Dysregulation of the autonomic nervous system is associated with pain intensity, not with the presence of chronic widespread pain

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Abstract

Objective. To test the hypotheses: (i) dysregulation of the autonomic nervous system (ANS) is associated with the presence of Chronic Widespread Pain (CWP); and (ii) dysregulation of the ANS is associated with higher pain intensity in CWP.

Methods. Cross-sectional data were obtained from 1574 subjects –healthy controls as well as persons with depressive and anxiety disorders– participating in the Netherlands Study of Depression and Anxiety. The Chronic Pain Grade was used to assess pain intensity and pain-related disability. Heart rate (HR), standard deviation of the normal-to-normal interval (SDNN), the pre-ejection period (PEP) and respiratory sinus arrhythmia (RSA) were used to assess the ANS. Logistic regression analyses and linear regression analyses were conducted with adjustment for potential confounders.

Results. No differences in HR, PEP, SDNN or RSA values were found between CWP subjects and controls after adjustment for confounders. However, lower SDNN and lower RSA were associated with higher pain intensity in subjects with CWP.

Conclusion. Lower parasympathetic activity, as assessed with SDNN and RSA, is associated with higher pain intensity in subjects with CWP. This large and well controlled study does not provide evidence for an association between dysregulation of the ANS and the presence of CWP.
Significance and Innovations

1. The results from this large and well controlled study are not in line with a role of dysregulation of the ANS in the development of CWP.

2. Lower parasympathetic activity is associated with higher pain intensity in subjects with CWP.

3. A longitudinal study is required to examine the direction of the association between low parasympathetic activity and pain intensity in CWP.
Introduction

Chronic widespread pain (CWP), one of the cardinal symptoms of fibromyalgia, is defined as pain, lasting at least 3 months, above and below the waist, on the right and left sides of the body and in the axial skeleton (1). CWP is one of the most common reasons for referral to a rheumatologist: it is highly prevalent and disabling, and has a large impact on the individual and society (2). Treatment modalities for CWP include both pharmacological and non-pharmacological interventions. Currently, the effects of these interventions are moderate: the mean effect size of the efficacy of 120 treatments was 0.49, which is considered as a medium size effect (3). Better knowledge on risk factors and explanatory mechanisms for the development and perpetuation of CWP is highly crucial to identify targets for effective prevention and treatment.

One of the possible risk factors for CWP is dysregulation of the autonomic nervous system (ANS). Emerging evidence points towards an association between dysfunction of the ANS and CWP. A recent review of Maletic and Raison (4) summarized evidence suggesting that dysregulation of the ANS (i.e. increased sympathetic and/or decreased parasympathetic tone) has a crucial role in initiating and perpetuating central sensitization in the cortico-limbic circuitry. In turn, central sensitization predisposes individuals for the development of chronic pain in response to trigger events (i.e. daily hassles and major life events). Several other studies, not included in the review of Maletic and Raison, have also found alterations in the ANS activity of fibromyalgia patients. These studies indicated increased tonic sympathetic and/or decreased parasympathetic nervous system activity (5-14), as well as hypo-reactive ANS response to applied stressors (10) in patients with fibromyalgia.

Although these studies suggest a link, the evidence for an association between ANS activity and CWP is still limited. One of the methodological weaknesses of the currently available studies is the limited number of participants (the largest study had n = 60; (12)). Furthermore, confounders
such as sociodemographic characteristics, lifestyle and health variables were generally not sufficiently taken into account. The present study reports analyses from a large cohort study; this study also offers the possibility to adjust for potential confounders (15).

The aim of the present study was to assess the association between activity of the ANS and CWP. The hypotheses were: (i) dysregulation of ANS is associated with the presence of CWP; and (ii) dysregulation of ANS is associated with higher pain intensity in subjects with CWP. We examined whether heart rate (HR), standard deviation of the normal-to-normal interval (SDNN), the pre-ejection period (PEP), and respiratory sinus arrhythmia (RSA) differed between subjects with CWP and controls, and whether these variables were associated with pain intensity in subjects with CWP.

**Subjects and Methods**

**Study population**

Study data came from the NESDA study (Netherlands Study of Depression and Anxiety), a large cohort study conducted among 2981 adults, age between 18–65 years, at the baseline assessment in 2004–2007. The study examines the long-term course and consequences of depressive and anxiety disorders and included persons with depressive and anxiety disorders as well as controls without a psychiatric diagnosis. To ensure representative healthcare settings, respondents were recruited from the community, general practice and secondary mental health care. Further details of the study have been described elsewhere (15). For the present study both subjects with CWP and controls were selected (see below). The research protocol was approved by the ethical committees of participating universities. All respondents provided written informed consent.

**Measurements**

*Chronic widespread pain*
The Chronic Pain Grade (CPG) was used to assess pain intensity and pain-related disability (16). The CPG first inquires about the presence of pain in the prior 6 months on several locations, i.e. extremities (joint of arms, hands, legs, or feet), back, neck, head, abdomen, chest, and orofacial. The pain measures employed in the CPG all refer to the most painful location and include: a) days in pain in the prior 6 months (scale 0 - 180); b) pain at this moment (scale 0-10); c) worst pain in the prior 6 months (scale 0-10); d) average pain in the prior 6 months (scale 0-10); e) disability days in the prior 6 months (score 0 -180); f) disability in daily activities (scale 0 -10); g) disability in spare time, social life and family activities (scale 0 -10); h) disability in work (scale 0 -10). From these measures, five grades are categorized, according to the CPG protocol (16): Grade 0 (Pain free, no pain problem in the prior 6 months); Grade I: Low disability-low intensity; Grade II: Low disability-high intensity; Grade III: High disability-moderately limiting; and Grade IV: High disability-severely limiting. The CPG has been extensively tested and found to be reliable, valid and responsive to change (16-18).

We used CPG to select subjects with CWP and controls. Subjects were classified as CWP if they met both of the following criteria: (i) grade I, II, III or IV on the CPG; and (ii) pain present in extremities, back and neck. CWP subjects were further differentiated as grade I, II, III or IV. Subjects were classified as control if they met both of the following criteria: (i) grade 0 or I on the CPG; and (ii) pain in ≤2 locations. Subjects with grade I, and pain in 3 or more locations other than extremities, back and neck were excluded, as well as subjects with grade II, III or IV, and pain elsewhere than extremities, back and neck.

To assess pain intensity in subjects with CWP, three questions on the GCP were used (question b, c and d, see above). The total pain intensity of a subject was the average of 0-10 ratings of the three questions multiplied by 10 to yield a 0 to 100 score (16).
The autonomic nervous system (ANS) was assessed with the VU University Ambulatory Monitoring System (VU-AMS). The VU-AMS is a simple, non-invasive, lightweight ambulatory device recording the electrocardiogram (ECG) and changes in thorax impedance from 6 electrodes placed at chest and back of the subjects, of which recording methodology has been described previously (19;20). Subjects wore the VU-AMS monitor during the assessment unobtrusively underneath clothing for about two hours. The start of the various assessments was indicated by an event marker to divide the total recording into fixed periods (resting baseline, breaks, interview 1, computer task, and interview 2). Movement registration by a vertical accelerometer was used to excise periods in which subjects were not stationary. Removal of breaks and non-stationary moments (~15 minutes) left an average registration of 97.2 (SD = 24.7) minutes (duration concerns subjects in the present study). The registration consisted of a supine resting condition (with 3 blood pressure measurements; mean time, 9.7 minutes, SD, 3.0 minutes) and 3 test conditions in which the participants were sitting upright: interview session 1 (investigating somatic health, functioning, and health care use; mean, 37.7 minutes, SD, 13.5 minutes), interview session 2 (investigating family and personal history and life events; mean, 35.1 minutes, SD, 12.7 minutes), and a computer task (Implicit Association Task; mean, 16.3 minutes, SD, 4.2 minutes).

From the electrocardiogram and the thorax impedance data, the following variables were obtained: mean heart rate (HR); pre-ejection period (PEP): the time from the beginning of electrical activity to the beginning of left ventricular ejection (longer PEP reflecting lower sympathetic activity); standard deviation of the normal-to-normal interval (SDNN; a parasympathetic dominated mixture of parasympathetic and sympathetic nervous activity; high SDNN reflecting high parasympathetic activity); and respiratory sinus arrhythmia (RSA; high RSA reflecting high parasympathetic activity). Reliability and validity of these measures of cardiac ANS activity have been demonstrated previously (21-26). Details of the ANS assessment procedures in NESDA have been described elsewhere (25;27;28).
Covariates

Potential confounders included socio-demographic characteristics (age, gender and years of education), and lifestyle and health variables. Alcohol use was assessed using the first two questions of the Alcohol Use Disorders Identification Test (AUDIT) (29). Alcohol use was categorized into no drinker, mild/moderate drinker (men: 1-21 glasses/week; women: 1-14 glasses/week) and heavy drinker (men: > 21 glasses/week; women: > 14 glasses/week). Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Smoking, which was assessed by self-report, was categorized into never smoked – former smoker – current smoker. Heart disease (including coronary disease, cardiac arrhythmia, angina, heart failure, and myocardial infarction) and other chronic conditions (epilepsy, diabetes, osteoarthritis, stroke, cancer, chronic lung disease, thyroid disease, liver disease, chronic fatigue syndrome, intestinal disorders, and ulcer) were assessed by self-report and considered present if persons received treatment. Medication use was assessed based on drug container inspection of all drugs used in the past month and classified according to the WHO’s anatomical therapeutic chemical (ATC) classification (30). Heart medication was divided in two categories 1) beta blocking agents (ATC code C07) and 2) and other heart medication (cardiac therapy (ATC code C01), antihypertensives (ATC code C02), diuretics (ATC code C03), peripheral vasodilators (ATC code C04), vasoprotectives (ATC code C05), calcium channel blockers (ATC code C08) and agents acting on the renin-angiotensin system (ATC code C09)). Pain medication included (ATC code M01A, M02, M03A, N02, N03AX12 and N03AX16) (31;32). In addition, frequent use (daily or > 50% of the time) of antidepressant medications (tricyclic antidepressants [TCA; ATC code N06AA], selective serotonin reuptake inhibitors [SSRI; ATC code N06AB], and other antidepressant medication [ATC codes N06AF/AG/AX]) were considered as covariates because of the previously reported impact of antidepressants on heart rate, SDNN and RSA in depressed patients (28). Respiration rate (breaths/min) was obtained from
the thorax impedance data as it has been asserted that research investigating RSA should take respiration rate into account (19).

Another set of potential confounders was evaluated as well: physical activity, insomnia, and diagnosis and severity of depressive and anxiety disorders. Physical activity was assessed with the International Physical Activity Questionnaire (33), and expressed in metabolic equivalent minutes per week. Insomnia was evaluated with the Insomnia Rating Scale (range 0-20), with 9 as a cut-off point (34). Although we found diagnoses and severity to be largely unrelated to ANS activity (25;27), depressive and anxiety disorders were considered as potential confounders as well. Lifetime depressive and anxiety disorders were established with the Composite International Diagnostic Interview (CIDI, WHO version 2.1) (35). Severity of depressive symptoms was measured with the Inventory of Depressive Symptomatology (IDS) self-report version (range 0 -84) (36). Severity of anxiety and panic symptoms was measured using the 21-item Beck Anxiety Inventory (range 0 -63) (BAI) (37). These variables are not merely potential confounders but could also be mediators, explaining the link between ANS activity and pain: for this reason, these potential confounders/mediators were analyzed in a separate step (38).

Statistical analyses

Descriptive baseline characteristics were tabulated as mean and SD, or as percentages. Between-group differences at baseline were examined using Chi-square tests for categorical variables and analyses of variance (ANOVA) for continuous variables. Binary (no CWP vs. CWP) and multinomial (no CWP, CWP-grade I, CWP-grade II, CWP-grade III, and CWP-grade IV) logistic regression analyses were performed to analyse associations between ANS functioning and the presence of CWP. To examine whether ANS activity was associated with pain intensity in subjects with CWP, we conducted linear regression analyses in subjects with CWP. In all analyses, ANS functioning was the independent variable; presence of CWP and intensity of pain were the dependent variables,
respectively.

Three models were used in binary and multinomial logistic regression and linear regression analyses. First an unadjusted model was used. In the second model, we adjusted for potential confounders, i.e. gender, age, education, BMI, smoking, alcohol use, heart disease, number of chronic diseases, beta blocking agents, other heart medication, pain medication, TCA, SSRI, and antidepressant medication. In the third model we additionally adjusted for the potential confounders/mediators, i.e. physical activity, insomnia, diagnosis of lifetime depressive or anxiety disorders, and depression and anxiety severity. For all statistical tests, a probability level of equal or less than 5% was regarded as significant. The statistical calculations were performed using SPSS version 15.0.

Results

Subjects

The total study sample consisted of 1574 subjects. In total 1654 subjects met the selection criteria for the CWP group (N= 767) or the control group (N= 887). Of these subjects, 80 persons were excluded because no ANS data were available, leaving 843 control subjects and 731 subjects with CWP. The excluded subjects (N=80) did not differ from the included subjects with regard to the presence of CWP (data not shown). Included subjects were younger (43.1 versus 46.4; P=0.03), more often a smoker (37.5% versus 33.8%, P= 0.02), had a lower BMI (25.6 versus 26.8; P=0.04), had less heart disease (5.8% versus 15.0%, P= 0.003), and more often used pain medication (45.3% versus 35.0%; P=0.04), compared to excluded subjects. For all other baseline characteristics there were no significant differences between excluded and included subjects.

Baseline characteristics of the study population are shown in Table 1. In subjects with CWP, the mean days in pain in the prior 6 months was 108.2 (SD= 69.7) and the mean pain intensity was
53.1 (SD= 18.0). Compared to controls, subjects with CWP were significantly older, more often women, had less education, more often non-alcohol drinkers, had higher BMI, were more often current smokers, used more other heart medication, pain medication, SSRIs and other antidepressant medication, had more heart disease and other chronic diseases, suffered more frequently from insomnia, had more frequently lifetime depressive and/or anxiety disorders. Differences between controls and CWP subjects in the use of beta-blocking agents, TCA use and physical activity were not significant. With regard to ANS measures, SDNN and RSA were significantly higher in the control group compared to the CWP group, but HR and PEP did not differ between controls and CWP subjects.

ANS activity and the presence of chronic widespread pain

Table 2 shows the results of the unadjusted and adjusted binary and multinomial logistic regression analyses assessing the association between ANS activity and the presence of CWP. In the binary logistic regression model, before adjustment, SDNN and RSA were significantly associated with the presence of CWP: lower SDNN and RSA were associated with a higher odds of CWP. All potential confounders and confounders/mediators were separately tested: each individually resulted in a change in the beta of more than 10%. After adjustment for confounders, SDNN and RSA were not significantly associated with the presence of CWP. Further adjustment for potential confounder/mediators had no further impact.

In the unadjusted multinomial logistic model HR, SDNN and RSA showed a significant association with the presence of CWP: higher HR, lower SDNN and lower RSA were associated with higher odds of having “High disability-moderately limiting CWP” or “High disability-severely limiting CWP”. After adjustment for confounders these associations became weaker and were no longer significant. In fact, adjustment for age only reduced all associations to non-significance (data not shown). Adjusting for the potential confounder/mediators hardly affected these results. PEP did
not show a statistically significant effect in any CWP group, before or after adjustment for confounders and confounders/mediators. Thus, overall, there were no associations between ANS measurements and the presence of CWP, after adjustment for confounders.

**ANS activity and pain intensity in CWP**

Table 3 shows the results of the unadjusted and adjusted linear regression analyses assessing the association between ANS activity and pain intensity in subjects with CWP (N=731). Both SDNN and RSA were significantly associated with pain intensity, before and after full adjustment for potential confounders and confounders/mediators (SDNN: unadjusted: B -3.25, 95% CI= -4.60 -1.89, P<0.001; fully adjusted: B= -2.25, 95% CI= -3.52 -0.97, P = 0.001) (RSA: unadjusted: B= -2.58, 95% CI= -3.99 -1.17, P<0.001; fully adjusted: B= -1.95, CI = -3.44 -0.46, P=0.01). Neither HR nor PEP was associated with pain intensity, in the unadjusted and fully adjusted analyses, although PEP tended to be shorter in the CWP group after adjustments. Thus, lower SDNN and RSA were significantly associated with higher pain intensity in subjects with CWP, before and after correction for all potential confounders and confounders/mediators.

**Discussion**

In this well controlled study with a large sample, we examined the association between functioning of the autonomic nervous system and chronic widespread pain. We found that (i) ANS activity is not associated with the presence of CWP, and (ii) lower parasympathetic activity, as assessed with SDNN and RSA, is associated with higher pain intensity in subjects with CWP.

Our findings do not confirm our first hypothesis, that dysregulation of ANS is associated with the presence of CWP. This negative finding applies to the presence of CWP treated as a dichotomy (presence vs absence) as well as to CWP treated as an ordinal variable (grades 0 – IV), making a dose
response relationship unlikely. Our findings are in contradiction with other studies, which have suggested that ANS activity is altered in CWP (4). Previous studies which suggested an association between ANS activity and CWP suffered from limited sample size and insufficient control of potential confounders. In unadjusted analyses, we observed several significant associations between dysregulation of the ANS and the presence of CWP. These associations were not significant after controlling for confounders; in fact, controlling for age eliminated significant associations: age has been shown to be correlated with both ANS activity and CWP (39-41) and is therefore a potential confounder which should be controlled for. Previous studies have mostly examined fibromyalgia patients: it is still a possibility that dysregulation of the ANS is a factor in the development or persistence of fibromyalgia, as opposed to the broader category of CWP.

We did find an association between SDNN and RSA and pain intensity in subjects with CWP, confirming our second hypothesis. These associations remained significant, after controlling for confounders and even potential confounder/mediators. These findings are in line with other studies (e.g. (7;42)) which have shown a decrease in parasympathetic activity in fibromyalgia patients. In the present cross-sectional study, the causality of this relationship cannot be determined. Yet, lower parasympathetic activity was not associated with the presence of CWP (hypothesis 1), while it was associated with pain intensity in subjects with CWP (hypothesis 2): this pattern of results suggests that intense pain is a chronic stressor, interfering with parasympathetic activity, as has been suggested previously (10). Longitudinal studies are required to determine the direction of the relationship between parasympathetic activity and pain intensity.

HR and PEP did not show a significant association with pain intensity in subjects with CWP. This suggests that there is no association between dysregulated sympathetic tone and pain intensity in CWP subjects, which is in line with the results in fibromyalgia patients (9;43). Thus, our study does not support the idea that stress-related sympathetic tone is a driver of pain intensity, or that pain intensity enhances sympathetic tone.
For this study the NESDA data has been used. The NESDA data has a high rate of subjects with lifetime depressive and anxiety disorders. One could argue that the statistical adjustment to account for depression and anxiety has affected our conclusions. We do not think that this is a likely explanation for our conclusions. In unadjusted analyses, we found SDNN and RSA to be associated with the presence of CWP. After adjustment for confounders (i.e. gender, age, education, BMI, smoking, alcohol use, heart disease, chronic diseases, and medication), these associations became weaker and were no longer significant (see Table 2). Further adjustment for depression and anxiety did not have much influence on the associations (see Table 2). Therefore, it is unlikely that the statistical adjustment for the nature of the NESDA study population explains our conclusions. The same reasoning applies to the results with regard to parasympathetic activity and pain intensity: it is unlikely that our conclusions are due to the adjustment for depression and anxiety. Furthermore, we repeated the binary logistic and linear regression analyses, excluding subjects with a life-time diagnosis of depression or anxiety. The regression estimates derived from these analyses confirmed our conclusions, although p-values showed some change as result of the lower number of subjects (N=408, of whom N=86 had CWP; data not shown).

In a similar vein, one could argue that incorporating chronic fatigue syndrome and intestinal disorders among the potential confounders resulted in over-adjustment: like chronic widespread pain, chronic fatigue syndrome and intestinal disorders could be the result of central sensitization in the cortico-limbic circuitry. Again, we think that this is an unlikely explanation of our findings: adjustment for age only reduced all associations to non-significance.

Several methodological issues need to be taken into account when considering the conclusion of our study. First, one of the criteria for CWP is pain for more than 3 months, while we used the CPG, which asks about the number of days in pain in the prior 6 months. As shown in Table 1, subjects with CWP had on average 108 days of pain (~3.5 months) in the prior 180 days: it is likely that these subjects meet the criterion of pain for more than 3 months. Therefore, it is unlikely
that the slight deviation with regard to the criterion of pain, explains our findings. Second, we 
excluded from the control group subjects with grade I on the CPG and pain in 3 or more locations 
other than extremities, back and neck. These subjects were excluded in order to enhance the 
contrast between CWP and control. We did not exclude subjects with Grade I and pain in ≤2 
locations, limiting the control group to subjects with Grade 0 only: this would have left us with little 
subjects in the control group (only n = 170 had Grade 0). Including subjects with CPG level 1 and 
pain in ≤2 locations in the control group weakens the contrast between controls and subjects with 
CWP and increases the possibility of false negative findings. On the other hand, chronic pain in 1 or 
2 locations is quite common in the population (44): our controls resemble the population in this 
respect. Third, because the analyses were cross-sectional, the results do not indicate any causal 
direction of the associations found. As mentioned before, a longitudinal study is recommended to 
elucidate the directionality of the association between ANS activity and CWP. Fourth, we used HR, 
PEP, SDNN and RSA as measures of ANS activity. It should be noted that, strictly speaking, HR, PEP, 
SDNN and RSA are measures of the impact of ANS activity on the heart, instead of direct measures of 
ANS activity.

In conclusion, this large scale and well controlled study shows that lower parasympathetic 
activity, as assessed with SDNN and RSA, is associated with higher pain intensity in subjects with 
CWP. No evidence was found for an association between dysregulation of the ANS and the presence 
of CWP. A longitudinal study is required to examine the direction of the relationship between low 
parasympathetic activity and pain intensity in CWP.

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and Care Research, VU University Medical Center, Amsterdam; and Neuroscience Campus Amsterdam, VU University Amsterdam, the Netherlands.
Table 1: Baseline characteristics

| CHARACTERISTIC | Control N=843 | CWP N=731 | P-value  
|----------------|--------------|-----------|----------
| Days of pain in the prior 6 months, mean (SD) | 27.6 (49.0) | 108.2 (69.7) | <0.001 |
| Pain intensity, mean (SD) | 21.5 (15.2) | 53.1 (18.0) | <0.001 |

Potential confounders

| Age, years, mean (SD) | 41.9 (13.6) | 44.5 (12.2) | <0.001 |
| Gender, % women | 56.7 | 74.1 | <0.001 |
| Education in years, mean (SD) | 13.0 (3.3) | 11.3 (3.2) | <0.001 |
| Alcohol use, % yes |  
| Non-drinker | 23.6 | 40.5 | <0.001 |
| Mild-moderate drinker | 63.9 | 48.4 |  
| Heavy drinker | 12.5 | 11.1 |  
| BMI, mean (SD) | 25.0 (4.2) | 26.4 (5.2) | <0.001 |
| Smoking, % yes |  
| Non-smoker | 31.9 | 26.5 | <0.001 |
| Former smoker | 35.2 | 30.5 |  
| Current smoker | 32.9 | 43.0 |  
| Medication use, yes% |  
| Beta-blocking agents | 7.7 | 9.8 | 0.08 |
| Other heart medication | 11.0 | 14.1 | 0.04 |
| Pain medication | 31.2 | 61.6 | <0.001 |
| SSRI | 12.1 | 21.2 | <0.001 |
| TCA | 2.0 | 3.0 | 0.14 |
| Other antidepressant medication | 3.8 | 7.7 | 0.001 |
| Heart disease, % yes | 4.5 | 7.4 | 0.01 |
| Number of other chronic diseases, mean (SD) | 0.5 (0.8) | 1.4 (1.2) | <0.001 |

Potential confounders/mediators

| Physical activity, MET min a week, mean (SD) | 3309 (3027) | 3584 (3345) | 0.09 |
| Insomnia, % yes | 28.2 | 55.1 | <0.001 |
| Depressive disorder, % yes | 48.0 | 78.7 | <0.001 |
| Anxiety disorder, % yes | 43.7 | 71.3 | <0.001 |
| Depression or anxiety disorder, % yes | 61.8 | 88.2 | <0.001 |
| Depressive symptoms (IDS), mean (SD) | 13.7 (11.5) | 28.5 (13.8) | <0.001 |
| Anxiety symptoms (BAI), mean (SD) | 6.6 (7.6) | 17.6 (11.7) | <0.001 |

Autonomic nervous system measures

| HR, beats/min, mean (SD) | 72.5 (9.6) | 73.0 (9.5) | 0.29 |
| PEP, ms, mean (SD) | 119.6 (18.9) | 120.5 (18.3) | 0.36 |
| SDNN, ms, mean (SD) | 66.4 (26.4) | 63.3 (24.1) | 0.02 |
| RSA, ms, mean (SD) | 44.3 (26.9) | 41.3 (23.3) | 0.02 |
| Respiration rate, breaths/min, mean (SD) | 16.9 (1.2) | 16.8 (1.1) | 0.12 |

A: Based on X² test for dichotomous and categorical variables and ANOVA for continuous variables.
Table 2: Association between ANS activity and the presence of chronic widespread pain

<table>
<thead>
<tr>
<th>Parameters autonomic nervous system</th>
<th>Control (N= 843) vs. CWP (N= 731) ¹</th>
<th>Control (N=843) vs. grades of CWP ²</th>
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<tbody>
<tr>
<td></td>
<td>OR ²  95% CI  P</td>
<td>OR ²  95% CI  P</td>
</tr>
<tr>
<td>HR</td>
<td></td>
<td></td>
</tr>
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<td>1.06  0.96  1.17  0.29</td>
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<td>adjusted ⁴</td>
<td>0.99  0.87  1.11  0.81</td>
<td>1.0  0.85  1.17  0.97</td>
</tr>
<tr>
<td>adjusted ⁵</td>
<td>0.94  0.87  1.14  0.99</td>
<td>1.0  0.85  1.17  0.97</td>
</tr>
<tr>
<td>PEP</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>1.05  0.95  1.16  0.36</td>
<td>1.07  0.93  1.23  0.35</td>
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<tr>
<td>adjusted ⁴</td>
<td>1.09  0.97  1.23  0.18</td>
<td>1.08  0.93  1.26  0.30</td>
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<tr>
<td>adjusted ⁵</td>
<td>1.05  0.91  1.20  0.52</td>
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<td>SDNN</td>
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<tr>
<td>unadjusted</td>
<td>0.88  0.80  0.98  ⁰ 0.02</td>
<td>1.00  0.88  1.15  0.96</td>
</tr>
<tr>
<td>adjusted ⁴</td>
<td>1.09  0.97  1.24  0.17</td>
<td>1.13  0.97  1.23  0.11</td>
</tr>
<tr>
<td>adjusted ⁵</td>
<td>1.10  0.95  1.26  0.20</td>
<td>1.12  0.96  1.32  0.20</td>
</tr>
<tr>
<td>RSA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>unadjusted</td>
<td>0.88  0.80  0.98  ⁰ 0.02</td>
<td>1.01  0.89  1.16  0.85</td>
</tr>
<tr>
<td>adjusted ⁴</td>
<td>1.02  0.89  1.17  0.80</td>
<td>1.10  0.93  1.30  0.25</td>
</tr>
<tr>
<td>adjusted ⁵</td>
<td>1.06  0.90  1.24  0.50</td>
<td>1.12  0.94  1.33  0.22</td>
</tr>
</tbody>
</table>

1: Based on logistic regression analysis, total N= 1574.
2: Based on multinomial logistic regression analysis, total N= 1574. Control group as reference group.
³ Adjusted for confounders: age, gender, education, alcohol use, BMI, smoking, heart disease, chronic disease, beta-blocking agents, other heart medication, pain medication, TCA, SSRI and other antidepressant medication.
⁴ Additionally adjusted for physical activity, insomnia, lifetime depressive or anxiety disorder, IDS and BAI.
⁵: Per SD increase.
+ Also adjusted for respiration rate.
### Table 3: Association between ANS activity and pain intensity in subjects with chronic widespread pain

<table>
<thead>
<tr>
<th>Parameters autonomic nervous system</th>
<th>Pain intensity(^1)</th>
<th>(\beta^c)</th>
<th>95% CI</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HR unadjusted</td>
<td>0.85</td>
<td>-0.47</td>
<td>2.17</td>
<td>0.21</td>
</tr>
<tr>
<td>adjusted (^A)</td>
<td>0.94</td>
<td>-0.35</td>
<td>2.24</td>
<td>0.15</td>
</tr>
<tr>
<td>adjusted (^B)</td>
<td>0.92</td>
<td>-0.31</td>
<td>2.16</td>
<td>0.14</td>
</tr>
<tr>
<td>PEP unadjusted</td>
<td>-0.77</td>
<td>-2.10</td>
<td>0.56</td>
<td>0.26</td>
</tr>
<tr>
<td>adjusted (^A)</td>
<td>-1.09</td>
<td>-2.38</td>
<td>0.19</td>
<td>0.10</td>
</tr>
<tr>
<td>adjusted (^B)</td>
<td>-1.11</td>
<td>-2.33</td>
<td>0.11</td>
<td>0.07</td>
</tr>
<tr>
<td>SDNN unadjusted</td>
<td>-3.25</td>
<td>-4.60</td>
<td>-1.89</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>adjusted (^A)</td>
<td>-2.14</td>
<td>-3.50</td>
<td>-0.80</td>
<td>0.002</td>
</tr>
<tr>
<td>adjusted (^B)</td>
<td>-2.25</td>
<td>-3.52</td>
<td>-0.97</td>
<td>0.001</td>
</tr>
<tr>
<td>RSA(^*) unadjusted</td>
<td>-2.58</td>
<td>-3.99</td>
<td>-1.17</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>adjusted (^A)</td>
<td>-2.24</td>
<td>-3.81</td>
<td>-0.67</td>
<td>0.005</td>
</tr>
<tr>
<td>adjusted (^B)</td>
<td>-1.95</td>
<td>-3.44</td>
<td>-0.46</td>
<td>0.01</td>
</tr>
</tbody>
</table>

1: Based on linear regression, \(N=731\).

\(^A\): Adjusted for confounders: age, gender, education, alcohol use, BMI, smoking, heart disease, chronic diseases, beta-blocking agents, other heart medication, pain medication, TCA, SSRI and other antidepressant medication.

\(^B\): Additionally adjusted for physical activity, insomnia, lifetime anxiety or depression disorder, IDS and BAI.

\(^c\): Per SD increase.

\(^*\): Also adjusted for respiration rate.
Reference List


