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Review article

Sex differences in healthy human heart rate variability: A meta-analysis

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ABSTRACT

The present meta-analysis aimed to quantify current evidence on sex differences in the autonomic control of the heart, indexed by measures of heart rate variability (HRV) in healthy human subjects. An extensive search of the literature yielded 2020 titles and abstracts, of which 172 provided sufficient reporting of sex difference in HRV. Data from 63,612 participants (31,970 females) were available for analysis. Meta-analysis yielded a total of 1154 effect size estimates (k) across 50 different measures of HRV in a cumulated total of 296,247 participants. Females showed a significantly lower mean RR interval and standard deviation of RR intervals (SDNN). The power spectral density of HRV in females is characterized by significantly less total power that contains significantly greater high- (HF) and less low-frequency (LF) power. This is further reflected by a lower LF/HF ratio. Meta-regression revealed significant effects of age, respiration control and the length of recording available for analysis. Although women showed greater mean heart rate, they showed greater vagal activity indexed by HF power of HRV. Underlying mechanisms of these findings are discussed.

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Contents

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1. Introduction

Two households, both alike in dignity (Shakespeare, 1914). Cardiovascular disease is the leading cause of death worldwide for both men and women (Mozaffarian et al., 2015). However, significant health disparities exist between men and women such that men have earlier onset of cardiovascular disease (CVD) and greater CVD-related mortality and morbidity compared to women (Berry et al., 2012; Mikkola et al., 2013). Elevated resting heart rate (HR) is an independent risk factor for CVD (Cooney et al., 2010; Perret-Guillaume et al., 2009). However, despite greater resting HR, women don't have an increased risk for CVD compared to men (Cordero and Alegria, 2006). Consequently, numerous studies have shown that HR does not have the same predictive power for mortality and morbidity in women as it does in men (Palatini, 2001; Sacha, 2014). Clearly additional research is necessary to understand this paradoxical situation.

Sex differences in the autonomic control of the heart, indexed by heart rate variability (HRV), may potentially underlie these conflicting findings. The variability in the time series of adjacent heart beats provides insights into the interplay and contribution of the sympathetic and parasympathetic branches of the autonomic nervous system (ANS) in regulating human HR. The HR is under tonic inhibitory control via parasympathetic influences (Jose and Collison, 1970; Levy, 1997).

Since the publication of the first guidelines for the measurement and interpretation of HRV in 1996 (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996) thousands of studies utilizing measures of HRV have been published according to the PubMed database. HRV is widely recognized as a marker of cardiovascular health and overall mortality (Thayer et al., 2010). Despites its popularity and feasibility for research across different domains, several essential covariates of HRV remain to be systematically addressed. Here we investigate if HRV differs between men and women.

Numerous studies have explicitly addressed this question and were published on this topic, but yielded inconsistent findings. Some reported that the tonic vagal modulation of HR is augmented in women compared to men (Huikuri et al., 1996), others suggested, that "*gender [. . .] might not strongly influence autonomic nervous system function*" (Murata et al., 1992). However, to date, the existing literature on sex differences in HRV in healthy individuals has not been systematically quantified using meta-analysis.

We sought to rectify this situation by summarizing the available evidence using meta-analysis to quantify the effects across all studies reporting sex differences on measures of HRV in healthy human subjects.

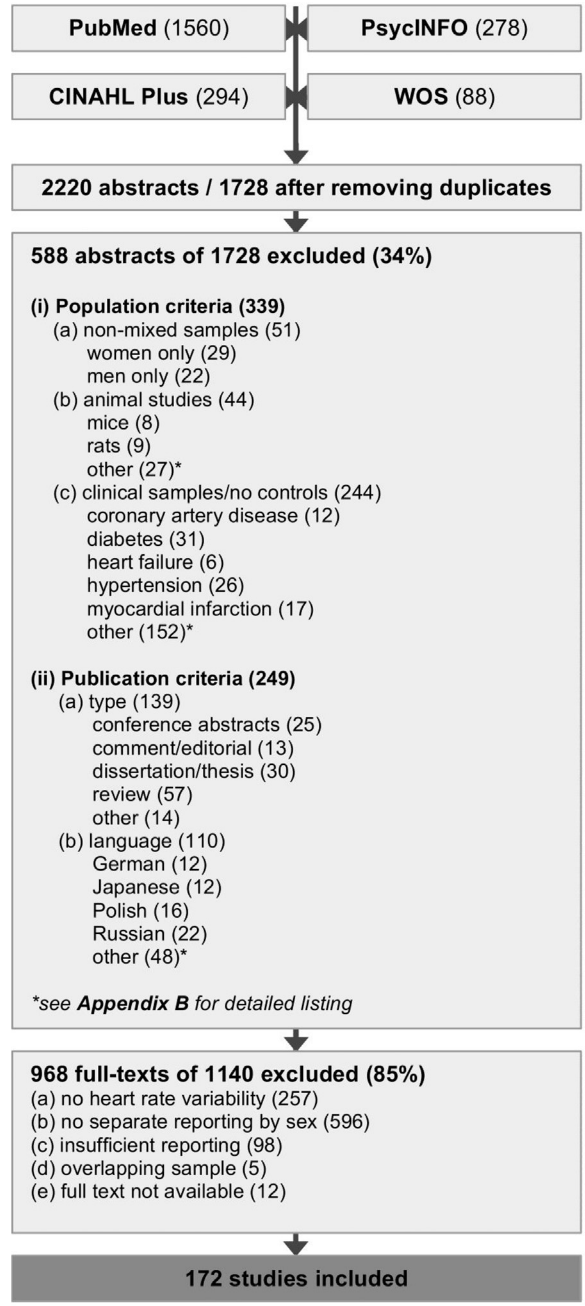

Fig. 1. Flow-chart of the systematic literature search.

2. Methods

2.1. Literature search

A systematic search of the literature, according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Moher et al., 2009) was employed. *PubMed*, *Web of Science* (WOS), *PsycINFO*, and *CINAHL Plus* databases were searched for studies reporting sex differences in measures of HRV (see Appendix A, for search strategy by database). The number of initial hits was recorded. After removing duplicates, abstracts of all identified articles were screened based on pre-defined inclusion criteria.

Abstracts were included and full-texts were retrieved if the abstract reported (i) an empirical investigation in (ii) healthy (iii) humans and (iii) if the full-text was published in the English language. Empirical investigations were defined as studies involving active data collection. Reviews, meta-analysis, comments, or single-case reports were excluded. Furthermore, dissertations, theses, as well as conference abstracts were excluded.

All studies reporting clinical samples of patients with any kind of disease or health-related distress were excluded. Studies were included if a clinical sample was reported in comparison to a group of healthy controls, of which only data from healthy controls was extracted for later analysis. Animal studies and studies published in any language other than English were excluded. The number of studies meeting the pre-defined inclusion criteria, the number of studies excluded, and reasons for exclusion were recorded (Fig. 1). In case insufficient information was provided in the abstract, the full-text of the title was screened.

All remaining studies were screened in full-text, given the likelihood that sex differences are not reported in the abstract but the full-text. Studies were included if the full-text reported

Table 1
Frequently used indices of heart rate variability.

Index	Definition
RR (ms)	Mean interval between consecutive R spikes in milliseconds
SDNN (ms) (log)	Standard deviation of RR intervals in milliseconds or log-transformed values
SDANN (ms)	Standard deviation of the average RR intervals in milliseconds; used for short-term recordings
SDNNi (ms)	Mean score of the standard deviations of all RR intervals in 5-min segments in milliseconds
MSD (ms)	Mean score of differences between successive RR intervals
RMSSD (ms) (log)	Root mean square of successive differences between adjacent RR intervals in milliseconds or log-transformed values
NN50 (*n*)	Number of pairs of successive RR intervals differing by more than 50 ms (count)
pNN50 (%)	Proportion of pairs of successive RR intervals differing by more than 50 ms divided by the total number of RR intervals (percentage)
TP (ms^2) (log)	Total frequency power in milliseconds squared, or in log-transformed values
VLF (ms^2) (nu) (log)	Very low frequency component in the power spectrum <0.04 Hz in milliseconds squared, normalized units, or log-transformed values
LF (ms^2) (nu) (log)	Low frequency component in the power spectrum range between 0.04 and 0.15 Hz in milliseconds squared, normalized units, or log-transformed values
HF (ms^2) (nu) (log)	High frequency component in the power spectrum range between 0.15 and 0.4 Hz in milliseconds squared, normalized units, or log-transformed values
LF/HF	Ratio between the low- and high frequency component
CVRR (%), CVR (log)	Coefficient of variation of RR intervals, in percentage or log-transformed values
CCV-HF (%)	Coefficient of variance of the high frequency component; high frequency component corrected for mean RR intervals
CCV-LF (%)	Coefficient of component variance of the low frequency component; low frequency component corrected for mean RR intervals
SD1 (ms)	Indicator for short-term variability in milliseconds; standard deviation of the instantaneous beat-to-beat RR interval variability (minor axis of the ellipse)
SD2 (ms)	Indicator for long-term variability in milliseconds; standard deviation of the continuous long-term RR interval variability (major axis of the ellipse)
ApEn	Approximate entropy; algorithm indicating regularity in heart rate variability; low values suggest regularity; higher values suggest higher complexity
SamEn	Sample entropy; algorithm indicating regularity under the exclusion of self-matches
DFAα1	Detrended fluctuation analysis short-term fractal scaling component; lower values indicate greater variability
TI	Triangular index; integral of the total number of RRs divided by the maximum of RRs; reflect overall heart rate variability

(i) sufficient descriptive data (*see below*) of (ii) any given measure of HRV, (iii) separately for female and male participants. Studies reporting overlapping samples were excluded. In case overlapping samples were reported by multiple titles, the report published earlier was included. If overlapping samples reported different measures of HRV they were included in the meta-analysis for all measures other than those previously reported. A summary of HRV measures included and a brief description on their statistical basis is given in Table 1.

2.2. Data extraction and transformations

The name of the authors, the year of publication, the sample size studied the relative *n* of female and male subjects and the age of females and males respectively were retrieved from all included studies. Furthermore, information on several covariates was extracted for meta-regression (see below).

The basis for the calculation of all the HRV measures is the recording and analysis of the sequence of time intervals between adjacent heartbeats, the inter-beat interval (IBI in ms). Despite several methods to record the IBI sequence, electrocardiography (ECG) is the most prominent. Methods of operationalizing HRV fall broadly into three classes of measures: *time-domain*, *frequency-domain* and *non-linear* measures.

Time-domain indices are derived directly from the R-R interval series and generally measure the variability contained therein, by applying simple statistical computations, such as deriving the standard deviation (SD) of IBIs (SDNN) across a particular recording length for analysis.

Frequency-domain measures quantify power spectral density (PSD) within pre-specified frequency bands via spectral analytic techniques (i.e., *Fast Fourier Transform* or *Autoregressive Algorithm*). The power spectrum of short-term recordings usually contains three major components, a high- (HF: 0.15–0.40 Hz), a low- (LF: 0.01–0.15 Hz), and a very-low (VLF: < 0.04 Hz) frequency component. Given that the influence of the parasympathetic branch of the ANS in regulating HR produces rapid changes in the beat-to-beat timing of the heart (Uijtdehaage and Thayer, 2000), power in the HF band and time-domain measures reflecting these fast changes (i.e., the root mean square of successive differences, RMSSD) are regarded as readily available indices of vagal activity. While the interpretation of activity in the LF band has generated a lively debate (Reyes del Paso et al., 2013; Goldstein et al., 2011), it is safe to consider, that it most likely reflects joint activation of the sympathetic and parasympathetic branches of the ANS.

For the present meta-analysis we included all measures of HRV reported, including time-domain, frequency-domain and non-linear measures as well as some exotic indices derived from further computations (Table 1). Descriptive data on the reported measures were extracted for female and male subjects separately. Meta-analytical effect size estimates were based on means, standard deviations (SD) and the sample size (n). In case descriptive data was presented other than as mean and SDs, data transformations were applied. If the median (m) and the range with upper (a) and lower (b) limits were reported, the mean ($\bar{x}$) was derived as proposed by Hozo et al. (2005), where $\bar{x} = (a + 2m + b)/4$.

For moderately sized samples ($15 < n \leq 70$) the SD was derived by dividing the length of the range (b–a) by 4. For larger samples ($n > 70$), the length of the range was divided by 6. In case the female and male samples were unevenly weighted, the formula for the lower sized sample was used for both groups to avoid introducing error. If the interquartile range was reported the length of the range was divided by 1.35 (Wiebe et al., 2006). When only the standard error (SE) of the mean was reported, the SD was calculated by multiplying the SE by the square root of the sample size (Higgins and Green, 2011). In case the confidence interval for the mean was given (i.e., 95%) the SD was derived by dividing the length of the confidence interval by 3.92, and then multiplying by the square root of the sample size (Higgins and Green, 2011), where $SD = (\sqrt{n} \times (b - a))/3.92$. Different factors for different confidence levels were applied (Higgins and Green, 2011).

Measures of PSD are frequently reported in different units. In addition to the raw values in ms^2, normalized units (nu) are quite common. These reflect the relative portion of the selected frequency band in the total power of the PSD. While different methods are used to derive nu (i.e., the *Italian formula*, (e.g., LF/(TP-VLF)), or the *Japanese formula* LF/TP), we combined reported values of *nu* irrespective of the formula used. Furthermore, time- and frequency domain measures of HRV are frequently skewed and authors apply a natural logarithmic (log) transformation to meet the assumptions of linear analysis (Ellis et al., 2008). These *log* transformed measures were extracted separately form ms^2 and nu, with the exception of the LF/HF ratio, that always reflects a relative ratio of the LF and HF band, irrespective of previous data transformations, and thus was treated independent of the reported units.

If possible, only measures of resting baseline conditions were extracted. However, studies reporting long-term measures of HRV were also included, and the length of recording was later addressed as a potential covariate in meta-regression (see below). If studies reported measures of HRV that were further stratified by the time of recoding (e.g., *day*- vs. *nighttime*), age (e.g., *young* vs. *middle-aged subjects*), ethnicity (e.g., *European Americans* vs. *African Americans*) or other categorical variables (e.g., *genotype*), data was extracted for all sub groups and labeled respectively, as long as female and male subjects were compared under the same characteristic (i.e., *African American Women* vs. *African American Men*), and as long as multiple reporting of participants in the same recording segment could be avoided to prevent effect size inflation.

2.3. Meta-analysis

True effect estimates were computed as adjusted standardized mean differences (SMD, Hedge's *g*) for all measures. We preferred using SMDs over *mean differences* (although we treated measures independently by the expression of units), given potential differences in the actual values reported that might relate to different techniques of handling or post-processing data. We undertook meta-analyses using both fixed- and random-effect models and results from both models are presented. Generally speaking, we aimed to apply a conservative approach given the large number of effect estimates expected. We considered measures of HRV holding a true effect, if both (fixed- and random-effect models) yielded significant effects.

Heterogeneity or inconsistency among trials in the magnitude or direction of effects estimated was investigated. Heterogeneity was assessed using the standard I^2 *index*, Chi^2, and Tau^2 tests (Higgins and Thompson, 2002). Bias was further examined using funnel plots from random-effect models, illustrating the effect size (SMD) against standard error for asymmetry. Meta-analytic computations were based on random-effects only and performed using RevMan (*Version 5.3.4, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014*). With respect to the number of computations performed, forest- and funnel-plots are available on request.

2.4. Meta-regression

Four population- and study-level covariates were documented and the respective information was extracted and subjected to meta-regression. Among those were: (i) age (continuous), (ii) respiration (*controlled* vs. *spontaneous*), (iii) position at recording (*supine* vs. *other*), and (iv) the length of recording used for analysis (*short*- vs. *long-term*).

First, as HRV decreases with age (Yeragani et al., 1997), we aimed to control for such an effect by using the reported sample mean age as a continuous covariate. In case the mean age was reported separately for males and females, we estimated the sample mean. In case the median or range was reported, similar data transformations as described for estimating effect sizes were applied.

Next, the effect of controlling for respiration during the recording of HRV (i.e., fixed breathing at a particular rate e.g., 0.25 Hz) was investigated. Similarly, we explored the effect of the participants' position (i.e., seated, lying, standing) during the recording. Finally, we controlled for the recording length by coding a categorical covariate, distinguishing short-term (<20 min) from long-term recordings (>1 h). The method of recording the IBI sequence (e.g., ECG, photoplethysmography) was also extracted from included studies. However, given that the majority of studies used ECG and insufficient data were available on other methods, it was not subjected as a covariate for further meta-regression. All factorial covariates were dummy coded and transformed as a numerical expression (0 vs. 1). All meta-regression computations were performed using the OpenMetaAnalyst software (Wallace et al., 2012a, 2012b), and only HRV indices with at least 40 effect-size estimates ($k \geq 40$) were subjected to meta-regression.

3. Results

3.1. Included studies

The systematic search identified a total of 2,020 titles and abstracts. After excluding duplicates, 1728 abstracts were screened for inclusion (Fig. 1). A detailed listing of reasons for exclusion is provided in Appendix B. 588 abstracts were excluded and 1140 papers were screened in full-text. Of these, 986 were excluded for various reasons (Fig. 1), leaving 172 studies that were included in the meta-analysis (Huikuri et al., 1996; Murata et al., 1992; Abhishekh et al., 2013; Agelink et al., 2001; Allen et al., 2015a, 2009; Arai et al., 2013; Arroyo-Morales et al., 2012; Arzeno et al., 2013; Aziz et al., 2012; Barantke et al., 2008; Beckers et al., 2006; Berkoff et al., 2007; Bigger et al., 1995; Bonnemeier et al., 2003; Brosschot et al., 2007; Brown and Brown, 2007; Brunetto et al., 2005; Brydon et al., 2008; BuSha et al., 2009; Byrne et al., 1996; Cankar and Finderle, 2003; Carnethon et al., 2002; Carrère et al., 2005; Carter et al., 2003; Castiglioni and Di Rienzo, 2010; Chang et al., 2014a, 2014b; Chang and Shen, 2011; Charles et al., 2014; Chen et al., 2010; Corrêa et al., 2013; Costa and Brody, 2012; Cowan et al., 1994; Čukić and Bates, 2014; Desai et al., 1997; Dishman et al., 2002; Dishman et al., 2000; Dubreuil et al., 2003; Dutra et al., 2013; Evans et al., 2001; Extramiana et al., 1999; Eyre et al., 2013; Fagard et al., 1999; Faulkner et al., 2003; Faust et al., 2013; Flanagan et al., 1999, 2007; Franke et al., 2000; Fregonezi et al., 2012; Fujikawa et al., 2009; Funada et al., 2010; Fürholz et al., 2013; Garcia et al., 2012; Genovesi et al., 2007; Gentile et al., 2015; Gerbase et al., 2014; Gerritsen et al., 2003; Grandjean et al., 2004; Greaves-Lord et al., 2007; Gregoire et al., 1996; Guillén-Mandujano and Carrasco-Sosa, 2014; Gutin et al., 2005; Han et al., 2000; Hedelin et al., 2000; Henriksen et al., 2014; Hering et al., 2008; Hintsanen et al., 2007; Huang et al., 2013; Hughes and Stoney, 2000; Huynh et al., 2006; Jarrin et al., 2015; Jones et al., 2007; Kamkwalala et al., 2012; Kapidžić et al., 2014; Kashiwagi et al., 2000; Keet et al., 2013; Kim and Woo, 2011; Kim et al., 2005; Kim and Nam, 2010; Kiviniemi et al., 2010; Koch and Pollatos, 2014; Koskinen et al., 2009; Krauss et al., 2009; Kuch et al., 2001; Kuo et al., 1999; Kupari et al., 1993; Kwon et al., 2014; Laitinen et al., 1998, 2004; Lauritzen et al., 2008; Lévesque et al., 2010; Li et al., 2011, 2009; Liao et al., 1995; Lin, 2013; Lin et al., 2013; Liu et al., 2014; Lutfi and Sukkar, 2011; Malan et al., 2013; Mann et al., 2012; Mellingsæter et al., 2013; Mendonca et al., 2010; Michels et al., 2013; Molnar et al., 1996; Moodithaya and Avadhany, 2012; Naumova and Zemtsova, 2009; Ohira et al., 2008; Ottaviani et al., 2009; Pal et al., 2014, 2012, 2013; Park et al., 2007; Perseguini et al., 2011; Pikkujämsä et al., 2001, 1999; Pitzalis et al., 2001; Ramaekers et al., 1998; Reed et al., 2006; Resmini et al., 2008; Rodríguez-Colón et al., 2014; Rossy and Thayer, 1998; Roy et al., 2013; Ryan et al., 1994; Saleem et al., 2012; Schechter et al., 1998; Sharpley et al., 2000; Sharshenova et al., 2006; Silvetti et al., 2001; Singh et al., 1998; Sinnreich et al., 1999, 1998a, 1998b; Sloan et al., 2001, 2008; Smith et al., 2011; Snieder et al., 2007; Sookan

Table 2
Study and sample characteristics.

Authors	Year	F *n*	M *n*	F Age	M Age	Sample type	Method	Position	Respiration	Length	Indices	Units PSD	Subgroups/notes	Source/transoformations
Abhishekh et al.	2013	75	114	35.7 (12.6)	32.3 (11.3)	Healthy subjects	ECG	supine	12–15 breaths/min	5 min	LF, HF	nu		Assumably reported as mean and SD (not specified)
Agelink et al.	2001	158	151	stratified	stratified	Hospital employees	ECG	supine	regularly and calmly	5 min	VLF, LF, HF, TP, CVR, RMSSD	log	5 age stratified groups	Mean and SD
Allen et al.	2009	43	40	18.9 (1.1)	19.5 (1.7)	Undergraduate students	ECG	seated	nr	3 min	MSD		*n* after drop-outs; baseline data used	Mean and SD
Allen et al.	2014	183	179	43 (6)	41 (7)	Residents	ECG	seated	paced respiration	5 min	HF	log		Mean and SD
Arai et al.	2013	86	64	20 (18–26)	20 (18–26)	Students	ECG	supine	nr	5 min/100 consecu-tive RRs	CVRR, CCVHF, CCVLF, LF, HF, LF/HF	ms^2, nu		Mean and SD; median and range for LF/HF, HF (ms2), LF (ms2), HF (%)
Arroyo-Morales et al.	2012	25	25	Sample mean: 22.4 (3.42)		Healthy active volunteers	ECG	supine	nr	5 min	SDNN, RMSSD, HRV index		Pretest data used; HRV index: n of all NN inter-vals/maximum of all NN intervals	Mean and SD
Arzeno et al.	2013	10	20	37.2 (2.8)	32.5 (1.3)	Healthy	ECG	supine	nr	20 min	RR, LF, HF	ms^2	Bed rest 1 values during normal saline infusion in the phenylephrine condition used	Mean and SE
Aziz et al.	2012	12	21	Sample mean: 8.96 (0.72)		Normal children	ECG	n/a	n/a	24 h	SDNN, SDANN, NN50, pNN50, RMSSD, LF, HF, LF/HF, SD1, SD2, ApEn, SamEn	ms^2	Only normal children included	Assumably reported as mean and SD (not specified)
Barantke et al.	2008	206	156	45 (16)	44 (16)	Volunteers	ECG	supine	spontanous	5 min	LF, HF, TP, LF/HF	ms^2, nu	Only supine data used	Assumably reported as mean and SD (not specified)
Beckers et al.	2006	135	141	Sample range: 18–71		Healthy population	ECG	n/a	n/a	24 h	RR, SDNN, RMSSD, pNN50, LF, HF, TP, 1/f slope, FD, Ap En, DFAα1, DFAα2, CD, %CD difference, S value, Lyapunov exponent	ms^2, nu	Values reported for day and night	Mean and SD
Berkoff et al.	2007	58	87	24.81 (3.98)	24.59 (2.89)	Elite-level athletes	ECG	supine	nr	2.5 min	LF, HF, LF/HF, TP, RMSSD, SDNN, pNN50	ms^2, nu		Mean and SD
Bigger et al.	1995	72	202	Sample mean: 57 (8.2)		Middle-aged persons	ECG	n/a	n/a	24 h	RR, ULF, VLF, LF, HF, TP, LF/HF	log	Only healthy controls incldued in analysis	Mean and SD
Bonnemeier et al.	2003	81	85	Sample mean: 42 (15)		Healthy volunteers	ECG	n/a	n/a	24 h	RR, RMSSD, SDNN, SDANN, NN50, TI, SDNNI			Mean and SD

Table 2 (*Continued*)

Authors	Year	F *n*	M *n*	F Age	M Age	Sample type	Method	Position	Respiration	Length	Indices	Units PSD	Subgroups/notes	Source/transoformations
Brosschot et al.	2006	39	13	Sample mean: 33.8 (13.9)		General population	ECG	n/a	n/a	varied*	RMSSD		*Waking and sleeping period; sleeping period used for meta-analysis	Mean and SD
Brown & Brown	2007	6	7	50.5 (2.9)	52.1 (3.3)	Endurance-trained subjects	ECG	seated	spontaneous	6 min	RR, SDNN, TP, VLF, LF, HF, LF/HF	ms^2, nu	Pre exercise period used	Mean and SD
Brunetto et al.	2005	21	20	15.2 (1.1)	15.4 (0.8)	Healthy adolescents	Polar	supine*	nr	10 min	RR, SDNN, RMSSD		*Multiple positions reported; supine used for analysis	Mean and SD
Brydon et al.	2008	62	32	21.4 (2.11)	21.4 (2.14)	Volunteers	Impedance	nr	nr	5 min	RMSSD			Mean and SD
BuSha et al.	2009	12	12	Sample range: 18–22		Healthy subjects	ECG	seated	varied*	15 min	RR, SDNN		Oral breathing included	Mean and SD
Byrne et al.	1996	70	57	21–82	20–87	Population-based	ECG	supine*	spontaneous	3 min	RR, RSA, 0.10 Hz	log	3 (7 by decade) age stratified groups; *supine values used; *n* after drop-out	Mean and SD
Cankar & Finderle	2003	10	10	34.9 (2.4)	32.6 (3.3)	Healthy subjects	ECG	supine	nr	5 min	LF, HF, LF/HF, LF/(LF + HF)	s^2/Hz, nu	Early follicular phase values for female participants used	Mean and SE
Carnethon et al.	2002	4544	3142	Sample range: 45–64		Population	ECG	supine*	nr	2 min	RR, SDNN, HF	ms^2	Supine position used; means adjusted for HR	Mean and SE
Carrère et al.	2005	54	54	nr	nr	Married couples	ECG	n/a	n/a	15 min	RR, HF	log	Marital interaction session not conflict discussion used	Mean and SD
Carter et al.	2003	12	12	Stratified	Stratified	Volunteers	ECG	supine	15 breaths/min	10 min	RR, SDNN, LF, HF, TP, Fractal Power, SNS indicator, PNS indicator	ms^2	2 age groups (20 and 40) per sex; pre training scores used	Mean and SD
Castiglioni & Di Rienzo	2010	23	33	34.5 (10)	34.6 (9.3)	Healthy volunteers	ECG	supine*	nr	10 min	RR, HF, LF/HF	log, LF/HF in %	Supine values reported	Mean and SD
Chang & Shen	2011	29	25	Estimaed sample mean: 38		Elementary school teachers	ANSWatch	sitting	nr	7 min	SDNN, LF, HF, LF/HF	nu	Values before aroma therapy used	Assumably reported as mean and SD (not specified)
Chang et al.	2014 (a)	228	355	Sub groups	Sub groups	Volunteers	ECG	sitting	spontaneous	5 min	LF, HF, LF/HF	log, nu	3 groups by geno-type per sex; adjusted means for covariates	Mean and SE
Chang et al.	2014 (b)	228	352	Sub groups	Sub groups	Volunteers	ECG	sitting	spontaneous	5 min	LF, HF, LF/HF, RMSSD	log	2 groups by geno-type per sex; different splitting by genotype therefore included	Mean and SE
Charles et al.	2014	91	264	40.3 (5.9)	40.7 (7.1)	Police officers	ECG	supine	nr	5 min	HF, LF	ms^2		Assumably reported as mean and range (incorrectly specified as SD)
Chen et al.	2009	252	354	Sample mean: 77.9 (5.2)		Elderly men and women	ECG	sitting	spontaneous	5 min	HF, LF	log		Mean and SD
Corrêa et al.	2012	42	36	Estimated sample mean: 55		Healthy sedentary or non-trained participants	Polar	nr	nr	1 min	RR, RMSSD, SD1, SD2		4 age stratified groups but no n per group therefore total reported; only rest values included	Median and interquartile range
Costa et al.	2012	68	75	25.72 (6.89)	26.44 (7.58)	Volunteers	Polar	nr	nr	5 min	LF, HF	ms^2		Mean and SD
Cowan et al.	1994	71	40	52 (15)	57 (15)	Healthy volunteers	ECG	n/a	n/a	24 h	RR, SDANN, SDNN, SDNNi, NN50, pNN50, RMSSD, LF, HF, LF/HF, TP	ms^2	Only data from healthy controls included	Assumably reported as mean and SD (not specified)
Čukić & Bates	2014	523	429	54.03 (11.3)	55.3 (11.9)	Population-based	ECG	nr	nr	6 min	LF, HF	log	Baseline measures used	Mean and SD
Desai et al.	1997	6	7	Sample mean: 27 (6)		Normal volunteers	ECG	nr	nr	15 s	RR		3 different baselines for every condition; nitroprusside baseline used	Mean and SD

Table 2 (*Continued*)

Authors	Year	F *n*	M *n*	F Age	M Age	Sample type	Method	Position	Respiration	Length	Indices	Units PSD	Subgroups/notes	Source/transoformations
Dishman et al.	2000	44	59	40.3 (12.5)	39.7 (9.9)	Apparently healthy participants	Polar	supine	spontaneous	5 min	RR, SDNN, LF, HF, TP, LF/HF, HF/TP	ms^2, log		Mean and SD
Dishman et al.	2002	13	13	26 (5)	24 (4)	Healthy	ECG	seated	spontaneous	2-3 blocks, >64 beats	RR, SDNN, LF, HF	ms^2, nu	Only baseline measure included	Mean and SD
Dubreuil et al.	2003	272	266	5 months	5 months	Twin pairs	ECG	seated	spontaneous	> 100 beats	RR, LF, HF	log, nu	*n* before drop outs	Mean and SE
Dutra et al.	2013	43	53	Sub groups	Sub groups	Healthy subjects	ECG	supine	nr	40 min (decomposed)	RR, Variance, LF, HF, LF/HF	ms^2, nu	3 groups based on aerobic physical capacity	Mean and SE
Evans et al.	2001	10	10	25.2 (0.7)	24.9 (0.8)	Healthy volunteers	ECG	nr	nr	200 s	VLF, LF, HF, TP, TP/HF, (VLF + LF)/HF, fractal and harmonic power	ms^2, nu	Unblocked data (group 1) used	Mean and SE
Extramiana et al.	1999	30	30	Sample mean: 33.9 (9.2)		Healthy volunteers	ECG	n/a	n/a	24 h	RR, SDNN, pNN50, RMSSD		Day and night values reported	Mean and SD
Eyre et al.	2013	94	61	9.0 (0.4)	9.0 (0.4)	Primary school children	ECG	n/a	n/a	24 h/7d	SDANN		School and sleep values reported	Assumably reported as mean and SD (not specified)
Fagard et al.	1999	222	202	47.5 (11.8)	49.6 (13.7)	Population-based	ECG	supine	spontaneous	512 consecutive beats	RR, TP, partial P, LF, HF, LF/HF	ms^2, nu, log	Restricted sample reported; supine data used	Mean and SD
Faulkner et al.	2003	49	26	Sub groups	Sub groups	Healthy adolescents	ECG	n/a	n/a	24 h	SDNN, SDANN,RMSSD, pNN50, TP, LF, HF	log	3 sub groups by age	Mean and SD
Faust	2013	75	75	Sub groups	Sub groups	Healthy subjects	ECG	sitting/supine	nr	20 min	SDNN, pNN50, TI, LF/HF, SD1/SD2, ApEn, CD		4 sub groups by age	Mean and SD
Flanagan et al.	1999	64	73	20.9 (0.29)	20.9 (0.28)	Cohort of young adults	ECG	supine	nr	15 min	LF, HF, Hlratio	nu		Mean and SD
Flanagan et al.	2007	62	68	20.9 (0.33)	20.9 (0.22)	Cohort of young adults	ECG	supine	nr	15 min	LF, HF, Hlratio	nu		Mean and SD
Franke et al.	2000	15	15	22.3 (0.4)	23.6 (1.1)	College-age men and women	ECG	nr	nr	236 RRs	LF, HF, LF/HF, TP	ms^2, nu	Rest period data used	Assumably reported as mean and SD (not specified)
Fregonezi et al.	2011	7	10	40.14 (8.33)	41.2 (2.9)	Healthy volunteers	Polar	supine*	nr	15 min	TP, LF, HF, LF/HF	ms^2, nu	Only data from healthy controls included; *supine position used	Mean and SE
Fujikawa et al.	2009	129	202	22.5 (2.0)	23.1 (2.5)	Medical students	ECG	n/a	n/a	24 h	HF, LF/HF	ms^2		Mean and SD
Funada et al.	2010	24	20	45 (22–6)	41 (19–62)	Healthy volunteers	ECG	semi-supine	9–11 breaths/min	5 min (from two recordings)	SDNN		*n* after drop-outs	Median and range
Fürholz et al.	2013	57	57	43 (7)	41 (7)	Non-elite athletes	ECG	n/a	n/a	24 h	SDNN, RMSSD, TP, LF, HF	m^2, nu	Night and daytime values reported	Mean and SD
Garcia et al.	2012	34	16	23.5 (5.7)	23.1 (3.5)	Healthy hispanic subjects	ECG	supine*	15 breaths/min)	10 min	RMSSD, pNN50, LF, HF, LF/HF	ms^2	Only data from healthy controls included; *supine data used	Assumably reported as mean and SD (not specified)
Genovesi et al.	2007	40	40	Sub groups	Sub groups	Apparently healthy subjects	ECG	n/a	n/a	24 h	SDNN, CVRR		Two sub groups each (trained and untrained); day and noight reported; due to insufficient reporting 24 h means used	Mean and SD
Gentile et al.	2014	115	78	42.8 (11.46)	39.1 (11.23)	Healthy adults	ECG	nr	nr	10 min	LF, HF, LF/HF	m^2, nu	Data at initial recruitment used	Mean and SD
Gerbase et al.	2014	731	652	60.0 (6.3)	59.7 (6.0)	Population-based cohort	ECG	n/a	n/a	24 h	VLF	nu		Mean and range

Table 2 (*Continued*)

Authors	Year	F *n*	M *n*	F Age	M Age	Sample type	Method	Position	Respiration	Length	Indices	Units PSD	Subgroups/notes	Source/transofomations
Gerritsen et al.	2003	93	98	63.3 (7.4)	62.0 (7.4)	General population	ECG	supine	spontaneous	3 min	RR, SDNN, LF, HF, LF/(LF + HF)	ms^2		Mean and SD/median and 10 to 90th percentiles (treated as range)
Grandjean et al.	2004	411	402	Sub groups	Sub groups	Birth cohort study	ECG	supine	spontaneous	100 consecutive R-R	CVRR, LF, HF, LF/HF	ms^2	Values reported at 7 and 14 years of age	Mean and interquartile range
Greaves-Lord et al.	2007	543	484	Sample range: 10–13		Young adolescents	ECG	supine*	spontaneous	4 min	LF, RSA	ms^2, log	*Supine position used	Mean and SD
Gregoire et al.	1996	40	40	Sub groups	Sub groups	Healthy subjects	ECG	supine	nr	10 min	RR, SDNN, TP, LF, HF	ms^2	4 sub-groups each (young/mature/trained/untrained); resting baseline used	Mean and SE
Guillén-Mandujano & Carrasco-Sosa	2014	18	20	20.7 (1.7)	21.3 (1.8)	Long-term residents of Mexico City	ECG	sitting	different	5 min	RR, HF	ms^2	Three controlled-breathingmaneuvers; only control data used for RF condition	Mean and SD
Gutin et al.	2005	171	123	Sample range: 14–18		Apparently healthy youths	ECG	supine	spontaneous	256 R-R intervals	RMSSD, HF, LH/HF	ms^2, nu	Subgroups by ethnicity	Mean and SD
Han et al.	2000	21	18	Age matched; patient range: 6–18		Healthy controls	ECG	n/a	n/a	24 h	RR, SDNN, SDANN, RMSSD, pNN50, LF, HF, LF/HF	log	Only data from controls included	Assumably reported as mean and SD (not specified)
Hedelin et al.	2000	11	8	Sample range: 16–19		Cross-country skiers	ECG	supine*	12 breaths/min	1 min	TP, LF, HF	log	Data from pre-season test 1 used; *supine data used	Mean and range
Henriksen et al.	2014	18	13	Sample median: 64 (50–75)		Healthy elderly subjects	MRI VCG	supine	nr	2 × 4 min	LF/HF			Median range
Hering et al.	2008	20	20	47 (3)	46 (3)	Habitual smokers	ECG	supine	nr	10 min	SDNN		Resting measures used	Mean and SE
Hintsanen et al.	2007	457	406	32.3 (4.9)	32.2 (4.8)	Population-based cohort	ECG	supine	0.25 Hz	3 min	RMSSD, pNN50, HF, LF/HF	log		Mean and SD
Huang et al.	2013	30	30	32.27 (8.49)	34.40 (10.61)	Healthy adults	ECG	seated	spontaneous	5 min	TP, LF, HF, LF/HF	log, nu		Mean and SD
Hughes & Stoney	2000	14	11	18.8 (2.5)	18.7 (1.4)	College students	ECG	nr	nr	5 min	HF	ln	Only data in subjects with low depression scores included	Mean and SD
Huikuri et al.	1996	186	188	50 (6)	50 (6)	Healthy volunteers	ECG	supine*	spontaneous	15 min	RR, SDNN, LF, HF, LF/HF	ms^2, nu	*Supine data used	Mean and SD
Huynh et al.	2006	10	10	Sample mean: 24.2 (5)		Control subjects	ECG	nr	nr	3 min	RR, LF, HF/LF/HF	nu	Only data on control subjects included, overall data used	Assumably reported as mean and SD (not specified)
Jarrin et al.	2015	555	481	10.2 (0.3)	10.2 (0.3)	Population-based	ECG	nr	nr	1 h	SDNN, SDANN, SDNNi, RMSSD, pNN50, VLF, LF, HF, LF/HF	ms^2, ln		Mean and SD
Jones et al.	2007	76	103	Sample mean: 26.3 (0.4)		Cohort of adults	Portapres	nr	nr	20 min	LF, HF, LF/HF	ms^2, nu	Rest data used	Mean and SD
Kamkwalala et al.	2012	57	37	Sample mean: 39.95 (11.62)		Controls	ECG	nr	nr	1 min	HF	log	Only non PTSD participants included; block 1 light data used	Mean and SE
Kapidžićí et al.	2014	28	28	Stratified	Stratified	Apparently healthy subjects	ECG	supine	spontaneous	20 min	RR, VLF, LF, HF, TP, SampEn, other measures of entropy		2 sub-groups each (young/middle-aged)	Mean and SE

Table 2 (*Continued*)

Authors	Year	F *n*	M *n*	F Age	M Age	Sample type	Method	Position	Respiration	Length	Indices	Units PSD	Subgroups/notes	Source/transoformations
Kashiwagi et al.	2000	17	15	51.9 (13.0)	49.4 (14.2)	Normal control subjects	ECG	n/a	n/a	48 h	LF, HF	ms^2	Only data from normal subjects used; data reported for activy dat span and resting night span	Mean and SD
Keet et al.	2013	43	50	Sample range: 18–50		Healthy adult subjects	nr	nr	nr	nr	RR, SDNN, RMSSD, VLF, LF, HF, TP, LF/(LF + HF)	ms^2		Reported as median, interquartile range and range (range used), or mean and SD
Kim & Nam	2010	32	77	nr	nr	Medical students	SA-6000	supine	spontaneous	5 min	LF, HF, TP, LF/HF	ms^2, nu	Adjusted values for age and academic performance	Mean and SD
Kim & Woo	2011	717	2679	38.0 (10.5)	42.3 (8.3)	Healthy participants	nr	seated	spontaneous	5 min	SDNN, RMSSD, LF, HF, TP, LF/HF	ms^2	4 age stratified groups; *n* before drop outs	Assumably reported as mean and SD (not specified)
Kim et al.	2005	22	19	Sample range: 20-65		Healthy persons	SA-2000	supine	nr	5 min	SDNN, RMSSD, LF, HF, LF/HF	log		Mean and SD
Kiviniemi et al.	2010	14	14	Subgroups	Subgroups	Healthy participants	Polar	nr	nr	nr	SD1		Pre scores used for ST and HRV-I groups	Mean and SD
Koch & Pollatos	2014	693	657	Sample mean: 8.39 (0 .94)		Elementary school children	Polar	seated	spontaneous	3 min	RMSSD, LF, HF	ms^2		Mean and SD
Koskinen et al.	2009	949	831	31.6 (5)	31.5 (5)	Population-based cohort	ECG	supine	0.25 Hz	3 min	SDNN, RMSSD, LF, HF, LF/HF	log		Assumably reported as mean and SD (not specified)
Krauss et al.	2009	76	63	42.3	40.9	Healthy volunteers	ECG	n/a	n/a	24 h	RR, SDNN, RMSSD		2 subgroups each stratified on age	Mean and SD
Kuch et al.	2001	137	149	55.9 (5.6)	56.0 (5.9)	Population-based	ECG	supine	spontaneous and controlled	5 min	LF, HF, TP	log, nu	Crude unadjusted means used	Mean and SD
Kuo et al.	1999	598	471	Sample range: 40–79		Normal volunteers	ECG	supine	spontaneous	5 min	RR, SDNN, VLF, LF, HF, LF/HF	log, nu		Mean and SE
Kupari et al.	1993	47	41	Birth year	Birth year	People living in Helsinki and born in 1954	ECG	supine	15/min	256 beats	RMSSD, VLF, LF, HF	log	Adjusted means for HR; *n* before drop out	Mean and SD
Kwon et al.	2014	183	202	Fetuses	Fetuses	Fetuses	ultrasound cardiotocogra-phy	nr	nr	2 h	LF, MF, HF, TP, LF/HF	ms^2, nu	Only non small-for-gestational-age included	Median and interquartile range
Laitinen et al.	1998	58	59	47.4 (2.2)	47.7 (2.1)	Healthy subjects	ECG	supine	0.2 Hz	150–511 beats	SDNN, RMSSD, VLF, LF, HF, LF/HF, TP	ms^2		Mean and SE
Laitinen et al.	2004	34	29	Sample range: 23-77		Healthy subjects	ECG	supine*	0.2 Hz	2.5–5 min	VLF, LF, HF, LF/HF	ms^2	*Supine data used	Mean and SE
Lauritzen et al.	2008	16	15	Subgroups	Subgroups	Healthy danish infants	ECG	nr	nr	0.5 h	RR		Only no-fish oil group reported, values given at 9 and 12 month of age	Mean and SE
Lévesque et al.	2010	118	81	42.7 (11.37)	39.4 (11.38)	Healthy working men and women	ECG	nr	nr	10 min	HF, LF/HF	ms^2	Only resting baseline condition used	Mean and SD
Li et al.	2009	209	190	Sample mean: 23.1		Overtly healthy participants	ECG	supine	nr	4 × 30 s	RMSSD, HF	ms^2	Split by ethnicity; data from visit 1 during rest used	Mean and SD

Table 2 (*Continued*)

Authors	Year	F *n*	M *n*	F Age	M Age	Sample type	Method	Position	Respiration	Length	Indices	Units PSD	Subgroups/notes	Source/transoformations
Li et al.	2011	60	35	57.5 (8.1)	54.6 (7.7)	Population-based	ECG	n/a	n/a	24 h	SDNN, RMSSD, LF, HF	log		Mean and SD
Liao et al.	1995	1046	938	Stratified	Stratified	Population-based	nr	nr	nr	2 min	HF, LF, LF/HF	assumed nu	Stratified by age (2 groups) and ethnicity (2 groups)	Mean and SE
Lin	2013	20	20	Sample mean: 22.38 (1.55)		Healthy volunteers	ANSWatch	nr	nr	7 min	SDNN, LF, HF, TP, LF/HF	ms^2, nu	Pre-game values used	Mean and SD
Lin et al.	2013	9	29	Sample mean: 24.6 (1.2)		Medical interns	SS1C	nr	nr	5 min	RR, SDNN, LF, HF, LF/HF, TP	nu, log	Intercept values used	Mean and SE
Liu et al.	2014	10	10	63.8 (3.29)	67.8 (5.20)	Healthy elderly subjects	waist-worn ECG	seated	nr	5 min	ApEn, SamEn		Descriptive reporting only in the lederly group	Mean and SD
Lutfi & Sukkar	2011	28	28	Sample range: 20–40		Healthy adults	ECG	supine	spontaneous	5 min	RR, SDNN, RMSSD, VLF, LF, HF, LF/HF, TP	ms^2, nu	Only healthy subjects included; only total n in healhty controls reported (56), sex specific n's are assumed to be equally distributed	Mean and SD
Malan et al.	2013	137	140	Sample range: 25–65		Teachers	ECG	n/a	n/a	24 h	SDNN, RMSSD, HRVti, LF, HF, LF/HF	ms^2, nu	Split by ethnicity; data from active coping groups reported	Mean and 95% CI
Mann et al.	2012	21	15	39 (3)	34 (2)	Healthy subjects	ECG	supine	nr	nr	SDNN, SDANN, RMSSD, LH, HF, LF/HF	log, nu	Baseline values used	Mean and SE
Mellingsæter et al.	2013	24	24	73.0 (6.2)	70.9 (5.7)	Healthy persons	ECG	nr	nr	4 min	LF, HF, LF/HF	ms^2, nu	Rest values used	Median and interquartile range
Mendonca et al.	2010	12	13	22.7 (3.5)	24.0 (2.4)	Healthy individuals	ECG	supine	12/min	5 min	LF, HF, LF/HF, DFAα1	log, nu	Pre-exercise values used	Mean and SE
Michels et al.	2013	220	240	Sample range: 5–10		Population-based cohort	Polar	supine	spontaneous	10 min	RR, SDNN, RMSSD, pNN50, VLF, LF, HF, LF/HF	ms^2, nu		Median and interquartile range
Molnar et al.	1996	10	11	57 (15)	57 (12)	Healthy subjects	ECG	n/a	n/a	24 h	RR			Mean and SD
Moodithaya & Avadhany	2012	141	126	Stratified	Stratified	Healthy volunteers	ECG	supine	nr	5 min	TP, LF, HF	m^2	4 stratified age groups	Mean and SE
Murata et al.	1992	33	68	38 (12)	45 (11)	Healthy men and women	ECG	supine	spontaneous	100 R-R	CVRR, CCVRSA, CCVMWSA, PSDRR, PSDRSA,PSDMWSA			Mean and SD
Naumovaa & Zemtsova	2009	61	61	27.1 (4.4)	27.2 (3.8)	Healthy subjects	ECG	nr	nr	500 values	ULF, VLF, LF, HF	nu	Only nu values used (not score values)	Median and interquartile range
Ohira et al.	2008	3528	3124	Sample range: 45–84		Cohort free from cardiovascular disease	ECG	seated	nr	30 s	SDNN, RMSSD			Mean and interquartile range
Ottaviani et al.	2009	29	16	32.6 (22–48)	35.4 (25–48)	Full-time employees	ECG	nr	nr	10 min	HF, LF/HF	log	Baseline data used	Assumably reported as mean and SD (not specified)
Pal et al.	2012	30	32	37.42 (7.30)	38.50 (6.25)	Institute staff	ECG	supine	nr	5 min	RR, RMSSD, NN50, pNN50, LF, HF, LF/HF	ms^2, nu	Only normotensive group used	Mean and SD
Pal et al.	2013	137	207	19.64 (2.40)	20.05 (2.85)	First-year course students	ECG	supine	nr	5 min	RR, RMSSD, NN50, pNN50, LF, HF, LF/HF	ms^2, nu	Only normotensive group used	Mean and SD
Pal et al.	2014	65	60	20.32 (2.38)	21.16 (2.70)	Medical students	ECG	supine	nr	10 min	SDNN, RMSSD, NN50, pNN50, TP, LF, HF, LF/HF		Only control group subjects	Mean and SD

Table 2 (*Continued*)

Authors	Year	F *n*	M *n*	F Age	M Age	Sample type	Method	Position	Respiration	Length	Indices	Units PSD	Subgroups/notes	Source/transoformations
Park et al.	2007	271	366	44.5 (11.2)	45.5 (10.4)	Healthy subjects	ECG	nr	nr	5 min	SDNN, RMSSD, LF, HF, LF/HF, TP	ms^2		Assumably reported as mean and SD (not specified)
Perseguini et al.	2011	10	14	65.3 (3.3)	66.1 (3.5)	Healthy elderly volunteers	ECG	supine*	spontaneous	250 RR	RR, RRi, LF, HF, LF/HF, Shannon entropy	nu	*Supine values used	Mean and SD
Pikkujämsä et al.	1999	48	66	Stratified	Stratified	Healthy subjects	ECG	n/a	n/a	24 h	α1, VLF, beta	log		Assumably reported as mean and SD (not specified)
Pikkujämsä et al.	2001	200	192	51 (6)	50 (6)	Healthy middle-aged subjects	ECG	supine*	nr	15 min	RR, ApEn, α1, SDNN, LF, HF, LF/HF	ms^2, nu	*Supine values used	Mean and SD
Pitzalis et al.	2001	25	22	27 (4)	26 (6)	Normotensive subjects without a family history of hypertension	ECG	n/a	n/a	24 h	RR, SDNN, RMSSD		Data from subjects without family history of hypertension used	Assumably reported as mean and SD (not specified)
Ramaekers et al.	1998	135	141	42.6 (14.8)	40.8 (14.4)	Healthy subjects	ECG	n/a	n/a	24 h	pNN50, SDNN, SDANN, RMSSD, LF, HF, LF/HF, TP	ms^2, nu		Mean and SD
Reed et al.	2006	32	30	10.5 (0.6)	10.2 (0.6)	Healthy children	Polar	supine	nr	5 min	SDNN, LF, HF, LF/HF, TP	nu, log	Only LF/HF in log used	Mean and SD
Resmini et al.	2008	17	17	34.59 (8.21)	36.18 (14.77)	Volunteers	ECG	supine*	nr	30 s	LF, HF	ms^2	Only subjects from the control groups (group 3 and 4) included; *clinostatism values used	Median and interquartile range
Rodríguez-Colón et al.	2014	182	206	17.05 (2.15)	16.86 (2.15)	Cohort of children	ECG	n/a	n/a	39 h	SDNN, RMSSD, LF, HF, LF/HF	log		Mean and SD
Rossy & Thayer	1998	19	21	Sample range: 17–25		Students	ECG	seated	nr	5 min	RR, SDNN, MSD, pNN50, LF, HF, LF/HF	ms^2, nu	Baseline values used	Mean and SD
Roy et al.	2013	30	30	Sample range: 18–25		Normotensive, non-obese and non-smokers	ECG	autonomic test	nr	30 s	30:15 RR			Assumably reported as mean and SD (not specified)
Ryan et al.	1994	27	40	Stratified	Stratified	Healthy subjects	ECG	supine	spontaneous and controlled	10/15 min	LF, HF, TP, LF/HF	log	3 stratified age groups (young/middle-aged/elderly); n before drop-outs	Mean and SE
Saleem et al.	2012	18	27	Sample mean: 42 (14)		Healthy individuals	ECG	nr	nr	10 cardiac cycles	SDNN, SDANN, SDNNi, RMSSD, pNN50, VLF, LF, HF,	ms^2		Assumably reported as mean and SD (not specified)

Table 2 (*Continued*)

Authors	Year	F *n*	M *n*	F Age	M Age	Sample type	Method	Position	Respiration	Length	Indices	Units PSD	Subgroups/notes	Source/transoformations
Schechter et al.	1998	50	48	57 (8)	57 (8)	Sedentary, middle-aged patients	ECG	supine	nr	5 min	RR, SDNN, pNN50%, RMSSD, VLF, LF, HF, LF/HF	ms^2	Only subjects with myocardial perfusion scans included (group 1)	Mean and SD
Sharpley et al.	2000	45	35	Sample range: 18–27		Healthy volunteer participants	ECG	supine	nr	20 min	SDNN, SDDNN			Mean and SD
Sharshenova et al.	2006	36	38	Sample range: 9–10		Apparently healthy children	ECG	supine*	nr	nr	RR, SDNN, LF, HF, TP, LF/HF	log, nu	*Supine position used	Assumably reported as mean and SD (not specified)
Silvetti et al.	2001	46	57	Stratified	Stratified	Healthy children and adolescents	ECG	n/a	n/a	>20 h	SDNN, SDNNi, SDANN, RMSSD, pNN50		4 stratified age groups	Mean and SD
Singh et al.	1998	884	686	49.3 (0.4)	48.4 (0.5)	Normotensive subjects	ECG	n/a	n/a	2 h	SDNN, VLF, LF, HF, LF/HF, RMSSD, pNN50, TP	log	Only data from normotensive subjects included; adjusted means reported	Mean and SE
Sinnreich et al.	1998 (a)	236	215	Stratified	Stratified	Families	ECG	supine	spontaneous and controlled	6 min	SDNN, RMSSD	log	4 stratified age groups	Mean and SD
Sinnreich et al.	1998 (b)	38	32	48.5 (7.2)	48.9 (6.8)	Families	ECG	supine	spontaneous*	6 min	SDNN, RMSSD, VLF, LF, HF, LF/HF, TP	log	*Free breathing used; values adjusted for age	Mean and SD
Sinnreich et al.	1999	236	215	Sample range: 15–97		Families	ECG	supine	spontaneous and controlled	6 min	SDNN, RMSSD, LF, HF, LF/HF, TP	ms^2	4 stratified age groups; only frequency domain measures used (partially overlapping sample with Sinnreich 1998 (a))	Mean and SD
Sloan et al.	2001	15	15	Sample mean: 30.9 (6.9)		Healthy, nonsmoking volunteers	ECG	supine	spontaneous	60/240 s	SDNN, RMSSD, LF, MF, HF	log	Only baseline values used	Assumably reported as mean and SD (not specified)
Sloan et al.	2008	436	321	Sample mean: 40.0 (3.7)		Population-based cohort	ECG	seated	nr	10 min	SDNN, HF, LF, LF/HF	ms^2	Split by ethnicity	Mean and SD
Smith et al.	2011	114	114	30.1	28.5	Wives and husbands	ECG	seated	nr	3 min	HF	log	Baseline 1 values used	Mean and SD
Snieder et al.	2007	210	196	44.5 (6.6)	43.7 (6.4)	Middle-aged twins	ECG	seated	nr	8.5 min	RSA, ApEn		Resting recovery period	Mean and SD
Sookan & McKune	2012	23	21	19.75 (1.76)	21.17 (1.55)	Physically active young adults	Suunto t6	supine	nr	5 min	RR, SDNN, pNN50, RMSSD, LF, HF, LF/HF	nu	Aggreagted data on days 2, 3, and 4 used	Mean and SD
Sosnowski et al.	2005	38	172	Sample mean: 49.5 (6.0)		Middle-aged subjects	ECG	n/a	n/a	24 h	RR, SDNN, SDANN, pNN50, TI, HRVF			Mean and SD
Spoelstra-De Man et al.	2005	130	122	64 (7)	62 (8)	Subjects with normal glucose metabolism	ECG	supine	spontaneous	3 min	RR, SDNN, LF, HF, LF/(LF + HF)	ms^2	Only data from subjects with normal glucose metabolism used	Mean and SD/mean and range
Stein et al.	1997	30	30	Stratified	Stratified	Healthy adults	ECG	n/a	n/a	24 h	RR, SDNN, SDANN, SDNNi, RMSSD, pNN50, TP, ULF, VLF, LF, HF, LF/HF		2 stratified age groups each (younger/older); day and nigh time values reported asides the 24 h mean	Assumably reported as mean and SD (not specified)
Stein et al.	2004	18	18	Sample mean: 37 (9)		Healthy controls	ECG	n/a	n/a	24 h	RR, SDNN, SDANN, SDNNi, RMSSD, pNN50, TP, ULF, VLF, LF, HF, LF/HF	log	Only control group subjects	Mean and SD

Table 2 (*Continued*)

Authors	Year	F n	M n	F Age	M Age	Sample type	Method	Position	Respiration	Length	Indices	Units PSD	Subgroups/notes	Source/transoformations
Steptoe et al.	2002	105	123	Stratified	Stratified	Healthy volunteers	ECG	nr	nr	nr	RMSSD		Stratified by three employment grades; HRV assessed in 159 participants only (no reporting of corrected n)	Mean and SE
Sztajzel et al.	2008	18	14	Sample mean: 29 (3)		Medical students	ECG	n/a	n/a	24 h	RR, SDNN, SDANN, RMSSD, pNN50, HRV index, VLF, LF, HF, LF/HF	ms^2, nu, log	24 h mean data from day 1 used because more measures reported; log transformed LF/HF used	Mean and SE
Thayer et al.	1998	6	5	Sample mean: 20.37		College students	ECG	seated	nr	5 min	RR, SDNN, MSD, pNN50, LF, HF, TP	nu, ms^2	Only data from nondepressed participants used; mean age includes depressed	Mean and SD
Tillisch et al.	2005	22	29	Sample mean: 40.2 (11)		Healthy control subjects	ECG	nr	nr	10 min	PPHF, PPR		Only data from controls used	Mean and SD
Tsao et al.	2013	64	60	13.4 (2.8)	13.0 (3.1)	Healthy children	ECG	nr	nr	2 min	RMSSD		Pre-task baseline used	Mean and SD
Tsuji et al.	1996 (a)	1486	1236	Sample mean: 55 (21–93)		Population-based cohort	ECG	n/a	n/a	2 h	SDNN, LF, HF	log		Mean and SD
Tsuji et al.	1996 (b)	1400	1101	54 (14)	52 (13)	Population-based cohort	ECG	n/a	n/a	2 h	SDNN, pNN50, RMSSD, VLF, LF, HF, LF/HF, TP	ms^2, nu	SDNN log, LF log, HF log not used (potentially overlapping)	Assumably reported as mean and SD (not specified)
Udo et al.	2009	16	20	21.6 (.96)	22.0 (1.00)	Social drinkers	ECG	nr	nr	5 min	0.1-Hz HRV index		Pre-drinking baseline used	Mean and SD
Umetani et al.	1998	148	112	Stratified	Stratified	Healthy subjects	ECG	n/a	n/a	24 h	SDNN, SDANN, SDNNi, RMSSD, pNN50,		4 stratified age groups	Mean and SD
Utsey & Hook	2007	116	82	Sample mean: 19.41 (2.50)		Graduate college students	Polar	nr	nr	5 min	RR, RMSSD			Mean and SD
Van Hoogen-huyze et al.	1991	14	19	Sample mean: 34 (24–54)		Healthy volunteers	ECG	n/a	n/a	2 × 24 h	RR, SDNN, SDANN, CV%		Only data from normal subjects included	Mean and SD
Vandeput et al.	2012	135	141	Sample range: 18–71		Healthy subjects	ECG	n/a	n/a	24 h	Nlmean, NLdr		Day and night time data reported asides 24 h mean	Mean and SD
Virtanen et al.	2003 (a)	79	71	48.2 (8.1)	47.3 (7.8)	Healthy participants	ECG	supine	0.25 Hz	5 min	LF, HF	ms^2		Mean and SD
Virtanen et al.	2003 (b)	56	49	44.4 (5.2)	44.1 (5.2)	Normotensive subjects	ECG	supine	spontaneous	5 min	SDNN, RMSSD, VLF, LF, HF, TP, LF/HF	ms^2, nu, log	Only data from normotensive subjects usedl LF/HF log used	Mean and SE
Virtanen et al.	2004	204	159	Sub groups	Sub groups	Population-based cohort	ECG	supine/nr	0.25 Hz/nr	5/45 min	SDNN, VLF, LF, HF, TP, LF/HF	ms^2, nu	2 populations reported	Mean and SE

Table 2 (*Continued*)

Authors	Year	F *n*	M *n*	F Age	M Age	Sample type	Method	Position	Respiration	Length	Indices	Units PSD	Subgroups/notes	Source/transoformations
von Känel et al.	2009	64	495	34.1 (12.5)	42.4 (10.9)	Working men and women	ECG	n/a	n/a	nr	RMSSD			Mean and SD
Voss et al.	2011	18	18	30 (4)	34 (7)	Healthy controls	ECG	nr	spontaneous	30 min	LF/HF, plvar, phvar		Only data from controls used	Mean and SD
Walleín et al.	2012	202	139	Sub groups	Sub groups	Nationally representative	ECG*	supine	spontanous	300 s	SDNN, RMSSD, LF, LH	ms^2	4 age stratified groups, *ECG and Polar reported, ECG used, total n before drop-outs	Mean and 95% CI
Wang et al.	2013	47	41	5.64 (0.56)	5.59 (0.51)	Preschool-age children	ECG	supine	spontaneous	228 s	RR, Var, VLF, LF, HF, LF/HF, TP	nu, log		Mean and SD
Wang et al.	2005	196	189	Sub groups	Sub groups	Subjects from a longitudinal cohort	ECG	supine	nr	256 RR	RR, SDNN, RMSSD, LF, HF, LF/HF	ms^2	Stratified by ethnicity	Mean and SD
Wang et al.	2009	399	336	Sub groups	Sub groups	Participants from a twin study	ECG	nr	nr	3 × 30 s	RR, RMSSD, HF	ms^2	Stratified by ethnicity; rest measures used	Assumably reported as mean and SD (not specified)
Wilhelm et al.	2011	61	60	43 (7)	42 (8)	Nonelite athletes	ECG	n/a	n/a	24 h	RR, SDNN, SDANN, RMSSD, LF, HF, LF/HF	ms^2, nu	Day and night time data reported asides 24 h mean	Mean and SD
Williams et al.	2011	156	331	Sub groups	Sub groups	Healthy men and women	ECG	supine	spontaneous	45 min	HF	nu	Stratified by ethnicity	Mean and SD
Wirch et al.	2006	12	12	27.2 (1.6)	27.2 (1.3)	Healthy, normotensive, physically active men and women	ECG	seated	spontaneous	512 R–R	RR, LF, HF	ms^2	Baseline values used	Mean SE
Xue-Rui et al.	2008	20	16	40.3 (7.8)	40.6 (7.8)	Healthy adults	nr	nr	nr	nr	SDNN, LF/HF		Baseline data used, age and n before drop outs; different n for measures	Mean and SD
Yoo et al.	2011	30	55	Sample mean: 48 (8)		Healthy adults	SA6000	sitting	nr	nr	RR, SDNN, RMSSD, pNN10, pNN20, pNN30, pNN50, LF, HF, LF/HF	log, nu		Median and interquartile range
Young & Leicht	2011	16	14	24.9 (7.8)	24.2 (5.9)	Healthy adults	ECG	supine*	nr	10 min	SDNN, SDANN, RMSSD, VLF, LF, HF, TP, LF/HF, SD1, SD2,	ms^2, nu	*Supine used	Mean and SD
Yüksel et al.	2013	13	12	Sample mean: 35.2 (6.3)		Healthy adult subjects	ECG	seated	nr	5 min	SDNN, SDANN, RMSSD, pNN50, VLF, LF, HF, LF/HF	assumed nu	Condition I data used	Mean and SD
Zhang	2007	303	167	Sample mean: 44 (16)		Pooled data, healthy samples	ECG	nr	nr	nr	RR, RMSSD, VLF, LF, HF, TP, LF/HF	ms^2, nu		Mean and SD
Ziegler et al.	2006	957	1030	64 (55–74)	65 (55–74)	Population-based cohort	ECG	supine	nr	20 s	SDNN, CV%			Median and range

and McKune, 2012; Sosnowski et al., 2005; Spoelstra-De Man et al., 2005; Stein et al., 2004, 1997; Steptoe et al., 2002; Sztajzel and Jung, 2008; Thayer et al., 1998; Tillisch et al., 2005; Tsao et al., 2013; Tsuji et al., 1996a, 1996b; Udo et al., 2009; Umetani et al., 1998; Utsey and Hook, 2007; Van Hoogenhuyze et al., 1991; Vandeput et al., 2012; Virtanen et al., 2004, 2003a, 2003b; von Känel et al., 2009; Voss et al., 2011; Wallén et al., 2012; Wang et al., 2013, 2009, 2005; Wilhelm et al., 2011; Williams et al., 2011; Wirch et al., 2006; Xue-Rui et al., 2008; Yoo et al., 2011; Young and Leicht, 2011; Yüksel et al., 2013; Zhang, 2007; Ziegler et al., 2006). Sample and study characteristics of included studies are summarized in Table 2. Studies reported data in a total of 63,612 participants (31,970 females, 31,642 males).

3.2. Meta-analysis main effects

Data on all available measures of HRV were extracted from studies and entered intro *RevMan* for meta-analytical computations, yielding a total of 1154 effect size estimates (k) across 50 different measures of HRV in a cumulated total of 296,247 participants. Only results from analysis on 32 measures of HRV with $k \geq 3$ are reported. Indices included in the analysis are described and explained in Table 2.

First, main effect estimates across all participants and age groups were derived using fixed- and random-effect models. Here, only significant findings that were consistent for fixed- and random effect models are reported, providing statistics derived from random-effect models. Complete reporting of effect size estimates and test results for heterogeneity is provided in Table 3, and an illustrative summary for measures reported most frequently is given in Fig. 2.

Analysis of mean RR and time-domain measures of HRV revealed, that females show a decreased mean RR interval ($g = -0.44$; [95%CI: -0.54: -0.34], $Z = 8.72$, $p < 0.0001$, $k = 79$), SDNN independent of the reported units (in **ms**: $g = -0.24$; [95%CI: -0.30: -0.18], $Z = 7.67$, $p < 0.0001$, $k = 99$; **log**: $g = -0.17$; [95%CI: -0.25: -0.09], $Z = 4.04$, $p < 0.0001$, $k = 16$), and SDNNi ($g = -0.44$; [95%CI: -0.63: -0.26], $Z = 4.70$, $p < 0.0001$, $k = 18$) compared to males. Analysis on SDANN, MSD, RMSSD (ms and log-transformed), as well as NN50 and pNN50 yielded no significant and inconsistent findings for both fixed- and random-effect models (Table 3).

Meta-analysis on frequency-domain measures of PSD showed lower TP in females (in **ms**^{2}: $g = -0.19$; [95%CI: -0.26: -0.12], $Z = 5.02$, $p < 0.0001$, $k = 48$; **log**: $g = -0.23$; [95%CI: -0.33: -0.12], $Z = 4.23$, $p < 0.0001$, $k = 29$). Furthermore, females showed decreased VLF power (in **ms**^{2}: $g = -0.21$; [95%CI: -0.29: -0.13], $Z = 4.92$, $p < 0.0001$, $k = 17$; **log**: $g = -0.21$; [95%CI: -0.34: -0.07], $Z = 3.04$, $p = 0.002$, $k = 19$), and LF power (in **ms**^{2}: $g = -0.34$; [95%CI: -0.45: -0.24], $Z = 6.60$, $p < 0.0001$, $k = 82$; **log**: $g = -0.34$; [95%CI: -0.43: -0.26], $Z = 7.97$, $p < 0.0001$, $k = 50$; **nu**: $g = -0.38$; [95%CI: -0.46: -0.31], $Z = 9.86$, $p < 0.0001$, $k = 67$).

Compared to males, females showed greater HF power (in **ms**^{2}: $g = 0.14$; [95%CI: 0.05: 0.23], $Z = 2.97$, $p = 0.003$, $k = 92$; **nu**: $g = 0.38$; [95%CI: 0.29: 0.047], $Z = 8.60$, $p < 0.0001$, $k = 67$). Respectively, females showed a lower LF/HF ratio ($g = -0.39$; [95%CI: -0.47: -0.32], $Z = 10.07$, $p < 0.0001$, $k = 92$). VLF in **nu** and HF in **log** values, showed no significant and consistent findings for both fixed- and random-effect models, although the direction of effects was in line with the findings reported for other units (see Table 3).

Furthermore, females showed a greater CCV-HF ($g = 0.48$; [95%CI: 0.20: 0.75], $Z = 3.38$, $p < 0.0005$, $k = 3$) and a greater CCV-LF ($g = 0.39$; [95%CI: 0.09: 0.68], $Z = 2.57$, $p = 0.01$, $k = 3$). Non-linear measures of HRV only revealed consistent results across fixed- and random-effect models for SamEn and DFAα1. Females showed greater SamEn ($g = 0.67$; [95%CI: 0.23: 1.10], $Z = 3.02$, $p = 0.003$, $k = 4$) and lower DFAα1 ($g = -0.17$; [95%CI: -0.68: -0.22], $Z = 3.87$, $p < 0.0001$, $k = 5$). However, all the later analyses are based on a relatively small number of available comparisons ($k = 3$–5).

CVRR (%), CVRR in log-transformed values, SD1 and SD2, as well as ApEn and TI showed no significant and consistent findings for both fixed- and random-effect models (Table 3). Most of the analysis on included measures of HRV, revealed significant heterogeneity across studies (Table 3)

3.3. Meta-regression

Meta-regression on random-effects was performed for RR, SDNN (ms), RMSSD (ms), pNN50 (%), TP (ms^2), LF (ms^2, nu, log), HF (ms^2, nu, log), and LF/HF. Here, only significant effects are reported. Full reporting is provided in Table 4. Meta-regression on time-domain measures of HRV with age (continuous) as a covariate, revealed small, but significant effects on SDNN (in ms; $\beta = 0.005$, [95%CI: 0.001: 0.008], SE = 0.002, $p = 0.017$, $k = 99$) and RMSSD (in ms; $\beta = 0.005$, [95%CI: 0.002: 0.008], SE = 0.002, $p < 0.001$, $k = 82$). With greater age, the previously reported sex differences on SDDN (*lower* in females, Fig. 2) were diminished. While meta-analysis on RMSSD (ms) showed no consistent effects (Fig. 2), females showed greater RMSSD compared to males with increasing age. Meta-regression on frequency-domain measures showed that with increasing age, the previously reported effect for LF (nu) power (*lower* in females) was further increased ($\beta = -0.006$, [95%CI: -0.011: -0.002], SE = 0.002, $p = 0.004$, $k = 67$).

Controlling for respiration (*controlled* vs. *spontaneous*) was a significant covariate for LF (nu) (*controlled* $k = 5$; *spontaneous* $k = 15$; $\beta = 0.309$, [95%CI: 0.076: 0.541], SE = 0.118, $p = 0.009$) and HF (log) (*controlled* $k = 15$; *spontaneous* $k = 25$; $\beta = -0.264$, [95%CI: -0.448: -0.080], SE = 0.094, $p = 0.005$). The reported main effects for LF (nu) (*lower* in females) and HF (log) (*greater* in females), were attenuated during spontaneous breathing. However, meta-regression on estimates of PSD expressed in other units didn't show such effect. Meta-regression on respiration control showed no significant effects for time-domain measures of HRV. Meta-regression on position at recording showed no effects on any of the included measures of HRV (Table 4).

Meta-regression on the length of recording (*short* vs. *long*) available for analysis of HRV, showed significant effects on SDNN (ms), RMSSD (ms), pNN50 (%) and TP (ms^2). Sex differences on SDNN (*lower* in females, Fig. 2) were further enhanced in long-term recordings (*short* $k = 55$; *long* $k = 39$; $\beta = -0.320$, [95%CI: -0.433: -0.206], SE = 0.058, $p < 0.001$). Similarly, *lower* TP in females (independent of recording length) was shown in particular in long-term recordings (*short* $k = 37$; *long* $k = 9$; $\beta = -0.267$, [95%CI: -0.419: -0.123], SE = 0.073, $p < 0.001$). RMSSD (*short* $k = 39$; *long* $k = 36$; $\beta = -0.122$, [95%CI: -0.229: -0.015], SE = 0.054, $p = 0.025$) and pNN50 (*short* $k = 18$; *long* $k = 27$; $\beta = -0.285$, [95%CI: -0.419: -0.150], SE = 0.069, $p < 0.001$), were lower in females during long-term recordings.

4. Discussion

This is the first meta-analysis on sex differences in HRV. In line with previous findings, we show that females have a greater mean HR reflected by a smaller mean RR interval. Females show less variability within the time-series of heartbeats indexed by SDNN and SDNNi—in particular in long-term recordings. Meta-analysis on frequency-domain measures of HRV showed that females have lower total power in the spectral density. Importantly, the composition of the PSD significantly differs between males and females. While females show less power in the very-low and LF bands they show greater power in the HF band. Consistent with a large body of animal and human research (Dart et al., 2002; Du et al., 2006),

Table 3
Effect estimates from fixed- and random-effect meta-analysis and test results from tests for heterogeneity. *k*: number of included comparisons; ES: effect size (Hedge's *g*); 95%CI: 95% confidence interval.

Index	Females (*n*)	Males (*n*)	*k*	Fixed effect					Random effect					Chi^2	*p*	I^2	Tau^2
				ES	95%CI		*Z*	*p*	ES	95%CI		*Z*	*p*				
RR (ms)	9775	8494	79	**−0.36**	−0.39	−0.33	23.77	<0. 0001	**−0.44**	−0.54	−0.34	8.72	<0. 0001	481.60	<0.0001	84%	0.12
SDNN (ms)	16307	16144	99	**−0.08**	−0.10	−0.06	6.81	<0. 0001	**−0.24**	−0.30	−0.18	7.67	<0. 0001	392.40	<0.0001	75%	0.04
SDNN (log)	4412	3706	16	**−0.13**	−0.17	−0.09	5.86	<0. 0001	**−0.17**	−0.25	−0.09	4.04	<0. 0001	27.00	0.03	44%	0.01
SDANN (ms)	1530	1466	29	**0.20**	0.12	0.28	5.09	<0. 0001	**−0.33**	−0.74	0.08	1.60	0.11	650.59	<0.0001	96%	1.13
SDNNi (ms)	1011	876	18	**−0.33**	−0.42	−0.23	6.95	<0. 0001	**−0.44**	−0.63	−0.26	4.70	<0. 0001	36.28	0.004	53%	0.06
MSD (ms)	68	66	3	**0.08**	−0.27	0.42	0.43	0.67	**0.10**	−0.29	0.48	0.49	0.62	2.31	0.31	13%	0.02
RMSSD (ms)	11629	12949	82	**−0.01**	−0.04	0.01	1.05	0.29	**−0.08**	−0.14	−0.02	2.69	0.007	242.81	<0.0001	67%	0.03
RMSSD (log)	4522	3928	21	**−0.04**	−0.09	0.00	1.98	0.05	**−0.07**	−0.16	0.01	1.65	0.10	44.47	0.001	55%	0.01
NN50 (n)	396	445	6	**0.05**	−0.09	0.18	0.65	0.52	**0.05**	−0.09	0.18	0.65	0.52	3.81	0.58	0%	0.00
pNN50 (%)	5192	4764	47	**−0.07**	−0.11	−0.03	3.39	<0. 0001	**−0.06**	−0.14	0.02	1.54	0.12	98.82	0.12	53%	0.02
TP (ms2)	4974	6606	48	**−0.18**	−0.22	−0.14	8.96	<0. 0001	**−0.19**	−0.26	−0.12	5.02	<0. 0001	115.63	<0.0001	59%	0.03
TP (log)	4238	3739	29	**−0.21**	−0.26	−0.17	9.43	<0. 0001	**−0.23**	−0.33	−0.12	4.23	<0. 0001	73.96	<0.0001	62%	0.03
VLF (ms2)	3005	2474	17	**−0.22**	−0.27	−0.16	7.87	<0. 0001	**−0.21**	−0.29	−0.13	4.92	<0. 0001	22.60	<0.0001	29%	0.01
VLF (nu)	805	635	3	**−0.34**	−0.45	−0.23	6.34	<0. 0001	**−0.13**	−0.61	0.35	0.53	0.60	10.84	0.004	82%	0.53
VLF (log)	3964	3379	19	**−0.21**	−0.26	−0.16	8.91	<0. 0001	**−0.21**	−0.34	−0.07	3.04	0.002	80.64	<0.0001	78%	0.04
LF (ms2)	9677	11077	82	**−0.23**	−0.26	−0.21	15.96	<0. 0001	**−0.34**	−0.45	−0.24	6.60	<0. 0001	854.01	<0.0001	91%	0.17
LF (nu)	6029	5984	67	**−0.31**	−0.34	−0.27	16.48	<0. 0001	**−0.38**	−0.46	−0.31	9.86	<0. 0001	222.49	<0.0001	70%	0.06
LF (log)	7948	7499	50	**−0.30**	−0.33	−0.26	18.12	<0. 0001	**−0.34**	−0.43	−0.26	7.97	<0. 0001	209.56	<0.0001	77%	0.05
HF (ms^2)	15259	15172	92	**0.05**	0.03	0.07	4.26	<0. 0001	**0.14**	0.05	0.23	2.97	0.003	1068.83	<0.0001	91%	0.15
HF (nu)	6412	6288	67	**0.27**	0.24	0.31	14.98	<0. 0001	**0.38**	0.29	0.47	8.60	<0. 0001	315.70	<0.0001	79%	0.08
HF (log)	8966	8426	66	**0.03**	0.00	0.06	1.85	0.06	**0.03**	−0.05	0.10	0.57	0.50	229.08	<0.0001	72%	0.04
LF/HF	14056	15459	113	**−0.34**	−0.36	−0.31	27.60	<0. 0001	**−0.39**	−0.47	−0.32	10.07	<0. 0001	903.67	<0.0001	83%	0.12
CVRR (%)	1952	2023	8	**0.09**	0.02	0.15	2.68	0.007	**0.07**	−0.08	0.22	0.87	0.39	21.45	0.003	67%	0.02
CVR (log)	158	151	5	**−0.23**	−0.45	0.00	1.94	0.05	**−0.23**	−0.49	0.04	1.69	0.09	4.97	0.29	20%	0.02
CCV-HF (%)	908	866	3	**0.42**	0.32	0.51	8.71	<0. 0001	**0.48**	0.20	0.75	3.38	<0. 0005	13.85	0.001	86%	0.05
CCV-LF (%)	908	866	3	**0.39**	0.29	0.48	8.09	<0. 0001	**0.39**	0.09	0.68	2.57	0.01	16.04	0.0003	88%	0.06
SD1 (ms)	77	78	4	**−0.24**	−0.56	0.08	1.49	0.14	**−0.24**	−0.56	0.08	1.49	0.14	1.00	0.80	0%	0.00
SD2 (ms)	70	71	3	**−0.31**	−0.65	0.03	1.78	0.08	**−0.24**	−0.96	0.49	0.64	0.52	7.88	0.02	75%	0.31
ApEn	507	484	8	**0.15**	0.03	0.28	2.39	0.02	**0.02**	−0.27	0.30	0.11	0.92	20.92	0.004	67%	0.09
SamEn	50	59	4	**0.66**	0.26	1.05	3.25	0.001	**0.67**	0.23	1.10	3.02	0.003	3.57	0.31	16%	0.03
DFAα1	530	553	5	**−0.45**	−0.57	−0.33	7.31	<0. 0001	**−0.45**	−0.68	−0.22	3.87	<0. 0001	11.70	0.02	66%	0.04
TI	392	522	9	**−0.21**	−0.35	−0.07	2.97	0.003	**−0.17**	−0.40	0.06	1.45	0.15	20.15	0.01	60%	0.07

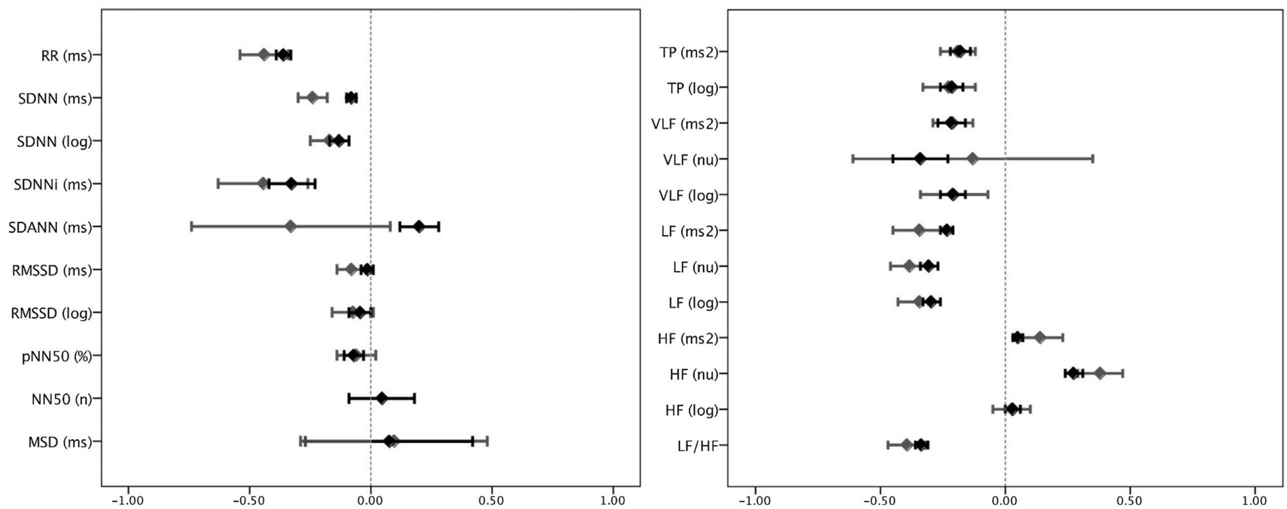

Fig. 2. Meta-analysis on sex differences on HRV measures reported most frequently, Black: fix-effect models; gray: random-effect models; a positive effect size indicates that the respective measure is greater in women compared to men.

Table 4
(A) Results from random-effect meta-regression on age (continuous) and respiration control (factorial). (B) Results from random-effect meta-regression on position (factorial) and recording length (factorial).

(A) Covariate		Age (continuous)					Respiration control (factorial)					
Index	*k*	*β*	Low	Up	SE	*p*	Cont/spont	*β*	Low	Up	SE	*p*
RR (ms)	79	−0.020	−0.040	0.000	0.01	0.055	23/4	−1.860	−4.418	0.698	1.305	0.154
SDNN (ms)	99	0.005	0.001	0.008	0.002	0.017	7/14	−0.060	−0.286	0.166	0.115	0.602
RMSSD (ms)	82	0.005	0.002	0.008	0.002	<0.001	2/13	0.082	−0.298	0.462	0.194	0.673
pNN50 (%)	47	0.004	−0.001	0.009	0.002	0.108	2/2	−0.184	−0.373	0.004	0.096	0.055
TP (ms^2)	48	−0.000	−0.005	0.005	0.003	0.994	6/15	−0.157	−0.394	0.080	0.121	0.194
LF (ms^2)	82	0.009	−0.017	0.035	0.013	0.483	8/26	−0.100	−0.326	0.126	0.115	0.386
LF (nu)	67	−0.006	−0.011	−0.002	0.002	0.004	5/15	0.309	0.076	0.541	0.118	0.009
LF (log)	50	0.001	−0.004	0.006	0.002	0.693	13/18	−0.057	−0.294	0.180	0.121	0.636
HF (ms^2)	92	−0.005	−0.035	0.026	0.015	0.767	8/29	−0.060	−0.293	0.173	0.119	0.615
HF (nu)	67	0.003	−0.002	0.008	0.003	0.299	5/16	−0.180	−0.440	0.080	0.132	0.174
HF (log)	66	0.004	−0.000	0.008	0.002	0.056	15/25	−0.264	−0.448	−0.080	0.094	0.005
LF/HF	113	−0.002	−0.007	0.002	0.002	0.330	11/33	0.165	−0.033	0.362	0.101	0.102

(B) Covariate	Position (factorial)						Recording Length (factorial)					
Index	Sup/other	*β*	Low	Up	SE	*p*	Short/long	*β*	Low	Up	SE	*p*
RR (ms)	40/10	0.525	−0.735	1.785	0.643	0.414	57/18	−0.284	−1.195	0.626	0.465	0.540
SDNN (ms)	35/20	0.092	−0.043	0.226	0.069	0.183	55/39	−0.320	−0.433	−0.206	0.058	<0.001
RMSSD (ms)	24/8	0.060	−0.084	0.204	0.073	0.418	39/36	−0.122	−0.229	−0.015	0.054	0.025
pNN50 (%)	11/8	−0.008	−0.289	0.272	0.143	0.953	18/27	−0.285	−0.419	−0.150	0.069	<0.001
TP (ms^2)	26/7	0.113	−0.047	0.272	0.081	0.167	37/9	−0.267	−0.419	−0.123	0.073	<0.001
LF (ms^2)	44/10	0.087	−0.223	0.398	0.159	0.582	63/17	0.133	−0.924	1.190	0.539	0.805
LF (nu)	31/12	0.073	−0.127	0.273	0.102	0.475	50/12	−0.184	−0.377	0.009	0.099	0.062
LF (log)	27/10	−0.135	−0.357	0.087	0.113	0.234	35/12	−0.092	−0.306	0.123	0.109	0.401
HF (ms^2)	50/11	−0.094	−0.491	0.304	0.203	0.645	72/18	−0.431	−1.665	0.803	0.630	0.493
HF (nu)	34/9	−0.184	−0.399	0.032	0.110	0.95	53/11	0.155	−0.052	0.361	0.105	0.143
HF (log)	37/13	−0.138	−0.322	0.047	0.094	0.144	52/11	−0.026	−0.232	0.180	0.105	0.804
LF/HF	53/23	0.058	−0.137	0.253	0.100	0.561	88/20	−0.144	−0.355	0.066	0.108	0.179

these findings indicate that the autonomic control of the female heart is characterized by a relative dominance of vagal, parasympathetic activity, despite greater mean HR, whereas the male heart is characterized by relative sympathetic dominance, despite lower HR. These findings have several important implications.

Altered function of the ANS, characterized by autonomic imbalance (i.e., relatively high sympathetic activity and relatively low parasympathetic activity) is one posited mechanism underlying the increased risk for adverse somatic health outcomes, such as CVD, hypertension, diabetes, and stroke as well as all-cause mortality (Thayer et al., 2010; Thayer and Lane, 2007). Greater vagal activity is considered to be *cardio-protective* and is associated with overall greater self-reported health (Jarczok et al., 2015), wellbeing and longevity.

One easily obtainable, albeit crude, index of autonomic imbalance is resting HR. Numerous studies have shown that higher resting HR is associated with increased mortality and morbidity (Palatini and Julius, 1997; Palatini and Julius, 2014; Palatini and Julius, 1999; Palatini and Julius, 2009). Given that the present results found shorter RR intervals (higher resting HR) in women one might expect that women would have greater CVD related mortality and morbidity. However, this is not the case as women have longer life expectancies and reduced CVD risk (at least premenopausal) (Matthews et al., 2001). In addition, it has been reported that the association between tachycardia or elevated HR and cardiovascular disease risk is stronger in men than in women (Palatini, 2001). Thus this paradoxical state of affairs requires explanation.

Our findings highlight that women show greater vagal activity compared to men, providing a potential mechanism underlying the health disparity between the sexes. Most interestingly, although women show greater parasympathetic activity, they show a decreased mean RR interval compared to men and less total variability in the time-series of heartbeats. Although a complete explication of the potential mechanisms by which females come to have greater parasympathetic cardiac control is beyond the scope of the present paper, as several reviews have summarized much of this literature (Dart et al., 2002; Du et al., 2006), we will briefly outline a few of those previously suggested and propose some others.

Both animal and human studies have reported sex differences in autonomic control such that females show greater parasympathetic modulation of cardiovascular activity compared to males. For example, in response to coronary artery occlusion both rodent and human females show greater vagally-mediated cardioprotective responses such as bradycardia, increased HRV, and simultaneous bradycardia and decreased blood pressure (Bezold-Jarisch type reactions (Aviado and Guevara Aviado, 2001; Mark, 1983)) compared to males (Airaksinen et al., 1998; Du et al., 1995). Research has suggested that this is due to the effects of estrogen as ovareictomy and vagotomy in females reversed these effects and produced more “male-like” responses (Du et al., 2006).

In addition, oxytocin has been implicated as stimulation of oxytocin neurons has been shown to induce HR slowing (bradycardia) and increased vagal tone (Rogers and Hermann, 1986; Higa et al., 2002). Importantly, it has been shown that these oxytocin neurons are associated with stress buffering in that they are more active during stressful events and thus serve to reduce the impact of such events by lowering HR via increased vagal tone (Higa et al., 2002). Further elaboration of the exact central nervous system (CNS) pathways via which oxytocin produces its stress buffering effects comes from animal studies. Oxytocin-type neurons from the paraventricular nucleus (PVN) have been shown to synapse on cardiovagal neurons in the nucleus of the solitary tract (NTS), the dorsal motor nucleus of the vagus (DMX), and the nucleus ambiguus (NA) (Higa et al., 2002; Luiten et al., 1985; Coote, 2013). Excitation of these neurons increase vagal outflow and decrease HR while having no effect on sympathetic outflow (Higa et al., 2002). Furthermore, both human and animal studies suggest that the amygdala plays a decisive role in the CNS stress attenuating effects of oxytocin (Landgraf and Neumann, 2004; Kirsch et al., 2005; Viviani et al., 2011).

Finally, neural control of the heart may differ significantly as a function of sex. HRV is related to brain structures such as the amygdala and the ventromedial prefrontal cortex (Thayer et al., 2012). For example, we have shown that amygdala activity is positively associated with HRV in women but negatively associated with HRV in men (Nugent et al., 2011). Furthermore, resting HF-HRV is related to resting brain perfusion (Allen et al., 2015c). Of note, higher resting HF-HRV was related to less perfusion in the left parahippocampal gyrus, the left amygdala, and the right hippocampus in women but not men (Allen et al., 2015b). Most interestingly, a recent meta-analysis on sex differences in brain structure showed regional sex differences in volume and tissue density in the amygdala, hippocampus and insula (Ruigrok et al., 2014). Taken together these effects of estrogen, oxytocin, and neural control are consistent with models of parental investment and differential stress coping as exemplified in the tend-and-befriend model to provide a functional basis for these structural physiological differences (Taylor et al., 2000).

Of the major limitations of the present analysis is the fact that a large amount of studies had to be excluded because of insufficient reporting of descriptive data (Fig. 1). Given the exclusion of these studies with potential data of interest, the present analysis is not completely reflective of the existing evidence. While not all studies which were excluded for not reporting results separately for men and women, did also not control for sex differences (i.e., in adjusted analysis), our findings highlight the necessity of adequate reporting of sex differences in the literature. Researchers are encouraged to provide descriptive statistics for HRV in women and men to further add to the existing body of literature. Furthermore, we think that sex differences in HRV should be critically noted within an update of the guidelines for the measurement and interpretation of HRV (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996)—in particular for the measurement of long-term recordings. This final recommendation is consistent with recent guidelines from the US National Institutes of Health on the inclusion of females in both basic and clinical research.

While our analyses provide solid evidence for the general existence of sex difference in HRV, we didn’t control for some covariates that need to be considered in future analyses. It has repeatedly been shown, that HRV is related to body composition, using measures of body mass index (Koenig et al., 2014), waist-to-height ratio, or waist-circumference (Windham et al., 2012). Furthermore, HRV is strongly related to physical activity (Rennie et al., 2003), which was rarely reported in the included studies and thus couldn’t be controlled for in our analysis.

From a methodological perspective we didn’t address the influence of the method of PSD estimation (i.e., *Autoregressive* vs. Fast-*Fourier*), sample rate of recording, and there was insufficient data to compare different methods of recording HRV (e.g., photoplethysmography vs. ECG). Other confounds such as electrode placement, post-processing of data and the use of different software tools for analysis of HRV were beyond the scope of the present paper and not addressed. Furthermore, the present analysis didn’t address the influence of other variables that have been identified by previous meta-analysis such as ethnicity (Hill et al., 2015) that has been shown to account for individual differences in HRV.

However, to our knowledge the present meta-analysis is the most extensive meta-analysis on HRV ever performed, providing further potential to derive estimates of norm-values in the general healthy population. Again, here we only focused on sex-differences. To summarize, we provide compelling evidence, that HRV data obtained in men and women cannot be treated equally and that studies need to emphasize these differences. Furthermore, our analyses show that differences in the autonomic regulation of mean HR are complex. Measures of mean HR alone cannot replace measures of HRV in understanding important health disparities. Most importantly, despite greater mean HR the female heart is characterized by a relative dominance of vagal, parasympathetic activity. Thus, mean HR alone provides limited insight into CVD risk—in particular in females. Research on HRV needs to emphasize and report sex differences in healthy samples. Further research on how these sex differences translate into pathological processes is desperately needed.

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Appendix A. : Search strategy by database

PubMed (search performed on Friday, November 28, 2014): 1560 hits

((“sex”[MeSH Terms] OR “sex”[All Fields]) OR (“sex”[MeSH Terms] OR “sex”[All Fields] OR “gender”[All Fields] OR “gender identity”[MeSH Terms] OR (“gender”[All Fields] AND “identity”[All Fields]) OR “gender identity”[All Fields])) AND (((“heart rate”[MeSH Terms] OR (“heart”[All Fields] AND “rate”[All Fields]) OR “heart rate”[All Fields]) AND variability[All Fields]) OR HRV[All Fields])

Web of Science (search performed on Friday, November 28, 2014): 88 hits

#1 TITLE: (heart rate variability) OR TITLE: (HRV); Timespan = All years; Search language = Auto.

#2 TITLE: (sex) OR TITLE: (gender); Timespan = All years; Search language = Auto.

#1 AND #2; Timespan = All years; Search language = Auto.

CINAHL Plus (search performed on Saturday, February 21, 2015): 294 hits

#1 Search modes—Find all my search terms: (heart rate variability) OR Search modes—Find all my search terms: (HRV).

#2 Search modes—Find all my search terms: (sex) OR Search modes—Find all my search terms: (gender).

#1 Search modes—Find all my search terms: AND #2.

PsycINFO (search performed on Saturday, February 28, 2015): 278 hits

#1 Search modes—Find all my search terms: (heart rate variability) OR Search modes—Find all my search terms: (HRV).

#2 Search modes—Find all my search terms: (sex) OR Search modes—Find all my search terms: (gender).

#1 Search modes—Find all my search terms: AND #2.

Appendix B. : Detailed listing of reasons for excluding studies

Animal studies (alphabetical order, *n* in brackets): birds (1); cats (2); cattle (1); chamois (1); dogs (6); drosophila (1); horses (3); koalas (1); macaque (1); mice (8); rats (9); salmon (2); sheep (3); swine/pigs (4); ungulate (1).

Clinical samples without healthy control group (alphabetical order, *n* in brackets): acute coronary syndrome (2); acute myocardial infarction (2); acute respiratory illness (2); adults living with HIV (1); alcoholic subjects (1); anatomic brainstem abnormalities (1); angina pectoris (1); angiography patients (1); aortic stenosis (2); aortic valve disease (1); artery bypass surgery (1); atrial fibrillation (4); bereaved spouses and parents (1); bone tumor survivors (1); CAD patients (1); cancer (1); cardiac arrest (3); cardiac patients (4); cardiac rehabilitation (1); cardiomyopathy (2); carotid endarterectomy (1); chagas disease (1); chronic benign pain (1); chronic fatigue syndrome (3); chronic heart failure (2); chronic hemodialysis patients (1); chronic kidney disease (1); chronic neck pain (1); chronic renal failure (1); chronic tension-type headache (1); cirrhotic patients (1); congenital long-QT syndrome (1); congestive heart failure (5); coronary angioplasty patients (1); coronary artery bypass surgery (4); coronary artery disease (12); coronary heart disease (4); defibrillator patients (1); depression (1); diabetes (31); diabetic foot problems (1); diabetic neuropathy (4); end-stage lung disease (1); end-stage renal disease (1); epilepsy (3); familial amyloidotic polyneuropathy (1); familial dysautonomia (1); fibromyalgia (1); gastric bypass (1); general anaesthesia (1); general surgery (1); heart failure (6); heart transplant recipients (1); hemodialysis (4); hereditary transthyretin amyloidosis (1); hospice cancer patients (1); hospitalized patients (1); hyperlipidemia (1); hypertension (25); hypertrophic cardiomyopathy (1); Idiopathic dilated cardiomyopathy (1); implanted defibrillation device (2); intensive care unit (1); invasive mold infections (1); ischemic attack or minor stroke (1); ischemic stroke (1); kidney disease (2); low heart rate patients (1); lower respiratory tract infections (1); lung cancer (1); lung function impairments (1); major depression (3); methadone-exposed infants (1); multiple sclerosis (2); muscular dystrophy (1); myasthenia gravis (1); myocardial infarction (17); nonischemic dilated cardiomyopathy (1); obesity (4); obstructive sleep apnea (2); other CVD (1); other heart disease (1); parkinson's disease (2); periodontal surgery (1); post myocardial infarction patients (1); post-operative patients (1); postinfarction (1); preterm infant (3); pulmonary vascular disease (1); psychosomatic inpatients (1); renal disease (1); renal transplant (1); schizophrenia (2); sepsis (1); sinus bradycardia (1); sleep apnea (2); social phobia (1); stroke (1); stroke survivors (1); trauma patients (2); traumatized civilian population (1); unstable angina (1); valvular and subvalvular deformity (1); valvular heart disease (1); very low birth weight infants (1); war veterans/PTSD (1).

Language (alphabetical order, *n* in brackets): Bulgarian (1); Chinese (7); Czech (3); French (10); German (12); Hungarian (1); Italian (5); Japanese (12); Polish (16); Portuguese (8); Russian (22); Spanish (11); Turkish (1); Ukrainian (2).

Type (alphabetical order, *n* in brackets): book (1); case study (5); comment/editorial (13); conference abstracts (25); correction (1); dissertation/thesis (30); meta-analysis (4); review (57); retracted paper (1); study protocol (2).

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