Meta-Analysis of Observational Studies in Epidemiology

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Heart rate variability and inflammatory bowel disease in humans

A systematic review and meta-analysis

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Abstract

The autonomic nervous system (ANS) maintains homeostasis in the gastrointestinal tract, including immunity, inflammation and motility, through the brain-gut axis. To date, the associations between ANS function and inflammatory bowel disease (IBD) have been controversial and inconclusive in human studies. PubMed, Cochrane Library, and Embase were searched through February 2020 for articles reporting these association between heart rate variability (HRV), an indirect measure of ANS activity, and IBD. The standardized mean differences and 95% confidence intervals (CIs) were calculated. Ten eligible studies involving 273 ulcerative colitis patients, 167 Crohn's disease patients and 208 healthy controls were included. The values of the total power (SMD = −0.83, 95% CI = −1.44, −0.21), high frequency (SMD = −0.79, 95% CI = −1.20, −0.38), RR interval (SMD = −0.66, 95% CI = −1.04, −0.27), standard deviation of the RR intervals (SMD = −1.00, 95% CI = −1.73, −0.27), percentage of RR intervals with a greater than 50-millisecond variation (SMD = −0.82, 95% CI = −1.33, −0.30) and the square root of the mean squared differences in successive RR intervals (SMD = −0.71, 95% CI = −1.15, −0.26) of the IBD patients were lower than those of the healthy controls, and moderate to large effect sizes were observed in all HRV indices, except for low frequency (SMD = −0.41, 95% CI = 0.95, 0.13). IBD was strongly associated with an overall decrease in HRV, indicating substantially decreased ANS activity. Furthermore, the parasympathetic nerve displayed a stronger inverse association with ANS activity than the sympathetic nerve, indicating ANS dysfunction in patients with IBD.

Abbreviations: ANS = autonomic nervous system, BMI = body mass index, CD = Crohn's disease, CIs = confidence intervals, HF = high frequency, HRV = between heart rate variability, IBD = inflammatory bowel disease, IL = interleukin, IRB = Institutional Review Board, LF = low frequency, pNN50 = percentage of RR intervals with a greater than 50-millisecond variation, RMSSD = square root of the mean squared differences of successive RR intervals, SDNN = standard deviation of the RR intervals, SDs = standard deviations, SMDs = standardized mean differences, TNF = tumor necrosis factor, TP = total power, UC = ulcerative colitis.

Keywords: autonomic nervous system, Crohn's disease, heart rate variability, inflammatory bowel disease, parasympathetic nerve, sympathetic nerve, ulcerative colitis

1. Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are the major forms of idiopathic inflammatory bowel disease (IBD) and are characterized by recurrent and chronic inflammation in the digestive tract. According to a recent study, the prevalence of IBD in 2017 is nearly 3.9 million in females and nearly 3.0 million in males worldwide, and the number of cases is increasing.[1] IBD is a disease that requires considerable health care attention because it is associated with various digestive symptoms and devastating complication effects. Although the etiology of IBD may involve many factors, such as genetic or environmental factors, gut dysbiosis and the mucosal immune response, the pathogenesis of this disease remains unknown.[2]

In recent years, emerging evidence has suggested that the brain-gut axis may influence the pathogenesis of IBD. Clinical studies have shown that changes in the brain-gut axis are associated with dysfunction of the autonomic nervous system (ANS), which is connected to the central nervous system and the gastrointestinal system. ANS impairment has been found in UC and CD patients.[3] Ganguli et al and Sharma et al reported that an increase in sympathetic activity is associated with UC.[4,5] Coruzzi et al reported impairment in cardiac vagal activity in UC.[6] Aghdasi-Bornaun et al reported a relative tendency of parasympathetic suppression and sympathetic predominance in IBD.[7] In addition, the function of the ANS is affected by mental stress, a factor that exacerbates IBD. Therefore, ANS dysfunction may be involved in the development of IBD.

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Because beat-to-beat fluctuations in heart rate are controlled by the combined effects of the sympathetic and parasympathetic nerves, ANS function is clinically evaluated by heart rate variability (HRV).[8,9] The results of studies examining the association between IBD and autonomic nerve activity are controversial, particularly for UC and CD.[3,5,10,11] Some studies have reported that patients with UC have lower absolute high frequency (HF) power values than patients with CD, implying parasympathetic tone, while others have reported that low frequency (LF) power components indicative of a predominant sympathetic tone are lower in patients with CD than in healthy individuals.[4,5,11,12] Therefore, the objective of the current meta-analysis based on previous human studies was to investigate whether HRV values in healthy individuals differ from those in patients with IBD, including CD and UC.

2. Methods

We planned, conducted and reported this systematic review according to widely accepted standards of quality for reporting meta-analyses of observational studies in epidemiology. Ethical approval for this study was waived by the Institutional Review Board (IRB) of Uijeongbu St. Mary's Hospital as we used only published data. As this study was a systematic review based on published studies, the requirement for informed consent was waived by the IRB.

2.1. Literature search

A medical librarian experienced in systematic reviews helped design the search strategy. We systematically searched the PubMed, Cochrane Library, and Embase databases via Elsevier for articles published by February 2020. A PubMed search for studies related to HRV and IBD was conducted without restrictions by combining search terms that are synonymous with or related to HRV and IBD (Supplementary Table 1, http://links.lww.com/MD/F287). The keywords used in the PubMed search were converted into search tags for the Cochrane Library and Embase databases. Furthermore, manual searches of the bibliographies and conference abstracts of relevant articles were conducted to identify additional studies.

2.2. Inclusion and exclusion criteria

Published articles were included in this meta-analysis if they met the following criteria:

1. case-control studies that were conducted in humans rather than animals;
2. studies that provided data on HRV in both individuals with and without UC or CD; and
3. studies that were written in English and published in their entirety.

The exclusion criteria for this meta-analysis were as follows:

1. articles that did not satisfy the inclusion criteria,
2. publications described as animal studies, reviews, case reports, and systematic reviews;
3. studies that did not provide sufficient data regarding the HRV indices, including the means, medians, standard deviations (SDs), or standard errors of individuals with and without IBD (UC or CD); and
4. studies in which the HRV data of patients with UC and CD were not analyzed separately.

2.3. Data extraction and quality assessment

Two investigators (Sang-Yhun Ju and Kyu-Nam Kim), the coauthors of the present study, independently extracted data from the original reports. The following information was extracted: the first authors last name, year of publication, country in which the study was conducted, age, sex, sample size, body mass index (BMI), HRV indices, disease duration, HRV recording length, patient position, and variables used for matching control groups to case groups. Disagreements between the 2 reviewers were resolved by consensus. The methodological quality of the included studies was evaluated using the Newcastle-Ottawa Scale criteria for case-control studies, which contained 9 items that were grouped into three major categories.[13] The maximum scores were 4 for selection, 2 for comparability, and 3 for exposure. A final score of 7 or higher was indicative of a high-quality study.

2.4. HRV Indices of Interests

HRV comprises time and frequency-domain components. The time-domain indices of HRV include the mean of the RR intervals, standard deviation of the RR intervals (SDNN), square root of the mean squared differences of successive RR intervals (RMSSD) and percentage of RR intervals with a greater than 50-millisecond variation (pNN50).[8] The frequency domain indices of HRV include the total power (TP), LF (0.04–0.15 Hz), and the HF power (0.15–0.4 Hz). RMSSD, pNN50 and HF power are associated with parasympathetic (vagal) activity, while the RR interval, SDNN, and TP reflect a combination of both parasympathetic and sympathetic activity.[9] LF mainly represents sympathetic activity. The ratio of LF to HF power is an estimate of the sympathovagal balance of the ANS.[8] The outcomes of interest were the frequency-domain indices, such as the TP, LF, HF, and LF/HF ratio, and time domain indices, such as the RR interval, SDNN, pNN50, and RMSSD.

2.5. Statistical analysis

Data were analyzed separately according to HRV indices, including indices in the frequency and time domains. The data of interest, presented as continuous values (means and SDs), were used to perform the meta-analysis to obtain the standardized mean differences (SMDs) and 95% confidence intervals (CIs) of the HRV indices of participants with UC or CD and of controls. Thus, studies in which the difference in the means is the same proportion of the standard deviation will have the same SMD, regardless of the actual scales used to perform the HRV measurements. An SMD less than 0.5 was considered small, an SMD from 0.5 to 0.8 was considered moderate, and an SMD larger than 0.8 was considered large.[14] We performed a random–effects meta-analysis of UC and CD.[15] The statistical heterogeneity across studies was assessed using Q and I^2 statistics. For the Q statistic, heterogeneity was considered present if $P < .1$.[16] I^2 values greater than 50% were considered to indicate a high degree of heterogeneity, $I^2 > 25\%$ indicated a moderate or high degree of heterogeneity, and $I^2 < 25\%$ indicated a low degree of heterogeneity.

The subgroup analyses were conducted by comparing the results from studies grouped according to predefined criteria, such as whether the study had a matched case-control design (yes vs no), all patients were in remission from disease (yes vs no), and 24-hours HRV recordings were reported (yes vs no). We also performed meta-regression and sensitivity analyses to explore the potential sources of heterogeneity. The possibility of publication bias was assessed using Begg test[17] and a visual inspection of the funnel plot. We also used the trim-and-fill algorithm[18] to identify and correct for funnel plot asymmetry. In the presence of publication bias, the *P* value of Begg test was less than .1. All statistical analyses were performed using Stata software, version 15.0 (Stata Corp., College Station, TX, USA).

3. Results

3.1. Study retrieval and selection and characteristics of the eligible studies

Fig. 1 shows the details of the study selection process. In brief, a total of 433 articles were identified via Cochrane Central, PubMed, and Embase. Of these studies, 38 duplicate articles were excluded, and another 395 articles were excluded on the basis of their titles and abstracts; 39 articles remained for further evaluation. After obtaining the full articles, we excluded an additional 29 articles according to the exclusion criteria (Supplementary Table 2, http://links.lww.com/MD/F288); 10 articles that were appropriate for the meta-analysis remained.[4–7,11,12,19–22] The interrater reliability of the 2 reviewers for the initial screening of the studies was good (agreement 97.7%, $\propto = 0.67$). The overall quality of the studies averaged 8 stars (range, 7–9) on a scale from zero to 9 stars (Supplementary Table 3, http://links.lww.com/MD/F289).

The characteristics of the ten included studies are summarized in Table 1. All of the studies were published from 2006 to 2019. Four studies[4,19–21] only included patients with UC, 3 studies[11,12,22] only included patients with CD and 3 studies[5–7] included UC and CD patients. The numbers of UC patients, CD patients and healthy controls were 273, 167 and 208, respectively. The participants mean age ranged from 11.55 to 48.6 years. All the studies included both men and women and the percentage of women ranged from 18.99 to 86.2. The mean duration of IBD ranged from 3 to 4 months, as reported by Gunterberg et al[20] to 15.3 years, as reported by Rubio et al.[22] Regarding disease activity, 6 studies[5–7,11,20,22] evaluated HRV in patients with IBD during the only remission phase, and 4 studies[4,12,19,20] evaluated HRV in patients during the remission and active phases. Seven studies[4,6,7,11,12,21,22] matched the case and control groups by age, sex or BMI, but 3 studies[5,19,20] did not match groups according to characteristics. The HRV recording length ranged from 5 minutes, as reported by Sharma et al,[5] to 24 hours, as reported by Aghdasi-Bornaun et al[7] and Gunterberg et al.[20] The data of the HRV indices were extracted from the 10 case-control studies. The time-domain indices were TP, LF, HF, and the LF/HF ratio, and the frequency domain indices were the RR interval, SDNN, pNN50 and RMSSD.

3.2. Frequency-domain indices of HRV in patients with IBD

Forest plots of the effect sizes of the frequency-domain indices of HRV with respect to IBD are shown in Fig. 2. A separate meta-

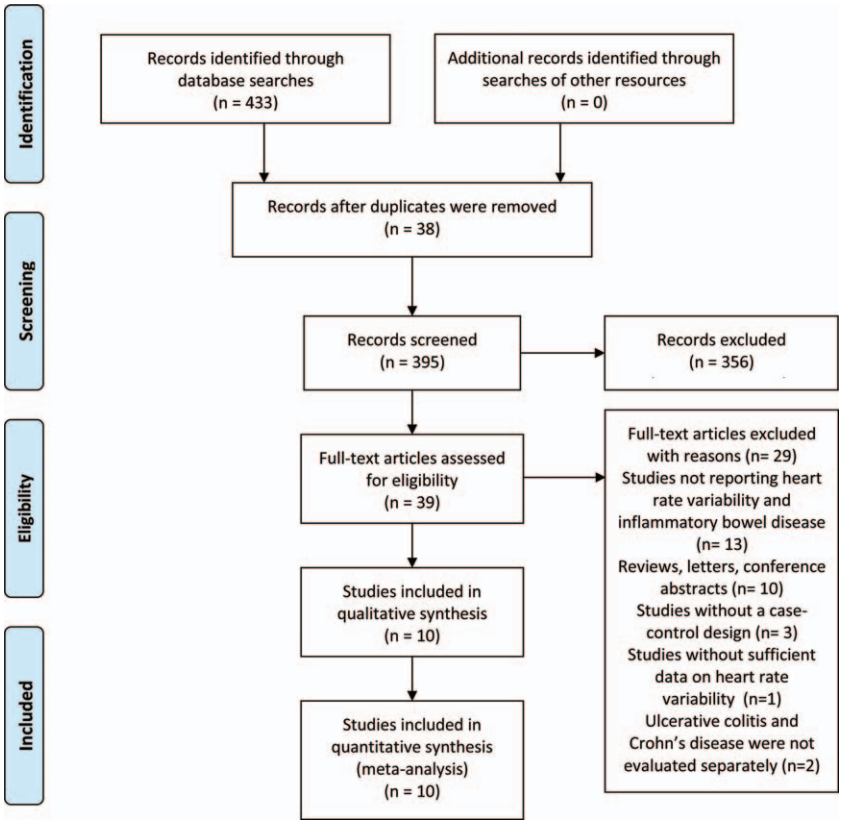

Figure 1. Flow diagram of the search strategy and study selection process.

Table 1

General Characteristics of Studies Included in the Meta-Analysis.

Author Year, country	Cases Controls (N)	Mean age (SD, range) year	Female (%)	Mean BMI (SD) kg/m2	Matched case-control design	Duration of disease year (mon)	All patients in remission from the disease	HRV recording Subject position	HRV indices time-domain (ms) frequency-domain (Hz)
Aghdasi-Bornaun et al [7]	UC (20)	11.55 (4.8)	60	19.58	Yes	1.4 (16.5)	Yes	24-h Holter ECG	RR interval, SDNN
2018, Turkey	CD (16)	12.8 (3.97)	43.75	(3.98)	(Age and sex)	1.4 (16.8)	Yes		RMSSD, pNN50
	HC (36)	12.11 (4.49)	18.99	18.99 (2.89)					TP, LF, HF, LF/HF
Coruzzi et al [6]	UC (26)	46 (11)	50	23.8 (2.6)	Yes	11	Yes	20-minutes FP	RR interval
2007, Italy	CD (26)	44 (13)	46	22.9 (2.6)	(Age, sex, and BMI)	9	Yes	Rest supine	RMSSD, pNN50
	HC (23)	45 (13)	48	23.6 (1.8)					LF, HF, LF/HF
Engel et al [12]	CD (30)	33.2 (11.29)	53.3	21.78 (4.65)	Yes	12.2	No	13-minutes ECG	SDNN, RMSSD
2015, Israel	HC (30)	32.7 (11.49)	50	23.1 (3.32)	(Age and sex)			Seat-siren-standing	LF, HF, LF/HF
Furlan et al [19]	UC (23)	42 (3)	34.8	NA	No	5.6	No	15-minutes ECG	TP, LF, HF, LF/HF
2006, Italy	HC (20)	38 (3)	40	NA				Rest recumbent	
Ganguli et al [4]	UC (15)	47.5 (18.5)	25	NA	Yes	11.08	No	20-min ECG	TP, LF, HF, LF/HF
2007, Canada	HC (18)	48.6 (19.6)	NA	NA	(Age and sex)			Rest supine	
Gunterberg et al. [20]	UC (51)	36 (13)	39.2	23 (3)	No	0.3	Yes	24-h ours Holter ECG	RMSSD
2016, Sweden	HC (34)	35 (11)	52.9	24 (3)		(3–4)			LF/HF
Maule [21]	UC (11)	33 (27–55)	36.4	NA	Yes	11	No	30-minutes FP	RR interval
2007, Italy	HC (17)	NA (25–60)	NA	NA	(Age and sex)			Rest supine	TP, LF†, HF†, LF/HF
Rubio et al [22]	CD (9)	43 (25–58)	50	23 (3)*	Yes	15.3	Yes	10-minutes ECG	RMSSD
2016, France	HC (8)	37 (24–58)	69.7	25 (5.7)*	(Age)				TP, LF, HF
Sharma et al [5]	UC (62)	35 (11)	30.8	21.93 (4.24)	No	6.0 (72)	Yes	5-minutes ECG	RR interval,
2009, India	CD (56)	31 (8)	50	22.31 (6.85)		5.0 (60)	Yes	Rest supine	SDNN, RMSSD
	HC (58)	35 (13)	31.03	22.45 (3.82)					TP, LF, HF, LF/HF
Zawadka-Kunikowska et al [11]	CD (30)	30.8 (7.4)	66.7	23.2 (3.8)	Yes	8.6	Yes	10-min utes FP	TP, LF†, HF†, LF/HF
2018, Poland	HC (29)	32.5 (6.2)	86.2	25 (4)	(Age)			Rest supine	

* Calculated SD = standard error× $\sqrt{\text{sample size}}$.

† Normalized value.

BMI = body mass index, CD = Crohn's disease, ECG = electrocardiography, LF = low frequency, HRV = heart rate variability, HC = healthy controls, HF = high frequency, ms = millisecond, N = number, NA = no available, NN = RR intervals, mon = month, pNN50 = percentage of RR intervals with more than 50 milliseconds variation, RMSSD = square root of mean squared differences of successive RR intervals, SDNN = standard deviation of RR intervals, TP = total power, UC = ulcerative colitis.

analysis was performed for the frequency-domain indices. IBD was significantly associated with a decrease in TP (SMD = −0.83, 95% CI = −1.44, −0.21, I^2 = 89.8%, Fig. 2A). Both UC and CD were related to decreases in TP, but the differences were not significant (UC; SMD = −0.71, 95% CI = −1.58, 0.16, I^2 = 90.6%; CD, SMD = −0.97, 95% CI = −2.01, 0.06, I^2 = 91.7%). IBD was associated with a decrease in LF, but the difference was not significant (SMD = −0.41, 95% CI = −0.95, 0.13, I^2 = 90.6%, Fig. 2B). Both UC and CD were related to decreases in LF, but the differences were not significant (UC, SMD = −0.26, 95% CI = −1.12, 0.06, I^2 = 92.1%; CD, SMD = −0.55, 95% CI = −1.31, 0.21, I^2 = 90.7%). IBD was significantly associated with a decrease in HF (SMD = −0.79, 95% CI = −1.20, −0.38, I^2 = 83.6%, Fig. 2C). UC was significantly correlated with a decrease in HF (SMD = −0.99, CI = −1.53, −0.46, I^2 = 79.0%), while CD was related to a decrease in HF but the difference was not significant (SMD = −0.58, CI = −1.22, 0.06, I^2 = 87.0). IBD was significantly associated with an increase in the LF/HF ratio (SMD = 0.48, 95% CI = 0.14, 0.83, I^2 = 80.0%, Fig. 2D). UC was significantly correlated with an increase in the LF/HF ratio (SMD = 0.59, CI = 0.05, 1.13, I^2 = 84.7%), while CD was related to an increase in the LF/HF ratio but the difference was not significant (SMD = 0.35, CI = −0.09, 0.79, I^2 = 73.3%).

3.3. Time-domain indices of HRV in patients with IBD

Forest plots of the effect sizes of time-domain indices of HRV with respect to IBD are shown in Fig. 3. A separate meta-analysis was performed for the time-domain indices. IBD was significantly associated with a decrease in the RR interval (SMD = −0.66, 95% CI = −1.04, −0.27, I^2 = 72.7%, Fig. 3A). Both UC and CD were significantly correlated with reduced RR interval (UC, SMD = −0.56, 95% CI = −1.12, −0.01, I^2 = 75.0%; CD, SMD = −0.76, 95% CI = −1.41, −0.10, I^2 = 78.9%). IBD was significantly associated with a decrease in the SDNN (SMD = −1.00, 95% CI = −1.73, −0.27, I^2 = 90.7%, Fig. 3B). Both CD and UC were related to a decrease in the SDNN, but the differences were not significant (UC, SMD = −1.30, 95% CI = −2.64, 0.04, I^2 = 93.0%; CD, SMD = −0.79, 95% CI = −1.79, 0.21, I^2 = 91.5%). IBD was significantly associated with a decrease in the pNN50 (SMD = −0.82, 95% CI = −1.33, −0.3, I^2 = 83.9%, Fig. 3C). UC was significantly correlated with a decrease in the pNN50 (SMD = −1.09, CI = −1.90, −0.28, I^2 = 86.4%), while CD correlated with a decrease in the pNN50, but the difference was not significant (SMD = −0.55, CI = −1.19, 0.10, I^2 = 79.0%). IBD was significantly associated with a decrease in the RMSSD (SMD = −0.71, CI = −1.15, −0.26, I^2 = 84.4%, Fig. 3D). CD was significantly correlated with a decrease in the RMSSD (SMD = −0.60, CI = −1.07 −0.12, I^2 = 79.0), while UC was related to a decrease in the RMSSD, but the difference was not significant (SMD = −0.83, CI = −1.69, 0.03, I^2 = 86.4%).

3.4. Publication bias

Figure 4 shows funnel plots with Beggs symmetry test of the association between HRV indices and IBD. A visual inspection of

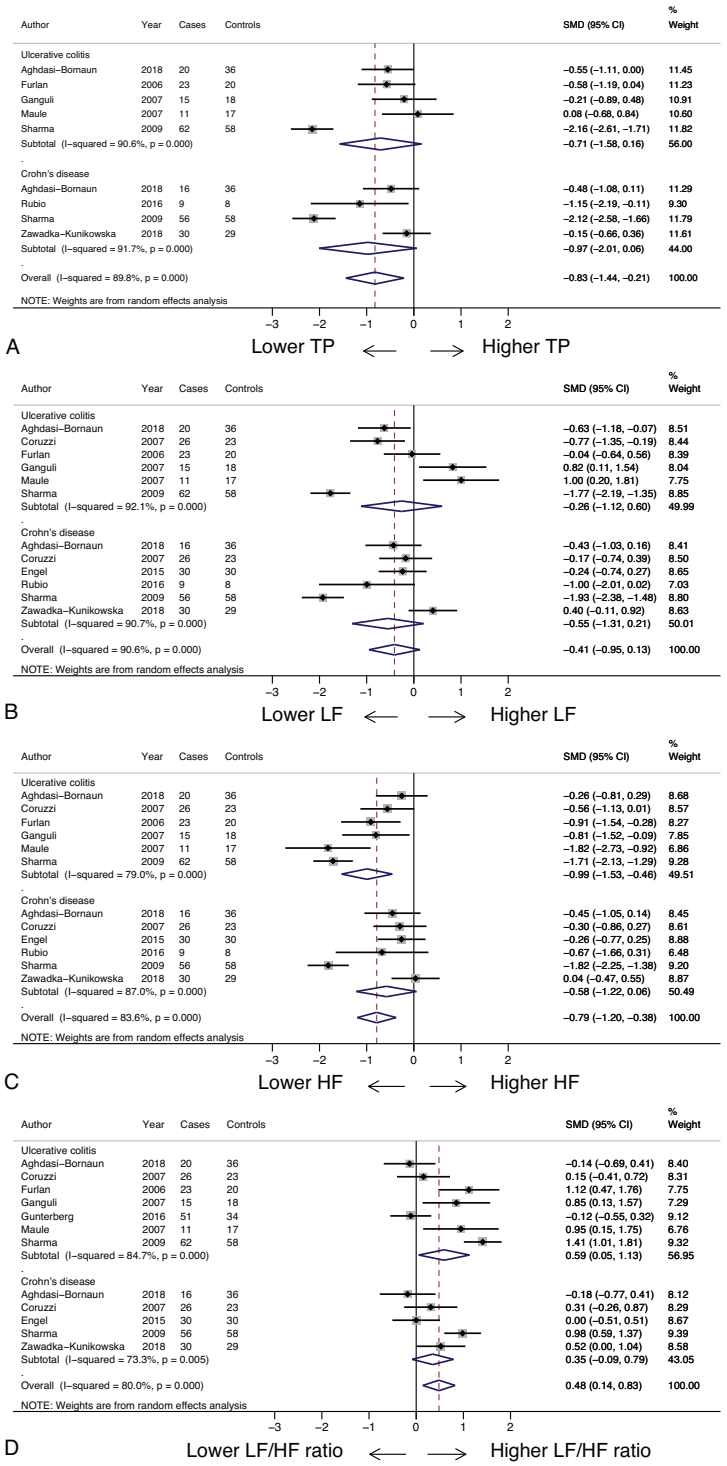

Figure 2. Forest plots of studies investigating the frequency-domain indices of HRV in healthy controls and patients with IBD. The combined SMDs and 95% CIs were separately calculated using random-effects models of TP (A), LF (B), HF (C) and the LF/HF ratio (D). CI = confidence interval, HF = high frequency, HRV = heart rate variability, LF = low frequency, SMD = standardized mean differences.

the funnel plot revealed evidence of effects of a small study size on the association between the RR interval and IBD, which was statistically supported by the results of Begg test ($P = .051$). The other funnel plots showed no evidence of publication bias according to Begg test ($P > .1$). The trim-and-fill analysis results identified 3 imputed studies in the association between the RR interval and IBD, which yielded a symmetrical funnel plot. The random-effects meta-analysis incorporating the hypothetical studies suggested that IBD was significantly associated with a reduced RR interval (SMD = −0.99, CI = −1.39, −0.59).

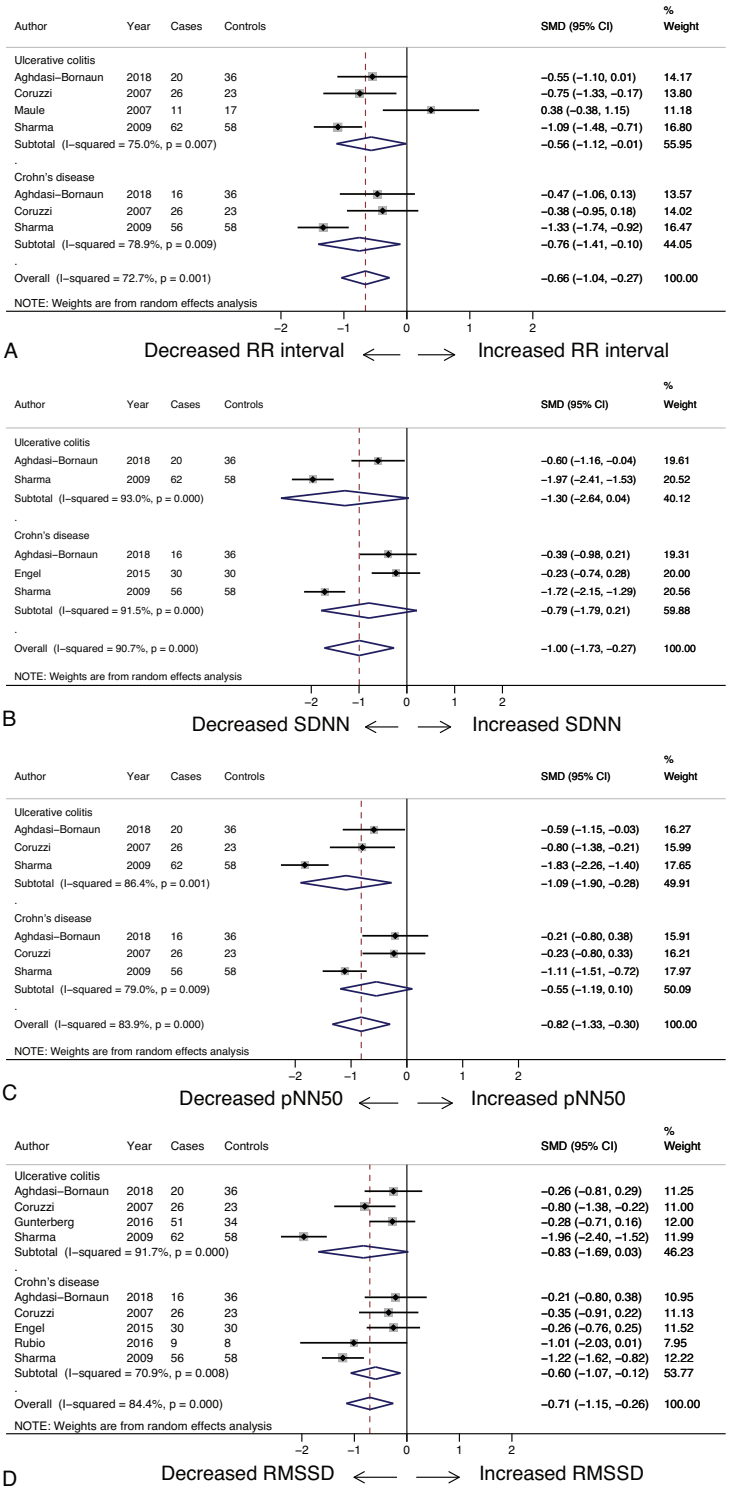

Figure 3. Forest plots of studies investigating the time-domain indices of HRV in healthy controls and patients with IBD. The combined SMDs and 95% CIs were separately calculated using random-effects models of the RR interval (A), SDNN (B), pNN50 (C) and RMSSD (D). pNN50 = percentage of RR intervals with greater than 50 milliseconds of variation, RMSSD = square root of the mean squared differences of successive RR intervals, SMD = standardized mean difference, SDNN = standard deviation of the RR intervals.

3.5. Subgroup analysis

Subgroup analyses using random effects were performed according to whether a matched case-control design was used (yes vs no), 24-hours HRV recordings were present (yes vs no) and all patients were in remission from disease (yes vs no). Subgroup analysis was performed separately for each HRV index.

Supplementary Figure 1, http://links.lww.com/MD/F282 shows the results of the subgroup analysis of the frequency-domain

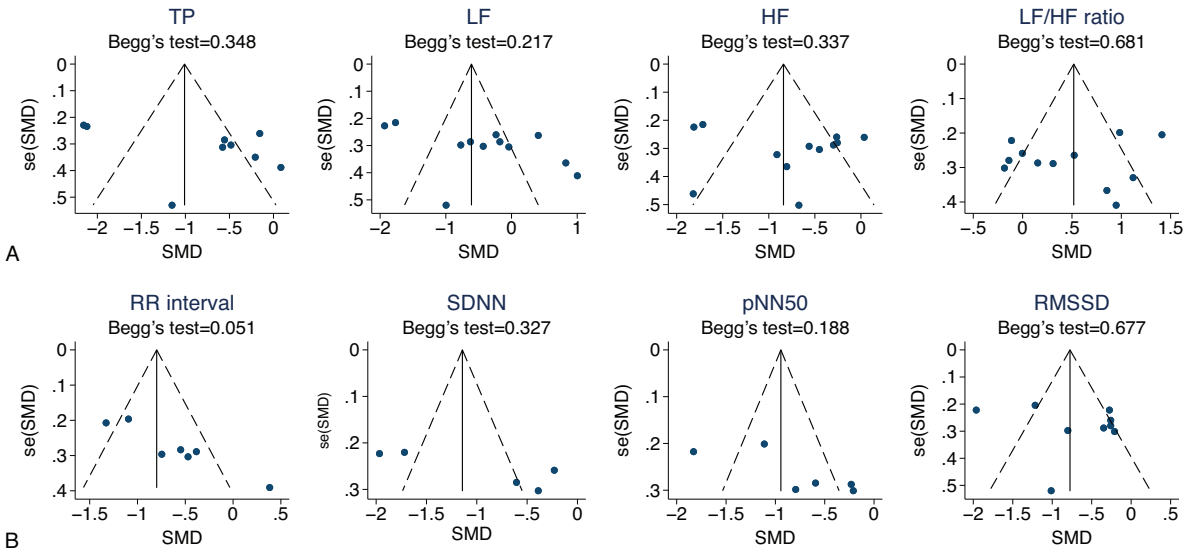

Figure 4. Begg's Funnel plots with Begg test of the meta-analysis of the HRV indices and IBD. Plots of the frequency-domain HRV indices (A) and time-domain HRV indices (B) are shown. LF = low frequency, HF = high frequency, LF/HF = low frequency to high frequency ratio, HRV = heart rate variability, pNN50 = percentage of RR intervals with greater than 50 milliseconds of variation, RMSSD = square root of the mean squared differences of successive RR intervals, SDNN = standard deviation of the RR intervals, se = standard error, SMD = standardized mean difference.

indices of HRV stratified by the matched case-control design (yes vs no). The SMDs (95% CIs) between the patients and the controls were attenuated in the matched case-control design (yes) subgroup compared to the matched case-control design (no) subgroup, and the differences were significant (TP, −0.35 [−0.61, −0.09] vs −1.64 [−2.55, −0.73]; LF, −0.11 [−0.51, 0.29] vs −1.27 [−2.31, −0.22]; HF, −0.47 [−0.75, −0.19] vs −1.53 [−2.01, −1.06]). An increase in the LF/HF ratio was significantly associated with IBD in the matched case-control design (no) subgroup (SMD = 0.84, 95% CI = 0.16, 1.53) but not associated with IBD in the matched case-control design (yes) subgroup (SMD = 0.26, 95% CI = −0.01, 0.53). In addition, heterogeneity was reduced in the matched case-control design (yes) subgroup compared to the matched case-control design (no) subgroup (TP, 0% vs 89.8%; LF, 73.5% vs 92.8%; HF 45.9% vs 65.4%; LF/HF ratio, 40.6% vs 89.1%).

Supplementary Figure 2, http://links.lww.com/MD/F283 shows the results of the subgroup analysis of the time-domain indices of HRV stratified by the matched case-control design (yes vs no). The SMD (95% CI) between the patients and the controls was attenuated in the matched case-control design (yes) subgroup compared to the matched case-control design (no) subgroup and the differences were significant (RR interval −0.41[−0.73, −0.08] vs −1.20 [−1.48, −0.93]; SDNN −0.39 [−0.71, −0.08] vs −1.84 [−2.15, −1.54]; pNN50, −0.46 [−0.74, −0.17] vs −1.47 [−2.17, −0.77]; RMSSD, −0.40 [−0.64, −0.16] vs −1.15 [−2.08, −0.22]). In addition, no evidence of heterogeneity was observed for any index among the matched case-control design (yes) subgroup (*P* for heterogeneity >.1)

In the analysis stratified by 24-hours recording (yes vs no) for frequency domain indices of HRV, the differences between the case and control groups were inconsistent across the indices of HRV (Supplementary Fig. 3, http://links.lww.com/MD/F284). The inverse association between TP and IBD was attenuated in 24-hours recording (yes) subgroup (SMD = −0.52, 95% CI = −0.93, −0.11) compared to 24-hours recording (no) subgroup (SMD = −0.88, 95% CI = −1.35, −0.40). The inverse association between LF and IBD was significant in 24-hours recording (yes) subgroup (SMD = −0.53, 95% CI = −0.94, −0.13) but not in 24-hours recording (no) subgroup (SMD = −0.38, 95% CI = −1.04, 0.27). Conversely, the inverse association between HF and IBD was significant in 24-hours recording (no) subgroup (SMD = −0.88, 95% CI = −1.35, −0.40) but not in 24-hours recording (yes) subgroup (SMD = −0.35, 95% CI = −0.75, 0.06). Additionally, an increase in the LF/HF ratio was significantly associated with IBD in the 24-hours recording (no) subgroup (SMD = 0.70, 95% CI = 0.36, 1.05), but was not associated with IBD in 24-hours recording (yes) subgroup (SMD = −0.14, 95% CI = −0.43, 0.16). No evidence of heterogeneity was observed among the 24-hours recording (yes) subgroups (*P* for heterogeneity >.1).

Supplementary Figure 4, http://links.lww.com/MD/F285 shows the results of the subgroup analysis of the frequency-domain indices of HRV stratified by all patients in remission (yes vs no). A decrease in TP was significantly associated with IBD in the all in remission (yes) subgroup (SMD = −1.11, 95% CI = −1.89, −0.33) but not associated with IBD in the all in remission (no) subgroup (SMD = −0.28 95% CI = −0.67, 0.11). A decrease in LF was significantly associated with IBD in the all in remission (yes) subgroup (SMD = −0.79, 95% CI = −1.41, −0.17), while an increase in LF was associated with IBD in the all in remission (no) subgroup, but the differences were not significant (SMD = 0.33, 95% CI = −0.26, 0.93). The inverse association between HF and IBD was significant in both the all in remission (yes) subgroup (SMD = −0.73, 95% CI = −1.28, −0.18) and in the all in remission (no) subgroup (SMD = −0.88, 95% CI = −1.46, −0.29). An increase in the LF/HF ratio was significantly associated with IBD in the all in remission (no) subgroup (SMD = 0.69, 95% CI = 0.12, 1.26), but not associated with IBD in the all in remission (yes) subgroup (SMD = 0.39, 95% CI = −0.06, 0.83). Evidence of heterogeneity was observed in the frequency-domain indices, except for TP, between the all in remission (yes vs no) subgroups (*P* for heterogeneity <0.1).

Table 2

Sensitivity Analysis of Studies Investigating the HRV indices between Patients with IBD and Healthy Controls.

HRV indices	N	SMD (95% CI)	I^2	Studies omitted
Ulcerative colitis				
Total power	4 [4,7,19,21]	−0.37 (−0.69, −0.05)	0%	Sharma et al [5]
pNN50	2 [6,7]	−0.69 (−1.09, −0.29)	0%	Sharma et al. [5]
RR interval	3 [5–7]	−0.85 (−1.19, −0.52)	27.5%	Maule et al [21]
RMSSD	3 [6,7,20]	−0.41 (−0.73, −0.09)	15.8%	Sharma et al [5]
Crohn's disease				
High frequency	5 [6,7,11,12,22]	−0.26 (−0.52, 0.00)	0%	Sharma et al [5]
RR interval	2 [6,7]	−0.42 (−0.84, −0.01)	0%	Sharma et al [5]
RMSSD	4 [6,7,12,22]	−0.34 (−0.64, −0.03)	0%	Sharma et al [5]

HRV = heart rate variability, IBD = inflammatory bowel disease, N = number of studies, pNN50 = percentage of RR intervals with greater than 50 milliseconds of variation, RMSSD = square root of the mean squared differences of successive RR intervals, SMD = standardized mean difference.

3.6. Sensitivity and meta-regression analyses

We performed separate sensitivity analyses for UC and CD by omitting one study at a time and calculating the combined SMDs for the remaining studies to exclude the studies with a high risk of bias (Table 2). After we excluded the single study by Sharma et al,[5] low heterogeneity was observed in TP ($I^2=0\%$), the pNN50 ($I^2=0\%$) and the RMSSD ($I^2=15.8\%$) in the patients with UC and in HF ($I^2=0\%$), the RR interval ($I^2=0\%$) and the RMSSD ($I^2=0\%$) in the patients with CD. The SMDs (95% CI) for TP, the pNN50 and the RMSSD in UC patients were −0.37 (−0.69, −0.05), −0.69 (−1.09, −0.29) and −0.41 (−0.73, −0.09), respectively. The SMDs (95% CI) for HF, the RR interval and the RMSSD in CD patients were −0.26 (−0.52, 0.00), −0.42 (−0.84, −0.01), and −0.34 (−0.64, −0.03), respectively.

In addition, after we excluded the single study by Maule et al,[21] moderate heterogeneity was observed in the RR interval ($I^2=27.5\%$) in patients with UC and the SMD (95% CI) was −0.85 (−1.19, −0.52). A random-effects meta-regression was performed for important covariates such as the mean age, percentage of female patients, BMI and disease duration. No factor contributed to heterogeneity in the analysis of HRV and IBD ($P>.05$, Supplementary Figure 5, http://links.lww.com/MD/F286).

4. Discussion

As shown in the present study, patients with IBD have a lower TP, lower HF, and higher LF/HF ratio in terms of the frequency-domain indices of HRV and a lower RR interval, lower SDNN, lower pNN50 and lower RMSSD in terms of the time-domain indices of HRV. The disease-specific analyses produced results similar to the main analyses. Large effect sizes of the association with IBD were observed in the pNN50 for parasympathetic activity as well as TP, the RR interval and the SDNN for comprehensive ANS activity. The effect size of the RMSSD and HF, markers of parasympathetic activity was substantially larger than the effect size of LF.

Parasympathetic nerve activity may be decreased in response to a stressor by a reduction in the efferent vagal tone.[23] Stress alters physiological gastrointestinal functions, including those related to motility, secretion, visceral perception, intestinal permeability, the mucosal regeneration capacity and mucosal blood flow.[24] The effect of stress on IBD might be mediated by the ANS and hypothalamic pituitary adrenal axis interactions. These stress-mediated pathways link gastrointestinal integrity and the central nervous system in response to a variety of physiological and psychological stimuli.[25] Psychological stress is involved in the pathophysiology of organic diseases of the gastrointestinal tract such as CD and UC.[26] Furthermore, a longitudinal study demonstrated that a bidirectional association between anxiety and disease activity exists in CD or UC patients.[27] Uncoupling between the ANS and the hypothalamic pituitary adrenal axis has been reported in IBD patients in whom the serum cortisol concentration did not correlate with the plasma neuropeptide Y.[28,29] This uncoupling is induced by stress, which cause an imbalance between the prefrontal cortex and the amygdala in the central nervous system.[30] An inverse association between HRV and IBD may reflect dysregulation of negative feedback by the prefrontal cortex and amygdala in the central nervous system.

Thus, the restoration of the ANS through drugs such as those that act on the cholinergic system, relaxation therapy (meditation, hypnosis, etc.), exercise or vagus nerve stimulation may be important in the treatment of these patients.[31–33] In addition, low-intensity parasympathetic nerve stimulation that activates vagal afferent Aδ fibers reduces visceral pain, and decreased parasympathetic nerve activity may contribute to visceral pain.[34] Furthermore, since the activity of the parasympathetic nerve is associated with anti-inflammatory action, low parasympathetic tone in preterm infants is considered a predictor of necrotizing enterocolitis, which is an exaggerated inflammatory response due to increased proinflammatory cytokines.[35] Taken together, the results of the aforementioned studies may explain how the reduction in parasympathetic nerve activity identified in this study is related to the development of intestinal symptoms in patients with IBD. In this sense, stimulation of the parasympathetic nerve may be helpful for patients with these diseases. Indeed, one study showed that by stimulating the parasympathetic vagus nerve, patients with mild to moderate active CD went into remission of clinical indicators, and the ANS became balanced, similar to that observed in healthy individuals.[36] However, since a large-scale study on the causal relationship between IBD and HRV has not yet been conducted, additional research is required to determine whether decreased vagal tone plays a pathogenic role in the progression and development of IBD or whether IBD causes low parasympathetic nervous system activity.

Interestingly, the subgroup analyses based on disease activity regardless of whether patients were in remission from disease (yes vs no) revealed a significant association between TP, which reflects both the sympathetic and parasympathetic tone, and IBD in the all in remission (yes) subgroup, but not the all in remission (no) subgroup. Although the combined estimates for the association of the LF index reflecting mainly sympathetic tone with IBD was not significant, decreased LF was significantly

associated with IBD in the all in remission (yes) subgroup, while increased LF was related to IBD in the all in remission (no) subgroup, but the association was not significant. However, the association between HF, which only reflects the parasympathetic tone, and IBD was significant, and the effect sizes were similar between the subgroups. One possible explanation is that ANS dysfunction in patients with IBD is probably mediated by the modulation of inflammation by the sympathetic nervous system. The sympathetic nervous system plays a proinflammatory role in the acute phase of these diseases and an anti-inflammatory role in the chronic phase of disease.[37,38] In the early phase of inflammation, norepinephrine from the postganglionic sympathetic nerve induces vasodilatation, chemotaxis and extravasation of immune cells, especially leucocytes. As an inflammatory response process mediated by the innate immune system, macrophages and fibroblasts produce and secrete proinflammatory cytokines, such as tumor necrosis factor (TNF), interleukin (IL)-6 and IL-8, and sympathetic nerve repellent factors, such as semaphorin 3C and semaphorin 3F.[38–40] Then, norepinephrine release is inhibited, and a loss of sympathetic nerves occurs. Sympathetic nerve modulation in relation to inflammation using norepinephrine depends on the immune cell and respective receptor that are activated. With low levels of norepinephrine, norepinephrine binds to the α adrenergic receptor and subsequently stimulates the immune response by increasing the production of Th1 lymphocytes TNF, IL-2, and interferon-γ.[37] At high concentrations of norepinephrine, activation of the β adrenergic receptor expressed in Th2 lymphocytes suppresses inflammation via the canonical pathway.[41] In some animal studies, IBD has been shown to be associated with reduced norepinephrine release, which deprives the inhibition of inflammation by the β adrenergic receptor.[42–44] Furthermore, several studies have described enteric nervous system structural changes including nerve hypertrophy, hyperplasia and axonal degeneration in humans with IBD.[45–47]

In the subgroup analysis by the matched case-control design (yes vs. no), the inverse association between HRV and IBD was attenuated in the subgroup stratified by age-, sex- or BMI-matched controls. Furthermore, it is generally agreed that HRV is influenced by age, sex and obesity.[48] In the subgroup analysis stratified by all remission in disease (yes vs. no), the all in remission (no) from disease subgroup exhibited a stronger positive association between the LF/HF ratio than the all in remission (yes) subgroup, indicating the presence of an apparent sympathovagal imbalance in the acute stage of inflammation. However, disease duration as a surrogate marker of disease chronicity was not a significant factor of the inverse association between HRV and IBD in the meta-regression.

Our study is the first meta-analysis to evaluate the relationship between IBD and HRV, which is a strength of this study, and the results showing an overall reduction in autonomic nerve activity and an imbalance between sympathetic and parasympathetic system activity in IBD patients compared to healthy individuals are valuable. Sensitivity analyses excluded the evident heterogeneity across the studies and showed consistent effects of ANS dysfunction on CD or UC. However, our study has several limitations. First, we evaluated only 10 case-control studies, some of which had relatively small sample sizes. Second, substantial heterogeneity was observed among the studies due to differences in the research methods used and subject characteristics among the studies. According to the meta-regression analysis, age, sex, and BMI were not significant sources of the heterogeneity in our observed results. However, psychosocial factors, such as depression, anxiety, smoking, alcohol, and exercise, may also modulate such heterogeneity, but these factors were not considered in this meta-analysis. Third, HRV was considered a measure of cardiac vagal tone, and thus it may not reflect abdominal vagal tone. Nevertheless, HRV is a widely used method for evaluating the ANS in these patients in clinical practice, independent of risk factors for cardiovascular events.[8]

IBD is strongly associated with an overall decrease in HRV indices, representing general ANS dysfunction. Furthermore, the inverse association with ANS activity was stronger for the parasympathetic nerve than for the sympathetic nerve, which indicated ANS dysfunction in patients with IBD. Therefore, the parasympathetic pathway is likely the underlying mechanism facilitating the consistent inverse relationship between the ANS and IBD. Further research into the effectiveness of interventions aimed to improving pathological features related to the imbalance between sympathetic and parasympathetic activity is needed to determine the causal relationship between IBD and the ANS.

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Author contributions

S.-Y. J drafted the initial manuscript. S.-Y. J had full access to the entire study dataset; was responsible for the study's integrity and the accuracy of the data analysis; designed the study; drafted, reviewed and revised the final manuscript; and contributed to the conception, design, statistical analysis, and data interpretation of this study. S.-Y. J and K.-N. K contributed to the data extraction by evaluating the quality of each study's methodology according to previously established criteria. K.D.H. and Y.Y. contributed to the interpretation of the data and drafted, reviewed and revised the final manuscript. All authors approved the final manuscript for submission.

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