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Dietary intake of polychlorinated dibenzo-p-dioxins and furans, adiposity and obesity status.

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Abbreviations: CVD, Cardiovascular diasease; EDC, Endocrine disrupting chemicals; EFSA, European Food Safety Authority; er-MedDiet, energy-reduced Mediterranean diet; FFQs, food frequency questionnaires; OR, odds ratios; PCDD/Fs, polychlorinated dibenzo-p-furans; PREDIMED-Plus, PREvención con DIeta MEDiterránea; PRs, prevalence ratios; TCDD/F, 2,3,7,8-tetrachlorodibenzo-p-dioxin/furan; TEQ, Toxic Equivalents; TWI, Tolerable weekly intake; WHO, World Health Organization; BMI, Body Mass Index; MET, Metabolic Equivalent of Task.

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A R T I C L E I N F O

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A B S T R A C T

Introduction: The principal source of exposure to Polychlorinated dibenzo-p-dioxins and polychlorinated dibenzo-p-furans (PCDD/Fs) in humans comes from food intake. PCDD/Fs, are a family of potential endocrine disruptors and have been associated with different chronic diseases such as diabetes and hypertension. However, studies assessing the relationship between dietary exposure to PCDD/Fs and adiposity or obesity status in a middle-aged population are limited.

Objective: To assess cross-sectionally and longitudinally the associations between estimated dietary intake (DI) of PCDD/Fs and body mass index (BMI), waist circumference, and the prevalence/incidence of obesity and abdominal obesity in a middle-aged population.

Methods: In 5899 participants aged 55–75 years (48% women) living with overweight/obesity from the PREDIMED-plus cohort, PCDD/Fs DI was estimated using a 143-item validated food-frequency questionnaire, and the levels of food PCDD/F expressed as Toxic Equivalents (TEQ). Consequently, cross-sectional and prospective associations between baseline PCDD/Fs DI (in pgTEQ/week) and adiposity or obesity status were assessed at baseline and after 1-year follow-up using multivariable cox, logistic or linear regression models.

Results: Compared to participants in the first PCDD/F DI tertile, those in the highest tertile presented a higher BMI (β-coefficient [confidence interval]) (0.43kg/m2 [0.22; 0.64]; P-trend <0.001), a higher waist circumference (1.11 cm [0.55; 1.66]; P-trend <0.001), and a higher prevalence of obesity and abdominal obesity (1.05 [1.01; 1.09] and 1.02 [1.00; 1.03]; P-trend = 0.09 and 0.027, respectively). In the prospective analysis, participants in the top PCDD/F DI baseline tertile showed an increase in waist circumference compared with those in the first tertile after 1-year of follow-up (β-coefficient 0.37 cm [0.06; 0.70]; P-trend = 0.015).

Conclusion: Higher DI of PCDD/Fs was positively associated with adiposity parameters and obesity status at baseline and with changes in waist circumference after 1-year of follow-up in subjects living with overweight/obesity. Further large prospective studies using a different population with longer follow-up periods are warranted in the future to strengthen our results.

1. Introduction

Nowadays, overweight and obesity are a major public health concern worldwide, with nearly one out of every three adults (30.7%) are living with overweight and more than two out of five adults (42.4%) are living with obesity (Ogden et al., 2021). In addition, in the next two decades, a potential 120% increase in the prevalence of severe obesity is estimated to occur (Finkelstein et al., 2012). Studies also have shown that obesity is associated with the onset of chronic diseases, such as cardiovascular diseases (CVD) and some types of cancer, but also premature death (Matsunaga et al., 2022; Célind et al., 2022; MacMahon et al., 2009).

It is well established that obesity is a complex and multidimensional condition caused by the interaction of several factors such as diet, physical activity and other behavioral factors, genetic predisposition and environmental exposures (Qasim et al., 2018; Sun et al., 2017; Ramos-Lopez et al., 2021). While some factors are already long studied and well-known, those concerning environmental exposure, specifically endocrine disrupting chemicals (EDCs) in our daily life have just started to gain important consideration (Street et al., 2018).

EDCs are synthetic compounds capable of binding to cell receptors and mimicking or blocking the functioning of natural hormones, thus could cause adverse health effects (Lauretta et al., 2019; Diamanti-Kandarakis et al., 2009). They can be bio-accumulated in the human body from the food chain. Consequently, they can be also referred to as persistent organic pollutants (Van den Berg et al., 1994). Among the most hazardous ones, the Polychlorinated dibenzo-p-dioxins and polychlorinated dibenzo-p-furans (PCDD/Fs) are considered to pose serious risks for humans (Srogi, 2008). The sources of PCDD/Fs were described either from their natural occurrence in some food manufacture, agricultural practices, industrial applications and atmospheric deposition into the food chain. The most relevant reported exposure to PCDD/Fs worldwide comes from the consumption of food, being meat, dairy, and fish products as the main contributors, accounting for almost 98% of human exposure (Air Quality Guidelines for Europe Second Edition, 2000; Fries, 1995). These EDCs could reach the human body and become significant because of chronic exposure and the tendency of these contaminants to accumulate due to their high metabolic stability, lipid solubility in the body, and resistance to degradation (Srogi, 2008; Schuhmacher et al., 1999).

There is a growing body of evidence coming from the literature

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examining the associations between exposure to PCDD/Fs and the risk of insulin resistance (Chang et al., 2016a), diabetes (Fierens et al., 2003), metabolic syndrome (Uemura et al., 2009a) or CVD (Donat-Vargas et al., 2020). However, the epidemiological evidence in middle-aged people is limited and mostly cross-sectionally analysed. Moreover, most of the studies conducted until now have not specifically assessed dietary exposure to PCDD/Fs.

Given the public health burden of the obesity epidemic and the increasing health effects of dietary exposure to these EDCs could cause, it is essential to understand and better delimitate potential associations between these compounds in everyday life and the risk of obesity or other related non-communicable diseases. We hypothesized that high exposure to dioxins and furans through the diet may have a relationship with adiposity and obesity development, therefore, the aim of the present study was to cross-sectionally and prospectively assess the associations between the estimated dietary intake of PCDD/Fs and adiposity or obesity risk in a middle-aged Spanish Mediterranean cohort. This will provide new insights to grow the evidence and to implement public health strategies in the future.

2. Materials and methods

2.1. Study population and design: the PREDIMED-plus study

A cross-sectional and prospective analysis was conducted using the data of the PREDIMED-Plus (PREvención con DIeta MEDiterránea) cohort. The PREDIMED-Plus study is a randomized and ongoing controlled trial, conducted in 23 Spanish centres with the objective to compare the effect of an intensive weight loss intervention based on an energy-reduced Mediterranean diet -er-MedDiet-, physical activity promotion, and behavioral support (intervention group), to an intervention consisting in recommending a non-caloric reduced MedDiet following usual care advice (control group), on the incidence of CVD and mortality. More available details of the PREDIMED-Plus study can be found at https://www.predimedplus.com and have been described elsewhere (Sayón-Orea et al., 2019; Salas-Salvadó et al., 2019). Participants were recruited (between October 2013 and December 2016) in Spain. A total of 6874 participants were randomly assigned to the intervention group or the control group in a 1:1 ratio. Eligible participants are living with overweight or obesity (BMI = 27–40 kg/m^2), men and women aged 55–75 years without documented history of CVD, who met at least three of the following metabolic syndrome criteria: a) waist circumference of more than 102 cm in men and more than 88 cm in women; b) serum triglycerides equal to or more than 150 mg/dl or drug treatment for elevated triglycerides; c) HDL-c less than 40 mg/dl in men and less than 50 mg/dl in women or drug treatment for low HDL-cholesterol; d) blood pressure equal or higher than 130/85 mmHg or antihypertensive drug treatment; e) and fasting plasma glucose level equals or more than 100 mg/dl or hypoglycemic treatment. Extensive descriptions of inclusion and exclusion criteria can be found elsewhere (Martínez-González et al., 2019). All subjects provided written informed consent, and the final project protocol was approved by the ethical review boards of each centre involved. Participants without complete food frequency questionnaires (FFQs) at baseline and after 1-year of follow-up or those with an energy intake outside the pre-specified energy limits (less than 500 and more than 3500 kcal/day, and less than 800 and higher than 4000 kcal/day in women and men respectively) and participants without data for BMI and waist circumference after 1 year of follow-up n = 22 were excluded (Supplementary Material, File S1). Participants included (n = 5899) in the present study showed no differences in sociodemographic, dietary, and biomedical characteristics compared to the total randomized PREDIMED-plus participants (n = 6874) (Supplementary Material, Table S1).

2.2. Theory and calculation of the dietary intake assessment

Validated face-to-face baseline FFQs were administrated to our study cohort population by trained staff (De La Fuente-Arrillaga et al., 2010). The participants documented their average frequency and quantity of consumption for 143 food and beverage items over the preceding year. The frequency of consumption was shown through nine categories ranging from never or almost never, one to three times per month, once per week, two to four times per week, five to six times per week, once per day, two to three times per day, four to six and more than 6 times per day.

The dietary intake was estimated using the frequency of consumption previously mentioned and the levels of the PCDD/F expressed as Toxic Equivalents (TEQ). The TEQ is established by the World Health Organization (WHO) (Van den Berg et al., 2006) to assess total PCDD/F exposure by the sum of an individual's congener concentration multiplied by their relative toxicity factor. This factor's scale ranges from [0 to 1], where 0 corresponds to the less toxic compound and the value of 1 corresponds to 2,3,7,8-tetrachlorodibenzo-p-dioxin/furan (TCDD/F) which is the most toxic PCDD/F known (Van den Berg et al., 2006).

The TEQ for each food item was obtained from the most updated published studies with a first priority for studies from the Mediterranean region since our participants are from Spain and they technically follow a Mediterranean diet. Therefore, the hierarchy rule followed to gather the TEQ for each food item was: data from Spain > data from other Mediterranean countries > Europe > other available data (Supplementary Material, Table S2).

TEQ data was available for most products and reported as pg TEQ/g (on a fresh weight basis). For some particular food products, the TEQ/g was estimated (as an average) from related food items as previously performed by other studies such as Kiviranta et al., 2001 (Supplementary material, Table S2). Alcoholic beverages and coffee were excluded from the dietary intake assessment since they generally contain very low levels of PCDD/Fs and will, therefore, add little to the total dietary TEQ intake (Air Quality Guidelines for Europe Second Edition, 2000; Kiviranta et al., 2001).

The estimated dietary intake of PCDD/F (expressed in TEQ pg/week) was the sum of each TEQ (in TEQ pg/day) from a specific food item multiplied by the amount of each specific food consumed for each participant (in g/day) multiplied by seven considering the following equation:

$$\textit{Dietary intake of PCDD/F}_{(pg\ /week)} = (\sum TEQ_i * A_i) * \quad 7$$

Where TEQ_i *represents the toxic equivalency of a specific food item (in pg* PCDD/F/*g),* A_i *represents the amount of a specific food consumed (in g/day) and it was multiplied by 7 to obtain the weekly dietary intake of PCDD/F in pg TEQ/week.*

2.3. Estimation of dietary exposure to PCDD/Fs

Dietary exposure to dioxins and furans was estimated according to the following equation:

$$\text{Dietary exposure to PCDD/F}_{(\text{pg/kg of body weight/week})} = (\sum \text{TEQ}_i * \text{A}_i * 7) / \text{BW}_i$$

Where TEQi represents the toxic equivalency of a specific food item (in pg PCDD/F/g), Ai represents the amount of a specific food consumed (in g/day), BWi represents the body weight (kg) of each participant, and the result was multiplied by 7 to obtain the weekly dietary exposure of PCDD/F in pg TEQ/Kg of body weight/week.

3. Outcomes

Measurements of different anthropometric variables at baseline and 1 year of follow-up were assessed by PREDIMED-Plus staff. Body weight was measured twice with light clothes using high-quality electronic

calibrated scales, and the mean of both measurements were used. Height was measured using a wall-mounted stadiometer. Waist circumference was measured midway between the lowest rib and the iliac crest using an anthropometric tape. Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of height in meters. On one hand, obesity was defined when BMI was higher than or equal to 30 kg/m^2. On the other hand, abdominal obesity was defined when waist circumference was higher than or equal to 88 cm for women and higher than or equals to 102 cm for men (Alberti et al., 2009). Therefore, the prevalence of obesity and abdominal obesity were defined as participants having higher levels of BMI and waist circumference at baseline than those indicated above. In addition, the incidence of obesity and abdominal obesity were defined when participants did not present these conditions (obesity and abdominal obesity) at baseline but showed higher levels of BMI and waist circumference than those indicated above after 1-year of follow-up.

4. Assessment of covariates

Covariates were evaluated using general face-to-face questionnaires that collect information on lifestyle (smoking habits and physical activity), socio-demographics (sex, marital status, age, and level of education), history of type 2 diabetes, hypertension, hypercholesterolemia, and medication use. A validated Minnesota-REGICOR Short Physical Activity questionnaire was used to assess the physical activity (Molina et al., 2017). In addition, adherence to the traditional MedDiet was using a validated 14-item MEDAS questionnaire was provided (Schröder et al., 2011).

4.1. Statistical analyses

For the statistical analyses, the PREDIMED-Plus database updated in December 2020 was used. Descriptive baseline sociodemographic, dietary, and biomedical characteristics by tertiles of energy-adjusted PCDD/F intake are shown in Table 1, and expressed as mean ± SD for continuous variables and percentages (number) for categorical variables.

The dietary intake of PCDD/F (expressed in TEQ pg/week) was adjusted for total energy intake using the residual-regression method (Willett and Stampfer, 1986) and categorized in tertiles of energy-adjusted (TEQ pg/week) corresponding to lower (first tertile), intermediate (second tertile), and higher (third tertile) dietary intake of PCDD/F. The Chi-square test for categorical variables and one-way ANOVA for continuous variables were used to compare the baseline characteristics across the tertiles.

Linear regression models were fitted to cross-sectionally assess the associations [β-coefficient (95% confidence interval (CI)] between energy-adjusted dietary intake of PCDD/F and adiposity parameters (BMI and waist circumference) at baseline. We also used linear regression models to explore the prospective associations between baseline energy-adjusted PCDD/F and changes in BMI and waist circumference after 1 year of follow-up.

Cox proportional hazards regression with a robust variance estimator and constant follow-up time (t = 1) were fitted to estimate prevalence ratios (PRs) and 95% confidence interval (95% CI) for the prevalence of obesity and abdominal obesity across tertiles of energy-adjusted dietary intake of PCDD/F. This method has been described to be more appropriate than logistic regression in cross-sectional studies when the outcome prevalence is >10%, as odds ratios (OR) could overestimate or underestimate the risk in logistic regression (Barros and Hirakata, 2003).

Logistic regression models were also fitted to estimate the Odd Ratio (OR) and 95% confidence interval (95% CI) for the incidence of obesity and abdominal obesity across tertiles of energy-adjusted dietary intake of PCDD/F. To assess the linear trend, the median values for each tertile of PCDD/F dietary intake were assigned and used as continuous

Table 1
Characteristics of included participants overall and across energy-adjusted total PCDD/F dietary intake tertiles.

	All	Energy-adjusted total PCDD/F dietary intake – (TEQ pg/week)			
		T1 n=1,970	T2 n=1,964	T3 n=1,965	P-value
Energy adjusted total PCDD/F dietary intake (TEQ pg/week) **range**	73.6 - 496	73.6 - 223	224 - 271	272 - 496	<0.001
Sex					
Women	48.3 (2,847)	39.6 (781)	49.1 (965)	56.0 (1,101)	<0.001
Age (years) (n=5,899)	65.0 ± 4.90	65.0 ± 5.00	65.1 ± 4.90	64.9 ± 4.80	0.72
Educational level (n=5,899)					
Up to primary	49.7 (2,931)	48.0 (945)	50.0 (981)	51.1 (1,005)	0.196
Secondary	28.8 (1,696)	29.0 (572)	29.4 (578)	27.8 (546)	
University	21.5 (1,272)	23.0 (453)	20.6 (405)	21.1 (414)	
Marital status (n=5,899)					
Single	12.5 (738)	14.8 (291)	11.9 (234)	10.8 (213)	0.001
Married	77.1 (4,546)	76.0 (1,498)	77.4 (1,520)	77.8 (1,528)	
Widowed	10.4 (615)	9.20 (181)	10.7 (210)	11.4 (224)	
Smoking status (n=5,899)					
Never	44.7 (2,636)	40.1 (791)	45.3 (890)	48.6 (955)	<0.001
Former	43.0 (2,535)	46.0 (905)	42.2 (829)	40.8 (801)	
Current	12.3 (728)	14.0 (274)	12.5 (245)	10.6 (209)	
Physical activity (MET min/week) (n=5,899)	2509 ± 2325	2454 ± 2306	2464 ± 2291	2610 ± 2375	0.06
Waist circumference (cm) (n=5,899)					
Men	110 ± 8.70	110 ± 8.70	111 ± 9.00	111 ± 8.40	0.06
Women	103 ± 9.20	103 ± 9.20	103 ± 8.90	104 ± 9.30	0.06
BMI (kg/m^2) (n=5,899)	32.5 ± 3.40	32.2 ± 3.30	32.5 ± 3.50	32.7 ± 3.50	<0.001
Intervention group (%)	48.9	49.6	49.6	47.7	0.34
Energy-reduced Mediterranean diet adherence (0-14 points) (n=5,899)	8.18 ± 1.94	7.88 ± 1.97	8.24 ± 1.83	8.42 ± 1.96	<0.001
Dietary assessment (n=5,899)					
Fruits and vegetables (g/d)	666 ± 260	605 ± 194	676 ± 266	747 ± 315	<0.001
Legumes (g/d)	20.6 ± 11.0	20.1 ± 11.5	20.3 ± 10.2	21.3 ± 11.4	0.001
Total cereals (g/d)	151 ± 78.0	170 ± 87.5	144 ± 71.0	136 ± 70.5	<0.001
Unrefined cereals (g/d)	41.0 ± 63.2	38.3 ± 68.9	40.3 ± 60.1	44.4 ± 60.2	0.009
Dairy products (g/d)	345 ± 201	345 ± 207	334 ± 188	353 ± 205	0.009
Red meat and derivatives (g/d)	82.3 ± 44.8	73.7 ± 43.8	77.2 ± 39.2	95.9 ± 47.8	<0.001
White meat (g/d)	62.0 ± 34.0	47.6 ± 28.0	63.9 ± 30.5	74.4 ± 37.6	<0.001
Fish and shellfish (g/d)	102 ± 47.4	82.5 ± 40.4	102 ± 42.2	122 ± 50.0	<0.001
Virgin olive oil (g/d)	31.9 ± 20.8	30.9 ± 20.8	32.4 ± 20.7	32.6 ± 20.5	0.02
Total energy (Kcal/d)	2367 ± 550	2422 ± 578	2293 ± 522	2386 ± 541	<0.001

(*continued on next page*)

Table 1 (*continued*)

	All	Energy-adjusted total PCDD/F dietary intake – (TEQ pg/week)			
		T1 n=1,970	T2 n=1,964	T3 n=1,965	P-value
Proteins (g/d)	97.7 ± 22.0	90.2 ± 20.5	95.4 ± 19.6	107 ± 22.0	<0.001
Saturated fatty acids (g/d)	26.2 ± 8.40	26.4 ± 8.90	25.4 ± 7.80	26.8 ± 8.49	<0.001
Polyunsaturated fatty acids (g/d)	18.0 ± 6.5	17.8 ± 6.86	17.6 ± 6.24	18.5 ± 6.46	<0.001
Carbohydrates (g/d)	241 ± 72.7	257 ± 76.3	231 ± 66.9	234 ± 71.4	<0.001
Dietary fibre (g/d)	26.1 ± 8.7	25.2 ± 8.73	25.6 ± 8.17	27.6 ± 9.05	<0.001
Total sugar (g/d)	6.70 ± 12.0	8.63 ± 13.3	6.04 ± 11.2	5.56 ± 11.0	<0.001
Obesity prevalence					
Yes	72.7 (4,286)	71.6 (1,411)	71.5 (1,405)	74.8 (1,470)	0.03
Abdominal obesity prevalence					
Yes	93.1 (5,490)	92.0 (1,812)	92.4 (1,815)	94.8 (1,863)	0.001
Hormonal treatment (n=5,899)					
Yes	2.23 (131)	1.94 (38)	2.55 (50)	2.19 (43)	0.42

Abbreviations: PCCD/F: Polychlorinated dibenzo-p-dioxins or dibenzofurans; TEQ: Toxic Equivalency; BMI: body mass index; MET: Metabolic Equivalent of Task.Data are expressed as mean ± SD and percentages (number) for continuous and categorical variables, respectively.P-values for comparisons were tested by one-way ANOVA or Chi-square test, as appropriate across tertiles.

variables in the models. Additionally, statistical analyses were conducted to evaluate whether the associations observed could be modified by the intervention group. Therefore, interaction analyses were conducted by intervention group using the likelihood ratio test.

Three multivariable-adjusted models with progressive adjustment for covariates that may confound the association were used. 1) Model 1: adjusted for age and sex; 2) Model 2: model 1 additionally adjusted for physical activity (METs min/week), marital status (married, widowed, single or divorced or separated, or religious), smoking status (never, former, or current), education level (primary or lower, secondary or academic, or graduate) and the size of the recruitment centres representing the total field centre workload (<250, 250 to <300, 300 to <400, ≥400 randomized participants); 3) Fully adjusted: Model 2 additionally adjusted for adherence to Mediterranean diet using the 14-item MEDAS score, hormonal treatment, and prevalence of having diabetes (yes/no), hypertension (yes/no) and hypercholesterolemia (yes/no) or taking medications for their control. In the prospective analysis, each adiposity parameter was further adjusted for its baseline measurement (in the fully adjusted model) and the intervention group.

The statistical significance threshold for the results was set at $p < 0.05$. All analyses were conducted with robust estimates of the variance to correct for intra-cluster correlation and using the Stata 14 software program (StataCorp).

5. Results

5899 participants (52% men and 48% women, with a mean age of 65 years) were included in this study after excluding 953 participants lacking FFQ and with an energy intake out of the specified limits. The baseline characteristics of the participants overall and according to tertiles of total energy-adjusted dietary PCDD/F intake (TEQ pg/week) are shown in Table 1. A total of 72.7% of participants had obesity and 93.1% had abdominal obesity at baseline.

In this cohort, the participants' PCDD/Fs dietary intake ranged between 73.6 and 496 pg/week and the leading food groups responsible for PCDD/F intake were red meat (28%), fish and seafood (18%), and fruits and vegetables (17%), followed by white meat (11%) and oils and fats (10%) (Fig. 1).

Compared to participants with lower dietary intake of PCDD/Fs (Tertile 1, range between 73.6 and 223 pg/week), those participants with highest PCDD/Fs intake (Tertile 3, range between 272 and 496 pg/week) were more frequently women, more physically active and were less frequently smokers and consume higher amounts of fruits and vegetables, legumes, unrefined cereals, dairy products, red meat and derivatives, white meat, fish and shellfish, virgin olive oil, dietary fibre, protein, and saturated and polyunsaturated fatty acids. On the other hand, they consumed lower amounts of refined cereals, biscuits, and sugar.

In the cross-sectional analysis (Table 2), positive and linear associations were observed between the energy-adjusted dietary intake of PCDD/F and BMI or waist circumference and significantly increased through models 1 and 2 after controlling for different confounders reaching the most significant association in the fully-adjusted model (β coefficient [95%CI]) (0.43 kg/m^2 [0.22 to 0.64] and 1.11 cm [0.55 to 1.66], P for trend <0.001 for BMI and waist circumference respectively).

Compared to those participants in the lowest tertile of energy-adjusted dietary intake of PCDD/F, those in the highest tertile showed a higher prevalence of obesity and abdominal obesity PRs [95% CI] = 1.05 [1.01 to 1.09] and 1.02 [1.00 to 1.03], respectively.

In the prospective analysis (Table 3), participants in the top tertile of baseline energy-adjusted dietary intake of PCDD/F (pg/week) showed an increase in waist circumference (β coefficient [95%CI]; 0.37 cm [0.06 to 0.70]; P for trend = 0.01) compared to those in the lowest tertile after 1-year of follow-up. No other significant associations were observed for BMI nor for obesity or abdominal obesity incidence, although the direction of these associations remains as those observed in the cross-sectional analysis. In addition, cross-sectional and prospective associations between dietary intake of PCDD/Fs in each food group and adiposity parameters, prevalence/incidence of obesity, and abdominal obesity are found in the Supplementary Material (Tables S3-S12).

Interactions of the likelihood ratio tests between tertiles of PCDD/Fs and the stratified subgroup variable (intervention and control groups) were not significant ($p > 0.05$).

6. Discussion

In this large cohort of middle-aged subjects at high cardiovascular risk, higher dietary exposure to PCDD/Fs was shown to be cross-sectionally associated with higher measures of adiposity parameters and a higher prevalence of obesity and abdominal obesity. In addition, a higher dietary intake of PCDD/Fs at baseline was positively associated with changes in waist circumference after 1 year of follow-up. No other significant associations were observed for BMI nor for obesity or abdominal obesity incidence, although the direction of these associations was the same as those observed in the cross-sectional analysis. Consequently, our results support the hypothesis that there is a positive relationship between the dietary intake of PCDD/Fs and adiposity and obesity parameters.

Current results are in line with other epidemiological and mechanistic studies (Windal et al., 2010b; Fattore et al., 2006). The present study provides data concerning the associations between dietary intake of PCDD/Fs and adiposity parameters and prevalence/incidence of obesity in a large cohort study population, being to the best of our knowledge, the first article on this topic. However, some studies have also investigated the association between similar chemical substances such as dioxin-like polychlorinated biphenyls (DL-PCBs) and adiposity through the dietary intake (Windal et al., 2010b; Fattore et al., 2006). For example, in a prospective Spanish study conducted with healthy participants, a positive association between higher dietary intake of DL-PCBs and obesity risk was found (Donat-Vargas et al., 2014). As reviewed by Hassan et al., 2021), excessive exposure to PCB in humans was also related to different metabolic disorders including hepatic steatosis, obesity, diabetes mellitus, endocrine metabolism, thyroid

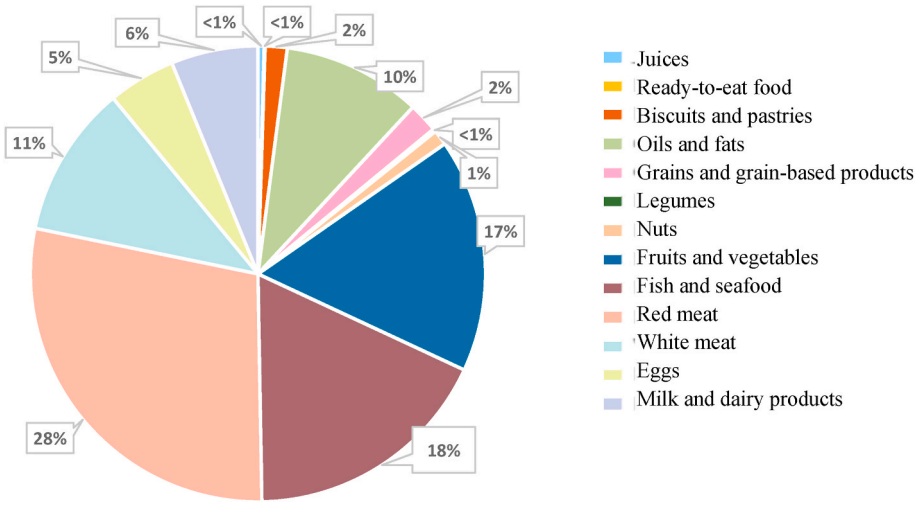

Fig. 1. Percentage of dietary PCDD/Fs intake coming from the different food groups consumed by the PREDIMED-Plus participants.

metabolism, and dyslipidaemia (Hassan et al., 2021).

It was determined that red meat (28%), fish and seafood (18%) and fruits and vegetables (17%) were the main food groups contributing to the total PCDD/Fs dietary intake in our study (Fig. 1), being also the main food groups contributors in each PCDD/Fs dietary intake tertile (data not shown). Our results showed a higher dietary intake of PCDD/Fs in women compared to men ($p < 0.001$), this could be explained because women present a higher consumption of fish, seafood and fruits and vegetables. This is in line with other studies reporting that red meat and seafood were the most contributors to the total intake of PCDD/Fs (Schwarz et al., 2014; Törnkvist et al., 2011; Windal et al., 2010a). The high dietary intake of PCDD/Fs coming from fruits and vegetables could be explained due to the high consumption of these food items in our study population and not by the high levels of TEQ detected in this food category. According to the literature, it is important to consider the concentration levels of these chemicals and the specific frequency of consumption of each food item from each population profile to estimate the exposure (Barone et al., 2021; Sirot et al., 2012; Windal et al., 2010b). In fact, the major contributors detected here could be different in other cohort study populations depending on their lifestyle and dietary patterns. In our PREDIMED-plus study, participants have a high adherence to the Mediterranean diet. Because of that, fruits and vegetables (instead of dairy products) are one of the main contributors to total dioxin exposure along with meat and fish.

Our findings are also in line with other studies measuring PCDD/F in blood. Fattore et al., 2006 reported higher serum PCDD/F levels in middle-aged women than in men (Fattore et al., 2006). Beyond the dietary intake, it is reasonable to expect that women present higher PCDD/Fs serum levels than men since PCDD/Fs are principally stored in adipose tissue, and women tend to have naturally greater percentage of body fat (Van den Berg et al., 1994). Moreover, in the cross-sectional analyses of Chang et al., 2016b, it has been found a positive and significant association between serum PCDD/Fs concentrations and the prevalence of abdominal obesity. They also found that participants with abdominal obesity had significantly higher serum dioxin levels compared to those participants without abdominal obesity (Chang et al., 2016b). In addition, a study conducted by Lee et al., 2007, found a positive relationship between serum concentrations of dioxins and waist circumference and prevalence of metabolic syndrome (Lee et al., 2007). Furthermore, Uemura et al., 2009b reported that body levels of dioxins and related compounds, particularly those of DL-PCBs, were cross-sectionally associated with BMI and the risk of metabolic syndrome (Uemura et al., 2009b).

Animal studies also suggest that these compounds can have potential effects on adiposity. Hoyeck et al., 2020 demostrated in animals that low-dose TCDD exposure in female mice impair metabolic adaptability to a high fat diet, indicating that dioxin exposure may be a causative factor of obesity and diabetes pathogenesis in females (Hoyeck et al., 2020). Brulport et al., 2017 also provided new evidence that dioxins, could present obesogenic effects and metabolic disturbances in adult mice (Brulport et al., 2017).

According to the European Food Safety Authority (EFSA), the tolerable weekly intake (TWI) of dioxins and furans in food (established in 2018) is 2.0 pgTEQ/kg of body weight/week (Knutsen et al., 2018). The TWI set by the European Commission's Scientific Committee on Food in 2001 was seven times higher than the current EFSA TWI (EFSA, 2018). It is important to consider that in this current study the 87% of our population exceeded the PCDD/Fs TWI with a mean of 2.99 pg TEQ/kg of body weight/week. The current TWI mean is similar to other studies conducted around the world and in accordance, even slightly above, with a previous study carried out in Spain (Llobet et al., 2008) in which dietary mean exposure also exceeded the EFSA TWI limits. Compared to other countries, the mean level of exposure of our participants is similar to other studies conducted in Netherlands or Ireland (De Mul et al., 2008). In contrast, studies from Italy (Diletti et al., 2018), France (Sirot et al., 2012) and Ireland (Tlustos et al., 2014) reported lower PCDD/Fs exposure compared to our participants. On the other hand, in countries such as Germany (Schwarz et al., 2014), the United Kingdom (Bramwell et al., 2016) and Taiwan (Wang et al., 2009) a higher PCDD/Fs exposure has been detected. It has been observed that the PCDD/Fs dietary exposure in healthy general populations of numerous countries in Europe has been declining in the last years (Llobet et al., 2008; Arisawa, 2018). Dioxin emissions have been decreased as a result of demanding laws governing waste treatment and disposal, which may account for the majority of this decline. According to several studies, food consumption of PCDDs/PCDFs decreased to a greater extent than DL-PCBs (González and Domingo, 2021; Tard et al., 2007). The improvements and efforts made in the waste incineration process concerning PCDDs/PCDFs emissions in recent years could be the reason for these decreases (González and Domingo, 2021; Tard et al., 2007). However, the problem is that due to the large discharges produced and the lack of periodic review of the legislation, we still have high levels of dioxins remaining, especially in the trophic chain (Arisawa, 2018). Dioxins can be bioaccumulated in the human body for almost a decade, and it is known that between 90 and 95% of dioxin absorption occurs via dietary sources (WHO, 2016).

Our study has several limitations that deserve to be discussed. The results cannot be generalized to other populations since participants included in the analysis were middle-aged Mediterranean individuals with overweight/obesity and metabolic syndrome. In addition, the

Table 2
Multivariable-adjusted β-coefficients or prevalence ratios and its 95% confidence interval for adiposity parameters and obesity prevalence, respectively, across baseline energy-adjusted total PCDD/F dietary intake tertiles.

	Energy-adjusted total PCDD/F dietary intake tertiles (TEQ pg/week)				
	Tertile 1 n=1,970	**Tertile 2** n=1,964	**Tertile 3** n=1,965	***P-trend***	**Continuous n=5,899**
Energy adjusted total PCDD/F dietary intake (TEQ pg/week), mean ± SD	189 ± 27	247 ± 14	324 ± 59		
β-coefficients (95%CI) BMI (kg/m^2)					
Model 1	**0 (Ref.)**	0.21 (-0.01 to 0.42)	**0.33 (0.12 to 0.55)**	**0.003**	**0.002 (0.00 to 0.002)**
Model 2	**0 (Ref.)**	0.21 (-0.00 to 0.43)	**0.38 (0.16 to 0.59)**	**0.001**	**0.002 (0.00 to 0.003)**
Fully-adjusted model	**0 (Ref.)**	**0.25 (0.03 to 0.46)**	**0.43 (0.22 to 0.64)**	**<0.001**	**0.002 (0.00 to 0.003)**
Waist circumference (cm)					
Model 1	**0 (Ref.)**	0.37 (-0.19 to 0.94)	**0.86 (0.29 to 1.42)**	**0.003**	**0.01 (0.00 to 0.02)**
Model 2	**0 (Ref.)**	0.47 (-0.09 to 1.04)	**1.06 (0.5 to 1.62)**	**<0.001**	**0.01 (0.00 to 0.01)**
Fully-adjusted model	**0 (Ref.)**	0.51 (-0.05 to 1.06)	**1.11 (0.55 to 1.66)**	**<0.001**	**0.01 (0.00 to 0.01)**
Prevalence ratios (95%CI)					
Obesity					
Prevalence, % (n)	71.6 (1,411)	71.5 (1,405)	74.8 (1,470)		72.7 (4,286)
Model 1	**1 (Ref.)**	0.99 (0.96 to 1.03)	1.04 (0.99 to 1.08)	**0.049**	1.00 (0.099 to 1.00)
Model 2	**1 (Ref.)**	0.99 (0.95 to 1.03)	**1.04 (1.00 to 1.08)**	**0.030**	**1.00 (1.00 to 1.00)**
Fully -adjusted model	**1 (Ref.)**	1.00 (0.96 to 1.04)	**1.05 (1.01 to 1.09)**	**0.009**	**1.00 (1.00 to 1.001)**
Abdominal obesity					
Prevalence, % (n)	92.0 (1,812)	92.4 (1,815)	94.8 (1,863)		93.1 (5,490)
Model 1	**1 (Ref.)**	0.99 (0.98 to 1.01)	1.01 (0.99 to 1.03)	0.065	**1.00 (1.00 to 1.00)**
Model 2	**1 (Ref.)**	0.99 (0.98 to 1.01)	1.02 (0.99 to 1.03)	**0029**	**1.00 (1.00 to 1.00)**
Fully -adjusted model	**1 (Ref.)**	0.99 (0.98 to 1.01)	**1.02 (1.00 to 1.03)**	**0.027**	**1.00 (1.00 to 1.00)**

Abbreviations: PCCD/F: Polychlorinated dibenzo-p-dioxins or dibenzofurans; TEQ: Toxic Equivalency; CI: confidence interval; BMI: body mass index. SD: Standard deviation.
Linear and cox regression models were fitted to assess the β-coefficients or prevalence ratio, and its 95%CI for adiposity parameters and obesity/overweight prevalence, respectively, across energy-adjusted total dietary PCDD/F intake. Model 1: adjusted for age and sex. Model 2: Model 1 additionally adjusted for physical activity (MET min/week), marital status (single, married, widowed), smoking status (current, former, never), education level (up to primary, secondary, university) and the size of the recruitment center (<250, 250 to <300, 300 to <400, ≥400). Fully adjusted: Model 2 additionally adjusted for adherence to Mediterranean diet MEDAS score (0-14 points) and type 2 diabetes (yes/no), hypertension (yes/no), and hypercholesterolemia (yes/no), or prevalence or taking medications for their control, and hormonal treatment. The robust estimate of variance was used in all analyses to account for the intra-cluster correlation.

limitation of the food intake assessment through FFQ (Food Frequency Questionnaire) is that it is susceptible to measurement errors. However, despite this drawback, FFQs have been widely adopted as a tool in epidemiological studies since the 1990s (Shim et al., 2014). The present study only assessed exposure to PCDDs/PCDFs through dietary sources, but not from other sources such as inhalation or dermal contact. However, the exposure to these chemicals occurs largely (90%) through the diet (Air Quality Guidelines for Europe Second Edition, 2000). Nowadays, estimation of PCDD/F from food sources is feasible. However, more detailed information in the literature on different foods, including their origin, production methods, content and packaging, would be helpful for more accurate estimations. Additionally, it was challenging to compare current results with other articles based on dietary exposure estimations, due to the limited literature data available on that topic. Moreover, we lacked information about the food preparation or cooking techniques that could change PCDD/Fs levels in the finished food product.

7. Conclusion

In conclusion, to our knowledge, this is the first study to explore the association between dietary intake of PCDD/Fs and adiposity. We found that in this middle-aged population, a higher dietary intake of PCDD/Fs was associated with a higher prevalence of obesity and higher adiposity parameters at baseline. In addition, a higher baseline dietary intake of PCDD/Fs was positively associated with changes in waist circumference after 1 year of follow-up. These findings support the growing epidemiological data linking the current exposure to PCDD/Fs with adiposity. Even though the production of PCDD/Fs has stopped in the 80s, PCDD/Fs continue to pose a serious health risk since the DI of our population and of other countries are still above the levels recommended by the EFSA. It is therefore very important to assess the unintentionally exposed population and to keep establishing awareness and prophylactic measures to reduce these levels. Further large prospective studies using different population and with longer follow-up period are warranted in the future to strengthen our results.

Credit author statement

NK, MÁM, NB, and JS-S conceived and designed the study. MÁM-G, DC, MF, JAM, ÁA-G, JW, JV, DR, JL-M, RE, FJT, JL, LS-M, AB-C, JAT, VMS, XP, MD-R, PM-M, JVi, CV, LD, and JS-S, conducted data acquisition. NK, MÁ.M, IP and JS-S performed statistical analyses. NK, MÁ.M, NB, and JS-S carried out interpretation of the data for the study. NK, MÁM, NB and JS-S conducted the first draft. All authors were involved in draft redaction, revision for important intellectual content, read, and approved the final manuscript.

Ethics statement

The studies involving human participants were reviewed and approved by JW: CEI Provincial de Málaga-Servicio Andaluz de Salud (O01_feb_PR2), José Lapetra: CEI de los Hospitales Universitarios Virgen Macarena y Virgen del Rocío-Servicio Andaluz de Salud (PI13/00673), JAM: CEIC Universidad de Navarra (053/2013), DR: CEI de las Illes Balears – Conselleria de Salut Direcció General de Salut Publica i Consum (IB 2242/14 PI), MF: CEIC Parc de Salut Mar y IDIAP Jordi Gol (PI13/120), JSS: CEIC del Hospital Universitari Sant Joan de Reus y IDIAB Jordi Gol (13-07-25/7proj2), Aurora Bueno: CEI de la Provincia de Granada- Servicio Andaluz de Salud (MAB/BGP/pg), CV: CEIC de la Fundacion Jiménez Díaz (EC 26–14/IIS-FJD), MM-G: CEIC Universidad de Navarra (053/2013), Fernando Aros: CEIC Euskadi (PI2014044), DC: CEIC Corporativo de Atención Primaria de la Comunitat Valenciana

Table 3
Multivariable-adjusted β-coefficients or Odds ratios and its 95% confidence intervals for adiposity changes or obesity incidence, respectively, after 1-year of follow-up across baseline energy-adjusted total dietary PCDD/F intake.

	Energy-adjusted total PCDD/F dietary intake tertiles (TEQ pg/week)				
	Tertile 1	**Tertile 2**	**Tertile 3**	***P- trend***	**Continuous**
β-coefficients (95%CI)					
BMI changes **(kg/m^2)**	(n=1,970)	(n=1,964)	(n=1,965)		(n=5,899)
Energy adjusted total PCDD/F dietary intake **(TEQ pg/week), mean ± SD**	189 ± 27	247 ± 14	324 ± 59		
Model 1	**0 (Ref.)**	0.21 (-0.08 to 0.12)	0.09 (-0.00 to 0.20)	0.050	**0.001 (0.000 to 0.001)**
Model 2	**0 (Ref.)**	0.04 (-0.04 to 0.13)	0.09 (-0.01 to 0.19)	0.053	**0.001 (0.000 to 0.001)**
Fully- adjusted model	**0 (Ref.)**	0.03 (-0.05 to 0.13)	0.08 (-0.01 to 0.17)	0.113	0.00 (-0.000 to 0.001)
Waist circumference changes (cm)	(n=1,967)	(n=1,966)	(n=1,966)		(n=5,5899)
Energy adjusted total PCDD/F dietary intake **(TEQ pg/week), mean ± SD**	189 ± 27	247 ± 14	324 ± 59		
Model 1	**0 (Ref.)**	0.11 (-0.22 to 0.44)	**0.36 (0.09 to 0.69)**	**0.029**	0.001 (-0.000 to 0.003)
Model 2	**0 (Ref.)**	0.16 (-0.14 to 0.46)	**0.38 (0.07 to 0.69)**	**0.013**	**0.002 (0.000 to 0.004)**
Fully-adjusted model	**0 (Ref.)**	0.15 (-0.15 to 0.45)	**0.37 (0.06 to 0.70)**	**0.015**	0.002 (-0.000 to 0.004)
Odds ratios (95%CI)					
Obesity	(n= 538)	(n= 538)	(n= 537)		(n=1,613)
Incidence, % (n)	6.8 (38)	8.59 (48)	8.08 (40)		
Energy adjusted total PCDD/F dietary intake **(TEQ pg/week) mean ± SD**	188 ± 27.0	244 ± 13.1	318 ± 56.3		
Model 1	**1 (Ref.)**	1.17 (0.74 to 1.85)	1.28 (0.80 to 2.01)	0.310	1.00 (0.998 to 1.003)
Model 2	**1 (Ref.)**	1.17 (0.73 to 1.86)	1.24 (0.78 to 1.97)	0.651	1.00 (0.997 to 1.003)
Fully-adjusted model	**1 (Ref.)**	1.19 (0.74 to 1.91)	1.25 (0.77 to 2.02)	0.635	1.00 (0.997 to 1.003)
Abdominal obesity	(n=137)	(n=136)	(n=136)		(n=409)
Incidence, % (n)	15.1 (24)	18.2 (27)	20.59 (21)		
Energy adjusted total PCDD/F dietary intake **(TEQ pg/week) mean ± SD**	184 ± 26	236 ± 11	300 ± 42		
Model 1	**1 (Ref.)**	1.20 (0.64 to 2.26)	1.15 (0.60 to 2.19)	0.759	1.00 (0.995 to 1.005)
Model 2	**1 (Ref.)**	1.28 (0.64 to 2.52)	1.11 (0.57 to 2.14)	0.485	0.99 (0.994 to 1.004)
Fully-adjusted model	**1 (Ref.)**	1.28 (0.66 to 2.51)	1.08 (0.56 to 2.08)	0.571	0.99 (0.994 to 1.004)

Abbreviations: PCCD/F: Polychlorinated dibenzo-p-dioxins or dibenzofurans; TEQ: Toxic Equivalency; CI: confidence interval; BMI: body mass index; SD: Standard Deviation.

Linear regression models and logistic regression models were fitted to assess the β-coefficients or odd ratio, and its 95%CI for adiposity parameters and obesity/overweight incidence, respectively across energy-adjusted total dietary PCDD/F intake. Model 1: adjusted for age, sex. Model 2: Model 1 additionally adjusted for physical activity (MET min/week), marital status (single, married, widowed), smoking status (current, former, never), education level (up to primary, secondary, university) and the size of the recruitment centres (<250, 250 to <300, 300 to <400, ≥400). Fully adjusted: Model 2 additionally adjusted to adherence to Mediterranean diet MEDAS score (0–14 points) and the prevalence of having and type 2 diabetes (yes/no), hypertension (yes/no), and hypercholesterolemia (yes/no), or prevalence or taking medications for their control, and hormonal treatment, intervention group and outcome variable at baseline. The robust estimate of variance was used in all analyses to account for the intra-cluster correlation.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.envres.2023.115697.

References

Alberti, K.G.M.M., Eckel, R.H., Grundy, S.M., Zimmet, P.Z., Cleeman, J.I., Donato, K.A., Fruchart, J.C., James, W.P.T., Loria, C.M., Smith, S.C., 2009. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood Institute; American heart association; world heart federation; international atherosclerosis society; and international association for the study of obesity. Circulation 120, 1640–1645. https://doi.org/10.1161/CIRCULATIONAHA.109.192644.

Arisawa, K., 2018. Recent decreasing trends of exposure to PCDDs/PCDFs/dioxin-like PCBs in general populations, and associations with diabetes, metabolic syndrome, and gout/hyperuricemia. J. Med. Invest. 65, 151–161. https://doi.org/10.2152/jmi.65.151.

Barone, G., Storelli, A., Busco, A., Mallamaci, R., Storelli, M.M., 2021. Polychlorinated dioxins, furans (PCDD/Fs) and dioxin-like polychlorinated biphenyls (dl-PCBs) in food from Italy: estimates of dietaryintake and assessment. J. Food Sci. 86, 4741–4753. https://doi.org/10.1111/1750-3841.15901.

Barros, A.J.D., Hirakata, V.N., 2003. Alternatives for logistic regression in cross-sectional studies: an empirical comparison of models that directly estimate the prevalence ratio. BMC Med. Res. Methodol. 3, 1–13. https://doi.org/10.1186/1471-2288-3-21/TABLES/9.

Bramwell, L., Mortimer, D., Rose, M., Fernandes, A., Harrad, S., Pless-Mulloli, T., 2016. UK dietary exposure to PCDD/Fs, PCBs, PBDD/Fs, PBBs and PBDEs: comparison of results from 24-h duplicate diets and total diet studies 34, 65–77. https://doi.org/10.1080/19440049.2016.1258493.

Brulport, A., Le Corre, L., Chagnon, M.C., 2017. Chronic exposure of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) induces an obesogenic effect in C57BL/6J mice fed a high fat diet. Toxicology 390, 43–52. https://doi.org/10.1016/J.TOX.2017.07.017.

Célind, J., Bygdell, M., Martikainen, J., Ohlsson, C., Kindblom, J.M., 2022. Childhood overweight and risk of obesity-related adult cancer in men. Cancer Commun. 42, 576. https://doi.org/10.1002/CAC2.12286.

Chang, J.W., Chen, H.L., Su, H.J., Lee, C.C., 2016a. Abdominal obesity and insulin resistance in people exposed to moderate-to-high levels of dioxin. PLoS One 11, 145818. https://doi.org/10.1371/JOURNAL.PONE.0145818.

Chang, J.W., Chen, H.L., Su, H.J., Lee, C.C., 2016b. Abdominal obesity and insulin resistance in people exposed to moderate-to-high levels of dioxin. PLoS One 11, e0145818. https://doi.org/10.1371/JOURNAL.PONE.0145818.

De La Fuente-Arrillaga, C., Vzquez Ruiz, Z., Bes-Rastrollo, M., Sampson, L., Martinez-González, M.A., 2010. Reproducibility of an FFQ validated in Spain. Publ. Health Nutr. 13, 1364–1372. https://doi.org/10.1017/S1368980009993065.

De Mul, A., Bakker, M.I., Zeilmaker, M.J., Traag, W.A., Leeuwen, SPJ va, Hoogenboom, R.L.A.P., Boon, P.E., Klaveren, JD va, 2008. Dietary exposure to dioxins and dioxin-like PCBs in The Netherlands anno 2004. Regul. Toxicol. Pharmacol. 51, 278–287. https://doi.org/10.1016/j.yrtph.2008.04.010.

Diamanti-Kandarakis, E., Bourguignon, J.P., Giudice, L.C., Hauser, R., Prins, G.S., Soto, A.M., Zoeller, R.T., Gore, A.C., 2009. Endocrine-disrupting chemicals: an endocrine society scientific statement. Endocr. Rev. 30, 293. https://doi.org/10.1210/ER.2009-0002.

Diletti, G., Scortichini, G., Abete, M.C., Binato, G., Candeloro, L., Ceci, R., Chessa, G., Conte, A., Di Sandro, A., Esposito, M., et al., 2018. Intake estimates of dioxins and dioxin-like polychlorobiphenyls in the Italian general population from the 2013-2016 results of official monitoring plans in food. Sci. Total Environ. 627, 11–19. https://doi.org/10.1016/J.SCITOTENV.2018.01.181.

Donat-Vargas, C., Gea, A., Sayon-Orea, C., Carlos, S., Martinez-Gonzalez, M.A., Bes-Rastrollo, M., 2014. Association between dietary intakes of PCBs and the risk of obesity: the SUN project. J. Epidemiol. Community Health 68, 834–841. https://doi.org/10.1136/jech-2013-203752.

Donat-Vargas, C., Moreno-Franco, B., Laclaustra, M., Sandoval-Insausti, H., Jarauta, E., Guallar-Castillon, P., 2020. Exposure to dietary polychlorinated biphenyls and dioxins, and its relationship with subclinical coronary atherosclerosis: the Aragon Workers' Health Study. Environ. Int. 136, 105433 https://doi.org/10.1016/j.envint.2019.105433.

EFSA (European Food Safety Authority), 2018. Dioxins and related PCBs: tolerable intake level updated. https://www.efsa.europa.eu/en/press/news/dioxins-and-related-pcbs-tolerable-intake-level-updated. (Accessed 28 November 2022).

Fattore, E., Fanelli, R., Turrini, A., Di Domenico, A., 2006. Current dietary exposure to polychlorodibenzo-p-dioxins, polychlorodibenzofurans, and dioxin-like polychlorobiphenyls in Italy. Mol. Nutr. Food Res. 50, 915–921. https://doi.org/10.1002/MNFR.200500212.

Fierens, S., Mairesse, H., Heilier, J.F., de Burbure, C., Focant, J.F., Eppe, G., de Pauw, E., Bernard, A., 2003. Dioxin/polychlorinated biphenyl body burden, diabetes and endometriosis: findings in a population-based study in Belgium. Biomarkers 8, 529–534. https://doi.org/10.1080/1354750032000158420.

Finkelstein, E.A., Khavjou, O.A., Thompson, H., Trogdon, J.G., Pan, L., Sherry, B., Dietz, W., 2012. Obesity and severe obesity forecasts through 2030. Am. J. Prev. Med. 42, 563–570. https://doi.org/10.1016/j.amepre.2011.10.026.

Fries, G.F., 1995. A review of the significance of animal food products as potential pathways of human exposures to dioxins. J. Anim. Sci. 73, 1639–1650. https://doi.org/10.2527/1995.7361639X.

González, N., Domingo, J.L., 2021. Polychlorinated dibenzo-p-dioxins and dibenzofurans (PCDD/Fs) in food and human dietary intake: an update of the scientific literature. Food Chem. Toxicol. 157. https://doi.org/10.1016/J.FCT.2021.112585.

Hassan, W., Ahmed, H., Murtaza, G., Umar, M.I., Iqbal, F.M., 2021. Role of Polychlorinated Biphenyls as EDCs in Metabolic Disorders, pp. 161–174. https://doi.org/10.1007/978-3-030-45923-9_11.

Hoyeck, M.P., Merhi, R.C., Blair, H.L., Spencer, C.D., Payant, M.A., Martin Alfonso, D.I., Zhang, M., Matteo, G., Chee, M.J., Bruin, J.E., 2020. Female mice exposed to low doses of dioxin during pregnancy and lactation have increased susceptibility to diet-induced obesity and diabetes. Mol. Metabol. 42. https://doi.org/10.1016/J.MOLMET.2020.101104.

Kiviranta, H., Hallikainen, A., Ovaskainen, M.L., Kumpulainen, J., Vartiainen, T., 2001. Dietary intakes of polychlorinated dibenzo-p-dioxins, dibenzofurans and polychlorinated biphenyls in Finland. Food Addit. Contam. 18, 945–953. https://doi.org/10.1080/02652030110057134.

Knutsen, H.K., Alexander, J., Barregård, L., Bignami, M., Brüschweiler, B., Ceccatelli, S., Cottrill, B., Dinovi, M., Edler, L., Grasl-Kraupp, B., et al., 2018. Risk for animal and human health related to the presence of dioxins and dioxin-like PCBs in feed and food. EFSA J. 16. https://doi.org/10.2903/J.EFSA.2018.5333.

Lauretta, R., Sansone, A., Sansone, M., Romanelli, F., Appetecchia, M., 2019. Endocrine disrupting chemicals: effects on endocrine glands. Front. Endocrinol. 10, 178. https://doi.org/10.3389/FENDO.2019.00178.

Lee, D.H., Lee, I.K., Porta, M., Steffes, M., Jacobs, D.R., 2007. Relationship between serum concentrations of persistent organic pollutants and the prevalence of metabolic syndrome among non-diabetic adults: results from the National Health and Nutrition Examination Survey 1999-2002. Diabetologia 50, 1841–1851. https://doi.org/10.1007/s00125-007-0755-4.

Llobet, J.M., Martí-Cid, R., Castell, V., Domingo, J.L., 2008. Significant decreasing trend in human dietary exposure to PCDD/PCDFs and PCBs in Catalonia, Spain. Toxicol. Lett. 178, 117–126. https://doi.org/10.1016/J.TOXLET.2008.02.012.

MacMahon, S., Baigent, C., Duffy, S., Rodgers, A., Tominaga, S., Chambless, L., De Backer, G., De Bacquer, D., Kornitzer, M., Whincup, P., et al., 2009. Body-mass index and cause-specific mortality in 900 000 adults: collaborative analyses of 57 prospective studies. London, England Lancet 373, 1083–1096. https://doi.org/10.1016/S0140-6736(09)60318-4.

Martínez-González, M.A., Buil-Cosiales, P., Corella, D., Bulló, M., Fitó, M., Vioque, J., Romaguera, D., Alfredo Martínez, J., Wärnberg, J., López-Miranda, J., et al., 2019. Cohort profile: design and methods of the PREDIMED-Plus randomized trial. Int. J. Epidemiol. 48, 387–388o. https://doi.org/10.1093/ije/dyy225.

Matsunaga, M., Yatsuya, H., Iso, H., Li, Y., Yamagishi, K., Tanabe, N., Wada, Y., Ota, A., Tamakoshi, K., Tamakoshi, A., 2022. Impact of body mass index on obesity-related cancer and cardiovascular disease mortality; the Japan collaborative cohort study. J. Atherosclerosis Thromb. 29, 1547–1562. https://doi.org/10.5551/JAT.63143.

Molina, L., Sarmiento, M., Peñafiel, J., Donaire, D., Garcia-Aymerich, J., Gomez, M., Ble, M., Ruiz, S., Frances, A., Schröder, H., et al., 2017. Validation of the regicor Short physical activity questionnaire for the adult population. PLoS One 12, e0168148. https://doi.org/10.1371/JOURNAL.PONE.0168148.

Ogden, C.L., Fryar, C.D., Martin, C.B., Freedman, D.S., Carroll, M.D., Gu, Q., Hales, C.M., 2021. Trends in obesity prevalence by race and hispanic origin - 1999-2000 to 2017-2018. JAMA, J. Am. Med. Assoc. 324, 1208–1210. https://doi.org/10.1001/JAMA.2020.14590.

Qasim, A., Turcotte, M., de Souza, R.J., Samaan, M.C., Champredon, D., Dushoff, J., Speakman, J.R., Meyre, D., 2018. On the origin of obesity: identifying the biological, environmental and cultural drivers of genetic risk among human populations. Obes. Rev. 19, 121–149. https://doi.org/10.1111/obr.12625.

Ramos-Lopez, O., Milagro, F.I., Riezu-Boj, J.I., Martinez, J.A., 2021. Epigenetic signatures underlying inflammation: an interplay of nutrition, physical activity, metabolic diseases, and environmental factors for personalized nutrition. Inflamm. Res. 70, 29–49. https://doi.org/10.1007/S00011-020-01425-Y/TABLES/4.

Salas-Salvadó, J., Díaz-López, A., Ruiz-Canela, M., Basora, J., Fitó, M., Corella, D., Serra-Majem, L., Wärnberg, J., Romaguera, D., Estruch, R., et al., 2019. Effect of a lifestyle intervention program with energy-restricted mediterranean diet and exercise on

weight loss and cardiovascular risk factors: one-year results of the PREDIMED-plus trial. Diabetes Care 42, 777–788. https://doi.org/10.2337/DC18-0836.

Sayón-Orea, C., Razquin, C., Bulló, M., Corella, D., Fitó, M., Romaguera, D., Vioque, J., Alonso-Gómez, Á.M., Wärnberg, J., Martínez, J.A., et al., 2019. Effect of a nutritional and behavioral intervention on energy-reduced mediterranean diet adherence among patients with metabolic syndrome: interim analysis of the PREDIMED-plus randomized clinical trial. JAMA 322, 1486–1499. https://doi.org/10.1001/JAMA.2019.14630.

Schröder, H., Fitó, M., Estruch, R., Martínez-González, M.A., Corella, D., Salas-Salvadó, J., Lamuela-Raventós, R., Ros, E., Salaverría, I., Fiol, M., et al., 2011. A Short screener is valid for assessing mediterranean diet adherence among older Spanish men and women. J. Nutr. 141, 1140–1145. https://doi.org/10.3945/JN.110.135566.

Schuhmacher, M., Domingo, J.L., Llobet, J.M., Lindström, G., Wingfors, H., 1999. Dioxin and dibenzofuran concentrations in blood of a general population from Tarragona, Spain. Chemosphere 38, 1123–1133. https://doi.org/10.1016/S0045-6535(98)00363-4.

Schwarz, M.A., Lindtner, O., Blume, K., Heinemeyer, G., Schneider, K., 2014. Dioxin and dl-PCB exposure from food. the German LExUKon project 31, 688–702. https://doi.org/10.1080/19440049.2013.878041.

Shim, J.-S., Oh, K., Kim, H.C., 2014. Dietary assessment methods in epidemiologic studies. Epidemiol Health 36, e2014009. https://doi.org/10.4178/EPIH/E2014009.

Sirot, V., Tard, A., Venisseau, A., Brosseaud, A., Marchand, P., Le Bizec, B., Leblanc, J.C., 2012. Dietary exposure to polychlorinated dibenzo-p-dioxins, polychlorinated dibenzofurans and polychlorinated biphenyls of the French population: results of the second French Total Diet Study. Chemosphere 88, 492–500. https://doi.org/10.1016/J.CHEMOSPHERE.2012.03.004.

Srogi, K., 2008. Levels and congener distributions of PCDDs, PCDFs and dioxin-like PCBs in environmental and human samples: a review. Environ. Chem. Lett. 6, 1–28. https://doi.org/10.1007/s10311-007-0105-2.

Street, M.E., Angelini, S., Bernasconi, S., Burgio, E., Cassio, A., Catellani, C., Cirillo, F., Deodati, A., Fabbrizi, E., Fanos, V., et al., 2018. Current knowledge on endocrine disrupting chemicals (EDCs) from animal biology to humans, from pregnancy to adulthood: highlights from a national Italian meeting. Int. J. Mol. Sci. 19 https://doi.org/10.3390/IJMS19061647.

Sun, X., Li, P., Yang, X., Li, W., Qiu, X., Zhu, S., 2017. From genetics and epigenetics to the future of precision treatment for obesity. Gastroenterol Rep 5, 266–270. https://doi.org/10.1093/GASTRO/GOX033.

Tard, A., Gallotti, S., Leblanc, J.C., Volatier, J.L., 2007. Dioxins. furans and dioxin-like PCBs: Occurrence in food and dietary intake in France 24, 1007–1017. https://doi.org/10.1080/02652030701317293.

Tlustos, C., Anderson, W., Flynn, A., Pratt, I., 2014. Exposure of the adult population resident in Ireland to dioxins and PCBs from the diet 31, 1100–1113. https://doi.org/10.1080/19440049.2014.905713.

Törnkvist, A., Glynn, A., Aune, M., Darnerud, P.O., Ankarberg, E.H., 2011. PCDD/F, PCB, PBDE, HBCD and chlorinated pesticides in a Swedish market basket from 2005 – levels and dietary intake estimations. Chemosphere 83, 193–199. https://doi.org/10.1016/J.CHEMOSPHERE.2010.12.042.

Uemura, H., Arisawa, K., Hiyoshi, M., Kitayama, A., Takami, H., Sewachika, F., Dakeshita, S., Nii, K., Satoh, H., Sumiyoshi, Y., et al., 2009a. Prevalence of metabolic syndrome associated with body burden levels of dioxin and related compounds among Japan's general population. Environ. Health Perspect. 117, 568. https://doi.org/10.1289/EHP.0800012.

Uemura, H., Arisawa, K., Hiyoshi, M., Kitayama, A., Takami, H., Sewachika, F., Dakeshita, S., Nii, K., Satoh, H., Sumiyoshi, Y., et al., 2009b. Prevalence of metabolic syndrome associated with body burden levels of dioxin and related compounds among Japan's general population. Environ. Health Perspect. 117, 568. https://doi.org/10.1289/EHP.0800012.

Van den Berg, M., De Jongh, J., Poiger, H., Olson, J.R., 1994. The toxicokinetics and metabolism of polychlorinated dibenzo-p-dioxins (PCDDs) and dibenzofurans (PCDFs) and their relevance for toxicity. Crit. Rev. Toxicol. 24, 1–74. https://doi.org/10.3109/10408449409017919.

Van den Berg, M., Birnbaum, L.S., Denison, M., De Vito, M., Farland, W., Feeley, M., Fiedler, H., Hakansson, H., Hanberg, A., Haws, L., et al., 2006. The 2005 World Health Organization reevaluation of human and Mammalian toxic equivalency factors for dioxins and dioxin-like compounds. Toxicol. Sci. 93, 223–241. https://doi.org/10.1093/TOXSCI/KFL055.

Wang, I.C., Wu, Y.L., Lin, L.F., Chang-Chien, G.P., 2009. Human dietary exposure to polychlorinated dibenzo-p-dioxins and polychlorinated dibenzofurans in Taiwan. J. Hazard Mater. 164, 621–626. https://doi.org/10.1016/J.JHAZMAT.2008.08.040.

Willett, W., Stampfer, M.J., 1986. Total energy intake: implications for epidemiologic analyses. Am. J. Epidemiol. 124, 17–27. https://doi.org/10.1093/OXFORDJOURNALS.AJE.A114366.

Windal, I., Vandevijvere, S., Maleki, M., Goscinny, S., Vinkx, C., Focant, J.F., Eppe, G., Hanot, V., Van Loco, J., 2010a. Dietary intake of PCDD/Fs and dioxin-like PCBs of the Belgian population. Chemosphere 79, 334–340. https://doi.org/10.1016/J.CHEMOSPHERE.2010.01.031.

Windal, I., Vandevijvere, S., Maleki, M., Goscinny, S., Vinkx, C., Focant, J.F., Eppe, G., Hanot, V., Van Loco, J., 2010b. Dietary intake of PCDD/Fs and dioxin-like PCBs of the Belgian population. Chemosphere 79, 334–340. https://doi.org/10.1016/J.CHEMOSPHERE.2010.01.031.

WHO (World Health Organization), 2000. Air Quality Guidelines for Europe Second Edition. https://www.who.int/publications/i/item/9789289013581. (Accessed 9 December 2022).

WHO (World Health Organization), 2016. Dioxins and their effects on human health. https://www.who.int/news-room/fact-sheets/detail/dioxins-and-their-effects-on-human-health. (Accessed 9 December 2022).