
Supplementary materials and methods

Supplementary methods

SM1 Multi-omics sample preparation

SM1.1 Transcriptomics

The quantity and quality of the RNAs were evaluated using Qubit RNA HS Assay Kit (Thermo Fisher Scientific, Cat. # Q32855) and Agilent RNA 6000 Nano Chips (Agilent Technologies, Cat. # 5067-1511) or Agilent RNA 6000 Pico Chips (Agilent Technologies, Cat.# 5067-1513).

mRNA sequencing libraries were prepared following "TruSeq Stranded mRNA Sample Preparation Guide (Part # 15031058 Rev. E) using the TruSeq™ Stranded mRNA Library Prep kit (Illumina Inc. Cat. # 20020594) and TruSeq RNA CD Index Plate (96 Indexes, 96 Samples) (Illumina Inc. Cat. # 20019792). Briefly, starting from 700 ng of total RNA, mRNA was purified, fragmented and primed for cDNA synthesis. cDNA first strand was synthesized with SuperScript-II Reverse Transcriptase (Thermo Fisher Scientific, Cat. # 18064-014) for 10 min at 25°C, 15 min at 42°C, 15 min at 70°C and pause at 4°C. cDNA second strand was synthesized with Illumina reagents at 16°C for 1 hour. Then, A-tailing and adaptor ligation were performed. Finally, enrichment of libraries was achieved by PCR (30 sec at 98°C; 15 cycles of 10 sec at 98°C, 30 sec at 60°C, 30 sec at 72°C; 5 min at 72°C and pause at 4°C).

Afterwards, libraries were quantified using Qubit dsDNA HS DNA Kit (Thermo Fisher Scientific, Cat. # Q32854) and visualized on an Agilent 2100 Bioanalyzer using Agilent High Sensitivity DNA kit (Agilent Technologies, Cat. # 5067-4626).

microRNA sequencing libraries were prepared following the protocol included with the kit NEXTFlex™ Small RNA-Seq Kit v4 with UDIs, (©Bioo Scientific Corp. Cat. # 5132-31, 5132-32, 5132-41, 5132-42, 5132-43, 5132-44). Briefly, 300 ng of total RNA were used at starting material. 3' 4N adenylated adapter and ligase enzyme were added to the RNA input and ligation was conducted by incubation of this mix at 25°C for 1 hour. After excess 3' adapter removal, 5'-adapter was added alongside with ligase enzyme, and the mix was incubated at 20°C for 1 hour. The ligation product was used for the reverse transcription with the Reverse Transcriptase in a thermocycler for 1 hour at 50°C, 5 min 90°C and 5 min 4°C. Following first strand synthesis reaction product clean-up, enrichment of the cDNA and UDIs addition was performed using PCR cycling: 30 sec at 98°C; 19 cycles of 10 sec at 98°C, 20 sec at 65°C and 15 sec at 72°C; a final elongation of 2 min at 72°C and pause at 4°C. Then, PCR product size-selection and clean-up was carried out using Nextflex Cleanup beads.

Afterwards, libraries were visualized on an Agilent 2100 Bioanalyzer using Agilent High Sensitivity DNA kit (Agilent Technologies, Cat. # 5067-4626) and quantified using Qubit dsDNA HS DNA Kit (Thermo Fisher Scientific, Cat. # Q32854).

Both mRNA and microRNA libraries were sequenced on a NovaSeq 6000 (Illumina Inc.), using paired-end 150bp and paired-end 100bp reads, respectively.

Generated RNASeq reads shorter than < 20 nt after adapters removal or trimming based on Phred33 quality < 20 were removed with CUTADAPT (v1.18) [1] and the remaining reads were mapped to the human reference GRCh38.p13 with STAR (v2.6) [2]. From the aligned reads, those that were not uniquely mapped or had a mapping quality below 20 were removed with SAMTOOLS (v1.11) [3] and the remaining reads were used for gene quantification with HTSeq (v0.11) [4].

MicroRNA reads were quantified using the sRNAbench webserver [5], based on the miR-Base release 22.1 and the human reference GRCh38.p13. The alignment and filtering param-

eters were configured as follows: a minimum mean Phred33 score of 20, a seed length for alignment of 17, a minimum read count of 5, a minimum read length of 15, a maximum of 1 allowed mismatch, and a maximum of 10 multiple mappings.

SM1.2 Proteomics sample preparation

Tissue samples were disposed on Extraction Buffer (7M urea, 2M thiourea, 4% CHAPS and 200 mM DTT) and homogenized by using Precellys universal tissue homogenizer (Bertin Technologies) using a standard procedure using zirconium oxide beads of 1.4mm (Bertin Technologies) and two cycles of 30 sec at 6.0 speed and a 30 sec pause between cycles. After this step, samples were ready to perform FASP digestion protocol, as described in the following section.

For mass spectrometry analysis, samples were analyzed in a timsTOF PRO with PASEF (Bruker Daltonics) coupled online to a Evosep ONE liquid chromatograph (Evosep). 200ng were directly loaded onto the Evosep ONE and resolved using the 30 samples-per-day protocol (44 min. gradient). Data acquisition was made using Brukers DIA-PASEF method (Data Independent Acquisition).

DIA data was processed with DIA-NN software for protein identification and quantification using default parameters. Searches were carried out against a database consisting of *Homo sapiens* protein entries from Uniprot in library-free mode. Carbamidomethylation of cysteines was considered as fixed modification and oxidation of methionines as variable modification.

SM1.3 Metataxonomics sample preparation

Participants collected stool samples at home, 24 hours prior to the colonoscopy or at least 7 days after the colonoscopy and samples were stored at -80°C. DNA extraction from stool samples was performed from 200mg of fecal material using the QIAamp DNA stool minikit (QIAGEN) following the manufacturers instructions. DNA concentration and purity were assessed using a Nanodrop spectrophotometer (Nanodrop Technologies, Wilmington, DE, USA).

The generation of the amplicons from the 16S rRNA were assessed with the commercial Ion 16S Metagenomics kit (Thermo Fisher Scientific, Waltham, Massachusetts, USA), which contains primer pools to amplify multiple variable regions of the 16S ribosomal RNA gene (V2, 3, 4, 6, 7, 8 and 9). After that, the generation of the sequencing libraries was performed with the Ion Plus Fragment Library Kit (Thermo Fisher Scientific, Waltham, Massachusetts, USA), which was used to ligate the barcode adapters with the Ion Xpress™ Barcode Adapters kit (Thermo Fischer Scientific Waltham, Massachusetts, USA) and synthesize the libraries. The emulsion PCR and 400bp sequencing of the libraries were performed on an Ion 530 chip (Ion 530TM Chip Kit) using the Ion Chef System and a Torrent S5TM system, respectively (Ion 510/520/530 Kit-Chef, Thermo Fisher Scientific).

Base calling and run demultiplexing were performed using Torrent Suite™ Server software (Thermo Fisher Scientific), version 5.4.0, with default parameters for targeted sequencing of 16S (bead loading ≤ 30 , key signal ≤ 30 , and usable sequences ≤ 30).

SM1.4 Lipoproteomics, metabolomics and inflammation biomarkers sample preparation

Fasting venous blood samples were drawn according to standard operating procedures. Following room-temperature coagulation and subsequent centrifugation, the isolated serum was separated into cryogenic vials and immediately frozen at -80°C to preserve metabolic stability and ensure comparability until measurement. Prior to NMR analysis, the cryopreserved serum

was thawed at 4°C. Following standard *in vitro* diagnostic guidelines, 300uL of each serum sample was combined in a 1:1 ratio with 300uL of phosphate buffer. This 600uL mixture was then carefully transferred into a 5mm outer-diameter SampleJet NMR tube.

Spectral acquisition was carried out on Bruker Avance III HD or Neo 600 MHz spectrometers featuring BBI or TXI probes alongside SampleJet automation. All measurements were conducted at 310 K, applying rigorous calibration and quality control standards to guarantee quantitative reproducibility. Three main spectral profiles were acquired for each serum sample: a 1D ¹H NOESY equence with water presaturation (noesygppr1d) for absolute quantification; (ii) a 1D CPMG (CarrPurcellMeiboomGill) experiment (cpmgpr1d) designed to suppress broad macromolecular signals (e.g., proteins and lipoproteins), thereby highlighting low-molecular-weight metabolites; and (iii) a rapid 2D J-resolved experiment (jrespprqf) to aid in peak disambiguation and accurate metabolite identification. Furthermore, 1D-PGPE (Pulsed Gradient Perfect Echo, zgpgpezf.ivdr) experiments were performed specifically to quantify markers of inflammation.

Supplementary tables

Features	UC-all	UC-Rs	UC-NRs	CD-all	CD-Rs	CD-NRs	non-IBD
sex (M/F)	10/9	6/5	4/4	6/8	3/3	3/5	11/9
age ($\mu \pm \sigma$)	44.79 $\pm$ 16.38	46.18 $\pm$ 18.83	42.88 $\pm$ 13.26	49.21 $\pm$ 8.92	50.17 $\pm$ 10.91	48.5 $\pm$ 7.84	54.0 $\pm$ 10.37
BMI ($\mu \pm \sigma$)	24.85 $\pm$ 5.73	23.26 $\pm$ 3.54	27.03 $\pm$ 7.55	27.3 $\pm$ 5.71	27.43 $\pm$ 6.42	27.2 $\pm$ 5.58	27.2 $\pm$ 5.71
smoking (Y/N)	0/19	0/11	0/8	5/9	3/3	2/6	4/16
disease index ($\mu \pm \sigma$)	2.47 $\pm$ 0.51	2.63 $\pm$ 0.5	2.25 $\pm$ 0.46	8.14 $\pm$ 3.55	9.0 $\pm$ 5.02	7.5 $\pm$ 2.07	NaN
CRP ($\mu \pm \sigma$)	2.1 $\pm$ 4.36	3.25 $\pm$ 5.53	0.52 $\pm$ 0.49	1.39 $\pm$ 1.58	0.78 $\pm$ 0.96	1.85 $\pm$ 1.85	0.09 $\pm$ 0.06

Table ST1: Demographic characteristics of the cohort along with baseline values for disease index (Mayo endoscopic subscore for UC and Simple Endoscopic Score for CD) and C-reactive protein levels (CRP). Values are given for each IBD type (UC or CD) and corresponding responders (Rs) and non-responders (NRs) patients. The CRP parameters for the non-IBD were based on the available observations of three individuals.

	mean	sd	hdi_3%	hdi_97%	mcse_mean	mcse_sd	ess_bulk	ess_tail	r_hat
β_0_NIBD	0.433	0.304	-0.156	0.982	0.003	0.003	10568.0	5930.0	1.0
β_1_IBD	4.285	0.459	3.45	5.177	0.005	0.005	9545.0	6706.0	1.0
β_2_IBDxW	0.087	0.471	-0.766	1.026	0.005	0.005	10751.0	6723.0	1.0
β_3_IBDxR	-0.637	0.483	-1.516	0.28	0.005	0.005	10059.0	6472.0	1.0
$\beta_4_IBDxWxR$	-1.781	0.598	-2.893	-0.636	0.006	0.006	10064.0	6635.0	1.0

Table ST2: Summary statistics and convergence diagnostics for the PyMC model parameters for latent factor 1. Values represent the posterior mean, standard deviation (sd), and 94% highest density intervals (hdi). The split- $\hat{R}$ (r_hat) and effective sample size (ess_bulk and ess_tail) metrics indicate chain convergence and sampling efficiency across all estimated parameters.

	mean	sd	hdi_3%	hdi_97%	mcse_mean	mcse_sd	ess_bulk	ess_tail	r_hat
β_0_NIBD	0.037	0.215	-0.367	0.427	0.002	0.003	11063.0	6355.0	1.0
β_1_IBD	0.695	0.316	0.08	1.261	0.003	0.003	8804.0	6059.0	1.0
β_2_IBDxW	-0.337	0.32	-0.923	0.277	0.003	0.003	9734.0	7368.0	1.0
β_3_IBDxR	-0.211	0.33	-0.803	0.432	0.003	0.003	9269.0	6875.0	1.0
$\beta_4_IBDxWxR$	0.013	0.432	-0.79	0.829	0.005	0.004	8942.0	6976.0	1.0

Table ST3: Summary statistics and convergence diagnostics for the PyMC model parameters for latent factor 2. Values represent the posterior mean, standard deviation (sd), and 94% highest density intervals (hdi). The split- $\hat{R}$ (r_hat) and effective sample size (ess_bulk and ess_tail) metrics indicate chain convergence and sampling efficiency across all estimated parameters.

	mean	sd	hdi_3%	hdi_97%	mcse_mean	mcse_sd	ess_bulk	ess_tail	r_hat
β_0_NIBD	0.036	0.185	-0.299	0.387	0.002	0.002	8638.0	5945.0	1.0
β_1_IBD	0.948	0.275	0.43	1.458	0.003	0.003	6548.0	6032.0	1.0
β_2_IBDxW	0.17	0.271	-0.327	0.689	0.003	0.003	7716.0	5802.0	1.0
β_3_IBDxR	0.063	0.293	-0.49	0.596	0.003	0.003	7376.0	6285.0	1.0
$\beta_4_IBDxWxR$	-0.683	0.372	-1.395	0.011	0.004	0.004	7397.0	6299.0	1.0

Table ST4: Summary statistics and convergence diagnostics for the PyMC model parameters for latent factor 3. Values represent the posterior mean, standard deviation (sd), and 94% highest density intervals (hdi). The split- $\hat{R}$ (r_hat) and effective sample size (ess_bulk and ess_tail) metrics indicate chain convergence and sampling efficiency across all estimated parameters.

	mean	sd	hdi_3%	hdi_97%	mcse_mean	mcse_sd	ess_bulk	ess_tail	r_hat
β_0_NIBD	0.227	0.295	-0.333	0.786	0.004	0.003	7022.0	5979.0	1.0
β_1_IBD	2.387	0.454	1.543	3.249	0.006	0.005	5512.0	5190.0	1.0
β_2_IBDxW	-0.426	0.389	-1.124	0.334	0.004	0.004	8200.0	6083.0	1.0
β_3_IBDxR	-0.974	0.504	-1.916	-0.026	0.007	0.006	5350.0	5721.0	1.0
$\beta_4_IBDxWxR$	0.78	0.521	-0.197	1.75	0.006	0.005	7177.0	5735.0	1.0

Table ST5: Summary statistics and convergence diagnostics for the PyMC model parameters for latent factor 4. Values represent the posterior mean, standard deviation (sd), and 94% highest density intervals (hdi). The split- $\hat{R}$ (r_hat) and effective sample size (ess_bulk and ess_tail) metrics indicate chain convergence and sampling efficiency across all estimated parameters.

	mean	sd	hdi_3%	hdi_97%	mcse_mean	mcse_sd	ess_bulk	ess_tail	r_hat
β_0_NIBD	0.068	0.243	-0.384	0.524	0.003	0.003	6018.0	5932.0	1.0
β_1_IBD	1.165	0.366	0.461	1.835	0.005	0.004	5004.0	5122.0	1.0
β_2_IBDxW	0.198	0.258	-0.278	0.686	0.003	0.003	9718.0	6107.0	1.0
β_3_IBDxR	-0.415	0.393	-1.131	0.352	0.006	0.004	4597.0	5309.0	1.0
$\beta_4_IBDxWxR$	-0.394	0.355	-1.07	0.259	0.004	0.004	9739.0	7009.0	1.0

Table ST6: Summary statistics and convergence diagnostics for the PyMC model parameters for latent factor 5. Values represent the posterior mean, standard deviation (sd), and 94% highest density intervals (hdi). The split- $\hat{R}$ (r_hat) and effective sample size (ess_bulk and ess_tail) metrics indicate chain convergence and sampling efficiency across all estimated parameters.

	mean	sd	hdi_3%	hdi_97%	mcse_mean	mcse_sd	ess_bulk	ess_tail	r_hat
β_0_NIBD	0.016	0.191	-0.356	0.372	0.002	0.002	11659.0	6193.0	1.0
β_1_IBD	0.393	0.282	-0.124	0.926	0.003	0.003	8390.0	6348.0	1.0
β_2_IBDxW	0.096	0.292	-0.444	0.633	0.003	0.003	9865.0	6858.0	1.0
β_3_IBDxR	-0.334	0.293	-0.868	0.236	0.003	0.003	8624.0	6310.0	1.0
$\beta_4_IBDxWxR$	0.167	0.392	-0.582	0.894	0.004	0.004	9499.0	6704.0	1.0

Table ST7: Summary statistics and convergence diagnostics for the PyMC model parameters for latent factor 6. Values represent the posterior mean, standard deviation (sd), and 94% highest density intervals (hdi). The split- $\hat{R}$ (r_hat) and effective sample size (ess_bulk and ess_tail) metrics indicate chain convergence and sampling efficiency across all estimated parameters.

	mean	sd	hdi_3%	hdi_97%	mcse_mean	mcse_sd	ess_bulk	ess_tail	r_hat
β_0_NIBD	0.008	0.208	-0.379	0.397	0.002	0.002	9379.0	6188.0	1.0
β_1_IBD	0.171	0.308	-0.417	0.733	0.004	0.003	6738.0	6086.0	1.0
$\beta_2_IBD \times W$	-0.249	0.287	-0.8	0.281	0.003	0.003	8192.0	6079.0	1.0
$\beta_3_IBD \times R$	0.018	0.33	-0.609	0.632	0.004	0.004	6650.0	6331.0	1.0
$\beta_4_IBD \times W \times R$	-0.61	0.39	-1.342	0.111	0.004	0.004	8417.0	5852.0	1.0

Table ST8: Summary statistics and convergence diagnostics for the PyMC model parameters for latent factor 7. Values represent the posterior mean, standard deviation (sd), and 94% highest density intervals (hdi). The split- $\hat{R}$ (r_hat) and effective sample size (ess_bulk and ess_tail) metrics indicate chain convergence and sampling efficiency across all estimated parameters.

	mean	sd	hdi_3%	hdi_97%	mcse_mean	mcse_sd	ess_bulk	ess_tail	r_hat
β_0_NIBD	0.008	0.153	-0.274	0.292	0.002	0.002	9881.0	6249.0	1.0
β_1_IBD	0.373	0.228	-0.083	0.774	0.003	0.003	7818.0	6293.0	1.0
$\beta_2_IBD \times W$	-0.098	0.233	-0.544	0.342	0.003	0.002	8605.0	6555.0	1.0
$\beta_3_IBD \times R$	0.359	0.238	-0.08	0.809	0.003	0.002	7715.0	6554.0	1.0
$\beta_4_IBD \times W \times R$	-0.268	0.315	-0.86	0.317	0.004	0.003	7791.0	6090.0	1.0

Table ST9: Summary statistics and convergence diagnostics for the PyMC model parameters for latent factor 8. Values represent the posterior mean, standard deviation (sd), and 94% highest density intervals (hdi). The split- $\hat{R}$ (r_hat) and effective sample size (ess_bulk and ess_tail) metrics indicate chain convergence and sampling efficiency across all estimated parameters.

	mean	sd	hdi_3%	hdi_97%	mcse_mean	mcse_sd	ess_bulk	ess_tail	r_hat
β_0_NIBD	0.057	0.268	-0.45	0.558	0.003	0.003	8426.0	5990.0	1.0
β_1_IBD	0.702	0.398	-0.075	1.433	0.005	0.004	6984.0	5345.0	1.0
$\beta_2_IBD \times W$	0.086	0.378	-0.621	0.793	0.004	0.004	8692.0	6325.0	1.0
$\beta_3_IBD \times R$	0.237	0.427	-0.582	1.031	0.005	0.004	7175.0	6404.0	1.0
$\beta_4_IBD \times W \times R$	-0.017	0.5	-1.018	0.876	0.005	0.005	8484.0	6067.0	1.0

Table ST10: Summary statistics and convergence diagnostics for the PyMC model parameters for latent factor 9. Values represent the posterior mean, standard deviation (sd), and 94% highest density intervals (hdi). The split- $\hat{R}$ (r_hat) and effective sample size (ess_bulk and ess_tail) metrics indicate chain convergence and sampling efficiency across all estimated parameters.

	mean	sd	hdi_3%	hdi_97%	mcse_mean	mcse_sd	ess_bulk	ess_tail	r_hat
intercept	-0.204	0.493	-1.108	0.749	0.007	0.005	5653	6227	1
β_1 _distance	-1.057	0.44	-1.855	-0.204	0.005	0.005	7547	5705	1
β_2 _sex	0.711	0.634	-0.508	1.868	0.009	0.006	5514	6001	1
β_3 _age	0.318	0.413	-0.47	1.088	0.005	0.004	8166	6235	1
β_4 _bmi	-0.327	0.425	-1.16	0.438	0.005	0.004	7437	6580	1
β_5 _smoking	-0.14	0.778	-1.587	1.317	0.009	0.009	7099	5543	1

Table ST11: Summary statistics and convergence diagnostics for the PyMC logistic regression model using as covariate the baseline Euclidean distance (based on latent factors) of IBD patients to the non-IBD group and response to treatment as outcome. Values represent the posterior mean, standard deviation (sd), and 94% highest density intervals (hdi). The split- $\hat{R}$ (r_hat) and effective sample size (ess_bulk and ess_tail) metrics indicate chain convergence and sampling efficiency across all estimated parameters.

Features	T-all	T-Rs	T-NRs	V-all	V-Rs	V-NRs	U-all	U-Rs	U-NRs
sex (M/F)	5/6	2/3	3/3	8/4	4/4	4/0	10/5	2/2	8/3
age ($\mu \pm \sigma$)	35.82 $\pm$ 10.89	33.8 $\pm$ 13.14	37.5 $\pm$ 9.57	51.33 $\pm$ 15.83	52.5 $\pm$ 15.0	49.0 $\pm$ 19.58	37.93 $\pm$ 14.03	32.25 $\pm$ 12.55	40.0 $\pm$ 14.52
BMI ($\mu \pm \sigma$)	23.66 $\pm$ 5.57	22.11 $\pm$ 4.2	24.95 $\pm$ 6.6	28.03 $\pm$ 4.87	29.3 $\pm$ 4.21	25.49 $\pm$ 5.72	25.26 $\pm$ 5.67	24.89 $\pm$ 4.68	25.39 $\pm$ 6.19
smoking (Y/N)	1/10	1/4	0/6	1/11	1/7	0/4	0/15	0/4	0/11
disease index ($\mu \pm \sigma$)	2.72 $\pm$ 0.46	2.8 $\pm$ 0.44	2.66 $\pm$ 0.51	2.75 $\pm$ 0.45	2.75 $\pm$ 0.46	2.75 $\pm$ 0.5	9.67 $\pm$ 3.22	10.0 $\pm$ 2.45	9.55 $\pm$ 3.56
CRP ($\mu \pm \sigma$)	1.3 $\pm$ 1.41	1.78 $\pm$ 1.85	0.9 $\pm$ 0.9	0.93 $\pm$ 1.0	0.6 $\pm$ 0.61	1.5 $\pm$ 1.37	1.14 $\pm$ 0.89	1.0 $\pm$ 0.47	1.19 $\pm$ 1.02

Table ST12: Demographic characteristics of UC cohorts treated with tofacitinib (T) or vedolizumab (V) and CD cohort treated with ustekinumab (U). Disease index (Mayo endoscopic subscore for UC and Simple Endoscopic Score for CD) and C-reactive protein (CRP) indicate baseline values. Each group is further subdivided into responders (Rs) and non-responders (NRs) patients.

Supplementary figures

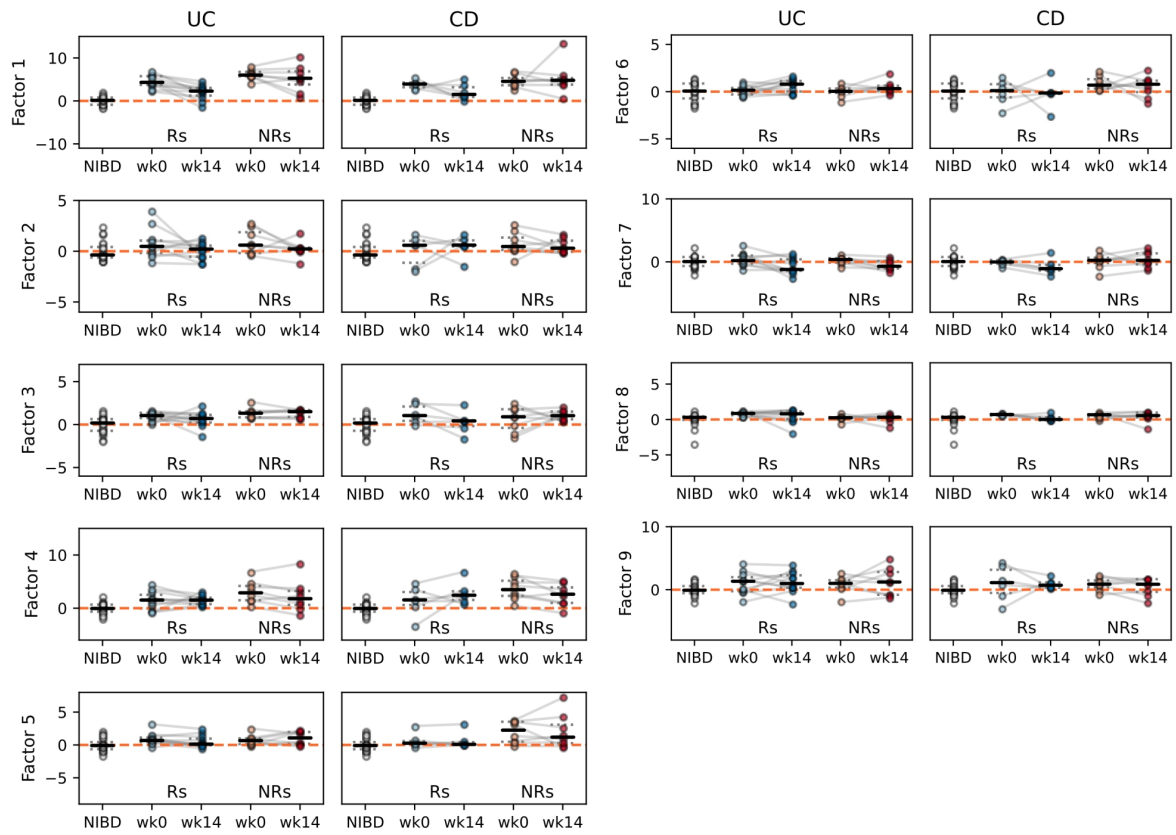


Figure SF1: Latent factors scores of UC and CD responders (Rs) and non-responders (NRs) at baseline (wk0) and post-anti-TNF treatment (wk14), compared to non-IBD individuals (NIBD). For each clinical group, solid lines represent the median and dotted lines indicate the interquartile range (IQR). The horizontal colored dashed line marks the median value of the non-IBD group.

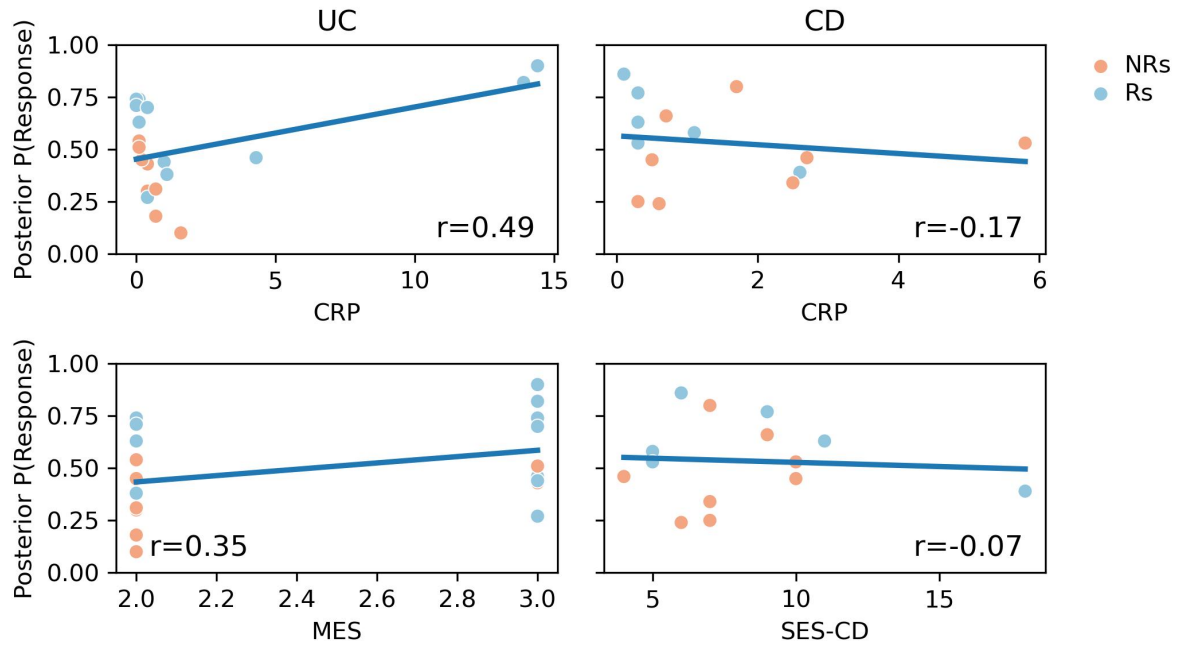


Figure SF2: Correlation between posterior probability of response to anti-TNF treatment, based on Euclidean distance to non-IBD group, and CRP or disease index. The latter included Mayo endoscopic subscore for UC (MES) and simple endoscopic score for CD (SES-CD). Points correspond to IBD responders (Rs) or non-responders (NRs).

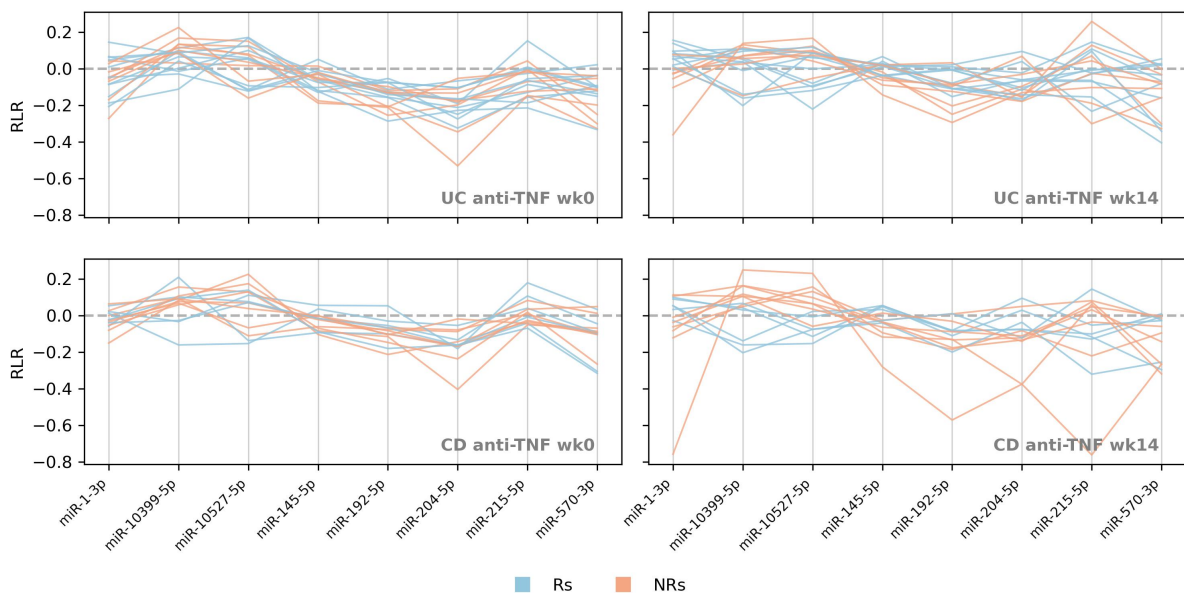


Figure SF3: Confounded-adjusted and rlr-transformed levels of microRNAs included in the protein secretion module. Each line represents an IBD responder (Rs) or non-responder (NRs) before (wk0) and after (wk14) treatment.

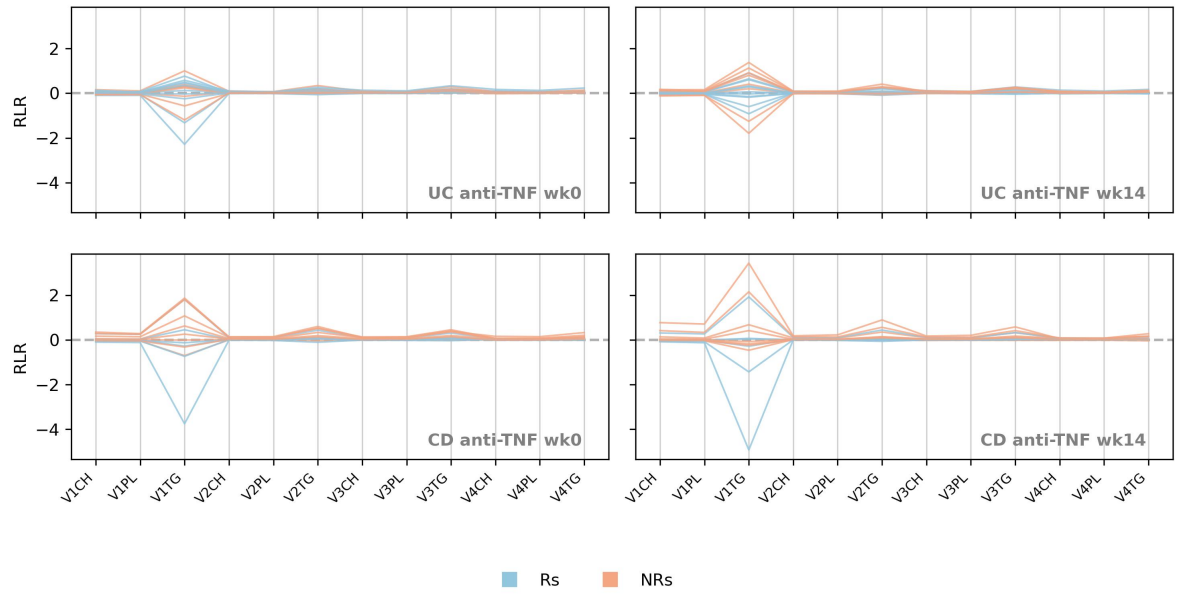


Figure SF4: Confounded-adjusted and rlr-transformed levels of lipoproteins included in the VLDL lipid export signal module. Each line represents an IBD responder (Rs) or non-responder (NRs) before (wk0) and after (wk14) treatment.

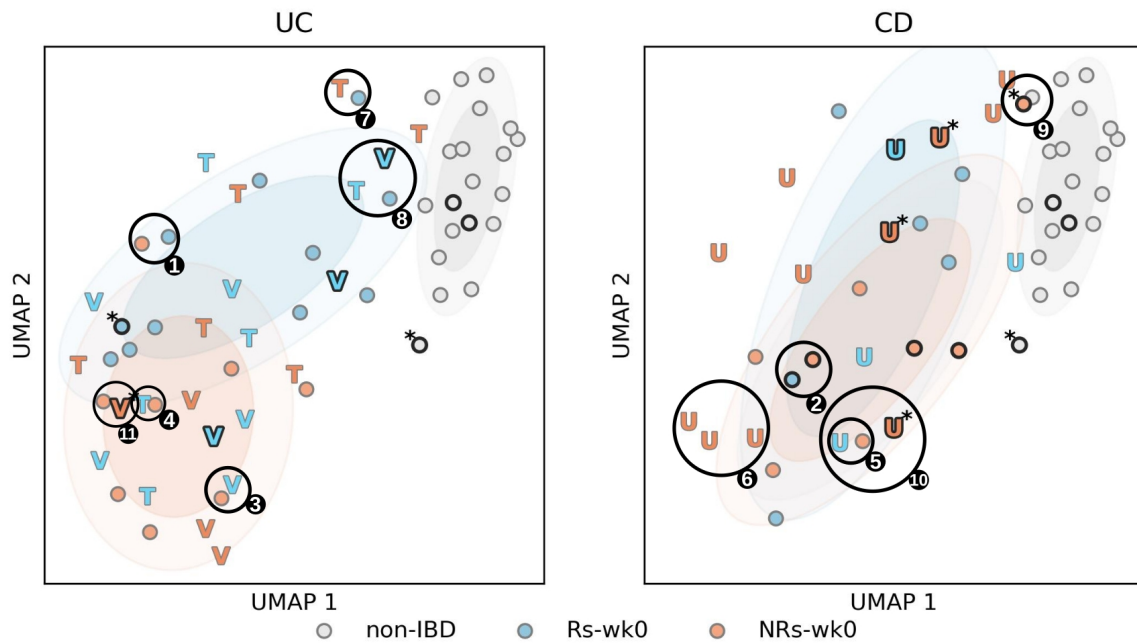


Figure SF5: 11 cases of IBD patients that clustered in close proximity and their relation is discussed in the results section of the manuscript. Patients that were treated with anti-TNF are denoted with circle, whereas patients that were treated with vedolizumab, tofacitinib or ustekinumab are indicated with the first letter of treatment. Patients that were classified with dyslipoproteinemia are denoted with thick black lines, and asterisks mark those patients that were specifically classified with VLDL or VLDL+LDL dyslipoproteinemia.

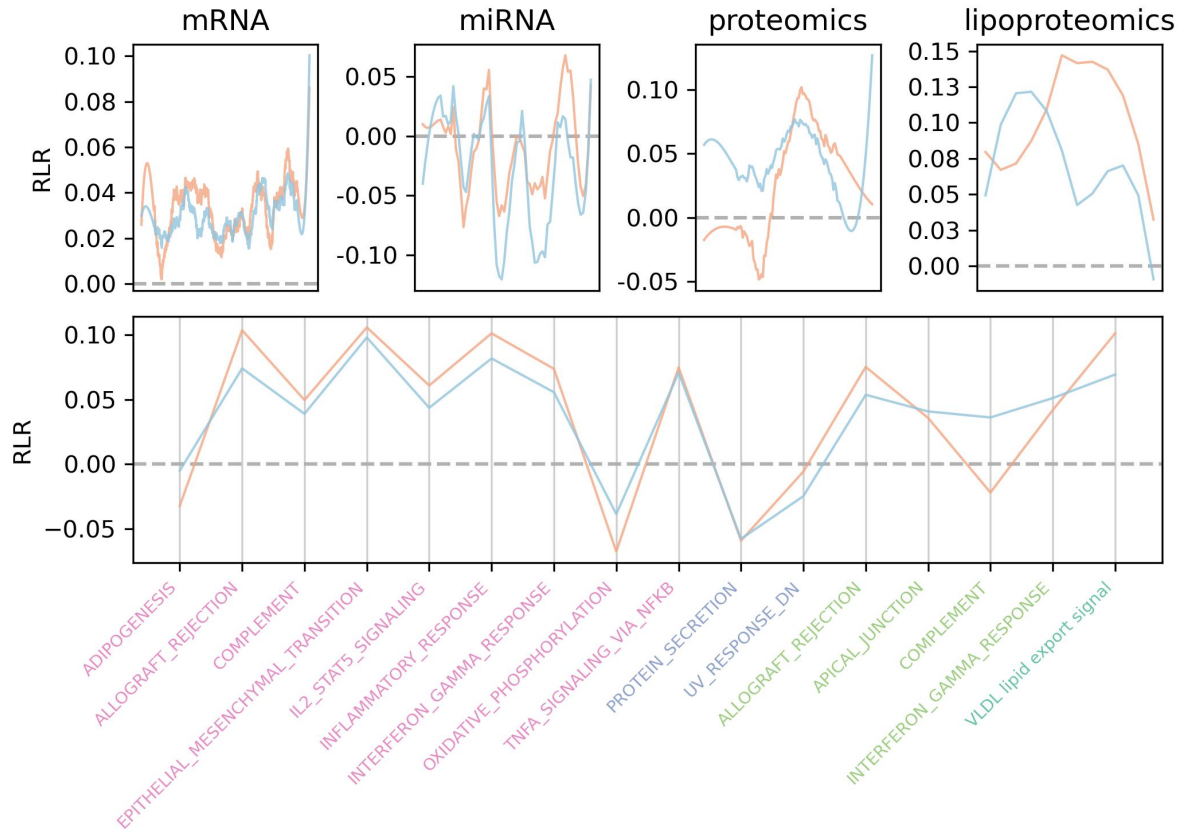


Figure SF6: Comparison of the multi-omic profile that includes 1,589 features between a responder (blue line) and non-responder (orange line) to anti-TNF UC patient (case 1 supplementary Figure SF5). Upper panels show confounded-adjusted and rlr-transformed levels of the features separated by corresponding omic layer (mRNA=1,383, miRNA=67, proteomics=127, lipoproteomics=12 features). Feature levels were smoothed using the Savitzky-Golay filter to reduce noise while preserving peak dynamics. Bottom panel shows confounded-adjusted and rlr-transformed mean levels of the features arranged by corresponding omic module.

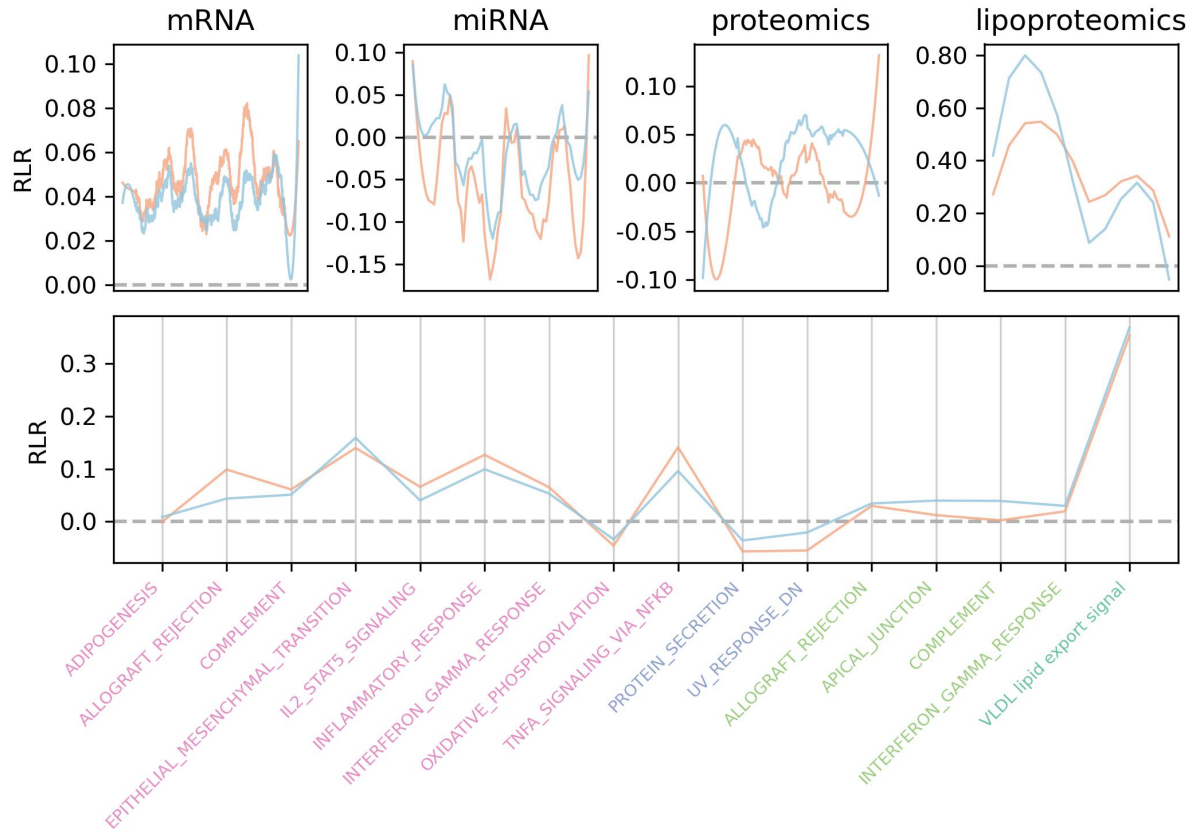


Figure SF7: Comparison of the multi-omic profile that includes 1,589 features between a responder (blue line) and non-responder (orange line) to anti-TNF CD patient (case 2 supplementary Figure SF5). Upper panels show confounded-adjusted and rlr-transformed levels of the features separated by corresponding omic layer (mRNA=1,383, miRNA=67, proteomics=127, lipoproteomics=12 features). Feature levels were smoothed using the Savitzky-Golay filter to reduce noise while preserving peak dynamics. Bottom panel shows confounded-adjusted and rlr-transformed mean levels of the features arranged by corresponding omic module.

105 **SM2 Code for accessing provided multi-omic datasets**

106 The multi-omic datasets used in this study have been stored in a DuckDB [6] instance using the
107 Python package Omilayers [7], and have been deposited in Zenodo under the accession code:
108 <https://doi.org/10.5281/zenodo.21471655>. After downloading the data, Omilayers needs to be
109 installed using the following command:

```
110 1 pip install omilayers
```

111 To access the stored data, use the following Python code snippet:

```
112 1 from omilayers import Omilayers
113 2
114 3 # Instantiate omilayers.
115 4 omi = Omilayers("multi_omic_data_IBD.duckdb")
116 5
117 6 # View available data along with brief description.
118 7 print(omi.layers)
119 8
120 9 # Load specific layer as pandas.DataFrame. Example load layer "cohort".
121 10 cohort = omi.layers["cohort"].to_df()
```

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