
Ultra-processed foods and food additives in gut health and disease

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Kevin Whelan, Aaron S. Bancel, James O. Lindsay, Benoit Chassaing

Supplementary Table 1 - Epidemiological studies of UPF and risk of gut disease

Reference	Study design and population	Numbers in cohort or number of controls in case-control	Follow-up period	Dietary assessment method and UPF classification	Disease diagnosis method	Risk reporting	Disease (number of incident cases)	Risk of gut disease (unadjusted or minimally adjusted)	Risk of gut disease (adjusted)	Variables adjusted for
Inflammatory bowel disease										
Narula et al, 2021 ¹	Cohort study (PURE) 21 countries, 59.2% female 50.2 y (SD 9.7 y)	116,037	Median 9.7 y (IQR 8.9-11.2)	FFQ (country specific, 1 year recall) Researcher-defined UPF	Self-report, followed by medical record confirmation in 20% of positive cases	HR (95% CI) ≥5 serves/d Reference <1 serves/d	IBD (467)	3.18 (2.49 to 4.07) P<0.001	1.92 (1.28 to 2.90) P=0.004	Age, sex, geographical region, education, alcohol intake, smoking status, location, BMI, energy intake, Alternate Health Eating Index (AHEI)
							Crohn's (90)	5.84 (3.57 to 9.54) P<0.001	4.90 (1.78 to 13.45) P=0.008	
							UC (377)	2.63 (1.97 to 3.51) <0.001	1.52 (0.96 to 2.41) P=0.06	
Lo et al, 2022 ²	Cohort study (Nurses' Health Study I and II; Health Professionals Follow-up Study) USA 83.0% female	245,112	5,468,444 person years (mean 22.3 y)	FFQ (1 year recall) NOVA	Self-report, followed by medical record confirmation in all positive cases	HR (95% CI) Q4 (median 46.4% energy from UPF) Reference Q1 (median 21.0% energy from UPF)	Crohn's (369)	1.75 (1.29 to 2.35) P=0.0001	1.70 (1.23 to 2.35) P=0.0008	Age, cohort, questionnaire cycle, race/ethnicity, family history of IBD, smoking status, BMI, physical activity, energy intake, AHEI, regular NSAID use, oral contraceptives;
							UC (488)	1.25 (0.97 to 1.62) P=0.11	1.20 (0.91 to 1.58) P=0.25	

	44.7-45.7 y mean									menopausal hormone therapy.
Vasseur et al, 2021 ³	Cohort study (NutriNet-Santé) France 78.0% female 43.3 y (SD 14.7)	105,832	238,924 person years (mean 2.3 y, SD 2.2 y)	≥3 x online 24h recall NOVA	Self-report, followed by medical record confirmation in 15% of cases	RR (95% CI) Q3 (>19.1% food weight as UPF) Reference Q1 (<12.4% food weight as UPF)	IBD (75)	1.81 (1.05 to 3.12) P=0.03	1.44 (0.70 to 2.94) P=0.30	Age, sex, income, education, marital status, residence, BMI, physical activity, smoking status, hormonal contraception, number of 24h recalls, energy intake, “healthy” dietary pattern
Meyer et al, 2022 ⁴	Cohort study (EPIC) 8 European countries 68.6% female 51.7 y (SD 10.1)	413,590	4,920,526 person years (mean 13.2 y)	EPIC FFQ (1 year recall) NOVA	Self-report, followed by medical record confirmation in all cases	HR (95% CI) Q4 (mean 50.6% energy from UPF) Reference Q1 (mean 13.3% energy from UPF)	Crohn's (179)	NR	1.48 (0.79 to 2.76)	Age, sex, centre, education, smoking status, BMI, physical activity, energy intake, alcohol consumption
							UC (431)	NR	0.93 (0.61 to 1.43)	
Chen et al, 2022 ⁵	Cohort study (UK Biobank) United Kingdom 54.8% female 56.2 y (SD 7.9)	185,849	16,247 person years (mean 9.8 years, IQR 9.5-10.8)	≥1 x online 24h recall NOVA	Hospital or primary care record review	HR (95% CI) Q5 (per serving, energy kJ from UPF, % energy from UPF) Reference Q1	IBD (841)	Per serving 1.34 (1.07 to 1.67) P=0.001 Energy from UPF 1.20 (0.97, 1.49) P=0.010 % energy from UPF 1.21 (0.98, 1.50) P=0.016	Per serving 1.16 (0.91, 1.48) P=0.091 Energy from UPF 1.18 (0.95, 1.46) P=0.017 % energy from UPF 1.15 (0.93, 1.42) P=0.097	Age, age-squared, sex, ethnicity, deprivation, smoking status, drinking status, education, physical activity, BMI, IBD genetic risk, and total energy (for ‘per serving’ only).

							Crohn's (251)	Per serving 1.52 (1.02 to 2.27) P=0.001 Energy from UPF 1.49 (1.01 to 2.20) P=0.007 % energy from UPF 2.09 (1.39 to 3.16) P<0.001	Per serving 1.61 (1.03 to 2.51) P=0.002 Energy from UPF 1.46 (0.98 to 2.16) P=0.011) % energy from UPF 2.00 (1.32 to 3.03) P=0.001	
							UC (590)	Per serving 1.27 (0.97 to 1.65) P=0.070 Energy from UPF 1.10 (0.85 to 1.42) P=0.174 % energy from UPF 0.97 (0.75 to 1.25) P=0.581	Per serving 1.01 (0.75 to 1.35) P=0.956 Energy from UPF 1.08 (0.83 to 1.39) P=0.235 % energy from UPF 0.91 (0.70 to 1.18) P=0.948	
Functional gastrointestinal disorders										
Schnabel et al, 2018 ⁶	Case-control study (NutriNet- Santé) France 76.4% female	27,119	NR	≥3 x online 24h recall NOVA	Rome III questionnai re (self- report)	OR (95% CI) Q4 (>20.6% food weight as UPF) Reference Q1 (<9.7% food weight as UPF)	IBS (3516)	1.21 (1.09 to 1.34), P<0.0001	1.25 (1.12 to 1.39) P<0.0001	Sex, age, income, education, marital status, residence, BMI, physical activity, smoking, energy intake, season of
							Functional constipati on (1785)	1.02 (0.89 to 1.16) P=0.91	0.98 (0.85 to 1.12) P=0.66	
							Functional diarrhoea	1.02 (0.77 to 1.36) P=0.77	0.92 (0.69 to 1.24) P=0.70	

	50.4 y (SD 14.0)						(368)			food records, time between food and FGIDs questionnaire, Adherence to national diet recommendation score
							Functional dyspepsia (1303)	1.32 (1.12 to 1.55) P=0.0002	1.25 (1.05 to 1.47) P=0.004	
Gastrointestinal cancer										
Fiolet et al, 2018 ⁷	Cohort study (NutriNet-Santé) France 78.3% female 42.8 y (SD 14.8)	104,980	426, 362 person years (median 5 y)	≥2 x online 24h recall NOVA	Self-report, followed by medical record confirmation in >90% of positive cases	HR (95% CI) Q4 (>23.2% of food weight as UPF) Reference to Q1 (<11.8% of food weight as UPF)	Colorectal cancer (153)	1.49 (0.92 to 2.43) P=0.1	1.23 (1.08 to 1.40) P=0.07	Age, sex, energy intake, number of dietary records, smoking, education, physical activity, height, BMI, alcohol intake, family history; intakes of lipids, sodium, carbohydrates, ‘Western’ dietary pattern.
Wang et al, 2022 ⁸	Cohort study (Health Professionals Follow-up Study, Nurses’ Health Study I and II) USA Men 53.5-54.9 y mean	Men 46,341	24-28 years	FFQ (1 year recall)	Self-report, followed by medical record confirmation in all positive cases where possible	HR (95% CI) Q5 (Men ≥7.9, Women ≥7.2 energy-adjusted servings /d of UPF)	Colorectal cancer (1,294 men; 1,922 women)	Men 1.24 (1.04 to 1.47) P=0.04 Women 1.08 (0.94 to 1.24) P=0.08	Men 1.29 (1.08 to 1.53) P=0.01 Women 1.04 (0.90 to 1.20) P=0.29	Age, year of questionnaire, race, family history of cancer, endoscopy history, alcohol intake, physical activity, smoking status, smoking pack years, energy intake, aspirin use, menopausal
		Women 159,907		NOVA		Reference Q1 (Men ≤4.1, Women ≤4.0 energy-adjusted	Proximal colon cancer (443 men; 797 women)	Men 1.32 (0.97 to 1.79) P=0.22 Women 1.16 (0.93 to 1.45)	Men 1.34 (0.98 to 1.82) P=0.20 Women 1.11 (0.89 to 1.39)	

	Women 52.0-53.0 y mean					servings /d of UPF)		P=0.11	P=0.24	status, postmenopausal hormone use
							Distal colon cancer (368 men; 455 women)	Men 1.62 (1.18 to 2.23) P=0.002 Women 1.10 (0.82 to 1.46) P=0.13	Men 1.72 (1.24 to 2.37) P<0.001 Women 1.07 (0.80 to 1.43) P=0.19	
							Rectal cancer (267 men; 398 women)	Men 1.01 (0.68 to 1.48) P=0.72 Women 1.10 (0.81 to 1.51) P=0.70	Men 1.05 (0.71 to 1.56) P=0.89 Women 1.08 (0.79 to 1.49) P=0.84	
Romague ra et a., 2021 ⁹	Case-control study (Multi-Case-Control) Spain 49.4% female 62.9 y (SD 12.0)	3543 controls	N/A	FFQ (1 year recall) NOVA	Colonoscopy and histology (cases only)	OR (95% CI) Q3 (>14.6% of food weight as UPF) Reference Q1 (<6.9% of food weight as UPF)	Colorectal cancer (1852)	1.44 (1.24 to 1.67) P<0.001	1.30 (1.11 to 1.51) P=0.001	Sex, age, study area, education, BMI, physical activity, smoking, NSAIDs, family history, energy intake, ethanol intake
Kinany et al, 2022 ¹⁰	Matched case-control study Morocco 50.7% female 56.0 y (SD 13.8)	1453 controls	N/A	FFQ (1 year recall) NOVA	Colonoscopy and histology (cases only)	OR (95% CI) Q3 (≥37.3 g/d UPF) Reference Q1 (<3.9 g/d UPF)	Colorectal cancer (1453)	1.28 (1.13 to 1.46)	1.40 (1.22 to 1.61)	Age, education, family history of CRC, smoking status, physical activity, BMI, energy intake
							Colonic cancer (729)	1.26 (1.06 to 1.51)	1.36 (1.12 to 1.66)	
							Rectal cancer (724)	1.31 (1.09 to 1.57)	1.44 (1.18 to 1.76)	
	Case-control study	358 controls	N/A	FFQ (1 year recall)	Colonoscopy in all and	OR (95% CI)	Adenoma (294)	N/R	1.75 (1.14 to 2.68) P=0.009	Age, gender, BMI, energy intake,

Fliss-Isakov et al, 2020 ¹¹	Egypt 49.2% female 58.5 y (SD 6.6)			NOVA	histology in cases	Q3 (≥44.9% of total E from UPF)	Non-advanced adenoma (147)	N/R	1.31 (0.76 to 2.25) P=0.325	aspirin use, indication for colonoscopy
						Reference Q1 (<30.4% of total E from UPF)	Advanced adenoma (147)	N/R	2.17 (1.29 to 3.65) P=0.003	
							Proximal adenoma (143)	N/R	2.38 (1.37–4.11) P=0.002	
							Distal adenoma (151)	N/R	1.39 (0.82–2.34) P=0.212	
Zhong et al, 2023 ¹²	Cohort study (PLCO) USA 52.5% female 65.6 y mean (SD 5.7)	98,265	871040 person years (mean 8.9 y, SD 1.9)	FFQ (1 year recall) NOVA	Self-report, followed by medical record confirmation in all positive cases where possible	HR (95% CI) Q4 (>3.7 servings/d of UPF, energy adjusted) Reference Q1 (<0.9 servings/d of UPF)	Pancreatic cancer (387)	1.47 (1.10 to 1.97) P=0.012	1.49 (1.07 to 2.07) P=0.021	Age, sex, race, smoking, alcohol, BMI, aspirin, diabetes, family history of pancreatic cancer, energy intake

BMI, body mass index

FFQ, food frequency questionnaire

N/A, not applicable

NR, not reported

OR, odds ratio; RR, relative risk; HR, hazard ratio

Where quantiles are used, data represent the highest quantile reported (e.g. Q3 is tertile 3, Q4 is quartile 4, Q5 is quintile 5) compared with the reference quantile Q1

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