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: University hospital in Germany

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 = 4.14, P < .0001; g = -0.34; 95% CI [-0.50, -0.18]; k = 25) and HF (Z = 4.30, P < .0001; g = -0.29; 95% CI [-0.42, -0.16]; 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 Aristotle 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 Aβ 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 periaqueductual 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 track, 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 baroreceptor-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 hypoaesthesia) (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 SNS (sp) 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. Heart rate (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 (sp) 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 (0.01 – 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 ms2 [HFP]). Regarding the recording and analysis of frequency-domain measures of vHRV (a) the unit of HF-HRV and (b) the method of power spectral density (PSD) estimation were recorded.

Descriptive statistics means and standard deviations (SD) of time (RMSSD) and frequency (HF-HRV) domain measures of vHRV 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 vHRV was included to minimize confounding effects by experimental manipulation and confilation 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-
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Random 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 I2 index, Chi-Square, and Tau2 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 ms2 or s2) 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 periodogram 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 pre-specified 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
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 65 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 was 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 males (n = 1 / 1.5%, no information on age).

**Meta-Analysis: Main Effect**

Meta-analyses on HF-HRV revealed a sizeable and significant ($Z = 4.30, P < .0001$) difference between CPPs ($n = 3,418$) and HCs ($n = 1,997$) (Hedges' $g = -0.29; 95\% CI [-0.42, -0.16]; k = 61$) 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 ($Z = 4.14, P < .0001$) lower RMSSD compared to HCs ($n = 938$) ($g = -0.34; 95\% CI [-0.50, -0.18]; k = 25$)

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**Fig. 1.** (a) FFT and (b) AR spectrum of HRV frequency analysis.
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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 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 CCPs 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 = 7) and RMSSD (Z = 3.01, P = .003; g = -0.32;
Fig. 3. Forest Plot of Random Effect Meta-Analysis on HF-HRV; 95% CI: 95% Confidence Interval; SD: Standard Deviation.
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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.
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 \((\beta = -0.370, P < 0.0001)\). 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 \((\beta = -0.352, P = 0.020)\) and RMSSD \((\beta = -0.391, P < 0.0001)\). 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 \((\beta = -0.268, P = 0.004)\) and RMSSD \((\beta = -0.217, P = 0.041)\), however, both long- and short-term recordings revealed significant differences on vmHRV between CPPs...
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 RMS-SD 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 (\( \beta = -0.290, P = 0.181 \)), indicating that both – FFT and AR – were capable of revealing differences on frequency-domain measures of vmHRV (HF) between CPPs and HCs.

### Summary of Findings

The meta-analysis revealed a significant main effect of group (HCs vs. CPPs) on time (RMS-SD) and frequency domain measures of vmHRV. CPPs showed lower RMSSD (Z = 4.14, \( P < .0001 \); g = -0.34; 95% CI [-0.50, -0.18]; k = 25) and lower HF-HRV (Z = 4.30, \( P < .0001 \); g = -0.29; 95% CI [-0.42, -0.16]; 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 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.

### 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
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 be 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 difference was found in subsamples of men (and HCs) 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 APS 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 stressor 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 disease – 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 heart rate (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 de-activation 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 circuitry 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-
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 circuitry in the brain can be observed in chronic pain (125). Efficacy in emotion regulation is related to quality of life and negative effect in patients with chronic pain (142). Resting HRV may therefore provide an index of the integrity of central-peripheral feedback that is necessary for effective 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 potential target for therapeutic interventions. An important area involved in descending inhibitory modulation of pain is the periaqueductal grey. 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 grey 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-analysis 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.

**APPENDIX 1. List of abbreviations**

ANS: autonomic nervous system  
AR: Autoressive 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: Cardiovascular 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  
HF-P: 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  
IFS: SCA patients who had not experienced any pain crises during the year prior to recruitment  
InHF: Natural log transformed High-Frequency Power  
MA: Migraine with Aura  
MMP: Masticatory Muscle Pain  
MO: Migraine without Aura  
MSD: Multisomatoform disorder  
NCCP: Non-Cancer Chest Pain  
NCCP-AI: NCCP acid insensitive  
NCCP-AS: NCCP acid sensitive  
OAP: Organic Abdominal Pain  
OP: Orofacial Pain  
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  
Sc: 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**

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].  
Psynindex (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.

<table>
<thead>
<tr>
<th>#</th>
<th>Authors</th>
<th>Year</th>
<th>Country</th>
<th>Language</th>
<th>N total</th>
<th>Comparison</th>
<th>Etiology</th>
<th>n PP/HC (n female)</th>
<th>Group</th>
<th>Age PP/HC mean (SD or range)</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Bajocchi et al.</td>
<td>2009</td>
<td>Italy</td>
<td>English</td>
<td>37</td>
<td>SSc vs. HC</td>
<td>OTHERS</td>
<td>12 (11) / 25 (23)</td>
<td>Mixed</td>
<td>33 (30–69) / 50 (15)</td>
<td>Adults</td>
</tr>
<tr>
<td>2a</td>
<td>Burr et al.</td>
<td>2000</td>
<td>USA</td>
<td>English</td>
<td>75</td>
<td>Mild AP-PP vs. HC</td>
<td>OTHERS</td>
<td>34 (34) / 41 (41)</td>
<td>Female</td>
<td>31.8 (7.4) / 32.2 (8.1)</td>
<td>Adults</td>
</tr>
<tr>
<td>2b</td>
<td>Burr et al.</td>
<td>2000</td>
<td>USA</td>
<td>English</td>
<td>79</td>
<td>Mild AP no PP vs. HC</td>
<td>OTHERS</td>
<td>38 (38) / 41 (41)</td>
<td>Female</td>
<td>33.6 (8.1) / 32.2 (8.1)</td>
<td>Adults</td>
</tr>
<tr>
<td>2c</td>
<td>Burr et al.</td>
<td>2000</td>
<td>USA</td>
<td>English</td>
<td>59</td>
<td>Severe AP PP vs. HC</td>
<td>OTHERS</td>
<td>18 (8) / 41 (41)</td>
<td>Female</td>
<td>29.9 (8.5) / 32.2 (8.1)</td>
<td>Adults</td>
</tr>
<tr>
<td>2d</td>
<td>Burr et al.</td>
<td>2000</td>
<td>USA</td>
<td>English</td>
<td>57</td>
<td>Severe AP no PP vs. HC</td>
<td>OTHERS</td>
<td>16 (16) / 41 (41)</td>
<td>Female</td>
<td>35.9 (6.5) / 32.2 (8.1)</td>
<td>Adults</td>
</tr>
<tr>
<td>3a</td>
<td>Chalaye et al.</td>
<td>2012</td>
<td>Canada</td>
<td>English</td>
<td>33</td>
<td>FM vs. HC</td>
<td>OTHERS</td>
<td>10 (10) / 10 (10)</td>
<td>Female</td>
<td>46.7 (7.1) / 41 (8.5)</td>
<td>Adults</td>
</tr>
<tr>
<td>3b</td>
<td>Chalaye et al.</td>
<td>2012</td>
<td>Canada</td>
<td>English</td>
<td>33</td>
<td>IBS vs. HC</td>
<td>OTHERS</td>
<td>13 (13) / 10 (10)</td>
<td>Female</td>
<td>37 (15.8) / 41 (8.5)</td>
<td>Adults</td>
</tr>
<tr>
<td>4a</td>
<td>Chelimsky et al.</td>
<td>2013</td>
<td>USA</td>
<td>English</td>
<td>52</td>
<td>IC/BPS+MPP vs. HC</td>
<td>OTHERS</td>
<td>34 (34) / 28 (28)</td>
<td>Female</td>
<td>37.89 (1.79) / 37.26 (1.83)</td>
<td>Adults</td>
</tr>
<tr>
<td>4b</td>
<td>Chelimsky et al.</td>
<td>2013</td>
<td>USA</td>
<td>English</td>
<td>45</td>
<td>IC/BPS vs. HC</td>
<td>OTHERS</td>
<td>17 (17) / 28 (28)</td>
<td>Female</td>
<td>43.3 (10.4) / 38.9 (15.7)</td>
<td>Adults</td>
</tr>
<tr>
<td>4c</td>
<td>Chelimsky et al.</td>
<td>2013</td>
<td>USA</td>
<td>English</td>
<td>37</td>
<td>MPP vs. HC</td>
<td>OTHERS</td>
<td>9 (9) / 28 (28)</td>
<td>Female</td>
<td>33.3 (10.1) / 38.9 (15.7)</td>
<td>Adults</td>
</tr>
<tr>
<td>5</td>
<td>Cheng et al.</td>
<td>2013</td>
<td>USA</td>
<td>English</td>
<td>67</td>
<td>IBS vs. HC</td>
<td>OTHERS</td>
<td>36 (19) / 31 (18)</td>
<td>Mixed</td>
<td>37.89 (1.79) / 37.26 (1.83)</td>
<td>Adults</td>
</tr>
<tr>
<td>6</td>
<td>Chervin et al.</td>
<td>2009</td>
<td>USA</td>
<td>English</td>
<td>30</td>
<td>FM vs. HC</td>
<td>OTHERS</td>
<td>15 (15) / 15 (15)</td>
<td>Female</td>
<td>37.3 (3.5) / 42.5 (3.3)</td>
<td>Adults</td>
</tr>
<tr>
<td>7</td>
<td>Cho et al.</td>
<td>2011</td>
<td>Korea</td>
<td>English</td>
<td>153</td>
<td>CP/CPPS vs. HC</td>
<td>OTHERS</td>
<td>59 (0) / 94 (0)</td>
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<td>Adults</td>
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<td>8</td>
<td>Cohen et al.</td>
<td>2000</td>
<td>Israel</td>
<td>English</td>
<td>44</td>
<td>FM vs. HC</td>
<td>OTHERS</td>
<td>22 (22) / 22 (22)</td>
<td>Female</td>
<td>47 (7.1) / 47 (7)</td>
<td>Adults</td>
</tr>
<tr>
<td>9</td>
<td>Cohen et al.</td>
<td>2001</td>
<td>Israel</td>
<td>English</td>
<td>38</td>
<td>FM vs. HC</td>
<td>OTHERS</td>
<td>19 (0) / 19 (n.r.)</td>
<td>Male</td>
<td>45.8 (7.1) / n.r. (n.r.)</td>
<td>Adults</td>
</tr>
<tr>
<td>10</td>
<td>De Kooning et al.</td>
<td>2013</td>
<td>Belgium</td>
<td>English</td>
<td>61</td>
<td>WAD vs. HC</td>
<td>OTHERS</td>
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<td>Adults</td>
</tr>
<tr>
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<td>Dobrek et al.</td>
<td>2006</td>
<td>n.r.</td>
<td>Polish</td>
<td>20</td>
<td>IBS vs. HC</td>
<td>OTHERS</td>
<td>10 (n.r.) / 10 (n.r.)</td>
<td>-</td>
<td>47.3 (12.5) / 49.1 (8)</td>
<td>Adults</td>
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<td>Evans et al.</td>
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<td>USA</td>
<td>English</td>
<td>152</td>
<td>Mixed vs. HC</td>
<td>OTHERS</td>
<td>48 (30) / 104 (56)</td>
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<td>Adults</td>
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<td>13</td>
<td>Evrengül et al.</td>
<td>2004</td>
<td>Turkey</td>
<td>English</td>
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<td>RA vs. HC</td>
<td>OTHERS</td>
<td>42 (31) / 44 (31)</td>
<td>Mixed</td>
<td>48 (10.8) / 45 (8.4)</td>
<td>Adults</td>
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<tr>
<td>14</td>
<td>Figueroa et al.</td>
<td>2008</td>
<td>USA</td>
<td>English</td>
<td>19</td>
<td>FM vs. HC</td>
<td>OTHERS</td>
<td>10 (10) / 9 (9)</td>
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<td>50 (10) / 49 (8)</td>
<td>Adults</td>
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<td>15</td>
<td>Friederich et al.</td>
<td>2005</td>
<td>Germany</td>
<td>German</td>
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<td>FM vs. HC</td>
<td>OTHERS</td>
<td>28 (28) / 15 (15)</td>
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<td>54.5 (6.3) / 51.8 (6.8)</td>
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<td>Furlan et al.</td>
<td>2005</td>
<td>Italy</td>
<td>English</td>
<td>32</td>
<td>FM vs. HC</td>
<td>OTHERS</td>
<td>16 (15) / 16 (15)</td>
<td>Female</td>
<td>43.9 (3.2) / 37.2 (3.6)</td>
<td>Adults</td>
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<tr>
<td>17</td>
<td>Gass &amp; Glaros</td>
<td>2013</td>
<td>USA</td>
<td>English</td>
<td>40</td>
<td>PHD vs. HC</td>
<td>OTHERS</td>
<td>21 (19) / 19 (17)</td>
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<td>32.86 (11.74) / 30.37 (11.20)</td>
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<td>Hallman &amp; Lysek</td>
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<td>English</td>
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<td>CNSP vs. HC</td>
<td>OTHERS</td>
<td>23 (21) / 22 (20)</td>
<td>Mixed</td>
<td>40.5 (7.1) / 41.0 (6.9)</td>
<td>Adults</td>
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<td>19</td>
<td>Hallman et al.</td>
<td>2011</td>
<td>USA</td>
<td>English</td>
<td>44</td>
<td>CNSP vs. HC</td>
<td>OTHERS</td>
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<td>40.5 (7.1) / 40.8 (7)</td>
<td>Adults</td>
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<td>20</td>
<td>Hallman et al.</td>
<td>2013</td>
<td>USA</td>
<td>English</td>
<td>56</td>
<td>CNSP vs. HC</td>
<td>OTHERS</td>
<td>29 (13) / 27 (12)</td>
<td>Mixed</td>
<td>41 (10) / 41 (9)</td>
<td>Adults</td>
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<td>21</td>
<td>Hettemper et al.</td>
<td>1998</td>
<td>USA</td>
<td>English</td>
<td>40</td>
<td>IBS vs. HC</td>
<td>OTHERS</td>
<td>25 (25) / 15 (15)</td>
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<td>32.6 (8.0) / 32.5 (8.6)</td>
<td>Adults</td>
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<tr>
<td>22</td>
<td>Hettemper et al.</td>
<td>2001</td>
<td>USA</td>
<td>English</td>
<td>152</td>
<td>IBS vs. HC</td>
<td>OTHERS</td>
<td>103 (103) / 49 (49)</td>
<td>Female</td>
<td>32.6 (8.1) / 32.2 (7.7)</td>
<td>Adults</td>
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<td>23</td>
<td>Hollerbach et al.</td>
<td>2000</td>
<td>Canada</td>
<td>English</td>
<td>20</td>
<td>NCP vs. HC</td>
<td>OTHERS</td>
<td>8 (3) / 12 (1)</td>
<td>Mixed</td>
<td>43.5 (10) / 32 (8)</td>
<td>Adults</td>
</tr>
<tr>
<td>24a</td>
<td>Jarrett et al.</td>
<td>2012</td>
<td>USA</td>
<td>English</td>
<td>162</td>
<td>Girls FAP/IBS vs. HC</td>
<td>OTHERS</td>
<td>100 (70) / 62 (44)</td>
<td>Female</td>
<td>8.9 (1.1) / 9.3 (1.1)</td>
<td>Children</td>
</tr>
<tr>
<td>24b</td>
<td>Jarrett et al.</td>
<td>2012</td>
<td>USA</td>
<td>English</td>
<td>162</td>
<td>Boys FAP/IBS vs. HC</td>
<td>OTHERS</td>
<td>100 (70) / 62 (44)</td>
<td>Male</td>
<td>8.9 (1.1) / 9.3 (1.1)</td>
<td>Children</td>
</tr>
<tr>
<td>25</td>
<td>Jarrett et al.</td>
<td>2008</td>
<td>USA</td>
<td>English</td>
<td>73</td>
<td>IBS vs. HC</td>
<td>OTHERS</td>
<td>35 (35) / 38 (38)</td>
<td>Female</td>
<td>31.06 (7.96) / 32.16 (6.72)</td>
<td>Adults</td>
</tr>
<tr>
<td>26</td>
<td>Karling et al.</td>
<td>1998</td>
<td>Sweden</td>
<td>English</td>
<td>54</td>
<td>IBS vs. HC</td>
<td>OTHERS</td>
<td>18 (14) / 36 (n.r.)</td>
<td>Mixed</td>
<td>31.6 (20.6–49.2) / 31.4 (20.8–52.3)</td>
<td>Adults</td>
</tr>
<tr>
<td>27</td>
<td>Kim et al.</td>
<td>2013</td>
<td>Korea</td>
<td>English</td>
<td>137</td>
<td>RA vs. HC</td>
<td>OTHERS</td>
<td>94 (94) / 43 (43)</td>
<td>Female</td>
<td>49.7 (9.6) / 37.9 (7.2)</td>
<td>Adults</td>
</tr>
<tr>
<td>28</td>
<td>Kingsley et al.</td>
<td>2010</td>
<td>USA</td>
<td>English</td>
<td>24</td>
<td>FM vs. HC</td>
<td>OTHERS</td>
<td>9 (9) / 15 (15)</td>
<td>Female</td>
<td>42 (5) / 45 (5)</td>
<td>Adults</td>
</tr>
</tbody>
</table>
### APPENDIX 3. Sample Characteristics of Included Studies by First-Author in Alphabetical Order.

<table>
<thead>
<tr>
<th>#</th>
<th>Authors</th>
<th>Year</th>
<th>Country</th>
<th>Language</th>
<th>N total</th>
<th>Comparison</th>
<th>Etiology</th>
<th>n PP/HC</th>
<th>Group</th>
<th>Age PP/HC</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>Koszewicz et al. 2012</td>
<td>Poland</td>
<td>English</td>
<td>83</td>
<td>BM vs. HC</td>
<td>OTHERS</td>
<td>33 (27) / 30 (20)</td>
<td>Mixed</td>
<td>61.4 (9.4) / 60.5 (10.5)</td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>Lavigne et al. 2011</td>
<td>Canada</td>
<td>English</td>
<td>48/12</td>
<td>CWP vs. HC</td>
<td>OTHERS</td>
<td>24 (13) / 24 (12)</td>
<td>Mixed</td>
<td>n.r. (n.r.) / n.r. (n.r.)</td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>31</td>
<td>Lerma et al. 2011</td>
<td>Mexico</td>
<td>English</td>
<td>44</td>
<td>FM vs. HC</td>
<td>FM</td>
<td>22 (22) / 22 (22)</td>
<td>Female</td>
<td>32.4 (7.9) / 30.4 (7.4)</td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>Luong et al. 2010</td>
<td>USA</td>
<td>English</td>
<td>99</td>
<td>FM vs. HC</td>
<td>FM</td>
<td>55 (n.r.) / 44 (n.r.)</td>
<td>-</td>
<td>n.r. (n.r.) / n.r. (n.r.)</td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>33</td>
<td>Maixner et al. 2011</td>
<td>USA</td>
<td>English</td>
<td>34/48</td>
<td>TMD vs. HC</td>
<td>OTHERS</td>
<td>1494 (n.r.) / 166 (n.r.)</td>
<td>Mixed</td>
<td>n.r. (n.r.) / n.r. (n.r.)</td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>Martinez-Lavin et al. 1997</td>
<td>Mexico</td>
<td>English</td>
<td>38</td>
<td>FM vs. HC</td>
<td>FM</td>
<td>19 (19) / 19 (19)</td>
<td>Female</td>
<td>46 (10.5) / 38 (9.1)</td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>Martinez-Lavin et al. 1998</td>
<td>Spain</td>
<td>English</td>
<td>60</td>
<td>FM vs. HC</td>
<td>FM</td>
<td>30 (n.r.) / 30 (n.r.)</td>
<td>Mixed</td>
<td>386 (10.5) / n.r. (n.r.)</td>
<td>Adults</td>
<td></td>
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<tr>
<td>36</td>
<td>Mazur et al. 2012</td>
<td>Poland</td>
<td>English</td>
<td>60</td>
<td>IBS-C vs. HC</td>
<td>IBS</td>
<td>30 (18) / 30 (19)</td>
<td>Female</td>
<td>42.2 (14.0) / 38.9 (11.6)</td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>37</td>
<td>Mork et al. 2013</td>
<td>n.r.</td>
<td>English</td>
<td>45</td>
<td>FM vs. HC</td>
<td>FM</td>
<td>23 (23) / 22 (n.r.)</td>
<td>Female</td>
<td>52.3 (8.1) / 54.2 (8.2)</td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>38a</td>
<td>Mosek et al. 1999</td>
<td>n.r.</td>
<td>English</td>
<td>33</td>
<td>MWOA vs. HC</td>
<td>PHD</td>
<td>9 (9) / 16 (16)</td>
<td>Female</td>
<td>35 (7) / 33 (7)</td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>38b</td>
<td>Mosek et al. 1999</td>
<td>n.r.</td>
<td>English</td>
<td>33</td>
<td>MWA vs. HC</td>
<td>PHD</td>
<td>8 (8) / 16 (16)</td>
<td>Female</td>
<td>36 (7) / 33 (7)</td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>39a</td>
<td>Nebor et al. 2011</td>
<td>Jamaica</td>
<td>English</td>
<td>59</td>
<td>FSCA vs. HC</td>
<td>OTHERS</td>
<td>15 (10) / 24 (11)</td>
<td>Mixed</td>
<td>31.3 (8.4) / 31.9 (9.2)</td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>39b</td>
<td>Nebor et al. 2011</td>
<td>Jamaica</td>
<td>English</td>
<td>59</td>
<td>FSCA vs. HC</td>
<td>OTHERS</td>
<td>20 (11) / 24 (11)</td>
<td>Mixed</td>
<td>26.5 (9.0) / 31.9 (9.2)</td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>Nilsen et al. 2009</td>
<td>Norway</td>
<td>English</td>
<td>30</td>
<td>MO vs. HC</td>
<td>PHD</td>
<td>16 (16) / 14 (14)</td>
<td>Female</td>
<td>23.4 (3.2) / 22.8 (15)</td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>41</td>
<td>Olafsdottir et al. 2001</td>
<td>Norway</td>
<td>English</td>
<td>48</td>
<td>RAP vs. HC</td>
<td>OTHERS</td>
<td>25 (15) / 23 (n.r.)</td>
<td>Mixed</td>
<td>10.7 (7-15) / 10.4 (7-13)</td>
<td>Children</td>
<td></td>
</tr>
<tr>
<td>42</td>
<td>Raj et al. 2000</td>
<td>Canada</td>
<td>English</td>
<td>31</td>
<td>FM vs. HC</td>
<td>FM</td>
<td>17 (17) / 14 (14)</td>
<td>Female</td>
<td>41.8 (6.5) / 35.1 (77)</td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>43</td>
<td>Reyes del Paso et al. 2010</td>
<td>Spain</td>
<td>English</td>
<td>64</td>
<td>FM vs. HC</td>
<td>FM</td>
<td>35 (32) / 29 (27)</td>
<td>Mixed</td>
<td>50.5 (6.7) / 49.4 (94)</td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>44</td>
<td>Schmidt &amp; Carlson 2009</td>
<td>USA</td>
<td>English</td>
<td>45</td>
<td>MMP vs. HC</td>
<td>OTHERS</td>
<td>22 (22) / 23 (23)</td>
<td>Female</td>
<td>41.0 (12.6) / 41.0 (5)</td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>45</td>
<td>Singh et al. 2012</td>
<td>USA</td>
<td>English</td>
<td>34</td>
<td>PP vs. HC</td>
<td>OTHERS</td>
<td>20 (n.r.) / 16 (14)</td>
<td>Female</td>
<td>n.r. (n.r.) / n.r. (n.r.)</td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>46</td>
<td>Sodervall et al. 2013</td>
<td>Finland</td>
<td>English</td>
<td>339</td>
<td>Sciatica vs. HC</td>
<td>OTHERS</td>
<td>201 (88) / 138 (99)</td>
<td>Mixed</td>
<td>42 (11) / 42 (11)</td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>47</td>
<td>Solberg Nes et al. 2010</td>
<td>USA</td>
<td>English</td>
<td>100</td>
<td>FM/TMD vs. HC</td>
<td>FM</td>
<td>50 (50) / 50 (50)</td>
<td>Female</td>
<td>43.5 (n.r.) / 42.2 (n.r.)</td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>48</td>
<td>Stein et al. 2004</td>
<td>USA</td>
<td>English</td>
<td>813</td>
<td>FM vs. HC</td>
<td>FM</td>
<td>29 (21) / 39 (18)</td>
<td>Female</td>
<td>40.9 (19) / 37 (9)</td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>49</td>
<td>Taneyama et al. 2013</td>
<td>USA</td>
<td>English</td>
<td>20</td>
<td>CRPS-1 vs. HC</td>
<td>OTHERS</td>
<td>10 (6) / 10 (5)</td>
<td>Mixed</td>
<td>50.9 (13.4) / 46.9 (10.3)</td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>50</td>
<td>Terkelsen et al. 2012</td>
<td>Denmark</td>
<td>English</td>
<td>40</td>
<td>CRPS vs. HC</td>
<td>OTHERS</td>
<td>20 (12) / 20 (12)</td>
<td>Mixed</td>
<td>43 (12) / 43 (14)</td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>51a</td>
<td>Tillisch et al. 2005</td>
<td>USA</td>
<td>English</td>
<td>185f</td>
<td>Female IBS vs. HC</td>
<td>IBS</td>
<td>130 (65) / 55 (24)</td>
<td>Female</td>
<td>41.1 (10) / 40.2 (11)</td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>51b</td>
<td>Tillisch et al. 2005</td>
<td>USA</td>
<td>English</td>
<td>185</td>
<td>Male IBS vs. HC</td>
<td>IBS</td>
<td>130 (65) / 55 (24)</td>
<td>Male</td>
<td>413 (10) / 402 (11)</td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>52</td>
<td>Tibani et al. 2003</td>
<td>Italy</td>
<td>English</td>
<td>151</td>
<td>CH vs. HC</td>
<td>PHD</td>
<td>8 (0) / 7 (n.r)</td>
<td>Male</td>
<td>n.r. (n.r.) / n.r. (n.r.)</td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>53</td>
<td>Van Middendorp et al. 2013</td>
<td>Netherlands</td>
<td>English</td>
<td>121</td>
<td>FM vs. HC</td>
<td>FM</td>
<td>62 (62) / 59 (59)</td>
<td>Female</td>
<td>46.3 (10.8) / 48.9 (11.4)</td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>54</td>
<td>Waring et al. 2004</td>
<td>Scotland</td>
<td>English</td>
<td>60</td>
<td>IBS vs. HC</td>
<td>IBS</td>
<td>30 (30) / 30 (30)</td>
<td>Female</td>
<td>34 (2) / 38 (29)</td>
<td>Adults</td>
<td></td>
</tr>
<tr>
<td>55</td>
<td>Yilmaz et al. 2007</td>
<td>USA</td>
<td>English</td>
<td>87</td>
<td>CUPS vs. HC</td>
<td>OTHERS</td>
<td>22 (0) / 20 (n.r.)</td>
<td>Male</td>
<td>42.8 (9.4) / 40.4 (132)</td>
<td>Adults</td>
<td></td>
</tr>
</tbody>
</table>

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.

<table>
<thead>
<tr>
<th>#</th>
<th>First Author</th>
<th>Year</th>
<th>Comparison</th>
<th>Rec. Length</th>
<th>Code</th>
<th>Technique</th>
<th>Sample Rate</th>
<th>HF Units</th>
<th>PSD Est.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Baijocchi et al.</td>
<td>2009</td>
<td>SSc vs. HC</td>
<td>30 min</td>
<td>Short-term</td>
<td>Supine position</td>
<td></td>
<td>ECG, n.r.</td>
<td>Log ms2</td>
</tr>
<tr>
<td>2a</td>
<td>Burr et al.</td>
<td>2000</td>
<td>Mild AP PP vs. HC</td>
<td>24 h</td>
<td>Long-term</td>
<td>ECG, n.r.</td>
<td></td>
<td>ECG, n.r.</td>
<td>Log ms2</td>
</tr>
<tr>
<td>2b</td>
<td>Burr et al.</td>
<td>2000</td>
<td>Severe AP PP vs. HC</td>
<td>24 h</td>
<td>Long-term</td>
<td>ECG, n.r.</td>
<td></td>
<td>ECG, n.r.</td>
<td>Log ms2</td>
</tr>
<tr>
<td>2c</td>
<td>Burr et al.</td>
<td>2000</td>
<td>Mild AP no PP vs. HC</td>
<td>24 h</td>
<td>Long-term</td>
<td>ECG, n.r.</td>
<td></td>
<td>ECG, n.r.</td>
<td>Log ms2</td>
</tr>
<tr>
<td>2d</td>
<td>Burr et al.</td>
<td>2000</td>
<td>Severe AP no PP vs. HC</td>
<td>24 h</td>
<td>Long-term</td>
<td>ECG, n.r.</td>
<td></td>
<td>ECG, n.r.</td>
<td>Log ms2</td>
</tr>
<tr>
<td>3a</td>
<td>Chalaye et al.</td>
<td>2012</td>
<td>FM vs. HC</td>
<td>5 min</td>
<td>Short-term</td>
<td>Instructed to relax</td>
<td></td>
<td>ECG, 3-lead</td>
<td>FFT</td>
</tr>
<tr>
<td>3b</td>
<td>Chalaye et al.</td>
<td>2012</td>
<td>IBS vs. HC</td>
<td>5 min</td>
<td>Short-term</td>
<td>Instructed to relax</td>
<td></td>
<td>ECG, 3-lead</td>
<td>FFT</td>
</tr>
<tr>
<td>4a</td>
<td>Chelimsky et al.</td>
<td>2013</td>
<td>IC/BPS+MPP vs. HC</td>
<td>10 min</td>
<td>Short-term</td>
<td>Supine baseline</td>
<td></td>
<td>ECG, n.r.</td>
<td>Log ms2</td>
</tr>
<tr>
<td>4b</td>
<td>Chelimsky et al.</td>
<td>2013</td>
<td>IC/BPS vs. HC</td>
<td>10 min</td>
<td>Short-term</td>
<td>Supine baseline</td>
<td></td>
<td>ECG, n.r.</td>
<td>Log ms2</td>
</tr>
<tr>
<td>4c</td>
<td>Chelimsky et al.</td>
<td>2013</td>
<td>MPP vs. HC</td>
<td>10 min</td>
<td>Short-term</td>
<td>Supine baseline</td>
<td></td>
<td>ECG, n.r.</td>
<td>Log ms2</td>
</tr>
<tr>
<td>5</td>
<td>Cheng et al.</td>
<td>2013</td>
<td>IBS vs. HC</td>
<td>2 min</td>
<td>Short-term</td>
<td>before sigmoidoscopy</td>
<td></td>
<td>ECG, n.r.</td>
<td>Log ms2</td>
</tr>
<tr>
<td>6</td>
<td>Cohen et al.</td>
<td>2000</td>
<td>FM vs. HC</td>
<td>5 min</td>
<td>Short-term</td>
<td>Rest</td>
<td></td>
<td>ECG, 3-lead</td>
<td>FFT</td>
</tr>
<tr>
<td>7</td>
<td>Cohen et al.</td>
<td>2000</td>
<td>FM vs. HC</td>
<td>5 min</td>
<td>Short-term</td>
<td>Rest</td>
<td></td>
<td>ECG, 3-lead</td>
<td>FFT</td>
</tr>
<tr>
<td>8</td>
<td>Cohen et al.</td>
<td>2011</td>
<td>CPT/SYS vs. HC</td>
<td>5 min</td>
<td>Short-term</td>
<td>Supine baseline</td>
<td></td>
<td>ECG, n.r.</td>
<td>Log ms2</td>
</tr>
<tr>
<td>9</td>
<td>Cohen et al.</td>
<td>2011</td>
<td>FM vs. HC</td>
<td>5 min</td>
<td>Short-term</td>
<td>Supine baseline</td>
<td></td>
<td>ECG, n.r.</td>
<td>Log ms2</td>
</tr>
<tr>
<td>10</td>
<td>De Kooning et al.</td>
<td>2013</td>
<td>CWAD vs. HC</td>
<td>5 min</td>
<td>Short-term</td>
<td>Rest</td>
<td></td>
<td>ECG, 3-lead</td>
<td>FFT</td>
</tr>
<tr>
<td>11</td>
<td>Dobrucki et al.</td>
<td>2013</td>
<td>RA vs. HC</td>
<td>5 min</td>
<td>Short-term</td>
<td>Rest</td>
<td></td>
<td>ECG, n.r.</td>
<td>Log ms2</td>
</tr>
<tr>
<td>12</td>
<td>Dobrucki et al.</td>
<td>2013</td>
<td>RA vs. HC</td>
<td>5 min</td>
<td>Short-term</td>
<td>Rest</td>
<td></td>
<td>ECG, n.r.</td>
<td>Log ms2</td>
</tr>
<tr>
<td>13</td>
<td>Evrengül et al.</td>
<td>2004</td>
<td>FM vs. HC</td>
<td>5 min</td>
<td>Short-term</td>
<td>Supine baseline</td>
<td></td>
<td>ECG, n.r.</td>
<td>Log ms2</td>
</tr>
<tr>
<td>14</td>
<td>Evrengül et al.</td>
<td>2004</td>
<td>FM vs. HC</td>
<td>5 min</td>
<td>Short-term</td>
<td>Supine baseline</td>
<td></td>
<td>ECG, n.r.</td>
<td>Log ms2</td>
</tr>
<tr>
<td>15</td>
<td>Freelton et al.</td>
<td>2013</td>
<td>CHL vs. HC</td>
<td>5 min</td>
<td>Short-term</td>
<td>Rest</td>
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<td>ECG, n.r.</td>
<td>Log ms2</td>
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<tr>
<td>16</td>
<td>Friedman et al.</td>
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<td>Short-term</td>
<td>Rest</td>
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<tr>
<td>17</td>
<td>Freuler et al.</td>
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<td>5 min</td>
<td>Short-term</td>
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<td>18</td>
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<td>Short-term</td>
<td>Rest</td>
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<td>Rest</td>
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<td>22</td>
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<td>Rest</td>
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<td>ECG, n.r.</td>
<td>Log ms2</td>
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<td>Rest</td>
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<td>Jarrett et al.</td>
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<td>IBS vs. HC</td>
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<td>Long-term</td>
<td>Supine baseline</td>
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<td>Short-term</td>
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<td>Year</td>
<td>Comparison</td>
<td>Rec Length</td>
<td>Code</td>
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<td>Technique</td>
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<td>29</td>
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<td>30</td>
<td>Lavigne et al.</td>
<td>2011</td>
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<td>1 night</td>
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<td>Sleep</td>
<td>ECG, n.r.</td>
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<td>31</td>
<td>Lerma et al.</td>
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<td>Long-term</td>
<td>24 h</td>
<td>Holter, n.r.</td>
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<td>32</td>
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<td>Short-tem</td>
<td>Rest</td>
<td>n.r.</td>
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<td>33</td>
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<td>2011</td>
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<td>20 min</td>
<td>Short-tem</td>
<td>Seated in a chair</td>
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<td>34</td>
<td>Martinez-Lavin et al.</td>
<td>1997</td>
<td>FM vs. HC</td>
<td>&gt; 256 RR</td>
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<td>Supine position</td>
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<td>35</td>
<td>Martinez-Lavin et al.</td>
<td>1998</td>
<td>FM vs. HC</td>
<td>24 h</td>
<td>Long-term</td>
<td>24 h</td>
<td>ECG, n.r.</td>
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<td>36</td>
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<td>30 min</td>
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<td>37</td>
<td>Mork et al.</td>
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<td>Long-term</td>
<td>REM sleep</td>
<td>ECG, mod lead II</td>
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<td>38a</td>
<td>Mosék et al.</td>
<td>1999</td>
<td>MWA vs. HC</td>
<td>10 min</td>
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<td>Supine position</td>
<td>n.r.</td>
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<td>MWOA vs. HC</td>
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<td>Supine position</td>
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<td>39a</td>
<td>Nebor et al.</td>
<td>2011</td>
<td>IFSCA vs. HC</td>
<td>7 h</td>
<td>Long-term</td>
<td>Sleep (12 to 7 am)</td>
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<td>n.r.</td>
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<td>39b</td>
<td>Nebor et al.</td>
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<td>FSCA vs. HC</td>
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<td>Long-term</td>
<td>Sleep (12 to 7 am)</td>
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<td>24 h</td>
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<td>41</td>
<td>Olafsdottir et al.</td>
<td>2001</td>
<td>RAP vs. HC</td>
<td>n.r.</td>
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<td>after 10min stabilization</td>
<td>ECG, n.r.</td>
<td>n.r.</td>
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<td>42</td>
<td>Raj et al.</td>
<td>2000</td>
<td>FM vs. HC</td>
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<td>24 h</td>
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<td>n.r.</td>
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<td>43</td>
<td>Reyes del Paso et al.</td>
<td>2010</td>
<td>FM vs. HC</td>
<td>5 min</td>
<td>Short-tem</td>
<td>Resting Period</td>
<td>ECG, bipolar</td>
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<td>ms2</td>
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<td>Schmidt &amp; Carlson</td>
<td>2009</td>
<td>MMP vs. HC</td>
<td>10 min</td>
<td>Short-tem</td>
<td>Baseline</td>
<td>ECG, 3 electrodes</td>
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<td>45</td>
<td>Singh et al 2</td>
<td>2012</td>
<td>PP vs. HC</td>
<td>5 min</td>
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<td>n.r.</td>
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<td>46</td>
<td>Södervall et al.</td>
<td>2013</td>
<td>Sciatica vs. HC</td>
<td>5 min</td>
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<td>Supine</td>
<td>Polar HR monitor</td>
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<td>47</td>
<td>Solberg Nes et al.</td>
<td>2010</td>
<td>FM/TMD vs. HC</td>
<td>10 min</td>
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<td>Sitting</td>
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<td>48</td>
<td>Stein et al.</td>
<td>2004</td>
<td>FM vs. HC</td>
<td>24 h</td>
<td>Long-term</td>
<td>24 h</td>
<td>ECG, n.r.</td>
<td>n.r.</td>
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<td>49a</td>
<td>Taneyama et al.</td>
<td>2013</td>
<td>CRPS-1 vs. HC</td>
<td>280 sec</td>
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<td>n.r.</td>
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<td>Taneyama et al.</td>
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<td>CRPS vs. HC</td>
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<td>50a</td>
<td>Terkelson et al.</td>
<td>2005</td>
<td>Females IBS vs. HC</td>
<td>10 min</td>
<td>Short-tem</td>
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<td>51a</td>
<td>Turani et al.</td>
<td>2003</td>
<td>CH vs. HC</td>
<td>24 h</td>
<td>Long-term</td>
<td>24 h</td>
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<td>51b</td>
<td>Van Middendorp et al.</td>
<td>2013</td>
<td>FM vs. HC</td>
<td>90 sec</td>
<td>Short-tem</td>
<td>Neutral recall condition</td>
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<td>Waring et al.</td>
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<td>Yilmaz et al.</td>
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<td>Resting supine</td>
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<td>Ms2</td>
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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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