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Original article

A high consumption of ultra-processed foods is associated with higher total mortality in an adult Mediterranean population

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SUMMARY

Background & aims: The consumption of ultra-processed foods (UPF) has been associated with higher all-cause and cardiovascular disease (CVD) mortality, although this association has not been sufficiently investigated in Mediterranean populations. We aimed to evaluate the association between UPF consumption and all-cause, CVD and cancer mortality in an adult population in Spain.

Methods: We analysed data from 1,538 participants aged 20 years and above in the Valencia Nutrition Survey in 1995. Diet was assessed at baseline using a validated food frequency questionnaire and the consumption of UPF was calculated using the NOVA system. Information on socio-demographic characteristics, lifestyles, and presence of diseases was also collected at baseline. Cause of death was ascertained during an 18-year follow-up period. We used Cox regression and competing risk models as proposed by Fine and Gray's to estimate adjusted hazard ratios (HR) and 95 % confidence intervals (95 % CI).

Results: After 18 years of follow-up, we documented 312 deaths (36.5 % of CVD and 25.6 % of cancer). Compared with participants in the lowest tertile of UPF consumption, those in the highest tertile showed 40 % higher risk of all-cause mortality, HR 1.40 (95 %CI: 1.04–1.90), and evidence of a higher CVD mortality, HR 1.39 (95 %CI: 0.80–2.41) and of cancer mortality, HR 1.53 (95 %CI: 0.83–2.82).

Conclusions: This study suggests that a high UPF consumption is associated with a higher all-cause mortality in a Mediterranean population after a long follow-up period. Considering the increase in UPF consumption and their detrimental health effects on mortality, these results should be confirmed by other studies in other populations.

1. Introduction

Ultra-processed foods (UPF) are industrial products mainly composed of ingredients extracted from foods which have previously been processed [1]. UPF are characterized by a high content of total, trans, and saturated fats, salt, and simple sugars, with a low content of fibre and micronutrients [2]. In addition, the advances in food processing have made UPF more appetizing and low-cost, with a longer shelf-life, increasing their palatability, convenience, and easy accessibility. This can lead to uncontrolled UPF consumption resulting in excessive calorie intake and unbalanced micro- and macronutrient intake [3]. Increased UPF consumption and the resulting shifts in dietary habits have concurred with the rising prevalence of non-communicable diseases (NCDs) - e.g., cardiovascular disease (CVD), diabetes, and several cancers - which are now responsible for around 70 % and 90 % of all deaths worldwide and in Spain, respectively [4,5].

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To the best of our knowledge, only a few studies assessed UPF-associated mortality in Mediterranean countries, and only five were prospective cohort studies: NutriNet-Santé (France), Moli-Sani (Italy), SUN, ENRICA and DRECE (from Spain) [6–10]. In the NutriNet-Santé study, each 10 % increase in UPF consumption was associated with a 14 % rise in the risk of all-cause mortality after 6.6 years of follow-up [6]. Similar results were observed in the DRECE cohort study, in which each 10 % increase in energy intake derived from UPF consumption was associated with a 15 % rise in the risk of all-cause mortality [9]. In the study by Blanco-Rojo et al., conducted in a Spanish population, individuals with the highest quartile of UPF consumption (mean consumption corresponded to 42.8 % of the total energy intake) showed a 44 % higher risk of all-cause mortality than those in the lowest quartile (mean consumption of 8.68 %) [8]. Similar results were observed in another prospective study with a selected population of university graduates in Spain, in which the highest quartile of UPF consumption (>4 servings/day) was associated with a 62 % higher hazard ratio for all-cause mortality compared with the lowest quartile (<2 servings/day) [7]. In the Moli-Sani study in Italy, a 26 % higher all-cause mortality was observed in participants with the highest UPF consumption (18.5) compared to those with the lowest consumption (median of total dietary UPF consumption of 4.8 %) [10]. There is also evidence from studies in non-Mediterranean countries that reported a positive association between UPF consumption and mortality, although other studies did not find the association. In the PURE study, a prospective study conducted among 138,076 adults from non-Mediterranean countries in five continents, the consumption of UPF was associated with 28 % higher risk of all-cause mortality after 10,2 years of follow-up [11]. In another study conducted with kidney transplanted patients, a positive association was also observed [12]. However, in a prospective study carried out with 77,060 American participants (SCCS study), the UPF consumption was not associated with higher all-cause mortality [13].

Less is known about the association between UPF consumption and mortality by specific causes such as CVD and cancer. In the above mentioned Moli-Sani study, no association was observed between UPF consumption and cancer mortality. However, the results from NutriNet-Santé showed that a 10 % increase in the proportion of UPF significantly increased the risk of overall cancer by 12 % and the risk of breast cancer by 11 % [10,14]. Regarding CVD mortality, in the Moli-Sani study, individuals with the highest UPF consumption had a 58 % higher risk of CVD mortality [10]. Moreover, in this study when the participants were stratified by prior cardiovascular events, those with the highest UPF consumption (≥11.3 % of total consumption) had a 65 % increased risk of CVD mortality when compared with those with the lowest UPF consumption (<4.7 %) [15]. In contrast, the PURE study no association was reported between UPF consumption and CVD mortality [11]. Finally, in the SUN cohort and the SCCS studies, no significant associations were found between UPF consumption and either CVD or cancer mortality [7,13].

The consumption of UPF is increasing in many countries including Mediterranean countries like Spain although knowledge regarding the long-term health effects of UPF consumption is still insufficient [4,16]. We consider justified to provide new evidence on the long-term effect of UPF consumption on mortality in different populations. Thus, we aimed to evaluate the effect of UPF consumption on all-cause, CVD and cancer mortality after 18 years of follow-up in a representative sample of adults in a Mediterranean area.

2. Materials and methods

2.1. Study design and population

Data were obtained from the population-based Valencia Nutrition Survey (VNS) conducted in 1994–95. The VNS aimed to assess the health and nutrition status in a representative sample of 1,811 individuals aged 15 years and older in the Valencian region. Detailed information about the design of the VNS has been published previously [17–19]. Inclusion criteria for the study were people 15 years and older, able to read and write in Spanish, who gave their informed consent. We did not exclude participants based on their self-reported health status, although we adjusted for the presence of most prevalent self-reported diseases such as diabetes (6 %), hypertension (13 %) and high cholesterol (12 %). For this study, we included data from 1,538 participants aged 20 years and older (689 men and 849 women) with complete dietary information. We excluded participants aged between 15 and 19 years as we consider that the usual diet among adolescents is not sufficiently stable ($n = 247$). We also excluded 29 participants with implausible dietary information according to established cut offs [20]: <800 or >4000 kcal/day for men or <500 or >3500 kcal/day for women. Informed consent was obtained from all participants, and the Ethical Committees of the Hospital of San Juan and Miguel Hernandez University approved the study (AUT.DSP.JVL.04.21).

2.2. Dietary assessment

We used a semi-quantitative food frequency questionnaire (FFQ) of 93 food items to assess the usual daily intake of foods and nutrients (available at: https://epinut.umh.es/cfa-93-encv/). The FFQ was a modified version from a previous one based on the Harvard questionnaire [21], which we developed and validated using four 1-week dietary records in an adult population in Valencian region [22–24]. The validity correlation coefficients (adjusted by energy intake) ranged from 0.27 for folate intake to 0.67 for calcium intake (average 0.44), and the reproducibility correlation coefficients ranged from 0.30 for carotene intake to 0.65 for calcium intake (average 0.44); this is a similar range to other established diet questionnaires [20].

Participants were asked how often, on average, they had consumed a standard portion size of each food item during the previous year. There were nine options of frequency consumption ranging from “never or less than once a month” to “six or more a day” [22]. Two trained dietitians categorized the 93 food items in the FFQ according to NOVA classification based on their degree of processing. A third dietitian assisted in the classification when a mismatch occurred. NOVA classification is one of the most used nutritional system to assess the extent of food processing, and categorizes foods and food products based on the purpose, extent and nature of the processing [25]. Previous evidence have pointed out that NOVA classification system contains fewer UPF items compared to other systems of classification such as International Agency for Research on Cancer, International Food Information Council or the University of North Carolina, and it could produce an underestimation of the health effects of UPF [26]. However, recent studies have shown that NOVA classification can be an accurately method to evaluate consumption of UPF and its association with different points in health [27–29]. It divides foods into four groups depending on the biological, physical, and chemical techniques used. Group 1, includes unprocessed and minimally processed foods such as edible parts from plants, animals and fungi, algae, water, and non-alcoholic fermented beverages. Group 2, includes

processed culinary ingredients which are used to prepare, season, and cook products from the Group 1. Group 3, includes processed foods which combine products from the first and second groups as well as several fermented beverages (e.g., wine or beer). Group 4 includes ultra-processed, hyper-palatable foods, mostly pre-prepared and ready-to-consume products with a high content of food additives. In addition, group 4 includes soft drinks and distilled beverages. Our study primarily focused on the UPF from group 4. Classification of the FFQ into the four NOVA groups can be found in Supplementary Table 1.

Finally, we calculated UPF consumption as the sum of each food item. Consumption of UPF was calculated for each participant as the % of UPF within total daily dietary intake using the following formula: $\left(\frac{UPF\ intake(g/day)}{Total\ dietary\ intake(g/day)}*100\right)$ Consumption of UPF was analysed in tertiles, in order to classify participants according to their total UPF consumption as low, medium and high.

2.3. Ascertainment of mortality

During the 18-year follow-up period, the date and cause of death were verified through the Spanish Statistical Office's National Death Index and the Valencian Region's Mortality Registry. The 10th version of the International Classification of Diseases (ICD-10) was used for coding causes of death. We classified causes of death into the following three categories: CVD (ICD-10: I00–I99), cancer (ICD-10: C00-D49), and all-cause mortality which included deaths from any cause.

2.4. Other variables

Sociodemographic, medical, and lifestyle information was collected at baseline using structured and validated questionnaires: sex (women, men); age (years); educational level (<primary school, primary school, ≥secondary school); waist circumference [healthy range (78–94 cm in men and 64–80 cm in women), moderate risk (94–102 cm in men and 80–88 cm in women) and increased risk (>102 cm in men and >88 cm in women)]; smoking habit (never, ex-smoker, current); television (TV) watching (hours/day); sleep (hours/day) and pre-existing self-reported diabetes and hypertension at baseline (yes/no).

2.5. Statistical analysis

We performed a descriptive analysis of sociodemographic factors using number (n), percentages (%) and a chi-square test to describe and compare categorical variables, and for continuous variables, we used means, standard deviations (SD), and ANOVA test. We estimated person-years for each participant from the date of the interview at baseline to the date of death or completion of the 18-year follow-up, whichever came first. Hazard ratios (HRs) and 95 % confidence intervals (95 %CI) were obtained by Cox's regression models for each tertile of UPF consumption from all-cause mortality, CVD, and cancer mortality. Competing risk models as proposed by Fine and Gray's were also performed for CVD and cancer mortality using the *stcrreg* command in STATA v. 16.1®. In addition, we calculated the proportion of change per 10 % increase in UPF consumption. We carried out two models, model one was adjusted for age and sex, and another, more adjusted for factors - identified in the literature as possible confounders and those variables showing p-values <0.20 in bivariate analysis. Model 2 was adjusted by age, sex, educational level (<primary, primary, ≥secondary), waist circumference (healthy range, moderate risk and increased risk), smoking habit (current; ex-smoker, never smoker), self-reported diabetes (no/yes), self-reported hypertension (no/yes), sleep (hours/day) and TV watching (hours/day).

We checked the proportional hazard assumption using the scaled Schoenfeld residuals. We calculated the likelihood ratio test (LRT) to estimate the overall significance of UPF consumption as a categorical variable. Trend tests were also calculated to explore the dose–response for total UPF using tertiles of consumption as a continuous variable. We also estimated survival curves for categories of UPF and all-cause mortality and cumulative incidence curves for CVD and cancer mortality adjusted by age and sex according Cox regression and competing risk models (using *stcurve* command). Statistical significance was set at 0.05 and all reported *p*-values are from two-sided tests.

3. Results

Table 1 shows the main sociodemographic and lifestyle characteristics of the study participants according to UPF consumption. Participants in the highest tertile of UPF consumption had a mean age of 37.2 years and more than a half were men. They were mainly never smokers, had a low educational level, lower proportion of self-reported diabetes, cholesterol and hypertension, higher waist circumference and reported a greater time watching TV in hours and sleeping and had low consumption of fruits and vegetables. Regarding nutrient intake, those with the highest UPF consumption had higher intakes of calories, protein, carbohydrates, fats (total, monounsaturated, polyunsaturated, saturated and trans), sugar and sodium ($p < 0.001$).

Table 2 shows the main associations observed between UPF consumption and all-cause, CVD and cancer mortality. A total of 312 deaths occurred during the 18 years of follow-up (25047.7 person-year), 114 deaths (36.5 %) due to CVD and 80 deaths (25.6 %) to cancer. Survival curves for all-cause mortality adjusted by model 2 showed that the highest category of UPF consumption presented lower survival than the lowest categories of UPF consumption after 18-years of follow-up (Fig. 1). Similarly, cumulative incidence curves for CVD and cancer mortality showed that the highest UPF consumption presented higher risk of mortality than the lowest consumption of UPF (Fig. 2).

A higher UPF consumption was associated with higher all-cause, CVD and cancer mortality in the fully adjusted model (Table 2). Compared with participants in the lowest tertile of UPF consumption, participants in the highest tertile showed a 40 % higher risk of all-cause mortality, HR = 1.40 (95 %CI: 1.04–1.90). Evidence of a higher CVD and cancer mortality was also observed in the highest tertile of UPF consumption compared to the lowest tertile in the Cox regression models, HR = 1.39 (95 %CI: 0.80–2.41) and HR = 1.53 (95 %CI:0.83–2.82) respectively, although these associations were not statistically significant (Table 2). No significant dose–response trends were observed. When using competing risk models, a higher CVD mortality was also evident for the second tertile of UPF consumption, HR = 1.24 (0.80–1.96), and the highest tertile, HR = 1.35 (95 %CI: 0.80–2.26) although not statistically significant; however, the association with cancer mortality was lost, HR = 1.06 (95 %CI: 0.56–2.02).

When we explored the effect of 10 % increase of UPF consumption on all-cause, CVD and cancer mortality, we observed increased mortality, although these associations were not statistically significant (Table 2).

4. Discussion

This study shows that higher UPF consumption is associated with higher all-cause mortality in an adult Mediterranean population after an 18-year follow-up. There was also some evidence

Table 1
Sociodemographic and lifestyle characteristics according to UPF consumption (% of total daily intake in g/d) among participants aged 20 years and above of the Valencian Nutrition Study in Spain (n = 1.538).

	Tertiles of UPF consumption				
	Total	Low intake (<6.7 %) N = 513	Medium intake (6.7–12.6 %) N = 513	High intake (>12.6 %) N = 512	p-value[a]
Study, *n* (%)	1.538	513 (33.4)	513 (33.4)	512 (33.2)	
Sex, *n* (%)					
Men	689 (44.8)	203 (39.6)	225 (43.8)	261 (51.0)	<0.001
Women	849 (55.2)	310 (60.4)	288 (56.1)	251 (49.0)	
Age, mean (SD)	46.2 (18.0)	55.0 (15.0)	46.0 (17.3)	37.4 (17.2)	<0.001
Education level, *n* (%)					
< Primary school	703 (45.7)	314 (61.2)	228 (44.4)	161 (31.4)	<0.001
Primary school	367 (23.9)	102 (19.9)	126 (24.6)	139 (27.2)	
≥ Secondary school	468 (30.4)	97 (18.9)	159 (31.0)	212 (41.4)	
Waist circumference, *n* (%)					
Healthy range	567 (37.3)	127 (25.1)	200 (39.4)	240 (47.4)	<0.001
Moderate risk	365 (24.0)	129 (25.5)	120 (23.6)	116 (22.9)	
Increased risk	587 (38.6)	249 (49.3)	188 (37.0)	150 (29.6)	
Smoking status, *n* (%)					
Never	770 (50.1)	283 (55.2)	257 (50.1)	230 (44.9)	<0.001
Ex-smoker	255 (16.6)	99 (19.3)	79 (15.4)	77 (15.0)	
Current	513 (33.4)	131 (25.5)	177 (34.5)	205 (40.1)	
Diabetes[b] (yes), *n* (%)	120 (7.8)	79 (5.1)	30 (6.0)	12 (2.3)	<0.001
Hypertension[b] (yes), *n* (%)	278 (18.1)	123 (24.0)	91 (17.7)	64 (12.5)	<0.001
Cholesterol[b] (yes), *n* (%)	201 (13.1)	108 (21.1)	62 (12.1)	31 (6.0)	<0.001
TV, hours/day, mean (SD)	2.5 (1.8)	2.5 (1.7)	2.5 (1.6)	2.6 (1.9)	0.467
Sleep, hours/day, mean (SD)	7.5 (1.4)	7.3 (1.5)	7.5 (1.4)	7.6 (1.3)	<0.001
Fruit and vegetables, grams/day, mean (SD)	685.8 (342.9)	781.7 (391.5)	700.3 (324.6)	575.2 (270.1)	<0.001
Nutrient intake/day, mean (SD)					
Calories	2217.0 (732.2)	1885.0 (599.2)	2250.5 (637.4)	2516.2 (802.7)	<0.001
Proteins	94.7 (30.1)	84.3 (26.7)	96.7 (27.5)	103.1 (32.7)	<0.001
Carbohydrates	253.0 (90.5)	221.4 (77.6)	251.1 (79.7)	286.6 (100.5)	<0.001
Total FAT	90.6 (37.0)	73.1 (29.6)	93.5 (32.3)	105.1 (40.8)	<0.001
PUFA	15.8 (7.9)	13.1 (6.7)	16.2 (7.6)	17.9 (8.5)	<0.001
MUFA	40.7 (17.3)	33.9 (15.3)	42.2 (15.7)	45.9 (18.6)	<0.001
STA	26.9 (12.9)	20.4 (9.7)	27.7 (10.9)	32.8 (14.6)	<0.001
Trans	1.8 (1.2)	1.1 (0.69)	1.8 (0.9)	2.5 (1.5)	<0.001
Total sugar	105.5 (45.8)	92.2 (38.9)	102.0 (39.4)	122.4 (52.5)	<0.001
Sodium	3066.9 (1325.4)	2488.8 (1065.0)	3153.0 (11147.3)	3559.8 (1497.2)	<0.001

Abbreviations; SD, Standard Deviation; PUFA, total polyunsaturated fat intake in grams; MUFA, total monosaturated fat intake in grams, STA, total saturated fat intake in grams. Waist circumference: healthy range (78–94 cm in men and 64–80 cm in women), moderate risk (94–102 cm in men and 80–88 cm in women), increased risk (>102 cm in men and >88 cm in women).

[a] P-value from chi-square test (categorical variables) and ANOVA (continuous variables).

[b] Self-reported diabetes (no/yes), hypertension (no/yes) and cholesterol (no/yes).

that a higher UPF consumption might increase the risk of CVD and cancer mortality, although these associations were not statistically significant.

We should note that we observed a lower proportion of self-reported hypertension and diabetes among participants with higher UPF consumption in our study. This inverse association with UPF consumption has been previously reported [30], probably due to these subjects being more conscious on their health status and their physicians recommend them to follow diets with foods with lower sugar o salt content.

4.1. Ultra-processed food consumption and all-cause mortality

The association between UPF consumption and all-cause mortality is consistent with the results from other prospective studies conducted in Mediterranean [6–9,14,15] and non-Mediterranean countries [31,32], as well as those from meta-analyses and systematic reviews [33,34]. In line with our results, other studies conducted in adults from Mediterranean countries like Spain, France, and Italy have also reported increased all-cause mortality in participants with a highest UPF consumption compared to those with a lowest intake [6–10]. In the 19-year follow-up NHANES III study, participants with the highest UPF consumption had a 31 % higher risk of all-cause mortality when compared to those with the lowest consumption [31]. Similarly, in a prospective study carried out with 60,298 participants from the UK after 10.9 years of follow-up, participants in the highest quartile of UPF consumption had 22 % higher risk of all-cause mortality [35]. Furthermore, a positive association between UPF consumption and all-cause mortality was observed in a systematic review of 20 studies [33]. In a recently published meta-analysis, the highest intake of UPF was significantly associated with an increased risk of all-cause mortality RR = 1.29 (95 %CI: 1.17–1.42) [34].

4.2. Ultra-processed food consumption and cardiovascular mortality

In this study, we found increased risk of CVD mortality for the highest tertiles of UPF consumption in both cox regression and competing risk models, although these associations were not statistically significant. This result is similar to that reported in previous studies in which they also observed a non-significant increased risk of CVD mortality [7,31]. However, several studies have shown a statistically significant increased risk of CVD mortality. In one US study with adult population, after an average follow-up of 13.5 years, participants in the highest (>4 serving/day) vs lowest (<0.5 servings/day) quintiles of UPF consumption had higher risk of CVD mortality, HR = 1.50 (95 %CI: 1.36–1.64) and

Table 2
Associations between ultra-processed food (UPF) consumption (% of total daily intake in g/d) and all-cause, cardiovascular disease (CVD) and cancer mortality and among participants of Valencian Nutrition Survey in Spain after 18 years of follow-up (n = 1538). Cox regression (models 1 and 2) and Competing risk models (model3).

	Tertiles of UPF consumption							10 % increase of UPF consumption	
	Low intake (<6.7 %) N = 513	Medium intake (6.7–12.6 %) N = 513		High intake (>12.6 %) N = 512					
		HR (95 % CI)	*p*-value[a]	HR (95 % CI)	*p*-value[a]	p-trend[b]	*p*-value[c]	HR (95 % CI)	*p*-value[a]
All-cause									
Deaths, *n*	152	86		74					
Person-years	7967.3	8544.5		8535.9					
Model 1	1.00	0.74 (0.56–0.96)	0.024	1.33 (1.01–1.76)	0.044	0.269	0.001	1.15 (0.98–1.34)	0.084
Model 2	1.00	0.79 (0.60–1.03)	0.086	1.40 (1.04–1.90)	0.028	0.174	0.003	1.17 (0.99–1.38)	0.057
CVD									
Deaths, *n*	54	35		25					
Person-years	7069.7	8019.4		8100.1					
Model 1	1.00	0.80 (0.52–1.23)	0.309	1.25 (0.77–2.03)	0.353	0.626	0.237	1.11 (0.86–1.44)	0.415
Model 2	1.00	1.03 (0.66–1.60)	0.909	1.39 (0.80–2.41)	0.238	0.310	0.488	1.19 (0.90–1.58)	0.217
Model 3	1.00	1.24 (0.80–1.96)	0.342	1.35 (0.80–2.26)	0.261	–	–	1.20 (0.93–1.55)	0.161
Cancer									
Deaths, *n*	39	23		18					
Person-years	6851.9	7933.2		8024.1					
Model 1	1.00	0.65 (0.39–1.08)	0.099	1.56 (0.88–2.80)	0.129	0.530	0.026	1.19 (0.85–1.67)	0.314
Model 2	1.00	0.64 (0.37–1.11)	0.114	1.53 (0.83–2.82)	0.173	0.557	0.041	1.18 (0.83–1.68)	0.341
Model 3	1.00	0.90 (0.52–1.54)	0.695	1.06 (0.56–2.02)	0.853	–	–	0.96 (0.68–1.36)	0.806

Model 1: Cox regression model adjusted for age and sex adjusted.
Model 2. Cox regression model adjusted for model 1 plus educational level (<primary, primary ≥ secondary), waist circumference: healthy range (78–94 cm in men and 64–80 cm in women), moderate risk (94–102 cm in men and 80–88 cm in women), increased risk (>102 cm in men and >88 cm in women), smoking habit (current, ex- and never smoker), self-reported diabetes (no/yes), hypertension (no/yes), cholesterol (no/yes), sleeping time (hours/day), TV watching (hours/day) and fruits and vegetables consumption (grams/day).
Model 3: Competing risk model adjusting for the same variables as in model 2.
HR (95 % CI) = Hazard or Sub-hazard ratios and 95 % Confidence Intervals.
[a] Wald test p-values from Cox and competing risk models.
[b] P-value from trend test from Cox models.
[c] Likehood ratio test p-value from Cox models.

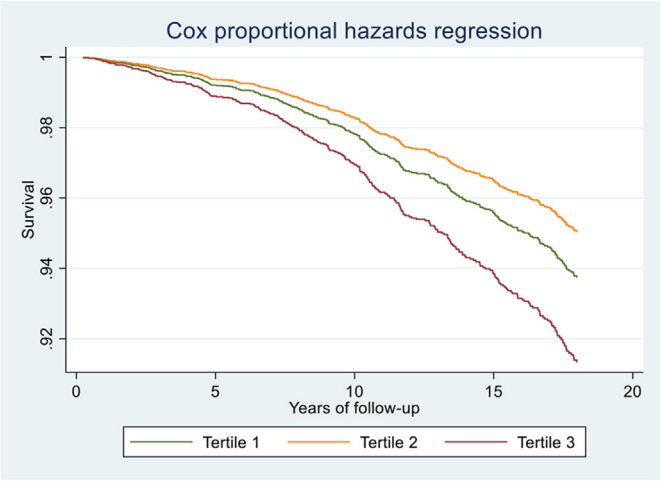

Fig. 1. Survival curves for all-cause mortality according to tertiles of UPF consumption adjusted by model 2 after 18 years of follow-up.

heart disease, HR = 1.68 (95 %CI: 1.50–1.87) [36]. Interestingly, in this study the association between UPF consumption and CVD mortality was stronger in women, HR = 1.93 (95 %CI: 1.68–2.21). Higher CVD mortality associated with the UPF consumption has also been reported in other populations, including individuals with prior CVD events [15].

4.3. Ultra-processed food consumption and cancer mortality

Data on the association between UPF consumption and cancer mortality is scarce. In our study, we observed a non-significant increased risk of cancer mortality in the participants in the highest tertile of UPF consumption. Higher cancer mortality has also been reported in the NutriNet-Santé (France) prospective study [14], for every 10 % increase in UPF consumption a 12 % increase in cancer mortality was reported. However, other studies did not find significant positive associations between UPF consumption and cancer mortality [7,37].

Although the consumption of UPF in Spain could be considered low compared to other European countries [38], it is drifting towards higher UPF consumption [16]. Overall, several mechanisms and factors could explain the positive association between UPF consumption and increased mortality rates. Firstly, increased UPF consumption is associated with poor overall diet quality and overconsumption of kilocalories due to high-energy density and low satiety which characterize UPF [3], all of which can be related to higher mortality rates. In fact, in one of the studies discussed above [8], a theoretical isocaloric substitution of UPF for minimally or unprocessed products was associated with a significant decrease in mortality. Secondly, a diet with a high content of UPF provides significant amounts of trans fatty acids, salt, and/or sugar, as shown in our study (Table 1) which have been associated with increased mortality rates in observational studies [39–41]. Thirdly, a higher intake of UPF is associated with unhealthy behavioural patterns, such as smoking or a sedentary lifestyle [14], and for this reason we have adjusted our regression models for smoking and other factors (e.g. sedentary behaviours, such as TV watching or pre-existing diseases). Fourthly, few studies have observed a significant association between CVD mortality and UPF consumption although the characteristic of a UPF-rich diet such as low-fat quality, low fresh fruits and vegetables consumption as well as high sodium content, would suggest a harmful effect on CVD mortality [15,36]. Based on this context it would be interesting to consider the influence of sex in the association between UPF consumption and CVD mortality [36]. In this sense, more focuses are currently put on CVD-related

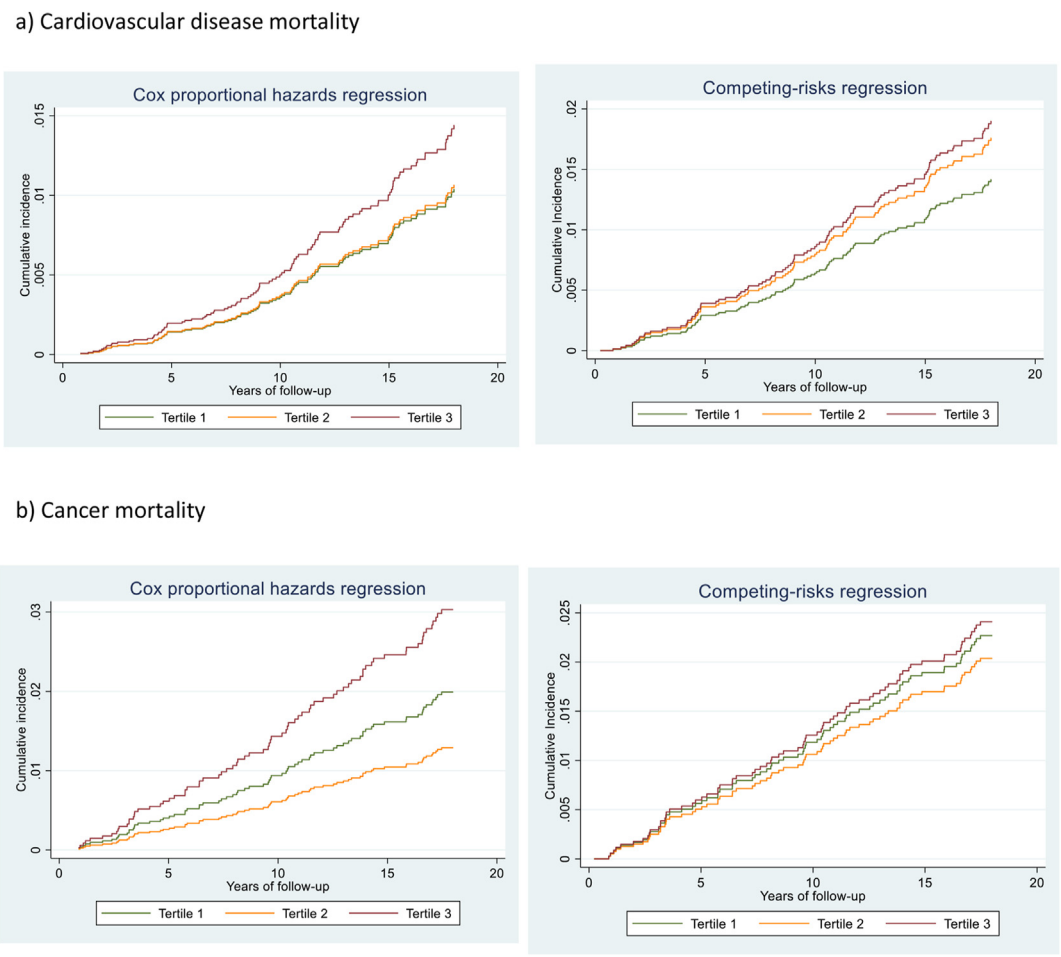

Fig. 2. Cumulative incidence curves of cardiovascular disease (a) and cancer (b) mortality according to tertiles of UPF consumption after 18 years of follow-up (Curves adjusted for the variables of models 2 and 3 in Table 2).

differences between women and men [42,43] and it could constitute an important and missing link in the context of UPF consumption and CVD mortality assessment. When we explored the effect of UPF consumption separately in men and women, the associations remained like those observed for the whole cohort, although the number of deaths by sex was much lower, particularly for CVD and cancer, and estimates were less precise (data not shown). Thus, more studies with bigger sample size would be required to confirm the hypothesis of a differential effect by sex.

In this study, we evaluated the association between UPF consumption and cause-specific mortality using Cox regression and competing risk models. Regarding CVD mortality, competing risk models still showed evidence of a positive association although not statistically significant, whereas for cancer mortality, the initial association observed with UPF consumption in cox regression, it was not observed in competing risk models. This may suggest that the detrimental effect of UPF consumption may be more related to specific mechanisms of cardiometabolic factors (e.g. inflammatory), rather than those observed for cancer risk.

4.4. Strengths and limitations

Our study has several limitations that should be discussed. First, we only measured dietary intake at baseline, and then we were not able to control changes in UPF consumption during the 18-years of follow-up. However, previous studies have noted that dietary intake is a habit that remains unchanged over time. In fact, previous studies have shown that a single diet assessment at baseline is a valid method for epidemiological studies to analyse long-term effects on the risk of chronic diseases [44,45]. However, the consumption of UPF may have increased over the study period due to a higher food supply [4,38]. Thus, any misclassification in UPF consumption categories, if any, could be non-differential, and therefore, lead to an underestimation of the effects of UPF on mortality. Second, our participants were volunteers and some response bias is possible, although collecting dietary information rarely influences the participation rate in studies. Third, the sample size in our study was not estimated a priori for survival analyses but it was calculated in order to assess differences in the main lifestyles and dietary variables from the VNS which was carried out in the nineties on a representative sample of the adult population. Therefore, we must consider that our sample size may have limited the statistical power to detect some associations as significant (e.g., cancer or CVD), although the follow-up period was long enough to notice significant associations with all-cause mortality after 18 years. Finally, we did not collect information on relevant variables such as the use of vitamin supplements, the antioxidant capacity, or the presence of specific diseases (e.g. atherosclerosis, autoimmune diseases, liver or kidney failure) that overall may have a confounding role. However, the percentage of multivitamin use was very low (>6 %) and in the multivariable analyses, we adjusted for the intake of fruit and vegetables (the main sources of fiber and vitamins on the diet), and

self-reported diseases like diabetes, hypertension, and high cholesterol. Moreover, the effect of other variables with a potential confounding role like socio-economic and physical activity, were controlled using indicators such as educational level and television watching.

Nevertheless, our study has several strengths. It was conducted on a well-defined population with available data regarding dietary intake, lifestyles and socioeconomic characteristics. Trained field-workers using standardized and validated questionnaires collected all this information. In addition, two trained dietitians categorized the food products into NOVA classification and a third dietitian assisted in the classification when a mismatch occurred. Further, even after adjusting for several known factors related to mortality, our results remained statistically significant. Another strength of this study is the long period of follow-up of the participants. We would like to highlight that our results add new evidence on a relevant and increasingly studied public health issue, namely UPF consumption. In addition, our findings can serve as a basis for initiating health promotion and mortality prevention strategies with the aim to reduce UPF consumption in Mediterranean adults.

5. Conclusions

Our study shows that a high consumption of UPF may increase the risk of all-cause mortality in a Mediterranean population after a long follow-up period. Therefore, considering the increase in UPF consumption and their detrimental health effects on mortality, further prospective studies should be carried out to confirm if UPF consumption also increase the incidence of CVD and cancer, and consequently, to enhance more attention should be put in population nutritional education and nutritional policies.

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Conflict of interest

None of the authors declares conflict of interest.

Author contributions

Conceptualization, J.V.; Formal analysis, L.T.C. and S.G.P; Writing—original draft preparation, L.T.C and A.R.; Writing—review and editing, all authors; Supervision, J.V. All authors have read and agreed to the published version of the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2024.01.014.

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