Reduced heart rate variability in patients with medically unexplained physical symptoms: a meta-analysis of HF-HRV and RMSSD

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Reduced Heart Rate Variability in Patients With Medically Unexplained Physical Symptoms: A Meta-Analysis of HF-HRV and RMSSD

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ABSTRACT

Objective: Medically unexplained physical symptoms (MUPS) and related syndromes are common and place a substantial burden on both patients and society. Chronic psychological distress and dysregulation of the autonomic nervous system may be common factors associated with MUPS, although previous studies have reported mixed results. The aims of this meta-analysis are to provide an updated synthesis of studies investigating heart rate variability (HRV) indices associated with autonomic nervous system functioning in three common MUPS syndromes and to explain inconsistencies in previous study findings.

Methods: Literature search yielded 58 studies comparing HRV indices of reduced parasympathetic activity of healthy individuals with those of patients with chronic fatigue syndrome ($n_{patients}$ = 271), irritable bowel syndrome ($n_{patients}$ = 1005), and fibromyalgia ($n_{patients}$ = 534). Separate random-effects meta-analyses were conducted on studies measuring root mean square of successive differences (RMSSD) and high-frequency HRV (HF-HRV).

Results: Regardless of syndrome type, patients had significantly lower RMSSD (k = 22, Hedges g = −0.37 [−0.53 to −0.21], p < .001) and HF-HRV (k = 52, Hedges g = −0.69 [−1.03 to −0.36], p < .001) than did healthy individuals. Sample age and publication year explained a substantial variation in RMSSD, whereas controlling for confounders in statistical analyses explained variation in HF-HRV.

Conclusions: Lower RMSSD and HF-HRV in patients with MUPS versus healthy controls indicates that autonomic nervous system dysregulation, particularly lower parasympathetic activity, may play a role in patients with these conditions. This conclusion may have important implications for the underlying mechanisms and treatment of MUPS and related syndromes.

Key words: medically unexplained physical symptoms, fibromyalgia, irritable bowel syndrome, chronic fatigue syndrome, chronic stress responses, heart rate variability.

INTRODUCTION

Patients with chronic or recurring physical complaints are common in all health care sectors. A large number of these patients experience persistent complaints that cannot be attributed to a conventionally defined medical condition or are out of proportion to an underlying medical condition (1). These complaints are defined as medically unexplained physical symptoms (MUPS), but several other terms are often used as well, such as persistent somatic symptoms, functional somatic symptoms, or psychosomatic symptoms (2). MUPS include a wide range of generic symptoms or symptoms specific for one or more organs or structures in the body. These symptoms severely affect patients' quality of life and place a substantial burden on health care (3–6).

Widely acknowledged and prevalent syndrome clusters of MUPS include fibromyalgia, irritable bowel syndrome, and chronic fatigue syndrome (7,8), which show a substantial overlap in etiology and patient characteristics and also high comorbidity (8–10). It has been argued that different syndromes are a reflection of a common core phenomenon of bodily distress and are therefore best captured into a single diagnosis of bodily distress syndrome (11–13). Although a common underlying pathogenesis is therefore assumed (8), it is still unclear which mechanisms are involved in the pathogenesis of MUPS. Of note, it is likely that there are multiple underlying mechanisms, and it is thus necessary to unravel the complex and multifaceted system of etiological and perpetuating factors.

Dysfunction of the stress responsive system, particularly the autonomic nervous system, has been implicated in MUPS and may be one potential underlying mechanism of various MUPS syndromes (14,15). Previous studies have found indications of autonomic imbalance, reflected by heart rate variability (HRV) indices, such as low high-frequency HRV (HF-HRV) and root mean square of successive differences (RMSSD), in patients with fibromyalgia, irritable bowel syndrome, and chronic fatigue syndrome compared with healthy individuals (16,17). HRV indices are based on the time changes between successive heart beats, and several HRV indices can be used as a measure of parasympathetic activity (18). HRV indices associated with decreased parasympathetic

HF-HRV = high-frequency heart rate variability, **HRV** = heart rate variability, **MUPS** = medically unexplained physical symptoms, **RMSSD** = root mean square of successive differences

SDC Supplemental Content

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activity have been related to poor health outcomes, an increased risk of cardiovascular disease, and early mortality (19,20).

Although there may be biological causes for decreased HF-HRV and RMSSD in patients with MUPS that originate in their physical condition, an alternative explanation that has been suggested is that, conversely, decreased HF-HRV and RMSSD in these patients are causal to their condition and reflect a chronic psychological stress response (16,21). A chronic psychological stress response may be implicated in MUPS in at least three ways that can be simultaneously present. First, a chronic stress response may play a role in the development of MUPS. Second, it may be a consequence of MUPS. Third, the interaction between chronic stress responses and MUPS may become a self-perpetuating cycle, which maintains and intensifies distress and symptom experience. Unfortunately, there is a lack of longitudinal studies in this field that observe MUPS and HRV indices of reduced parasympathetic activity, possibly reflecting chronic psychological stress responses, over a period of time to establish potential sequences of events, providing insight into causality and direction of effects. Thus, it remains unclear which of the three aforementioned pathways is most likely the case.

Although longitudinal studies, by virtue of their scope, can suggest causal relationships, cross-sectional studies are able to assess whether variables are related in the first place, that is, a prerequisite for making causal inferences. Findings of cross-sectional studies that assessed HRV indices of parasympathetic activity in patients with MUPS and healthy controls are mixed (14,16). Studies that report differences in these HRV measures consistently show lower HF-HRV in patients as compared with healthy controls, irrespective of syndrome type (15). Although the reason for these mixed findings is still unclear, possible explanations are differences between studies in selection of participants, assessment and quantification of HRV, and common confounding factors (e.g., medication and smoking).

A meta-analysis of studies that measured HF-HRV in fibromyalgia, chronic fatigue syndrome, and irritable bowel syndrome, published around 10 years ago, found indications of decreased HF-HRV in patients compared with controls (17). However, the authors concluded that the available studies substantially lacked methodological quality and were therefore not sufficient to provide a definitive summary estimate of the role of HF-HRV in these MUPS syndromes, suggesting that study quality is an important factor to take into account when summarizing this literature.

Previous contradictory findings may further be clarified by exploring the role of several potential moderators, such as severity and duration of the disorder. In addition, differences in how HRV is recorded and presented may introduce heterogeneity in effect sizes. There are short-term (2 minutes–1 hour) and long-term (24 hours) assessments, and correlations between these are relatively weak (22). Finally, HF-HRV is often expressed in absolute or log-transformed values of power in squared milliseconds, but can also be measured in normalized units that adjust for changes in the total power of the HRV spectrum (23). It is not clear how these measurement methods can influence the results, but they often have been found to differ within studies that used more than one of them.

Over the last 10 years, meta-analyses that demonstrated decreased HF-HRV in irritable bowel syndrome (24) and chronic pain syndromes such as fibromyalgia (25) have been published. However, to the best of our knowledge, no recent meta-analysis on MUPS syndromes has been published that may include methodologically improved studies since the meta-analysis by Tak et al. (17) and addressed the potential moderators discussed here. The aim of the current study is to provide an updated synthesis of the existing evidence of HF-HRV and RMSSD in fibromyalgia, irritable bowel syndrome, and chronic fatigue syndrome. It is hypothesized that patients with these syndromes show reductions in HF-HRV and RMSSD compared with healthy individuals. Furthermore, we explore the role of study quality, publication year, sample characteristics, syndrome types and their characteristics, and HRV assessment/quantification methods.

METHODS

The present study follows the Preferred Reporting Items for Systematic Reviews and Meta-Analysis statement (26).

Search Strategy

A search of the electronic database Web of Science was conducted for empirical studies investigating HRV in patients with fibromyalgia, irritable bowel syndrome, and chronic fatigue syndrome. To build an inclusive key word profile, first a list of potential keywords was created including fibromyalgia, irritable bowel syndrome, and chronic fatigue syndrome and their synonyms. Relevance of each potential keyword was systematically assessed by combining it with HRV and related terms, while excluding the keywords that produced relevant results in previous searches, using the NOT operator (see Text, Supplemental Digital Content, for an example, http://links.lww.com/PSYMED/A692). For the final search, the following keyword profile was used: ("fibromyalgia" or "chronic fatigue syndrome" or "irritable bowel syndrome") AND (parasympath* or vagal* or sympathovagal* or "heart rate variability" or HRV* or "heart period variability" or RSA or "HF-HRV" or RMSSD). The search was conducted on January 7, 2019, with no limitation on time period. In addition, reference lists of included studies and review articles were examined to identify other relevant studies.

Eligibility Criteria

Studies were included if they a) included a short-term (2 minutes–1 hour) or long-term (10–24 hours) HF-HRV or RMSSD assessment in patients with fibromyalgia, irritable bowel syndrome, or chronic fatigue syndrome and in healthy controls and b) provided quantitative data from which effect sizes could be computed (i.e., means and standard deviations). Exclusion criteria were a) animal studies or studies with unconscious patients, b) not available as full-text article, c) published in a language other than English, d) age of sample <18 or >65 years, and e) inclusion of patients diagnosed with more than one MUPS syndrome or reporting subthreshold or temporary (≤3 months) symptoms. For intervention studies or studies that recorded HF-HRV or RMSSD under specific conditions, such as during exercise, task performance, or sleep, the baseline or presleep phase was considered. Studies that did not include a baseline or presleep phase were excluded.

Study Selection

Titles and abstracts of records from the literature search were screened for relevance based on inclusion and exclusion criteria. Of the potential eligible studies, full-text articles were collected and screened again to determine whether the studies were in accordance with the inclusion and exclusion criteria. When a full-text article was not available, a reprint request was sent to the authors. Discrepancies between two independent reviewers (S.R.V. and Y.T.) in the screening and selection of the articles were resolved by discussion (interrater reliability was 0.92). An overview of the study selection procedure is presented in Figure 1.

Quality Appraisal

Appraisal of individual study quality was conducted by S.R.V. and Y.T. based on a quality tool that has specifically been developed to assess bias in case-control studies that assess short-term HRV in MUPS syndromes across three key domains: appropriate selection of participants, appropriate quantification of HRV, and appropriate control for confounding (17). One item about the methods of HRV assessment was adjusted for studies using long-term measures of HRV based on the criteria from the Guidelines for Reporting Articles on Psychiatry and Heart rate Variability (27) as well as the recommended standards of measurement from the Task Force Paper (23). For each item, a score of 0, 1, or 2 can be obtained based on predefined response categories (Table S1, Supplemental Digital Content, http://links.lww.com/PSYMED/A692). The total quality score of a study is calculated by summing the item scores with a maximum obtainable score of 18 points.

Data Extraction

A standardized coding form was developed to extract information from each study on a) authors and publication year, b) sample size per group, c) demographic information of patients and controls, d) syndrome type and duration of the disorder, e) type of HRV index (HF-HRV, RMSSD, or both), f) recording time and position, g) HF-HRV or RMSSD (or both) per group, and h) units of reporting.

Data Analyses

The software of Rstudio Version 1.1.383 was used to conduct the analyses. Based on means, standard deviations, and sample sizes per group, standardized mean differences (Hedges *g* effect sizes) and corresponding estimated sampling variances for all included studies were obtained through the "metafor" package in Rstudio. Hedges *g* is a parametric effect size estimator and thus assumes normally distributed data. Studies presenting descriptive data in median and ranges instead of means and standard deviations ($k = 8$) were excluded because median and range are typically used to describe the distribution of data that are not normally distributed.

Separate meta-analyses were carried out for studies that measured RMSSD and HF-HRV. Because heterogeneous effect sizes were assumed a priori because of variability between the studies in terms of study population and HRV recording conditions, a random-effects model was considered more appropriate compared with a fixed-effect model to analyze the combined effect size for the cross-sectional association between MUPS and HF-HRV/RMSSD. The Q test was performed to assess the expected heterogeneity in the variances of the effect sizes, complemented by the I^2 statistic. Small, medium, and large heterogeneities are indicated by an I^2 statistic of 25, 50, and 75, respectively (28). Results were presented in a forest plot of Hedges *g* effect sizes for all included studies. Hedges *g* effect sizes can be interpreted as small (0.20), medium (0.5), or large (0.80) (29). Standardized residuals of the effect sizes were examined to identify potential outliers (absolute z value >3), and sensitivity analyses excluding these studies were performed.

Publication bias was assessed by funnel plots and the rank correlation test for funnel plot asymmetry (30). In addition, fail-safe numbers were calculated according to two methods. The Rosenthal method calculates the number of studies with nonsignificant results the sample needs to include to reduce a significant combined effect size to an insignificant value. The Orwin method calculates how many of such studies are needed get to a "trivial" effect size, that is, an effect size that is half as large as the observed combined effect size (31,32).

For both RMSSD and HF-HRV, subgroup analyses were performed to investigate moderation by syndrome type, sex distribution in the sample (all female versus mixed), recording length (short versus long-term), and

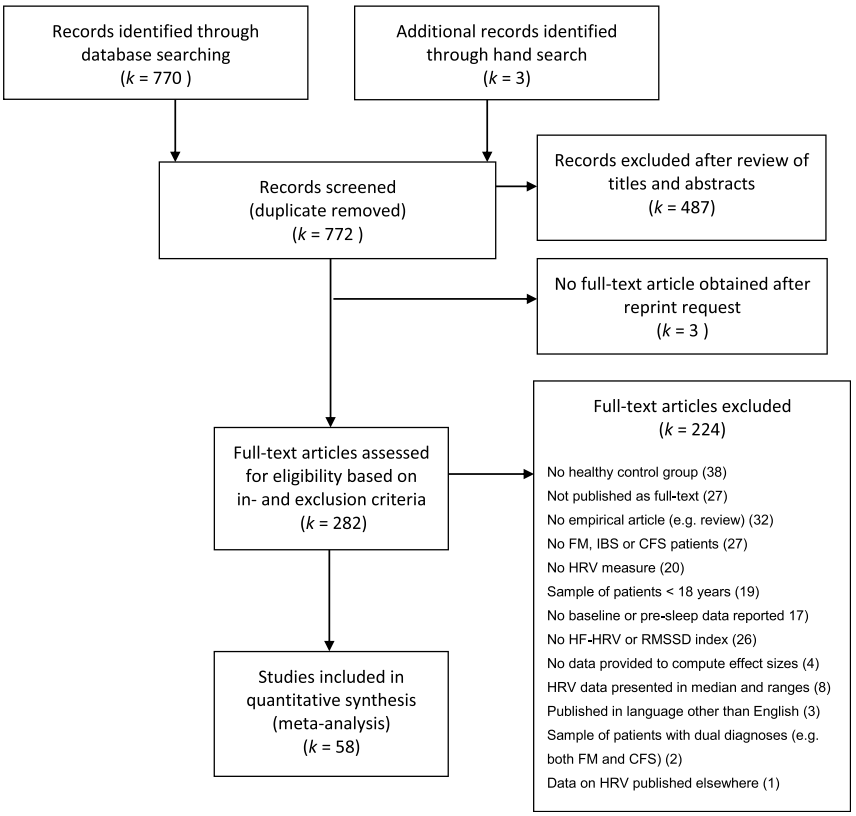

FIGURE 1. PRISMA flowchart of study screening and selection procedure. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analysis; HF-HRV = high-frequency heart rate variability; RMSSD = root mean square of successive differences; FM = fibromyalgia; CFS = chronic fatigue syndrome; IBS = irritable bowel syndrome.

position (supine versus seated). For studies that measured HF-HRV, an additional subgroup analysis was performed to assess units of reporting (absolute values in milliseconds squared, log-transformed values in milliseconds squared, or normalized units) as a moderator. The following continuous moderators were subjected to meta-regression: average age of the sample, publication year, quality score, and quality scores per domain of the quality tool. A minimum of three studies per subgroup was required for subgroup analysis and a minimum of 10 studies for meta-regression analysis. We were not able to test severity of the disorder as a moderator in both analyses because of inconsistencies in assessment and a lack of reporting.

RESULTS

Study Selection and Characteristics

The literature search yielded 770 studies. A total of 58 studies met the criteria for inclusion ($n_{patients}$ = 1810, $n_{controls}$ = 1582), of which 15 studies were also included in the meta-analysis by Tak et al. (17). Table 1 summarizes the sample and study characteristics of the included studies. Most studies recruited patients with irritable bowel syndrome (k = 23, 40%, $n_{patients}$ = 1005) or fibromyalgia (k = 22, 38%, $n_{patients}$ = 534). Studies that recruited patients with chronic fatigue syndrome were less common (k = 12, 21%, $n_{patients}$ = 271). One study recruited both patients with fibromyalgia and patients with irritable bowel syndrome (36). Because both patient groups in this study were compared with a single control group, effect sizes for both comparisons were computed using half the sample size of the control group.

Quality Appraisal of the Included Studies

Quality scores ranged from 5 to 16 (theoretical range, 0–18) and the average (standard quality) quality score was 9.67 (2.60). The total quality score for each study is displayed in Table 1. Studies scored best on items about the selection of control participants and the presentation of HF-HRV/RMSSD and worst on items about blinding of assessors and controlling for common confounders (Figure 2). However, a majority of studies matched cases and controls on the basis of sex, age, and body mass index and additionally assessed whether the groups significantly differed in terms of these variables. Furthermore, potential confounders such as sex and age are assessed as moderators of the current meta-analyses.

Meta-Analysis on RMSSD

Meta-analysis of 22 studies showed reduced RMSSD in patients, regardless of syndrome type, relative to healthy controls (n = 1385, g = −0.37 [−0.53 to −0.21], SE = 0.08, p < .001), which is a small-to-medium association. Figure 3 presents the forest plot of the effect sizes for the included studies. The Q test indicated the presence of heterogeneity among study findings (Q(21) = 42.79, p = .003, I^2 = 48.13%). No outliers were detected. Publication bias was detected by significant funnel plot asymmetry (Kendall τ = −0.41, p = .007; Figure 4A). Fail safe numbers indicated an addition of 299 studies with null results to reduce the combined effect size to an insignificant value (p > .05) and 22 insignificant studies to reduce the combined effect size into half the effect size (g = 0.23), which would still indicate a small association between reduced RMSSD and MUPS.

Meta-Analysis on HR-HRV

Meta-analysis of 52 studies showed that HF-HRV was significantly lower in patients than in healthy controls (n = 3026, g = −0.69 [−1.03 to −0.36], SE = 0.18, p < .001), which is a medium-to-large association. A forest plot of effect sizes for the included studies is displayed in Figure 5. The Q test showed a substantial heterogeneity in effect sizes between studies (Q(51) = 493.98, p < .001) complemented by a high I^2 statistic of 93.91%. Two outliers were detected, demonstrating relatively large differences in HF-HRV between patients with fibromyalgia and healthy controls in the expected direction (44,89). Exclusion of these studies lowered the strength of the association between reduced HF-HRV and MUPS (n = 2906, g = −0.52 [−0.76 to −0.28], SE = 0.12, p < .001) and resulted in less study heterogeneity (Q (49) = 353.32, p < .001, I^2 = 87.78%). The rank correlation rest for funnel plot asymmetry suggested the presence of publication bias (Kendall τ = −0.26, p = .006; Figure 4B). Comparable results were obtained for this test after exclusion of outliers (Kendall τ = −0.19, p = .048). Fail-safe number calculation using the Rosenthal and Orwin approach yielded 3314 and 52 studies, respectively, indicating the need for substantial counterevidence to reduce the strength of the effect size to an insignificant or trivial value.

Moderator Analyses

For RMSSD and HF-HFV, subgroup analyses did not indicate significant moderators. Meta-regression analyses revealed that publication year and sample age were associated with smaller associations between MUPS and RMSSD. Quality score in the domain of "appropriate control for confounders" was associated with smaller associations between MUPS and HF-HRV. Exclusion of outliers did not change the significance of the results of the moderator analyses on HF-HRV. Table 2 displays an overview of results for these moderator analyses.

DISCUSSION

Meta-analyses indicate that patients with fibromyalgia, irritable bowel syndrome, and chronic fatigue syndrome have lower HRV than do healthy individuals on both a time domain measure (RMSSD; small-to-medium association) and a frequency domain measure (HF-HRV; medium-to-large association). These findings have important implications for patients because HRV indices of reduced parasympathetic activity are associated with poor health and decreased life expectancy (19,91). Before considering the theoretical implications of our findings in detail, we will briefly discuss the difference in strength of the associations between MUPS and both HRV indices.

The overall association between MUPS and low RMMSD was smaller than between MUPS and low HF-HRV, which is surprising because these measures are known to be highly correlated (92) and is inconsistent with a previous meta-analysis on HRV in chronic pain that also included studies on fibromyalgia and irritable bowel syndrome (93). However, a similar meta-analysis that included studies on fibromyalgia but not on irritable bowel syndrome demonstrated significant differences between patients and controls only in HF-HRV and not in RMSSD (25). Although these findings suggest that associations between MUPS and the two HRV indices may differ as a function of syndrome type, this was not supported by our data.

In a further exploration of the different effect sizes for RMSSD and HF-HRV, it seemed that the number of studies that recorded HRV on the long-term, usually during a period of 24 hours, was

TABLE 1. Overview of Characteristics of the Included Studies ($k = 58$)

Study Characteristics			Sample Characteristics				Disease Characteristics			HRV Assessment	
Author	Country	Quality		*n*	Age, y	Sex	Type	Diagnostic Criteria	Duration, y	Recording Condition	HRV Index
Bardal et al. (33)	Norway	10	Cases:	25	54 (7.3)	25♀	FM	ACR	8.3 (6.5)	30 min/supine	RMSSD
			Controls:	25	52 (8.8)	25♀					
Beaumont et al. (34)	Australia	7	Cases:	30	36 (11.8)	12♂ 20♀	CFS	Fukuda	NR	3 min/seated	RMSSD
			Controls:	40	34.6 (12.1)	16♂ 24♀					
Burr et al. (35)	United States	12	Cases:	106	32.7 (7.8)	106♀	IBS	ROME I	NR	24 h	HF-HRV, RMSSD
			Controls:	41	32.2 (8.1)	24♀					
Chalaye et al. (36)	Canada	5	Cases:	10	46.7 (7.1)	10♀	FM	ACR	NR	24 h	HF-HRV
			Controls:	10*	41 (8.5)	10♀					
Chalaye et al. (36)	Canada	5	Cases:	13	37 (15.8)	13♀	IBS	ROME II	NR	24 h	HF-HRV
			Controls:	10*	41 (8.5)	10♀					
Cheng et al. (37)	United States	12	Cases:	36	37.9 (NR)	17♂ 19♀	IBS	ROME III	13 (NR)	5 min/supine	HF-HRV
			Controls:	31	37.3 (NR)	13♂ 18♀					
Chervin et al. (38)	United States	12	Cases:	15	43.7 (3.5)	15♀	FM	ACR	NR	24 h	HF-HRV, RMSSD
			Controls:	15	42.5 (3.3)	15♀					
Cohen et al. (39)	Israel	13	Cases:	22	47 (7)	22♀	FM	ACR	8 (8)	20 min/supine	HF-HRV
			Controls:	22	47 (7)	22♀					
Cohen et al. (40)	Israel	10	Cases:	19	45.8 (7.1)	19♀	FM	ACR	8 (9)	20 min/supine	HF-HRV
			Controls:	19	NR (NR)	19♀					
Cordero et al. (41)	United States	6	Cases:	11	NR (NR)	1♂ 10♀	CFS	Holmes	NR	4 min/seated	HF-HRV
			Controls:	11	NR (NR)	1♂ 10♀					
Davydov et al. (42)	Russia	15	Cases:	78	35.3 (12.8)	78♀	IBS	CDC	13.7 (11.2)	NR/seated	HF-HRV
			Controls:	27	33.3 (11.7)	27♀					
De Becker et al. (43)	Belgium	8	Cases:	21	31.7 (10.6)	6♂ 15♀	CFS	ACR	2.7 (range, 1–12)	10 min/supine	HF-HRV
			Controls:	13	28.1 (5.2)	5♂ 8♀					
Doğru et al. (44)	Turkey	9	Cases:	50	38 (7)	50♀	FM	ACR	NR	24 h	HF-HRV
			Controls:	30	36 (9)	30♀					
Duprez et al. (45)	Belgium	9	Cases:	38	34.8 (8)	9♂ 29♀	CFS	Holmes	NR	24 h	HF-HRV, RMSSD
			Controls:	38	35.6 (10.5)	9♂ 29♀					
Durakoğlugil et al. (46)	Turkey	11	Cases:	30	45 (12)	30♀	IBS	ROME III	NR	24 h	HF-HRV, RMSSD
			Controls:	30	47 (10)	30♀					
Elsenbruch and Orr (47)	United States	13	Cases:	24	32.8 (NR)	24♀	IBS	ROME	13.2 (2.2)	30 min/supine	HF-HRV
			Controls:	20	32.2 (NR)	20♀					
Figueroa et al. (48)	United States	11	Cases:	10	49 (8)	10♀	FM	Rheumatologist	NR	5 min/supine	HF-HRV, RMSSD
			Controls:	9	50 (10)	9♀					
Fournier et al. (49)	France	12	Cases:	25	36.2 (10.7)	7♂ 18♀	IBS	ROME II	10.2 (range, 0.3–31)	10 min/NR	HF-HRV
			Controls:	26	39 (11.7)	8♂ 18♀					
Hansen et al. (50)	Norway	10	Cases:	19	40.1 (9.9)	19♀	CFS	Oxford	4 (range, 1–10)	3 min/seated	RMSSD
			Controls:	21	43.2 (11.3)	21♀					

Heitkemper et al. (51)	United States	8	Cases: Controls:	25 125	32.6 (8) 32.5 (8.6)	25♀ 125♀	IBS	ROME	NR	24 h	HF-HRV
Heitkemper et al. (52)	United States	9	Cases: Controls:	103 106	32.6 (8) 32.2 (7.7)	103♀ 106♀	IBS	ROME I	NR	24 h	HF-HRV, RMSSD
Jarrett et al. (53)	United States	10	Cases: Controls:	103 46	33 (8) 33 (8)	103♀ 46♀	IBS	ROME I	NR	24 h	HF-HRV, RMSSD
Jones et al. (54)	United Kingdom	7	Cases: Controls:	16 8	NR (NR) NR (NR)	16♀ 8♀	CFS	Fukuda	NR	10 min/supine	HF-HRV
Kang et al. (55)	Korea	10	Cases: Controls:	16 16	49.8 (7.4) 49.9 (7.6)	4♂ 12♀ 4♂ 12♀	FM	Rheumatologist	3–20	NR/supine	RMSSD
Kano et al. (56)	Japan	5	Cases: Controls:	28 34	21.9 (2.7) 22.2 (2.7)	14♂ 14♀ 17♂ 14♀	IBS	NR	8 (5.6)	5 min/NR	HF-HRV
Karling et al. (57)	Sweden	6	Cases: Controls:	18 36	31.6 (NR) 31.4 (NR)	4♂ 14♀ NR	IBS	ROME	NR	NR/supine	HF-HRV
Kingsley et al. (58)	United States	13	Cases: Controls:	9 20	42 (5) 45 (5)	9♀ 20♀	FM	Rheumatologist	7 (3)	2-5 min/NR	HF-HRV
Kingsley et al. (59)	United States	9	Cases: Controls:	9 9	48 (NR) 48 (NR)	9♀ 9♀	FM	ACR	NR	5 min/seated	HF-HRV
Kosek et al. (60)	Sweden	10	Cases: Controls:	15 15	46.2 (1.1) 44.4 (10.7)	15♀ 15♀	FM	ACR	2.9 (2.7)	24 h	HF-HRV, RMSSD
Lerma et al. (61)	Mexico	11	Cases: Controls:	22 22	32.4 (7.9) 30.4 (7.4)	22♀ 22♀	FM	ACR	6.8 (6.1)	24 h	RMSSD
Malfliet et al. (62)	Belgium	8	Cases: Controls:	20 20	41.1 (8.9) 39.9 (14.2)	20♀ 20♀	CFS	ACR	NR	10 min/seated	RMSSD
Martinez-Lavin et al. (63)	Mexico	10	Cases: Controls:	19 19	46 (10.5) 45 (NR)	19♀ 19♀	FM	ACR	6.7 (6.4)	15 min/supine	HF-HRV
Martínez-Lavín et al. (64)	Mexico	12	Cases: Controls:	30 30	38.6 (10.5) NR (NR)	2♂ 28♀ NR	FM	ACR	6.5 (5.5)	24 h	RMSSD
Mazur et al. (65)	Poland	5	Cases: Controls:	23 30	45 (13) 47 (5)	8♂ 15♀ 15♂ 15♀	IBS	ROME II	NR	30 min/NR	HF-HRV
Mazur et al. (66)	Poland	5	Cases: Controls:	30 30	42.2 (14) 38.9 (11.6)	12♂ 18♀ 11♂ 19♀	IBS	ROME III	NR	30 min/NR	HF-HRV
Mazurak et al. (67)	Germany	9	Cases: Controls:	21 42	34 (10.4) 38.2 (11.4)	21♀ 42♀	IBS	ROME II	NR	3 min/supine	HF-HRV, RMSSD
Ng et al. (68)	Australia	9	Cases: Controls:	8 8	39 (3.8) 38 (4.4)	NR NR	IBS	ROME II	NR	2 min/NR	HF-HRV
Orr et al. (69)	United States	6	Cases: Controls:	15 15	34.9 (2.1) 36.2 (2.3)	2♂ 13♀ 2♂ 13♀	IBS	ROME I	NR	10 h	HF-HRV
Pellissier et al. (70)	France	12	Cases: Controls:	26 26	36 (10) 38 (11)	8♂ 18♀ 7♂ 19♀	IBS	ROME II	13.4 (range, 1–28)	10 min/seated	HF-HRV

Continued on next page

TABLE 1. *(Continued)*

Study Characteristics			Sample Characteristics				Disease Characteristics			HRV Assessment	
Author	Country	Quality		*n*	Age, y	Sex	Type	Diagnostic Criteria	Duration, y	Recording Condition	HRV Index
Pellissier et al. (71)	France	13	Cases: Controls:	27 21	39 (NR) 40 (14)	9♂ 18♀ 8♂ 13♀	IBS	ROME II	9.1 (range, 1–21)	10 min/seated	HF-HRV, RMSSD
Raj et al. (72)	Canada	9	Cases: Controls:	17 14	41.8 (6.5) 35.1 (7.7)	17♀ 14♀	FM	ACR	NR	5 min/supine, 24 h	HF-HRV
Reis et al. (73)	Brazil	9	Cases: Controls:	10 10	52 (10) 45 (9)	10♀ 10♀	FM	ACR	NR	10 min/supine	HF-HRV, RMSSD
del Paso et al. (74)	Spain	12	Cases: Controls:	35 29	50.5 (49.4) 50.5 (49.4)	3♂ 32♀ 2♂ 27♀	FM	ACR	NR	5 min/seated	HF-HRV
del Paso et al. (75)	Spain	12	Cases: Controls:	35 29	50.5 (49.4) 50.5 (49.4)	3♂ 32♀ 2♂ 27♀	FM	ACR	NR	5 min/seated	HF-HRV
Rizzi et al. (76)	Italy	9	Cases: Controls:	50 45	53.6 (8.4) 44.4 (8)	50♀ 45♀	FM	ACR	7.6 (3.2)	5 min/supine	HF-HRV
Robinson et al. (77)	United Kingdom	8	Cases: Controls:	35 10	46.9 (11.9) 49.4 (15.3)	12♂ 23♀ 3♂ 7♀	CFS	NICE	14.5 (10)	10 min/supine	HF-HRV
Rost et al. (78)	Luxembourg	7	Cases: Controls:	47 45	45.5 (9.2) 44.9 (12.2)	8♂ 39♀ 8♂ 37♀	FM	ACR	NR	5 min/seated	HF-HRV, RMSSD
Salvioli et al. (79)	Italy	10	Cases: Controls:	41 42	40 (2) 41 (2)	12♂ 29♀ 14♂ 28♀	IBS	ROME III	NR	10 min/supine	HF-HRV
Stein et al. (80)	United States	10	Cases: Controls:	29 39	40 (9) 37 (9)	8♂ 21♀ 20♂ 19♀	FM	ACR	NR	24 h	HF-HRV, RMSSD
Tanaka et al. (81)	Japan	10	Cases: Controls:	165 31	35 (11) 37 (12)	34♂131♀ 7♂ 24♀	IBS	ROME III	NR	24 h	HF-HRV
Thompson et al. (82)	United States	13	Cases: Controls:	16 21	37 (NR) 38 (NR)	16♀ 21♀	IBS	ROME I	NR	30 min/supine	HF-HRV
Tousignant-Laflamme et al. (83)	Canada	9	Cases: Controls:	14 13	NR (NR) NR (NR)	14♀ 13♀	IBS	ROME II	NR	2 min/NR	HF-HRV
Van Oosterwijck et al. (84)	Belgium	10	Cases: Controls:	20 20	41.6 (9.8) 34.6 (15.2)	20♀ 20♀	CFS	CDC/Canadian criteria	5.9 (range, 0–13.5)	10 min/supine	HF-HRV, RMSSD
Waring et al. (85)	Scotland	10	Cases: Controls:	30 30	34 (NR) 38 (NR)	30♀ 30♀	IBS	ROME II	NR	5 min/supine	HF-HRV
Yamamoto et al. (86)	Japan	8	Cases: Controls:	24 22	NR (NR) NR (NR)	24♀ 26♀	CFS	CDC	NR	5 min/supine	HF-HRV
Yataco et al. (87)	United States	8	Cases: Controls:	19 11	29 (12) 34 (9)	5♂ 14♀ 4♂ 7♀	CFS	CDC	4 (range, 1–7)	5 min/supine	HF-HRV
Yoshiuchi et al. (88)	United States	5	Cases: Controls:	18 25	36.6 (7.1) 40.4 (7.4)	3♂ 15♀ 5♂ 20♀	CFS	CDC	NR	5 min/supine	HF-HRV

Zamunér et al. (89)	Brazil	14	Cases:	20	48 (7)	20♀	FM	ACR	8 (4.6)	15 min/supine	HF-HRV
			Controls:	20	46 (7)	20♀					
Zamunér et al. (90)	Brazil	16	Cases:	20	48.2 (6.1)	20♀	FM	ACR	7.05 (4.5)	15 min/supine	HF-HRV, RMSSD
			Controls:	20	45.8 (7.3)	20♀					

HRV = heart rate variability; FM = fibromyalgia; ACR = American College of Rheumatology; RMSSD = root mean square of the successive differences; CFS = chronic fatigue syndrome; NR = not reported; IBS = irritable bowel syndrome; HF-HRV = high-frequency heart rate variability; CDC = Centers for Disease Control and Prevention; NICE = National Institute for Health and Care Excellence.
*These are the same control participants, half this sample size is used for effect size calculation.

relatively higher in the analyses on RMSSD (47.62%) than on HF-HRV data (27.45%). Compared with short-term standardized laboratory assessments, 24-hour recordings may be influenced by unstandardized individual and environmental factors (94). On the other hand, the generalizability of laboratory-based measures is questionable, as the reaction of the participant to being measured in an artificial setting may induce physiological processes that are not representative of HRV in daily life. However, potential reliability issues in these studies are unlikely to explain the overall smaller association between MUPS and low RMSSD than between MUPS and low HF-HRV because recording length did not moderate findings in both analyses. It should be noted that spectral power analysis methods such as autoregression or fast Fourier transformation of HF-HRV generally used in the included studies require stationary data, implying that the shape of the distribution of a series does not change over time. Stationarity of the signal is strongly associated with recoding duration, as rapid changes in the physiological state of an individual during a longer observation period are quite common, whereas this is not the case for short-term recordings (23). Although the interpretation of HF-HRV on long-term recordings is generally limited by nonstationary data, most of the included studies did not take this into account.

Theoretical Implications

Based on the current synthesis of cross-sectional studies, it is clear that there is a relation between HRV indices reflecting reduced parasympathetic activity, a typical autonomic nervous system response to acute and chronic psychological distress, and MUPS syndromes (fibromyalgia, irritable bowel syndrome, and chronic fatigue syndrome). Because of a lack of longitudinal studies, the existing evidence is at this point insufficient to draw definitive conclusions about potential underlying mechanisms of reduced parasympathetic activity, which possibly reflects a chronic psychological stress response, in patients with MUPS. Still, some speculations seem warranted because they might help to focus future research. In our view, there are three possible pathways of how chronic stress responses may be implicated in MUPS. Theoretical arguments and suggestive empirical evidence for these three pathways will be described in detail in the three sections hereinafter.

Chronic Stress Responses Implicated in the Development of MUPS

Many physical symptoms may represent normal bodily reactions to stressors. Increased muscle tension, HPA-axis activity, and autonomic arousal are evolutionary adaptive mechanisms, allowing for efficient responding to acute stressors, that is, a fight or flight response. In the case of chronic stress responses, however, the stage of efficient responding is surpassed, and these bodily responses can have detrimental effects on the body (95). For example, extended periods of muscle tension can induce pain symptoms and chronic activation of neuroendocrine and autonomic systems may lead to altered sleep patterns and a dysfunctional immune system (96). Because a sympathovagal balance shift toward sympathetic predominance is central in these bodily stress responses, it might explain why HRV indices of reduced parasympathetic activity are associated with MUPS. These direct effects of chronic stress responses on bodily functioning have been proposed to explain symptoms of chronic fatigue syndrome and fibromyalgia

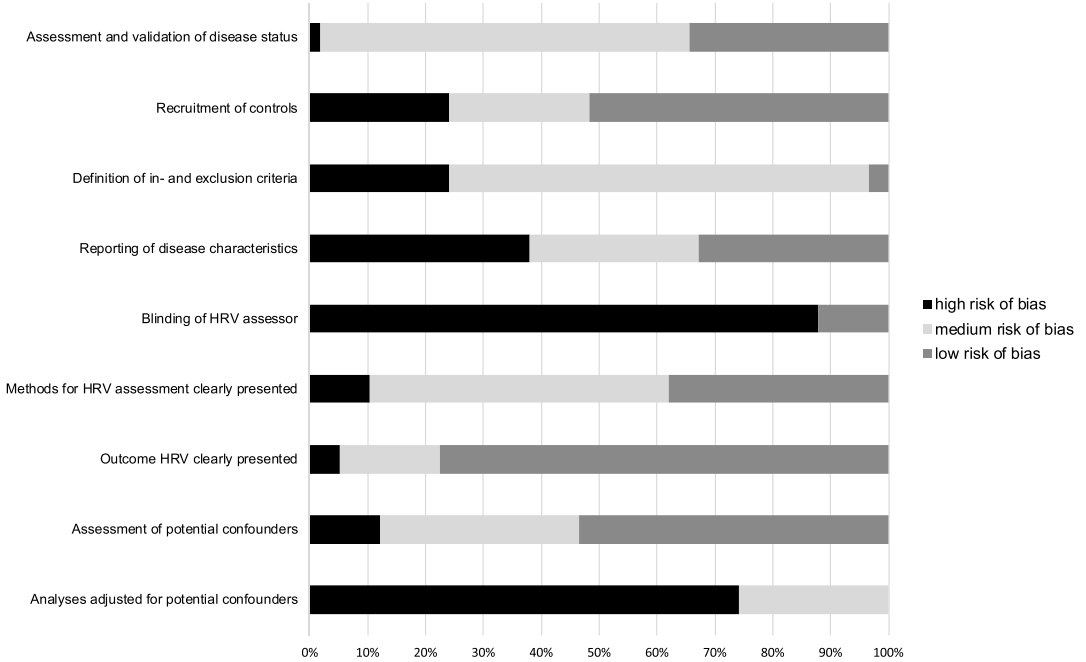

FIGURE 2. Quality appraisal of the included studies. HRV = heart rate variability.

(97), but may also be involved in other types of MUPS. Second, somatic symptoms may be accounted for by changes in cardiovascular, immunological, and endocrine systems through prolonged physiological activation as a consequence of childhood adversities and stressful life events (98). A number of studies have demonstrated physical and sexual abuse during childhood as a risk factor for irritable bowel syndrome and chronic fatigue syndrome (99,100), and there is evidence for autonomic nervous system dysregulation in adults with early life stress histories (52,101–104). Moreover, besides physiological aspects, there are several cognitive aspects of chronic psychological

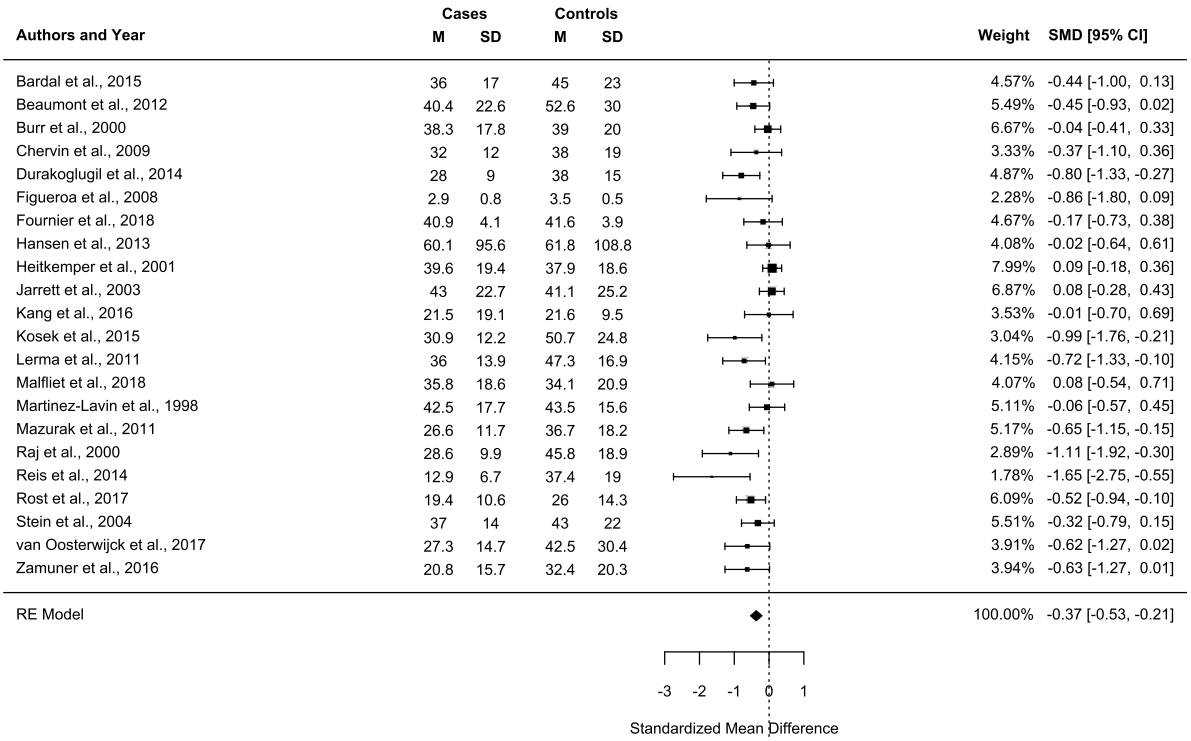

FIGURE 3. Forest plot of the random-effects meta-analysis of case-control studies with RMSSD as an outcome variable ($k = 22$). RMSSD = root mean square of successive differences; M = mean; SD = standard deviation; SMD = standardized mean difference; CI = confidence interval; RE = Random Effects.

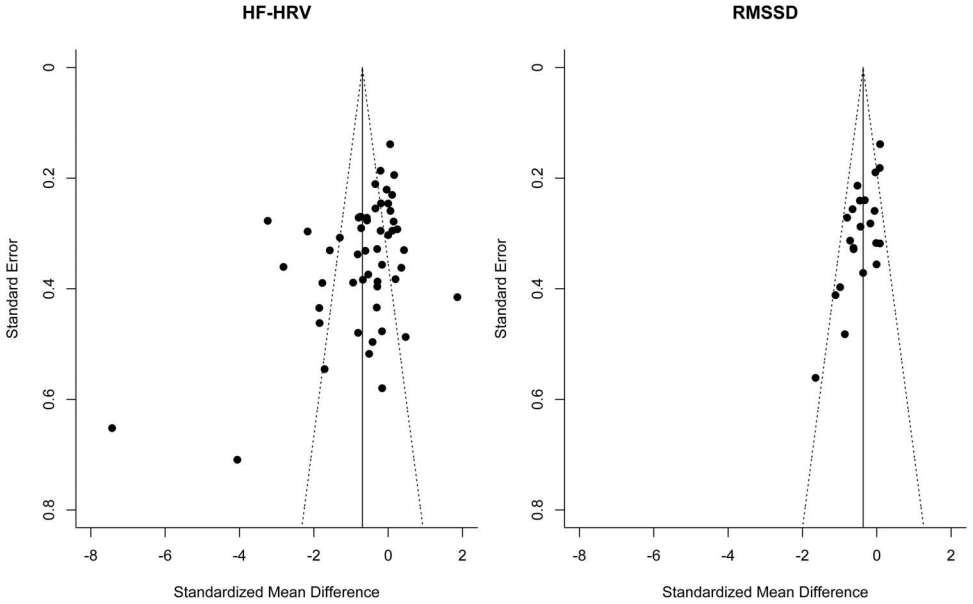

FIGURE 4. Funnel plots of Hedges *g* by the standard error for studies that measured RMSSD and HF-HRV. RMSSD = root mean square of successive difference; HF-HRV = high-frequency heart rate variability.

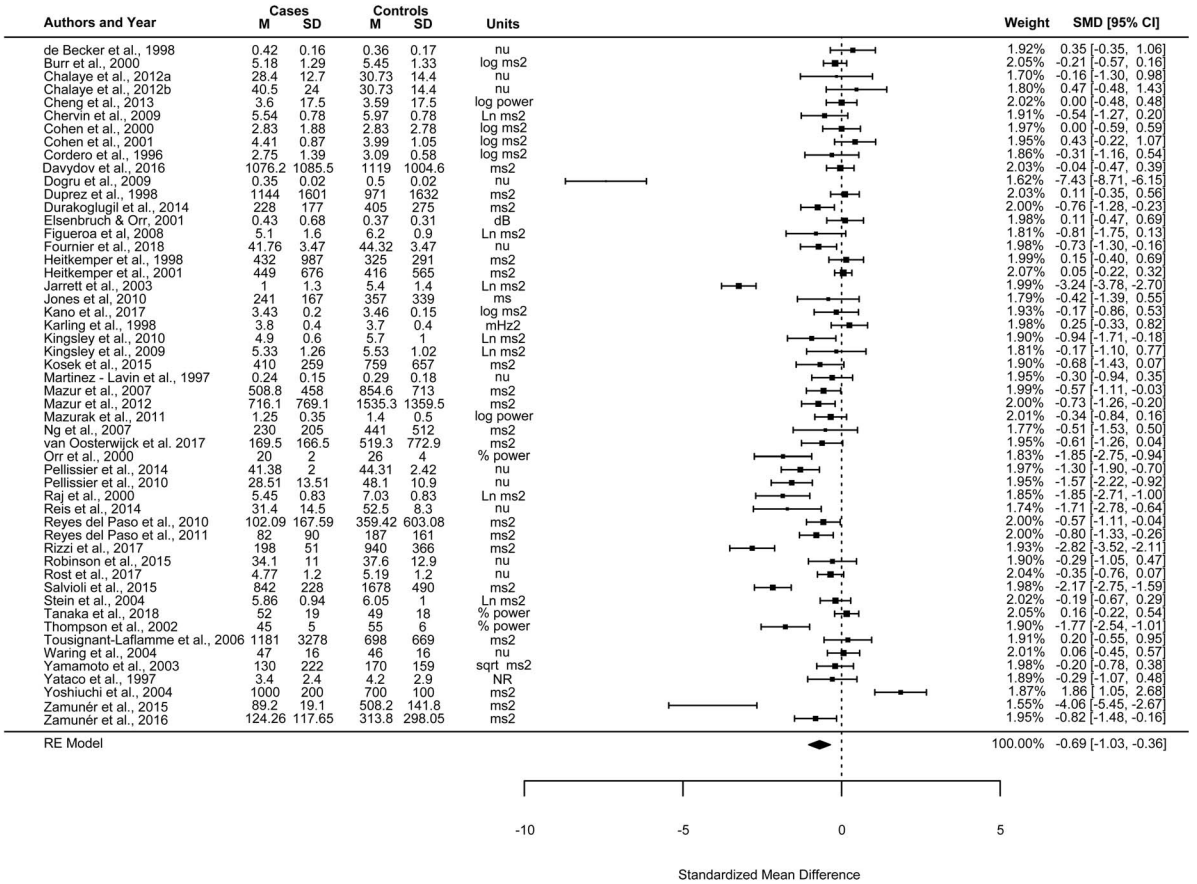

FIGURE 5. Forest plot of the random-effects meta-analysis of case-control studies with HF-HRV as an outcome variable (k = 52). HF-HRV = high-frequency heart rate variability; M = mean; SD = standard deviation; SMD = standardized mean difference; CI = confidence interval; RE = Random Effects.

TABLE 2. Results of Moderator Analyses

	RMSSD (k = 22)			HF-HRV (k = 52)		
	β	Q	p	β	Q	p
Syndrome type		4.49	.11		4.02	.13
Sex		1.34	.25		0.83	.36
Recording length		0.64	.42		0.66	.42
Recording position		2.00	.37		0.01	.92
Units of reporting		NA	NA		3.54	.32
Study quality	0.004		.93	−0.09		.15
Selection of participants	−0.02		.81	−0.03		.76
Quantification of HRV	−0.02		.77	−0.08		.66
Control for confounders	0.03		.75	−0.49		**.002**
Age	−0.03		**.023**	−0.02		.11
Publication year	−0.02		**.026**	−0.04		.13
Disease duration	0.03		.52	0.01		.83

Subgroup random-effects meta-analyses were performed for categorical variables. Continuous variables were subjected to meta-regression.

RMSSD = root mean square of successive differences; HF-HRV = high-frequency heart rate variability; HRV = heart rate variability.

p Values <.05 are presented in bold.

stress responses that may increase somatic symptom experience. Stressed individuals are susceptible to negative and catastrophic thinking and to making disease-related attributions for bodily sensations, which may eventually contribute to the development of MUPS (105–107). There is abundant evidence that HRV indices of reduced parasympathetic activity are associated with these negative cognitive phenomena (19,108).

Chronic Stress Responses as a Consequence of MUPS

Chronic stress responses may also be a *consequence* of MUPS. In this view, the experience of symptoms on itself can act as a strong stressor triggering these chronic stress responses. MUPS are even more stressful because of the lack of explanation as to the origin of the symptoms and uncertainty about the prognosis and consequences of the condition (98). Second, the effect of MUPS might be of a much more unconscious nature. From an evolutionary perspective, a healthy body is essential for an adequate fight or flight response in the face of potential stressors. Our physical ability to deal with potential stressors is thus an important source of perceived safety. There is reason to believe that a mere reduction in this ability might be enough for a continuous stress response, as reflected by reduced HF-HRV and RMSSD.

According to a novel theory of chronic stress, lack of perceived safety is a sufficient requirement for a chronic stress response, even in the absence of stressors (threats or thoughts about threats). This theory, named Generalized Unsafety Theory of Stress (109,110), argues that the stress response is not triggered by a stressor but is a "default response, that is left on" when safety is not perceived. This idea is based on recent neurobiological insights that the amygdala is activated *by default* but is tonically inhibited by the prefrontal cortex under conditions of perceived safety. In contrast, a lack of appraisal of safety maintains the default stress response by means of prefrontal disinhibition, which is reflected by reduced HRV indices of parasympathetic activity. Because this mechanism is phylogenetically ancient, it remains largely unconscious. It is thought to explain the chronic stress response found in many conditions without sufficient stressors to account for it, such as in loneliness, low social economic status, and in adults with a history of childhood stress. An unfit body is believed to be such a condition too (110). Organisms that chronically preemptively disinhibited their stress response when they were—temporarily or chronically—less able to realize an adequate fight or flight response in the face of possible future danger had a survival advantage. Indeed, low HF-HRV and RMSSD have been found in several other conditions of bodily unfitness, such as obesity and low aerobic fitness (50,111). Thus, a Generalized Unsafety Theory of Stress explanation for the findings of this meta-analysis would be that because of a "compromised" bodily state, MUPS is associated with unconsciously experienced generalized unsafety, indicated by low HF-HRV and RMSSD. Most likely both mechanisms are at work at the same time, the conscious one due to "MUPS as stressor" and the current one due to unconscious unsafety. Thus, stress responses may co-determine MUPS and also be the consequence of them.

The Self-Perpetuating Cycle of Chronic Stress Responses and MUPS

Chronic stress responses are thus assumed a potential cause and consequence of MUPS, and so the patient can theoretically become locked into a self-perpetuating cycle of increased distress and symptom maintenance. For example, early life stress can lead to prolonged physiological activation (i.e., chronic disinhibited default stress response) due to generalized perceptions that the world is an unsafe place. This chronic default stress response may in turn cause somatic symptoms (either medically explained or unexplained) through detrimental effects on cardiovascular, immunological, and endocrinal systems. These somatic symptoms and illness experiences may further amplify the chronic stress response (or further disinhibit the default stress response), at least to some extent, because now also the body is no longer perceived as safe.

Limitations and Future Directions

This study has several potential limitations. First, we exclusively searched for articles in the electronic database Web of Science. Second, studies reporting HRV data in median and ranges were excluded from the analyses. However, because most of these studies are in line with our findings, we do not expect that these data would have altered the observed effects. Third, publication bias was supported by the asymmetric funnel plot but did not correspond with the high fail-safe numbers. Fourth, substantial variation among study findings in our meta-analyses remained unexplained, so there may be potential moderators that we have overlooked.

Throughout this article, we have emphasized the need for longitudinal research to elucidate the mechanisms underlying reduced HF-HRV and RMSSD in fibromyalgia, irritable bowel syndrome, and chronic fatigue syndrome, as well as in other MUPS syndromes, and explore potential differences between and within the MUPS syndromes. There are also a number of nonlinear methods, such as the short-term fractal scaling exponent or the ratio of the

axes of the Poincare plot (SD1/SD2) that capture the balance between randomness and predictability of the heart rate pattern (112). However, studies using nonlinear methods (73) have not accumulated to the point that it is reasonable to conduct a meta-analysis. Future studies using graphic or nonlinear analysis are needed to evaluate HRV in MUPS, while considering the organization of heart rate patterns. Follow-up longitudinal studies should also be undertaken for further elucidation of the nature of the association between HRV and MUPS. Because this meta-analysis is quite robust, new (small) cross-sectional studies on HF-HRV and RMSSD are not necessary. Moreover, future research should continue to focus on the development of standards for the use and interpretation of HRV measures and consensus in terms of reporting.

CONCLUSIONS

The current study provides updated meta-analytic evidence of studies that measured HF-HRV in the three most common MUPS syndromes since the meta-analysis by Tak et al. (17). Ten years later and including twice as many studies, we find support for an association between HRV indices of reduced parasympathetic activity and MUPS, possibly reflecting chronic psychological distress. Future research is needed to understand potential causal pathways in this relation. A first step would be to assess whether dysfunction of the autonomic nervous system precedes MUPS syndromes and whether it normalizes when MUPS syndromes are effectively treated (113,114).

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