Supplementary Table 1. Outcomes of studies on neurological disorders (neurodegenerative diseases and sleep disorders)

Author/Year	Neurological disorder	Assessment method	Outcome
Shadrin et al. 2021 [20]	Multiple System Atrophy	Genome-Wide Association Study Data	Multiple System Atrophy and CD share a genetic etiology, highlighting a locus on chromosome 5 at 5p13.1 containing the C7 gene. This locus exhibited high deleterious and moderate regulatory scores, suggesting that genetic variability within C7 could modulate the risks of MSA and CD.
Sand et al. 2022 [21]	Dementias	Analysis of electronic medical record database	Patients with CD had an increased risk for all-cause dementia (HR = 1.15 [95% CI: 1.05-1.27]), with a higher risk observed for frontotemporal dementia (HR = 2.70 [95% CI: 1.44-5.05]).
Zingel et al. 2021 [22]	Dementias	Analysis of electronic medical record database	CD is not significantly associated with an increased risk of dementia (HR: 1.17 [95% CI: 0.93-1.47]).
Bar-Gil Shitrit et al. 2018 [23]	Sleep disorders	Ambulatory Polysomnography	CD patients had less REM sleep (P = 0.03) and less light sleep (P = 0.05) than control patients.
Chen et al. 2021 [24]	Sleep disorders	Genome-Wide Association Study Data	Results indicated that none of the investigated sleep characteristics had a significant causal impact on CD.
Chrobak et al. 2018 [25]	Sleep disorders	Pittsburg Sleep Quality Index (PSQI) and Inflammatory bowel disease questionnaire (IBDQ)	CD patients had significantly lower total PSQI scores than controls, indicating a greater tendency for eveningness. Correlational analysis reveals that in the CD group, PSQI scores are significantly negatively associated with total IBDQ score, systemic symptoms, intestinal symptoms, and emotional and social functions.
Georgiana-Emmanuela et al. 2020 [26]	Sleep disorders	Clinical (CDAI), biochemical parameters for disease activity analysis and use of the PSQI questionnaire	Sleep quality was impaired in CD patients compared to controls (P = 0.00905).
Hastaliklari et al. 2019 [27]	Sleep disorders	PSQI and Morningness-Eveningness Questionnaire	Investigations into differences in chronotype and sleep quality between individuals with Crohn's disease (CD) and controls showed that eveningness (preference for the afternoon or evening) was more common in CD patients (P < 0.0001). Additionally, there was no significant difference in CD patients' PSQI scores.
Iskandar et al. 2020 [28]	Sleep disorders	PSQI, Epworth Sleepiness Scale (ESS), Actigraphy, and Harvey Bradshaw Index (HBI)	Sleep disorders were more subjectively self-reported in CD patients compared to controls (PSQI: 57% vs. 35%, P = 0.02) and in patients with disease activity compared to patients in remission (PSQI: 75.8% vs. 33.3%, P < 0.01; ESS: 45.5% vs. 19%, P = 0.03). However, there was no significant change in objective sleep quality analysis between groups.

Kyle Hoffman et al. 2022 [29]	Sleep disorders	Analysis of electronic medical record database	Increased risk of developing Obstructive Sleep Apnea in CD patients compared to control patients (P < 0.0001).
Sofia et al. 2020 [30]	Sleep disorders	PSQI and HBI	CD patients and controls shared similar PSQI (P = 0.31), and 77% of the CD population had PSQI > 5. The Cox proportional hazards model for hospitalization or surgery showed that PSQI > 8 predicted surgery or hospitalization (hazard ratio 5.37; 95% CI 1.39-27.54).
Aggarwal et al. 2020 [31]	Alzheimer's Disease	Analysis of electronic medical record database	CD was associated with higher AD risk (P < 0.0001).
Camacho-Soto et al. 2018 [32]	Parkinson's Disease	Analysis of electronic medical record database	PD was inversely associated with CD (OR = 0.83 [95% CI: 0.74-0.93]).
Freuer et al. 2022 [33]	Parkinson's Disease	Genome-Wide Association Study Data	No causal association between PD and CD (P = 0.48).
Hui et al. 2018 [34]	Parkinson's Disease	Exome sequencing	Association in the LRRK2 gene with similar genetic effects in PD and CD. The CD risk allele LRRK2 N2081D is located in the same kinase domain as G2019S, a mutation that is the leading genetic cause of familial and sporadic Parkinson's disease.
Kang et al. 2022 [35]	Parkinson's Disease	Genome-Wide Association Study Data	Weak but statistically significant genetic correlations were detected between PD and CD (P = 0.01). Genetic variants and shared genomic loci were identified in both diseases, indicating a possible common genetic basis.
Loosen et al. 2023 [36]	Parkinson's Disease	Analysis of electronic medical record database	There was no significant association between CD and PD in the total study cohort (patients evaluated were over 40 years old).
Park et al. 2019 [37]	Parkinson's Disease	Analysis of electronic medical record database	CD patients had a 2.2 times higher chance of developing PD than healthy patients (P = 0.023). The average age of PD diagnosis in CD was lower than in controls (53.7 vs. 64.9 years; P = 0.014).
Wang et al. 2024 [38]	Parkinson's Disease	Analysis of electronic medical record database	Results suggest that CD presence does not influence PD's occurrence.
Weimers et al. 2019 [39]	Parkinson's Disease	Analysis of electronic medical record database	The overall risk of PD was 30% higher in CD patients compared to reference individuals.
Witoelar et al. 2017 [40]	Parkinson's Disease	Genome-Wide Association Study Data	Significant genetic overlap of PD and CD with shared susceptibility loci.
Zheng et al. 2022 [41]	Parkinson's Disease	Peripheral blood transcriptomic database	One hundred seventy-eight commonly differentially expressed genes (113 increased and 65 decreased) between PD and CD were found. Functional analysis showed they were related to immune response and lipid binding. Twelve core genes: BUB1B, BUB3, DLGAP5, AURKC, CBL, PCNA, RAF1, LYN, RPL39L, MRPL13, RSL24D1, and MRPS11.

Li et al. 2022 [42]	Neurodegenerative Diseases	Mendelian Randomization analysis of single nucleotide polymorphisms to explore causal association between CD and neurodegenerative diseases	No causal effect of CD on PD (P = 0.54), AD (P = 0.26), or ALS (P = 0.41) was suggested.
Li et al. 2021 [43]	Amyotrophic Lateral Sclerosis	Genome-Wide Association Study Data	There was a minimal genetic association between ALS and CD; the strongest signal, rs2076756 (NOD2), in the Manhattan conjunction plot was identified between ALS and CD. There was no significant difference in the incidence rate of ALS between patients with previous CD compared to controls.
Sonnenberg et al. 2023 [44]	Multiple Sclerosis	Analysis of electronic medical record database	Results showed a significant association between multiple sclerosis and the simultaneous diagnosis of CD.
Yang et al. 2021 [45]	Multiple Sclerosis	Genome-Wide Association Study Data	Three shared single nucleotide polymorphisms between MS and CD were identified; none genome-wide significant in the single-trait GWAS.

Supplementary Table 2. Results from studies employing neuroimaging, electroencephalography (EEG), or serum BDNF analysis in Crohn's disease

Author/Year	Assessment method	Outcome
Agostini et al. 2023 [46]	Structural Magnetic Resonance Imaging (MRI) and Resting-State Functional Magnetic Resonance Imaging (rs-fMRI)	Patients with active CD (CD-A) showed reduced gray matter within the posterior cingulate cortex compared to patients with CD in remission (CD-R). Analysis of resting-state fMRI data revealed the following patterns: (1) increased connectivity within the left fronto-parietal network (in the superior parietal lobe) in CD-R patients compared to CD-A patients; (2) decreased connectivity in the motor network (in parietal and motor areas) in the CD-A group compared to healthy controls (HC); (3) reduced connectivity in the motor network; and (4) in the language network (in parietal areas and the posterior cingulate cortex) in CD-R patients compared to HC.
Bao et al. 2018 [47]	rs-fMRI	Compared to controls, CD showed higher bilateral Amplitude of Low-Frequency Fluctuations (ALFF) in the hippocampus and parahippocampal regions, right insula, and prefrontal cortex; decreased Functional Connectivity (FC) in the left inferior cortex, middle cingulate cortex, hippocampus, and fusiform area; significant ALFF differences in the anterior cingulate cortex, precuneus, insula, precentral gyrus, medial prefrontal cortex, and secondary somatosensory cortex.
Chen et al. 2023 [48]	rs-fMRI	The results showed differences between groups related to the functional connectivity of subregions of the Periaqueductal Gray (PAG). A decrease in functional connectivity was observed successively in the order of control patients, patients with CD without abdominal pain, and patients with CD with abdominal pain. This suggests that the intensity of abdominal pain is associated with reduced functional connectivity between these regions.
Fan et al. 2020 [49]	rs-fMRI	Compared to control patients, CD showed altered Functional Connectivity (FC) in the amygdala, insula, parahippocampal gyrus, anterior cingulate cortex, and middle cingulate cortex. Patients with abdominal pain showed decreased FC in the insula.
Hall et al. 2023 [50]	Electroencephalogram (EEG)	They showed that CD patients presented altered states implicating the default mode network in parietal and visual regions, reflecting a shift in attentional modes' predominance. The results demonstrated that the diagnosis of CD is a determinant factor in the risk of developing altered brain network signatures.

Hou et al. 2019 [51]	MRI	In the Executive Control Network, resting-state FC was increased between the right middle frontal gyrus and the right inferior parietal lobule in CD compared to HC. In the Default Mode Network (DMN), resting-state FC showed increased CD patients between the right precuneus and the right posterior cingulate cortex compared to HC. Thus, the patient group exhibited elevated resting-state FC in both networks compared to the control group.
Hou et al. 2020 [52]	MRI	Fractional Anisotropy (FA) was significantly reduced in regions of the bilateral cingulate gyrus. Mean Diffusivity (MD) was significantly increased in areas of the left cingulate, left inferior frontal-occipital fasciculus, and bilateral superior longitudinal fasciculus. Axial Diffusivity (AD) was increased in regions of the bilateral cingulate and bilateral superior longitudinal fasciculus. Radial diffusivity values were significantly increased in areas of the right corticospinal tract, right inferior longitudinal fasciculus, and left superior longitudinal fasciculus (temporal part).
Kelleci et al. 2019 [53]	EEG	EEG alterations were significantly more common in CD patients than controls ($P = 0.001$). Slow wave abnormalities were the most common EEG abnormality detected in 13 (31%) patients. Epileptiform abnormalities were detected in 3 (7%) patients in the CD group. 94% (15/16) of EEG abnormalities were bilateral, and 6% (1/16) were on the right side.
Kong et al. 2022 [54]	HBI, Visual Analog Scale (VAS) and rs-fMRI	Patients with active CD showed higher spontaneous activity in the left anterior and medial cingulate cortex and higher levels of Glutamate in the anterior cingulate cortex ($P < 0.05$).
Kornelsen et al. 2020 [55]	MRI	In patients with CD, region of interest analyses showed increased FC between the frontoparietal network and salience network, decreased FC within the default mode network, increased FC between the right lateral prefrontal cortex of the frontoparietal network and the bilateral supramarginal gyrus of the salience network, decreased FC between the medial prefrontal cortex and the left lateral parietal node in the default mode network. Independent component analysis revealed cerebellar, visual, and salience network component alterations.
Li et al. 2021 [56]	rs-fMRI	The CD group showed higher Amplitude of Low-Frequency Fluctuations (ALFF) in the left anterior cingulate cortex, left superior frontal gyrus, and left supplementary motor cortex, and lower ALFF in the left hippocampus compared to controls ($P < 0.05$). They also exhibited higher Regional Homogeneity (ReHo) values in the left anterior cingulate cortex, bilateral superior frontal gyrus, left supplementary motor cortex, and left putamen compared to controls. In the FC analysis based on ALFF and ReHo, there was higher activity in the left precentral gyrus, left middle temporal gyrus, inferior frontal orbital cortex, middle frontal gyrus, and right rolandic operculum than controls.
Liu et al. 2018 [57]	rs-fMRI	Regarding Functional Connectivity (FC) in resting-state networks, the primary visual network showed decreased functional connectivity in the left calcarine cortex. In contrast, the language network showed increased functional connectivity in the left middle temporal gyrus (cluster-level $P < 0.01$). Significantly increased connectivity was found between the language network and the dorsal Default Mode Network (DMN) ($P < 0.05$). In the CD group, the connectivity strength related to the Left Calcarine Cortex within the primary network was significantly negatively correlated with disease duration ($P = 0.046$).
Nair et al. 2019 [58]	MRI and Verbal Fluency Score	There was no difference in Verbal Fluency Score between control patients and those with CD. In brain activation analyzed by MRI, regions activated in healthy controls in the left hemisphere included the inferior frontal gyrus, supplementary motor area, and fusiform gyrus. Right hemisphere activation involved the putamen and cerebellum. In patients with CD, activated regions in the left hemisphere included the insula, precuneus, angular gyrus, and supplementary motor area (SMA), and in the right hemisphere, the insula, SMA, cerebellum, and inferior frontal gyrus. Patients with CD in this study demonstrated activation patterns similar to those of older healthy individuals, as previously reported in the literature.

Qiu et al. 2022 [59]	Mean Apparent Propagator Magnetic Resonance Imaging (MAP-MRI) and rs-fMRI	The brain regions with different Mean Apparent Propagator (MAP) parameters are bilateral parahippocampal gyrus, bilateral thalamus, bilateral insula, left hippocampus, left putamen, left amygdala, left temporal pole: superior temporal gyrus, left rolandic operculum, left fusiform gyrus, right middle frontal gyrus, right superior medial frontal gyrus, and right anterior cingulate gyrus and right paracingulate gyrus. Regarding the FC analysis, they were lower in CD patients than in healthy controls. They were left thalamus-left parahippocampal gyrus (t = -3.117, P = 0.034), left thalamus-right parahippocampal gyrus (t = -3.407, P = 0.021), right thalamus-right parahippocampal gyrus (t = -2.959, P = 0.029), and right thalamus-left parahippocampal gyrus (t = -4.485, P = 0.006).
Sochai et al. 2021 [60]	Serum evaluation of BDNF, insomnia assessment: Athens Insomnia Scale (AIS) and VAS and Laitinen Pain Scale	Patients with CD had a higher serum BDNF level than healthy controls (P = 0.010). No correlation was found between clinical severity and BDNF. There were positive correlations between BDNF level and AIS scores (r = 0.253, P = 0.020), pain severity measured using VAS (r = 0.251, P = 0.021), and Laitinen Pain Scale (r = 0.218, P = 0.047). No differences were observed in BDNF levels before and after 14 weeks of anti-TNF-α therapy.
Thapaliya et al. 2023 [61]	rs-fMRI	They showed a significant reduction in the overall volume of cerebrospinal fluid in participants with CD compared to controls and a decrease in gray matter volume, white matter volume, and cortical thickness in the left precentral gyrus.
Thapaliya et al. 2023 [62]	rs-fMRI	Functional connectivity alterations at rest were documented in patients with CD in the frontoparietal network, visual networks, cerebellar networks, and attention networks, suggesting a specific neural phenotype of CD. Higher abdominal pain scores were associated with lower connectivity in the precuneus (visual network) and parietal operculum and connectivity in the cerebellum. Longer disease duration was associated with higher connectivity in the middle temporal gyrus and temporal plane (visual network).
Thomann et al. 2017 [6]	rs-fMRI	Abnormal connectivity was observed in CD patients only in the subsystems of the DMN (P < 0.05). Increased connectivity was found in the anterior cingulate, left superior medial frontal gyrus, and the middle cingulate cortex.
Thomann et al. 2021 [63]	MRI and rs-fMRI	Joint analysis of independent components detected structural alterations in the middle frontal and temporal regions and functional alterations in the superior frontal gyrus, middle and inferior frontal gyrus, inferior temporal gyrus, rectus, and subcallosal gyrus of CD patients compared to control patients.
Thommann et al. 2017 [64]	High-Resolution Magnetic Resonance Imaging	Transitivity, a measure of global segregation of the neural network, was significantly reduced in patients with CD (P = 0.003). Regionally, patients showed a reduction in nodal betweenness centrality in the right insula and cuneus and the left superior frontal cortex and a reduction in nodal degree in the left hemispheric cingulate, left lateral orbitofrontal cortex, and right medial orbitofrontal cortex.
Yeske et al. 2024 [65]	MRI	Patients with CD showed more significant brain similarity with older control patients than their healthy age-matched peers.
Zhang et al. 2021 [66]	rs-fMRI	Compared to controls, patients with CD showed gray matter volume in the left dorsal anterior insula and bilateral posterior insula. The Functional Connectivity (FC) of the parahippocampus/hippocampus with the left dorsal anterior insula and bilateral posterior insula was negatively correlated with the Crohn's Disease Activity Index (CDAI).

Supplementary Table 3. Outcome of the study on vagotomy

Neurological disorder	Assessment method	Outcome
Vagotomy [67]	Analysis of electronic medical record database	It showed a positive association between vagotomy and CD (HR = 3.63, 95% CI = 1.94-6.80 for truncal vagotomy, HR = 2.06, 95% CI = 1.49-2.84 for selective vagotomy).