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DOI:
10.1136/bmjopen-2022-069327

Document Version
Publisher's PDF, also known as Version of record

Citation for published version (Harvard):
Asquini, G, Devecchi, V, Edoardo Bianchi, A, Borromeo, G, Tessera, P & Falla, D 2023, 'External validation of a clinical prediction tool for the use of manual therapy for patients with temporomandibular disorders: a protocol for a prospective observational study', *BMJ open*, vol. 13, no. 7, e069327. https://doi.org/10.1136/bmjopen-2022-069327

BMJ Open

External validation of a clinical prediction tool for the use of manual therapy for patients with temporomandibular disorders: a protocol for a prospective observational study

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To cite: Asquini G, Devecchi V, Edoardo Bianchi A, *et al*. External validation of a clinical prediction tool for the use of manual therapy for patients with temporomandibular disorders: a protocol for a prospective observational study. *BMJ Open* 2023;**13**:e069327. doi:10.1136/bmjopen-2022-069327

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2022-069327).

Received 18 October 2022
Accepted 21 June 2023

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ABSTRACT

Introduction Clinical guidelines recommend conservative treatment for the management of temporomandibular disorders (TMD), and manual therapy directed to temporomandibular structures is commonly applied to reduce pain and improve function. In a recent prospective study, we developed a clinical prediction tool based on an array of predictors to identify people with TMD who are likely to experience significant pain relief and functional improvements following a programme of manual therapies (MTP) applied to temporomandibular structures. The purpose of this study is to externally validate in a different sample (temporal validation) the prediction model obtained in the initial study.

Methods/analysis This observational prospective study will recruit a cohort of 120 adults with TMD from a Dental Hospital in Italy. The intervention will be an MTP consisting of four sessions (once per week) of manual therapy applied to temporomandibular structures. Candidate predictors included in the predictive model will be pain intensity during mouth opening, treatment expectations, number of pain locations, central sensitisation, TMD pain duration and maximal mouth opening. Outcome measures (i.e., pain intensity, functional improvement) will be collected before starting the MTP, after the last session and after 1 month (2 months from baseline). A reduction of pain intensity by at least 30% will be considered a good outcome. External validity of the prediction model will be evaluated after the last session by measuring its calibration, discrimination and overall fit. Additionally, the performance of the model will be evaluated considering the clinical outcomes collected 1 month after the last MTP session.

Ethics and dissemination Ethical approval was obtained from the Ethics Committee of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Italy. The results will be submitted for publication in a peer-reviewed journal, and the prediction model will be implemented in a web-based calculator to facilitate its use by clinicians.

Trial registration number NCT03990662.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ Compared with the development study, this validation study includes an additional follow-up-assessment, 2 months after the initial assessment.
⇒ The predictive variables included in the clinical prediction tool are reliable measures that can be easily evaluated during clinical assessment.
⇒ Although the external validation will be in a different sample, the lack of a control group and a long-term follow-up will limit the strength of the results.
⇒ The study could potentially generate a non-representative sample since patients will be excluded if they recieved treatment for their temporomandibular disorders 6 months before the study.

INTRODUCTION

Recent epidemiological evidence showed that approximately 30% of adults present with some clinical signs of temporomandibular disorders (TMD) and about 10% suffered from TMD-related pain, with a growing trend over the last decades.[1–3] People with TMD usually experience facial pain and limitations of jaw opening with a significant impact on quality of life, predominantly for those with chronic forms of TMD.[4 5] In addition, many people with TMD complain of neck and back pain or pain at other sites[6] thus, the prevalence of comorbid chronic pain conditions (e.g., chronic back pain, myofascial syndrome, chronic migraine headache) among those with TMD is high.[7] Over the last decade, several authors have investigated the aetiology of TMD revealing that it is a complex multifactorial process.[8 9] Considering the biopsychosocial model, numerous factors have been associated with TMD aetiology including psychosocial status and genetics.[8–10] As a result, current evidence suggeststhe need for a multidisciplinary approach for the management of TMD.[11 12]

Physical therapy is one of the most commonly used conservative treatments for managing TMD since it reduces pain, improves altered motor function and increases joint range of motion.[13–16] In particular, hands-on treatment such as manual therapy (MT) aims to restore joint mobility, mobilise or manipulate soft tissues and joints, thereby relieving pain.[17 18] MT targeted to the temporomandibular region significantly reduces pain in patients with TMD, even if the superiority of MT in comparison to other interventions (e.g., exercise or education) remains unknown.[19 20] It is often a challenge for manual therapists managing people with TMD to identify which treatment modalities are more likely to lead to a positive outcome because of the unclear origin of TMD and variability of clinical presentations. When managing patients with TMD, the clinician's choice of the best intervention for the patient is impacted by many considerations including the clinician's expertise and knowledge of the current evidence, professional principles and routines and clinical reasoning skills.[21] Clinical improvements can be enhanced by identifying patients who respond better to a specific intervention. Hancock *et al*, defined treatment effect modifiers as factors identifying subgroups of patients who show different responses to a particular therapeutic intervention.[22] Few studies have investigated predictors of pain reduction for people with TMD in response to a specific treatment.

In a recent prospective study, we developed a clinical prediction tool based on an array of predictors to identify people with TMD who are likely to experience significant pain reduction following a programme of manual therapies (MTP) applied to temporomandibular structures.[23] A pain intensity reduction equal to or greater than 30% was defined as a good outcome.[23] Our results showed that participants reporting pain intensity greater than 2 out of 10 during mouth opening, positive expectations of outcome following MT, pain localised in the craniocervical region and a low Central Sensitisation Inventory (CSI) score had significant pain reduction after four sessions of the MTP targeted to temporomandibular structures. Likewise, participants with a shorter pain duration and limitations in maximal mouth opening (MMO) showed greater functional improvements.[23] The purpose of this study is to externally validate the prediction model in a new cohort (temporal validation) of patients with TMD. Only after external validation, can a clinical prediction tool be confidently introduced in clinical practice.[22] If the performance of the clinical prediction tool in a new sample will be satisfactory, the knowledge gained from this validation study will facilitate clinical decision-making for manual therapists managing people with TMD, which will ultimately enhance patient outcomes.

This study aims to externally validate, in a different cohort of patients with TMD, the prediction model developed in a previous study investigating predictors of pain reduction following an MTP.[23]

METHODS AND ANALYSIS

Source of data

In a prospective observational study, a cohort of patients with a TMD diagnosis according to the diagnostic criteria for TMDs (DC/TMD) will be recruited at the Italian Stomatologic Institute (Milan, Italy).[24] This protocol is written following prediction model development and validation recommendations, reported in the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis statement.[25] Ethical approval has been received from the Ethics Committee of the Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico (acceptance no. '534_2019bis'). The study will be conducted in conformity with the Declaration of Helsinki. Baseline collection data will be completed before starting the treatment programme. The follow-up assessment will occur at the end of the fourth session of the MTP.[23 26] In the current study, we will also add a follow-up 1 month after the last MTP session to reduce the possibility that acute treatment effects influence the first follow-up assessment.

Setting and participants

Participants will be recruited from the Italian Stomatologic Institute (Dental Hospital in Milan, Italy) over a period of approximately 24 months. All eligible participants attending the Temporomandibular Joint (TMJ) Unit of the Italian Stomatologic Institute will be considered for recruitment until the sample size is achieved. In this validation study, we will recruit patients from the same setting and use the same eligibility criteria adopted in the development study.[23 26]

Eligibility criteria

Inclusion criteria: (1) age ≥18 years; (2) TMD diagnosis in agreement with the DC/TMD[14]; (3) no treatment received for their TMD in the last 6 months[23 26]; (4) ability to comprehend and use verbal and written Italian language; (5) mental capacity to provide informed consent.

Exclusion criteria: (1) TMD pain associated with rheumatoid or inflammatory arthritis (2) any physical (eg, facial paralysis, neurological disorders, neuropathic pain) or mental condition (eg, cognitive deficit, mental illness and/or disorders) that could potentially affect outcomes of the study; (3) participants starting another TMD treatment (eg, pharmacology, oral appliance, others) for the study; (4) taking medications potentially affecting neuromuscular function for reasons other than TMD; (5) malignancy; (6) pregnancy; (7) drug and/or alcohol addiction.

Recruitment

Based on data from our previous study, a period of approximately 24 months will be necessary to recruit at least 120 participants completing all phases of the study.[23 26] All patients with a potential TMD will be screened at the TMJ Unit of the Italian Stomatologic Institute. Two expert

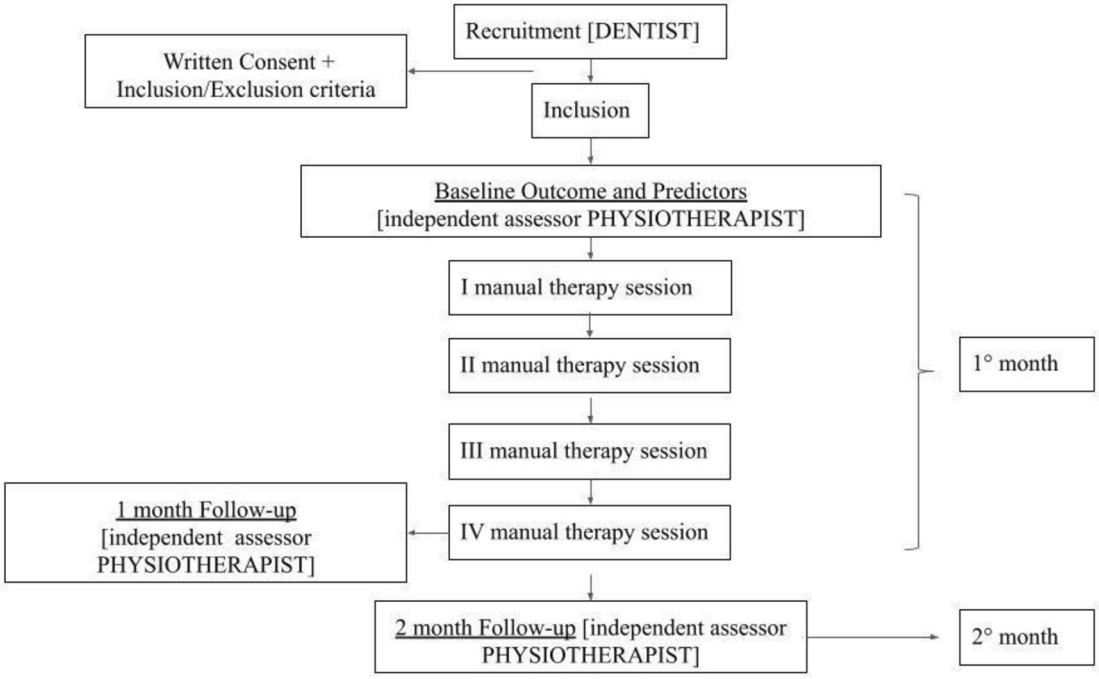

Figure 1 Participant flow through the study.

dentists with more than 10 years' experience in the management of TMD will apply the Italian version of the DC/TMD protocol to confirm the diagnosis.[27] Afterwards, if the eligibility criteria are met, they will explain the study process and provide the patient information sheet. Participants will be included in the study after giving their written informed consent. Later, baseline data will be obtained by a physiotherapist (independent assessor) with more than 5 years of experience in TMD management. The MTP will initiate in the same week. At the end of the last session (i.e., 1 month from baseline) and 1 month later (ie, 2 months from baseline), the same independent physiotherapist will assess participants to measure outcomes. Participant flow through the study is illustrated in figure 1.

Intervention

The intervention will be an MTP consisting of four sessions (once per week) of MT applied to the temporomandibular structures over a period of 4 weeks. This treatment plan was successful in the previous study and other authors adopted a similar treatment programme in comparable studies.[28–30] Further details are reported elsewhere.[23 26] This intervention is part of the usual care for patients with TMD attending the TMJ Unit at the Italian Stomatologic Institute. The two physiotherapists which will provide all treatments have more than 5 years of experience in the use of MT applied to temporomandibular structures and specific training on TMD assessment and management. These physiotherapists will not take part in participant recruitment or the assessments. MT techniques will be targeted only to temporomandibular structures and not to other areas (e.g., the neck), and will be selected based on individual clinical presentation and clinical reasoning.[31] During the MT sessions, any questions will be answered by providing explanations and promoting general advice. Participants will be withdrawn from the study if they start another treatment for their TMD (e.g., oral appliance) and/or seek treatment for an acute episode of pain at another site (e.g., neck pain).

Outcome measures

As described in the original development study, pain intensity will be the primary outcome since patients with TMD commonly identify pain as their main problem.[5] Pain intensity will be measured with the Visual Analogue Scale (VAS) as an average score of current pain, average pain in the last week and worst pain in the last week.[23 26] The VAS is a reliable and valid tool to measure pain intensity in intervention studies.[32 33] According to the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials recommendations about TMD, a pain VAS score reduction of at least 30% is clinically significant.[34] Consistent with our previous study, a VAS score reduction of ≥30% will be considered a good outcome.[23 26]

The Patient-Specific Functional Scale (PSFS) will be administered as a secondary outcome to assess for any functional modifications.[35 36] The PSFS is a valid, reliable and self-reported outcome measure evaluating functional change in patients with musculoskeletal disorders.[37–41] The same independent assessor will assess all outcome measures to reduce detection bias.[42] All outcome measures will be collected before starting the MTP, after the last session and after 1 month (2 months from baseline).

Predictive variables

In the development study, the prediction model included four predictors of pain reduction and two predictors of

functional improvement for patients with TMD.[23] The same independent physiotherapist assessor collecting outcomes will collect demographic variables (age and gender) and these predictors by following the standardised procedures described in the development study.[23]

Pain during maximal mouth opening

Pain intensity during maximal mouth opening will be measured via a Numerical Rating Scale (NRS).[43] Participants will be asked: 'Rate your pain by indicating the number that best describes pain during maximal mouth opening, with 0 meaning 'No pain' and '10' meaning 'Pain as bad as you can imagine'.[33 43] NRS is a reliable and valid tool to detect pain modification in clinical trials.[33]

Central sensitisation

Participants will be asked to complete the Italian version of the CSI.[44] Part A examines existing health symptoms through a 0–100 score for 25 items, each with 5 alternatives from 'never' (score 0) to 'always' (score 4).[45] Part B asks about seven previous diagnoses.[45] The CSI has adequate test–retest reliability and internal consistency in people with and without pain.[45] The Italian version of the CSI has an acceptable Cronbach's alpha (0.87).[44]

Treatment expectations

Treatment expectations will be measured by applying the same procedure used in our previous study.[23 26] Participants will report if they 'Completely disagree', 'Somewhat disagree', 'Neutral', 'Somewhat agree', 'Completely agree' with the following statement: 'I believe that manual techniques applied to my jaw will significantly help to improve my pain'. Only answers 'somewhat agree' or 'completely agree' are considered positive treatment expectations.

Duration of TMD pain

The duration of TMD pain will be collected in days and obtained from open hospital records and patient interviews.

Number of pain locations

Participants will complete a pain drawing representing spatial pain distribution through a body frontal and dorsal view chart. Further details of the body charts are reported in the (online supplemental file 1) of the published protocol in the previous study.[26] The pain reported in distinct body regions (e.g., head, jaw area, back area, pelvic area, neck area) will be collected as the number of painful sites.

Maximal mouth opening

MMO measurements will be in millimetres and calculated with a ruler in a neutral craniocervical position (e.g., sitting or supine) as suggested by the DC/TMD.[24 27] The measurement procedure is fully described in our previous study and follows the DC/TMD protocol.[23 24 26 27] MMO in a neutral craniocervical position is a reliable clinical measures and has good inter and intrarater reliability.[24 46]

Pain during MMO and the extent of MMO will be re-evaluated at the end of the treatment period to investigate if they may act as mediators in the relationship between the treatment and the outcomes of interest. Selected predictors and outcomes for each stage of the study are displayed in table 1.

Data handling

Participants' personal details will be anonymised with ID codes. Data will be stored on a password-protected computer accessible only by the principal investigators (GA). All data will be securely transferred to a server at the Centre of Precision Rehabilitation for Spinal Pain at the University of Birmingham, UK for statistical analysis when

Table 1 Summary of variables collected for each stage of the study

Variables	Baseline	1° follow-up	2° follow-up
Demographic characteristics			
Age	X	–	–
Gender	X	–	–
Predictors			
Pain during maximal mouth opening	X	X	X
Central Sensitisation Inventory	X	–	–
Treatment expectations	X	–	–
Duration of temporomandibular disorders pain	X	–	–
Number of pain locations	X	–	–
Maximal mouth opening	X	X	X
Outcomes of interest			
Visual Analogue Scale pain intensity	X	X	X
Patient-Specific Functional Scale	X	X	X

data collection is complete. According to Research Governance procedures, all data will be secured on a protected server for 10 years at the University of Birmingham.

Sample size

The sample size of this study will ensure that at least 10 events per predictor will be available in the subgroup with the lowest number of patients,[23 47] which we anticipate to be the non-responder group since it represented around 30% of the sample investigated in the development study.[23] For this reason, if the proportion of responders and non-responders will be similar to the development study, a total sample size of 120 patients will be reached. Otherwise, if the proportion of responders and non-responders will differ, it will be ensured that at least 40 patients for each subgroup will be present since four predictors are included in the model to validate. Moreover, the heterogeneity of the performance measures (e.g., c-statistic, calibration slope) will be provided to inform on the strength of the results as recommended in case of a limited sample size.

Statistical analysis

Predictors will be coded in accordance with the development study.[23 26] Specifically, pain during MMO will be dichotomised to distinguish between patients with no/minimal pain (VAS ≤2) or pain (VAS >2). A similar approach will be used for pain locations since we will separate patients experiencing localised pain (ie, temporomandibular and cervical region) from patients experiencing widespread pain (ie, other body regions). Although dichotomisation of continuous variables is usually discouraged for the risk of losing information, we identified cut-off values with clinical meaning to facilitate the interpretation of the model and reduce the risk of overfitting (if compared with data-driven cut-offs). Missing data will be handled using multiple imputation.[48]

Primary analysis

External validation of the prediction model obtained from the development study will be conducted in accordance with the three-step approach suggested by Debray *et al* and other guidelines.[25 49–51] First, demographic characteristics (ie, age, gender), predictors and the proportion of good versus poor outcomes will be considered to assess to what extent samples of the development and validation studies are related (ie, relatedness). Summary measures including mean, SD and range will be presented for each continuous variable and frequency for categorical variables. High similarity between development and validation samples will allow us to evaluate the reproducibility of the model and understand if a model performance similar to the one obtained in the development sample should also be expected in the validation sample.

Second, model performance in the validation sample will be evaluated by measuring calibration, discrimination and overall fit. Measure of calibration will include calibration-in-the-large and calibration slope. A calibration plot comparing the predicted/observed risks based on the predicted probabilities will be presented. Discrimination will be assessed by the area under the receiver operating characteristic curve which can range from 0.5 (no discrimination) to 1.0 (perfect discrimination). Overall fit will be measured using the R^2 Nagelkerke's.

The results from model validation will be interpreted by examining the similarity between development and validation samples and the measure of performance compared with the development study. If necessary, the prediction model will be recalibrated by updating the intercept and the individual regression coefficients. Based on the obtained results, the prediction model will be implemented in a web-based calculator which will allow the assessor to enter the values of individual predictors of a patient with TMD and compute the predicted probability of a good outcome after the MTP.

Secondary analyses

The same approach described for the primary analysis will be used to evaluate the performance of the models reported in the development study with pain change (percentage of baseline) and functional improvement as dependent variables. Moreover, pain intensity and PSFS score collected 1 month after the end of the treatment (time point not assessed in the development study) will be used to assess the role of predictors in the mid-term. The outcome pain will be obtained as an average across three measures describing the level of pain over the previous week, 24 hours and at the time of completing the online questionnaire. The same change from baseline (30%) will be used to identify patients with good or poor outcomes.

DISCUSSION

The multifactorial origin of TMD and different clinical manifestations often make it challenging for clinicians to identify the most suitable intervention for their patients. For people with TMD, the treatment choice is driven by evidence-based knowledge, clinical expertise, professional habits and clinical reasoning.[21] To facilitate this process, factors identifying patients who are likely to respond to a specific intervention are useful.[22] We previously developed a clinical prediction tool to recognise factors predicting a significant pain reduction after an MTP.[23] Pain intensity during MMO, positive expectations, pain localised to the craniocervical region and a low CSI score predicted significant pain reduction following the MTP.[23] Additionally, a shorter pain duration and limitations in MMO predicted greater functional improvements.[23] However, it is only after an external validation that a clinical prediction tool can be included in clinical practice with confidence.[22] If the clinical prediction tool is deemed valid (i.e., predicts response to treatment), it will facilitate manual therapists treating patients with TMD, ultimately contributing to improving patient outcomes and likely, health-related costs.

Quality assurance

People that have received TMD treatment 6 months before the study will be excluded. This choice may result in a selection bias by excluding participants with higher pain intensity. Consequently, the number of eligible and included participants (with withdrawal reasons) will be recorded to manage this possible limitation.

Patient and public involvement

The development of the research question occurred following conversations with patients. Patients will participate in interpreting and summarising results without being involved in data analysis and collection.

Ethics and dissemination

Ethical approval has been obtained from the Ethics Committee of the 'Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico' (acceptance no. '534_2019bis'). The principal investigator (GA) will immediately notify any potential adverse event to the ethics committee. As reported above, a web-based calculator will be developed from the prediction model to calculate the personalised predicted probability of a good outcome following an MTP. Findings from this study will be submitted for publication in a peer-review journal and presented at conferences.

Limitations

Although this validation study will recruit a different sample from the previous development study,[23 26] it remains a single site study performed in the same clinical setting by the same clinicians. In addition, people reporting TMD treatment 6 months before the study will be excluded to conserve adequate internal validity and diminish confounding bias, by resulting in a possible selection bias because of the exclusion of participants with higher pain levels. For these two reasons, external validation and generalisability of results will be reduced. Moreover, if the temporal validation confirms the prediction model, future research will be needed to strengthen the evidence by conducting a randomised control trial with longer follow-up.

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Contributors GA is a PhD student supervised by DF. GA and DF formulated the research question and study focus. GA drafted the initial version of the manuscript. DF, VD, AEB, GB and PT provided guidance on topic, methodology and analyses. All authors reviewed and commented on each draft of the protocol. All authors have approved the final manuscript. DF is guarantor.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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PREDICTORS OF PAIN REDUCTION FOLLOWING MANUAL THERAPY IN PATIENTS WITH TEMPOROMANDIBULAR DISORDERS: A PROTOCOL FOR A PROSPECTIVE OBSERVATIONAL STUDY

Supplementary file 1 - Candidate predictors

Demographical variables

Participants' demographic variables [age, gender, education] will be collected at baseline from open hospital records and patient interview.

Age

Age is a significant factor in TMD incidence and prevalence. Lipton et al. found different age-specific prevalence for face/jaw pain: 6.5% in aged 18-34, 5.0% in 35-54 years old, 4.0% in 55-74 years old and 3.9% in people > 74 year old, showing a prevalence reduction across the lifetime[1]. By contrast, data from the OPPERA study[2] showed a 40% increased risk for TMD among individuals aged 25-34 years and a 50% increased risk for TMD among individuals aged 35-50 years.

Gender

Women are 1.5-2 times more likely to develop TMD than men[3-5]. Currently, there is no study examining the extent of recovery from TMD in men and women. Nevertheless, gender is a significant factor to be considered.

Education

The National Centre of Health and Statistic (NCHS)[6] found that the differences in jaw pain prevalence among different educational groups are minimal. On the other hand, there is evidence that people with lower levels of education adopt maladaptive coping strategies, including a tendency to catastrophize about their pain[7]. As a result, the education levels will be collected as candidate predictor of outcome by classifying education into three categories: basic education, intermediate education and university-level education.

General health variable

EuroQol Five Dimension Scale, 5-level [EQ-5D-5L]

According to Kapos et al.[8], health-related quality of life can be a significant factor influencing treatment outcome for TMD. The results showed that a higher health-related quality of life predicted lower TMD pain intensity at an 8 year follow-up. Health-related quality of life will be measured using the Italian version of the EQ-5D-5L [www.euroqol.org]. This instrument transforms different health states into a single value with range 0-1 where 1 is perfect health, and it measures the patient's own judgement about his/her health outcome through a visual analogue scale range 0–100, representing respectively 'worst' to 'best' imaginable health state[9]. The EQ-5D-5L, with 5 possible responses to each item, has increased inter-observer [ICC 2,1 0.57] and test-retest [ICC 2,1 0.69] reliability compared to the previous EQ-5D-3L[10]. Additionally, it has less ceiling effects [20.8% reduction] and adequate convergent validity when compared with the WHO-5 [Spearman rank 0.38-0.51][11].

Sleep quality

It is known that chronic pain patients may suffer from poor sleep quality, even if it is difficult to draw a causal relation[12]. Consequently, sleep quality will be assessed as a candidate predictor because of its possible role among other factors in the transition from acute to chronic pain. Sleep quality will be evaluated through an 11-point Numerical Rating Scale [NRS], where 0 is 'the best possible sleep' and 10 is 'the worst possible sleep'. This scale owns moderate psychometric properties in fibromyalgia patients to assess current sleep quality [over the previous 24 hour period] with a symptom diary[13]. We will use the 0-10 NRS to assess average sleep quality, related to the preceding 6-months at baseline[14], although no psychometric properties have previously been reported for this recall period.

Psychosocial features

Psychosocial factors are known to influence TMD onset and chronicity[15]. Psychological distress is significantly linked to a greater severity and persistence of TMD pain[16]. Moreover, depression and high levels of stress are significantly more common in people with chronic TMD[17-18]. In addition, there is agreement about the predictive strength of psychosocial factors in primary care among different musculoskeletal pain conditions[19-20].

<u>The Hospital Anxiety and Depression Scales [HADS]</u>

The Italian version of the HAD[21] will be utilised to investigate depression, anxiety and manifestations of somatic symptoms[22]. This scale consists of two subscales [anxiety: HADS-A; depression: HADS-D] with 7 items and a total score from 0 to 21, with a higher score indicating elevated levels of anxiety and depression[23].

HADS has been studied in different groups confirming adequate to excellent internal

consistency of HADS-A [0.68-0.93] and HADS-D [0.67-0.90][23]. In a coronary heart disease sample, the standard measurement of error was 1.37 for anxiety and 1.44 for depression; the minimal detectable change was 3.80 for anxiety and 3.99 for depression[24]. The HADS has excellent concurrent validity in comparison to other depression/anxiety scales[23].

Coping Strategies Questionnaire 27 [CSQ-27]

Forssell et al.[25] found that a low perceived ability to control pain increases the risk for poor prognosis of TMD pain at one year regardless of the type of treatment. The Italian version of the CSQ-27[26] will be used to provide an indication of coping strategies used by participants when they are in pain. This 27-item questionnaire contains six domains to assess the strategies for coping with pain: *Distraction, Catastrophizing, Ignoring pain sensations, Distancing from pain, Coping self-statements,* and *Praying*. Patients rate the specific strategies for coping with pain using a seven-point Likert scale [for each domain] ranging from 0 “Never do that” to 6 “Always do that”, with higher scores indicating greater use[27]. A recent study in a low back pain cohort[28], in which individual items from multiple questionnaires were factorised, suggested that diversion, reinterpreting and cognitive coping clustered together as a single factor, representing coping cognitions; by contrast, catastrophizing clustered with pain-related distress items. The original form was examined in English-speaking subjects and revealed acceptable internal consistency [Cronbach’s alpha estimates ranging from 0.72 to 0.86] and satisfying construct validity[27].

Treatment expectation

A positive treatment expectation is considered as a treatment moderator because of its influence on treatment outcome[29]. A positive treatment expectation is predictive of good outcome

because the expectation of benefit (placebo) has a robust effect on pain[30]. In the current study we will investigate treatment expectation following the same protocol used by Puentedura et al[31]. Participants will be asked whether they "Completely disagree", "Somewhat disagree", "Neutral", "Somewhat agree", "Completely agree" with the following statement: "I believe that *manual techniques applied to my jaw* will significantly help to improve my pain". If the participant chooses "completely disagree," "somewhat disagree," or "neutral," there is not a positive expectation that manual therapy applied to craniomandibular structures will significantly help their temporomandibular disorder. If the participant chooses "somewhat agree" or "completely agree," there is a positive expectation that manual therapy applied to craniomandibular structures will significantly help their temporomandibular disorder.

TMD characteristics

Based on previous studies on predictive factors of outcome in TMD patients[8,25,32], pain characteristics [e.g. pain duration, pain intensity, pain location] are good predictors for pain change in the long-term. In addition, across a variety of different conditions, pain features were reported to hold predictive value for pain modulation[19,33-35].

Pain Duration

According to Grossman et al.[32], pain duration could be a significant factor influencing the treatment outcome for TMD. Their results underline the fact that a longer pain duration is associated with a more refractory therapeutic approach. Consequently, the pain duration [measured in "days"] will be collected as candidate predictor of outcome from open hospital records and patient interview.

Pain intensity

As shown in a previous study[32], high levels of pain intensity at baseline in people with TMD, can be associated with no-clinically significant results at a midterm [3-4 months] follow up. Pain intensity will be calculated by averaging ratings of current pain, average pain, and worst pain in the past week using the visual analogue scale (VAS), consisting of a horizontal line measuring 10 cm (without marks), with "no pain" written at the left extremity, and "unbearable pain" written at the right extremity[36]. Patients will be educated to trace a perpendicular line on the horizontal line to intend the pain intensity. The distance from the 0 points will be after measured in millimetres. The VAS is a reliable and valid scale to assess pain intensity[37].

Pain location and extent

Forssell et al.[25] found that a high number of pain conditions increases the risk for poor prognosis of TMD pain at one year regardless of the type of treatment. Comorbid painful areas are common in patients with TMD pain[38]. Therefore, the pain location and the pain extent will be collected as a candidate predictor of outcome. This will be recorded as described in the DC/TMD protocol[16,39-44]. Patients will be asked to complete a pain drawing symbolising the spatial distribution of the pain, over one chart with a frontal view of the body, one with a dorsal view and one with a dental setting (more specific for the jaw and teeth pain). Pain reported in different body areas (e.g., headache, back pain, pelvic pain, neck pain) can be summarised as a count variable. The extent of pain will be calculated as % of the body area by using an image scanning software (ImageJ: Image Processing and Analysis in Java, http://imagej.nih.gov/ij/; Klong Image Measurement: http://www.imagemeasurement.com/experience-image-measurement/pain-assessment-image-measurement)

Central Sensitization Inventory (CSI)[45]

Central sensitization can be present in different pain disorders including low back pain[46], neck pain[47], fibromyalgia[48], and TMD[49]. The Italian version of the Central Sensitization Inventory (CSI)[50] will be used. Part A consists of a 0-100 score for 25 items on current health symptoms with five options ranging from 'never' (0) to 'always' (4). Part B examines previous physician diagnoses among seven different conditions[45]. The CSI has significant test-retest reliability and internal consistency in subjects with and without pain[45]. The Italian version of the CSI showed a satisfactory Cronbach's alpha [0.87][50].

Classification of TMD

Manual therapy could potentially be beneficial for both myogenous and arthrogenous TMD[51]. The TMD type will therefore be collected as a candidate predictor of outcome. As stated in the inclusion criteria, every patient included in the study will be diagnosed according to the Axis I of the Diagnostic Criteria for TMD DC/TMD[39]. Based on these criteria, Peck et al.[52] reported different types of TMD. This Taxonomic Classification of TMD includes four main domains: TMJ Disorders, Masticatory Muscle Disorders, Headache and Associated Disorders. An additional domain, called Mixed TMD (simultaneous presence of TMJ Disorders and Masticatory Muscle Disorders) will be included. For every patient the type of TMD (total of 5 domains) will be collected as candidate predictors from the patient medical records.

Characteristic pain intensity and disability

A greater number of disability days increases the risk of having clinically significant pain one year after an initial assessment[25]. In this study we will use the Italian version of Graded Chronic Pain Scale [GCPS] version 2.0 [www.rdc-tmdinternational.org][53] following the DC/TMD protocol recommendations[39,42,44]. This scale has good internal consistency in temporomandibular pain [Cronbach's alpha of 0.84][54]. The GCPS measures the facial pain severity over the preceding 6-months by unifying pain intensity and pain-related disability. The characteristic pain intensity score [range: 0-100] is the mean of three pain intensity measurements: 'at the present time' and 'worst pain' and the 'average' pain over the preceding 6 months. The disability status is measured with a 0-6 point score derived from a combination of the number of disability days and the disability level [range: 0-100; limitation given by pain in performing activities of daily living]. Based on these scores, the participant's chronic pain and disability status can be classified into one of the five ordinal categories of chronic pain severity[55].

Oral Behaviour

People with abnormal oral behaviours with scores above 25 in the Oral Behaviours Checklist [OBC] are 75% more likely to develop TMD than individuals with a score below 17[42,44,56]. Parafunctional habits could play a significant role in the development and the persistence of TMD pain[58]. In this study we will use the Italian version of the RDC/TMD questionnaire Axis II Oral Behaviours Checklist [www.rdc-tmdinternational.org][42,56] following the DC/TMD protocol recommendations[39,56]. The OBC measures the self-reported frequency over the preceding month of each of 21 activities involving the jaw such as clenching the teeth or bracing the jaw (five ordinal response options, ranging from ''none of the time,'' coded 0, to ''all of the time,'' coded 4). Psychometric properties of this instrument suggest that it is valid, with patient behaviours matching those measured[56,57,59]. Scoring is computed as the sum of the number of items with non-

zero response or as a weighted sum [e.g. the sum of the endorsed frequencies of the respective items][56].

Clinical tests of the TMJ and masticatory muscles

TMJ range of motion

Mobility testing of the TMJ denotes an essential sign of TMD, it is one of the most reliable clinical measures[39]. Grossman et al.[8] examined the preoperative variables of TMD patients with articular disc displacement without reduction that may alter the effects of arthrocentesis on joint effusion. They observed that small maximum interincisal distance influences treatment outcome. As a result, we will use the Maximal Mouth Opening (MMO) without pain as measure of TMJ range of motion. The measurements will be in millimeters and will be taken with a ruler in a neutral craniocervical position [e.g. sitting or supine]. The distance between the incisal edges of the maxillary and mandibular reference teeth, as described in the DC/TMD protocol[44], will be measured. Participants will be asked to open the mouth as wide as they can without feeling any pain, or without increasing any present pain. The tip of the ruler will be located against the incisal edge of the mandibular reference incisor, and the distance to the mesial-distal center of the edge of the maxillary central incisor will be read. The test will be repeated twice if the pain-free opening if less than 30mm[44]. Assessment of mandibular ROM in a neutral craniocervical position obtained good inter- and intra-rater reliability for MMO[60].

TMJ palpation pain:

Pain induced in joints via palpation is a useful clinical test that allows to understand if the provoked pain duplicates or replicates the patient's pain complaint by identifying potential joint

origin[44]. For this palpation, finger pressure is calibrated [1.0 kg], as described in the DC/TMD protocol[44], using a simple hand-held algometer prior to palpation examination. While the participant mandible is in a comfortable position or in a slightly protruded position, the examiner's index finger will be placed just anterior to the tragus of the ear and dorsal to the TMJ with the participant in neutral craniocervical position e.g. sitting or supine. The index finger will press while orbiting around the lateral pole in a circular fashion over the superior aspect of the condyle and then anteriorly [from the 9:00 to the 3:00 position, and then continuing fully around the condyle]. Palpation will last 5 seconds for each pressed point[44]. If a participant complains of familiar pain in at least one pressed point the point score of this test will be 1; if there is no pain at any points the point score of this test will be 0 [range 0-1: no pain =0; pain = 1]. Palpation will be performed in the left and right side. The interexaminer reliability values of TMJ palpation in TMD patients is 0.59 and the specificity values is acceptable [above 0.90][61].

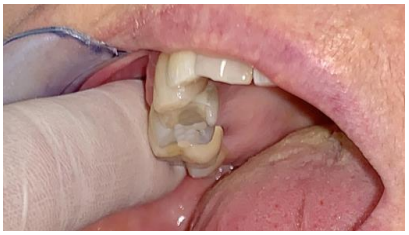
Muscle palpation pain

For this assessment, finger pressure is calibrated to 1.0 kg for masseter muscles and 0.5 kg for lateral pterygoid area and temporalis tendons as described in the DC/TMD protocol[44], using a simple hand-held algometer prior to palpation examination. Pain induced in muscles via palpation is a useful clinical test that allows to understand whether the provoked pain duplicates or replicates the patient's pain complaint by identifying potential muscular origin[44]. Palpation will be performed with the participant in a neutral craniocervical position (e.g. sitting or supine), on the left and right side and will last 5 seconds for each testing point[44]. The inter-examiner reliability values of palpation in TMD patients is 0.59 and the specificity values are acceptable [above 0.90][61]. The feasibility of the lateral pterygoid muscle palpation is controversial. Some authors defined it as a feasible palpation technique[62], and others considered this muscle unaccessible[63]. Therefore, in this

study, this parameter [pain at lateral pterygoid site] will not be considered alone but in combination with pain at other muscular sites.

Lateral pterygoid area: palpation will be performed with a finger pressure calibrated at 0.5 kg (DC/TMD protocol[44]). The palpation will take place as described in FIG.1. If a participant complains of familiar pain during palpation the lateral pterygoid area will be considered as a painful site.

FIG. 1 Lateral pterygoid area: Finger is placed as shown. Palpate the vestibule in posterior-superior-medial direction while the mandible is omolaterally deviated.

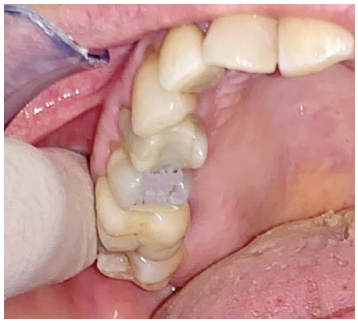


Masseter muscle: masseter palpation consists of a sequence of three palpation sites with finger pressure calibrated to 1.0 kg (DC/TMD protocol[44]): origin zone [inferior to the bony margin of the zygomatic process], body zone [in front of ear lobe] and insertion zone [superior to the mandibular angle]. In each zone, the palpation continues until the anterior boundary of the muscle is reached[44]. If a participant complains of familiar pain in at least one pressed point, the masseter muscle will be considered as a painful site.

Temporalis tendon area: the palpation will be performed with a finger pressure calibrated to 0.5 kg (DC/TMD protocol[44]). The palpation will take place as described in FIG.2. If a participant

complains of familiar pain during the palpation the temporalis tendon area will be considered as a painful site.

FIG. 2 Temporalis tendon area: Finger is located against the ascending mandibular ramus while the mouth is slightly open. The palpation direction is superior as far as possible by following the bone surface.



Total score: if a participant complains of familiar pain in at least three of the six examined sites the score will be 1, otherwise it will be 0 [score range 0–1: < 3 sites with familiar pain = 0; ≥ 3 sites with familiar pain = 1][64].

JAw-test

The JAw-test is a clinical test that aims to investigate the immediate effects of four brief intraoral manual therapy techniques on pain and on TMJ range of motion. The participant will be positioned in supine position. Before starting the test, the TMJ range of motion without pain will be measured [MMO - millimeters] with a ruler, as described above, according to DC/TMD protocol[44]. Then the participant will be asked to rate his/her pain through the Verbal Rating Scale (VRS) “at rest”, “during clenching” and “during the maximal opening of the mouth”; an average of the three pain scores will be registered. For this test, finger pressure is calibrated [1.0 kg], in the same way described in the DC/TMD protocol[44], using a simple hand-held algometer prior to

palpation examination.

Participants will be informed with the following words: "*I am going to perform four manual techniques on some muscles and joints in your jaw region. You may feel a little pain, if the pain increases and becomes too intense, let me know, I will reduce the pressure until the pain returns to acceptable levels".*

First technique: Lateral pterygoid area

This techniques will be performed on the most painful side. While one hand stabilizes the participant's head on the least painful side, the other hand will be used to apply pressure over the lateral pterygoid area as described above and in accordance with the DC/TMD protocol[44]. In this position, compression [1.0 kg] is applied for 30-60 seconds.

Second technique: Temporalis tendon area

This techniques will be performed on the most painful side. While one hand stabilizes the participant's head on the least painful side, the other hand (index finger) will be used to apply pressure over the Temporalis tendon area as described above and in accordance with the DC/TMD protocol[44]. In this position, compression [1.0 kg] is applied for 30-60 seconds.

Third technique: Mylohyoid area

The participant will be instructed to open the mouth to let the examiner's finger reach the mylohyoid area in a central position on the mylohyoid raphe. The other hand of the examiner will reach the same area using a finger through an extraoral approach. In this position a combined compression (1.0 kg) will be applied for 30-60 seconds.

Fourth technique: TMJ mobilization

An intraoral ventral and caudal anterior glide [mobilisation grades I and II] of both the TMJs will be performed for 30 seconds as described by Cleland et al.[65]

Final scores:

After the tests, the TMJ range of motion without pain will be measured [MMO - millimeters] with a ruler, as described above, according to DC/TMD protocol[44]. Then the participant will be asked to rate his/her pain using the Verbal Rating Scale (VRS) “at rest”, “during clenching” and “during the maximal opening of the mouth”; an average oh this three pain scores will be registered. If a participant shows only an improvement in pain [average score VRS pre-test > average score VRS post-test] the score will be 1; if a participant shows only an improvement of TMJ mobility [MMO pre-test < MMO post-test at least 2 millimeters] the score will be 1; if a participant shows improvements in both pain and TMJ mobility, the score will be 2; if a participant shows no improvements the score will be 0 [Score range 0-2: 0 = no change; 1 = VRS improvement or MMO improvement; 2 = improvement of both].

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