PAPER

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Dietary quercetin intake is associated with lower ulcerative colitis risk but not Crohn's disease in a prospective cohort study and *in vivo* experiments†

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Objectives: Previous preclinical evidence indicates a protective role of quercetin against inflammatory bowel disease (IBD). However, there is no evidence from human populations, resulting in knowledge gaps regarding the role of quercetin in the IBD development. We aimed to prospectively evaluate the associations between dietary quercetin intake and IBD in humans and *in vivo* animal models. **Methods**: We included 187 709 IBD-free participants from the UK Biobank. Dietary information was collected using validated 24-hour dietary recalls and the quercetin intake was estimated based on national nutrient databases. Incident IBD was ascertained *via* inpatient and primary care data. Cox proportional hazard models were used to estimate the multi-variable adjusted hazard ratios (aHRs) and 95% confidence intervals (CIs). Experiments were conducted in two chemical-induced (dextran sulfate sodium salt and trinitro-benzene-sulfonic acid) mouse models orally pretreated with quercetin (CAS number: 117-39-5) solution to evaluate the effects of quercetin at physiological levels. **Results**: After a mean follow-up of 9.7 years, we documented 863 incident IBD. Compared to participants with the lowest quintile intake of quercetin, those in the highest quintiles were associated with a lower risk of IBD (aHR 0.76, 95% CI 0.60−0.95; *P*-trend = 0.004) and ulcerative colitis (aHR 0.69, 95% CI 0.53−0.91; *P*-trend = 0.001), but not Crohn's disease (aHR 0.95, 95% CI 0.62−1.45; *P*-trend = 0.765). Mouse models showed that pretreatment with quercetin could attenuate the chemically induced colitis. **Conclusions**: Higher quercetin intake was associated with a lower risk of IBD, especially UC. The protective role of quercetin is promising in humans and warrants further investigation into downstream mechanisms.

1. Introduction

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), is an immune-related chronic gastrointestinal disease with a rapidly increasing global incidence.[1] As a crucial modifiable behavioral risk factor, the diet has received widespread attention in the aetiopathogenesis of IBD.[1] Among phytonutrients, there is emerging evidence of various flavonoids to play an important role in the development of IBD. They may be useful in alleviating acute or chronic intestinal inflammation through different mechanisms, including protecting against oxidative stress, enhancing intestinal epithelial barrier function, and modulating the immune response in the gut.[2]

Quercetin is a flavonoid commonly enriched in many vegetables and fruits with various pharmacological functions.[3,4] A meta-analysis of 11 preclinical experiments concluded a protective effect of quercetin against IBD in animal models *via* multiple mechanisms.[5] However, there is no available evidence in humans. Previous randomized clinical trials reported that quercetin supplementation could significantly improve disease activity and reduce serum tumor necrosis factor (TNF)-α levels in patients with rheumatoid arthritis compared with the placebo group.[6] In addition, as top sources of dietary quercetin, tea,[7] vegetables,[8] and fruits[8] have been linked to a lower risk of IBD. These pieces of evidence make it rational for the possible benefits of quercetin in IBD prevention, but there are still knowledge gaps in further understanding the role of quercetin in the development of IBD in humans.

Therefore, in a prospective cohort of 187 709 participants free of IBD, we aimed to examine the association between dietary quercetin intake and the subsequent development of

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IBD and of CD and UC separately. Secondly, we aimed to examine this association in different participant subgroups to identify populations that may benefit more from dietary quercetin intake. Animal experiments in mouse models were conducted to evaluate the effects of quercetin at physiological levels *in vivo*.

2. Methods

2.1 Study population

This study leveraged data from the UK Biobank, which is an ongoing national prospective cohort project that enrolled over half a million volunteers from 22 assessment centers in the UK between 2006 and 2010.[9,10] All participants have signed an electronic consent and received a touchscreen questionnaire, a verbal interview, a physical examination, and biological sample collection. The details are described in detail elsewhere.[9] The North West–Haydock Research Ethics Committee granted ethical approval to use the UK Biobank database (REC reference: 16/NW/0274).

A web-based 24-hour dietary recall questionnaire (Oxford WebQ) was administered for five rounds in April 2009–September 2010, February 2011–April 2011, June 2011–August 2011, October 2011–December 2011, and April 2012–June 2012. In the present study (Fig. 1), a subset of UK Biobank participants has available 24-hour dietary data ($n = 210\,948$). Then, we excluded: (1) participants reporting implausible energy intake (defined as <800 or >4200 kcal per day for males, <600 or >3500 kcal per day for females)[11] or a non-typical diet ($n = 19\,883$);[12] (2) participants with a dietary quercetin intake outside the normal distribution ($n = 978$) based on Rosner's generalized extreme studentized deviate test;[13] (3) participants with diagnosis of IBD before the baseline (*i.e.*, the completion date of the last round of recalls in this study, $n = 2378$). This study followed the strengthening the reporting of observational studies in epidemiology (STROBE) guidelines.

2.2 Assessment of quercetin intake

The dietary information was collected using a 24 h WebQ. Participants were presented with a list of up to 206 foods and 32 beverages commonly consumed in the UK and selected the number of portions consumed from each food. The exposure was the daily intake of quercetin from the diet and was estimated using the sum of the portion size multiplied by the corresponding quercetin content of each food. The portion size recorded in grams of each food was obtained from the publication by the Food Standards Agency.[14] The quercetin content (in mg per 100 g) was obtained from the United States Department of Agriculture (USDA) database on flavonoids[15]
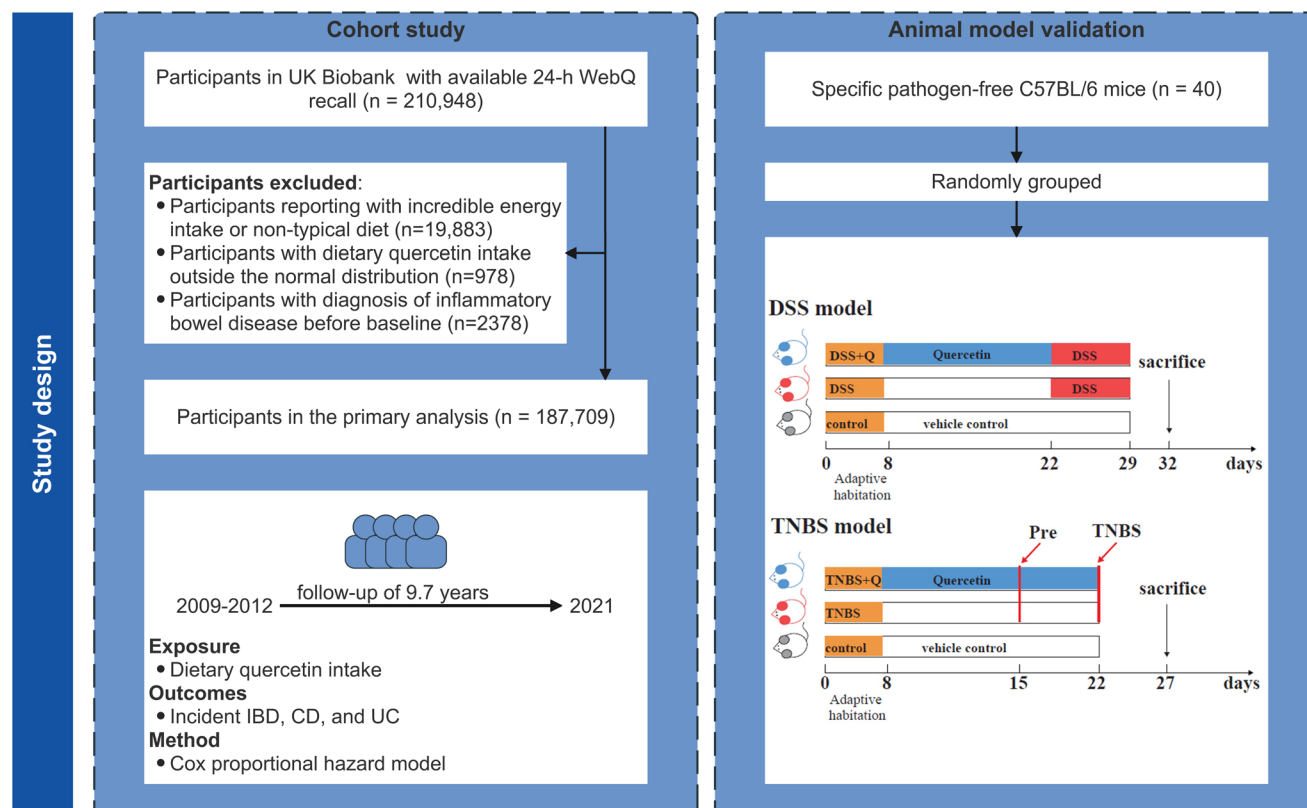

Fig. 1 Flow chart of the current study.

and expanded with values from Phenol-Explorer,[16] a French database on polyphenols. The two databases were previously applied to estimate dietary intakes of flavonoids in European and other populations and the results show that the intake estimates from both are in good agreement.[17–19] These studies suggested the rationale for using these databases to estimate participants in the current cohort.

The web-based 24-hour dietary assessment was compared with an interviewer-administered 24-hour recall completed on the same day, and Spearman correlation coefficients calculated from the web-based questionnaire ranged from 0.5 and 0.9 (mean 0.6) for most nutrients.[20] In the subgroup of participants who completed all five rounds of WebQ (n = 2218), comparing dietary measures based on a single recall *versus* the mean of all completed questionnaires, the Pearson correlation coefficients of the quercetin intake between the two measures were 0.703–0.767. Moreover, 86%–93% of participants were classified into the same or adjacent category of quercetin intake between the measures from a single recall and the average of five recalls.

In addition, a single round of a 24-hour WebQ recall has also shown good agreement with long-term consumption and frequency of food groups collected by baseline food frequency questionnaires.[21] Therefore, we included participants with at least one 24 h recall in the primary analysis, given the sample size and the incidence of outcomes.

2.3 Ascertainment of outcomes

The primary outcomes of interest were inflammatory bowel disease during the follow-up, obtained through hospital inpatient data (International Classification of Disease ninth and tenth editions [ICD-9 and ICD-10]) and coded primary care data. Incident IBD cases were defined as CD (ICD-9 codes 555, ICD-10 codes K50) or UC (ICD-9 codes 556, ICD-10 codes K51). We use a single diagnostic code in the primary analysis to maximize the statistical power. Previous studies in the UK had reported acceptable diagnostic accuracy using at least one diagnosis code in inpatient data (PPV 87%)[22] and primary care data (sensitivity 94%).[23] Moreover, the UK Audit Commission review of 2009 to 2010 concluded that a single diagnostic coding ICD-10 has an overall accuracy of 87%.[24] Therefore, we used a single diagnostic code to identify IBD in the primary analysis. A stricter definition, using at least two diagnostic codes or one diagnostic code plus one prescription that was described in detail in a previous study,[25] was applied in a sensitivity analysis.

Participants were followed up from the completed date of the last available 24-h WebQ to the date of incidence of IBD, death, loss, or the end of the follow-up (latest updated time for health data, September 2021 for participants in England, July 2021 for participants in Scotland, and February 2018 for participants in Wales), whichever came first.

2.4 Assessment of covariates

In this study, we used predefined covariates. We included age, sex (female and male), race (white and non-white), education level (college and below college), smoking status (never, previous or current), physical activity level (adequate and inadequate),[26] and body mass index (BMI). We controlled the socioeconomic status using the Townsend Deprivation Index (TDI).[27] Baseline comorbidities were evaluated using the Charlson Comorbidity Index (CCI).[28] Serum C-reactive protein (CRP) was measured by immunoturbidimetric-high sensitivity analysis on a Beckman Coulter AU5800, with full details regarding sample and data processing available on the UKB website.[29] Medication information was recorded in interviews with trained nurses, including the use of non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors, antibiotics, and oral contraceptive pills. Dietary variables were collected using the 24 h WebQ, including total energy, common nutrients, and food groups. The details of nutrient and food group calculation are published elsewhere.[30] Details of the definition and process of the covariates are presented in Table S1.† The intake of ultra-processed food defined by NOVA classification was included in the sensitivity analysis, the calculation of which has been described previously.[31] If covariate information was missing or recorded as "unknown", we imputed the median values for continuous variables or applied a most frequently used category for categorical variables.

2.5 Statistical analysis for cohort study

Baseline characteristics were displayed by the quintiles of dietary quercetin intake. Characteristics were summarized in number (percentage) for categorical variables and in mean (standard deviation (SD)) for continuous variables. The associations between quercetin intake in quintiles and subsequent IBD, CD, and UC were first presented as a cumulative incidence plot. The Cox model was applied to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs). Four multivariable models were constructed: model 1 (minimally adjusted model) adjusted for age, sex, and ethnic background; model 2 further adjusted for physical activity, TDI, smoking status, alcoholic drink (excluding wine) consumption, and the BMI based on model 1; model 3 further adjusted for total energy based on model 2; model 4 (fully adjusted model) further adjusted for the intake of cereal, meat, fish, and sugar-sweetened beverages based on model 3. The usage of oral contraceptive pills was included in the fully adjusted model when investigating associations in females. Proportional hazard assumptions were confirmed using a weighted residual method ($P > 0.79$).

To visualize the association between quercetin and IBD, we also used restricted cubic splines (RCS) with three knots at the 10th, 50th, and 90th percentile based on the fully adjusted mode. We set the zero intake as the reference level for analysis using the RCS method. In a secondary analysis, we evaluated associations of energy-adjusted quercetin intake and quercetin intake by body weight with IBD. The energy-adjusted quercetin was calculated using the residual method, which can mitigate the effects of measurement error in data collected using self-reported dietary assessment instruments.[32]

Subgroup analyses were conducted and multiplication interactions were tested in population by age (<60, ≥60), sex, smoking status, alcohol consumption (none, moderate, heavy), physical activity, and BMI (<30, ≥30 kg m^{-2}). The categorization for physical activity and the BMI in the subgroup analysis was based on the same definition found to be associated with an elevated risk of IBD in previous studies.[33] We also conducted several sensitivity analyses: (1) lagged analysis excluding IBD within the first 2 and 4 years of follow-up; (2) restricting the analysis to individuals at 2 rounds of 24 h recalls; (3) further adjusting for CCI; (4) further adjusting for IBD-related medication; (5) further adjusting for CRP and conducting mediation analysis to quantify the contribution of CRP in quercetin-IBD/UC associations using R packages "mediation" (version 4.5.0) with 1000 bootstrap samples to estimate the bias-corrected bootstrap CI; (6) additionally adjusting for ultra-processed food and n-3 polyunsaturated fatty acid consumption; (7) identifying individuals with IBD using at least two medical records. All analyses were performed using R (version 4.2.1; R Development Core Team), and all statistical tests were two-sided, with a P value < 0.05 considered as statistically significant.

2.6 Validation in animal models

Animal experiments were conducted to verify the inverse associations between the quercetin intake and subsequent IBD. The objective of the animal experiments was to supplementally validate the credibility of observational studies in a framework and the quercetin dose matched our cohort study, not solely to pursue novel mechanistic discoveries. C57BL/6 male mice were purchased from and raised at Shanghai Model Organisms Center, Co., Ltd (Shanghai, China). All animals were randomly grouped and hosted under standardized specific pathogen-free (SPF) conditions with *ad libitum* access to water and chow. Quercetin (Solarbio, SQ8030; CAS number: 117-39-5) was dissolved in 2%-Tween 80 (Sigma, P4780)-containing ddH$_2$O. Referring to the dosage of previous studies, we chose the dose of 15 mg kg^{-1} daily for quercetin treatment in mice, which was approximately equal to 84 mg d^{-1} in humans. After a one-week adaptive growth period, mice were gavaged with quercetin solution daily (15 mg kg^{-1}) for 14 days. Then, we took the classical Dextran Sulfate Sodium Salt (DSS)-induced and trinitro-benzene-sulfonic acid (TNBS)-induced mouse models to establish the mouse models of UC (Fig. 1). We evaluated the disease activity, histological presentation, and specific mRNA expression among different groups. The detailed reagents, experiments, and analysis are provided in the ESI.† All mouse experiments were conducted as per the National Institutes of Health Guidelines for the Care and Use of Laboratory Animals. All of the study procedures were approved by the Institutional Animal Care and Use Committee of The Second Affiliated Hospital, School of Medicine, Zhejiang University (iACUC No.2023-130).

3. Results

3.1 Characteristics of the study sample

In this study, 187 709 individuals were included and followed up for a mean (SD) of 9.7 (1.6) years. Baseline characteristics are summarized in Table 1. Among the included study samples, the mean (SD) age was 59.0 (8.0) years and 103 241 (55.0%) were female. The mean (SD) intake of quercetin was 22.61 (18.52) mg d^{-1}. Compared with participants in the lowest quintiles of quercetin intake, those in the higher categories are more likely to be non-smokers, with a higher educational level, a lower BMI, and more physical activity.

3.2 Primary and secondary analyses

Throughout the follow-up, we documented 863 IBD events (4.74 cases per 10 000 person-years) including 256 CD (1.40 cases per 10 000 person-years) and 607 UC (3.33 cases per 10 000 person-years). As shown in Fig. 2, inverse associations were observed between quercetin and incident IBD and UC, but not CD. Based on the fully adjusted model, the dose–response associations of the dietary quercetin intake with IBD and UC seemed to reach a plateau at an intake amount of about 35 mg d^{-1} (both P-nonlinearity < 0.05). We observed that a higher intake of dietary quercetin was significantly associated with a lower risk of IBD and UC in different multi-variable adjusted models (Fig. S1, Table S2† and Table 2). Specifically, compared to individuals in the lowest quintiles of quercetin intake, the HRs (95% CIs) of the second to highest quintiles in the fully-adjusted model were 0.80 (0.65–0.98), 0.73 (0.60–0.91), 0.65 (0.52–0.82) and 0.76 (0.60–0.95) for IBD and 0.74 (0.59–0.94), 0.68 (0.53–0.87), 0.56 (0.43–0.74), 0.69 (0.53–0.91) for UC. We observed consistent inverse associations of energy-adjusted quercetin intake and quercetin intake by body weight with the risk of IBD and UC (all P-trend < 0.05, Table 3).

3.3 Subgroup and sensitivity analyses

In subgroup analyses, the inverse associations between quercetin and UC remained significant across age groups and sex (Table S3,† all P-trend < 0.05). When stratified by the smoking status, alcohol consumption, and physical activity level, not all subgroups showed a statistically significant inverse trend between a higher dietary quercetin intake and a lower risk of UC. However, we did not detect evidence of heterogeneity in the associations across these subgroups (Tables S4 and S5,† all P-interaction > 0.05). The direction of the associations was consistent with the primary analysis and the observed non-significant associations may be due to the inadequate statistical power. When comparing extreme quintile intake of dietary quercetin, the HR (95% CI) for UC risk was 0.59 (0.43–0.83) among individuals with BMI < 30 kg m^{-2} and 0.89 (0.52–1.54) among individuals with a higher BMI (Table S5†). Although the overall trend of the dietary quercetin–UC association remained inverse in individuals with obesity, it was observed that this association appeared to be statistically different from that in individuals with a lower BMI (P-interaction = 0.038).

Table 1 Baseline characteristics of the study sample at the baseline visit according to the dietary quercetin intake in quintiles[a]

| Characteristics | Total (n = 187 709) | Dietary quercetin intake in quintiles (lowest to highest, mg d^{-1}) | | | | |
		Q1 (n = 37 542, 0–<8.9)	Q2 (n = 37 542, 8.9–<15.0)	Q3 (n = 37 541, 15.0–<21.6)	Q4 (n = 37 542, 21.6–<31.9)	Q5 (n = 37 542, ≥31.9)
Age at the baseline (mean (SD))	59.04 (8.01)	57.15 (8.19)	58.83 (8.00)	59.43 (7.89)	59.84 (7.80)	59.97 (7.81)
Sex (%)						
Female	103 241 (55.0)	17 088 (45.6)	19 437 (51.8)	20 590 (54.8)	22 152 (59.0)	23 948 (63.8)
Male	84 468 (45.0)	20 390 (54.4)	18 105 (48.2)	16 951 (45.2)	15 390 (41.0)	13 594 (36.2)
Townsend deprivation index (mean (SD))	−1.60 (2.86)	−1.26 (3.02)	−1.66 (2.82)	−1.71 (2.80)	−1.69 (2.80)	−1.66 (2.84)
Education (%)						
Below college degree	106 976 (57.3)	25 584 (68.8)	22 146 (59.3)	20 387 (54.5)	19 077 (51.0)	19 735 (52.8)
College degree	79 823 (42.7)	11 621 (31.2)	15 202 (40.7)	17 001 (45.5)	18 322 (49.0)	17 662 (47.2)
Ethnicity (%)						
White	179 449 (95.9)	35 229 (94.4)	35 859 (95.9)	36 178 (96.7)	36 192 (96.7)	35 939 (96.1)
Others	7595 (4.1)	2109 (5.6)	1546 (4.1)	1245 (3.3)	1220 (3.3)	1464 (3.9)
Smoking status (%)						
Never smoked	106 358 (56.8)	19 731 (52.8)	21 070 (56.3)	21 419 (57.2)	21 568 (57.6)	22 525 (60.1)
Previous or current smokers	80 868 (43.2)	17 631 (47.2)	16 371 (43.7)	16 025 (42.8)	15 888 (42.4)	14 934 (39.9)
Physical activity (%)						
Inadequate	53 357 (28.4)	13 192 (35.2)	11 491 (30.6)	10 378 (27.6)	9358 (24.9)	8915 (23.7)
Adequate	134 352 (71.6)	24 286 (64.8)	26 051 (69.4)	27 163 (72.4)	28 184 (75.1)	28 627 (76.3)
BMI, kg m^{-2} (mean (SD))	26.91 (4.63)	27.96 (4.97)	27.19 (4.66)	26.77 (4.51)	26.37 (4.34)	26.24 (4.45)
Charlson comorbidity index (mean (SD))	0.24 (0.83)	0.25 (0.85)	0.23 (0.83)	0.22 (0.78)	0.22 (0.80)	0.25 (0.88)
Non-steroidal anti-inflammatory drugs use (%)	68 419 (36.4)	14 843 (39.6)	13 853 (36.9)	13 366 (35.6)	13 216 (35.2)	13 118 (34.9)
Proton pump inhibitors use (%)	15 168 (8.1)	3566 (9.5)	3062 (8.2)	2882 (7.7)	2695 (7.2)	2958 (7.9)
Antibiotic use (%)	2124 (1.1)	465 (1.2)	469 (1.2)	389 (1.0)	372 (1.0)	428 (1.1)
Alcohol, g d^{-1} (mean (SD))	15.22 (20.69)	14.11 (21.52)	15.49 (20.34)	16.58 (20.95)	16.71 (21.25)	13.22 (19.10)
Total energy, KJ d^{-1} (mean (SD))	8464.46 (2265.29)	8056.27 (2411.93)	8298.58 (2217.72)	8456.86 (2171.47)	8635.49 (2177.10)	8877.20 (2250.93)
Quercetin, mg d^{-1} (mean (SD))	22.61 (18.52)	4.98 (2.53)	11.98 (1.78)	18.18 (1.89)	26.10 (2.90)	51.84 (19.58)
From vegetables	4.13 (3.80)	1.66 (1.84)	3.33 (2.70)	4.18 (3.25)	5.32 (3.84)	6.14 (4.91)
From fruits	3.98 (4.21)	1.15 (1.67)	2.78 (2.62)	3.91 (3.32)	5.45 (4.14)	6.60 (5.68)
From alcoholic beverages	1.34 (2.63)	0.40 (1.08)	1.15 (2.17)	1.63 (2.83)	1.94 (3.22)	1.59 (2.99)
From non-alcoholic beverages	7.30 (15.21)	0.87 (0.87)	1.45 (1.84)	2.27 (3.07)	4.47 (5.56)	27.46 (24.42)
Cereal intake, g d^{-1} (mean (SD))	52.72 (69.63)	17.70 (22.37)	27.75 (33.08)	51.61 (63.65)	77.63 (81.91)	88.91 (90.04)
Meat intake, g d^{-1} (mean (SD))	86.68 (70.06)	94.36 (76.53)	91.31 (69.51)	86.99 (67.76)	82.82 (67.08)	77.90 (67.73)
Fish intake, g d^{-1} (mean (SD))	26.07 (41.65)	21.49 (42.19)	24.12 (40.01)	26.48 (41.04)	28.38 (41.45)	29.88 (42.97)
Ultra-processed food intake, serving per d (mean (SD))	8.48 (4.47)	9.52 (4.92)	8.72 (4.44)	8.33 (4.32)	7.91 (4.15)	7.92 (4.28)
Sugar-sweetened beverage intake, serving per d (mean (SD))	0.28 (0.63)	0.40 (0.78)	0.30 (0.64)	0.26 (0.59)	0.23 (0.54)	0.24 (0.57)
Alcoholic drink intake (excl. wine), g d^{-1} (mean (SD))[b]	127.48 (369.62)	225.62 (538.75)	144.67 (381.85)	113.65 (322.44)	89.27 (272.98)	64.18 (230.20)
Carbohydrate intake, g d^{-1} (mean (SD))	251.77 (75.02)	233.59 (77.72)	243.29 (71.97)	249.59 (70.70)	258.30 (71.97)	274.07 (76.10)
Dietary fiber intake, g d^{-1} (mean (SD))	18.06 (6.57)	13.49 (5.17)	16.64 (5.21)	18.31 (5.55)	20.13 (6.04)	21.75 (7.35)
Fat intake, g d^{-1} (mean (SD))	71.25 (27.02)	70.89 (28.60)	70.81 (26.85)	70.87 (26.45)	71.11 (26.26)	72.57 (26.83)
Protein intake, g d^{-1} (mean (SD))	80.01 (23.26)	75.62 (25.04)	78.70 (22.69)	80.08 (22.05)	81.71 (22.18)	83.93 (23.38)
n-3 polyunsaturated fatty acid, g d^{-1} (mean (SD))	1.96 (1.01)	1.78 (0.97)	1.89 (0.96)	1.96 (0.98)	2.04 (1.01)	2.14 (1.08)
n-6 polyunsaturated fatty acid, g d^{-1} (mean (SD))	10.73 (5.04)	10.14 (5.00)	10.43 (4.87)	10.65 (4.88)	11.00 (5.02)	11.43 (5.33)

BMI, body mass index; SD, standard deviation. [a] Mean (SD) values and percentages are reported for continuous and categorical variables, respectively. [b] Including intake of beer/cider, spirits, and other alcoholic drinks.

In the sensitivity analysis (Table S6†), we obtained similar results after excluding incident IBD in the first 2/4 years of follow-up, restricting to individuals with at least 2 rounds of 24 h recalls, further adjusting for CCI/IBD-related medication/ CRP/ultra-processed food/n-6 polyunsaturated fatty acids, or when identifying individuals with IBD using at least two
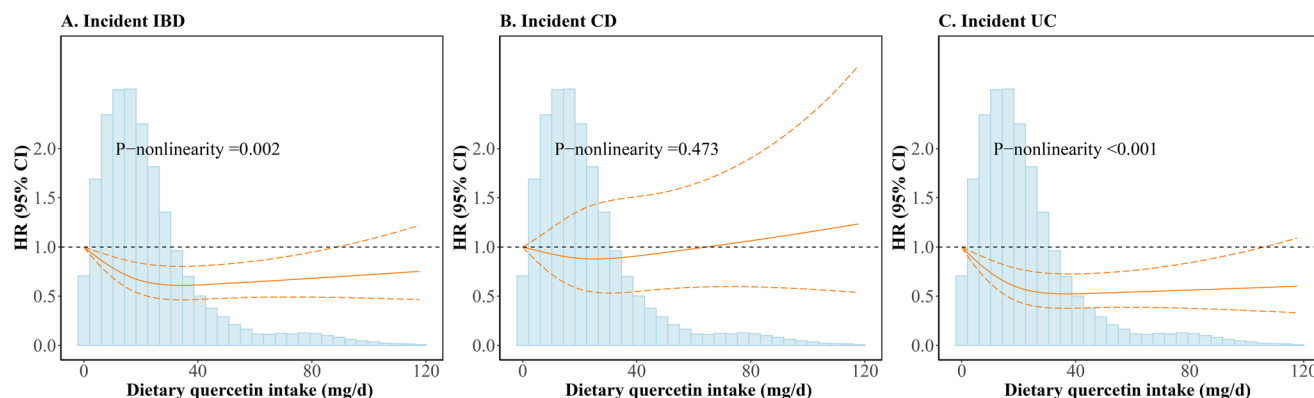
Fig. 2 Associations of dietary quercetin with the risk of IBD, CD, and UC using restricted cubic curves. The results were based on the fully adjusted model. The vertical axis represents the risk of IBD based on the fully adjusted model. The solid line in orange represents hazard ratios, and the dashed lines in orange represent 95% confidence intervals. Density plots of quercetin are presented in blue. CI, confidence interval; HR, hazard ratio.

medical records only. Mediation analysis showed that CRP partially mediated the associations between quercetin and IBD and UC risk (Table S7,† mediating proportion = 7.15% [95% CI 0.54–11.31%] and 2.74% [95% CI 1.00–4.94%]).

3.4 Evaluation in an animal model

The flow frame of the experiment is shown in Fig. 1. We found that pretreatment of quercetin (15 mg kg^{-1}, oral, daily) for 14 days before colitis induction could significantly reduce the DAI score (Fig. 3A and B) and the histological score (Fig. 3C and D). PAS-AB stain and immunohistochemistry stain of Claudin-1 (Fig. 3E and F) showed that quercetin pretreatment could protect the mouse mucosal barrier.

Then, we conducted quantified real-time PCR of some common inflammatory markers in each group. We saw reduced expression of several reported inflammation-related genes (*S100a8*, *S100a9*, *Lcn2*) in colonic tissues (Fig. 3G and H), of which, *S100a8* and *S100a9* were components of calprotectin. Interestingly, we also found a decreased *Cxcl9* mRNA expression level in colonic tissues of quercetin-pretreated mice (Fig. 3I and J), which was the potential target for UC treatment that we unearthed in a previous work.[34] Therefore, we have demonstrated that pretreatment of quercetin can attenuate colitis in mouse models and contribute to intestinal barrier hemostasis.

4. Discussion

In the current study, we demonstrated that a higher quercetin intake was associated with 24% and 31% reduced risk of IBD and UC, respectively, when comparing extreme quintile intake. We did not observe significant associations between dietary quercetin intake and CD incidence. The associations were consistent in most subgroup and sensitivity analyses. In the *in vivo* mouse experiment, we found that oral pretreatment with quercetin can partially prevent chemical-induced inflammation in mouse models.

The prevention and therapeutic potential of food or nutrients are receiving growing attention, such as quercetin. Previous preclinical experiments conclude a protective effect of quercetin against IBD in animal models *via* multiple mechanisms but lack the results in humans. Currently, there is no evidence directly linked to the quercetin intake and the development of IBD and UC. Previous umbrella reviews concluded an inverse association of tea consumption, vegetable consumption, and fruit consumption with UC,[7] which were reported to be top sources of quercetin in UK.[35] However, all results from these *meta*-analyses were mostly extracted from studies that comprehensively investigated food groups as dietary risk factors with a lack of separate estimates of specified food and nutrients. Therefore, our study provided a novel finding in humans that directly linked higher dietary quercetin to lower risk of IBD and UC.

We did not observe a significant association between dietary quercetin and CD. A possible explanation was the discrepancies in lesion sites between the two disease subtypes. The entire gastrointestinal tract can be affected in patients with CD while the lesion is localized to the colon and rectum in patients with UC. The pathways through which quercetin is absorbed, distributed, and metabolized in the digestive system and the bioactivities of different quercetin metabolites have been demonstrated before. The absorption of quercetin and related compounds partially (about 5 to 10%) is initiated from the small intestine, while most quercetin could be easily absorbed in the form of conjugates in the colon catabolized by the microflora and exert subsequent bioactivities.[36,37,38–40] Accordingly, previous evidence showed quercetin could inhibit chemical-induced colorectal cancer but failed to reduce tumor incidence found in an APC$^{min/+}$ mouse model (a model with spontaneous tumor development mainly in the small intestine and also some in the colon).[41]

In subgroup analysis, we found that the association between quercetin and UC was statistically stronger in individuals with BMI < 30 kg m^{-2} than in those with a higher BMI. A previous cohort study in Danish found a similar weaker associ-

Table 2 Associations of dietary quercetin with the risk of IBD, CD, and UC

Quercetin intake (mg d^{-1})	Case/person-years	Crude model HR (95% CI)	Minimally adjusted model (model 1)[a] HR (95% CI)	Fully adjusted model (model 4)[b] HR (95% CI)
Inflammatory bowel disease				
Q1 (0–<8.9)	227/365 342	Ref	Ref	Ref
Q2 (8.9–<15.0)	174/358 585	**0.78 (0.64, 0.95)[c]**	**0.78 (0.64, 0.95)**	**0.80 (0.65, 0.98)**
Q3 (15.0–<21.6)	159/358 282	**0.71 (0.58, 0.87)**	**0.71 (0.58, 0.87)**	**0.73 (0.60, 0.91)**
Q4 (21.6–<31.9)	141/357 536	**0.63 (0.51, 0.78)**	**0.63 (0.51, 0.78)**	**0.65 (0.52, 0.82)**
Q5 (≥31.9)	162/356 681	**0.73 (0.60, 0.89)**	**0.73 (0.60, 0.90)**	**0.76 (0.60, 0.95)**
P-trend		**<0.001**	**<0.001**	**0.004**
Crohn's disease				
Q1 (0–<8.9)	58/369 497	Ref	Ref	Ref
Q2 (8.9–<15.0)	53/363 798	0.93 (0.64, 1.36)	0.94 (0.64, 1.36)	0.96 (0.66, 1.41)
Q3 (15.0–<21.6)	48/363 588	0.85 (0.58, 1.24)	0.85 (0.58, 1.25)	0.90 (0.60, 1.33)
Q4 (21.6–<31.9)	48/362 847	0.85 (0.58, 1.24)	0.86 (0.58, 1.26)	0.92 (0.61, 1.39)
Q5 (≥31.9)	49/362 093	0.87 (0.59, 1.27)	0.89 (0.60, 1.30)	0.95 (0.62, 1.45)
P-trend		0.377	0.447	0.765
Ulcerative colitis				
Q1 (0–<8.9)	169/368 980	Ref	Ref	Ref
Q2 (8.9–<15.0)	121/363 462	**0.73 (0.58, 0.92)**	**0.72 (0.57, 0.91)**	**0.74 (0.59, 0.94)**
Q3 (15.0–<21.6)	111/363 321	**0.67 (0.53, 0.85)**	**0.66 (0.52, 0.84)**	**0.68 (0.53, 0.87)**
Q4 (21.6–<31.9)	93/362 627	**0.56 (0.44, 0.72)**	**0.56 (0.43, 0.72)**	**0.56 (0.43, 0.74)**
Q5 (≥31.9)	113/361 764	**0.68 (0.54, 0.87)**	**0.68 (0.54, 0.87)**	**0.69 (0.53, 0.91)**
P-trend		**<0.001**	**<0.001**	**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] Based on the minimally adjusted model adjusted for age, sex, and ethnic background. [b] Further adjusted for physical activity, BMI, TDI, smoking status, alcoholic drink consumption (exclude wine), intake of cereal, meat, fish, and sugar-sweetened beverages, and total energy based on model 1. [c] *P* < 0.05. Bold values indicate significant associations with *P* values < 0.05.

ation between flavonoid intake and mortality among participants with BMI > 30 kg m^{-2}.[42] Microbiota was considered important to make quercetin and related metabolites bioactive.[43] Reduction in the enrichment level of several probiotics (such as *Bifidobacterium* and *Lactobacillus)* was reported to decrease the bioactive transformation of quercetin.[43] In fact, obesity will reshape the gut microbiota in humans,[44] which also play driven roles in the inter-individual variability in absorption, metabolism, and excretion of polyphenols.[45] However, there was no evidence to connect these clues and give biologically plausible explanations for the observed differences in the dietary quercetin intake–UC association

Table 3 Associations of daily quercetin intake calibrated by energy and weight with the risk of IBD, CD, and UC

Daily quercetin intake	Inflammatory bowel disease		Crohn's disease		Ulcerative colitis	
	Case/person-years	HR (95% CI)[a]	Case/person-years	HR (95% CI)	Case/person-years	HR (95% CI)
Intake adjusted by energy[b] (mg)						
Q1 (<9.1)	222/365 568	Ref	56/369 760	Ref	166/369 244	Ref
Q2 (9.1–15.2)	186/358 614	0.90 (0.73, 1.09)	56/363 795	1.08 (0.74, 1.58)	130/363 422	0.83 (0.66, 1.05)
Q3 (15.2–<21.6)	150/358 425	**0.73 (0.59, 0.91)[c]**	45/363 717	0.90 (0.60, 1.35)	105/363 494	**0.68 (0.52, 0.87)**
Q4 (21.6–<31.7)	145/357 816	**0.72 (0.57, 0.90)**	48/363 154	1.00 (0.66, 1.51)	97/362 898	**0.62 (0.47, 0.82)**
Q5 (≥31.7)	160/356 668	**0.80 (0.64, 1.01)**	51/362 067	1.08 (0.71, 1.63)	109/361 772	**0.71 (0.54, 0.93)**
P-trend		**0.011**		0.989		**0.002**
Intake according to weight[d] (mg kg^{-1})						
Q1 (<0.1)	229/364 320	Ref	55/368 557	Ref	174/367 999	Ref
Q2 (0.1–<0.2)	184/358 031	0.85 (0.70, 1.04)	56/363 080	1.10 (0.75, 1.61)	128/362 709	0.77 (0.61, 0.97)
Q3 (0.2–<0.3)	161/357 758	**0.76 (0.61, 0.94)**	54/362 913	1.11 (0.75, 1.64)	107/362 709	**0.65 (0.50, 0.83)**
Q4 (0.3–<0.45)	143/356 824	**0.69 (0.55, 0.86)**	41/362 330	0.88 (0.57, 1.36)	102/362 016	**0.62 (0.48, 0.81)**
Q5 (≥0.45)	145/356 113	**0.71 (0.56, 0.89)**	50/361 523	1.10 (0.71, 1.68)	95/361 306	**0.59 (0.44, 0.78)**
P-trend		**0.001**		0.971		**<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] Based on the fully adjusted model for age, sex, and ethnic background, adjusted for physical activity, BMI, TDI, smoking status, alcoholic drink consumption (excluding wine), intake of cereal, meat, fish, and sugar-sweetened beverages, and total energy. [b] The quercetin intake was adjusted by the energy intake using the residual method. Adjusted quercetin was the residual from a regression model in which the total energy intake is the independent variable and the absolute nutrient intake is the dependent variable. [c] *P* < 0.05. [d] Calculated using quercetin intake divided by participants' weight. Bold values indicate significant associations with *P* values < 0.05.

across populations by BMI categories. The underlying mechanisms of the role of obesity in the associations still need more research.

In mediation analyses, we found that decreased CRP levels partially mediated (proportions of 7.15% and 2.74%) the protective association of dietary quercetin intake with IBD and UC. Subclinical inflammation is one of the most prominent features of the preclinical stage of IBD.[46] Reversal of this pathologic process by decreasing the level of inflammation in the body is a reasonable assumption for the protective effect of quercetin against IBD. However, the low mediation proportion in our study may suggest an important role of other pathways in the effect of dietary quercetin, such as the contribution to intestinal barrier homeostasis found in our animal experiments. In addition, subsequent studies are needed to explore the mediating role of inflammation biomarkers other than CRP that are more closely associated with IBD, such as fecal calprotectin levels, in the quercetin–IBD association.

Previous studies have established mouse models and proven the protective role of quercetin in reducing colitis.[5] These studies, however, varied much in quercetin dosage and feeding time. To match the prevention purpose, we only gave
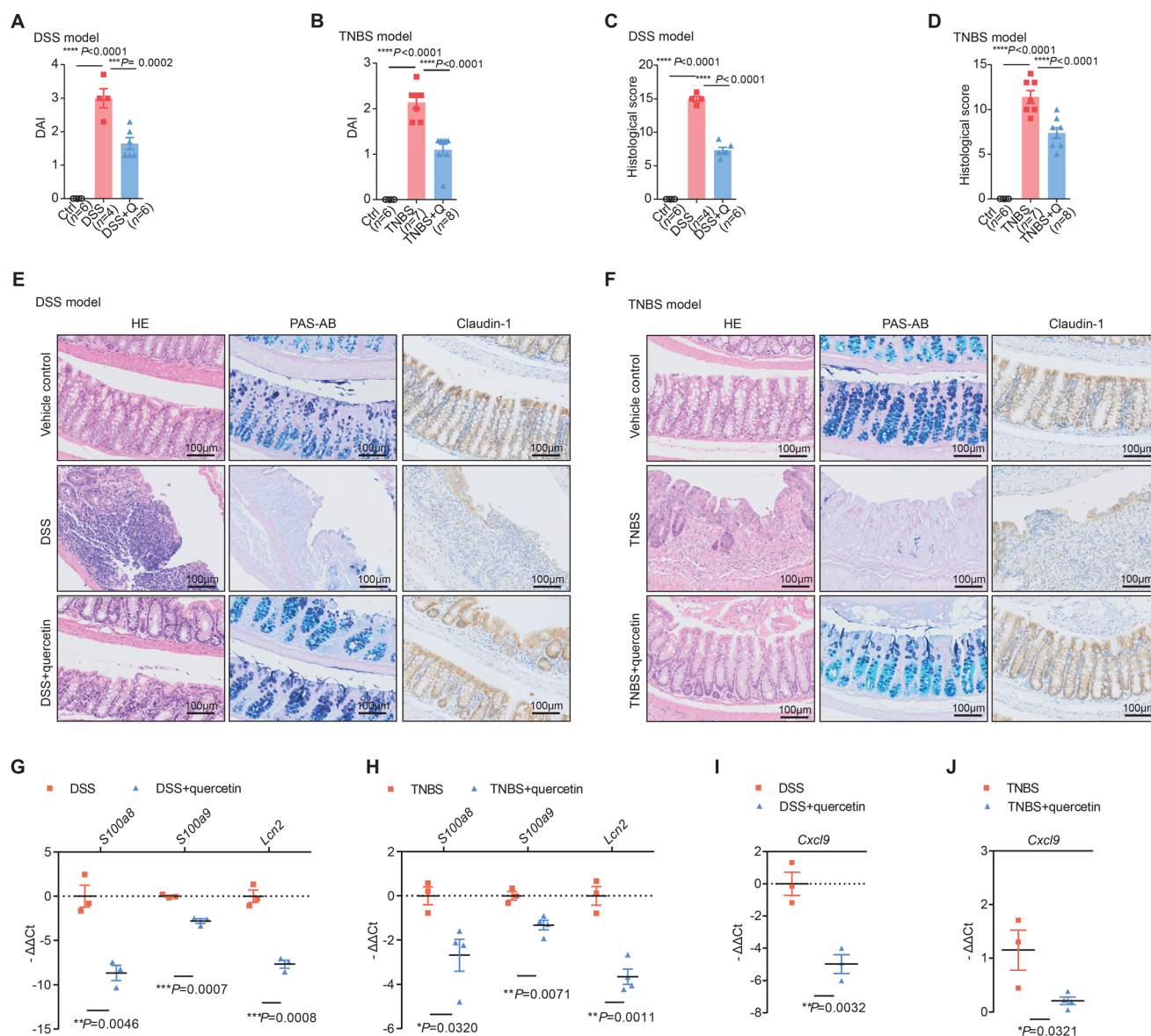

Fig. 3 Quercetin pretreatment could partially prevent ulcerative colitis in mouse models. (A and B) Disease activity index (DAI) score of each experimental group in DSS-induced (A) and TNBS-induced (B) mouse models. (C and D) Histological score of each experiment. (E and F) Representative image of Hematoxylin–Eosin (HE) stain, PAS-AB stain, and Claudin-1 stain in each experimental group. (G and H) Relative gene expression (referred to the colitis group) of inflammatory markers between the colitis group and the quercetin pretreated colitis group in DSS-induced (G) and TNBS-induced (H) mouse models. (I and J) Relative gene expression (referred to the colitis group) of Cxcl9 between the colitis group and the quercetin pretreated colitis group.

mice quercetin (generally matched to human protective dose) before colitis induction. Matched to the previous studies,[5] we found prior quercetin feed was enough to significantly reduce the colitis severity, though it couldn't totally prevent the chemical-induced inflammation. Also, we found the significant downregulated colonic mRNA expression level of several recognized molecules that reflected gut inflammatory levels, in addition to serum cytokines that were reported in the previous studies.[5] It is worth noticing that *S100a8* and *S100a9* are components of fecal calprotectin, a widely used clinical biomarker for evaluating gastro inflammation.[47] Of note is that the expression of *Cxcl9*, which was found to be strongly related to the risk of a UC onset *via* our previous research,[34] was also found to be induced upon colitis induction and reduced after quercetin treatment. As a detected potential target to prevent and ameliorate IBD, the inhibition of *Cxcl9* expression could make sense to explain the potential mechanism of quercetin.[34]

We used 15 mg kg^{-1} quercetin in the *in vivo* study, equivalent to 84 mg d^{-1} (1.2 mg kg^{-1}) for humans (weight 70 kg) based on the body surface area according to the US Food and Drug Administration.[48] In the cohort study, we found that the protective association between quercetin and IBD risk remained significant when the quercetin intake peaked at around 80 mg (Fig. 2), which is comparable to the dosage in the animal study. Besides, though it was a little higher than the quercetin intake calculated in the human cohort, different quercetin forms (pure quercetin powder without conjugates was used in mouse models) and bioactivities in mice and humans should be considered.

To our knowledge, this is the first human study that investigated the association between quercetin intake and IBD risk. The strength of our study is the use of data from the large cohort UK Biobank, with a rich set of variables such as lifestyle, medication information, dietary intake, and a complete follow-up over time.

Nonetheless, our study also has several limitations. Firstly, although we included many potential confounders, we cannot rule out the possibility of residual confounding caused by unmeasured factors (*e.g.*, use of prebiotics and probiotics) in an observational research design. Moreover, reverse causation that cannot be ruled out prevents us from proving the causality of our conclusions. However, we have obtained consistent results in analyses and experiments that demonstrate that our conclusions are not likely to be greatly affected by the above bias. For reverse causation, the lagged analysis excluding incident IBD cases in the first 2- and 4-year follow-up demonstrated that the delay in diagnosis of IBD was less likely to affect main conclusions. Results in animal experiments designed to match the design of our cohort study supported our primary findings. For potential confounding factors, we used multivariable adjustment and a propensity score to minimize the bias and obtain consistent results. Secondly, the quercetin we administered in the experiments was in the form of an aglycone while dietary quercetin is present mainly in *O*-glycosidic forms.[49] This limitation should be noted when exploring the mechanisms of dietary quercetin effects on

health in the future. Thirdly, although we used a validated 24 h WebQ, approximately 38% of the study sample had only 1 questionnaire data. We minimized the bias seen in self-reported diet information by excluding extreme energy intake and non-typical diets, as suggested by previous studies in the UK Biobank.[12,50] Also, assessing the dietary quercetin intake using nutrient databases may introduce biases due to large variability in the polyphenol content of a given food and insufficient data on the composition of certain foods, though we have demonstrated the feasibility of the used databases in the European countries in the *Methods* section. In addition, the mean intake of dietary quercetin is 22 mg d^{-1} in our study, which is within the estimated intake (10–100 mg) by the previous review.[51] In the Epic-Oxford study (∼30% vegetarians), the average intake of flavonoids was 54 mg d^{-1}, of which quercetin accounted for 70% (*i.e.*, 37.8 mg d^{-1}).[52] This may demonstrate the reliability of our estimate of the dietary quercetin intake to some extent. Finally, the vast majority of participants in our study were over 40 years of age and white, and caution is needed in generalizing our findings to other IBD populations.

In conclusion, higher quercetin intake was associated with a lower risk of IBD, especially UC. The protection role of quercetin against IBD was validated in two colitis mouse models. Together, our study showed the possibility of quercetin to prevent IBD in humans for the first time. These findings require further clinical interventional studies to validate and more in-depth experiments to elucidate the underlying mechanisms.

Author contributions

Shi-Yuan Lu: conceptualization (lead), methodology (equal), writing – original draft (lead), formal analysis (supporting), and validation (equal); Lintao Dan: formal analysis (lead) and writing – original draft (equal); Sishen Sun: methodology (supporting), validation (equal), and writing – review and editing (supporting); Tian Fu: methodology (supporting), writing – review and editing (supporting), and formal analysis (supporting); Jie Chen: conceptualization (equal), methodology (equal), writing – review and editing (lead), and project administration (lead). All authors have read and agreed to the published version of the manuscript.

Ethical considerations

Ethical approval for the UK Biobank was granted by the North West-Haydock Research Ethics Committee (REC reference: 21/NW/0157). Written informed consent has been obtained from the patients to publish this study.

Data availability

Researchers can require the data and approval from the UK Biobank (**https://www.ukbiobank.ac.uk**).

Conflicts of interest

Acknowledgements

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