Case-Control Study

Lack of Gender and Age Differences in Pain Measurements Following Exercise in People with Chronic Whiplash-Associated Disorders

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Background: Individuals with chronic whiplash associated disorders (WAD) present persistent pain in the absence of structural pathology. In these people, altered central pain processing and central sensitization are observed. The role of personal factors, such as gender and age, on pain processing mechanisms in chronic WAD, however, is still unclear.

Objectives: This study investigated possible gender- and age-related differences in self-reported and experimental pain measurements in people with chronic WAD. Besides the exercise-induced response on pain measurements between gender and age subgroups was recorded.

Study Design: Case-control study.

Setting: University Hospital, Brussels.

Methods: Self-reported pain and experimental pain measurements (pressure pain thresholds [PPT], occlusion cuff pressure, temporal summation, and conditioned pain modulation) were performed in 52 individuals (26 chronic WAD patients and 26 healthy controls), before and after a submaximal cycle exercise.

Results: Lower PPTs and occlusion cuff pressures were shown in chronic WAD in comparison with healthy controls. No gender and age differences regarding PPTs, occlusion cuff pressures and conditioned pain modulation were found in chronic WAD.

Within the chronic WAD group, men showed higher self-reported pain compared to women and younger adults showed enhanced generalized pain facilitation compared to older adults. In addition, chronic WAD patients are able to inhibit exercise-induced hyperalgesia, but no gender and age differences in pain response following exercise were found.

Limitations: This study was sufficiently powered to detect differences between the chronic WAD and control group. However, a sufficient power was not reached when patients were divided in age and gender groups. Furthermore, only mechanical stimuli were included in the experimental pain measurements. Besides, psychosocial factors were not taken into account.

Conclusion: Some alterations of altered pain processing are present in chronic WAD patients, however not in response to exercise. No gender and age differences in pain measurements were observed in people with chronic WAD.

Key words: Neck pain, whiplash associated disorders, chronic pain, personal factors, age, gender, central sensitization, exercise induced hyperalgesia, pressure pain thresholds, self reported pain

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Whiplash injuries occur due to an acceleration-deceleration mechanism of forces acting on the neck (e.g., motor vehicle collisions, diving, cycling, or other incidents). The indirect impact at the cervical spine may lead to the development of various clinical manifestations usually termed as whiplash-associated disorders (WAD). The main complaints of people with WAD are characterized by pain and disability (1). A substantial proportion of patients recover in the initial 3 months after the accident. After this period, recovery rates level off and people frequently develop chronic (pain) complaints (i.e., chronic WAD) (2,3).

Individuals with chronic WAD present persistent pain in the absence of structural pathology, with radiological imaging findings being more related to age than to the person's symptoms (3,4). There is indeed a growing body of evidence demonstrating the involvement of the central nervous system in the maintenance of symptoms after a whiplash trauma. Widespread hyperalgesia and impaired endogenous pain modulation, indicative for altered central pain processing and central sensitization (CS), were observed in people with chronic WAD (5-8).

The role of personal factors, such as gender and age, in experimental and clinical pain perception acquired more interest in the recent years (9-11). Gender differences appear to depend on the nature of the experimental paradigm. Women often show lower pain thresholds and experience greater temporal summation (TS) of pain to brief, repeated, stimuli or stimuli with a dynamic component, compared to men (12,13). On the other hand, a recent systematic literature review concluded that, among other factors, male gender is related to better conditioned pain modulation (CPM) (14). It is however suggested that women have mechanisms to modulate and cope with pain more effectively over longer time periods (12). These gender differences in human pain perception could underlie the increased incidence of some chronic pain conditions predominantly seen in females (13,15).

Studies investigating age differences in healthy adults have demonstrated mixed findings for measures of pain thresholds (16). Likewise, age differences for TS of pain are conflicting in healthy persons, with studies demonstrating greater TS at the forearm (17,18) and less TS at the foot in older individuals compared to their younger counterparts (19). Regarding CPM, in general, younger adults seem to present with better CPM than older adults (14).

It is appropriate to question whether such laboratory studies in healthy people are the best option to investigate individual differences in pain perception and whether we can extrapolate these results to chronic pain populations. Conducting laboratory studies of individual differences in participants with painful pathologies should enhance the clinical relevance of these experiments. Therefore, the primary purpose of this study is to examine possible gender- and age-related differences in self-reported pain, pain thresholds, TS, and CPM in people with chronic WAD.

Furthermore, it seems that people with chronic WAD are unable to activate central descending nociceptive inhibition in response to aerobic exercise as they demonstrate decreased pain thresholds and show symptom flares in response to aerobic exercise (20). Conversely, in healthy people aerobic exercise triggers the production of endorphins and activates other pain inhibitory mechanisms orchestrated by the brain (a phenomenon termed exercise-induced hypoalgesia) (21,22). Therefore, self-reported pain, pain thresholds, TS, and CPM will also be studied in response to aerobic exercise in men and women, and young and older adults with chronic WAD. Pre- to post-exercise differences will be compared between people with chronic WAD and healthy controls on the one hand, and between chronic WAD gender and age groups on the other hand.

We hypothesize that both older adults and women with chronic WAD will report higher pain levels, decreased pain thresholds, less efficient CPM, and enhanced TS compared to their younger and male counterparts, respectively. We expect to observe exercise-induced hyperalgesia and less efficacious endogenous pain modulation in all subgroups with larger insufficiencies in older adults and women with chronic WAD.

Methods

Study Design and Setting

This study was designed as a cross-sectional study in line with the STROBE Statement (www.strobe-statement.org/). All assessments took place at the University Hospital of Brussels. The study was approved by the ethics committee of the University Hospital Brussels/Vrije Universiteit Brussel and all participants gave written informed consent prior to the study.

Participants and Assessments

The study sample consisted of people with chronic WAD and a group of healthy inactive controls. Each

study participant had to be Dutch speaking and aged between 18 and 65 years. People with chronic WAD were recruited via the emergency department and the department of physical medicine and physiotherapy of the University Hospital Brussels (Belgium), a peripheral center for emergency medicine and rehabilitation, and through advertisements placed in the newsletter and on the website of a Belgian patient support group (vzw Whiplash). Individuals who had suffered a whiplash trauma at least 3 months ago and who initially did not fulfil the criteria of WAD grade IV (implying fracture or dislocation of the cervical spine) as defined by the Quebec Task Force classification (1) were eligible for study participation.

Healthy [pain-free and without any (chronic) disease] inactive controls were recruited from relatives, friends or acquaintances of researchers, students, university personnel, or patients participating in the study. Additionally, controls were also recruited through advertisements in public and private buildings (universities, hospitals, companies, and medical and physical therapy practices) and through social media (Facebook, Twitter). Being inactive was defined as practicing a profession that does not involve physical labor, and performing a maximum of 3 hours of moderate physical activity/week. Moderate physical activity was defined as activity demanding at least threefold the energy spent passively (23).

General exclusion criteria were the presence of neurologic, metabolic, orthopedic, cardiovascular, or inflammatory disorders. In order to preclude confounding factors, women who were pregnant or within one year postnatal were excluded. If applicable, participants were instructed to stop the use of opioid analgesics, and anti-depressive and anti-epileptic medications 2 weeks prior to study participation. On the day of the assessments they were asked not to undertake physical exertion and to refrain from non-opioid analgesics, beta-adrenergic blocking agents, caffeine, alcohol, and nicotine (if applicable).

On the day of data collection, study participants were first asked to read an information leaflet and had the chance to ask additional questions. Afterwards, they were asked to provide written informed consent. Secondly, after collecting personal characteristics (age, gender, height, body mass, disease duration, and occupational status) and checking for the presence of possible confounders, self-reported and experimental pain measurements were carried out. Finally, participants undertook a submaximal exercise bout on a cycle ergometer. Immediately after finishing the exercise, self-reported and experimental pain measurements were repeated.

Self-reported Pain

Self-reported pain intensity was measured using a 100 mm visual analogue scale. Participants were instructed to indicate their present pain intensity by drawing a vertical line on a 100 mm horizontal line, with utmost left representing no pain and utmost right representing unbearable pain. Hence, a score ranging from 0 to 100 was obtained. This self-reported measure demonstrated good validity and reliability (24,25). This outcome was registered at baseline, post exercise, and 24 hours post exercise.

Experimental Pain Measurements

Pressure Hyperalgesia: Pressure Pain Thresholds

Pressure pain thresholds (PPTs) were measured at the middle of the right trapezius belly (PPT shoulder = local site) and at the proximal third of the calf muscle belly 10 cm distal to the fossa poplitea (PPT calf = remote site) with an analogue Fisher algometer (Force Dial, Wagner Instruments, Greenwich CT, USA) (26,27). Participants' PPTs were determined by gradually increasing the pressure provided by the algometer (at a rate of 1 kg/s) until the point when the sensation first became painful (participants were instructed to say stop at this point). This was performed 2 times (30 seconds apart) at the shoulder and at the calf in order to calculate the mean PPT for every site. Pressure algometry has been found to be efficient and reliable in the exploration of pathophysiological mechanisms involved in pain (28,29).

Deep-tissue Hyperalgesia: Occlusion Cuff Pressure

Deep-tissue hyperalgesia was investigated by inflating an occlusion cuff placed around the left arm. Cuff inflation rate was increased manually and at a constant rate (20 mmHg/s) until the participant reported the sensation first became painful (participants were instructed to say stop at this point). The pressure at this moment was registered (cuff pressure threshold) and used for further data analyses. Participants then adapted to the stimulus for 30 seconds and rated the pain on a verbal numeric rating scale (VNRS) ranging from 0 (= no pain) to 10 (= worst possible pain). Cuff inflation was then adjusted until participants indicated pain at a level 3 of 10 on the VNRS. Subsequently, this

pressure (cuff pressure VNRS3) was saved and used for further data analyses.

Endogenous Pain Facilitation: Temporal Summation

TS was examined 2 minutes after the final PPT was taken at each site (shoulder and calf). Ten pulses at the previously determined mean PPT intensity were applied at the right trapezius and this pressure was maintained for one second before being released. Pressure was increased at a rate of approximately 2 kg/s for each pulse and pulses were presented with an interstimulus interval of one second. After the first, fifth, and tenth pulse, participants were asked to verbally rate their pain on a VNRS. The outcome measure for TS is the difference between the tenth and the first VNRS score (26,27).

Endogenous Pain Inhibition: Conditioned Pain Modulation

To assess CPM, TS was measured while an occlusion cuff was inflated to a painful intensity and maintained at that level on the opposing (left) arm (as a heterotopic noxious conditioning stimulus). The cuff was inflated at approximately 20 mmHg/s until the point that the sensation first became painful (participants were instructed to say stop at this point). Next, they adapted for 30 seconds to the stimulus and subsequently rated their pain on a VNRS. Cuff inflation was then increased or decreased until the participant indicated the pain level was equal to a score of 3/10 on the VNRS. The left arm was then rested on a table and CPM was assessed by replicating the TS assessment as described above. The outcome measure for CPM is obtained by subtracting the first VNRS score "before cuff inflation" from the first VNRS score "during cuff inflation" (26,27).

Submaximal Aerobic Exercise

The submaximal aerobic exercise was performed on a cycle ergometer (Kardiomed 520 basic cycle, Proxomed, Alzenau, Germany). The seat was adjusted to suit each participant. The exercise protocol that was used is known as the Aerobic Power Index test (30). Multiple studies demonstrated that this test has a reliable protocol to administer a submaximal exercise in several populations, including people with chronic pain (31-33). The duration of the test is kept below 15 minutes, thus avoiding early fatigue in the lower extremities due to insufficient physical fitness. Once the heart rate telemetry band (Polar Electro OY, Kempele, Finland) was put on and the participant was adjusted to the resting position for 2 minutes, resting heart rate (HRrest) was recorded. The workload started at 25 watt and was increased by 25 watt every minute until the participant reached his submaximal level. This level (i.e., target heart rate) is defined as 75% of the age-predicted maximal heart rate [(220 – age) x 0.75]. Participants were instructed to cycle at a constant pedaling rate of approximately 60 rpm. Heart rate was recorded at the end of every minute. The exercise was terminated when participants reached their individual target heart rate. Cooling-down included one minute of cycling at a rate of 60 rpm and a workload of 25 watt.

Data Analysis

All data were analysed using the Statistical Package for Social Sciences 23.0 for Windows (IBM Corp., Armonk, NY, USA). Normality of the variables was tested using the Kolmogorov-Smirnov goodness-of-fit test. To answer our research questions, the chronic WAD group was divided into a group of young and old (age groups), and men and women (gender groups) patients.

Primary outcome measures (pain measures) and demographic variables were compared between the different age (young vs. older adults) and gender groups (men vs. women) and between people with chronic WAD and healthy controls. These baseline (pre-exercise) comparisons were performed using independent-samples t-testing (normal distribution) and Mann-Whitney U-testing (non-normal distribution). Furthermore, pre- to post-exercise evolution in primary outcome measures was examined within each group (young, old, men, women, WAD, and control) using the Paired-Samples t-test or for non-normal data the Wilcoxon signed-rank test or related-samples Friedman's 2-way analysis of variance with subsequent pairwise comparisons. Finally, post minus pre-exercise differences (Δ post-pre-exercise) in pain data were compared between groups with independent samples t-testing (or independent samples Mann-Whitney U testing). The significance level was set at .05 and 2-sided tests were used for all analyses.

An a priori sample size calculation was conducted with the program G*Power 3.1.5 (Kiel, Germany) (34). An analysis was performed for the within- and between-group comparisons. Based on the study results of Ge et al (35), a total sample size of 16 participants is necessary for the between-group analysis (gender). The sample size calculation for the within-group analysis (pre vs. post exercise) is based on the results of the study of Van Oosterwijck et al (20). The sample size was calculated

using a desired power of .80, a significance level of .05, and a medium effect size of .30. Based on this a priori sample size calculation, we aimed at enrolling at least 15 participants per group (WAD, control, young WAD, older WAD, female WAD, and male WAD).

Results

Group Characteristics

A total of 26 people with chronic WAD participated in this study (11 men and 15 women). When divided based on their age, there were 13 participants in the age group of 18 – 42 years (young adults) and 13 in the age group of 43 – 65 years (older adults). The healthy control group consisted of 26 participants (11 men and 15 women). All demographic variables are presented in Table 1.

The total group of people with chronic WAD and the control group were comparable for age, body mass, and height ($P > 0.05$). Body mass index (BMI) was significantly higher in people with chronic WAD ($t(50) = -0.55$, $P = 0.036$). Young and older people with chronic WAD were comparable for body mass ($P = 0.091$), height ($P = 0.479$), and BMI ($P = 0.113$). The WAD gender groups had a similar age distribution ($P = 0.134$), but men showed significantly higher body mass ($U = 150$, $P < 0.001$), height ($U = 145.5$, $P = 0.001$), and BMI ($U = 131$, $P = 0.011$).

The Pearson Chi-square test showed an equal distribution of genders (matched) among the group of people with chronic WAD and the healthy control group, but a significant difference in occupational status ($\chi^2(3) = 2.71$, $P = 0.01$) with more healthy controls working in a fulltime job (65.4% controls vs. 34.6% WAD) and more people with chronic WAD being currently unemployed (3.8% controls vs. 38.5% WAD). Occupational status was comparable within the gender and age WAD groups ($P > 0.05$).

Table 1. *Demographic data of the study samples.*

	C-WAD (n = 26)	Controls (n = 26)	*P*-values	C-WAD gender groups			C-WAD age groups		
				Women (n = 15)	Men (n = 11)	*P*-values	Young adults (n = 13)	Older adults (n = 13)	*P*-values
Age, years	43.5 (30.8-47.3)	37.0 (25.8-53)	0.614[b]	33 (29-47)	45 (41-49)	0.134[b]	31 (29-40.5)	47 (45-52)	<0.001[b]
Women, n (%)	15 (57.7)	15 (57.7)	1.0[c]	15 (100)	0 (0)	< 0.001[c]	10 (76.9)	5 (38.5)	0.111[c]
Body Mass, kg	74.9 (14.4)	70.3 (13.7)	0.246[a]	65 (60 – 69)	84 (81 – 95)	< 0.001[b]	66 (60 – 83.9)	80 (68.5 – 86)	0.091[b]
Height, cm	171.5 (8.7)	173 (9.5)	0.582[a]	166.5 (162 – 172)	178.4 (173 – 185)	0.001[b]	170 (162 – 175)	172 (165 – 181.5)	0.479[b]
Body Mass Index, kg/m^2	25.3 (3.6)	23.3 (3)	0.036[a]	23.5 (22 – 26.5)	27.4 (26 – 30)	0.011[b]	23.5 (21 – 27.8)	26.3 (24.7 – 29)	0.113[b]
Disease duration, months	28.5 (6.8 – 77.3)	NA	< 0.001[b]	29 (7 – 105)	28 (5 – 71)	0.610[b]	28 (7.5 – 88)	36 (5.5 – 74.5)	0.920[b]
Occupational status, n (%)			0.010[c]			0.383[c]			0.438[c]
Unemployed	10 (38.5)	1 (3.8)		4 (26.7)	6 (22.2)		4 (30.8)	6 (46.2)	
Part-time job	5 (19.2)	3 (11.5)		3 (11.5)	2 (7.4)		2 (15.4)	3 (23.1)	
Fulltime job	9 (34.6)	17 (65.4)		6 (23.1)	3 (11.1)		5 (38.5)	4 (30.8)	
Student	2 (7.7)	2 (7.7)		2 (7.7)	0 (0)		2 (15.4)	0 (0)	
Retired	0 (0)	3 (11.5)		0 (0)	0 (0)		0 (0)	0 (0)	

Values are mean (SD), median (IQR), or number (%).
C-WAD Chronic whiplash-associated disorders, NA not applicable
[a] Statistical analysis performed using an Independent Samples t-test.
[b] Statistical analysis performed using an Independent Samples Mann-Whitney U Test.
[c] Statistical analyses were performed using a Pearson Chi-Square test (Fisher's Exact test for gender).
Statistically significant results are printed in bold.

Exercise Variables and Baseline Self-reported and Experimental Pain Measurements

Table 2 presents the baseline values (pre-exercise) and changes in response to exercise in pain measurements of the different study samples. Changes in PPT values at the calf and shoulder are displayed in Figs. 1 and 2, respectively.

People with Chronic WAD vs. Healthy Controls

Mean resting heart rates were 82.5 (12) and 80 (11.1) bpm in people with chronic WAD and healthy controls, respectively. Median maximal workload showed 125 (IQR WAD: 100 – 150 and IQR controls: 125 – 150) watt in both groups and median duration of the cycling exercise was 5 (IQR WAD: 4 – 6 and IQR controls: 5 – 6) minutes in both groups as well. People with chronic WAD and healthy controls did not differ regarding any of these exercise variables ($P > 0.05$).

At baseline, people with chronic WAD self-reported significantly more pain (U = 41, $P < 0.001$), showed lower PPTs at the shoulder (i.e., neck region) (t(50) = -4.4, $P < 0.001$) as well as at the calf (i.e., remote site) (t(50) = -3.78, $P = 0.001$), and displayed a lower cuff pressure threshold (t(50) = -3.35, $P = 0.002$) and cuff pressure at VNRS3 (t(50) = -3, $P = 0.004$) compared to healthy controls. However, CPM at the shoulder (neck region) and calf (remote site) as well as TS at the shoulder (neck region) and calf (remote site) were not different between people with chronic WAD and healthy controls ($P > 0.05$).

Gender Groups – women with Chronic WAD vs. Men with Chronic WAD

Men with chronic WAD displayed a significantly higher median maximal workload (women: 125 (100 – 125) watt, men: 150 (100 – 175) watt, U = 125, $P = 0.027$)

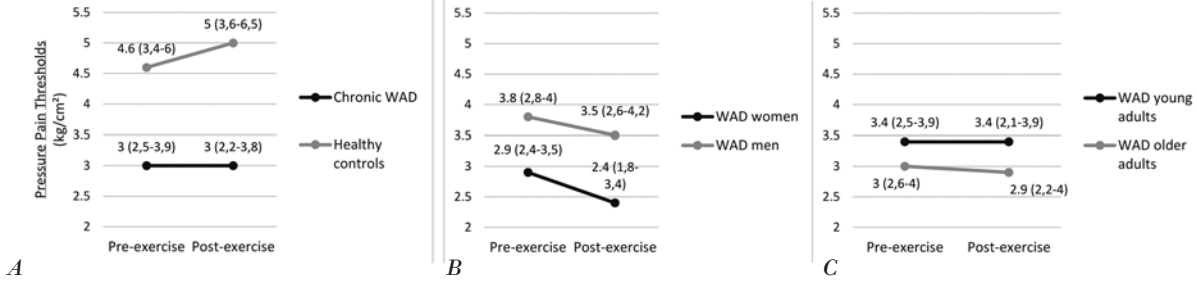

Fig. 1. *Changes in pressure pain thresholds at the calf (i.e., remote site) in response to submaximal exercise in (A) people with chronic WAD (n=26) and healthy controls (n=26), (B) women (n=15) and men (n=11) with chronic WAD, and (C) young (n=13) and older (n=13) people with chronic WAD.*
Values are median (IQR).

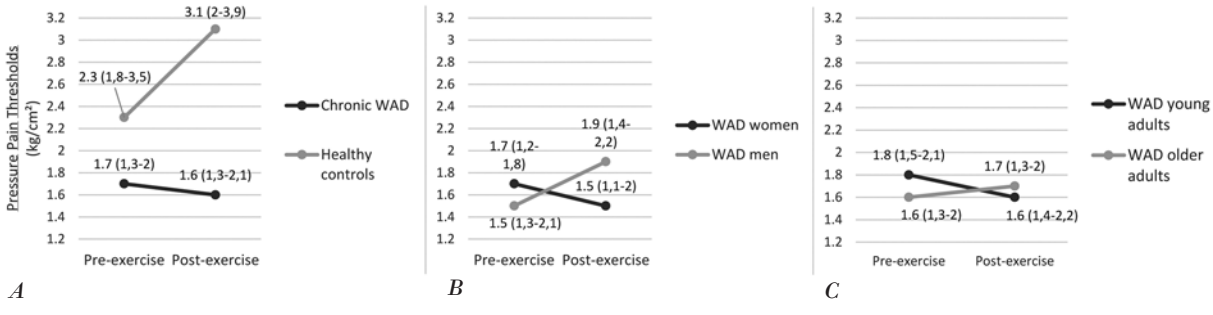

Fig. 2. *Changes in pressure pain thresholds at the shoulder (i.e., neck region) in response to submaximal exercise in (A) people with chronic WAD (n=26) and healthy controls (n=26), (B) women (n=15) and men (n=11) with chronic WAD, and (C) young (n=13) and older (n=13) people with chronic WAD.*
Values are median (IQR)

Table 2. *Baseline (pre-exercise) and post exercise values and post minus pre-exercise differences (Δ post–pre-exercise) in self-reported and experimental pain measurements.*

	C-WAD (n = 26)	Controls (n = 26)	Between groups comparisons *P*-values	C-WAD sex groups			C-WAD age groups		
				Women (n = 15)	Men (n = 11)	Between groups comparisons *P*-values	Young adults (n=13)	Older adults (n=13)	Between groups comparisons *P*-values
VAS pain, mm									
Pre-exercise Post exercise 24h post exercise Δ 24h post – pre-exercise	57 (21.5 – 73.8) 60.5 (16.1 – 78.4) 60.5 (22 – 81.8) -1.5 (-8.8 – 12.3)	1.5 (0 – 9.6) 2 (0.4 – 10.4) 0.3 (0 – 4.5) 0 (-5 – 0)	0.552[b]	30 (12.5 – 67) 56 (6.5 – 72.5) 56.8 (13 – 77.9) 10.1 (28.1)	71 (42 – 84.5) 65 (26 – 79.5) 60.5 (25.5 – 83) -8.6 (12.5)	0.053[a]	57 (22 – 75.5) 65 (15 – 78.8) 65.5 (20 – 85.3) 5.2 (28.7)	57 (21.5 – 74.2) 39 (13.5 – 78.8) 56.5 (20.6 – 79.4) -1.7 (18.7)	0.492[a]
Cuff pressure threshold, mmHg									
Pre-exercise Post exercise Δ post – pre-exercise	129.2 (58.7) 119 (64.3) -10.2 (34)	188.1 (67.8) 187.5 (82.3) -0.5 (34.8)	0.317[a]	120 (60 – 140) 80 (60 – 140) -6.2 (40.1)	170 (110 – 180) 120 (70 – 180) -15.6 (24.2)	0.496[a]	120 (74 – 136) 100 (70 – 150) -4.2 (33.3)	170 (79 – 180) 120 (69 – 175) -16.2 (35)	0.383[a]
Cuff pressure VNRS3, mmHg									
Pre-exercise Post exercise Δ post – pre-exercise	97.3 (58.5) 84.7 (47.6) -8.5 (-30 – 11)	153.1 (74.7) 163 (85.4) 7.5 (-17.8 – 30)	0.078[b]	90 (44 – 140) 60 (48 – 120) -7 (-30 – 10)	90 (60 – 142) 90 (60 – 120) -10 (-52 – 10)	1.000[b]	90 (47 – 126) 60 (49 – 100) 0 (-41 – 7.5)	100 (55 – 150) 108 (50 – 130) -10 (-30 – 20)	1.000[b]
TS calf									
Pre-exercise Post exercise Δ post – pre-exercise	1 (0 – 2.3) 0 (0 – 2) 0 (-1 – 0)	1 (0 – 2) 1 (0 – 1.3) 0 (-1 – 0)	0.591[b]	1 (0.5 – 3) 1 (0 – 2) -5 (-1 – 0)	0 (0 – 2) 0 (0 – 2) 0 (-1 – 0)	0.474[b]	1 (1 – 3) 1 (0 – 2) -1 (-1 – 0)	0 (0 – 1) 0 (-0.5 – 1) 0 (-0.3 – 0)	0.153[b]
TS shoulder									
Pre-exercise Post exercise Δ post – pre-exercise	1 (0 – 1.3) 1 (0 – 2) 0 (-5 – 1)	1 (0 – 2) 1 (0 – 2) 0 (-1 – 1)	0.977[b]	1 (0 – 1) 1 (0 – 2) 1 (-0.5 – 1)	0 (-1 – 2) 0 (0 – 3) 0 (0 – 1)	0.878[b]	1 (0 – 1.5) 2 (0.8 – 2.5) 1 (-0.3 – 1)	0 (0 – 1.5) 0 (-0.3 – 1) 0 (-0.8 – 0.5)	0.091[b]
CPM calf									
Pre-exercise Post exercise Δ post – pre-exercise	0 (-1 – 0) 0 (-1 – 0) 0 (-0.3 – 1)	0 (-1 – 1) 0 (-1 – 0) 0 (-1 – 0)	0.127[b]	0 (-1 – 0) 0 (-1 – 0) 0.1 (2.1)	0 (-1 – 0) 0 (0 – 0) 0.3 (1.1)	0.841[a]	-1 (-1 – 0) 0 (-1 – 0) 0 (-0.5 – 1.5)	0 (-1 – 0) 0 (-0.5 – 0) 0 (-0.5 – 1)	0.650[b]
CPM shoulder									
Pre-exercise Post exercise Δ post – pre-exercise	0 (0 –1) 0 (-0.3 – 1) 0 (-1 – 1)	0 (0 – 1) 0 (0 – 1) 0 (-0.6 – 0.3)	0.260[b]	0 (-1 – 1) 0 (-1 – 1) -0.5 (1.8)	0 (0 – 2) 0 (0 – 1) -0.5 (1.2)	0.903[a]	0 (-1 – 1) 0 (-1 – 1) 0 (-2.5 – 1)	0 (0 – 1.5) 0 (0 – 1) 0 (-1 – 0.5)	0.687[b]
PPT calf, kg/m^2									
Δ post – pre-exercise	-0.1 (-0.4 – 0)	0.3 (-0.3 – 0.7)	**0.023[b]**	-0.2 (0.5)	-0.1 (0.7)	0.664[a]	-0.1 (-0.4 – 0.2)	-0.1 (-0.3 – 0)	0.960[b]
PPT shoulder, kg/m^2									
Δ post – pre-exercise	0 (0.3)	0.2 (0.7)	0.140[a]	0 (0.3)	0 (0.2)	0.536[a]	0 (0.4)	0 (0.2)	0.524[a]

Values are mean (SD), median (IQR). or number (%). C-WAD Chronic whiplash-associated disorders, VAS Visual analogue scale, TS Temporal summation, CPM Conditioned pain modulation, PPT Pressure pain threshold. [a]Statistical analysis performed using an Independent Samples t-test. [b]Statistical analysis performed using an Independent Samples Mann-Whitney U Test. Statistically significant results are printed in bold.

and median duration of the cycling exercise (women: 5 (4 – 5) minutes, men: 6 (4 – 7) minutes, U = 125, *P* = 0.027) compared to their female counterparts. The median resting heart rate was not different between both groups (women: 80 (70 – 89) bpm, men: 85 (77 – 96) bpm, U = 104.5, *P* = 0.259).

Regarding baseline pain measurements, men self-reported significantly higher pain levels compared to women (U = 126.5, *P* = 0,020). PPTs, cuff pressures, TS, and CPM were not different among the gender groups (*P* > 0.05).

Age Groups – Young Adults with Chronic WAD vs. Older Adults with Chronic WAD

Median resting heart rate was 86 (73 – 91.5) and 79 (74.5 – 89) bpm in younger and older adults with chronic WAD, respectively. Median maximal workload showed 125 (IQR younger WAD: 100 – 125 and IQR older WAD: 87.5 – 162.5) watt in both groups and median duration of the cycling exercise was 5 (IQR younger WAD: 4 – 5 and IQR older WAD: 3.5 – 6.5) minutes in both groups as well. All exercise variables were comparable among both chronic WAD age groups (*P* > 0.5).

TS at the calf (remote site) was significantly higher in younger adults with chronic WAD than in their older counterparts (U = 41.5, *P* = 0.026). There were no differences among age groups regarding self-reported pain, PPTs, cuff pressures, TS at the shoulder (neck region), and CPM (remote site and neck region) (*P* > 0.1).

Influence of Exercise on Self-reported and Experimental Pain Measurements

Changes in Response to Submaximal Exercise within the Different Study Samples

Men with chronic WAD self-reported significantly lower pain intensity immediately after the exercise compared to before the exercise (Z = 7.364, *P* = 0.007). There was no significant change 24 hours post exercise in this subgroup (*P* > 0.05). Pre to post and 24 hours post exercise changes in self-reported pain were not significant in any of the other study samples (i.e., people with chronic WAD, healthy controls, younger and older adults, and women with chronic WAD) (*P* > 0.05) (Table 2).

PPTs (Figs. 1 and 2) and occlusion cuff pressures (thresholds and at VNRS3) (Table 2) did not change significantly in response to the submaximal exercise in any of the groups that were studied (*P* > 0.05).

TS measured at the calf (remote site) significantly decreased in response to exercise in people with chronic WAD (Z = -2.275, *P* = 0.023). When the chronic WAD group was divided according to gender, only women still showed a significant reduction in TS at the calf in response to exercise (Z = 5.444, *P* = 0.020). The other (sub)groups did not show any significant changes regarding the measures of endogenous pain modulation (i.e., pain inhibition [CPM] and facilitation [TS]) in response to exercise (*P* > 0.05) (Table 2).

Comparison of Post- Minus Pre-exercise Differences (Δ Post-pre-exercise)

As shown in Table 2, for all pain measurement values, deltas were compared between (1) people with chronic WAD and healthy controls, (2) subgroups of men and women with chronic WAD, and (3) subgroups of younger and older adults with chronic WAD. The delta of PPTs at the calf was significantly lower in people with chronic WAD compared to the healthy control group (U = 462.5, *P* = 0,023), whereas they were not significantly different among the gender and age subgroups (*P* > 0.05). There were no significant differences between the deltas of the other pain data (*P* > 0.05).

Discussion

This is the first study to test for gender and age differences in self-reported and experimental pain measurements in people with chronic WAD. Repeating these assessments immediately after an aerobic exercise allowed us to compare exercise-induced responses on pain measurements between gender and age subgroups as well. Summarized, people with chronic WAD showed significantly lower PPTs and occlusion cuff pressures in comparison with healthy controls. Moreover, the results suggest that there were no gender and age differences regarding PPTs, occlusion cuff pressures, and endogenous pain inhibition in people with chronic WAD. Within the chronic WAD group, men showed higher self-reported pain than women and younger adults showed enhanced generalized pain facilitation compared to their older counterparts. In addition, our results suggest that patients with chronic WAD are able to inhibit exercise-induced hyperalgesia, however, there were no gender and age differences in pain response following exercise.

Empirical inquiry advocates that the central nervous system has become hypersensitized in patients with chronic WAD and that this process of central sensitization plays a crucial role in the persisting pain complaints experienced by these patients (8). Central

sensitization encompasses various related dysfunctions within the central nervous system, all contributing to altered (often increased) responsiveness to a variety of stimuli like mechanical pressure, chemical substances, light, sound, cold, heat, stress, and electricity (36). Such central nervous system dysfunctions include altered sensory processing in the brain (37), poor functioning of descending anti-nociceptive mechanisms (38), and increased activity of nociceptive faciliatory pathways (37). In this study, the findings regarding PPTs and cuff pressure measurements at baseline confirm this evidence by demonstrating the presence of local and generalized hyperalgesia among people with chronic WAD. Interestingly, on the other hand, efficient CPM and TS were preserved in our chronic WAD study sample. Some previous studies demonstrated inefficient CPM (before termed as diffuse noxious inhibitory controls or DNIC) activation (39) and enhanced TS of pain (6) in chronic WAD, while others have found results that are similar to ours (40,41). Efficient CPM was also found in a recent study performed in patients with chronic low back pain (37).

CPM is the psychophysical test paradigm to measure DNIC, which is one of the most explored mechanisms underlying the nociceptive inhibitory system in healthy people and clinical populations. DNIC, also known as the "pain inhibits pain" paradigm, acts as a filter separating irrelevant from relevant stimuli (8,26).

TS is a psychophysical correlate of the physiological phenomenon of wind-up. TS, which has been increasingly used to investigate nociceptive facilitation in healthy people and clinical populations, is defined as the increase in pain rating after repetitive stimulation at a constant stimulus intensity (8,26).

The contradictory results regarding CPM and TS in chronic WAD may be explained by the different types of stimuli (thermal, electrical, mechanical) that were used to induce CPM and TS in these different studies. Mechanical stimuli seem to have another, less pronounced, effect on measurements of pain modulation. Thus, examining CPM and TS in response to different types of stimuli may be useful to provide a better understanding of the underlying mechanisms involved in altered central processing in chronic WAD. Furthermore, our chronic WAD group demonstrated a significantly higher BMI compared to the control group. In the general population obesity has been described to be associated with an increased occurrence of severe pain and the likelihood of experiencing pain in multiple parts of the body (42). Therefore, in this study, BMI could be a possible confounder, responsible for the lack of between-group differences in pain measures.

Our hypothesis that both women and older adults with chronic WAD would report higher pain levels, lower PPTs and occlusion cuff pressures, less efficient CPM, and enhanced TS compared to their male and younger counterparts, respectively, is not supported by our results. On the contrary, in general we did not find gender and age differences apart from the findings that men showed higher self-reported pain than women with chronic WAD and younger adults showed more distinct generalized pain facilitation compared to older chronic WAD patients. Ge et al (35) reported higher pain intensity and lower PPTs in healthy women in comparison with men. These discrepancies might be explained by the characteristic of the sample, since this study only included healthy volunteers. Moreover, pain is a multidimensional phenomenon influenced by cognitive-emotional factors as well. Therefore, self-reported pain (i.e., pain perception) will most likely have been influenced by previous experiences and beliefs in these men with chronic WAD. Indeed, patients with chronic WAD show negative pain-related cognitions (41) and Wijnhoven et al (43) demonstrated that pain catastrophizing seems to be stronger associated with chronic pain among men.

On the other hand, there were no age-related differences in pain response, with the exception of TS. This finding is not in line with previous research (17,18). Lautenbacher et al (17) reported that TS of heat pain is markedly increased in older individuals whereas TS of pressure pain was not vulnerable to age effects. In the study of Edwards and Fillingim (18), older adults exhibited higher ratings of thermal pain and enhanced TS relative to younger adults. The discrepancies with our results may be explained by the different noxious stimuli applied (thermal vs. mechanical and ischemic) and the mean age of the participants. In our study we considered older adults between 43 to 65 years old (mean age 47 years), however, mean age was significantly higher in the studies discussed above (71.6 and 65 years, respectively). In addition, these studies were performed in healthy people without any chronic pain condition.

Our results showed that people with chronic WAD are able to inhibit hyperalgesia following exercise, however no gender and age differences were found in response to exercise. In contrast, Van Oosterwijck et al (20) demonstrated that women with chronic WAD show more pain and widespread hyperalgesia following an

aerobic exercise compared to healthy women. Meeus et al (44) reported fairly similar results as ours in patients with chronic low back pain. They even showed exercise-induced hypoalgesia in these patients, suggesting the presence of adequate pain inhibition following submaximal aerobic exercise in at least a subgroup of these patients. Additionally, it has been shown that people with fibromyalgia experience less pain and have the ability to activate brain regions involved in descending nociceptive inhibition (i.e., anterior insula and left dorsolateral prefrontal cortex) after an aerobic exercise (45), while other authors have demonstrated that patients with fibromyalgia report no changes or an increase in pain after an isometric muscle contraction (46).

The common physiological response during and following exercise is a decrease in pain perception and an increase in pain thresholds. Currently, the underlying mechanisms responsible for this are poorly understood. It is thought that the release of endogenous opioids and growth factors plays an important role (21,47) as well as activation of (supra)spinal nociceptive inhibitory mechanisms ("descending inhibition") orchestrated by the central nervous system (22). Recently, preliminary evidence for the involvement of the endocannabinoid system (47) and psychosocial variables, such as the family environment and mood states (48) was raised as well.

Based on the contradictory findings in people with chronic WAD and other overlapping chronic pain conditions, we cannot make the generalized statement that patients with chronic WAD exhibit adequate endogenous pain modulation in response to exercise. It is more likely that a subset of patients display altered central pain processing in response to exercise while others do not. With regard to clinical practice, these findings support the need to identify this subgroup of patients who react abnormally to exercise, in order to adapt (exercise) therapy.

Strengths and Limitations

The present study should be interpreted in the light of its strengths and limitations. An important strength of this study is that our patient and control groups were matched for age and gender. Additionally, healthy controls had to be inactive. This way, observed differences between people with chronic WAD and healthy people could not be due to a higher activity level of the control group. Another important strength of this study is that we anticipated sources of bias like pregnancy; use of medication, caffeine, alcohol, and nicotine; and execution of physical exertion on the days of the assessments. However, psychosocial factors were not taken into account. Therefore, influences of certain psychosocial factors cannot be ruled out.

This study was sufficiently powered to detect differences between the chronic WAD and control group. However, a sufficient power was not reached when patients were divided in age and gender groups. With larger samples sizes per subgroup, probable effects would have been easier to detect. Furthermore, we only included measurements with mechanical pain stimuli. Because of the contradictory findings between studies, it seems interesting to include other types of stimuli (i.e., chemical, electrical, and thermal) in futures studies. Additionally, psychosocial factors such as catastrophizing, depression, or pain hypervigilance may have influenced pain measurement outcomes. Thus, future studies should include such variables as possible moderators of pain assessment in different gender and age groups of people with chronic pain.

Conclusion

In conclusion, this study provides evidence for some alterations in pain processing in chronic WAD, however not in response to exercise. Furthermore, it demonstrates a lack of gender and age differences in pain measurements in patients with chronic WAD.

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IRB approval: The study protocol was approved by the Ethics committee of the University Hospital Brussels/Vrije Universiteit Brussel. Appropriate written and informed consent was obtained from each participant in accordance with institutional policies. ClinicalTrials.gov identifier: NCT01601912.

Dorien Goubert and Maria Encarnacion Aguilar-Ferrandiz contributed equally to this paper. We would therefore like to give them equal credit for this paper by indicating that they share the last authorship.

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