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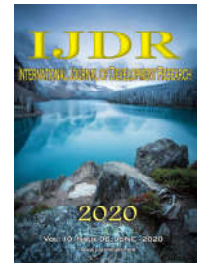
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RESEARCH ARTICLE

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## EFFICIENCY OF AEROBIC PHYSICAL EXERCISE IN CHRONIC OROFACIAL PAIN: A SYSTEMATIC REVIEW

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Pain; Exercise; Chronic Pain.

### ABSTRACT

**Objective:** This systematic review was conducted to the following central question: In adults with chronic or facial pain, which is the efficiency of aerobic physical exercise in reducing pain?

**Design:** Search strategies were developed to electronic database. **Results:** Four studies were included in the qualitative synthesis. In three transversal studies included it was observed that physical exercise led to an improvement in chronic or ofacial pain, that simple advice is equally as effective as a more intense and comprehensive physiotherapy exercise programme. **Conclusion:** available evidence on the subject suggests that there is effect of analgesia through aerobic physical exercise in patients with chronic or ofacialpain, however, further studies on the subject should be performed for a quantitative analysis to be performed.

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Odilon Guariza-Filho

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## INTRODUCTION

Chronic pain is characterized as continuous or recurrent pain, which does not disappear with conventional therapeutic procedures, becoming the cause of prolonged disabilities and inabilities, many times with ambiguous etiology<sup>1</sup>. Orofacial pain (OFP) includes a heterogeneous group of conditions, such as dental, mucosal, musculoskeletal, neurovascular and neuropathic pain<sup>2</sup>. Epidemiological studies have shown that OFP is prevalent in the general population around 17–26%, (excluding dental pain), in which 7–11% is classified as chronic<sup>3</sup>. Chronic pain plays an important role on functional capacity, which results in disrupted work and social activities; leading to a high economic cost. Multidisciplinary approaches with physical exercise have shown to improve pain and function in chronic pain patients<sup>4</sup>.

Specifically, aerobic exercise has been shown to provide temporary pain relief, and it may have clinical utility as a complementary method for pain management<sup>5,6</sup>. Exercise-induced hypoalgesia (EIH) is characterized by a reduced sensitivity to noxious stimulation or a decrease in pain perception as a result of exercise, possibly due to stimulating release of pain-relieving peptides include nonopioid compounds (eg, serotonin, norepinephrine) and endogenous opioid substances<sup>7</sup>. These pain-relieving peptides have been implicated in the analgesic response after muscle contraction<sup>8</sup>. The mechanism responsible for exercise-induced analgesia are poorly understood. Although involvement of the endogenous opioid system has received mixed support in human research, results from animal research seem to indicate that there are multiple analgesia systems, including opioid and non-opioid systems<sup>9</sup>.

Due to the lack of systematic reviews on this topic and based on the above, this systematic review was conducted to answer the following central question: In adults with chronic orofacial pain, which is the efficiency of aerobic physical exercise in reducing pain?

## MATERIALS AND METHODS

### Protocol and registration

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Checklist<sup>10</sup>. International Prospective Register of Systematic Reviews, database was used to register this systematic review protocol under the number CRD42017063780<sup>11</sup>.

**Eligibility criteria:** Studies that met the following criteria, using the acronym 'PICOS or PECOS', were considered eligible for this systematic review:

- P = *participants* - Studies evaluating physical exercise in adults (>18 years old) with chronic orofacial pain.
- I = *intervention/or/exposition* - Chronic pain will be define as persistent pain lasting more than 3 months (patient's report) and physical exercise such as walking, running, dancing, cycling and other ones.
- C = *comparison* - Compared to no exercise in adults (>18 years old) with chronic orofacial pain.
- O = *outcomes* - Pain intensity was measured through questionnaires and/or pain scales, such as Visual Analogue Scale (VAS), Numerical Rating Scale (NRS) or Numerical Analogue Scale (NAS).
- S = *types of studies included* - Randomized or non-randomized clinical trials and observational studies were included. No restrictions on language and publication's time were applied.

**Inclusion criteria:** Studies evaluating aerobic physical exercise compared to no exercise in adults (> 18 years old) with chronic orofacial pain. Chronic pain will be define as persistent pain lasting more than 3 months (patient's report). Aerobic exercise include walking, running, dancing, cycling and other. Physical activity was considered any body movement produced by skeletal muscles requiring energy expenditure. Pain intensity was considered measured through questionnaires and/or pain scales. Clinical trials Randomized or not and observational studies it was possible to be included. No restrictions on language and publication's time were applied.

### Exclusion criteria

**Studies were not selected based on the following exclusion criteria:**

- Studies in children and adolescents (<18 years old) and elderly (>65 years);
- Studies with chronic pain in other region than orofacial one, and with systemic chronic diseases such as fibromyalgia;
- Studies reporting pain that lasts less than 3 months;
- Studies which did not evaluate aerobic exercises;
- Reviews, letters, conference abstract, personal opinions.

**Search Methods to Identify Studies:** Search strategies were specifically developed to the following electronic database: Cochrane, Latin American and Caribbean Health Sciences (LILACS) PubMed (including Medline), Scopus and Web of Science (More information on the search strategies is provided in Appendix 1). Appropriate truncation and word combinations were selected and adapted for each database search. Furthermore, partial grey literature search through Google Scholar, Open Grey and ProQuest (dissertations and thesis) were performed. In addition to the electronic search, articles were indicated by the experts, hand-search was made and references list of the selected articles were looked at. The experts were selected based on their expertise in pain, which was based on numerous of paper published on the field. A contact was made with the experts to carry out their participation in this work. Once accepted the invitation they received our protocol, to indicate some papers. The references were managed and the duplicates were removed by using EndNote® X7 (Thomson Reuters, Philadelphia, PA). Both electronic database searches and the grey literature searches were conducted from their starting coverage date through Nov 4<sup>th</sup>, 2017. An updated search with the same word combinations for each database above mentioned was performed on Oct 24<sup>th</sup>, 2019.

**Study selection:** The selection was completed in two phases. In the first phase, titles and abstracts of all electronic data base were screened independently by two reviewers (B.L.C. and C.M.A.). In phase 2 the same authors worked independently (B.L.C. and C.M.A.), where the complete text reading. The reference lists of the included articles were evaluated. Final selection was always based on the full text of the publication. Any disagreements in either phase were resolved by discussion by the same reviewers. A third and fourth author (J.A and A.D.) was involved when required to make a final decision.

**Data items and data collection process** Two authors (B.L.C. and C.M.A.) collected the required information from the selected studies, and the accuracy of the information collected was discussed. Any mistyping in this process was evaluated by a third and fourth author (J.A and A.D.). The data collected consisted of: study characteristics (authors, year of publication and country), population characteristics (sample size, mean age, and percentage of female), intervention characteristics (methods) and outcome characteristics (therapy, control, results and main conclusions). If the required data were not complete, efforts were made to contact the authors to retrieve any pertinent unpublished data.

**Risk of bias within individual studies:** The methodological quality of the included RCTs will be evaluated through the Cochrane Collaboration's tool for assessing risk of bias<sup>12</sup>. Briefly, the randomization and allocation methods will be classified as adequate, inadequate, or unclear, whereas the completeness of the follow-up period, blinding of examiners, selective reporting and other forms of bias will be coded as "yes/no" responses. The methodological quality of observational studies will be evaluated using Meta-Analysis of Statistics Assessment and Review Instrument (MASTAR). Risk of bias will be categorized as "high" when the study reaches up to 49% score "yes"; "moderate" when the study reached 50% to 69% score "yes"; and "low" when the study reached more than 70% score "yes".

**Studiesslection:** In phase 1, we found 1252 references across the five electronic databases. After the duplicate articles were removed, 883 references retained. Thereafter, applying the eligibility criteria, 878 studies were excluded, resulting in five articles. A partial grey literature search was done and five more studies were identified, whereas none study was selected. From the references lists, two studies were screened and both additional studies were included. The expert indicates 18 studies, however only 5 were selected. An updated search with the same word combinations for each database above mentioned was performed on Oct 24<sup>th</sup>, 2018. No more studies were included. Therefore, articles were retrieved for phase-2. Twelve of them were excluded (Appendix 2), resulting on four studies included in the qualitative synthesis. A flowchart of the process of identification, inclusion and exclusion of studies is shown in Figure 1.

**Study Description:** The four studies were published between 2012 and 2017. The studies were conducted in Australia, Scandinavia, Spain, in Belgium and United Kingdom. Sample size ranged from 40 to 244 subjects. Pain intensity was measured through questionnaires and/or pain scales, such as VAS<sup>13</sup>, NRS or NAS<sup>14</sup>, Short Form Health Survey (SF-36), the Checklist Individual Strength (CIS)<sup>13</sup>, Numerical Pain Rating<sup>15</sup>, the Neck Disability Index (NDI) and Pain Catastrophizing Scale (PCS)<sup>15</sup>, the Tampa Scale of Kinesiophobia (TSK) and the Symptom Severity Scale (i.e. questions 22–38) of the Posttraumatic Stress Diagnostic Scale (PDS)<sup>15</sup>, the Standardized Extended Version of the EQ-5D<sup>16</sup>. One Study evaluate chronic musculoskeletal disorders<sup>16</sup> and the other ones evaluated chronic whiplash<sup>13-15</sup>. Three studies did not report the use of Temporomandibular Disorders Diagnostic Method (TMD)<sup>14-16</sup> and the other one used the WAD grade I-III<sup>13</sup>. A summary of the studies descriptive characteristics can be found in Table 1.

One selected study<sup>14</sup> was randomized controlled trial and three<sup>13,15,16</sup> were observational studies. Related of active therapy, two of them presented therapy program combining therapeutic exercise and health education intervention to the participants<sup>14,16</sup>. Smith, 2017<sup>15</sup> used single session of aerobic exercise and a single session of isometric exercise. Van Oosterwijck, 2012<sup>13</sup> did a cycle test known as the Aerobic Power Index while in control group a self-paced and physiologically limited bicycle exercise was performed. The age of the patients in all included studies ranged from 18-65 years. In the study by Van Oosterwijck et al.<sup>13</sup> the sample consisted of 100% women, Cuesta-Vargas et al.<sup>16</sup>, 56% of women, Smith et al.<sup>15</sup>, 55%, and Michael et al.<sup>14</sup>, did not report this information. Two studies not presented a well-defined control group with healthy subjects<sup>17,18</sup> and the other seven presented control<sup>19-25</sup>.

**Risk of bias within studies:** All studies were methodologically acceptable and were considered at low risk of bias. The complete analysis of quality assessment items list is presented in Appendix 3 and Figure 2.

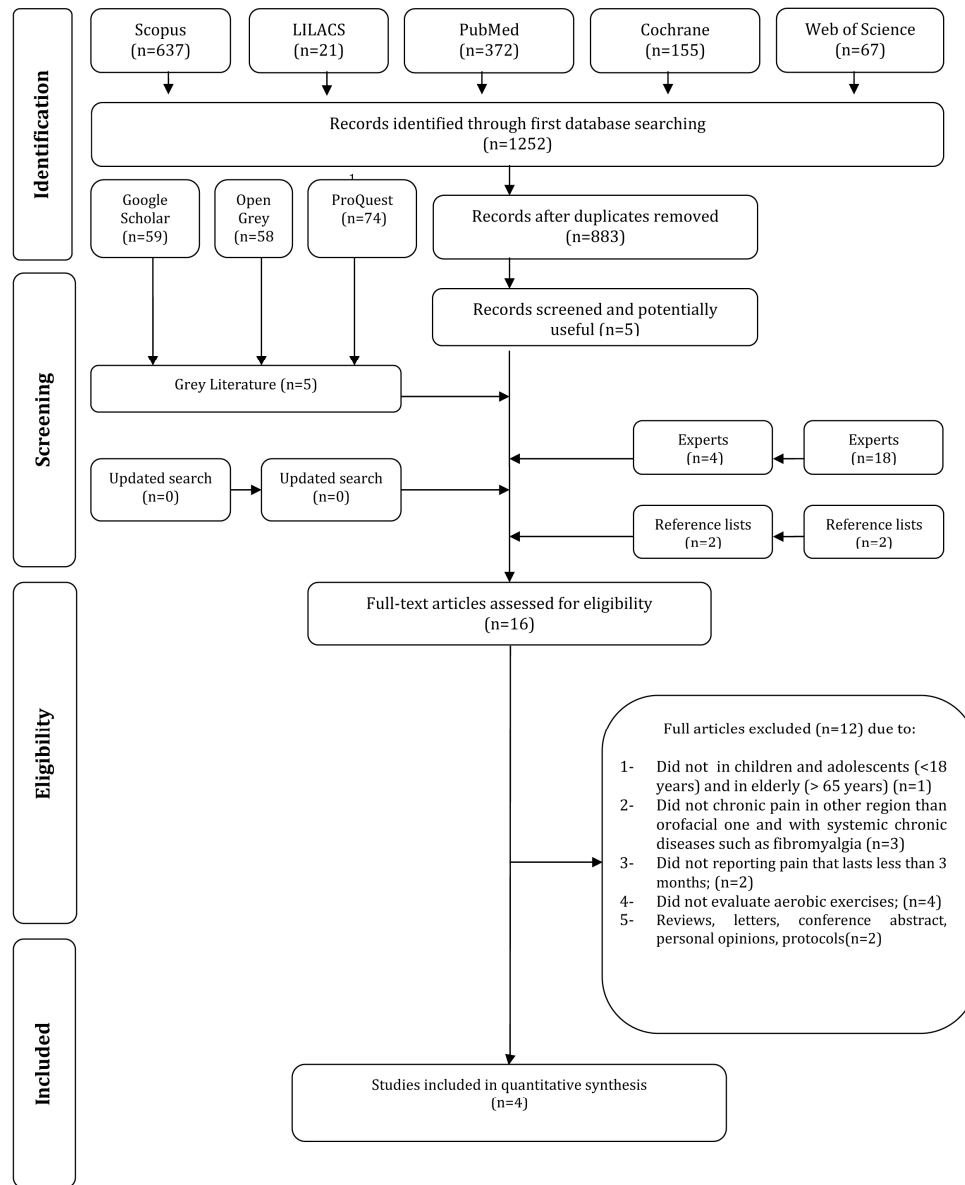
**Synthesis of Results:** Two studies evaluated Chronic Whiplash-associate disorders<sup>13,15</sup>. One study evaluated Chronic Whiplash<sup>15</sup> and another study evaluated chronic musculoskeletal disorders<sup>16</sup>, where exercise therapy presented combining therapeutic exercise and health education, could be recommended to patients at least in the short-term. One study evaluated chronic whiplash-associated disorders<sup>13</sup> showing a self-paced and physiologically limited exercise more appropriate for chronic WAD patients.

Smith, 2017<sup>15</sup>, suggests that isometric exercise may be more effective than aerobic exercise in inducing hypoalgesia in individuals with mild to moderate WAD symptoms. In the three transversal studies<sup>13,15,16</sup> included it was observed that physical exercise in these patients led to an improvement in chronic orofacial pain, however, Michaleff, et al.<sup>14</sup>, shown that simple advice is equally as effective as a more intense and comprehensive physiotherapy exercise programme. Because the different outcomes and different groups characteristics related to the absence of a controlled TMD group or a controlled TMD therapy, neither descriptive clustering nor quantitative meta-analysis was performed in this systematic review.

## DISCUSSION

This systematic review investigated the available evidence about the efficiency of aerobic physical exercise in chronic orofacial pain. We found several types of proposed exercises: physiotherapy, cycle ergometer, wall squat exercise and therapeutic exercise and different ways to evaluate chronic pain since health related quality of life determined through questionnaire<sup>16</sup>, until scales of pain like Numerical Pain Rating<sup>15</sup> and the results indicated that aerobic exercises can bring an improvement in painful symptoms. One of the pivotal mechanisms that could explain the chronification of pain, as well as its resistance to classical forms of treatment, is the concept of pain centralization, where initial sensory events following trauma can gradually alter the central nervous system (CNS), resulting in amplified pain and/or aberrant pain that exists without peripheral tissue damage or sensitization<sup>26</sup>. The circuitry of pain in the brain is complex, mainly because pain is a multidimensional experience that incorporates nociceptive, affective, and cognitive networks. In brief, the dorsal posterior insula, the primary and secondary somatosensory cortices, the anterior insula, the ventrolateral and medial thalamus, the hypothalamus, and the dorsal anterior cingulate cortex have been implicated in the nociceptive processing of pain, while limbic systems including the nucleus accumbens, amygdala, and hippocampus could become involved with persistent nociceptive input, eventually engaging prefrontal cortical circuitry<sup>27,28</sup>. It is important to note, however, that this pain “matrix” is not a static entity but rather a dynamic network that is characterized by specific spatiotemporal neural expression patterns in painful conditions<sup>29</sup>.

Exercise-induced hypoalgesia (EIH) is characterized by a diminished sensitivity to noxious stimulation or a decrease in pain perception as a result of exercise, possibly due to stimulating release of pain-relieving peptides include nonopioid compounds (eg, serotonin, norepinephrine) and endogenous opioid substances<sup>7,30</sup>. These pain-relieving peptides have been implicated in the analgesic response after muscle contraction<sup>8</sup>. Any increased sensitization of the nociceptive receptors could affect the response of the afferent nerve fibers, causing central hyperexcitability of the neurons in the dorsal horn of the spinal cord affecting trigeminal nucleus and facilitating headache symptoms<sup>31</sup>. The antinociceptive and analgesic effects of physical exercise have been shown in rodent models of pain as well, both as prophylactic and therapeutic interventions. One possible mechanism by which exercise could prevent some of the maladaptive neuroplasticity observed in chronic pain is limiting blood-brain Barrier permeability after peripheral injury<sup>26</sup>.



<sup>1</sup> Adapted from PRISMA REF.

Figure 1 - Flow Diagram of Literature Search and Selection Criteria

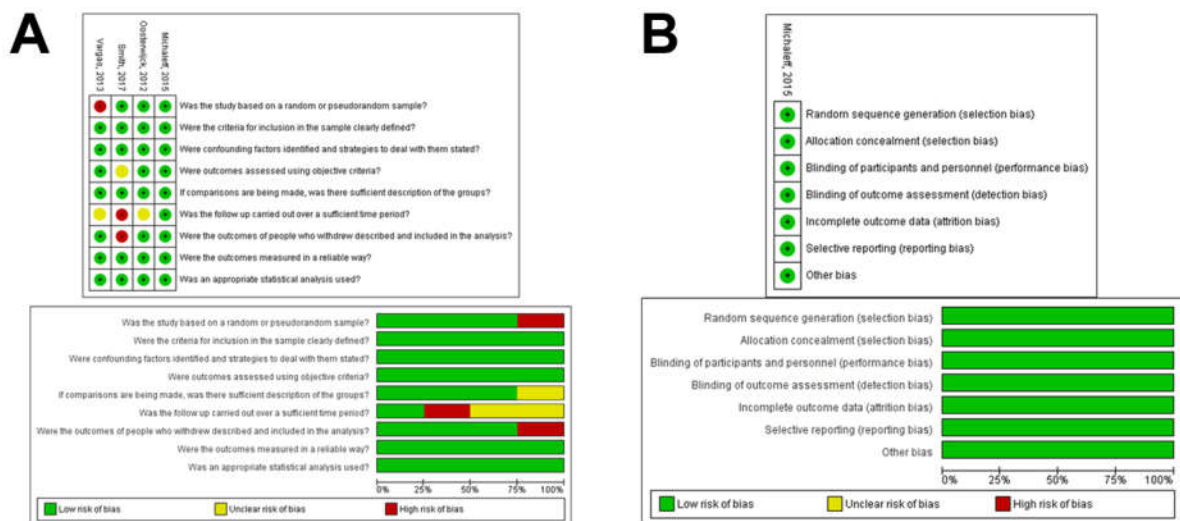


Figure 2 -A) Observational studies assessed by means of Meta-Analysis of Statistics Assessment and Review Instrument critical appraisal tools. Green indicates low risk of bias, yellow indicates unclear risk of bias, and red indicates high risk of bias. Risk of bias summary and graph. B) Cochrane's tool to assessed risk of bias in randomized controlled trials. Risk of bias summary and graph.

Table 1 - Summary of the descriptive characteristics of the included studies.n=4

Author Year Country	Sample (n) Mean age(SD) % fem	Active TherapySample(aer obic Exercise (n/%fem)	ControlTherapy Sample(no exercise (n/%fem)	Information about Active Therapy	Information about Placebo Therapy	Results	Main conclusion
Michaleff et al, 2015 Australia	172 NR	86 NR	86 NR	Participants will be provided with the patient educational booklet 'Whiplash injury recovery: a self-management plus twenty, one-hour individually tailored and supervised exercise sessions over a 12 week period at physiotherapy clinics	Participants will be provided with the patient educational booklet 'Whiplash injury recovery: a self-management guide' and advice session: thirty-minute consultation with a physiotherapist.	The addition of a comprehensive exercise program was not more effective than advice alone in reducing pain: at 14 weeks the treatment effect was 0.0 (95%CI -0.7 to 0.7), 6 months 0.2 (-0.5 to 1.0)and at 12 months-0.1 (-0.8 to 0.6).	The comprehensive exercise program provided no additional benefit to a single physiotherapy advice session supplemented with telephone support.
Oostewijk , 2012 Belgium United Kingdom	44 (38.4± 9.2 y) Control groups (37.1±14.6 Y)	22 100%	22 100%	cycle test known as the Aerobic Power Index were performed in a sitting position on an electrically braked cycle ergometer	A self-paced and physiologically limited bicycle exercise was performed by all subjects with 3 safety breaks or exercise limits For the controls, the estimated time was always decreased by 25%.	Significant differences were found in terms of symptom occurrence and quality of life (visual analogue scales and SF-36) between the chronic WAD and the control group, only the "general health" subscale from the SF-36 showed a significant different evolution over time between the 2 exercise tests in the patient group (P = .038). Patients reported a small improvement in general health immediately after the submaximal exercise, but scores declined significantly 24 hours post exercise.	Chronic people with WAD demonstrated lowered PPTs and symptom exacerbations following exercise, which is suggestive for an impaired descending endogenous pain inhibition during exercise in these patients. Although chronic WAD patients' symptoms increased in response to both types of exercise, a self paced and physiologically limited exercise will trigger less severe symptoms and therefore seems more appropriate for chronic WAD patients
Smith, 2017 Scandinavi an	40 44.5 ± 10.5 years, 55%female , healthy controls (age = 37.4 ± 10.8 years, 74%female)	21 55%female	19 74%	Single session of aerobic exercise and a single session of isometric exercise. These sessions were scheduled 5–10 days apart.	Single session of aerobic exercise and a single session of isometric exercise. These sessions were scheduled 5–10 days apart.	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.	Individuals with chronic WAD and mild to moderate pain and disability, and no evidence of dysfunctional CPM, demonstrated reduced pain sensitivity, both in the cervical spine and over the tibialis anterior following an isometric, timed wall squat exercise. Cycling exercise did not increase pain sensitivity.
Vargas 2013 Spain	244 45.17 yearsold, 56%	244 56% female	N	Therapy Program ((combining therapeutic exercise and health education) intervention was used and individualized to the participants	N	Intervention resulted in an improvement in all outcome measures.	Eight weeks of a Multimodal Physical Therapy Program seemed to moderately enhance the general health state and HRQoL of patients with chronic musculoskeletal diseases. This kind of therapeutic exercise can be recommended to patients with CLBP, CNP and OA, at least in the short term.

## Conclusion

In conclusion, the available evidence on the subject suggests that there is an improvement in the effect of analgesia through aerobic physical exercise in patients with chronic orofacial pain, however, further studies on the subject should be performed for a quantitative analysis to be performed.

## Compliance with Ethical Standards

**Funding:** There were no source of funding for this systematic review.

**Conflicts of interest:** There were no conflicts of interest in the performance of this study.

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## Appendix 1 - Database search strategy.

Database	Search(Oct 24, 2019)
LILACS	(Adult)OR (adults) OR (male) OR (female) OR (adulto) OR (adultos) AND (Pain) OR (pains) OR (ache) AND (head) OR (face) OR (orofacial) OR (bucomaxillofacial) OR (buccofacial) OR (mouth) OR (oral) OR (buccal) OR (temporomandibular) OR (dor facial) OR (dolor facial) OR (Dor craniofacial) OR (Dor miofacial) AND (chronic OR chronicity) OR (persistent OR Longlasting) AND (aerobicphysicalexercise) OR (exercise, aerobic) OR (aerobicexercise) OR exercise OR (physicalexercise) OR dance OR dancing OR walking OR walk OR running OR run OR cycling
PubMed	"adult"[MeSHTerms] OR "adult"[AllFields] OR "adult"[MeSHTerms] OR "adult"[AllFields] OR "adults"[AllFields] OR "male"[MeSHTerms] OR "male"[AllFields] OR "female"[MeSHTerms] OR "female"[AllFields]AND "Pain"[MeSHTerms] OR "pain"[AllFields] OR "pains"[AllFields] OR "ache"[AllFields] AND "head"[MeSHTerms] OR "head"[AllFields] OR ("face"[MeSHTerms] OR "face"[AllFields] OR orofacial[AllFields] OR "face"[MeSHTerms] OR "face"[AllFields] OR "facial"[AllFields] OR bucomaxillofacial[AllFields] OR buccofacial[AllFields] OR "mouth"[MeSHTerms] OR "mouth"[AllFields] OR "oral"[AllFields] OR buccal[AllFields] OR temporomandibular[AllFields] AND chronic[AllFields] OR chronicity[AllFields] OR persistent[AllFields] OR "Longlasting"[AllFields] AND "aerobicphysicalexercise"[AllFields] OR "exercise, aerobic"[AllFields] OR "aerobicexercise"[AllFields] OR "exercise"[AllFields] OR "physicalexercise"[AllFields] OR dance OR dancing OR walking OR walk OR running OR run OR cycling
SCOPUS COCHRANE	"adult" OR "adults" OR "male" OR "female" "Pain" OR "pains" OR "ache" "head" OR "head" OR "face" OR "orofacial" OR "bucomaxillofacial" OR "buccofacial" OR "mouth" OR "oral" OR "buccal" OR "temporomandibular" "chronic" OR "chronicity" OR "persistente" OR "Longlasting" "aerobicphysicalexercise" OR "exercise, aerobic" OR "aerobicexercise" OR "exercise" OR "physicalexercise" OR "dance" OR "dancing" OR "walking" OR "walk" OR "running" OR "run" OR "cycling"
Web of Science	"adult" OR "adults" OR "male" OR "female" "Pain" OR "pains" OR "ache" "head" OR "head" OR "face" OR orofacial OR bucomaxillofacial OR buccofacial OR "mouth" OR "oral" OR buccal OR temporomandibular chronic OR chronicity OR persistent OR "Longlasting" "aerobicphysicalexercise" OR "exercise, aerobic" OR "aerobicexercise" OR "exercise" OR "physicalexercise" OR dance OR dancing OR walking OR walk OR running OR run OR cycling
Google Scholar	"physicalexercise" OR "aerobicexercise", "orofacial pain" filetype:pdf
ProQuest	(head OR head OR face OR orofacial OR bucomaxillofacial OR buccofacial OR mouth OR oral OR buccal OR temporomandibular) AND (chronic OR chronicity OR persistent OR "Longlasting") AND (adult OR adults OR male OR female)
Open Grey	Exercise AND paindoctype (U-Thesis)

## Appendix 2 Excluded articles and reasons for exclusion n=12.

Author, Year	Reason for exclusion
Arai Y.C.P. et al 2015 <sup>1</sup>	4
Benoliel, R. et al 2003 <sup>2</sup>	4
Bron C. et al 2011 <sup>3</sup>	2
Carlson et al 2001 <sup>4</sup>	2
AustralianGovernmentDepartmentofVeteran'sAffairs. 2004 <sup>5</sup>	5
Cinciripini et al 1983 <sup>6</sup>	4
Costa et al 2016 <sup>7</sup>	5
Fricton J. et al 2009 <sup>8</sup>	1
Hoffman D.M. et al 2004	3
Kvale A., Wilhelmsen K., Fiske H. A. et al 2009 <sup>9</sup>	1
Souza et al 2009 <sup>10</sup>	5
Saklecha et al 2015 <sup>11</sup>	3

Legend: 1. Studies in children and adolescents (<18 years) and in elderly (> 65 years) 2. Studies with chronic pain in other region than orofacial one and with systemic chronic diseases such as fibromyalgia 3. Studies reporting pain that lasts less than 3 months; 4. Studies which did not evaluate aerobic exercises; 5. Reviews, letters, conference abstract, personal opinions, protocols.

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**Appendix 3** - Risk of bias assessed by “Meta-Analysis of Statistics Assessment and Review Instrument” (MAStARI)<sup>15</sup> critical appraisal tools.

A – Cross-sectional.Descriptive Studies.

Question	Answer		
	Smith, 2017[1]	Cuesta-Vargas, 2013[2]	Van Oosterwijck, 2012[3]
1. Was the study based on a random or pseudorandom sample?	Y	N	Y
2. Were the criteria for inclusion in the sample clearly defined?	Y	Y	Y
3. Were confounding factors identified and strategies to deal with them stated?	Y	Y	Y
4. Were outcomes assessed using objective criteria?	Y	Y	Y
5. If comparisons are being made, was there sufficient description of the groups?	NA	Y	Y
6. Was the follow up carried out over a sufficient time period?	N	NA	NA
7. Were the outcomes of people who withdrew described and included in the analysis?	N	Y	Y
8. Were the outcomes measured in a reliable way?	Y	Y	Y
9. Was an appropriate statistical analysis used?	Y	Y	Y
% yes/risk	75% Low	87.5% Low	100% Low

Legend - \*Y=Yes, N=No, U=Unclear, NA=Not applicable

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**Appendix 3b** – Cochrane’s tool to assessed risk of bias in randomized controlled trials (Higgins et al 2011)<sup>1</sup>

Author, year	Questions	Support for judgement	Risk of Bias
Michaleff, Z. A., et al., 2014	Blinding of participants and personnel (performance bias)	To ensure allocation was concealed, participants were randomly assigned immediately after baseline assessment by opening the next sealed, sequentially numbered, opaque envelope. Participants were deemed to have entered the study at the time that the envelope was opened	LOW RISK
	Allocation concealment (selection bias)	The researcher did participate in analysis and interpretation of trial results, but only after masked results were recoded to ensure all authors were masked to group allocation.	LOW RISK
	Random sequence generation (selection bias)	A computer-generated randomisation schedule, stratified for recruitment site (Sydney and Brisbane) was produced	LOW RISK
	Blinding of outcome assessment (detection bias)	All outcome measures were obtained by an investigator who was unaware of group allocation at baseline, 14 weeks, 6 months, and 12 months after randomisation.	LOW RISK
	Incomplete outcome data (attrition bias)	No missing outcome data.	LOW RISK
	Selective reporting (reporting bias)	All of the study's pre-specified (primary and secondary) outcomes that are of interest in the review have been reported.	LOW RISK

Higgins Julian P T, Altman Douglas G, Gøtzsche Peter C, Jüni Peter, Moher David, Oxman Andrew D et al. “The Cochrane Collaboration’s tool for assessing risk of bias in randomised trials”. *BMJ* 2011; 343:d5928

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