Systematic Review

Pneumogastric (Vagus) Nerve Activity Indexed by Heart Rate Variability in Chronic Pain Patients Compared to Healthy Controls: A Systematic Review and Meta-Analysis

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Background: A large body of scientific literature derived from experimental studies emphasizes the vital role of vagal-nociceptive networks in acute pain processing. However, research on vagal activity, indexed by vagally-mediated heart rate variability (vmHRV) in chronic pain patients (CPPs), has not yet been summarized.

Objectives: To systematically investigate differences in vagus nerve activity indexed by time- and frequency-domain measures of vmHRV in CPPs compared to healthy controls (HCs).

Study Design: A systematic review and meta-analysis, including meta-regression on a variety of populations (i.e., clinical etiology) and study-level (i.e., length of HRV recording) covariates.

Setting: Not applicable (variety of studies included in the meta-analysis)

Methods: Eight computerized databases (PubMed via MEDLINE, PsycNET, PsycINFO, Embase, CINAHL, Web of Science, PSYNDEX, and the Cochrane Library) in addition to a hand search were systematically screened for eligible studies based on pre-defined inclusion criteria. A meta-analysis on all empirical investigations reporting short- and long-term recordings of continuous time- (root-mean-square of successive R-R-interval differences [RMSSD]) and frequency-domain measures (high-frequency [HF] HRV) of vmHRV in CPPs and HCs was performed. True effect estimates as adjusted standardized mean differences (SMD; Hedges g) combined with inverse variance weights using a random effects model were computed.

Results: CPPs show lower vmHRV than HCs indexed by RMSSD ($Z = 5.47$, $P < .0001$; $g = -0.24$;95% CI [-0.33, -0.16]; $k = 25$) and HF ($Z = 4.54$, $P < .0001$; $g = -0.30$; 95% CI [-0.44, -0.17]; $k = 61$).Meta-regression on covariates revealed significant differences by clinical etiology, age, gender, and length of HRV recording.

Limitations: We did not control for other potential covariates (i.e., duration of chronic pain, medication intake) which may carry potential risk of bias.

Conclusion(s): The present meta-analysis is the most extensive review of the current evidence on vagal activity indexed by vmHRV in CPPs. CPPs were shown to have lower vagal activity, indexed by vmHRV, compared to HCs. Several covariates in this relationship have been identified. Further research is needed to investigate vagal activity in CPPs, in particular prospective and longitudinal follow-up studies are encouraged.

Key words: Vagus nerve, heart rate variability, chronic pain, irritable bowel syndrome, fibromyalgia, primary headache disorders, meta-analysis, systematic review

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Ancient pain theory in the age of Aristotele suggested that pain is perceived by the soul that is located in the heart. Linton (1) noted that in those days, "the brain was not believed to have any direct influence" and that "for years the heart was considered to be the center for pain sensation." While nowadays the fact that nociceptive information is processed in the brain (2), and the sensation of pain is related to brain function is indisputable, some of the ancient ideas still hold truth. The networks and neural structures controlling cardiovascular function are closely coupled to the networks modulating the perception of acute pain (3,4) and extensive interactions between the neural structures involved in pain sensation and the autonomic control of the heart can be observed (5,6). The functional interaction of these systems (7) is an important component involved in the endogenous modulation of pain, and there is strong evidence that the functionality of these networks is altered in patients with chronic pain (4).

An important structure linking cardiovascular and pain regulatory systems is the pneumogastric nerve – the vagus. French physiologist Claude Bernard was the first to investigate the manifold connections between peripheral organs (including the heart) and the brain. His idea that the vagus serves as a structural and functional, bidirectional link between the brain and the heart is nowadays widely received (8). Most interestingly, it was also Bernard to first characterize a pain syndrome accompanied by changes in the autonomic nervous system (ANS), later described by Bernard's student Mitchell as causalgia (9) and nowadays known as complex regional pain syndrome (CRPS) (10).

Vagal-Nociceptive Networks

Nociception is the process by which information about actual or potential tissue damage is relayed to the brain. Sensory receptors (nociceptors) located in the skin, muscles, joints, and viscera are capable of transducing and encoding noxious stimuli from the peripheral branches to the central branches (presynaptic terminals in the spinal cord) of nociceptive neurons involved in processing noxious stimuli (11). Peripheral nociceptors are attached to thin myelinated Aδ and unmyelinated C fibers, which terminate in the dorsal horn of the spine. Interneuronal networks in the dorsal horn transmit nociceptive information to neurons that project to the brain, and further on to other spinal cord neurons, including nociceptive projection neurons and flexor motoneurons. The spinothalamic tract is the major central pathway for processing nociceptive information about noxious stimuli to a number of regions of the brainstem and diencephalon. Three major ascending nociceptive pathways, which originate in the spinal cord and terminate in the brain, process specific pain-related information: (a) the lateral sensory-discriminative component, (b) autonomic components of the pain response, and (c) the medial affective-motivational component.

The spinothalamic tract communicates the location and intensity of nociceptive stimulation (sensory-discriminative component) to the sensory cortex. The sensory cortex further relays information to many sites throughout the brain stem reticular formation, where neurons further relay nociceptive information to many areas of the brain, including the thalamus and the hypothalamus. These areas of the brain process and integrate the different components to produce the holistic pain experience. Connections between the reticular system (formation reticularis) and the thalamus and hypothalamus explain the autonomic components of the pain response. The spinomesencephalic tract on the other hand projects to the periaqueductal gray, the superior colliculus, and the nucleus cuneiformis located in the midbrain. The periaqueductal gray in turn has reciprocal connections with the limbic system and is an important modulator of the pain experience (affective-motivational component).

The influence of the vagus nerve on these (acute) nociceptive processes can be described at different levels of the nociceptive pathway. At the level of spinal nociceptive transmission, early experimental work in rats established that the experimental activation of vagal afferent fibers by electrical stimulation could facilitate or inhibit responses of dorsal horn neurons to noxious heating of the skin (12). The authors concluded, that "the role of vagal afferents in nociception may be interpreted in two ways: facilitation of the perception of relevant stimuli, which is beneficial to the organism, and inhibition of nociceptive transmission via linkage with known endogenous pain control systems" (12).

We will return to this idea later; however, it is important to note that this network is bi-directional and also links to descending inhibitory pathways from cerebral structures to the dorsal horn. These descending pathways are capable of suppressing or potentiating the processing of nociceptive information (13) in addition to the ascending pathways (vagal afferents) involved in transducing noxious stimuli to the central branches (presynaptic terminals in the spinal cord). This descending inhibition is relayed via the nucleus

tractus solitarius (NTS) that receives major input from the vagus nerve and thus represents the initial relay for descending vagally mediated nociceptive effects. As a consequence of impaired vagal control (14), the descending control within the spinal cord dorsal horn may be disrupted and contribute to the central sensitization increasing the excitability of neurons in the central nervous system (CNS) in chronic pain (15). Decreased vagal activity may therefore result in greater somatic and visceral input via the spinothalamic tract, which in turn provides a mechanism for decreased pain threshold and increased pain sensitivity in those with chronic pain.

On the other end of this chain and related to the autonomic outflow, sympathetic and parasympathetic preganglionic nuclei in the spinal cord receive input from descending inhibitory pathways (13). These preganglionic nuclei influence pain thresholds and modify autonomic outflow by baroceptor-mediated changes in arterial pressure (16,17) leading to well described phenomena characterized by alterations in the nociception of acute painful stimuli (i.e., hypertension-related hypoalgesia) (18-20). Blood pressure and heart rate (HR) – both products of the ANS – have been widely studied in investigations of the relationship between acute pain stimuli and autonomic reactions (21-24).

Autonomic Dysfunction and Heart Rate Variability

The dysregulation (dysautonomia) of the ANS – the relative dominance of the sympathetic nervous system (SNS) or decreased activity of the parasympathetic nervous system (PNS) – is considered to play a major role in several chronic painful conditions (25,26). A convenient way to measure ANS function is the widely used recording of heart rate variability (HRV) (27). Chronotropic control of the heart is achieved via the complex interplay of the SNS and PNS branches of the ANS. HR is under tonic inhibitory control (PNS dominance over SNS influences) (28), and because of the rapid breakdown of acetylcholine, the PNS modulation of the HR is fast (timescale of milliseconds) and short-lived, while SNS effects are slow on the timescale of seconds (29). The recording and analysis of the sequence of time intervals between adjacent heartbeats – the inter-beat interval (IBI) in milliseconds – is therefore the basis for the calculation of all the measures of HRV. Among the several methods to record the IBI sequence, electrocardiography (ECG) is the most prominent. Numerous methods of operationalizing HRV exist but fall broadly into 3 classes of measures: time domain, frequency domain, and non-linear measures.

Time domain measures range from short-term (e.g., the standard deviation of IBIs or the root mean square successive differences in an IBI series within a 5-minute window) to long-term (e.g., the standard deviation of all IBIs in a 24-hour window). Frequency domain measures submit an IBI time series to spectral analysis and quantify power spectral density within pre-specified frequency bands. Time domain indices are derived directly from the R-R interval series and generally measure the variability contained therein, whereas frequency domain measures are derived via spectral analytic techniques (i.e. Fast Fourier Transform [FFT] or Autoregressive [AR] algorithm) applied to the R-R interval series. The power spectrum of short-term time series contains 2 major components, a high (0.15 – 0.40 Hz) and a low (0.04 – 0.15 Hz) frequency component. Given that the PNS influences are the only ones capable of producing rapid changes in the beat-to-beat timing of the heart (30), power in the HF band (.15 – .4 Hz) is regarded as largely attributable to PNS activity. Activity in the low-frequency (LF) band (.04 – .15 Hz) is considered to reflect joint activity of the PNS and SNS (27).

Aim and Innovation of the Present Study

The aim of the present meta-analysis is to quantify differences in vagal activity indexed by measures of vagally-mediated HRV (vmHRV) across existing studies comparing chronic pain patients (CPPs) with healthy controls (HCs). An existing meta-analysis on HRV in functional somatic disorders from 2009 (31) was comprised of 31 studies, including studies on patients with irritable bowel syndrome (IBS) and fibromyalgia (FM), but also samples of patients with other non-chronic pain related disorders such as chronic fatigue syndrome. Existing systematic reviews on chronic pain and HRV without a meta-analytical approach addressed HRV differences in patients with IBS (32) or FM (33,34). This is the first meta-analysis exclusively looking at vmHRV in CPPs compared to HCs, including different chronic pain conditions and a large variety of covariates, allowing for the comparison and exploration of different clinical etiologies, age, gender effects, and methods of HRV recording and analysis.

Methods

Data Sources and Searches

A systematic search of the literature according to

the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (35) was employed. The initial search, conducted for a systematic review on HRV and experimentally induced pain back in March 2013 (36), was updated in April 2014. Eight computerized databases (PubMed via MEDLINE, PsycNET, PsycINFO, Embase, CINAHL, Web of Science, PSYNDEX, and the Cochrane Library) were searched (see Appendix 2 for search terms and strategy applied by database). The number of initial hits was recorded for each database. In addition a hand search (i.e., Google, Google scholar, and other sources) was performed.

Study Selection

After duplicates were removed, abstracts of all articles were independently screened based on predefined inclusion criteria by JK and DF. Studies were included if they reported (a) an empirical investigation that was performed in (b) humans, comparing (c) CPPs to (d) a group of HCs and (e) reported HRV. All titles meeting the inclusion criteria were retrieved and reviewed in full text. The number of studies meeting the pre-specified inclusion criteria, number of studies excluded, and reasons for exclusion were recorded. Empirical investigations were defined as studies involving active data collection in a sample of human patients. Reviews, meta-analyses, comments, or single-case reports were excluded. Also, animal studies and studies using a computational modeling approach (i.e., virtual data) were excluded. Unpublished dissertations, poster abstracts, and conference proceedings were included. CPPs were defined as patients reporting medical conditions that are commonly characterized by long-lasting or recurrent pain with pain as the primary or among the leading symptoms. Patients with stable angina or pain related to other cardiovascular diseases (CVD) were excluded. However, studies on patients with non-cardiac chest pain were included. Studies that reported more than 2 groups (CPPs vs. HCs) were included as long as they reported at least one group of CPPs and HCs each, excluding studies that compared different groups of CPPs only. In case multiple CPPs groups and at least one group of HCs was reported, each group of CPPs was compared to the same group of HCs.

Data Extraction

The following meta-data from included studies was extracted (a) year of publication. (b) language of publication, and (c) country where research took place. Regarding the patients studied, information was extracted on the (a) sample size, (b) size of CPPs and HCs group(s), (c) age and (d) gender of participants, and (e) the kind of chronic painful condition (clinical etiology/diagnosis). Furthermore, details on the HRV recording, including (a) the method of HRV measurement (e.g., ECG), (b) electrode placement, (c) sample rate of HRV recording, the (d) condition at HRV recording (e.g., supine), and the (e) length of HRV recording were obtained.

Guidelines from the Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology (27) were used to define the HRV measurements included for analysis. Only components thought to reflect primarily vagal cardiac modulation were included. Studies had to report the root-mean-square of successive R-R-interval differences (RMSSD) or any spectral measure in the HF range of 0.15 – 0.14Hz (natural log transformed [lnHF], normalized [HFnu], or expressed as absolute power in ms^2 [HFP]). Regarding the recording and analysis of frequency-domain measures of vmHRV (a) the unit of HF-HRV and (b) the method of power spectral density (PSD) estimation were recorded.

Means and standard deviations (SD) of time (RMSSD) and frequency (HF-HRV) domain measures of vmHRV were extracted by group (CPPs vs. HCs) from resting baseline recordings if available. In case the standard error of the mean (SEM) but not the SD was reported, the SD was obtained from the SEM by multiplying by the square root of the sample size (37). Where longitudinal or pre-post data were reported, only the baseline resting vmHRV was included to minimize confounding effects by experimental manipulation and conflation of effect size estimates. Where multiple citations provided data from overlapping samples, only the citation that contained the most information relevant to covariate testing (e.g., stratification by age and gender) was retained. Authors who reported baseline HRV but who did not report sufficient quantitative data (e.g., only a graphical display) were contacted to request the necessary information to derive effect size estimates and confidence limits. Furthermore, authors with potential access to data of interest (i.e., reporting a sample including CPPs and HCs, and HRV but no analysis on group differences) were contacted. All data extraction was performed independently by DF, AC, JW, and JK.

Data Synthesis, Analysis, and Covariates

True effect estimates were computed as adjusted standardized mean differences (Hedges g) using a ran-

dom effects model. Each covariate was tested using meta-regression with a single covariate at a time (38), in line with a previous meta-analysis on HRV variables (39). Heterogeneity was tested with the standard I^2 index, Chi-Square, and Tau^2 tests (40). Bias was examined using a funnel plot of effect size against standard error for asymmetry. Meta-analytic computations were performed using RevMan (Version 5.3.4, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and meta-regression computations were performed using the OpenMetaAnalyst software (41).

Three population- and study-level covariates were documented and subjected to meta-regression (a) age, (b) gender, and (c) clinical etiology (i.e., type of chronic painful condition). First, as HRV decreases with age (42-45), we aimed to control for such effect by stratifying samples of included studies by the reported mean age. According to the nature of included studies, 2 groups were formed. If the mean age of the study sample was < 18 years, the sample was classified as "children/adolescents"; if the mean age of the study sample was > 18 years, the sample was classified as "adults." Thus, age was coded and analyzed as children/adolescents (< 18 years) vs. adults (> 18 years).

Secondly, evidence supports gender differences in the experience of experimentally induced pain and clinical pain reports. Women report more severe levels of clinical pain, more frequent pain, and pain of longer duration compared to men (46). Furthermore, population based studies report that likewise more women report chronic pain and higher chronic pain intensity than men (47,48). However, in treatment-seeking samples with chronic pain, studies show that men report higher levels of pain and disability (49). Several studies support gender differences on HRV in healthy controls (50-53). A recent meta-analysis (54) reports greater vagally mediated HRV in women and higher relative sympathetic dominance in men. To explore potential gender differences within the present meta-analysis, included studies were stratified by gender (women vs. men vs. mixed). Thirdly, in addition to age and gender effects, differences between major clinical etiologies were explored by comparing studies on FM, IBS, primary headache disorders (PHD), and other chronic pain (CP) conditions.

Furthermore, 2 major methodological covariates were explored: (a) the length of HRV recording and (b) the method of PSD estimation. For this, the recording length of HRV measurements was contrasted as short- (< 1 hour) vs. long-term recordings (e.g., 24 hours), and the method of PSD estimation of HRV frequency-domain measures was subjected to meta-regression. Frequency-domain measures (27,55,56,57) quantify HRV from an IBI time series that has been detrended (to remove slow nonstationarities) using a moving polynomial filter, such as a cubic spline (56) or a smoothness priors regularization (57). The detrended IBI time series is then decomposed into its underlying periodicities, and a power spectrum density plot is created, plotting spectral power density (in ms^2 or s^2) as a function of frequency (in Hz). Two common solutions are used: a nonparametric FFT and a parametric autoregressive algorithm (AR) (58). Common FFT algorithms utilize Welch's periodigram method. This divides the sample into 256-ms windows that overlap by 50% and averages overlapping segments. This decreases the variance of the FFT spectrum. Absolute power values are then obtained by integrating the spectrum within 2 prespecified frequency bands (Fig. 1a). The AR algorithm uses a factorization procedure to obtain distinct LF and HF components (Fig. 1b). Power values are obtained as the powers of those components. The advantages of an AR solution are smoother spectral components that are independent of pre-specified frequency bands, clear central frequencies of each component, and an accurate estimation of power spectral density even on a small number of (stationary) samples (27). Furthermore, the central frequency of the HF component has been shown to quantify respiration rate (i.e., frequency in Hz × 60 = respiration rate) (59). The use of these 2 different methods of HRV frequency-domain estimation was recorded for each included study that reports HF-HRV. The factorial covariate (FFT vs. AR) was included in the meta-regression.

Results

Retrieved Literature and Included Studies

The search in the selected databases revealed a total of 1,832 articles. After removing duplicates, 1,140 abstracts were screened (Fig. 2). Systematic screening of abstracts left 97 papers potentially eligible for inclusion that were retrieved in full text if possible. Seven manuscripts could not be retrieved even after contacting the authors. Thirty-six studies reported insufficient data (i.e., range of values instead of SD) and corresponding authors were contacted to retrieve missing data. Finally, a total of 55 studies (60-114) were

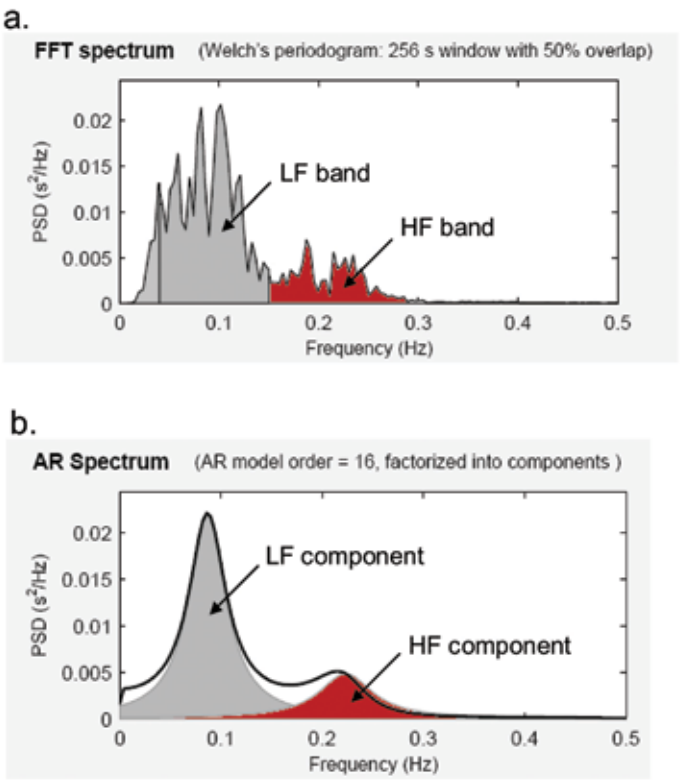


Fig. 1. (a) FFT and (b) AR spectrum of HRV frequency analysis.

included in the meta-analysis. Several studies reported multiple comparisons (i.e., different clinical etiologies or analysis stratified by gender). In case different clinical subgroups (i.e., severe vs. mild pain) were reported in comparison to one group of HC, every subgroup was compared to the respective group of HCs. A total of 86 comparisons were subjected to meta-analysis, of which 61 reported HF (93.9%) and 25 reported RMSSD (38.5%) as outcome. Twenty-one studies reported both measures (32.3%).

Study and Sample Characteristics

Study and sample characteristics are summarized in Appendix 3 and details on the HRV measurement are presented in Appendix 4. Meta-regression coefficients and confidence limits for each tested covariate are reported in Table 1. The majority of studies were published within the past 10 years and conducted within the USA (Appendix 3). Data from a total of 3,418 CPPs on HF and 2,232 on RMSSD were available for analysis. Twenty-five comparisons (38.5%) comprised a mixed sample of women and men, while 32 comparisons (49.2%) exclusively reported data from women, and 6 (9.2%) from men (n = 2 / 3.1%, no information on gender). Sixty comparisons were in adults (92.3%) and 4 (6.2%) in children/adolescent (n = 1 / 1.5%, no information on age).

Meta-Analysis: Main Effect

Meta-analyses on HF-HRV revealed a sizeable and significant (Z = 4.54, $P < .0001$) difference between CPPs (n = 3,418) and HCs (n = 1,997) (Hedges' g = -0.30; 95% CI [-0.44, -0.17]; k = 61) suggesting lower vagal activity, as indexed by HF-HRV, in CPPs compared to HCs (Fig. 3; negative effect estimates reflect lower HF in CPPs). Significant heterogeneity across all true effects was found (see test results in Fig. 3). A similar pattern of results was observed for RMSSD. CPPs (n = 2,232) showed significantly (Z = 5.47, $P < .0001$) lower RMSSD compared to HCs (n = 938) (g = -0.24; 95% CI [-0.33, -0.16]; k = 25)

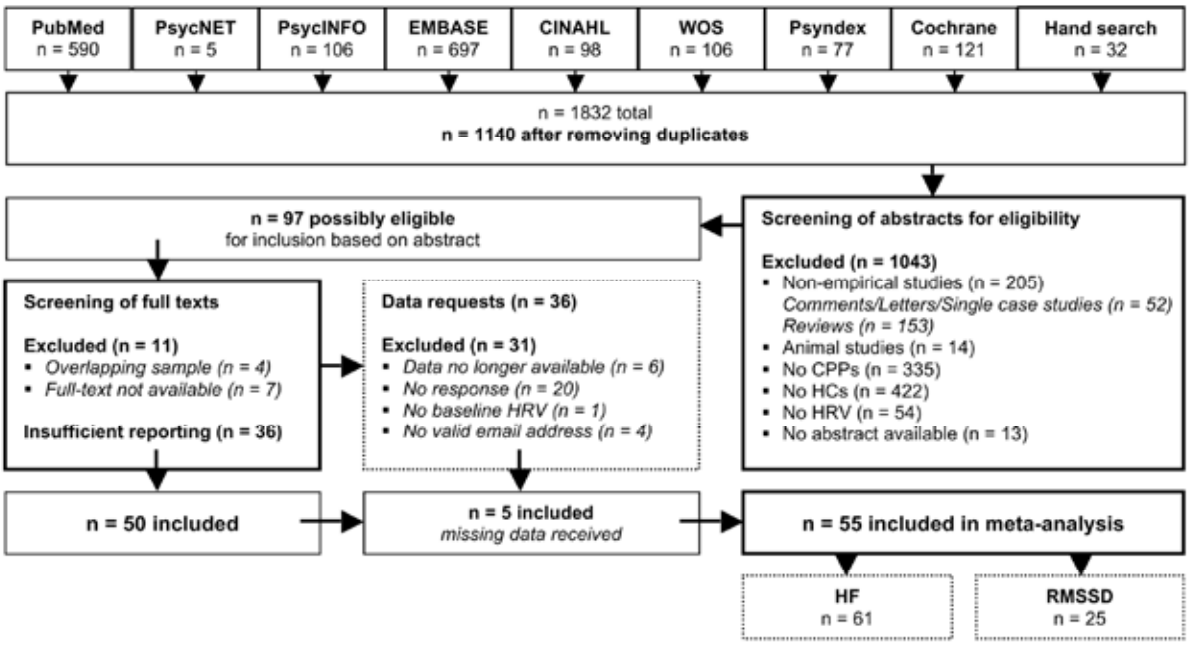


Fig. 2. PRISMA search flow chart; WOS: Web of Science.

Table 1. *Meta-Regression Covariate results for HF and RMSSD.*

	HF					RMSSD				
Covariate	β	**SE** β	**95%CI Lower**	**95%CI Upper**	***P*-value**	β	**SE** β	**95%CI Lower**	**95%CI Upper**	***P*-value**
Age	-0.322	0.079	-0.477	-0.167	< 0.0001	-	-	-	-	-
Gender	-0.370	0.118	-0.601	-0.139	0.002	-0.391	0.106	-0.599	-0.183	< 0.0001
Etiology	-0.352	0.151	-0.649	-0.055	0.020	-0.056	0.313	-0.669	0.557	0.859
PSD estimation	-0.290	0.217	-0.715	0.135	0.181	-	-	-	-	-
Recording length	-0.268	0.094	-0.452	-0.084	0.004	-0.217	0.106	-0.425	-0.009	0.041

suggesting lower vagal activity, as indexed by RMSSD, in CPPs compared to HCs (see Fig. 4; negative effect estimates reflect lower RMSSD in CPPs). Again, significant heterogeneity was found (see test results in Fig. 4). Visual examination of funnel plots for HF (Fig. 5a) and RMSSD (Fig. 5b) revealed no significant asymmetry.

Vagal Activity by Clinical Etiology

Studies were grouped based on major clinical etiologies of CPPs. In 16 cases (24.6%) HF was reported in FM patients, 13 comparisons in IBS patients (20.0%), 5 in PHD patients (7.7%), and 27 other CP related disorders (41.5%). Clinical etiology was a significant covariate of HF (β = -0.352, P = 0.020, Table 1). Seven comparisons (10.8%) on RMSSD addressed FM patients, 2 (3.2%) IBS, 2 (3.2%) PHD, and 14 (21.5%) any other CP disorder. Clinical etiology was not a significant covariate of RMSSD (β = -0.056, P = 0.859). Meta-analysis for these subgroups by etiology is illustrated in Fig. 6. Group differences between CPPs and HC were robust for FM patients regarding HF (Z = 2.50, P = .001; g = -0.48; 95% CI [-0.85, -0.10]; k = 16) and RMSSD (Z = 3.65, P = .0003; g = -0.57; 95% CI [-0.88, -0.27]; k = 7), as were differences between HCs and patients with other CP conditions regarding HF (Z = 3.54, P = .0004; g = -0.32; 95% CI [-0.50, -0.14]; k = 27) and RMSSD (Z = 3.01, P = .003; g = -0.32;

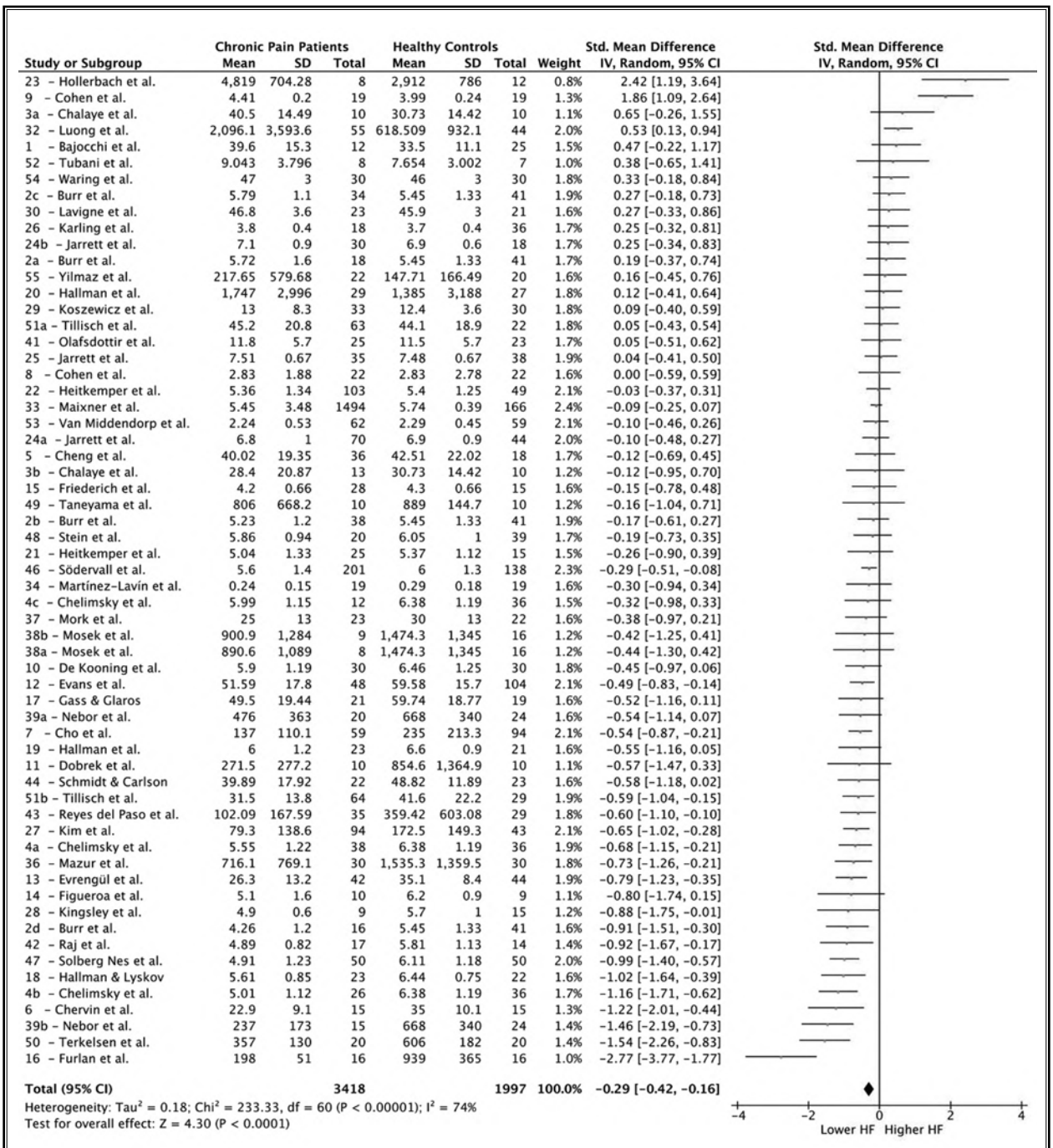
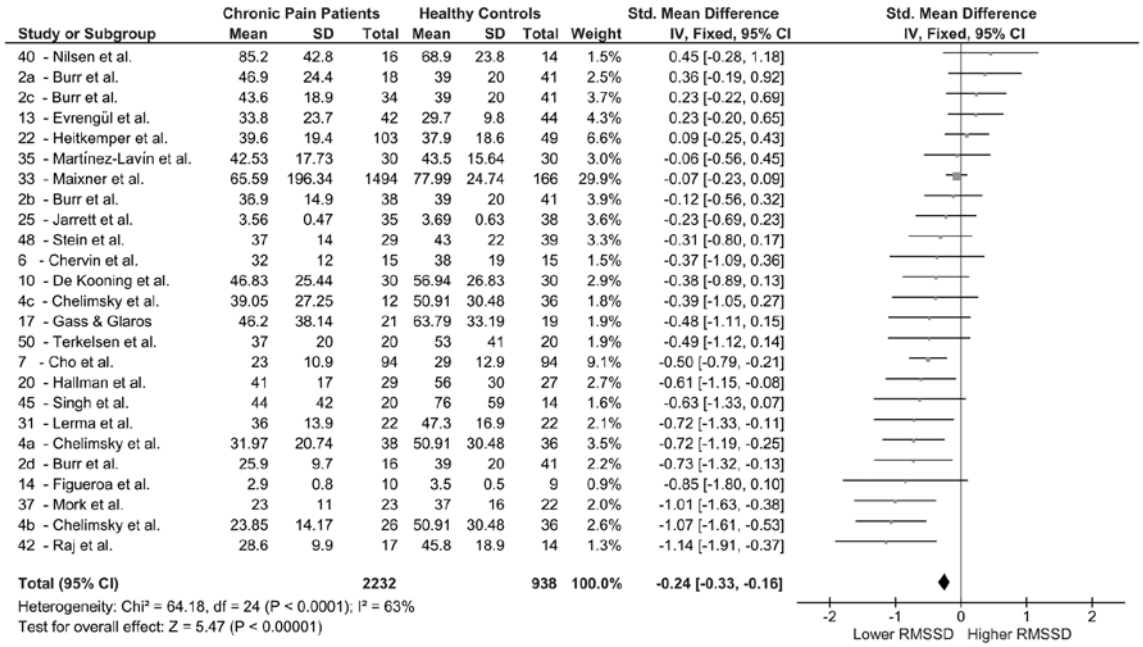


Fig. 3. orrest Plot of Random Effect Meta-Analysis on HF-HRV; 95% CI: 95% Confidence Interval; SD: Standard Deviation.



Study or Subgroup	Chronic Pain Patients Mean	SD	Total	Healthy Controls Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
40 - Nilsen et al.	85.2	42.8	16	68.9	23.8	14	1.5%	0.45 [-0.28, 1.18]
2a - Burr et al.	46.9	24.4	18	39	20	41	2.5%	0.36 [-0.19, 0.92]
2c - Burr et al.	43.6	18.9	34	39	20	41	3.7%	0.23 [-0.22, 0.69]
13 - Evrengül et al.	33.8	23.7	42	29.7	9.8	44	4.3%	0.23 [-0.20, 0.65]
22 - Heitkemper et al.	39.6	19.4	103	37.9	18.6	49	6.6%	0.09 [-0.25, 0.43]
35 - Martínez-Lavín et al.	42.53	17.73	30	43.5	15.64	30	3.0%	-0.06 [-0.56, 0.45]
33 - Maixner et al.	65.59	196.34	1494	77.99	24.74	166	29.9%	-0.07 [-0.23, 0.09]
2b - Burr et al.	36.9	14.9	38	39	20	41	3.9%	-0.12 [-0.56, 0.32]
25 - Jarrett et al.	3.56	0.47	35	3.69	0.63	38	3.6%	-0.23 [-0.69, 0.23]
48 - Stein et al.	37	14	29	43	22	39	3.3%	-0.31 [-0.80, 0.17]
6 - Chervin et al.	32	12	15	38	19	15	1.5%	-0.37 [-1.09, 0.36]
10 - De Kooning et al.	46.83	25.44	30	56.94	26.83	30	2.9%	-0.38 [-0.89, 0.13]
4c - Chelimsky et al.	39.05	27.25	12	50.91	30.48	36	1.8%	-0.39 [-1.05, 0.27]
17 - Gass & Glaros	46.2	38.14	21	63.79	33.19	19	1.9%	-0.48 [-1.11, 0.15]
50 - Terkelsen et al.	37	20	20	53	41	20	1.9%	-0.49 [-1.12, 0.14]
7 - Cho et al.	23	10.9	94	29	12.9	94	9.1%	-0.50 [-0.79, -0.21]
20 - Hallman et al.	41	17	29	56	30	27	2.7%	-0.61 [-1.15, -0.08]
45 - Singh et al.	44	42	20	76	59	14	1.6%	-0.63 [-1.33, 0.07]
31 - Lerma et al.	36	13.9	22	47.3	16.9	22	2.1%	-0.72 [-1.33, -0.11]
4a - Chelimsky et al.	31.97	20.74	38	50.91	30.48	36	3.5%	-0.72 [-1.19, -0.25]
2d - Burr et al.	25.9	9.7	16	39	20	41	2.2%	-0.73 [-1.32, -0.13]
14 - Figueroa et al.	2.9	0.8	10	3.5	0.5	9	0.9%	-0.85 [-1.80, 0.10]
37 - Mork et al.	23	11	23	37	16	22	2.0%	-1.01 [-1.63, -0.38]
4b - Chelimsky et al.	23.85	14.17	26	50.91	30.48	36	2.6%	-1.07 [-1.61, -0.53]
42 - Raj et al.	28.6	9.9	17	45.8	18.9	14	1.3%	-1.14 [-1.91, -0.37]
Total (95% CI)			**2232**			**938**	**100.0%**	**-0.24 [-0.33, -0.16]**

Heterogeneity: Chi² = 64.18, df = 24 (P < 0.0001); I² = 63%
Test for overall effect: Z = 5.47 (P < 0.00001)

Fig. 4. Forrest Plot of Random Effect Meta-Analysis on RMSSD; 95% CI: 95% Confidence Interval; SD: Standard Deviation.

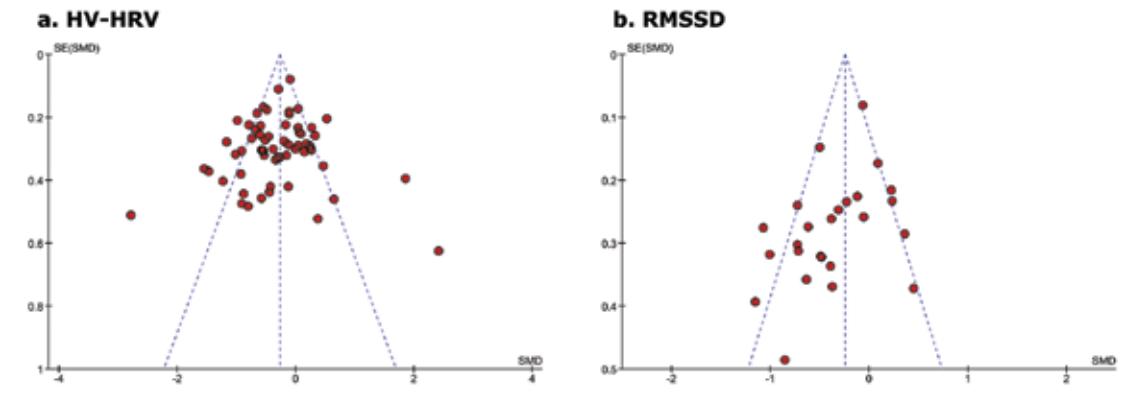


Fig. 5. Funnel Plots for (a) HF-HRV (a) and (b) RMSSD.

95% CI [-0.53, -0.11]; k = 14). However, comparisons in IBS patients showed no significant differences on HF (Z = 1.19, *P* = .23, g = -0.11; 95% CI [-0.28, 0.07]; k = 13) and RMSSD (Z = 0.20, *P* = .84, g = -0.03; 95% CI [-0.33, 0.27]; k = 2). Differences in patients with PHD compared to HCs were significant regarding HF (Z = 2.50, *P* = .001; g = -0.51; 95% CI [-0.91, -0.11]; k = 5) but not in RMSSD (Z = 0.07, *P* = .94, g = -0.03; 95% CI [-0.94, 0.88]; k = 2).

Other Covariates

Age and Gender Differences

Meta-regression on age as a covariate was only possible for HF, as all studies on RMSSD were in adults only.

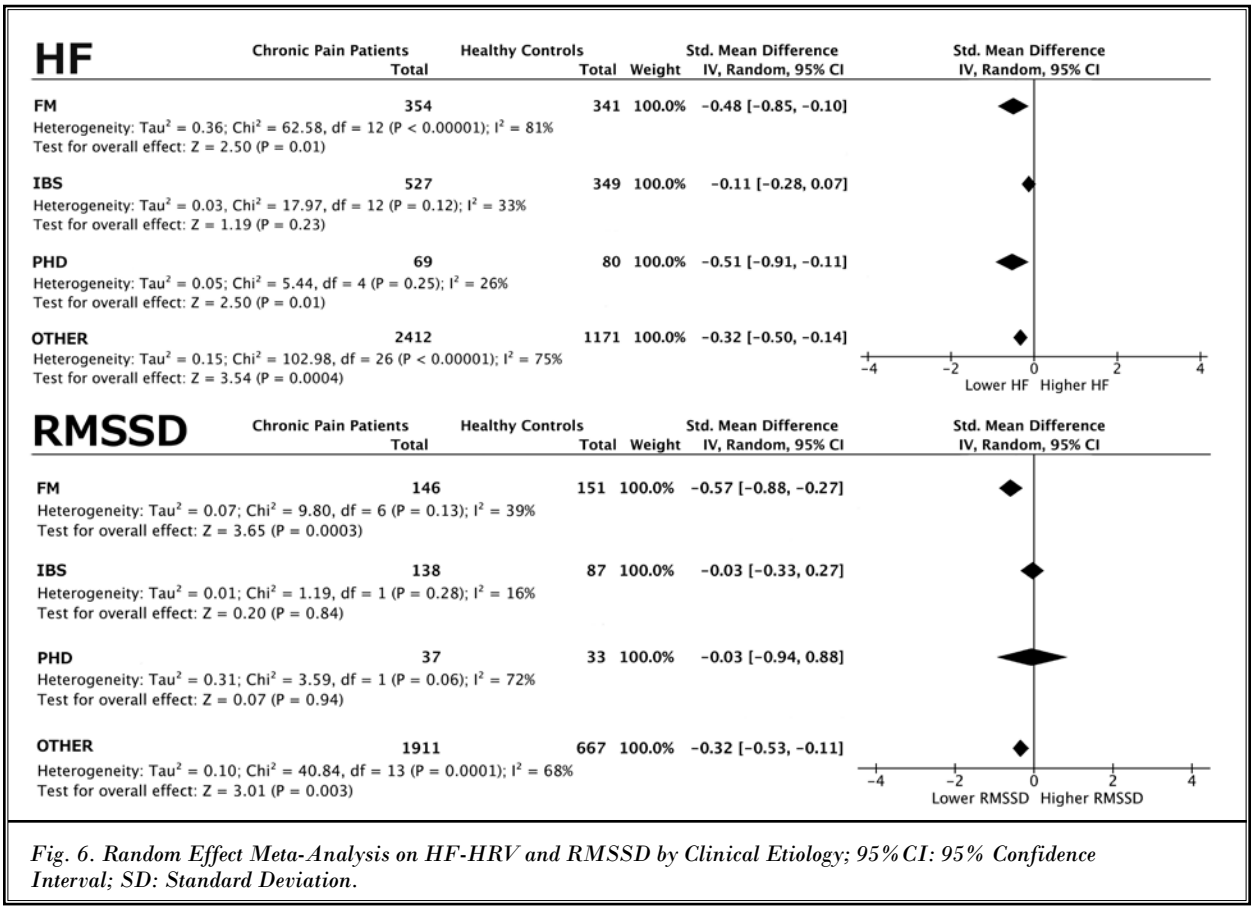


Fig. 6. Random Effect Meta-Analysis on HF-HRV and RMSSD by Clinical Etiology; 95% CI: 95% Confidence Interval; SD: Standard Deviation.

The majority of studies included in the meta-regression were on adults (n = 56, 86.2). Four studies (6.2%) were on children/adolescents (n = 1 [1.5%] missing information). Age was a significant covariate on HF (β = -0.370, P < 0.0001). Adults with CP showed significantly lower HF (Z = 4.24, P < 0.0001; g = -0.30; 95% CI [-0.44, -0.16]; k = 56), while no significant effect in children and adolescents was observed (Z = 0.82, P = 0.41, g = -0.13; 95% CI [-0.45, 0.18]; k = 4), as illustrated in Fig. 7.

Among the studies reporting HF, 29 were exclusively on women (44.6%) and 6 on men (9.2%). Twenty-four (36.9%) reported results from mixed samples (n = 2 [3.1%] missing information). RMSSD comparisons were reported for 16 female (24.6%), one male (1.5%), and 8 mixed (12.3%) samples (no missing information). Gender was a significant covariate of HF (β = -0.352, P = 0.020) and RMSSD (β = -0.391, P < 0.0001). Women with CP showed significantly lower HF (Z = 2.77, P = 0.006; g = -0.26; 95% CI [-0.44, -0.08]; k = 29) and RMSSD (Z = 3.10, P = 0.002; g = -0.40; 95% CI [-0.65, -0.15]; k = 16). While significant differences were also found for mixed samples in HF (Z = 4.15, P < 0.0001; g = -0.42; 95% CI [-0.62, -0.22]; k = 2) and RMSSD (Z = 2.07, P = 0.04; g = -0.20; 95% CI [-0.38, -0.01]; k = 8), no significant differences between male CPPs and HCs in HF were found (Z = 0.60, P =0.55, g = 0.20; 95% CI [-0.44, 0.83]; k = 6) (only one study on RMSSD). These findings are illustrated in Fig. 8.

Methodological Differences

Of the studies that reported HF, 21 obtained long-term recording (32.3%) and 43 (66.2%) obtained short-term recordings (n = 1 [1.5%] missing information, Table 2). Meta-regression for RMSSD was performed on 14 studies (21.5%) reporting long-term recordings and 11 studies (16.9%) reporting short-term recordings. Recording length was a significant covariate on HF (β = -0.268, P = 0.004) and RMSSD (β = -0.217, P = 0.041), however, both long- and short-term recordings revealed significant differences on vmHRV between CPPs

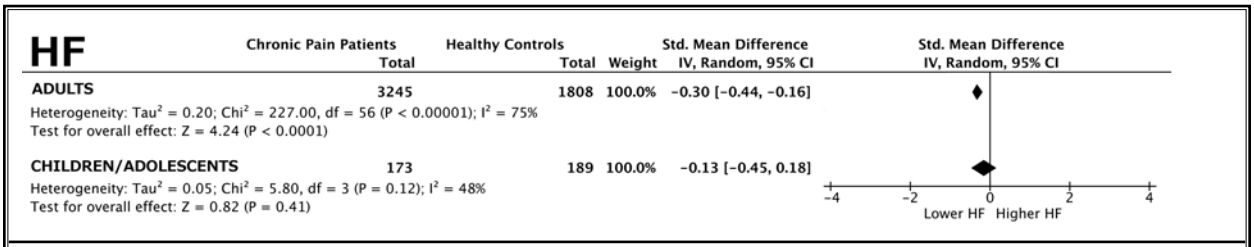


Fig. 7. Random Effect Meta-Analysis on HF-HRV by Age Group; 95% CI: 95% Confidence Interval; SD: Standard Deviation.

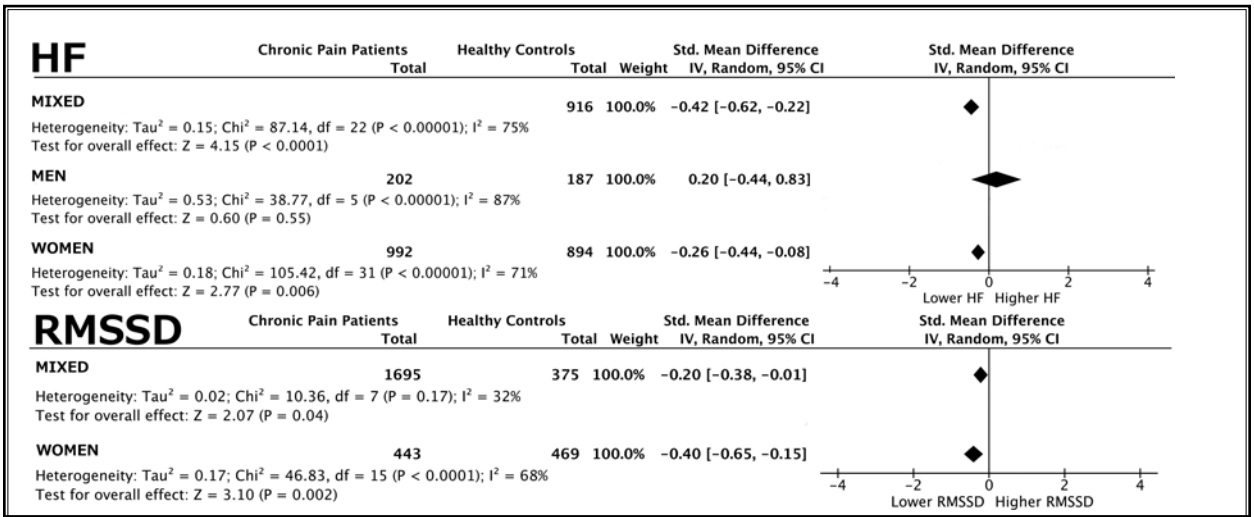


Fig. 8. Random Effect Meta-Analysis on HF-HRV and RMSSD by Gender; 95% CI: 95% Confidence Interval; SD: Standard Deviation.

and HCs as illustrated in Fig. 9 (all $P > 0.05$). HF long-term recordings showed a greater effect compared to short-term recordings (g = -0.35 vs. g = -0.26); for RMSSD short-term recordings showed a greater effect compared to long-term recordings (g = -0.46 vs. g = -0.24).

Regarding the method of PSD estimation, 25 studies on HF (38.5%) used the FFT for the estimation of the PSD estimation. Nine (13.8%) used the AR approach, and one study used a different approach (n = 26 (40.0%) missing information). The method of PSD estimation was not a significant covariate (β = -0.290, $P = 0.181$), indicating that both – FFT and AR – were capable of revealing differences on frequency-domain measures of vmHRV (HF) between CPPs and HCs.

Discussion

Within the present meta-analysis we aimed to investigate differences in vmHRV between CPPs and HCs. After an extensive search of the literature, we identified 55 studies that were eligible for inclusion based on predefined inclusion criteria. Included studies yielded a total of 86 comparisons of time- and frequency-domain measures of vmHRV. Within the following paragraphs, we will summarize our results and discuss the implications as well as potential underlying mechanisms of the present findings.

Summary of Findings

The meta-analysis revealed a significant main effect of group (HCs vs. CPPs) on time (RMSSD) and frequency domain measures of vmHRV. CPPs showed lower RMSSD (Z = 5.47, $P < .0001$; g = -0.24; 95% CI [-0.33, -0.16]; k = 25)and lower HF-HRV (Z = 4.54, $P < .0001$; g = -0.30; 95% CI [-0.44, -0.17]; k = 61) compared to HCs. This effect has several covariates that were identified by subsequent meta-regressions.

We were able to show that vagal activity differs as a function of different clinical etiologies. While differences between CPPs with FM or other chronic painful conditions were robust independent of the measure of

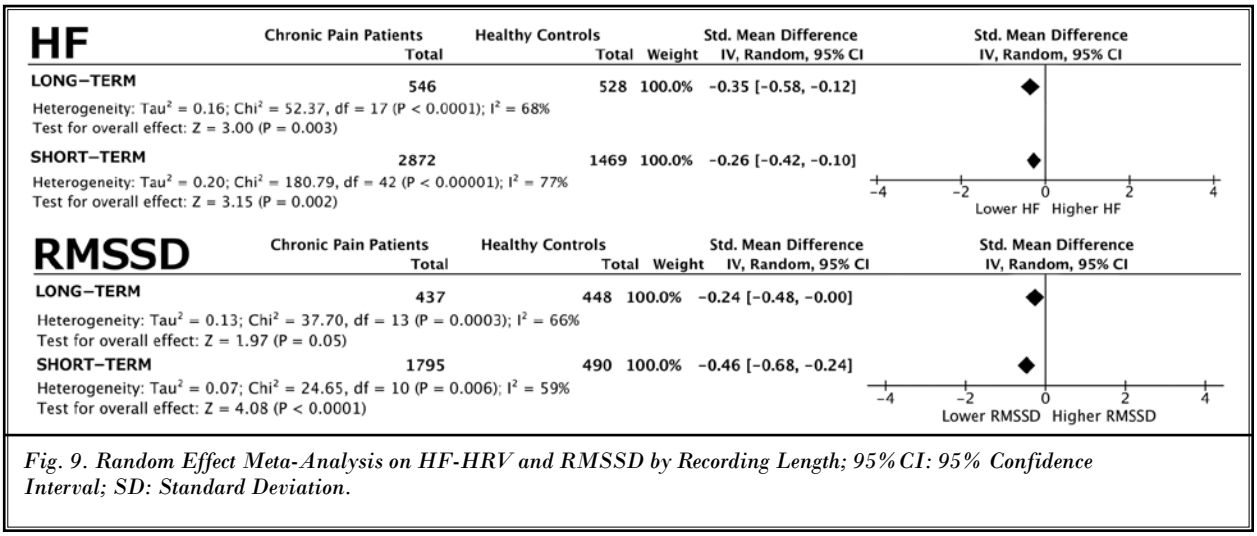


Fig. 9. Random Effect Meta-Analysis on HF-HRV and RMSSD by Recording Length; 95% CI: 95% Confidence Interval; SD: Standard Deviation.

vmHRV, we found no differences within the subgroup of patients with IBS), and differences between CPPs with PHD and HCs only held for HF, not RMSSD (Fig. 6). While we aimed to explore the general effect of the experience of recurrent or chronic pain, the unique association of vmHRV and pain in a defined disorder should the subject of further in-depth analysis and exploration.

A meta-regression on age as a covariate showed that vmHRV differs between CPPs and HCs when examined in adults but not in children (Fig. 7). While one of the primary studies on children or adolescents reported that children with chronic pain had significantly lower resting HRV compared to healthy children (70), 2 studies in children found no significant difference between CPPs and HCs (81,97). However, the studies on children/adolescents included different disorders which may account at least partly for the reported differences.

While differences on vmHRV (independent of measure) between CPPs and HCs were found for samples comprising only women and mixed samples, no significant differences was found in subsamples of men only (Fig. 8). While gender difference in the experience of pain and reporting of clinical pain are well described within the literature, research on HRV is just beginning to explore gender differences (54). While women in general tend to have greater HRV, not much is known about the basis for this finding. However, research suggests that these differences are likely to represent gender differences in emotion regulation that may be reflected by different coping strategies in CPPs.

Another meta-regression and subsequent analysis revealed that recording-length of HRV is a significant covariate. Meta-analysis on sub-samples (short-term vs. long-term recording) showed that short- and long-term recordings revealed significant differences on vmHRV between CPPs and HCs. As illustrated in Fig. 9, it seems that HF should be considered as the preferred measure for long-term recordings, while RMSSD is more likely to show effects within short-term recordings. While previous meta-analysis on HRV excluded 24-hour measurements (31), we were able to show that short- and long-term recordings carry potential valuable information on vagal-activity in CPPs. It is noted that guidelines for the measurement of HRV (27) suggest that spectral analysis of 24-hour long-term HRV (where spectral estimates are calculated over long data epochs that are not likely to be stationary) may not accurately reflect autonomic modulation, which may be better captured by estimates based on shorter data epochs. The method of frequency-domain power estimation of HRV (AR vs. FFT) was not a significant covariate.

Implications and Mechanisms

While the meta-analytical approach taken cannot clarify if altered vagal-activity in CPPs is the cause or consequence of the recurrent experience of pain, we will highlight several associations of HRV and pain that go well beyond a simplistic view of autonomic dysfunction in CPPs and carries the potential to frame future research on HRV in CPPs.

Beyond Autonomic Dysfunction: Neurovisceral Integration

Gebhardt and Randich, 2 pioneers, who attempted

to delineate the vagal network modulating nociception for more than 20 years, stated in a focus commentary of the first issue of the American Pain Society Journal: "In closing, it is not clear why vagal afferents serve a role in the modulation of pain, but it is plausible to assume that any biological adaptive nociceptive system should require moment-by-moment integration with other bodily functions. Vagal afferents, by virtue of their innervation and control of so many peripheral functions, are clearly well-suited to convey such information to nociceptive systems" (115).

A comprehensive framework to view the way in which organisms function and adapt to diverse types of stressors such as pain, and how the vagus nerve mediates such "biological adaptive […] moment-by-moment integration [of] bodily functions" (115) is the model of Neurovisceral Integration (116). It posits flexibility in the face of changing physiological and environmental demands as a hallmark of successful adaptation. The model proposes that a core set of neural structures, operating as a "super-system" integrate "the activity in perceptual, motor, interoceptive, and memory systems into gestalt representations of situations and likely adaptive responses, provides an organism with the ability to continuously assess the environment for signs of threat and safety and to prepare the organism for appropriate action" (8). Later work by the authors emphasizes "that such systems can also become unbalanced, and a particular process [author commentary: like pain] can come to dominate the system's behavior, rendering it unresponsive to the normal range of inputs," and that such a system that is "locked in" to a particular pattern is dysregulated (8). CP – like other chronic diseases – represents such a dysregulated, locked in system, characterized by a loss of biological adaptive functions.

In the context of physiology, the ANS adaptively regulates visceral function. A balanced system is healthy, because the system itself can adaptively respond to physical and environmental demands (117). In particular, the ANS has a dominant role in the regulation of the cardiovascular system. In the light of the Neurovisceral Integration Model, the HR of a healthy heart oscillates spontaneously (i.e., shows high variability), whereas a diseased heart shows almost no variability (8). The characteristic beat-to-beat variability in the time series of the HR –HRV – has therefore been proposed to "be more than just an index of healthy heart function, and may in fact provide an index of the degree to which the brain's 'integrative' system for adaptive regulation provides flexible control over the periphery" (8).

Brain Morphology in Chronic Pain

It is well known that the recurrent or chronic experience of pain alters brain morphology (118). "Irrespective of the location, nature or course of the different pain syndromes, the most common finding is a decrease of gray matter in the cingulate cortex, the orbitofrontal cortex, the insula and the dorsal pons, suggesting a common [neural] basis" of CP (119). There is evidence, that these "gray matter abnormalities […] are not the cause, but […] due to changes in motor function and bodily integration" in CPPs (34). This is further supported by studies showing that gray matter decrease is reversible when pain is successfully treated (120).

These alterations result in different pain processing in CPPs (121,122). However, not only pain related information seems to be processed differently in CPPs. Recent experimental research has shown that the long-term experience of pain may alter the functional connectivity of components of the "default mode network" (DMN), comprising cortical regions known to be active at rest (123). The authors report a significant deactivation failure (increased prefrontal activity) in the medial prefrontal cortex (mPFC) – a key component of the DMN that is anatomically connected with the descending pain modulatory system – in CPPs during a cognitive task (rest-to-active phase task transition).

Recent studies extend these findings providing evidence that functional connectivity of the mPFC is positively correlated to pain rumination in CPPs (124). Generally speaking, CP is characterized by a shift from nociceptive to emotion-related circuit activity in the brain (125,126). Most interestingly, HRV has been shown to be associated with regional cerebral blood flow in the mPFC during emotional tasks (127), and "may index the degree of functional integration in the axis connecting the ventral mPFC, brainstem, and peripheral physiology — and, in psychological terms, the degree to which affective context provides flexible control over the peripheral autonomic nervous system" (8).

Besides these shared neural networks that provide a mechanism underlying differences in vagal activity in CPPs caused by pain, several top-down metabolic processes are associated with HRV and may play a significant role in the onset and chronification of persistent pain. For example, efferent activity of the vagus nerve is also associated with inflammation via the release of acetylcholine that inhibits the release of pro-inflammatory cytokines. These inflammatory processes may cause prolonged, ongoing excitation of primary nociceptive neu-

rons leading to CP, and have been linked to vagal activity and HRV (128-133).

Comorbidities and the Treatment of Chronic Pain

The vagus nerve innervates a wide range of organs and is associated with many functional systems in the human body. Decreased vagal activity leads to organic dysfunction, associated with disease and adaptive malfunction far beyond a particular medical condition. Lower vagal activity, indexed by decreased vmHRV, may therefore mediate frequently found comorbidities in CPPs. For example, higher cardiac sympathetic regulation and lower vagal tone due to the continuous experience of pain might explain frequent comorbidities associated with CP, like poorer sleep quality (134-136) that has been linked to HRV (137-140). Furthermore, as emphasized by the Model of Neurovisceral Integration, vagal activity bridges purely physiological function to psychological concepts, linking lower vagal activity to psychosomatic research on CP. To name a few critical concepts in this context, HRV serves as an index of regulation and dysregulation of emotion (116,141). As mentioned earlier, a shift to emotion-related circuit activity in the brain can be observed in chronic pain (125). Efficacy in emotion regulation is related to quality of life and negative affect in patients with chronic pain (142). Resting HRV may therefore provide an index of the integrity of central-peripheral feedback that is necessary for affective emotion regulation including effective regulation of pain. A loss of sensory integration due to decreased vagal activity may result in greater effective processing of nociceptive information that results in overstraining adaptive capabilities. This is further reflected by literature linking HRV to emotion (127,143), depression and anxiety (145,146), cognition (147,148), and executive function.

The present findings have further major implications for the treatment of CP, as they highlight the vagus nerve as a potential target for therapeutic interventions. An important area involved in descending inhibitory modulation of pain is the periaqueductal gray. Recent research has shown that ventral periaqueductal grey stimulation increases HRV and decreases pain in humans with CP (149). This pathway is distinct from dorsal periaqueductal gray deep brain stimulation, suggesting that analgesia with deep brain stimulation in CP is associated with increased vagal parasympathetic activity, indexed by vmHRV (149). Considering these anatomical connections, results from the present meta-analysis provide further evidence for the prominent role of the vagus nerve in pain processing, and a rational for therapeutic vagus nerve stimulation in patients with CP (150-155) and HRV as an additional outcome measure of manifold therapeutic interventions in the treatment of CPPs (156).

Limitations and Future Directions

The present meta-analysis is the most extensive analysis of vmHRV in CPPs compared to HCs. However, there are limitations that need to be addressed. While our results support the general hypothesis of altered vagal function in CPPs, we did not address important study-level covariates in detail given the vast amount of studies included, and the major scope of the analysis. In particular, several clinical variables are likely to confound the reported effects. For example, we did not address medication intake nor comorbidities specific for several disorders as potential covariates in the meta-regression that are likely to differ among the large variety of clinical entities included. As every clinical condition represents its own etiology, further in-depth analysis of studies by clinical condition is necessary. Therefore, we will release a series of systematic reviews – taking a more narrative and exploratory approach – focusing on a single condition at a time, to further analyze the presented results and the potential risk of bias. A major limitation of the present analysis is that we had to exclude a large number of studies due to insufficient reporting of means and standard deviations of measures or because authors did not reply to our data requests in a reasonable amount of time or because the data were no longer available. We cannot deny that these data may have influenced the observed effects. That said, we agree with others authors of meta-analyses within this field of research (31), who claim that standards and a consensus on reporting HRV measures are necessary.

In the light of the theoretical framework outlined, we encourage future research on vagal activity, indexed by vmHRV in CPPs. In particular, longitudinal studies with follow-up assessments in CPPs over a longer period of time (i.e., follow-up over treatment, prospective cohort studies) are promising to extend our knowledge on ANS alterations and the role of vagal-nociceptive networks in the chronification of pain. Recently, we were able to show that vmHRV predicts increased levels of C-reactive protein 4 years later in a sample of healthy adults (157), providing in vivo support for the importance of the cholinergic anti-inflammatory pathway. As outlined above and well described in the literature inflammatory processes contribute to a large variety of

chronic painful conditions. Investigating the prospective association of vmHRV and chronic pain within prospective cohort studies may help to identify risk factors associated with the onset of persistent pain in a variety of settings. Furthermore, experimental studies that address the association of cortical networks, brain morphology, pain perception, and HRV in CPPs using fMRI studies seem promising.

Conclusions

Chronic pain patients have lower vagal activity indexed by measures of vmHRV compared to HCs. Exploring the potential mechanism underlying these findings and discussing the implications of our results, we provided evidence for (i) a role of the vagus nerve in spontaneous pain processing at the level of nociceptive transmission to the brain, (ii) highlighted shared neural networks underlying this association, referred to (iii) a model of neurovisceral integration in pain processing that links physiology to psychological concepts of interest in the study of chronic pain (i.e., comorbidities), and reviewed (iv) alterations in brain morphology in CPPs related to brain regions that are commonly associated with HRV, providing a rational why vagal activity, indexed by HRV, is altered in CPPs. We briefly discussed the vagus nerve as a target and outcome of manifold therapeutic interventions in chronic pain patients and provided suggestions for future research. It is hoped that this review will stimulate further research in this important area of CP research.

APPENDIX 1. List of abbreviations

ANS: Autonomic Nervous System
AR: Autoregressive algorithm
BM: Burning Mouth Syndrome
BP: Blood Pressure
BVP: Blood Volume Pulse
CAP: Chronic Abdominal Pain
CH: Cluster Headache
CI: Confidence interval
CNSP: Chronic Neck and Shoulder Pain
COV: Coefficient of Variance
CPPs: Chronic Pain Patients
CPPS: Chronic Pelvic Pain Syndrome
CRPS-1: Complex Regional Pain Syndrome Type 1
CVD: Cardio Vascular Diseases
ECG: Electrocardiography
FAP: Functional Abdominal Pain
FFT: Fast Fourier Transform
FM: Fibromyalgia
FSCA: SCA patients with at least three episodes of acute vaso-occlusive pain crises requiring day care or hospital admission, and opioid analgesia within the previous year
GERD: Gastroesophageal Reflux Disease
GWI: Gulf War Illness
HCs: Healthy Controls
HF-HRV: High-Frequency Heart Rate Variability
HFnu: Normalized High-Frequency Power
HFP: Absolute High-Frequency Power in MS^2
HRV: Heart Rate Variability
IBS-A: IBS-Alternating
IBS-C: Constipation-Predominant IBS
IBS-D: Diarrhea-predominant or alternating IBS
IBS: Irritable Bowel Syndrome
IBS+D: IBS with Dyspeptic Symptoms
IFSCA: SCA patients who had not experienced any pain crises during the year prior to recruitment
lnHF: Natural log transformed High-Frequency Power
MA: Migraine with Aura
MMP: Masticatory Muscle Pain
MO: Migraine without Aura
MSD: Multisomatoform Disorder
NCCP-AI: NCCP Acid Insensitive
NCCP-AS: NCCP Acid Sensitive
NCCP: Non-Cardiac Chest Pain
OAP: Organic Abdominal Pain
OP: Orofacial Pain
PHD: Primary Headache Disorders
PP: Pain Patients
PPHF: High-Frequency Peak Power
RA: Rheumatoid Arthritis
RAP: Recurrent Abdominal Pain
RMSSD: Root-Mean-Square of Successive R-R-Interval Differences
MSSD: Mean-Square of Successive R-R-Interval Differences
SD: Standard Deviation
SE: Standard Error
SEM: Standard Error of the Mean
SSc: Systemic Sclerosis
TMD: Temporomandibular Disorders
TTH: Tension-Type Headache
UAE: United Arab Emirates
vmHRV: Vagally-Mediated Heart Rate Variability

APPENDIX 2. Search strategy by database

Search terms for all databases: #1: pain; #2: heart rate variability OR HRV; #3: #1 AND #2.
PubMed: 04/03/2014: 590 results for (pain) AND ((heart rate variability) OR HRV) [ABSTRACT AVAILABLE, HUMANS].
PsycNET (via APA): 04/03/2014: 5 results for Any Field: pain AND Any Field: heart rate variability [no results for pain AND HRV].
PsycINFO (via DIMDI): 04/03/2014, 106 results for FT=pain AND (FT=heart rate variability OR FT=HRV).
EMBASE: 04/03/2014: 697 results for FT=pain AND (FT=heart rate variability OR FT=HRV) [FILTERS: AI=ABSTRACT ONLINE AND LA=ENGLISH AND pps=human].
CINAHL: 04/03/2014: 98 results for AB pain AND (AB heart rate variability OR AB HRV).
WEB OF SCIENCE: 04/03/2014: 106 results for TI pain AND (TI heart rate variability OR TI HRV) [Timespan=All years; Search language=English].
Psyndex (via MEDPILOT): 04/03/2014: 77 results for TI pain AND TI heart rate variability [English only].
The Cochrane Library: 04/03/2014: 121 results (2 reviews/119 trials) for pain:ti,ab,kw AND (heart rate variability:ti,ab,kw or HRV:ti,ab,kw) (Word variations have been searched).

APPENDIX 3. Sample Characteristics of Included Studies by First-Author in Alphabetical Order.

#	Authors	Year	Country	Language	N total	Comparison	Etiology	n PP/HC (n female)	Group	Age PP/HC mean (SD or range)	Group
1	Bajocchi et al.	2009	Italy	English	37	SSc vs. HC	OTHERS	12*1* (11) / 25 (23)	Mixed	53 (30–69) / 50 (15)	Adults
2a	Burr et al.	2000	USA	English	75	Mild AP PP vs. HC	OTHERS	34 (34) / 41 (41)	Female	31.8 (7.4) / 32.2 (8.1)	Adults
2b	Burr et al.	2000	USA	English	79	Mild AP no PP vs. HC	OTHERS	38 (38) / 41 (41)	Female	33.6 (8.1) / 32.2 (8.1)	Adults
2c	Burr et al.	2000	USA	English	59	Severe AP PP vs. HC	OTHERS	18 (8) / 41 (41)	Female	29.9 (8.5) / 32.2 (8.1)	Adults
2d	Burr et al.	2000	USA	English	57	Severe AP no PP vs. HC	OTHERS	16 (16) / 41 (41)	Female	35.9 (6.5) / 32.2 (8.1)	Adults
3a	Chalaye et al.	2012	Canada	English	33	FM vs. HC	FM	10 (10) / 10 (10)	Female	46.7 (7.1) / 41 (8.5)	Adults
3b	Chalaye et al.	2012	Canada	English	33	IBS vs. HC	IBS	13 (13) / 10 (10)	Female	37 (15.8) / 41 (8.5)	Adults
4a	Chelimsky et al.	2013	USA	English	52	IC/BPS+MPP vs. HC	OTHERS	34 (34) / 28 (28)	Female	38.7 (12.9) / 38.9 (15.71)	Adults
4b	Chelimsky et al.	2013	USA	English	45	IC/BPS vs. HC	OTHERS	17 (17) / 28 (28)	Female	43.3 (10.4) / 38.9 (15.71)	Adults
4c	Chelimsky et al.	2013	USA	English	37	MPP vs. HC	OTHERS	9 (9) / 28 (28)	Female	33.3 (10.11) / 38.9 (15.71)	Adults
5	Cheng et al.	2013	USA	English	67	IBS vs. HC	IBS	36 (19) / 31 (18)	Mixed	37.89 (1.79) / 37.26 (1.83)*2*	Adults
6	Chervin et al.	2009	USA	English	30	FM vs. HC	FM	15 (15) / 15 (15)	Female	43.7 (3.5) / 42.5 (3.3)*3*	Adults
7	Cho et al.	2011	Korea	English	153	CP/CPPS vs. HC	OTHERS	59 (0) / 94 (0)	Male	46.5 (7.02) / 48.4 (5.96)*4*	Adults
8	Cohen et al.	2000	Israel	English	44	FM vs. HC	FM	22 (22) / 22 (22)	Female	47 (7.1) / 47 (7)	Adults
9	Cohen et al.	2001	Israel	English	38	FM vs. HC	FM	19 (0) / 19 (n.r.*5*)	Male	45.8 (7.1) / n.r. (n.r.)*6*	Adults
10	De Kooning et al.	2013	Belgium	English	61	WAD vs. HC	OTHERS	30 (24) / 317 (24)	Mixed	43.6 (9.44) / 43.45 (15.87)	Adults
11	Dobrek et al.	2006	n.r.	Polish	20	IBS vs. HC	IBS	10 (n.r.) / 10 (n.r.)	-	47.3 (12.5) / 49.1 (8)	Adults
12	Evans et al.	2013	USA	English	152	Mixed vs. HC	OTHERS	48 (30) / 104 (56)	Mixed	14.2 (2.6) / 13.4 (2.8)	Children
13	Evrengül et al.	2004	Turkey	English	86	RA vs. HC	OTHERS	42 (31) /44 (31)	Mixed	48 (10.4) / 45 (8.4)	Adults
14	Figueroa et al.	2008	USA	English	19	FM vs. HC	FM	10 (10) / 9 (9)	Female	50 (10) / 49 (8)	Adults
15	Friederich et al.	2005	Germany	German	43	FM vs. HC	FM	28 (28) / 15 (15)	Female	54.5 (6.3) / 51.8 (6.8)	Adults
16	Furlan et al.	2005	Italy	English	32	FM vs. HC	FM	16 (15) / 16 (15)	Mixed	43.9 (3.2) / 37.2 (3.6)	Adults
17	Gass & Glaros	2013	USA	English	40	PHD vs. HC	PHD	21 (19) / 19 (17)	Mixed	32.86 (11.74) / 30.37 (11.20)	Adults
18	Hallman & Lyskov	2012	Sweden	English	45	CNSP vs. HC	PHD	23 (21) / 22 (20)	Mixed	40.5 (7.1) / 41.0 (6.9)	Adults
19	Hallman et al.	2011	USA	English	44	CNSP vs. HC	OTHERS	23 (21) / 21 (19)	Mixed	40.5 (7.1) / 40.8 (7)	Adults
20	Hallman et al.	2013	USA	English	56	CNSP vs. HC	OTHERS	29 (13) / 27 (12)	Mixed	41 (10) / 41 (9)	Adults
21	Heitkemper et al.	1998	USA	English	40	IBS vs. HC	IBS	25 (25) / 15 (15)	Female	32.6 (8.0) / 32.5 (8.6)	Adults
22	Heitkemper et al.	2001	USA	English	152	IBS vs. HC	IBS	103 (103) / 49 (49)	Female	32.6 (8.1) / 32.2 (7.7)	Adults
23	Hollerbach et al.	2000	Canada	English	20	NCCP vs. HC	OTHERS	8 (3) / 12 (1)	Mixed	43.5 (10) / 32 (8)	Adults
24a	Jarrett et al.	2012	USA	English	162*8*	Girls FAP/IBS vs. HC*9*	IBS	100 (70) / 62 (44)	Female	8.9 (1.1) / 9.3 (1.1)	Children
24b	Jarrett et al.	2012	USA	English	162	Boys FAP/IBS vs. HC*10*	IBS	100 (70) / 62 (44)	Male	8.9 (1.1) / 9.3 (1.1)	Children
25	Jarrett et al.	2008	USA	English	73	IBS vs. HC	IBS	35 (35) / 38 (38)	Female	31.06 (7.96) / 32.16 (6.72)	Adults
26	Karling et al.	1998	Sweden	English	54	IBS vs. HC	IBS	18 (14) / 36 (n.r.*11*)	Mixed	31.6 (20.6–49.2) / 31.4 (20.8–52.3)	Adults
27	Kim et al.	2013	Korea	English	137	RA vs. HC	OTHERS	94 (94) / 43 (43)	Female	49.7 (9.6) / 37.9 (7.2)	Adults
28	Kingsley et al.	2010	USA	English	24	FM vs. HC	FM	9 (9) / 15 (15)	Female	42 (5) / 45 (5)	Adults

APPENDIX 3. Sample Characteristics of Included Studies by First-Author in Alphabetical Order.

#	Authors	Year	Country	Language	N total	Comparison	Etiology	n PP/HC (n female)	Group	Age PP/HC mean (SD or range)	Group
29	Koszewicz et al.	2012	Poland	English	83	BM vs. HC	OTHERS	33 (27) / 30 (20)	Mixed	61.4 (9.4) / 60.5 (10.5)	Adults
30	Lavigne et al.	2011	Canada	English	48*12*	CWP vs. HC	OTHERS	24 (13) / 24 (12)	Mixed	n.r. (n.r.) / n.r. (n.r.)*13*	Adults
31	Lerma et al.	2011	Mexico	English	44	FM vs. HC	FM	22 (22) / 22 (22)	Female	32.4 (7.9) / 30.4 (7.4)	Adults
32	Luong et al.	2010	USA	English	99	FM vs. HC	FM	55 (n.r.) / 44 (n.r.)	-	n.r. (n.r.) / n.r. (n.r.)	-
33	Maixner et al.	2011	USA	English	344*814*	TMD vs. HC	OTHERS	1494 (n.r.) / 166 (n.r.)*15*	Mixed	n.r. (n.r.) / n.r. (n.r.)	Adults
34	Martínez-Lavín et al.	1997	Mexico	English	38	FM vs. HC	FM	19 (19) / 19 (19)	Female	46 (10.5) / n.r. (n.r.)*16*	Adults
35	Martínez-Lavín et al.	1998	Spain	English	60	FM vs. HC	FM	30 (n.r.*17*) / 30 (n.r.)*18*	Mixed	38.6 (10.5) / n.r. (n.r.)*19*	Adults
36	Mazur et al.	2012	Poland	English	60	IBS-C vs. HC	IBS	30 (18) / 30 (19)	Mixed	42.2 (14.0) / 38.9 (11.6)	Adults
37	Mork et al.	2013	n.r.	English	45	FM vs. HC	FM	23 (23) / 22 (n.r.)*20*	Female	52.3 (8.1) / 54.2 (8.2)	Adults
38a	Mosek et al.	1999	n.r.	English	33	MWOA vs. HC	PHD	9 (9) / 16 (16)	Female	35 (7) / 33 (7)	Adults
38b	Mosek et al.	1999	n.r.	English	33	MWA vs. HC	PHD	8 (8) / 16 (16)	Female	36 (7) / 33 (7)	Adults
39a	Nebor et al.	2011	Jamaica	English	59	FSCA vs. HC	OTHERS	15 (10) / 24 (11)	Mixed	31.3 (8.4) / 31.9 (9.2)	Adults
39b	Nebor et al.	2011	Jamaica	English	59	IFSCA vs. HC	OTHERS	20 (11) / 24 (11)	Mixed	26.5 (9.0) / 31.9 (9.2)	Adults
40	Nilsen et al.	2009	Norway	English	30	MO vs. HC	PHD	16 (16) / 14 (14)	Female	23.4 (3.2) / 22.8 (1.5)	Adults
41	Olafsdottir et al.	2001	Norway	English	48	RAP vs. HC	OTHERS	25 (15) / 23 (n.r.)	Mixed	10.7 (7–15) / 10.4 (7–13)	Children
42	Raj et al.	2000	Canada	English	31	FM vs. HC	FM	17 (17) / 14 (14)	Female	41.8 (6.5) / 35.1 (7.7)	Adults
43	Reyes del Paso et al.	2010	Spain	English	64	FM vs. HC	FM	35 (32) / 29 (27)	Mixed	50.5 (6.7) / 49.4 (9.4)	Adults
44	Schmidt & Carlson	2009	USA	English	45	MMP vs. HC	OTHERS	22 (22) / 23 (23)	Female	41.0 (12.6) / 41.0 (5)	Adults
45	Singh et al.	2012	USA	English	34	PP vs. HC	OTHERS	20 (n.r.*1*) / 14 (14)	Female	n.r. (n.r.) / n.r. (n.r.)*2*	Adults
46	Södervall et al.	2013	Finland	English	339	Sciatica vs. HC	OTHERS	201 (88) / 138 (99)	Mixed	42 (11) / 42 (11)	Adults
47	Solberg Nes et al.	2010	USA	English	100	FM/TMD vs. HC	FM	50 (50) / 50 (50)	Female	43.5 (n.r.) / 42.2 (n.r.)	Adults
48	Stein et al.	2004	USA	English	81*3*	FM vs. HC	FM	29 (21) / 39 (18)	Mixed	40 (9) / 37 (9)	Adults
49	Taneyama et al.	2013	USA	English	20	CRPS-1 vs. HC	OTHERS	10 (6) / 10 (5)	Mixed	50.9 (13.4) / 46.9 (10.3)	Adults
50	Terkelsen et al.	2012	Denmark	English	40	CRPS vs. HC	OTHERS	20 (12) /20 (12)	Mixed	43 (12) / 43 (14)	Adults
51a	Tillisch et al.	2005	USA	English	185*4*	Female IBS vs. HC	IBS	130 (65) / 55 (24)	Female	41.1 (10) / 40.2 (11)	Adults
51b	Tillisch et al.	2005	USA	English	185	Male IBS vs. HC	IBS	130 (65) / 55 (24)	Male	41.1 (10) / 40.2 (11)	Adults
52	Tubani et al.	2003	Italy	English	155	CH vs. HC	PHD	8 (0) / 7 (n.r.*6*)	Male	n.r. (n.r.) / n.r. (n.r.)*7,8*	Adults
53	Van Middendorp et al.	2013	Netherlands	English	121	FM vs. HC	FM	62 (62) / 59 (59)	Female	46.3 (10.8) / 48.9 (11.4)	Adults
54	Waring et al.	2004	Scotland	English	60	IBS vs. HC	IBS	30 (30) / 30 (30)	Female	34 (2) / 38 (2)*9*	Adults
55	Yilmaz et al.	2007	USA	English	42	CPPS vs. HC	OTHERS	22 (0) / 20 (n.r.)	Male	42.8 (9.4) / 40.4 (13.2)	Adults

1. HRV was not obtained in three patients. 2. Reported as SEM not SD. 3. Reported as SEM not SD. 4. Reported as SEM not SD. 5 Reported as "matched". 6. Reported as "matched". 7. 30 used for analysis. 8. Data available for vagal activity, sample characteristics not stratified by gender, values relate to the entire sample. 9. Separate analysis for girls and boys. 10. Separate analysis for girls and boys. 11. Reported as "matched". 12. ECG data for 23(13)/21(10). 13. Age only reported by sex: female: 46.0(SEM 3.4)/47.0(SEM 3.9); male: 41.9(SEM 2.1)/46.0(SEM 2.6) 14. 1818 analyzed in case control study. 15. Based on available data for HF-HRV. 16. Reported as "matched". 17. 93% female. 18. Reported as "matched". 19. Reported as "matched". 20. Reported as "matched"

APPENDIX 4. Methodological Characteristics of Included Studies by First-Author in Alphabetical Order.

#	First Author	Year	Comparison	Rec Length	Code	Condition	Technique	Sample Rate	HF Units	PSD Est.
1	Bajocchi et al.	2009	SSc vs. HC	30 min	Short-tem	Supine position	Plethysm.	n.r.	Normalized	n.r.
2a	Burr et al.	2000	Mild AP PP vs. HC	24 h	Long-term	24h	ECG, n.r.	n.r.	Log ms2	n.r.
2b	Burr et al.	2000	Mild AP no PP vs. HC	24 h	Long-term	24h	ECG, n.r.	n.r.	Log ms2	n.r.
2c	Burr et al.	2000	Severe AP PP vs. HC	24 h	Long-term	24h	ECG, n.r.	n.r.	Log ms2	n.r.
2d	Burr et al.	2000	Severe AP no PP vs. HC	24 h	Long-term	24h	ECG, n.r.	n.r.	Log ms2	n.r.
3a	Chalaye et al.	2012	FM vs. HC	2 min	Short-tem	Instructed to relax	ECG, 3-lead	1000 Hz	Normalized*1*	FFT
3b	Chalaye et al.	2012	IBS vs. HC	2 min	Short-tem	Instructed to relax	ECG, 3-lead	1000 Hz	Normalized*2*	FFT
4a	Chelimsky et al.	2013	IC/BPS+MPP vs. HC	10 min	Short-tem	Supine baseline	ECG, n.r.	n.r.	Log ms2	AR
4b	Chelimsky et al.	2013	IC/BPS vs. HC	10 min	Short-tem	Supine baseline	ECG, n.r.	n.r.	Log ms2	AR
4c	Chelimsky et al.	2013	MPP vs. HC	10 min	Short-tem	Supine baseline	ECG, n.r.	n.r.	Log ms2	AR
5	Cheng et al.	2013	IBS vs. HC	2 min	Short-tem	Before sigmoidoscopy	ECG, 2-lead	n.r.	Normalized	FFT/AR3
6	Chervin et al.	2009	FM vs. HC	24 h	Long-term	24h	ECG, n.r.	128 Hz	Normalized	n.r.
7	Cho et al.	2011	CPPS VS. HC	5 min	Short-tem	Seated after 30 min rest	ECG, n.r.	n.r.	ms2	n.r.
8	Cohen et al.	2000	FM vs. HC	20 min	Short-tem	Supine rest after 15 min	ECG, lead II	250Hz	Log ms2	FFT
9	Cohen et al.	2001	FM vs. HC	20 min	Short-tem	Supine rest after 15 min	ECG, lead II	500 Hz	Log ms2	FFT
10	De Kooning et al.	2013	CWAD vs. HC	5 min	Short-tem	Rest	BVP, Photoplethys.	n.r.	Log ms2	FFT
11	Dobrek et al.	2006	IBS vs. HC	5 min	Short-tem	Rest	ECG, n.r.	n.r.	ms2	n.r.
12	Evans et al.	2013	CP vs. HC	5 min	Short-tem	Sit quietly	ECG, two-lead	1000 Hz	Normalized	FFT
13	Evrengül et al.	2004	RA vs. HC	1 h	Long-term	Recumbent position	ECG, 3 channel	n.r.	ms2	FFT
14	Figueroa et al.	2008	FM vs. HC	5 min	Short-tem	Supine rest	ECG, CM5 lead	1000/200 Hz	Log ms2	FFT
15	Friederich et al.	2005	FM vs. HC	5 min	Short-tem	Supine rest	ECG, Einthoven II	1000 Hz	Log ms2	AR
16	Furlan et al.	2005	FM vs. HC	5 min	Short-tem	Supine rest	ECG, unipolar	300	ms2	n.r.
17	Gass & Glaros	2013	CHH vs. HC	5 min	Short-tem	Sitting after 10 min	ECG, 3 electrodes	n.r.	n.r.	n.r.
18	Hallman & Lyskov	2012	PHD vs. HC	24 h	Long-term	Sleep	ECG, bipolar	256 Hz	Log ms2	FFT
19	Hallman et al.	2011	CNSP vs. HC	15 min	Short-tem	Baseline, seated	ECG, bipolar	2000 Hz	Log ms2	n.r.
20	Hallman et al.	2013	CNSP vs. HC	72 h	Long-term	Sleep	ECG, two-lead	n.r.	ms2	n.r.
21	Heitkemper et al.	1998	IBS vs. HC	24 h	Long-term	24h	ECG, 3 channel	n.r.	Log ms2	FFT
22	Heitkemper et al.	2001	IBS vs. HC	24 h	Long-term	24h	ECG, 3 channel	n.r.	Log ms2	FFT
23	Hollerbach et al.	2000	NCCP vs. HC	n.r.	Short-tem	Supine rest, baseline	ECG, lead II	500Hz	ms24	AR
24a	Jarrett et al.	2012	Girls FAP/IBS vs. HC	24 h	Long-term	24h	ECG, 7 electrodes	n.r.	n.r.	FFT
24b	Jarrett et al.	2012	Boys FAP/IBS vs. HC	24 h	Long-term	24h	ECG, 7 electrodes	n.r.	n.r.	FFT
25	Jarrett et al.	2008	IBS vs. HC	>15min	Short-tem	NREM Period 1	ECG, mod lead II	200Hz	Log ms25	FFT
26	Karling et al.	1998	IBS vs. HC	120 sec	Short-tem	Supine	ECG, n.r.	500Hz	mHz2	AR
27	Kim et al.	2013	RA vs. HC	5 min	Short-tem	Resting	ECG, n,r,	500Hz	ms2	n.r.
28	Kingsley et al.	2010	FM vs. HC	5 min	Short-tem	Seated	ECG, mod CM5	1000Hz	Log ms2	FFT

APPENDIX 4. Methodological Characteristics of Included Studies by First-Author in Alphabetical Order.

29	Koszewicz et al.	2012	BMS vs. HC	n.r.	n.r.	n.r.	n.r.	n.r.	Bpm2	FFT
30	Lavigne et al.	2011	CWSP vs. HC	1 night	Short-tem	Sleep	ECG, n.r.	128 Hz	Normalized	n.r.
31	Lerma et al.	2011	FM vs. HC	24 h	Long-term	24 h	Holter, n.r.	n.r.	n.a.	n.a.

#	First Author	Year	Comparison	Rec Length	Code	Condition	Technique	Sample Rate	HF Units	PSD Est.
32	Luong et al.	2010	FM vs. HC	5 min	Short-tem	Rest	n.r.	n.r.	n.r.	n.r.
33	Maixner et al.	2011	TMD vs. HC	20 min	Short-tem	Seated in a chair	ECG, 3-lead	1024 Hz	Log ms21	n.r.
34	Martínez-Lavín et al.	1997	FM vs. HC	>256 RRs	Short-tem	Supine position	ECG, n.r.	High res	Normalized	FFT
35	Martínez-Lavín et al.	1998	FM vs. HC	24 h	Long-term	24 h	ECG, n.r.	n.r.	n.a.	n.a.
36	Mazur et al.	2012	IBS-C vs. HC	30 min	Short-term	Resting	ECG, 4-channel	n.r.	ms2	FFT
37	Mork et al.	2013	FM vs. HC	Varied	Long-term	REM sleep	ECG, mod lead II	1000 Hz	Normalized	n.r.
38a	Mosek et al.	1999	MWA vs. HC	10 min	Short-tem	Supine position	n.r.	n.r.	RF	n.r.
38b	Mosek et al.	1999	MWOA vs. HC	10 min	Short-tem	Supine position	n.r.	n.r.	RF	n.r.
39a	Nebor et al.	2011	IFSCA vs. HC	7 h	Long-term	Sleep (12 to 7 am)	ECG, n.r.	n.r.	ms2/Hz	FFT
39b	Nebor et al.	2011	FSCA vs. HC	7 h	Long-term	Sleep (12 to 7 am)	ECG, n.r.	n.r.	ms2/Hz	FFT
40	Nilsen et al.	2009	MWOA vs. HC	24h	Long-term	24h	ECG, 3 channel	1 kHz	n.a.	n.a.
41	Olafsdottir et al.	2001	RAP vs. HC	n.r.	Short-tem	after 10min stabilization	ECG, n.r.	n.r.	RSA	n.a.
42	Raj et al.	2000	FM vs. HC	24h	Long-term	24h	ECG, n.r.	n.r.	Log ms2	FFT
43	Reyes del Paso et al.	2010	FM vs. HC	5 min	Short-tem	Resting Period	ECG, bipolar	1000HZ	ms2	FFT
44	Schmidt & Carlson	2009	MMP vs. HC	10 min	Short-tem	Baseline	ECG, 3 electrodes	1000Hz	Normalized	FFT
45	Singh et al.2	2012	PP vs. HC	5 min	Short-tem	Supine rest	n.r., n.r.	n.r.	n.a.	n.a.
46	Södervall et al.	2013	Sciatica vs. HC	5 min	Short-tem	Supine	Polar HR monitor	n.r.	Log ms2	AR
47	Solberg Nes et al.	2010	FM/TMD vs. HC	10 min	Short-tem	Sitting	ECG, type II	1000Hz	Log ms2	n.r.
48	Stein et al.	2004	FM vs. HC.	24 h	Long-term	24 h	ECG, n.r.	n.r.	Log ms2	n.r.
49	Taneyama et al.	2013	CRPS-1 vs. HC	280 sec	Short-tem	Supine position	ECG, n.r.	n.r.	ms2/Hz	n.r.
50	Terkelsen et al.	2012	CRPS vs. HC	10 min	Short-tem	Supine Baseline	ECG, lead II	1000Hz	ms2/Hz	AR
51a	Tillisch et al.	2005	Females IBS vs. HC	10 min	Short-tem	Baseline	ECG, 2 lead	500 Hz	PPHF	n.r.
51b	Tillisch et al.	2005	Males IBS vs. HC	10 min	Short-tem	Baseline	ECG, 2 lead	500 Hz	PPHF	n.r.
52	Tubani et al.	2003	CH vs. HC	24 h	Long-term	24 h	ECG, n.r.	n.r.	Normalized	n.r.
53	Van Middendorp et al.	2013	FM vs. HC	90 sec	Short-tem	Neutral recall condition	ECG, lead II	1000Hz	Log ms2	DWT
54	Waring et al.	2004	IBS vs. HC	5 min	Short-tem	Baseline	ECG, n.r.	n.r.	Normalized	FFT
55	Yilmaz et al.	2007	CPPS vs. HC	5 min	Short-tem	Resting supine	ECG, 4 electrodes	n.r.	Ms2	FFT

1. SD obtained from reported SE . 2. SD obtained from reported SE . 3. Primary measures of HRV based on AR approach, author provided both FFT and AR (AR used). 4. SD obtained from reported SE. 5. RMSSD also log-transformed

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