Alterations in Heart Rate Variability Associated With Irritable Bowel Syndrome or Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis

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INTRODUCTION: **Irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) are gastrointestinal pathologies affecting large numbers of the global population and incurring significant healthcare costs. Disruptions in the gut-brain axis occurring in these conditions can lead to increased inflammation, affecting gastrointestinal and autonomic nervous system function. Heart rate variability (HRV) is commonly used to assess the state of the sympathetic and parasympathetic function of the autonomic nervous system, but it remains unclear how HRV measures are associated with gastrointestinal pathologies. Here, we conduct a systematic review of the literature comparing HRV of subjects diagnosed with IBS or IBD to HRV in healthy controls (HC).**

METHODS: **We searched PubMed, Cochrane Library, and CINAHL (EBSCO) for eligible studies up to 2018. We included any study comparing a recognized measure of HRV between a group of patients with either IBS or IBD to a group of matched HC before any intervention. Studies were screened, and data were extracted from included articles using predefined criteria. Random effects meta-analysis was performed for each outcome, with effect size reported as the standardized mean difference.**

RESULTS: **There were significant differences between IBD and HC in time domain HRV and significant decreases in high-frequency power measures were also noted, in both IBS and IBD compared with HC.**

DISCUSSION: **Parasympathetic nervous system activity, represented through high-frequency power, seems to be lower in people with IBS and IBD, but conclusions are limited by the small number of studies that provide usable data, methodological heterogeneity, and high risks of bias in primary study methods and measures.**

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A467

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INTRODUCTION

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder (FGID) consisting of 4 subtypes (constipation, diarrhea, mixed, and unclassified) in the absence of organic or structural etiologies and diagnosed with Rome or Manning criteria (1). Its global prevalence remains elusive because of the methodological heterogeneity, symptom perception, and reporting concerns (2). Its global prevalence rate has been estimated at 11.2% (95% confidence interval [CI], 9.8%–12.8%) and more recently at 8.8% (95% CI, 8.7–8.9%) (2,3). In North America, the prevalence is estimated at 11.8% (95% CI, 7.4–17.2) (3) with direct and indirect annual healthcare costs exceeding 20 billion dollars (4).

Unlike IBS, inflammatory bowel disease (IBD), comprising of Crohn's disease (CD) and ulcerative colitis (UC), is a chronic, potentially fatal illness diagnosed via gastrointestinal imaging and histological findings. Greater than 5 million individuals are affected globally (5,6) and its direct healthcare costs in the United States are estimated at 6.3 billion dollars, with a lack of data on indirect costs (7).

The ability to actively monitor or even predict flares before their occurrence may reduce costs and improve patient outcomes in these conditions. Such monitoring might be achieved through a set of noninvasive electrocardiography parameters, collectively referred to as heart rate variability (HRV), that provides an indirect measure of the autonomic nervous system (ANS) (8–14).

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Excessive sympathetic or parasympathetic activity in the ANS can lead to dysregulation within the gut-brain axis contributing to maladaptive gastrointestinal responses and resulting in symptomatic flares (8–12,14).

Despite suggestions that lowered HRV is associated with pathological processes and mortality, definitive reference ranges constituting normal or healthy HRV values remain unclear (13–15), and there remains a knowledge gap associating HRV values with incidence or severity of gastrointestinal disorders despite several published reviews pertaining to IBS and none assessing IBD studies (16–20). We aim to systematically review the literature comparing HRV of individuals diagnosed with IBS and IBD with HRV in healthy controls (HC) to determine whether these disorders are associated with low HRV.

METHODS

This study was registered through the International Prospective Register of Systematic Reviews (PROSPERO) registration: CRD4201800072.

Eligibility for inclusion

Any study that presented HRV data in both an IBS or IBD group and a healthy group, at a single point in time and before any intervention, was considered eligible for inclusion. No restrictions were placed on age, sex, or weight of participants; setting; or language of publication. HRV data in original studies must be available from continuous recordings collected between 5 minutes and 24 hours in a lying, seated, or ambulatory state. Studies using participants with cardiovascular diseases, central or peripheral nervous system comorbidities, diabetes, renal failure, alcoholism, or on beta-blockers, beta-adrenergic agonists, or calcium channel blockers were excluded because these conditions may influence HRV (14). FGIDs can coexist with other functional disorders such as dyspepsia, functional abdominal pain, or fibromyalgia, and studies in which participants with IBS were not separated from participants with other functional disorders were excluded, unless authors could be contacted for clarification or appropriate subgroup data.

Studies were included if IBS participants were diagnosed by a physician and/or met Manning or Rome I-IV criteria as assessed by study investigators. Participants with IBD had to be diagnosed by a physician or have evidence of IBD via imaging such as colonoscopy. Primary study authors were contacted by email 3 times for any missing or unclear information. If they did not respond after 3 attempts, those studies were excluded. If the same participants seemed to give data in multiple studies assessing HRV, authors were contacted for clarification and failure to respond resulted in earliest dated study used if otherwise eligible.

Search strategy

We searched PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL EBSCO interface), and the Cochrane Database until June 2018. Reference lists of included studies, previous reviews, and meta-analyses were hand searched. ClinicalTrials.gov and the International Clinical Trials Registry Platform Search Portal were searched for ongoing or recently completed trials. PROSPERO was searched for similar ongoing or recently completed systematic reviews. A complete literature search strategy can be seen in Supplemental Digital Content 1 (see http://links.lww.com/CTG/A467).

Study selection, storage, and screening

Authors used Mendeley Desktop and DistillerSR for literature search results and management of screening results. Studies meeting inclusion criteria were entered into Review Manager (RevMan) version 5.3 software to assess studies, create comparison tables, examine and extract data from studies for meta-analysis, and present results in graphs if appropriate (21). The primary investigator (A.S.) screened titles and abstracts with coinvestigator CD, and level 2 screening with D.H. disagreement was settled via consensus between A.S. and D.H.

Data collection/data items

A.S. and D.H. conducted all data extraction after agreement, and data were recorded into a data extraction form and uploaded into RevMan5.3. Data items collected can be seen in Tables 1–3.

Primary outcomes

Primary outcomes consist of the HRV time-domain measurements of standard deviation of the inter-beat-interval of normal sinus beats (SDNN), number of consecutive intervals differing from each other by more than 50 milliseconds (NN50), the NN50 represented as a percentage (pNN50), and the root mean square of successive differences between normal heartbeats (RMSSD) (13).

Secondary outcomes

Secondary outcomes consist of the HRV frequency-domain measurements of high-frequency (HF) band power ranging from 0.15 to 0.4 Hz, low-frequency (LF) band power ranging from 0.04 to 0.15 Hz, and the very low frequency (VLF) band power ranging from 0.003 to 0.04 Hz (22). HF and LF are sometimes expressed as a log-transformed measure (LnHF and LnLF) or as normalized units (HFnu and LFnu). Although these transformed measures are usually intended to represent the same characteristics of the ANS, log-transformed and untransformed data cannot be synthesized together in a meta-analysis (23).

Synthesis of results

Authors followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (24). Owing to the heterogeneity across study methodologies, a random-effects meta-analysis was used to derive pooled standardized mean difference (SMD) with 95% CIs using an inverse variance model (25). SMD expressed as a negative value indicates HC having greater mean values than IBS or IBD groups. The I^2 statistic was used to assess heterogeneity between primary study results. I^2 = 0%–24% is considered low heterogeneity, 25%–49% considered mild heterogeneity, 50%–74% considered high heterogeneity, and $I^2 >$ 75% considered extensive heterogeneity (16,26). We attempted to address high levels of heterogeneity with follow-up subanalyses. Evidence for potential publication bias was investigated visually using funnel plots.

Data for all primary and secondary HRV outcomes were compared with HC only because there was insufficient evidence for a comparison of IBS to IBD. Subanalysis was also performed for studies that used methods intended to match participants on the factors of age, sex, and body mass index (BMI). Pooling of data was based on length of HRV recording, separating studies according to short or long recording periods because these

Table 1. Characteristics of studies comparing irritable bowel syndrome with healthy controls

Study	Location	Design	Sample size (disease/control)	No. of men (disease/control)	Rome criteria	IBS type	Position and length of recordings	Time of HRV recording	Frequency ranges (Hz)	HRV software
Heitkemper et al. (31)	USA	Cross-sectional	25/15	0/0	I	IBS-C/D/M	Seated/standing/ supine, 24 hr	Unclear	HF: 0.15–0.40; MF: 0.04–015; LF: 0.016–0.04	SpaceLabs Systems
Orr et al. (32)	USA	Cross-sectional	15/15	2/2	I	IBS-C/M	Supine, 15 min	10:00 PM	HF:0.15–0.50; LF: 0.05–0.15	MATLAB
Elsenbruch et al. (33)	USA	Cross-sectional	24/20	0/0	I	IBS-C/D/M	Supine, 30 min	12:00 PM to 6:00 PM	HF: 0.15–0.40; LF: 0.014–0.15	MATLAB
Heitkemper et al. (34)	USA	Cohort	103/49	0/0	I	IBS-C/D/M	Seated/standing/ supine, 24 hr	Unclear	HF: 0.15–0.40; LF: 0.016–0.15	SpaceLabs Systems
Thompson et al. (35)	USA	Cross-sectional	16/21	0/0	I	IBS-C/D/M	Supine, 15 min	Unclear	HF: 0.15–0.50; LF: 0.04–0.15	MATLAB
Robert et al. (36)	USA	Cross-sectional	44/21	0/0	II	IBS-C/D/M	Supine, 15 min	Unclear	HF: 0.15–0.50; LF: 0.04–0.15	MATLAB
Waring et al. (37)	Scotland	Cross-sectional	30/30	0/0	II	IBS-C/D/M	Supine/standing, 5 min	Unclear	HF: 0.15–0.50; LF: 0.04–0.15; VLF: <0.04	Chart Software
Cain et al. (38)	USA	Cross-sectional	165/50	0/0	I/II	IBS-C/D/M	Seated/standing/ supine, 24 hr	Unclear	HF: 0.15–0.40; LF: 0.04–0.15	Space Labs Systems
Mazur et al. (39)	Poland	Cross-sectional	23/30	N/A	II	IBS-C	Unclear, 30 min	Unclear	HF: 0.15–0.40; LF: 0.04–0.15	Task Force Monitor
Jarrett et al. (40)	USA	Cross-sectional	35/38	0/0	II	IBS-C/D/M	Supine, 5 min	Unclear	HF: 0.15–0.40; LF: 0.04–0.15	Somnologica Software
Pellissier et al. (41)	France	Cross-sectional	27/21	9/8	II	Unclear	Seated, 10 min	8:00 AM to 12:00 AM	HF: 0.15–0.40; LF: 0.04–0.15; VLF: 0.0033–0.04	Heart Rhythm Scanner
Heitkemper et al. (42)	USA	Cross-sectional	40/32	0/0	II	Unclear	Supine, unclear "overnight"	Unclear	HF: 0.15–0.40; LF:0.04–0.15	Unclear
Mazur et al. (43)	Poland	Cross-sectional	30/30	12/11	III	IBS-C	Unclear, 30 min	Unclear	HF: 0.15–0.40; LF: 0.04–0.15	Task Force Monitor
Pellissier et al. (44)	France	Cross-sectional	26/26	7/8	II	IBS-C/D/M	Seated, 10 min	8:00 AM to 10:00 AM	HF: 0.15–0.40; LF: 0.04–0.15; VLF: 0.0033–0.04	Heart Rhythm Scanner
Jarrett et al. (45)	USA	Cohort	54/37	0/0	III	IBS-C/D/M	Seated/standing/ supine 4 hr	2:00 AM to 6:00 AM	HF: 0.15–0.40; LF: 0.04–0.15	Vision Premier Software
Davydov et al. (46)	USA	Cross-sectional	78/27	0/0	III	IBS-C/D/M/U	Seated, 10 min	Unclear	HF: 0.125–0.50; LF: 0.075–0.125	Biopac MP 100
Walker et al. (47)	USA	Cross sectional	63/123	16/57	III	Unclear	Seated, 5 min	Unclear	HF: 0.15–0.40	MATLAB
Fournier et al. (48)	France	Cross-sectional	25/26	7/8	II	IBS-C/D/M	Seated, 10 min	8:00 AM to 10:00 AM	HF: 0.15–0.40	Heart Rhythm Scanner
Polster et al. (49)	Sweden	Cross-sectional	158/39	45/17	III	IBS-C/D/M/U	Seated/standing/ supine 24 –hr	Unclear	HF: 0.15–0.40; LF: 0.04–0.15	Impressario CardioNavigator Plus

Sample size of Pellissier et al. 2010 and 2014 reflect IBS/healthy controls, as this study assessed IBS, inflammatory bowel disease, and healthy controls.
HF, high frequency; HRV, heart rate variability; IBS, irritable bowel syndrome; IBS-C/D/M/U, IBS with constipation predominant, IBS with diarrhea predominant, IBS mixed presentation, IBS with undetermined predominance; LF, low frequency; MF, moderate frequency; VLF, very low frequency.

measures can represent different facets of ANS function (27,28). To obtain adequate data for meta-analysis of our primary outcome of interest, however, short and long RMSSD recordings were combined.

Quality appraisal

A modified Cochrane Collaboration's Risk of Bias in Non-Randomized Studies of Interventions was used to evaluate the risk of bias in selected studies as low, moderate, serious, and critical based on 6 domains (Table 3) (29,30). A modified tool was used because study authors were only interested in the initial HRV results and not the HRV results after an intervention. Remaining relevant domains were bias because of confounding, selection bias, classification of exposure, missing data, measurement of outcomes, and selective outcome reporting bias.

The overall risk of bias was graded as follows (29):

Low = Low risk of bias in all 6 domains
Moderate = Mostly low risk of bias or unclear risk of bias.
Serious = At least one domain at serious risk.
Critical = At least one domain at critical risk
No Information = No information on which to base a judgment about the risk of bias.

RESULTS

A total of 154 studies were identified; 27 were eligible for inclusion in the systematic review; an additional 5 were accessed through evaluation of references from included studies, of which one met the inclusion criteria. Eighteen of the 28 included studies provided suitable data for meta-analysis (Figure 1). No studies met inclusion criteria in ClinicalTrials.gov, and no relevant reviews were identified through PROSPERO.

Study characteristics

Study characteristics can be seen in Tables 1 and 2. Nineteen studies compared IBS with HC (31–49), 9 compared IBD with HC (50–58), and 2 compared HRV across all 3 comparators (41,44).

Specific to IBS studies, one combined IBS with diarrhea predominant (IBS-D) and IBS mixed presentation (IBS-M) into one group (32), one combined IBS with constipation predominant (IBS-C) and IBS-M into one group (45), 2 recruited only IBS-C participants (39,43), and 3 did not report subtype (41,42,47); although one reported data on a combined group of FGIDs including IBS and functional abdominal pain (47), data for IBS-only participants were available after contacting the primary author. In addition, because 2 studies (44,48) used the same participants in successive appraisals, we excluded data from the latter study in meta-analysis; both, however, were included in the narrative review.

Specific to IBD studies, 3 compared UC with HC (51,52,58), 2 compared CD only with HC (44,56), and 4 presented data on both subgroups (41,53–55).

Diagnosis. All participants with IBS were diagnosed using the Rome criteria. Five studies used Rome I (31–35), 8 used Rome II (36,39–42,44,48), 5 used Rome III (43,45–47,49), none used Rome IV, one used both Rome I and II (38), and one used both Manning and Rome II criteria(39). Eight studies (35,36,41,44,46–49) used physician diagnosis in addition to Rome criteria during enrolment; the remainder relied on a previous medical diagnosis and confirmed with Rome criteria in a study interview. All IBD participants were recruited with an already established diagnosis of CD or UC via imaging.

Short duration laboratory collection of HRV. Studies conducted HRV in a seated (41,44,46–48,56), supine (32,33,35,36,40,51–53,55), and both a supine and standing position (37,54,57). Two studies were unclear in which position short recordings were conducted (39,43).

Long duration collection of HRV. Six studies conducted 24-hour HRV recordings (31,34,38,49,50,58) and one conducted 12-hour recordings (45); 4 were conducted while sleeping (32,35,36,45), of which 3 separated data into sleep stages (32,35,40).

Specific HRV software was unclear in 4 studies (42,51–53); MATLAB software was the most commonly reported (n = 5) (32,33,35,36,47). Frequency ranges were not consistent across all studies, without sufficient reasoning for deviations from the 1996 European Task Force guidelines (22). Studies not using recommended reference ranges were still included for review and meta-analysis, provided that the reference ranges used seemed qualitatively similar to the guideline ranges. HF was recorded in all studies, LF was recorded in 26 (96.8%) (31–47,50–58), and VLF was recorded in 6 (21.4%) (37,41,44,52,56,57). HF was mostly calculated over the frequency range of 0.15–0.40 Hz (n = 18) (31,33,34,38–45,47–50,56–58); LF was usually calculated over 0.04–0.15 Hz (n = 15) (35–45,49,55–57); VLF was most commonly calculated over 0.0033–0.04 Hz (n = 3) (41,44,57).

Data presented as medium frequency represent LF data and low frequency represent VLF in meta-analysis for Heitkemper 1998 (31) because those respective ranges are consistent with the task force guidelines.

Participant characteristics

A total of n = 2,314 participants across 28 studies were included in the review (n = 1,447 participants across 18 studies were able to be included in meta-analysis.) The review sample contained a total of n = 956 IBS, n = 438 IBD, and n = 895 HC participants. 27.3% (n = 628) of study participants were men, and the mean ages of HC, IBS, and IBD participants were 31.6, 33.3, and 37.9 years, respectively. Mean BMI of participants was 23.7, 24.3, and 22.5 for HC, IBS, and IB, respectively. Baseline demographics according to groups were not reported in several studies (31,40–42,50–52,54,57).

Outcome characteristics

Of the primary outcomes of interest, SDNN (34,42,49,50,55,56), the natural log of SDNN (42), RMSSD (34,42,48–50,53,55,56,58), and pNN50 (34,49,50,53,55) were presented. NN50 was not presented in any study. One study used HRV methods before the 1996 guidelines and was not included in the meta-analysis (54).

HF and LF outcomes were presented in absolute units (31,34,38,39,43,45–47,51,53,55–57), normalized units (37,39,41,43,44,48,49,51,52,55), natural log form (31,34,39,40,42,46,50), and as frequency percentages (32,35,54). VLF was presented in absolute units (31,37,43,44,56) and as the natural log only (31,41). Three studies only represented data graphically, and no adequate response was provided from authors, when contacted to request numerical values (32,33,35). One study did not include adequate

Table 2. Characteristics of studies comparing inflammatory bowel disease with healthy controls

Study	Location	Design	Sample size (disease/control)	Men (n) (disease/control)	IBD types	Position and length of recordings	Time of HRV recording	Frequency range (Hz)	HRV software
Mouzas et al. (50)	Greece	Cross-sectional	27/26	21/20	CD and UC	Seated/standing/supine, 24 hr	Unclear	HF: 0.15–0.40; LF: 0.06–0.15	Marquette laser Holter scanner software 5.8
Furlan et al. (51)	Italy	Cross-sectional	23/20	15/12	UC	Supine, 15 min	Unclear	HF: 0.25; LF: 0.10	Unclear
Maule et al. (52)	Italy	Cross-sectional	11/17	7/NA	UC	Supine, 30 min	Unclear	HF: 0.25; LF: 0.10; VLF: <0.03	Unclear
Coruzzi et al. (53)	Italy	Cross-sectional	52/23	29/12	CD and UC	Supine, 5 min	Unclear	HF: 0.14–0.50; LF: 0.04–0.14	Unclear
Ganguli et al. (54)	Canada	Cross-sectional	28/28	19/18	CD and UC	Supine/standing, 20 min/10 min	8:00 AM to 11:00 AM	HF: 0.15–0.50; LF: 0.02–0.15	Windaq/EX
Sharma et al. (55)	India	Cross-sectional	118/58	74/40	CD and UC	Supine, 15 min	10:00 AM to 1:00 PM	HF: 0.15–0.50; LF: 0.04–0.15	Nevrokard version 6.4.0
Pellissier et al. (41)	France	Cross-sectional	48/21	17/8	CD and UC	Seated, 10 min	8:00 AM to 12:00 AM	HF: 0.15–0.40; LF: 0.04–0.15	Heart Rhythm Scanner
Pellissier et al. (44)	France	Cross-sectional	21/26	9/8	CD	Seated, 10 min	8:00 AM to 10:00 AM	HF: 0.15–0.40; LF: 0.04–0.15; VLF: 0.0033–0.04	Heart Rhythm Scanner
Engel et al. (56)	Israel	Cross-sectional	30/30	14/15	CD	Seated, 5 min	Unclear	HF: 0.15–0.40; LF: 0.04–0.15; VLF: <0.04	BioGraph Infiniti
Jelenova et al. (57)	Czech Republic	Cross-sectional	29/35	15/27	CD and UC	Supine/standing 15 min	Unclear	HF: 0.15–0.40; LF: 0.04–0.15; VLF: 0.0033–0.04	ProComp Infiniti
Gunterberg et al. (58)	Sweden	Cohort	51/34	31/16	UC	Seated/supine/standing 24-hr	Unclear	HF: 0.15–0.40; LF: 0.05–0.15	Impresario Analyzer

CD, Crohn's disease; HF, high frequency; HRV, heart rate variability; LF, low frequency; MF, moderate frequency; UC, ulcerative colitis; VLF, very low frequency.

Table 3. Modified Risk of Bias in Nonrandomized Studies of Interventions table for all studies included in the review

Study	Confounding	Selection	Classification of exposure	Missing data	Measurement of outcomes	Selective outcome reporting	Overall bias
Heitkemper et al. (31)	Serious	Low	Low	Low	Moderate	Moderate	Serious
Orr et al. (32)	Serious	Low	Low	Low	Moderate	Moderate	Serious
Elsenbruch et al. (33)	Low	Low	Low	Low	Moderate	Serious	Serious
Heitkemper et al. (34)	Serious	Low	Low	Low	Moderate	Moderate	Serious
Thompson et al. (35)	Serious	Low	Low	Low	Moderate	Serious	Serious
Robert et al. (36)	Serious	Low	Low	Low	Moderate	Serious	Serious
Waring et al. (37)	Serious	Low	Low	Low	Moderate	Serious	Serious
Cain et al. (38)	Serious	Low	Low	Low	Moderate	Critical	Critical
Mazur et al. (39)	Critical	Low	Low	Low	Moderate	Moderate	Critical
Jarrett et al. (40)	Serious	Low	Low	Moderate	Moderate	Moderate	Serious
Pellisier et al. (41)	Serious	Critical	Low	Moderate	Moderate	Serious	Critical
Heitkemper et al. (42)	Serious	Low	Low	Low	Moderate	Serious	Serious
Mazur et al. (43)	Serious	Low	Low	Low	Moderate	Moderate	Serious
Pellisier et al. (44)	Serious	Low	Low	Low	Moderate	Serious	Serious
Jarrett et al. (45)	Serious	Low	Critical	Low	Moderate	Serious	Critical
Davydov et al. (46)	Serious	Low	Low	Moderate	Moderate	Moderate	Serious
Walker et al. (47)	Serious	Low	Low	Low	Low	Moderate	Serious
Fournier et al. (48)	Serious	Low	Low	Low	Moderate	Low	Serious
Polster et al. (49)	Critical	Low	Low	Low	Low	Moderate	Critical
Mouzas et al. (50)	Serious	Low	Low	Low	Moderate	Serious	Critical
Furlan et al. (51)	Critical	Low	Low	Low	Moderate	Moderate	Critical
Maule et al. (52)	Critical	Low	Low	Low	Moderate	Serious	Critical
Coruzzi et al. (53)	Low	Low	Low	Low	Moderate	Moderate	Moderate
Ganguli et al. (54)	Serious	Low	Low	Low	Moderate	Serious	Serious
Sharma et al. (55)	Serious	Low	Low	Low	Moderate	Moderate	Serious
Engel et al. (56)	Low	Low	Low	Low	Moderate	Moderate	Moderate
Jelenova et al. (57)	Serious	Low	Low	Serious	Moderate	Low	Serious
Gunterberg et al. (58)	Serious	Low	Low	Serious	Moderate	Moderate	Serious

Pellissier et al. 2010 and 2014 included as study authors compared HRV across all 3 subgroups.
CD, Crohn's disease; HF, high frequency; HRV, heart rate variability; LF, low frequency; MF, moderate frequency; UC, ulcerative colitis; VLF, very low frequency.

data regarding IBS-M in their analysis despite comparing results between all 3 IBS subgroups and HC (38).

Meta-analysis

The results of meta-analyses can be seen in Figures 2–5. Comparison of RMSSD between IBD and HC was the only primary outcome with adequate data for meta-analysis, with significantly lower RMSSD in IBD relative to HC (3 studies; pooled SMD = −0.37 [−0.66, −0.07], $P = 0.02$, $I^2 = 0\%$).

Absolute HF (Figure 3) in short recordings remained significantly lower in IBD compared with HC even after subanalysis in adults only (3 studies; pooled SMD = −0.51 [−0.85, −0.17], $P = 0.003$, $I^2 = 16\%$). There was a lack of adequate absolute HF data to investigate CD or UC subgroups, during short or long recordings. HFnu was significantly lower in IBD compared with HC ($P = 0.0002$), and the difference remained significant when analyzing UC only ($P = 0.001$).

Absolute frequency data for short HF recordings (4 studies; pooled SMD = −0.35 [−0.63, −0.08], $P = 0.01$, $I^2 = 37\%$) but not long HF recordings (3 studies; pooled SMD = −0.06 [−0.31, 0.19], $P = 0.64$, $I^2 = 4\%$) were significantly lower in IBS than HC (Figure 4). The results remained significant in IBS-C (3 studies; pooled SMD = −0.55 [−0.86, −0.23], $P = 0.0007$, $I^2 = 0\%$) with a lack of adequate data to investigate IBS-D, IBS-M, or IBS with undetermined predominance subgroups during any recording length.

Publication bias

Only HFnu and LFnu in studies comparing IBS with HC pooled from more than 4 primary studies, and as such funnel plots are

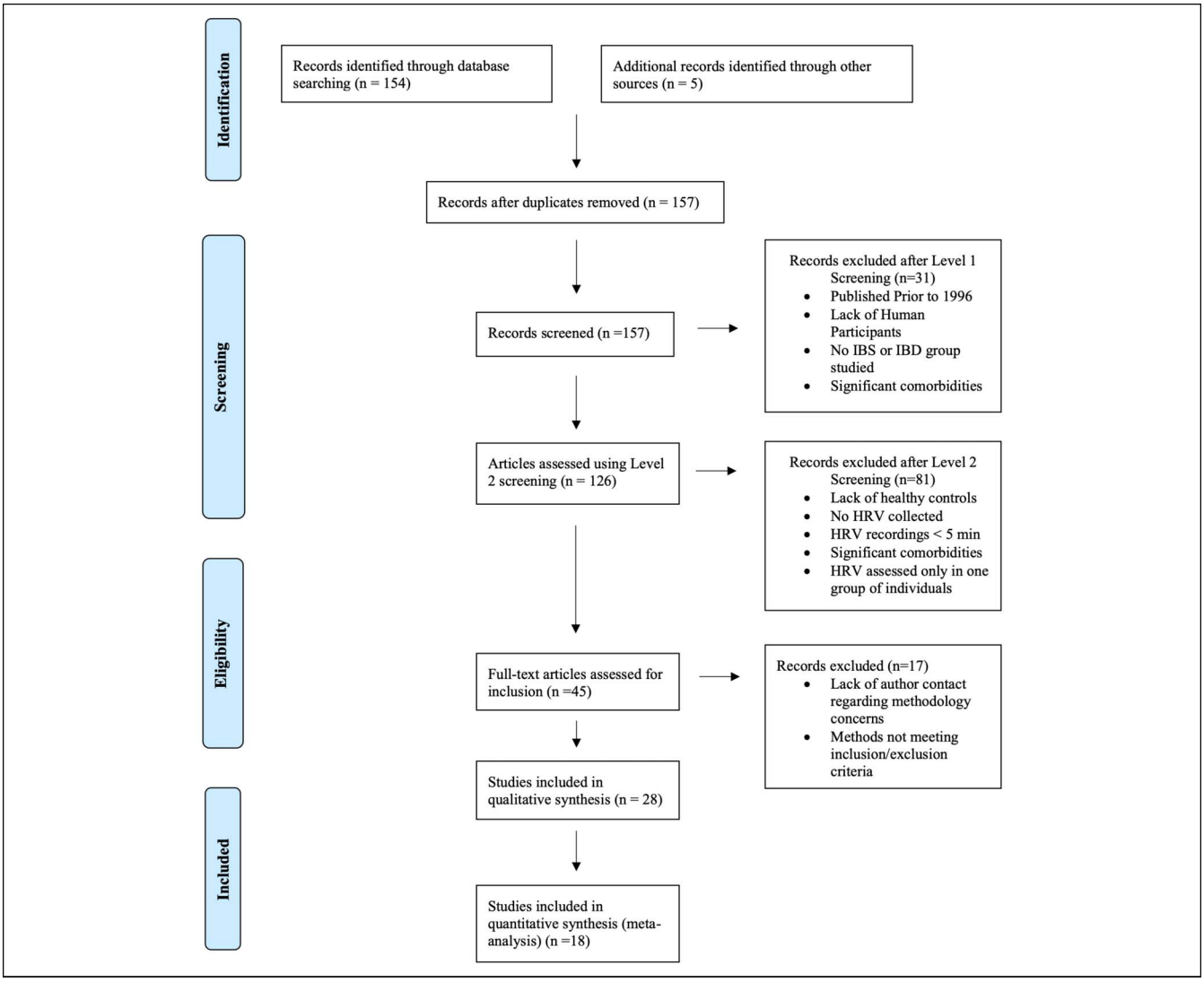

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram. IBD inflammatory bowel disease; IBS, irritable bowel syndrome; HRV, heart rate variability.

not shown; however, visual inspection showed no signs of publication bias for any analysis.

Risk of bias in individual studies

Most studies had a moderate or serious amount of bias (Table 3). Confounding bias was largely because of a lack of matching between disease and healthy groups, or sufficiently controlling for one or more factors including age, sex, BMI, smoking status, and medication use. We did not treat anxiety or depression as confounding comorbidities because these are common in, and could even result from, IBS and IBD. Only 2 studies confirmed the use of blinded HRV assessment (47,49), resulting in substantial potential for bias in measurement of outcomes, and there was substantial variation in *selection of* HRV outcome measures to report. Studies further differed in HRV collection methods and time and length of recordings.

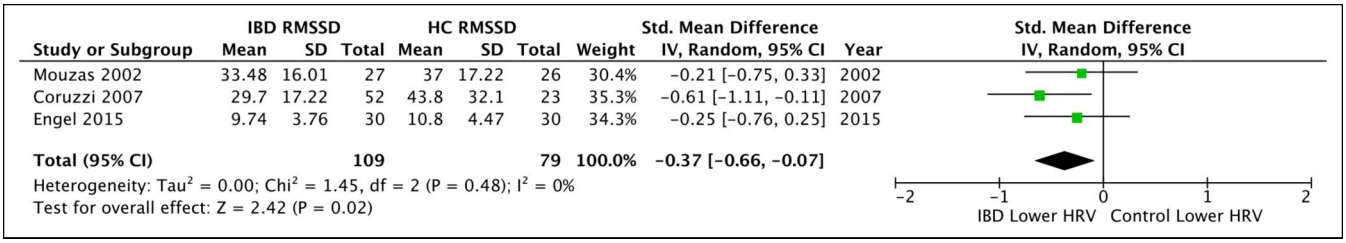

Figure 2. Forest plot for primary outcome comparing inflammatory bowel disease (IBD) with healthy controls (HC). CI, confidence interval; RMSSD, root mean square of successive RR interval differences.

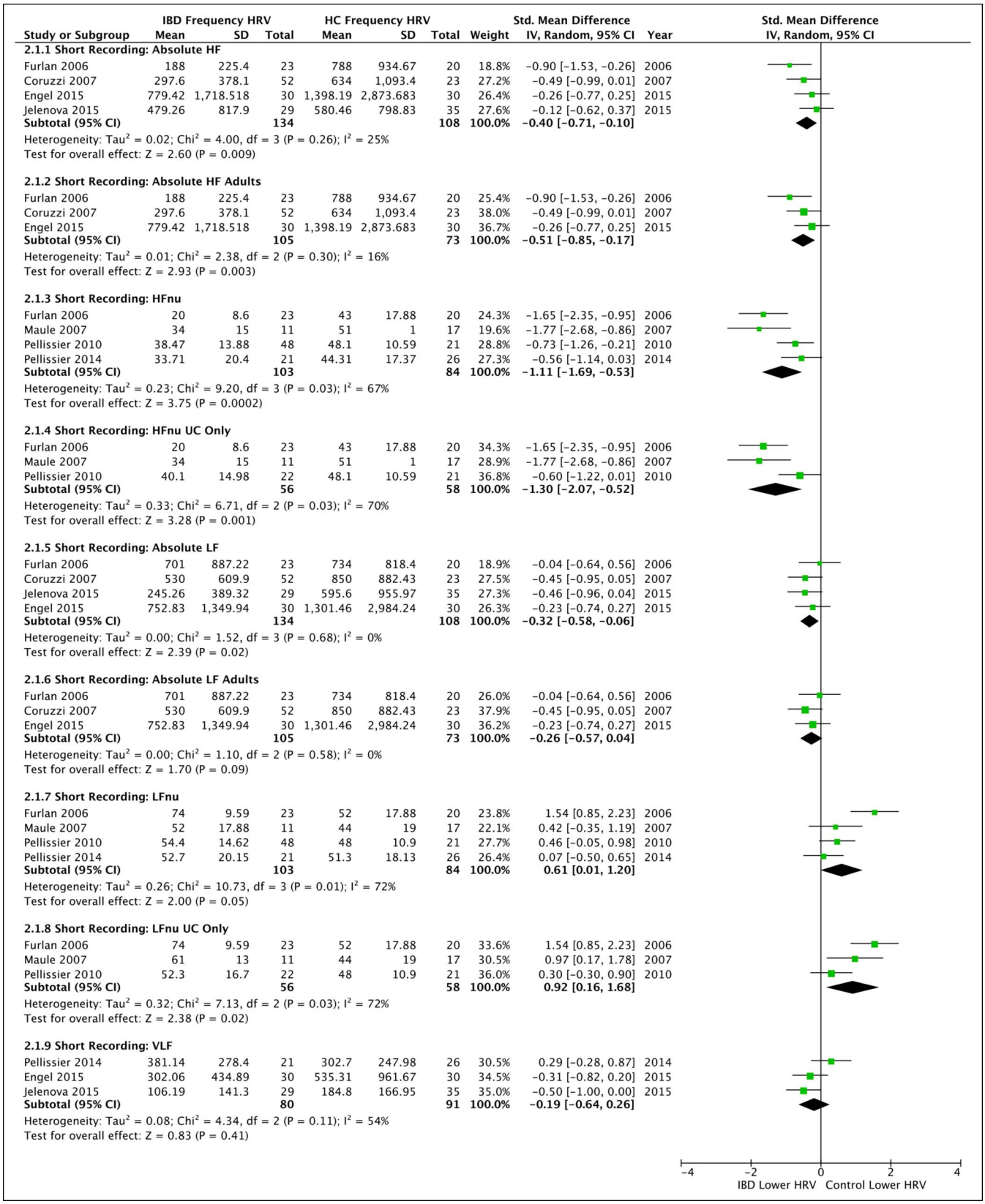

Figure 3. Forest plots for all secondary outcomes available for meta-analysis comparing frequency domain heart rate variability (HRV) between inflammatory bowel disease (IBD) and healthy controls (HC). All studies were conducted over short recording lengths. Subanalyses were only possible for age and ulcerative colitis (UC) where indicated. High-frequency (HF), HF represented in normalized units (HFnu), low frequency (LF), LF represented in normalized units (LFnu), and very low frequency (VLF). CI, confidence interval.

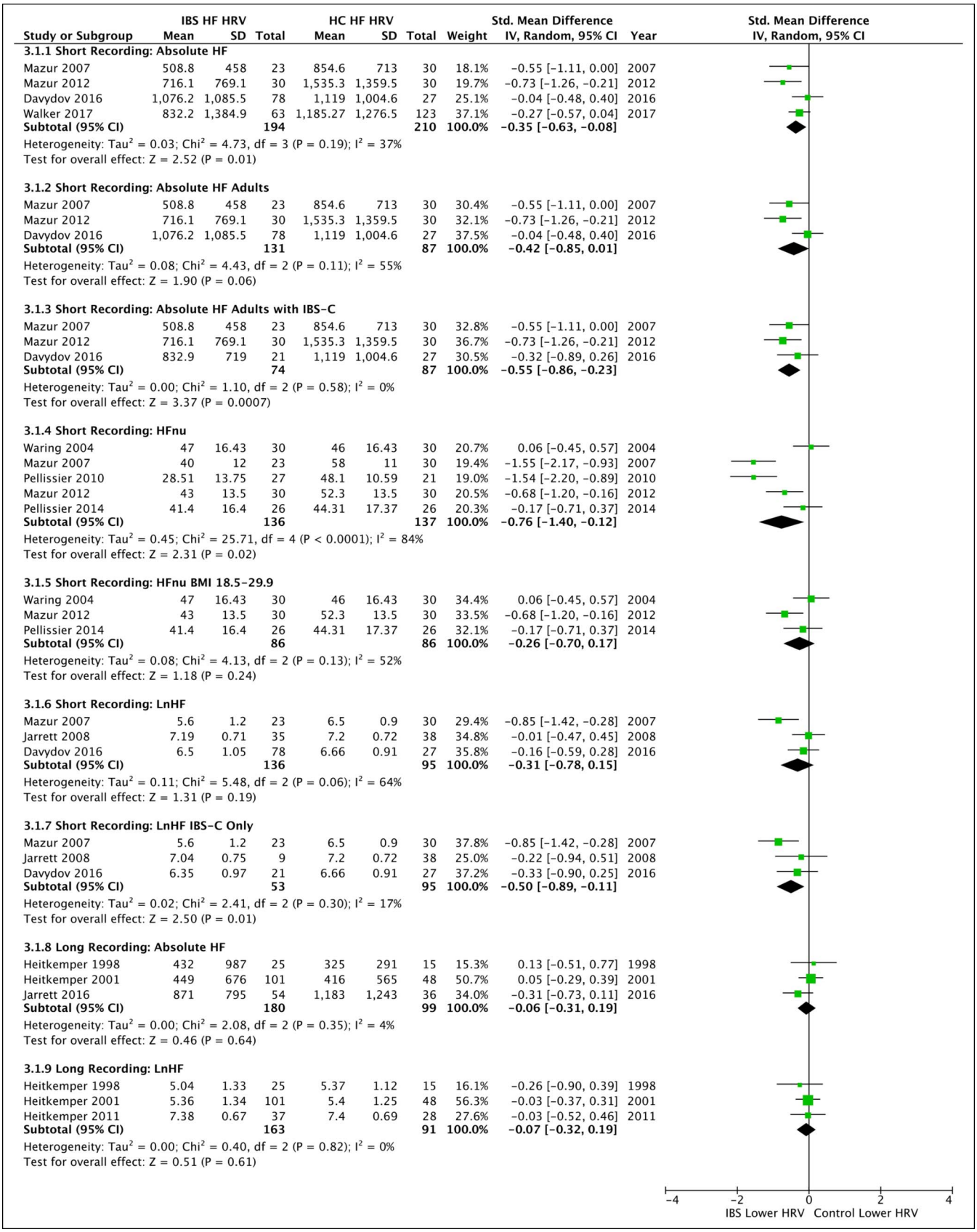

Figure 4. Forest plots for all secondary outcomes available for meta-analysis comparing high-frequency (HF) domain heart rate variability (HRV) between irritable bowel syndrome (IBS) and healthy controls (HC). Studies were separated by short and long duration recordings, with subanalyses for age, IBS subtype, and body mass index (BMI) where indicated. IBS with constipation predominant (IBS-C), HF represented in normalized units (HFnu), HF represented in the natural log (lnHF), low frequency (LF), LF represented in normalized units (LFnu). CI, confidence interval.

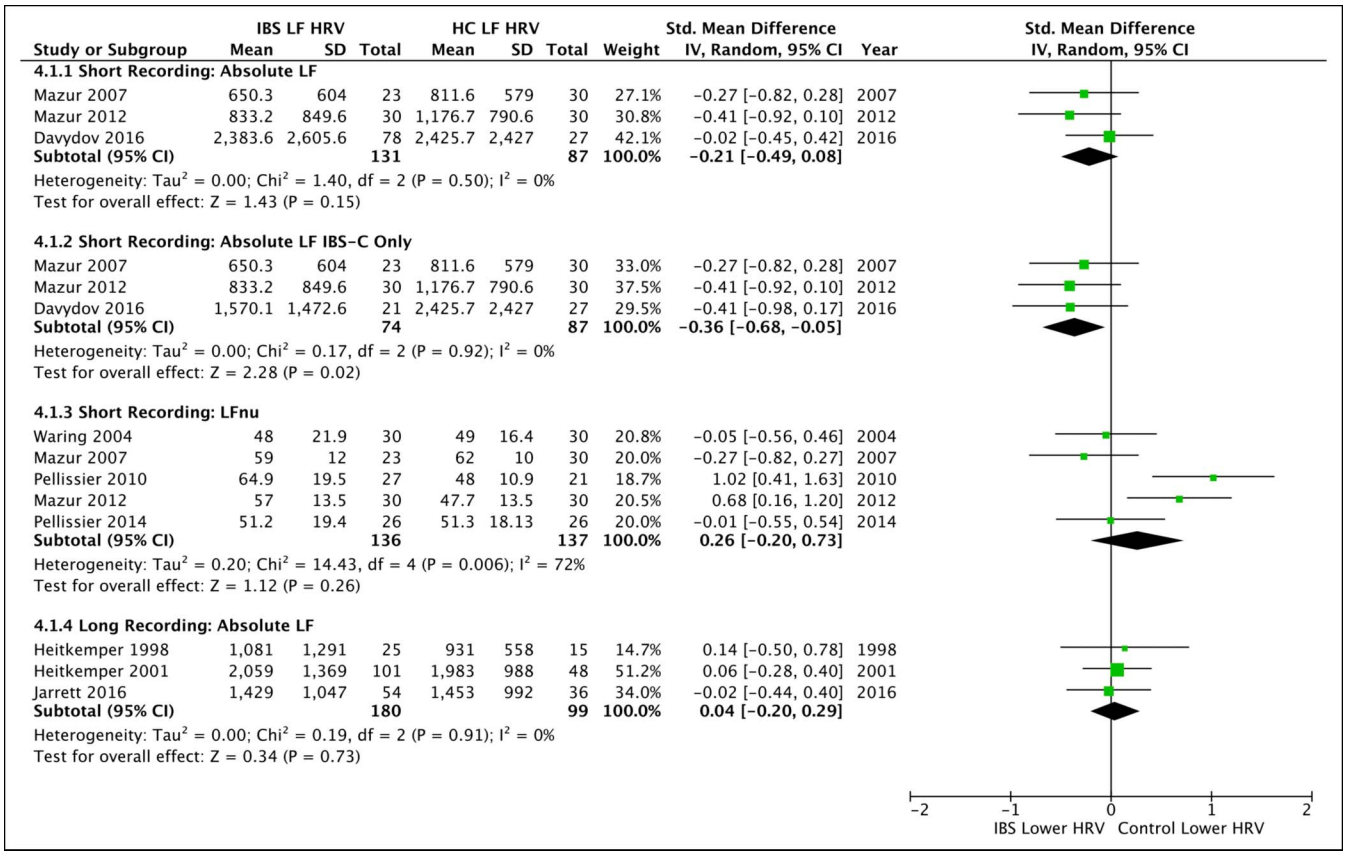

Figure 5. Forest plots for all secondary outcomes available for meta-analysis comparing low-frequency (LF) domain heart rate variability (HRV) between irritable bowel syndrome (IBS) and healthy controls (HC). Studies were separated by short and long duration recordings, with subanalysis available for IBS with constipation predominant (IBS-C). LF represented in normalized units (LFnu). CI, confidence interval.

DISCUSSION

Twenty-eight studies compared HRV measurements in individuals with either IBS or IBD with HC at rest, showing some evidence for an association of HRV with gastrointestinal disorders, evidenced by decreased RMSSD and HF relative to HC. It is unknown whether decreases in HF may be indicative of ANS dysregulation via parasympathetic withdrawal or of sympathetic dominance.

Quality of evidence assessing HRV in IBS and IBD remains low, as seen in the paucity of included studies and the high risks of bias in individual studies. There is limited evidence to associate HRV parameters with health outcomes in individuals with gastrointestinal pathology, and what should be considered healthy or unhealthy HRV in gastrointestinal pathologies can only be speculative at this time. Caution is strongly advised when using metrics developed to measure neuronal functions of the heart to noncardiac health outcomes (28).

Strengths

The strengths of this review include the incorporation of both IBS and IBD as compared to HC, an assessment of overall initial HRV measures across groups, and methods guided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist. Both time and frequency domain outcomes were assessed and limiting data collection to initial collection prevented confounding from interventions.

Limitations

The main limitations consisted of including studies of small sample sizes, significant amounts of heterogeneity in primary study methods and measures, and studies at high risk of bias. There was inconsistent reporting of HRV measures, recording software, timing of HRV collection, and lack of HRV assessor blinding. There were inconsistencies regarding disease severity (34,35,38,41,44–46,49,50,52,53,55,56,58), association of disease severity with HRV parameters, and lack of sufficient data to make any conclusions regarding associations with severity within diseased populations.

Implications/recommendations for research

HRV research on IBS and IBD should follow the 1996 guidelines in the absence of an update in addition to the recommendations by Tak et al. (22,59). We currently recommend future studies report all initial HRV parameters only using either 24-hour measures or short recordings over 5 min to strengthen the consistency in methods used to collect HRV. We do not recommend the use of the LF/HF ratio, given the significant evidence against its use, and because the usefulness of VLF remains unknown, we recommend increased reporting to determine its relationship to gastrointestinal pathologies (14,27,28,60–63). As all outcomes can be computed from the same interbeat-interval data, we recommend that studies report on all common measures, even when transforming skewed data. Future studies comparing HRV of

distinct populations should match participants for age, sex, BMI, smoking status, comorbidities, and medication use, and should explicitly blind HRV assessors. To reduce heterogeneity across studies, future research should conduct repeated measures to produce more reliable measures and assess intrasubject variability. To our knowledge, reliability has not been assessed in the IBS or IBD patient populations, and there are inconsistencies regarding the reproducibility of HRV measures in a variety of unrelated populations (64–66). In addition, we recommend focusing research on a specific disease subtype (such as IBS-C, IBS-D, CD, or UC), or presenting results separately for these subgroups, whenever possible, because HRV patterns could vary dramatically between different forms of the conditions.

If cross-sectional associations of IBS/IBD with altered HRV continues to be seen, investigators should conduct longitudinal study to determine whether HRV measures are responsive to changes in symptoms or severity (whether occurring spontaneously or because of treatment). In particular, they should attempt to identify whether improvements in HRV precede improved disease course or whether improvements in the disease course are accompanied by improvements in HRV. Only a limited number of clinical trials in IBS have evaluated associations between improvements in the disease course and changes in HRV outcomes, with conflicting results; no such trials have been conducted for IBD (67,68). In addition, the role of inflammation should be assessed to determine whether it is a driving factor in HRV outcomes, especially because inflammation is characteristic of IBD but not always present in IBS. When Pellissier et al. used HFnu to categorize subjects into high or low parasympathetic activity across CD, IBS, and HC groups, individuals in the CD group with low parasympathetic activity had significantly greater tumor necrosis factor-α levels compared with IBS and HC groups. When categorized into high parasympathetic activity; however, there were no differences in tumor necrosis factor-α levels between CD, IBS, or HC groups (44). Increased evidence for the direct comparison of IBS to IBD could help to elucidate the role of inflammation.

Implications for clinical practice

The use of HRV to clinically monitor symptoms in IBS and IBD cannot currently be made and further research is required. Validation of HRV regarding established markers of disease severity, as well as enhanced standardization of HRV recording processes, are needed. If HRV differs between diseased states and healthy, it is still unclear how HRV correlates to disease severity, within diseased populations, or if changes in HRV are associated with successful treatment.

CONCLUSIONS

This is the first review that study authors are aware of evaluating initial differences in HRV between both IBS and IBD as compared to HC. There is evidence to suggest that individuals with these conditions have reduced HF variability, relative to HC. Despite some significant findings, these results need to be interpreted with great caution, and further studies are warranted, especially with improvements in study quality and increased homogeneity across study methods and data collection. In addition, future studies should rely on updated Rome Criteria for diagnosis of IBS because the most recent guidelines suggest that IBS subgroups exist on a spectrum and not as distinct entities (69).

CONFLICTS OF INTEREST

Guarantor of the article: Adam Sadowski, ND, MS.
Specific author contributions: A.S. and D.H.: planned the study, collected and interpreted data, and wrote all manuscript drafts. A.S.: approved the final draft submitted. C.D.: aided in the planning of the study and data collection. A.L.: aided in the planning of the study.
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