Metabolic syndrome is associated with decreased heart rate variability in a sex-dependent manner: a comparison between 252 men and 249 women

Short title: Heart rate variability in metabolic syndrome

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Summary

Impaired heart rate variability (HRV) is associated with increased risk of cardiovascular disease, but evidence regarding alterations of HRV in metabolic syndrome (MetS) remains elusive. In order to examine HRV in MetS, we subjected 501 volunteers without atherosclerosis, diabetes, or antihypertensive medication, mean age 48 years, to passive head-up tilt. The subjects were divided to control men (n=131), men with MetS (n=121), control women (n=191), and women with MetS (n=58) according to the criteria by Alberti et al. 2009. In unadjusted analyses 1) men and women with MetS had lower total power and high frequency (HF) power of HRV than controls whether supine or upright ($p < 0.05$ for all). 2) Supine low frequency (LF) power of HRV was lower in men ($p = 0.012$) but not in women ($p = 0.064$) with MetS than in controls, while men and women with MetS had lower upright LF power of HRV than controls ($p < 0.01$ for both). 3) The LF:HF ratio did not differ between subjects with and without MetS. After adjustment for age, smoking habits, alcohol intake, height, heart rate, and breathing frequency, only the differences in upright total power and HF power of HRV between women with MetS and control women remained significant ($p < 0.05$). In conclusion, reduced total and HF power of HRV in the upright position may partially explain why the relative increase in cardiovascular risk associated with MetS is greater in women than in men. Additionally, the present results emphasize that the confounding factors must be carefully taken into consideration when evaluating HRV.

Keywords: cardiac autonomic tone, heart rate variability, head-up tilt, sex, cardiovascular risk

Introduction

Metabolic syndrome (MetS), a disorder characterized by a cluster of unfavourable changes in lipid profile, blood pressure, glucose metabolism, and waist circumference is very common, especially in the Western countries. MetS is related to an increased risk of diabetes and cardiovascular disease (CVD) (Alberti *et al.*, 2009), while CVDs are the most important factor causing mortality worldwide (Mendis S, 2011). Consequently, MetS has been under active investigation during the last decades. However, the mechanisms linking MetS with increased risk of CVD are still incompletely understood (Mottillo *et al.*, 2010).

Imbalance in the autonomic nervous system with sympathetic overdrive has been linked with MetS (Grassi, 2006). An applicable, non-invasive method for the evaluation of cardiac autonomic tone is the measurement of heart rate variability (HRV). Decreased vagal activity, as indicated by HRV, has been shown to predict mortality in both high risk and low risk populations (Thayer *et al.*, 2010; Wulsin *et al.*, 2015). According to a recent systematic review (Stuckey *et al.*, 2014), numerous cross-sectional studies have revealed impaired cardiac autonomic function associated with MetS. Furthermore, a longitudinal study showed that low HRV increased the odds of developing MetS during 12 years of follow-up (Wulsin *et al.*, 2016).

In previous studies, MetS was associated with lower indices of HRV, but the results have not been consistent (Stuckey *et al.*, 2014). In many reports, the changes of cardiac autonomic tone in MetS seemed to be more pronounced in women than in men (Koskinen *et al.*, 2009; Stuckey et al., 2014; Stuckey *et al.*, 2015). Several

studies suggested that the association of MetS with cardiovascular end-points is also stronger in women than in men (Hunt *et al.*, 2004; Schillaci *et al.*, 2006). This raises the question whether the sex-related differences in autonomic tone in MetS could play a role to explain these differences.

In addition to various medical conditions, also age (Bonnemeier *et al.*, 2003), sex (Koenig & Thayer, 2016), heart rate (HR) (Billman, 2013a; Sacha, 2014), circadian rhythm (Bonnemeier et al., 2003), and breathing frequency (Stolarz *et al.*, 2003; Billman, 2011) can influence HRV. In many studies evaluating HRV in MetS these factors were somewhat neglected, and this may explain some of the discrepancies in the published results (Stuckey et al., 2014). According to a review published in 2014 (Stuckey et al., 2014), only three reports had separated the analyses by sex, while only one study in young adults had adjusted the HRV results for HR (Koskinen et al., 2009), although increased HR is characteristic of subjects with MetS (Mancia *et al.*, 2007). To our knowledge, no HR adjusted results of HRV in MetS have been published thereafter.

Importantly, many antihypertensive medications like beta-blockers (Vaile *et al.*, 1999), calcium channel blockers (Karas *et al.*, 2005), angiotensin receptor blockers (Karas et al., 2005; Okano *et al.*, 2009) and angiotensin-converting enzyme inhibitors (Karas et al., 2005) can influence HRV. Hypertension is very common in MetS, and in many studies evaluating HRV in MetS, subjects with antihypertensive medication were included (Stuckey et al., 2014), and this has probably also contributed the discrepancy in the published results.

In the current study, we examined changes in HRV associated with MetS separately in men and women. None of the subjects used antihypertensive agents or other

medications with direct cardiovascular influences, and the differences of HR and breathing frequency were also taken into account. As upright position is characterised by differences in the haemodynamic responses between men and women (Kangas *et al.*, 2016), we examined HRV during supine and upright positions.

Methods

Study subjects

This study is part of an ongoing investigation of haemodynamics in the University of Tampere (DYNAMIC-study, ClinicalTrials.gov identifier NCT01742702). The recruiting of participants and the data collection have been previously described (Kangas et al., 2016). The population of the current study was screened from 1091 subjects. The exclusion criteria were diagnosed atherosclerosis, cardiac insufficiency or cerebrovascular disease, diabetes, and use of antihypertensive drugs or other medications having influences on haemodynamics (like β-blocker eye drops for glaucoma, $β_2$-adrenoceptor agonists, $α_1$-adrenoceptor blockers for prostate problems, and digoxin). After the exclusion process, 501 subjects aged 19-72 years were eligible for the study population. Clinical cardiovascular status was examined, lifestyle habits, medical history, family history, and use of medicines were recorded, and laboratory tests were taken before the haemodynamic recordings.

For the definition of MetS, the criteria of Alberti et al. from 2009 (Alberti et al., 2009) were used, so that three or more of the following criteria were met: waist circumference ≥ 94 cm (men) and ≥ 80 cm (women); high density lipoprotein cholesterol (HDL-C) <1.0 mmol/l (men) and <1.3 mmol/l (women); triglycerides ≥ 1.7

mmol/l; fasting plasma glucose ≥ 5.6 mmol/l; systolic BP ≥ 130 mmHg and/or diastolic BP ≥ 85 mmHg. The study subjects were allocated to 4 groups: men without MetS (M-control, n=131), men with MetS (M-MetS, n=121), women without MetS (W-control, n=191), and women with MetS (W-MetS, n=58).

Although none of the subjects used antihypertensive agents, medications not affecting haemodynamics were allowed. Altogether 186 subjects (37%) used some medication. Thirteen had statins for dyslipidemia, 77 female participants (31%) used systemic female hormones (hormone replacement therapy or contraception). In the use of female hormones, no difference was found between W-control and W-MetS groups (p=0.761). Additionally, some other drugs (e.g. antihistamines, thyroid hormones, proton pump inhibitors, acetylsalicylic acid, selective serotonin re-uptake inhibitors, and intranasal or inhaled corticosteroids) were used by the participants. One subject had anti-phospholipid syndrome without any symptoms or findings, and he was receiving warfarin.

Measuring heart rate variability during passive head up tilt test

The participants were instructed to refrain from smoking, caffeine containing products and heavy meals for ≥ 4 hours, and from alcohol for ≥ 24 hours prior to the recordings. The recordings were performed in a temperature-controlled laboratory by a trained research nurse during two consecutive 5-minute periods with continuous capture of data: 5 minutes of supine recordings followed by 5 minutes of passive head-up tilt to >60°. The actual recordings were preceded by an introductory head-up tilt. The HRV values of the last three minutes of the supine and the upright periods were used in the analyses, since the signal of these periods was most stable

(Tikkakoski *et al.*, 2013). Continuous radial tonometric blood pressure values were recorded during the measurements, and the average systolic and diastolic values of the last supine three minutes were used for the definition of MetS. The detailed description of the measurement protocol has been previously published (Kangas *et al.*, 2013; Koskela *et al.*, 2013).

For assessing cardiac autonomic tone, HRV analysis from a single channel electrocardiogram (ECG) was used. The ECG was recorded by the CircMon[R] device (CircMon; JR Medical Ltd) with 200 Hz sampling rate, and Matlab software (MathWorks Inc., Natick, Massachusetts, USA) was used for data analyses. Normal R-R intervals were recognized, and if the interval differed more than 20% from the previous values, the beat was considered ectopic. The processing of artefacts was performed using the cubic spline interpolation method (Peltola, 2012). Since the data was collected from short-term recordings, the frequency domain method was applied (1996). The following HRV variables were calculated using the Fast Fourier transformation: (1) total power, (2) power in the low-frequency (LF) range (0.04-0.15 Hz), (3) power in the high-frequency (HF) range (0.15-0.40 Hz), and (4) LF:HF ratio. The recordings were performed in both supine and upright positions. Breathing frequency was captured from the CircMon[R] data, the focus being on the last three minutes of the supine and upright phases of recording.

Laboratory tests

Blood samples were obtained after ~12 hours of fasting, and plasma total cholesterol, HDL-C and low-density lipoprotein cholesterol (LDL-C), triglycerides, glucose,

creatinine, and cystatin C were determined using the Cobas Integra 700/800 or Cobas 6000 (Roche Diagnostics, Basel, Swizerland), and insulin using electrochemiluminescence immunoassay (Cobas e 422, Roche Diagnostics). A standard 12-lead electrocardiogram was recorded and Cornell voltage QRS duration product was calculated for evaluating left ventricular mass ((ESC), 2007). Insulin sensitivity was estimated using the Quantitative insulin sensitivity check index (QUICKI) (Katz *et al.*, 2000). Estimated glomerulus filtration rate (eGFR) was calculated using the CKD-EPI formula (Inker *et al.*, 2012).

Statistical analyses

The skewed distributions of total power, LF power, HF power, LF:HF ratio, and triglycerides were logarithmically transformed before the statistical analyses. The original values of the HRV variables are represented in the figures. The statistical analyses were performed separately in men and women. In the comparisons of HRV variables and the characteristics between control and MetS groups, the independent samples of *t*-test was used. Pearson chi-square test was applied to compare smoking habits (current, previous, never) and the use of female hormones between the study groups, while Mann-Whitney U-test was used for the comparisons of alcohol intake due to its skewed distribution.

To assess the influence of different confounding factors on the HRV results, three separate models of adjustment were crafted. The results adjusted for 1) age, smoking (current smoking amount), alcohol intake, and height; 2) model 1 plus HR(Billman, 2013a; Sacha, 2013; Monfredi *et al.*, 2014); 3) model 2 plus breathing

frequency (Brown *et al.*, 1993; Billman, 2013b). In the adjusted analyses, analysis of covariance (ANCOVA) was used with the above variables as covariates.

HRV data was captured from all 501 participants. However, some of the additional data were missing: Information about alcohol intake was missing from 14, and about smoking from 5 subjects. LDL-C value was missing from 4, and ECG from 1 subject. QUICKI could not be calculate from 47 participants. Due to technical problems, breathing frequency was not obtained from 77 subjects in the supine position, and from 76 subjects in the upright position. Altogether 482 (96%) subjects were included in the adjusted models 1 and 2, while 407-408 (81%) subjects were included in the adjusted model 3.

All testing was 2-sided, and the results in the table were reported as means and standard deviations for normally distributed variables, and medians and lower and upper quartiles for variables with skewed distribution. For categorical variables, numbers of cases and percentages are shown. P-values < 0.05 were considered significant. The statistical analyses were performed using IBM SPSS Statistics (software version 24, Armonk, New York, USA).

Results

Study population

The characteristics of the study participants are presented in Table 1. The MetS and the control groups did not differ in age or in alcohol use (p > 0.1 for all). In women, the proportion of previous smokers was higher in the MetS group than in the control

group (p=0.047), but the proportions of current smokers were similar in the MetS and control groups, in both women and men (p > 0.1). As expected, female and male subjects with MetS had higher systolic and diastolic blood pressure, BMI, and waist circumference; and higher fasting plasma glucose, total cholesterol, triglycerides, LDL-C (p < 0.001 for all), and lower HDL-C and QUICKI (p < 0.001 for all) than the control subjects. Creatinine was higher in the W-control group than in the W-MetS group (p=0.004), but eGFR did not differ between the W-MetS and the W-control groups, or between the M-MetS and the M-control groups (p > 0.1 for both). Both women and men with MetS had higher Cornell voltage product in ECG than controls (p < 0.05).

HRV in supine and upright positions

Unadjusted supine analyses: Supine total power (Figure 1A) and HF power (Figure 1B) of HRV were lower in the MetS groups than in the control groups (p < 0.05 for analyses in men and in women). The M-MetS group had lower supine LF power (Figure 2A) than the M-control group (p = 0.012), while in women supine LF power did not differ between the two groups (p = 0.064). The supine LF:HF ratio (Figure 2B) did not differ between the MetS and the control groups (p > 0.1).

Unadjusted upright analyses: Upright total power (Figure 1A), HF power (Figure 1B), and LF power (figure 2A) were all different in the comparisons between the M-MetS and the M-control groups, and between the W-MetS and the W-control groups (p < 0.05 for all). The upright LF:HF ratio (Figure 2B) did not differ between the MetS and the control groups (p > 0.1).

When the results were adjusted for the confounding factors, the differences between the MetS and the control groups were not as clear as in the unadjusted analyses. The detailed comparisons with the three models of adjustment with the exact p-values are presented in the Figures 1 and 2. The results of model 1, with adjustments for age, smoking habits, alcohol intake, and height, paralleled well the unadjusted results. In model 2 with additional adjustments for HR, the differences between the MetS and the control groups in supine total power and HF power in women, and supine LF power in men, were no longer significant.

In model 3, where the HRV results were also adjusted for breathing frequency, only the differences in upright total power (Figure 1A), and upright HF power (Figure 1B), between the MetS and the control groups remained statistically significant, and these differences were only found in women ($p < 0.05$ for both). In men, all of the adjusted p-values in model 3 were not significant ($p \geq 0.105$).

Discussion

The present study demonstrates sex-dependent characteristics of cardiac autonomic tone in MetS using the frequency domain analyses of HRV. In HRV indices, the HF component represents cardiac parasympathetic activity (Eckberg, 1997; Cooke *et al.*, 1999; Xhyheri *et al.*, 2012), while the LF component predominantly reflects sympathetic activity, although it contains parasympathetic contributions (Eckberg, 1997; Xhyheri et al., 2012). The interpretation of LF:HF ratio remains somewhat controversial. It has been suggested to represent sympathovagal balance (Task Force of the European Society of Cardiology and the North American Society of

Pacing and Electrophysiology, 1996; Xhyheri et al., 2012), but this interpretation has been criticized, and conclusions should be drawn with caution (Eckberg, 1997; Cooke et al., 1999; Billman, 2013b).

Impaired cardiac autonomic tone is associated with cardiovascular risk (Tsuji *et al.*, 1996; Schuster *et al.*, 2016; Patel *et al.*, 2017) and mortality (Thayer et al., 2010; Wulsin et al., 2015). Several studies have reported changes in the HRV indices in MetS (Stuckey et al., 2014), and disturbances in autonomic nervous tone have been suggested as an important link between MetS and cardiovascular diseases (Grassi, 2006). However, although the HRV indices are known to be affected by multiple factors, aspects like HR, sex, and breathing frequency have been somewhat neglected in many reports evaluating the association between MetS and HRV (Stuckey et al., 2014). In the current study we found that MetS was associated with lower total power, HF power, and LF power of HRV in both women and men. These findings are in accordance with previous studies. When the results were adjusted for age, smoking habits, alcohol intake, height, HR, and breathing frequency, the differences between the MetS and the control groups diminished. Even after all adjustments, the total power and HF power, measured in the upright position, were still lower in women with MetS than in control women. Similar results were not found in men.

HR has a significant influence on HRV. Higher HRV represents higher parasympathetic nervous system activity, which leads to slower HR (Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Thus, there is a physiological association between HR and HRV indices. In addition, a nonlinear relationship exists between the heart period

(RR interval) and HR, causing a mathematical dependence between HRV and HR (Sacha & Pluta, 2008; Sacha, 2014). Furthermore, the impact of HR on the prognostic value of HRV has been found to differ between sexes: as the HRV indices became more dependent on HR, the predictive power of spectral indices increased for cardiac death in men, whereas the prognostic power of the indices decreased in women (Sacha *et al.*, 2014). Monfredi et al. have concluded that HRV is primarily dependent on HR and it cannot be used in any simple way to assess autonomic nerve activity to the heart (Monfredi et al., 2014). Therefore, all studies concerning HRV should carefully correct for differences in HR before drawing conclusions (Monfredi et al., 2014). In comparisons between sexes, women have presented with greater vagal activity as indexed by the HF power, but higher HR is also characteristic for women (Koenig et al., 2016). Therefore, the relationship between the HRV indices and HR is not straightforward. In the present study, HR was taken into account in the adjusting process, and this clearly influenced the results.

Breathing frequency is another important factor that influences the HRV indices (Stolarz et al., 2003; Billman, 2011). HRV increases when respiratory frequency decreases, while HRV decreases when the tidal volume of ventilation decreases (Brown et al., 1993). Furthermore, mechanical factors that occur during respiration (stretch of the atria that results from changes in thoracic pressure and cardiac filling) influence HRV independent of changes in cardiac autonomic nerve activity (Billman, 2013b). Several studies have shown that slow, paced breathing strengthens vagal activity and modifies HRV (Howorka *et al.*, 2013; Prinsloo *et al.*, 2013; Kromenacker *et al.*, 2018; Li *et al.*, 2018). In the current study, the influence of breathing on the HRV indices was taken into account by adjusting the results for breathing frequency.

The underlying pathophysiology for the association of MetS with impaired HRV is not clear, but some factors have been suggested. Insulin resistance is commonly found in MetS, and several studies have revealed an association of insulin resistance with impaired HRV (Rodriguez-Colon *et al.*, 2010; Hillebrand *et al.*, 2015; Saito *et al.*, 2015). However, a study that examined HRV in subjects with and without MetS and comprised 220 subjects, found that insulin resistance was associated with HR, but not with HRV (Stuckey et al., 2015). Inflammatory markers, like interleukin-6 have been shown to inversely associate with HRV (Brunner *et al.*, 2002; Haensel *et al.*, 2008). Also increased plasma leptin level seems to associate with a shift of the sympathovagal balance toward sympathetic predominance (Paolisso *et al.*, 2000), and this relationship was found to be stronger in women than in men (Flanagan *et al.*, 2007). Both interleukin-6 and leptin are associated with obesity, and influence in the pathogenesis of MetS (Kaur, 2014). When the influence of the different MetS components (waist circumference, HDL-C, triglycerides, fasting glucose, and blood pressure) on HRV were evaluated in a large cohort of men, all components had a strong, linear association (Hemingway *et al.*, 2005), but the strongest association was found between HRV and waist circumference (Hemingway et al., 2005; Stuckey et al., 2015). However, a study with 2441 participants emphasized the role of glycemic status above all other components of MetS as a cause for the impaired HRV (Jarczok *et al.*, 2013).

In the current study the association of MetS with reduced HRV indices was found to be stronger in women than in men. This is in good concordance with previous studies (Stuckey et al., 2014; Stuckey et al., 2015). The tilt test challenges the autonomic nervous system (Avolio & Parati, 2011; Teodorovich & Swissa, 2016), thus it is logical that the differences between MetS and control groups found in women were

accentuated in the upright position. The reason why women with MetS seem to have relatively more disturbances in HRV than men with MetS, remains unknown. However, hormonal factors may play an important role in this process.

Our study has some limitations. 1) The observational design does not allow conclusions about causal relationship. 2) The collection of the breathing frequency data was not complete from all participants, and the depth of respiration was not measured. 3) The information about the hormonal status like menstrual cycle and testosterone level could have given additional information, as hormonal factors potentially influence HRV. However, the use of exogenous female hormones was reported, and no difference was found between the W-MetS and W-control groups. 4) Subjects using medications that are known to influence HRV were excluded, but it remains uncertain whether the medications that were used by some of the participants had an effect on the results. 5) The criteria by Alberti et al.(Alberti et al., 2009) were used for the definition of MetS, instead of the definition by National Cholesterol Education Program (NCEP, 2001). Using the criteria of Alberti et al., healthier subjects are defined as MetS patients. Of note, despite this MetS definition used in the current study, the results showed impaired HRV in women with MetS.

In conclusion, when the confounding factors were taken into account, the MetS-related changes in HRV seemed to be more pronounced in women than in men, especially in the upright position. It is possible that changes in cardiac autonomic tone, presented as lower total power and lower HF power of HRV, may contribute to the previously reported greater relative increase in cardiovascular risk in women than in men with MetS (Hunt et al., 2004; Iglseder *et al.*, 2005; Schillaci et al., 2006).

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Conflict of Interest

The authors declare that the research was performed in the absence of any commercial or financial relationship that could be considered a potential conflict of interest.

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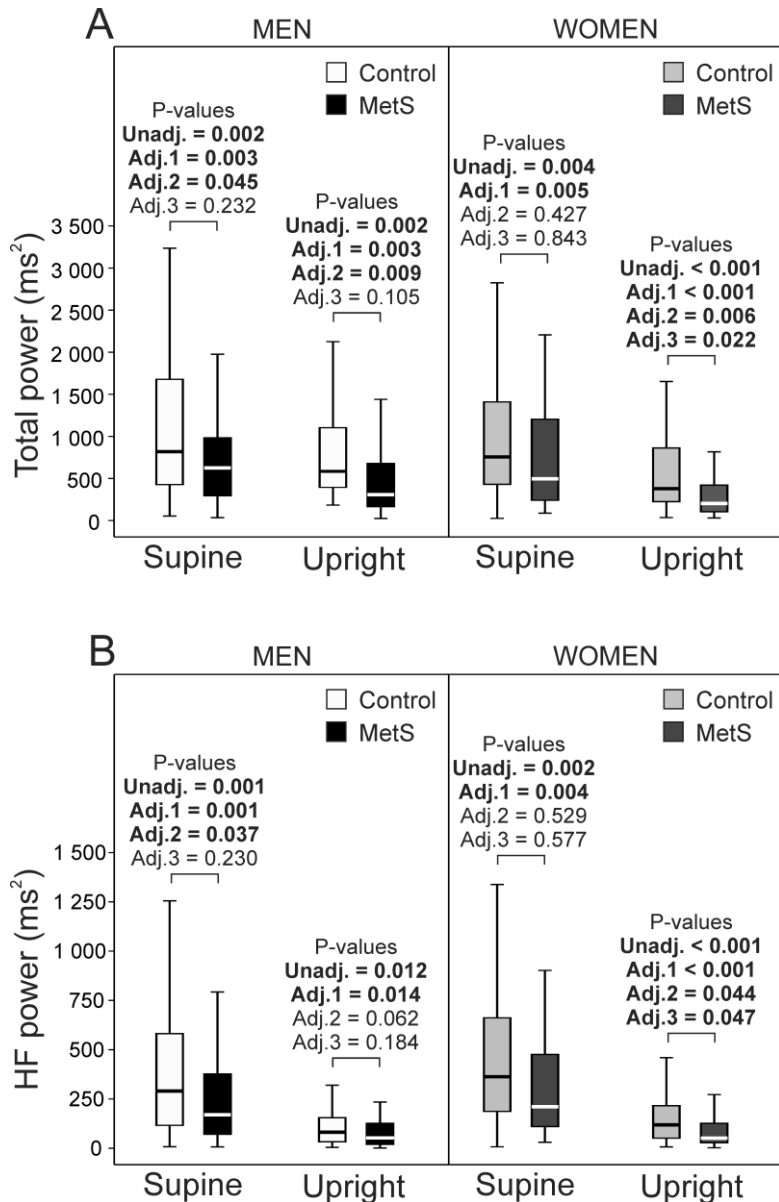
Figure 1. Box plots of total power (A) and high frequency (HF) power (B) of heart rate variability in the study groups (median [line inside box], 25th to 75th percentile [box], and range [whiskers]; outliers were excluded from the figure, but were included in the statistics). Supine and upright P values in unadjusted analyses and in analyses adjusted for 1) age, smoking (current smoking amount), alcohol intake, and height; 2) model 1 plus heart rate; 3) model 2 plus breathing frequency. Numbers of subjects in the groups of men without metabolic syndrome (MetS), men with MetS, women without MetS, and women with MetS, respectively: unadjusted n=131, n=121, n=191, and n=58; adjusted models 1 and 2 n=125, n=120, n=180, and n=57; adjusted model 3 n=110, n=90; n=160, and n=47-48.
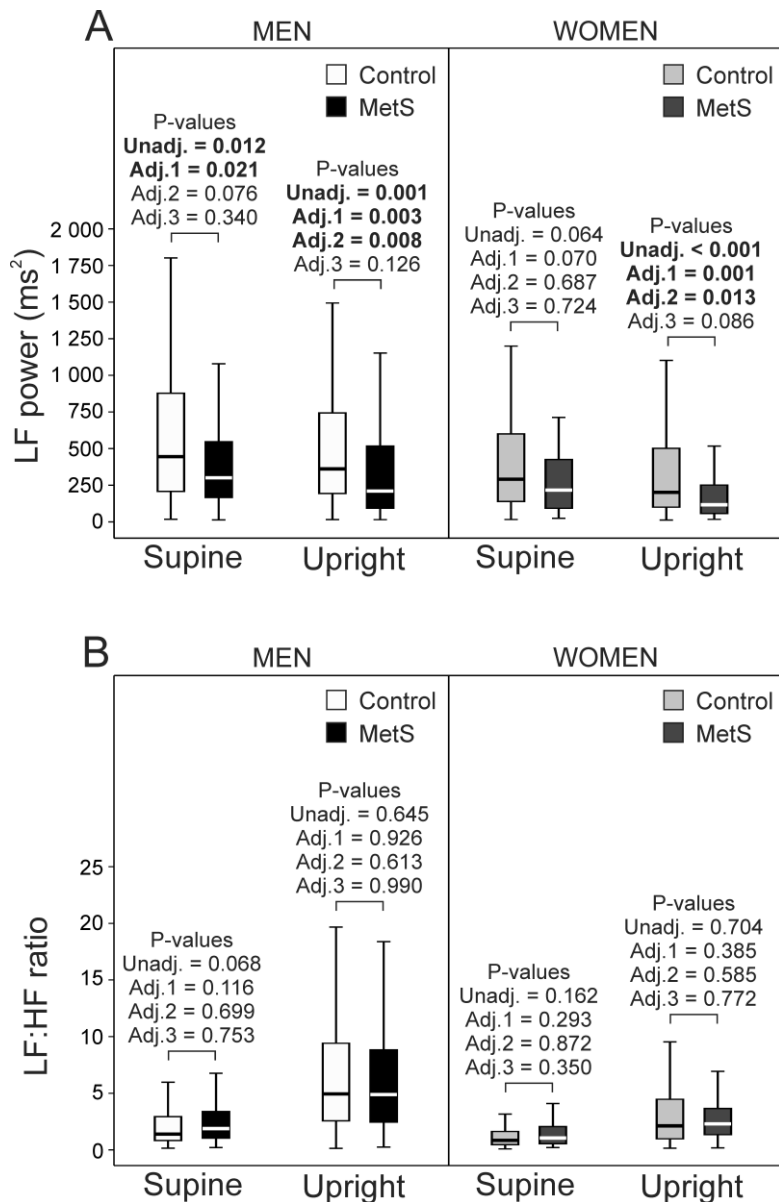
Figure 2. Box plots of low frequency (LF) power (A) and LF:HF ratio (B) in the study groups (median [line inside box], 25th to 75th percentile [box], and range [whiskers]; outliers were excluded from the figure, but were included in the statistics). Supine and upright P values in unadjusted analyses and in analyses adjusted for 1) age, smoking (current smoking amount), alcohol intake, and height; 2) model 1 plus heart rate; 3) model 2 plus breathing frequency. Numbers of subjects in the unadjusted and adjusted models as in Figure 1.

Table 1. Clinical and metabolic characteristics in the study groups.

Variable	M-control	M-MetS	P-value	W-control	W-MetS	P-value
Number of subjects	131	121		191	58	
Age (years)	48 ± 10	49 ± 9	0.457	47 ± 9	49 ± 10	0.113
BMI (kg/m^2)	26 ± 3	30 ± 4	< 0.001	25 ± 4	30 ± 5	< 0.001
Waist circumference (cm)	95 ± 10	106 ± 8	< 0.001	85 ± 12	98 ± 14	< 0.001
Systolic blood pressure (mmHg)	130 ± 16	144 ± 15	< 0.001	125 ± 18	142 ± 19	< 0.001
Diastolic blood pressure (mmHg)	75 ± 11	84 ± 10	< 0.001	72 ± 12	81 ± 13	< 0.001
Smoking status						
Never smoked (n / %)	70 / 53%	57 / 47%	0.316	118 / 62%	28 / 48%	0.067
Current smoker (n / %)	21 / 16%	18 / 15%	0.800	26 / 14%	8 / 14%	0.972
Previous smoker (n / %)	40 / 31%	46 / 38%	0.211	47 / 25%	22 / 38%	0.047
Alcohol intake (standard doses/week)	4 (1-9)	4 (2-11)	0.410	2 (0-3)	2 (0-4)	0.697
Creatinine (µmol/l)	82 ± 12	82 ± 11	0.551	66 ± 9	62 ± 9	0.004
eGFR (ml/min/1.73 m^2)	95 ± 13	96 ± 13	0.842	95 ± 13	98 ± 13	0.122
Fasting plasma glucose (mmol/l)	5.4 ± 0.4	5.9 ± 0.5	< 0.001	5,2 ± 0.4	5.8 ± 0.5	< 0.001
Total cholesterol (mmol/l)	5.2 ± 0.9	5.6 ± 1.1	< 0.001	5,1 ± 1.0	5.6 ± 0.9	< 0.001
Triglycerides (mmol/l)	1.0 (0.7 - 1.4)	1.7 (1.1 - 2.3)	< 0.001	0.9 (0.6 - 1.2)	1.5 (1.0 - 2.0)	< 0.001
High-density lipoprotein cholesterol (mmol/l)	1.5 ± 0.3	1.2 ± 0.3	< 0.001	1.9 ± 0.4	1.5 ± 0.4	< 0.001
Low-density lipoprotein cholesterol (mmol/l)	3.2 ± 0.9	3.7 ± 1.0	< 0.001	2.8 ± 0.9	3.4 ± 0.8	< 0.001
Quantitative insulin sensitivity check index	0.365 ± 0.046	0.343 ± 0.042	< 0.001	0.372 ± 0.042	0.339 ± 0.032	< 0.001
Cornell voltage product in ECG (ms*mm)	1624 ± 823	1807 ± 584*	0.044	1543 ± 523	1739 ± 506*	0.012

Values are means ± SD except the values for smoking, which are the number of cases and percentages, and the values for triglycerides and alcohol intake, which are shown as medians (lower and upper quartiles) due to skewed distribution. M-control, men without MetS; M-MetS, men with MetS; W-control, women without MetS; W-MetS, women with MetS; BMI, body mass index; eGFR, estimated glomerulus filtration rate (Inker et al., 2012).