HOCHSCHULE OSNABRÜCK
UNIVERSITY OF APPLIED SCIENCES

SPECIFIC AGREEMENT OF INTERNATIONAL COOPERATION

UFSCar
N.º: 006/2023
Processo: 23112.039117/2022-35

Specific agreement of academic, scientific, technical and cultural cooperation between the Federal University of São Carlos (Brazil) and *Hochschule Osnabrück* (Germany) in the area of and/or regarding topics on Physiotherapy

The Federal University of São Carlos, with registered offices on São Carlos campus, at *Rodovia* Washington Luís, km 235, in São Carlos, in the state of São Paulo, Brazil, represented by its Rector, Prof. Dr. Ana Beatriz de Oliveira, hereinafter referred to as "UFSCar", on behalf of its Department of Physiotherapy and Graduate Program on Physiotherapy, and *Hochschule Osnabrück*, with registered offices at 30 *Albrechtstr.*, in Osnabrück, in Lower Saxony, Germany, represented herein by its Vice President and Dean of its Faculty of Business Management and Social Sciences, Prof. Dr. Andrea Braun von Reinersdorff, on behalf of its Faculty of Economics and Social Sciences,

WHEREAS both Institutions are interested in the development of Higher Education, scientific knowledge and research, and technology,

WHEREAS they wish to formally establish an institutional relationship between them, aiming to promote their continuous strengthening, enhancement and advancement by jointly developing academic, scientific, technical and cultural activities in the area of and/or regarding topics on Physiotherapy, for the interest of their respective academic and/or research unities mentioned above,

ENTER INTO THIS AGREEMENT, which will be governed by the following terms and conditions:

SECTION 1 – Purpose

This Agreement establishes and governs academic, scientific, technical and cultural cooperation between the Parties in the area of and/or regarding topics on Physiotherapy, for the interest of the Department of Physiotherapy and Graduate Program on Physiotherapy of UFSCar, and the Faculty of Economics and Social Sciences of *Hochschule Osnabrück*.

Said collaboration may comprise the development of the following activities:

I. Exchange of undergraduate and/or graduate students, so as to attend courses, take part in research activities and/or do academic internship/practicum at the host institution.

II. Exchange of professors and researchers, so as to give lectures and workshops, teach courses and/or carry out or participate in research activities at the host institution.

III. Joint supervision of doctoral (Ph.D.) dissertations/theses, by supervisors from each institution, by duly executing proper, distinct, separate agreements, referring to each dissertation/thesis and its respective doctoral (Ph.D.) student.

IV. Joint development of research projects, which proposals, work plans or, at least, abstracts shall be timely attached hereto, like the projects "What is the minimal important difference (MID) of outcomes measures related to urinary incontinence? A systematic review" (see Annex A), "Global prevalence of dysmenorrhea: a systematic review and metanalysis" (see Annex B), "Prognostic factors of the urinary incontinence: a systematic review" (see Annex C) and "Immediate effects of cervical spine motor control and aerobic exercise on individuals with orofacial and neck pain: a randomized clinical trial" (see Annex D).

V. Sharing and exchange of scientific, technical and cultural information, as well as joint production of academic, scientific and technical publications.

VI. Co-organization of academic, scientific and cultural events, *e.g.*, conferences, symposia, seminars and colloquia.

SECTION 2 – Coordination

In order to coordinate the implementation of this Agreement and the pursuit of its purpose, UFSCar indicates Dr. Ana Beatriz de Oliveira and Dr. Patricia Driusso, both professors at its Department of Physiotherapy and Graduate Program on Physiotherapy, and *Hochschule Osnabrück* indicates Dr. Susan Armijo-Olivo, professor at its Faculty of Economics and Social Sciences.

The coordinators shall supervise the study plans/learning agreements, research plans and the internship/practicum projects or plans corresponding to the exchanges under this Agreement, as well as seek solution for the academic and administrative issues referring hereto from its effective date.

SECTION 3 – Exchange of students, professors and researchers

When promoting the exchanges provided in the First Clause hereof, both Parties shall observe the following rules, to the extent of their respective rules and regulations on international academic mobility:

I. The maximum number of exchange students, professors and researchers from any institution in mobility at the other, as well as the length of their respective stay at the host institution, will be set forth timely by the Parties, in accordance with what is possible and feasible for them, subject to the limits stipulated in their by-laws.

II. The coordinator at the home institution will select the students who apply for exchange. Such selection shall be based on their academic performance. The final acceptance (admission) of each selected applicant will be decided by the host institution.

III. The exchange of professors and researchers requires formal invitation by professor or researcher from the host institution.

IV. An individual study plan/learning agreement, research plan and/or internship/practicum project or plan must be elaborated for each student. For each professor and researcher a research plan and/or work plan shall be elaborated. Those plans, which will be executed at the host institution, must be prepared before the arrival of the corresponding students, professors and researchers at said institution.

V. Students, professors and researchers accepted by the host institution will be subject not only to the rules and regulations in force there, but also to the immigration law of the country where said institution is situated.

VI. Before arriving in the country of the host institution, accepted students, professors and researchers must purchase health, personal accident, civil liability, and medical and mortal remains repatriation insurances featuring coverage for the whole period of their respective exchange.

VII. Both institutions shall facilitate the access and use of its own facilities, equipments, laboratories and library material by exchange students, professors and researchers, so as to enable the proper development of their respective activities.

VIII. The host institution shall waive the academic fees, where required, regarding the mobility of students, professors and researchers from the other institution.

IX. Participants in the exchanges will bear the costs referring to their own participation in said activity, *e.g.*, travels, housing, food, transportation, insurance, visa, and others.

X. Exchange students will not be entitled to diploma issued by the host institution and will remain as degree-seeking students at their respective home institution.

XI. The host institution shall send to the home institution document(s) informing the academic and scientific activities developed by each of its students during his/her respective exchange and, where applicable, informing also the result of the evaluation of his/her performance in such activities. Where necessary or requested, this provision may apply also to professors and researchers participating in the exchanges, to the possible extent.

XII. Participation in any activity under this Agreement does not generate any formal employer-employee relationship between any person from either Party and the other Party.

SECTION 4 – Financial resources

Unless otherwise agreed in an amendment hereto, this Agreement does not create any financial obligation from either Party to the other. Each Party shall bear the costs of its own effective participation in the development hereof.

The Parties may carry out activities hereunder using funds granted from agencies and organizations devoted to funding research and development, as well as from companies and other private and public institutions.

SECTION 5 – Confidentiality of information, intellectual property rights and publications

I. Both Parties ensure that themselves, their respective employees and agents, as well as any other person in connection with the Parties, will respect the confidentiality of all the information, data, projects, know-how and any other information or documents provided by either Party to the other under this Agreement. Both Parties shall not disclose such information, documents, data, projects and know-how to third parties without the prior written consent of the Disclosing Party.

II. Throughout the duration of this Agreement and for five (5) years after its termination, both Parties shall keep strictly confidential the confidential information exchanged between them or generated by them hereunder. Both Parties shall not directly or indirectly disclose such confidential information to third parties or make it public

without the prior written consent of the Disclosing Party, or use such confidential information for purposes not set forth in this Agreement, except under a legal rule or court order.

III. Notwithstanding the previous provisions, information will not be deemed confidential if:

a) it is publicly known or is known by the Receiving Party before its receipt, without any breach of this Agreement;
b) it becomes publicly known in the future, without either Party being responsible for its disclosure.

IV. If a court order requires the Parties to disclose confidential information to third parties, the Party receiving the court order shall communicate the Disclosing Party about such court order and take all the appropriate legal actions, at its own expenses, in order to prevent disclosing said confidential information or, where it is not possible, disclose only the piece of information that is strictly necessary to comply with such court order.

V. Any data, technology, technical and commercial information, software, procedure and routine, registered or not, belonging to any of the Parties and/or to third parties, but under the responsibility of this Party, prior to the effective date of this Agreement, and which has been disclosed to the other Party for the sole purpose of supporting the development of programs, projects or activities hereunder, will remain belonging to the Party that has possessed such goods already.

VI. The Parties hereby agree that any result able of being protected by intellectual property rights, resulting from programs, projects or activities developed under this Agreement, will be jointly owned by UFSCar and *Hochschule Osnabrück*. Such intellectual property rights, as well as other rights and duties of the Parties, shall be set forth in a further specific agreement or contract, which shall observe the relevant legislation.

VII. By signing this Agreement, *Hochschule Osnabrück* explicitly acknowledges that UFSCar features an innovation agency, which is in charge of managing said university's policy on innovation. As a consequence, any further result arising from the development of this Agreement, which may become property of both Parties, shall be communicated to UFSCar Innovation Agency, so as to execute the appropriate procedures to protect such result.

VIII. The Parties shall communicate each other about the generation of any new process and/or product able of being protected by intellectual property rights resulting from the development of programs, projects or activities hereunder.

IX. Provided that clauses on confidentiality stipulated in this Agreement are observed, both Parties are entitled to publish or present results from the development hereof. Any publication or presentation resulting from this Agreement shall mention the cooperation set forth herein, as well as duly protect proprietary information or intellectual property regarding those results or confidential information disclosed by either Party.

X. Any publication or presentation by any Party of any result jointly obtained under this Agreement requires the prior written consent from the other Party. Thus, the Party wishing to publish or present such results shall show the content of the publication or presentation to the other Party, which will give its consent or disallow the publication or presentation, along with the corresponding reasons, within sixty (60) days from the date

when it receives the content of the publication or presentation in an electronic document. In the event that such decision is not communicated within the abovementioned period, the publication or presentation of said document will be deemed authorized.

SECTION 6 – Duration, amendments and termination

This Agreement is valid as from the date of the last signature by both Parties and will remain in force for five (5) years. The duration hereof may be extended by means of a duly signed amendment.

Any amendment hereto shall be agreed in writing and signed by the authorized representatives of both Parties.

Any Party can terminate this Agreement at any time by giving the other Party a reasoned termination notice in writing at least three (3) months in advance, along with return receipt. In the event of termination hereof, eventually ongoing activities will be duly concluded.

SECTION 7 – Settlement of disputes

Questions and disputes arising from the interpretation or execution of this Agreement will be friendly settled by both Parties. In case an amicable solution is not possible, they shall jointly appoint a third party, natural person, to act as arbitrator.

Both Parties sign this agreement in four identical copies, two in Portuguese and two in English, to the same effect.

FEDERAL UNIVERSITY OF SÃO CARLOS

Prof. Dr. Ana Beatriz de Oliveira
Rector

São Carlos, São Paulo (Brazil), 19/12/2022

HOCHSCHULE OSNABRÜCK

Prof. Dr. Andrea Braun von Reinersdorff
Vice President and Dean of Faculty of Business Management and Social Sciences

Osnabrück, Lower Saxony (Germany), 17.1.2023

ANNEX A – Proposal/Work plan referring to the joint research project "What is the minimal important difference (MID) of outcomes measures related to urinary incontinence? A systematic review"

See proposal/work plan on the following pages.

Citation

Jordana Barbosa da Silva, Leticia Calixtre, Daniela von Piekartz, Patricia Driusso, Susan Armijo-Olivo. What is the minimal important difference (MID) of outcomes measures related to urinary incontinence? A systematic review. PROSPERO 2022 CRD42022299686 Available from: https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42022299686

Review question

1. What are the most common methods to determine the MID estimates for outcomes related to urinary incontinency available in the literature?

2. What are the MIDs estimates available in the literature for the most commonly used outcomes related to urinary incontinency?

3. What is the credibility (i.e. methodological quality) of the studies that generated MIDs for outcomes related to urinary incontinency?

Searches

To conduct the present systematic review, the following five databases were consulted: MEDLINE (Ovid MEDLINE(R) ALL), Embase (Ovid interface), CINAHL PLUS with Full text (EBSSCOhost interface), Web of Science (Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI) and Scopus. The final version of the search included the principal terms for UI and MID and resulted in 1, 662 papers. However, 719 references were duplicated and were excluded. Therefore, the final number of papers included in the data screening was 943. No limits were applied on the databases for the date, language or publication status but conference abstracts were removed. Manual search will be performed after data extraction in order to look for relevant references.

Types of study to be included

Any study generating MID for UI outcomes (RCT and controlled trial, secondary analysis of clinical trials, cohort studies, cross-sectional studies and reliability, responsiveness and validity studies) will be included.

The following types of studies will be excluded, case report, reviews, systematic reviews, meta-analysis, commentaries, letters to the editor, conference papers, books chapter, protocol's registration, abstracts without full text, and animal's studies. However, reviews will be carefully looked for relevant references.

Condition or domain being studied

Urinary incontinence (UI) is defined as any loss of urine1. In the present systematic review, the International Society Continence definitions for stress, urgency and mixed urinary incontinence will be considered1:

• Stress urinary incontinence (SUI): urine loss that occurs with the increased in abdominal pressure such coughing, sneezing, exertion or physical exertion. Women usually present SUI when the urethral closure mechanism is poorly functioning in association with the weakness of the pelvic floor muscles42;

• Urgency urinary incontinence (UUI): loss of urine associated with urinary urgency (a sudden and strong urge to urinate). This dysfunction is associated to the inability to inhibit the detrusor muscles contraction42. The women can also complain about an increased in urinary frequency both day and night43;

• Mixed urinary incontinence: stress and urinary incontinence, concomitantly.

Participants/population

Population: Women more than 18 years old, with SUI (urine loss associate with coughing, sneezing, exertion or physical exertion) and/or UUI (loss of urine associate with urinary urgency, a sudden and strong urge to urinate) and/or MUI (both stress and urgency urinary incontinence); with diagnostic of UI according the results of a subjective interview or validated questionnaires that assess urinary symptoms or physical tests (pad-test, cough test or/and urodynamic).

Studies will be excluded if the aim was to analyze urinary symptoms of children or male incontinence; if they included only continent women and/or if authors analyzed only other pelvic floor dysfunctions (e.g., fecal and/or anal incontinence, pelvic organ prolapse, sexual dysfunctions).

Intervention(s), exposure(s)

Interventions: Studies will be included if they assessed any outcome measure relevant to UI. We are open to all constructs that could be related to UI such as quality of life and/or amount of leakage, pelvic floor muscles function (evaluated through by physical tests that include the vaginal palpation, dynamometry, vaginal cones, manometry, electromyography, imagining tools, urodynamic and/or urine stream interruption test) among others.

Comparator(s)/control

Not applicable.

Main outcome(s)

The primary outcome of this review will be the estimates of minimal important difference (MID) for outcome measures related to UI. The MID can be reported by distribution- and anchor-based methods as described in a previous study18. The methods available to measure MID are presented in Appendix 1. Moreover, UI can be identified by questionnaires or physical exams (e.i. cough test, pad test). The present systematic review will include studies that applied any tool or questionnaires or physical test that measures UI.

Additional outcome(s)

Not applicable.

Data extraction (selection and coding)

An excel form will be development exclusively for the present systematic review. Pilot testing and regular revision through discussions will be taken to standardize the DE form. One researcher will conduct the data extraction and organize the data on the excel form and a second researcher will review the extracted data for accuracy and completeness. In case of disagreement, a consensus meeting will be performed. If the two researchers do not reach a consensus, a third evaluator will make the final decision. Data extracted will be based on characteristics that include, but are not limited to article information; participants information; MID determination (e.g. analytical approach, sample size included in MID calculation, duration of follow-up (when applicable)); MID estimate (distribution- and/or anchor-based method; range of options/categories/values; the specific anchor applied during data collection, MID values); constructs evaluated (e.g. quality of life , pelvic floor function, urinary loss); tool description (value of the tool (e.g. categorical, ordinal, numerical); type (e.g. questionnaire or physical test); Other study characteristics (study design, number of groups, number of examiners, time between each assessment, type of randomization, number of assessments, blinded process, treatment characteristics if applicable (such as type of intervention, if the intervention was applied alone or combined, if the intervention was individual or in a group, duration of the whole treatment, number of sessions, percentage of compliance with the treatment, number of follow-ups, intervention fidelity); Results Summary (MID estimation, correlations between the outcome and anchor, precise of the MID (e.g. 95%CI/MID*100), time between baseline and follow-up, directions of both anchor and PROM, correlations of the PROM and the transition item during baseline and follow-up); Data Analysis; Conclusion; Limitations/Comments; and Recommendations. In the case of missing quantitative data, the authors of the primary studies will be contacted in order to get unreported data.

Risk of bias (quality) assessment

Two independent researchers will be responsible for conducting the credibility and methodological quality assessment independently.

The credibility of the MID estimate will be performed on studies that applied anchor-based methods by an instrument developed by Devji et al. composed by a 1) core criteria with five items related to anchor-based

methods and 2) four items related to the transition rating anchors.
The risk of bias of RCTs and controlled trials will be performed by the Cochrane Collaboration's tool for assessing the risk of bias of randomized trials, following the guidelines outlined in the Cochrane Handbook for Systematic Reviews of Interventions Version 5.1. The risk of bias of cross-sectional studies will be evaluated by the checklist proposed by the Joanna Briggs Institute (JBI).

Methodological studies evaluating any psychometric property (i.e. reliability, validity and responsiveness) will be assessed by completing the checklist for assessing the risk of bias proposed by the Consensus-based Standards for the Selection of Health Measurement Instruments (COSMIN).

To determine the level of agreement between reviewers, the kappa statistics test will be performed.

Strategy for data synthesis

Tables will be used to summarize findings and outcomes; and facilitate the analysis. The findings will be synthetized in a narrative (descriptive) synthesis. Data synthesis will be performed according to the type of UI (e.g. stress, urgency of mixed) and type of instrument that reported MID (questionnaires or physical test to assess leakage urine, quality of life and pelvic floor muscles function). The findings will also be summarized according to the risk of bias and the strength of the overall evidence will also be evaluated and synthesized according to the GRADE approach (see below for more details).

After data synthesis, we will plot all MID estimates based on anchor methods together by triangulation according to the recommendations published by Trigg and Griffiths50: I) to apply a credibility assessment tool to assess the correlation between the anchor and the outcome; II) to conduct the triangulate assessment by the inverse-variance using random-effects meta-analysis models. Therefore, we expect to define a single value for each instrument included in the present review, if we found evidence from multiple studies. We will perform the triangulation from multiple estimates arising from different studies by conducting a namely inverse-variance meta-analysis using random-effects models, which have been applied in previous systematic reviews28, 29.

If possible, a meta-analysis will be conducted using the RevMan 5 software (Review Manager (RevMan))51 or STATA software. The studies will be grouped according to the instruments that reported MID and the similarity between the comparison of the study groups. The effect size will be measured using the standardized mean differences for continuous outcomes and the 95% confidence intervals will be reported. The Index I^2 will be used to analyze the consistency between studies based on the assessment of heterogeneity. Heterogeneity will be classified as low (25%), moderate (50%) or high (75%) as recommended in the literarure;

Analysis of subgroups or subsets

Subgroups analyses will be done when feasible considering the type of urinary incontinence (e.g. stress, urge and mixed), credibility of MIDs, risk of bias and according the outcomes related to questionaries and physical tests.

Contact details for further information

Jordana Barbosa da Silva
jordanabsilva@gmail.com

Organisational affiliation of the review

Federal University of SÃ£o Carlos

Review team members and their organisational affiliations

Miss Jordana Barbosa da Silva. Federal University of SÃ£o Carlos
Dr Leticia Calixtre. Federal University of São Carlos
Daniela von Piekartz. University of Applied Osnabrück
Dr Patricia Driusso. Federal University of São Carlos
Dr Susan Armijo-Olivo. University of Applied Osnabrück; University of Alberta

Type and method of review

Systematic review

Anticipated or actual start date
01 June 2021

Anticipated completion date
31 July 2022

Funding sources/sponsors
CAPES

Grant number(s)

State the funder, grant or award number and the date of award

Financial code 001

Conflicts of interest

Language
English

Country
Brazil

Stage of review
Review Ongoing

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
MeSH headings have not been applied to this record

Date of registration in PROSPERO
21 January 2022

Date of first submission
21 December 2021

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

The record owner confirms that the information they have supplied for this submission is accurate and complete and they understand that deliberate provision of inaccurate information or omission of data may be

construed as scientific misconduct.

The record owner confirms that they will update the status of the review when it is completed and will add publication details in due course.

Versions

21 January 2022
21 January 2022

ANNEX B – Proposal/Work plan referring to the joint research project "Global prevalence of dysmenorrhea: a systematic review and metanalysis"

REGISTRATION IN PROSPERO

1. Review title

"GLOBAL PREVALENCE OF DYSMENORRHEA: A SYSTEMATIC REVIEW AND META-ANALYSIS"

2. Original language title

"GLOBAL PREVALENCE OF DYSMENORRHEA: A SYSTEMATIC REVIEW AND META-ANALYSIS"

3. Authorship

Guilherme Tavares de Arruda, Jordana Barbosa da Silva, Susan Armijo-Olivo, Cinthuja Pathmanathan, Patricia Driusso, Mariana Arias Avila

4. Background

Dysmenorrhea is a gynecological condition defined as menstrual pain of uterine origin more common among women of reproductive age [1]. The pain is usually located in the pelvic region or lower abdomen and is often accompanied by symptoms such as fatigue, mood swings, insomnia, nausea, headache and gastrointestinal discomfort [2].

Based on the pathophysiology, dysmenorrhea can be classified into primary (PD) and secondary (SD). PD is defined as spasmodic menstrual pain immediately before and/or during menstruation, without any associated pelvic affection; pain is believed to be caused by increased release of prostaglandins during endometrial desquamation, along with uterine muscle ischemia and hypoxia. On the other hand, secondary dysmenorrhea is associated with the presence of some pelvic affection, usually endometriosis and myomas [2].

Studies have reported the effect of pain on decreasing quality of life [3–5], limitation in physical and social activities [6] and presenteeism/absenteeism from school and work in women with dysmenorrhea [2,7]. Some women may avoid social contact and recreational activity, remain isolated at home, and diminish relationships with family and friends. Although there are no studies on the cost of treating PD, medical and surgical treatment for endometriosis-related dysmenorrhea has an effective cost of $100,000 per quality-adjusted life years gains [8]. This shows that dysmenorrhea is a global public health, social and economic problem.

Although the interference of dysmenorrhea on various aspects and quality of life of women is recognized, the prevalence of dysmenorrhea varies widely in the literature [9–11]. Thus, women

commonly do not report this problem to the health professionals, and therefore, the prevalence of dysmenorrhea is underestimated.

Four systematic reviews [9–12] have been conducted on the prevalence of dysmenorrhea. However, these reviews had some limitations. Although one [10] of the reviews did meta-analysis and assessed by country, dysmenorrhea was included along with other terms for pelvic pain, such as dysmenorrhea, dyspareunia and noncyclical pelvic pain, which may have limited the search for dysmenorrhea, and this review included studies prior to 2004. Other systematic reviews were limited to specific populations such as adolescents [11], Iranian women [12], and women in school or university [9]. In addition, the search period and selection of studies was not presented in one of the reviews [12] and the other two reviews [9,11] only included studies published in English. Thus, no comprehensive systematic review and meta-analysis with studies without limitation of language and women of all ages has been carried out on the prevalence of dysmenorrhea in the world. It is important to know the worldwide prevalence and divided by continent and countries of dysmenorrhea. In addition, current epidemiological data are needed to monitor the evolution of this problem in the world and also gather information to establish strategies to improve the quality of life of women with dysmenorrhea.

5. Aim

The aims of the present systematic review are:

- To systematically analyze and synthetize the literature on the global prevalence of dysmenorrhea.
- To determine the prevalence of dysmenorrhea by different continents and countries.
- When possible, to provide a (pooled) quantitative estimate of the prevalence of dysmenorrhea in the world by carrying out meta-analysis.

6. Anticipated or actual start date

2nd February, 2022

7. Anticipated completion date

December 20th, 2022

8. Stage of review at time of this submission

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes

Formal screening of search results against eligibility criteria	Yes	No
Data extraction	No	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

REVIEW TEAM DETAILS

9. Named contact

Mr. Guilherme Tavares de Arruda

10. Named contact email

gui_tavares007@hotmail.com

11. Named contact address

Rodovia Washington Luis, km 235 – SP-310; zip code: 13565-905

12. Named contact phone number

+55 55991360953

13. Organizational affiliation of the review

Federal University of São Carlos and University of Applied Sciences Osnabrück

14. Review team members and their organizational affiliations

Title	First name	Last name	Affiliation
Msc	Guilherme Tavares de	Arruda	Federal University of São Carlos
Msc	Jordana Barbosa	Silva	Federal University of São Carlos/University of Applied Osnabrück
MRes	Cinthuja	Pathmanathan	University of Colombo
PhD	Patricia	Driusso	Federal University of São Carlos
PhD	Mariana Arias	Ávila	Federal University of São Carlos
PhD	Susan	Armijo-Olivo	University of Applied Osnabrück/University of Alberta

15. Funding sources/sponsors

CAPES

16. Conflict of interest

None

17. Collaborators

None

REVIEW METHODS

18. Review question

1. What is the global prevalence of dysmenorrhea?
2. What is the difference between continents regarding the prevalence of dysmenorrhea?

19. CoCoPop elements

Co – Dysmenorrhea;

Co – Global prevalence between 2000 and 2022;

Pop – Women of any age.

This systematic review will include:

Studies whose primary aim was to assess the prevalence of dysmenorrhea (either primary or secondary), published between 2000 and 2022, without language restriction. Prevalence in cohort studies will be included at the end of the follow-up; Studies on menstrual characteristics, premenstrual syndrome, menstrual disorders, premenstrual dysphoric disorder, pelvic pain that reported the prevalence of dysmenorrhea separately; Studies that associated endometriosis, uterine myoma, polycystic ovaries and adenomyosis to dysmenorrhea. Studies of women with any kind of comorbidities as long as the ***primary aim of the study*** is to assess the prevalence of dysmenorrhea in this specific population.

This systematic review will exclude:

Studies available only as abstracts or event proceedings, literature reviews and book chapters; Case report, commentaries, letters to the editor, conference papers, protocol's registration, interventional (e.g., Intra Uterine Device, medication, oral or intravaginal contraceptive, hysterectomy, organ transplantation, acupuncture, ablation, bariatric surgery, mastectomy, tubal ligation or sterilization, assisted reproduction technology, etc.), qualitative study, clinical trials;

Animal or in vitro studies; In studies with more than one publication, the study with the smallest number of individuals will be excluded.

20. Searches

The search will be carried out in the databases Medline (Ovid), EMBASE, Web of Science, SciELO, CINAHL and LILACS. A manual search will be performed in the first 10 pages of Google Scholar. For each database, a search filter. The descriptors “dysmenorrhea”, “painful menstruation”, “pelvic pain” and “epidemiology” will be combined with their acronyms and used in a search filter for each database. We will also search the reference list of published systematic reviews of dysmenorrhea prevalence.

21. Url to search strategy

None

22. Condition or domain being studied

Dysmenorrhea is a gynecological condition defined as menstrual pain of uterine origin more common among women of reproductive age [1]. In this systematic review, we will consider:

- **Primary dysmenorrhea:** spasmodic menstrual pain immediately before and/or during menstruation, without any associated pelvic affection.
- **Secondary dysmenorrhea:** dysmenorrhea associated with the presence of some pelvic affection, usually endometriosis and myomas.
- **Dysmenorrhea (non-specific):** dysmenorrhea unclassified.

23. Primary outcome

Prevalence measured in absolute frequency and percentage, or prevalence, or standard error, or 95% confidence intervals, and country.

24. Secondary outcomes

25. Data extraction

Studies will be selected through Covidence. Data extraction, including type of dysmenorrhea, age, sample size, population, assessment of dysmenorrhea and study objective, will be performed manually in Microsoft Excel. The selection of studies and data extraction will be performed by two independent researchers. Data will be extracted on the prevalence of dysmenorrhea,

characteristics of the studied sample, country and study objective. In case of disagreement between reviewers, a third reviewer will be consulted. Data from studies that evaluated women with comorbidities and who underwent cesarean section will be analyzed separately.

26. Methodological quality assessment

The assessment of methodological quality will be carried out by Joanna Briggs Institute (JBI) Critical Appraisal Tools for cross-sectional study [13] by two independent researchers.

27. Strategy for data synthesis

Data will be analyzed by two independent reviewers in an Excel spreadsheet.

28. Data synthesis

The assessment of methodological quality will be carried out by Joanna Briggs Institute (JBI) Critical Appraisal Tools for cross-sectional study [13] by two independent researchers.

29. Analysis of subgroups or subsets

If possible, the analysis of subgroups will be performed considering different health conditions.

REVIEW GENERAL INFORMATION

30. Type of review

Systematic review related to prevalence.

31. Language

English

32. Country

Brazil, Germany

33. Other registration detail

None

34. Reference and/or URL for publishes protocol

None

35. Dissemination plans

The finding of this systematic review will be submitted for peer-reviewed journal publications, international conferences for the consideration of oral and poster presentations. In addition, the results will be presented to clinicians, colleagues, and students interested in this area.

36. Keywords

Dysmenorrhea, Prevalence, Epidemiology

37. Details of any existing review of the same topic by the same authors

None

38. Current review status

Ongoing

39. Any additional information

None

40. Details of final report/publications

None

41. Relevance of the project

The results of the current project may help health professionals and public organizations to know the global prevalence of dysmenorrhea, as well as knowing regions that should receive greater attention on public care for people with pain related to menstruation. Considering the prevalence of dysmenorrhea in some regions and the quality of the evidence, it is possible that more studies are needed with better methodological quality to fill the gap in the literature on the topic.

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ANNEX C – Proposal/Work plan referring to the joint research project "Prognostic factors of the urinary incontinence: a systematic review"

REGISTRATION IN PROSPERO

1. **Review title**

   "Prognostic factors of the urinary incontinence: a systematic review"

2. **Original language title**

   "Prognostic factors of the urinary incontinence: a systematic review"

3. **Authorship**

   Jordana Barbosa da Silva; Leticia Bojikian Calixtre; Guilherme Tavares de Arruda; Patricia Driusso; Susan Armijo-Olivo

4. **Background**

The worldwide prevalence of urinary incontinence (UI) is estimated to be 8.7%. Numerically, it represents 421 million people affected by urinary symptoms, which is larger than the population of the United States of America[1]. It seems that women are more affected by UI than men, as 1 in 4 women will be incontinent at some point in life[2,3]. This is a concerning factor, as the presence of UI is significantly associated with an increased in mortality rate[4] and also depression, embarrassment and social isolation [5,6].

Nonetheless, previous studies reported an association between urinary symptoms severity and quality of life[7–9]. Authors reported that even a very small urine leakage may cause a significative impact on the quality of life[8]. However, prior to the increase of severity symptoms, conservative approaches of prevention can help to reduce the UI prevalence and severity rate, regardless of the woman's age.

Prognostic studies aim to investigate the relationship between the occurrence of a certain outcome of interest and the predictors of the clinical profile in a population that already has the disease and/or condition of interest[10]. The outcomes of this type of study result in an understanding of the progression of a certain disease, which can result in actions to limit this progression[11]. From the analysis of these studies, it is possible to classify the variables that can reduce or settle the presence of possible dysfunctions[12], which can contribute to the decision-making process of health professionals during the management of patients[13]. Besides that, in clinical practice, by identifying the variables associated with UI, the physiotherapist can encourage the active participation of women, in order to make them autonomous in relation to the management of their own health, assuming that the patient adapts behaviors based on the previous health education, in order to

eliminate the risks inherent to the increase in the severity of the dysfunction and/or to prevent the onset of the symptom[14]. One possible way to apply this strategy is to direct attention to modifiable factors, such as changes in lifestyle habits[15] (i.e. change in diet, smoking cessation, regular physical activity, weight reduction, among others)[16].

Prognostic factors for UI can also be identified as possible covariates to be controlled in investigative research, such as randomized and controlled clinical trials, in order to allow the researcher to balance the presence and/or absence of variables between the participants included in control and intervention groups. This bias control strategy can be used to minimize differences in the prevalence of prognostic factors between groups[15,17].

However, it is still inconclusive how modifiable and non-modifiable factor may influence the severity of UI. Most part of the previous reviews published in literature reported only the risk factors associated with UI[18–25]. Only a single systematic review aimed to reported the presence of all prognostic factors in the literature, related to UI[26]. However, authors limited the searchers only to papers published in English language and had not performed a meta-analysis. In addition, the previous systematic review was published in 2016, which is equivalent a five years ago.

Therefore, the results of the present project will contribute to the scientific dissemination of the assessment and management of UI in women. It is expected to synthesize evidence regarding the presence of prognostic factors associated with UI and encourage further scientific research that seeks to fill possible gaps related to the increase of UI severity. Our results may encourage researchers and clinicians to incorporate the assessment of factors associated with UI into their routine care, as well as the implementation of new practices that could result in and reduce the severity of this dysfunction in women.

5. Aim

The aims of the present systematic review are:

1. To identify and synthesize all the prognostic factors related to the severity of UI available in the literature;
2. To summarize the odds related to the UI severity according the prognostic factors;
3. To compare the odds of the severity of UI between modifiable and non-modifiable variables.

6. Anticipated or actual start date

March 8th, 2021

7. Anticipated completion date

December 31th, 2021

8. Stage of review at time of this submission

Review stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	No
Risk of bias (quality) assessment	No	No
Data analysis	No	No

REVIEW TEAM DETAILS

9. Named contact

Mrs. Jordana Barbosa da Silva

10. Named contact email

jordanabsilva@gmail.com

11. Named contact address

Rodovia Washington Luis, km 235 – SP-310; zip code: 13565-905

12. Named contact phone number

+49 15752852653

13. Organizational affiliation of the review

Federal University of São Carlos and University of Applied Sciences Osnabrück

14. Review team members and their organizational affiliations

Title	First name	Last name	Affiliation
Msc	Jordana Barbosa	Silva	Federal University of São Carlos/University of Applied Osnabrück
PhD	Leticia	Calixtre	Federal University of São Carlos
Msc	Guilherme	De Arruda	Federal University of São Carlos
PhD	Patricia	Driusso	Federal University of São Carlos

PhD Susan Armijo-Olivo University of Applied Osnabrück/University of Alberta

15. Funding sources/sponsors

CAPES

16. Conflict of interest

None

17. Collaborators

None

REVIEW METHODS

18. Review question

1. What are the prognostic factors associated with female urinary incontinence?
2. What are the odds for UI according to the prognostic factors?
3. Is there a difference between the odds for UI according the prognostic factors considered non-modifiable and modifiable?

19. PICO elements

P – Women more than 18 years old with stress urinary incontinence and/or urgency urinary incontinence and/or mixed urinary incontinence;

I – Prognostic factors associated to UI;

C – Not applicable;

O –Severity of UI (improving or worsening symptoms);

S – Cohort studies that generated odds for severity of UI (retrospective and prospective longitudinal studies).

This systematic review will include studies involving:

Population: Women with more than 18 years old, with SUI (urine loss associate with coughing, sneezing, exertion or physical exertion) and/or UUI (loss of urine associate with urinary urgency, a sudden and strong urge to urinate) and/or MUI (both stress and urgency urinary incontinence).

Studies will be excluded if the aim was to analyze urinary symptoms of children or male incontinence; if they included only continent women and if authors analyzed only other pelvic

floor dysfunctions (i.e. fecal and/or anal incontinence, pelvic organ prolapse, sexual dysfunctions); if authors included pregnant women or postpartum women until 1 year in their analysis, if they included women continent and analyzed the risk factors for UI, if they analyzed predictive factors (i.e., any intervention related to the management of UI symptoms).

Interventions: Studies will be included if they assessed any prognostic factor, that can be classified as modifiable and non-modifiable.
Papers will be excluded if they aimed to analyze the risk factor of UI, if they tried to analyzed the prognostic of UI before or after any intervention (i.e., surgery, conservative treatment).

Outcomes: This review will include studies that reported the odds of UI severity in incontinent women. A detailed description of the outcomes is described below.

Designs: Cohort studies that generated odds for severity of UI (retrospective and prospective longitudinal studies). The following types of studies will be excluded: RCTs, controlled-trials, case report, cross-sectional, reviews, systematic reviews, meta-analysis, commentaries, letters to the editor, conference papers, books chapter, protocol's registration, abstracts without full text and animal's studies.

20. Searches

To conduct the present systematic review, the following five databases were consulted: Medline (Ovid MEDLINE(R) ALL), Embase (Ovid interface), CINAHL PLUS with Full text (EBSSCOhost interface), Web of Science (Indexes=SCI-EXPANDED, SSCI, A&HCI, ESCI) and Cochrane. The final version of the search included the principal terms for UI and prognostic factors. No limits were applied on the databases for the date, language or publication status but conference abstracts were removed.

21. Url to search strategy

None

22. Condition or domain being studied

Urinary incontinence (UI) is defined as any loss of urine[27]. In the present systematic review, the International Society Continence definitions for stress, urgency and mixed urinary incontinence will be considered[27]:

- **Stress urinary incontinence:** urine loss associate with coughing, sneezing, exertion or physical exertion;
- **Urgency urinary incontinence:** loss of urine associated with urinary urgency (a sudden and strong urge to urinate);
- **Mixed urinary incontinence:** stress and urinary incontinence, concomitantly.

23. Primary outcome

The primary outcome of this study will be the prognostic factors for the outcomes related to the severity of UI. The present systematic review will include studies that provided any description of odds related to the UI severity after statistical analysis.

24. Secondary outcomes

The following secondary outcome can be anticipated and is the following: tools available to assess the severity of UI. In the present systematic review, will be include studies that applied any tool or questionnaires that measures the primary outcome. A brief description of the secondary outcome is following:

1) **Tools applied to assess the UI severity**: The severity of UI can be measured by different tools. In the literature, it is possible to find studies that applied questionnaires (i.e. Incontinence Severity Index)[28] and also physical tests and exams (i.e., pad test and urodynamics)[8,29] to identify the presence of the symptom in different populations. Our aim in analyzing this secondary outcome is to reported which tool is available to measure the UI severity according to the evaluation of a prognostic factor. Recommended tools to assess the UI severity include bladder diary, pad test and the Patient Perception of Bladder Condition and Urogenital Distress Inventory. Alternative tools that can be applied to assess the impact of the severity of UI in quality of life are the following: Bristol Female Lower Urinary Tract Symptoms Short Form, International Consultation on Incontinence Questionnaire-Urinary Incontinence Short Form, Incontinence Impact Questionnaire, Incontinence Quality of Life Questionnaire and King's Health Questionnaire[30].

25. Data extraction

Study selection: One researcher will search the databases cited above and will compiled them into the software ENDNOTE. Sequentially, the researcher will import them to Covidence (www.covidence.org), which will be used during the screening process. Two

researchers will evaluate the studies' eligibility according to inclusion and exclusion criteria development in three sequential evaluation phases: (I) analysis of titles; (II) evaluation of the abstracts; and (III) analysis of full papers. The selection of the studies will be done independently by two researchers that will be blinded to each other's decision. In case of disagreement, a consensus meeting will be performed. If the two researchers did not reach a consensus, a third evaluator will make the final decision. A flowchart will be organized according to the PRIMA guidelines to report the results of the selection process.

Data extraction (DE): An excel form will be development exclusively for the present systematic review, so the researchers can extract data from the primary studies. Pilot testing and regular revision, discussions and comparison will be taken to standard the form during data extraction. To optimize this process, the drop-down Excel's menus will be used where applicable to contribute to the consistency of data extracted. One researcher will conduct the data extraction and organize the data on the excel form and a second researcher will review the extracted data. Reviewers will be instructed about the process, in order to make it consistent. In case of disagreement, a consensus meeting will be performed. If the two researchers did not reach a consensus, a third evaluator will make the final decision. Data extracted will be based on characteristics that include, but are not limited to **article information** (name of the first author, year of publication, language, funding, country where the study was conducted and ethical approval); **participants information** (e.g. population age, body mass index, ethnicity, diagnosis, tool for the diagnosis, parity); **study information** (e.g. main aim, study design, sample size); **prognostic information** (e.g. type of the variable analyzed, duration of follow-up or cohort, type of test applied during the statistical analysis, numerical variable related to the odds for UI) **Outcomes** (e.g. severity of UI, number of assessments); **Secondary outcomes** (e.g. tool applied to identify the severity of UI); **Results Summary; Data Analysis; Conclusion; Limitations/Comments; and Recommendations**. In the case of missing quantitative data, the authors of the primary studies will be contacted in order to get unreported data.

26. Methodological quality assessment

Two independent researchers will be responsible for conducting the credibility and methodological quality assessment independently.

The risk of bias of cross-sectional studies will be evaluated by the Quality in Prognosis Studies (QUIPS), composed by six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, statistical analysis and reporting. Each

domain has multiple items that are classified separately and are classified in high, moderate and low risk of bias[31].

If there is any disagreement between reviewers, a consensus meeting will be schedule. A third person will be asked for input if the consensus cannot be reached and will make the final decision.

To determine the level of agreement between reviewers, the kappa statistics test will be performed and will be classified the researchers as excellent agreement (0.93-1.00), very good agreement (0.61-0.80), good agreement (0.41-0.60), fair agreement (0.21-0.40), slight agreement (0.01-0.20), poor agreement (0.00) or less were considered to have no agreement, according to Byrt[32].

27. Strategy for data synthesis

Tables will be used to present the studies' details, summarize findings and outcomes; and performed analysis. The findings will be synthetized in a narrative (descriptive) synthesis. Data synthesis will be performed according the type of UI (i.e., stress, urgency of mixed). The findings will also be summarized according the methodological assessment and the strength of the overall evidence will also be evaluated and synthesized according to the GRADE approach (see below for more details).

After data synthesis, we will plot the estimates of the odds of UI severity based on the triangulation method, according to the recommendations published by Trigg and Griffiths[33]. Therefore, we expect to define a single value for the prognostic analysis related to the increased of UI severity, if we found accumulative evidence from multiple studies. We will perform the triangulation from multiple estimates arising from different studies by conducting a namely inverse-variance meta-analysis using random-effects models, which have been applied in previous systematic reviews[34,35]. This calculation will only be possible if authors from the included studies reported sufficient data for analysis.

If possible, a meta-analysis will be conducted using the RevMan 5 software (Review Manager (RevMan))[36]. The studies will be grouped according to the instruments that reported the odds for prognosis of UI severity and the similarity between the comparison of the study groups. The effect size will be measured using the standardized mean differences for continuous outcomes and risk ratios will be used for dichotomous results, and the 95% confidence intervals will be reported. The Index I^2 will be used to analyze the consistency between studies based on the assessment of heterogeneity. Heterogeneity will be classified as low (25%), moderate (50%) or high (75%)[37].

28. Data synthesis

To evaluate the quality of the body of the evidence, we will use the Grades of

Recommendation, Assessment, Development and Evaluation (GRADE), considering the following domains: study design, risk of bias, inconsistency of results, indirectness, imprecision (insufficient data) and bias of the publication. The quality of the evidence will be classified as high, moderate, low, and very low, according to GRADE[38,39].

29. Analysis of subgroups or subsets

Subgroups analyses will be done when feasible considering the type of urinary incontinence (e.g. stress, urge and mixed) and according the variables classified as modifiable and non-modifiable.

REVIEW GENERAL INFORMATION

30. Type of review

Systematic review related to prognostic factors

31. Language

English

32. Country

Brazil, Germany

33. Other registration detail

None

34. Reference and/or URL for publishes protocol

None

35. Dissemination plans

The finding of this systematic review will be submitted for peer-reviewed journal publications, international conferences for the consideration of oral and poster presentations. In addition, the results will be presented to clinicians, colleagues, and students interested in this area.

36. Keywords

Urinary incontinence, Prognosis, Women's Health

37. Details of any existing review of the same topic by the same authors

None

38. Current review status

Ongoing

39. Any additional information

None

40. Details of final report/publications

None

41. Relevance of the project

The results of the present project may help health professionals of clinical and research practice to understand the progression of UI, which can also reflect in new practices to reduce the rate of urinary symptoms that can be considered severe. This type of result can contribute to the decision-making process of health professionals during the management of patients with UI[13].

Considering the variables that may increase the severity of UI, the physiotherapist can encourage the active participation of women by health education strategies, in order to make them autonomous in relation to the management of their own health, to eliminate the risks inherent to the increase in the severity of the dysfunction[14].

It is expected to synthesize evidence regarding the presence of prognostic factors associated with UI and encourage further scientific research that seeks to fill possible gaps related to the increased of UI severity.

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ANNEX D – Proposal/Work plan referring to the joint research project "Immediate effects of cervical spine motor control and aerobic exercise on individuals with orofacial and neck pain: a randomized clinical trial"

FEDERAL UNIVERSITY OF SÃO CARLOS
CENTER FOR BIOLOGICAL AND HEALTH SCIENCES
PHYSIOTHERAPY DEPARTMENT
GRADUATE PROGRAM IN PHYSIOTHERAPY

INTERNSHIP DOCTORATE RESEARCH PROJECT (CAPES/Print)

IMMEDIATE EFFECTS OF CERVICAL SPINE MOTOR CONTROL AND AEROBIC EXERCISE ON INDIVIDUALS WITH OROFACIAL AND NECK PAIN: A RANDOMIZED CLINICAL TRIAL

ACUTE EFFECTS OF NECK MOTOR CONTROL AND AEROBIC EXERCISES IN INDIVIDUALS WITH OROFACIAL AND NECK PAIN: A RANDOMIZED CLINICAL TRIAL

LUIZ FELIPE TAVARES

ADVISOR: Prof. Dr. Ana Beatriz de Oliveira
CO-ADVISOR: Prof. Dr. Leticia Bojikian Calixtre
SUPERVISOR Overseas: Prof. Dr. Susan Armijo-Olivo

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SUMMARY

Musculoskeletal disorders are some of the world's most costly health problems and leading causes of disability. Among them, orofacial and neck pain are highly prevalent among the general population. Treatment of the cervical spine by motor control exercises of the neck muscles can decrease painful symptoms related to orofacial and neck pain. On the other hand, aerobic exercise is known to have direct benefits in reducing pain, and improving quality of

life and mental health in patients with different chronic conditions. Decreases in pain levels are observed from 8 to 12 weeks of exercise of various types, but a single session of exercise can cause the effect of exercise-induced hypoalgesia (EIH), a phenomenon that has been widely studied in recent years. There is limited evidence evaluating EIA immediately after either motor control or aerobic exercise in people with chronic musculoskeletal pain, and in particular in individuals with orofacial and/or neck pain. Traditionally, health professionals use drugs as the first form of treatment and often underestimate the effect of physical activity in combating chronic pain, disregarding the immediate effects of exercise as a treatment option with few adverse effects that can decrease pain severity and functional capacity in patients with chronic pain. Studies investigating the acute and chronic effects of physical exercise in individuals with orofacial and neck pain are necessary and currently scarce. The main objective of this proposal is to evaluate whether a single session of motor control exercises for the cervical spine or aerobic exercise is able to cause exercise-induced hypoalgesia, identified by a reduction in pain intensity and an increase in pain pressure threshold (PPT) and pain pressure tolerance (PPT), in individuals with orofacial and neck pain. This study will be conducted at the University of Applied Sciences, Osnabruck (Germany), in partnership with Prof. Susan Armijo-Olivo, who represents a reference in the investigation of orofacial and cervical dysfunctions. This proposal also includes the analysis of data from a randomized clinical trial (RCT) that is currently being carried out at the Federal University of São Carlos, whose protocol and subject matter are similar to the sandwich Ph.D. proposal. It is believed that the development of this study plan will contribute to the greater success of interventions aimed at the treatment of such dysfunctions with complex and multifactorial factors and symptoms. In addition, the opportunity to do an internship abroad will provide the candidate with a unique opportunity to further develop his academic and scientific potential.

SUMMARY

1. INTRODUCTION

Musculoskeletal disorders, including orofacial and neck pain, are some of the world's most costly health problems and leading causes of disability.[1] Orofacial pain (OFP) is a term that embrace different conditions such as temporomandibular disorders (TMD, headaches, and associated disorders. Individuals with TMD have pain and disability as their main symptoms.[2] The worldwide prevalence data of TMD is inconsistent, ranging from 10% to 60%.[3–5] TMD contributes to a large part of public health expenses[6] due to their disabling impact, compromising the quality of life of affected individuals.[4] Neck pain, on the other hand, according to the 2010 *Global Burden of Disease*, is the fourth leading cause of years lost to disability.[7] About half of all individuals will experience an episode of neck pain during their lifetime. Neck pain is a complex condition, in which the association of individual, ergonomic, sociocultural, and psychosocial risk factors contribute to its occurrence and chronicity.[8] About 70% of TMD patients also have complaints related to the cervical spine.[9] Thus, treatment of the cervical spine by means of neck muscle exercises may reduce the painful symptoms related to TMD[10]and neck pain.[11,12] There is evidence that specific neck training using motor control exercises may reduce the risk of neck pain recurrence and may improve reduced muscle strength, endurance, altered range of motion and motor control, as well as potentially work on better abnormal brain connectivity observed in patients with chronic neck pain.[13]

On the other hand, it is known that aerobic exercise has direct benefits in reducing pain in chronic patients, improving quality of life and mental health of people with various pathologies such as fibromyalgia, obesity, depression, headaches, and orofacial pain,[14] and that its mechanism of action is potentially based on the release of endogenous opioids.[15] However, there is little evidence in the literature about the effects of aerobic exercise on pain in people with TMD and neck pain.[14,16] There are two clinical trials being developed to answer this research question at the moment, one by the present research group in Brazil, and the other by Professor Susan Armijo-Olivo's research group in Germany.

Exercise is widely recommended to treat a variety of chronic conditions, including painful conditions. Decreases in pain levels are observed from 8 to 12 weeks of exercise treatment, however a single session may cause the effect of exercise-induced hypoalgesia (EIH), a phenomenon that has been widely studied in recent years,[17–20] and represents the decrease in sensitivity to painful stimuli induced by exercise. The EIH may occur by several mechanisms, such as activation of the opioid and cannabioid systems, release of hormones and/or neurotransmitters in response to induced stress, changes in the cardiovascular system, and pain modulation by the central nervous system.[21]

Studies evaluating the effects of aerobic or resistance exercise on IEA in people with chronic musculoskeletal pain were found to be limited (in quantity and quality) and therefore there is low quality of evidence and uncertainty in their risk of bias.[17] One review study noted a trend toward impaired pain inhibition in patients with orofacial pain using the temporal summation test, but the estimate of the total effect size was not robust, indicating that variations in the protocols of the primary studies may have influenced the test responses, explaining the conflicting results.[19] Another recent systematic review pointed out that several studies have been conducted verifying the acute effects of exercise in different chronic conditions, however the minority used a control group design.[21] In addition, the number of studies investigating EIH in individuals with orofacial and/or neck pain is scarce.

Traditionally, health professionals use drugs as the first form of treatment and often underestimate the immediate effects of physical activity in managing chronic pain,[22] disregarding the immediate effects of exercise as a treatment option with few adverse effects that can decrease pain severity and functional capacity in patients with chronic pain.[15] Thus, it becomes important to determine how a *single bout of exercise* affects pain in people with chronic pain, as this may influence their adherence to exercise training. The inclusion of a multimodal treatment, which includes aerobic fitness along with strength exercises has significantly improved the functionality of people with pain. Thus, personalized exercise can ensure a significant improvement in patient compliance and motivation and is necessary for individuals with chronic pain.[23] Due to the similarity in the symptoms of individuals with orofacial and neck pain, researches investigating the acute and chronic effects of physical exercise in this population are necessary and currently scarce.

2. PROPOSAL GOALS

1. To evaluate whether a single session of motor control exercises for the cervical spine, or aerobic exercise is able to cause exercise-induced hypoalgesia (EIH), identified through reduced pain intensity and increased Pressure Pain Threshold (PPT), and Pressure Pain Tolerance (PPT) in individuals with orofacial and neck pain .
2. Analyze the data from the study "Additional effects of aerobic exercise to cervical exercises on pain in women with TMD", developed in Brazil, and compare its results with those of a similar study being developed in Germany.

3. METHODS

Study 1. exercise-induced analgesia in patients with orofacial pain

3.1 Study design

This is a randomized controlled clinical trial that will be conducted at the University of Applied Sciences Osnabruck, Germany. This study will be part of an umbrella project and will include subjects recruited from a larger study already registered at *clinicaltrials.gov (NCT05232604).*

3.2 Participants

Subjects will be between 18 and 60 years of age, diagnosed with chronic nonspecific neck pain (as described by the IASP) and/or diagnosed with temporomandibular dysfunction according to the *Diagnostic Criteria for Temporomandibular Disorders - DC/TMD*,[24] both diagnoses will require a moderate or severe baseline pain score of 30mm or greater using a 100mm Visual Analog Scale. Subjects with severe pathologies (red flags) related to neck pain, reporting comorbidities (e.g. fibromyalgia); having been diagnosed with psychiatric disorders; having received therapy within 3 months prior to study entry; having contraindications to MRI scanning will be excluded. all patients will answer anamnestic questionnaires to assess readiness to exercise. The Central Sensitization Inventory (CSI) recommended for chronic pain patients will also be applied. This is an easy-to-apply self-report questionnaire that tracks and assesses symptoms related to central sensitization.[25]

3.3 Evaluation procedures and endpoints

To evaluate the acute effects of exercise protocols, subjects will be assessed before, immediately after, and 30 minutes after a single intervention session. Individuals with orofacial and/or neck pain may be randomly assigned to one of the treatment groups: cervical motor control exercises or aerobic exercise.

3.3.1 Intensity of orofacial and neck pain

The intensity of pain at the time of the evaluation will be measured by means of the Visual Analog Scale (VAS) in which the participants will rate the pain on an increasing scale from 0-100 millimeters, referring to the orofacial region and the cervical region, separately, considering that 100 indicates the "worst imaginable pain.

3.3.2 Quantitative sensory testing

Pressure Pain Thresholds (PPL): The PPL will be defined as the minimum pressure that induces pain or discomfort. This will be done in the masticatory and neck muscles using a calibrated algometer following the protocol described in Silveira et al.[9] Because these muscles are the most prone to pain in this population.[9] The masseter (1 cm superior and 2 cm anterior to the mandibular angle), anterior temporalis (2 cm above the zygomatic arch, sternocleidomastoid (near its origin, 2 cm below the mastoid process) and upper trapezius (halfway between the C7 vertebra and the acromion) muscles will be evaluated bilaterally in the sitting position[9]. Measurements will also be taken in the muscle at a distance (belly of the tibialis anterior muscle[26–28]). The PPT measurements have been shown to have good to excellent inter- and intra-rater reliability (0.74 to 0.99). All measurements will be measured in Newtons (N), and higher values mean less pain sensitivity.

Temporal summation (ST): Participants will complete a mechanical temporal summation task involving a needle-like stimulator with a contact area of 0.2 mm in diameter. Stimuli will be applied separately to the dorsal surface of the middle finger and the upper trapezius region, with an interval between stimuli of 1s. Pain scores by VAS will be recorded after the first stimulus and also after the 5th stimulus. The difference between the maximum pain score of the 5 repeated stimuli and the single stimulus will be calculated as the final score.[29,30] ST for each participant and each test site will be calculated by subtracting the first stimulus mean from the final stimulus mean, also considering the right and left side mean.

3.3.3 Exercise-induced analgesia (EIA)

The AIE will be calculated by subtracting the post-exercise LDP values from the pre-exercise values, as proposed by McPhee et al.[20] After subtraction of the values, an increase in the thresholds will be considered as a positive analgesia response. The difference between the pre- and post-exercise values of the visual analog scales will also be considered.

3.3.4 Additional variable: the brain activity of individuals with neck pain*.

The project titled: "*How do localized neck Motor and Aerobic exercises influence Pain intensity, pain modulation, and Brain activity in patients with chronic Neck pain: A randomized controlled trial: The* ***MAPBraiN*** *Trial"* is under evaluation by the German funding agency, and if approved, will enable the collection of MRI data.

To collect variables related to pain processing, image scanning will be performed on a 3T Siemens MAGNETOM Skyra (Siemens, Erlangen, Germany) with a 32-channel head coil. Whole-brain data acquisition will

use a planar echo imaging sequence. Subjects will undergo electrocutaneous stimulation of the right upper trapezius muscle (midpoint between the C7 vertebrae and the acromion) that will elicit a moderate level of pain. Stimulation will be delivered using a DS8 model stimulator. This method has been used previously to evaluate brain-related changes in patients with neck pain.[31] Preprocessing and analysis of MRI variables will be performed according to recognized standards.

3.4 Intervention Protocol

Aerobic exercise group: The session will have a total duration of 60 minutes, and will be divided into three parts: warm-up, main exercise period, and cool-down. The training will be performed on a cycle ergometer. The intensity will be based on maximum heart rate (HRmax), heart rate reserve (HRres) and the subjective perception of effort (Borg Scale), which will be monitored. The HRmax will be calculated by the ramp protocol for the cycle ergometer and confirmed by standard formulas. The intensity of the aerobic exercise program will be targeted at moderate intensity (55-70% HRmax or 12-14 on the Borg scale) for the first 10 min to allow adaptation and then high intensity interval training (HIIT) (75-90% HRmax or 15-17 on the Borg scale) will be targeted for the remaining 20 min.

Localized neck motor control exercises (LNMCE): A one session of localized motor control of neck muscles, supervised by a physical therapist will be performed. This exercise protocol has been successfully tested in subjects with neck pain. Low load craniocervical exercises (head nods) will be performed in early stages (first 6 weeks) guided by visual feedback from a pressure unit. Higher load neck exercises will be performed in later stages (last 6 weeks). During the first month, subjects will receive 30-45 min of this protocol three times per week, in the second month twice per week, and in the third month once per week. This duration of treatment is commonly used in clinical settings and has proven sufficient to improve muscle function, and clinical and brain outcomes.

Control condition for EIH protocol: The evaluation measurements will be collected initially and after 30 minutes of rest on a stretcher, and during this time no intervention will be performed. This procedure will allow us to obtain a measure that represents the natural course of the variables during the same period as the intervention, allowing the subjects to be controls of themselves.

Thereafter, subjects will be assigned to treatment groups, based on a previously computer-generated sequence where the participant will perform 30 minutes of aerobic or cervical exercise or a control condition. In this way, it will be possible to compare the outcomes obtained at baseline (evaluation 1), at a second moment without intervention (evaluation 2), and after one of the interventions (evaluation 3).

3.5 Data Analysis

All analyses will be performed by the statistical program SPSS version 26. The Kolmogorov-Smirnov test will be used to verify the normality distribution of the data. Then, descriptive statistics will be performed to characterize the sample through the ANOVA test. The results will be presented as mean and standard deviation when parametric, or as median and interquartile range when the data distribution is not normal. A 95% confidence interval will be adopted, a $p < 0.05$ as a significant difference. To achieve the study objectives, comparisons will be made using the mixed-factor ANOVA test (2x3) intra (time factor - baseline, immediately after, and 30 minutes after) and between-subjects (group factor). If there is a significant interaction, Tukey's post-hoc test will be applied to see where the differences are. If the data are non-parametric, comparisons will be made using the Friedman test, considering the Wilcoxon test to detect where the differences are in the comparisons between the evaluations. Bonferroni correction for multiple comparisons will be applied. Effect sizes (EF) will be calculated by Cohen's d (large EF if >0.8; moderate, >0.5; small >0.2),[32] if parametric and by Cliff's Delta if the data are non-parametric.[33,34] Per-protocol and intention-to-treat analyses will be performed with the data from excluded subjects, through data imputation, keeping the last data collected.

Study 2. analysis and writing of the randomized controlled clinical trial developed in Brazil

The overall objective of the clinical trial being conducted at UFSCar is to identify the additional effects of aerobic exercise to cervical motor control exercises on pain in women with temporomandibular dysfunction. This study was registered and approved by the site ethics committee (CAAE: 53219021.0.0000.5504) and is ongoing, with an expected completion date of December 2022. The primary endpoints are pain intensity and neck disability. In addition, pain thresholds to masticatory and cervical muscle pressure, jaw function, quality of life, perceived change scale, otologic symptom intensity, and self-efficacy will be considered as secondary endpoints. Subjects are being randomized into two groups: one group with aerobic exercise and one group with motor control exercises for the cervical muscles. The intervention lasts from 30 minutes to 1 hour, twice a week and for a total period of 8 weeks, with *follow-up* evaluation 4 weeks after intervention, for a total of 12 weeks of study. The analysis of the data from this study will contribute to the knowledge about the additional effects of aerobic exercise as a new treatment option with few adverse effects for this population, so that these data can be compared with the study that has been carried

out in Germany, with a similar objective, to evaluate the effects of aerobic exercise in individuals with orofacial pain. The cervical motor control exercise protocol in the German study was based on the same protocol used in Brazil, and the aerobic exercise protocol uses a cycle ergometer, which is different from the treadmill used in the Brazilian protocol. Furthermore, the total intervention time of 12 weeks, with different evaluation times (2 weeks, 6 weeks, 12 weeks, and 3 and 6 months after the end of treatment), will allow us to see the influence of the different treatment protocols regarding intensity and duration in individuals with orofacial and neck pain.

4. Activity schedule

Table 1. Schedule of activities to be carried out during the development of the sandwich doctorate program.

Steps	Activities
1	Laboratory Familiarization
2	Literature review and scientific update
3	Summary and analysis of data from study 1 conducted in Brazil
4	Preparation and submission of manuscripts of study 1 conducted in Brazil
5	Conducting a pilot study 2 in Germany
6	Study 2 data collection
7	Processing, data analysis and discussion of the results of study 2
8	Presentation of partial results at scientific conferences of study 2
9	Preparation and submission of study 2 manuscript
10	Preparation of the final report

Steps	March April 2023		May June 2023		July August 2023		September October 2023		November December 2023		January February 2024	
1												
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5. Contribution of the syllabus to the promotion of teaching, training and learning

The realization of this study plan will bring a great contribution to strengthen the partnership already established between the Laboratory of Clinical and Occupational Kinesiology (LACO) of the Postgraduate Program in Physical Therapy at the Federal University of São Carlos and the research group of Professor Susan Armijo-Olivo, from the University of Applied Sciences Osnabruk - Germany, which represents a reference group in the investigation of orofacial and neck pain, as well as other topics relevant to Physical Therapy, focusing on studies of high methodological quality. Due to the increase of cases of individuals with orofacial and neck pain in recent years, this theme has been investigated with more attention, aiming to identify the possible factors related to this increase, especially among women, and the best forms of treatment, given the complexity of the symptoms. In addition, the internship abroad will provide the candidate with a unique opportunity to further develop his academic-scientific potential, with a group of researchers of reference in TMD research, who are already collaborating with our laboratory, resulting in impact publications in good journals in the field.

6. Potential for increasing the research and education network, with new techniques and partnerships, and wide dissemination of the results

The completion of this study plan will consolidate the partnership established between the research group to which the candidate belongs and Prof. Susan, as well as other national and international researchers who already cooperate with our research group. The studies developed will contribute to a better understanding of the behavior of pain in individuals with orofacial and cervical complaints, considering the multifactoriality of the symptoms. The joint findings (combining the research underway in Brazil with that of Germany) will increase the potential for dissemination of the results, both in scientific meetings, lectures, national and international conferences and through scientific articles, bringing opportunities for broad discussion and scientific advances about the management of orofacial and neck pain, enabling answers about the acute and chronic effects of physical exercise, whether localized or more global, and the development of new themes to be studied in the population with chronic pain.

7. Relevance for the scientific and technological development of the area in Brazil in the medium and long term

The realization of the study plan will contribute to the scientific and technological/clinical development of Physical Therapy in Brazil, especially in the management of patients with chronic pain related to the head and neck. The subject addressed in the studies still has important gaps regarding the effectiveness of physical exercises in controlling acute and chronic pain in individuals with orofacial and neck pain, as well as the effects of these non-pharmacological therapies on pain processing in the central nervous system. From the results obtained with this proposal, it will be possible to contribute to the national and international scientific knowledge about a subject that has been increasingly studied in the literature and that still needs to be better investigated (medium-term development). Moreover, the results found will contribute to a greater success of interventions aimed at the prevention and control of musculoskeletal symptoms in the head/neck region in men and women, considering physical exercise as a low cost tool, easy to access, and that provides other health benefits, such as reducing the demand in our single health system (SUS), allowing professionals inserted in the primary care system to emphasize and guide about the importance of this type of exercise in combating chronic orofacial and neck pain, and in improving quality of life and stimulating the independence of each individual (long-term development).

8. Relevance for the economic development and social welfare of Brazil in the medium and long term

Orofacial and neck pain are complex conditions, in which the association of individual, psychosocial, and sociocultural risk factors contribute to their occurrence and chronicity. Brazil is undergoing an accelerated population aging process; a higher prevalence of neck pain in middle-aged and elderly individuals highlights the need for prevention initiatives.[8] The impact of chronic pain on the economy is significant and includes costs related to treatment, decreased productivity, and missed work attendance. About five million out of 211 million Brazilians presented with neck pain in a study conducted in 2019,[8] and therefore greater investments in public health policies are needed to avoid individual and financial losses. The realization of the study plan will contribute to the economic development and social welfare in our country, since from the interpretation of the results obtained, we will be able to contribute in the medium and long term with planning interventions that seek to prevent and control pain in men and women, especially when considering a non-pharmacological treatment, of easy applicability, and with few adverse effects. The knowledge produced from this study may provide support for a new approach, both scientific and clinical.

9. Compliance with national and international ethical standards

The development of the study involving data collection in Germany will be in accordance with national and international ethical standards and will comply with the ethical policies of the University of Applied Sciences

Osnabrück and the University of Lübeck. The study will be conducted in accordance with the Declaration of Helsinki, and will be approved by the local Ethics Committee. In addition, the data from the clinical trial conducted in Brazil and to be analyzed in Germany have passed the local ethics and registration procedures. All volunteers have signed an informed consent form prior to their participation in the study.

10. Justification for the choice of destination HEI and supervisor abroad

The University of Applied Sciences Osnabrück, Germany, has a high reputation in the region as one of the largest universities of applied sciences in Lower Saxony. The university has an outstanding research orientation, with the approach of a "University of Applied Sciences". That is, the university is actively involved in society and sees research as an essential contribution to helping in practice to solve socially relevant issues. Prof. Dr. Susan Armijo-Olivo, a physiotherapist and world renowned researcher in the study of chronic pain, joined the university team in recent years from the University of Alberta in Canada. Due to the great affinity of the studies we have in progress, she is the best choice to develop this project and sandwich PhD program.

In addition, the applicant's doctoral project entitled "Physical therapy rehabilitation of patients with temporomandibular dysfunction: effect of manual therapy and cervical spine exercises on otologic symptoms and additional effect of aerobic training on orofacial pain" will continue to advance this line of research in the Laboratory of Clinical and Occupational Kinesiology (LACO). The candidate is currently participating in a reference course on systematic review writing taught by Prof. Susan, which has culminated in the candidate participating in four different review projects with international collaborations. Thus, we believe that the face-to-face period with Prof. Susan will bring even more contributions on this subject both nationally and internationally, since she represents a reference on the subject, with over 110 scientific publications, H-Index of 41, and over 7000 citations.

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