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ORIGINAL REPORT

LOW HEART RATE VARIABILITY IS ASSOCIATED WITH EXTENDED PAIN-RELATED SICK LEAVE AMONG EMPLOYED CARE-SEEKERS

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Objective: **To examine the association between autonomic regulation and length of pain-related sick leave in subjects receiving a cognitive behavioural therapy-based return to work intervention.**

Methods: **Sixty-five persons (29 men, 36 women) on pain-related sick leave participated in the study. Electrocardiograms were recorded in the clinic during supine rest, passive head-up tilt, standing, and seated rest, and in the home during seated rest and sleep. Spectral components of heart rate variability were derived from short-term (5 min) segments of electrocardiogram recordings. The number of days on sick leave was obtained from register data for 3 months before to 6 months after seeking care at the primary healthcare clinic.**

Results: **Extended sick leave (>121 days) compared with short sick leave (<29 days) was associated with higher heart rate, and lower heart rate variability in supine rest and the seated position. The associations in supine rest were marginally weakened by adjusting for offensive behaviours at work. (for example, exposure to bullying, sexual harassment, unpleasant teasing, etc.)**

Conclusion: **Higher heart rate and lower heart rate variability measured in the awake resting condition predicts extended sick leave in care-seeking individuals. Further research is needed to clarify the underlying nature and causal role of altered autonomic regulation with regard to extended pain-related sick leave.**

Key words: autonomic nervous system; cardiac autonomic regulation; return to work; sick leave; multimodal rehabilitation; pain treatment; cognitive behavioural rehabilitation; treatment.

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INTRODUCTION

Musculoskeletal pain-related sick leave is a problem in Western countries. There is evidence that psychosocial factors play an important role for the development of unspecific musculoskeletal pain. To identify the few patients who are in need of a specialized multimodal intervention aimed at minimizing the risk of extended sick leave, screening with focus on psychosocial factors has been suggested as a possible solution (1–3). Compared with psychosocial factors, physiological factors have received little attention as predictors of extended sick leave. Yet the detection of early physiological mechanisms could be an important aid when it comes to diagnosing, monitoring and treating the underlying musculoskeletal pains that are grounds for extended sick leave. The autonomic nervous system may be important in this context. For example, the ability to adjust behaviour and emotional expressions to environmental demands seems to be associated with the ability to dynamically regulate the activity in the autonomic nervous system (4, 5). Thus, exertion of impulse control (6), persistence in solving difficult tasks (7), cognitive functioning during stress and non-stress situations (8, 9), and low emotional arousal and constructive coping in response to daily life stressors (10) have all been observed to be associated with autonomic functioning. The central role of the autonomic nervous system in modifying and adjusting behaviour in the face of environmental challenges suggests that it also could influence the decision about returning to work of care-seekers on sick leave.

Frequency domain analysis of short-term heart rate variability (HRV) can be used to assess the vagal component and the sympathovagal balance in the autonomic modulation of heart rate (11, 12). The aim of the present study was to explore the association between autonomic regulation as assessed by HRV and the length of sick leave. This was done in the context of employed subjects on pain-related sick leave who received an individually tailored cognitive behavioural therapy (CBT)-based return to work intervention based on the individual subject's needs. The following questions were asked: (*i*) Is longer sick leave associated with an altered autonomic cardiac regulation? (*ii*) Is the physiological association explained (mediated) by known psychosocial risk factors of extended sick leave?

METHODS

Subjects

Participants were identified through data sampled from 54 public sector primary healthcare physiotherapists, located at 17 outpatient clinics, in primary care in the city of Malmö from December 2005 to July 2008.

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Inclusion criteria for care-seekers were: age 18–65 years, having adequate Swedish language skills to communicate without an interpreter and being sick-listed at the time of identification. In order to avoid subjects with a history of long sick leave, care-seekers with more than 3 months of pain-related sick leave during the previous 12 months at the time of inclusion were excluded. After identification, care-seekers were randomly allocated to an intervention or a control group.

Care-seekers were provided with an opportunity to participate in CBT and the possibility to participate in a research project concerning biological stress markers. Due to ethical considerations, these 2 options were unlinked, making participation in CBT-rehabilitation possible without participation in the research project and vice versa. Positive responders to the research project were scheduled for appointments on two consecutive days with a research assistant, during which data sampling for HRV took place. Questionnaires were completed by the care-seekers between the two appointments.

All care-seekers in the intervention group received individually tailored CBT according to their need for rehabilitation. The need for CBT was based on a validated CBT team evaluation employing functional behaviour analysis. An in-depth description of the evaluation is given elsewhere (13).

In total, 566 care-seekers were identified by the physiotherapist in primary care. Of these, 374 were randomly allocated to the intervention group, while the remaining 192 care-seekers formed a control group. The control group, however, is not part of the present study, which investigates contrasts within the intervention group. Ninety-one care-seekers in the intervention group could not be reached by telephone. Of the remaining 283 cases, 91 volunteered to participate in the research project concerning biological markers. Three care-seekers did not fulfil the inclusion criteria. Details concerning enrolment are presented elsewhere (Ektor-Andersen et al., submitted).

Thus, in total, 88 care-seekers participated in the research project. However, as the present research aim presupposed that the care-seekers were employed; only the 72 employed persons were included. Lastly, 7 care-seekers using β_1-receptor blockers were excluded, as this medication may interfere with autonomic cardiac regulation (14). This left 65 persons for investigation in the present study of HRV.

Characteristics of the participants

Among the 65 employed care-seekers 55% were women (Table I). The median age was 44 years for men and 40 years for women. Twenty-four percent of the men and 39% of the women were born outside Sweden. Thirty-six percent of the women were educated above the level of Swedish senior high school (12 years), which was 22% points more than the proportion of men. Fourteen percent of the women, the same proportion as for the men, were classified as middle- or high-level non-manual employees.

The subjects had mixed types of pain. Employing the International Association for the Study of Pain (IASP) definitions of pain types, 37% had nociceptive pain (demanding objective structural post-traumatic or degenerative changes or rheumatic inflammatory disorders), 6% had neuropathic pain fulfilling the IASP revised criteria 2007 (15), 14% had psychogenic pain and 52% idiopathic pain. The total exceeding 100% is due to 14% fulfilling the criteria for nociceptive or neuropathic pain and also diagnosed with prominent psychiatric disorders (depression or anxiety). In terms of pain models (16) the 43% with nociceptive or neuropathic pains exemplified end-organ dysfunction models (EODM), whereas 57% exemplified altered nervous system processing models (ANSPM). Eight percent (5 subjects) with ANSPM had generalized pain (fibromyalgia), whereas the remaining subjects had localized or regional pains.

Thirty-one subjects (48%) used one or more forms of pain medication. The most frequently used pain medication was paracetamol (22 subjects, 34%), non-steroidal anti-inflammatory drugs (12 subjects, 18%) and opioid analgesics (11 subjects, 17%). Sleeping medication was used by 6 subjects (9%). Antidepressants (selective serotonin reuptake inhibitors) were used by 9 subjects (14%).

Test conditions for heart rate variability measurements

During the first appointment a 24-h electrocardiogram (ECG) was recorded using 3-lead Lifecard CF Holter monitors (Del Mar Reynolds Medical Inc., Irvine, CA, USA). Electrocardiogram recording segments were sampled during standardized test conditions at the clinic and at home (17), as described below.

Supine rest, head-up tilt and standing. The care-seeker rested lying horizontally on an electric tilt table (TR Classic Art. Nr 718030) for 10 min (supine rest 1). The table was then tilted to the vertical position for 8 min (head-up tilt) and was then tilted down to the horizontal position for 10 min (supine rest 2). Following this, the care-seeker got up to upright standing position beside the board, leaning against the wall, and remained in this position for 8 min (standing).

Seated in clinic. The care-seeker sat in the clinic waiting-room for 16 min. The instruction was to sit and relax as much as possible. Talking or moving was not allowed, but reading was.

Seated at home. The care-seeker was instructed to repeat the 16-min relaxation period at home at a time of own choice during the 24-h period. The care-seeker was allowed to do whatever he or she felt was relaxing, as long as he or she sat still. For example watch television, listen to music, read, etc.

Sleep. When turning off the light to go to sleep at night the care-seeker was asked to note the time. This was repeated immediately after waking up in the morning. HRV was calculated for the 15-min period starting 1 h after bed-time.

Table I. *Socio-demographic and sick leave characteristics for the examined 29 men and 36 women seeking care due to recent start of musculoskeletal pain-related sick leave*

	Men	Women
Age, years, *n* (IQR)	44 (32–53)	40 (30–48)
Sex, *n* (%)	29 (45)	36 (55)
Born in Sweden	75.9	61.1
Educational level, %		
≤9 years	6.9	5.6
10–12 years	75.9	58.3
>12 years	13.8	36.1
Missing data	3.4	–
Occupational class, %		
High-level, non-manual	–	5.6
Middle-level, non-manual	13.8	8.3
Low-level, non-manual	13.8	13.9
Skilled, manual	24.1	44.4
Unskilled, manual	44.8	27.8
Missing data/other (e.g. self-employed)	3.4	–
Sick leave 1–3 year before, %		
<1 week	58.6	63.9
1 week–1 month	24.1	5.6
1–3 months	13.8	19.4
3–6 months	3.4	11.1
>6 months	0.0	0.0
Sick leave the previous year, %		
<1 week	34.5	41.7
1 week–1 month	37.9	27.8
1–3 months	27.6	30.6
OMPQ score, median (IQR)	106 (84–125)	114 (87–130.5)

IQR: interquartile range; OMPQ: Örebro Musculoskeletal Pain Questionnaire.

Reactivity. Cardiovascular reactivity in the orthostatic manoeuvre was expressed as the difference between head-up tilt and supine rest 1 results (reactivity 1). Reactivity in the standing challenge was expressed as the difference between standing and supine rest 2 (reactivity 2).

Spectral components of heart rate variability

The electrocardiograms (ECGs) were sampled with a sampling frequency of 128 Hz. Artefacts and non-normal beats in the ECG segments were autodetected by commercial software (Impresario version 2.8, Del Mar Reynolds Medical Inc., Hertford, UK) and verified by visual inspection. To calculate the heart interbeat (RR) interval series, the ECGs were processed as described previously (17). In brief, the fiducial point of each R-peak was determined after cubic-spline interpolation to 512 Hz. Next, the RR-intervals were filtered for possible outliers (ectopic beats, falsely detected beats, missed beats, etc.). Finally, the RR-intervals were resampled with a frequency of 4 Hz and linearly detrended. The spectral components of the HRV for 5-min segments of the RR-interval series were estimated by Welch's averaged, modified periodogram method (Hamming window size 256 points, 50% overlap). The total power (TP) was calculated for the frequency range 0.0003–0.5 Hz, low-frequency power (LF) in the range 0.04–0.15 Hz and high-frequency power (HF) in the range 0.15–0.4 Hz. Power was expressed in absolute units (ms^2). Lastly, the ratio of power in the low-frequency range to the power in the high-frequency range, LF/HF, was calculated. To conform to a Gaussian distribution, the natural logarithms of the spectral components were used in all analyses.

Questionnaires

Örebro Musculoskeletal Pain Questionnaire (OMPQ). The OMPQ contains 21 items that assess the care-seeker's reaction to the situation and symptoms in terms of cognitions, behaviours and psycho-physiological reactions (2). Answers to the 21 items are summed up to a total score (0–210). Higher OMPQ scores indicate greater presence and severity of biopsychosocial risk factors. The median OMPQ score of men and women are presented in Table I.

Copenhagen Psychosocial Questionnaire (COPSOQ). The COPSOQ II (18) was used to assess psychosocial factors at work. It contains 7 domains: (*i*) demands at work, (*ii*) work organization and content, (*iii*) social relations and leadership, (*iv*) job insecurity and job satisfaction, (*v*) values at the workplace, (*vi*) self-rated health and lack of well-being, and (*vii*) personal skills and offensive behaviours (for example, exposure to bullying, sexual harassment, unpleasant teasing, etc.).

In a previous study on the same group of subjects we have shown that the OMPQ score and the work pace and offensive behaviours in the COPSOQ are independent predictors of extended sick leave (Ektor-Andersen et al., submitted).

Sick leave registration

Register data on spells of sick leave during the period from 3 years before to 1 year after seeking care at the primary care unit were obtained from the Swedish National Social Insurance Board 1 year after inclusion in the study. Data were gathered on the number of spells of sick leave, the number of days in each period and on the proportion (25%, 50%, 75% or 100%) of full-time employment. The total number of days on sick leave was calculated for the period 3 months before to 6 months after seeking care at the primary care unit. Days compensated with sickness benefit or rehabilitation benefit were summed up. For each new period of sick leave found in the register, a period of 14 days paid for by the employer were added. Part-time compensation was converted to full-time (e.g. 10 days on half-time sick leave was registered as 5 whole days during that period). The enrolled group of care-seekers was divided into tertiles (<29, 29–121, and >121 days) based on the distribution of the length of their sick leave.

Statistical methods

Analysis of the associations between HRV and the length of sick leave was performed using repeated measures mixed models, using an autoregressive model for the covariance structure. Sick leave was entered as categorical variables using the first tertile (i.e. <29 days) as reference. An initial analysis showed that men and women could be combined, and therefore the fully adjusted statistical models included gender, age, and test condition as covariates, as well as the total OMPQ score and work pace and offensive behaviours from COPSOQ. When analysing the association with sick leave, the analysis indicated that comparable test conditions could be combined. Therefore, *supine rest 1* and *supine rest 2* were considered repeated measurements in the *supine rest* condition; *seated clinic* and *seated home* were considered repeated measurements in the *seated* condition; and lastly, *head-up tilt* and *standing* repeated measurements in the *upright* condition. *Sleep* was retained as a condition of its own. The two reactivity variables (*reactivity 1* and *reactivity 2*) were considered to be 2 repeated measurements of the *supine-to-upright change*. In hypothesis testing, a 2-tailed probability $p \leq 0.05$ was considered significant. *p*-values in *post-hoc* statistical testing were adjusted for multiple comparisons using Bonferroni correction. All analyses were made by use of SPSS/PASW version 18.0.

RESULTS

Influence of test condition on heart rate variabilty

Table II shows heart rate and HRV in the orthostatic test, standing, seated rest and sleep situations. As expected, and in accordance with previous results in healthy subjects (11, 19), head-up tilt resulted in increased heart rate, lower HRV, and a significant decrease in ln(LF/HF). Standing induced the same changes in HRV, except that there was no significant change in ln(LF). HRV measured during the second supine rest, seated in the clinic or during sleep did not differ significantly from HRV measured during the first supine rest. Seated at home was associated with lower ln(LF) and higher heart rate compared with supine rest 1.

Table II. *Heart rate variability (HRV) in different conditions (supine rest, head up tilt, standing, seated in the clinic, seated at home, and during sleep)*

HRV	Supine rest 1 (n=61) Mean (SD)	Head up tilt (n=64) Mean (SD)	Supine rest 2 (n=58) Mean (SD)	Standing (n=64) Mean (SD)	Seated clinic (n=62) Mean (SD)	Seated home (n=59) Mean (SD)	Sleep (n=63) Mean (SD)
BPM	69.2 (8.6)	83.4 (10.8)***	67.0 (7.9)	82.9 (10.1)***	70.4 (9.1)	76.1 (11.6)**	68.1 (8.1)
ln(TP)	7.54 (0.79)	6.84 (0.93)***	7.62 (0.80)	7.11 (0.90)**	7.65 (0.77)	7.21 (0.88)	7.21 (0.96)
ln(LF/HF)	0.82 (0.68)	1.85 (0.79)***	0.75 (0.79)	1.94 (0.77)***	0.93 (0.78)	0.85 (0.82)	0.53 (1.08)
ln(LF)	6.36 (0.85)	5.97 (0.94)*	6.43 (0.80)	6.25 (1.07)	6.46 (0.92)	5.94 (1.00)**	5.94 (1.05)
ln(HF)	5.54 (1.17)	4.12 (1.22)***	5.68 (1.18)	4.31 (1.16)***	5.53 (1.19)	5.09 (1.43)**	5.40 (1.26)

Significantly different from mean at supine rest 1: *$p<0.05$; **$p<0.01$; ***$p<0.001$ (mixed model).

BPM: beats per min; TP: total power; LF: low-frequency power; HF: high-frequency power.

Association between heart rate variability and length of sick leave

Table III shows the effect estimates of intermediate length sick leave and extended sick leave with short sick leave as reference adjusted for gender and age, by test condition (supine rest, seated, upright, supine-to-upright change, and sleep) (Model 1). For the two resting conditions, supine rest and seated, there was a consistent pattern of increased heart rate and lower HRV (in particular, ln(TP) and ln(LF)) associated with extended sick leave, but not with intermediate length sick leave. With regard to HRV in the upright body posture the effect estimates point in the same direction, but they did not obtain significance ($0.05 < p < 0.10$). There was no association between length of sick leave and HRV measured during sleep, nor between cardiovascular reactivity and length of sick leave.

Influence of psychosocial risk factors on the association between HRV and sick leave

The mediating roles of the total OMPQ score, work pace and offensive behaviours experienced at work were investigated by entering these variable in Model 1. A strong association between sick leave and heart rate and HRV remained after entering all 3 psychosocial variables (Table III, Model 2). Adjusting for offensive behaviours alone (in addition to gender and age) resulted in a marginal weakening of the associations between sick leave and ln(LFP) in the supine position, but did not alter the other associations (results not shown). Also, adjusting for total OMPQ score or work pace individually had no influence on the associations. Furthermore, adjusting for pain (OMPQ ratings of intensity and frequency of pain episodes) also did not weaken the associations between length of sick leave and HRV (results not shown).

Finally, we investigated the possible influence of medication and pain diagnosis on the associations between HRV and sick leave. Since widespread pain may be caused by autonomic nervous system dysfunction (20), we tentatively excluded subjects diagnosed with generalized pain (fibromyalgia). This did not alter the magnitude or the significance of the statistical associations between sick leave and HRV. Next, categorical variables encoding diagnosis classification (EODM vs ANSPM), use of centrally acting opioid analgesics (yes vs no), SSRI antidepressant (yes vs no) and sleeping medication (yes vs no) were inserted in Model 2 (Table III). Adjustment for these factors strengthened the associations. For example, supine position ln(LF/HF) became significant (difference between the long sick leave group and the reference group 0.50 (SD 0.22), $p = 0.05$). Among the medication and diagnosis variables, the use of opioid

Table III. *Heart rate variability (HRV) differences between sick leave groups (reference <29 days) by condition (supine rest, seated, upright, supine-to-upright change, sleep), adjusted for sex and age (model 1), and furthermore adjusted for total the Örebro Musculoskeletal Pain Questionnaire (OMPQ) score, work pace, and offensive behaviours at the workplace (model 2)*

		Model 1: Adjusted for gender and age				Model 2: Further adjusted for total OMPQ score, work pace, and offensive behaviours at work			
Activity	HRV	*p*-value	29–121 days vs <29 days Mean (SD)	>121 days vs <29 days Mean (SD)		*p*-value	29–121 days vs <29 days Mean (SD)	>121 days vs <29 days Mean (SD)	
Supine	BPM	0.024	2.9 (2.4)	7.3 (2.6)	*	0.033	2.6 (2.6)	8.9 (3.3)	*
	ln(TP)	0.025	0.01 (0.20)	–0.54 (0.21)	*	0.011	0.00 (0.21)	–0.75 (0.27)	*
	ln(LF/HF)	0.737	0.10 (0.17)	0.14 (0.18)		0.092	0.20 (0.18)	0.50 (0.23)	
	ln(LF)	0.036	0.02 (0.21)	–0.54 (0.23)	*	0.022	0.03 (0.22)	–0.71 (0.29)	*
	ln(HF)	0.082	–0.07 (0.29)	–0.67 (0.31)		0.006	–0.15 (0.30)	–1.21 (0.38)	**
Seated	BPM	0.018	1.9 (2.6)	8.0 (2.8)	*	0.020	2.8 (2.8)	10.5 (3.7)	*
	ln(TP)	0.064	–0.16 (0.20)	–0.50 (0.21)	*	0.005	–0.28 (0.21)	–0.91 (0.26)	**
	ln(LF/HF)	0.685	–0.15 (0.18)	–0.12 (0.19)		0.852	–0.07 (0.19)	0.06 (0.25)	
	ln(LF)	0.018	–0.10 (0.21)	–0.63 (0.23)	*	0.001	–0.20 (0.22)	–1.05 (0.28)	***
	ln(HF)	0.182	0.06 (0.31)	–0.52 (0.32)		0.022	–0.13 (0.32)	–1.11 (0.41)	*
Upright	BPM	0.066	5.9 (3.0)	6.5 (3.2)		–	–	–	
	ln(TP)	0.068	0.13 (0.23)	–0.45 (0.25)		–	–	–	
	ln(LF/HF)	0.559	0.21 (0.20)	0.02 (0.22)		–	–	–	
	ln(LF)	0.058	0.14 (0.25)	–0.50 (0.26)		–	–	–	
	ln(HF)	0.232	–0.06 (0.29)	–0.52 (0.31)		–	–	–	
Supine-to-upright change	BPM	0.188	3.7 (2.1)	0.7 (2.2)		–	–	–	
	ln(TP)	0.689	0.16 (0.19)	0.02 (0.20)		–	–	–	
	ln(LF/HF)	0.506	0.20 (0.22)	–0.07 (0.23)		–	–	–	
	ln(LF)	0.538	0.19 (0.20)	–0.03 (0.21)		–	–	–	
	ln(HF)	0.994	–0.01 (0.26)	0.02 (0.27)		–	–	–	
Sleep	BPM	0.270	0.1 (2.4)	3.8 (2.6)		–	–	–	
	ln(TP)	0.362	0.38 (0.26)	0.16 (0.28)		–	–	–	
	ln(LF/HF)	0.782	0.20 (0.29)	0.08 (0.31)		–	–	–	
	ln(LF)	0.427	0.31 (0.29)	–0.05 (0.31)		–	–	–	
	ln(HF)	0.784	0.11 (0.32)	–0.13 (0.34)		–	–	–	

Post-hoc test of difference between sick leave groups (reference: <29 days): significantly different from zero, *$p<0.05$; **$p<0.01$; ***$p<0.001$ (mixed model, Bonferroni corrected).

SD: standard deviation; BPM: beats per min; TP: total power; LF: low-frequency power; HF: high-frequency power.

analgesics and sleeping medication were both associated with increased heart rate. Moreover, the use of opioid analgesics was associated with increased ln(LF/HF) (results not shown). These effects were significant after adjustment for other effects, including gender, age, diagnosis classification and uses of the other medications mentioned above.

DISCUSSION

The present results show that a higher heart rate and a lower HRV during resting conditions in the wake state were longitudinally related to prolonged sick leave beyond 121 days in care-seeking individuals in spite of the fact that they received an evidence-based CBT-team intervention. Low HRV, which was observed both in LF and HF, indicates a reduced autonomic modulation of the heart rate with no overall change in the sympatho-vagal balance.

To our knowledge, this is the first time autonomic regulation has been shown to be associated with length of sick leave in persons on musculoskeletal pain-related sick leave. It has, however, long been known that various chronic pain states are associated with signs of altered autonomic functioning. Thus, patients with fibromyalgia syndrome show higher heart rate and lower HRV in the supine position compared with controls (21) as well as changed dynamics, for example, a loss of circadian variation in sympatho-vagal balance (22) and blunted autonomic response to orthostatic challenge (23). Likewise, subjects with localized chronic pain, for example, low back pain or shoulder-neck pain also show signs of altered autonomic regulation (24–26). Interestingly, Gockel et al. (27) found that perceived disability but not pain ratings, was associated with lower total HRV and lower parasympathetic modulation of heart rate in patients with low back pain. Also relevant is the finding that autonomic dysfunction is associated with reduced psychomotor abilities in a group of elderly subjects (28). In general, a role of autonomic dysfunction has been suggested in unspecific symptoms, such as pain, discomfort, fatigue, mood changes, etc. (20, 29, 30). Thus, the lines of evidence suggest that autonomic dysregulation is associated with some forms of reduced well-being, deteriorated health and complicated psychosocial interactions, which could translate into longer sick leave in persons on musculoskeletal pain-related sick leave.

However, HRV is not only an indicator of physical health. HRV in apparently healthy subjects indexes the dynamic balance between central nervous system (CNS) structures involved in adaptation of the organism to perceived environmental challenges (4), and it therefore correlates with emotional and behavioural flexibility (4, 5). The associations between HRV and behaviours such as persistence and self-regulatory strength (7) and coping with daily life stressors (10) suggests that behavioural and emotional tendencies associated with high HRV could play a role in tackling the daily life challenges, and this, rather than reduced wellbeing or poor health, may be the mechanism linking autonomic functioning with sick leave.

The association between HRV and length of sick leave remained unaffected by adjustment for perceived pain and psychosocial factors. This suggests that the type of reduced well-being measured by OMPQ does not explain the associations. Work-related stress also does not explain the associations between HRV and sick leave.

There was no significant association between length of sick leave and HRV measured in the upright body posture, although the association was close to being statistically significant. The lack of significance may be due the higher variability in HRV during this condition. There was also no association between HRV measured during sleep and sick leave. This supports the above-mentioned interpretation of the importance of the cognitive component in the mechanism of association.

A lack of association with sick leave was also found for the supine-to-upright difference in HRV. Altered HRV responses to an orthostatic challenge are seen in fibromyalgia syndrome patients (23) as well in relation to certain personality traits, such as anxiety (31, 32) and anger (33), where it might reflect a dysregulation of cerebral structures involved in controlling emotional expressions (34, 35). Thus, our results are not in accordance with a central dysregulation of the kind observed in fibromyalgia patients or in subjects with prominent anger or anxiety personality traits.

Some strengths and limitations of this study need to be addressed. Among the strengths of the study are the objective nature of the outcome and main predictor, the longitudinal nature of the study, and the use of an internal reference group. Excluding subjects with fibromyalgia, which is known to possibly be associated with autonomic dysfunction, or adjusting for class of diagnosis (EODM vs ANSPM) did not affect the associations. In addition, adjusting for the use of various classes of medication did not change the results. Hence, it is unlikely that associations between HRV and sick leave are due to confounding from these factors. Among the limitations are the limited number of subjects, which reduced the possibilities to investigate the moderating effects of age and gender. Because of the lack of information about physical fitness we were not able to investigate the role of this factor. It is likely that physical fitness may shorten the length of sick leave. Both leisure-time physical activity levels and objectively measured cardiorespiratory fitness has been found to correlate with high HRV (36, 37). Hence, it might be the case that people with sedentary lifestyles and poor physical resources more easy develop pain-related conditions and need longer to recover. On the other hand, other studies have found little or no association between autonomic regulation and physical activity levels (38). With regard to HRV measured during sleep, it should be mentioned that cardiac autonomic activity is strongly dependent on the sleep stage. In particular, rapid eye movement (REM) sleep is associated with activity similar to that of the awake state, in contrast to non-REM sleep, which is associated with predominant parasympathetic autonomic activity (39). We have no information about the sleep stage during our measurements. However, HRV measurements were conducted early in the sleep cycle, as it is well-known that REM sleep mainly occurs late in the sleep cycle in normal sleep (40).

In conclusion, we demonstrated that higher heart rate and altered autonomic regulation expressed as reduced sympathetic and parasympathetic modulation of heart rate in wake-resting conditions were associated with prolonged sick leave in care-seeking individuals, in spite of receiving an evidence-based CBT-team intervention in order to facilitate the process of return to work.

Because of the explorative nature of this study, further research is needed to clarify the underlying nature and causal role of altered autonomic regulation with regard to pain-related sick leave.

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