Does consumption of ultra-processed foods matter for liver health? Prospective analysis among older adults with metabolic syndrome.

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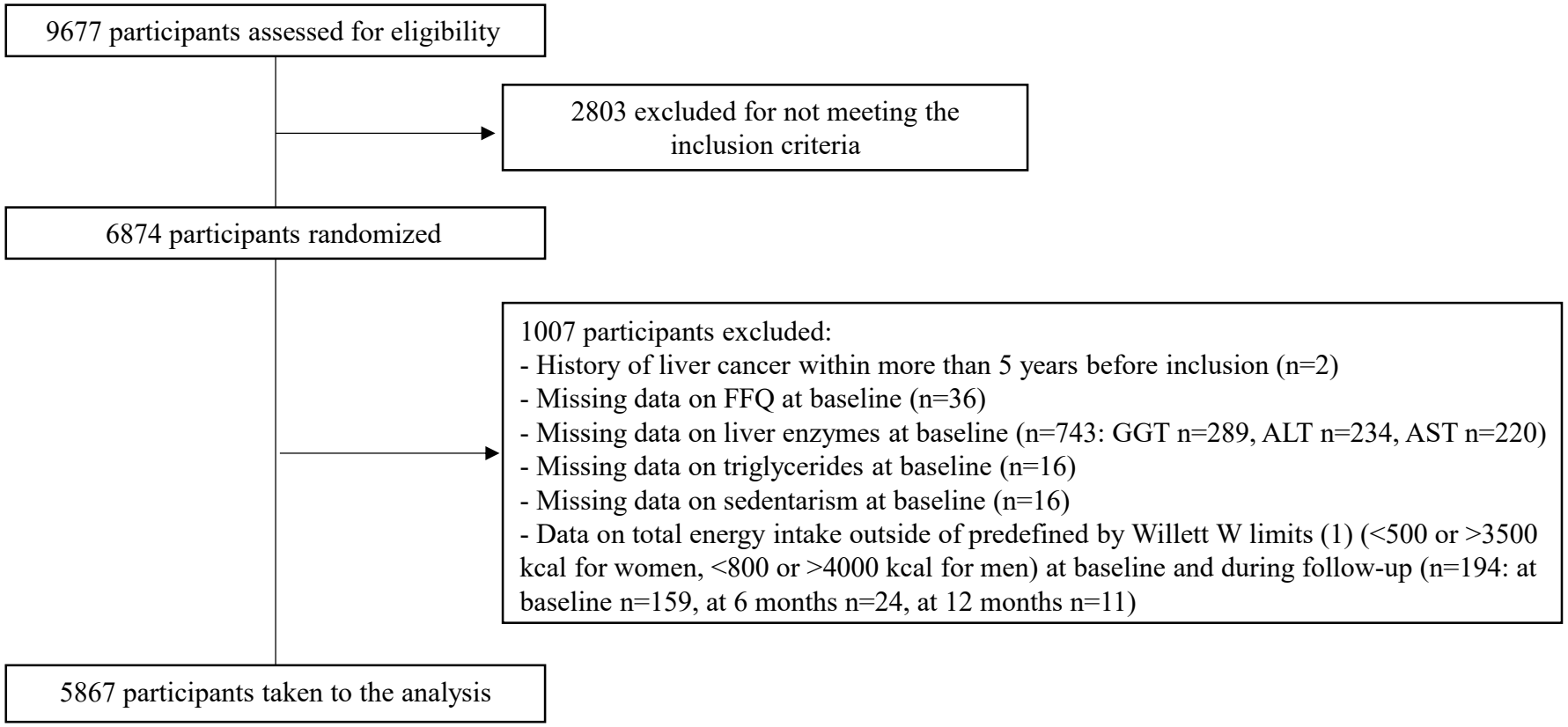
Supplementary Figure S1.



Flow chart for the selection of participants for analysis.

Abbreviations: ALT - alanine aminotransferase; AST - aspartate aminotransferase; FFQ – Food frequency questionnaire; FLI – Fatty liver index; GGT - gamma-glutamyltransferase; HSI – Hepatic steatosis index

Supplementary Table S1. Examples of food and beverage items considered as NOVA processing groups.

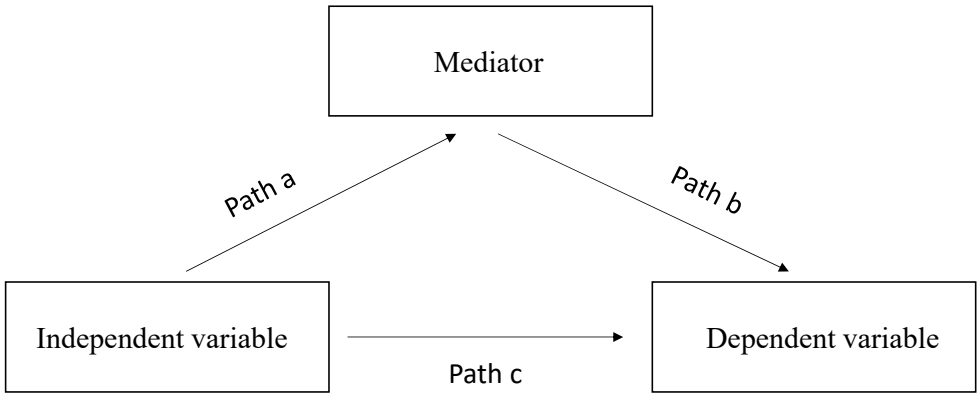
Group 1: Unprocessed or minimally processed foods	milk (whole-fat, semi-skimmed and skimmed), yogurt (whole-fat and skimmed), eggs, meats (chicken, turkey, beef, pork, lamb, rabbit), liver, offal, fish and seafoods, fresh vegetables, gazpacho, boiled potatoes, fresh fruits, dried fruits, nuts, legumes, whole-grain cereals, rice (whole-grain and refined), pasta (whole-grain and refined), natural fruit juices, coffee and tea.
Group 2: Processed culinary ingredients	vegetable oils (regular and virgin-extra olive oil, oils from sunflower seeds, corn and soybean), butter, lard, salt, sugar and honey
Group 3: Processed foods	condensed milk, cream, cheeses (cured, semi-cured, cottage and fresh), bacon, cured ham, canned fish, salt-curing and drying fish, breads (white and whole-grain), artisanal pastries, home-made French fries, olives, fruits in syrup, marmalade, beer, wine, champagne and decaffeinated coffee.
Group 4: UPF	Petit suisse, creamy cheese spreads, margarine, custard, flan, pudding, ice-cream, milkshakes, processed meat (ham, chorizo, mortadella, sausages, hamburgers, meat balls, pate, foie-gras), potato chips, breakfast cereals, cookies, industrial and commercial pastries (croissant, ensaimada, donuts, muffins, cakes, churros), chocolates, sugary cocoa powder, marzipan, nougat, pre-prepared dishes (croquettes, empanadillas, pizza), instant soups, mayonnaise, mustard, ketchup, packed fried tomato sauce, savoury packed snacks, soft drinks (sugar- and artificially-sweetened), commercial fruit juices, alcoholic drinks produced by fermentation followed by distillation (whisky, vodka, gin, liquors)

Process of classification of FFQ items into four NOVA groups according to the degree and purpose of their processing.

The classification of food and beverage items from food frequency questionnaire (FFQ) (2) into one of the four food groups (staring from minimally processed products to ultra-processed foods (UPF)) according to NOVA system (3) was performed by two independent dietitians. Posteriori, the classification was independently revised by specialists in nutritional epidemiology - members of four recruiting centers participating in the trial. Discrepancies in classification were discussed and decision was made by consensus taking some assumptions. For an example, fruit juices, milkshakes, meatballs, hamburgers and pizza can be consumed as artisanal or industrial varieties - we assumed that they were industrial and classified them as ultra-processed products. Regarding yogurts and whole-grain cereals, the FFQ used does not distinguish between plain, sweetened or flavored varieties; these foods were considered to belong to unprocessed or minimally processed foods group.

Supplementary Text S1. Procedure for mediation analysis.

Mediation analyses were performed to determine the extent to which the association between independent variable (ultra-processed foods (UPF)), continuous variable) and each dependent variable (Fatty liver index (FLI) and Hepatic steatosis index (HSI)) was mediated through individual nutritional factors, characteristics of UPF (total energy intake, saturated and trans fatty acids, cholesterol, fiber, glycemic index, and sodium), and adherence to energy-restricted Mediterranean Diet, as well as NAFLD-related biomarkers (known risk factors and components of hepatic steatosis indices). Mediation analyses were performed following standard steps proposed by Baron and Kenny (1986) with adjustments introduced by Iacobucci et al (4) to evaluate direct and indirect effect and the proportion mediated by each of these variables, following the schema below.



The indirect effect was estimated as the multiplicative product of paths a (the effect of independent variable on the mediator) and b (effect of the mediator on the dependent variable, controlling for the independent variable), whereas the direct effect as the effect of the independent variable on the dependent variable (Path c). Mediation was considered plausible if either Path a or Path b were statistically significant, otherwise the indirect effect and the mediation were considered null. The proportion mediated was calculated as the ratio of indirect effect by the sum of the direct and indirect effect (a*b/(a*b)+c).

For these analyses mixed-effects linear modelling for repeated measure with random intercepts at recruiting center, cluster family and patient level were used after controlling in fully adjusted model 2 for baseline variables, such as age, sex, study arm, educational level, smoking habits, height, as well as repeatedly measured physical activity, sedentary behavior, alcohol intake, and follow-up time.

Supplementary Table S2. Characteristics of the study participants at baseline, 6 months and 12 months of follow-up.

	Baseline		6 months		12 months		
	n	**Mean (SD)**	**n**	**Mean (SD)**	**n**	**Mean (SD)**	***p-value***
Sociodemographic factors							
Women, n (%)	5867	2807 (47.8)					
Age (years)	5867	65.0 (4.9)					
Higher education, n (%)	5867	1233 (21.0)					
Current smokers, n (%)	5867	732 (12.5)					
Lifestyle factors							
Physical activity (METs min/week)	5867	2477 (2297)	5448	2914 (2463)	5403	3042 (2478)	*<0.001*
Sedentary behavior (h/day)	5867	6.00 (1.96)	5449	5.98 (1.92)	5404	5.96 (1.89)	*0.011*
FFQ:							
Total energy intake (kcal/day)	5867	2360 (550)	5173	2213 (450)	5281	2208 (457)	*<0.001*
Saturated FA (% of energy intake)	5867	9.95 (1.99)	5173	9.16 (1.72)	5281	9.20 (1.69)	*<0.001*
Trans FA (% of energy intake)	5867	0.22 (0.13)	5173	0.15 (0.10)	5281	0.15 (0.10)	*<0.001*
Cholesterol (mg/day)	5867	380 (115)	5173	352 (99)	5281	350 (95)	*<0.001*
Sodium (mg/day)	5867	3281 (1016)	5173	2906 (873)	5281	2892 (868)	*<0.001*
Glycemic load	5867	131 (46)	5173	111 (37)	5281	110 (36)	*<0.001*
Fiber intake (g/day)	5867	25.9 (8.7)	5173	29.7 (8.6)	5281	29.6 (8.3)	*<0.001*
Alcohol intake (g/day)	5867	11.1 (15.1)	5173	9.62 (13.2)	5281	9.99 (14.0)	*<0.001*
Adherence to erMedDiet (17p score)	5867	8.45 (2.7)	5433	11.5 (2.9)	5386	11.7 (2.8)	*<0.001*
NOVA processing groups:							
Unprocessed or minimally processed foods (% of g/day)	5867	68.1 (12.5)	5173	74.8 (10.8)	5281	74.9 (10.8)	*<0.001*
Processed culinary ingredients (% of g/day)	5867	2.79 (1.28)	5173	2.68 (1.07)	5281	2.73 (1.10)	*<0.001*
Processed foods (% of g/day)	5867	20.9 (10.8)	5173	17.3 (9.4)	5281	17.4 (9.4)	*<0.001*
UPF (% of g/day)	5867	8.19 (6.95)	5173	5.20 (5.29)	5281	5.00 (5.07)	*<0.001*
Liver health risk factors							
BMI (kg/m^2)	5867	32.5 (3.4)	5630	31.8 (3.6)	5628	31.7 (3.6)	*<0.001*
Overall obesity prevalence, n (%)	5867	4289 (73.1)	5630	3677 (65.3)	5628	3601 (64.0)	
History of overweight from childhood, n (%)	5867	334 (5.69)					
Waist circumference (cm)	5867	107.5 (9.6)	5415	105.3 (9.8)	5365	104.8 (10.0)	*<0.001*

Abdominal obesity prevalence, n (%)	5867	5454 (93.0)	5415	4597 (84.9)	5365	4440 (82.8)	
HbA1c (%)	5464	6.12 (0.87)	4817	6.06 (0.86)	4976	6.05 (0.82)	*<0.001*
Type 2 diabetes prevalence at baseline, n (%)	5867	1828 (31.2)					
Number of MetS factors at baseline	5844	3.38 (0.98)	5121	3.16 (1.06)	5198	3.12 (1.09)	*<0.001*
Liver health biomarkers							
FLI (arbitrary units)	5867	77.9 (17.1)	5064	72.6 (19.8)	5181	71.7 (20.5)	*<0.001*
NAFLD prevalence (FLI ≥ 60), n (%)	5867	4934 (84.1)	5064	3768 (74.4)	5181	3761 (72.6)	
HSI (arbitrary units)	5867	43.4 (5.87)	5001	42.2 (5.91)	5097	42.0 (5.65)	*<0.001*
NAFLD prevalence (HSI ≥ 36), n (%)	5867	5585 (95.2)	5001	4495 (89.9)	5097	4515 (88.6)	
ALT (U/L)	5867	27.0 (15.4)	5184	25.1 (17.5)	5310	24.8 (15.6)	*<0.001*
AST (U/L)	5867	23.3 (9.92)	5037	22.7 (11.4)	5140	22.9 (16.9)	*0.032*
ALT/AST ratio	5867	1.16 (0.53)	5026	1.11 (0.51)	5125	1.09 (0.45)	*<0.001*
AST/ALT ratio	5867	0.95 (0.30)	5026	1.00 (0.38)	5125	1.02 (0.75)	*<0.001*
GGT (U/L)	5867	37.6 (37.2)	5135	35.4 (36.0)	5255	34.9 (37.1)	*<0.001*
Triglycerides (mg/dL)	5867	151 (77)	5212	143 (74)	5333	143 (73)	*<0.001*

Abbreviations: ALT - alanine aminotransferase; AST - aspartate aminotransferase; BMI – body mass index; erMedDiet – energy-restricted Mediterranean Diet; GGT - gamma-glutamyltransferase; FA – fatty acids; FFQ – Food frequency questionnaire; FLI – fatty liver index; HbA1c – glycated hemoglobin; HSI – hepatic steatosis index; MetS – metabolic syndrome; NAFLD – non-alcoholic fatty liver disease; UPF – ultra-processed foods.

Values shown are mean (SD) unless otherwise specified. Overall obesity was defined as body mass index ≥ 30.0 kg/m^2, and abdominal obesity as waist circumference ≥ 88 cm in women or ≥ 102 cm in men.

The consumption of NOVA processing groups was expressed as a percentage of total food and beverage intake in g/day. Daily intake of beverages was collected in cubic centimeters and then converted into milliliters (1 cc = 1 ml), and further into grams, assuming that 1 ml = 1 g.

P-values for changes in repeatedly measured characteristics over follow-up time were determined using mixed-effects linear modelling with random intercepts at recruiting center, cluster family and patient level.

Out of the total analytical sample of 5867 participants, baseline data on HbA1c was available for 93.1% participants and on number of MetS factors for 99.6%. Although all the participants presented MetS (5) at inclusion (factors medically-diagnosed within one year proceeding the inclusion), we recalculated this variable using data on blood parameters and medication use available at baseline and follow-up. Participants with insufficient data on smoking habits were 26 (0.44 %), and were classified in separate category.

Supplementary Figure S2.

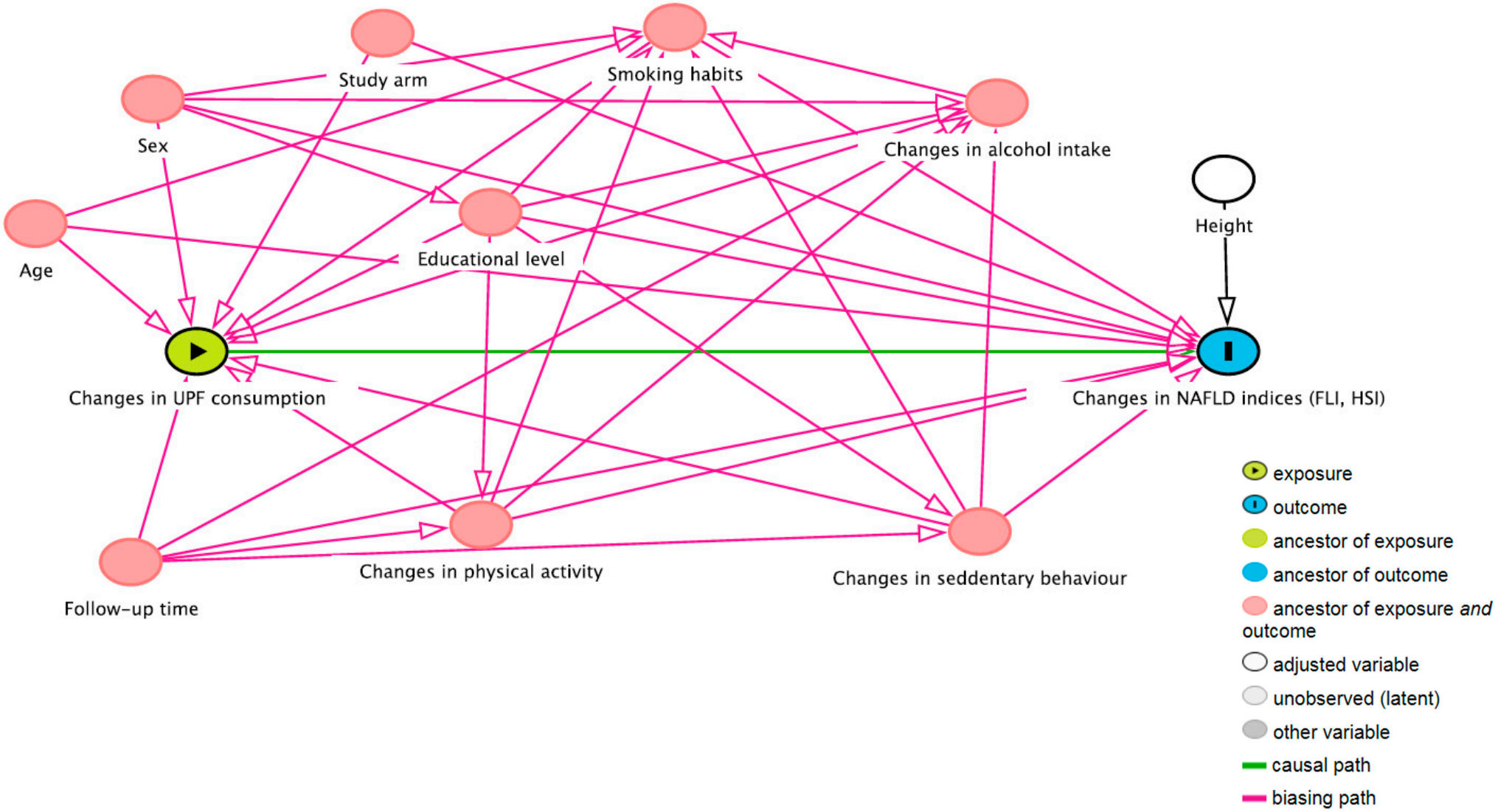


Figure legend. Directed acyclic graph (DAG).

The total unconfounded effect of changes in UPF cosnumption on NAFLD indices was drawn and analyzed using available free online application DAGitty (www.dagitty.net). The minimally sufficient adjustment set was age, sex, study arm, baseline educational level, smoking habits, height, as well as changes in physical activity, sedentary behavior, alcohol intake, and follow-up time.

Abbreviations: FLI – fatty liver index; HSI – hepatic steatosis index; NAFLD – non-alcoholic fatty liver disease; UPF – ultra-processed foods.

Supplementary Table S3. Association between concurrent changes in UPF consumption (% of g/day) and changes in NAFLD indices during 1-year of follow-up.

	Continuous[a]		Quintiles of changes in UPF consumption[b]					
	Per 10% change in UPF consumption		Q1	Q2	Q3	Q4	Q5	
	β (95% CI)	*p-value*	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	*p for trend*
FLI score								
Model 1	1.88 (1.52; 2.24)	*<0.001*	reference	0.93 (0.41; 1.46)	2.31 (1.76; 2.87)	3.43 (2.85; 4.01)	4.30 (3.66; 4.93)	*<0.001*
Model 2	1.60 (1.24; 1.96)	*<0.001*	reference	0.77 (0.25; 1.28)	2.01 (1.46; 2.55)	3.00 (2.43; 3.58)	3.73 (3.10; 4.35)	*<0.001*
HSI score								
Model 1	0.50 (0.36; 0.64)	*<0.001*	reference	0.44 (0.22; 0.65)	0.60 (0.37; 0.83)	0.70 (0.46; 0.94)	1.08 (0.83; 1.33)	*<0.001*
Model 2	0.43 (0.29; 0.57)	*<0.001*	reference	0.39 (0.17; 0.60)	0.51 (0.29; 0.74)	0.58 (0.35; 0.82)	0.93 (0.67; 1.18)	*<0.001*

Abbreviations: FLI – Fatty liver index; HSI – Hepatic steatosis index; NAFLD – non-alcoholic fatty liver disease; UPF – ultra-processed foods.

The consumption of UPF was expressed as a percentage of total food and beverage intake in g/day. Daily intake of beverages was collected in cubic centimeters and then converted into milliliters (1 cc = 1 ml), and further into grams, assuming that 1 ml = 1 g.

Mixed-effects linear models for repeated measures with random intercepts at recruiting center, cluster family and patient level were used. Model 1 was adjusted for age, sex, study arm and follow-up time; model 2 was further adjusted for baseline variables, such as educational level, smoking habits, height, as well as repeatedly measured physical activity, sedentary behavior, and alcohol intake.

[a]Estimates β are interpreted as changes in NAFLD indices associated with increments of 10% in UPF. [b]Estimates β are interpreted as changes in NAFLD indices in each sex-specific quintile of UPF consumption, compared to quintile 1, the reference category.

Supplementary Table S4. Sensitivity analysis for the association between concurrent changes in UPF consumption (% of g/day) and changes in NAFLD indices during 1-year of follow-up.

A. FLI score	Continuous[a]		Quintiles of changes in UPF consumption[b]					
	Per 10% change in UPF consumption		Q1	Q2	Q3	Q4	Q5	
	β (95% CI)	*p-value*	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	*p for trend*
Overall	1.60 (1.24; 1.96)	*<0.001*	reference	0.77 (0.25; 1.28)	2.01 (1.46; 2.55)	3.00 (2.43; 3.58)	3.73 (3.10; 4.35)	*<0.001*
Nutritional factors								
+ changes in total energy intake (kcal/day)	1.47 (1.11; 1.84)	*<0.001*	reference	0.72 (0.20; 1.23)	1.91 (1.36; 2.46)	2.86 (2.28; 3.44)	3.54 (2.90; 4.17)	*<0.001*
+ changes in saturated FA intake (g/day)	1.31 (0.94; 1.68)	*<0.001*	reference	0.64 (0.12; 1.16)	1.77 (1.21; 2.32)	2.67 (2.08; 3.26)	3.29 (2.64; 3.94)	*<0.001*
+ changes in trans FA intake (g/day)	1.31 (0.94; 1.68)	*<0.001*	reference	0.64 (0.12; 1.15)	1.76 (1.20; 2.31)	2.66 (2.07; 3.25)	3.29 (2.65; 3.94)	*<0.001*
+ changes in cholesterol intake (mg/day)	1.60 (1.23; 1.96)	*<0.001*	reference	0.77 (0.26; 1.29)	2.02 (1.47; 2.57)	3.02 (2.44; 3.60)	3.75 (3.12; 4.38)	*<0.001*
+ changes in fiber intake (g/day)	1.34 (0.98; 1.70)	*<0.001*	reference	0.65 (0.14; 1.17)	1.82 (1.27; 2.37)	2.71 (2.13; 3.29)	3.31 (2.68; 3.94)	*<0.001*
+ changes in glycemic load	1.43 (1.07; 1.79)	*<0.001*	reference	0.72 (0.20; 1.23)	1.89 (1.35; 2.44)	2.83 (2.25; 3.41)	3.45 (2.82; 4.08)	*<0.001*
+ changes in sodium intake (mg/day)	1.48 (1.12; 1.84)	*<0.001*	reference	0.71 (0.19; 1.22)	1.89 (1.34; 2.44)	2.85 (2.27; 3.43)	3.52 (2.89; 4.16)	*<0.001*
+ changes in intake of saturated and trans FA, cholesterol, fiber, glycemic load and sodium	0.50 (0.12; 0.87)	*0.010*	reference	0.35 (-0.17; 0.85)	1.23 (0.67; 1.78)	1.82 (1.23; 2.42)	2.02 (1.35; 2.68)	*<0.001*
+ changes in adherence to erMedDiet (17p score)	0.68 (0.32; 1.04)	*<0.001*	reference	0.36 (-0.15; 0.86)	1.22 (0.68; 1.77)	1.80 (1.22; 2.38)	2.08 (1.44; 2.71)	*<0.001*
NAFLD-related risk factors								
+ changes in BMI (kg/m^2)	0.49 (0.21; 0.77)	*<0.001*	reference	-0.01 (-0.42; 0.39)	0.50 (0.07; 0.93)	1.02 (0.57; 1.47)	1.32 (0.83; 1.80)	*<0.001*
+ changes in waist circumference (cm)	0.67 (0.40; 0.95)	*<0.001*	reference	0.35 (-0.06; 0.75)	0.71 (0.28; 1.14)	1.27 (0.82; 1.72)	1.63 (1.14; 2.11)	*<0.001*
+ changes in HbA1c (%)	1.25 (0.87; 1.63)	*<0.001*	reference	0.60 (0.06; 1.14)	1.84 (1.27; 2.41)	2.69 (2.08; 3.29)	3.22 (2.55; 3.88)	*<0.001*
+ changes in number of MetS factors	1.22 (0.89; 1.55)	*<0.001*	reference	0.55 (0.08; 1.02)	1.57 (1.07; 2.07)	2.34 (1.81; 2.86)	2.91 (2.34; 3.49)	*<0.001*
+ history of overweight	1.60 (1.24; 1.96)	*<0.001*	reference	0.76 (0.24; 1.27)	1.99 (1.45; 2.54)	2.99 (2.42; 3.57)	3.72 (3.09; 4.35)	*<0.001*
+ Type 2 diabetes prevalence at baseline	1.60 (1.24; 1.96)	*<0.001*	reference	0.78 (0.26; 1.29)	2.01 (1.46; 2.56)	2.99 (2.42; 3.57)	3.73 (3.10; 4.35)	*<0.001*
Elimination of FLI outliers (1st, 99th percentile)[c]	1.53 (1.17; 1.89)	*<0.001*	reference	0.84 (0.32; 1.36)	2.06 (1.51; 2.61)	2.99 (2.42; 3.57)	3.62 (2.99; 4.24)	*<0.001*
Dealing with missing follow-up data with LOCF	1.71 (1.38; 2.04)	*<0.001*	reference	0.73 (0.25; 1.21)	1.91 (1.40; 2.42)	2.86 (2.33; 3.40)	3.55 (2.97; 4.14)	*<0.001*

B. HSI score	Continuous[a]		Quintiles of changes in UPF consumption[b]					
	Per 10% change in UPF consumption		Q1	Q2	Q3	Q4	Q5	
	β (95% CI)	*p-value*	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	β (95% CI)	*p for trend*
Overall	0.43 (0.29; 0.57)	*<0.0001*	reference	0.39 (0.17; 0.60)	0.51 (0.29; 0.74)	0.58 (0.35; 0.82)	0.93 (0.67; 1.18)	*<0.001*
Nutritional factors								
+ changes in total energy intake (kcal/day)	0.39 (0.25; 0.54)	*<0.001*	reference	0.37 (0.16; 0.59)	0.48 (0.26; 0.71)	0.54 (0.30; 0.77)	0.87 (0.61; 1.12)	*<0.001*
+ changes in saturated FA intake (g/day)	0.34 (0.20; 0.49)	*<0.001*	reference	0.34 (0.13; 0.56)	0.43 (0.20; 0.66)	0.46 (0.22; 0.70)	0.77 (0.51; 1.04)	*<0.001*
+ changes in trans FA intake (g/day)	0.35 (0.21; 0.50)	*<0.001*	reference	0.35 (0.14; 0.56)	0.44 (0.21; 0.67)	0.48 (0.24; 0.72)	0.80 (0.54; 1.06)	*<0.001*
+ changes in cholesterol intake (mg/day)	0.41 (0.26; 0.55)	*<0.001*	reference	0.37 (0.16; 0.59)	0.49 (0.26; 0.71)	0.54 (0.31; 0.78)	0.88 (0.63; 1.14)	*<0.001*
+ changes in fiber intake (g/day)	0.41 (0.27; 0.55)	*<0.001*	reference	0.38 (0.17; 0.60)	0.50 (0.28; 0.73)	0.56 (0.33; 0.80)	0.90 (0.65; 1.16)	*<0.001*
+ changes in glycemic load	0.39 (0.25; 0.53)	*<0.001*	reference	0.37 (0.16; 0.59)	0.49 (0.26; 0.71)	0.54 (0.31; 0.78)	0.86 (0.61; 1.12)	*<0.001*
+ changes in sodium intake (mg/day)	0.38 (0.24; 0.52)	*<0.001*	reference	0.36 (0.15; 0.57)	0.46 (0.23; 0.68)	0.51 (0.27; 0.75)	0.83 (0.58; 1.09)	*<0.001*
+ changes in intake of saturated and trans FA, cholesterol, fiber, glycemic load and sodium	0.25 (0.10; 0.40)	*0.001*	reference	0.30 (0.09; 0.52)	0.35 (0.12; 0.58)	0.35 (0.11; 0.60)	0.61 (0.34; 0.88)	*<0.001*
+ changes in adherence to erMedDiet (17p score)	0.25 (0.11; 0.40)	*0.001*	reference	0.30 (0.09; 0.52)	0.36 (0.13; 0.59)	0.35 (0.11; 0.59)	0.60 (0.34; 0.86)	*<0.001*
NAFLD-related risk factors								
+ changes in BMI (kg/m^2)	0.13 (0.01; 0.24)	*0.033*	reference	0.15 (-0.04; 0.34)	0.07 (-0.13; 0.27)	0.04 (-0.17; 0.24)	0.27 (0.06; 0.48)	*0.015*
+ changes in waist circumference (cm)	0.18 (0.06; 0.31)	*0.004*	reference	0.27 (0.06; 0.47)	0.18 (-0.03; 0.39)	0.13 (-0.09; 0.35)	0.38 (0.15; 0.61)	*0.005*
+ changes in HbA1c (%)	0.35 (0.21; 0.50)	*<0.001*	reference	0.41 (0.19; 0.63)	0.41 (0.18; 0.65)	0.48 (0.23; 0.72)	0.83 (0.57; 1.10)	*<0.001*
+ changes in number of MetS factors	0.36 (0.22; 0.49)	*<0.001*	reference	0.35 (0.14; 0.56)	0.44 (0.22; 0.67)	0.46 (0.23; 0.70)	0.79 (0.54; 1.04)	*<0.001*
+ history of overweight	0.43 (0.29; 0.57)	*<0.001*	reference	0.38 (0.17; 0.60)	0.51 (0.28; 0.73)	0.58 (0.34; 0.81)	0.92 (0.67; 1.17)	*<0.001*
+ Type 2 diabetes prevalence at baseline	0.42 (0.28; 0.56)	*<0.001*	reference	0.40 (0.19; 0.62)	0.52 (0.30; 0.74)	0.57 (0.33; 0.80)	0.92 (0.67; 1.17)	*<0.001*
Elimination of HSI outliers (1st, 99th percentile)[c]	0.32 (0.24; 0.41)	*<0.001*	reference	0.19 (0.07; 0.31)	0.34 (0.21; 0.47)	0.52 (0.39; 0.66)	0.67 (0.52; 0.82)	*<0.001*
Dealing with missing follow-up data with LOCF	0.44 (0.30; 0.57)	*<0.001*	reference	0.37 (0.17; 0.57)	0.48 (0.27; 0.69)	0.57 (0.34; 0.79)	0.85 (0.61; 1.09)	*<0.001*

Abbreviations: BMI – body mass index; erMedDiet – energy-restricted Mediterranean Diet; FA – fatty acids; FLI – Fatty liver index; HbA1c – glycated hemoglobin; HSI – Hepatic steatosis index; LOCF – last observation carried forward; MetS – metabolic syndrome; NAFLD – non-alcoholic fatty liver disease; UPF – ultra-processed foods.

The consumption of UPF was expressed as a percentage of total food and beverage intake in g/day. Daily intake of beverages was collected in cubic centimeters and then converted into milliliters (1 cc = 1 ml), and further into grams, assuming that 1 ml = 1 g.

Mixed-effects linear modelling for repeated measures with random intercepts at recruiting center, cluster family and patient level were used after controlling in fully adjusted model 2 for baseline variables, such as age, sex, study arm, educational level, smoking habits, height, as well as repeatedly measured physical activity, sedentary behavior, alcohol intake, follow-up time, and use of antidiabetic medications (for models with HbA1c).

[a]Estimates β are interpreted as changes in NAFLD indices associated with increments of 10% in UPF products consumption. [b]Estimates β are interpreted as changes in NAFLD indices in each sex-specific quintile of UPF consumption, compared to quintile 1, the reference category.

[c]Outliers (1^{st}, 99^{th} percentile) in the outcome variables were eliminated at baseline and follow-up (for FLI total n=318, for HSI total n=316)

Supplementary Table S5. Mediation analysis for the association between concurrent changes in UPF consumption (% of g/day, continuous variable) and changes in NAFLD indices during 1-year of follow-up, through nutritional factors and NAFLD-related biomarkers.

A. FLI score	Indirect effect					Direct effect		% mediated
	Path a		Path b		a*b	Path c		
	β (95% CI)	*p-value*	β (95% CI)	*p-value*		β (95% CI)	*p-value*	
Nutritional factors								
+ changes in total energy intake (kcal/day)	124 (112; 136)	*<0.001*	0.00 (0.00; 0.00)	*<0.001*	0.00	1.47 (1.11; 1.84)	*<0.001*	0%
+ changes in saturated FA intake (g/day)	3.07 (2.88; 3.25)	*<0.001*	0.10 (0.07; 0.13)	*<0.001*	0.31	1.31 (0.94; 1.68)	*<0.001*	19%
+ changes in trans FA intake (g/day)	0.13 (0.12; 0.14)	*<0.001*	2.25 (1.62; 2.89)	*<0.001*	0.29	1.31 (0.94; 1.68)	*<0.001*	18%
+ changes in cholesterol intake (mg/day)	19.7 (17.0; 22.5)	*<0.001*	0.00 (0.00; 0.00)	*0.695*	0.00	1.60 (1.23; 1.96)	*<0.001*	0%
+ changes in fiber intake (g/day)	-2.41 (-2.64; -2.19)	*<0.001*	-0.10 (-0.13; -0.08)	*<0.001*	0.24	1.34 (0.98; 1.70)	*<0.001*	15%
+ changes in glycemic load	8.88 (7.83; 9.94)	*<0.001*	0.02 (0.02; 0.03)	*<0.001*	0.18	1.43 (1.07; 1.79)	*<0.001*	11%
+ changes in sodium intake (mg/day)	197 (174; 221)	*<0.001*	0.00 (0.00; 0.00)	*<0.001*	0.00	1.48 (1.12; 1.84)	*<0.001*	0%
+ changes in adherence to erMedDiet (17p score)	-1.17 (-1.24; -1.10)	*<0.001*	-0.81 (-0.89; -0.74)	*<0.001*	0.95	0.68 (0.32; 1.04)	*<0.001*	58%
NAFLD-related biomarkers								
+ changes in BMI (kg/m^2)	0.26 (0.22; 0.30)	*<0.001*	4.26 (4.19; 4.33)	*<0.001*	1.11	0.49 (0.21; 0.77)	*<0.001*	69%
+ changes in waist circumference (cm)	0.54 (0.40; 0.68)	*<0.001*	1.56 (1.54; 1.59)	*<0.001*	0.84	0.67 (0.40; 0.95)	*<0.001*	56%
+ changes in HbA1c (%)	0.05 (0.04; 0.07)	*<0.001*	4.13 (3.76; 4.49)	*<0.001*	0.21	1.25 (0.87; 1.63)	*<0.001*	14%
+ changes in number of MetS factors	0.07 (0.04; 0.09)	*<0.001*	5.93 (5.73; 6.13)	*<0.001*	0.42	1.22 (0.89; 1.55)	*<0.001*	26%
+ changes in GGT (U/L)	-0.07 (-0.86; 0.73)	*0.869*	0.13 (0.13; 0.14)	*<0.001*	0.00	1.61 (1.26; 1.95)	*<0.001*	0%
+ changes in triglycerides (mg/dL)	4.80 (2.90; 6.71)	*<0.001*	0.09 (0.08; 0.09)	*<0.001*	0.43	1.22 (0.91; 1.54)	*<0.001*	26%

B. HSI score	Indirect effect					Direct effect		% mediated
	Path a		Path b		a*b	Path c		
	β (95% CI)	*p-value*	β (95% CI)	*p-value*		β (95% CI)	*p-value*	β (95% CI)
Nutritional factors								
+ changes in total energy intake (kcal/day)	124 (112; 136)	*<0.001*	0.00 (0.00; 0.00)	*0.002*	0.00	0.39 (0.25; 0.54)	*<0.001*	0%
+ changes in saturated FA intake (g/day)	3.07 (2.88; 3.25)	*<0.001*	0.03 (0.02; 0.04)	*<0.001*	0.09	0.34 (0.20; 0.49)	*<0.001*	21%
+ changes in trans FA intake (g/day)	0.13 (0.12; 0.14)	*<0.001*	0.57 (0.31; 0.83)	*<0.001*	0.07	0.35 (0.21; 0.50)	*<0.001*	17%
+ changes in cholesterol intake (mg/day)	19.7 (17.0; 22.5)	*<0.001*	0.00 (0.00; 0.00)	*0.004*	0.00	0.41 (0.26; 0.55)	*<0.001*	0%
+ changes in fiber intake (g/day)	-2.41 (-2.64; -2.19)	*<0.001*	-0.01 (-0.02; 0.00)	*0.148*	0.00	0.41 (0.27; 0.55)	*<0.001*	0%
+ changes in glycemic load	8.88 (7.83; 9.94)	*<0.001*	0.00 (0.00; 0.01)	*<0.001*	0.00	0.39 (0.25; 0.53)	*<0.001*	0%
+ changes in sodium intake (mg/day)	197 (174; 221)	*<0.001*	0.00 (0.00; 0.00)	*<0.001*	0.00	0.38 (0.24; 0.52)	*<0.001*	0%
+ changes in adherence to erMedDiet (17p score)	-1.17 (-1.24; -1.10)	*<0.001*	-0.16 (-0.19; -0.13)	*<0.001*	0.19	0.25 (0.11; 0.40)	*0.001*	43%
NAFLD-related biomarkers								
+ changes in BMI (kg/m^2)	0.26 (0.22; 0.30)	*<0.001*	1.12 (1.10; 1.15)	*<0.001*	0.29	0.13 (0.01; 0.24)	*0.033*	69%
+ changes in waist circumference (cm)	0.54 (0.40; 0.68)	*<0.001*	1.56 (1.54; 1.59)	*<0.001*	0.84	0.18 (0.06; 0.31)	*0.004*	82%
+ changes in HbA1c (%)	0.05 (0.04; 0.07)	*<0.001*	1.24 (1.10; 1.37)	*<0.001*	0.06	0.35 (0.21; 0.50)	*<0.001*	15%
+ changes in number of MetS factors	0.07 (0.04; 0.09)	*<0.001*	1.06 (0.98; 1.15)	*<0.001*	0.07	0.36 (0.22; 0.49)	*<0.001*	16%
+ changes in ALT (U/L)	0.59 (0.15; 1.03)	*0.009*	0.12 (0.11; 0.12)	*<0.001*	0.07	0.36 (0.23; 0.49)	*<0.001*	16%
+ changes in AST (U/L)	0.27 (-0.10; 0.64)	*0.158*	-0.02 (-0.02; -0.01)	*<0.001*	0.00	0.43 (0.29; 0.57)	*<0.001*	0%
+ changes in ALT/AST	0.02 (0.00; 0.03)	*0.009*	8.21 (8.17; 8.26)	*<0.001*	0.16	0.25 (0.21; 0.29)	*<0.001*	39%

Abbreviations: ALT - alanine aminotransferase; AST - aspartate aminotransferase; BMI – body mass index; erMedDiet – energy-restricted Mediterranean Diet; FA – fatty acids; FLI – Fatty liver index; GGT - gamma-glutamyltransferase; HbA1c – glycated hemoglobin; HSI – Hepatic steatosis index; MetS – metabolic syndrome; NAFLD – non-alcoholic fatty liver disease; UPF – ultra-processed foods.

Mediation analyses were performed following procedure described in **Supplementary Text 1**. Briefly, the indirect effect was estimated as the multiplicative product of paths a (the effect of independent variable on the mediator) and b (effect of the mediator on the dependent variable, controlling for the independent variable), whereas the direct effect as the effect of the independent variable on the dependent variable (Path c). Mediation was considered plausible if either Path a or Path b were statistically significant, otherwise the indirect effect and the mediation were considered null. The proportion mediated was calculated as the ratio of indirect effect by the sum of the direct and indirect effect (a*b/(a*b)+c).

Mixed-effects linear modelling for repeated measures with random intercepts at recruiting center, cluster family and patient level were used after controlling in fully adjusted model 2 for baseline variables, such as age, sex, study arm, educational level, smoking habits, height, as well as repeatedly measured physical activity, sedentary behavior, alcohol intake, follow-up time, and use of antidiabetic medications (for models with HbA1c). Estimates β are interpreted as changes in NAFLD indices associated with increments of 10% in UPF consumption.

Supplementary Table S6. Association between concurrent changes in UPF consumption (% of g/day) and changes in NAFLD indices during 1-year of follow-up by subgroups.

Continuous (per 10% change in UPF consumption)	FLI score		HSI score	
	β (95% CI)	*p-value*	β (95% CI)	*p-value*
Sex				
Men (n=3060 (52.2%))	1.54 (1.08; 2.00)	*<0.001*	0.49 (0.30; 0.69)	*<0.001*
Women (n=2807 (47.8%))	1.66 (1.10; 2.22)	*<0.001*	0.35 (0.14; 0.56)	*0.001*
p for interaction		*0.813*		*0.208*
Age				
<65 y (n=2688 (45.8%))	1.76 (1.25; 2.27)	*<0.001*	0.52 (0.32; 0.73)	*<0.001*
≥65 y (n=3179 (54.2%))	1.50 (1.00; 2.01)	*<0.001*	0.36 (0.17; 0.56)	*<0.001*
p for interaction		*0.639*		*0.074*
Type 2 diabetes status				
Non-diabetics (n=4039 (68.8%))	1.73 (1.29; 2.18)	*<0.001*	0.42 (0.27; 0.58)	*<0.001*
Diabetics (n=1828 (31.2%))	1.29 (0.68; 1.90)	*<0.001*	0.40 (0.10; 0.69)	*0.008*
p for interaction		*0.027*		*0.352*
Alcohol intake				
<20g/day for women and < 30g/d for men (n=5123 (87.3%))	1.63 (1.24; 2.01)	*<0.001*	0.46 (0.31; 0.61)	*<0.001*
≥20g/day for women and ≥ 30g/d for men (n=744 (12.7%))	1.52 (0.52; 2.53)	*0.003*	0.25 (-0.18; 0.67)	*0.253*
p for interaction		*0.616*		*0.908*
Adherence to erMedDiet				
<8 points (n=2171 (37.0%))	1.47 (0.97; 1.97)	*<0.001*	0.41 (0.21; 0.62)	*<0.001*
≥8 points (n=3696 (63.0%))	1.66 (1.14; 2.18)	*<0.001*	0.45 (0.25; 0.65)	*<0.001*
p for interaction		*0.830*		*0.695*

Abbreviations: erMedDiet – energy-restricted Mediterranean Diet; FLI – Fatty liver index; HSI – Hepatic steatosis index; NAFLD – non-alcoholic fatty liver disease; UPF – ultra-processed foods.

The consumption of UPF was expressed as a percentage of total food and beverage intake in g/day. Daily intake of beverages was collected in cubic centimeters and then converted into milliliters (1 cc = 1 ml), and further into grams, assuming that 1 ml = 1 g.

Mixed-effects linear modelling for repeated measures with random intercepts at recruiting center, cluster family and patient level were used after controlling in fully adjusted model 2 for baseline variables, such as age, sex, study arm, educational level, smoking habits, height, as well as repeatedly measured physical activity, sedentary behavior, alcohol intake, and follow-up time. Estimates β are interpreted as changes in NAFLD indices associated with increments of 10% in UPF consumption.

Supplementary Table S7. Association between concurrent changes in consumption of specific food subgroups within UPF (% of g/day) and changes in NAFLD indices during 1-year of follow-up.

Continuous (per 10% change in UPF subgroup consumption)	FLI score		HSI score	
	β (95% CI)	*p-value*	β (95% CI)	*p-value*
Dairy products	2.59 (1.06; 4.13)	*0.001*	0.36 (-0.27; 0.98)	*0.262*
Processed meats	6.18 (3.88; 8.47)	*<0.001*	1.75 (0.82; 2.68)	*<0.001*
Pre-prepared dishes, snacks and fast-foods	9.11 (6.14; 12.07)	*<0.001*	2.17 (0.99; 3.36)	*<0.001*
Sweets	5.32 (3.98; 6.65)	*<0.001*	1.33 (0.79; 1.87)	*<0.001*
Non-alcoholic beverages	1.03 (0.62; 1.45)	*<0.001*	0.32 (0.15; 0.48)	*<0.001*
Alcoholic beverages	9.25 (4.62; 13.87)	*<0.001*	1.22 (-0.60; 3.04)	*0.189*

Abbreviations: FLI – Fatty liver index; HSI – Hepatic steatosis index; NAFLD – non-alcoholic fatty liver disease; UPF – ultra-processed foods.

The consumption of each specific food group within UPF was expressed as a percentage of total food and beverage intake in g/day. Daily intake of beverages was collected in cubic centimeters and then converted into milliliters (1 cc = 1 ml), and further into grams, assuming that 1 ml = 1 g.

Mixed-effects linear modelling for repeated measures with random intercepts at recruiting center, cluster family and patient level were used after controlling in fully adjusted model 2 for baseline variables, such as age, sex, study arm, educational level, smoking habits, height, as well as repeatedly measured physical activity, sedentary behavior, alcohol intake (except for alcoholic beverages subgroup), and follow-up time. Estimates β are interpreted as changes in NAFLD indices associated with increments of 10% in UPF subgroup consumption.

File S1: Group information.

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References

1. Willett W. Nutritional epidemiology. 3rd ed. Oxford University Press; 2013. p. 529.

2. Fernández-Ballart JD, Piñol JL, Zazpe I, Corella D, Carrasco P, Toledo E, et al. Relative validity of a semi-quantitative food-frequency questionnaire in an elderly Mediterranean population of Spain. Br J Nutr. 2010;103(12):1808–16.

3. Monteiro CA, Cannon G, Levy RB, Moubarac J-C, Louzada ML, Rauber F, et al. Ultra-processed foods: what they are and how to identify them. Public Health Nutr. 2019 Apr 12;22(5):936–41.

4. Iacobucci D, Saldanha N, Deng X. A Meditation on Mediation: Evidence That Structural Equations Models Perform Better Than Regressions. J Consum Psychol. 2007 Apr 1;17(2):139–53.

5. Alberti KGMM, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. 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. Circulation. 2009;120(16):1640–5.