeneity was assessed by calculating  $I^2$  statistics and corresponding P values. Subgroup analyses were also performed based on model 3 between sex, BMI category, baseline age and abdominal obesity, to evaluate potential effect modification. Finally, analyses were also stratified by the median follow-up time to explore long-term effects.

All statistical analyses were conducted using SAS software (version 9.4, SAS Institute) and R (version 4.3.1). Tests were two-sided, with statistical significance defined as  $P < 0.05$ .

## 3. Results

The baseline characteristics of the study population, categorized by quartile of dietary intake of NDL-PCBs or dioxins + DL-PCBs, are presented in Table 1 and Supp Table 1, respectively. The median dietary intakes values were 41.96 pg TEQ/day for dioxins + DL-PCBs and 128.22 ng/day for NDL-PCBs (Table 1). The highest dietary intakes of both dioxins + DL-PCBs (66.50 pg TEQ/day) and NDL-PCBs (282.21 ng/day) were reported from France. Participants from Denmark and Germany accounted for the largest proportion of the study population (20 % each) (Supp Table 2).

The association between the 5-year weight change and intakes of dioxins + DL-PCBs and NDL-PCBs are presented in Table 2. In model 1, a higher intake of NDL-PCBs was associated with weight increase after 5 years (Q4 vs. Q1: 0.27 kg/5y (95 % CI: 0.20, 0.34),  $P$ -trend <0.001). After adjusting for potential confounders in models 2 and 3, significant association were observed for both dioxins + DL-PCBs (model 3: Q4 vs. Q1: 0.07 kg/5y (95 % CI: 0.01, 0.13),  $P$ -trend = 0.001) and NDL-PCBs (model 3: Q4 vs. Q1: 0.27 kg/5y (95 % CI: 0.20, 0.35),  $P$ -trend <0.001). However, the association with dioxins + DL-PCBs was weak at lower intake ranges and

**Table 1**  
Baseline characteristics of study participants from the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort for the overall population and by quartile groups of dietary intakes of NDL-PCBs (median [interquartile range] or %).

	All N = 215,556	Q1 N = 53,889	Q2 N = 53,889	Q3 N = 53,889	Q4 N = 53,889
<b>NDL-PCBs (ng/day)</b>	128.22 (95.13–179.10)	77.22 (64.82–86.75)	111.23 (103.28–119.46)	149.05 (137.99–162.34)	242.00 (202.38–351.52)
<b>Dioxin + DL-PCBs (pg TEQ/day)</b>	41.96 (30.04–59.79)	28.80 (20.48–42.87)	36.28 (27.81–52.03)	42.33 (34.12–57.74)	59.27 (46.52–78.67)
<b>Dioxins (pg TEQ/day)</b>	9.78 (6.77–14.22)	5.91 (4.32–8.63)	8.21 (6.46–10.95)	10.48 (8.52–13.17)	15.25 (11.96–20.03)
<b>DL-PCBs (pg TEQ/day)</b>	31.53 (22.29–45.62)	22.34 (15.32–33.84)	27.75 (20.48–40.40)	31.54 (24.65–44.25)	43.61 (33.57–59.02)
<b>Age at recruitment (years)</b>	52.39 (45.83–59.20)	50.81 (43.43–57.36)	51.96 (44.86–58.02)	53.07 (46.86–58.71)	53.30 (47.81–58.58)
<b>Sex</b>					
Male	36.17	21.09	32.58	44.05	46.95
Female	63.83	78.91	67.42	55.95	53.05
<b>Anthropometric at baseline</b>					
<b>BMI (kg/m<sup>2</sup>)</b>	25.42 (22.98–28.25)	25.05 (22.63–28.05)	25.30 (22.97–28.05)	25.54 (23.19–28.26)	25.77 (23.19–28.63)
≤18.5	1.04	1.27	0.93	0.79	1.12
18.5–25	44.66	48.30	45.89	43.19	41.28
25–30	39.13	35.63	39.01	40.94	40.93
≥30	15.16	14.81	14.17	15.01	16.67
<b>Waist circumference (cm)</b>	83.00 (74.00–92.00)	82.00 (73.50–91.30)	84.00 (75.00–93.00)	87.00 (77.00–95.50)	88.00 (78.00–97.00)
Men	93.00 (87.00–100.00)	91.00 (86.00–97.00)	92.00 (87.00–98.90)	93.00 (88.00–100.00)	95.00 (89.00–101.00)
Women	77.00 (71.80–85.00)	77.00 (71.00–84.00)	78.00 (72.00–85.00)	78.00 (72.00–86.00)	77.00 (71.00–84.00)
<b>Anthropometric at follow-up</b>					
<b>BMI (kg/m<sup>2</sup>)</b>	25.65 (23.23–28.44)	25.36 (22.84–28.34)	25.58 (23.24–28.33)	25.78 (23.42–28.46)	25.87 (23.42–28.68)
≤18.5	0.96	1.23	0.85	0.79	0.95
18.5–25	42.19	45.30	42.85	40.63	39.98
25–30	40.97	37.85	41.08	42.70	42.25
≥30	15.88	15.61	15.23	15.87	16.82
<b>Waist circumference(cm)</b>	89.00 (80.24–98.00)	87.00 (79.00–95.00)	88.00 (80.72–97.00)	90.00 (82.00–99.00)	89.00 (80.00–98.00)
Men	97.00 (92.00–104.00)	97.00 (91.00–103.00)	97.00 (92.00–103.00)	97.00 (92.00–104.00)	98.00 (92.00–104.00)
Women	78.00 (84.00–92.00)	85.00 (78.00–92.00)	85.00 (78.00–93.00)	85.00 (78.00–93.00)	80.85 (75.00–89.00)
<b>Weight change (kg/5y)</b>	0.35 (–1.80–2.33)	0.35 (–1.75–2.45)	0.40 (–1.60–2.40)	0.35 (–1.80–2.35)	0.25 (–2.00–2.05)
<b>Waist circumference change (cm/5y)</b>	3.12 (0.79–6.15)	3.43 (1.22–6.05)	3.56 (1.06–6.46)	3.41 (0.73–6.77)	2.51 (0–5.49)
<b>Total energy intake without alcohol (kcal/day)</b>	2046.48 (1687.66–2466.61)	1650.89 (1396.79–1927.83)	2005.27 (1714.85–2326.07)	2244.00 (1897.21–2632.79)	2375.88 (1986.82–2835.39)
<b>Alcohol (g/day)</b>	7.58 (1.29–19.92)	4.43 (0.50–13.23)	6.81 (1.13–17.46)	9.14 (1.91–22.24)	11.16 (2.49–26.09)
<b>Vegetables (g/day)</b>	169.20 (110.22–256.71)	146.54 (95.23–232.97)	154.06 (104.46–231.99)	170.23 (114.98–250.68)	209.67 (118.94–305.04)
<b>Fruits, nuts and seeds (g/day)</b>	202.09 (109.26–328.71)	199.64 (103.95–325.58)	199.68 (108.00–324.68)	195.71 (109.30–319.47)	215.12 (118.94–345.25)
<b>Dairy products (g/day)</b>	265.85 (153.39–421.33)	211.27 (111.26–336.94)	258.89 (152.54–401.41)	296.26 (175.96–468.38)	303.23 (185.98–484.76)
<b>Cereals and cereal products (g/day)</b>	207.43 (149.07–280.99)	176.77 (126.00–239.40)	208.77 (150.63–284.10)	222.26 (162.95–299.52)	223.84 (163.47–295.51)
<b>Meat and meat products (g/day)</b>	103.87 (70.13–143.95)	69.21 (41.70–97.74)	96.00 (69.29–126.20)	119.51 (89.81–153.98)	139.39 (100.52–184.38)
<b>Fish and shellfish (g/day)</b>	29.17 (15.89–49.71)	15.89 (5.75–28.20)	23.04 (14.22–36.30)	32.52 (21.28–46.65)	54.31 (36.51–79.37)
<b>Total fat (g/day)</b>	80.62 (63.60–100.93)	63.26 (51.1–76.90)	79.08 (64.56–94.74)	89.36 (71.84–108.88)	95.88 (77.06–118.30)
<b>PUFA (g/day)</b>	14.21 (10.88–18.62)	10.90 (8.58–14.16)	13.42 (10.80–16.94)	15.55 (12.43–19.57)	17.50 (13.64–22.53)
<b>Relative Mediterranean Diet Score</b>					
Low		29.44	18.08	24.04	29.30
Medium		44.62	44.39	46.76	47.38
High		25.94	37.53	29.20	23.31
<b>Smoking</b>					
Never		49.18	52.36	49.85	46.65
Former		28.13	27.04	28.78	29.82
Current		29.73	20.60	21.36	23.53

(continued on next page)

Table 1 (continued)

	All N = 215,556	Q1 N = 53,889	Q2 N = 53,889	Q3 N = 53,889	Q4 N = 53,889
<b>Education level</b>					
None		6.22	4.56	4.38	7.42
Primary school completed		31.19	31.51	31.75	31.17
Technical/professional school		24.18	26.25	27.17	19.39
Secondary school		15.17	14.64	14.49	18.12
Longer education (incl. University deg.)		23.24	23.05	22.21	23.90
<b>Physical activity</b>					
Inactive		19.36	19.34	20.63	19.34
Moderately inactive		29.31	27.65	28.52	33.87
Moderately active		41.98	43.93	40.74	36.90
Active		9.35	9.09	10.11	9.89

Table 2

Association between dietary intake of dioxins + DL-PCBs (pg TEQ/d) and NDL-PCBs (ng/d) and estimated weight change (kg/5y) (N = 215,556) in EPIC.

		Model 1	Model 2	Model 3
Beta (95 % CI)				
Dioxins + DL-PCBs				
Restricted cubic spline		<b>0.001</b>	<b>0.004</b>	<b>0.005</b>
(P-overall*)				
Quartiles	Q1	0.00 (Ref.)	0.00 (Ref.)	0.00 (Ref.)
	Q2	-0.01 (-0.07, 0.05)	-0.01 (-0.07, 0.05)	0.004 (-0.05, 0.05)
	Q3	-0.01 (-0.07, 0.05)	-0.01 (-0.07, 0.05)	0.01 (-0.05, 0.06)
	Q4	0.06 (-0.002, 0.13)	0.06 (-0.002, 0.13)	<b>0.07</b> <b>(0.01, 0.13)</b>
P trend		<b>0.04</b>	<b>0.04</b>	<b>0.001</b>
NDL-PCBs				
Restricted cubic spline		<b>0.001</b>	<b>0.001</b>	<b>0.001</b>
(P-overall*)				
Quartiles	Q1	0.00 (Ref.)	0.00 (Ref.)	0.00 (Ref.)
	Q2	<b>0.08</b> <b>(0.02, 0.13)</b>	<b>0.09</b> <b>(0.03, 0.15)</b>	<b>0.09</b> <b>(0.03, 0.14)</b>
	Q3	<b>0.18</b> <b>(0.12, 0.24)</b>	<b>0.19</b> <b>(0.12, 0.25)</b>	<b>0.18</b> <b>(0.11, 0.24)</b>
	Q4	<b>0.27</b> <b>(0.20, 0.34)</b>	<b>0.27</b> <b>(0.19, 0.34)</b>	<b>0.27</b> <b>(0.20, 0.35)</b>
P trend		<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>

Model 1: Stratified by centre adjusted for age, BMI at baseline and sex.

Model 2: Model 1 + smoking, alcohol, education level, physical activity, and follow-up duration.

Model 3: Model 2 + total energy intake without alcohol and rMED score.

\* P-values for overall association corresponds to the test of all terms of the exposure variable (i.e., linear and non-linear terms); they are reported only when non-linear associations are detected; Restricted cubic spline plot is shown in Figure 2 and 3.

became positive only in the highest quartile, while NDL-PCBs intake showed a progressively higher weight gain across quartile groups.

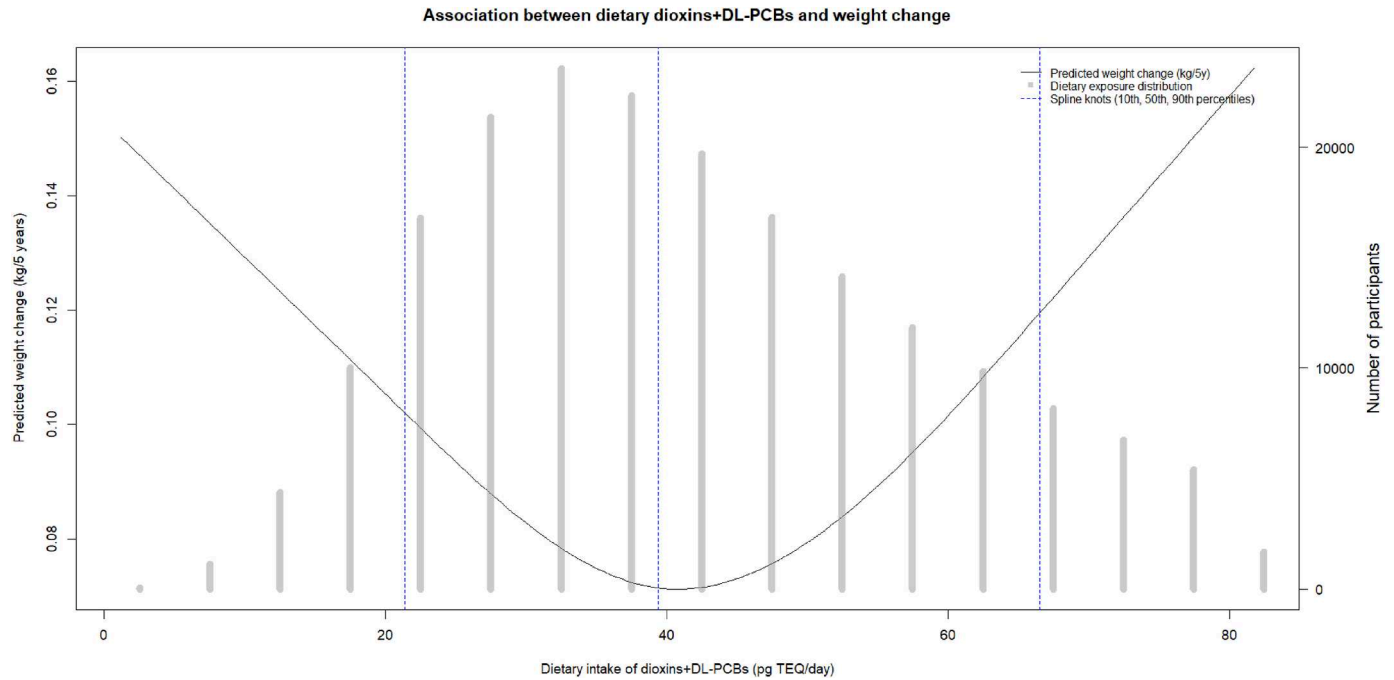
There was evidence of non-linearity in the association between weight change and dietary intake of Dioxins + DL-PCBs, and a U-shaped association was observed, with a turning point at 41.71 pg TEQ/day (P non-linearity < 0.001, P-overall = 0.005) (Fig. 3). Non-linearity was also observed for NDL-PCBs (P non-linearity = 0.001, P-overall = 0.001), with higher intakes associated with more rapid weight gain (Fig. 4). However, when the population was limited to 0–90th percentile of NDL-PCBs intake, the association almost appeared linear (P non-linearity = 0.10).

Table 3 presents the association between the 5-year waist circumference change and intakes of dioxins + DL-PCBs and NDL-PCBs. The 5-year waist circumference change was inversely related with intakes of dioxins + DL-PCBs (Model 3: Q4 vs Q1: -0.44 cm/5y (-0.56, -0.31), P-trend < 0.001) and NDL-PCBs across all models (Model 3: Q4 vs Q1: -0.21 cm/5y (-0.34, -0.07), P-trend < 0.001).

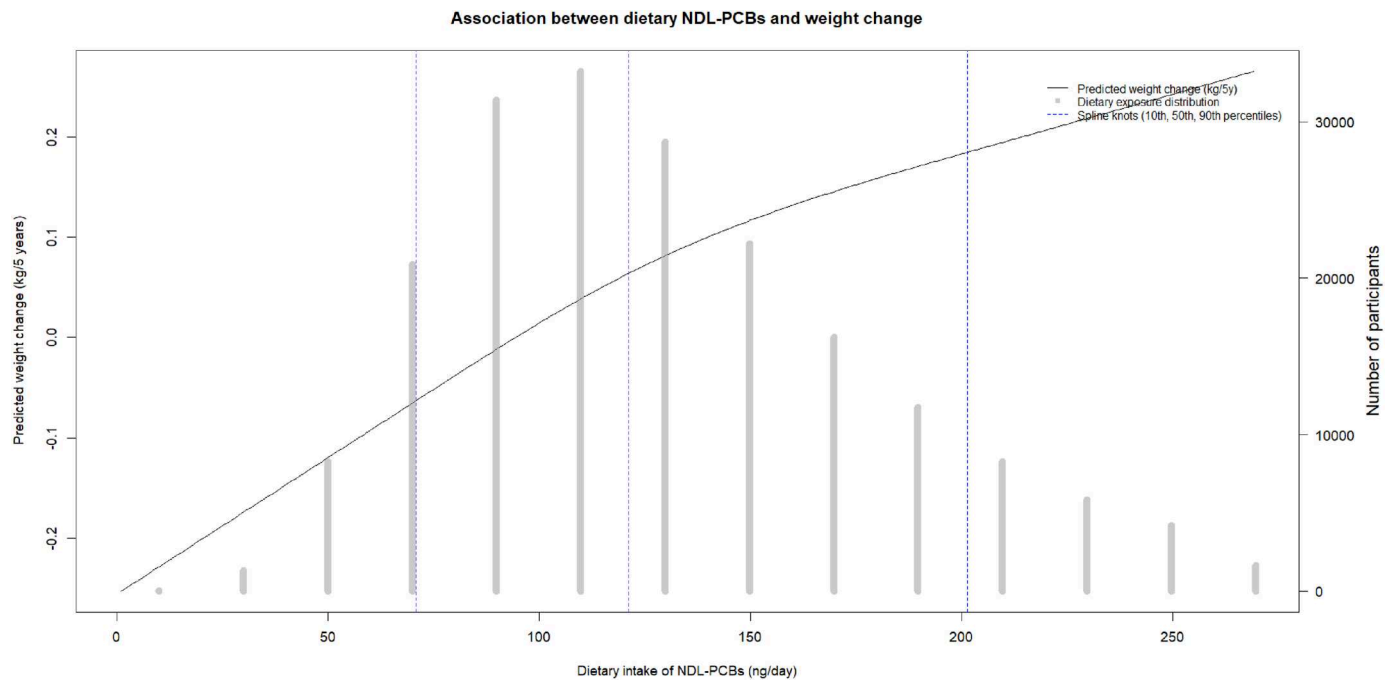
To address potential concerns about model assumptions, we assessed the distribution of residuals and observed deviations from normality primarily in the upper tail (99th percentile). Evidence of non-linearity was observed for the association between waist circumference change and dioxins + DL-PCB and NDL-PCB; a U-shaped form for Dioxins + DL-PCBs (P non-linearity < 0.001, P-overall < 0.001, turning point = 40.61 pg TEQ/day) and an inverse U-shaped form for NDL-PCBs (P non-linearity = 0.001, P-overall < 0.001, turning point = 141.72 ng/day) were identified using spline functions in model 3 (Figs. 4 and 5).

### 3.1. Sensitivity analyses

As shown in Supp Table 3, after further adjusting for total fat intake, PUFAs intake, fish intake or using the energy residual



**Fig. 2.** Association between dietary dioxins + DL-PCBs and estimated weight change (Model 3) using restricted cubic splines with three knots (10th: 21.34, 50th: 39.39, 90th: 66.51 pg TEQ/day); analysis limited to 0–90th percentile of intake ( $P$  non-linearity = 0.07).

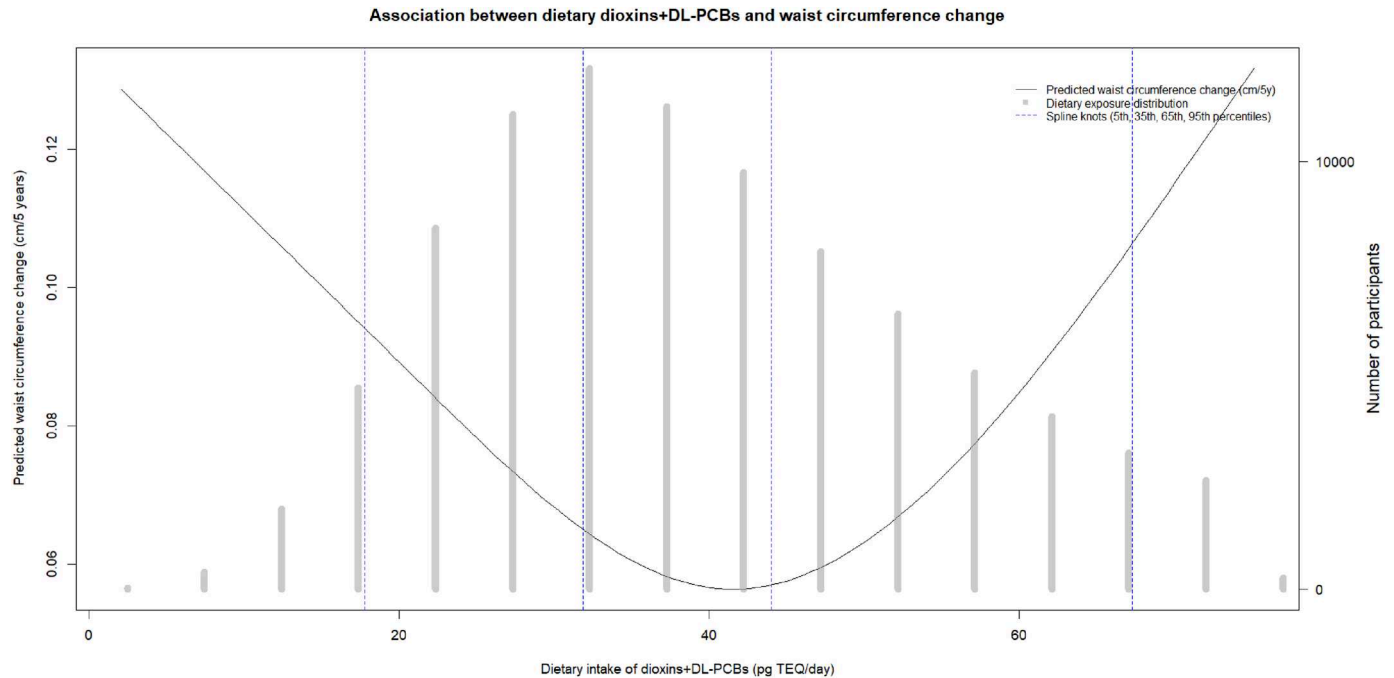


**Fig. 3.** Association between dietary NDL-PCBs and estimated weight change (Model 3) using restricted cubic splines with three knots (10th: 70.85, 50th: 121.17, 90th: 201.23 ng/day); analysis limited to 0–90th percentile of intake ( $P$  non-linearity = 0.10).

model, most results remained consistent with the main analyses (Supp Tables 3a and 3b), except that the association between dioxins + DL-PCBs and weight change was no longer statistically significant. Similarly, when using food contamination data from different periods of food sampling (2005–2018 and 2010–2018) and conducting complete-case analyses for covariates, the relationship between dietary intakes of dioxins + DL-PCBs/NDL-PCBs and both outcomes remained unchanged (data not shown).

### 3.2. Stratified analyses

In separate analyses for each country, a positive association between dietary intake of dioxins + DL-PCBs/NDL-PCBs and weight change was observed in most countries. However, in Denmark, the associations with weight change were either inverse or showed a trend toward being inverse ( $I^2 = 82\%$ ,  $P < 0.01$ ) (Fig. 6). Moreover, stratified analyses revealed that the inverse



**Fig. 4.** Association between dietary dioxins + DL-PCBs and estimated waist circumference change (Model 3) using restricted cubic splines with four knots (5th:17.78, 35th: 31.86, 65th: 44.02, 95th: 67.26 pg TEQ/day); analysis limited to 0–90th percentile of intake ( $P$  non-linearity<0.001).

**Table 3**

Association between dietary intake of dioxins + DL-PCBs (pg TEQ/d) and NDL-PCBs (ng/d) and estimated waist circumference change (cm/5y) (N = 99,046) in EPIC.

	Model 1	Model 2	Model 3
Beta (95 % CI)			
Dioxins + DL-PCBs			
Restricted cubic spline ( $P$ -overall*)	<b>0.001</b>	<b>0.001</b>	<b>&lt;0.001</b>
Quartiles			
Q1	<b>0.00 (Ref.)</b>	<b>0.00 (Ref.)</b>	<b>0.00 (Ref.)</b>
Q2	<b>-0.17 (-0.27, -0.07)</b>	<b>-0.18 (-0.28, -0.08)</b>	<b>-0.19 (-0.29, -0.09)</b>
Q3	<b>-0.32 (-0.27, -0.07)</b>	<b>-0.34 (-0.45, -0.23)</b>	<b>-0.35 (-0.46, -0.24)</b>
Q4	<b>-0.39 (-0.50, -0.27)</b>	<b>-0.42 (-0.55, -0.30)</b>	<b>-0.44 (-0.56, -0.31)</b>
$P$ trend	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>
NDL-PCBs			
Restricted cubic spline ( $P$ -overall*)	<b>0.001</b>	<b>0.001</b>	<b>&lt;0.001</b>
Quartiles			
Q1	0.00 (Ref.)	0.00 (Ref.)	0.00 (Ref.)
Q2	0.08 (-0.06, 0.18)	0.05 (-0.06, 0.15)	0.05 (-0.06, 0.15)
Q3	<b>0.12 (0.02, 0.23)</b>	0.07 (-0.05, 0.18)	0.07 (-0.05, 0.18)
Q4	<b>-0.14 (-0.26, -0.02)</b>	<b>-0.20 (-0.34, -0.07)</b>	<b>-0.21 (-0.34, -0.07)</b>
$P$ trend	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>

Model 1: Stratified by centre adjusted for age, BMI at baseline and sex.

Model 2: Model 1 + smoking, alcohol, education level, physical activity, and follow-up duration.

Model 3: Model 2 + total energy intake without alcohol and rMED score.

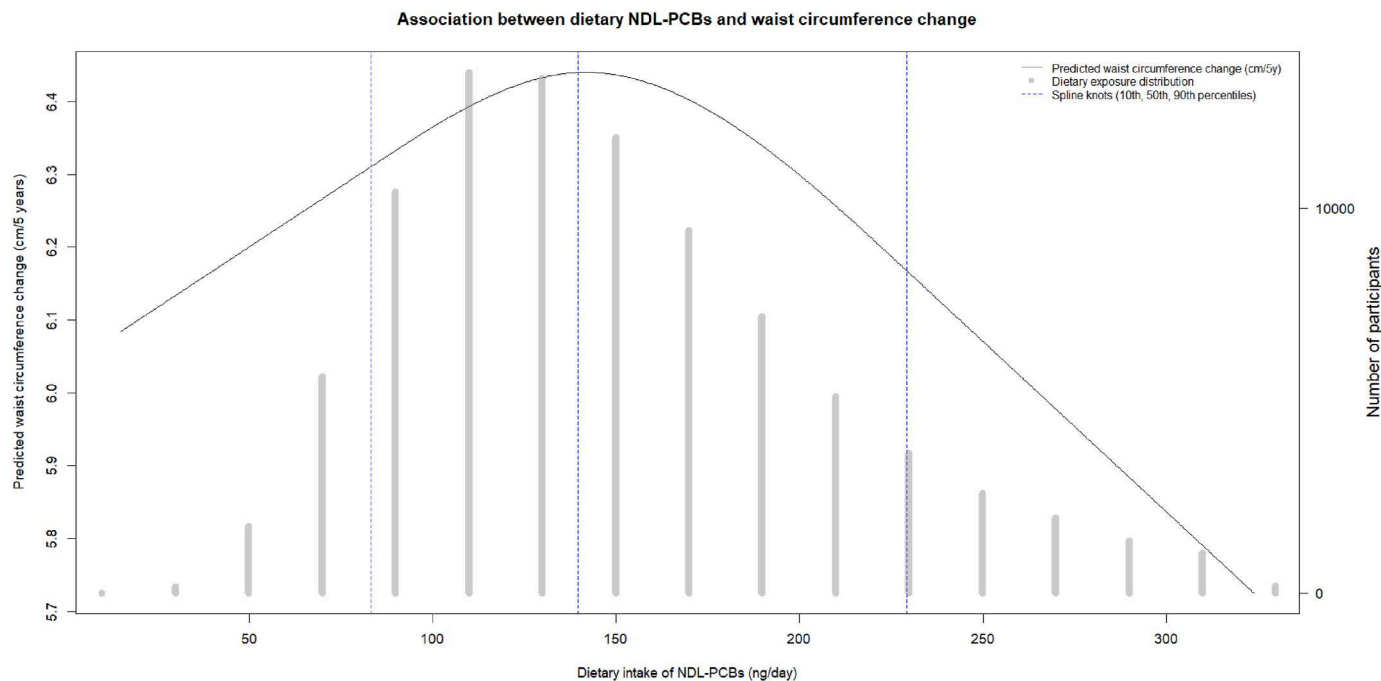
\*  $P$ -values for overall association corresponds to the test of all terms of the exposure variable (i.e., linear and non-linear terms); they are reported only when non-linear associations are detected; Restricted cubic spline plot is shown in [Figure 4](#) and [5](#).

association between dietary intake of dioxins + DL-PCBs/NDL-PCBs and waist circumference change was only observed in Denmark, which accounted for 44 % of the population included in the analysis ( $I^2 = 86 \%$ ,  $P < 0.01$ ) ([Fig. 7](#)). Considerable heterogeneity across countries was observed for both outcomes.

These associations were further assessed according to the median follow-up time ([Table 4](#)). The association between the intake of dioxins + DL-PCBs/NDL-PCBs and the 5-year weight change remained positive and significant and appeared stronger when the follow-up period lasted more than median (5.51 y). Regarding waist circumference change, different associations were observed depending on the follow-up duration. Specifically, when the follow-up duration was shorter than the median, the association remained inverse. However, when the follow-up duration was longer than the median, no association was found between

dioxins + DL-PCBs and waist circumference change, while a positive association was found for NDL-PCBs and waist circumference change. In the analyses stratified by median follow-up, participants from Denmark accounted for 31.04 % of those with follow-up durations shorter than 5.51 years (weight change). Furthermore, all Danish participants had follow-up durations of less than 8.91 years, representing 88.34 % of the group with follow-up durations shorter than the median for waist circumference change.

Moreover, when analyses were stratified by sex, the associations appeared stronger among women than men for both outcomes ([Supp Table 4](#)). Regarding waist circumference change, no association was observed in men ([Supp Table 4](#)). Stratification by baseline BMI (4 groups; underweight normal weight, overweight, obesity) showed that associations remained consistent with the main analyses for participants with a BMI above 18.5 kg/m<sup>2</sup>.



**Fig. 5.** Association between dietary NDL-PCBs and estimated waist circumference change (Model 3) using restricted cubic splines with three knots (10th: 83.30, 50th: 139.61, 90th: 229.14 ng/day); analysis limited to 0–90th percentile of intake ( $P$  non-linearity = 0.001).

However, no association was found between dioxins + DL-PCBs and either weight or waist circumference change in participants with a BMI below 18.5 kg/m<sup>2</sup> (data not shown). Results were similar to those from the main analyses when stratified by abdominal obesity and age groups (data not shown).

#### 4. Discussion

This large prospective study provides new evidence that dietary exposure to dioxins and/or PCBs may contribute to long-term weight changes in European adults. Specifically, higher dietary intakes of NDL-PCBs were consistently associated with modest weight gain over five years, while associations with waist circumference showed marked geographic heterogeneity, with inverse associations observed primarily in Denmark.

In the present study, a positive association was also observed between intakes of NDL-PCBs and weight gain (0.23 kg/5y). Although data on NDL-PCBs remain limited, our findings align with most previous studies reporting positive associations between NDL-PCB exposure and weight gain [9,29], although other studies did not [30].

Similarly, the obtained results suggest that individuals in the highest dioxins + DL-PCBs group experienced a 0.07 kg/5 y greater increase in weight than individuals in the lowest quartile group, although this association was characterized by a U-shape. These findings are consistent with previous *in vitro* and *in vivo* studies that have demonstrated the obesogenic effects of dioxins and DL-PCBs. Dioxins and DL-PCBs can activate the aryl hydrocarbon receptor, disrupting lipid metabolism, and potentially promoting adiposity and long-term weight gain [3,31]. Exposure to dioxins and DL-PCBs may also be linked with impair glucose metabolism and lead to elevated glycated hemoglobin A1c concentrations, which may further contribute to weight gain [32]. Several studies have also reported positive associations between dioxins or DL-PCBs and the risk of obesity [9–11], although one found no

relationship between serum PCBs concentrations and obesity [14]. Another study highlighted the specific contribution of certain congeners, such as 1,2,3,4,6,7,8-HpCDD, to the risk of obesity [32].

In our main analyses, non-linear associations were found between dioxins and/or PCBs intakes and waist circumference change. In particular, a U-shaped association was observed between dioxins + DL-PCBs dietary intake and waist circumference change. These results are not completely in line with previous studies which have reported positive associations between waist circumference or abdominal obesity and serum concentrations of all PCBs [33], dioxins or DL-PCBs [12,13,32,34]. In addition, in the present study NDL-PCBs intake presented an inverted U-shaped association with waist circumference. In a previous study including 98 individuals with obesity, negative correlations were observed between waist, BMI, fat mass percentage and abdominal adipose tissue and serum levels of NDL-PCBs and sum of PCBs [35]. An inverted U-shaped association between serum NDL-PCBs and the risk of metabolic syndrome was also observed in another study [13]. These non-linear associations may reflect dual biological effects of dioxins and/or PCBs, different exposure levels show different effect on fat accumulation or metabolic dysfunction [36]. Nevertheless comparison with previous studies is not easy since most previous studies measured PCBs concentrations in the blood, which probably reflect overall body burden, but may be influenced by several factors, such as age, sex, and ethnicity [37]. Furthermore, studies differed in terms of study design, study population, adjusted confounders, exposure levels, compositions of the mixtures, and follow-up duration. While these factors may partly explain the discrepancies in the findings, they also complicate direct comparisons among studies, even when similar associations are observed.

While weight gain is generally linked to increased health risks, an annual change of less than 0.2 kg may be considered relatively stable [38]. Waist circumference is recognized as a stronger indicator of health risks than weight alone [39], and an increase of

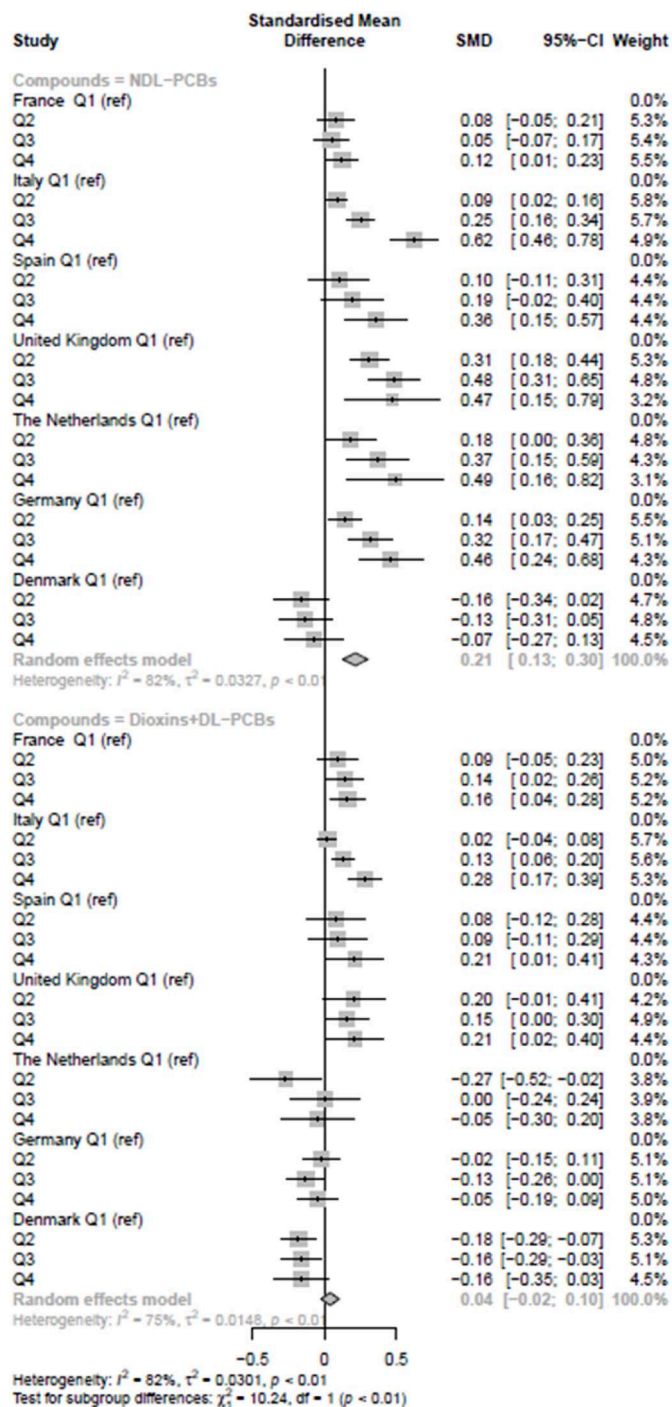


Fig. 6. Forest plot presenting the between dietary intake of dioxins + DL-PCBs (pg TEQ/d) and NDL-PCBs (ng/d) and estimated weight change (kg/5y) stratified analyses by EPIC country.

5 cm or more in waist circumference related to a higher risk of mortality [40,41]. In this study, although the associations were statistically significant, the observed effect sizes for both outcomes are relatively small and may be influenced by measurements errors. While these effect sizes suggest limited clinical relevance, it has to be considered that, at the population scale, even small shifts in weight or waist circumference distributions may have meaningful public health impacts. Moreover, although our exposure assessment focussed on the most relevant congeners, there were

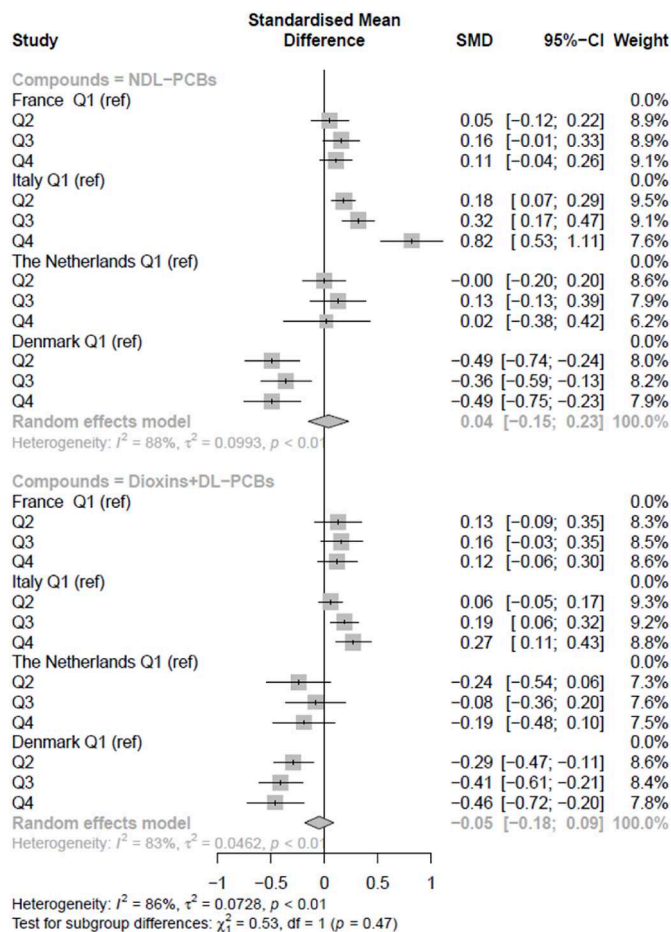


Fig. 7. Forest plot presenting the between dietary intake of dioxins + DL-PCBs (pg TEQ/d) and NDL-PCBs (ng/d) and estimated waist circumference change (cm/5y) stratified analyses by EPIC country.

still some additional congeners not included in the analyses, which may have led to an underestimation of overall effects. Given the widespread and lifelong exposure to dioxins and PCBs, the present results highlight the need for continued attention to dioxins and PCB's potential long-term health effects.

Stratified and sensitivity analyses revealed that the significant inverse association between dietary intakes of dioxins and/or PCBs and waist circumference change was primarily driven by participants from Denmark, who accounted for 44 % of the total study population. In all other countries, higher intake of dioxins and/or PCBs intake were either not associated with changes in waist circumference or were linked to an increase in waist circumference. The factors underlying this divergent association in Denmark remain unclear. Danish participants in the cohort were older and had shorter follow-up periods compared to those from other countries. However, stratified analyses based on age and follow-up duration did not reveal significant variations, suggesting that these factors do not fully explain the discrepancy. The first possibility relates to dietary habits in Denmark. A previous study within the EPIC cohort noted that the Danish and Norwegian populations had the highest consumption of fish products among the included countries, with approximately 50 % of the fish consumption in Denmark being fatty or very fatty fish (fat 14g/100g or more) [42]. The consumption of fatty fish corresponds to high intake of n-3 PUFAs, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) [42], which have been suggested to reduce waist

**Table 4** Association between dietary intake of dioxins + DL-PCBs (pg TEQ/d) and NDL-PCBs (ng/d) and estimated weight (kg/5y) or waist circumference change (cm/5y) in EPIC stratified by median follow-up.

	Weight change (5.51 years)		Waist circumference change (8.91 years)	
	Follow-up less than median (n = 107,799)		Follow-up more than median (n = 49,525)	
	Follow-up less than median (n = 107,757)	Follow-up more than median (n = 49,521)	Follow-up less than median (n = 107,757)	Follow-up more than median (n = 49,521)
<b>Dioxins + DL-PCBs</b>				
Restricted cubic spline (P-overall*)	<b>0.001</b>	-	<b>0.01</b>	<b>0.01</b>
Continuous (per 1 SD increment)	0.00 (Ref.)	<b>0.03 (0.01, 0.06)</b>	0.00 (Ref.)	0.00 (Ref.)
Quartiles				
Q1	-0.05 (-0.15, 0.04)	0.01 (-0.05, 0.07)	<b>-0.27 (-0.45, -0.11)</b>	0.04 (-0.05, 0.13)
Q2	-0.06 (-0.16, 0.04)	0.03 (-0.04, 0.09)	<b>-0.42 (-0.60, -0.23)</b>	0.09 (-0.01, 0.18)
Q3	0.04 (-0.07, 0.16)	0.04 (-0.03, 0.11)	<b>-0.48 (-0.72, -0.24)</b>	0.01 (-0.09, 0.11)
Q4	0.27	0.20	<b>&lt;0.001</b>	0.98
P trend				
<b>NDL-PCBs</b>				
Restricted cubic spline (P-overall*)	<b>0.001</b>	<b>0.001</b>	<b>0.02</b>	<b>0.01</b>
Continuous (per 1 SD increment)	1.00 (Ref.)	0.00 (Ref.)	0.00 (Ref.)	0.00 (Ref.)
Quartiles				
Q1	0.10 (-0.01, 0.20)	<b>0.12 (0.07, 0.18)</b>	<b>-0.26 (-0.46, -0.06)</b>	<b>0.10 (0.02, 0.18)</b>
Q2	<b>0.15 (0.05, 0.26)</b>	<b>0.26 (0.19, 0.32)</b>	-0.17 (-0.38, 0.03)	<b>0.17 (0.07, 0.27)</b>
Q3	<b>0.28 (0.15, 0.40)</b>	<b>0.32 (0.23, 0.40)</b>	<b>-0.40 (-0.65, -0.16)</b>	<b>0.17 (0.06, 0.28)</b>
Q4	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>0.003</b>	<b>0.004</b>
P trend				

circumference [43]. Nevertheless, in the present study, the results of the sensitivity analyses, which were further adjusted for fish intake, fat intake, and PUFA intake were comparable to those of the main analyses. Furthermore, during the EPIC data collection period, the intake of industrially produced trans fatty acids (TFA) started to decline [44]. Positive associations between TFAs and weight gain have been reported, although previous research in the Danish population did not find such links [45]. Another hypothesis is that these inverse associations may partly reflect cancer-related weight loss, given that Denmark has reported higher cancer incidence rates than some other European countries over recent decades [46]. While both dietary factors and reduced TFA exposure may have contributed to the observed inverse associations in Denmark, further investigation is needed to clarify these findings.

#### 4.1. Strengths and limitations

Several limitations need to be considered when interpreting the results of the present study. First, in the EPIC cohort, dietary intakes were assessed at baseline using self-administrated questionnaires, which may be subject to memory or psychological biases, potentially leading to over- or underestimation and measurement errors [47]. Nevertheless, the questionnaires used in the EPIC cohort were validated to address potential misestimations in dietary assessment and have been shown to provide reliable estimates for main food sources of dioxins and PCBs, including fish, meat, and dairy products [18]. Second, in most centres, follow-up weights and waist circumferences were self-reported, and individuals who are overweight or obese tend to under-report their weight. Nevertheless, self-reported and measured anthropometric data generally show high correlations and are considered reasonably valid [48]. Similarly, strong correlations between self-reported and measured weights and waist circumferences have been reported in the EPIC-Oxford cohort [25]. In addition, the prospective design of this study ensures that such measurement errors are likely to be non-differential, potentially attenuating the real association between the extreme exposure and the outcome of interest, while their effect on the analysis of middle exposure may bias the results in either direction. Third, food contamination data from EFSA were not matched with food consumption data at a country level. This discrepancy could potentially introduce exposure classification bias. However, we assume a similar food market across European countries, where individuals consume both locally produced and imported foods. Moreover, dietary information was collected in the 1990s, which does not fully align with the food contamination data gathered between 2000 and 2018. Nevertheless, the widespread presence, bio-accumulative nature, and long half-lives of dioxins and PCBs likely minimize the potential exposure misclassification due to changes in food contamination levels [6]. Furthermore, the results of our sensitivity analysis were consistent regardless of the time period in which the food contamination data were collected. Fourth, the EPIC cohort is not representative of the general European population, which may limit the generalizability of our findings. In addition, despite adjusting for several confounding factors, our results may still be influenced by residual confounders, such as exposure to other contaminants and dietary components.

The present study also has several strengths. First, the large sample size and diverse range of exposure allowed for more precise estimations of associations and enabled sensitivity and subgroup analyses, which further confirmed the associations between dietary intake of dioxins and PCBs and weight change. By including participants from seven European countries, this study captures a broad spectrum of dietary habits, reflecting significant heterogeneity in dioxin and PCB intake, which contributes to

considerable exposure contrast. Furthermore, this study evaluated dietary intakes of dioxins and PCBs using the EFSA food contamination dataset, which provides a representative of food contamination levels across Europe.

## 5. Conclusion

This large prospective study provides evidence that dietary exposure to both dioxins + DL-PCBs and NDL-PCBs may play a role in long-term weight regulation in European populations. Although the observed associations were modest and we cannot fully exclude the influence of measurement error, the consistency across multiple stratified and sensitivity analyses strengthens the validity of the findings. The findings also highlight geographic differences, in particular the inverse association observed in Denmark. Further studies are needed to clarify the underlying biological mechanisms, potential modifying role of dietary patterns and residual confounding. These findings also suggest that, despite the regulation those POPs remain present in the food chain, highlighting the need for continued efforts to reduce exposure and prevent obesity and related chronic conditions.

### Patient consent

All participants provided written informed consent to participate in the EPIC study.

### Ethical approval

This study was approved by the ethics committee of IARC and all study centres.

### Data sharing statement

EPIC data and biospecimens are available for investigators who seek to answer important questions on health and disease in the context of research projects that are consistent with the legal and ethical standard practices of the International Agency for Research on Cancer (IARC), WHO, and the EPIC centres. The primary responsibility for accessing the data, obtained in the frame of the present publication, belongs to the EPIC centres that provided them. The use of a random sample of anonymised data from the EPIC study can be requested by contacting [epic@iarc.fr](mailto:epic@iarc.fr). The request will then be passed on to members of the EPIC Steering Committee for deliberation and approval.

### Contributors

XR, FRM, IH conceived the study and defined the analytical strategy. XR performed statistical analyses and provided preliminary interpretation of findings. XR and the writing group (IH, FRM, GN) drafted the manuscript. All authors critically interpreted the results, revised the manuscript, provided relevant intellectual input, and read and approved the final manuscript. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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### Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors used ChatGPT (GPT-5, OpenAI, 2025) to assist with grammar checking.

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### Conflict of interest

We declare no conflicts of interest.

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## Appendix A. Supplementary data

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