Research Square

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# Stromal enrichment and ulcerative colitis-associated loss of quinoid dihydropteridine reductase (QDPR) in the inflamed colon: a compartment-resolved immunohistochemical study in inflammatory bowel disease

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## Abstract

# Background

Quinoid dihydropteridine reductase (QDPR) is the key enzyme that regenerates tetrahydrobiopterin (BH4) and contributes to redox control. Its expression in the colon in inflammatory bowel disease (IBD) is undefined.

# Methods

In 76 patients with ulcerative colitis (UC) and 25 with Crohn's disease (CD), we used immunohistochemistry to compare QDPR expression between colonic lesions and paired adjacent healthy tissue. We distinguished epithelial from stromal compartments and related expression to clinical activity and biologic therapy.

# Results

QDPR staining was higher in the colonic stroma than in the epithelium. In UC, lesional QDPR in both epithelium and stroma was lower than in the patient's own healthy tissue ($P < 0.05$), and CD lesional QDPR was higher than in UC. QDPR correlated weakly and negatively with serum hs-CRP. UC patients receiving biologic therapy had higher lesional QDPR than untreated patients.

# Conclusions

QDPR shows a stroma-enriched pattern in the colon. UC and CD differ in QDPR expression, and CD may retain greater antioxidant compensatory capacity. Tissue QDPR may help distinguish UC from CD and gauge mucosal repair, pending prospective validation.

## 1. Introduction

Inflammatory bowel disease (IBD), which comprises ulcerative colitis (UC) and Crohn's disease (CD), is a chronic, relapsing, non-specific inflammatory disorder of the gastrointestinal tract. Its global burden continues to rise, with the steepest increases in newly industrialized countries [1]. UC inflammation is typically confined to the colonic mucosa in a continuous, diffuse distribution. CD can be transmural and segmental and may involve any part of the gut. Despite these clinical, endoscopic and pathological differences, both share a pathogenesis that involves genetic susceptibility, environmental exposures, gut-microbial dysbiosis and dysregulated mucosal immunity [2]. In active IBD, over-activated neutrophils, macrophages and T lymphocytes release large amounts of reactive oxygen species (ROS) and nitric oxide (NO), which drive oxidative tissue injury. The functional state of the local antioxidant system in turn influences whether inflammation resolves and whether the mucosa can repair [3, 4].

NO has a dual role in intestinal inflammation. Low-output NO from constitutive NO synthases (eNOS and nNOS) helps maintain blood flow, the epithelial barrier and immune homeostasis. High-output NO from inducible NOS (iNOS) is instead associated with tissue injury and amplified inflammation [5]. Tetrahydrobiopterin (BH4) is an essential cofactor for NOS. When BH4 is sufficient, NOS converts L-arginine to NO; when BH4 is deficient, NOS uncouples and generates superoxide rather than NO, which aggravates oxidative stress [6]. Maintaining intracellular BH4 is therefore important for preventing NOS uncoupling and limiting tissue damage. QDPR is the key enzyme of the BH4 salvage cycle and reduces oxidized quinoid dihydrobiopterin (qBH2) back to active BH4 [7]. Altered QDPR expression or function can lower BH4 and shift the mode of NO production. BH4 salvage and QDPR are altered, and participate in redox regulation, in several oxidative-stress-related diseases, including atherosclerosis, diabetic nephropathy and ischaemia-reperfusion injury [8–11]. How QDPR is expressed and localized in the IBD colon, and whether this differs between UC and CD, has not been studied systematically.

Only limited evidence links the BH4 pathway to intestinal inflammation. In dextran-sulfate-sodium (DSS) colitis, oral BH4 attenuated disease severity, lowered ROS and remodelled lipid signalling. Inhibiting BH4 synthesis, for example of its rate-limiting enzyme GTP cyclohydrolase I, worsened weight loss, epithelial haemorrhage and ulceration, and neutrophil infiltration [12]. This evidence comes largely from animal models or whole-organism intervention. It lacks a fine-grained description of where QDPR, the salvage enzyme itself, sits within the human colon. Four questions follow. Does lesional QDPR differ from adjacent healthy mucosa? Is any such difference consistent between UC and CD? Is QDPR predominantly epithelial or stromal? And does its level track disease activity or biologic therapy? Answering these questions would clarify the cellular basis of BH4 dysregulation in IBD and could point to markers for histological differential diagnosis and treatment-response assessment.

Drawing on linked clinical, pathological and treatment data, we used immunohistochemistry to compare QDPR expression between colonic lesions and paired adjacent healthy tissue in UC and CD, resolving epithelial and stromal compartments. Our aims were to (1) define overall QDPR changes in the IBD colon and any difference between UC and CD; (2) describe the epithelial versus stromal distribution; (3) analyse lesion versus healthy changes within each compartment; and (4) explore the relationship of QDPR to clinical activity and biologic therapy. Given the antioxidant salvage function of QDPR, we hypothesized that persistent oxidative stress in UC lesional mucosa would deplete QDPR and lower its expression. By mapping the spatial distribution of QDPR in the IBD colon, we aimed to inform the compensatory logic of intestinal oxidative stress and BH4-pathway-based intervention.

# 2. Methods

This single-centre, retrospective, observational study enrolled outpatients and inpatients at Xinqiao Hospital, the Second Affiliated Hospital of Army Medical University, China. It was approved by the Army Medical University ethics committee(No. 2026-yandi 261-02). This study was conducted in accordance with the Declaration of Helsinki. Reporting follows the STROBE statement for observational studies.

## 2.1 Patient enrolment

Archived endoscopic mucosal biopsies from routine outpatients and inpatients with UC or CD, obtained between April 2023 and September 2025, were retrieved from the pathology department. Samples included lesional tissue and relatively healthy tissue away from lesions. All patients gave verbal telephone consent.

## 2.2 Data collection

Patient data were extracted from hospital records into a spreadsheet: sampling date, disease type, age at sampling, age at diagnosis, disease duration, sex, smoking history, BMI, Montreal-classification location and extent, treatments, biologic use, and serum high-sensitivity C-reactive protein (hs-CRP) and haemoglobin at sampling.

## 2.3 Sample collection and storage

Mucosal biopsies were fixed in 4% paraformaldehyde and paraffin-embedded by the pathology department for storage.

## 2.4 Immunohistochemistry

Paraffin blocks were sectioned at 4 μm. After baking and dewaxing, antigen retrieval used Biosharp EDTA buffer (pH 8.0) at 100°C for 20 min, followed by cooling to room temperature. Sections were washed three times in PBS (5 min each), circled with a pap pen, incubated in 3% hydrogen peroxide (15 min, room temperature, in the dark) and washed. After 5% BSA blocking (30 min), sections were incubated overnight at 4°C with anti-QDPR (abcam ab126150). The next day they were rewarmed for 30 min, washed in PBST, incubated with secondary antibody (abcam ab101; 1 h, room temperature) and washed. Signal was developed with a DAB kit (Beyotime; 15 min, in the dark), counterstained with haematoxylin (1 min 40 s), dehydrated, cleared and mounted in neutral resin.

## 2.5 Quantification and scoring of QDPR expression

For overall tissue QDPR expression, the mean optical density of the entire tissue section was measured using ImageJ (National Institutes of Health, USA) and taken as the representative value for that specimen. The epithelial compartment was defined as the region above the epithelial basement membrane, whereas the stromal compartment was defined as the region below the basement membrane. For epithelial and stromal QDPR expression separately, the same densitometric approach was applied. For each tissue section, three random fields of view were selected within the epithelial region and three within the stromal region; the mean optical density was calculated for each selected area using ImageJ, and the average of the three measurements was used as the final QDPR expression value for that compartment in that tissue. No automated thresholding algorithm was applied; instead, manual delineation of each compartment was performed on haematoxylin-counterstained images to ensure accurate separation of epithelium and stroma.

## 2.6 Statistical analysis

Data were analysed and visualized in R (v4.5.1) and Prism (v10.1.2). Categorical variables were summarized as frequencies and continuous variables as median with interquartile range. Categorical variables were compared with the chi-square or Fisher's exact test. Continuous variables were compared with the t-test for normally distributed data or the Mann-Whitney U test otherwise for two groups, and with ANOVA or Kruskal-Wallis for more than two groups. Correlations used Pearson or Spearman rank analysis.

## 3. Results

# 3.1 Baseline characteristics (Table 1)

A total of 101 patients were enrolled (76 UC, 25 CD). Median age at sampling was 51 years (IQR 41–59) for UC and 25 years (IQR 22–31) for CD ($P < 0.001$). UC extent was proctitis (E1) in 9 (12%), left-sided colitis (E2) in 24 (32%) and extensive colitis (E3) in 43 (57%); 61 (81%) UC patients had active disease, and 52% and 25% were receiving steroids or biologics (infliximab, vedolizumab, ustekinumab and others), respectively. Among CD patients, 0 (0%) had ileal, 4 (16%) colonic and 21 (84%) ileocolonic involvement; 72% and 84% were receiving steroids or biologics, respectively.

Table 1
Characteristics of the Ulcerative colitis (UC) and Crohn's disease (CD) patients.

| **Characteristic** | **UC** **N = 76** | **CD** **N = 25** | **p-value[1]** |
|---|---|---|---|
| Age at sampling (years), Median (IQR) | 51 (41–59) | 25 (22–31) | <0.001 |
| Age at diagnosis (years), Median (IQR) | 49 (35– 57) | 25 (22–29) | <0.001 |
| Disease duration (months), Median (IQR) | 24 (12–60) | 14 (7–24) | 0.056 |
| Sex, n (%) | | | 0.2 |
| Female | 26 (34) | 5 (20) | |
| Male | 50 (66) | 20 (80) | |
| Smoking status, n (%) | | | 0.035 |
| Active smoker | 2 (3.6) | 4 (16) | |
| Former smoker | 13 (23) | 2 (8) | |
| Never smoker | 41 (73) | 18 (72) | |
| BMI (kg/m²), Mean (SD) | 22.45 (3.18) | 20.40 (3.16) | 0.008 |
| Montreal classification (UC) Extension, n (%) | | | NA |
| E1 | 9 (12) | NA | |
| E2 | 24 (32) | NA | |
| E3 | 43 (57) | NA | |
| Disease activity (UC) PMS, n (%) | | | NA |
| 0 | 2 (2.7) | NA | |
| 1 | 12 (16) | NA | |
| 2 | 34 (45) | NA | |
| 3 | 27 (36) | NA | |
| Disease activity (UC) PMS (≥ 2), n (%) | 61 (81) | NA | NA |
| Montreal classification (CD) Age, n (%) | | | NA |
| A1 | NA | 0 | |
| A2 | NA | 24 (96) | |
| A3 | NA | 1 (4) | |
| Montreal classification (CD) Location, n (%) | | | NA |

| Characteristic | UC<br>N = 76 | CD<br>N = 25 | p-value[1] |
|---|---|---|---|
| L1 | NA | 0 | |
| L2 | NA | 4 (16) | |
| L3 | NA | 21 (84) | |
| Montreal classification (CD) Behavior, n (%) | | | NA |
| B1 | NA | 17 (68) | |
| B2 | NA | 8 (32) | |
| B3 | NA | 0 | |
| Perianal disease, n (%) | NA | 22 (88) | NA |
| SES-CD, Median (IQR) | NA | 7 (4–10) | NA |
| History of treatment: | | | |
| Steroid, n (%) | 30 (52) | 18 (72) | 0.086 |
| Mesalazine, n (%) | 58 (100) | 11 (44) | <0.001 |
| Immunosuppressive, n (%) | 0 (0) | 4 (16) | 0.007 |
| Advanced therapies, n (%) | 25 (34) | 21 (84) | <0.001 |
| Biologic therapy time, n (%) | | | 0.004 |
| Pre | 14 (19) | 12 (48) | |
| Post | 61 (81) | 13 (52) | |
| History of anemia, n (%) | 12 (22) | 8 (32) | 0.4 |
| Hb (g/L), Median (IQR) | 134 (115– 148) | 125 (119–144) | 0.8 |
| hs-CRP (mg/ml), Median (IQR) | 3.92 (1.32–12.52) | 19.10 (3.34–52.10) | 0.032 |

Continuous variables are expressed as medians (and interquartile ranges) and categorical variables as absolute frequencies and percentages. Chi-square test or Fisher’s exact test, when appropriate, was used to compare categorical variables, and Mann–Whitney U-test was used for the continuous variables.

N, total number; NA, not applicable; IQR, interquartile range; PMS, partial Mayo score; SES-CD, Simple Endoscopic Score for Crohn's Disease; Pre, Biological therapy was administered prior to sample collection; Post, Biological therapy was administered after sample collection.

## 3.2 Lesional QDPR is lower than adjacent healthy tissue in UC (Fig. 1)

Across all IBD patients, lesional QDPR was lower than in adjacent healthy tissue. By subtype, UC lesions showed lower QDPR than adjacent healthy tissue, whereas CD showed no significant difference. The lesion-versus-healthy difference is therefore driven mainly by UC. Direct UC-versus-CD comparison of lesional and adjacent-healthy tissue showed no significant difference.

## 3.3 Colonic QDPR is concentrated in the stroma (Fig. 2)

In all IBD patients, stromal QDPR exceeded epithelial QDPR in both lesional and adjacent-healthy tissue. The same held within each subtype: in both UC and CD, stromal QDPR exceeded epithelial QDPR in lesional and adjacent-healthy tissue. QDPR is thus concentrated in the stroma rather than the epithelium, and the stroma may be where QDPR participates in an anti-inflammatory role.

## 3.4 Lesional epithelial QDPR is lower in UC than CD (Fig. 3)

Because epithelial integrity is central to the mucosal barrier in IBD, we examined epithelial QDPR. Lesional epithelial QDPR was lower than adjacent-healthy epithelial QDPR across IBD and within UC, with no significant difference in CD. UC and CD did not differ in adjacent-healthy epithelial QDPR, but UC lesional epithelial QDPR was lower than that of CD. The lesion-versus-healthy epithelial difference is therefore driven mainly by UC, with more pronounced lesional epithelial loss in UC than CD.

## 3.5 Stromal QDPR differences (Fig. 4)

Given the stromal concentration of QDPR, we examined stromal expression by subtype. Lesional stromal QDPR was lower than adjacent-healthy stromal QDPR across IBD and within UC, with no significant difference in CD. UC lesional stromal QDPR was lower than that of CD, with no significant difference in adjacent-healthy tissue. As in the epithelium, the lesion-versus-healthy stromal difference is driven mainly by UC, with more severe stromal loss in UC than CD.

## 3.6 QDPR tends to correlate negatively with inflammatory markers (Fig. 5)

We related inflammatory markers to QDPR in UC and CD. In UC, QDPR tended to correlate negatively with hs-CRP in both lesional and adjacent-healthy tissue, except in lesional epithelium. In CD, hs-CRP correlated negatively with QDPR, most evidently for lesional epithelial QDPR.

## 3.7 Lesional QDPR is higher in biologic-treated UC patients (Fig. 6)

Because the QDPR-BH4 cycle regulates oxidative stress, we related biologic therapy to QDPR. Adjacent-healthy QDPR did not differ by treatment, whereas lesional QDPR was higher in biologic-treated than untreated patients. This difference was driven mainly by UC, with no significant difference in CD for

either tissue. Biologic therapy is thus associated with higher QDPR. This is a cross-sectional association rather than a causal effect, as discussed below.

# 4. Discussion

This study provides the first compartment-resolved description of QDPR distribution in the IBD colon. It characterizes QDPR across lesional versus healthy tissue, epithelium versus stroma, UC versus CD, and biologic-treatment status. The main observations are as follows. First, QDPR is strongly stroma-enriched, independent of disease state and subtype. Second, UC lesions in both epithelium and stroma show lower QDPR than the patient's own healthy tissue, whereas CD shows no such difference, and CD lesional QDPR exceeds UC. Third, QDPR correlates weakly and negatively with serum hs-CRP. Fourth, biologic-treated UC patients show higher lesional QDPR, with no effect in CD. Because this is a single-time-point, cross-sectional study, the interpretations below are inferences from the present data and require prospective and functional validation.

Stromal QDPR exceeded epithelial QDPR in UC and CD and in both lesional and healthy tissue. This stromal predominance is already present in healthy tissue, which suggests an intrinsic distribution rather than an inflammation-induced rearrangement. In the kidney, QDPR is more often reported in the parenchymal or tubular epithelium [13]. This comparison should be drawn cautiously, because public-database annotations for renal QDPR are not fully consistent across assay levels. Stromal enrichment in the colon suggests a function relatively independent of the epithelium. The colonic stroma is rich in fibroblasts, endothelial cells and macrophages, which are both targets of oxidative stress and sources of inflammatory mediators in IBD. High stromal QDPR may act as a local BH4 reservoir that helps stromal cells maintain NO homeostasis and resist peroxynitrite injury. This interpretation is consistent with the protective role of BH4 in intestinal inflammation. In DSS colitis, oral BH4 attenuated disease by reducing oxidative stress and remodelling lipid signalling, whereas inhibiting BH4 synthesis worsened weight loss, epithelial haemorrhage and ulceration, neutrophil infiltration and ROS production [14]. This study shows only where QDPR is expressed, not its function, so the idea that the stroma is where QDPR exerts an anti-inflammatory role remains a hypothesis. Cell sorting and single-cell transcriptomics are needed to identify which stromal subsets, whether fibroblasts, endothelial or immune cells, predominantly express QDPR, and to test its function in the inflammatory microenvironment.

We observed an apparent paradox with interpretive value. Although lesional QDPR was lower than healthy tissue across IBD, this difference was contributed mainly by UC, with no lesion-versus-healthy difference in CD. In both epithelium and stroma, CD lesional QDPR exceeded UC. This contrasts with a multi-omics Mendelian randomization study by Zhang et al., which reported that higher QDPR is associated with increased UC risk (OR = 1.17, 95% CI 1.07–1.28) and that QDPR methylation (cg08808571 and cg26689483) correlates inversely with its expression, consistent with a detrimental role in UC [15]. Mendelian randomization reflects an association between germline-predicted expression and disease risk, which is a different level from the protein expression we measured directly in inflamed tissue. The two should not be equated, and we juxtapose them only to indicate that QDPR may play a

complex role in UC. We therefore propose cautiously that in UC, persistent diffuse mucosal inflammation may consume QDPR more rapidly and lower its expression. In CD, segmental transmural inflammation with granuloma and fibrosis may allow stromal cells such as fibroblasts and myofibroblasts to up-regulate antioxidant defences adaptively, for example through Nrf2. This could relatively preserve QDPR [16]. This consumption-versus-maintenance account describes a dynamic process that a cross-sectional design cannot establish, and it remains a hypothesis to be tested. Extra-intestinal evidence also suggests more active pterin metabolism in CD. Faecal neopterin, a metabolic marker of the BH4-synthesis branch, is elevated in CD and reflects endoscopic activity, with predictive accuracy comparable to calprotectin [17]. This offers indirect support at the systemic level for stronger pterin and redox compensation in CD.

In the analysis of biologic use and QDPR, biologic-treated UC patients had higher lesional QDPR than untreated patients, with no significant change in CD. This is a cross-sectional comparison of treated versus untreated patients, and biologic use is linked to disease severity and duration. The association is therefore confounded by indication and cannot be equated with a causal up-regulation of QDPR by therapy. If the association is real, one interpretation applies to UC, where inflammation is largely mucosal. Controlling inflammation with biologics may reduce ongoing QDPR consumption, so higher QDPR may partly reflect molecular-level mucosal repair even when mild endoscopic activity persists. The transmural inflammation and fibrosis of CD are more refractory, and mucosal control alone may not restore QDPR. The subtype difference in epithelial QDPR, with UC lesional epithelium lower than CD, points to a use for QDPR immunohistochemistry. It could serve as a candidate histological clue for distinguishing UC from colonic CD, especially with limited or atypical biopsies. This rests on group means without ROC curves, cut-offs or sensitivity and specificity, so it remains hypothesis-generating and requires validation with diagnostic-performance metrics in independent, larger cohorts. Together with the inverse QDPR methylation-expression relationship reported by Zhang et al. [18], QDPR regulation may be shaped by both the inflammatory microenvironment and epigenetic mechanisms, which future work could examine alongside DNA-methylation profiling.

QDPR correlated only weakly and negatively with hs-CRP. This suggests that QDPR may reflect a chronic, metabolic redox adaptation rather than an immediate response to acute inflammatory fluctuation. As an acute-phase reactant, hs-CRP would be expected to relate loosely to QDPR if the two operate on different timescales. Future work should relate QDPR to markers that better reflect tissue-level inflammation, such as faecal calprotectin or neopterin and endoscopic and histological scores, and to long-term outcomes such as stricture formation, colectomy and treatment non-response, to clarify its clinical meaning.

# 5. Conclusions

This spatial analysis supports several conclusions. First, QDPR is natively stroma-enriched in the colon, independent of inflammation and disease type. Second, UC lesions in both epithelium and stroma show lower QDPR than the patient's own healthy tissue, whereas CD shows no such difference and CD lesional QDPR exceeds UC, which suggests that CD may retain greater antioxidant compensatory capacity. Third,

biologic-treated UC patients show higher lesional QDPR, which suggests QDPR as a candidate marker of micro-scale mucosal repair; the current evidence is a cross-sectional association rather than a causal effect and needs prospective validation. The spatial-distribution framework helps interpret the regional and cell-type heterogeneity of redox metabolism in IBD. Future work should pursue mechanistic studies in stromal cells, especially fibroblasts, and test whether QDPR plays a dual role in CD-associated fibrosis. The subtype difference in epithelial QDPR may serve as a candidate immunohistochemical clue for distinguishing UC from colonic CD and merits validation with diagnostic-performance endpoints in multicentre cohorts.

There are also several limitations apply. First, and most important, this is a retrospective, cross-sectional study in which UC and CD differed markedly in age (median 51 versus 25 years, $P < 0.001$), as well as in disease duration and treatment. Differences in QDPR between UC and CD may therefore be driven partly by age, duration or treatment rather than intrinsic subtype biology. We did not adjust for these confounders, so UC and CD comparisons should be read cautiously and confirmed with age-matched or multivariable-adjusted analyses. Second, a single-time-point cross-sectional design cannot establish dynamic processes such as consumption or up-regulation, so the related mechanisms are hypotheses. Third, the sample size is limited, and non-significant subgroup findings, such as those in the CD treatment subgroup, may reflect insufficient power. Fourth, QDPR immunohistochemical quantification and scoring must be specified and standardized (see Methods 2.5), and the QDPR antibody requires further validation, because the Human Protein Atlas notes that its staining and RNA-expression data are not fully concordant; future work should cross-validate with in situ hybridization and multiplex immunofluorescence. Fifth, this is a single-centre study with limited generalizability.

In summary, QDPR shows a stroma-enriched pattern in the IBD colon and differential expression between UC and CD. This offers a histological perspective on the heterogeneity of redox metabolism across IBD subtypes. Tissue QDPR may become a candidate molecular tool to aid UC-versus-CD differentiation and mucosal-repair assessment, and it warrants further validation in multicentre prospective cohorts.

# Abbreviations

IBD (inflammatory bowel disease), UC(ulcerative colitis), CD(Crohn's disease), QDPR(quinoid dihydropteridine reductase), BH4(tetrahydrobiopterin), ROS(reactive oxygen species), NO(nitric oxide), NOS(nitric oxide synthase), eNOS(endothelial NOS), nNOS(neuronal NOS), iNOS(inducible NOS)、qBH2(quinoid dihydrobiopterin)、GTP(guanosine triphosphate)、DSS(dextran sulfate sodium)、hs-CRP(high-sensitivity C-reactive protein)、BMI(body mass index)、PBS(phosphate-buffered saline)、BSA(bovine serum albumin)、DAB(3,3'-diaminobenzidine)、EDTA(ethylenediaminetetraacetic acid)、STROBE(Strengthening the Reporting of Observational Studies in Epidemiology)、ANOVA(analysis of variance)、Nrf2(nuclear factor erythroid 2-related factor 2)、ROC(receiver operating characteristic)

# Declarations

**Contribution**

Xia Xie conceived this study and revised the manuscript. Jianyun Zhou supervised and secured funding for the project; Hongli Zhou revised the manuscript; Yannan Ma completed the experiment and drafted the manuscript; Zewen Wang collected the data. Zuo Zhang and Xiaomei He were responsible for coordinating. All authors have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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**Conflict of Interest**

The authors declare that they have no competing interests.

**Ethical Considerations**

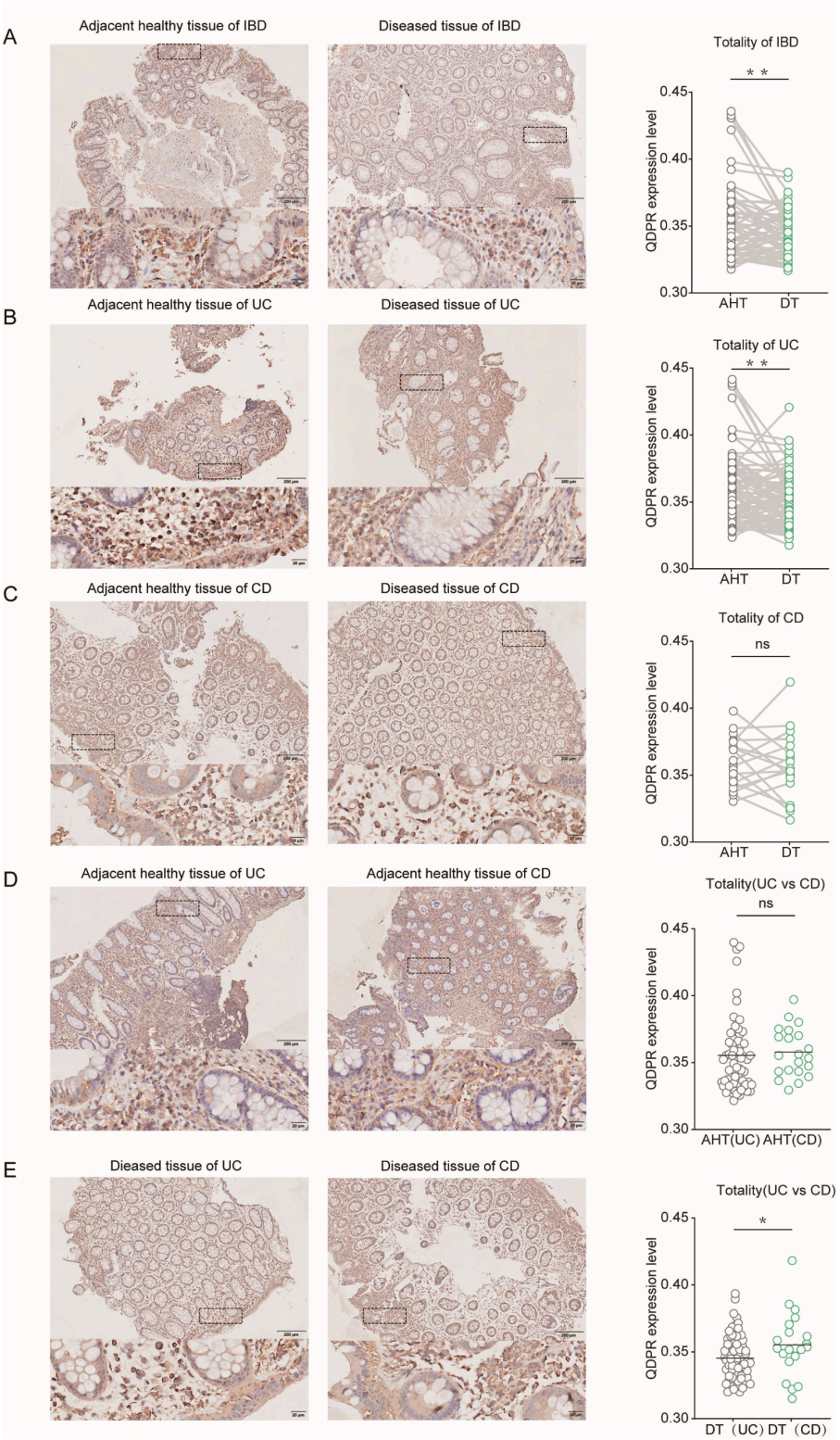
All patients gave verbal telephone consent. And it was approved by the Army Medical University ethics committee(No. 2026-yandi 261-02). This study was conducted in accordance with the Declaration of Helsinki. Reporting follows the STROBE statement for observational studies.

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# Figures




## Figure 1

Overall QDPR expression in adjacent healthy versus lesional colonic tissues from IBD patients.(A) In all IBD patients, QDPR expression was significantly higher in adjacent healthy tissues than in lesional tissues ($P < 0.05$).(B) In UC patients, QDPR expression was significantly higher in adjacent healthy tissues than in lesional tissues ($P < 0.05$).(C) In CD patients, no significant difference was observed between adjacent healthy and lesional tissues ($P > 0.05$).(D) No significant difference in QDPR

expression was found between UC and CD in adjacent healthy tissues (P > 0.05).(E) QDPR expression in UC lesional tissues was significantly lower than that in CD lesional tissues (P < 0.05). AHT, adjacent healthy tissue; DT, diseased tissue

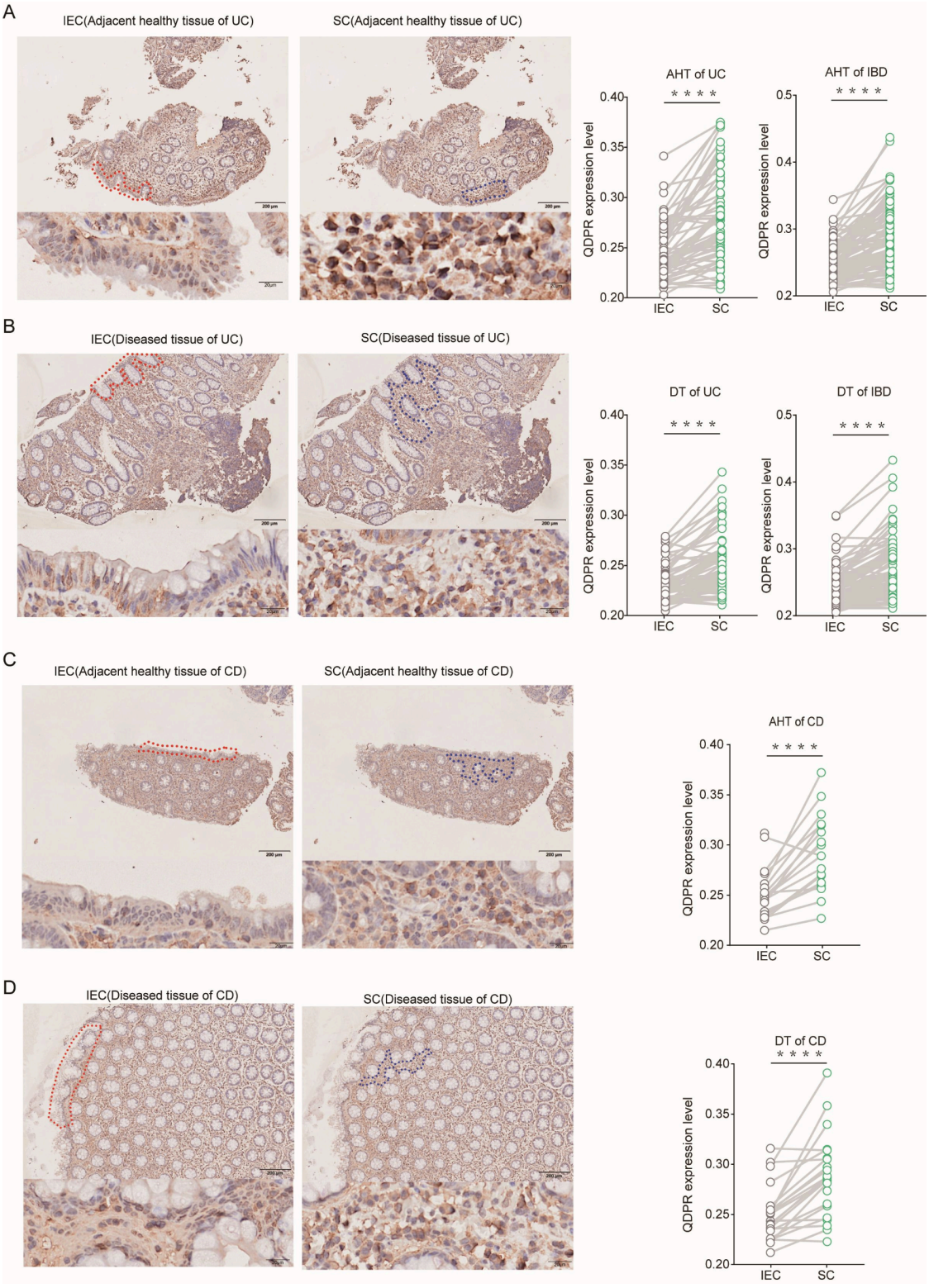
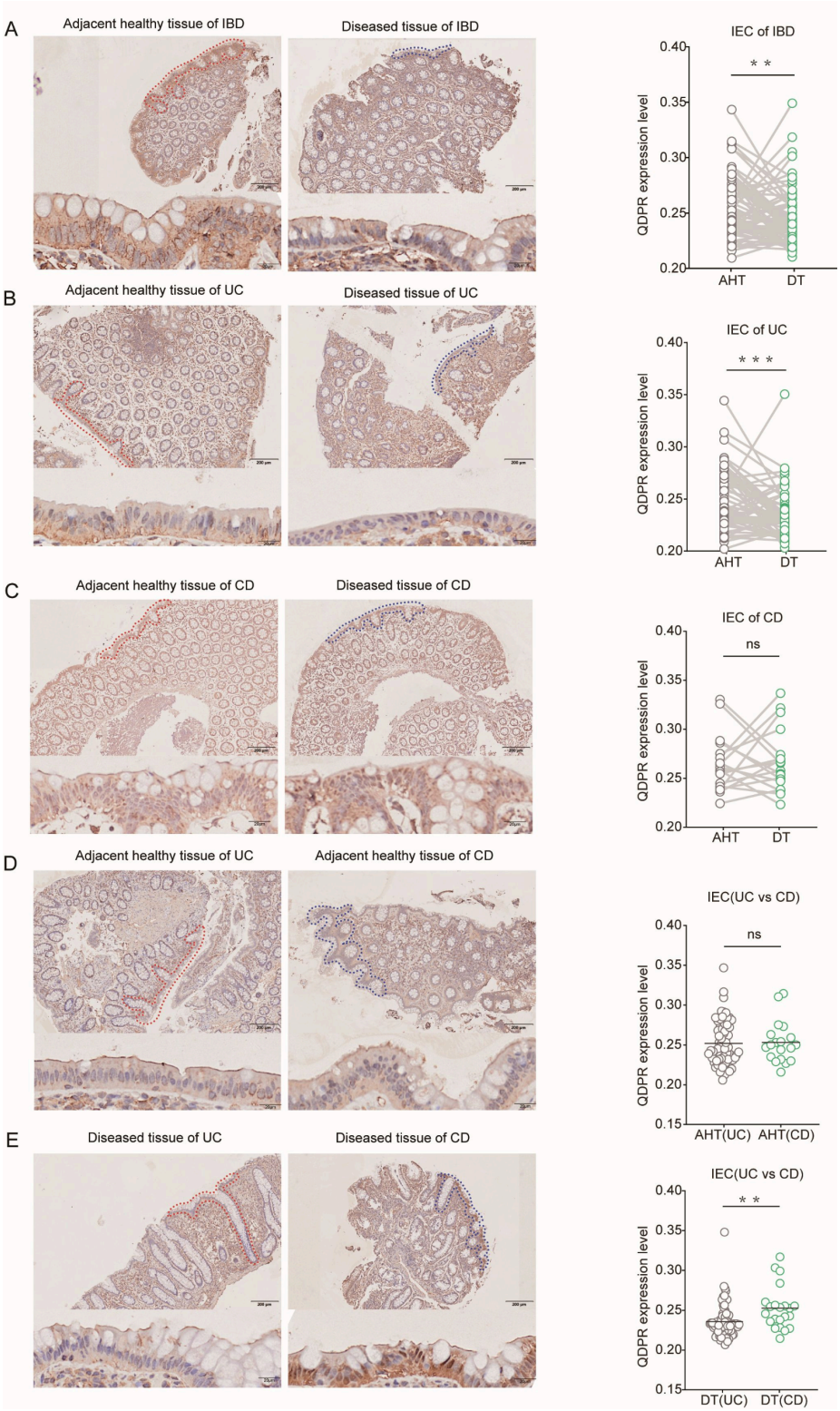



**Figure 2**

Comparison of epithelial versus stromal QDPR expression in adjacent healthy and lesional colonic tissues from IBD patients.(A) In adjacent healthy tissues from all IBD patients, epithelial QDPR expression (red boxes) was significantly lower than stromal QDPR expression (blue boxes) ($P < 0.0001$); the same pattern was observed in UC patients ($P < 0.0001$).(B) In UC lesional tissues, epithelial QDPR expression (red boxes) was significantly lower than stromal QDPR expression (blue boxes) ($P < 0.0001$). (C) In CD adjacent healthy tissues, epithelial QDPR expression (red boxes) was significantly lower than stromal QDPR expression (blue boxes) ($P < 0.0001$).(D) In CD lesional tissues, epithelial QDPR expression (red boxes) was significantly lower than stromal QDPR expression (blue boxes) ($P < 0.0001$). IEC, Intestinal Epithelial Cell; SC, Stromal Cell; AHT, adjacent healthy tissue; DT, diseased tissue.




## Figure 3

Differences in epithelial QDPR expression in colonic tissues from IBD patients.(A) In all IBD patients, epithelial QDPR expression was significantly higher in adjacent healthy tissues than in lesional tissues ($P < 0.01$).(B) In UC patients, epithelial QDPR expression was significantly higher in adjacent healthy tissues than in lesional tissues ($P < 0.001$).(C) In CD patients, no significant difference was observed between adjacent healthy and lesional epithelial QDPR expression ($P > 0.05$).(D) No significant difference was

found between UC and CD in epithelial QDPR expression of adjacent healthy tissues (P > 0.05).(E) Epithelial QDPR expression in CD lesional tissues was significantly higher than that in UC lesional tissues (P < 0.01).IEC, Intestinal Epithelial Cell; AHT, adjacent healthy tissue; DT, diseased tissue.

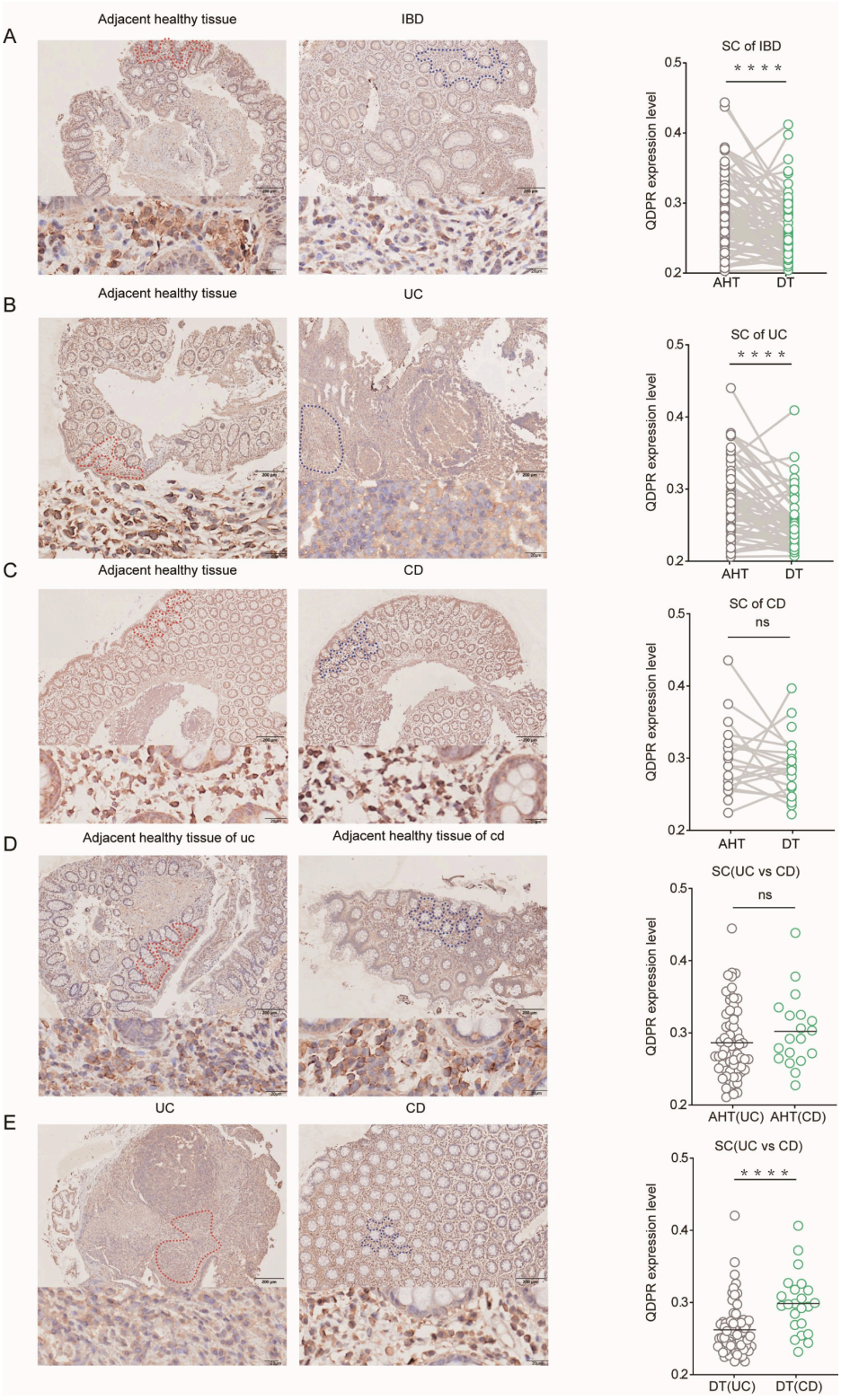
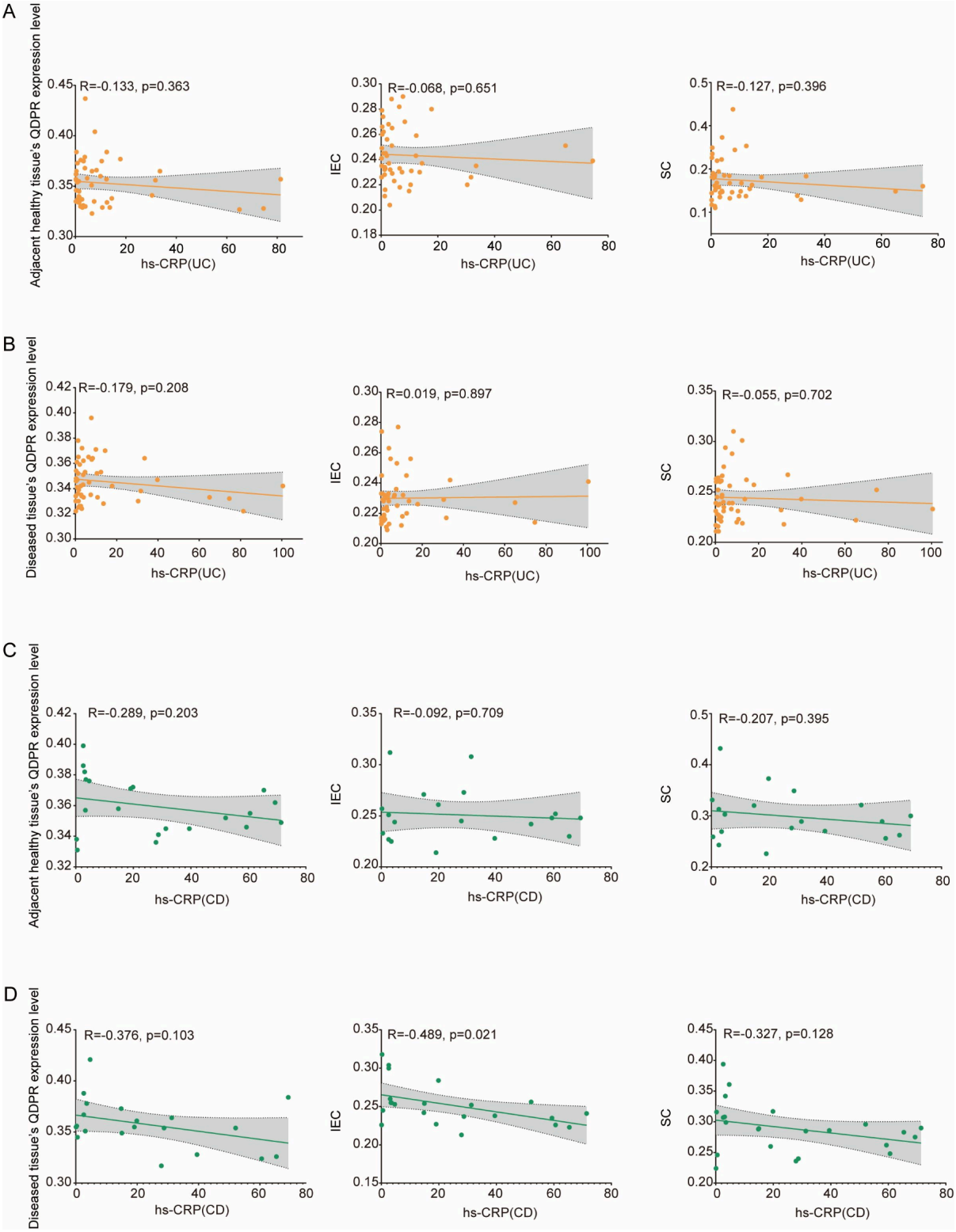



**Figure 4**

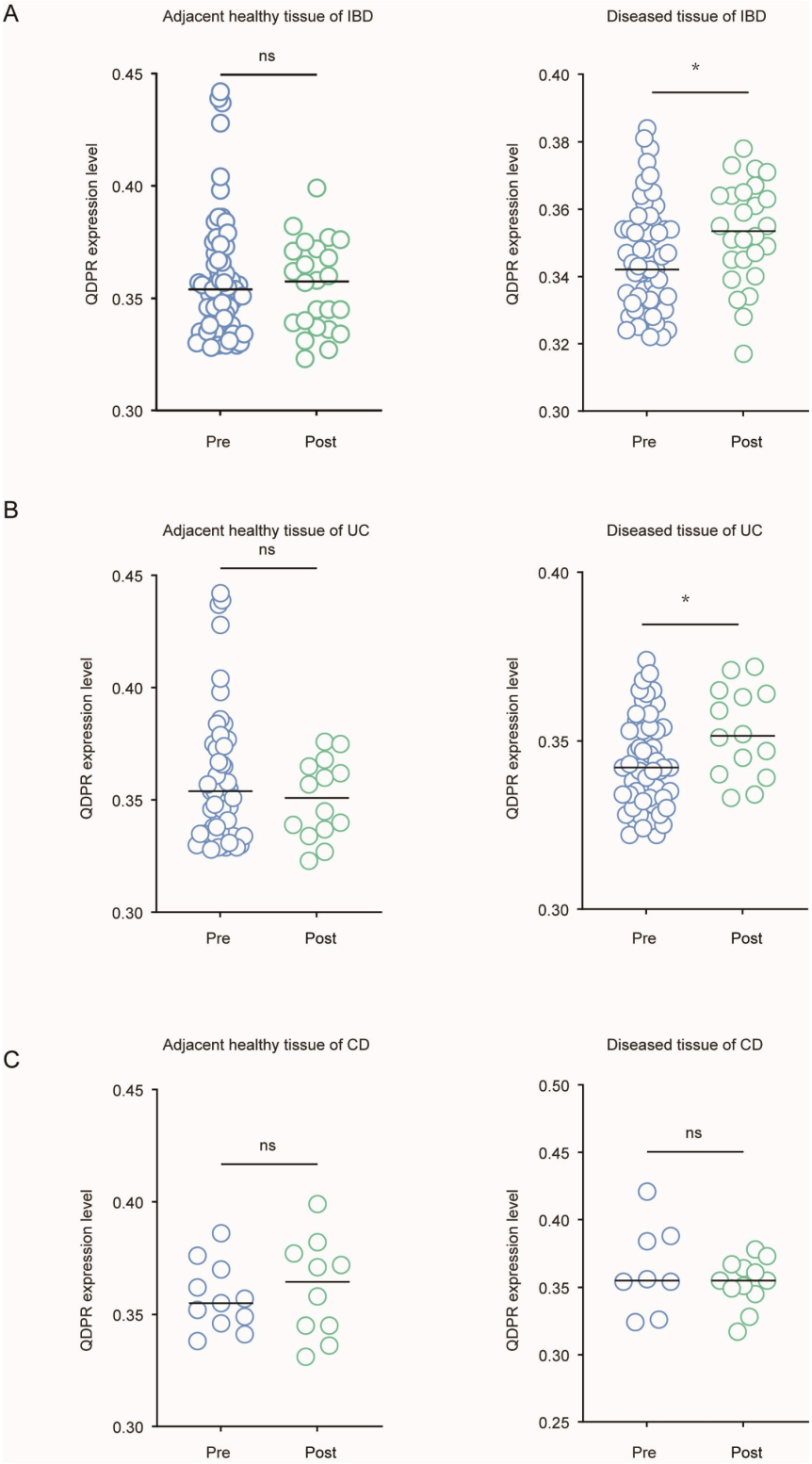
Differences in stromal QDPR expression in colonic tissues from IBD patients.(A) In all IBD patients, stromal QDPR expression was significantly higher in adjacent healthy tissues than in lesional tissues ($P < 0.0001$).(B) In UC patients, stromal QDPR expression was significantly higher in adjacent healthy tissues than in lesional tissues ($P < 0.0001$).(C) In CD patients, no significant difference was observed between adjacent healthy and lesional stromal QDPR expression ($P > 0.05$).(D) No significant difference was found between UC and CD in stromal QDPR expression of adjacent healthy tissues ($P > 0.05$).(E) Stromal QDPR expression in CD lesional tissues was significantly higher than that in UC lesional tissues ($P < 0.0001$). SC, Stromal Cell; AHT, adjacent healthy tissue; DT, diseased tissue.




## Figure 5

Correlation between serum high sensitivity C reactive protein (hs CRP) levels and QDPR expression in different colonic compartments of IBD patients.(A) In UC patients, serum hs CRP showed non significant negative correlations with overall QDPR expression in adjacent healthy tissues (R = −0.133, P = 0.363), epithelial QDPR in adjacent healthy tissues (R = −0.068, P = 0.651), and stromal QDPR in adjacent healthy tissues (R = −0.127, P = 0.396).(B) In UC patients, serum hs CRP showed non significant negative

correlations with overall lesional QDPR (R = –0.179, P = 0.208) and stromal lesional QDPR (R = –0.055, P = 0.702), but a weak positive correlation with epithelial lesional QDPR (R = 0.019, P = 0.897).(C) In CD patients, serum hs CRP showed non significant negative correlations with overall QDPR in adjacent healthy tissues (R = –0.289, P = 0.203), epithelial QDPR in adjacent healthy tissues (R = –0.092, P = 0.709), and stromal QDPR in adjacent healthy tissues (R = –0.207, P = 0.395).(D) In CD patients, serum hs CRP showed non significant negative correlations with overall lesional QDPR (R = –0.376, P = 0.103) and stromal lesional QDPR (R = –0.327, P = 0.128), but a significant negative correlation with epithelial lesional QDPR (R = –0.489, P = 0.021). IEC, Intestinal Epithelial Cell; SC, Stromal Cell; hs-CRP, high-sensitivity C-reactive protein.




## Figure 6

Differences in colonic QDPR expression between patients before and after biologic therapy.(A) In all IBD patients, no significant difference was observed in adjacent healthy QDPR expression between pre therapy and post therapy groups ($P > 0.05$), whereas lesional QDPR expression was significantly higher in post therapy patients than in pre therapy patients ($P < 0.05$).(B) In UC patients, no significant difference was found in adjacent healthy QDPR expression between pre therapy and post therapy groups

(P > 0.05), but lesional QDPR expression was significantly higher in post therapy patients (P < 0.05).(C) In CD patients, no significant differences were observed in either adjacent healthy or lesional QDPR expression between pre therapy and post therapy groups (P > 0.05).Pre, before biologic therapy; Post, after biologic therapy.