BMJ Open

Prognostic factor analysis in patients with temporomandibular disorders after conservative treatment: study protocol for a prospective cohort study in China

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-048011
Article Type:	Protocol
Date Submitted by the Author:	15-Dec-2020
Complete List of Authors:	zhang, LING; Department of Rehabilitation, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, Department of Rehabilitation, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China Shi, Wentao Lu, Shenji Cai, Bin; Shanghai Ninth People's Hospital Shanghai Jiao Tong University School of Medicine, Fan, Shuai; Department of Rehabilitation, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China Yang, Yang xu, lili; Department of Rehabilitation, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
Keywords:	Rehabilitation medicine < INTERNAL MEDICINE, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, Adult palliative care < PALLIATIVE CARE, Oral & maxillofacial surgery < SURGERY, Clinical trials < THERAPEUTICS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Prognostic factor analysis in patients with temporomandibular disorders after conservative treatment: study protocol for a prospective cohort study in China

Ling Zhang[a], MPE, Wentao Shi[b], PhD, Shenji Lu[a], PhD, Bin Cai[a], PhD, Shuai Fan[a], MPT, Yang Yang[a], MPE, Lili Xu[a], PhD

Author affiliations

[a]Department of Rehabilitation, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, 200010, People's Republic of China

[b]Clinical Research Center, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, 200010, People's Republic of China

Corresponding author

Lili Xu

Department of Rehabilitation, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine

639 Zhizaoju Road, Huangpu District, Shanghai 200011, China

Email: heblll@163.com

Phone: +86 21 18817892605

Fax: +86 021 64189920

Keywords: prognostic factor; temporomandibular disorders; conservative treatment; cohort study; protocol

Total word count: 3394

ABSTRACT

Introduction: Temporomandibular disorders (TMDs) are complex multifactorial disorders.

Conservative treatment has been suggested for the initial management of TMD; however, comparable therapeutic effects of different conservative intervention modalities remain controversial. Various biopsychosocial factors, which may be putative prognostic factors that influence the response to conservative treatment for TMD, have been reported to increase the risk of developing first-onset TMD. However, there is a paucity of research that aims to identify prognostic factors associated with the clinical outcomes of conservative treatment in people with TMD. The objective of this prospective cohort study is to identify prognostic factors that are associated with clinical outcomes of conservative treatment in patients with TMD and to analyse the risk factors that influence the development of chronic TMD.

Methods and analysis: We plan to recruit 834 patients with TMD who meet the inclusion criteria. Following provision of informed consent, baseline data including anamnestic data, physical assessments, and self-reported questionnaires will be collected from participants at their first clinic visit, and then they will receive 1–4 weeks of conservative treatment. Primary treatment outcome measures will be change in the anterior maximal opening, worse TMD pain score registered on a visual analogue scale (VAS), and a reduction in characteristic pain intensity. A good outcome will be defined as an anterior maximal opening ≥ 35 mm and at least a 30% reduction on VAS post-treatment. The association between candidate prognostic factors and clinical outcomes of conservative TMD treatment will be analysed.

Ethics and dissemination: The protocol has been approved by the Ethics Committee of Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, based on the guidelines outlined in the Declaration of Helsinki (SH9H-2019-T316-4). The results of this study will be reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. The authors intend to publish the results in a peer-reviewed source.

Trial Registration Number: ChiCTR2000033328.

Strengths and limitations of this study

■ This study will identify the prognostic factors that are associated with clinical outcomes of conservative treatment in patients with TMD and analyse risk factors that influence the

development of chronic TMD.

■ The heterogeneity of patient material and psychosocial factors may be considered in treatment planning.

■ This study will provide evidence to appropriately manage Chinese patients with TMD.

■ This study will be performed in China; thus, it limits applicability to other populations.

INTRODUCTION

Temporomandibular disorders (TMDs) are painful musculoskeletal conditions that are associated with pain and dysfunction of the temporomandibular joint (TMJ) and masticatory muscles.[1 2] Approximately 5% to 12% of adults experience TMD.[2] The most common TMD symptoms and signs are facial pain, impaired jaw mobility, deviations of mandibular movements, and TMJ sounds, affecting the patient's wellbeing and quality of life.[3]

TMD is a complex disorder resulting from multiple physical, psychological, genetic, sensory processing, and environmental domains, and clinical characteristics have been identified to predict the increased risk of developing TMD.[4] Previous reports from the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) study have concluded that numerous biopsychosocial factors increase the risk of developing first-onset TMD.[4-6] The OPPERA study findings demonstrated that a complex pattern of considerable changes in psychologic functioning (i.e., perceived stress, depression, and somatisation),[7] pain sensitivity,[8] clinical jaw function,[9] sleep disturbance, and other health conditions[10] is associated with changes in the TMD status.

Various interventions have been suggested for TMD, but to date, the most effective treatment programme remains unclear.[11-14] These interventions are grouped into three categories based on the level of invasiveness, including conservative (e.g., education, self-management, splint therapy, and physiotherapy), minimally invasive (e.g., arthrocentesis), and surgical interventions (e.g., arthroscopic and open joint surgeries).[11] The similar pain-reducing effect of physiotherapy and splint therapy has been confirmed for patients with myofascial TMD pain.[14] Diraçoğlu et al.[13] concluded that neither conservative methods nor arthrocentesis is beneficial in the early treatment of TMD. A previous randomised controlled trial found no

difference between medical management, non-surgical rehabilitation, arthroscopic surgery, and arthroplasty relative to TMJ pain and mandibular mobility at a 60-month follow-up.[12] The comparable therapeutic effects of different intervention modalities suggest that the least expensive, least invasive, and simplest interventions should be employed for the initial management of TMD.[11]

Although promising outcomes have been reported with conservative treatment, the results remain controversial.[15] One prospective cohort study followed 40 TMD patients for 2.5 years and found that 43% of the patients were free of symptoms, 33% of the patients had decreased symptoms, and 25% showed no improvement or required further treatment.[15] Similarly, nearly 50% of patients who received conservative treatment reported no pain 5 years later, and another 14% of patients continued to report significant pain.[16] Little is known about clinical characteristics of these TMD patients with poor prognosis following conservative treatment. These findings suggest that the prognostic information is critical when predicting the impact of conservative interventions in a population with TMD. However, there is a paucity of research that aims to identify prognostic factors associated with the clinical outcomes of conservative treatment in people with TMD. Previous studies have concluded that numerous biopsychosocial factors increase the risk of developing first-onset TMD; therefore, we speculated that these factors may have a theoretical association with prognosis in individuals with TMD. Moreover, the TMD status changes substantially over time, and acute TMD becomes chronic in 25% of patients along the highly variable course of TMD.[17] Long-term follow-up studies are needed to investigate the prognostic factors that influence the response to conservative treatment and the risk factors that are associated with the development of chronic TMD.

The aim of this prospective cohort study is 1) to identify prognostic factors that are associated with clinical outcomes of conservative treatment in patients with TMD and 2) to analyse risk factors that influence development of chronic TMD during the 1-year follow-up period. Based on current knowledge of risk factors for the development of TMD that have been reported in epidemiological studies, putative prognostic factors, including demographic data, self-reported questionnaires, and measures of physical function, will be collected and analysed.

Specific aims

Aim 1: To determine whether demographic characteristics and biopsychosocial factors are associated with the prognosis of conservative treatment for TMD.

Aim 2: To determine the risk factors associated with chronic TMD.

TRIAL DESIGN AND METHODS

This population-based prospective cohort study will be conducted in Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine. This protocol has been designed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement and Prognosis Research Strategy (PROGRESS).[18] The results of this study will be reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[19]

Participants

We will recruit 834 patients with TMD presenting to the rehabilitation department. Consecutive eligible patients will receive 1–4 weeks of conservative treatment and will be followed-up for 12 months post-treatment. The conservative treatment programme has been reproduced from a previous systematic review on patients with TMD.[20] The 1-year follow-up has been pre-registered before the patients participated. Study recruitment will commence on December 2020 and will be completed by December 2021.

The participants must meet the following criteria:

1. Aged 12–75 years.
2. Fulfil the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD).[21]
3. Maximal mouth opening < 35 mm and/or a visual analogue scale (VAS) score for orofacial pain ≥ 4.
4. Understanding of the survey and independent completion of the questionnaires.
5. Volunteers to participate in the study and signs the consent form.

The participants will be excluded if they meet one of the following conditions at baseline:

1. History of traumatic facial injury or surgery.

2. Malignant disease, active rheumatologic disease, haemorrhagic disease, heart disease, or heart failure.

3. Pregnant or lactating women or women who plan to be pregnant within the next 1 year.

Drop-out criteria: Participants will have the right to drop out of the study at any time. Participants who meet one of the following conditions will be removed from the study:

1. The researcher believes that removal from the study will benefit the patient.

2. Not following the follow-up time schedule or refusal to answer the required questionnaires.

Recruitment

Patients will be recruited from the rehabilitation department in Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine. We will recruit eligible patients at their first clinic visit. Prior to study initiation, training will be delivered to the clinical examiners working at the physiotherapy clinic to inform them of the study and how to screen patients for eligibility. X.L. will serve as the reference examiner throughout the study. In a separate training session, each study examiner will conduct more than 10 blinded, replicated examinations of non-study volunteers. Data from the blinded, replicate examinations will be analysed for interexaminer reliability computed using the Kappa statistic. Providers will have copies of the screening form to screen potential patients according to the inclusion and exclusion criteria. At the first outpatient visit, a potential patient will be informed about the study. All study patients will provide written informed consent at the time of recruitment.

Candidate prognostic factors

Owing to the lack of consensus on prognostic factors that influence the response to conservative treatment for TMD, demographic data, physical measures, self-reported questionnaires, and type of treatment modality will be collected. Putative factors have been selected based on current knowledge of risk factors for the development of TMD in epidemiological studies that may have a theoretical association with prognosis in individuals with TMD, as confirmed by the biopsychosocial model of developing TMD. These selected factors are feasible to measure in clinical settings. Candidate prognostic factors are summarised in Table 1. All data collection

will be standardised using clinical report forms and protocols.

Data collection

Baseline data including demographic data, self-reported questionnaires, and physical assessments will be collected by a trained assessor at the first clinic visit. Patients will receive 1–4 weeks of conservative treatment within 2 weeks following recruitment, and treatment modalities that patients receive will be recorded. Patients will be contacted by the same assessor by telephone 3, 6, and 12 months after treatment to complete physical examination and functional questionnaires (Figure 1).

Baseline interview, self-reported questionnaires, and physical examination

During the first clinic visit, the researcher will collect the patient's demographic data (e.g., gender, age distribution, educational attainment, marital status), case histories, intercurrent diseases (e.g., pain related to the neck and TMJ region, general musculoskeletal pain elsewhere), and use of medication. Anamnestic data will be collected at baseline, including the nature, duration, and intensity of the pain. The intensity of the present facial pain, including masticatory muscle pain and TMJ pain at rest and during movements of the mandible according to the DC/TMD criteria, will be assessed with VAS. VAS is a measurement instrument that measures an attitude or characteristic that ranges across a continuum of values and cannot be directly measured.[22] Operationally, it usually takes the form of a horizontal line, 100 mm in length, with word descriptors at each end. The patient marks the point on the line that represents their current feelings. The VAS score, measured in millimetres, is determined from the left end to the point that the patient marks.

Patients will be asked to complete self-reported questionnaires. The patients will follow the procedure shown in Table 1. The Oral Behaviors Checklist is a self-reported questionnaire with 21 items used to quantify the frequency of oral behaviours, which is considered as part of a larger study of diagnostic validity and reliability for TMD.[23]

The Patient Health Questionnaire (PHQ) is a self-administered diagnostic instrument for common mental disorders. The PHQ-15 consists of 15 somatic symptoms from the PHQ, and

the PHQ-9 comprises nine items to establish a depressive disorder diagnosis as well as grade depressive symptom severity.[24] Generalised anxiety disorder (GAD) is a common mental disorder among TMD patients, and a 7-item anxiety scale (GAD-7) is a self-reported scale to determine probable cases of GAD with good reliability and procedural validity.[25]

The Pittsburgh Sleep Quality Index provides a valid, standardised, clinically useful measure of a variety of sleep disturbances that may affect sleep quality.[26]

The Jaw Functional Limitation Scale (JFLS) comprises 20 items used to assess the limitation of the jaw function in TMD patients.[27]

Finally, a functional examination of the masticatory system and diagnosis of patients according to the DC/TMD criteria[21] will be made by the same clinician. Clinical stomatognathic assessments of TMD include the ranges of movements of the mandible, TMJ sounds, and patients' head and neck posture.[28] The ranges of movements of the mandible will be measured with a vernier caliper.[22] When performing measurement of the anterior maximal opening, the examiner will ask the patient to place the mandible in a comfortable position. The patient will be asked to open the mouth as far as possible without assistance. The edge of the millimetre ruler will be placed at the incisal edge of the maxillary central incisor for maximal vertical orientation to the labioincisal edge of the opposing mandibular incisor. This measurement will be considered the interincisal opening. If subjects open their mouth less than 30 mm, the opening will be repeated to insure understanding. If the second opening still produces an opening less than 30 mm, the measurement will be recorded as the interincisal opening. To measure the vertical incisal overlap, the patient will be asked to perform the action of biting to bring the teeth together. The line where the incisal edge of the same maxillary central incisor used before for measurements overlaps the mandibular incisor will be marked with a pen. The distance from the mandibular incisal edge to the marked line will be recorded as the vertical incisal overlap. The anterior maximal opening will be considered as the sum of the interincisal opening and the vertical incisal overlap.[29]

The objective method of assessing head and neck posture will be to measure the craniovertebral (CV) angle and the cranial rotation angle.[30] The CV angle will be defined as the angle between the horizontal plane (the line perpendicular to true vertical axis) and the line

extending from the tragus of the ear to the C7 spinous process.[31] The cranial rotation angle will be formed by a line connecting the lateral canthus and the tragus with a horizontal line.[31] Measurement of the cervical angle will be performed using a protractor. The digitisation procedure has been proven to be highly reliable.[30] The sagittal plane images of the upper body of each patient will be taken using a digital camera in a habitual relaxation sitting position. The patient will be asked to assume a comfortable habitual sitting position with the eyes focused towards the front, and the height of the chair will be 45 cm. Red markers will be placed over the tragus and C7 spinous process by the same examiner. To ensure consistency in images, the distance between the camera and the patient will be 1.5 m and the camera will be adjusted to keep with the patient's shoulder.

Interventions

Patients included in the study will be invited to attend a study session at the physiotherapy clinic. At this session, patients will receive a standardised conservative treatment programme within 2 weeks of recruitment and will be followed-up for a period of 12 months after treatment. According to the recommendations from the current systematic reviews and meta-analyses, the least invasive, simplest, and reversible interventions are considered as first-line therapy for TMD. An experienced physiotherapist will design a conservative treatment programme according to each patient's clinical symptoms, characteristics, and willingness. The programme will include education, self-management, medication, therapeutic exercise, manual therapy, and occlusal splint therapy, as previously reported.[20] Patients will be informed of the reasoning behind the treatment plan and provided detailed information about the treatment programme.

For those patients who meet the inclusion criteria but refuse to participate in the study, the standard of care treatment will be given. To promote patient retention, the researcher will inform the potential patient that although they can withdraw at any time, dropping out without reason reduces the ability to answer the research question and therefore weakens the study. Patients will be advised to carry on with their usual daily routines, and any interventions received during conservative therapy sessions will be recorded for a descriptive analysis. The detail of treatment (eg, time, number, duration, modality), leave requests and reasons will be

documented and reported, as well as any adverse events during the study. Participants will be monitored during the 1 to 4-week programme and 12-month follow-up.

Outcomes

The primary treatment outcome measures will be change in the anterior maximal opening, worse TMD pain registered on the VAS, and characteristic pain intensity. An anterior maximal opening ≥ 35 mm and at least 30% reduction on VAS post-treatment will be defined as good outcomes. Additional outcome measures will include change in frequency of TMD pain (recurrent, persistent, and one-time experience), the JFLS scores, and diagnosis of chronic TMD. The patients will be asked to report discomfort and complications associated with the conservative treatment and how often they perform the treatment. Additionally, all outcome measures will be collected 3, 6, and 12 months after treatment and assessed for the prediction model.

Data management

All data will be entered into the research folder, and a researcher will transfer them into the master data spreadsheet. Privacy of patient data will be maintained through data handling (collection transfer, storage, and processing). Accuracy of data will be guaranteed by a secondary review by co-authors. Data from each participant will be recorded by research numbers and will be accessible only by members of this research team. A spreadsheet will be stored on a portable drive, and the research folders will be locked in a cabinet.

Trial organisation and monitoring

The research team will consist of the authors listed in this article, in addition to administrative staff at the physiotherapy clinic who will assist with the entire process of the study and data entry. The primary investigator will manage the study flow and perform inspections of enrolment, treatment, and procedures throughout the entire study. Other investigators will monitor data collection and facilitate data integrity performed with periodic evaluations during the data collection phase.

Data analysis

Numbers of individuals will be recorded, including those potentially eligible, confirmed eligible, recruited into the study, receiving conservative treatment, and completing follow-up. Withdrawals and loss to follow-up will be reported with reasons. Descriptive analyses of patients at baseline will include demographics, self-reported questionnaires, and physical assessment data.

All analyses will be performed with the use of SPSS software (version 25.0). All analyses will be conducted with a 2-sided significance level, with a threshold of $P < 0.05$. Linear regression analysis, as the primary analysis, will be used to develop a linear model to determine the association between candidate prognostic factors and the response to conservative treatment in patients with TMD. For risk factors for the development of chronic TMD, univariate associations between categorical variables (treatment, sex et.) and the diagnose of chronic TMD according to DC/TMD will be tested using $\chi 2$ tests. Continuous variable (age, height et.) and the diagnose of chronic TMD according to DC/TMD will be tested using students unpaired t tests. Multivariable analyses will be performed using binary logistic regression with forced entry of all independent variables.

Sample size calculation

This prospective cohort study was designed with a target sample size of 834 enrolled patients with TMD. This is expected to investigate the association between 20 candidate prognostic factors and the clinical outcome of conservative treatment in patients with TMD over the 1-year follow-up, assuming 20% loss to follow-up. The researchers will ensure at least 10 participants per prognostic factor to develop an adequately powered linear regression analysis.[33] In a previous study, 70% of TMD patients who received conservative treatment reported good outcomes.[12] Therefore, a sample size of 834 participants will be adequate to power a linear regression analysis of 20 candidate prognostic factors.

Management of missing data

For each variable of interest, numbers of patients with missing data will be reported. Any potential bias due to loss to follow-up will be assessed and compared using baseline data of patients who withdraw or were lost to follow-up.[32] Multiple imputation will be used to deal with missing outcome data, if necessary.[34] Participants will be excluded from the predictive model and subsequent analyses if they request to withdraw from the study following recruitment.[32]

Patient and public involvement

No patients were involved with the design or will be involved in data provision, analysis, or publication of the study.

DISCUSSION

This will be the first protocol to describe the methods and analysis for identifying prognostic factors for clinical outcomes of conservative treatment in individuals with TMD. In particular, self-reported measures together with physical examination will be incorporated to predict poor outcome of conservative treatment in individuals with TMD. The candidate prognostic factors have been selected based on current knowledge of risk factors for developing first-onset TMD and its possible utilisation in clinical practice. The knowledge gained through this study will provide a better understanding of how these prognostic factors can be used to improve clinical outcomes, including whether conservative treatment is useful in the clinical management of TMD patients.

This study will be conducted in accordance with the SPIRIT statement and PROGRESS framework.[18 32] The results from this study will provide new insights into who is likely to benefit from conservative treatment versus who is likely to develop chronic TMD. Between 57% and 71% of patients seeking treatment for acute TMD continue to report significant pain 6 months later.[9 35] Therefore, the evaluation of prognoses will be valuable for treatment planning of patients with TMD. In clinical practice, the heterogeneity of the patient material and psychosocial factors may be considered in treatment planning.

Despite the novelty of this trial, this study has some limitations. First, the candidate

prognostic factors are selected based on those reported risk factors for developing first-onset TMD, however, some possible prognostic factors may be ignored. For future studies, we may include more candidate prognostic factors. Second, since the conservative treatment is a combined treatment, we cannot ascertain the effects of medication only or manual therapy only; however, we will explore the prognose of each treatment component.

ETHICS AND DISSEMINATION

The protocol was approved by the Ethics Committee of Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, based on the guidelines set forth in the Declaration of Helsinki (SH9H-2019-T316-4). An ethics review protects human medical research participants to ensure compliance with federal regulations. Any modifications to the protocol which may impact study procedures or the conduct of the study will require approval by the Institutional Review Board and a formal amendment to the protocol. This clinical trial has been registered with Chinese Clinical Trial Registry (www.chictr.org.cn) with a registration number ChiCTR2000033328.

All study participants will provide written informed consent prior to randomisation. Patients included in this study have rights to withdraw at any time, and the reasons will be documented. If participants have trouble complying with the intervention or completing follow-up testing, they can discuss these challenges with the study coordinator. If participants miss measurement appointments, up to three reminders will be sent, and if needed, the participant will be contacted by telephone to rearrange measurements at an appropriate time. Regardless of the outcome, the results of the trial will be reported following the STROBE statement in a relevant scientific journal.

TRIAL STATUS

Recruitment started in December 2020 and is estimated to be completed in December 2021.

Contributors All authors are involved in the design of the study. LX initiated the study. BC, LX, SL, LZ and SF contributed to planning and design. LZ, BC and LX drafted the study

protocol and design. SW and SF perform statistical analysis. LX and ZF are responsible for communications through different centres and research management. LX is the supervisor of the project.

Funding This work is supported by the Clinical Research Program (Grant no. JYLJ201901) and the Shanghai Municipal Science and Technology Major Project (Grant No. 19441908400).

Competing interests None declared.

Patient consent for publication Obtained.

Ethics approval Ethics Committee of Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China (SH9H-2019-T316-4).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request.

REFERENCE

1. Duckro PN, Tait RC, Margolis RB, *et al.* Estimated prevalence and distribution of reported orofacial pain in the United States. *J Am Dent Assoc* 1993;124:115-21.
2. Sharma S, Wactawski-Wende J, LaMonte M, *et al.* Incident injury is strongly associated with subsequent incident temporomandibular disorder: results from the OPPERA study. *J Pain* 2019;160:1551-61.
3. Wänman A, Marklund S. Treatment outcome of supervised exercise, home exercise and bite splint therapy, respectively, in patients with symptomatic disc displacement with reduction: a randomised clinical trial. *J Oral Rehab* 2020;47:143-9.
4. Slade G, Ohrbach R, Greenspan J, *et al.* Painful temporomandibular disorder: decade of discovery from OPPERA studies. *J Dental Res* 2016;95:1084-92.
5. Ohrbach R, Bair E, Fillingim R, *et al.* Clinical orofacial characteristics associated with risk of first-onset TMD: the OPPERA prospective cohort study. *J Pain* 2013;14:33-50.
6. Sanders A, Slade G, Bair E, *et al.* General health status and incidence of first-onset temporomandibular disorder: the OPPERA prospective cohort study. *J Pain* 2013;14:51-62.
7. Fillingim R, Ohrbach R, Greenspan J, *et al.* Associations of psychologic factors with multiple chronic overlapping pain conditions. *J Oral Facial Pain Headache* 2020;34:85-100.

8. Greenspan J, Slade G, Rathnayaka N, *et al.* Experimental pain sensitivity in subjects with temporomandibular disorders and multiple other chronic pain conditions: the OPPERA prospective cohort study. *J Oral Facial Pain Headache* 2020;34:43-56.
9. Fillingim R, Slade G, Greenspan J, *et al.* Long-term changes in biopsychosocial characteristics related to temporomandibular disorder: findings from the OPPERA study. *J Pain* 2018;159:2403-13.
10. Sanders A, Greenspan J, Fillingim R, *et al.* Associations of sleep disturbance, atopy, and other health measures with chronic overlapping pain conditions. *J Oral Facial Pain Headache* 2020;34:73-84.
11. Al-Baghdadi M, Durham J, Araujo-Soares V, *et al.* TMJ disc displacement without reduction management: a systematic review. *J Dental Res* 2014;93:37-51.
12. Schiffman E, Velly A, Look J, *et al.* Effects of four treatment strategies for temporomandibular joint closed lock. *Int J Oral Maxillofac Surg* 2014;43:217-26.
13. Diraçoğlu D, Saral I, Keklik B, *et al.* Arthrocentesis versus nonsurgical methods in the treatment of temporomandibular disc displacement without reduction. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009;108:3-8.
14. Giannakopoulos N, Rauer A, Hellmann D, *et al.* Comparison of device-supported sensorimotor training and splint intervention for myofascial temporomandibular disorder pain patients. *J Oral Rehab* 2018;45:669-76.
15. Kurita K, Westesson P, Yuasa H, *et al.* Natural course of untreated symptomatic temporomandibular joint disc displacement without reduction. *J Dent Res* 1998;77:361-5.
16. Ohrbach R, Dworkin S. Five-year outcomes in TMD: relationship of changes in pain to changes in physical and psychological variables. *J Pain* 1998;74:315-26.
17. Rollman A, Visscher C, Gorter R, *et al.* Improvement in patients with a TMD-pain report. A 6-month follow-up study. *J Oral Rehab* 2013;40:5-14.
18. Chan A, Tetzlaff J, Altman D, *et al.* SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200-7.
19. Elm V, Erik, Altman, *et al.* The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern*

Med 2007;156:568-75.

20. Gauer RL, Semidey MJ. Diagnosis and treatment of temporomandibular disorders. *Am Family Phys* 2015;91:378-86.
21. Türp G, Christoph J. Diagnostic criteria for temporomandibular disorders (DC/TMD) - presentation of the axis I classification. *J Craniomandibular Function* 2014;23:45-51.
22. Katyayan P, Katyayan M, Shah R, *et al.* Efficacy of appliance therapy on temporomandibular disorder related facial pain and mandibular mobility: a randomized controlled study. *J Indian Prosthodont Soc* 2014;14:251-61.
23. Vand M, Lobbezoo F, Aartman IHA, *et al.* Validity of the Oral Behaviours Checklist: correlations between OBC scores and intensity of facial pain. *J Oral Rehab* 2014;41:115-21.
24. Kroenke K, Spitzer RL, Williams JBW. The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms. *Psychosom Med* 2002;64(2):258-66.
25. Spitzer RL, Kroenke K, Williams JB, *et al.* A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med* 2006;166:1092.
26. Buysse D. The Pittsburgh sleep quality index (PSQI). An instrument for psychiatric practice and research. *Psychiatr Res* 1989;28:234-9.
27. Zhang Y, Chung SC, Chung JW. Evaluation of jaw functional limitation in TMD patients using a korean version of jaw functional limitation scale (JFLS). *J Oral Med Pain* 2004;29:346-54.
28. Ohrbach R, Fillingim R, Mulkey F, *et al.* Clinical findings and pain symptoms as potential risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case-control study. *J Pain* 2011;12:27-45.
29. Dworkin S, LeResche L. Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. *J Craniomandibular Disorders* 1992;6:301-55.
30. Lau HMC, Chiu TTW, Lam TH. Clinical measurement of craniovertebral angle by electronic head posture instrument: a test of reliability and validity. *Manual Ther* 2009;14:363-8.
31. Joy T, Tanuja S, Pillai R, *et al.* Assessment of craniocervical posture in TMJ disorders using lateral radiographic view: A cross-sectional study. *Cranio* 2019;34:1-7.
32. Riley R, Hayden J, Steyerberg E, *et al.* Prognosis Research Strategy (PROGRESS) 2: prognostic

factor research. *PLoS Med* 2013;10: 100-8.

33. Royston P, Moons K, Altman D, *et al.* Prognosis and prognostic research: developing a prognostic model. *BMJ* 2009;338: 604.

34. Sterne JAC, White IR, Carlin JB, *et al.* Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;338:2393.

35. Garofalo J, Gatchel R, Wesley A, *et al.* Predicting chronicity in acute temporomandibular joint disorders using the research diagnostic criteria. *J Am Dent Assoc* 1998;129:438-47.

Table 1 Summary of measures that will be collected

Domain/candidate predictor	Baseline	After treatment	Month 3	Month 6	Month 12
Fill out by clinicians					
Inclusion or exclusion standard table	√				
Sign informed notice	√				
Demographic data and case history	√				
Intercurrent diseases	√				
Anterior maximal opening	√	√	√	√	√
Head and neck posture	√				
Adverse events	√	√	√	√	√
Clinical routine inspection	√				
CPI		√	√	√	√
Filled out by subjects					
VAS score	√	√	√	√	√

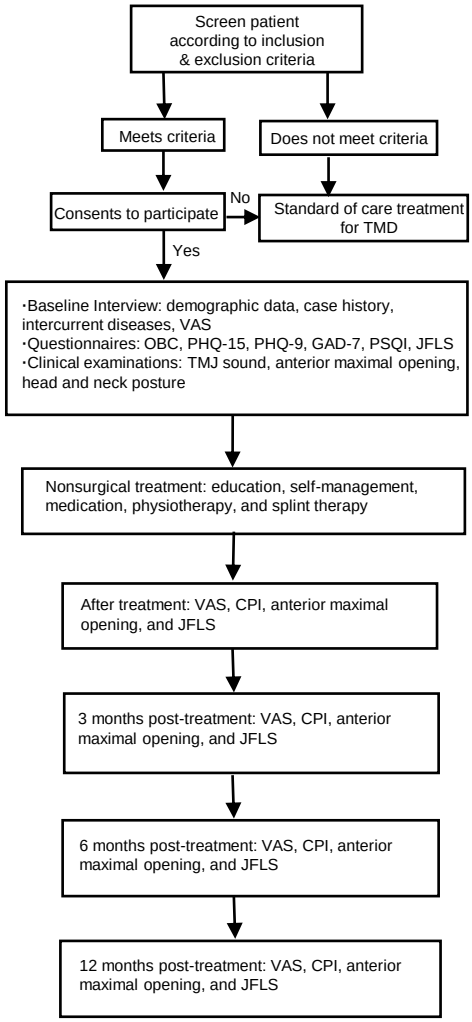
OBC	√				
PHQ-15	√				
PHQ-9	√				
GAD-7	√				
PSQI	√				
JFLS	√	√	√	√	√

CPI, characteristic pain intensity; VAS, visual analogue scale; OBC, Oral Behaviors Checklist; PHQ, Patient Health Questionnaire; GAD, generalized anxiety scale; PSQI, Pittsburgh Sleep Quality Index; JFLS, Jaw Functional Limitation Scale

Figure Legends

Figure 1 Participants recruitment and flow of the study.

TMD, temporomandibular disorders; VAS, visual analogue scale; OBC, Oral Behaviors Checklist; PHQ, Patient Health Questionnaire; GAD, generalized anxiety disorder; PSQI, Pittsburgh Sleep Quality Index; JFLS, Jaw Functional Limitation Scale; TMJ, temporomandibular joint; CPI, characteristic pain intensity


Screen patient according to inclusion & exclusion criteria
Meets criteria
Does not meet criteria
Consents to participate
No
Standard of care treatment for TMD
Yes
·Baseline Interview: demographic data, case history, intercurrent diseases, VAS
·Questionnaires: OBC, PHQ-15, PHQ-9, GAD-7, PSQI, JFLS
·Clinical examinations: TMJ sound, anterior maximal opening, head and neck posture
Nonsurgical treatment: education, self-management, medication, physiotherapy, and splint therapy
After treatment: VAS, CPI, anterior maximal opening, and JFLS
3 months post-treatment: VAS, CPI, anterior maximal opening, and JFLS
6 months post-treatment: VAS, CPI, anterior maximal opening, and JFLS
12 months post-treatment: VAS, CPI, anterior maximal opening, and JFLS

BMJ Open

Prognostic factor analysis in patients with temporomandibular disorders after reversible treatment: study protocol for a prospective cohort study in China

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-048011.R1
Article Type:	Protocol
Date Submitted by the Author:	27-May-2021
Complete List of Authors:	zhang, LING; Shanghai Jiao Tong University School of Medicine Affiliated Ninth People's Hospital, Department of Rehabilitation Shi, Wentao; Shanghai Jiao Tong University School of Medicine Affiliated Ninth People's Hospital, Clinical Research Center Lu, Shenji; Shanghai Jiao Tong University School of Medicine Affiliated Ninth People's Hospital, Department of Rehabilitation Cai, Bin; Shanghai Jiao Tong University School of Medicine Affiliated Ninth People's Hospital, Department of Rehabilitation Fan, Shuai; Shanghai Jiao Tong University School of Medicine Affiliated Ninth People's Hospital, Department of Rehabilitation Yang, Yang; Shanghai Jiao Tong University School of Medicine Affiliated Ninth People's Hospital, Department of Rehabilitation Xu, Lili; Shanghai Jiao Tong University School of Medicine Affiliated Ninth People's Hospital, Department of Rehabilitation
Primary Subject Heading:	Rehabilitation medicine
Secondary Subject Heading:	Dentistry and oral medicine, Rehabilitation medicine, Public health, Research methods
Keywords:	Rehabilitation medicine < INTERNAL MEDICINE, Musculoskeletal disorders < ORTHOPAEDIC & TRAUMA SURGERY, Adult palliative care < PALLIATIVE CARE, Oral & maxillofacial surgery < SURGERY, Clinical trials < THERAPEUTICS

I, the Submitting Author has the right to grant and does grant on behalf of all authors of the Work (as defined in the below author licence), an exclusive licence and/or a non-exclusive licence for contributions from authors who are: i) UK Crown employees; ii) where BMJ has agreed a CC-BY licence shall apply, and/or iii) in accordance with the terms applicable for US Federal Government officers or employees acting as part of their official duties; on a worldwide, perpetual, irrevocable, royalty-free basis to BMJ Publishing Group Ltd ("BMJ") its licensees and where the relevant Journal is co-owned by BMJ to the co-owners of the Journal, to publish the Work in this journal and any other BMJ products and to exploit all rights, as set out in our licence.

The Submitting Author accepts and understands that any supply made under these terms is made by BMJ to the Submitting Author unless you are acting as an employee on behalf of your employer or a postgraduate student of an affiliated institution which is paying any applicable article publishing charge ("APC") for Open Access articles. Where the Submitting Author wishes to make the Work available on an Open Access basis (and intends to pay the relevant APC), the terms of reuse of such Open Access shall be governed by a Creative Commons licence – details of these licences and which Creative Commons licence will apply to this Work are set out in our licence referred to above.

Other than as permitted in any relevant BMJ Author's Self Archiving Policies, I confirm this Work has not been accepted for publication elsewhere, is not being considered for publication elsewhere and does not duplicate material already published. I confirm all authors consent to publication of this Work and authorise the granting of this licence.

Prognostic factor analysis in patients with temporomandibular disorders after reversible treatment: study protocol for a prospective cohort study in China

Ling Zhang[a], MPE, Wentao Shi[b], PhD, Shenji Lu[a], PhD, Bin Cai[a], PhD, Shuai Fan[a], MPT, Yang Yang[a], MPE, Lili Xu[a], PhD

Author affiliations

[a]Department of Rehabilitation, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, 200010, People's Republic of China

[b]Clinical Research Center, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, 200010, People's Republic of China

Corresponding author

Lili Xu

Department of Rehabilitation, Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine

639 Zhizaoju Road, Huangpu District, Shanghai 200011, China

Email: heblll@163.com

Phone: +86 21 18221878206

Fax: +86 021 64189920

Keywords: prognostic factor; temporomandibular disorders; reversible treatment; cohort study; protocol

Total word count: 3720

ABSTRACT

Introduction: Temporomandibular disorders (TMDs) are complex multifactorial disorders. Reversible treatment has been suggested for the initial management of TMD; however, comparable therapeutic effects of different reversible intervention modalities remain controversial. Various biopsychosocial factors, which may be putative prognostic factors that influence the response to reversible treatment for TMD, have been reported to increase the risk of developing first-onset TMD. However, there is a paucity of research that aims to identify prognostic factors associated with the clinical outcomes of reversible treatment in people with TMD. The objective of this prospective cohort study is to identify prognostic factors that are associated with clinical outcomes of reversible treatment in patients with TMD and to analyse the risk factors that influence the development of chronic TMD.

Methods and analysis: We plan to recruit 834 patients with TMD who meet the inclusion criteria. Once informed consent is obtained, baseline data, including anamnestic data, physical assessments, and self-report questionnaires, will be collected from participants at their first clinic visit; subsequently, they will receive 1–4 weeks of reversible treatment. The primary treatment outcome measures will be a change in the anterior maximum mouth opening, worsening of TMD pain scores assessed using a visual analogue scale (VAS), and a reduction in characteristic pain intensity. A good outcome will be defined as an anterior maximal opening ≥35 mm and at least a 30% reduction in VAS scores 3 months after baseline. The association between candidate prognostic factors and clinical outcomes of reversible TMD treatment will be analysed.

Ethics and dissemination: The protocol has been approved by the Ethics Committee of Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, based on the guidelines outlined in the Declaration of Helsinki (SH9H-2019-T316-4). The results of this study will be reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement. The authors intend to publish the results in a peer-reviewed journal.

Trial Registration Number: ChiCTR2000033328.

Strengths and limitations of this study

■ A battery of assessments of demographic characteristics and biopsychosocial factors will be

conducted to evaluate the associations between those variables and the prognosis of patients with TMD.

■ Putative risk factors that are associated with the development of chronic TMD will be explored so that the heterogeneity of patient characteristics and psychosocial factors may be considered during treatment planning.

■ Anterior maximal opening of the mouth and TMD pain will be included as outcome measures, providing evidence that will be useful for appropriately managing Chinese patients with TMD.

■ As putative prognostic factors are selected based on current knowledge of risk factors associated with the development of TMD, some possible biopsychosocial factors may not be assessed in this study.

■ Considering that the ethnic background of TMD patients may be associated with psychological variables, the influence of these psychological factors on the prognosis of patients with TMD may also differ based on ethnicity.

INTRODUCTION

Temporomandibular disorders (TMDs) are painful musculoskeletal conditions that are associated with pain and dysfunction of the temporomandibular joint (TMJ) and masticatory muscles.[1 2] Approximately 5% to 12% of adults experience TMD.[2] The most common TMD symptoms and signs are facial pain, impaired jaw mobility, deviations of mandibular movements, and TMJ sounds, affecting the patient's well-being and quality of life.[3]

TMD is a complex disorder associated with multiple physical, psychological, genetic, sensory processing, and environmental domains, and clinical characteristics have been identified to predict the increased risk of developing TMD.[4] Previous reports from the Orofacial Pain: Prospective Evaluation and Risk Assessment (OPPERA) study have concluded that numerous biopsychosocial factors increase the risk of developing first-onset TMD.[4-6] The OPPERA study findings demonstrated that a complex pattern of considerable changes in psychological functioning (i.e., perceived stress, depression, and somatisation),[7] pain sensitivity,[8] clinical jaw function,[9] sleep disturbance, and other health conditions[10] is

associated with changes in the TMD status.

Various interventions have been suggested for TMD, although to date, the most effective treatment programme remains unclear.[11-14] These interventions are grouped into three categories based on the level of invasiveness, including reversible (e.g., education, self-management, splint therapy, and physiotherapy), minimally invasive (e.g., arthrocentesis), and surgical (e.g., arthroscopic and open joint surgeries) interventions.[11] A similar pain-reducing effect of physiotherapy and splint therapy has been confirmed in patients with myofascial TMD pain.[14] Diraçoğlu et al.[13] concluded that neither reversible methods nor arthrocentesis was beneficial in the early treatment of TMD. A previous randomised controlled trial found no difference between medical management, non-surgical rehabilitation, arthroscopic surgery, and arthroplasty in terms of TMJ pain and mandibular mobility at a 60-month follow-up.[12] The comparable therapeutic effects of different intervention modalities suggest that the least expensive, least invasive, and simplest interventions should be employed for the initial management of TMD.[11]

Although promising outcomes have been reported with reversible treatment, the results remain controversial.[15] One prospective cohort study followed 40 TMD patients for 2.5 years and found that 43% of the patients were free of symptoms, 33% of the patients had decreased symptoms, and 25% showed no improvement or required further treatment.[15] Similarly, nearly 50% of patients who received reversible treatment reported no pain five years later, although 14% of patients continued to report significant pain.[16] Little is known about the clinical characteristics of these TMD patients who experience a poor prognosis following reversible treatment. These findings suggest that prognostic information is critical when predicting the impact of reversible interventions in a population with TMD. However, there is a paucity of research that aims to identify prognostic factors associated with the clinical outcomes of reversible treatment in people with TMD.[17-19] Previous studies have concluded that numerous biopsychosocial factors increase the risk of developing first-onset TMD; therefore, we speculated that these factors may have a theoretical association with prognosis in individuals with TMD. Moreover, the TMD status changes substantially over time, and acute TMD becomes chronic in 25% of patients, as the course of TMD progression can be

highly variable.[20] Long-term follow-up studies are needed to investigate the prognostic factors that influence the response to reversible treatment and the risk factors that are associated with the development of chronic TMD.

The aims of this prospective cohort study are: 1) to identify prognostic factors that are associated with clinical outcomes of reversible treatment in patients with TMD; and 2) to analyse risk factors that influence the development of chronic TMD during a 1-year follow-up period. Based on current knowledge of risk factors for the development of TMD that have been reported in epidemiological studies, putative prognostic factors, including demographic data, data from self-report questionnaires, and measures of physical function will be collected and analysed.

Specific aims

Aim 1: To determine whether demographic characteristics and biopsychosocial factors are associated with the prognosis of reversible treatment for TMD.

Aim 2: To determine the risk factors associated with chronic TMD.

TRIAL DESIGN AND METHODS

This clinical-based, prospective, cohort study will be conducted at Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine. This protocol has been designed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement and Prognosis Research Strategy (PROGRESS) guidelines.[21] The results of this study will be reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[22]

Participants

We will recruit 834 patients with TMD presenting to the rehabilitation department. Consecutive eligible patients will receive 1–4 weeks of reversible treatment and will be followed up for 12 months after baseline measurements. The reversible treatment programme

has been reproduced from a previous systematic review on patients with TMD.[23] The 1-year follow-up has been pre-registered before patient enrolment. Study recruitment will commence in December 2020 and will be completed by December 2021.

The participants must meet the following inclusion criteria:

1. Patients aged 20–45 years.

2. Patients fulfilling the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD).[24]

3. Patients with myofascial pain or reducible or non-reducible disc displacement.

4. Patients should have one of the following symptoms:

    a: visual analogue scale (VAS) score for orofacial pain ≥ 4;

    b: maximal mouth opening < 35 mm.

5. Understanding of the survey and ability to independently complete the questionnaires.

6. Patients must volunteer to participate in the study and sign the consent form.

7. Patients receiving at least one type of reversible treatment (e.g., education, self-management, medication, therapeutic exercise, manual therapy, and occlusal splint therapy).

The participants will be excluded if they meet one of the following conditions at baseline:

1. History of traumatic facial injury or surgery.

2. Malignant disease, active rheumatologic disease, haemorrhagic disease, heart disease, or heart failure.

3. Pregnant or lactating women or women who plan to be pregnant within the next year.

Drop-out criteria: Participants will have the right to drop out of the study at any time. Participants who meet one of the following conditions will be removed from the study:

1. The researcher believes that removal from the study will benefit the patient.

2. Failure to adhere to the follow-up time schedule or refusal to respond to the required questionnaires.

Recruitment

Patients will be recruited from the rehabilitation department of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine. We will recruit eligible patients

at their first clinic visit. Prior to study initiation, training will be delivered to the clinical examiners working at the physiotherapy clinic to inform them of the study and how to screen patients for eligibility. X.L. will serve as the reference examiner throughout the study. In a separate training session, each study examiner will conduct more than 10 blinded, replicated examinations of non-study volunteers. Data from the blinded, replicate examinations will be analysed for inter-examiner reliability computed using the Kappa statistic. Providers will have copies of the screening form to screen potential patients according to the inclusion and exclusion criteria. At the first outpatient visit, a potential patient will be informed about the study. All study participants will be required to provide written informed consent at the time of recruitment.

Candidate prognostic factors

Owing to the lack of consensus on the prognostic factors that influence the response to reversible treatment for TMD, demographic data, physical measurements, data from self-report questionnaires, and information about the type of treatment modality will be collected. Putative factors have been selected based on current knowledge of risk factors for the development of TMD from epidemiological studies that may have a theoretical association with prognosis in individuals with TMD, as confirmed by the biopsychosocial model of developing TMD. These selected factors are feasible to measure in clinical settings. The candidate prognostic factors are summarised in Table 1. All data collection will be standardised using clinical report forms and protocols.

Data collection

Baseline data, including demographic data, data from self-report questionnaires, and physical assessments will be collected by a trained assessor at the first clinic visit. Patients will receive 1–4 weeks of reversible treatment within 2 weeks following recruitment, and the treatment modalities that patients receive will be recorded. Patients will be contacted by the same assessor by telephone 3, 6, and 12 months after baseline measurements to complete the physical examination and functional questionnaires (Figure 1).

Baseline interview, self-report questionnaires, and physical examination

During the first clinic visit, the researcher will collect each patient's demographic data (e.g., sex, age distribution, educational attainment, marital status), case histories, intercurrent diseases (e.g., pain related to the neck and TMJ region, general musculoskeletal pain elsewhere), and use of medication. Anamnestic data will be collected at baseline, including the nature, duration, and intensity of the pain. The intensity of the present facial pain, including masticatory muscle pain and TMJ pain at rest and during movements of the mandible according to the DC/TMD criteria, will be assessed with the VAS. The VAS scale is a measurement instrument that quantifies an attitude or characteristic that ranges across a continuum of values and cannot be directly measured.[25] Operationally, it is usually depicted using a horizontal line, 100 mm in length, with word descriptors at each end. The patient marks the point on the line that represents their current feelings. The VAS score, measured in millimetres, is determined as the distance from the left end to the point that the patient marks.

Patients will be asked to complete self-report questionnaires and will follow the procedure shown in Table 1. Oral behaviours will be assessed at baseline using the Oral Behaviours Checklist, which is a self-report questionnaire comprising 21 items used to quantify the frequency of oral behaviours and has been evaluated as part of a larger study of the diagnostic validity and reliability of techniques for diagnosing TMD.[26]

The Patient Health Questionnaire (PHQ) is a self-administered diagnostic instrument for common mental disorders. The PHQ-15 assessed 15 somatic symptoms from the PHQ, and the PHQ-9 comprises nine items to establish a depressive disorder diagnosis, in addition to grading depressive symptom severity.[27] Generalised anxiety disorder (GAD) is a common mental disorder among TMD patients, and a 7-item anxiety scale (GAD-7) is a self-report scale to determine probable cases of GAD, with good reliability and procedural validity.[28]

The Pittsburgh Sleep Quality Index provides a valid, standardised, clinically useful measure of a variety of sleep disturbances that may affect sleep quality.[29]

The Jaw Functional Limitation Scale (JFLS) comprises 20 items used to assess limitations of jaw function in patients with TMD.[30]

Finally, a functional examination of the masticatory system and diagnosis of patients according to the DC/TMD criteria[24] will be conducted by the same clinician. Clinical stomatognathic assessments of TMD include the range of motion of the mandible, TMJ sounds, and a patient's head and neck posture.[31] The range of motion of the mandible will be measured with a Vernier caliper.[25] When performing measurement of the anterior maximal opening, the examiner will ask the patient to place the mandible in a comfortable position. The patient will be asked to open the mouth as far as possible without assistance. The edge of the millimetre ruler will be placed at the incisal edge of the maxillary central incisor for maximal vertical orientation to the labio-incisal edge of the opposing mandibular incisor. This measurement will be considered the interincisal opening. If subjects open their mouth less than 30 mm, the process will be repeated to ensure understanding. If the second opening is still less than 30 mm, the measurement will be recorded as the interincisal opening. To measure the vertical incisal overlap, the patient will be asked to perform the action of biting to bring the teeth together. The line where the incisal edge of the same previously measured maxillary central incisor overlaps the mandibular incisor will be marked with a pen. The distance from the mandibular incisal edge to the marked line will be recorded as the vertical incisal overlap. The anterior maximal opening will be considered as the sum of the interincisal opening and the vertical incisal overlap.[32]

The objective method of assessing head and neck posture will be to measure the craniovertebral (CV) angle and the cranial rotation angle.[33] The CV angle will be defined as the angle between the horizontal plane (the line perpendicular to true vertical axis) and the line extending from the tragus of the ear to the C7 spinous process.[34] The cranial rotation angle will be formed by a line connecting the lateral canthus and the tragus with a horizontal line.[34] Measurement of the cervical angle will be performed using a protractor. The digitisation procedure has been proven to be highly reliable.[33] Sagittal plane imaging of the upper body of each patient will be conducted using a digital camera in a habitual relaxed, seated position. The patient will be asked to assume a comfortable habitual sitting position with the eyes focused toward the front, and the height of the chair will be 45 cm. Red markers will be placed over the tragus and C7 spinous process by the same examiner. To ensure

consistency in the images, the distance between the camera and the patient will be 1.5 m, and the camera will be adjusted to remain aligned with the patient's shoulder.

Interventions

Patients included in the study will be invited to attend a study session at the physiotherapy clinic. At this session, patients will receive a standardised reversible treatment programme within 2 weeks of recruitment and will be followed up for a period of 12 months after baseline. According to the recommendations from the current systematic reviews and meta-analyses, the least invasive, simplest, and reversible interventions are considered as first-line therapy options for TMD. An experienced physiotherapist will design a reversible treatment programme according to each patient's clinical symptoms, characteristics, and willingness. The programme will include education, self-management, medication, therapeutic exercise, manual therapy, and occlusal splint therapy, as previously reported.[23] Patients will be informed of the reasoning behind the treatment plan and provided detailed information about it.

For patients who meet the inclusion criteria but refuse to participate in the study, the standard of care treatment will be given. To promote patient retention, the researcher will inform the potential patient that although they can withdraw at any time, dropping out without a reason reduces the ability to answer the research question and, therefore, weakens the study. Patients will be advised to carry on with their usual daily routines, and any interventions received during reversible therapy sessions will be recorded for a descriptive analysis. The details of the treatment (e.g., time, number, duration, modality) and the number of and reasons for dropouts will be documented and reported, as well as any adverse events during the study. Participants will be monitored during the 1- to 4-week programme and the 12-month follow-up period. Data from patients receiving monotherapy or adjuvant therapy will be analysed separately.

Outcomes

The primary treatment outcome measures will be changes in the anterior maximal opening,

worsening of TMD pain assessed using the VAS, and changes in pain characteristics. A previous study concluded that the greatest improvement occurs between 3 and 4 months after baseline;[35] therefore, 3 months was chosen as the treatment outcome evaluation time point in this study. An anterior maximal opening of ≥ 35 mm and a reduction in VAS scores of at least 30% three months after baseline will be defined as good clinical outcomes.[17] Additional outcome measures will include changes in the frequency of TMD pain (recurrent, persistent, and one-time experience), JFLS scores, and the diagnosis of chronic TMD. The patients will be asked to report discomfort and complications associated with the reversible treatment and how often they perform the treatment. Additionally, all outcome measures will be evaluated 6 and 12 months after baseline measurements and will be assessed using predictive modelling.

Data management

All data will be entered into the research folder, and a researcher will transfer them into the master data spreadsheet. Privacy of patient data will be maintained for all data handling procedures (collection transfer, storage, and processing). The accuracy of the data will be guaranteed through a secondary review by study co-authors. Data recorded from each participant will anonymized using research numbers and will be accessible only by members of this research team. A spreadsheet will be stored on a portable drive, and the research folders will be locked in a cabinet.

Trial organisation and monitoring

The research team will consist of the authors listed in this article, in addition to administrative staff at the physiotherapy clinic who will assist with the entire process of the study and data entry. The primary investigator will manage the study flow and perform inspections of enrolment, treatment, and procedures throughout the entire study. Other investigators will monitor data collection and facilitate the maintenance of data integrity through periodic evaluations during the data collection phase.

Data analysis

Numbers of individuals will be recorded, including those who are potentially eligible, confirmed eligible, recruited into the study, receiving reversible treatment, and completing follow-up. Numbers related to withdrawals and loss to follow-up will be reported, along with reasons for removal from the study. Descriptive analyses of patients at baseline will include demographic, self-report questionnaire, and physical assessment data.

All analyses will be performed using Statistical Package for the Social Sciences (SPSS) software (version 25.0). The Kolmogorov–Smirnov test will be performed to assess whether the data are normally distributed ($p>0.05$), considering that both parametric and non-parametric tests will be used in the data analyses. Linear regression, unpaired t-tests, chi square tests, and logistic regression will be used depending on the analysis to be performed. A multiple linear regression analysis will be conducted to develop a linear model to determine the associations between candidate prognostic factors and the response to reversible treatment in patients with TMD, with anterior maximal opening and TMD pain as continuous dependent variables. For assessing risk factors for the development of chronic TMD, univariate associations between categorical variables (treatment, sex, etc.) and the diagnosis of chronic TMD according to the DC/TMD criteria will be evaluated using $\chi 2$ tests. Continuous variables (age, height, etc.) and the diagnosis of chronic TMD according to the DC/TMD criteria will be evaluated using student's unpaired *t*-tests with a Bonferroni correction. Multivariate analyses will be performed using binary logistic regression with forced entry of all independent variables. All analyses will be two-tailed, with a threshold for statistical significance of $P<0.05$.

Sample size calculation

This prospective cohort study was designed with a target sample size of 834 enrolled patients with TMD to investigate the association between 20 candidate prognostic factors and the clinical outcome of reversible treatment in patients with TMD over the 1-year follow-up period, assuming 20% loss to follow-up. The researchers will ensure that there are at least 10 participants per prognostic factor to conduct an adequately powered linear regression analysis.[36] In a previous study, 70% of TMD patients who received reversible treatment

reported good outcomes.[12] Therefore, a sample size of 834 participants will be adequate to power a linear regression analysis of 20 candidate prognostic factors.

Management of missing data

For each variable of interest, the number of patients with missing data will be reported. Any potential bias due to loss to follow-up will be assessed and compared using baseline data of patients who withdraw or are lost to follow-up.[37] Multiple imputation will be used to deal with missing outcome data, if necessary.[38] Participants will be excluded from the predictive model and subsequent analyses if they request to withdraw from the study following recruitment.[37]

Patient and public involvement

No patients were involved with the design or will be involved in data collection, analysis, or publication of the study.

DISCUSSION

This will be the first protocol to describe methods and analysis for identifying prognostic factors associated with clinical outcomes of reversible treatment in individuals with TMD. In particular, self-report measures combined with physical examinations will be incorporated to predict poor outcomes of reversible treatments in individuals with TMD. The candidate prognostic factors have been selected based on current knowledge of risk factors for developing first-onset TMD and their possible utilisation in clinical practice. The knowledge gained through this study will provide a better understanding of how these prognostic factors can be used to improve clinical outcomes, including whether reversible treatment is useful in the clinical management of TMD patients.

This study will be conducted in accordance with the SPIRIT statement and PROGRESS framework.[21 37] The results of this study will provide new insights into who is likely to benefit from reversible treatment versus who is likely to develop chronic TMD. Between 57% and 71% of patients seeking treatment for acute TMD continue to report significant pain 6 months

later.[9 39] Therefore, the evaluation of prognoses will be valuable for treatment planning for patients with TMD. In clinical practice, the heterogeneity of patient characteristics and psychosocial factors may be considered in treatment planning.

Despite the novelty of this trial, this study has some limitations. Firstly, the candidate prognostic factors have been selected based on reported risk factors for developing first-onset TMD; however, some possible prognostic factors may be ignored. In future studies, we may include more candidate prognostic factors. Secondly, since the reversible treatment is a combined treatment, we cannot ascertain the effects of medication or manual therapy alone; however, we will explore the prognosis associated with each treatment component.

ETHICS AND DISSEMINATION

The protocol was approved by the Ethics Committee of Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China, based on the guidelines set forth in the Declaration of Helsinki (SH9H-2019-T316-4). An ethics review protects human medical research participants to ensure compliance with federal regulations. Any modifications to the protocol that may impact study procedures or the conduct of the study will require approval by the Institutional Review Board and a formal amendment to the protocol. This clinical trial has been registered with the Chinese Clinical Trial Registry (www.chictr.org.cn), with the registration number ChiCTR2000033328.

All study participants will provide written informed consent prior to randomisation. Patients included in this study have the right to withdraw at any time, and the reasons will be documented. If participants have trouble complying with the intervention or completing follow-up testing, they can discuss these challenges with the study coordinator. If participants miss measurement appointments, up to three reminders will be sent, and, if necessary, the participant will be contacted by telephone to rearrange an appointment for measurements at an appropriate time. Regardless of the outcome, the results of the trial will be reported in accordance with the STROBE guidelines in a relevant scientific journal.

TRIAL STATUS

Recruitment started in December 2020 and is estimated to be completed in December 2021.

Authors' contributions All authors are involved in the design of the study. LX initiated the study. BC, LX, SL, LZ and SF contributed to the planning and design. LZ, BC and LX drafted the study protocol and design. WS and SF will perform the statistical analysis. LX, LZ, YY and SF are responsible for managing the research. LX is the supervisor of the project.

Funding This work is supported by the Clinical Research Program (Grant no. JYLJ201901) and the Shanghai Municipal Science and Technology Major Project (Grant No. 19441908400).

Competing interests None declared.

Patient consent for publication Obtained.

Ethics approval Ethics Committee of Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China (SH9H-2019-T316-4).

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request.

REFERENCE

1. Duckro PN, Tait RC, Margolis RB, *et al.* Estimated prevalence and distribution of reported orofacial pain in the United States. *J Am Dent Assoc* 1993;124:115-21.
2. Sharma S, Wactawski-Wende J, LaMonte M, *et al.* Incident injury is strongly associated with subsequent incident temporomandibular disorder: results from the OPPERA study. *J Pain* 2019;160:1551-61.
3. Wänman A, Marklund S. Treatment outcome of supervised exercise, home exercise and

bite splint therapy, respectively, in patients with symptomatic disc displacement with reduction: a randomised clinical trial. *J Oral Rehab* 2020;47:143-9.

4. Slade G, Ohrbach R, Greenspan J, *et al.* Painful temporomandibular disorder: decade of discovery from OPPERA studies. *J Dental Res* 2016;95:1084-92.
5. Ohrbach R, Bair E, Fillingim R, *et al.* Clinical orofacial characteristics associated with risk of first-onset TMD: the OPPERA prospective cohort study. *J Pain* 2013;14:33-50.
6. Sanders A, Slade G, Bair E, *et al.* General health status and incidence of first-onset temporomandibular disorder: the OPPERA prospective cohort study. *J Pain* 2013;14:51-62.
7. Fillingim R, Ohrbach R, Greenspan J, *et al.* Associations of psychologic factors with multiple chronic overlapping pain conditions. *J Oral Facial Pain Headache* 2020;34:85-100.
8. Greenspan J, Slade G, Rathnayaka N, *et al.* Experimental pain sensitivity in subjects with temporomandibular disorders and multiple other chronic pain conditions: the OPPERA prospective cohort study. *J Oral Facial Pain Headache* 2020;34:43-56.
9. Fillingim R, Slade G, Greenspan J, *et al.* Long-term changes in biopsychosocial characteristics related to temporomandibular disorder: findings from the OPPERA study. *J Pain* 2018;159:2403-13.
10. Sanders A, Greenspan J, Fillingim R, *et al.* Associations of sleep disturbance, atopy, and other health measures with chronic overlapping pain conditions. *J Oral Facial Pain Headache* 2020;34:73-84.
11. Al-Baghdadi M, Durham J, Araujo-Soares V, *et al.* TMJ disc displacement without reduction management: a systematic review. *J Dental Res* 2014;93:37-51.
12. Schiffman E, Velly A, Look J, *et al.* Effects of four treatment strategies for temporomandibular joint closed lock. *Int J Oral Maxillofac Surg* 2014;43:217-26.
13. Diraçoğlu D, Saral I, Keklik B, *et al.* Arthrocentesis versus nonsurgical methods in the treatment of temporomandibular disc displacement without reduction. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009;108:3-8.
14. Giannakopoulos N, Rauer A, Hellmann D, *et al.* Comparison of device-supported

sensorimotor training and splint intervention for myofascial temporomandibular disorder pain patients. *J Oral Rehab* 2018;45:669-76.

15. Kurita K, Westesson P, Yuasa H, *et al.* Natural course of untreated symptomatic temporomandibular joint disc displacement without reduction. *J Dent Res* 1998;77:361-5.
16. Ohrbach R, Dworkin S. Five-year outcomes in TMD: relationship of changes in pain to changes in physical and psychological variables. *J Pain* 1998;74:315-26.
17. Grossi M, Goldberg M, Locker D, *et al.* Reduced neuropsychologic measures as predictors of treatment outcome in patients with temporomandibular disorders. *J Orofac Pain* 2001;15:329-39.
18. Burris JL, Evans DR, Carlson CR. Psychological correlates of medical comorbidities in patients with temporomandibular disorders. *J Am Dent Assoc* 2010;141:22-31.
19. Lipton JA, Marbach JJ. Predictors of treatment outcome in patients with myofascial pain-dysfunction syndrome and organic temporomandibular joint disorders. *J Prosthodont Dent* 1984;51:387-93.
20. Rollman A, Visscher C, Gorter R, *et al.* Improvement in patients with a TMD-pain report. A 6-month follow-up study. *J Oral Rehab* 2013;40:5-14.
21. Chan A, Tetzlaff J, Altman D, *et al.* SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med* 2013;158:200-7.
22. Elm V, Erik, Altman, *et al.* The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. *Ann Intern Med* 2007;156:568-75.
23. Gauer RL, Semidey MJ. Diagnosis and treatment of temporomandibular disorders. *Am Family Phys* 2015;91:378-86.
24. Türp G, Christoph J. Diagnostic criteria for temporomandibular disorders (DC/TMD) - presentation of the axis I classification. *J Craniomandibular Function* 2014;23:45-51.
25. Katyayan P, Katyayan M, Shah R, *et al.* Efficacy of appliance therapy on temporomandibular disorder related facial pain and mandibular mobility: a randomized controlled study. *J Indian Prosthodont Soc* 2014;14:251-61.
26. Vand M, Lobbezoo F, Aartman IHA, *et al.* Validity of the Oral Behaviours Checklist:

correlations between OBC scores and intensity of facial pain. *J Oral Rehab* 2014;41:115-21.

27. Kroenke K, Spitzer RL, Williams JBW. The PHQ-15: validity of a new measure for evaluating the severity of somatic symptoms. *Psychosom Med* 2002;64(2):258-66.
28. Spitzer RL, Kroenke K, Williams JB, *et al.* A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med* 2006;166:1092.
29. Buysse D. The Pittsburgh sleep quality index (PSQI). An instrument for psychiatric practice and research. *Psychiatr Res* 1989;28:234-9.
30. Zhang Y, Chung SC, Chung JW. Evaluation of jaw functional limitation in TMD patients using a korean version of jaw functional limitation scale (JFLS). *J Oral Med Pain* 2004;29:346-54.
31. Ohrbach R, Fillingim R, Mulkey F, *et al.* Clinical findings and pain symptoms as potential risk factors for chronic TMD: descriptive data and empirically identified domains from the OPPERA case-control study. *J Pain* 2011;12:27-45.
32. Dworkin S, LeResche L. Research diagnostic criteria for temporomandibular disorders: review, criteria, examinations and specifications, critique. *J Craniomandibular Disorders* 1992;6:301-55.
33. Lau HMC, Chiu TTW, Lam TH. Clinical measurement of craniovertebral angle by electronic head posture instrument: a test of reliability and validity. *Manual Ther* 2009;14:363-8.
34. Joy T, Tanuja S, Pillai R, *et al.* Assessment of craniocervical posture in TMJ disorders using lateral radiographic view: A cross-sectional study. *Cranio* 2019;34:1-7.
35. Duc J, Hüning S, Grossi ML. Parallel randomized controlled clinical trial in patients with temporomandibular disorders treated with a CAD/CAM versus a conventional stabilization splint. *Int J Prosthodont* 2016;29:340-50.
36. Royston P, Moons K, Altman D, *et al.* Prognosis and prognostic research: developing a prognostic model. *BMJ* 2009;338: 604.
37. Riley R, Hayden J, Steyerberg E, *et al.* Prognosis Research Strategy (PROGRESS) 2: prognostic factor research. *PLoS Med* 2013;10: 100-8.

38. Sterne JAC, White IR, Carlin JB, *et al.* Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;338:2393.

39. Garofalo J, Gatchel R, Wesley A, *et al.* Predicting chronicity in acute temporomandibular joint disorders using the research diagnostic criteria. *J Am Dent Assoc* 1998;129:438-47.

552

553

Table 1 Summary of measures that will be collected

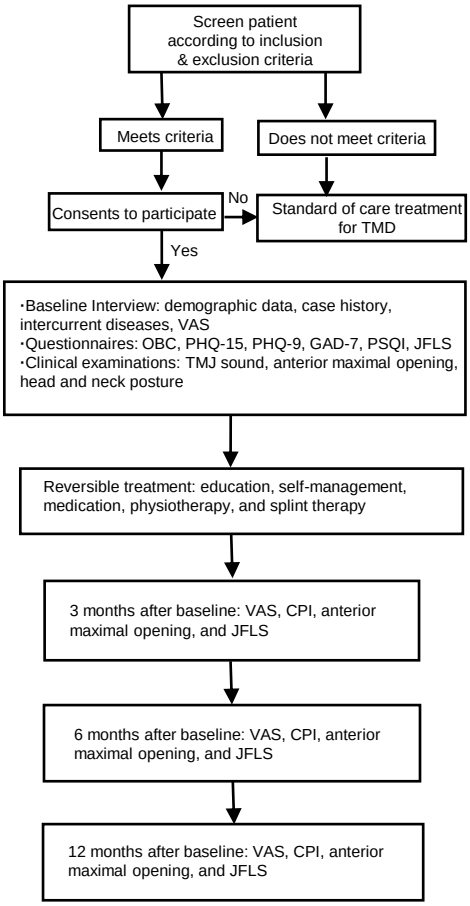
Domain/candidate predictor	Baseline	Month 3	Month 6	Month 12
Fill out by clinicians				
Inclusion or exclusion standard table	√			
Sign informed notice	√			
Demographic data and case history	√			
Intercurrent diseases	√			
Anterior maximal opening	√	√	√	√
Head and neck posture	√			
Adverse events	√	√	√	√
Clinical routine inspection	√			
CPI		√	√	√
Filled out by subjects				
VAS score	√	√	√	√
OBC	√			
PHQ-15	√			
PHQ-9	√			
GAD-7	√			
PSQI	√			
JFLS	√	√	√	√

554 CPI, characteristic pain intensity; VAS, visual analogue scale; OBC, Oral Behaviors Checklist;
555 PHQ, Patient Health Questionnaire; GAD, generalized anxiety scale; PSQI, Pittsburgh Sleep
556 Quality Index; JFLS, Jaw Functional Limitation Scale

Figure Legends

Figure 1 Participants recruitment and flow of the study.

TMD, temporomandibular disorders; VAS, visual analogue scale; OBC, Oral Behaviors Checklist; PHQ, Patient Health Questionnaire; GAD,generalized anxiety disorder; PSQI, Pittsburgh Sleep Quality Index; JFLS, Jaw Functional Limitation Scale; TMJ, temporomandibular joint; CPI, characteristic pain intensity


Screen patient according to inclusion & exclusion criteria
Meets criteria
Does not meet criteria
Consents to participate
No
Standard of care treatment for TMD
Yes
·Baseline Interview: demographic data, case history, intercurrent diseases, VAS
·Questionnaires: OBC, PHQ-15, PHQ-9, GAD-7, PSQI, JFLS
·Clinical examinations: TMJ sound, anterior maximal opening, head and neck posture
Reversible treatment: education, self-management, medication, physiotherapy, and splint therapy
3 months after baseline: VAS, CPI, anterior maximal opening, and JFLS
6 months after baseline: VAS, CPI, anterior maximal opening, and JFLS
12 months after baseline: VAS, CPI, anterior maximal opening, and JFLS

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	1-2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3-5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5-10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (*b*) For matched studies, give matching criteria and number of exposed and unexposed	6 6-7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7--9
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	11
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding (*b*) Describe any methods used to examine subgroups and interactions (*c*) Explain how missing data were addressed (*d*) If applicable, explain how loss to follow-up was addressed (*e*) Describe any sensitivity analyses	11 11 11 11 11
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	None
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	None
Outcome data	15*	Report numbers of outcome events or summary measures over time	None

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included (*b*) Report category boundaries when continuous variables were categorized (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	None
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	None
Discussion			
Key results	18	Summarise key results with reference to study objectives	N/A
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	N/A
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	N/A
Generalisability	21	Discuss the generalisability (external validity) of the study results	N/A
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	13

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.