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Exercise induced hypoalgesia and *exercise induced hyperalgesia* in pazienti con dolore cronico e acuto: *A Sistematic Review.*

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Indice

1. INTRODUZIONE 1

2. MATERIALI E METODI 4

2.1 OBIETTIVI DELLA REVISIONE 4

2.2 CRITERI DI INCLUSIONE ED ESCLUSIONE 4

2.3 STRATEGIA DI RICERCA 5

2.4 CRITERI DI SELEZIONE DEGLI STUDI 7

2.5 VALUTAZIONE DELLA VALIDITÀ INTERNA 7

3. RISULTATI 8

3.1 SELEZIONE DEGLI STUDI 8

3.2 ESTRAZIONE DEI DATI 10

3.3 VALUTAZIONE DEGLI STUDI E CRITICAL APPRAISAL 29

3.4 VALUTAZIONE DEL RISCHIO DI BIAS 30

3.5 SINOSSI DEI RISULTATI 31

3.5.1 ENDOPOINT 31

3.5.2 APPROCCI TERAPEUTICI 32

4. DISCUSSIONE 46

4.1 LIMITI 52

5. CONCLUSIONI 52

5.1 IMPLICAZIONI PER LA PRATICA: KEYPOINT 53

BIBLIOGRAFIA 54

APPENDICE 57

INTRODUZIONE

Il legame tra esercizio ed analgesia è stato indagato da diversi studi negli ultimi trent'anni confermando la sua efficacia nel trattamento di diversi disturbi acuti e cronici come il *chronic neck pain,* l'artrosi, l'artrite reumatoide ed il *chronic low back*.

Precedenti lavori hanno dimostrato che l'esercizio fisico riduce la sensibilità verso gli stimoli dolorosi, provocando nei soggetti una risposta ipoalgesica. Questo fenomeno è stato definito "*exercise-induced analgesia*" (EIA) o, più precisamente, "*exercise-induced hypoalgesia*" (EIH).

Sebbene l'esercizio fisico sembri aiutare chi soffre di dolore cronico attraverso il suo effetto ipoalgesico, alcuni pazienti, per esempio quelli con fibromialgia o *chronic fatigue syndrome* o *chronic WAD*, sviluppano una risposta iperalgesica all'esercizio.

Obiettivo di questa revisione sistematica è quindi quello di analizzare le attuali evidenze disponibili in letteratura riguardanti gli effetti ipoalgesici o iperalgeisci delle diverse tipologie di esercizio fisico sulla percezione del dolore.

MATERIALI E METODI

La revisione è stata condotta secondo il PRISMA statement. La ricerca è stata eseguita sui seguenti database: PubMed, Web of Science, PEDro, e Cochrane. Sono stati inclusi studi in lingua inglese o italiana, che comprendevano almeno un gruppo di pazienti con dolore muscolo scheletrico o associato (es. neuropatie) che valutavano l'efficacia di un singolo esercizio e le cui misurazione di outcome fossero effettuate al massimo dopo 48 h. La selezione degli studi è stata fatta in modo indipendente dagli autori della review per lettura di titolo, abstract e full text, dopo eliminazione di articoli ripetuti dalla ricerca nelle varie banche dati ed infine confrontata

reciprocamente. La valutazione della validità interna degli studi è stata fatta attraverso il Cochrane Risk of Bias ed il Quality Assessment Tool dell'NIH.

RISULTATI

Le stringhe di ricerca hanno prodotto un totale di 6600 articoli. Per giungere alla selezione degli articoli inerenti al quesito di ricerca è stata utilizzata l'applicazione web Rayyan che ha permesso agli autori di selezionare 22 lavori attinenti al quesito di ricerca e ai criteri di inclusione ed esclusione. Di questi 4 sono RCT con un rischio di bias estremamente variabile mentre i restanti 18 sono case-control e cross sectional.

CONCLUSIONI

Dalla presente *review* appare evidente l'efficacia dell'esercizio fisico nei soggetti sani cosi come in quelli patologici, con le dovute eccezioni. Se da un lato l'esercizio, che sia esso aerobico, isometrico o isotonico porta ad una fisiologica *exercise induced hypolagesia* in pazienti con osteoartrite e con dolore lombare meccanico, dall'altro i pazienti con *chronic WAD*, fibromialgia, *chronic fatigue* s*yndrome* e *Gulf War Illnes* mostrano un comportamento diametralmente opposto: l'esercizio sembra infatti determinare un incremento del dolore post-intervento. Tale caratteristica non è comune a tutti i pazienti con dolore cronico ma solo nei casi in cui si evidenzia la presenza di sensibilizzazione centrale. In questi pazienti l'esercizio ad intensità moderata e *self paced* risulte essere una valida alternativa rispetto a quello sub-massimale e isometrico, garantendo un'adeguata risposta ipoalgesica.

1. INTRODUZIONE

L'esercizio fisico è ormai considerato un trattamento efficace in soggetti con dolore acuto o cronico.

Il legame tra esercizio ed analgesia è stato indagato da numerosi studi negli ultimi trent'anni e si è confermata la sua efficacia nel trattamento di disturbi come la fibromialgia, il dolore cronico al collo, l'artrosi, l'artrite reumatoide e la lombalgia cronica[1–3].

Precedenti lavori hanno dimostrato che l'esercizio fisico riduce la sensibilità agli stimoli dolorosi, cioè stimola nei soggetti una risposta ipoalgesica. Questo fenomeno è stato definito "*exercise-induced analgesia*" (EIA) o, più precisamente, "*exercise-induced hypoalgesia*" (EIH): l'*International Association for the Study of Pain* sottolinea come infatti non si verifichi una completa assenza di dolore ma piuttosto una diminuzione della sensibilità agli stimoli nocicettivi[1,4].

Clinicamente il fenomeno dell'EIH si riscontra quando i Pain Tresholds (soglie in cui un individuo percepisce uno stimolo come doloroso) e la Pain Tolerance (soglia in cui un individuo non riesce più a tollerare uno stimolo doloroso) aumentano durante e dopo l'esercizio[5] così come diminuiscono le percezioni di intensità del dolore[6].

Una possibile spiegazione di questi effetti analgesici è che la natura stressante dell'esercizio fisico alteri l'omeostasi e attivi l'asse ipotalamo-ipofisi-surrene (HPA) provocando il rilascio di oppioidi endogeni sia nei siti periferici che centrali contribuendo così alla modulazione del dolore. Le contrazioni muscolari attivano il Gruppo III (A-delta) e le afferenze primarie IV (C) nel muscolo scheletrico che a loro volta attivano il sistema oppioide endogeno. Aumenti nelle concentrazioni di beta-endorfina nel sangue periferico sono state infatti riscontrate dopo esercizio fisico.

Inoltre, meccanismi mediati da endocannabinoidi sono stati suggeriti come meccanismo

alternativo per EIH. La presenza di recettori cannabinoidi (CB) nelle aree di elaborazione del dolore del cervello e del midollo spinale suggerisce che questi possano contribuire al controllo della trasmissione del dolore all'interno del sistema nervoso centrale attraverso la loro attivazione. Come i peptidi oppioidi endogeni, gli endocannabinoidi sono aumentati nella circolazione durante l'esercizio, quindi l'attivazione del recettore CB produrrebbe analgesia(1,7).

Per di più, l'esercizio fisico metterebbe alla prova il sistema cardiovascolare(8) e il conseguente aumento della pressione sanguigna (BP) potrebbe essere responsabile dell'EIH perché attiva recettori e barocettori oppioidi endogeni.

Questi sistemi possono influenzare l'elaborazione del dolore tramite percorsi inibitori discendenti, che sono una componente importante del sistema di analgesia endogeno.

Sebbene l'esercizio fisico sembri aiutare chi soffre di dolore cronico attraverso il suo effetto ipoalgesico, alcuni pazienti, per esempio quelli con fibromialgia o *chronic fatigue syndrome* o *chronic WAD,* sviluppano una risposta iperalgesica all'esercizio.

Questa "*exercise induced hyperalgesia*" corrisponde clinicamente ad una diminuzione dei Pain Treshold e della Pain Tolerance, determinata dall'incapacità del sistema di attivare l'inibizione nocicettiva centrale discendente, disfunzione che spiegherebbe in parte l'aumento del sintomo doloroso dopo l'esercizio in questi pazienti(9,10).

Numerosi studi hanno quindi esaminato l'effetto acuto dell'esercizio sulle risposte alla stimolazione nocicettiva sperimentalmente indotta. Questi hanno incluso diverse modalità di esercizio (aerobico, isometrico, isotonico) su soggetti con dolore cronico che hanno mostrato risposte funzionali (ipoalgesia) o disfunzionali (iperalgesia) nella modulazione del dolore.

Le metodologie di studi che hanno indagato l'"*exercise-induced hypoalgesia*" sono state diverse e non sempre consistenti: obiettivo di questa revisione sistematica è quindi quello di

analizzare le attuali evidenze disponibili in letteratura riguardanti gli effetti ipoalgesici o iperalgesici delle diverse tipologie di esercizio fisico sulla percezione del dolore.

Riuscire ad applicare nella pratica clinica fisioterapica questi risultati utilizzando l'esercizio come metodo di gestione del sintomo doloroso presuppone infatti la scelta di un esercizio che sia su misura del singolo paziente.

2. MATERIALI E METODI

2.1 OBIETTIVI DELLA REVISIONE

La seguente revisione si pone l'obiettivo di indagare l'effetto analgesico, ipo o iper algesico dell'esercizio in pazienti con dolore sia cronico che acuto. L'esercizio fisico ha generalmente un effetto ipoalgesico in soggetti sani, per contro, in pazienti con dolore cronico, questo effetto non viene sempre osservato, e addirittura in alcuni casi i pazienti riferiscono un peggioramento dei sintomi dopo l'esercizio. Con la presente revisione si è deciso di interrogare i maggiori database ed analizzare quanto la letteratura dice a riguardo.

2.2 CRITERI DI INCLUSIONE ED ESCLUSIONE

Criteri di inclusione sono stati:

- Studi che includono almeno un gruppo di pazienti con dolore
- Dolore muscolo scheletrico e associato (es. neuropatie)
- Studi che valutano l'efficacia di un singolo esercizio
- Studi le cui misurazioni post esercizio vengono effettuate massimo dopo 48h.

Criteri di esclusione sono stati:

- Lingua non conosciuta dagli autori (sono stati inclusi solo studi in lingua inglese, italiana e francese)
- Sistematic reviews, editoriali, punti di vista nonché case study e case report;
- Studi in cui analizzava l'efficacia di programmi di esercizi o attività fisica prolungata, stretching, yoga, pilates ed efficacia della neurodinamica
- Studi relativi agli animali, pazienti oncologici e soggetti con dismenorrea

- Studi in cui le misurazioni post-esercizio erano effettuate dopo 48h
- Studi in cui mancava un gruppo controllo.

2.3 STRATEGIA DI RICERCA

Nell'elaborare le strategie di ricerca, abbiamo utilizzato l'acronimo PICO. Di seguito è stata riportata la specifica tabella utilizzata per proceder nella ricerca (*Tabella 1)*

	Patients		**I / E (intervention/exposure)**		**Comparison**		**Outcome**
Mesh terms	"Chronic Pain"[Mesh]		"Exercise"[Mesh] "Exercise Movement Techniques"[Mesh] "Exercise Therapy"[Mesh] "Breathing Exercises"[Mesh]				"Analgesia" [Mesh]
	OR		OR		OR		OR
Termini liberi	"Chronic Pain*" "Persistent Pain*" "Constant Pain" "Recurr* pain*"	AND	Exercise* "Exercise Movement Techniques" "Exercise Therap*" "Breathing Exercise*" "Physical activit*" "Physical exercise*" "Acute exercise*" "Isometric exercise*" "Aerobic exercise*" "Exercise training*" "pilates-based exercise*" "pilates training" "exercise* rehabilitation" "remedial exercise*" "respiratory muscle training*"	AND		AND	Hypoalgesia* Analgesia*

Tabella 1: PICO

Per condurre la ricerca sono state indagate le seguenti fonti:

- PubMed
- Web of science
- PEDro
- Cochrane database for clinical trial (CENTRAL)

Le specifiche stringhe sono riportate in *Tabella 2*.

Database	Stringhe utilizzate	Note
• **Pubmed** • **Cochrane database for clinical trial**	((((((((((hyperalgesia) OR hypoalgesia) OR analgesia) OR hyperalgesia[mesh]) OR analgesia[mesh])) AND (((((((training) OR physical activit*) OR exercise*) OR "Breathing Exercises"[Mesh]) OR "Exercise Therapy"[Mesh]) OR "Exercise Movement Techniques"[Mesh]) OR exercise[mesh])) AND (((pains) OR pain) OR pain[mesh]))) NOT review[Publication Type]	
Web Of Science	((((((((((hyperalgesia) OR hypoalgesia) OR analgesia) OR hyperalgesia[mesh]) OR analgesia[mesh])) AND (((((((training) OR physical activit*) OR exercise*) OR "Breathing Exercises"[Mesh]) OR "Exercise Therapy"[Mesh]) OR "Exercise Movement Techniques"[Mesh]) OR exercise[mesh])) AND (((pains) OR pain) OR pain[mesh]))) NOT review[Publication Type]	
PEDro	**algesia exercis* pain**	*È stata utilizzata la modalità di ricerca semplice*.

Tabella 2 Stringhe di ricerca

2.4 CRITERI DI SELEZIONE DEGLI STUDI

Lo screening degli studi inclusi è stato effettuato utilizzando l'applicazione web **Rayyan** seguendo alcuni step chiave:

Step 1: Rimozione dei duplicati

Step 2: Selezione degli studi per titolo

Step 3: Selezione degli studi per lettura di abstract

Step 4: Selezione degli studi per lettura dei full text

Step 5: Reporting della strategia di ricerca in un flow chart (usando il PRISMA Diagram) in cui saranno riportati gli inclusi ed i motivi di esclusione degli studi scartati.

2.5 VALUTAZIONE DELLA VALIDITÀ INTERNA

Per la valutazione della qualità interna ed il rischio di BIAS degli articoli inclusi verrà utilizzata la *Quality Assessment of Controlled Intervention Studies* e l'Analisi dei Rischio di BIAS della Cochrane Collaboration per gli RCT (11) mentre *il Qualitity Assessment Tool of Case-Control Studies* per i case-control e i cross-sectional

3. RISULTATI

3.1 SELEZIONE DEGLI STUDI

Le stringhe individuate hanno prodotto un totale di 6600 articoli.

Per giungere alla selezione degli articoli inerenti al quesito di ricerca è stata utilizzata l'applicazione web Rayyan ed è stata adottata la seguente metodologia: prima sono stati esclusi 437 duplicati, comuni alle ricerche effettuate sulle diverse banche dati. Poi sono stati esclusi 6081 articoli con titolo ed abstract non pertinenti al quesito di ricerca e/o non conformi ai criteri di inclusione definiti nel capitolo precedente. Infinite tramite la lettura dei full text sono stati esclusi ulteriori 60articoli perché anche questi classificati come non attinenti allo scopo della revisione sistematica e/o non conformi con i criteri di inclusione.

Il processo di selezione degli studi di diagnosi è riportato nel flow chart PRISMA (*Figura 1)*

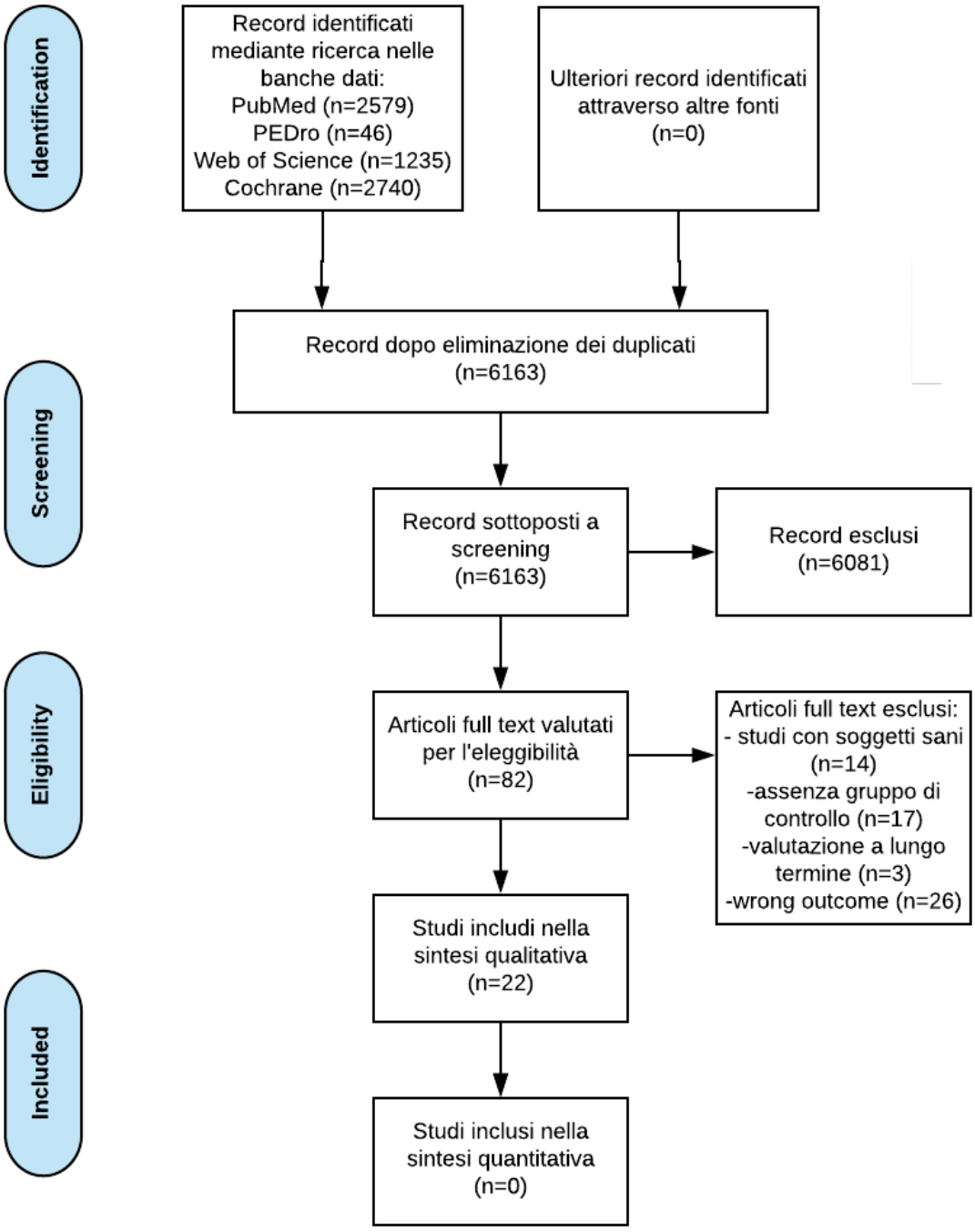

Figure 1 Flow chart di selezione degli studi

3.2 ESTRAZIONE DEI DATI

È stata fatta un'estrazione e una sintesi dei dati di ogni articolo (*Tabella 3*), nel tentativo di raggruppare e mettere in risalto i punti chiave di ognuno di essi e facilitare l'analisi dei risultati.

Studio	Soggetti	Disegno di studio	Intervento	Misure di outcome	Risultati
Ickmans 2017	52 individuals between 18 and 65 years (26 chronic WAD patients; 26 healthy controls)	Case Control Study	The submaximal aerobic exercise was performed on a cycle ergometer. Aerobic Power Index test (15 minutes, approx 60 rpm) Cooling-down: 1 minute of cycling at a rate of 60 rpm and a workload of 25 watt.	100 mm VAS (baseline, post exercise, and24 hours post exercise) PPTs conditioned pain modulation (CPM) temporal summation (TS) Deep-tissue Hyperalgesia with Occlusion Cuff Pressure (VNRS)	Lower PPTs and occlusion cuff pressures were shown in chronic WAD in comparison with healthy controls. 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. [Men with chronic WAD self-reported significantly lower pain intensity immediately after the exercise compared to before the exercise ($Z = 7.364$, $P = 0.007$).

					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) ($P > 0.05$). PPTs and occlusion cuff pressures (thresholds and at VNRS3) 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 ($P > 0.05$).] No gender and age differences in pain measurements ($P = 0,020$). PPTs, cuff pressures, TS, and CPM were not different among the gender groups ($P > 0.05$)
Christensen 2017	25 neck pain patients with bilateral neck pain and 25 healthy age- and sex-matched controls. 16 of the 25 neck pain patients had neck pain of insidious onset (IONP) and 9 were due to WAD.	Cross Sectional Study	6 series of arm abduction movements: first three series (Bout-I) of arm movements were 8 min and the last three series (Bout II) of arm movements were separated by 42 s. Bout-I and Bout-II were separated by a 10-min break. [abduction in the scapular plane, 30° scaption to a 140° angle with stretched arm. One movement series consisted of three slow movements 3-s up phase and 3-s down phase followed by three fast movements where only the fast-up movement was recorded. Each movement was separated by a 6-s break before moving the contralateral arm.]	EMG PPT VAS Drawing the perceived pain area on a body map McGill pain questionnaire	For both neck pain groups, the mean VAS score was significantly higher at baseline, during Bout-I and Bout-II compared with pain-free controls $H(2) > 42.0$, $p < 0.001$; Mann–Whitney U: $p < 0.001$). The post hoc test revealed increasing VAS score throughout the study for IONP when comparing baseline with Bout-I (Wilcoxon: $p = 0.013$) and for both neck pain groups when this was compared with Bout-II (Wilcoxon: IONP $p = 0.008$; WAD $p = 0.015$). A significant increase during Bout-II compared with Bout-I was seen for both neck pain groups (Wilcoxon: IONP

					p = 0.007; WAD p = 0.015). Decreased PPT at all time points was found when comparing both the IONP (NK: p < 0.03) and WAD (NK: p < 0.001) with controls. In WAD, compared with IONP, the PPT was decreased at baseline (NK: p = 0.041). For controls, the PPTs were progressively increasing and different between all time points (NK: p < 0.04), while for the IONP group, the post hoc test showed decreased PPT after Bout-I and Bout-II compared with baseline (NK: p < 0.001). For the TEMP site, an interaction (ANOVA: F [4,18] = 9.8; p < 0.001) showed that both neck pain groups had decreased PPTs compared with controls at all time points (NK: p <0.001). Furthermore, for the IONP group, the PPT was decreased after Bout-I and Bout-II compared with baseline (NK: p < 0.03). For controls, an increase in PPTs was found after Bout-II when compared with baseline and Bout-I

					(NK: $p < 0.002$). For the ECRB site, an interaction (ANOVA: $F[4,18] = 6.9$; $p < 0.001$) demonstrated that both neck pain groups displayed decreased PPT at all time points when compared with the control group (NK: $p < 0.001$). For the IONP group, the post hoc test revealed decreased PPT at Bout-I and Bout-II compared with baseline (NK: $p < 0.002$). ⇨ hyperalgesia for neck pain patients compared with controls ⇨ Repeated arm movements in controls were non painful and showed pressure hypoalgesia in the neck and head site, while IONP developed hyperalgesia
Smith 2017	participants with chronic WAD (n = 21) asymptomatic controls (n = 19).	Cross Sectional Study	two testing sessions: 1.submaximal aerobic bicycle exercise (cycle at 25 W and the power output was increased by 25 W every minute until attainment of 75% of age predicted maximum heart rate for 30 min) 2.isometric exercise: a wall squat for a maximum of 3 min [The sessions were scheduled 5–10 days apart]	Primary outcomes: PPTs Secondary outcomes: Thermal pain thresholds Conditioned pain modulation (CPM) ->VAS	The isometric wall squat exercise but not the aerobic cycling exercise resulted in EIH in both groups ($P < .023$) with no between-group differences ($P > .55$) demonstrated for either exercise. There were no significant associations measured

					between EIH (for either exercise performed), and CPM, or any of the psychological variables. [PPTs were significantly increased following the wall squat exercise (P = .001), however there were no significant changes following the bicycle test (P = .17). PPTs were significantly increased following the wall squat exercise (P = .015), however there were no significant changes following the bicycle test (P = .96).] ⇨ Hyperalgesia for aerobic ex and Hypoalgesia for isometric ex
Kuppens 2016	24 musicians with shoulder pain and 12 musicians without shoulder pain	A single-blinded randomized and controlled crossover study design	Physical protocol: isometric contraction (20 – 25% of MVC) of the gleno-humeral external rotators until exhaustion or for a maximum of 5 minutes in the same test position. Emotional protocol: 32 selected and unpleasant images were presented in random order	PPTs (SF-36; PVAQ; PCS; SDQ)	Similar effects of both protocols in either group, i.e., musicians with and without shoulder pain (P > 0.05). All musicians showed elevated PPTs at local and remote areas after isometric exercise (P < 0.05). The emotional stress task increased PPTs at remote areas only (P < 0.05).

Ellingson 2016	11 patients with FM: Age(years) 38,58 (11,17) Height(cm) 165,18 (6,77) Weight(kg) 65.55 (13,06) FIQ 52,95 (13,06) 12 controls: Age(years) 43,67 (7,02) Height(cm) 1165,92 (5,77) Weight(kg) 68,41 (10,20) FIQ NA	RCT	EX Condition: participants completed 25 min of moderate intensity cycling on a Vision Fitness 2150, semi-recumbent stationary bicycle (Vision Fitness, Lake Mills, WI, USA). Following a 1-min warm-up, participants were instructed to achieve and maintain a pedaling rate of 60–70 revolutions per minute. They were also encouraged to increase or decrease the resistance level as needed to maintain a perception of effort that was "somewhat hard" or approximately "13" on Borg's 6–20 ratings of perceived exertion (RPE) scale. This intensity and duration of cycling was selected based on evidence from our group demonstrating that patients would be willing and able to complete the exercise. Pedaling rate and RPE were monitored and recorded by research staff throughout cycling. QR: participants rested on the same bike for the same amount of time as the exercise condition	fMRI Short Form McGill Pain Questionnaire (MPQ)	Following the scan post-EX, FM patients experienced a decrease in pain symptoms as reported from the MPQ visual analog scale (pre = 57.8˘29.1; post = 53.1˘27.6; d = 0.39) whereas after the QR scan there was an increase in pain symptoms (pre = 50.5˘18.2; post = 57.3˘20.5; d = 0.17). Following EX, HR was significantly elevated ($p <$ 0.001) and $ETCO_2$ was significantly lower across runs (p = 0.013) compared to QR. Groups did not differ significantly in HR ($p > 0.05$) and there were no significant interactions ($p >$ 0.05). However, $ETCO_2$ was significantly higher in FM compared to CO across runs ($p <$ 0.001). Exercise appeared to stimulate brain regions involved in descending pain inhibition in FM patients, decreasing their sensitivity to pain. Exercise may benefit patient with FM via improving the functional capacity of the pain modulatory system.

Gellego Izquierdo 2016	28 Subjects (18women and 10 men) with chronic non specific neck pain	RCT	CCF Training (n.14) Proprioception training (N.14)	CCFT PPT VAS Neck Pain Disability index	Both groups showed a significant increase in the PPT over the right anterior scalene muscle from baseline to post month 2. In addition, the proprioceptive training group showed an increase in the PPT over the right upper trapezius ($p <$ 0.05), right splenius ($p <$ 0.05) and right elevator scapulae ($p < 0.05$) at post month 2 compared with baseline
Knauf and Kolty 2014	N. participants: 18 (6 men and 12 women) with type 2 diabetes with or without painful diabetic neuropathy	Case control study	Three minutes of isometric exercise performed at 25% MVC	Pain Ratings Short McGill Questionnaire (VAS, Present Pain Index and SF-MPQ Total) IPAQ and pedometer for physical activity	Temporal summation pain ratings were significantly lower ($p < 0.05$) following exercise for the diabetic adults without PDN, however, for diabetics with PDN no significant differences were found after exercise. The results indicated that ratings were significantly lower following exercise for diabetic adults without PDN for the SF-MPQ total, VAS, and PPI; however, for diabetic adults with PDN only PPI ratings were significantly lower following exercise.
Kosek 2013	134 OA patients (83 knee, 51 hip)	Longitudinal Cohort Study	Subjects were instructed to perform an isometric	PTTs PP VAS	We found a normal function of EIA in OA

	40 controls		contraction (knee extension) corresponding to 50% of their individual MVC (afflicted side). The contraction was performed in a sitting position pushing against a resistance attached horizontally to the ankle with the knee joint flexed to about 90 degrees. PPTs were assessed at the contracting m. quadriceps and at the resting contralateral m. deltoideus starting 5 s after beginning of contraction and then every 30 s during contraction. Subjects were asked to keep the contraction until exhaustion (maximum 5 min)	HADS, KOOS, HOOS PPTs	patients at baseline <u>EIA at baseline and following exercise:</u> Normalized PPTs at m. quadriceps and at m. deltoideus increased during contraction in OA patients and controls alike (P <0.0001). No statistically significant change in normalized PPTs following exercise compared to baseline in OA patients, nor between the first and second assessment in controls. There was a positive correlation between baseline localized and generalized EIA in the OA group (r = 0.401, P < 0.0001) <u>Sensitivity to pressure pain at baseline and following exercise:</u> There was a significant difference between groups in PPTs (P = 0.026) and also a statistically significant difference between groups related to the assessed sites (i.e., GROUP _ SITE interaction) (PPT: P < 0.0001, PP4: P = 0.031, PP7: P=0.004). PP4 (P =0.038) and PP7 (P

					=0.006) were lower following exercise,
Rayhan 2013	28 Gulf War veterans 10 controls	Case Control Study	fMRI scan before and after two exercise stress tests (25 minute duration at 70% predicted hear rate followed by a climb to 85% HR to reach anaerobic threshold) Exercise induced two clinical Gulf War Illness subgroups. One subgroup presented with orthostatic tachycardia (n=10, START phenotype) The other subgroup developed exercise induced hyperalgesia (n=18, STOPP phenotype) associated with cortical atrophy and baseline working memory compensation in the basal ganglia.	fMRI indeces Supine and standing heart rate (HR) systolic (SBP) and diastolic blood pressure (DBP) pain perception: digital palpation at 18 traditional fibromyalgia tender point sites SF-36	Sixty-eight percent (19 out of 28) of the GWI subjects met the criteria for fibromyalgia. We repeated this digital palpation to assess longitudinal changes. At baseline controls had significantly fewer positive tender points than GWI subjects ($F_{2,35} = 5.58$, $P=0.007$). GWI subjects (n =18) had a significant increase in positive tender points after the two exercises compared to baseline ($P=0.007$, 2-tailed paired t-test, STOPP phenotype)
Ge 2012	22 women with fibromyalgia and 22 age-matched healthy controls (control group)	Case Control Study	Both arms in 90° abduction until exhaustion	PPTs	Following the contraction, PPTs were increased significantly and heterogeneously in the upper trapezius over time, but not, in the tibialis anterior muscle in healthy controls. However, PPT were significantly decreased over time in the tibialis anterior ($P < 0.05$), but not, in the upper trapezius in FM.
Van Oosterwijck 2012	N. participants: 22 female chronic WAD patients and	Case Control Study	Submaximal exercise stress test: the workload was increased by 25 W every min- ute, and the submaximal level	SF-36 CIS VAS PPTs	The change in PPTs over time was found to be significantly different between the chronic WAD

	22 healthy women.		was defined as 75% of the age-predicted target heart rate. Self- paced and physiologically limited exercise: bicycle exercise was performed by all subjects with 3safety breaks or exercise limits.		and the control group (hand P = .044, back P = .021, and calf P = .029),
Kumar 2011	18 adults (12 men, 6 women), mean age 22.5 ± 1.09 yrs who scored 7/13 in subjective aspects and 8/14 in objective aspects of Delphi criteria for lumbar segmental instability	Observer-blinded randomized placebo-controlled crossover clinical trial.	1.placebo-control (prone lying with pillow under the legs for 15 minutes) 2. experimental lumbar segmental stabilization ex: in a quadruped position the subject was instructed to tuck in the chin and hollow the abdomen with a posterior pelvic tilt. Then lift one arm while maintaining the earlier neutral spinal position. The steps were then repeated with lifting other arm. Ten repetitions were given for each side.	VAS PPT Joint play grading scale (0-6 scale)	Visual analogue scale changed significantly in both the periods of intervention-in control (*P* =.016) and experimental (*P*=.000) periods. However this improvement was more significant in the experimental period. The Pressure pain threshold also improved significantly in the experimental condition (*P* =.000) while the changes in control condition was not statistically significant (*P*=.816).
Conti 2011	The MFP group consisted of 29 consecutive Caucasian women (mean age 29.83±8.43 years, ranged from 18 to 49) Control group was comprised by 15 asymptomatic Caucasian women (25.47±1.23	Case Control Study	asked to chew a gum stick for 9 min and to stay at rest for another 9 min	VAS PPT	Patients with myofascial pain reported increase (76%) and no change (24%) on the pain intensity measured with the VAS. A significant main effect for group (MFP vs. control, P=0.002) and for time (p<0.001), but not for activity (chewing or rest). Also a significant interaction between group, activity and time

	years, from 20 to 35)				(p=0.01) was found. These findings reveal the effect of the chewing activity on the pain level in both groups over time, but do not indicate a significant recovery at rest. A reduction of the PPT at all muscular sites after the exercise and a non-significant recovery after rest were also observed.
Van Oosterwijck 2010	N. participants: Twenty-two women with ME/CFS and 22 healthy sedentary controls. The mean age of the patients was 34.3 ± 8.8 years and their mean BMI was 24.1 ± 4.7 kg m)2. The mean age of the control subjects was 38.9 ± 15 years and their BMI was 24.5 ± 4.8 kg m)2	Case Control Study	Submaximal exercise: the workload was increased by 25 W every minute, and the submaximal level was defined as 75% of the age-predicted target heart rate Self paced and physiologically limited exercise: the heart rate could not exceed 80% of the rate that corresponded to the anaerobic threshold during the sub- maximal exercise test.	PPT SF-36 CIS Immediately and after 24h exercise	In patients with ME/CFS, pain thresholds decreased following both types of exercise, whereas they increased in healthy subjects. This was accompanied by a worsening of the ME/CFS symptom complex post-exercise. Decreased pressure thresholds during submaximal exercise were associated with post exertional fatigue in the ME/CFS group (r = 0.454; P = 0.034).
Staud 2010	N. participants: 36 middle-aged healthy pain-free female subjects [mean age (SD): 44.7 (11.0) years] and 34 female FM	Case Control Study	2 rest and 2 arm exercise periods: 15 min rest, arm ergometer (the subjects were instructed to rotate the flywheel at 60 rpm) and repeat the same sequence	VAS PPT Tender point testing REP	Alternating strenuous exercise with brief rest periods not only decreased overall clinical pain of FM subjects but also their mechanical hyperalgesia.

	subjects [44.6 (12.2) years				
Meeus 2010	N. participants: Twenty-six patients with chronic fatigue syndrome suffering of chronic pain, 21 patients with chronic low back pain and 31 healthy subjects.	Comparative study	Submaximal aerobic exercise protocol on a bicycle ergometer	PPT VAS ADQ SF36 Nitric oxide assay	The mean PPT increased following exercise in healthy subjects and in patients with CLBP, and decreased in patients with CFS. These changes were statistically significant (p = 0.001) for all 3 groups. When comparing the patients with CFS with the 2 other groups, they differed significantly from patients with CLBP (p = 0.002) and from healthy controls (p = 0.009).
Cook 2010	N. partecipants: 15 GVs with CMP and 17 healthy GVs	Case Control Study	Sub-Maximal exercise test: resistance set at a power output associated with 70% of the participant's previously determined VO2peak. The exercise test began at 30 watts for the first minute of exercise. Resistance was then increased over the first 3 minutes until the target intensity was achieved by the beginning of the fourth minute. Participants were instructed to maintain a pedal rate between 50 and 60 rpm throughout the test	Heat and pressure pain threshold Suprathreshold pain testing RPE BDI DDS HSCL-12 MPQ SF-36 PBQ PARQ	No significant main or interaction effects were observed for heat or pressure-pain thresholds either prior to or following submaximal exercise (P > .05). Independent t-tests conducted to compare the MPQ ratings of the heat and pressure stimuli between groups also yielded insignificant (P > .05) differences
Kadetoff and Kosek 2007	17 FM female patients with the average age of 38.8 years (range 22–56)	Case Control Study	isometric contraction (39.2 N) m. quadriceps femoris dx. Performed in a sitting position, with the hip and knee held in approximately 90	Blood pressure (BP) heart rate (HR) Borg scale PPTs	FM patients had higher ratings of exertion/fatigue ($p<0.003$) and pain ($p<0.001$) at all times

	Controls: 17 healthy sex- and age matched subjects with the average age of 37.4 years (range 22–53)		flexion pushing against a resistance (4 kg · 9.81 m/s2 = 39.2 N) attached horizontally to the ankle. Held until exhaustion or for a maximum of 15 min. During the contraction period PPTs were assessed every 30 s alternating between the contracting m. quadriceps femoris and the resting m. deltoideus		compared to controls. The increase in pain ratings compared to baseline was more pronounced in FM patients than in controls during (2 min; $p < 0.005$: exhaustion; $p < 0.001$) and following (relaxation; $p < 0.001$: 5 min; $p < 0.005$: 10 min; $p < 0.05$) contraction. No statistically significant difference in the increase of pain ratings from baseline was seen between the groups at 15 min following contraction. PPTs were lower in patients compared to controls at both sites at all times ($p < 0.001$). FM patients had significantly lower PPTs than controls at both sites at all times ($p < 0.001$) . =>FM patients rated higher pain intensity during and following contraction of the same absolute force, but when subgroups performing the same relative force (same %MVC) were compared, only the pain ratings were elevated in FM patients

					compared to controls.
Staud 2005	11 female NC and 12 female FM subjects. The mean age of the NC and FM subjects was 45.7 and 48.4 years	Case Control Study	All subjects underwent submaximal ISOM hand grip exercise of the dominant forearm by squeezing a JAMAR hand dynamometer at 30% MVC for 90 s.	VAS Borg scale of exertion (0–20) Heart rate and blood pressure (systolic/diastolic) Medical College of Virginia (MCV) Pain Questionnaire Tender point testing	We found the effects of submaximal ISOM exercise on central pain modulation to be opposite in FM patients and NC. ISOM exercise reduced experimental heat pain ratings and increased PPTs in NC subjects both ipsilateral and contralateral to the exercised extremity. Opposite effects were detected in FM patients ipsilateral and contralateral to the exercised extremity. Thus, ISOM exercise evoked hypoalgesia in NC and hyperalgesia in FM patients. <u>Effects of ISOM exercise on thermal pain ratings</u> Ipsilateral thermal pain ratings: Compared to baseline ISOM exercise of 90 s duration resulted in a significant decrease of experimental heat pain ratings in NC ($F(1,10)=8.4$; $P=0.01$), whereas the same exercise manipulation significantly increased the pain ratings of FM subjects after 60 s and 90 s of exercise ($F(1,11)=8.0$; $P=0.02$ and

					F=13.0; P=0.001, respectively). Contralateral thermal pain ratings: the change in thermal pain ratings between baseline and 60 or 90 s significantly differed between NC and FM subjects (F(1,17)=5.9; P=0.27; F=13.3; P=0.002),ISOM exercise of 90 s duration resulted in a significant decrease of experimental pain ratings in NC (F(1,11) 5.7; P=0.04), whereas the same exercise manipulation significantly increased the pain ratings of FM subjects after 60 and 90 s of exercise (F(1,6)=6.3; P=0.04 and F=6.5; P=0.04). <u>Effect of ISOM exercise on mechanical pain thresholds</u> Ipsilateral mechanical pain thresholds: the change of PPTs between baseline and 30, 60, or 90 s of exercise was significantly different between NC and FM subjects (F(1,22)=11.7; P=0.002; F=18.1; P=0.001; F=27.9; P=0.001). Compared to baseline, exercise of NC resulted

					in a significant increase of PPTs after 30, 60, and 90 s (F(1,13)=8.2; P=0.01; F=23.4; P=0.001; F=24.1;P=0.001), whereas the same exercise manipulation significantly decreased the PPTs of FM subjects after 30 and 90 s (F(1,9)=37.6; P=0.001, F=11.5; P=0.008). Contralateral mechanical pain thresholds: Compared to baseline the PPT change at each time point was different between NC and FM subjects (F(1,22)=24.7; P=0.001; F=13.1; P=0.002; F=16.1; P=0.001) Compared to baseline exercise of NC resulted in a significant increase of PPT safter 30, 60, and 90 s (F (,13)=22.0; P=0.001; F=6.1;P=0.03; F=8.6; P=0.01), whereas the same exercise manipulation significantly decreased PPTs of FM subjects at all time points (F(1,9)Z7.7; P=0.02; F=9.1; P=0.02,F=39.0; P=0.001)
Hoffman 2005	8 individuals (4 male and 4 female) with chronic low back pain	Case Control Study	First pressure pain test + cycle ergometer 1 min after: cycling was initiated at the workload that	PPTs	Among the chronic low back pain group, pain ratings at both 2 minutes and 32

	participated in the study A separate group of 10 healthy subjects (7 male and 3 female, age = 34± 8)		generated 50 percent of peak oxygen uptake for 5 min than we increased the intensity to a level that generated 70 percent of peak continued for 20 min. After completion of the cycling, a second pressure pain test that was initiated 2 minutes after cycling ended. Then, the subjects rested quietly until the third pain test, 28 minutes after completion of the second pain test (32 minutes postex). The time between each of the three pain tests was 28 min, the subjects performed 25 min of cycling between the first and second pain tests.		minutes post-exercise were lower ($p < 0.05$) than pre-exercise values. Mean SD pain ratings for the first trial of the second test day were no different between the two subject groups. ⇨ that exercise-induced analgesia to an experimentally induced pressure pain can be evident for more than 30 minutes after aerobic exercise from leg cycling in people with minimal to moderate levels of disability caused by chronic low back pain
Whiteside, 2004	Five CFS patients (median age 46 years range 28 – 49) and five control subjects (median age 44 years range 30 – 54)	Case Control Study	The exercise consisted of three 5-min periods on a treadmill, set to a speed of 5 km h, with an increasing incline of 5, 10 and 15°at each stage of the graded exercise test	PT	The difference in baseline pain threshold between the single female participants in each group was not significant. The pain threshold for the female control did not change with exercise while it was reduced in the female CFS patient.
Vierck 2001	For ex 1: 6 pain-free subjects (3 men and 3 women),	Case Control Study	Experiment 1: evaluate the effect of exercise on temporal summation in healthy subjects-	Ex 1: Post exercise testing began either 1.5 or 10 minutes after completion of exercise,	Experiment1: The effects of exercise on temporal summation of late sensation

	ranging 17 - 60 y For ex 2: 10 female patients who fulfilled the 1990 American College of Rheumatology Criteria for FMS 10 age matched female control subjects and 10 male control subjects (average age in each group was 46 years)		Either the subjects 1) did not exercise before testing or 2) the level of exercise was controlled by pedaling on a stationary bicycle for 15 minutes at a low comfortable rate and not leading to exhaustion (mild exercise) or 3) pedaling at a comfortable rate for 15 minutes, followed by pedaling at a maximal rate to exhaustion. Experiment2:(designed to compare effects of exercise on control pain-free subjects and subjects with FMS) All subjects exercised on a treadmill according to a modified protocol of Bruce et al. The endpoint for exercise testing was physical exhaustion.	resulting in a total of 5 types of testing sessions. Each subject was tested 4 times at each condition, twice with stimulation of the right hand and twice on the left hand (20 sessions) the subjects with FMS rated their clinical pain using VAS (Ex Ex 2: Borg's rating scale of perceived exertion (RPE) Peak oxygen uptake (VO2) carbon dioxide production metabolic equivalent (MET) respiratory exchange ratio (RER) tender point evaluation Fibromyalgia Impact Questionnaire Medical College of Virginia (MCV) Pain Questionnaire Sensory testing temporal summation of second pain	intensities for pain-free subjects Comparisons between baseline and post exercise ratings of sensations during the first series revealed significant effects for mild exercise ($F = 165.6$, $P < .01$) and a greater reduction of temporal summation after exercise to exhaustion ($F = 246.7$, $P < .01$). When testing began 10 minutes after completion of exercise, smaller but significant effects were obtained for exercise to exhaustion ($F = 87.7$, $P < .01$) and mild exercise ($F = 121.8$, $P < .01$). Experiment 2: ratings of the initial and maximal sensation magnitudes and early and late after sensation intensities were significantly reduced by exercise for pain-free subjects ($F = 4.3$, $P < .05$), with the 4 response measures and 4 ISIs as dependent variables. In contrast, these same indices were significantly increased by exercise for subjects with FMS ($F = 7.2$, $P = .01$). Patients with FMS had high levels of clinical

					pain (mean, 64 VAS) before exercise, and their pain ratings were not significantly altered at 10 minutes or 24 hours after exercise. Also, contrary to the self-assessments of many patients with FMS, clinical pain levels did not increase during the 7 days after maximal exercise testing. A slight decrease in daily pain intensity was reported by a subset of 7 subjects with FMS ⇨ The principal finding of the present study was that strenuous exercise increased, rather than decreased, temporal summation of pain intensity for subjects with FMS.

Tabella 3 Analisi risultati degli articoli inclusi

3.3 VALUTAZIONE DEGLI STUDI E CRITICAL APPRAISAL

Per i diversi studi sono state utilizzate le scale dello "*Study Quality Assessment Tools*" del National Institute of Health (NIH).

Nel dettaglio:

- per gli *RCT* è stata utilizzata la ***Quality Assessment of Controlled Intervention Studies*****,** uno strumento di valutazione critica che comprende al suo interno 14 domande riguardanti il metodo di randomizzazione, l'assegnazione del trattamento, il blinding la somiglianza tra i gruppi basali nonché tasso di abbandono, adesione al protocollo di trattamento e valutazione delle misure di esito;
- per i *case-control* è stata utilizzata la ***Quality Assessment of Case-Control Studies***, uno strumento di valutazione critica che comprende al suo interno 12 domande inerenti al quesito di ricerca, la popolazione target e la relativa selezione dei partecipanti, la dimensione del campione, i criteri di inclusione ed esclusione nonché il blinding dei valutatori e l'analisi statistica;
- per i *cross-sectional* è stata utilizzata la stessa scala di misurazione dei case-control.

In appendice sono state riportate le tabelle complete.

3.4 VALUTAZIONE DEL RISCHIO DI BIAS

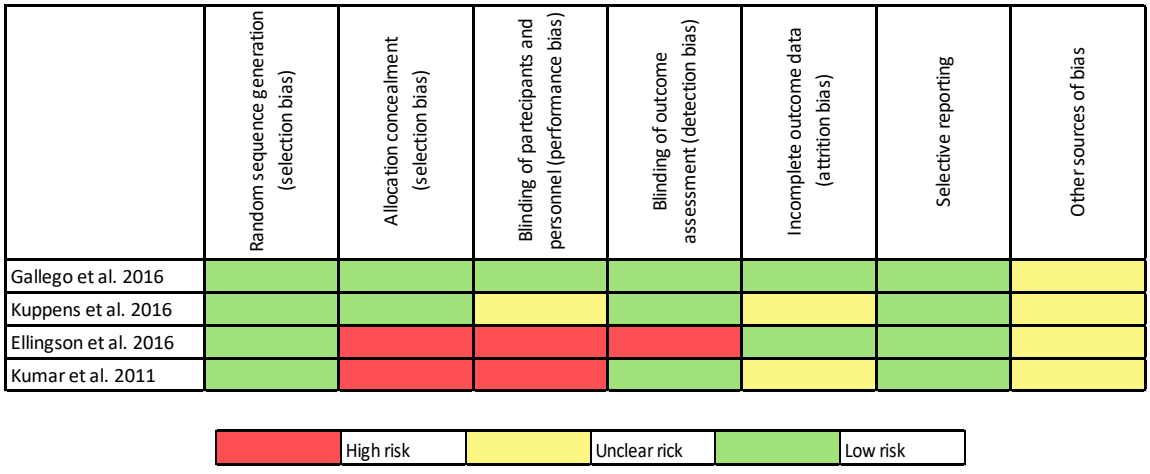

Tabella 4: Risk of Bias RCT

	Was the research question or objective in this paper clearly stated and appropriate?	Was the study population clearly specified and defined?	Did the authors include a sample size justification?	Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?	Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?	Were the cases clearly defined and differentiated from controls?	If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?	Was there use of concurrent controls?	Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?	Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?	Were the assessors of exposure/risk blinded to the case or control status of participants?	Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?
Ickmans et al, 2017							NA	CD		CD		
Christensen et al, 2017							NR					NA
Smith et al., 2017				NR			NR					
Knauf, 2014							NA					NA
Kosek et al., 2013												
Rayhan et al.,2013								NR				CD
Van Oostervick et al., 2012							NA				NR	
Ge et al., 2012							NA				NR	NR
Conti et al., 2011							NA		NA			
Staud et al., 2010							NA				NR	
Meeus et al., 2010							NA					NR
Van Oostervick, 2010							NA				NR	NR
Cook et al., 2010							NA				NR	
Kadetoff, 2007				NR			NA		NA			
Hoffman et al., 2005				NR			NR		CD			NR
Staud et al., 2005							NA					
Whiteside et al., 2004				NR			NA				NR	NR
Vierck , 2001				NR			NA		NA			NR

yes | no | NA = not applicable | NR = not reported | CD= cannot determine

Tabella 5: Qualità case-control e cross-sectional

3.5 SINOSSI DEI RISULTATI

3.5.1 ENDOPOINT

Tutti gli studi hanno preso in considerazione il dolore come *endpoint*. La misurazione dell'outcome dolore è stata eseguita per tutti mediante il pressure pain threshold (PPT) fatta eccezione per Ellingson 2016[12] in cui l'autore si è servito di fMRI e del McGill Questionnaire. Associato al PPT altre forme di misurazione dell'outcome dolore sono stati la VAS, VNRS, il Conditioned Pain Modulation (CPM), la Pain Tolerance, la Temporal Summation, la palpazione dei tender point. In relazione poi alla specifica patologia analizzata nei singoli studi gli autori hanno selezionato la scala che meglio si addiceva per misurare disabilità, partecipazione o comunque la limitazione oggetto di indagine.

3.5.2 APPROCCI TERAPEUTICI

- *Esercizio aerobico*

Hoffman et al. (2005)[13] hanno analizzato 8 individui con *chronic low back pain* e 10 soggetti sani. I pazienti hanno effettuato esercizio su cicloergometro. Il test è iniziato con un carico di lavoro che ha generato il 50% del picco di assorbimento di ossigeno per 5 minuti poi è stata aumentata l'intensità a un livello che ha generato il 70% del picco continuato per 20 minuti. Come misure di outcome è stata utilizzata il PPTS misurato dopo 2 minuti dal termine dell'esercizio e di nuovo a distanza di 32minuti. Nel gruppo CLBP, le valutazioni del dolore a post esercizio sia a 2 minuti che a 32 minuti erano inferiori ($p < 0.05$) rispetto ai valori preesistenti. Si può dunque affermare che l'analgesia indotta da esercizio fisico per un dolore da pressione indotto sperimentalmente può essere evidente per più di 30 minuti dopo l'esercizio aerobico in persone con livelli da minimi a moderati di disabilità causati da lombalgia cronica.

Rayhan et al. (2013)[14] hanno indagato la relazione esistente tra esercizio, funzioni cerebrali e cambiamenti dei sintomi in un gruppo di veterani della Guerra del Golfo. 28 veterani e 10 controlli hanno completato una scansione fMRI ed una valutazione di tender points prima e dopo due prove di stress da sforzo di 25 minuti su bicicletta al 70% della frequenza cardiaca. Parte dei soggetti ha sviluppato iperalgesia mostrando un significativo aumento dei tender points dopo i due esercizi se confrontati con le misurazioni alla baseline ($P = 0.007$).

Staud et al. (2010)[29] hanno analizzato 36 femmine sane e 34 femmine con fibromialgia. L'esercizio prevedeva 15 min di riposo e 15 min di cicloergometro a 60 rpm ripetuto per due

volte (A+B+A+B). Come misure di outcome sono state usate la VAS, PPT, tender point testing, e REP. Alle misurazioni post esercizio è stato dimostrato che l'alternanza di un intenso esercizio fisico con brevi periodi di riposo non solo riduce il dolore clinico generale dei soggetti FM, ma anche la loro iperalgesia meccanica. Nessun peggioramento prolungato del dolore e dell'iperalgesia FM generali si è verificato nonostante la forte attività muscolare

Whiteside et al. (2004)[15] hanno analizzato 5 pazienti con *chronic fatigue syndrome* (CFS) e 5 soggetti sani. Entrambi i gruppi hanno eseguito un esercizio diviso in 3 fasi di 5 minuti ciascuna su tapis roulant, impostato ad una velocità di 5 km/h con una pendenza crescente di 5°,10°,15° in ciascuna fase del test. Come misura di outcome è stata utilizzata il Pain Thresholds. Dalle misurazioni post esercizio si rileva un incremento del PT nel gruppo controllo e una riduzione nel gruppo CFS.

Vierck et al. (2001)[6] hanno studiato gli effetti dell'esercizio fisico sulla Temporal Summation alla stimolazione di recettori nocicettivi. In soggetti normali, la Temporal Summation delle sensazioni dolorose tardive è attenuata quando i test iniziarono a 1,5 o 10 minuti dopo l'esercizio. Gli individui con diagnosi di sindrome di fibromialgia (FM) riferiscono generalizzato dolore cronico che aumenta dopo l'esercizio. Tutti i soggetti hanno eseguito il *Bruce Protocol Test* su di un *treadmill* fino all'esaurimento fisico generalmente per più di 11 minuti (un picco di *respiratory exercise* rate maggiore di 1.16 indicava il livello massimo di esercizio). I soggetti con FM sono riusciti a malapena a raggiunger il Maximal Heart Rate per la loro età (220-età), mentre i soggetti sani lo hanno lievemente sorpassato. In questo studio è stato dimostrato come l'esercizio aumenti, invece che diminuire la Temporal Summation dell'intensità del dolore in soggetti con FM. Questo risultato suggerisce una disfunzione

centrale in soggetti con FM e conferma il dato che indica che l'esercizio aumenta la loro sensibilità dolorosa a differenza dei soggetti sani.

- *Esercizio submassimale*

Ickmans et al. (2017)[16] hanno reclutato 52 pazienti (26 con WAD cronico e 26 sani). Entrambi i gruppi hanno effettuato esercizio sub-massimale su cicloergometro seguendo il protocollo "*Aerobic Power Index Test"*. Il carico di lavoro è iniziato ad una potenza di 25 watt ed è stato aumento di 25 watt ogni minuto fino a quando il partecipante ha raggiunto il suo livello sub-massimale pedalando ad una velocità di 60rpm. L'esercizio è stato interrotto quando i partecipanti hanno raggiunto la frequenza cardiaca target individuale. Come misure di outcome sono state utilizzate i PPTs, la VAS (baseline, post esercizio e 24 h post esercizio), il conditioned pain modulation (CPM), Temporal Summation (TS) e il Deep-Tissue Hyperalgesia with occlusione cuff pressure (VNRS). Alle misurazioni post trattamento si è osservato una riduzione maggiore dei PPTs delle persone con WAD cronico rispetto ai controlli sani. Si dimostra che i pazienti con WAD cronica sono in grado di inibire l'iperalgesia indotta dall'esercizio.

Smith et al. (2017)[17] hanno reclutato 21 pazienti con WAD cronico e 19 pazienti asintomatici. Entrambi i pazienti hanno compiuto due sessioni di test: 1. Esercizio sub-massimale su bicicletta (watt iniziale 25 con incremento di 25 watt ogni minuto per 30 min) e 2. Esercizio isometrico con squat a muro per massimo 3 min. Queste sessioni sono state programmate a distanza di 5-10giorni l'una dall'altra. Come misure di outcome sono stata utilizzate la PPT, la Thermal Pain Threshold e la Conditioned Pain Modulation. I PPTs sono significativamente aumentati dopo l'esercizio di squat (P = .001), tuttavia non si sono verificati cambiamenti

significativi dopo il test della bicicletta (P = .17). L'esercizio isometrico di squat al muro ma non l'esercizio ciclico aerobico ha portato a EIH in entrambi i gruppi (P <0.023) senza differenze tra i gruppi (P> 0.55) dimostrate per entrambi gli esercizi.

Van Oosterwijck et al. (2012)[10] hanno invece analizzato l'effetto dell'esercizio sub-massimale confrontandolo con quello "*self-paced*" in 22 pazienti con WAD cronico e 22 soggetti sani. Entrambi i gruppi hanno eseguito esercizio sub-massimale su bicicletta seguendo il protocollo "*Aerobic Power Index Test*" con una velocità di pedalata compresa tra 60 e 70 rmp e, a distanza di una settimana, lo stesso è stato effettuato con 3 interruzioni di sicurezza o limiti di esercizio (a. la frequenza cardiaca non poteva superare l'80% della velocità corrispondente alla soglia anaerobica durante il test massimale; b. il carico di lavoro era mantenuto al di sotto dell' 80% di quello corrispondente alla soglia anaerobica; c. la durata dell'allenamento è stata determinata chiedendo ai pazienti di stimolare se stessi stimando per quanto tempo sarebbero stati in grado di eseguire l'esercizio senza esacerbare i sintomi). Il Pressure Pain Threshold (PPT), lo stato di salute e i livelli di attività sono stati valutati in risposta ai 2 periodi di allenamento. Nel WAD cronico, la PPT diminuiva in seguito all'esercizio sub-massimale, mentre aumentava nei soggetti sani. Lo stesso effetto è stato stabilito in risposta all'esercizio auto-stimolato, fisiologicamente limitato, con l'eccezione del PPT al polpaccio che è aumentato. Un peggioramento del complesso cronico dei sintomi WAD è stato segnalato dopo l'esercizio. Sono stati riportati meno sintomi in risposta all'esercizio auto-stimolato, fisiologicamente limitato. Queste osservazioni suggeriscono un'anormale elaborazione del dolore centrale durante l'esercizio in pazienti con WAD cronico. L'esercizio sub-massimale innesca un malessere post-esercizio, mentre un esercizio "*self paced*" e fisiologicamente limitato scatena sintomi meno gravi e, pertanto, sembra più appropriato per i pazienti con WAD cronico.

Van Oosterwijck et al. (2010)[9] hanno esaminato 22 donne con encefalomielite mialgica/*chronic fatigue syndrome* (ME/CFS) e 22 soggetti sani. Tutti i soggetti hanno eseguito un test di esercizio sub-massimale e, a distanza di una settimana, un test di esercizio "*self-paced*", fisiologicamente limitato su un cicloergometro. Prima e dopo l'esercizio, i soggetti hanno compilato questionari per valutare lo stato di salute (SF-36, CSI) e sono stati sottoposti a misurazioni del Pressure Pain Threshold (PPT). Nei pazienti con ME / CFS, i PPTs si sono ridotti seguendo entrambi i tipi di esercizio, mentre sono aumentate nei soggetti sani. Questo è stato accompagnato da un peggioramento del complesso sintomatologico nei pazienti con ME/CFS post-esercizio. Le diminuzioni dei PPTs durante l'esercizio sub-massimale erano associate all'affaticamento post-sforzo fisico nel gruppo ME / CFS ($r = 0,454$; $P = 0,034$). Questo indica la presenza di un'anormale elaborazione del dolore centrale durante l'esercizio in pazienti con ME / CFS e dimostra che sia l'esercizio sub-massimale che l'esercizio "*self-paced*" e fisiologicamente limitato, attivano il malessere post- sforzo in questi pazienti.

Meeus et al. (2010)[18] hanno reclutato 26 pazienti con "*chronic fatigue syndrome*" (CFS), 21 pazienti con "*chronic low back pain"* e 31 soggetti sani. Tutti i soggetti hanno eseguito un protocollo completo che consisteva in massimo di 6 periodi di esercizio su un cicloergometro, ognuno dei quali seguito da 90 s di riposo. Il programma di esercizi è stato incrementale, a partire da 20 Watt e aumentando di 10 Watt / minuto. Ogni esercizio è stato introdotto da un breve periodo di riscaldamento per superare l'inerzia, partendo da zero e aumentando gradualmente di 1 Watt ogni 2 s. Successivamente, il periodo di esercizio effettivo consisteva in 2 passaggi incrementali di 1 min. Infine, ogni incontro è stato completato con un breve raffreddamento di 30 s per prevenire il pooling venoso. I partecipanti sono stati istruiti a interrompere il test quando si stancavano e hanno ritenuto di non poter più raggiungere una frequenza di pedalata di almeno 70 giri al minuto. Pre e post esercizio sono stati misurati i livelli

sierici di NO e 8 siti di PPT bilaterali. Il PPT medio è aumentato dopo l'esercizio in soggetti sani e in pazienti con CLBP e diminuita nei pazienti con CFS. Questi cambiamenti erano statisticamente significativi (p = 0,001) per tutti e 3 i gruppi. Confrontando i pazienti con CFS con gli altri 2 gruppi, essi differivano significativamente dai pazienti con CLBP (p = 0,002) e dai controlli sani (p = 0,009). I risultati suggeriscono l'iperalgesia e l'elaborazione anormale del dolore centrale durante l'esercizio aerobico sub-massimale nei pazienti con CFS, ma non in quelli con CLBP.

Cook et al. (2010)[19] hanno reclutato 32 veterani della guerra del Golfo persiano, 15 dei quali presentavano "*chronic musculoskeletal pain*" (CMP). Tutti i partecipanti hanno eseguito un esercizio sub-massimale su cicloergometro con una resistenza impostata ad una potenza erogata associata al 70% del VO_{2peak} precedentemente determinato. Il test è iniziato ad una potenza di 30 watt per il primo minuto, e la resistenza è stata poi aumentata nei primi 3 minuti fino a raggiungere l'intensità desiderata entro l'inizio del quarto minuto. I partecipanti sono stati istruiti a mantenere una frequenza di pedalata tra di 50 e 60 rpm durante il test. L'esercizio è durato 30minuti seguito da 3 minuti di riposo attivo. Prima e dopo l'esercizio sono state misurate la Heat e il Pressure Pain Thresholds e il Suprathreshold Pain Ratings. Non sono stati osservati effetti principali o interazioni significative per le soglie di calore o pressione-dolore prima o dopo l'esercizio sub-massimale (P> 0.05). Nelle misurazioni del Suprathreshold Pain Ratings i veterani con CMP hanno riportato livelli più elevati di intensità di dolore rispetto ai sani dopo esercizio sub-massimale. Si è dunque osservato che i veterani affetti da CMP sono: 1) più sensibili a una gamma di stimoli di dolore termico rispetto ai GV sani; 2) sperimentano un maggiore dolore muscolare durante l'esercizio rispetto ai GV sani; e 3) diventano più sensibili agli stimoli di dolore termico a seguito di esercizio.

- *Esercizio a intensità moderata*

Ellingson et al. (2016)[12] hanno analizzato 11 pazienti diagnosi di fibromialgia e 12 soggetti sani. I partecipanti sono stati sottoposti a due condizioni differenti: esercizio o riposo tranquillo. L'ordine delle condizioni è stato randomizzato e controbilanciato. Per la condizione EX, i partecipanti hanno completato un ciclo di intensità moderata di 25 minuti su una Vision Fitness 2150, una bicicletta stazionaria semi-sdraiata. Dopo un riscaldamento di 1 minuto, i partecipanti sono stati istruiti a raggiungere e mantenere una velocità di pedalata di 60-70 giri al minuto. Sono stati inoltre incoraggiati ad aumentare o diminuire il livello di resistenza necessario per mantenere una percezione dello sforzo "un po' difficile" o approssimativamente "13" sui valori di 6-20 di Borg della scala di sforzo percepito (RPE). L'intensità e la durata del ciclo sono state selezionate sulla base delle prove del nostro gruppo che dimostrano che i pazienti sarebbero disposti e in grado di completare l'esercizio. Per "*quiet rest*", i partecipanti si sono fermati sulla stessa bici per lo stesso periodo di tempo delle condizioni di esercizio. Sono state poi valutate le risposte cerebrali mediante fRMN e le valutazioni agli stimoli di calore nocivi confrontate all'interno e tra i due gruppi. Per le valutazioni del dolore, è stata riscontrata un'interazione significativa ($p < 0,05$) di tipo *Condition by Run* caratterizzata da livelli di dolore moderatamente inferiori post EX rispetto a QR ($d = 0,39\text{-}0,41$) per FM ma simili ai valori in CO ($d = 0,10\text{-}0,26$), dimostrando così che l'esercizio diminuiva la sensibilità al dolore nei pazienti affetti da FM a un livello analogo ai controlli senza dolore. Le risposte cerebrali hanno dimostrato una significativa differenza all'interno del gruppo nei pazienti fibromialgici, caratterizzata da una minore attività cerebrale bilaterale nell'insula anteriore dopo QR rispetto a EX. C'era anche un'interazione significativa per gruppo per condizione con i pazienti FM che mostrava meno attività nella corteccia prefrontale dorsolaterale sinistra dopo QR rispetto a post-EX e CO in seguito a entrambe le condizioni. Questi risultati suggeriscono che l'esercizio

sembra stimolare le regioni cerebrali coinvolte nella inibizione del dolore discendente nei pazienti affetti da FM, diminuendo la loro sensibilità al dolore. Pertanto, l'esercizio fisico può giovare ai pazienti con fibromialgia migliorando la capacità funzionale del sistema di regolazione del dolore.

- *Esercizio isometrico*

Kuppens et al. (2016)[20] hanno reclutato 24 musicisti con dolore alla spalla e 12 musicisti sani. Sono stati elaborati due differenti protocolli: 1. *physical task* (i partecipanti hanno effettuato una contrazione isometrica dei rotatori esterni della spalla al 20-25 % del MVC fino all'esaurimento o massimo 5 minuti nella stessa posizione di test); 2. *emotianal protocol* (i partecipanti hanno visualizzato 32 immagini sgradevoli in ordine randomizzato). Tutti i partecipanti sono stati allocati casualmente a uno dei due protocolli elaborati e a distante di 3/7 giorni sono stati incrociati in modo che ogni musicista li eseguisse entrambi. Come misure di outcome è stato utilizzato il PPT e sono stati somministrati questionari quali SF-36, PVAQ, PCS e la SDQ. I PPTs, sia alla spalla ipsilaterale che alla spalla controlaterale, sono aumentati significativamente in tutti i musicisti dopo aver eseguito un esercizio di rotazione unilaterale della spalla ipsilaterale. I PPTs sono aumentati in tutti i musicisti in luoghi remoti (quadricipite e tibiale anteriore), ma un aumento significativo è stato osservato solo in 2 su 4 misurazioni nei musicisti con dolore alla spalla e in 3 su 4 misure in musicisti senza dolore. Dopo l'*emotianal protocol,* tutti i musicisti hanno aumentato significativamente i loro PPTs agli arti inferiori (P <0,05) ma non alla spalla (P> 0,05). Nel complesso, i relativi cambiamenti nei PPTs non differiscono tra i musicisti con e senza dolore alla spalla (P> 0.05). Infine, non sono state osservate differenze significative nel cambiamento di PPT tra il compito emotivo e quello fisico nei musicisti con dolore alla spalla. Quelli senza dolore hanno mostrato un aumento significativamente più elevato di PPT ai quadricipiti ipsilaterali durante il protocollo emotivo e

all'infraspinato controlaterale durante il protocollo fisico. Questi risultati suggeriscono che l'ipoalgesia indotta sia dall'esercizio fisico sia dallo stress si verifica nei musicisti con e senza dolore alla spalla, ma in luoghi diversi.

Gallego Izquierdo et al. (2016)[21] hanno reclutato 28 soggetti con *chronic non specific neck pain* ed ha confrontato l'efficacia sul dolore del *Cranio Cervical Flexion Training* (n=14) contro un *training propriocettivo cervicale* (n=14). Per il CCF training il fisioterapista ha identificato il livello target che il paziente poteva mantenere stabilmente per 5 secondi senza ricorrere alla retrazione, senza l'uso dominante dei muscoli superficiali del collo, e senza un rapido movimento di flessione cranio-cervicale. Per ciascun livello target, la durata della contrazione è stata aumentata a 10 s, e il soggetto è stato addestrato a eseguire 10 ripetizioni con brevi periodi di riposo tra ogni contrazione (~ 3-5 s). Una volta raggiunto un set di 10 ripetizioni di 10 secondi a un livello target, il soggetto è stato portato a allenarsi al livello target successivo fino al target finale di 10 ripetizioni di 10 s a 30 mmHg. Per il training propriocettivo sono stati eseguiti esercizi di *head relocation, eye follow, gaze stability e eye-head coordination*. I partecipanti hanno effettuato in totale 6 giorni di esercizio distribuiti in 2 mesi. Come misure di outcome sono state utilizzate il PPT, il Cranio Cervical Flexion Test performance, la VAS, e il NDI prima, immediatamente dopo la prima seduta, dopo un mese dall'inizio del trattamento e a distanza di due mesi dalla sua fine. A 2 mesi, entrambi i gruppi hanno migliorato le loro prestazioni sul CCFT ($p < 0,05$), ma questo non differiva tra di loro ($p > 0,05$). Entrambi i gruppi hanno mostrato una riduzione del loro dolore a riposo e disabilità a 2 mesi, ma anche questo non era differente tra di loro($p > 0,05$). La sensibilità al dolore da pressione non è cambiata per nessuno dei due gruppi. Entrambi gli interventi hanno comportato una riduzione del dolore e della disabilità, il che conferma le proprietà di modulazione del

dolore degli esercizi del collo attivo e sottolinea l'importanza dell'esercizio come componente del trattamento per la gestione dei pazienti con dolore cronico al collo.

Knauf and Koltyn (2014) [22] hanno analizzato 18 pazienti con diabete di tipo 2 con e senza dolore neuropatico (PDN). Tutti i partecipanti hanno effettuato una contrazione isometrica schiacciando un dinamometro con la mano al 25% del MVC per 3minuti. Come misure di outcome sono state utilizzate la SF-MPQ, la VAS, e il Present Pain Index (PPI). I risultati hanno indicato che le valutazioni erano significativamente inferiori dopo l'esercizio per gli adulti diabetici senza PDN per il totale di SF-MPQ, VAS e PPI; tuttavia, per gli adulti diabetici con PDN solo i punteggi PPI erano significativamente inferiori dopo l'esercizio. Le valutazioni del dolore sperimentale sono risultate diminuire significativamente dopo l'esercizio per gli adulti diabetici senza PDN, indicando che l'EIH si è verificato dopo l'esercizio.

Kosek et al (2013)[23] hanno analizzato 130 pazienti con osteoartrosi (83 al ginocchio e 51 all'anca) e 40 soggetti sani. I soggetti sono stati istruiti a eseguire una contrazione isometrica (estensione del ginocchio) al 50% del loro MVC individuale sul lato deficitario mantenendo la contrazione fino all'esaurimento per massimo 5 min. Come misure di outcome sono state utilizzate il PPT, il Pressure Pain, la VAS e scale specifiche quali HADS, KOOS, HOOS. Dai risultati si evince che il valore del PPT normalizzati a m. quadricipite e alla m. il deltoide è aumentato durante la contrazione nei pazienti con OA e nei controlli allo stesso modo (P <0,0001). Non vi è stato alcun cambiamento statisticamente significativo nei PPT normalizzati dopo l'esercizio rispetto al basale nei pazienti con OA, né tra la prima e la seconda valutazione nei controlli. C'era una correlazione positiva tra l'EIA localizzata di base e l'EIA generalizzata nel gruppo OA (r 1/4 0,401, P <0,0001). Dopo l'esercizio, non ci sono state correlazioni

statisticamente significative tra la durata dell'esercizio neuromuscolare (settimane) e il cambio di VIA a m. quadricipite (r 1/4 0.089, P 1/4 0.424) o m. deltoide (r 1/4 0.162, P 1/4 0.146).

Kadetoff and Kosek (2007)[24] hanno analizzato 17 donne con diagnosi di fibromialgia e 17 soggetti sani. Entrambi i gruppi hanno effettuato una contrazione isometrica del quadricipite di dx tenuta fino all'esaurimento o per un massimo di 15 minuti. Durante la contrazione, i PPTs sono stati valutati ogni 30sec. Come misure di outcome sono state utilizzate il PPT, la scala di Borg, pressione arteriosa e frequenza cardiaca. I pazienti affetti da FM avevano punteggi più elevati di sforzo/fatica ($p < 0{,}003$) e dolore ($p < 0{,}001$) in ogni momento rispetto ai controlli. L'aumento nelle valutazioni del dolore rispetto al basale era maggiore nei pazienti FM che nei controlli durante (2 minuti; $p < 0{,}005$: esaurimento; $p < 0{,}001$) e dopo la contrazione (rilassamento; $p < 0.001$: 5 min; $p < 0.005$: 10 min; $p < 0.05$). Nessuna differenza statisticamente significativa nell'aumento delle misurazioni del dolore rispetto al basale è stata osservata tra i gruppi a 15 minuti dopo la contrazione. I PPTs erano più bassi nei pazienti rispetto ai controlli in entrambi i siti in ogni momento ($p < 0{,}001$). I pazienti con FM presentavano PPTs significativamente più bassi dei controlli in entrambi i siti in ogni momento ($p < 0{,}001$). I pazienti FM hanno valutato una maggiore intensità del dolore durante e dopo la contrazione della stessa forza assoluta, ma quando sono stati confrontati sottogruppi con la stessa forza relativa (stessa% MVC), solo i valori del dolore erano elevati nei pazienti fibromialgici rispetto ai controlli.

Ge et al. (2012)[25] hanno analizzato 22 donne con fibromialgia e 22 soggetti sani. Entrambi i gruppi hanno eseguito una abduzione a 90° di braccia bilaterale fino all'esaurimento. Come misura di outcome è stato utilizzato il PPT. Le soglie del dolore sotto pressione (PPTs) sono state misurate in 13 punti bilateralmente nel muscolo trapezio superiore e dal punto medio

bilateralmente nel tibiale anteriore prima-, immediatamente dopo- e 20 minuti dopo l'esercizio. Sono stati registrati il tasso di affaticamento, l'intensità del dolore e la durata della contrazione affaticante. La durata della contrazione affaticante era significativamente più breve in FM rispetto ai gruppi di controllo sani (P <0,05), l'intensità del dolore era significativamente più alta in FM rispetto ai controlli sani (P <0,01), mentre entrambi i gruppi riportavano una simile intensità di fatica (P> 0,05). Dopo la contrazione, i PPT sono aumentati in modo significativo ed eterogeneo nel trapezio superiore nel tempo, ma non nel muscolo tibiale anteriore nei controlli sani. Tuttavia, il PPT era significativamente diminuito nel tempo nel tibiale anteriore (P <0,05), ma non nel trapezio superiore in FM. Questo studio dimostra che la contrazione isometrica continua fino all'esaurimento diminuisce la soglia del dolore meccanico a livello extra-segmentale in FM, ma induce l'inibizione segmentale nei controlli sani.

Staud et al. (2005)[26] hanno analizzato 11 femmine sane e 11 con fibromialgia. Tutti i soggetti hanno effettuato una contrazione isometrica sub-massimale della mano del braccio dominante schiacciando un dinamometro a mano (JAMAR) al 30% MVC per 90sec. Come misure di outcome sono state utilizzate la VAS, la Borg scale of exertion, tender point testing. È stato riscontrato che l'effetto dell'esercizio isometrico sub-massimale sulla modulazione del dolore centrale è opposto nei pazienti FM e sani. L'esercizio isometrico sub-massimale ha ridotto il rating del dolore termico sperimentale e aumentato il PPT nei soggetti sani sia ipsilaterali che controlaterali all'estremità esercitata. Effetti opposti sono stati rilevati nei pazienti FM sia nelle valutazioni ipsilaterali che controlaterali all'estremità esercitata. Pertanto, l'esercizio ha evocato l'ipoalgesia in sani e iperalgesia nei pazienti con FM.

- *Esercizio isotonico*

Christensen et al. (2017)[27] hanno reclutato 25 soggetti con *neck pain* (16 IONP e 9 WAD) e 25 soggetti sani. A tutti i partecipanti è stato chiesto di eseguire un'abduzione di spalla nel piano scapolare a braccio allungato. Il test consisteva in 3 movimenti lenti composti da una fase di salita e di discesa di 3 secondi ciascuna e una seconda serie di movimenti più veloci in cui veniva registrato solo il movimento di accelerazione. Ogni momento è stato separato da una pausa di 6 secondi prima di muovere il braccio controlaterale. Come misure di outcome sono state utilizzate il PPT, la VAS, l'EMG. Per entrambi i gruppi di dolore al collo, il punteggio medio di VAS era significativamente più alto al basale, durante Bout-I e Bout-II rispetto ai controlli senza dolore (H (2)> 42,0, p <0,001; Mann-Whitney U: p <0,001). Il test post hoc ha rivelato un aumento del punteggio VAS durante lo studio per IONP confrontando il basale con Bout-I (Wilcoxon: p = 0,013) e per entrambi i gruppi di dolore al collo quando questo è stato confrontato con Bout-II (Wilcoxon: IONP p = 0,008; WAD p = 0,015). Un aumento significativo durante Bout-II rispetto a Bout-I è stato osservato per entrambi i gruppi di dolore al collo (Wilcoxon: IONP p = 0,007; WAD p = 0,015). Ridotto PPT in tutti i punti di tempo è stato trovato confrontando sia IONP (NK: p <0.03) e WAD (NK: p <0.001) con controlli. Nel WAD, rispetto a IONP, il PPT era diminuito al basale (NK: p = 0,041). Per i controlli, i PPT erano progressivamente in aumento e diversi tra tutti i punti temporali (NK: p <0,04), mentre per il gruppo IONP, il test post hoc mostrava una diminuzione del PPT dopo Bout-I e Bout-II rispetto al basale (NK: p <0,001). Per il sito TEMP, un'interazione (ANOVA: F [4,18] = 9,8; p <0,001) ha mostrato che entrambi i gruppi di dolore al collo avevano ridotti PPT rispetto ai controlli in tutti i punti temporali (NK: p <0,001). Inoltre, per il gruppo IONP, il PPT era diminuito dopo Bout-I e Bout-II rispetto al basale (NK: p <0,03). Per i controlli, è stato trovato un aumento dei PPT dopo Bout-II se confrontato con baseline e Bout-I(NK: p <0,002). Per il

sito ECRB, un'interazione (ANOVA: F [4,18] = 6,9; p <0,001) ha dimostrato che entrambi i gruppi di dolore al collo mostravano una riduzione del PPT in tutti i momenti rispetto al gruppo di controllo (NK: p <0,001). Per il gruppo IONP, il test post hoc ha rivelato una riduzione del PPT a Bout-I e Bout-II rispetto al basale (NK: p <0,002). Si rileva dunque iperalgesia per i pazienti con dolore al collo rispetto ai controlli. I movimenti ripetuti del braccio nei controlli non sono stati dolorosi e hanno mostrato pressione ipoalgesia nel collo e nel sito della testa, mentre IONP ha sviluppato iperalgesia

Conti et al. (2011)[28] hanno analizzato 29 soggetti con *myofascial pain* (MFP) e 15 soggetti asintomatici. A tutti i partecipanti è stato chiesto di masticare una gomma per 9min e riposare per altri 9. Come misure di outcome sono state utilizzate la VAS e il PPT. I pazienti con dolore miofasciale hanno riportato un aumento (76%) e nessun cambiamento (24%) sull'intensità del dolore misurata con il VAS. Un significativo effetto principale per il gruppo (MFP vs. controllo, P = 0,002) e per il tempo (p <0,001), ma non per l'attività (masticazione o riposo). È stata trovata una significativa interazione tra gruppo, attività e tempo (p = 0.01). Questi risultati rivelano l'effetto dell'attività di masticazione sul livello del dolore in entrambi i gruppi nel tempo, ma non indicano un significativo recupero a riposo. È stata inoltre osservata una riduzione del PPT in tutti i siti muscolari dopo l'esercizio e una ripresa non significativa dopo il riposo.

Kumar (2011)[30] ha reclutato 18 adulti che hanno ottenuto 7/13 in aspetti soggettivi e 8/14 in aspetti obiettivi di Delfi criteri per l'instabilità segmentaria lombare. I soggetti selezionati sono stati quindi randomizzati a ricevere un controllo placebo o sperimentale (stabilizzazione segmentaria lombare). L'intervento placebo consisteva nel mantenere una posizione distesa prona con un cuscino sotto le gambe per 15minuti mentre per al gruppo sperimentale è stato chiesto di assumere la posizione quadrupedica ed effettuare un tilt pelvico con sollevamento

delle braccia alternate (10 ripetizioni per lato per un totale di 15 minuti). Ogni trattamento è stato seguito da un periodo di wash-out di 24 ore. I risultati sono stati misurati quattro volte: intervento pre e post primo intervento pre e post secondo. Le misure di outcome utilizzate sono state dolore su Scala Analogica Visiva, il Pressure Pain Threshold e il Joint Play Grading Scale (scala 0-6) a quel livello. I punteggi della VAS sono cambiati significativamente in entrambi i periodi di intervento - nel gruppo del placebo da 6,05 ± 0,80 a 5,61 ± 0,77 (P = 0,016) e sperimentali da 5,98 ± 0,22 a 2,94 ± 1,11 (P = 0,000) periodi. Questo miglioramento è stato più significativo nel periodo sperimentale. I punteggi del joint play sono migliorati nella condizione sperimentale da 4.12 ± 0.08 a 3.00 ± .48 (p = .000) rispetto alla condizione del placebo da 4.33 ± 0.48 a 4.16 ± 51 (P = .25). La differenza era significativamente (P = .000) maggiore per l'intervento sperimentale. Anche le soglie del dolore pressorio sono migliorate significativamente nella condizione sperimentale da 4,04 ± 0,14 a 5,83 ± 68 sterline-forza (P = 0,000) mentre i cambiamenti nelle condizioni del placebo da 4,27 ± 0,5 a 4,26 ± 0,04 libbre-forza erano non statisticamente significativo (P = .816). Si conclude dunque l'esercizio di stabilizzazione segmentale è risultato più efficace dell'intervento del placebo nell'instabilità segmentaria lombare sintomatica tra le persone con lombalgia meccanica.

4. DISCUSSIONE

L'obiettivo della presente revisione è quello di indagare l'effetto a breve tempo dell'esercizio sul dolore sia acuto che cronico. La ricerca ha prodotto diversi risultati, mostrando come le diverse modalità di esercizio a intensità variabili possano avere effetti peculiari su specifiche patologie.

Per quanto riguarda la correlazione tra *exercise induced hypolgesia* (EIH) ed esercizio aerobico, gli studi che hanno risposto ai criteri d'inclusione definiti sono stati quattro (**Hoffman et al.**

2005 [13]; **Staud et al. 2010** [29] con una media qualità metodologica contro una bassa per **Whiteside et al. 2004** [15] e **Vierk et al. 2001**[6]. I pazienti presi in esame presentavano *chronic low back pain*, *chronic fatigue syndrome* e fibromialgia. Sia nei pazienti con CLBP che con CFS l'esercizio aerobico effettuato su cicloergometro (**Hoffman et al. 2005**)[13] e su *treadmill* (**Whiteside et al. 2004**)[15], ha determinato una riduzione del dolore post intervento in contrasto con quanto avviene nei pazienti con fibromialgia. **Vierk et a**[6] hanno dimostrato, infatti, come, l'esercizio su *treadmill* determina un incremento della Temporal Summation post-esercizio. Questo suggerisce che l'input anormale proveniente dai tessuti profondi e/o dall'affaticamento dei sistemi antinocicettivi centrali contribuisce alla sensibilizzazione centrale nei soggetti con FM. **Staud et al.** [29] analizzando un gruppo di pazienti con fibromialgia aveva dimostrato che l'uso del riposo alternato all'esercizio fornisce un efficace anti-iperalgesico indotto dall'esercizio stesso. Anche se i pazienti con FM hanno riportato un aumento a breve termine dell'intensità del dolore durante gli esercizi con le braccia, il loro dolore clinico è sempre diminuito rapidamente nei periodi di riposo. La modulazione del dolore dipende dalla quantità e dalla durata dello stress indotto dall'esercizio e dallo stato dei sistemi di regolazione del dolore attivati dall'esercizio. Mentre è stato dimostrato che i fattori di stress acuto attenuano i riflessi nocicettivi e possono inibire il dolore, lo stress cronico sembra aumentare la sensibilità al dolore. Allo stesso modo, l'attivazione acuta dei sistemi oppioidi endogeni è chiaramente antinocicettiva, ma questo sistema può diventare meno efficace in condizioni di dolore cronico. Pertanto, l'attivazione di tali sistemi mediante l'esercizio fisico potrebbe avere effetti diversi sull'elaborazione nocicettiva in pazienti sani e con fibromialgia.

Un numero importante di studi indaga nel dettaglio gli effetti dell'esercizio sub-massimale. Le patologie prese in esame sono state il *WAD* (**Ickmans et al. 2017**[16]**, Smith et al. 2017**[17], **Van Oosterwijick et al. 2012**[10]), *encefalomielite mialgica* (ME) e *chronic fatigue syndrome*

(**VanOosterwijick et al. 2010**[9]), *chronic low back pain* (**Meeus et al. 2010**[18]) e *Gulf War Illness* (**Cook at al. 2010**[19]).

Ickmans et al.[16] mettono in evidenza come l'esercizio sub-massimale su cicloergometro sia in grado di inibire l'iperalgesia indotta dall'esercizio nei pazienti con WAD cronico, in contrasto con quanto affermato da **Smith et al.**[17] che, confrontando l'efficacia dell'esercizio sub-massimale rispetto a quello isometrico, sottolineano come solo quest'ultimo abbia portato EIH. La discrepanza tra i due risultati è, molto probabilmente, da ricondurre ai differenti tempi di durata dell'esercizio stesso (15min per Ickmans VS 30 min per Smith). A tal proposito, per analizzare con maggiore criticità i due studi in esame, occorre sottolineare la differente qualità metodologica: **Ickmans et al.** [16] presentano un'alta qualità, mentre **Smith et al.** [17] bassa. Comparando l'esercizio *self paced* e fisiologicamente autolimitato con quello sub-massimale, **Van Oosterwijick et al.**[10] hanno visto come l'esercizio *self paced* riporti sintomi post esercizio ridotti. Questo non fa altro che confermare la tesi secondo la quale i pazienti con WAD cronico abbiano un'anomala elaborazione del dolore centrale, pertanto per questo gruppo di persone l'esercizio *self paced* sembra essere più appropriato rispetto a quello sub-massimale. Sembra inoltre che l'esercizio ad intensità moderata possa stimolare i meccanismi regolatori del dolore centrale[12].

Se da un lato l'esercizio sub-massimale nei pazienti con WAD si è dimostrato relativamente efficace nell'EIH, un effetto totalmente opposto si è evidenziato nei pazienti con *chronic fatigue syndrome*, encefalomielite mialgica e *Gulf War Illness* i quali non hanno avuto esperienza di EIH, ma hanno invece dimostrato una risposta iperalgesica agli stimoli sperimentali di calore-dolore dopo l'esercizio. La maggiore sensibilità al dolore è stata caratterizzata da aumenti sia delle intensità che delle valutazioni verbali soggettive[19]. Questi risultati suggeriscono che l'esercizio acuto può aumentare la sensibilità del sistema nervoso centrale alle informazioni sensoriali, lo stesso sottolineato precedentemente da **Vierck et al.**[6] nei soggetti con FM. Presi

insieme, i dati sull'esercizio in FM, GWI, CFS suggeriscono un fallimento della regolazione discendente dei processi nocicettivi che porta ad aumenti del dolore muscolare naturale durante l'esercizio e alla sensibilità centrale esagerata post-esercizio.

Per quanto riguarda la correlazione tra *exercise induced hypoalgesia* (EIH) ed esercizio isometrico gli studi che hanno risposto ai criteri d'inclusione definiti sono stati otto. I pazienti presi in esame presentavano *chronic neck pain (***Gallego Izquierdo et al., 2016**[21]*)*, *osteoartrite (***Kosek et al, 2013**[23]*) Chronic WAD (***Smith et al. 2017**[17]*) shoulder pain (***Kuppens et al. 2016**[20]*)* fibromialgia (**Kadetoff and Kosek 2007**[24]**, Staud et al. 2005**[26]**, Ge et al. 2012**[25]**)**e neuropatia diabetica (**Knauf and Koltyn 2014**[22]**)**

I risultati hanno evidenziato la comparsa di fenomeni ipoalgesici in soggetti con dolore muscolo-scheletrico e con osteoartrite ed iperalgesici quando l'esercizio isometrico era somministrato a pazienti con fibromi algia o neuropatia diabetica.

Kosek et al.[23] hanno indagato gli effetti dell'esercizio isometrico in pazienti con osteoartrite di anca e ginocchio dimostrando una normale funzione del sistema inibitorio del dolore alla baseline nonostante un aumento della sensibilità dolorifica dopo contrazione isometrica del quadricipite femorale del lato affetto al 50% dell'MVC sino all'esaurimento, così come **Kuppens et al.**[20] nel suo studio sul dolore cronico di spalla ha evidenziato un significativo aumento dei PPTs sia in zone vicine che lontane all'area di dolore dopo esercizio isometrico al 20-25% dell'MVC mostrando un effetto ipoalgesico adeguato in linea con i risultati ottenuti sui soggetti sani[31,32].

Gallego Izquierdo et al.[21] indagano il *chronic neck pain* ma, a differenza dei precedenti studi, è stato evidenziato un aumento dei PPTs solo sul medio termine (2 mesi), mentre immediatamente dopo la contrazione isometrica (nello specifico il *Cranio Cervical Flexion Test*) è stata rilevata una diminuzione degli stessi evidenziando fenomeni iperalgesici. Le valutazioni sul dolore invece, tramite VAS hanno mostrato una significativa riduzione del

dolore immediatamente dopo la prima seduta di trattamento ma rimangono valutazioni soggettive del dolore non accompagnate da una consistente misurazione oggettiva.

Molto interessante il lavoro di **Smith et al.** [17] dove si confronta l'esercizio isometrico con l'aerobico in pazienti con *chronic WAD*, patologia in cui è stato dimostrato in letteratura una disfunzione del controllo endogeno del dolore[32]. In questo studio son stati evidenziati fenomeni di EIH attraverso aumento significativo dei PPTs solo nell'esercizio isometrico (wall squat max 3 min) suggerendo un pratico approccio clinico nei confronti di pazienti con disfunzioni del controllo del dolore.

Knauf and Koltyn[22] trattano dell'effetto dell'esercizio isometrico nel paziente diabetico con o senza neuropatia diabetica: si è concluso che negli adulti diabetici con PDN si riscontrano aumentati livelli di dolore muscolare durante esercizio e mancanza di fenomeni ipoalgesici al contrario dei pazienti diabetici senza PDN.

Vi sono altre condizioni di dolore cronico in cui si riscontra una disfunzione del sistema di inibizione del dolore endogeno come ad esempio la fibromialgia ma è stato interessante notare come non tutti hanno riscontrato un aumento più o meno significativo dei PPTs dopo esercizio.

Staud et al.(26) ha esaminato gli effetti di contrazioni isometriche sulla sensibilità dolorifica lontano dal muscolo attivato. Riporta una diminuzione bilaterale nel Pressure Pain Sensitivity cutanea durante una contrazione unilaterale di 90 sec al 30% dell'MVC nei soggetti sani e un incremento paradosso nei Pressure Pain Sensitivity è stato riscontrato bilateralmente nei pazienti fibromialgici durante le contrazioni unilaterali, evidenziando la generalizzata carenza di EIH. Anche **Ge et al**.[26] evidenzia come la contrazione isometrica protratta sino ad affaticamento muscolare induca una facilitazione discendente generalizzata fonte di iperalgesia extrasegmentale in pazienti con FM. Risulta invece interessante il risultato di **Kadetoff et al.** [24] che evidenzia come la contrazione isometrica effettuata ad una bassa intensità (10% MVC)

aumenti i PPTs del muscolo deltoide. Questo risultato fa pensare che l'EIH nei pazienti fibromialgici potrebbe essere elicitata in risposta ad esercizi di bassa/media intensità.

Nell'indagare la correlazione tra EIH ed esercizio isotonico gli studi analizzati sono stati tre: **Christensen et al. 2017**[27], **Conti et al. 2011**[28], e **Kumar 2011**[30]. Ancora una volta si viene a delineare il contrasto tra gli effetti dell'esercizio nei pazienti con *chronic WAD* e *myofascial pain* (MFP) rispetto a quelli con LBP.

Christensen et al.[27] ha riscontato iperalgesia e dolore evocati in seguito a sei serie di abduzione del braccio sul piano scapolare in pazienti con IONP e WAD, rispetto ad un gruppo controllo di soggetti asintomatici dove si è verificata una risposta ipoalgesica. Come già visto in precedenza, **Van Oosterwijick et al.**[10] aveva dimostrato che nei pazienti con WAD l'esercizio *self paced* determinava un aumento del PPT al contrario di quanto accadeva nell'esercizio sub-massimale. Potenzialmente, i movimenti del braccio con un ritmo gestito dal paziente stesso rispetto a quelli usati da Christensen avrebbero potuto determinare una risposta diversa. Viene allora sottolineata la necessità di calibrare adeguatamente l'esercizio in base allo specifico patologico del paziente evitando di attenersi a dei target prestabiliti.

Anche **Conti et al.**[28] analizzando 29 soggetti con *myofascial pain* ha rilevato nel 76% dei pazienti un incremento della VAS in seguito a 9 minuti di masticazione di un bastoncino di gomma, mentre **Kumar et al.** [30] ha messo in evidenza l'efficacia di esercizi di stabilizzazione segmentali nei pazienti con instabilità lombare segmentale. In questo studio però, l'aspetto meccanico del problema è stato preso come focus di riferimento a dispetto di quanto fatto in quelli precedenti.

4.1 LIMITI

I principali limiti della seguente revisione sono stati principalmente l'esecuzione della ricerca e la valutazione degli studi da parte di solo due persone; l'indagine dei soli effetti acuti dell'esercizio (*cut-off* misurazioni post-esercizio 48h) e l'inclusione di studi in cui veniva analizzata l'efficacia di un singolo esercizio. La qualità metodologica variabile degli studi includi ed una minima parte di studi escludi per lingua non conosciuta agli autori (sono stati tenuti solo studi in lingua inglese, italiana e spagnola) definiscono un ulteriore limite.

5. CONCLUSIONI

Sulla base dell'analisi degli studi presi in considerazione nella presente *review* appare evidente l'efficacia dell'esercizio fisico nei soggetti sani cosi come in quelli patologici, con le dovute eccezioni.

Se da un lato l'esercizio, che sia esso aerobico, isometrico o isotonico porta ad una fisiologica *exercise induced hypolagesia* in pazienti con osteoatrite e con dolore lombare meccanico, dall'altro i pazienti con *chronic WAD,* fibromialgia, *chronic fatigue syndrome* e *Gulf War Illnes* mostrano un comportamento diametralmente opposto: l'esercizio sembra infatti determinare un incremento del dolore post-intervento. Tale caratteristica non è comune a tutti i pazienti con dolore cronico ma solo nei casi in cui si evidenzia la presenza di sensibilizzazione centrale. In questi pazienti l'esercizio ad intensità moderata e *self paced* risulte essere una valida alternativa rispetto a quello sub-massimale e isometrico, garantendo un'adeguata risposta ipoalgesica.

5.1 IMPLICAZIONI PER LA PRATICA: KEYPOINT

Sorge dunque spontaneo chiedersi quali pazienti beneficiano effettivamente dell'esercizio e con quali bisogna essere più cauti e ponderati. È necessario infatti porre la massima attenzione quando si propone dell'esercizio a pazienti con *chronic pain* ed EIH disfunzionale (pazienti con fobromialgia, *chronic fatigue syndrome*) onde evitare un'esacerbazione dei sintomi e la conseguente riduzione della *compliance* al trattamento da parte del soggetto.

L'esercizio opportunamente personalizzato e graduato è stato suggerito come trattamento efficace in pazienti con dolore cronico. Si consiglia di utilizzare l'esercizio aerobico rispetto all'isometrico o eccentrico, in quanto gli ultimi due sembrano aumentare l'ipereccitabilità del sistema nervoso, e di esercitare preferibilmente parti corporee non dolenti o lontane dal sito di dolore utilizzando regimi di allenamento a bassa intensità con lunghe e frequenti pause.

BIBLIOGRAFIA

1. Koltyn KF. Analgesia following exercise. A Review. 2000;29(2):85–98.
2. Janal MN. Pain sensitivity , exercise and stoicism. 1996;376–81.
3. O'Connor PJ., Cook DB. Exercise and pain: the neurobiology, measurement, and laboratory study of pain in relation to exercise in humans. 2011; 119-66
4. Koltyn KF. Exercise-Induced Hypoalgesia and Intensity of Exercise. 2002;32(8):477–87.
5. Gurevich M, Kohn PM, Davis C, Gurevich M, Kohn PM, Davis C. Exercise - induced analgesia and the role of reactivity in pain sensitivity Exercise-induced analgesia and the role of reactivity in pain sensitivity. (January 2015):37–41.
6. Vierck CJ, Staud R, Price DD, Cannon RL, Mauderli AP, Martin AD. The Effect of Maximal Exercise on Temporal Summation of Second Pain (Windup) in Patients With Fibromyalgia Syndrome. 2001;2(6):334–44.
7. Manuscript A. Mechanisms of Exercise-Induced Hypoalgesia. 2015;15(12):1294–304.
8. Ring C, Edwards L, Kavussanu M. Effects of isometric exercise on pain are mediated by blood pressure. 2008;78:123–8.
9. Oosterwijck J Van, Nijs J, Meeus M, Lefever I, Huybrechts L, Lambrecht L, et al. Pain inhibition and postexertional malaise in myalgic encephalomyelitis ⁄ chronic fatigue syndrome : An experimental study. 2010;265–78.
10. Oosterwijck J Van, Nijs J, Meeus M, Loo M Van, Paul L. Lack of Endogenous Pain Inhibition During Exercise in People With Chronic Whiplash Associated Disorders: An Experimental Study. J Pain [Internet]. 2012;13(3):242–54.
11. Cochrane Handbook for Systematic Reviews of Interventions Handbook for Systematic Reviews of Interventions Chapter 1 : 1–12.
12. Ellingson LD, Stegner AJ, Schwabacher IJ, Koltyn KF, Cook DB. brain sciences Modulation of Pain in Fibromyalgia.
13. Hoffmann MD., Shepanski M., MacKenzie SP., Clifford PS. Experimentally induced pain perception is acutely reduced by aerobic exercise in people with chronic low back pain, 2005.
14. Rayhan RU, Stevens BW, Raksit MP, Ripple JA, Timbol CR, Adewuyi O, et al. Exercise Challenge in Gulf War Illness Reveals Two Subgroups with Altered Brain Structure and Function. 2013;8(6).
15. Whiteside A, Hansen S, Chaudhuri A. Exercise lowers pain threshold in chronic fatigue

syndrome. 2004;109:497–9.

16. Ickmans K, Malfliet A, Kooning M De, Goudman L, Hubloue I, Schmitz T, et al. Lack of Gender and Age Differences in Pain Measurements Following Exercise in People with Chronic Whiplash-Associated Disorders. 2017;
17. Smith A, Ritchie C, Pedler A, Mccamley K, Roberts K, Sterling M. Exercise induced hypoalgesia is elicited by isometric , but not aerobic exercise in individuals with chronic whiplash associated disorders. Scand J Pain [Internet]. 2017;15(November 2016):14–21. Available from: http://dx.doi.org/10.1016/j.sjpain.2016.11.007
18. Meeus M, Roussel NA, Truijen S, Nijs J. original report reduced pressure pain thresholds in response to exercise in chronic fatigue syndrome but not in chronic low back pain : an experimental study. 2010;(15):884–90.
19. Cook DB, Stegner AJ, Ellingson LD, Middleton WS, Veterans M. Exercise Alters Pain Sensitivity in Gulf War Veterans With Chronic Musculoskeletal Pain. J Pain [Internet]. 2010;11(8):764–72. Available from: http://dx.doi.org/10.1016/j.jpain.2009.11.010
20. Kuppens K, Struyf F, Nijs J, Cras P, Fransen E, Hermans L, et al. Exercise- and Stress-Induced Hypoalgesia in Musicians with and without Shoulder Pain: A Randomized Controlled Crossover Study. 2016;59–68.
21. Izquierdo TG, Pecos-martin D, Girbés EL, Plaza-manzano G, Caldentey RR, Mayor R, et al. Original report comparison of cranio-cervical flexion training versus cervical proprioception training in patients with chronic neck pain : a randomized controlled clinical trial.2016;(13):48–55.
22. Knauf MT, Koltyn KF. Exercise-induced modulation of pain in adults with and without painful diabetic neuropathy. J Pain [Internet]. 2014;15(6):656–63. Available from: http://www.scopus.com/inward/record.url?eid=2-s2.0-84901802110&partnerID=tZOtx3y1
23. Kosek E, Roos EM, Ageberg E, Nilsdotter A. Increased pain sensitivity but normal function of exercise induced analgesia in hip and knee osteoarthritis e treatment effects of neuromuscular exercise and total joint replacement. YJOCA [Internet]. 2013;21(9):1299–307. Available from: http://dx.doi.org/10.1016/j.joca.2013.06.019
24. Kadetoff D, Kosek E. The effects of static muscular contraction on blood pressure , heart rate , pain ratings and pressure pain thresholds in healthy individuals and patients with fibromyalgia. 2007;11:39–47.
25. Ge H, Nie H. Descending pain modulation and its interaction with peripheral sensitization following sustained isometric muscle contraction in fibromyalgia.

2012;16:196–203.

26. Staud R, Robinson ME, Price DD. Isometric exercise has opposite effects on central pain mechanisms in fibromyalgia patients compared to normal controls. 2005;118:176–84.
27. Christensen SW, Hirata RP, Graven-nielsen T. Altered pain sensitivity and axioscapular muscle activity in neck pain patients compared with healthy controls. 2017;21:1763–71.
28. César P, Conti R, Silva S, Pereira R, N LM, Yassuda S, et al. Effect of experimental chewing on masticatory muscle pain onset. 2011;19(1):34–40.
29. Staud R, Robinson ME, Weyl EE, Price DD. NIH Public Access. 2011;11(12):1376–83.
30. Kumar S. Efficacy of segmental stabilization exercise for lumbar segmental instability in patients with mechanical low back pain : A randomized placebo controlled crossover study. 2011;3(10):1–6.
31. Naugle KM, Fillingim RB, Riley JI. A meta-analytic review of the hypoalegsic effects of exercise. J Pain. 2012;13(12):1139–50.
32. Nijs J, Kosek E, Oosterwijck J Van, Meeus M. Dysfunctional Endogenous Analgesia During Exercise in Patients with Chronic Pain: To Exercise or Not to Exercise? 2012;(1):205–14.
33. Koltyn KF., Brellenthin AG., Cook DB., Sehgal N., Hillard C. Mechanism of exercise-induced hypoalgesia. J Pain. 2014.1294-1304.
34. Naugle, K. M., Naugle, K. E., & Riley, J. L. Reduced modulation of pain in older adults following isometric and aerobic exercise. The Journal of Pain Official Journal of the American Pain Society, 2016. 17(6), 719–728
35. Kodesh E., Weissman-Fogel I., Exercise-induced hypoalgesia - interval versus continuous mode. 2014. 39 (7)829-34.
36. Koltyn KF., Arbogast RW. Perception of pain after resistance exercise. Br J Sports Med, 1998; 32:20-24.
37. Naugle KM, Fillingim RB, Riley JL 3rd. A meta-analytic review of the hypoalgesic effects of exercise. J Pain. 2012 Dec;13(12):1139-50.
38. Daenen L, Varkey E, Kellmann M, Nijs J. Exercise, not to exercise, or how to exercise in patients with chronic pain? Applying science to practice. Clin J Pain. 2015 Feb;31(2):108-14

APPENDICE

RCT	no	si	CD/NA/NR	motivazione	
Gallego 2016					GOOD
Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?				Randomized controlled clinical trial with parallel groups	
Was the method of randomization adequate (i.e., use of randomly generated assignment)?				Randomization was performed using computer-generated random numbers. Concealment of allocation was ensured using sequentially numbered opaque, sealed envelopes.	
Was the treatment allocation concealed (so that assignments could not be predicted)?			NR		
Were study participants and providers blinded to treatment group assignment?				Blinded assessors	
Were the people assessing the outcomes blinded to the participants' group assignments?				The assessor, who was blinded to subject group for the outcome assessments, was a physical therapist with 3 years of clinical experience in outpatient orthopaedic practice with a Master's degree in physical therapy.	
Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?				28 subjects with a history of chronic non specific neck pain. Age between 18 and 55 years, score ≤ 15/50 on the Neck Disability Index (NDI) (24), showing signs of cervi- cal movement control dysfunction (25), and manual physical examination revealing muscle tenderness.	
Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?				There were no drop-outs during the study period. All participants completed the 6 physiotherapist-supervised sessions and verbally con- rmed that they complied with the home-exercise programme.	
Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?				see above	
Was there high adherence to the intervention protocols for each treatment group?					
Were other interventions avoided or similar in the groups (e.g., similar background treatments)?				Participants were advised not to receive any other speci c treatments for neck pain, although their usual medication was not withdrawn.	
Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				CCFT, VAS, NDI, PPT	
Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?			NR		
Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?					
Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?				in order to analyse the effectiveness of the 2 interventions, an intention-to-treat analysis was performed	
Kuppens 2016					GOOD
Was the study described as randomized, a randomized				randomized controlled crossover study	

trial, a randomized clinical trial, or an RCT?					
Was the method of randomization adequate (i.e., use of randomly generated assignment)?				A single-blinded observer randomized and con- trolled crossover study design was used to compare the effect of a physical and an emotional stressor on pain thresholds in musicians with and without shoulder pain. All participants (i.e., the musicians with and without shoulder pain) were contacted and informed about the study by a researcher who was not involved in the test- ing of the participants. If the musicians agreed to par- ticipate, they were scheduled by this researcher, so that the assessors involved in the tests remained blinded to the participants' condition	
Was the treatment allocation concealed (so that assignments could not be predicted)?				see above	
Were study participants and providers blinded to treatment group assignment?				see above	
Were the people assessing the outcomes blinded to the participants' group assignments?					
Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?					
Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?				No drop-out	
Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?				no drop-out	
Was there high adherence to the intervention protocols for each treatment group?					
Were other interventions avoided or similar in the groups (e.g., similar background treatments)?				All patients were asked to stop medication use 24 hours prior to study participa- tion and to avoid alcohol, caffeine, and nicotine on the day of study participation.	
Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				PPTS, SF 36, PVAQ, PCS, SDQ	
Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?			NR		
Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?			NR		
Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?					
Ellingson 2016					FAIR
Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?				Order of conditions was randomized and counterbalanced.	
Was the method of randomization adequate (i.e.,			NR		

use of randomly generated assignment)?					
Was the treatment allocation concealed (so that assignments could not be predicted)?			NR		
Were study participants and providers blinded to treatment group assignment?			NR		
Were the people assessing the outcomes blinded to the participants' group assignments?			NR		
Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?				Female patients with a physician-confirmed diagnosis of FM who were between the ages of 18 and 60 years old, and age- and sex-matched pain-free controls	
Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?				One FM patient was unable to return for exercise due to scheduling complications	
Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?				see above	
Was there high adherence to the intervention protocols for each treatment group?					
Were other interventions avoided or similar in the groups (e.g., similar background treatments)?				participants abstained from caffeine for 4 h, cigarettes for 2 h, alcohol for 24 h, structured exercise for 24 h and any pain medications for 24 h.	
Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?				FIQ, MPQ,	
Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?				Our results demonstrated that a relatively short bout of cycling exercise resulted in improvements in pain modulation in FM. This research may lead to future studies aimed towards determining whether the therapeutic effects of exercise training result from changes in central pain regulatory mechanisms. Research examining these effects in FM using functional brain imaging methods in the context of an exercise intervention trial will be necessary to more fully test this hypothesis.	
Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?				Previous research regarding the effects of acute bouts of exercise on pain sensitivity in FM patients is largely equivocal. Some studies have demonstrated a hypoalgesic effect while other studies show either no changes in pain perception or an exacerbation of pain	
Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?					
Kumar 2011					FAIR
Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?				The study was an observer-blinded randomized placebo-controlled cross-over study	
Was the method of randomization adequate (i.e., use of randomly generated assignment)?			NR		
Was the treatment allocation concealed (so that assignments could not be predicted)?					

Were study participants and providers blinded to treatment group assignment?					
Were the people assessing the outcomes blinded to the participants' group assignments?				The three outcomes were taken four times by an indipendent blinded observer	
Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?				Out-patients referred by a physician to the physical therapy department in Kasturba Medical College Hospital, Mangalore, for conservative treatment of leg pain and/or low back pain or discomfort. The participants were selected based upon the criteria: Clinical diagnosis of segmental instability [9] for those who had localized midline pain in the low back and tenderness on palpation, painful arc during spinal movements, pain on jerky movements, positive prone segmental instability test, positive H-I instability test, hypermobility detected on passive accessory intervertebral testing using central postero-anterior pressure on that lumbar spinal level. Subjects with previous history of low back pain were also included and subjects with cognitive deficits were excluded. The diagnosis was confirmed by the tester using the Delphi checklist [16] provided in the appendix-I and only subjects who scored 7/13 in subjective aspects and 8/14 in objective aspects were included. This criterion was adapted from the earlier Delphi study findings and was validated and was found to be reliable predictors of spinal segmental instability. Patients who did not understand the instructions and who were unable to co-operate due to any other medical conditions were excluded	
Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?					
Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?					
Was there high adherence to the intervention protocols for each treatment group?					
Were other interventions avoided or similar in the groups (e.g., similar background treatments)?			NR		
Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?					
Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?					
Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?					
Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?					

CASE CONTROL					
Ickmans 2017	no	si	CD/NA/NR	motivazione	GOOD
Was the research question or objective in this paper clearly stated and appropriate?				the primary purpose was to examine gender and age related differeces of self reported pain, ppt ts and cpm in people with chronic wad	
Was the study population clearly specified and defined?				Dutch speaking and aged 18-65, who had suffered a wad at least 3 months ago, via the University Hospital Brussels	
Did the authors include a sample size justification?				sampe size was calculeted using a desired power of .80 a signifiance level of.05 and a medium effect size of .30	
Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?					
Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?					
Were the cases clearly defined and differentiated from controls?					
If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?			NA		
Was there use of concurrent controls?			CD		
Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?					
Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?			CD		
Were the assessors of exposure/risk blinded to the case or control status of participants?					
Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?				matched for gender and age	
Christensen, 2017					FAIR
Was the research question or objective in this paper clearly stated and appropriate?				This study set out to investigate activity and coordination between axioscapular muscles during repeated arm movements in groups of IONP, WAD and healthy controls as well as the effects on pain sensitivity and pain perception.	
Was the study population clearly specified and defined?				Participants between 18 and 50 years of age were recruited through advertisements in local newspapers, educational facilities and social media. The inclusion criteria for patients were neck pain classified as IONP or WAD lasting more than 3 months. Additionally,they had to have neck pain during active cervical range of motion and palpation soreness of posterior neck muscles, which both were exclusion criteria for the control group if present within the past 6 months. Neck pain patients	

				were excluded if they had referred or radiating pain down the arms. All participants were required to have pain-free shoulder active range of motion. Furthermore, exclusion criteria for all participants were signs or symptoms of neurological, rheumatological or other disorders that could influence the results of the study along with pregnancy	
Did the authors include a sample size justification?					
Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?					
Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?					
Were the cases clearly defined and differentiated from controls?					
If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?			NR		
Was there use of concurrent controls?				25 neck pain patients with bilateral neck pain and 25 healthy age- and sex-matched controls were enrolled in the study.	
Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?					
Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?				PPT, VAS	
Were the assessors of exposure/risk blinded to the case or control status of participants?				was impossible to blind participants to the fact that the effect of movements on PPTs were investigated	
Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?			NA		
Smith, 2017					FAIR
Was the research question or objective in this paper clearly stated and appropriate?				The aims of this study were: 1. To compare EIH responses to isometric and aerobic exercise inpatients with chronic WAD and healthy controls 2. To determine if there is a differential response of exercise typeon EIH 3. To investigate relationships between EIH and CPM in patientswith chronic WAD4. To investigate relationships between EIH and psychological fac-tors in patients with chronic WAD.	
Was the study population clearly specified and defined?				ParticipantsIndividuals with WAD were eligible to participate if theypresented with Whiplash Grade II (neck pain but no frac-ture/dislocation of the neck and no neurological deficit) of at least 3 months but less than 10 years duration and were agedbetween 18 and 65 years. Individuals were excluded if they hadknown or suspected serious spinal pathology; confirmed frac-ture	

				or dislocation at the time of injury; nerve root compromise(at least 2 of the following signs: weakness/reflex changes/sensoryloss associated with the same spinal nerve); spinal surgery in theprevious 12 months; history or presentation of psychosis, bipolardisorder, organic brain disorder or severe depression; were takinganti-depressant or anti-convulsant medication; or who answered‘yes’ to any of the 7 questions on the PAR-Q physical activityscreening questionnaire	
Did the authors include a sample size justification?				a sample size of 17 participants with WAD and17 controls was indicated to obtain the study power .80 and signifiance level of .05	
Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?			NR		
Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?					
Were the cases clearly defined and differentiated from controls?				Healthy control participants were eligible to participate if they did not have a history of WAD or recent (within the previous 12 months) musculoskeletal pain and did not answer ‘yes’ to any questions on the PAR-Q.	
If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?			NR		
Was there use of concurrent controls?					
Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?					
Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?				Participants attend two testing sessions: one to perform submaximal aerobic bicycle exercise; and a second to complete an isometric exercise. These sessions were scheduled 5–10 days apart. The participant started to cycle at 25 W and the power output was increased by 25 W every minute until attainment of 75% of age-predicted maximum heart rate. The participant continued to cycle at this power output for a total duration of 30 min	
Were the assessors of exposure/risk blinded to the case or control status of participants?					
Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?					
Knauf and Koltyn (2014)					GOOD
Was the research question or objective in this paper clearly stated and appropriate?					
Was the study population clearly specified and defined?				Adults (18 – 60 yrs) clinically diagnosed with type 2 diabetes mellitus with and without PDN	
Did the authors include a sample size justification?					
Were controls selected or recruited from the same or					

similar population that gave rise to the cases (including the same timeframe)?					
Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?				Exclusion criteria included: 1) any acute medical or psychiatric illness, 2) uncontrolled chronic medical conditions (e.g., hypertension, heart disease, hypercholestrolemia, hyperglycemia, etc.), 3) upper extremity neuropathy or arthritis that limits exercise, 4) neuropathies from other causes than diabetes, and 5) cognitive or reading impairments which would preclude completing the questionnaires	
Were the cases clearly defined and differentiated from controls?					
If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?			NA		
Was there use of concurrent controls?					
Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?					
Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?				Short forma McGill Questionnaire (VAS, Present Pain Index and SF-MPQ Total9. IPAQ and pedometer for physical activity	
Were the assessors of exposure/risk blinded to the case or control status of participants?					
Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?			NA		
Kosek, 2013					FAIR
Was the research question or objective in this paper clearly stated and appropriate?				The main purpose of the present studywas to assess the function of EIA in OA patients and to study the effects of neuromuscular exercise and surgery on these parametres	
Was the study population clearly specified and defined?				The patients were recruited consecutively at the Department of Orthopaedics at Lund University Hospital, Sweden, between September 2007 and March 2009. 134 patients who were assigned for total hip replacement (THR) (n= 51) or total knee replacement (TKR) (n= 83) at the Department of Orthopaedics at Lund University Hospital were included in the study.	
Did the authors include a sample size justification?				JUST FOR THE CONTROL GROUP:Power calculations based on previous studies indicated that at least 40 controls were needed	
Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?				random sample from the population, identified through the Swedish civil registration system, was recruited at the same time period as the patients.	
Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?				Inclusion criterion was primary OA. Exclusion criteria were post-traumatic OA (e.g., fractures), rheumatoid arthritis (RA), psoriatic arthritis, severe heart failure and neurological diseases that influence physical function, congenital hip deformities, Mb Perthes, patients who had been operated on with THR or TKR during the last 12 months, dementia and not Swedishspeaking	

				due to the high level of language skills required for questionnaires and quantitative sensory testing. Patients who were treated with antidepressants, neuroleptics, anticonvulsive drugs or steroids were also excluded.	
Were the cases clearly defined and differentiated from controls?					
If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?					
Was there use of concurrent controls?					
Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?					
Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?					
Were the assessors of exposure/risk blinded to the case or control status of participants?				the investigator performing the assessments was not blinded to the patient/control status	
Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?					
Rayhan 2013	no	si	CD/NA/NR		GOOD
Was the research question or objective in this paper clearly stated and appropriate?				study the casual relationship between exercise , the brain and changes in symptoms after two exercise stress test	
Was the study population clearly specified and defined?				veterans from the I gulf war and heathy controls between 2009 and 2011	
Did the authors include a sample size justification?					
Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?				controls are non military subjects	
Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?				I: healty and gulf war illness veterand from 2009 to 2011, screened for military service for at least 30 days between 1990-1991, servcein GWT, cdc criteria for gwi and CFS, current med, chronic medical and psychiatrc illness, factor s preventic fMRI. E: active duty militar personnel, neoplastic conditions...fear of needles.	
Were the cases clearly defined and differentiated from controls?					
If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?					
Was there use of concurrent controls?			NR		
Were the investigators able to confirm that the exposure/risk occurred prior to the					

development of the condition or event that defined a participant as a case?					
Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?					
Were the assessors of exposure/risk blinded to the case or control status of participants?					
Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?			CD		
Van Oosterwijik 2012					GOOD
Was the research question or objective in this paper clearly stated and appropriate?				A controlled experimental study was performed to examine the efficacy of the endoge- nous pain inhibitory systems and whether this (mal)functioning is associated with symptom increases following exercise in patients with chronic whiplash-associated disorders (WAD).	
Was the study population clearly specified and defined?				22 QFT+ 22 healthy.Patients with chronic neck pain as a result of a whiplash injury which fulfilled the criteria of WAD grade I-III as defined by the Quebec Task Force classification29 were el- igible for study participation	
Did the authors include a sample size justification?					
Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?				Patients were recruited through a local emergency unit. The medical files of patients who had attended the emergency unit from a Red Cross medical center with an acute whiplash injury at least 6 months ago were screened according to the inclusion criteria. Eighty-five patients who fulfilled the inclusion criteria were contacted. When patients reported persisting symptoms due to the whiplash injury, they were in- formed about the study and asked to participate	
Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?				vedi sopra. Patients with grade IV (implying fracture or dislocation of the cer- vical spine) were excluded from the study.	
Were the cases clearly defined and differentiated from controls?					
If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?			NA		
Was there use of concurrent controls?					
Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?				see above	
Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?				SF-36, CIS, VAS PPT	

Were the assessors of exposure/risk blinded to the case or control status of participants?			NR		
Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?				In the present study, a substantial portion of recruited patients reported chronic widespread pain, together with a large variation in symptom duration. However, these factors do not seem to influence the response to exercise in chronic WAD patients.	
Ge 2012					FAIR
Was the research question or objective in this paper clearly stated and appropriate?				We hypothesized that fatiguing contraction may shift descending pain modulation from inhibition towards facilitation and that the effect of descending pain modulation be dependent on peripheral muscle pain sensitivity.	
Was the study population clearly specified and defined?				The sample consisted of 22 women with fibromyalgia (FM group, mean age: 53.6 2.5 year; mean weight: 68.2 3.5 kg; mean height: 173 29.8 cm) and 22 age-matched healthy controls (control group, mean age: 52.4 2.4 year; mean weight: 65.2 3.1kg; mean height: 171 38.8 cm).	
Did the authors include a sample size justification?				The sample size was calculated with a minimum detectable difference in means of 50, a standard deviation of 40, an alpha level of 0.05, and a desired power of 0.95. This generated a desired sample size of at least 18 participants per group	
Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?				The participants were recruited through local FM support group and through rheuma- tology clinics.	
Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?				Only women between the ages of 18 and 70 were recruited for the study. The patients had their FM confirmed by a physician according to ACR criteria (Wolfe et al., 1990). The FM patients were not excluded if depressed or taking anti- depressant medications and/ or analgesics. The control group had no current spontaneous pain, no major pain experience during the past month prior to experi- ment, and no pain-related diagnoses	
Were the cases clearly defined and differentiated from controls?					
If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?			NA		
Was there use of concurrent controls?					
Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?					
Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?				PPT	
Were the assessors of exposure/risk blinded to the case or control status of participants?			NR		
Were key potential confounding variables measured and adjusted statistically in the analyses? If			NR		

matching was used, did the investigators account for matching during study analysis?					
Conti 2011	no	si	CD/NA/NR		FAIR
Was the research question or objective in this paper clearly stated and appropriate?				To evaluate the effect of a chewing exercise on pain intensity and pressurepain threshold in patients with myofascial pain.	
Was the study population clearly specified and defined?				The MFP group consisted of 29 consecutive caucasian women (mean age 29.83±8.43 years, ranged from 18 to 49)selected among those seeking for treatment at the Orofacial Pain Clinic of the Bauru School of Dentistry, University of São Paulo, Brazil. Inclusion criteria followed the diagnostic of MFP (Group Ia), according to the Research Diagnostic Criteria (RDC/TMD)6. Patients with more than two absent teeth, history of facial or cervical injury, cervical pain or limited range of motion, active periodontal disease or caries, history of general neurological disturbances cervical and/ or masticatory active trigger points were excluded from the study. The diagnosis of TMJ disorders, according to RDC/TMD6 (diagnostic II) were also an exclusion criterion, although individuals with asymptomatic disc displacement joint (IIa, without pain) concomitant with Ia diagnostic (RDC/TMD6) were allowed to participate. The patients should not have taken any analgesic medication within 24 h prior to the experimental procedure	
Did the authors include a sample size justification?					
Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?				at the regular dental clinics of the Bauru School of Dentistry. None of the subjects had any facial pain complaint or underwent TMD treatment 6 months prior to the experiment. Except for pain, the inclusion criteria for the control group were the same to the used for the MFP group	
Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?					
Were the cases clearly defined and differentiated from controls?					
If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?			NA		
Was there use of concurrent controls?					
Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?			NA		
Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?					
Were the assessors of exposure/risk blinded to the case or control status of participants?					
Were key potential confounding variables measured and adjusted					

statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?					
Staud 2010					FAIR
Was the research question or objective in this paper clearly stated and appropriate?				we examined the effects of alternating exercise with rest on clinical pain and thermal/mechanical hyperalgesia of 34 FM patients and 36 age-matched healthy controls (NC). Using an ergometer, all subjects performed arm exercise to exhaustion twice alternating with 15 min rest periods.	
Was the study population clearly specified and defined?				34 FM+ 36 healthy	
Did the authors include a sample size justification?					
Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?				local communiny and FM support groups	
Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?					
Were the cases clearly defined and differentiated from controls?					
If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?			NA		
Was there use of concurrent controls?					
Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?				parallel group classic reversal design	
Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?				VAS REP PPT Tender point testing	
Were the assessors of exposure/risk blinded to the case or control status of participants?			NR		
Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?				only women	
Meuus 2010					GOOD
Was the research question or objective in this paper clearly stated and appropriate?				The aims of this study were to examine: (i) base- line pressure pain thresholds in patients with chronic fatigue syndrome and those with chronic low back pain compared with healthy subjects; (ii) the change in mean pain threshold in response to exercise; and (iii) associations with exercise- induced increase in nitric oxide.	
Was the study population clearly specified and defined?					

Did the authors include a sample size justification?					
Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?					
Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?					
Were the cases clearly defined and differentiated from controls?					
If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?			NA		
Was there use of concurrent controls?					
Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?					
Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?				nitric oxide assay, PPts, VAS ODQ, SF36	
Were the assessors of exposure/risk blinded to the case or control status of participants?				the samples were analysed blindly.	
Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?			NR		
Van Oosterwijick 2010					GOOD
Was the research question or objective in this paper clearly stated and appropriate?				To examine the efficacy of the pain inhibitory systems in patients with myalgic encephalomyeli- tis/chronic fatigue syndrome (ME/CFS) during two different types of exercise and to examine whether the (mal)functioning of pain inhibitory systems is associ- ated with symptom increases following exercise.	
Was the study population clearly specified and defined?				Patients with ME/CFS were referred for study participation from a private practice for internal medicine. For study inclusion, subjects had to fulfil the Center for Disease Control and Prevention criteria for ME/CFS (i.e. a clinically evaluated, unexplained, per- sistent or relapsing chronic fatigue that is of new or definite onset and which results in a substantial reduction in the previous levels of occupational, edu- cational, social or personal activities. Sedentary was defined as having a seated occupation and performing a maximum of 1 h of sports per week.	
Did the authors include a sample size justification?				the power analysis revelead that 22 people with ME CFS were required for the study. The control group consisted pf 22 healthy women matched for age and body mass index	
Were controls selected or recruited from the same or				see above	

similar population that gave rise to the cases (including the same timeframe)?					
Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?				see above	
Were the cases clearly defined and differentiated from controls?					
If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?			NA		
Was there use of concurrent controls?					
Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?					
Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?				PPT SF 36 CIS	
Were the assessors of exposure/risk blinded to the case or control status of participants?			NR		
Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?			NR		
Cook 2010					POOR
Was the research question or objective in this paper clearly stated and appropriate?				This study examined the impact of an acute bout of exercise on pain sen- sitivity in GVs with CMP.	
Was the study population clearly specified and defined?				All participants were male, veterans of U.S. military service, and had been deployed to the Persian Gulf region (eg, Kuwait, Iraq, Saudi Arabia) during the first Gulf War (1990–1991). Participants were classified either as having chronic muscle pain (CMP) or as healthy controls.	
Did the authors include a sample size justification?					
Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?				see above	
Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?				Our inclusion criteria for CMP were based on examination of the epidemiological literature,30 the case definition for FM,49 and consultation with VA pain specialists.Veterans were excluded from participation if their pain was attributed to a clinically defined pain condition with a medically explained etiology/pathology (eg, rheumatoid arthritis) or current musculoskeletal injury, or if they exhibited neuropathic pain on the volar surface of the forearm or thenar eminence of the hand. In addition, participants were excluded if they had a history of cardiac disease, uncontrolled thyroid disease,	

				asthma, hypertension, stroke, HIV, cancer, drug or alcohol abuse within the previous 2 years, used vasoactive and other cardiovascular medications or pain medications within the 24 hours prior to testing. Criteria for assignment to the CMP group were: 1) report of widespread or generalized muscle and joint pain; 2) a rating of 2 (moderate) or more on a 6-point scale of current complaints of joint and muscle pain; 3) current musculoskeletal pain in 2 or more quadrants of the body not associated with a current acute injury; and 4) musculoskeletal pain complaints lasting for at least 3 months prior to testing.	
Were the cases clearly defined and differentiated from controls?					
If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?			NA		
Was there use of concurrent controls?					
Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?					
Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?				heat and pressure pain threshold, suprathreshold pain testing + questionari	
Were the assessors of exposure/risk blinded to the case or control status of participants?			NR		
Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?				Veterans with CMP and healthy Gulf-veteran controls were demographically similar and did not differ signifi-cantly (P > .05) in regards to age, height, weight, resting heart rate, resting blood pressure, or aerobic capacity.	
Kadetoff and Kosek (2005) 2007					POOR
Was the research question or objective in this paper clearly stated and appropriate?				investigate the interactions between cardiovascular regulation, subjective perception of pain and exertion/fatigue and the sensitivity to pressure pain in FM patients and healthy controls before, during and following a standardised isometric contraction of m. quadriceps femoris	
Was the study population clearly specified and defined?				17 female FM patients (average age 38.8)They were all outpatients at the Department of Rehabilitation Medicine and fulfilled the classification criteria proposed by the American College of Rheumatology 1990 for fibromyalgia (Wolfe et al., 1990). Had normal laboratory test results regarding erythrocyte sedimentation rate, hematology count, liver enzymes, creatinine kinase, thyroid function, rheumatoid factor and antinuclear antibodies. No medications were taken. Controls:17 healthy sex and aged matched average age 37.4	
Did the authors include a sample size justification?					
Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?			NR		

Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?					
Were the cases clearly defined and differentiated from controls?					
If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?			NA		
Was there use of concurrent controls?					
Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?			NA		
Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?					
Were the assessors of exposure/risk blinded to the case or control status of participants?					
Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?					
Hoffman, 2005	no	si	CD/NA/NR		FAIR
Was the research question or objective in this paper clearly stated and appropriate?				This study determined whether a single exercise bout would alter the perception of experimentally induced pressure pain in individuals with chronic low back pain. We hypothesized that pain perception after exercise would be decreased for individuals with chronic low back pain in a similar manner as has been previously demonstrated in normal healthy individuals. This study also compared pressure pain perception between normal healthy individuals and subjects with chronic low back pain.	
Was the study population clearly specified and defined?				8 individuals (4 males and 4 females) participated in the study. Criteria for participation in the study included the presence of back pain for at least 1 year and clinical evidence that the etiology of the back pain was stable and non neurological. Exclusion criteria included the use of narcotic analgesics, inability to walk without an assistive device, evidence of sacroiliac joint dysfunction as the primary etiology for symptoms, current involvement in a regular exercise or physical therapy program, major surgery within the past year, history of spondylo arthropathy, and presence of spinal infection, fracture, spondylolisthesis, or malignancy. Individuals with know cardiac, pulmonary, or metabolic disorders; diseases affecting sensory nerves; musculoskeletal disorders preventing safe participation in exercise; and pregnancy were also excluded. In effect, the chronic low back pain subject group was composed primarily of individuals with muscular and/or degenerative disk etiologies of pain. Their mean standard deviation (SD) Oswestry disability index score was 23	

Did the authors include a sample size justification?					
Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?			NR		
Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?					
Were the cases clearly defined and differentiated from controls?					
If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?			NR		
Was there use of concurrent controls?					
Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?			CD		
Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?					
Were the assessors of exposure/risk blinded to the case or control status of participants?					
Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?			NR		
Staud 2005					POOR
Was the research question or objective in this paper clearly stated and appropriate?				To test possible central abnormalities of pain modulation in FM, we studied peripheral (ipsilateral to handgrip exercise) versus central (contralateral to handgrip exercise) effects of ISOM exercise on pain inhibition. We hypothesized that ISOM exercise would reduce experimental muscle and heat pain in local as well as remote body areas of NC subjects but would have either no effect or opposite effects in FM patients.	
Was the study population clearly specified and defined?				11 female NC and 12 female FM subjects. The mean age of the NC and FM subjects was 45.7 and 48.4 years. FM subjects were recruited at the Health Science Center Outpatient Clinics and from FM support groups. All subjects underwent a clinical examination and would have been excluded from the study if they had abnormal findings unrelated to FM. However, none of the screened subjects met exclusion requirements. Continuation of analgesics, including non steroidal anti-inflammatory drugs (NSAID) and acetaminophen, was not allowed during the study. Subjects were asked to discontinue narcotic analgesics at least two weeks prior to study	
Did the authors include a sample size justification?					

Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?				NC subject s came from the University Health Science Center and the University campus, Gainesville	
Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?					
Were the cases clearly defined and differentiated from controls?					
If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?			NA		
Was there use of concurrent controls?				not specified	
Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?					
Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?				The subjects were tested during a minimum of four visits which were separated by at least seven days. The study included at least one initial training session to familiarize the subjects with the psychophysical testing procedures. Thermal supra-threshold testing and PPT testing were always done on separate days. Testing sessions for each subject were always conducted at about the same time of day. All study procedures except the hand grip exercise (the dominant arm was always used) were administered in a counterbalanced fashion to avoid order effects.	
Were the assessors of exposure/risk blinded to the case or control status of participants?					
Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?				Unpaired Student's t-tests were used for group comparisons of grip strength and cardiovascular data.	
Whiteside 2004					POOR
Was the research question or objective in this paper clearly stated and appropriate?				In this study, we compared changes in pain threshold in five CFS patient with five age and sex matched control subjects following exercise	
Was the study population clearly specified and defined?				Five CFS patients (median age 46 years range 28 – 49) and five control subjects (median age 44 years range 30 – 54)	
Did the authors include a sample size justification?					
Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?			NR		
Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and					

implemented consistently across all study participants?					
Were the cases clearly defined and differentiated from controls?					
If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls randomly selected from those eligible?			NA		
Was there use of concurrent controls?					
Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?					
Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?					
Were the assessors of exposure/risk blinded to the case or control status of participants?			NR		
Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?			NR		
Vierck 2001	no	si	CD/NA/NR		POOR
Was the research question or objective in this paper clearly stated and appropriate?				the present study directly compared effects of strenuous exercise on clinical pain and on temporal summation of experimental pain.	
Was the study population clearly specified and defined?				Ten female patients who fulfilled the 1990 American College of Rheumatology Criteria for FM, 10 age matched female control subjects, and 10 male control subjects of comparable age were enrolled in the study. All subjects were right handed, and all were white except for 2 black women. The average age of subjects in each group was 46 years. Patients with FM were recruited at the Health Science Center Outpatient Clinics and from FM support groups. Most normal volunteers were employees at the University of Florida Health Science Center	
Did the authors include a sample size justification?					
Were controls selected or recruited from the same or similar population that gave rise to the cases (including the same timeframe)?			NR		
Were the definitions, inclusion and exclusion criteria, algorithms or processes used to identify or select cases and controls valid, reliable, and implemented consistently across all study participants?					
Were the cases clearly defined and differentiated from controls?					
If less than 100 percent of eligible cases and/or controls were selected for the study, were the cases and/or controls			NA		

randomly selected from those eligible?					
Was there use of concurrent controls?					
Were the investigators able to confirm that the exposure/risk occurred prior to the development of the condition or event that defined a participant as a case?			NA		
Were the measures of exposure/risk clearly defined, valid, reliable, and implemented consistently (including the same time period) across all study participants?					
Were the assessors of exposure/risk blinded to the case or control status of participants?					
Were key potential confounding variables measured and adjusted statistically in the analyses? If matching was used, did the investigators account for matching during study analysis?			NR		