Heart rate and heart rate variability comparison between postural orthostatic tachycardia syndrome versus healthy participants; a systematic review and meta-analysis.

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Joel Dominic Swai
Benjamin Mkapa Hospital
joel.swai@hotmail.com
Corresponding Author
ORCiD: https://orcid.org/0000-0001-5363-3977

Zixuan Hu
Central South University Third Xiangya Hospital

Xiexiong Zhao
Central South University Third Xiangya Hospital

Tibera Rugambwa
Mbeya Referral Hospital

Gui Ming
Central South University Third Xiangya Hospital

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Abstract
Background A number of published literatures have reported that, physiologically, heart rate variability in patients with postural orthostatic tachycardia (POTS) to be greatly confounded by age, sex, race, physical fitness and circadian rhythm. The purpose of this study was to compare between postural orthostatic tachycardia syndrome (POTS) patients versus healthy patients, in terms of heart rate (HR) and heart rate variability (HRV) after Head-Up tilt test, by systematic review and meta-analysis of available published literature. Methods MEDLINE (using PubMed interphase), EMBASE and SCOPUS were systematically searched for observational studies comparing between POTS patients versus healthy patients, in terms of heart rate (HR) and heart rate variability (HRV). HRV was grouped into Time and frequency domain outcome measurements. Time domain was measured as mean RR-interval and mean square root of mean of squares of successive R-R waves (rMSSD) in milliseconds. Frequency domain was measured as mean values of Low frequency power (LF), High frequency power (HF), LF/HF-ratio, LF-normalized units (LF(n.u)) and HF-normalized units (HF(n.u)). Demographic data, comorbidities, and mean values of HR, RR-interval, rMSSD, LF, HF, LF/HF-ratio, LF-(n.u) and H.F-n.u were extracted from each group and compared, by their mean differences as overall outcome measure. Computer software, RevMan 5.3 was utilized, at 95% significance level. Results Twenty (20) eligible studies were found to report 717 POTS and 641 healthy participants. POTS group had higher mean heart rate (p<0.05), lower mean RR-Interval (p<0.05), lower rMSSD (p<0.05) than healthy participants. Furthermore, POTS group had lower mean HF(p>0.05), lower mean LF(p>0.05), and lower mean HF(n.u) (p>0.05), higher LF/HF-Ratio (p>0.05) and higher LF(n.u) (p>0.05) as compared to healthy participants. Conclusion Despite massively supported fact that POTS patients have higher heart rate than healthy patients after HUTT, POTS patients have lower heart rate variability in terms of time domain measure but not in terms of frequency domain measure.

Background
Blood circulation, blood pressure and adequate tissue perfusion are closely coordinated with autonomic nervous system in that, body postural changes will result in smaller and bearable changes in hemodynamics (1). Inadequate blood volume, dysfunctional autonomic nervous system and
sometimes, old-age and postprandial status, can result into altered hemodynamics when raising to upright position (Orthostasis) (1, 2). The altered hemodynamics result into a variety of symptoms collectively known as orthostatic intolerance (OI). Orthostatic intolerance could be classified as either Orthostatic Hypotension (OH), postprandial hypotension or Postural orthostatic tachycardia syndrome (POTS), also known as Chronic orthostatic intolerance (3).

Orthostatic intolerance presents with immediate clinical manifestations that follow cerebral hypoperfusion (4). These could range from, generalized weakness, dizziness or lightheadedness, visual blurring or darkening of the visual fields, hypotension, tachycardia, pallor and in severe cases, syncope (4, 5). Orthostatic hypotension is characterized by hypotension when raising to upright position without compensatory increase in heart rate while, postprandial hypotension results into hypotension characterized by hypotension when raising to an upright position after eating. On the other hand, Postural orthostatic tachycardia syndrome is characterized by tachycardia and normal blood pressure (6).

Postural tachycardia syndrome is the most prevalent form of orthostatic intolerance. It is diagnosed relying on sustained heart rate increase of greater than 40 beats per minute or an increase to 120 beats per minute or greater within the first 10 minutes of tilt, without arterial hypotension. It is estimated that 3,000,000 Americans, suffer from this disorder at female: male ratio of 4:5.1 (7). It occurs particularly in children and younger adults between 14 and 45 years, as compared to other OI which commonly occur in elderly (3). Adverse manifestations such as hypotension and syncope almost never occur in POTS patients because they have preserved autonomic nervous functions (8).

Among others, Autonomic nervous function, is one of key players in maintaining hemodynamics and preventing POTS. Sympathetic denervation in lower extremities, preserved cardiac innervation and increased sympathetic activities (hyper-adrenergic state) have been shown to be sole etiologies of POTS (2, 3, 6, 8). Other postulated theories include Cardiovascular deconditioning, abnormal venous function with reduced venous return, baroreflex abnormalities, hypovolemia and genetic abnormalities (4, 7). To assess cardiac autonomic innervation and function, a number of tests have been developed with heart rate variability (HRV) widely used (9).
Heart rate variability (HRV) analysis attempts to assess cardiac autonomic regulation through quantification of sinus rhythm variability. The sinus rhythm interval-time series is obtained from the QRS to QRS interval sequence of the electrocardiogram (ECG), by extracting only normal sinus to normal sinus in between two consecutive beats \((9, 10)\). High frequency alterations in sinus rhythm signifies parasympathetic modulation, while slower variations reflect a combination of both parasympathetic and sympathetic modulation and non-autonomic factors. Heart rate variability (HRV) measures are measured in two ways; time domain measures and frequency domain measures \((9-11)\).

A few published literatures have reported heart rate variability to be greatly confounded by factors including age, sex, race and circadian rhythm. This study compared between postural orthostatic tachycardia syndrome (POTS) patients versus healthy patients, in terms of their heart rate (HR) and heart rate variability (HRV) after head-up tilt test (HUTT), by systematic review and meta-analysis of available published literature.

**Methods**

**Eligibility criteria**

This study included two kinds of participants; patients with postural orthostatic tachycardia syndrome as cases, healthy participants as controls. The main outcomes were; Heart rate and Heart rate variability as time domain measurement (TDM) and frequency domain measurement (FDM). Only observational studies comparing suitable outcomes between the two groups were eligible for inclusion. To increase the external validity of this study, accessible literature from across the world were eligible for inclusion as long as they fulfill aforementioned inclusion criteria. Only English published literatures were eligible for inclusion.

**Information sources**

Three online databases, namely PubMed, EMBASE and the SCOPUS were systematically searched to come up with eligible included studies. The searches were not be customized for searching within any restricted date ranges. Secondary referencing of eligible studies was done to extend the search scope and the last date of search was 29\(^{th}\) September 2019.

**The search**
To generate a set of citations that are relevant to our study’s search question, advanced search tool was used, utilizing Mesh terms and keywords in all of the three databases aforementioned. Using PubMed, Mesh terms were generated, search was built and advanced search was done as; ("Postural Orthostatic Tachycardia Syndrome"[Mesh]) AND "Heart Rate"[Mesh]. Again the search was repeated with; ("postural orthostatic tachycardia syndrome"[MeSH Terms] OR ("postural"[All Fields] AND "orthostatic"[All Fields] AND "tachycardia"[All Fields] AND "syndrome"[All Fields])) OR "postural orthostatic tachycardia syndrome"[All Fields]) OR ("postural orthostatic tachycardia syndrome"[MeSH Terms] OR ("postural"[All Fields] AND "orthostatic"[All Fields] AND "tachycardia"[All Fields] AND "syndrome"[All Fields])) OR "postural orthostatic tachycardia syndrome"[All Fields]) OR ("postural orthostatic tachycardia syndrome" OR "pots"[All Fields])) AND ("heart rate"[MeSH Terms] OR ("heart"[All Fields] AND "rate"[All Fields])) OR "heart rate"[All Fields]) AND variability[All Fields]).

Using EMASE, on the other hand, advanced search tool was utilized firstly using Mesh terms ((postural AND orthostatic AND tachycardia AND syndrome OR pots) AND heart AND rate) and then a repeated by using a combination of key words (postural AND orthostatic AND tachycardia AND syndrome OR pots) AND heart AND rate AND variability. The searches were independently performed by two authors; JS and XZ. Results were exported to computer software, EndNote X9 (Build 12062) which was used to manage and keep track of references throughout this study.

**Study selection process**

All studies resulting from online database search independently conducted by two authors, were initially screened by their titles and abstracts to initially assess their relevance to our study question. This was, level-one screening, and was done independently by two authors, JS and XZ. Compiled results of level-one screening were exported to EndNote software and then searched for their full-text articles. Level-two screening involved assessing the retrieved full text articles for eligibility for inclusion or exclusion. Any differences of thoughts in the search process were settled by the third author, TR. The entire study search, screening and selection is summarized in the Figure 1.

**Data extraction**

Before data extraction process from full-text articles meting eligibility criteria for inclusion,
assessment for methodological biases was done. PRISMA (preferred reporting items for systematic reviews and meta-analyses) tool (12) was used for this study write-up to minimize reporting bias. The process of data extraction was independently performed by two authors, namely; JS and XZ. Any difference of thoughts was settled by the third author, TR. Data collected included participants’ demographics, study characteristics and reported outcomes in line with our study question. Demographic data included participants’ mean/median ages, setting and sample sizes in each group. Head-up Tilt test (HUTT) procedure details; angle of tilt, time of tilt, duration of orthostasis and device used to measure HR and HRV; whether ECG or Holter. Diagnoses and comorbidities among participants were also recorded.

In line with this study question, two outcomes were recorded from the eligible studies; Heart rate and Heart rate variability measured by either Time domain measures (TDM) and frequency domain measures (FDM). These outcomes were recorded on both comparison groups.

**Analysis**

Data was analyzed separately according to the two main outcomes of interest. Time domain measurement was sub-grouped into RR interval and rMSSD while Frequency domain measurement outcome was sub-grouped into LF, HF, LF/HF-ratio, LF (n.u) and HF (n.u). In that case, comparison of time domain measures (TDM) between postural orthostatic tachycardia versus healthy participants groups were in terms of the mean differences of RR-Interval and rMSSD. On the other hand, comparison of frequency domain measures (FDM) between postural orthostatic tachycardia versus healthy participants groups were in terms of the mean differences of LF, HF, LF/HF-ratio, LF (n.u) and HF (n.u).

Overall effect of postural orthostatic tachycardia was diagrammatically be depicted by forest-plots. Data synthesis, analysis and generation of forest-plots were done utilizing a computer software, **Review Manager (RevMan Version 5.3)**. The software was customized to random or fixed effect model depending on the heterogeneity ($I^2$) of the studies when analyzing the outcomes. Fixed effect model was used when $I^2$ was less than 50% and random effect model was used when $I^2$ was more
than 50%.

**Assumptions and Simplifications**

For this study purpose, all participants were considered to have been correctly diagnosed and correctly classified as to be having postural orthostatic tachycardia, or otherwise healthy. All participants, despite study country, were considered to have received standard care.

**Results**

**Study selection**

Literature search identified a total of twenty-eight (28) studies that seemed relevant and were sought for full-text. Nine of these were excluded due to various reasons; Nakao et al. (2012)(13) used comorbid than healthy control; Goldstein et al. (2005)(14) did not assess our outcome of interest; Yoshiuchi et al. (2004)(15) used POTS participants comorbid with chronic fatigue syndrome; Singer et al. (2003)(16) intervened the control group with isoproterenol infusion similarly Freitas et al. (2000)(17) who intervened with cardio-selective beta-blocker and/or fludrocortisone and Stewart et al. (2007)(18) who employed hand-grip maneuver than HUTT. Furthermore, Bongiovanni et al. (2013)(19) and Aoki et al. (2008)(20) were excluded for not accessible full-text and use of Japanese language in the full-text retrieved, respectively. A total of twenty (20) studies fulfilled eligible criteria for inclusion.

**Figure 1,** summarizes search results, screening and selection process.

**Study characteristics**

Table 1 summarizes the study characteristics of our twenty (20) studies that were eligible for inclusion in our study. Total number of participants reported was 1358, of these, 717 POTS and 641 were healthy participants. Regarding participants demographics, while other studies recruited both gender equally(21), other only recruited one gender participants (22), and other studies randomly involved both gender (23). While other studies matched the groups by age (14, 22), other studies did not (24). Furthermore, majority of studies reported participants’ ages central tendencies by mean, two studies utilized median instead (25, 26). While other studies used larger sample size (27), other used smaller sample sizes (28).
All twenty studies were case-control observational studies and none was interventional. These were conducted in different settings from a diverse number of countries all around the world. Eleven studies were done in USA, two in Australia and other were conducted in Israel (29), UK (23), Portugal (30), Japan (31), Germany (22), Korea republic (24) and The Netherlands (21), each contributing one study. This was thought to increase the external validity of this study.

Despite the fact that the search was not confined to any specified range of dates, none of the included study was found to have been published before the year 2000. Fifteen studies (75%) were published in the last decade.

Different studies reported different outcomes, but all aligned with our study questions. Eighteen studies compared heart rate, three studies compared RR-Interval, three studies compared rMSSD, six studies compared LF, eight studies compared HF, six compared LF/HF-Ratio and four studies compared LF(n.u) and HF(n.u) each. Studies comparing similar outcomes were analyzed together in the same forest-plot.

**Sources of bias**

All 20 eligible articles included in this study were assessed for risk of bias in two levels; at study level and at review level. Regarding study level bias assessment; different studies involved different number sample sizes. Other studies included large number of participants (27) while other used low (28). It follows that, large sample sizes are more representative of general population as compared to small sample sized studies. Furthermore, none of these 20 studies reported to have had calculated the required sample size prior to their conduction.

Despite the fact that all studies were similar in that, they compared POTS versus healthy participants, some studies matched the comparison groups to reduce confounding factors while other studies did not (32). This might have introduced confounding factors to our study as factors such as female gender, BMI, physical fitness and race, each has been reported to independently alter heart rate variability (41).

Different studies utilized different methods to induce orthostasis, with other using Head-up Tilt test,
physical standing (31), while others utilizing Valsalva-maneuvers. Regarding, HUTT, different angles of tilt were set, ranging from $40^0$ (37) to $70^0$ in other studies (28). While majority involved awake patients, other studies (22) utilized sleeping participants. While other studies used ECG to measure heart rate variability in a 40 minutes session (38), others used Holter device to record mean heart rate variability per 24 hours (32).

At review level on the other hand, a number of loopholes for biases were also identified. Although, other studies had our data of interest, readily available to extract from tables in text, from one (23) study data had to be extracted by estimations and extrapolation from a graphical figure. This led to conducting sensitivity analysis excluding this study. Furthermore, overall mean ages of POTS and/or healthy group could not be calculated because data could not be accessed in other studies (28, 32), because median was utilized than mean (25, 26).

**Heart rate**

**Figure 2** illustrates eighteen of twenty eligible studies that compared heart rate outcome between POTS versus Healthy participants. Overall mean difference between the two groups was 19.88 (15.24, 24.52) signifying higher heart rate in POTS group. This difference reached statistical significance (P-value < 0.05). Random-effect model was used since heterogeneity, $I^2$, was 99% (i.e. $I^2 > 50%$).

**RR- interval**

**Figure 3a** illustrates three of twenty eligible studies that compared time domain measure outcome between POTS versus Healthy participants in terms of mean RR intervals. Overall mean difference between the two groups was -162.89 (-172.65, -153.12) signifying lower Heart rate variability in terms of RR-interval in POTS group. This difference reached statistical significance (P-value < 0.05). Fixed-effect model was used since heterogeneity, $I^2$, was 0% (i.e. $I^2 < 50%$).

**Root of mean of squares of successive R-R interval differences (rMSSD)**
**Figure 3b** illustrates three of twenty eligible studies that compared time domain measure outcome between POTS versus Healthy participants in terms of rMSSD. Overall mean difference between the two groups was -15.16 (-18.28, -12.03) signifying lower Heart rate variability in terms of rMSSD in POTS group. The difference reached statistical significance (P-value<0.05). Fixed-effect model was used since heterogeneity, $I^2$, was 2% (i.e. $I^2<50\%$).

**Low frequency power (LF)**

**Figure 4a** illustrates five of twenty eligible studies that compared frequency domain measure outcome between POTS versus Healthy participants in terms of LF. Overall mean difference between the two groups was -80.89 (-211.37, 49.58) milliseconds$^2$ signifying lower heart rate variability in terms of LF in POTS group. The difference, however did not reach statistical significance (P-value>0.05). Random-effect model was used since heterogeneity, $I^2$, was 96% (i.e. $I^2>50\%$).

**High frequency power (HF)**

**Figure 4b** illustrates seven of twenty eligible studies that compared frequency domain measure outcome between POTS versus Healthy participants in terms of HF. Overall mean difference between the two groups was -113.20 (-275.52, 49.13) milliseconds$^2$ signifying lower heart rate variability in terms of HF in POTS group. The difference, did not reach statistical significance (P-value>0.05). Random-effect model was used since heterogeneity, $I^2$, was 84% (i.e. $I^2>50\%$).

**Low frequency power /High frequency power ratio (LF/HF- ratio)**

**Figure 4c** illustrates five of twenty eligible studies that compared frequency domain measure outcome between POTS versus Healthy participants in terms of LF/HF- ratio. Overall mean difference between the two groups was 0.29 (-0.25, 0.83) signifying higher heart rate variability in terms of LF/HF- ratio in POTS group. The difference, did not reach statistical significance (P-value>0.05). Random-effect model was used since heterogeneity, $I^2$, was 95% (i.e. $I^2>50\%$).
Low frequency power-normalized unit

**Figure 4d** illustrates four of twenty eligible studies that compared frequency domain measure outcome between POTS versus Healthy participants in terms of LF (n.u). Overall mean difference between the two groups was 0.05 (-0.04, 0.13) signifying higher heart rate variability in terms of LF (n.u.) in POTS group. The difference, however did not reach statistical significance (P-value>0.05).

Random-effect model was used since heterogeneity, $I^2$, was 96% (i.e. $I^2 > 50\%$).

High frequency power-normalized unit

**Figure 4e** illustrates four of twenty eligible studies that compared frequency domain measure outcome between POTS versus Healthy participants in terms of HF (n.u). Overall mean difference between the two groups was -0.03 (-0.11, 0.04) signifying lower Heart variability in terms of HF (n.u.) in POTS group. The difference, however did not reach statistical significance (P-value>0.05). Random-effect model was used since heterogeneity, $I^2$, was 91% (i.e. $I^2 > 50\%$).

Sensitivity analysis

Eliminating one study (23), in which data were collected by estimates and extrapolations from a graphical figure, none of the outcome results changed statistical significance.

Publication bias

**Figure 5** illustrates a funnel-plot to illustrate publication biases for studies included in comparing heart rate between POTS versus healthy groups. Medium sample sized studies at the middle of the funnel-plot were more symmetrically distributed as compared to large sample sized studies at the top. This suggest heterogeneity of the study estimates as well as likely publication bias favoring studies with medium sample sizes than large sample sizes.

Discussion

Age, sex, race, BMI, physical fitness and circadian rhythm are among a number of factors that have
been reported to physiologically influence heart rate variability. Heart rate variability in patients with postural orthostatic tachycardia is no exception. This study was aimed to compare between postural orthostatic tachycardia syndrome (POTS) patients versus healthy patients, in terms of their heart rate (HR) and heart rate variability (HRV) after head-up tilt test (HUTT), by systematic review and meta-analysis of available published literature.

From the results of our study, mean difference for time domain outcome measures between POTS versus healthy participants were found to be; RR interval = -162.89 (-197.93, -84.07), P-value<0.05; rMSSD = -15.16 (-18.28, 12.03), P-value<0.05. In this case both outcomes showed statistically significant results that illustrate lower heart rate variability in terms of time domain measure in POTS group than in comparison group. These findings concur with available base of literatures by; De Wandel et al. (2014) (42), Galland et al. (2008) (43), Gergont et al. (2019) (44), Lewis et al. (2013) (45) and Pengo et al. (2015) (46), all of whom reported reduced heart rate variability in POTS than in non-POTS patients or otherwise healthy individuals. On the other hand, mean differences for frequency domain outcome between POTS versus healthy participants were: LF, = -80.89 (-211.37, 49.58), P-value>0.05; HF, = -113.20 (-275.52, 49.13), P-value>0.05 and HF (n.u) = -0.03 (-0.11, 0.04), all of which did not show statistically significant results that POTS patients have lower heart rate variability than healthy participants in terms of frequency domain measure. Our study’s LF results aligns with those reported by Mallien et al. (2012) but contradicts with those reported by Stewart et al. (2006). Our results for HF align with those reported by Ocon et al. (2009) but contradicts with those of Freitas et al. (2005).

Moreover, from our study, LF/HF- ratio was found to be 0.29 (-0.25, 0.83), P-value>0.05; LF (n.u), = 0.05 (-0.04, 0.13), P-value>0.05; all of which showed higher heart rate variability in POTS patients in comparison to healthy participants in terms of frequency domain measures without reaching statistical significance. Our results for LF/HF-Ratio aligns with those reported by Yoshida et al. (2014) and contradicts with those reported by Mallien et al. (2014). Our LF(n.u) results aligns with those previously reported by Medow et al. (2014) but contradicts with those reported by Ocon et al. (2009).

Regarding heart rate, our study strongly shows statistically significant higher heart rate in POTS than
healthy patients following HUTT with mean difference of 19.88(15.24, 24.52), P-value<0.05. These results align with majority of previously published literatures but contradicts with those reported by Meier et al. (2006) who reported otherwise.

Authors of this study believe that the reasons for variations and contradictions among all aforementioned studies and their outcomes to greatly be due to methodological reasons, especially inadequate and/or improper matching of participants. Authors therefore recommend more robust researches to be conducted in the topic, matching participants with age, gender, ethnicity, BMI, physical fitness and circadian rhythm.

Amid a number of theories explaining low heart rate variability in POTS patients, one is hyperadrenergic state (14, 39, 47). Physiologically, POTS patients have been reported to have increased sympathetic activity following a suggested hyperadrenergic state. Another theory for low heart rate variability in POTS patient is, distal denervation predominantly in lower extremity, with preserved cardiac innervation leading to lower extremity anhidrosis, impaired norepinephrine spillover in the lower extremities and decreased muscle sympathetic activity recruitment in the lower extremity in response to a nitroprusside-induced hypotensive stimulus (21, 48, 49). Other studies have reported hypovolemia, decreased venous posture in upright position, baroreflex abnormality and cardiac deconditioning to contribute (50).

Despite promising results, the results of this study need to be addressed with care. This follows a number of bias sources that were encountered and assumptions that were made during the conduction of this study. Different studies involved different number sample sizes and none of these twenty studies reported to have calculated the required sample size prior to their conduction. Furthermore, improper matching as explained earlier, different methods of inducing orthostasis including variable angles of tilt from 40° to upright; different methods of measuring outcomes including the use of ECG and/or Holter device. Moreover, at review level, one study involved data extraction from graphical figure, though sensitivity analysis was thereafter conducted eliminating this study. To help mitigate biases, authors firstly appraised all eligible studies and used a team work in conducting database search and data extraction. To mitigate reporting biases, PRISMA tools was used
Conclusions
Despite a number of unavoidable sources of biases, it is worth to note that despite massively supported fact that POTS patients have higher heart rate than healthy patients after HUTT, POTS patients have lower heart rate variability in terms of time domain measure but not in terms of frequency domain measure. We, though, call upon more extensive observational and interventional studies to further mitigate biases encountered in this study.

Abbreviations
POTS - postural orthostatic tachycardia syndrome
OH – orthostatic hypotension
OI – orthostatic Intolerance
HRV – Heart Rate Variability
HR – Heart Rate
HUTT – Head Up Tilt Test
RR-Interval – Interval between R and R waves of electrocardiogram
rMSSD - square root of mean of squares of successive R-R waves
LF - Low Frequency Power
HF – High Frequency Power
LF(n.u) – Low Frequency - normalized unit
HF(n.u) – High Frequency – normalized unit
BMI – Basal Metabolic Index
ECG - Electrocardiogram
TDM – Time Domain Measure
FDM – Frequency Domain Measure
MeSH – Medical Subject Headings
PRISMA - Preferred Reporting Items for Systematic Reviews and Meta-Analyses
JS – Joel Swai (Author)
Declarations

All authors agreed the submission and publication of this study.

Data for study search results is attached as supplementary EndNote file.

Authors declared no competing interests.

No funds were given.

All authors contributed equally.

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Tables
Table 1: Study characteristics
| Study, Year   | Study size (POTS, Healthy) | Mean Aged (POTS, Healthy) | Matched case-control or not? | Country of study | Outcome F |
|--------------|---------------------------|---------------------------|-------------------------------|------------------|-----------|
| Jacob 2019(29) | 12,10                     | 30±1.8, 32±3              | Unmatched                     | Israel           | HF, rMSSD |
| Owens 2018 (23) | 20,20                     | 36±10.84, 35±7.56         | Unmatched                     | UK               | HF, rMSSD |
| Goff 2017(32)  | 9,20                      | NA, NA                    | Unmatched                     | Australia        | rMSSD     |
| Moon 2016(24)  | 46,67                     | 28.9±1.9, 49.4±2.1        | Unmatched                     | Korea Republic   | HF        |
| Freitas 2015(30) | 10,12                     | 29.4±8.5, 33.8±5.9        | Matched                       | Portugal         | HR        |
| Yoshida 2014(31) | 70,38                     | 13.7±0.1, 13.5±0.1        | Unmatched                     | Japan            | HR, LF/H |
| Medow 2014(25)  | 12,19                     | Median: 20.8, 21.4        | Unmatched                     | USA              | HR, LF(n.u)|
| Mallien 2014(22) | 38,31                     | 25.3±7, 26.2±6.3          | Matched                       | Germany          | HR, LF, HF|
| Plash 2013(33)  | 15,15                     | 36±3, 33±2                | Unmatched                     | USA              | HF        |
| Ocon 2012(34)  | 16,20                     | 21±1, 23±1                | Unmatched                     | USA              | HF        |
| Brewster 2012(35) | 54,26                    | 35±2, 27±1                | Unmatched                     | USA              | HF        |
| Galbreath 2011(36) | 17,17                   | 27±9, 31±10               | Unmatched                     | USA              | HR, HF, LF |
| Baumert 2011(37) | 13,12                     | (32±13, 23±2),            | Unmatched                     | Australia        | HF        |
| Fu 2010(38)     | 27,16                     | 26(21-33), 28(23,35)      | Unmatched                     | USA              | HF        |
| Ocon 2009(28)   | 9,7                       | NA, NA                    | Unmatched                     | USA              | RR-Interv |
| Garland 2007(39) | 150,63                    | 34.5±10.7, 30.2±9.3       | Unmatched                     | USA              | HF        |
| Stewart 2006(40) | 20,10                     | 17±2, 17±1                | Matched                       | USA              | HR, LF/HR |
| Meier 2006(21)  | 21,39                     | 15.5±2.2, 11.7±2.7        | Unmatched                     | The Netherlands  | HF        |
| Garland 2005(27) | 136,191                   | 29.1±8.0, 32.2±9.9        | Unmatched                     | USA              | HF        |
| Stewart 2000(26) | 22,10                     | Median: 15.2, 15.8        | Unmatched                     | USA              | HR, HF(n. |
|               |                           |                           |                               |                  | u) LF/HR |

POTS - Postural orthostatic tachycardia; rMSSD - square root of mean of squares of successive R-R interval; LF - Low frequency power; HF - High frequency power; LF(n.u) - Low frequency power - normalized units; HF(n.u) - High frequency power - normalized units; HR - Heart Rate; NA - Data not accessed

Figures
Records identified from PUBMED, SCOPUS and EMBASE (n = 1,219)

Records after duplicates removed (n = 835)

Records screened (n = 835)

Records excluded (n = 807)

Full-text articles assessed for eligibility (n = 28)

Full-text articles excluded, with reasons (n = 8)

Studies included in qualitative synthesis (n = 20)

Studies included in quantitative synthesis (meta-analysis) (n = 20)

Figure 1

PRISMA 2009 Flow Diagram
Heart rate comparison between the groups

**Figure 2**

Time domain measure comparison between the groups; Figure 3a illustrates three of twenty eligible studies that compared time domain measure outcome between POTS versus Healthy participants in terms of mean RR-intervals; Figure 3b illustrates three of twenty eligible studies that compared time domain measure outcome between POTS versus Healthy participants in terms of rMSSD.
Figure 4

Frequency domain measure between POTS versus healthy participants: Figure 4a illustrates
five of twenty eligible studies that compared frequency domain measure outcome in terms of LF. Figure 4b illustrates seven of twenty eligible studies that compared frequency domain measure outcome in terms of HF. Figure 4c illustrates five of twenty eligible studies that compared frequency domain measure in terms of LF/HF ratio. Figure 4d illustrates four of twenty eligible studies that compared frequency domain measure outcome in terms of LF (n.u). Figure 4e illustrates four of twenty eligible studies that compared frequency domain measure outcome in terms of HF (n.u).

Figure 5
Funnel-plot for publication biases for included studies

Supplementary Files
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