Reference values for short-term resting-state heart rate variability in healthy adults: Results from the Brazilian Longitudinal Study of Adult Health - ELSA-Brasil study.

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Reference values for heart rate variability indices

Abstract

Background: Heart rate variability (HRV) is a psychophysiological phenomenon with broad implications, providing a widely accessible index of vagal function, underpinning a variety of psychological constructs, including the capacity for social engagement and emotion regulation, and may predict future morbidity and mortality. However, the lack of reference values for short-term HRV indices for participants of both sexes across the age spectrum is a limiting factor. This was the objective the present study. **Method:** Resting electrocardiographic records were obtained from 13,214 participants (both sexes, 35-74 y) and HRV indices in time and frequency domains (mean ± SD) were determined. **Results:** Final results were based on a subsample of 2,874 non-medicated, healthy participants stratified by sex across 10-year age-groupings. Men showed lower heart rate (HR, 64 ± 8 bpm vs. 68 ± 8 bpm, $P<0.05$) and normalized HF (39.4 ± 18.0 n.u. vs. 50.4 ± 18.5 n.u., $P<0.05$) than women, and higher N-N variance (2214 ± 1890 ms^2 vs. 1883 ± 1635 ms^2, $P<0.05$), SDNN (43.7 ± 17.3 ms vs. 40.3 ± 15.8ms, $P<0.05$) and LF/HF (2.30 ± 2.68 vs. 1.33 ± 1.82, $P<0.05$). HR and HF (n.u.) were also higher in younger than older women. LF/HF was lower in women compared to men. Percentile curves showed almost all HRV indices decreasing with aging. **Conclusion:** The availability of short-term, resting-state HRV reference values in a large sample of healthy and non-medicated participants from 35-74 years will provide a valuable tool for use by researchers, clinicians and those in the quantified self-community.

Keywords: Heart rate variability; reference values; autonomic nervous system; cardiovascular diseases; frequency domain analysis.

Reference values for heart rate variability indices

Introduction

Resting-state heart rate variability (HRV) is a psychophysiological phenomenon with broad implications. It provides an index of vagal function (Reyes del Paso, Langewitz, Mulder, van, & Duschek, 2013), which supports various psychological functions such as the capacity for social engagement (Kemp et al., 2012) and emotion regulation (Williams et al., 2015), and may even predict risk for future morbidity and mortality (Hillebrand et al., 2013; May & Arildsen, 2011; Schroeder et al., 2003). We have previously reported on the adverse effects of common mental disorders on HRV (Brunoni et al., 2013), especially in participants with generalised anxiety disorder (Kemp et al., 2014). Others have subsequently shown that changes in HRV precede the appearance of depressive symptoms (Jandackova, Britton, Malik, & Steptoe, 2016), consistent with the possibility that functioning of the vagus nerve play an aetiological role in depression onset. We have also reported that reductions in vagal function – indexed by HRV – may provide a 'spark' that initiates a cascade of downstream effects, subsequently leading to cognitive impairment (Kemp et al., 2016b). In this study, we demonstrated a relationship between HRV and cognitive function, consistent with the proposal that HRV may reflect activity within prefrontal-vagal pathways (Thayer, Hansen, Saus-Rose, & Johnsen, 2009). We further demonstrated that this relationship was mediated by insulin resistance (a marker of type 2 diabetes mellitus) and carotid intima-media thickness (subclinical atherosclerosis) (Kemp et al., 2016b), lending further support to the possibility that HRV provides an early indicator of ill-health that may have psychological and physiological consequences. Two recently published, complimentary models provide a foundation on which much of the HRV literature spanning psychological science and epidemiology may be understood. These include the GENIAL model (Kemp, Arias, & Fisher, 2017), which describes a theoretical pathway involving genomic and environmental influences on the vagus nerve that both supports and is impacted on by social interaction, and plays an important regulatory role over allostatic processes that may lead to ill-health and premature mortality. The complementary NIACT model refers to neurovisceral integration across a continuum of time (Kemp, Koenig, & Thayer, 2017), which like GENIAL, helps to bridge the disciplinary divide

from psychological science to epidemiology and public health. Both models emphasise vagal function as a critical mediating factor of health and wellbeing and provide new insights into the complex interaction among factors that may lead to longevity or premature mortality.

A major goal of the present study is to provide reference values for short-term, resting-state HRV in a large healthy sample of males and females across different age groups ranging from 35-74 years. This contribution represents a valuable resource for researchers, clinicians, those in the quantitative-self movement, and will support future efforts to understand, identify and predict personalised pathways to health and wellbeing. Although reference values for short-term measures of HRV in the time and frequency domains have been reported (Nunan, Sandercock, & Brodie, 2010; Task Force, 1996), their use remains limited because of the low sample size, variable inclusion criteria, a lack of standardisation across methods of data collection and analysis, making it difficult to draw comparisons across studies. The more recent review paper (Nunan et al., 2010) reported values for short-term HRV based on data in studies on small samples and non-standardised data-collection procedures, and none of the reviewed studies had sufficient power to provide normal population values as we will do here. Importantly, a variety of factors influence HRV including age (Antelmi et al., 2004), sex (Koenig & Thayer, 2016; Koenig, Rash, Campbell, Thayer, & Kaess, 2017), medication (Kemp et al., 2014; Felber et al., 2006), and ill-health (Buccelletti et al., 2009; Kemp et al., 2010; May et al., 2011; Schroeder et al., 2003). A population-based study (Felber et al., 2006) provided normal values for long-term HRV measurements, however, since that study was published there is increasing interest in use of short-term measures. The sample was also unbalanced between sexes (329 women and 170 men) and included a restricted age-range of participants (50-72 years). Recently, another study (Sammito & Böckelmann, 2016) in a sample of 695 individuals (aged 20-60 years old) reported reference values for time and frequency domain HRV from 24h records. Yet methodological problems involving data pre-processing and analysis were detected (Bauer et al., 2017) leading to a report on new values (Sammito & Böckelmann, 2017). However, this report is based on longer (24-hour) ECG records, highlighting a continued need for short-term HRV reference values.

Therefore, the aim of the present study was to establish reference values for the most used linear indices of short-term HRV collected under standardised and resting-state condition while participants were in the supine position. Values were derived from a robust sample of adults (35-74 years) included in the Longitudinal Study of Adult Health (ELSA-Brasil study). Data were obtained from short-term electrocardiographic (ECG) recordings in healthy participants who were medication free allowing for future unbiased comparisons with patients from a variety of clinical conditions. Given the importance of the HRV metric as well as the increasing interest in short-term measures HRV, it is critical that standardized indices from large and representative populations are available.

Method

Design, participants and procedures

This study reports on baseline data from the ELSA-Brasil study collected between 2008 and 2010. A sample of 15,105 civil servants from five public universities and one research institute from three Brazilian regions (Northeast, Southeast, and South) were included. The Ethics Committees of each institution approved the research protocol and all participants, aged 35–74 years, active or retired, signed written consent before participation. Questionnaires were administered by trained interviewers, and clinical and laboratory exams were carried out during a scheduled visit to one of the six investigation centres. Personal data, demographic characteristics, and all medications under regular use were recorded during the interview. Venous blood samples, anthropometric (body weight and stature) and hemodynamic data (blood pressure) were collected by trained technicians. Blood pressure (BP) was recorded in the morning period, in fasting conditions, and all were instructed to avoid consumption of coffee, cigarettes, and alcoholic beverages, as well as not to exercise on the day before the exams. BP was recorded at rest in the left arm in the sitting position. Measurements were performed using a validated oscillometric device (Omron HEM 705CPINT). Three measures were taken at one-minute intervals and the arithmetic mean of the two last readings was used to determine the values of systolic, diastolic and mean BP. Biochemical analysis of blood

and urine were performed in a central laboratory using commercially available kits (Aquino et al., 2012).

Reference values for HRV were generated from a subsample of healthy participants with a validated ECG recording. The following exclusion criteria were used: a) current or recent (<4 months) pregnancy; b) use of any medication (N=8,892), except oral contraceptives and vitamins; c) self-report of previous cardiovascular or cerebrovascular disease or cardiac surgery (myocardial infarction, N=278; stroke, N=201), including vascular stents (N=268); d) presence of obesity (body mass index ≥ 30 kg/m^2, N=3,464), diabetes (fasting glycaemia ≥ 126 mg/dL, N=2,970), hypertension (blood pressure ≥ 140/90 mmHg, N=5,363), or chronic kidney disease (creatinine ≥ 1.4 mg/dL for men, N=341; and ≥ 1.2 mg/dL for women, N=130); and e) Common mental disorders (CMD, determined by Clinical Interview Schedule-Revised (CIS-R, (Lewis, Pelosi, Araya, & Dunn, 1992)), in which a score ≥ 12 indicated a current CMD (last week), N=4,036). After exclusions, 2,874 apparently healthy participants were available for analysis on which reference HRV indices were determined (figure 1).

ECG records and HRV analysis

A 10-minute continuous ECG recording was carried out on all participants (sampling rate of 250 Hz, Micromed, Brazil). Participants were in the supine position in a quiet and temperature-controlled room (20 – 24°C) while the ECG recording was obtained from a lead with the highest R wave amplitude (usually Lead 2). A computer program (WinCardio 4.4) generated the time series of R-R intervals, which were sent to a central cardiovascular physiology laboratory for further analyses (Mill et al., 2013).

The R–R series were automatically pre-processed to remove ectopic beats and artefacts. Linear interpolation was used to replace removed beats, in accordance with the following criteria: each R–R interval was compared to a reference called R–R$_{average}$. The R–R$_{average}$ was calculated as the

average of the last 10 normal R–R intervals. R–R intervals smaller than 80% of the $RR_{average}$, or greater than 120% of the $R–R_{average}$, were considered as ectopic beats and were removed from the R–R series. These beats were replaced by linear interpolation. If R–R series were changed by more than 20%, they were excluded from analyses (Dantas et al., 2012; Dantas et al., 2015). According to this criterion, 3.8% of the ECG records were invalid and excluded from HRV analysis.

Short-term HRV analyses were carried out on validated and artefact-free R-R series in the time and frequency domain using Matlab-customized software (Dantas et al., 2015). For this purpose, 5-minute segments were extracted from each 10 min R-R series. Based on criteria of greater stability, a standardised 5-minute segment of data was analysed from 2 minutes and 30 seconds until 7 minutes and 30 seconds. Each segment was pre-processed aiming to remove trends, subtracting the values of a linear regression function from the R-R series. Time domain analyses consisted of the mean and variance of all normal-to-normal intervals (NN), the standard deviation of all NN intervals (SDNN), the percentage of successive R–R intervals differing by more than 50 ms (pNN50), where NN50 is the number of pairs of adjacent NN intervals differing by more than 50 ms, and the square root of the mean of the sum of the squares of differences between adjacent NN intervals (RMSSD) (Task Force, 1996). Frequency domain analyses were performed by autoregressive (AR) modelling and Fast Fourier Transform (FFT). The AR model was estimated using the Yule Walker algorithm, using a constant model order set as 16 (Dantas et al., 2015; Dantas et al., 2012). For FFT analysis, the R-R series were resampled in the time at a sampling rate of 4Hz and the frequency spectrum was divided into 1024 points (Task Force, 1996). The very low frequency (VLF, 0–0.04 Hz), low frequency (LF, 0.04–0.15 Hz), and high frequency (HF, 0.15–0.40 Hz) were expressed in absolute values and in normalized units. Normalization was performed dividing the amount of power of each component by total power minus the power of the VLF component (Malliani, Pagani, Lombardi, & Cerutti, 1991; Task Force, 1996). The LF/HF ratio was also calculated.

Statistical analysis

Data normality was evaluated by Shapiro-Wilk test and variance homogeneity by Levene's test. Demographic categorical variables were compared between sexes by chi-square test, and continuous variables by Wilcoxon-Mann-Whitney test. Next, the participants were categorized into four age groups by decades (35-74 years). The mean, standard deviation, and 2.5^{th}, 10^{th}, 25^{th}, 50^{th}, 75^{th}, 90^{th}, and 97.5^{th} percentiles were calculated for each variable. A one-way ANOVA across age groups and a two-way ANOVA (including age and sex factors allowing for the interaction between age and sex to be determined) were carried out on HRV. Post-hoc tests were conducted using Fisher's protected least-significant difference (LSD) method. Quantile regression was used to estimate the percentiles (from 2.5^{th} to 97.5^{th}) of the HRV indices by age, and curves were generated for each HRV variable. In the body of the text, values are shown as mean ± SD. Comparisons were considered significant only when P was < 0.05. All statistics analyses were carried out with Stata 12.0/SE.

Results

Demographic characteristics of the participants (N=2,874) are shown in table 1. As expected, most of the participants were white, with medium to high level of education and non-smokers. In the entire group, 12.9% were current smokers, 23.7% were former smokers, and 63.3% never smoked. The proportion of current smokers were slightly higher in men than in women (14.1 *vs.* 11.4%; P<0.001). Characteristics of the sample are shown in table 2. Except for age and total cholesterol, all the other variables were significantly different between sexes.

Time and frequency domain analyses (table 3 and 4, respectively) show differences in age on most HRV indices, such that HRV was higher in younger than in older groups. However, there were no differences for heart rate, normalized LF, and LF/HF ratio.

Comparing both sexes (supplementary tables S1 and S2), men displayed lower mean heart rate (64 ± 8 bpm vs. 68 ± 8 bpm, P<0.05) and normalized HF (39.4 ± 18.0 n.u. vs. 50.4 ± 18.5 n.u.,

P<0.05) than women, but higher N-N variance (2214 ± 1890 ms^2 vs. 1883 ± 1635 ms^2, P<0.05), SDNN (43.7 ± 17.3 ms vs. 40.3 ± 15.8ms, P<0.05), VLF (1021.4 ± 1033.2 ms^2 vs. 832.1 ± 821.4 ms^2, P<0.05), absolute LF (580.3 ± 608.9 ms^2 vs. 385.6 ± 443.5 ms^2, P<0.05), normalized LF (56.3 ± 19.2 n.u. vs. 43.7 ± 19.0 n.u., P<0.05), and LF/HF ratio (2.30 ± 2.68 vs. 1.33 ± 1.82, P<0.05) in AR analyses. Similar differences between sexes were observed in FFT analyses (supplementary table S4). Considering the interaction between age and sex (supplementary tables S1, S2, and S4), significant differences were observed in heart rate, NN variance, SDNN, VLF (ms^2), LF (ms^2), HF (ms^2), LF (n.u.), HF (n.u.) and LF/HF ratio. NN variance, SDNN, pNN50 and RMSSD, LF (ms^2), HF (ms^2), HF (n.u.) were higher in younger participants of both sexes. Heart rate, HF (ms^2), and HF (n.u.) were higher in younger than older women. LF/HF ratio was lower in women compared to men.

Figures 2 and 3 show the changes of the HRV indices in percentiles as a function of age. It is noteworthy that almost all HRV indices decrease as the age increases in both time and frequency domain. While the LF/HF ratio (figure 2) determined using the AR method tends to decrease slightly (median or percentile 50) over age, LF/HF ratio increases when determined using FFT (supplementary figure S1). This fact occurs because in AR analyses the fall in LF component (absolute and normalized) is higher than that observed in HF component. Thus, the ratio tends to be reduced over age. On the other hand, in FFT analyses the reduction in LF component tends to be less than for the HF component. In fact, normalized LF increases while normalized HF decreases slightly over age, and LF/HF ratio become it higher (supplementary table S4).

Additional analyses were performed by age range and ethnic groups (supplementary tables S5 and S6) and clinical conditions such as hypertension (supplementary tables S7 and S8), and mental disorder (tables S9 and S10). Considering individuals of the same race, younger individuals (35-44 years) showed higher values of N-N variance and SDNN. Differences in between-race comparisons were noticed for time (N-N variance and SDNN) and frequency domain analyses (Ln LF ms^2). Young indigenous showed the highest values of N-N variance and SDNN, while white subjects showed higher values of Ln LFms^2 than brown subjects. Asiatic subjects showed lower Ln LF ms^2 than brown

and white subjects. For hypertensive participants no significant difference was observed among subjects of different age ranges. In participants with mental disorders there was a noticeable effect of age in time domain (N-N variance, SDNN, pNN50, RMSSD) and frequency domain (VLF, absolute LF and HF) indices, in that all were decreased in older subjects.

Finally, the analyses were performed in all individuals of the sample (supplementary tables S11 and S12). The same differences described above for apparently healthy individuals were also kept when were carried out without exclusion, highlighting the extensive impacts of gender and age. Again, most HRV variables in time and frequency domains decreased over age. The LF/HF ratio increased with age in both women and men, although in the older age-range values were lower in men.

Discussion

Although the need for HRV reference values in large population studies was identified many years ago by the Task Force of the European Society of Cardiology and the North American Society for Pacing and Electrophysiology (Task Force, 1996), few studies have addressed this need in relation to short-term HRV indices. Considering the broad interest in HRV spanning fields as diverse as psychological science and epidemiology, the hitherto lack of valid, short-term reference values is surprising. Therefore, our research will provide an important resource to researchers and clinicians as well as those involved in the quantified-self community. Our study also provides an important resource for personalised healthcare planning considering previously reported relationships between HRV and health behaviours, capacity to regulate emotion, cognitive flexibility, social functioning, mental and physical health, and future mortality (Kemp, Arias, & Fisher, 2017; Kemp, Koenig, & Thayer, 2017). To our knowledge, the present study is the first to provide reference values for short-term resting-state HRV measurements in a large, healthy and medication-free sample.

Reference values of HRV presented here were obtained from a large cohort study of the Brazilian population. HRV indices vary greatly among subjects as we demonstrate here. Autonomic

modulation is age-related: a major age-related change occurs primarily as a reduction in vagal modulation, while sympathetic modulation decreases at a slower rate (Antelmi et al., 2004; Lipsitz, Mietus, Moody, & Goldberger, 1990). Results of the present work are consistent with these earlier findings: almost all HRV variables were shown to decrease with age. Moreover, when the analyses were performed by sex, it was noticed that men show higher variance (mathematically equal to total power), LF (absolute and normalized), and lower HF (mainly the normalized) than women. Identic results were previously reported (Koenig et al., 2016). The possibility that the values established in this study are consistent with healthy individuals from other regions, such as North America, Europe or Asia cannot be dismissed, and we eagerly await for the publication of reference values from other large cohort studies around the world. However, it is important to reinforce the fact that many variables may impact on such comparisons.

Take for example ethnic factors, which exert considerable effects on HRV, as we have demonstrated previously (Kemp et al., 2016a). We have demonstrated previously that 'Black' and 'Brown' individuals display higher HRV than 'Whites', findings similar to those reported from North American samples (Hill et al., 2015). Extending beyond between-group differences, we further hypothesised (Kemp et al., 2016a) that black individuals may suffer repeated experience of discrimination, and that this discrimination might mediate the relationship between race and HRV, and this hypothesis was supported. We concluded that higher HRV in 'Blacks' and 'Browns' may reflect a sustained compensatory psychophysiological response to the adverse effects of discrimination.

While chronic reductions in a broad range of HRV indices in comparison to healthy controls – reference values for which we present here – are usually considered to reflect ill-health, there has been controversy over the interpretation of the LF component. Historically, the LF component has been considered as a marker of sympathetic nervous system function (Malliani et al., 1991; Montano et al., 1994; Rimoldi et al., 1990), especially when it has evaluated in normalized units, while others interpreted it as an unspecific index of sympathetic and parasympathetic activity (Berntson et al.,

1997; Task Force, 1996; Akselrod et al., 1981). More recently, others have argued that this component – as with other HRV indices – predominantly reflects parasympathetic nervous system activity (Reyes del Paso et al., 2013). We have provided reference values for both these variables as new insights may emerge in future work.

Our study has a number of strengths. First, our study provides reference values for males and females in a large sample of participants, once all potential confounding was addressed. Participants were removed from analysis if they presented with hypertension (Schroeder et al., 2003), diabetes (May et al., 2011), coronary heart disease and myocardial infarction (Buccelletti et al., 2009), obesity (Karason, Molgaard, Wikstrand, & Sjostrom, 1999), kidney disease (Furuland, Linde, Englund, & Wikstrom, 2008) and stroke (Graff et al., 2013) . Participants on medications including angiotensin converting enzyme inhibitors, antiarrhythmics, beta blockers, diuretics and sympathetic agonists (Felber et al., 2006), antidepressants (Kemp et al., 2010; Kemp et al., 2014), were also excluded from the present analysis. Therefore, analyses were conducted on a robust sample of healthy adults allowing for reference values by sex and age across four decades to be determined.

Second, we provide reference values based on two different methods, the FFT and the AR model, as described in international guidelines (Task Force, 1996). While FFT has been widely used due to algorithmic simplicity, the AR method has smoother spectral components and provides a more precise estimation of power spectral density even when short records are used (Task Force, 1996). Although there is a need to verify the complexity of the chosen model (that is, the order of the model), there is evidence (Dantas et al., 2012) demonstrating that model orders from 9 to 25 produce similar results. According to Taskforce (1996), results of FFT analyses are comparable to those of AR (Task Force, 1996), although more recent work is characterised by disagreement in adult populations (Silva et al., 2009) and even in 5-month-old infants (Poliakova et al., 2014). There are some possible explanations for these discrepancies including pre-processing steps, such as interpolation and detrending, as well as the processing itself. Firstly, according to a previous study (Poliakova et al., 2014), AR modelling is based on use of the most significant peaks, whereas FFT

tends to include all the components within a frequency band, and therefore, the tails of neighbouring components might be assigned into different bands by the FFT and AR approach. Moreover, discriminative capacity of FFT has been shown to be directly proportional to the record duration (Poliakova et al., 2014; Task Force, 1996). Thus, the AR method may provide a better resolution when short data frames are used (Kay & Marple, 1981; Poliakova et al., 2014; Task Force, 1996), and this may explain the small differences that we observed here between AR and FFT results.

Our study also has a number of limitations. First, the ECG evaluations on our participants were performed by using a digital electrocardiograph with 250 Hz of sampling rate. When the study was started in 2008, the technical specification of the used device was based on recommendations of international guidelines (Task Force, 1996). Although devices with higher sampling rates (> 1000 Hz) are available today, data from recent studies (Ellis, Zhu, Koenig, Thayer, & Wang, 2015; Mahdiani, Jeyhani, Peltokangas, & Vehkaoja, 2015) have shown that electrocardiographs with lower sampling rate (<100 Hz) might even be used without affecting HRV indices significantly. Second, we did not collect data on respiration rate or tidal volume, which may influence estimates of HRV. Thus, if we had performed the breathing control, spectral results, mainly the HF power (Driscoll & Dicicco, 2000), could have been quite different to those shown here. Nevertheless, we suggest that spontaneous respiration conditions are more comparable to clinical settings. Therefore, the reference values generated in our study are likely to be similar to those obtained in the clinical settings allowing better comparison with patient groups. We further note that the root mean square of successive differences, unlike frequency- based measures, may actually be more robust to changes in breathing patterns (Penttilä et al., 2001). Finally, the present work focuses on linear HRV indices only. Therefore, it will be necessary to describe non-harmonic and nonlinear components in future work once the underlying mechanisms are better understood.

In conclusion, we provide – for the first time – reference values along with percentile curves for major short-term resting-state HRV indices across age and sex in a large, healthy, and medication-free population allowing for unbiased comparisons in future work. These data provide a foundation

for reliable interpretation of HRV collected in research and clinical settings, and may also be of interest to those in the quantified-self community. There is now a need for longitudinal population-based studies to identify HRV thresholds for different age-groups beyond which adverse downstream psychological and physiological may arise.

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Conflicts of interest

None declared.

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Table 1 – Demographic characteristics of the participants

	All (N)	Men (N)	Women (N)	Pearson chi-square	P
Age range (years)					
35-44	982	593 (35.3%)	389 (32.6%)		
45-54	1,252	719 (42.8%)	533 (44.6%)	2.78	0.43
55-64	536	305 (18.2%)	231 (19.3%)		
65-74	104	63 (3.7%)	41 (3.4%)		
Race/ethnicity					
Black	381	213 (12.8%)	168 (14.3%)		
Brown	859	523 (31.5%)	336 (28.6%)		
White	1,491	871 (52.5%)	620 (52.7%)	14.72	0.005
Asiatic	82	35 (2.1%)	47 (4.0%)		
Indigenous	22	17 (1.0%)	5 (0.43%)		
Education level					
<8 years	122	102 (6.1%)	20 (1.7%)	55.22	<0.001
8-11 years	1,140	699 (41.6%)	441 (36.9%)		
≥12 years	1,612	879 (52.3%)	733 (61.4%)		
Smoking status					
Current	371	237 (14.1%)	134 (11.2%)		
Past	683	441 (26.2%)	242 (20.2%)	23.67	<0.001
Never	1,820	1,002 (59.6%)	818 (68.5%)		

Comparisons were performed with chi-square test.

Table 2- Characteristics of the participants

	All (N=2,871)	Men (N=1,680)	Women (N=1,191)	P
Age (years old)	47 (11)	47 (10)	47 (11)	0.2508
Height (cm)	167.3 (14.1)	172.6 (9.6)	159.3 (8.3)	< 0.0001
Body weight (kg)	68.7 (16.2)	74.1 (13.6)	61.15 (12.05)	< 0.0001
Body mass index (kg/m²)	24.6 (4.1)	25.0 (3.9)	24.1 (4.4)	< 0.0001
Waist circumference (cm)	85.7 (13.7)	89.5 (11.5)	80.4 (11.8)	< 0.0001
Systolic blood pressure (mmHg)	115 (17)	119 (16)	109 (16)	< 0.0001
Diastolic blood pressure (mmHg)	72 (13)	75 (12)	69 (11)	< 0.0001
Glycaemia (mg/dL)	102 (12)	104 (11)	100 (11)	< 0.0001
Creatinine (mg/dL)	0.90 (0.30)	1.00 (0.20)	0.80 (0.20)	< 0.0001
Total cholesterol (mg/dL)	211 (52)	210 (51)	212 (52)	0.3381
HDL (mg/dL)	54 (18)	50 (15)	61 (19)	< 0.0001
LDL (mg/dL)	130 (42)	132 (41)	128 (43)	0.0089
Triglycerides (mg/dL)	101 (74)	115 (85)	86 (55)	< 0.0001

Values are median and interquartile range (75-25). Comparisons between sexes were performed by Wilcoxon-Mann-Whitney test.

Table 3 - Time domain analysis

	Age range (years)	N	P ANOVA	Mean	SD	Percentiles 2.5	10	25	50	75	90	97.5
Heart rate (bpm)	35-44	982	0.2429	66	9	50	54	60	66	72	77	86
	45-54	1252		65	8	51	55	60	65	71	76	83
	55-64	536		65	8	51	56	60	65	70	75	82
	65-74	104		65	9	46	55	59	64	72	78	85
N-N Variance (ms^2)	35-44	982	0.0000	2378	1931	439	727	1145	1844	2966	4841	7484
	45-54	1252		1995 **	1644	360	544	882	1471	2583	4036	6685
	55-64	536		1769 **	1748	223	480	759	1249	2120	3435	7142
	65-74	104		1804 **	2046	221	380	619	1062	2031	4536	9101
SDNN (ms)	35-44	982	0.0000	45.7	17.0	21.0	27.0	33.8	42.9	54.5	69.6	86.5
	45-54	1252		41.6 **	16.2	19.0	23.3	29.7	38.3	50.8	63.5	81.8
	55-64	536		38.7 **	16.5	14.9	21.9	27.6	35.3	46.0	58.6	84.5
	65-74	104		37.9 **	19.2	14.9	19.5	24.9	32.6	45.1	67.3	95.4
pNN50 (%)	35-44	982	0.0000	14.0	15.4	0.0	0.4	2.2	8.0	20.6	37.2	55.1
	45-54	1252		10.0 **	12.9	0.0	0.0	0.9	4.7	14.1	28.4	47.1
	55-64	536		7.2 **	11.1	0.0	0.0	0.6	2.7	8.4	21.3	40.4
	65-74	104		7.3 **	13.2	0.0	0.0	0.3	1.7	8.9	21.9	60.6
RMSSD (ms)	35-44	982	0.0000	34.9	17.5	12.1	17.0	23.1	31.0	42.4	58.4	81.2
	45-54	1252		30.0 **	15.6	10.0	13.8	19.1	26.6	37.1	50.2	69.4
	55-64	536		26.7 **	15.3	9.5	12.6	17.5	23.1	31.9	44.0	67.5
	65-74	104		27.7 **	23.6	7.4	10.3	15.0	21.1	31.6	48.8	115.7

Comparisons between means performed by one-way ANOVA followed by Fisher's LSD multiple comparisons. Significant differences against 35-44 age range: ** - P<0.01.

Table 4 – Autoregressive frequency domain analysis

	Age range (years)	N	P ANOVA	Mean	SD	Percentiles 2.5	10	25	50	75	90	97.5
VLF (ms^2)	35-44	982	0.0326	1009.2	934.8	108.5	247.1	397.4	731.5	1258.5	2168.7	3654.4
	45-54	1252		920.5 *	936.5	113.4	207.6	346.8	642.3	1153.3	1986.3	3367.3
	55-64	536		900.8 *	1051.1	83.6	180.7	346.6	615.7	1115.8	1900.3	3375.9
	65-74	104		800.9 *	819.3	100.7	151.5	275.1	580.9	1024.3	1557.8	4201.8
LF (ms^2)	35-44	982	0.0000	594.8	582.3	52.2	121.3	222.8	423.8	738.5	1255.2	2194.8
	45-54	1252		487.7 **	538.7	36.7	83.5	153.1	311.3	593.8	1080.3	2069.6
	55-64	536		387.1 **	525.5	21.5	54.5	111.8	216.1	429.5	926.2	1733.3
	65-74	104		319.8 **	452.2	7.9	34.2	89.4	164.3	318.3	726.0	2314.3
HF (ms^2)	35-44	982	0.0000	575.5	667.6	41.4	94.0	182.7	343.6	700.4	1328.5	2637.4
	45-54	1252		410.8 **	491.6	23.7	61.1	117.3	257.5	495.7	930.5	1823.6
	55-64	536		325.9 **	487.3	27.3	54.7	103.5	201.1	373.0	673.8	1510.3
	65-74	104		383.3 **	684.2	13.3	35.8	67.8	149.6	358.5	949.1	3439.6
LF (n.u.)	35-44	982	0.0106	50.8	19.9	13.7	25.3	35.1	50.7	66.0	76.6	86.8
	45-54	1252		52.3	20.3	13.5	23.7	37.4	53.3	68.0	78.6	87.7
	55-64	536		49.6	20.0	13.1	23.1	33.9	49.4	65.0	75.9	86.4
	65-74	104		47.5	21.8	8.2	17.8	31.4	46.4	64.3	78.6	90.3
HF (n.u.)	35-44	982	0.0482	45.1	19.2	10.1	20.3	30.3	44.9	60.3	70.7	80.9
	45-54	1252		42.9 **	19.2	10.0	18.1	28.2	41.9	57.0	70.4	80.6
	55-64	536		44.3	18.0	11.7	20.9	30.1	43.9	58.2	67.9	79.6
	65-74	104		45.1	20.3	8.1	17.6	28.0	46.1	60.8	72.3	81.2
LF/HF	35-44	982	0.1685	1.86	2.42	0.17	0.37	0.58	1.12	2.17	3.74	8.13
	45-54	1252		2.01	2.48	0.18	0.35	0.66	1.24	2.40	4.23	8.66
	55-64	536		1.74	2.18	0.19	0.34	0.59	1.08	2.09	3.48	7.39
	65-74	104		1.91	2.60	0.14	0.28	0.52	1.03	2.39	4.46	11.73
Ln LF (ms^2)	35-44	982	0.0000	5.99	0.94	3.96	4.80	5.41	6.05	6.60	7.14	7.69
	45-54	1252		5.71 **	1.05	3.61	4.43	5.04	5.74	6.39	6.99	7.64
	55-64	536		5.38 **	1.10	3.07	4.00	4.72	5.38	6.06	6.83	7.46
	65-74	104		5.11 **	1.26	2.01	3.53	4.49	5.10	5.76	6.58	7.74
Ln HF (ms^2)	35-44	982	0.0000	5.86	1.03	3.72	4.54	5.21	5.84	6.55	7.19	7.88
	45-54	1252		5.48 **	1.08	3.17	4.12	4.77	5.55	6.20	6.84	7.51
	55-64	536		5.27 **	1.02	3.31	4.00	4.64	5.30	5.92	6.51	7.32
	65-74	104		5.07 **	1.29	2.58	3.58	4.22	5.01	5.88	6.85	8.14

Comparisons between means performed by one-way ANOVA followed by Fisher's LSD multiple comparisons. Significant differences against 35-44 age range: * - P<0.05. ** - P<0.01.

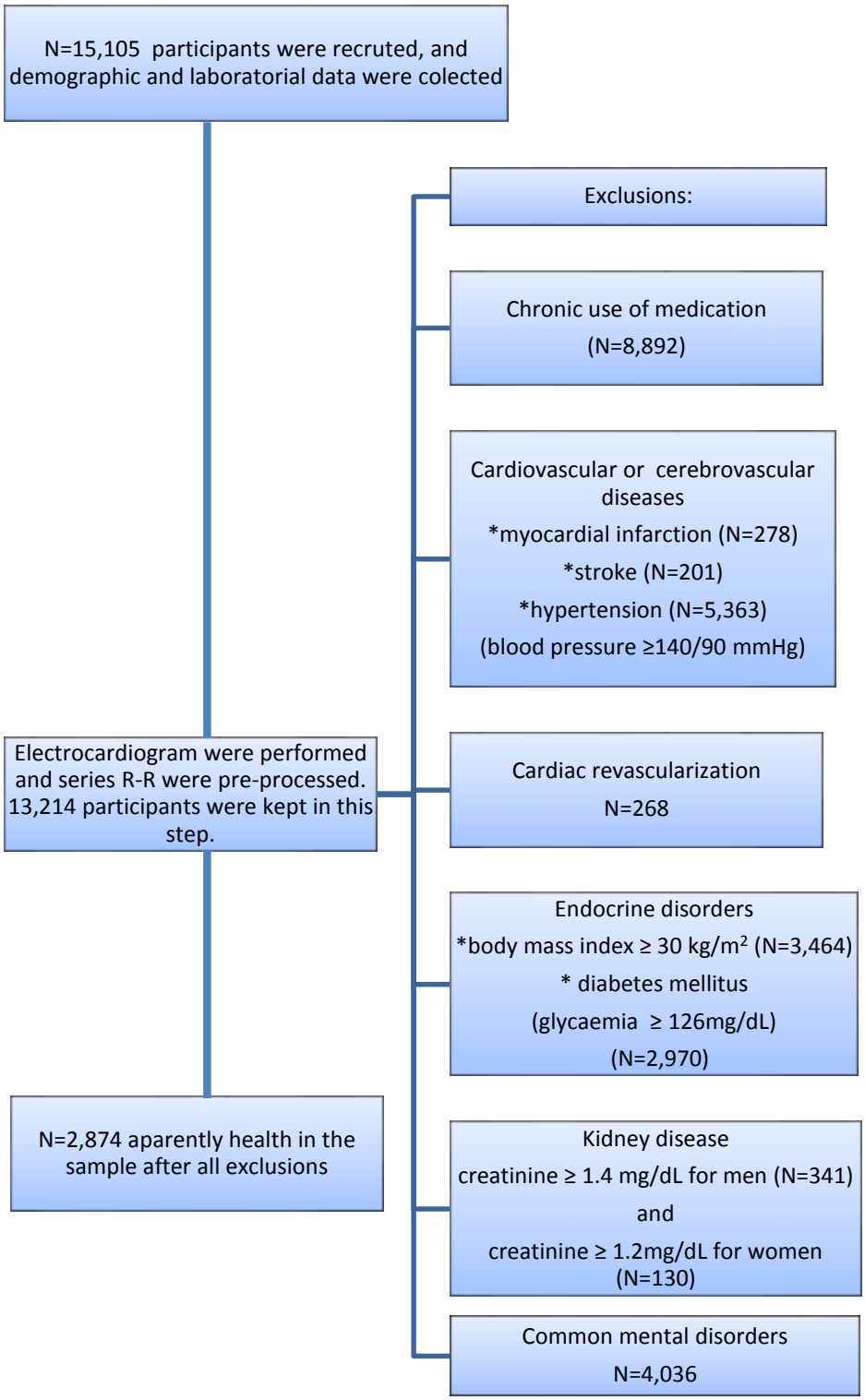

Figure 1. Exclusion criteria the sample.

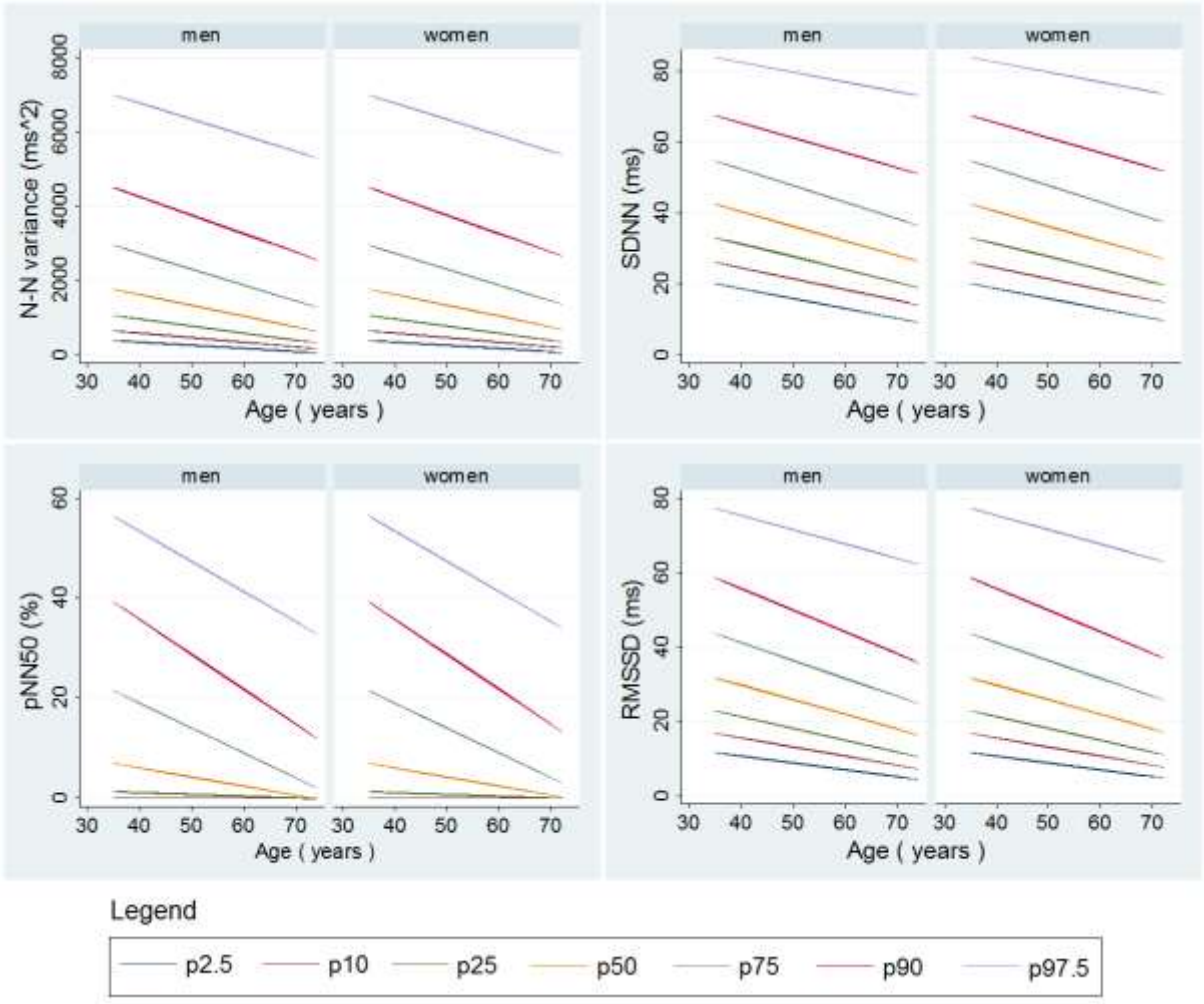

Figure 2. Percentile curves of time domain HRV indices by sex in function of age. N=2,874.

Reference values for heart rate variability indices

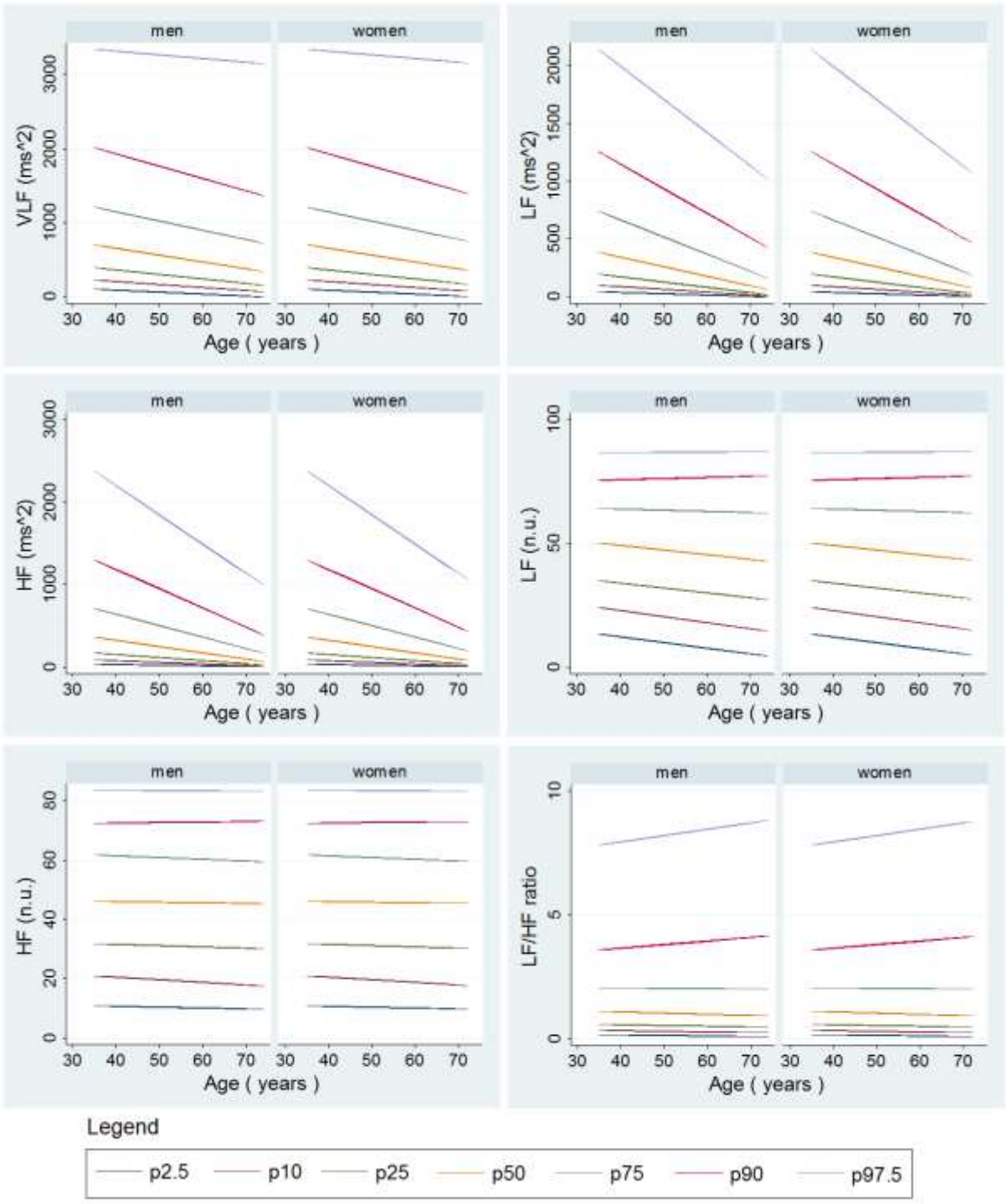

Figure 3. Percentile curves of frequency domain HRV indices by sex in function of age. N=2,874.

Indices were determined by AR method.