Systematic Review and Meta-Analysis

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# Evidence of altered cardiac autonomic regulation in myalgic encephalomyelitis/chronic fatigue syndrome

## A systematic review and meta-analysis

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**Abstract**

**Background:** Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a complex condition with no reliable diagnostic biomarkers. Studies have shown evidence of autonomic dysfunction in patients with ME/CFS, but results have been equivocal. Heart rate (HR) parameters can reflect changes in autonomic function in healthy individuals; however, this has not been thoroughly evaluated in ME/CFS.

**Methods:** A systematic database search for case-control literature was performed. Meta-analysis was performed to determine differences in HR parameters between ME/CFS patients and controls.

**Results:** Sixty-four articles were included in the systematic review. HR parameters assessed in ME/CFS patients and controls were grouped into ten categories: resting HR (RHR), maximal HR ($HR_{max}$), HR during submaximal exercise, HR response to head-up tilt testing ($HR_{tilt}$), resting HR variability ($HRV_{rest}$), HR variability during head-up tilt testing ($HRV_{tilt}$), orthostatic HR response ($HR_{OR}$), HR during mental task(s) ($HR_{mentaltask}$), daily average HR ($HR_{dailyaverage}$), and HR recovery (HRR) Meta-analysis revealed RHR (MD ± 95% CI = 4.14 ± 1.38, $P < .001$), $HR_{tilt}$ (SMD ± 95% CI = 0.92 ± 0.24, $P < .001$), $HR_{OR}$ (0.50 ± 0.27, $P < .001$), and the ratio of low frequency power to high frequency power of $HRV_{rest}$ (0.39 ± 0.22, $P < .001$) were higher in ME/CFS patients compared to controls, while $HR_{max}$ (MD ± 95% CI = −13.81 ± 4.15, $P < .001$), HR at anaerobic threshold (SMD ± 95% CI = −0.44 ± 0.30, $P = 0.005$) and the high frequency portion of $HRV_{rest}$ (−0.34 ± 0.22, $P = .002$) were lower in ME/CFS patients.

**Conclusions:** The differences in HR parameters identified by the meta-analysis indicate that ME/CFS patients have altered autonomic cardiac regulation when compared to healthy controls. These alterations in HR parameters may be symptomatic of the condition.

**Abbreviations:** ANS = autonomic nervous system, AT = anaerobic threshold, bpm = beats per minute, CCC = Canadian Consensus Criteria for diagnosis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, CDC = Centers for Disease Control and Prevention, CI = confidence interval, HFP = high frequency power of heart rate variability, HR = heart rate, $HR_{dailyaverage}$ = daily average heart rate, $HR_{max}$ = maximal heart rate, $HR_{mentaltask}$ = heart rate during mental task, $HR_{OR}$ = orthostatic heart rate response, $HR_{peak}$ = peak heart rate during maximal exercise, HRR = heart rate recovery, $HR_{steadystate}$ = steady state exercise heart rate, $HR_{threshold}$ = heart rate at submaximal exercise threshold, $HR_{tilt}$ = heart rate during head-up tilt testing, HRV = heart rate variability, $HRV_{tilt}$ = heart rate variability during head-up tilt testing, HUTT = head-up tilt testing, ICC = International Consensus Criteria for diagnosis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, LF/HF = ratio between low frequency and high frequency power of heart rate variability analysis, LFP = low frequency power, LT = lactate threshold, MD = mean difference, ME/CFS = Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, n = number, POTS = postural orthostatic tachycardia syndrome, PRISMA = Preferred Reporting Items for Systematic reviews and Meta-Analyses, PROSPERO = International Prospective register for Systematic Reviews, RHR = resting heart rate, RMSSD = root mean of the sum of squares of beat to beat deviations, SD = standard deviation, SE = standard error, SMD = standardized mean difference, $VO_2$ = volume of oxygen uptake, VT = ventilatory threshold.

**Keywords:** autonomic dysfunction, chronic fatigue syndrome, fatigue, heart rate, myalgic encephalomyelitis

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## 1. Introduction

Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS) is a condition with complex aetiology and is commonly characterised by debilitating fatigue that is not resolved with rest, with additional symptoms including muscle and joint pain, tender lymph nodes, sore throat, and cognitive difficulties.[2] Despite numerous hypotheses being proposed to explain the pathology of ME/CFS, there is a lack of conclusive evidence regarding the pathophysiology underlying this condition and no reliable clinical marker of ME/CFS exists.[3] As a result, diagnosis of ME/CFS has relied on patients meeting one of a range of consensus based diagnostic criteria, the most widely used being the Centers for Disease Control and Prevention (CDC) 1994 criteria.[1] The CDC 1994 criteria requires the presence of unexplained persistent or relapsing chronic fatigue which is of new or definite onset, and results in a substantial reduction in prior levels of occupational, educational, social or personal activities. In addition, to meet the diagnosis the person must also display at least 4 of the following secondary symptoms which must not have predated the fatigue:

1. impairment in short-term memory or concentration;
2. sore throat;
3. tender cervical or axillary lymph nodes;
4. muscle or multi-joint pain;
5. headache;
6. unrefreshing sleep;
7. post-exertional malaise that remains for a period of more than 24 hours.

More recently, other diagnostic criteria have emerged which have increased the emphasis on the importance of post-exertional malaise to help differentiate ME/CFS from other conditions with similar symptoms (e.g., Fibromyalgia).[3,4] Estimates of the prevalence of ME/CFS range from 0.2%[5] to 6.4%[6] in the developed world, with the variation in estimates likely due to differences in the diagnostic criteria applied.[7] Regardless of the prevalence, ME/CFS is a complex condition, for which diagnosis remains difficult. Accordingly, the identification of a reliable marker of ME/CFS remains highly desirable.

Evidence of altered autonomic nervous system (ANS) regulation of cardiovascular function has been observed in patients with ME/CFS.[8,9] Patients commonly present with concurrent cardiovascular conditions such as postural orthostatic tachycardia syndrome (POTS),[10] and disturbances in additional markers of ANS function including blood pressure variability, and altered responses to head-up tilt testing (HUTT).[11–13] However, these studies have used inconsistent methodologies and provided variable results, making it difficult to conclusively establish the nature and extent of any derangement of cardiovascular autonomic regulation.

One approach to assessing cardiovascular autonomic regulation which has commonly been used in ME/CFS patients is the assessment of a range of heart rate (HR) parameters such as HR variability (HRV),[14] HR recovery (HRR),[15] and HR acceleration.[16,17] A recent meta-analysis confirmed the ability of some HR markers of cardiac autonomic regulation to identify when athletes have become fatigued from too much exercise,[18] but there has been no systematic evaluation of whether these parameters are altered following other types of fatigue, including in patients whose fatigue originates from ME/CFS. The purpose of the present study was to systematically review, and meta-analyse, the literature reporting markers of cardiac autonomic regulation in patients with ME/CFS to determine whether there were differences in HR parameters between patients and controls. This was done in an effort to determine whether any markers of cardiac autonomic dysfunction might be useful to aid in the diagnosis of ME/CFS.

## 2. Methods

This systematic review was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).[19] The protocol for the review was registered with the International Prospective register for Systematic Reviews (PROSPERO; registration no. CRD 42016036731). As this study was a review of published literature, no ethics board approval was required.

### 2.1. Search strategy

The search strategy was formulated using the PICO (Population, Intervention, Comparator, Outcome) framework, and in consultation with an academic librarian.[20] To be included in the present meta-analysis, articles had to report on studies which reported assessing heart rate parameters (O) in patients diagnosed with ME/CFS (P) compared to healthy controls (C), with intervention (I) not being relevant to the current review and meta-analysis. In addition, the study design was limited to clinical case-control studies (S).

### 2.2. Database searching

A literature search was performed using MedLine, Embase, SportDiscus, CINAHL, Scopus and AMED with no date restrictions. Literature searches were performed by 2 authors (MJN and JSB) on the same day in January 2017. A mixture of keywords and MeSH headings where appropriate, linked with the appropriate Boolean operators was used to identify relevant articles. The complete search strategy was ('*Chronic Fatigue Syndrome*' OR '*CFS*' OR '*Myalgic Encephalomyelitis*' OR '*ME*') AND ('*Heart rate*' OR '*Heart rate variability*' OR '*HRV*' OR '*Heart rate recovery*' OR '*HRR*' OR '*Resting heart rate*' OR '*RHR*' OR '*Maximal heart rate*' OR '*HRmax*' OR '*Rate of heart rate increase*' OR '*rHRI*' OR '*Pulse rate*'). Reference lists of included articles were manually searched to identify additional articles. To ensure repeatability, agreement was required from the 2 relevant reviewers on the number of articles retrieved before proceeding.

### 2.3. Study selection

Articles were eligible for inclusion when the following criteria were fulfilled:

1. participants were adults (aged ≥ 18 years);
2. participants were diagnosed with ME/CFS based on recognised criteria: CDC 1988,[2] CDC 1994,[1] International Consensus Criteria (ICC),[4] Canadian Consensus Criteria (CCC),[3] or Oxford[21]);
3. studies included healthy control comparison group;
4. HR parameters were measured and reported, including, but not limited to: resting HR (RHR), maximal HR (HRmax), HRV, HRR and steady state exercise HR ($HR_{steadystate}$);

5. data were adequately reported (mean and standard deviation (SD) or standard error (SE) or 95% confidence intervals (CI));
6. the article was either written in English or had a detailed English summary available;
7. ME/CFS patients were free of comorbid conditions (Fibromyalgia, Diabetes, etc); and
8. ME/CFS patients were not reported to be taking HR altering medication (β-blockers, etc). In the case of data being inadequately reported, the corresponding author was contacted with a request for additional data. Citations retrieved from the searches were uploaded on an online systematic review platform (Covidence systematic review software, Veritas Health Innovation Ltd., Melbourne, Australia).

Citations retrieved from the search were independently screened by 2 reviewers (MJN and JSB) and any conflicts were resolved by discussion, or referred to a third reviewer (KD) if consensus was not reached. Titles that met the eligibility criteria were then retrieved as full manuscripts and reviewed independently by 2 reviewers (MJN and JSB). Conflicts were resolved using the same process as from the initial screening stage.

### 2.4. Critical appraisal

Critical appraisal of included studies was performed to assess the validity of the included studies using the Joanna Briggs Institute 'Checklist for Case Control Studies'.[22] Assessment was independently performed by two separate authors (MJN and JSB) who were blinded to the others evaluations. Disagreement between reviewers was resolved through discussion and via consultation with a third author (KD) if required. Articles were scored on description of the groups, exclusion of selection bias, detection and statistical methods, equal exposure and accounting for confounding factors. Articles were scored as either 'yes', 'no', 'unclear' or 'NA' for all questions, with each article being assessed on ten questions. Inter-rater agreement for each item of the risk of bias tool was evaluated using the Kappa (κ) statistic.

### 2.5. Data extraction and analysis

Information from each study was collected on publication details, participant characteristics and numbers, diagnostic criteria used for ME/CFS patients, and results of HR parameter assessment. All HR variables were extracted and where a HR variable was reported by more than one study, data were pooled to compute the between group differences in patients and controls. Random-effects meta-analysis was performed using Review Manager (RevMan, version 5.3, Cochrane Collaboration, Oxford, UK), using the inverse variance method. Due to the consistency of methods used for measurement of $HR_{max}$ and RHR, these parameters were expressed as the mean difference (MD) between groups ± 95% CI. All other data were expressed as the standardised mean difference (SMD) ± 95% CI, calculated by standardizing the mean difference between ME/CFS patients and controls by the pooled standard deviation from both patients and controls. Where data were reported separately based on gender or level of disease severity, mean and SD were pooled giving single values for ME/CFS patients and controls, rather than being reported separately. The presence of statistical heterogeneity was assessed through the $I^2$ statistic. Statistical significance for all outcome measures was set to $P < .05$.

## 3. Results

The literature search initially identified 412 unique records. The 317 studies did not meet the inclusion criteria and were excluded. Of the remaining 95 studies, data were inadequately reported in 31. None of the authors provided missing data upon request, resulting in a total of 64 studies for inclusion. A summary of the search outcomes, including the number of studies excluded at various phases is shown in Figure 1.

### 3.1. Critical appraisal of included studies

Inter-rater agreement for critical appraisal was high (κ = 0.75). Critical appraisal revealed that the majority of included studies were of moderate or good quality. Seventeen articles were found to be of 'moderate' quality (score between 50% and 59%), while 30 studies were found to be of 'good' quality (score between 60% and 69%). Four articles were found to be of 'low' quality (score below 50%), with each article scoring 45%. Thirteen articles were found to be 'high' quality (score over 70%) The most common questions which resulted in a response of 'No' during critical appraisal were "Were confounding factors identified?" (performed in 20% of studies), and "Were strategies to deal with confounding factors stated?" (23%). Few studies (30%) reported on the specific length of exposure to the condition so it was difficult to assess the question "Was the exposure period of interest long enough to be meaningful?". However, as this review only included studies which diagnosed ME/CFS through accepted criteria, and all of these criteria require the presence of the condition for at least 6 months, it is likely that all included studies reported on a meaningful exposure. That said, studies which did not explicitly report on the length of exposure to the condition were graded as "not available" for that question. Generally, patients and controls within the included studies were comparable, and both the exposure to the condition and all relevant HR parameters were assessed in a standard, valid and reliable manner. Appropriate statistical analysis were used in the vast majority of studies, however statistical analyses were unclear in 7 studies.[23–29]

### 3.2. Participants

In total, the 64 included studies reported on 2286 ME/CFS patients and 1758 healthy controls who had HR parameters assessed. Of these studies, 14 recruited exclusively female participants, and 50 studies recruited a mixed gender sample. Overall, 79% of ME/CFS patients were female (n = 1803), compared to 73% for controls (n = 1283), while 1 study[23] did not specify the gender of participants.

### 3.3. Diagnostic criteria

The 1994 CDC criteria were the most commonly used diagnostic criteria[1] (47 studies), followed by the 1988 CDC criteria[2] (8 studies), the Oxford criteria[21] (5 studies), and the ICC[4] (5 studies). Four studies employed the CCC, in each case in addition to another form of criteria (CDC alone,[30–32] CDC +ICC[33]).

### 3.4. Study outcomes

Overall, HR parameters extracted from the included studies were sorted into 10 categories, and included studies for each parameter

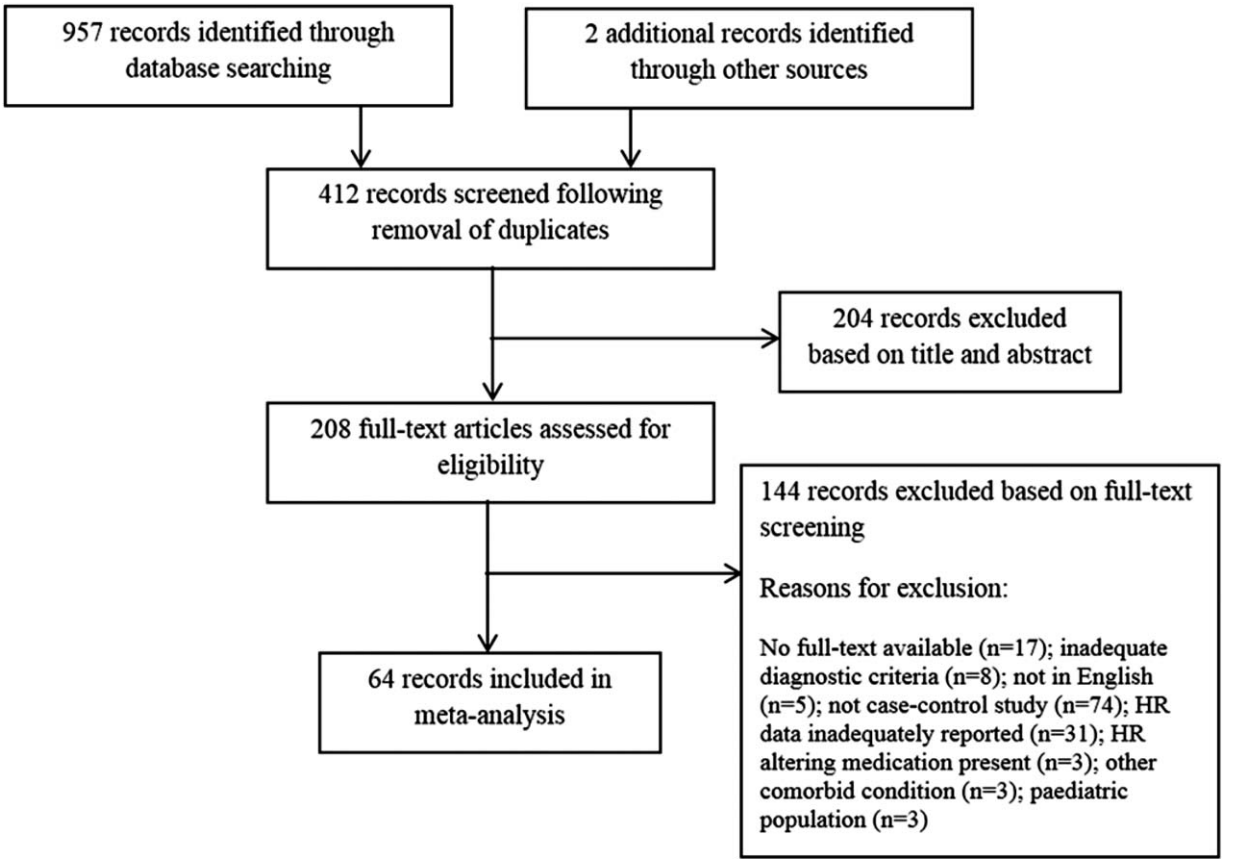


**Figure 1.** Literature search flow chart. *n* number of included studies.

are presented in Table 1 – resting HR (RHR), maximal HR ($HR_{max}$) HR during submaximal exercise, heart rate during HUTT ($HR_{tilt}$), Orthostatic HR response ($HR_{OR}$), resting HRV ($HRV_{rest}$), HRV during HUTT ($HRV_{tilt}$), HR during mental task ($HR_{mentaltask}$), daily average HR ($HR_{dailyaverage}$), and HRR

### 3.5. Resting heart rate

The most commonly assessed HR parameter was (RHR), which was assessed in 43 studies (patients n = 1766, controls n = 1291). Studies varied regarding the body position used to assess RHR, with 16 studies (patients n = 1059, controls n = 548) using a seated/reclined position ($RHR_{seated}$), and 26 (patients n = 707, controls n = 743) using a supine position ($RHR_{supine}$). Meta-analysis revealed ME/CFS patients had a RHR that was ~4 beats/minute faster compared to controls (MD ± 95% CI = 4.14 ± 1.30, $P < .001$; Fig. 2), but with significant heterogeneity between studies ($P < .001$, $I^2 = 62\%$). Subgroup analysis revealed a similar difference between ME/CFS patients and controls for $RHR_{supine}$ (4.02 ± 2.11, $P < .001$), and $RHR_{seated}$ (4.53 ± 2.40, $P < .001$), with significant heterogeneity amongst studies evaluating $RHR_{supine}$ ($P < .001$, $I^2 = 73\%$).

### 3.6. Maximal heart rate

$HR_{max}$ was reported in 20 studies (patients n = 989, controls n = 568), which used 2 different exercise modalities (cycling, 13 studies; and treadmill walking, 7 studies) to elicit a maximal response. Five studies (patients n = 111, controls n = 123) – four of which employed a cycling protocol – based the attainment of a maximal response on accepted criteria and assessed true $HR_{max}$, while the remaining 15 studies (patients n = 878, controls n = 445) only reported the highest HR achieved during testing, and is likely to represent symptom limited peak HR ($HR_{peak}$), rather than a true $HR_{max}$.

Meta-analysis showed $HR_{max}$ values were found to be lower for ME/CFS patients compared to controls (–13.81 ± 4.14, $P < .001$, Fig. 3), but were also affected by significant heterogeneity ($P < .001$, $I^2 = 78\%$). Subgroup analysis showed the difference between ME/CFS patients and controls was considerable in studies which measured symptom limited $HR_{peak}$ (–16.62 ± 4.68, $P < .001$), with significant heterogeneity between studies ($P < .001$, $I^2 = 74\%$). Comparatively, in studies which assessed true $HR_{max}$ the difference between ME/CFS patients and controls was smaller, albeit still significant (–5.81 ± 3.34, $P < .001$), with no heterogeneity present ($P = .88$, $I^2 = 0\%$).

### 3.7. Heart rate during submaximal exercise

HR during submaximal exercise was reported by 14 studies (patients n = 837, controls n = 496), with 10 studies using cycling exercise, and 4 studies using treadmill walking exercise (Table 1). Six studies (patients n = 539, controls n = 313) reported HR at a particular submaximal exercise 'threshold' (anaerobic threshold [AT], ventilatory threshold [VT], or lactate threshold [LT]), which were representative of the transition from predominately

**Table 1**

**Summary of included studies, grouped by HR parameters assessed.**

**Resting heart rate**

| Study (author, year) | *n* patients (*n* ♀) | *n* controls (*n* ♀) | Diagnostic criteria | Recording position | Recording length | MD [95% CI] |
|---|---|---|---|---|---|---|
| Barnden et al 2011[30] | 25 (19) | 25 (19) | CDC '94 & CCC | Seated | NA | 5.40 [0.53, 10.27] |
| Beaumont et al 2012[35] | 30 (20) | 40 (24) | CDC '94 | Reclined | 5 min | 5.00 [0.94, 9.06] |
| Blackwood et al 1998[36] | 10 (7) | 10 (7) | CDC '94 | Seated | NA | 6.30 [−0.15, 12.75] |
| Cook et al 2005[37] | 20 (13) | 26 (15) | CDC '94 | Supine | NA | 2.30 [−3.61, 8.21] |
| Cook et al 2006[38] | 29 (20) | 32 (17) | CDC '94 | Seated | NA | 0.00 [−5.03, 5.03] |
| Cordero et al 1996[39] | 11 (10) | 11 (10) | CDC '94 | Seated | 20 min | 2.00 [−6.91, 10.91] |
| De Becker et al 1998[40] | 21 (15) | 13 (8) | CDC '88 | Supine | 10 min | 2.30 [−3.61, 8.21] |
| De Becker et al 2000[41] | 427 (427) | 204 (204) | CDC '94 | Seated | 3–5 min | 6.10 [3.89, 8.31] |
| Farquhar et al 2002[42] | 17 (13) | 17 (12) | CDC '94 | Supine | 30 min | 9.00 [1.97, 16.03] |
| Freeman and Komaroff 1997[43] | 20 (14) | 20 (14) | CDC '88 | Supine | NA | 7.50 [0.78, 14.22] |
| Gibson et al 1993[24] | 12 (6) | 12 (6) | Oxford | Seated | NA | 4.70 [−7.24, 16.64] |
| Guillamo et al 2010[44] | 141 (141) | 20 (20) | CDC '94 | Seated | 2 min | 7.00 [2.64, 11.36] |
| Hansen et al 2013[45] | 19 (19) | 21 (21) | Oxford | Seated | 5 min | 8.78 [0.50, 17.06] |
| Hoad et al 2008[46] | 59 (41) | 52 (34) | CDC '94 | Seated | NA | 4.00 [−1.77, 9.77] |
| Hollingsworth et al 2012[47] | 12 (12) | 10 (10) | CDC '94 | Supine | NA | −3.00 [−11.79, 5.79] |
| Hurwitz et al 2010[48] | 56 (41) | 58 (43) | CDC '94 | Supine | >10 min | −3.27 [−6.37, −0.17] |
| Ickmans et al 2013[49] | 31 (31) | 13 (13) | CDC '94 | Seated | 3–5 min | −0.70 [−9.94, 8.54] |
| LaManca et al 1999[50] | 39 (32) | 31 (26) | CDC '88 | Supine | 20 min | 4.00 [−3.03, 11.03] |
| LaManca et al 2001[51] | 19 (19) | 20 (20) | CDC '94 | Supine | 5 min | 7.90 [1.76, 14.04] |
| Lavietes et al 1998[52] | 9 (9) | 10 (10) | CDC '94 | Seated | >10 min | 6.00 [−3.00, 15.00] |
| Miwa and Fujita 2011[53] | 20 (11) | 27 (17) | CDC '94 | Supine | NA | −2.00 [−6.82, 2.82] |
| Miwa and Fujita 2014[25] | 10 (7) | 10 (7) | ICC | Supine | 10 min | 2.00 [−5.28, 9.28] |
| Miwa 2017[54] | 18 (12) | 15 (10) | ICC | Supine | 15 min | 0.00 [−8.54, 8.54] |
| Naschitz et al 2000[26] | 32 (20) | 32 (20) | CDC '94 | Supine | 15 min | 2.40 [−2.41, 7.21] |
| Naschitz et al 2001[55] | 30 (17) | 37 (20) | CDC '94 | Supine | 10 min | 5.50 [−0.35, 11.35] |
| Naschitz et al 2002[56] | 21 (15) | 21 (10) | CDC '94 | Supine | 10 min | 7.90 [1.48, 14.32] |
| Neary et al 2008[57] | 6 (6) | 8 (8) | CDC '94 | Supine | NA | 15.00 [4.41, 25.59] |
| Newton et al 2009[58] | 38 (26) | 120 (94) | CDC '94 | Supine (sleep) | NA | 11.00 [7.35, 14.65] |
| Peckerman et al 2003[59] | 43 (11) | 29 (21) | CDC '94 | Supine | 20 min | 11.00 [7.35, 14.65] |
| Rahman et al 2011[60] | 15 (3) | 15 (10) | CDC '94 | Supine (sleep) | NA | 0.00 [−6.18, 6.18] |
| Razumovsky et al 2003[61] | 26 (23) | 23 (18) | CDC '94 | Supine | 10 min | 13.70 [7.99, 19.41] |
| Robinson et al 2015[62] | 51 (38) | 10 (7) | CDC '94 | Supine | 10 min | 0.90 [−4.01, 5.81] |
| Schondorf et al 1999[63] | 41 (38) | 48 (28) | CDC '94 | Supine | 10 min | 9.00 [5.13, 12.87] |
| Soetekouw et al 1999[64] | 37 (30) | 38 (28) | Oxford | Supine | 15 min | 4.80 [−1.48, 11.08] |
| Streeten and Streeten 2001[28] | 7 (5) | 7 (5) | CDC '94 | Seated | 30 min | −0.40 [−16.64, 15.84] |
| Streeten et al 2000[29] | 15 (12) | 15 (12) | CDC '94 | Seated | 30 min | 11.60 [3.53, 19.67] |
| Suarez et al 2010[65] | 44 (44) | 25 (25) | CDC '94 | Seated | NA | −2.00 [−8.14, 4.14] |
| Timmers et al 2002[66] | 36 (31) | 36 (31) | CDC '94 | Supine | 15 min | 9.00 [5.51, 12.49] |
| Van Oosterwijck et al 2017[31] | 20 (20) | 20 (20) | CDC '94/CCC | Supine | 10 min | −0.40 [−5.81, 5.01] |
| VanNess et al 2003[34] | 159 (97) | 20 (5) | CDC '88 | NA | NA | 2.30 [−1.84, 6.44] |
| Wallman et al 2003[67] | 31 (22) | 31 (22) | CDC '94 | Seated | NA | 4.00 [−0.66, 8.66] |
| Winkler et al 2004[68] | 22 (11) | 18 (15) | CDC '94 | Supine | 10 min | −3.90 [−12.89, 5.09] |
| Yataco et al 1997[69] | 19 (14) | 11 (7) | CDC '88 | Supine | 20 min | −1.00 [−13.96, 11.96] |

**Maximal heart rate**

| Study (author, year) | *n* patients (*n* ♀) | *n* controls (*n* ♀) | Diagnostic criteria | Protocol* (modality, start workload / rate of increase) | Definition of 'maximal' (% of age predicted $HR_{max}$ attained) | MD [95% CI] |
|---|---|---|---|---|---|---|
| Bazelmans et al 2001[70] | 20 (12) | 20 (12) | CDC '94 | Cycling, unknown, 10–30 W / min | Volitional exhaustion (89% $HR_{max}$) | −8.00 [−17.21, 1.21] |
| Cook et al 2006[38] | 29 (20) | 32 (17) | CDC '94 | Cycling, 20 W, 5 W / 20 sec | Criteria based, excluded if not met (93% $HR_{max}$) | −4.00 [−11.53, 3.53] |
| Cook et al 2003 (b)[71] | 15 (3) | 19 (3) | CDC '94 | Cycling, 0 W, 30 W / min | Criteria based, excluded if not met (87% $HR_{max}$) | −9.00 [−16.93, −1.07] |
| Cook et al 2003 (a)[72] | 19 (19) | 20 (20) | CDC '94 | Treadmill, 5.6 km/h, 2% incline / 2 mins | Criteria based, excluded if not met (94% $HR_{max}$) | −4.00 [−11.53, 3.53] |
| De Becker et al 2000[41] | 427 (427) | 204 (204) | CDC '94 | Cycling, 10 W, 10 W / min | Criteria based, unknown exclusions# (82% $HR_{max}$) | −19.40 [−22.68, −16.12] |
| Farquhar et al 2002[42] | 17 (13) | 17 (12) | CDC '94 | Cycling, unknown, 25 W / min | RQ value > 1.0 (93% $HR_{max}$) | −7.00 [−18.16, 4.16] |
| Fulcher and White 2002[73] | 66 (49) | 30 (22) | Oxford | | | −11.00 [−17.63, −4.37] |

(*continued*)

**Table 1**

**(continued).**

**Maximal heart rate**

| Study (author, year) | *n* patients (*n* ♀) | *n* controls (*n* ♀) | Diagnostic criteria | Protocol* (modality, start workload / rate of increase) | Definition of 'maximal' (% of age predicted $HR_{max}$ attained) | MD [95% CI] |
|---|---|---|---|---|---|---|
| | | | | Treadmill, 5 km/h, 2.5% incline / min | Volitional exhaustion (91% $HR_{max}$) | |
| Gibson et al 1993[24] | 12 (6) | 12 (6) | Oxford | Cycling, 60 W, 30 W / min | Volitional exhaustion (87% $HR_{max}$) | −28.00 [−45.06, −10.94] |
| Hodges et al 2017[33] | 10 (NA) | 17 (NA) | ICC/CCC/CDC '94 | Cycling, 15 W, 15 W / min | Volitional exhaustion (85% $HR_{max}$) | −7.00 [−24.10, 10.10] |
| Ickmans et al 2013[49] | 31 (31) | 13 (13) | CDC '94 | Cycling, 30 W / min | Volitional exhaustion (80% $HR_{max}$) | −19.60 [−28.36, −10.84] |
| Inbar et al 2001[74] | 15 (12) | 15 (12) | CDC '94 | Treadmill, 2% incline / min | Volitional exhaustion (83% $HR_{max}$) | −22.00 [−32.99, −11.01] |
| Nagelkirk et al 2003[75] | 15 (3) | 19 (3) | CDC '94 | Cycling, 30 W / min | Criteria based, unknown exclusions (87% $HR_{max}$) | −7.50 [−18.05, 3.05] |
| Neary et al 2008[57] | 6 (6) | 8 (8) | CDC '94 | Cycling, 25 W / min | Volitional exhaustion (86% $HR_{max}$) | −32.00 [−44.90, −19.10] |
| Riley et al 1990[27] | 13 (10) | 13 (10) | CDC '88 | Treadmill, Bruce protocol | Volitional exhaustion (unknown) | −5.00 [−15.50, 5.50] |
| Rowbottom et al 1998[76] | 16 (10) | 16 (10) | CDC '88 | Treadmill, modified Bruce to 6 km/h then 2% incline / 3 min | Volitional exhaustion (88% $HR_{max}$) | −15.00 [−29.13, −0.87] |
| Sargent et al 2002[77] | 33 (17) | 33 (17) | CDC '94 | Cycling, 0 W, 25 W / min | Criteria based, excluded if not met (99% $HR_{max}$) | −4.60 [−9.79, 0.59] |
| Sisto et al 1996[78] | 21 (21) | 22 (22) | CDC '94 | Treadmill, 5.6 km/h, 2.5% incline/min | Volitional exhaustion (87% $HR_{max}$) | −17.00 [−29.70, −4.30] |
| Strahler et al 2013[79] | 21 (11) | 20 (9) | CDC '94 | Cycling, 30–50 W, 30 W /min | Volitional exhaustion or 85% HRmax attained (91% $HR_{max}$) | −2.20 [−10.16, 5.76] |
| Suarez et al 2010[65] | 44 (44) | 25 (25) | CDC '94 | Cycling, 0 W, 20 W / min | Volitional exhaustion (77% $HR_{max}$) | −32.60 [−42.62, −22.58] |
| VanNess et al 2003[34] | 159 (97) | 20 (5) | CDC '88 | Treadmill, 3.2 km/h, 3% incline / 2 min | Volitional exhaustion (75% $HR_{max}$) | −26.60 [−34.40, −18.80] |

**Submaximal Exercise Heart rate**

| Study (author, year) | n patients (n ♀) | n controls (n ♀) | Diagnostic criteria | Exercise Protocol (modality, type of protocol) | HR parameter | SMD [95% CI] |
|---|---|---|---|---|---|---|
| Blackwood et al 1998[36] | 10 (7) | 10 (7) | CDC '94 | Treadmill, Bruce protocol to 85% of age predicted $HR_{max}$ | Mean HR during light stage | 0.18 [−0.70, 1.06] |
| | | | | | HR at 85% $HR_{max}$ | −0.35 [−1.24, 0.53] |
| Cook et al 2005[37] | 20 (13) | 26 (15) | CDC '94 | Cycling, steady-state workload at ~40% $VO_{2max}$ | Steady state HR during cycling | −0.13 [−0.72, 0.45] |
| Cook et al 2006[38] | 29 (20) | 32 (17) | CDC '94 | Cycling, ramp $VO_{2max}$ protocol | HR at VT (V-Slope method) | −0.17 [−0.68, 0.33] |
| Cook et al 2017[32] | 15 (15) | 15 (15) | CDC '94 & CCC | Cycling, steady state @ 70% $HR_{max}$ | Steady state HR during cycling | −0.16 [−0.88, 0.55] |
| De Becker et al 2000[41] | 427 (427) | 204 (204) | CDC '94 | Cycling, ramp $VO_{2max}$ protocol | HR at AT (RER >1.0) | −0.68 [−0.85, −0.51] |
| Guillamo et al 2010[44] | 141 (141) | 20 (20) | CDC '94 | Cycling, constant 0 W workload | Steady state HR during cycling | 0.65 [0.17, 1.12] |
| Hodges et al 2017[33] | 10 (NA) | 10 (NA) | ICC & CCC & CDC '94 | Cycling, ramp $VO_{2max}$ protocol | HR at VT (method unknown) | −0.20 [−1.07, 0.68] |
| Jones et al 2012[80] | 18 (16) | 12 (11) | CDC '94 | Cycling, ramp $VO_{2max}$ protocol | HR at VT (V-Slope method) | −0.90 [−1.67, −0.13] |
| Paul, Wood & Maclaren 2001[81] | 11 (10) | 11 (10) | CDC '94 | Cycling, steady-state workload at 90% of predicted workload at AT | Steady state HR during cycling | 0.33 [−0.52, 1.17] |
| Riley et al 1990[27] | 13 (10) | 13 (10) | CDC '88 | Treadmill, Bruce ramp to $VO_{2max}$ | Steady state HR during walking | 1.05 [0.22, 1.87] |
| Rowbottom et al 1998[76] | 16 (10) | 16 (10) | CDC '88 | Treadmill, Modified Bruce ramp to $VO2_{max}$ | Steady state HR during walking | 0.12 [−0.58, 0.81] |
| Sargent et al 2002[77] | 33 (17) | 33 (17) | CDC '94 | Cycling, ramp $VO_{2max}$ protocol | HR at LT [82] | 0.04 [−0.44, 0.52] |
| Sisto et al 1996[78] | 21 (21) | 22 (22) | CDC '94 | Treadmill, ramp $VO_{2max}$ protocol | Steady state HR at 3.5 mph | −0.36 [−0.86, 0.14] |
| | | | | | HR at VT (V-Slope method) | −0.65 [−1.26, −0.05] |
| Wallman et al 2003[67] | 31 (22) | 31 (22) | CDC '94 | Cycling, ramp to 75% $HR_{max}$ | Steady state HR cycling (150 W) | 0.20 [−0.30, 0.70] |

**Heart rate response to head-up tilt testing**

| Study (author, year) | n patients (n ♀) | n controls (n ♀) | Diagnostic criteria | Tilt Protocol | HR parameter reported | SMD [95% CI] |
|---|---|---|---|---|---|---|
| De Becker et al 1998[40] | 21 (15) | 13 (8) | CDC '88 | 10 min tilt @ 70° | Average tilt HR ΔHR during tilt | 0.96 [0.23, 1.70] 1.01 [0.27, 1.75] |
| Freeman and Komaroff 1997[43] | 20 (14) | 20 (14) | CDC '88 | 5 min tilt @ 60° | Peak tilt HR ΔHR during tilt | 1.43 [0.73, 2.14] 1.02 [0.36, 1.69] |

(*continued*)

**Table 1**

**(continued).**

**Heart rate response to head-up tilt testing**

| Study (author, year) | n patients (n ♀) | n controls (n ♀) | Diagnostic criteria | Tilt Protocol | HR parameter reported | SMD [95% CI] |
|---|---|---|---|---|---|---|
| LaManca et al 1999[50] | 39 (32) | 31 (26) | CDC '94 | 45 min tilt @ 70° | Peak tilt HR | 0.72 [0.23, 1.21] |
| Razumovsky et al 2003[61] | 26 (23) | 23 (18) | CDC '94 | 45 min tilt @ 70° | HR 5 min before end | 0.71 [0.13, 1.29] |
| Timmers et al 2002[66] | 36 (31) | 36 (31) | CDC '94 | 40 min tilt @ 70° | ΔHR during tilt | 0.40 [−0.07, 0.87] |
| Naschitz et al 2000[26] | 32 (20) | 32 (20) | CDC '94 | 30 min tilt @ 70° | Peak tilt HR | 1.45 [0.89, 2.00] |
| Naschitz et al 2002[56] | 21 (15) | 21 (10) | CDC '94 | 5–10 min tilt @ 70° | HR at tilt end | 1.27 [0.60, 1.94] |
| Naschitz et al 2001[55] | 30 (17) | 37 (20) | CDC '94 | 30 min tilt @ 70° | HR at tilt end | 1.06 [0.54, 1.57] |
| Yataco et al 1997[69] | 19 (14) | 11 (7) | CDC '88 | 45 min tilt @ 70° | Average tilt HR | 0.20 [−0.54, 0.95] |

**Orthostatic heart rate response**

| Study (author, year) | *n* patients (*n* ♀) | *n* controls (*n* ♀) | Diagnostic criteria | Positions of recording | HR parameter reported | SMD [95% CI] |
|---|---|---|---|---|---|---|
| Hoad et al 2008[46] | 59 (41) | 52 (34) | CDC '94 | Seated – 2 min standing | Max HR upon standing | 0.47 [0.09, 0.84] |
| Peckerman et al 2003[59] | 43 (31) | 29 (21) | CDC '94 | 10 min supine – 5 min standing | HR upon standing | 0.09 [−0.39, 0.56] |
| Streeten and Streeten 2001[28] | 7 (5) | 7 (5) | CDC '94 | 30 min supine – 10–30 min standing* | ΔHR at end of 30 min# | 0.93 [−0.19, 2.05] |
| Streeten, Thomas and Bell 2000[29] | 15 (12) | 15 (12) | CDC '94 | 30 min supine – 60 min standing* | ΔHR at end of 60 min# | 1.08 [0.31, 1.85] |
| Winkler et al 2004[68] | 22 (11) | 18 (15) | CDC '94 | 10 min supine – 5 min standing | ΔHR after 15 sec of standing | 0.69 [0.05, 1.34] |
| Robinson et al 2015[62] | 51 (38) | 10 (7) | CDC '94 | 10 min supine – 2 min standing | HR upon standing | 0.48 [−0.20, 1.16] |

**Resting heart rate variability**

| Study (author, year) | *n* patients (*n* ♀) | *n* controls (*n* ♀) | Diagnostic criteria | Recording posture | Recording Length | HRV parameters assessed | SMD [95% CI] |
|---|---|---|---|---|---|---|---|
| Beaumont et al 2012[35] | 30 (20) | 40 (24) | CDC '94 | Semi-reclined | 5 min | RMSSD | −0.45 [−0.92, 0.03] |
| Cordero et al 1996[39] | 11 (10) | 11 (10) | CDC '94 | Seated | 20 min | Vagal Power | −0.84 [−1.72, 0.04] |
| De Becker et al 1998[40] | 21 (15) | 13 (8) | CDC '88 | Supine | 10 min | LFP | 0.52 [−0.18, 1.23] |
| | | | | | | HFP | 0.38 [−0.32, 1.08 |
| | | | | | | LF/HF ratio | 0.06 [−0.64, 0.75] |
| Frith et al 2012[12] | 68 (33) | 68 (33) | CDC'94 | Supine | 10 min | LFP | 0.43 [0.09, 0.77] |
| | | | | | | HFP | −0.46 [−0.80, −0.12] |
| | | | | | | LF/HF ratio | 0.38 [0.04, 0.72] |
| Hansen et al 2012[45] | 19 (19) | 21 (18) | Oxford | Seated | 3–5 min | RMSSD | −0.02 [−0.64, 0.60] |
| | | | | | | LF/HF ratio | 0.50 [−0.13, 1.13] |
| Jones et al 2010[23] | 16 (NA) | 8 (NA) | CDC '94 | Supine | 10 min | LFP | 0.05 [−0.80, 0.90] |
| | | | | | | HFP | −0.48 [−1.34, 0.39] |
| | | | | | | LF/HF ratio | 0.60 [−0.26, 1.47] |
| Rahman et al 2011[60] | 15 (3) | 15 (10) | CDC '94 | Sleeping | Overnight | LF/HF ratio | 1.81 [0.94, 2.68] |
| Robinson et al 2015[62] | 51 (38) | 10 (7) | CDC '94 | Supine | 10 min | LFP | 0.25 [−0.43, 0.93] |
| | | | | | | HFP | −0.31 [−0.99, 0.37] |
| | | | | | | LF/HF ratio | 0.37 [−0.31, 1.05] |
| Shu et al 2016[83] | 15 (11) | 15 (10) | CDC '94 | Supine | 20 min | LFP | −0.29 [−1.01, 0.43] |
| | | | | | | HFP | −0.24 [−0.96, 0.47] |
| Sisto et al 1995[84] | 12 (12) | 12 (12) | CDC '88 | Seated | 6 min | Vagal Power | −2.97 [−4.19, −1.75] |
| Togo and Natelson 2013[85] | 26 (26) | 26 (26) | CDC '94 | Sleeping | Overnight | LF/HF ratio | −0.72 [−1.29, −0.16] |
| Van Oosterwijck et al 2017[31] | 20 (20) | 20 (20) | CDC '94/CCC | Supine | 10 mins | LFP | −0.28 [−0.91, 0.34] |
| | | | | | | HFP | −0.61 [−1.25, 0.02] |
| | | | | | | LF/HF ratio | 0.33 [−0.29, 0.96] |
| | | | | | | RMSSD | −0.63 [−1.26, 0.01] |
| Yataco et al 1997[69] | 19 (14) | 11 (7) | CDC '88 | Supine | 20 min | LFP | 0.25 [−0.50, 0.99] |
| | | | | | | HFP | −0.30 [−1.05, 0.45] |
| | | | | | | LF/HF ratio | 0.68 [−0.09, 1.44] |

**Heart rate variability during head-up tilt testing**

| Study (author, year) | *n* patients (*n* ♀) | *n* controls (*n* ♀) | Diagnostic criteria | Tilt protocol | Recording Length | HRV parameters assessed | SMD [95% CI] |
|---|---|---|---|---|---|---|---|
| De Becker et al 1998[40] | 21 (15) | 13 (8) | CDC '88 | 10 min tilt @ 70° | 10 min | LFP | 0.87 [0.15, 1.60] |
| | | | | | | HFP | 0.22 [−0.48, 0.91] |
| | | | | | | LF/HF ratio | 0.34 [−0.36, 1.04] |
| Yataco et al 1997[69] | 19 (14) | 11 (7) | CDC '88 | 45 min tilt @ 70° | 20 min | LFP | −0.01 [−0.75, 0.73] |
| | | | | | | HFP | 0.37 [−0.38, 1.12] |
| | | | | | | LF/HF ratio | 0.35 [−0.40, 1.10] |

(*continued*)

**Heart rate in response to mental task**

| Study (author, year) | *n* patients (*n* ♀) | *n* controls (*n* ♀) | Diagnostic criteria | Mental task | HR parameter | SMD [95% CI] |
|---|---|---|---|---|---|---|
| Beaumont et al 2012[35] | 30 (20) | 40 (24) | CDC '94 | Digit Symbol test, Spatial Working Memory task, Stroop Colour-Word test | Average HR during tasks | 0.47 [−0.01, 0.95] |
| Blackwood et al 1998[36] | 10 (7) | 10 (7) | CDC '94 | Lottery Recall test | Average HR during task | 0.30 [−0.58, 1.18] |
| LaManca et al 2001[51] | 19 (19) | 20 (20) | CDC '88 | Stroop Colour-Word test | Average HR during task | 0.07 [−0.55, 0.70] |
| Lavietes et al 1996[86] | 10 (10) | 9 (9) | CDC '88 | Mathematic subtraction task | Average HR during task | −0.19 [−1.09, 0.72] |
| Soetekouw et al 1999[64] | 37 (30) | 38 (28) | Oxford | Mental arithmetic test | ΔHR during task | −0.29 [−0.74, 0.17] |

**Daily average heart rate**

| Study (author, year) | n patients (n ♀) | n controls (n ♀) | Diagnostic criteria | HR parameter | Recording method | SMD [95% CI] |
|---|---|---|---|---|---|---|
| Gallagher et al 2005[87] | 42 (33) | 42 (34) | Oxford | 'Daily living average' HR | ECG | 0.01 [−0.42, 0.44] |
| Newton et al 2009[58] | 38 (NA) | 120 (NA) | CDC '94 | Average HR over 24 h period | ECG | 0.18 [−0.19, 0.54] |

**Post-exercise heart rate recovery**

| Study (author, year) | n patients (n ♀) | n controls (n ♀) | Diagnostic criteria | Protocol* (modality, start workload, rate of increase) | Duration of HRR | SMD [95% CI] |
|---|---|---|---|---|---|---|
| Fulcher and White 2000[73] | 66 (49) | 30 (22) | Oxford | Treadmill, 5 km/h, 2.5% incline / min | 3 min, position NA | −19.00 [−26.34, −11.66] |
| Gallagher et al 2005[87] | 42 (33) | 42 (34) | Oxford | Treadmill, 5 km/h, 2.5% incline / 2 mins | 3 min, position NA | −5.00 [−10.54, 0.54] |

Δ*HR* = change in heart rate, ♀ = female, *95% CI* = 95% confidence interval, *AT* = anaerobic threshold, *CCC* = Canadian Consensus Criteria, *NA* not available, *CDC '88* = 1988 Centre for Disease Control Chronic Fatigue Diagnostic criteria, *CDC '94* = 1994 Centre for Disease Control Chronic Fatigue Diagnostic criteria, *h* = hour, *HFP* = high frequency power from spectral analysis, *HR* = heart rate, *HRmax* = maximal heart rate, *HRR* = post-exercise heart rate recovery, *HRV* = heart rate variability, *ICC* = International Consensus Criteria, *km/h* = kilometres per hour, *LF/HF* = ratio between low frequency and high frequency power from spectral analysis, *LFP* = low frequency power from spectral analysis, *LT* = lactate threshold, *MD* = mean difference, *min* = minutes, *mph* = miles per hour, *n* = number of participants, *RER* = respiratory exchange ratio, *RMSSD* = root-mean-square difference of successive normal *R-R* intervals from time-domain analysis, *RQ* = respiratory quotient, *sec* = seconds, S*MD* = standardised mean difference, $VO_2max$ = maximal rate of oxygen uptake, *VT* = ventilatory threshold, *W* = watts.

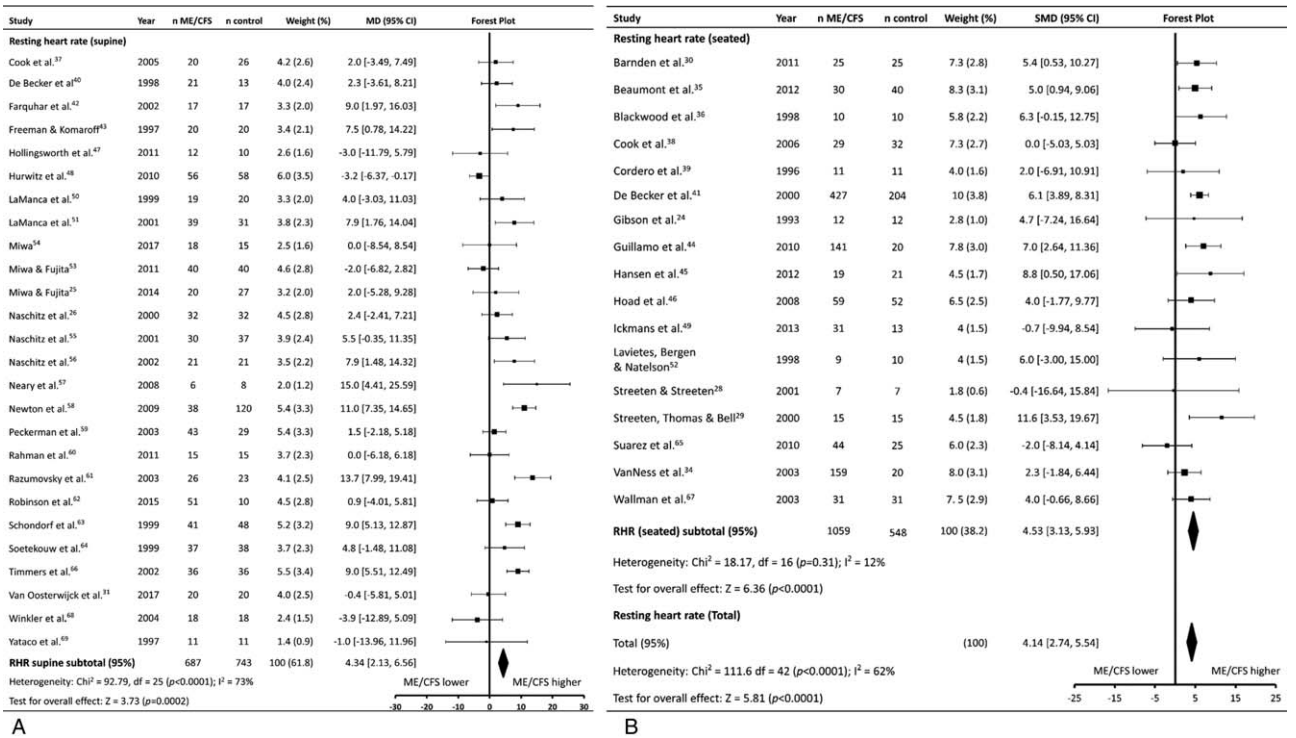


**Figure 2.** Effect of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome on resting heart rate. Weight outside of parentheses indicates weighting within relevant subgroup analysis, weight inside parentheses indicates weighting within total resting heart rate analysis. CI = confidence interval, HR = heart rate, MD = mean difference, n number of participants, ME/CFS = myalgic encephalomyelitis/ chronic fatigue syndrome.

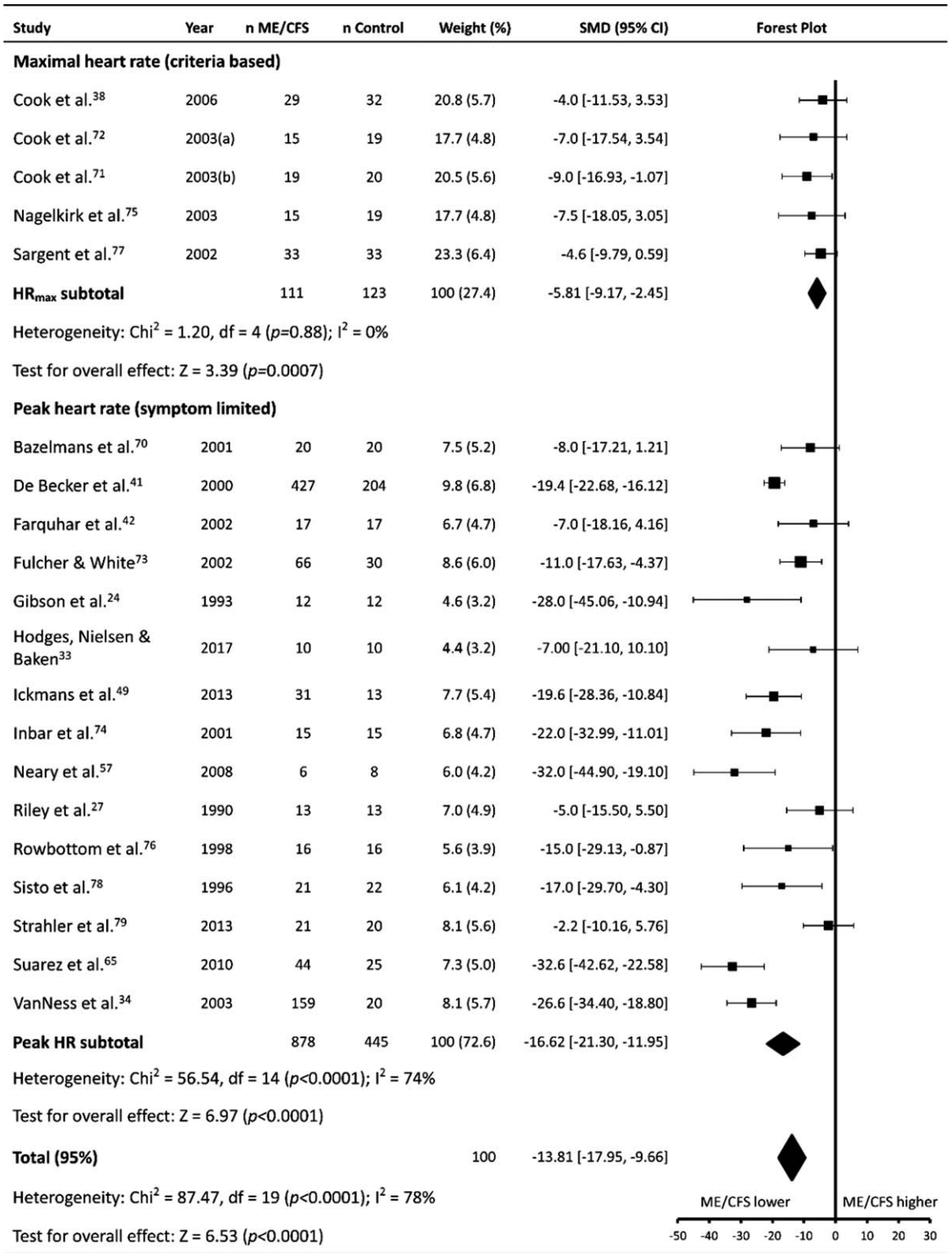


**Figure 3.** Effect of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome on maximal heart rate. Weight outside of parentheses indicates weighting within relevant subgroup analysis, weight inside parentheses indicates weighting within total maximal heart rate analysis. CI = confidence interval, HR = heart rate, HRmax = maximal heart rate, MD = mean difference, ME/CFS = myalgic encephalomyelitis/chronic fatigue syndrome, n = number of participants.

aerobic to predominately anaerobic energy systems ($HR_{threshold}$). In addition, nine studies reported a steady state HR response ($HR_{steadystate}$) at a given submaximal workload, with Blackwood et al[36] reporting HR's at both a light absolute workload, and at a workload designed to elicit 85% of maximal HR. Seven (patients n = 244, controls n = 129) studies reported $HR_{steadystate}$ during workloads that were likely below submaximal exercise threshold (AT, VT or LT), while 3 studies[27,36,67] (patients n = 54, controls

n = 54) reported a $HR_{steadystate}$ that was likely to be at or above submaximal exercise threshold (AT, VT, or LT).

Given the variations in the ways exercise HR was recorded and reported, with different thresholds being assessed in addition to varying exercise intensities at, above or below those thresholds, meta-analysis was performed separately for each HR parameter assessed during submaximal exercise. Analysis of $HR_{threshold}$ revealed a moderate difference, with HRs being lower in ME/CFS patients compared to healthy controls (SMD ± 95% CI = –0.44 ± 0.31, $P = .005$), albeit with significant heterogeneity ($P = .04$, $I^2 = 56\%$; Fig. 4). No difference was found between ME/CFS patients and controls for $HR_{steadystate}$ for workloads that were either likely

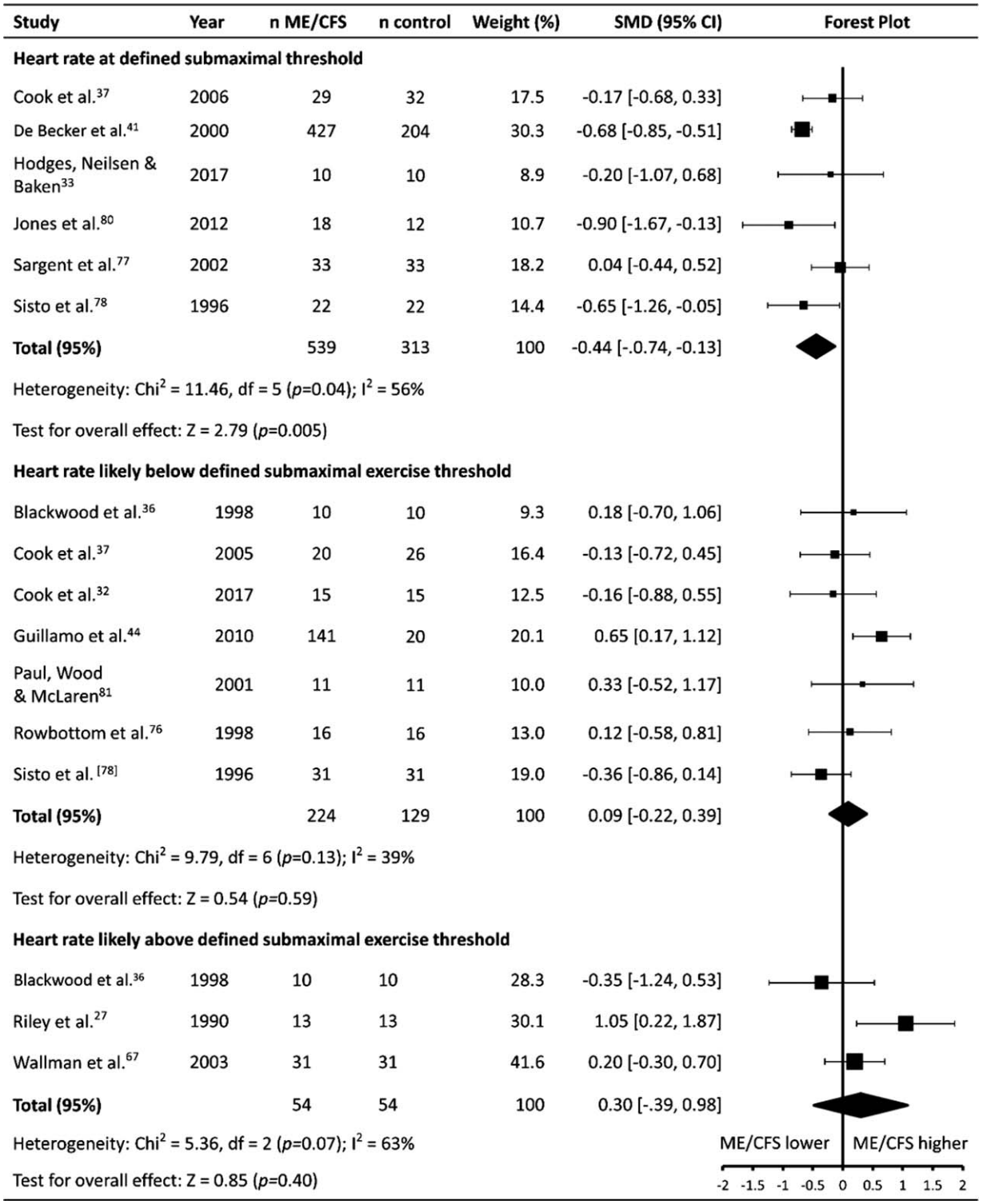


**Figure 4.** Effect of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome on submaximal exercise heart rate. CI = confidence interval, HR = heart rate, ME/CFS = myalgic encephalomyelitis/chronic fatigue syndrome, n = number of participants, SMD = standardized mean difference.

below (0.09 ± 0.30, $P = .59$) or likely above submaximal exercise threshold (AT, VT, or LT) (0.30 ± 0.69, $P = .40$).

### 3.8. Heart rate during head-up tilt testing

Nine studies (patients n = 285, controls n = 257) reported HR in response to HUTT ($HR_{tilt}$) (Table 1). Eight studies (patients n = 208, controls n = 188) reported an absolute HR value during HUTT (peak HR, end HR, etc) and 3 studies (patients n = 77, controls n = 69) reported the ΔHR in response to HUTT.[41,43,66] Meta-analysis revealed $HR_{tilt}$ was higher in ME/CFS patients than it was in controls (SMD ± 95% CI = 0.92 ± 0.24, $P < .001$; Fig. 5). Subgroup analysis revealed that $HR_{tilt}$ was increased in ME/CFS patients compared to controls, regardless of whether data were reported as the peak HR during a short (1.23 ± 0.40, $P < .001$) or long (0.86 ± 0.36, $P < .001$) duration HUTT, or if data were reported as the ΔHR during HUTT (0.74 ± 0.44, $P = .001$).

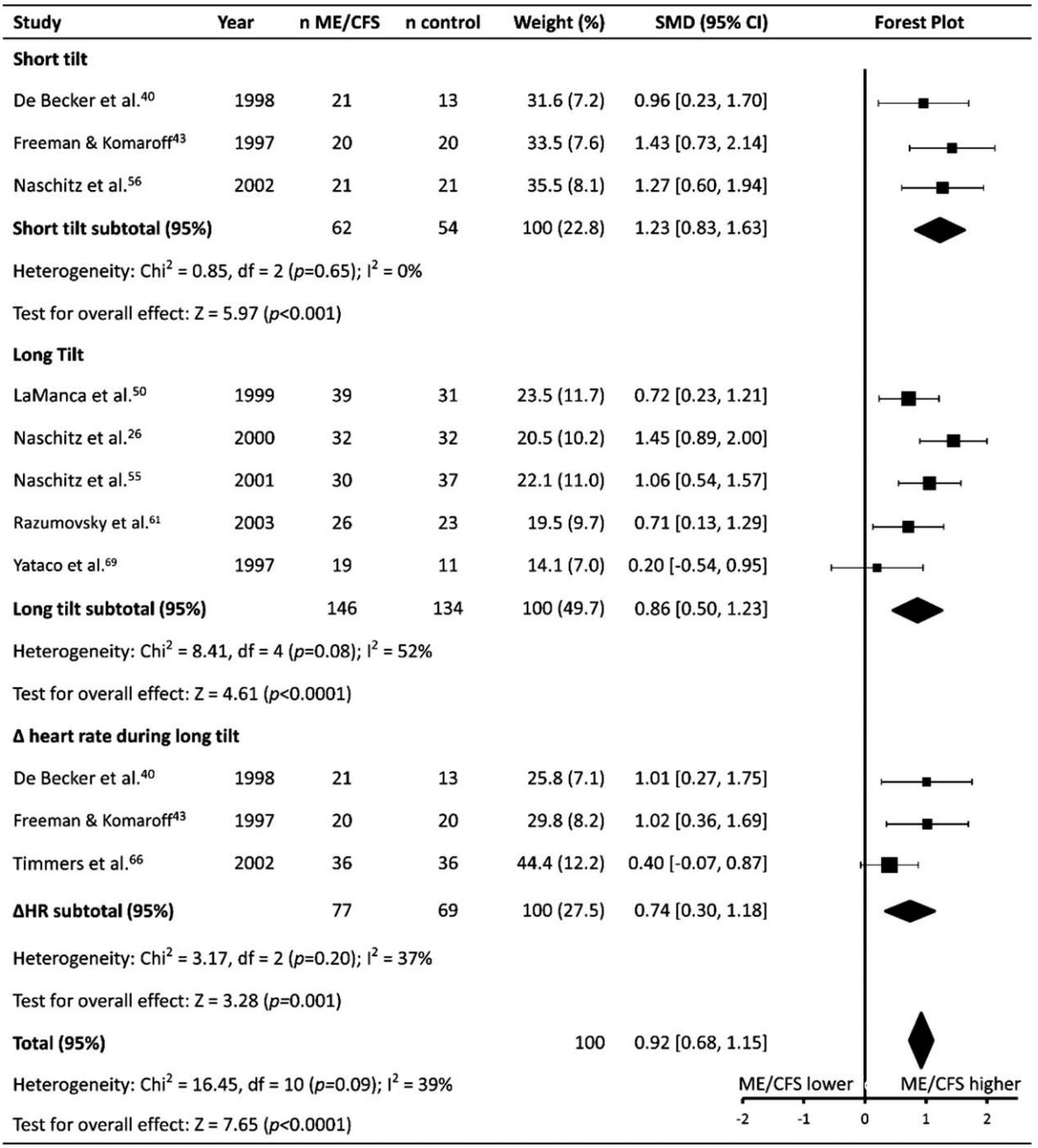


Figure 5. Effect of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome on heart rate in response to head-up tilt testing. Weight outside of parentheses indicates weighting within relevant subgroup analysis, weight inside parentheses indicates weighting within total heart rate during HUTT analysis. CI = confidence interval, HR = heart rate, ME/CFS = myalgic encephalomyelitis/chronic fatigue syndrome, n = number of participants, SMD = standardized mean difference.

### 3.9. Orthostatic heart rate response

The orthostatic HR response ($HR_{OR}$) was reported in 6 studies (patients n = 197, controls n = 131) (Table 1). Five studies[28,29,59,62,68] reported $HR_{OR}$ in response to standing up after a period of supine rest, while 1 study[46] reported the effect of standing up following sitting. Meta-analysis showed $HR_{OR}$ was higher for ME/CFS patients compared to controls (SMD ± 95% CI = 0.50 ± 0.27, $P < .001$; Fig. 6). Subgroup analysis revealed there was a moderate difference when $HR_{OR}$ was reported as the ΔHR upon moving from lying/sitting to standing, with ME/CFS patients having a higher ΔHR than controls (0.86 ± 0.46, $P < .001$), with a similar finding, albeit of a smaller magnitude, also found for the peak HR obtained upon standing (0.34 ± 0.27, $P = .01$).

### 3.10. Resting heart rate variability

Measures of resting HRV ($HRV_{rest}$) were reported in 13 studies (patients n = 294, controls n = 270) (Table 1). Seven studies recorded $HRV_{rest}$ in a supine position, while 3 [39,45,84] recorded $HRV_{rest}$ while seated/reclined. Two studies[60,85] recorded $HRV_{rest}$ during overnight sleep. Frequency domain $HRV_{rest}$ measures were used in 12 studies, with 1 study[35] reporting only time domain analyses, and 2 studies[31,45] reporting both frequency and time domain analyses.

Parameters of $HRV_{rest}$ from included studies were meta-analysed separately. ME/CFS patients had a higher ratio between low frequency and high frequency power (LF/HF) (SMD ± 95% CI = 0.20 ± 0.25, $P = .11$) than controls, and a lower high frequency power (HFP) (–0.34 ± 0.22, $P = .002$) and root mean of the sum of squares of beat to beat deviations (RMSSD) (–0.37 ± 0.32, $P = .02$) (Fig. 7). No differences were found for low frequency power (LFP) (0.39 ± 0.22, $P < .001$), Vagal Power (–1.86 ± 2.08, $P = .08$), or sleeping LF/HF ratio (–0.52 ± 2.48, $P = .68$), with significant heterogeneity for Vagal Power ($P = .006$, $I^2 = 87\%$), and sleeping LF/HF ($P < .001$, $I^2 = 96\%$).

### 3.11. Heart rate variability during head-up tilt testing

Two studies (patients n = 40, controls n = 24) reported HRV during HUTT[40,69] ($HRV_{tilt}$) (Table 1). Both studies reported exclusively frequency domain parameters, with each reporting on LFP, HFP, and LF/HF ratio. Meta-analysis found no difference between ME/CFS patients and controls for LFP (SMD ± 95% CI = 0.44 ± 0.87, $P = .32$; Fig. 8), HF power (0.29 ± 0.51, $P = .27$), or LF/HF ratio (0.35 ± 0.51, $P = .18$).

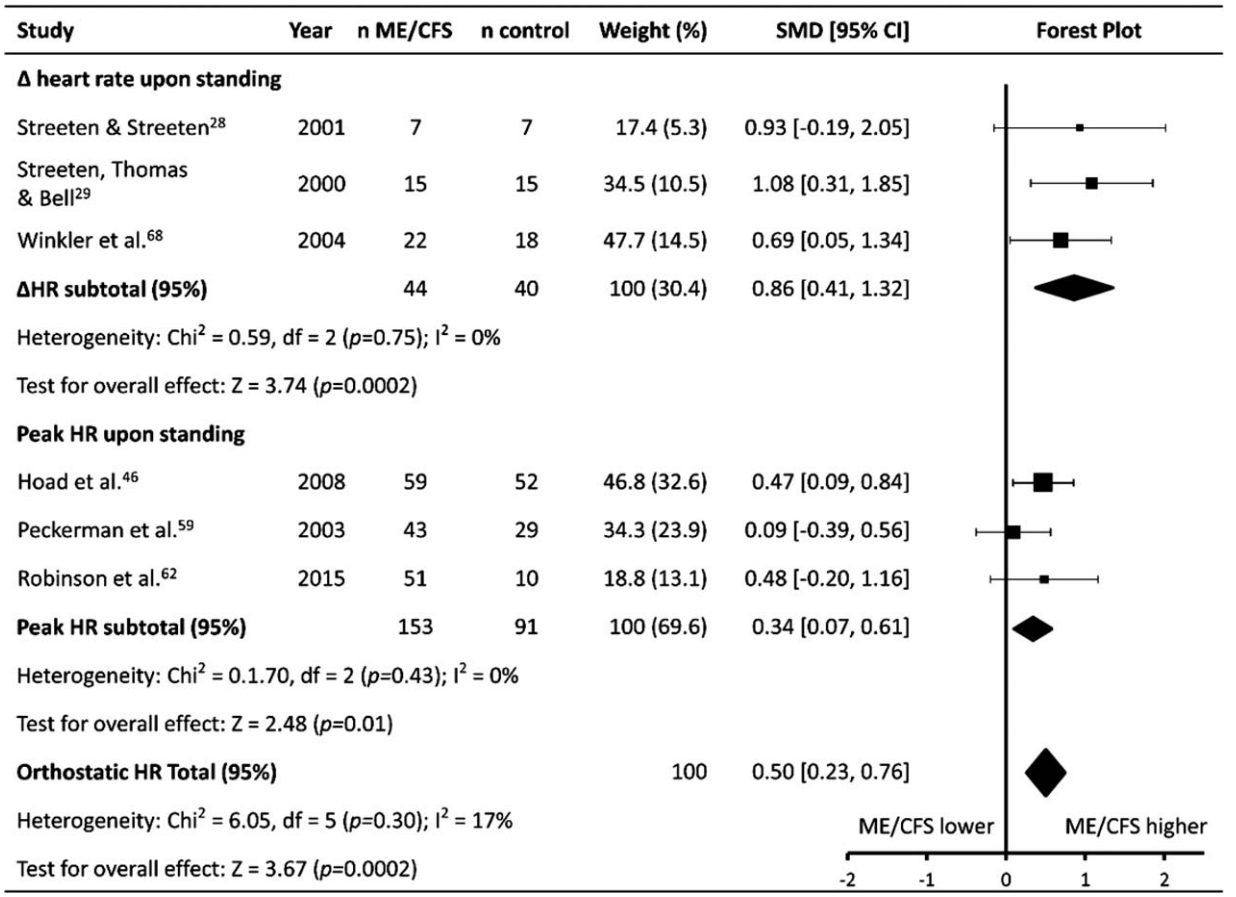


**Figure 6.** Effect of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome on orthostatic heart rate response. Weight outside of parentheses indicates weighting within relevant subgroup analysis, weight inside parentheses indicates weighting within total orthostatic response heart rate analysis. CI = confidence interval, HR = heart rate, ME/CFS = Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, n = number, SMD = standardized mean difference.

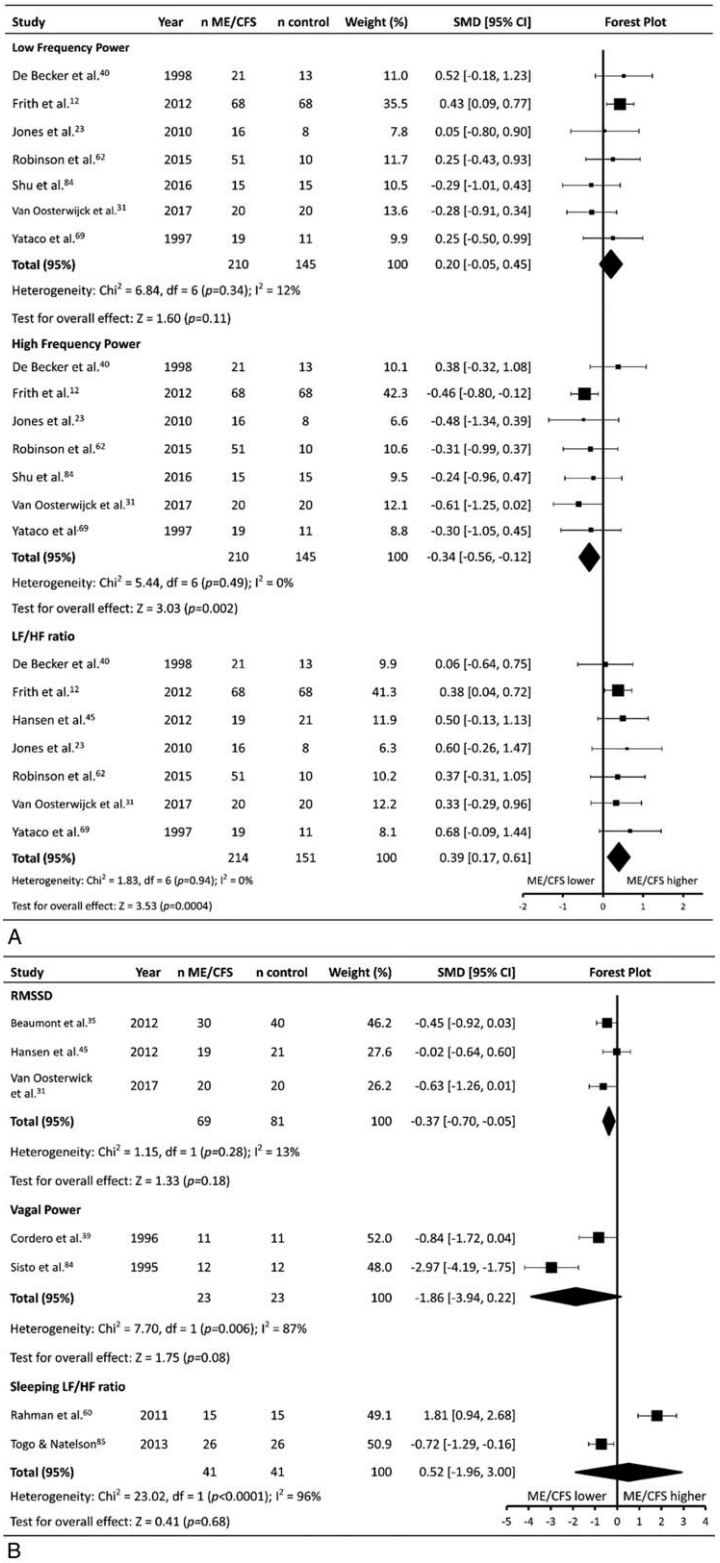


**Figure 7.** Effect of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome on resting heart rate variability. CI = confidence interval, LF/HF = low frequency power/high frequency power, ME/CFS = Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, n = number of participants, RMSSD = root-mean-square difference of successive normal R-R intervals from time-domain analysis, SMD = standardized mean difference.

### *3.12. Heart rate during mental task(s)*

Five studies (patients n = 107, controls n = 116) reported the HR response to a mental task ($HR_{mentaltask}$) (Table 1). Subgroup analysis revealed no significant effect for $HR_{mentaltask}$ when reported as the average HR during the tasks in 4 studies[35] 64,51,[86] (SMD ± 95% CI = 0.25 ± 0.32, $P = .57$) (Fig. 9). One study reported $HR_{mentaltask}$ as the ΔHR during task, again with no significant difference between ME/CFS and controls (-0.29 ± 0.45, $P = .21$).

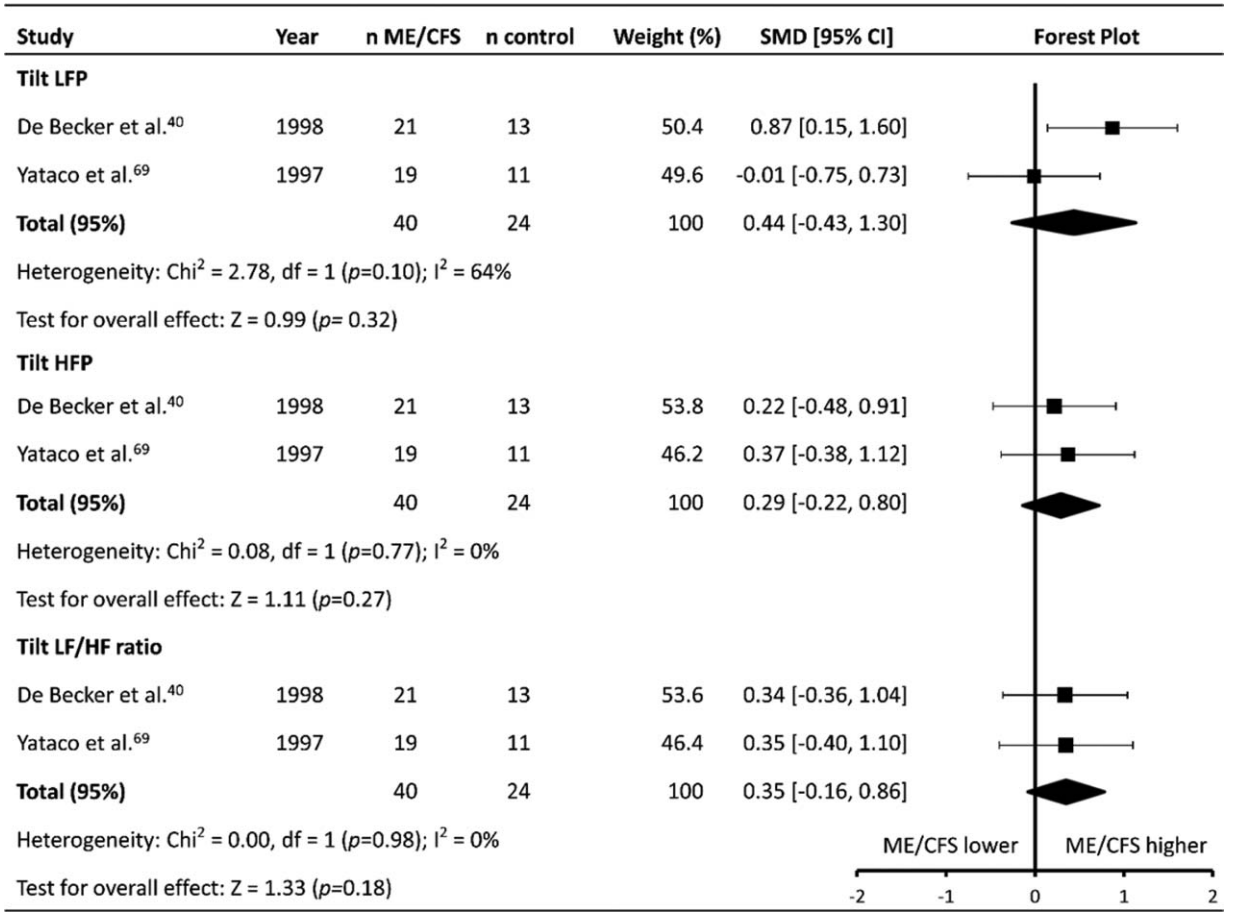


**Figure 8.** Effect of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome on heart rate variability during head-up tilt testing. CI = confidence interval, HFP = high frequency power, LF/HF = low frequency/high frequency, LFP = Low frequency power, ME/CFS = Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, n = number of participants, SMD = standardized mean difference.

### 3.13. Daily average heart rate

Daily average HR ($HR_{dailyaverage}$) was reported in 2 studies[58,87] (patients n = 80, controls n = 162) (Table 1). Both studies used the same measurement techniques and reported data in the same way – HR data were measured through ECG monitoring, and both studies reported the average HR over 24 hours. Meta-analysis revealed no difference between the ME/CFS patients and controls (SMD ± 95% CI = 0.11 ± 0.27, $P = .45$; Fig. 10), with no heterogeneity between the studies ($P = .56$, $I^2 = 0\%$).

### 3.14. Post-exertional heart rate recovery

HRR was reported in only 2 articles (patients n = 108, controls n = 72), both of which used similar methods to elicit and record HRR (Table 1). Meta-analysis found no difference in HRR between ME/CFS patients and controls (MD ± 95% CI = −11.78 ± 13.72, $P = .09$; Fig. 11), with results affected by significant statistical heterogeneity ($P = .003$, $I^2 = 89\%$).

## 4. Discussion

This review found a number of differences in HR parameters between patients with ME/CFS and controls. Meta-analysis identified that compared to controls, patients with ME/CFS exhibited higher resting HR (RHR), lower maximal/peak HR ($HR_{max}/HR_{peak}$), higher HR responses to HUTT ($HR_{tilt}$) and moving from sitting to standing ($HR_{OR}$), and lower HR at submaximal exercise threshold ($HR_{threshold}$). Resting HRV ($HRV_{rest}$) parameters also differed between ME/CFS patients and controls, with patients exhibiting higher LFP and lower HFP. Taken together, these results tend to suggest reduced vagal modulation and increased sympathetic modulation of HR in patients with ME/CFS. Included studies were generally of a moderate to good quality, and although confounding factors were rarely identified and dealt with it is unlikely that the quality of included articles played a major role on the results of this meta-analysis.

### 4.1. Resting heart rate (RHR)

RHR was higher for ME/CFS patients compared to controls, regardless of whether assessed when supine or seated. The higher RHR likely reflects a decrease in parasympathetic and increase in sympathetic cardiac modulation as multiple studies have shown that both parasympathetic blockade and an increase in sympathetic autonomic control result in an increase in RHR.[88,89] Interestingly, the analysis of $RHR_{supine}$ was affected by significant heterogeneity, which was not the case for $RHR_{seated}$. Very few studies made any effort to control breathing rate in either body position, and it is likely that the potential

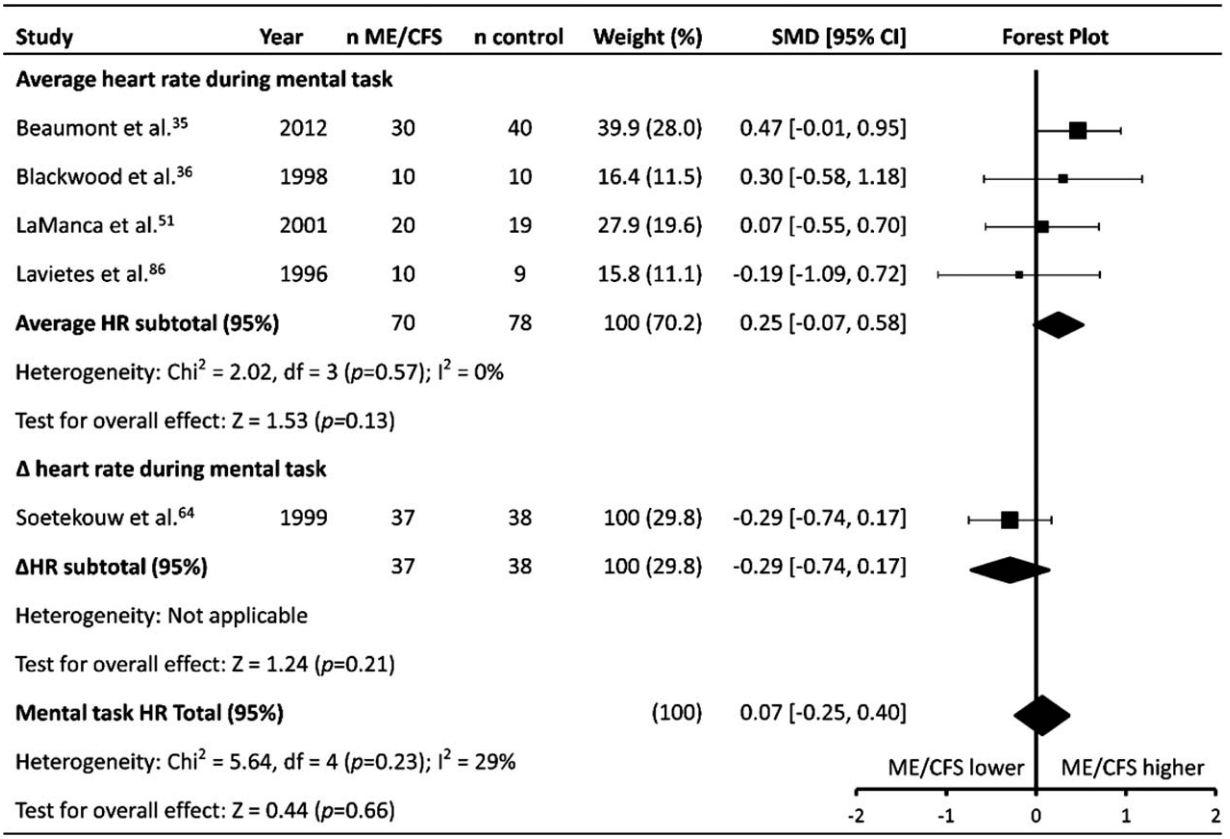


**Figure 9.** Effect of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome on heart rate response to mental task. Weight outside of parentheses indicates weighting within relevant subgroup analysis, weight inside parentheses indicates weighting within total mental task heart rate analysis. CI = confidence interval, HR = heart rate, ME/CFS = Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, n = number, SMD = standardized mean difference.

difference in breathing rates between studies may account for some of the variation in RHR values reported.[90] Although RHR appears to be higher for patients with ME/CFS than controls, the average difference between groups ($4.33 \pm 1.42$ bpm) is less than the typical day to day variation of RHR reported in the literature (~5 bpm).[91] Therefore, while the increased RHR experienced by ME/CFS patients may indicate an altered autonomic balance, it may not be a clinically relevant finding as the large amount of day to day variation in RHR will limit its potential utility as a diagnostic marker in ME/CFS. It must be acknowledged that there was a large amount of variability in the methods utilised to capture RHR data in the included studies including the duration of rest utilised, with rest periods ranging from $\leq 5$ minutes to 30 minutes, while 15 studies did not report the duration of rest utilised.

### 4.2. Heart rate variability ($HRV_{rest}$ and $HRV_{tilt}$)

In addition to ME/CFS patients having a higher RHR, they exhibited differences in $HRV_{rest}$ that also suggest the presence of reduced parasympathetic and increased sympathetic cardiac autonomic modulation. ME/CFS patients had lower HFP and

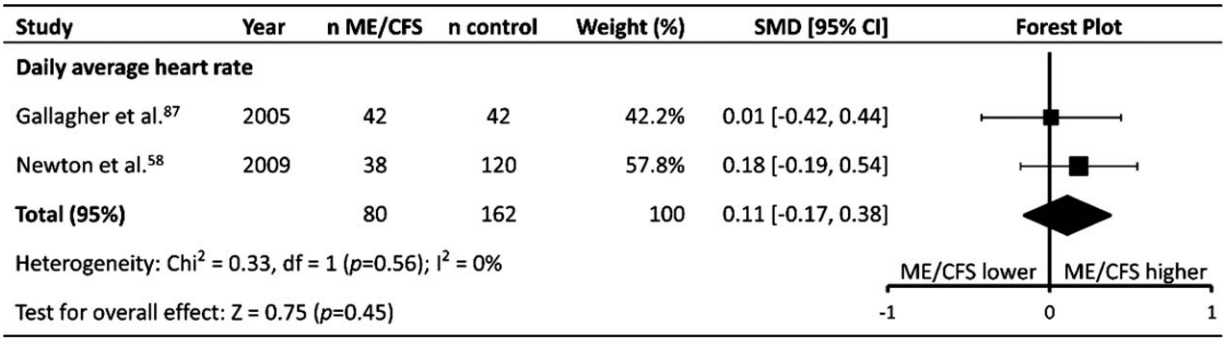


**Figure 10.** Effect of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome on daily average heart rate. CI = confidence interval, ME/CFS = Myalgic Encephalomyelitis/Chronic Fatigue Syndrome, n = number of participants, SMD = standardized mean difference.

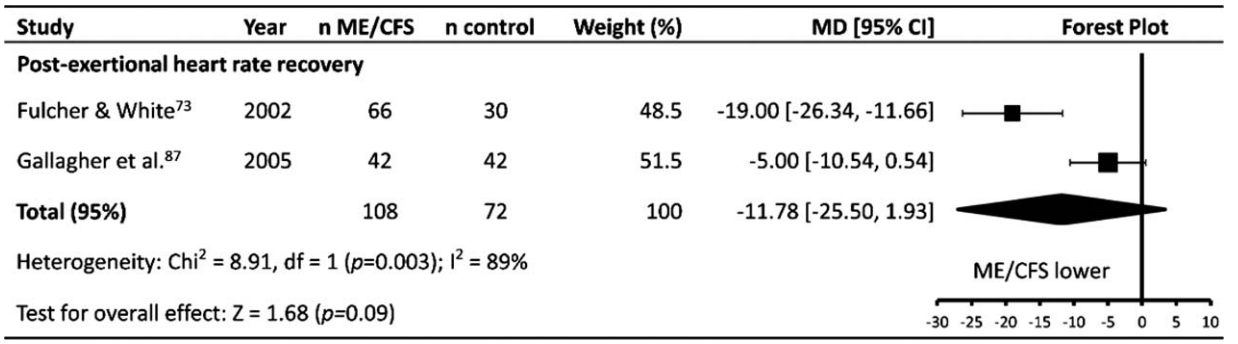


**Figure 11.** Effect of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome on post-exercise heart rate recovery. CI = confidence interval, MD = mean difference, ME/CFS = Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome, n = number of participants.

RMSSD, with both parameters representing primarily parasympathetic cardiac modulation.[92,93] ME/CFS patients also had a higher LF/HF ratio than controls, indicating increased sympathetic and decreased parasympathetic HR modulation compared to controls.[94] The effect sizes for the differences between ME/CFS patients and controls were consistently small (albeit significant), and this may explain why no significant effect was found for other $HRV_{rest}$ parameters which had fewer included studies. LFP, for example, reflects a combination of parasympathetic and sympathetic modulation of HR vagal cardiac modulation in a similar manner to HFP, however the small number of included studies for this parameter may limited the ability for the current meta-analysis to identify a significant effect. Although it is important to note that the effect sizes seen for the $HRV_{rest}$ analyses were small, and there were noticeably fewer included studies than for the analysis of parameters such as RHR, the consistent effect on HRV parameters (RMSSD HFP, LF/HF ratio) suggests that $HRV_{rest}$ may be a useful marker of autonomic dysfunction in ME/CFS patients to assist with the diagnosis of the condition. Interestingly, analysis of $HRV_{tilt}$ found no difference in any parameter between ME/CFS patients and controls, indicating there is no difference in HRV between the groups when an autonomic stressor is introduced, although again, this may be due to the small number of included studies (n = 2).

### 4.3. Maximal heart rate ($HR_{max}$)

Meta-analysis also revealed a lower $HR_{max}$ in ME/CFS patients compared to controls, which may represent further evidence of increased sympathetic modulation of HR. Lower $HR_{max}$ was found between ME/CFS patients and controls for studies which used set criteria to determine if a maximal effort had been produced and likely reported true $HR_{max}$, as well as studies which did not use a criteria approach and likely reported symptom-limited peak HR ($HR_{peak}$). Despite obvious differences arising from the 2 approaches, the fact that $HR_{max}$ was lower in ME/CFS patients in studies when criterion measures were applied suggests that there is a lowering of true $HR_{max}$ in patients with ME/CFS compared with controls. When considered in the context of resting HRV measures indicating increased sympathetic and decreased parasympathetic tone, the lower $HR_{max}$ in ME/CFS patients may be due to resting sympathetic hyperactivity. Alterations in blood pressure variability have also been found in ME/CFS patients[12,95,96] which indicate increased sympathetic autonomic regulation, and it is possible that prolonged pathological sympathetic activity has led to ME/CFS patients' autonomic effectors (such as heart and blood vessels) becoming resistant to sympathetic autonomic stimulation through down-regulation of receptors,[12] thus contributing to the lower $HR_{max}$ identified in this review. Additionally, patients with congestive heart failure have been shown to exhibit abnormally high levels of sympathetic activity, combined with decreased cardiac norepinephrine, suggesting that periods of increased sympathetic neural tone may result in a depletion of cardiac sympathetic neurotransmitters.[97] However, despite the clear differences in $HR_{max}/HR_{peak}$ between ME/CFS patients and controls, it is likely to have limited usefulness as a diagnostic marker in ME/CFS. It is notoriously difficult to elicit a reliable and valid maximal effort in clinical populations[98] and the high intensity exercise required to elicit $HR_{max}$ is likely to cause a significant exacerbation of symptoms for ME/CFS patients.[99] Additionally, the wide variability in individual $HR_{max}$ values (standard deviation ~ 10 bpm)[100] suggests that, despite the apparent differences between patients and controls, the diagnostic accuracy at an individual level would be low.

The assessment of peak $HR_{max}/HR_{peak}$ in the included studies was affected by numerous methodological issues which impacted on the consistency of results seen during studies which assessed symptom limited $HR_{peak}$, rather than true $HR_{max}$. The effect on true $HR_{max}$ was very consistent, with minimal heterogeneity ($P = .88$, $I^2 = 0\%$), compared to those which measured $HR_{peak}$ where the heterogeneity between studies was much larger ($P < .0001$, $I^2 = 74\%$). The heterogeneity in the studies which used reported $HR_{peak}$ is likely, in part, due to differences in encouragement given to participants during the maximal exercise testing. Some studies[78,79] reported that no encouragement was given during testing, while others[42,70] reported that verbal encouragement was given in an attempt to elicit a maximal response. Regular verbal encouragement during maximal exercise testing has been shown to elicit a greater maximum effort compared to when no encouragement is given.[101] As ME/CFS patients (similarly to most chronic health conditions) have been shown to catastrophize their symptoms of pain, leading to a negative effect on exercise performance,[102] the use of regular verbal encouragement during maximal exercise tests in ME/CFS may be particularly important in order to elicit a valid maximal response in this population. The ability for the included studies to elicit a valid maximal response in the patient group can be

established from analysis of the percentage of age predicted $HR_{max}$ achieved during data collection. Across the studies which reported $HR_{peak}$/true $HR_{max}$, the percentage of age predicted $HR_{max}$ obtained in each study varied from 99% in the study by Sargent et al[77] which relied on a criterion approach, to 75% in a study by VanNess et al[34] which reported symptom limited $HR_{peak}$. One study[27] did not report the age of the participants, so predicted maximal HR was unable to be calculated. The 3 highest % age predicted $HR_{max}$ attained by studies were all those which employed a criterion based approach to determine if a maximal effort was given[38,72,77] suggesting this approach may result in better assessment of $HR_{max}$ in this clinical population

### 4.4. Heart rate response to head-up tilt testing ($HR_{tilt}$)

In addition to the evidence of sympathetic overactivity in ME/CFS patients provided by analysis of RHR, $HRV_{rest}$, and $HR_{max}$, the results from the analysis of $HR_{tilt}$ further suggest an altered autonomic balance in ME/CFS patients compared to controls, revealing that ME/CFS patients had a significantly higher HR during HUTT, in addition to a higher ΔHR in response to HUTT. This difference in $HR_{tilt}$ is potentially due to an increased sympathetic tone which may be exhibited ME/CFS patients.[43] Additionally, Timmers et al[66] found a blunted plasma norepinephrine response to HUTT in patients who experienced presyncope without preceding tachycardia, further indicating the presence of altered autonomic function during HUTT in ME/CFS patients. However, it must be acknowledged that variability existed in the methodology utilised to collect $HR_{tilt}$ data. While studies were generally consistent in the tilt methodology used, (all studies using a 70° tilt, with the exception of Freeman and Komaroff[43] who used a 60° tilt) thre was large variability in the durations of tilt employed: 3 studies utilised durations of $\leq$10 minutes,[40,43,56] while the remainder used durations of 30 to 40 minutes.

### 4.5. Orthostatic heart rate response ($HR_{OR}$)

Similar to the findings for $HR_{tilt}$, ME/CFS patients were also found to have an increased $HR_{OR}$ compared to controls. This finding is not surprising given the well-known co-morbidities of ME/CFS and postural orthostatic tachycardia syndrome (POTS). Multiple studies have found that rates of POTS are significantly higher in ME/CFS populations,[103,104] and the greater $HR_{OR}$ seen in ME/CFS participants may be due to an increased sympathetic/parasympathetic balance.[68,105] Similar to $HR_{tilt}$ however, significant variability existed in the methodologies utilised to collect $HR_{OR}$ data which limits the ability to draw definite conclusions about the patterns observed. For example, 5 studies[28,29,59,62,68] reported $HR_{OR}$ in response to standing up after a period of supine rest, while 1 study[46] reported the effect of standing up following sitting, with durations spent in the resting position prior to standing also varying across studies (from 10 minutes[68] to 30 minutes[28]. Further, durations of standing differed greatly, ranging from short (2 minutes[46,62]) to long (60 minutes[29]).

Although the results of the meta-analysis suggest that ME/CFS patients have an altered autonomic balance compared to controls – consisting of higher resting sympathetic and lower resting parasympathetic cardiac modulation – it could be argued that these findings reflect the physical deconditioning that has been found in some ME/CFS patients.[106] Due to the exacerbation of post-exertional malaise which commonly occurs as a result of physical activity in this population, ME/CFS patients are candidates for physical deconditioning as a consequence of exercise avoidance.[102,107] For example, physical deconditioning is a potential cause of the increased RHR experienced by ME/CFS patients. Previous work by De Lorenzo et al,[106] which was subsequently confirmed by Miwa and Fujita,[108] found that ME/CFS patients had a reduced left ventricular size and mass, and such reductions in left ventricular size and mass are typically associated with deconditioning in healthy individuals.[109] Additionally, multiple studies have shown that a decreased level of aerobic fitness is associated with a lower vagal and increased sympathetic tone which can be reversed through aerobic training,[110,111] implying the altered $HRV_{rest}$ found in ME/CFS patients may result from the deconditioning typical of ME/CFS, rather than being a direct cause or symptom of the syndrome. Further, the elevated $HR_{tilt}$ for ME/CFS patients may also potentially be due to physical deconditioning. LaManca et al[50] measured stroke volume during HUTT in ME/CFS patients, and found stroke volume decreased in a similar manner to that seen in other deconditioned populations,[112] and suggested the increased $HR_{tilt}$ witnessed during that study attempted to counteract a hypovolaemic state which had led to decreased preload and decreased stroke volume. Similar observations have been made by other studies in ME/CFS populations.[43,66]

### 4.6. HR during submaximal exercise

The finding of lower HRs at submaximal exercise threshold, such as AT, LT, or VT ($HR_{threshold}$) in ME/CFS participants compared to controls may be further indication of potential physical deconditioning, given that it is well established that an increased level of aerobic fitness is associated with a later onset of submaximal exercise threshold.[113–115] Interestingly, in 4 of the 5 studies which reported on HR at VT/AT,[38,41,78,80] ME/CFS participants had a lower peak $VO_2$ than controls, providing further evidence of deconditioning while the fifth study[33] was underpowered to find a difference between the 2 groups for this parameter. It is important to note that the analysis of $HR_{threshold}$ was affected by significant, moderate heterogeneity ($I^2 = 56\%$), which likely resulted from the different methods used to quantify submaximal exercise threshold. Three of the studies[38,78,80] used the V-Slope method to determine VT, while De Becker et al[41] used an RER $< 1.0$ to determine that AT had been reached, and Sargent et al[77] calculated lactate threshold using the method of Beaver et al.[82] Hodges et al[33] reported on HR at VT, but did not state the method used to quantify VT. Indeed there remains debate as to whether or not there is a relationship between AT, LT, and VT, with some[114] arguing for a strong physiological link between the thresholds, and others believing the similar timing of the 2 thresholds to be purely coincidental.[116] The study by Sargent et al[77] which assessed HR at LT found no difference between ME/CFS patients and controls. Comparatively, 3 other studies which assessed HR at VT/AT found that HR was lower for patients than controls.[41,78,80] While this suggests plasma lactate measures may differ from ventilatory measures in their ability to reflect differences between ME/CFS patients and controls, the differences in $VO_{2max}$ in the studies which assessed HR at AT/VT suggest these differences may also result from physical deconditioning in the ME/CFS patients. Interestingly, there was no difference in the $HR_{steadystate}$ of ME/CFS patients

and controls. It is well known that $HR_{steadystate}$ in response to equal workload is generally higher in individuals with a lower level of aerobic fitness[117,118] and 2 of the 3 studies which reported both $HR_{steadystate}$ and $VO_{2max}$[27,78] found lower $VO_{2max}$ values for ME/CFS patients when compared to healthy controls. Therefore, it is surprising that there was no difference between the $HR_{steadystate}$ values reported between ME/CFS patients and controls in response to an equal workload.

### 4.7. Other heart rate parameters ($HR_{dailyaverage}$, $HR_{mentaltask}$, HRR)

No difference was found between ME/CFS patients and controls for $HR_{dailyaverage}$, $HR_{mentaltask}$, or HRR, potentially due to the small number of included studies for each parameter. $HR_{mentaltask}$ was reported in 5 studies, while $HR_{dailyaverage}$[58,87] and HRR[73,87] were both reported in 2 studies. Given that ME/CFS patients had a higher RHR than controls, it may be expected that a similar difference would be apparent during tasks which do not require physical exertion, such as a mental task. Similarly, it may be expected that ME/CFS patients would have a higher $HR_{dailyaverage}$ compared to controls due to a combination of physical deconditioning and an apparent sympathetic dominance at rest, however this does not appear to be the case. With regard to $HR_{dailyaverage}$, this may be due to increased patterns of exercise avoidance that ME/CFS patients exhibit[107,119] leading to lower daily physical activity,[120] and therefore an overall similar $HR_{dailyaverage}$ compared to controls. No difference was found between ME/CFS patients and controls with regard to post exercise HRR. The analysis only included 2 studies,[73,87] and was affected by significant statistical heterogeneity ($P = .003$, $I^2 = 89\%$), likely due to the small number of included studies. One study[73] found a 19 bpm difference between ME/CFS patients and controls, and the other[87] found no difference. Regardless, HRR is unlikely to be a suitable marker for use in an ME/CFS patient group, not only because of the lack of current evidence indicating any difference between patients and controls, but also because the assessment of HRR has been found to require exercise intensities of 88% of maximal HR in order to minimise day-to-day variation in athletes.[121] Given the difficulties that many ME/CFS patients may have in attempting to attain this elevated HR, the reliability of HRR may therefore be diminished in ME/CFS patients, in addition to the fact that high intensity exercise can exacerbate ME/CFS symptoms.[122]

Interestingly, of the studies which reported maximal HR in ME/CFS patients, the majority that also reported $VO_{2max}$ (10 of 17) found a lower $VO_{2max}$ in ME/CFS patients compared to controls, which could suggest that deconditioning is common in ME/CFS. However, of these studies, four of them were those which used a criterion approach to determine if a valid maximal effort had been given, and these studies found no difference in $VO_{2max}$ between ME/CFS and controls, implying that many ME/CFS patients may not be deconditioned compared to controls, but are unable to produce a valid voluntary maximal effort, possibly due to kinesiophobia.[102,107] While some studies have found differences in aerobic fitness between ME/CFS patients and controls, and it is possible that deconditioning may be a potential explanation for some of the differences in HR parameters seen between ME/CFS patients and controls, the equivocal findings regarding aerobic fitness parameters (with some studies reporting a difference between ME/CFS and controls,[42,74] and others not[38,75]) suggest that deconditioning cannot explain all of the variance in HR parameters between ME/CFS patients and controls. Rather, it is likely that an altered cardiac autonomic balance is present in ME/CFS patients, typified by increased sympathetic and decreased parasympathetic cardiac autonomic control. In any case, while deconditioning through avoidance of physical activity may have had an effect on the HR analyses in this meta-analysis, it is important to note that physical deconditioning is not a potential cause of ME/CFS, but rather it occurs as a consequence due to symptoms (i.e. fatigue, pain) reducing the capacity for participation in physical activity which may be further compounded by active avoidance of activity even when able, for fear of inducing post-exertional malaise and severe exacerbation of symptoms.[102]

## 5. Limitations

This review and meta-analysis included ME/CFS patients who were diagnosed with any of a number of recognised criteria. Although the 1994 CDC criteria[1] was by far the most commonly used criteria in the included studies, it may not be the most effective tool for clinical diagnoses, a function for which it was never intended.[3] In recent times, the 'Canadian Criteria' (CCC)[3] and the International Consensus Criteria on ME/CFS (ICC)[4] have been preferred by many clinicians as they require the patient to experience an acute worsening of symptoms with exercise, something which was not required as part of the 1988 or 1994 CDC definitions. However, very few of the articles included in this review employed the CCC or the ICC as their diagnostic criteria. Given the differences between the diagnostic criteria, it cannot be discounted that there are differences in the characteristics of the illnesses between studies which used different diagnostic criteria. Future research in ME/CFS populations should ideally report the number of included participants who met the 1994 CDC criteria (made to standardise research), and what number met the ICC or CCC (made for better clinical diagnosis).

Where possible, this review attempted to explain the reasons for any statistical heterogeneity that was identified during the meta-analysis process. Although this heterogeneity may be the result of methodological issues, it is likely that the results for each study are affected by the disease severity of included patients, in addition to the duration of illness. While some included studies[34,59] did classify patients into subcategories based on symptom severity, the majority of included studies did not. With particular regard to the HR parameters recorded during or following exercise ($HR_{max}$, HRR, exercise HR), selection bias is a potential issue that may limit the validity of the results from included studies, as patients who were more severely affected would be less likely to volunteer for exercise-based studies. Additionally, given that ME/CFS patients may be affected by cardiovascular deconditioning as a result of their condition, conceivably, ME/CFS patients who have had the illness for a longer duration are likely to have experienced greater deconditioning, and this increased deconditioning may explain some of the statistical heterogeneity witnessed for some parameters. Additionally, it must be acknowledged that it was not possible to analyse results based on other factors (e.g., level of physical activity) due to the under-reporting of such details within included studies, or a tendency to report all results within a single sample despite differences in participant characteristics (e.g., male or female).

## 6. Conclusions

Numerous HR parameters have been reported on in ME/CFS patients, with wide variations in study design and data acquisition methods, including body position and the duration/intensity of interventions (HUTT, exercise etc). Meta-analysis revealed significant differences between patients and controls in a number of parameters, including patients having: higher RHR, $HR_{tilt}$, orthostatic HR response, and LF/HF ratio; and lower $HR_{max}$, $HR_{threshold}$, HFP and RMSSD. These differences suggest an altered regulation of HR in ME/CFS patients that is suggestive of reduced vagal and increased sympathetic modulation of heart rate. It does not appear that any of the currently used HR parameters have the sensitivity to detect the presence of ME/CFS on their own, as demonstrated by the presence of high levels of statistical heterogeneity and methodological issues which limit the usefulness of these parameters. However, the results of this review suggest that there are quantifiable differences in autonomic HR regulation in ME/CFS patients, and future research in ME/CFS populations should therefore focus on determining if there are additional HR parameters which have diagnostic utility in this group.

## Author contributions

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