Online supplementary material

Dietary quercetin intake can reduce ulcerative colitis risk but not Crohn's disease in a prospective cohort study

Lu et al.

Menu

Supplementary Method for Animal Experiment

Mice, Reagents, and Colitis Model

Specific pathogen-free (SPF) C57BL/6 mice were purchased from and raised in Shanghai Model Organisms Center, Co., Ltd. (Shanghai, China). All animals were randomly grouped and hosted in laminar flow cabinets under conditions at 22℃ under a 12 h light/12 h dark cycle with ad libitum access to water and chow. A total of 40 male C57BL/6 at 5 weeks of age were kept in the SPF environment for adaptive growth for one week for further treatment. And 37 mice were analyzed finally with three dying because of chemical induction.

Dextran Sulfate Sodium Salt (DSS, MPbio 216011090, Mw 36000-50000Da) was bought from MP Biomedicals, and diluted in ddH2O at a concentration of 3%. Trinitro-benzene-sulfonic acid (TNBS, MB5523-1) was bought from MeilunBio, Co., Ltd. (Dalian, China), and dissolved in double distilled water (ddH_2O) and diluted with different solvents for different intentions. Quercetin (SQ8030; CAS number 117-39-5) was bought from Beijing Solarbio Science & Technology Co., Ltd.(Beijing, China), and dissolved in 2%-Tween80(Sigma, P4780)-containing ddH_2O in a concentration of 3mg/mL.

Mice at 6 weeks of age were used to conduct experiments after one week of adaptive growth. We set groups as follows: (1) DSS model. For the control (Ctrl.) group, 2%-Tween80 (Sigma, P4780)-containing ddH_2O was given in the pretreatment stage and ddH2O was given in the induction stage. For DSS group, 2%-Tween80(Sigma, P4780)-containing ddH2O was given in the pretreatment stage and 3% DSS solution was given for 7 days later, renewed every 2 to 3 days. For DSS+quercetin group, mice were pretreated with 100 μl of quercetin solution (at an amount of 15mg/kg, orally) daily for 14 days, and given DSS solution later. All mice were sacrificed 3 days later for the next examinations. (2) TNBS model. For the control (Ctrl.) group, 2%-Tween90-containing ddH_2O was given in gavage in the pretreatment stage and the 4:1 Acetone/olive oil mixture was applied to the skin in the presensitization stage. For TNBS group, 2%-Tween90-containing ddH_2O was given in gavage in the pretreatment stage and 150 μl of 1.0% (wt/vol) TNBS solution was applied to the skin, and 8 days after presensitization 100 μl of 2.5% (wt/vol) TNBS solution was injected into the mice colon to established TNBS-induce colitis model. For TNBS+quercetin group, mice were pretreated with 100 μl of quercetin solution (at an amount of 15mg/kg, orally) daily for 14 days, followed by TNBS induction. All mice were sacrificed 5 days later or next examinations.

Measurement of Disease Activity Index (DAI)

Body weight was measured and recorded from the first day of induction, and stools were collected the day before sacrifice. Fecal occult blood was tested according to the manual of fecal occult blood test kit (C027-1-1, Nanjing Jiancheng Bioengineering Institute). The mice were scored using the DAI according to the international criteria [1], and the formula was: (weight loss score + stool shape score + stool blood score)/3.

Histopathological Score Measurement, PAS-AB Stain, and Immunohistochemistry Analysis

Formaldehyde-fixed colon tissue was embedded in paraffin and sliced. For histopathological score measurement, the slices were dewaxed in xylene and gradient ethanol, then they were stained with hematoxylin and eosin successively, and the histopathological score was based on the Geboes criteria [2], and each group of slices was assessed by 2 observers who were blinded to the grouping of the mice. For the PAS-AB stain, dewaxed slices were sequentially stained with alcian blue, periodic acid, and Schiff reagent. For immunohistochemistry analysis of Claudin-1 expression, prepared slices were treated with 3% H_2O_2 to reduce endogenous background, then repaired in citrate solution, blocked the nonspecific antigenic epitopes by sheep serum, incubated under 4℃ overnight with Claudin-1 antibody (Servicebio, GB12032, dilution 1:500). Next day, the slices were incubated with secondary antibody and the color developing of DAB substrate system was finished under light microscope with the same developing time.

RNA extraction and quantified Real-time PCR

Mice colonic tissues were frozen and total RNA was extracted with TRIzol reagent (Invitrogen, USA), and reverse transcribed using the PrimeScript RT Reagent Kit (Takara, Japan). Relative mRNA expression was calculated using the -ΔΔCt method based on the Ct values obtained from StepOnePlus real-time PCR system (Applied Biosystems, FosterCity, California), referring to colitis group. The primers were synthesized by Tsingke Biotechnology Co., Ltd, and the sequences were listed in the following Table.

Primer sequences for qRT-PCR (Mus musculus)		
Name	**Sense (5'-3')**	**Antisense (5'-3')**
Actb	CATTGCTGACAGGATGCAGAAGG	TGCTGGAAGGTGGACAGTGAGG
S100a8	TGCCCTCTACAAGAATGACTTCAAG	TTATCACCATCGCAAGGAACTCC
S100a9	ATCTCCGTTCTTCAGTGTAGCAATG	ATCAGCATCATACACTCCTCAAAGC
Lcn2	ACCACGGACTACAACCAGTTCG	ACTTGGCAAAGCGGGTGAAAC
Cxcl9	CCAGCCGAGGCACGATCC	ATCTCCGTTCTTCAGTGTAGCAATG

The primer sequences for the above-mentioned genes were from the Tsingke (China).

Statistical analysis

Data were presented as the means ± SEM. Error bars in data represent SEM. OneSample Kolmogorov-Smirnov test was first utilized to evaluate whether data was normally distributed. For normally distributed data, independent student t-test was used for comparisons between two groups, and one-way ANOVA test was applied for comparisons among three groups. For skewed distributed data, nonparametric Mann-Whitney test was performed for data between two groups, and nonparametric Kruskal-Wallis test was utilized for comparisons within three groups. Statistical tests were two-tailed, adjusted using the Benjamini-Hochberg (BH) method, and a value of $P < 0.05$ was considered statistically

significant (* $P < 0.05$, ** $P < 0.011$, *** $P < 0.001$, ****$P < 0.0001$). For animal experiments, $n \geq 5$ biological samples for DSS model and $n \geq 6$ or TNBS. The sample size used for each experiment was marked in figures.

Reference

[1] Cooper HS, Murthy SN, Shah RS, Sedergran DJ. Clinicopathologic study of dextran sulfate sodium experimental murine colitis. Lab Invest. Aug 1993;69(2):238-49.

[2] Jauregui-Amezaga A, Geerits A, Das Y, et al. A Simplified Geboes Score for Ulcerative Colitis. Journal of Crohn's and Colitis. 2016;11(3):305-313. doi:10.1093/ecco-jcc/jjw154

Supplementary Figure

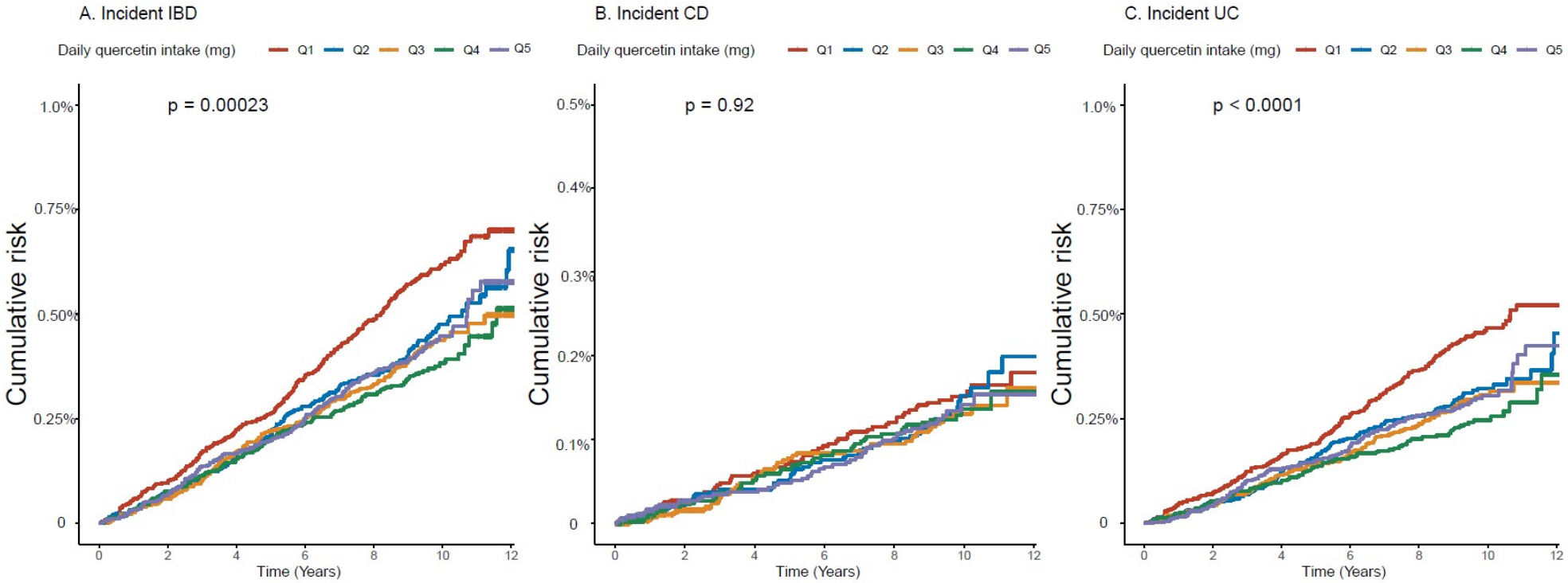

Figure S1 Cumulative incidence of incident IBD, CD, and UC in individuals according to daily quercetin intake in quintiles. CD, Crohn's disease; IBD, inflammatory bowel disease; UC, ulcerative colitis

Supplementary Table

Table S1 Definition of covariates

	UK Biobank
Age at recruitment	This is a derived variable based on date of birth and date of attending an initial assessment centre and refers to the age of the participant on the day they attended an Initial Assessment Centre, truncated to whole year. (response: as continues variable)
Sex	A mixture of the sex the National Health Service had recorded for the participant and self-reported sex (response: categorical variable "**Female**", "**Male**")
Ethnicity	Self-reported: "What is your ethnic background". We classified the responses into: **White** (White) and **Others** (Mixed, Asian or Asian British, Black or Black British, Chinese, and other ethnic group)
Education	Self-reported: "Which of the following qualifications do you have" We classified the responses into: **College** (College or University degree) and **Below college** (A levels/AS levels or equivalent, O levels/GCSEs or equivalent, CSEs or equivalent, NVQ or HND or HNC or equivalent, other professional qualifications eg: nursing, teaching, and none of the above)
Townsend deprivation index (TDI)	The higher, the more socioeconomic deprivation one was suffering. TDI was derived according to the unemployment rate, the percentage of overcrowded households, the percentage of people without cars, and the percentage of people without houses for each area in the UK, and baseline TDI calculated immediately before participant joining UK Biobank based on the preceding national census output areas. Each participant was assigned a score corresponding to the output area in which their postcode is located (ref). (response: as continues variable)
Smoking status	Self-reported current/past smoking status of the participant. We classified the

	UK Biobank
	responses into: **Never smoked** (Never) and **Former or current smoker** (Previous, current)
Physical activity	Self-reported: UK Biobank physical activity questionnaire. We classified the responses into **Adequate** (150 minutes moderate activity per week OR ≥ 75 minutes vigorous activity per week OR equivalent combination OR moderate physical activity at least 5 days a week or vigorous activity once a week) and **Inadequate** (below adequate level) recommended by the American Heart Association.
Body mass index (BMI)	BMI value is constructed from height and weight measured during the initial assessment centre visit. Relevant variable was measured by trained staff. (response: as continues variable)
Modified Alternative Healthy Eating Index (AHEI)	The modified AHEI included five items, including red meat, processed meat, fruit, vegetables and fat. Each dietary item scored 0 (unhealthiest), 5 and 10 (healthiest), respectively. (response: as continues variable)
Total energy	Total energy from overall diet estimating from the mean intake of the 24h WebQ
Nutrients intake	Including protein, fat, carbohydrate, sugar, vitamin D, vitamin E, vitamin B12, folate, zinc, and dietary fiber estimating from the mean intake of the 24h WebQ
Charlson Comorbidity Index (CCI)	CCI is a highly cited and well-established tool for measuring comorbidity in clinical research. We calculated CCI as a variable reflecting objective heath status. Mak JKL et al developed the calculation of CCI in the UK Biobank, which were constructed based on 17 comorbidities with assigned weights associated with ICD codes from hospital records. (as continues variable range from 0 to 16)

	UK Biobank
Non-steroidal anti-inflammatory drugs	We used the self-reported answer to “Do you regularly take any of the following?” We classified the usage of non-steroidal anti-inflammatory drugs into: Yes (Who chose option “aspirin”, “Ibuprofen”, or “Paracetamol”) and No (other choices). selection allowed for the usual names of the corresponding drugs will be verified in the verbal interview.
Proton pump inhibitors	We used the data from verbal interview by trained nurse on prescription medications. Data on any regular treatments taken weekly, monthly, etc. It does not include short-term medications (such as a 1week course of antibiotics) or prescribed medication that is not taken, or over-the-counter medications). For proton pump inhibitors, we classified the usage of proton pump inhibitors into: Yes (Who reported Lansoprazole, omeprazole, pantoprazole, esomeprazole, and rabeprazole) and No (other medicine) based on the previous study
Antibiotics	We used the data from verbal interview by trained nurse on prescription medications. Data on any regular treatments taken weekly, monthly, etc. It does not include short-term medications (such as a 1week course of antibiotics) or prescribed medication that is not taken, or over-the-counter medications). For proton pump inhibitors, we classified the usage of proton pump inhibitors into: Yes (Tetracyclines, Beta-lactam antibacterials and penicillins, xulfonamides and trimethoprim, macrolides, lincosamides, and streptogramins, aminoglycoside antibacterials, quinolone antibacterials, other antibacterials) and No (other medicine) based on the previous study
C-reactive protein	Assessed using immuno-turbidimetric method with platform (Beckman Coulter AU5800).
Oral contraceptive pills	We used the self-reported answer to “Have you ever taken the oral contraceptive pill? (include the 'mini-pill')” We classified the usage of oral contraceptive pills into: Yes (Who chose option “Yes”) and No (other

	UK Biobank
	choices).

Table S2 Associations of dietary quercetin with IBD, CD, and UC in step-wise Cox models

Quercetin intake (mg/d)	Model 2 [a]	Model 3 [b]
	HR (95% CI)	HR (95% CI)
Inflammatory bowel disease		
Q1 (0-<8.9)	Ref	Ref
Q2 (8.9-<15.0)	**0.80 (0.66, 0.98)** [c]	**0.79 (0.65, 0.97)**
Q3 (15.0-<21.6)	**0.74 (0.60, 0.91)**	**0.73 (0.59, 0.90)**
Q4 (21.6-<31.9)	**0.66 (0.54, 0.82)**	**0.65 (0.52, 0.80)**
Q5 (≥31.9)	**0.78 (0.63, 0.96)**	**0.75 (0.61, 0.93)**
P-trend	**0.003**	**0.001**
Crohn's disease		
Q1 (0-<8.9)	Ref	Ref
Q2 (8.9-<15.0)	0.95 (0.66, 1.39)	0.95 (0.65, 1.38)
Q3 (15.0-<21.6)	0.87 (0.59, 1.28)	0.86 (0.58, 1.27)
Q4 (21.6-<31.9)	0.88 (0.59, 1.30)	0.86 (0.58, 1.28)
Q5 (≥31.9)	0.91 (0.62, 1.35)	0.88 (0.59, 1.32)
P-trend	0.542	0.455
Ulcerative colitis		
Q1 (0-<8.9)	Ref	Ref
Q2 (8.9-<15.0)	**0.75 (0.59, 0.95)**	**0.74 (0.59, 0.94)**
Q3 (15.0-<21.6)	**0.70 (0.55, 0.89)**	**0.68 (0.54, 0.87)**
Q4 (21.6-<31.9)	**0.59 (0.46, 0.76)**	**0.57 (0.44, 0.75)**
Q5 (≥31.9)	**0.73 (0.57, 0.94)**	**0.71 (0.55, 0.91)**
P-trend	**0.002**	**0.001**

BMI, body mass index; CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; Ref, reference group; TDI, Townsend deprivation index; UC, ulcerative colitis

[a] adjusted for age, sex, ethnic background, physical activity, BMI, TDI, smoking status, alcoholic drinks consumption (exclude wine)

[b] adjusted for age, sex, ethnic background, physical activity, BMI, TDI, smoking status, alcoholic drinks consumption (exclude wine), and total energy

[c] represent P value<0.05

Table S3 Associations of dietary quercetin with risk of IBD, CD, and UC stratified by age and sex [a]

Quercetin intake	Age				Sex [b]			
	<60		>=60		Female		Male	
	Case/person-years	HR (95% CI)	Case/person-years	HR (95% CI)	Case/person-years	HR (95% CI)	Case/person-years	HR (95% CI)
IBD								
Q1	112/214,161	Ref	115/151,858	Ref	94/168,216	Ref	133/197,803	Ref
Q2	91/176,293	1.02 (0.77, 1.36)	83/182,292	0.63 (0.47, 0.83)	87/186,952	0.85 (0.63, 1.15)	87/171,633	**0.74 (0.56, 0.98)**
Q3	60/164,536	0.72 (0.52, 1.01)	99/193,746	0.71 (0.54, 0.95)	79/197,299	0.74 (0.54, 1.01)	80/160,983	**0.72 (0.53, 0.96)**
Q4	50/156,029	**0.63 (0.44, 0.91)** [c]	91/201,507	0.64 (0.47, 0.87)	79/211,816	**0.69 (0.49, 0.96)**	62/145,720	**0.60 (0.43, 0.84)**
Q5	70/152,888	0.88 (0.62, 1.25)	92/203,793	0.63 (0.46, 0.88)	87/228,518	**0.69 (0.49, 0.97)**	75/128,163	0.81 (0.58, 1.13)
P-trend		0.082		**0.021**		**0.02**		0.078
P-interaction				0.058				0.562
CD								
Q1	30/216,352	Ref	28/153,827	Ref	21/170,122	Ref	37/200,058	Ref
Q2	24/178,684	1.14 (0.65, 1.99)	29/185,114	0.91 (0.54, 1.55)	31/189,650	1.45 (0.82, 2.56)	22/174,148	0.73 (0.42, 1.25)
Q3	20/166,714	1.08 (0.59, 1.98)	28/196,874	0.85 (0.49, 1.48)	22/200,281	1.02 (0.54, 1.91)	26/163,306	0.93 (0.54, 1.60)
Q4	18/158,071	1.09 (0.57, 2.08)	30/204,777	0.90 (0.51, 1.59)	27/215,057	1.22 (0.65, 2.27)	21/147,791	0.84 (0.46, 1.54)

Q5	23/155,011	1.43 (0.76, 2.71)	26/207,082	0.73 (0.39, 1.35)	27/232,049	1.10 (0.57, 2.09)	22/130,044	0.99 (0.53, 1.85)
P-trend		0.367		0.369		0.899		0.926
P-interaction			□	0.827	□	□	□	0.401
				UC				
Q1	82/216,138	Ref	87/153,530	Ref	73/169,824	Ref	96/199,844	Ref
Q2	67/178,468	0.98 (0.70, 1.37)	54/184,994	**0.54 (0.38, 0.76)**	56/189,530	**0.69 (0.48, 0.99)**	65/173,932	0.75 (0.54, 1.04)
Q3	40/166,607	**0.61 (0.41, 0.92)**	71/196,715	**0.68 (0.48, 0.94)**	57/200,172	**0.66 (0.46, 0.96)**	54/163,149	**0.65 (0.46, 0.93)**
Q4	32/158,013	**0.50 (0.32, 0.79)**	61/204,614	**0.57 (0.39, 0.81)**	52/214,911	**0.56 (0.37, 0.83)**	41/147,716	**0.53 (0.36, 0.80)**
Q5	47/154,890	0.72 (0.47, 1.10)	66/206,874	**0.61 (0.42, 0.89)**	60/231,870	**0.59 (0.39, 0.88)**	53/129,895	0.76 (0.51, 1.12)
P-trend		**0.009**		**0.033**		**0.009**		**0.039**
P-interaction			□	**0.039**	□	□	□	0.667

CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; Ref, reference group; UC, ulcerative colitis

[a] Based on the fully adjusted model without adjustment for corresponding items

[b] additionally adjusted for ral contraceptive pills in females

[c] represent P value<0.05

Table S4 Associations of dietary quercetin with risk of IBD, CD, and UC stratified by smoking status and alcohol consumption [a]

Quercetin intake	Smoking				Alcohol consumption					
	Never		Previous or current		None		Moderate		Heavy	
	Case/person-years	HR (95% CI)	Case/person-years	HR (95% CI)	Case/person-years	HR (95% CI)	Case/person-years	HR (95% CI)	Case/person-years	HR (95% CI)
					IBD					
Q1	133/197,803	Ref	130/170,224	Ref	97/158,976	Ref	77/129,896	Ref	53/77,147	Ref
Q2	87/171,633	0.87 (0.65, 1.17)	83/155,161	**0.73 (0.55, 0.97)**	72/118,234	1.04 (0.76, 1.43)	60/152,841	**0.65 (0.46, 0.92)**	42/87,510	0.73 (0.48, 1.11)
Q3	80/160,983	**0.69 (0.50, 0.96)** [b]	84/151,885	0.77 (0.58, 1.04)	51/107,276	0.82 (0.57, 1.17)	66/156,169	**0.68 (0.48, 0.97)**	42/94,837	0.70 (0.45, 1.08)
Q4	62/145,720	**0.65 (0.46, 0.91)**	68/150,510	**0.65 (0.47, 0.90)**	36/101,526	**0.61 (0.40, 0.92)**	72/159,012	0.73 (0.51, 1.05)	33/96,998	**0.56 (0.34, 0.91)**
Q5	75/128,163	**0.65 (0.46, 0.93)**	82/141,120	0.83 (0.60, 1.15)	64/120,682	0.90 (0.62, 1.30)	66/161,271	**0.63 (0.43, 0.93)**	32/74,728	0.73 (0.43, 1.23)
P-trend		**0.006**		0.179		0.144		0.09		0.102
P-interaction		□		□		□ □		□		0.304
					CD					
Q1	37/200,058	Ref	39/172,157	Ref	28/160,400	Ref	16/131,746	Ref	14/78,034	Ref
Q2	22/174,148	**1.85 (1.04, 3.31)**	17/157,458	**0.57 (0.32, 1.03)**	21/119,645	1.23 (0.68, 2.23)	21/155,404	1.10 (0.56, 2.14)	11/88,749	0.73 (0.32, 1.64)
Q3	26/163,306	1.26 (0.67, 2.38)	23/154,159	0.87 (0.50, 1.51)	16/108,476	1.10 (0.57, 2.11)	20/158,884	1.01 (0.50, 2.02)	12/96,228	0.75 (0.33, 1.71)
Q4	21/147,791	1.39 (0.72, 2.65)	20/152,740	0.83 (0.45, 1.52)	13/102,683	1.01 (0.49, 2.07)	25/161,804	1.24 (0.61, 2.51)	10/98,360	0.63 (0.26, 1.57)

Q5	22/130,044	1.22 (0.62, 2.41)	22/143,299	0.98 (0.53, 1.80)	25/122,076	1.67 (0.89, 3.13)	16/164,196	0.73 (0.33, 1.62)	8/75,821	0.68 (0.24, 1.90)	
P-trend		0.846		0.821		0.215		0.556		0.416	
P-interaction		□	□	**0.013**		□ □	□	□	□	0.642	
UC											
Q1	96/199,844	Ref	91/171,916	Ref	69/160,175	Ref	61/131,534	Ref	39/77,958	Ref	
Q2	65/173,932	**0.65 (0.45, 0.93)**	66/157,222	0.79 (0.57, 1.09)	51/119,474	0.97 (0.66, 1.41)	39/155,320	**0.54 (0.35, 0.81)**	31/88,668	0.74 (0.45, 1.20)	
Q3	54/163,149	**0.57 (0.39, 0.83)**	61/153,989	0.75 (0.53, 1.06)	35/108,389	0.72 (0.47, 1.11)	46/158,785	**0.61 (0.40, 0.91)**	30/96,147	0.69 (0.41, 1.14)	
Q4	41/147,716	**0.49 (0.32, 0.74)**	48/152,613	**0.60 (0.41, 0.89)**	23/102,656	**0.48 (0.29, 0.81)**	47/161,677	**0.60 (0.39, 0.93)**	23/98,295	**0.54 (0.30, 0.95)**	
Q5	53/129,895	**0.53 (0.35, 0.80)**	60/143,084	0.79 (0.54, 1.16)	39/122,010	0.66 (0.42, 1.05)	50/164,026	**0.61 (0.39, 0.96)**	24/75,728	0.75 (0.41, 1.38)	
P-trend		**0.002**		0.096		**0.01**		0.113		0.164	
P-interaction		□	□	0.803		□ □	□	□	□	0.46	

CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; Ref, reference group; UC, ulcerative colitis

[a] Based on the fully adjusted model without adjustment for corresponding items

[b] represent P value<0.05

Table S5 Associations of dietary quercetin with risk of IBD, CD, and UC stratified by BMI and physical activity [a]

Quercetin intake	BMI				Physical activity			
	<30 Kg/m^2		>=30 Kg/m^2		Inadequate		Adequate	
	Case/person-years	HR (95% CI)	Case/person-years	HR (95% CI)	Case/person-years	HR (95% CI)	Case/person-years	HR (95% CI)
IBD								
Q1	159/263,111	Ref	68/102,908	Ref	82/127,380	Ref	145/238,639	Ref
Q2	133/278,272	0.80 (0.63, 1.02)	41/80,313	0.76 (0.51, 1.13)	60/108,750	0.89 (0.63, 1.26)	114/249,835	**0.75 (0.58, 0.96)**
Q3	109/289,293	**0.64 (0.49, 0.83)** [b]	50/68,989	1.07 (0.73, 1.59)	47/98,446	0.78 (0.53, 1.14)	112/259,836	**0.70 (0.54, 0.91)**
Q4	116/295,639	**0.66 (0.51, 0.87)**	25/61,897	0.59 (0.36, 0.98)	41/88,815	0.75 (0.50, 1.15)	100/268,721	**0.61 (0.46, 0.81)**
Q5	124/296,958	**0.70 (0.53, 0.92)**	38/59,723	0.88 (0.56, 1.40)	44/84,236	0.81 (0.53, 1.24)	118/272,445	**0.70 (0.52, 0.93)**
P-trend		**0.006**		0.418		0.222		**0.008**
P-interaction	□	□	□	0.054	□	□	□	0.95
CD								
Q1	39/266,189	Ref	19/103,990	Ref	23/128,845	Ref	35/241,334	Ref
Q2	38/282,396	1.03 (0.65, 1.64)	15/81,402	1.03 (0.51, 2.08)	18/110,362	1.07 (0.56, 2.04)	35/253,436	1.02 (0.63, 1.66)
Q3	32/293,636	0.88 (0.53, 1.44)	16/69,952	1.30 (0.64, 2.65)	13/99,923	0.93 (0.45, 1.92)	35/263,665	1.01 (0.61, 1.66)
Q4	36/300,132	1.00 (0.60,	12/62,716	1.10 (0.49,	14/90,059	1.15 (0.54,	34/272,788	0.98 (0.58,

		1.66)		2.44)		2.44)		1.65)
Q5	39/301,518	1.08 (0.64, 1.82)	10/60,575	0.87 (0.37, 2.05)	8/85,512	0.63 (0.26, 1.55)	41/276,581	1.17 (0.69, 1.98)
P-trend		0.843		0.89		0.477		0.646
P-interaction	□	□	□	0.771	□	□	□	0.55
UC								
Q1	120/265,799	Ref	49/103,869	Ref	59/128,684	Ref	110/240,984	Ref
Q2	95/282,141	**0.74 (0.56, 0.97)**	26/81,321	0.66 (0.41, 1.08)	42/110,232	0.83 (0.55, 1.26)	79/253,230	**0.67 (0.49, 0.90)**
Q3	77/293,452	**0.57 (0.42, 0.77)**	34/69,869	1.00 (0.62, 1.59)	34/99,835	0.74 (0.47, 1.17)	77/263,486	**0.61 (0.45, 0.84)**
Q4	80/299,926	**0.57 (0.42, 0.78)**	13/62,701	**0.42 (0.22, 0.80)**	27/90,000	0.64 (0.39, 1.06)	66/272,627	**0.50 (0.36, 0.70)**
Q5	85/301,273	**0.59 (0.43, 0.83)**	28/60,492	0.89 (0.52, 1.54)	36/85,372	0.87 (0.54, 1.42)	77/276,393	**0.57 (0.40, 0.80)**
P-trend		**0.001**		0.389		0.342		**0.001**
P-interaction	□	□	□	**0.038**	□	□	□	0.61

CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; Ref, reference group; UC, ulcerative colitis

[a] Based on the fully adjusted model without adjustment for corresponding items

[b] represent P value<0.05

Table S6 Sensitivity analysis for associations of dietary quercetin with risk of IBD, CD, and UC [a]

Daily quercetin intake	IBD	CD	UC
	HR (95% CI)	HR (95% CI)	HR (95% CI)
Excluding incident IBD in the first two years of follow-up			
Q1	Ref	Ref	Ref
Q2	0.80 (0.64, 1.00)	1.04 (0.68, 1.59)	**0.73 (0.56, 0.95)**
Q3	**0.75 (0.60, 0.95)**[b]	1.04 (0.67, 1.62)	**0.67 (0.51, 0.88)**
Q4	**0.62 (0.48, 0.80)**	1.01 (0.63, 1.62)	**0.51 (0.37, 0.70)**
Q5	**0.74 (0.57, 0.96)**	0.97 (0.60, 1.59)	**0.67 (0.50, 0.92)**
P-trend	**0.006**	0.877	**0.002**
Excluding incident IBD in the first four years of follow-up			
Q1	Ref	Ref	Ref
Q2	0.83 (0.64, 1.07)	1.22 (0.76, 1.97)	**0.71 (0.52, 0.96)**
Q3	**0.72 (0.55, 0.95)**	0.95 (0.56, 1.61)	**0.65 (0.47, 0.90)**
Q4	**0.64 (0.47, 0.86)**	1.03 (0.60, 1.78)	**0.52 (0.36, 0.75)**
Q5	0.75 (0.55, 1.01)	1.21 (0.70, 2.08)	**0.61 (0.42, 0.88)**
P-trend	**0.017**	0.756	**0.002**
Restrict analysis to individuals with at 2 rounds of 24h recalls			
Q1	Ref	Ref	Ref
Q2	**0.73 (0.55, 0.97)**	0.93 (0.54, 1.58)	**0.66 (0.47, 0.93)**
Q3	**0.68 (0.50, 0.91)**	0.70 (0.39, 1.27)	0.71 (0.49, 1.04)
Q4	**0.69 (0.51, 0.94)**	0.93 (0.51, 1.68)	**0.62 (0.43, 0.89)**
Q5	**0.71 (0.51, 0.98)**	0.71 (0.37, 1.36)	**0.67 (0.47, 0.95)**
P-trend	0.075	0.382	0.126
Identifying individuals with IBD using at least two medical records			
Q1	Ref	Ref	Ref
Q2	0.82 (0.63, 1.08)	0.89 (0.54, 1.45)	0.80 (0.58, 1.11)
Q3	**0.63 (0.46, 0.85)**	0.68 (0.39, 1.17)	**0.61 (0.42, 0.89)**
Q4	**0.67 (0.48, 0.91)**	0.74 (0.42, 1.31)	**0.64 (0.43, 0.93)**
Q5	**0.65 (0.47, 0.91)**	0.66 (0.36, 1.21)	**0.65 (0.43, 0.97)**

P-trend	**0.005**	0.148	**0.017**
Further adjusted for Charlson comorbidity index			
Q1	Ref	Ref	Ref
Q2	**0.79 (0.64, 0.97)**	1.01 (0.69, 1.49)	**0.72 (0.57, 0.91)**
Q3	**0.73 (0.58, 0.90)**	0.95 (0.63, 1.44)	**0.65 (0.51, 0.84)**
Q4	**0.64 (0.51, 0.81)**	0.99 (0.64, 1.52)	**0.54 (0.41, 0.72)**
Q5	**0.73 (0.57, 0.92)**	0.99 (0.64, 1.54)	**0.64 (0.49, 0.86)**
P-trend	**0.003**	0.930	**<0.001**
Further adjusted for C-reactive protein			
Q1	Ref	Ref	Ref
Q2	**0.79 (0.65, 0.97)**	1.02 (0.69, 1.50)	**0.72 (0.57, 0.92)**
Q3	**0.73 (0.59, 0.91)**	0.98 (0.65, 1.47)	**0.66 (0.51, 0.85)**
Q4	**0.65 (0.52, 0.83)**	1.01 (0.66, 1.56)	**0.55 (0.41, 0.72)**
Q5	**0.74 (0.58, 0.94)**	1.01 (0.65, 1.58)	**0.65 (0.49, 0.86)**
P-trend	**0.004**	0.974	**0.001**
Further adjusted for baseline medication [c]			
Q1	Ref	Ref	Ref
Q2	**0.80 (0.65, 0.98)**	1.03 (0.70, 1.52)	**0.72 (0.57, 0.92)**
Q3	**0.73 (0.59, 0.91)**	0.98 (0.65, 1.47)	**0.66 (0.51, 0.85)**
Q4	**0.65 (0.52, 0.83)**	1.02 (0.67, 1.57)	**0.55 (0.41, 0.72)**
Q5	**0.74 (0.58, 0.94)**	1.03 (0.66, 1.60)	**0.65 (0.49, 0.86)**
P-trend	**0.004**	0.942	**0.001**
Further adjusted for ultra-processed food			
Q1	Ref	Ref	Ref
Q2	**0.81 (0.66, 0.99)**	0.99 (0.68, 1.45)	**0.75 (0.59, 0.94)**
Q3	**0.75 (0.60, 0.92)**	0.94 (0.63, 1.41)	**0.68 (0.53, 0.87)**
Q4	**0.67 (0.53, 0.85)**	0.99 (0.65, 1.50)	**0.57 (0.43, 0.75)**
Q5	**0.78 (0.62, 0.99)**	1.03 (0.67, 1.59)	**0.70 (0.53, 0.92)**
P-trend	**0.013**	0.912	**0.002**
Further adjusted for n-3 polyunsaturated fatty acids			
Q1	Ref	Ref	Ref
Q2	**0.80 (0.65, 0.98)**	0.97 (0.66, 1.41)	**0.74 (0.59, 0.94)**

Q3	**0.74 (0.60, 0.91)**	0.90 (0.61, 1.34)	**0.68 (0.53, 0.87)**
Q4	**0.65 (0.52, 0.82)**	0.92 (0.61, 1.39)	**0.57 (0.43, 0.74)**
Q5	**0.76 (0.61, 0.95)**	0.95 (0.63, 1.45)	**0.69 (0.53, 0.91)**
P-trend	**0.004**	0.772	**0.001**

BMI, body mass index; CD, Crohn's disease; CI, confidence interval; HR, hazard ratio; IBD, inflammatory bowel disease; NSAIDs, nonsteroidal anti-inflammatory drugs; Ref, reference group; TDI, Townsend deprivation index; UC, ulcerative colitis

[a] based on the fully adjusted model age, sex, ethnic background, adjusted for physical activity, BMI, TDI, smoking status, alcoholic drinks consumption (exclude wine), intake of cereal, meat, fish, sugar-sweetened beverages, and total energy.

[b] represent P value<0.05

[c] including use of NSAIDs, proton pump inhibitors, and antibiotic

Table S7 Mediation analysis for C-reactive protein in associations of dietary quercetin with risk of IBD and UC [a]

Outcome	Mediating proportion (%)	Direct effect (E^{-04})	Indirect effect (E^{-04})
	Coefficient (95% CI)	Coefficient (95% CI)	Coefficient (95% CI)
IBD	7.15 (0.54, 11.31)	-12.2 (-21.9, -5.25)	-0.93 (-1.25, -0.67)
UC	2.74 (1.00, 4.94)	-11.9 (-20.0, -6.00)	-0.33 (-0.53, -0.13)

CI, confidence interval; HR, hazard ratio

[a] based on the fully adjusted model age, sex, ethnic background, adjusted for physical activity, BMI, TDI, smoking status, alcoholic drinks consumption (exclude wine), intake of cereal, meat, fish, sugar-sweetened beverages, and total energy.