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Brief Research Report

The Association of (Effective and Ineffective) Analgesic Intake, Pain Interference and Heart Rate Variability in a Cross-Sectional Occupational Sample

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Abstract

Objective. Persistent pain is associated with dysfunction of the autonomic nervous system, in particular a loss of vagal inhibitory control, that can be indexed by decreased vagally mediated heart rate variability (vmHRV). Effective treatment (e.g., analgesic self-medication) may lead to a restoration of vmHRV. The objective of this article was to further explore the relationship of pain and vagal control and to investigate the effect of analgesic self-medication on the association of vmHRV and pain.

Methods. We used a large cross-sectional data set on pain ratings and analgesic intake from the Mannheim Industrial Cohort Study for secondary analysis. The root mean square of successive differences, a measure of vmHRV corresponding to the parasympathetic regulation of the heart, was derived from 24-hour electrocardiogram recordings.

Results. The frequency of analgesic intake and interference of pain are significantly associated. Individuals that report greater pain interference with their normal work routine (including both work outside the home and housework) and frequent analgesic intake have significantly lower vmHRV. Subjects with ineffective analgesic intake (reporting great pain interference and high frequent analgesic intake) had the lowest vmHRV. Individuals effectively taking analgesics (reporting no or low pain interference and high frequent analgesic intake) showed greater vmHRV compared to those ineffectively taking. Analysis revealed significant differences and linear trends on vmHRV between all groups.

Conclusion. In line with previous research, vmHRV is inversely associated with pain interference. Analgesic intake mediates the association of vmHRV and pain. Effective analgesic self-medication may lead to a restoration in vmHRV. These results further support the vagus nerve as an objective indication of pain severity and treatment efficacy in patients with persistent pain.

Key Words. Analgesic Intake; Heart Rate Variability; Vagus Nerve; Inhibitory Pathways

Introduction

The persistent experience of pain can lead to dysfunction of the autonomic nervous system (ANS). The beat-

Table 1 Sample characteristics

Sample Characteristics	
N (w/m)	4742 (844/3898)
Age, mean years (SD)	41.07 (10.99)
BMI, mean kg/m^2 (SD)	25.87 (4.02)
Analgesic intake, *n* (%)	
Never	2487 (52.4)
Seldom	1695 (35.7)
Sometimes per month	458 (9.7)
Sometimes per week	71 (1.5)
Daily	31 (0.7)
Pain interference, *n* (%)	
Not at all	2635 (55.6)
A little bit	1467 (30.9)
Moderately	406 (8.6)
Quite a bit	195 (4.1)
Extremely	39 (0.8)
SF-12 scores, mean *t*-score (SD)	
Global health	47.33 (9.00)
Mental health	47.99 (9.71)
Physical health	52.22 (7.11)
Self-rated health, *n* (%)	
Poor	39 (0.8)
Fair	553 (11.7)
Good	2306 (48.6)
Very good	1570 (33.1)
Excellent	274 (5.8)
Night RMSSD, ms (SD)	42.75 (22.28)
Day RMSSD, ms (SD)	29.49 (13.29)
24-hour RMSSD, ms (SD)	36.12 (16.82)
Other medication, *n* (%)	
Blood pressure	440 (9.3)
Blood lipid	173 (3.6)
Blood glucose	43 (0.9)

to-beat variation in the heart rate (HR), heart rate variability (HRV), is mainly driven by the ANS and allows teasing out the relative contributions of sympathetic and parasympathetic activity underlying autonomic control of the heart. Reduced HRV compared with healthy controls is reported in patients with complex regional pain syndrome [1], fibromyalgia [2], chronic neck pain [3], irritable bowel syndrome [4], and headache [5,6]. Furthermore, lower HRV is associated with extended pain related sick leave in employees [7]. Thus, HRV is of interest as a potential biomarker for specific pain related diseases [8].

Recently, we provided evidence that pain is inversely correlated to decreased vagal control indexed by vagally mediated HRV (vmHRV) in healthy subjects [9] and a large cross-sectional occupational cohort [10]. A decrease in vagal activity mirrors a disruption in one of the major descending inhibitory pathways involved in the endogenous modulation of the processing of nociceptive information. Suppression of vagally mediated descending inhibitory pathways results in greater somatic and visceral input via the spinothalamic track, which in turn may provide a mechanism underlying increased pain sensitivity in those with chronic pain. We, therefore, propose that impaired vagal control contributes to the central sensitization in chronic pain leading to an increase in the excitability of neurons in the central nervous system [11] and a shift to emotion-related circuitry activity in the brain [12].

In addition to serving as a potential pathway involved in the chronification of pain, vmHRV may further provide an additional outcome for the relief of pain due to therapeutic interventions, resulting in a restoration of HRV measures [13–15]. Recent experimental research has shown that ventral periaqueductal gray stimulation increases vmHRV and decreases pain in individuals with chronic pain [16], suggesting that analgesia with deep brain stimulation in chronic pain is associated with increased vagal parasympathetic activity. Pharmaceutical analgesic self-medication is common and broadly accepted in individuals that experience pain. Recently, we found an association of ibuprofen use and HRV in a small sample of subjects [17]. This article aims to further explore the association of pain interference, analgesic self-medication, and HRV in a large cross-sectional sample of 4,742 individuals.

Methods

We used a large cross-sectional data set from the Mannheim Industrial Cohort Study for secondary analysis. The data was collected as part of a voluntary health risk assessment that was offered to all employees

Table 2 Contingency table analysis on the relation of analgesic intake and pain interference

	Analgesic Intake, *n* (%)					
Pain Interference, *n*	Never	Seldom	Sometimes/month	Sometimes/week	Daily	Total
Not at all	1656 (66.6)	854 (50.4)	116 (25.4)	5 (7.0)	4 (12.9)	2635 (55.6)
A little bit	621 (25.0)	616 (36.3)	204 (44.5)	23 (32.4)	3 (9.7)	1467 (30.9)
Moderately	141 (5.7)	160 (9.4)	79 (17.2)	19 (26.8)	7 (22.6)	406 (8.6)
Quite a bit	57 (2.3)	56 (3.3)	50 (10.9)	19 (26.8)	13 (41.9)	195 (4.1)
Extremely	12 (0.5)	9 (0.5)	9 (2.0)	5 (7.0)	4 (12.9)	39 (0.8)
Total	2487 (52.4)	1695 (35.7)	458 (9.7)	71 (1.5)	31 (0.7)	

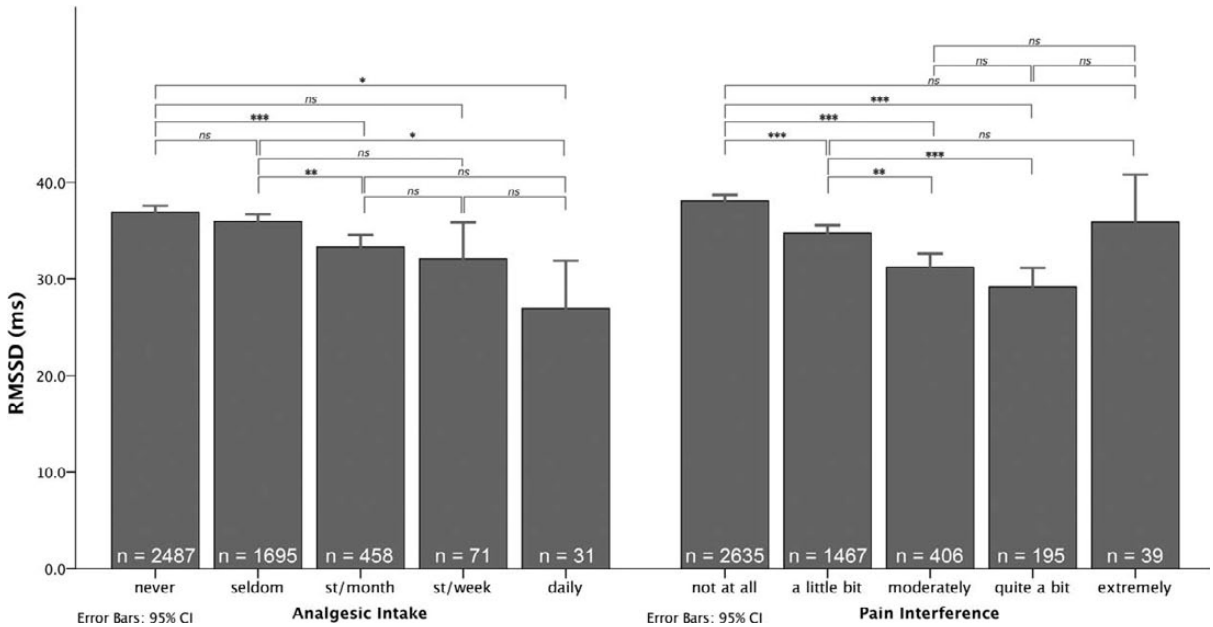

Figure 1 Group difference on RMSSD based on analgesic intake and pain interference; illustrated are Bonferroni-posthoc comparisons; *: indicates a significant difference $P < 0.05$; **: indicates a significant difference $P < 0.01$ ***: indicates a significant difference $P < 0.001$; ns: not significant.

during working hours. An agent independent from the employer conducted the health risk assessments and data collection (HealthVision Ltd., Berlingen, Switzerland). A total of 13 study sites (Companies from the secondary and tertiary sectors) from all over Germany with a total of 14,469 participants collected between 2010 and 2012 were available. Participants were invited to take part in the "Work Health Check" and were offered a detailed individual report containing their health status as assessed by medical examination and self reports. This sample encompassed the entire workforce between 17 and 65 years. The Ethical Committee of the Mannheim Medical Faculty, Heidelberg University, approved secondary analysis of this data. All participants gave written informed consent prior to examination. Details on the measurements and population are published elsewhere [18,19]. After completing an online questionnaire, participants were able to schedule a medical examination including a 24-hour recording of HR.

Demographic variables (age and sex) were obtained from the online questionnaire. The questionnaire had to be completed prior to being able to schedule the medical examination. All participants were enrolled and examined between 10 AM and 5 PM on a typical workday (Monday–Friday) during work hours. On arrival, a medical examination was performed. Subjects' body measures (weight and height) were taken and BMI was obtained according to common calculation (kg/m^2), as classified according to the WHO standard [20]. Three scores (general health, physical health, and mental health score) were derived from the SF-12 questionnaire [21] and used as a self-reported measure of health related quality of life, with greater T scores indicating greater health related quality of life. Self-rated health (SRH) was assessed using the first item of the SF-12 ("In general, would you say your health is…"), with response categories ("excellent," "very good," "good," "fair," "poor"). Item number 8 of the SF-12 questionnaire ("During the past 4 weeks how much did pain interfere with your normal work [including both work outside the home and housework]?") was used as pain-related measure for further analysis. Response categories were: 1) "not at all," 2) "a little bit," 3) "moderately," 4) "quite a bit," or 5) "extremely." Analgesic intake was assed by a single item, asking subjects "Do you take analgesics occasionally or regularly?" Participants had to indicate their answer as 1) "never," 2) "seldom," 3) "sometimes per month," 4) "sometimes per week," or 5) "daily."

Furthermore, we aimed to further control for medication intake other than analgesics. We were able to retrieve data on the intake of medication against high blood pressure, high blood lipid, and high blood glucose. These variables were scored dichotomously (taking/not taking) and some of the included subjects had missing data (blood pressure: $n = 30$; blood glucose: $n = 39$; blood lipid: $n = 38$).

HRV

HR was recorded as beat-to-beat intervals (IBI) using a t6 Suunto Memory Belt (SuuntoVantaa, Finland), sampling at a rate of 1,000 Hz. The IBI represents the time

Table 3 Differences between groups based on analgesic intake and pain interference

Groups by Analgesic Intake	Never	Seldom	Sometimes/month	Sometimes/week	Daily	*P*	Linearity
n, sex (m/w)	2487 (2193/294)	1695 (1320/375)	458 (307/151)	71 (52/19)	31 (26/5)		
Age, mean years (SD)	41.28 (11.28)	40.49 (10.66)	41.15 (10.46)	44.16 (10.21)	48.76 (10.29)	<0.001	0.094
BMI, mean kg/m^2 (SD)	25.75 (3.91)	25.92 (4.08)	26.02 (4.23)	26.96 (4.39)	28.02 (4.88)	0.002	0.001
Night RMSSD, mean ms (SD)	43.87 (22.83)	42.49 (22.19)	39.08 (19.18)	38.44 (21.18)	31.76 (17.33)	<0.001	<0.001
Day RMSSD, mean ms (SD)	30.02 (13.63)	29.59 (13.28)	27.12 (11.14)	26.96 (12.33)	22.75 (11.30)	<0.001	<0.001
24-hour RMSSD, mean ms (SD)	36.94 (17.32)	36.04 (16.69)	33.10 (14.11)	32.70 (15.83)	27.25 (13.91)	<0.001	<0.001
SF-12: General health, mean *T*-score (SD)	48.78 (8.4)	47.11 (8.70)	42.95 (9.48)	35.79 (9.57)	35.00 (11.73)	<0.001	<0.001
SF-12: Mental health, mean *T*-score (SD)	48.92 (9.30)	47.68(9.73)	45.09 (10.37)	42.33 (12.31)	46.62 (10.98)	<0.001	<0.001
SF-12: Physical health, mean *T*-score (SD)	53.49 (6.24)	52.09 (6.60)	48.38 (8.32)	42.00 (10.56)	36.89 (11.69)	<0.001	<0.001
Other medication: blood pressure,* *n* (%)	228 (9.2)	138 (8.2)	54 (11.9)	9 (13.0)	11 (42.3)	<0.001	
Other medication: blood lipid,* *n* (%)	80 (3.2)	53 (3.2)	26 (5.8)	7 (10.1)	7 (26.9)	<0.001	
Other medication: blood glucose,* *n* (%)	22 (0.9)	6 (0.4)	7 (1.6)	4 (5.9)	4 (15.4)	<0.001	
Groups by Pain Interference	**Not at All**	**A Little Bit**	**Moderately**	**Quite a Bit**	**Extremely**	***P***	**Linearity**
n, sex (m/w)	2635 (2194/441)	1467 (1179/288)	406 (323/83)	195 (166/29)	39 (36/3)		
Age, mean years (SD)	39.45 (11.03)	41.99 (10.66)	44.93 (10.16)	47.32 (9.58)	44.42 (9.94)	<0.001	<0.001
BMI, mean kg/m^2 (SD)	25.43 (3.84)	26.20 (4.11)	26.67 (4.24)	27.66 (4.45)	25.79 (3.16)	<0.001	<0.001
Night RMSSD, mean ms (SD)	45.27 (23.02)	40.95 (21.24)	36.84 (20.07)	34.88 (18.61)	41.11 (21.54)	<0.001	<0.001
Day RMSSD, mean ms (SD)	30.97 (13.61)	28.61 (13.16)	25.79 (11.08)	24.23 (10.85)	28.10 (11.18)	<0.001	<0.001
24-hour RMSSD, mean ms (SD)	38.12 (17.27)	34.78 (16.33)	31.32 (14.63)	29.55 (13.99)	34.60 (15.25)	<0.001	<0.001
SF-12: General health, mean *T*-score (SD)	50.7 (7.28)	45.36 (7.87)	40.02 (8.51)	33.79 (8.71)	33.19 (14.00)	<0.001	<0.001
SF-12: Mental health, mean *T*-score (SD)	49.53 (8.73)	46.95 (9.81)	44.57 (10.81)	42.60 (12.80)	45.44 (13.81)	<0.001	<0.001
SF-12: Physical health, mean *T*-score (SD)	56.17 (3.55)	50.26 (4.66)	43.57 (5.83)	35.78 (6.74)	30.41 (9.95)	<0.001	<0.001
Other Medication: Blood pressure,* *n* (%)	181 (6.9)	156 (10.7)	55 (13.8)	44 (23.3)	4 (11.1)	<0.001	
Other medication: blood lipid,* *n* (%)	69 (2.6)	49 (3.4)	33 (8.4)	18 (9.6)	4 (10.8)	<0.001	
Other medication: blood glucose,* *n* (%)	14 (0.5)	10 (0.7)	10 (2.5)	7 (3.7)	2 (5.4)	<0.001	

* Includes missing data; *P* values are derived from ANOVA or chi-square test for categorical variables.

Table 4 Posthoc comparison on RMSSD by analgesic intake and pain interference

RMSSD by Analgesic Intake, Bonferroni Posthoc Comparisons										
24-hour RMSSD	Never		Seldom		Sometimes/ month		Sometimes/week		Daily	
ANOVA	MD	*P*	MD	*P*	MD	*P*	MD	*P*	MD	*P*
Never	–	–	0.91	0.885	3.84	<0.001	4.25	0.358	9.69	0.014
Seldom	−0.90	0.885	–	–	2.94	0.009	3.34	1.00	8.79	0.039
Sometimes/month	−3.84	<0.001	−2.94	0.009	–	–	0.40	1.00	5.85	0.602
Sometimes/week	−4.25	0.358	−3.34	1.00	−0.40	1.00	–	–	5.45	1.00
Daily	−9.69	0.014	−8.79	0.039	−5.85	0.602	−5.45	1.00	–	–
RMSSD by Pain Interference, Bonferroni Posthoc Comparisons										
24-hour RMSSD	Not at all		A Little Bit		Moderately		Quite a Bit		Extremely	
ANOVA	MD	*P*	MD	*P*	MD	*P*	MD	*P*	MD	*P*
Not at all	–	–	3.34	<0.001	6.80	<0.001	8.57	<0.001	3.52	1.00
A little bit	−3.34	<0.001	–	–	3.46	0.002	5.22	<0.001	0.19	1.00
Moderately	−6.80	<0.001	−3.46	0.002	–	–	1.76	1.00	−3.29	1.00
Quite a bit	−8.57	<0.001	−5.22	<0.001	−1.76	1.00	–	–	−5.05	0.836
Extremely	−3.52	1.00	−0.18	1.00	3.29	1.00	5.05	0.836	–	–

in milliseconds between two adjacent heartbeats. The Suunto Memory Belt is a reliable measure of electrocardiography (ECG) compared with a five-lead ECG. IBIs were determined as the interval between two successive R-spikes. After attaching the ambulatory HR recorder, participants commenced their routine work duties followed by after work leisure and sleep activities. Participants were asked to return the HR recorder after a minimum of 22 hours of wearing or in case of any difficulties. The root mean-squared successive differences (RMSSD) between adjacent R-R intervals, measured in milliseconds, were averaged from 24-hour long-term HR monitoring (beat to beat) for daytime and nighttime as well as 24 hours as indicators of vagal tone. RMSSD is considered to be a stable [22], and valid [23], time-domain measure of vmHRV, reflecting parasympathetic influence. Raw IBIs were analyzed by researchers at the Center for Neuropsychological Research (University of Trier, Germany) according to the "Task Force Guidelines of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology" [24]. The 24-hour IBI-data was decomposed into blocks of 5.35 minutes each and subjected to further analysis if the artifact rate was below 5%.

Statistical Analysis

Only participants with complete data on all variables were included for the present analysis ($n = 4{,}742$). A contingency table analysis and chi-square test was used to examine the relationship between analgesic intake and interference of pain. Differences on continuous variables between groups based on ratings of analgesic intake and pain interference were analyzed using analysis of variance (factor: group), tests for linearity and Bonferroni posthoc comparisons. Differences on categorical variables (medication other than analgesics) between groups were analyzed using chi-square tests. Comparisons were further adjusted for age (continuous), sex (categorical), and BMI (continuous) within linear regression models on 24-hour RMSSD as the dependent variable. Finally, we addressed the effect of medication intake other than analgesics using an additional regression analysis.

A composite categorical variable was created to further investigate the association of analgesic intake and interference of pain and their impact on RMSSD. Subjects were stratified into four groups based on their reported analgesic intake and interference of pain within the last four weeks. Subjects that reported no interference of pain (1 or 2; "not at all" or "a little bit") and no analgesic intake (1 or 2; "seldom" or "never") were assigned to the group "not in need and not taking analgesics" ($n = 3747$). Subjects that reported interference of pain (3, 4, or 5; "moderately," "quite a bit," or "extremely") but did not use analgesics (1 or 2; "seldom" or "never") were assigned to the group "in need but not taking analgesics" ($n = 435$). Subjects that reported use of analgesics (3, 4, or 5*;* "sometimes a month," "daily," or "sometimes per week") and no more interference of pain (1 or 2; "not at all" or "a little bit") were assigned to the group "effectively taking analgesics" ($n = 355$). Finally, subjects that reported use of analgesics (3, 4, or 5; "sometimes a month," "daily," or "sometimes per week") and still pain interference (3, 4, or 5; "moderately," "quite a bit," or "extremely") were assigned to the group "ineffectively taking analgesics" ($n = 205$). Differences between these groups on RMSSD

Table 5 Results from linear regression analysis on predictors of 24-hour RMSSD

	Zero-Order *r*				Linear Regression Models 1–5				Full Model			
Variable/Model	Sex	Age	Pain Interference	Analgesic Intake	24-hour RMSSD	*B*	Std. Error	*β*	*P*	*B*	Std. Error	*β*	p
1. Analgesic intake					−0.077**	−1.68	0.315	−0.077	<0.001	−0.96	0.279	−0.044	.001
2. Pain interference				−0.335**	−0.144**	−2.60	0.297	−0.134	<0.001	−0.28	0.251	−0.014	.269
3. Age			0.192**	−0.017	−0.562**	−0.85	0.019	−0.558	<0.001	−0.86	0.019	−0.564	< .001
4. Sex		−0.165**	0.010	−0.164**	−0.005	−4.04	0.538	−0.092	<0.001	−4.42	0.547	−0.100	< .001
5. BMI		−0.209**	0.248**	0.131**	−0.049**	−0.169**				−0.19	0.052	−0.046	< .001

Zero-order correlations show the unadjusted correlation of the dependent variable (24-hour RMSSD) and each predictor variable; Linear Regression Models 1–5: show the stepwise regression models adding the predictor variables (1–4); Full-Model: shows the results from the full regression model including all predictor variables (1–5).
** Significant zero-order correlation on the $P < .01$ level.

were further analyzed using analysis of variance (factor group) and Bonferroni posthoc comparisons. All tests were considered statistically significant if $P < 0.05$. Data management and analysis were performed using SPSS (21, IBM Chicago, IL, USA).

Results

Characteristics of the study population are depicted in Table 1. The mean age was 41.07 years (standard deviation = 10.99), and 82.2% of the population was male. The majority of the study population reported not using analgesics (52.4%), no pain interference within the last 4 weeks (55.6%), and good SRH (48.6%). Analgesic intake and interference of pain were found to be significantly associated (χ^2 [16, $n = 4742$] = 727.18, $P < 0.001$), indicating that subjects with greater pain interference were more likely to report analgesic intake (Table 2).

Groups by analgesic intake as well as those formed based on the reporting of pain interference significantly differed on all included variables (Table 3), with linear trends. Bonferroni posthoc comparisons on differences on 24-hour RMSSD between groups based on analgesic intake (Table 4) revealed that subjects reporting more analgesic intake had lower RMSSD (Figure 1). Differences on 24-hour RMSSD were significant comparing subjects *never* using analgesics to those reporting to use analgesics *sometimes a month* (Mean difference [MD]: 3.84 ms; 95% confidence interval lower and upper bound [CI]: 2.17–5.52 ms) and on *daily* basis (MD: 9.69 ms; 95% CI: 3.75–15.63 ms). Subjects that reported *seldom* intake of analgesics significantly differed on 24-hour RMSSD from those reporting to use analgesics *sometimes a month* (MD: 2.94 ms; 95% CI: 1.20–4.67 ms) and on *daily* basis (MD: 8.79 ms; 95% CI: 2.83–14.74 ms).

Posthoc comparisons on differences on 24-hour RMSSD between groups based on pain interference (Table 4) showed a similar pattern revealing that subjects that reported greater interference of pain had lower 24-hour RMSSD (Figure 1)—except for those reporting that pain caused greatest interference with their work during the last 4 weeks ($n = 39$). Again, analysis revealed a significant linear trend. Subjects that reported to be *not at all* interfered by pain significantly differed on 24-hour RMSSD from those reporting to be interfered *a little bit* (MD: 3.34 ms; 95% CI: 2.28–4.40 ms), *moderately* (MD: 6.80 ms; 95% CI: 5.06–8.54 ms), and *quite a bit* (MD: 8.57 ms; 95% CI: 6.15–10.99 ms). Those reporting *a little bit* pain interference further differed on 24-hour RMSSD from those reporting *moderately* (MD: 3.46 ms; 95% CI: 1.63–5.29 ms) or *quite a bit* (MD: 5.22 ms; 95% CI: 2.74–7.71 ms) pain interference.

Multiple linear regression analysis was used to develop a model for predicting 24-hour RMSSD from reports on analgesic intake and pain interference controlling for *age*, *sex*, and *BMI*. Regression coefficients are given in

Table 6 Results from unadjusted and adjusted linear regression analysis on medication intake predicting 24-hour RMSSD; adjusted analysis control for age, sex, and BMI

	Unadjusted				Adjusted			
Medication Intake	*B*	Std. Error	β	*P*	*B*	Std. Error	β	*P*
1. Analgesic intake	−1.362	0.318	−0.062	<0.001	−1.037	0.269	−0.047	<0.001
2. Other medication: Blood pressure*	−7.273	0.880	−0.124	<0.001	0.941	0.766	0.016	0.219
3. Other medication: Blood lipid*	−6.418	1.366	−0.071	<0.001	−0.800	1.146	−0.009	0.485
4. Other medication: Blood glucose*	−4.405	2.686	−0.024	<0.001	0.122	2.241	−0.001	0.957

* Includes missing data.

Table 5. Except for *sex*, each of the predictor variables had a significant ($P < 0.001$) zero-order correlation with 24-hour RMSSD. Analgesic intake, age, sex, and BMI had significant ($P \leq 0.001$) partial effects in the full model. The regression model was able to account for 33% of the variance in 24-hour RMSDD ($F[5, 4736] = 468.513$, $P < 0.001$, $R^2 = 0.33$). Furthermore, regression analysis showed that analgesic intake significantly accounted for variance on 24-hour RMSSD even when controlling for other medication (Table 6).

Groups formed by the newly created composite variable combining analgesic intake and pain interference differed on all included variables (Table 7). Subjects with *ineffective analgesic intake* ($n = 205$, taking analgesics but still reporting pain) were significantly older than others and showed the poorest general health, mental health, and physical health. Bonferroni posthoc comparisons between groups on 24-hour RMSSD (Table 8) revealed that subjects with *ineffective analgesic intake* had the lowest RMSSD (Figure 2) significantly different from those *not in need (no pain) and not taking analgesics* (MD: −7.36 ms; 95% CI: −10.52 to −4.21 ms) and those *effectively taking anlgesics* (MD: −4.62 ms; 95% CI: −8.48 to −0.76 ms). Subjects *effectively taking analgesics* had greater 24-hour RMSSD (Figure 2) significantly different from those *not in need (no pain) and not taking analgesics* (MD: −2.74 ms; 95% CI: −5.18 to −0.30 ms).

Discussion

This analysis aimed to further explore the association of pain, analgesic intake, and vagal control, indexed by vmHRV. In line with previous studies, we found pain and vmHRV to be inversely related [9,10]. Individuals that reported greater pain interference within the last 4 weeks had lower RMSSD. A similar association was observed for vmHRV and the frequency of analgesic intake, as previously suggested by preliminary findings [17]. Again, individuals that reported frequent use of analgesics had lower RMSSD.

Pain interference and analgesic intake were significantly associated, indicating that those with greater pain interference are more likely to take analgesics on a regular basis. Furthermore and in line with common findings, subjects with greater pain interference were older and reported lower general, mental, and physical health related quality of life. The study adds two major findings. First, individuals that report frequent intake of analgesics but still report greatest pain interference (*ineffectively taking analgesics*) have the lowest vmHRV. Second, individuals that report frequent intake of analgesics and no pain interference (effectively taking analgesics) show a relative increase in vmHRV compared to those with ineffective analgesic intake. These findings have several implications. In line with interventional studies in chronic pain patients [13–15] and recent results from experimental trials, effective treatment of pain can be mirrored by a restoration in vmHRV. Furthermore, ineffective treatment can cause lower vmHRV than notreatment.

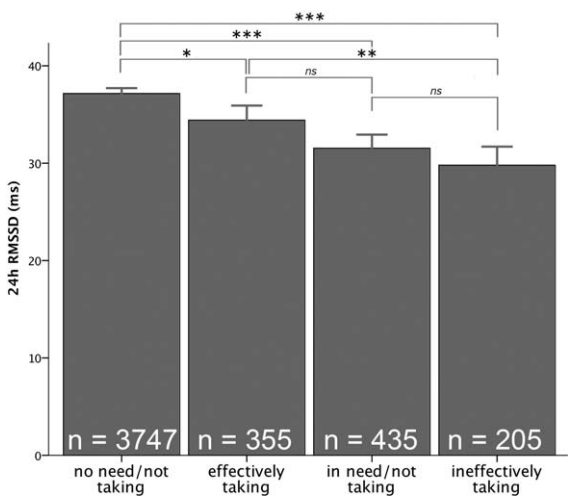

Figure 2 Group difference on RMSSD based on composite categorical variable; illustrated are Bonferroni-posthoc comparisons; *****: indicates a significant difference $P < 0.05$; ******: indicates a significant difference $P < 0.01$ *******: indicates a significant difference $P < 0.001$; ns: not significant.

Table 7 Differences between groups based on composite categorical variable

Groups by Composite Categorical Variable	No Need/Not Taking	Effectively Taking	In Need/Not Taking	Ineffectively Taking	*P*
n, sex (m/w)	3747 (3140/607)	355 (233/122)	435 (373/62)	205 (152/53)	
Age, mean years (SD)	40.46 (11.03)	39.40 (10.18)	45.28 (10.13)	46.36 (9.75)	<0.001
BMI, mean kg/m^2 (SD)	25.69 (3.93)	25.81 (4.17)	26.88 (4.19)	26.99 (4.74)	<0.001
Night RMSSD, mean ms (SD)	44.00 (22.72)	40.78 (19.68)	37.31 (20.40)	34.79 (18.24)	<0.001
Day RMSSD, mean ms (SD)	30.31 (13.67)	28.05 (11.23)	25.77 (10.97)	24.80 (11.20)	<0.001
24-hour RMSSD, mean ms (SD)	37.16 (17.22)	34.42 (14.39)	31.54 (14.79)	29.79 (13.84)	<0.001
SF-12: General health, mean *T*-score (SD)	49.15 (7.83)	45.49 (8.26)	39.08 (0.32)	34.79 (9.18)	<0.001
SF-12: Mental health, mean *T*-score (SD)	48.86 (9.10)	45.96 (10.00)	44.61 (11.68)	42.79 (11.56)	<0.001
SF-12: Physical health, mean *T*-score (SD)	54.25 (4.80)	52.08 (5.33)	41.52 (7.32)	38.01 (8.15)	<0.001
Other medication: Blood pressure,* *n* (%)	302 (8.1)	35 (9.9)	64 (14.9)	39 (20.1)	<0.001
Other medication: Blood lipid,* *n* (%)	108 (2.9)	10 (2.8)	25 (5.9)	30 (15.6)	<0.001
Other medication: Blood glucose,* *n* (%)	21 (0.6)	3 (0.8)	7 (1.6)	12 (6.3)	<0.001

* Includes missing data; *P* values are derived from ANOVA or chi-square test for categorical variables.

This analysis has several limitations that need to be addressed. First, respondents did not indicate the type and dose of analgesics used. Different analgesics and different dosages might lead to differential effects on vmHRV. Future studies could be refined with details of type of analgesics used and mg doses and more definite time intervals. As our analysis is based on a four-choice categorical variable, they may underestimate the effect of analgesic intake. Second, cardiac medications, antihypertensives, antidepressants, and other anticholinergics can have a significant impact on vmHRV. While, we were able to partially control for the intake of medication against high blood pressure, high blood glucose, and high blood lipid, these analyses are preliminary and future studies need to address this issue with greater rigor. Given that participants reporting the greatest pain interference and analgesic intake also reported poorer physical and mental health and older age, it is conceivable that this group would be taking additional confounding nonanalgesic medications. Within this analysis, those who reported greater pain interference and who used analgesics more frequently also reported greater intake of medications other than analgesics. In particular, we were not able to control for the use of antidepressive medication [25]. Future studies need to control for a broad range of medications in greater detail and need to control for potential interaction effects of different medications.

Third, the composite variable combining analgesic intake and pain interference classifies individuals based on the assumption that, for example, those with effective analgesic intake report no pain interference because of their regular or daily intake of painkillers. While our

Table 8 Posthoc comparison on RMSSD by composite categorical variable

	RMSSD by Composite Categorical Variable, Bonferroni Posthoc Comparisons							
24-hour RMSSD ANOVA	No Need/Not Taking		Effectively Taking		In Need/Not Taking		Ineffectively Taking	
	MD	*P*	MD	*P*	MD	*P*	MD	*P*
No need/not taking	–	–	−2.74	0.018	−5.61	<0.001	−7.36	<0.001
Effectively taking	2.74	0.018	–	–	−2.88	0.95	−4.62	0.009
In need/not taking	5.62	<0.001	2.88	0.095	–	–	−1.75	1.00
Ineffectively taking	7.36	<0.001	4.62	0.009	1.75	1.00	–	–

analysis proved a significant correlation of pain interference and frequency of analgesic intake, we cannot draw a causal relationship. Controlled trials are necessary to investigate the direct effect of effective versus ineffective analgesic intake on vmHRV in subjects with pain.

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