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SYSTEMATIC REVIEW

The influence of estrogen on temporomandibular disorders: an umbrella review of systematic reviews identifying critical knowledge gaps

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Abstract

Background: The higher prevalence of temporomandibular disorders (TMD) among women suggests a potential influence of female hormones, particularly estrogen. However, the existing evidence regarding the role of estrogen in development and progression TMD remains inconsistent and fragmented. This umbrella review aimed to synthesize evidence from published systematic reviews examining the influence of estrogen-related factors on TMD, and to identify critical gaps in the existing knowledge. **Methods**: A comprehensive literature search was performed across PubMed, Scopus, Web of Science, CiNii, and Google Scholar using Medical Subject Headings (MeSH) terms and Boolean operators. The search covered studies published between 01 January 2000 and 01 September 2025, limited to English-language articles. The risk of bias of the included reviews was assessed using Risk of Bias in Systematic Reviews (ROBIS), and the extent of overlap between studies was evaluated using the corrected covered area. **Results**: Twenty studies were selected for full-text assessment, of which eight systematic reviews met the inclusion criteria. There was moderate evidence to support the role of estrogen in temporomandibular joint (TMJ) pain modulation; however, this conclusion was primarily derived from systematic reviews with heterogeneous methodologies and variable risk-of-bias profiles. The interpretation of these findings was constrained by the methodological limitations and risk of bias identified in several of the included reviews. **Conclusions**: TMD are multifactorial conditions involving interactions among hormonal, genetic, and functional factors. Although current evidence suggests a potential role of estrogen in modulating TMJ pain, findings remain inconclusive due to methodological variability and the risk of bias among existing systematic reviews. Significant knowledge gaps remain, highlighting the need for well-designed, longitudinal studies using standardized methodologies to clarify the role of estrogen in the pathophysiology of TMD. **The PROSPERO Registration**: CRD420251129568.

Keywords

Estrogen; Temporomandibular joint; Temporomandibular diseases; Temporomandibular joint disorders; Systematic review; Meta-analysis

1. Introduction

The temporomandibular joint (TMJ) serves as the link between the mandible and the temporal bone of the skull. This joint allows for complex movements that are essential for the healthy functioning of the stomatognathic system. Its anatomy comprises various components, such as the condyle, the glenoid fossa, and the articular disc. These components work together to facilitate the joint functions smoothly. Ligaments provide joint stability, whereas the masticatory muscles coordinate mandibular movements. Healthy TMJ function involves the coordinated movement of the condyle and disc, consisting of condylar rotation around its axis, as well as the translation of the condyle–disc assembly when the mouth opens and closes [1].

Different terminologies are used in the literature to describe disorders affecting the temporomandibular region, which often leads to overlap and inconsistency in their usage. According to the Diagnostic Criteria for Temporomandibular Disorders (DC/TMD), TMD represent a broad and heterogeneous group of musculoskeletal and neuromuscular conditions affecting the TMJs, the masticatory muscles, and the associated structures. These conditions are categorized as myogenous or arthrogenous disorders [2]. Arthrogenous TMD includes intra-articular conditions such as disc displacement and degenerative joint disease, whereas myogenous TMD primarily

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involves the masticatory muscles. However, certain TMJ-specific pathologies—such as condylar resorption—are not categorized within the DC/TMD classification despite representing clinically significant structural joint alterations. Furthermore, many studies report findings at the level of TMD without distinguishing between muscular and joint-specific conditions, leading to heterogeneity and ambiguity in interpretation. In this umbrella review, the term "TMJ-related outcomes" is used to collectively describe pain-related, functional, inflammatory, and structural joint findings reported across the included reviews.

Epidemiological evidence consistently demonstrates a marked predominance in females, with women being affected 1.5 to 2 times more frequently than men, particularly during their reproductive and peri-menopausal years [3]. This sex-related disparity suggests the involvement of biological mechanisms, including hormonal and metabolic factors [3], and may also manifest as differences in TMD symptom presentation and functional limitations [4]. Given the presence of estrogen receptors (ERs) in TMJ tissues, this sex-related difference has prompted extensive investigations into the impact of estrogen levels on the pathogenesis of TMD. The effects of estrogen are mediated by binding to its receptors. The three types of ERs are two nuclear—alpha (ERα) and beta (ERβ), and one plasmatic—G-protein coupled ER 1 (GPER1) [5–7]. These ERs are involved in regulating various cellular processes, including those in cartilage tissue and intra-articular osteocytes [8–10]. ERs are known to modulate pain, inflammation, and tissue repair. Their presence in TMJ cartilage, as well as in adjacent structures such as the muscles and ligaments, suggests that fluctuations in estrogen levels can influence TMJ structure and function, potentially contributing to the onset or progression of TMD [11, 12]. Furthermore, estrogen has been shown to promote the release of matrix metalloproteinases (MMPs), which are enzymes responsible for breaking down collagen and other components of the extracellular matrix, leading to the remodelling of mandibular condyles [13, 14].

Previous animal studies have provided evidence that estrogen depletion causes significant structural changes in the TMJ [15–17]. However, existing research is fragmented with varying conclusions. This umbrella review aimed to synthesize evidence from existing systematic reviews on the influence of estrogen-related factors on TMD. The review also aimed to identify critical knowledge gaps in the current literature and evaluate the methodological quality and strength of the available evidence.

2. Materials and methods

The protocol of this umbrella review was registered with Prospective Register of Systematic Reviews (PROSPERO) under the number CRD420251129568. The search strategy was based on the Population, Exposure, and Outcome (PEO) framework to address the following clinical question: Do estrogen hormone levels influence TMD? The population (P) comprised human participants with TMD or populations in which TMJ-related outcomes were assessed. The exposure (E) was altered estrogen states (endogenous levels, menstrual cycle phases, menopause, oral contraceptives, hormone replacement therapy and ERs in the TMJ). The outcomes of interest (O) were the presence, severity, or clinical characteristics associated with TMD. A Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram summarizing the selection process was provided in Fig. 1.

2.1 Search strategy

A comprehensive literature search was performed using controlled vocabulary (MeSH terms) where applicable and free-text keywords combined with Boolean operators across 5 search engines: PubMed, Scopus, Web of Science, CiNii, and Google Scholar. The search spanned from 01 January 2000 to 01 September 2025. The time frame (2000–2025) was chosen to reflect the methodological standards in TMD research. The search was limited to English-language publications due to feasibility constraints and to ensure accurate assessment of methodological quality.

The full search strategy was developed for PubMed and subsequently adapted for other databases using equivalent keywords and database-specific field tags. The PubMed search strategy was as follows: Search keywords included terms for ("TMD"[MeSH] OR "TMD" OR "TMJ disorders" OR "temporomandibular dysfunction") AND ("estrogens"[MeSH] OR "estrogen" OR "estradiol" OR "hormone replacement therapy" OR "HRT" OR "oral contraceptives" OR "menstrual cycle" OR "menopause" OR "sex hormones") AND ("systematic review" OR "meta-analysis" OR "review"). For Scopus, the search was conducted using the TITLE-ABS-KEY field as follows: TITLE-ABS-KEY ("TMD" OR "TMJ disorders" OR "temporomandibular dysfunction" OR "temporomandibular disorder" OR "temporomandibular joint disorder") AND TITLE-ABS-KEY (estrogen OR oestrogen OR estradiol OR "sex hormone" OR "hormone replacement therapy" OR HRT OR "oral contraceptive" OR "menstrual cycle" OR menopause) AND TITLE-ABS-KEY ("systematic review" OR "meta-analysis" OR review). For Web of Science, the search was conducted using the Topic (TS) field as follows: TS = ("TMD" OR "TMJ disorders" OR "temporomandibular dysfunction" OR "temporomandibular disorder" OR "temporomandibular joint disorder") AND TS = (estrogen OR oestrogen OR estradiol OR "sex hormone" OR "hormone replacement therapy" OR HRT OR "oral contraceptive" OR "menstrual cycle" OR menopause) AND TS = ("systematic review" OR "meta-analysis" OR review). Equivalent keyword combinations were applied for Google Scholar and CiNii, without the use of controlled vocabulary including the search terms ("TMD" OR "TMJ disorders" OR "temporomandibular dysfunction" OR "temporomandibular disorder*" OR "temporomandibular joint disorder*") AND (estrogen OR oestrogen OR estradiol OR "sex hormone*" OR "hormone replacement therapy" OR HRT OR "oral contraceptive*" OR "menstrual cycle" OR menopause) AND ("systematic review" OR "meta-analysis" OR review). Due to the high volume of Google Scholar results, screening was limited to the first 200 results sorted by relevance, and titles and abstracts were assessed for eligibility. Grey literature

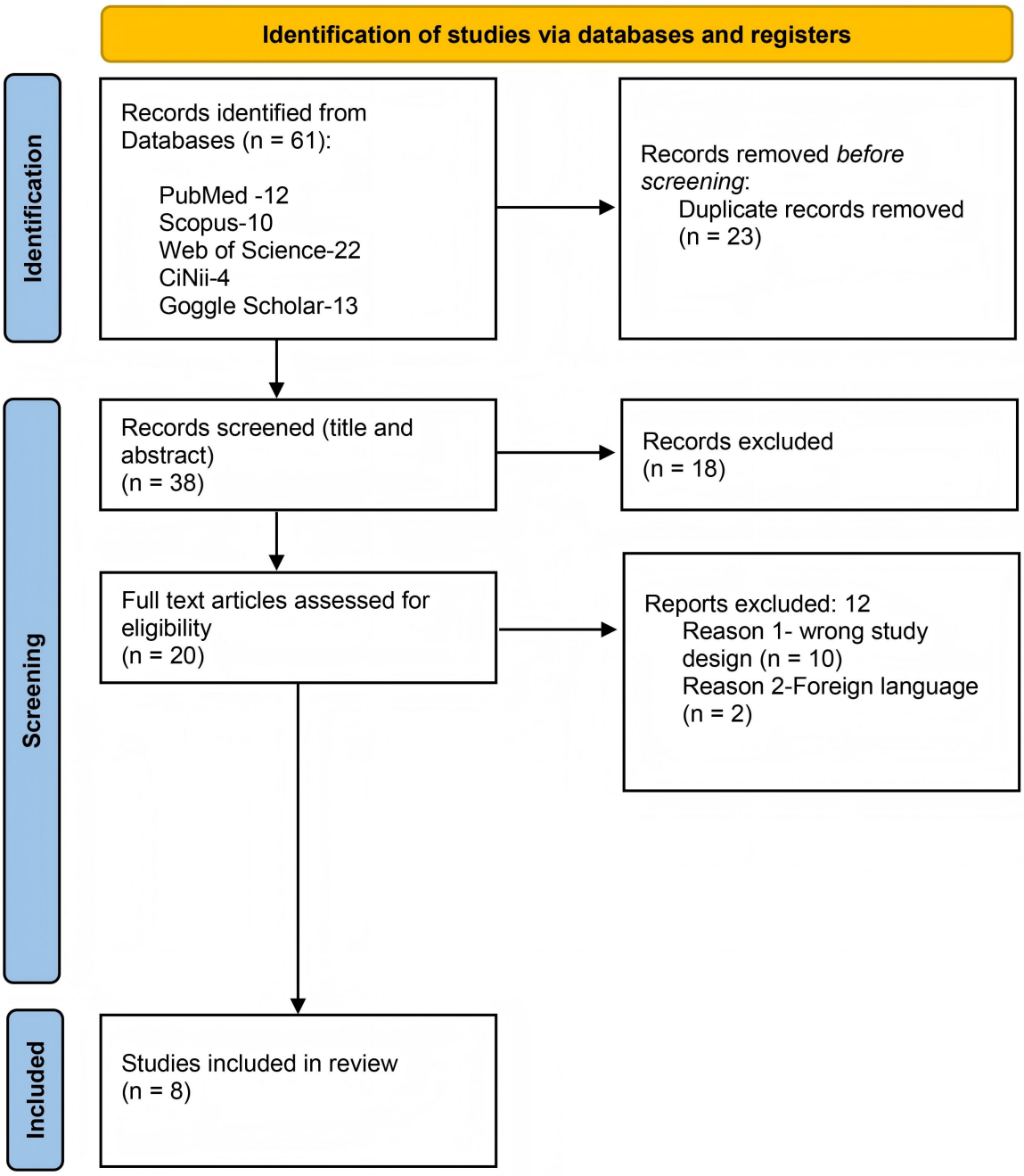


FIGURE 1. PRISMA flowchart for the study identification and inclusion.

sources, including preprints, dissertations, conference abstracts, and non-peer-reviewed repositories, were excluded, and only peer-reviewed systematic reviews were included. All the retrieved records were uploaded to Rayyan QCRI (https://rayyan.qcri.org/) for screening. Two independent reviewers screened the articles. Disagreements were resolved through discussion with a third reviewer until consensus was reached. Studies were evaluated based on their titles and abstracts; those meeting inclusion criteria underwent a full-text review.

2.2 Criteria for inclusion

We utilized the following inclusion criteria for this review:

Study design: Systematic reviews and/or meta-analyses.

Population: Human participants with TMD or populations in which TMJ-related outcomes were assessed.

Exposure/Intervention: altered estrogen states, including endogenous estrogen levels, hormonal status (*e.g.*, menstrual cycle, menopause), estrogen replacement therapy, oral contraceptive use, or ER expression or polymorphisms.

Outcomes: Presence, severity or clinical characteristics associated with TMD.

Language: English.

Publication type: Peer-reviewed journals.

2.3 Criteria for exclusion

We adopted the following exclusion criteria:

- Narrative reviews, scoping reviews, and case reports.
- Non-human studies.

2.4 Methodological quality assessment

The methodological quality of the included reviews was evaluated independently by two expert and certified reviewers using the risk of bias in systematic reviews (ROBIS) tool [18]. The evaluation was conducted in three main phases. Phase 1 assessed the relevance of the review; Phase 2 identified potential concerns in four key domains (study eligibility criteria, identification and selection of studies, data collection and appraisal, and synthesis and findings); and Phase 3 determined the overall risk of bias. In Phases 2 and 3, signalling questions within each domain were answered systematically, using the following response options: Yes (Y), Probably Yes (PY), Probably No (PN), No (N), and No Information (NI). Any discrepancies during the scoring process were resolved through discussion, and agreement was reached by consensus.

2.5 Data extraction and management

Data were extracted using a standardized form developed by the Joanna Briggs Institute for umbrella review and reported in accordance with the PRISMA 2020 guidelines [19, 20]. Two reviewers independently extracted data, with a third reviewer resolving eventual disagreements. The PRISMA checklist is provided as a **Supplementary material**.

Data extracted from each included systematic review comprised: author and year of publication; review objectives; population characteristics; number and design of included primary studies; estrogen-related exposures assessed; TMJ-related outcomes evaluated; main findings regarding the association between estrogen and TMD; methodological quality and risk-of-bias assessments; and authors' conclusions. These data were used to compare consistency of findings across reviews, evaluate methodological rigor, and assess the overall strength and limitations of the available evidence Greater interpretive emphasis was placed on systematic reviews with lower risk-of-bias ratings, while findings from higher-risk reviews were interpreted more cautiously, particularly where inconsistencies between studies were identified.

2.6 Study overlap

The Corrected Covered Area (CCA) was employed to quantify the degree of overlap among systematic reviews. The CCA is a standardized measure that accounts for the extent of shared primary studies across reviews. This helps to mitigate the risk of double-counting and ensures a balanced synthesis of evidence. A citation matrix was constructed, listing primary studies in rows and systematic reviews in columns, enabling the calculation of overlap using the CCA formula. To enhance the accuracy of the overlap assessment, the graphical representation of overlap for reviews (GROOVE) tool was utilized to provide a visual representation of the citation matrices and overlap proportions [21].

2.7 Quantitative heterogeneity matrix

To systematically characterize methodological heterogeneity across the included systematic reviews, a quantitative heterogeneity matrix was developed [22]. The matrix summarizes the frequency of major heterogeneity domains identified during data extraction and methodological appraisal.

2.8 Vote counting by direction-of-effect

A vote-counting approach based on direction-of-effect was performed to evaluate the consistency of findings across the included systematic reviews. This is a descriptive synthesis method that does not inherently account for methodological quality or risk of bias; therefore, all included systematic reviews contributed equally to the synthesis, irrespective of ROBIS ratings [23]. This represents a recognized limitation of the method. However, ROBIS assessments were considered during interpretation of the findings, with greater confidence assigned to trends supported by lower risk-of-bias reviews.

2.9 Certainty of evidence assessment

The certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) system, which provides a systematic method for rating the quality of evidence and strength of recommendations in systematic reviews [24]. In addition to methodological appraisal using the ROBIS tool, an umbrella-level qualitative certainty assessment was performed to improve interpretation of the synthesized evidence. The assessment considered five major domains: methodological limitations and risk of bias, inconsistency of findings, indirectness of evidence, imprecision of available data, and heterogeneity across studies. Certainty ratings were categorized as moderate, low, or very low depending on the overall confidence in the consistency and reliability of the available evidence.

3. Results

3.1 Study selection

A literature search across PubMed, Scopus, Web of Science, CiNii, and Google Scholar yielded a total of 61 records: 12 in PubMed; 10 in Scopus; 22 in Web of Science; 4 in CiNii; and 13 in Google Scholar. After removing 23 duplicates, 38 records remained for screening.

During title and abstract screening, 18 records were excluded as they did not meet the eligibility criteria, 6 were directly included, and 14 were marked as "maybe" and moved forward for full-text assessment.

A total of 20 full-text articles were evaluated (6 included + 14 maybe). Of these, 12 were excluded, primarily because they were narrative reviews, or did not assess estrogen-related exposures, or did not focus specifically on TMJ-related outcome. Ultimately, 8 systematic reviews or meta-analyses met the inclusion criteria and were included in the umbrella review [13, 14, 25–30]. Fig. 1 represents the PRISMA flow-chart.

3.2 Methodological quality of the included reviews

Using the ROBIS tool, the methodological quality of the included systematic reviews showed substantial variability. Two reviews were classified as a low risk of bias across all ROBIS domains. These reviews were characterized by well-defined eligibility criteria, comprehensive search strategies, appropri-

ate appraisal of primary studies, and cautious interpretation of findings [28, 29].

In contrast, four reviews were assessed as having a high risk of bias, primarily due to limitations in study identification, the use of non-validated or inappropriate appraisal tools, the inclusion of heterogeneous study designs and the reliance on narrative synthesis without adequate consideration of bias or certainty [13, 14, 25, 30]. Two reviews were judged to have a moderate risk of bias; these reviews generally demonstrated strong methodological processes, but were constrained by heterogeneity, restricted evidence bases, or synthesis approaches that limited the strength of inference [26, 27].

Consequently, findings derived from higher-quality reviews were given greater interpretive weight within this umbrella review. In particular, evidence supporting estrogen-associated pain modulation was more consistently supported by reviews with stronger methodological rigor, while evidence relating estrogen to disease occurrence, structural degeneration, and receptor polymorphism associations was more frequently derived from reviews with moderate-to-high risk of bias and heterogeneous evidence bases. This distinction is important because methodological limitations within weaker reviews may have amplified inconsistency and reduced confidence in causal interpretation (Fig. 2 (Ref. [13, 14, 25–30]) and Table 1 (Ref. [13, 14, 25–30])).

3.3 Study overlap analysis

Citation matrices were generated to determine the overlap in studies across systematic reviews. Corrected covered areas (CCAs) were calculated (CCA ≤5% (slight), 5% to <10% (moderate), 10% to <15% (high), and ≥15% (very high overlap)). Overall, CCA was found to be 6.54% in all 8 included studies, which is considered moderate (Fig. 3).

3.4 Study characteristics

Eight included systematic reviews/meta-analyses were published between 2015–2025 [13, 14, 25–30]. These reviews collectively addressed the relationship between estrogen (endogenous levels, menstrual cycle phases, menopausal status, oral contraceptives, hormone replacement therapy, or ER expression) and TMD.

Across these reviews, the primary studies included a mix of observational studies (cross-sectional, case-control, and cohort) and randomized trials evaluating hormonal interventions. The sample sizes of the primary studies varied widely and the diagnostic criteria for TMD differed between the reviews, with some using Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) or DC/TMD standards, and others relying on clinical definitions. A detailed summary of the characteristics of each review (population, exposure, outcomes, and study design) is shown in Table 2 (Ref. [13, 14, 25–30]).

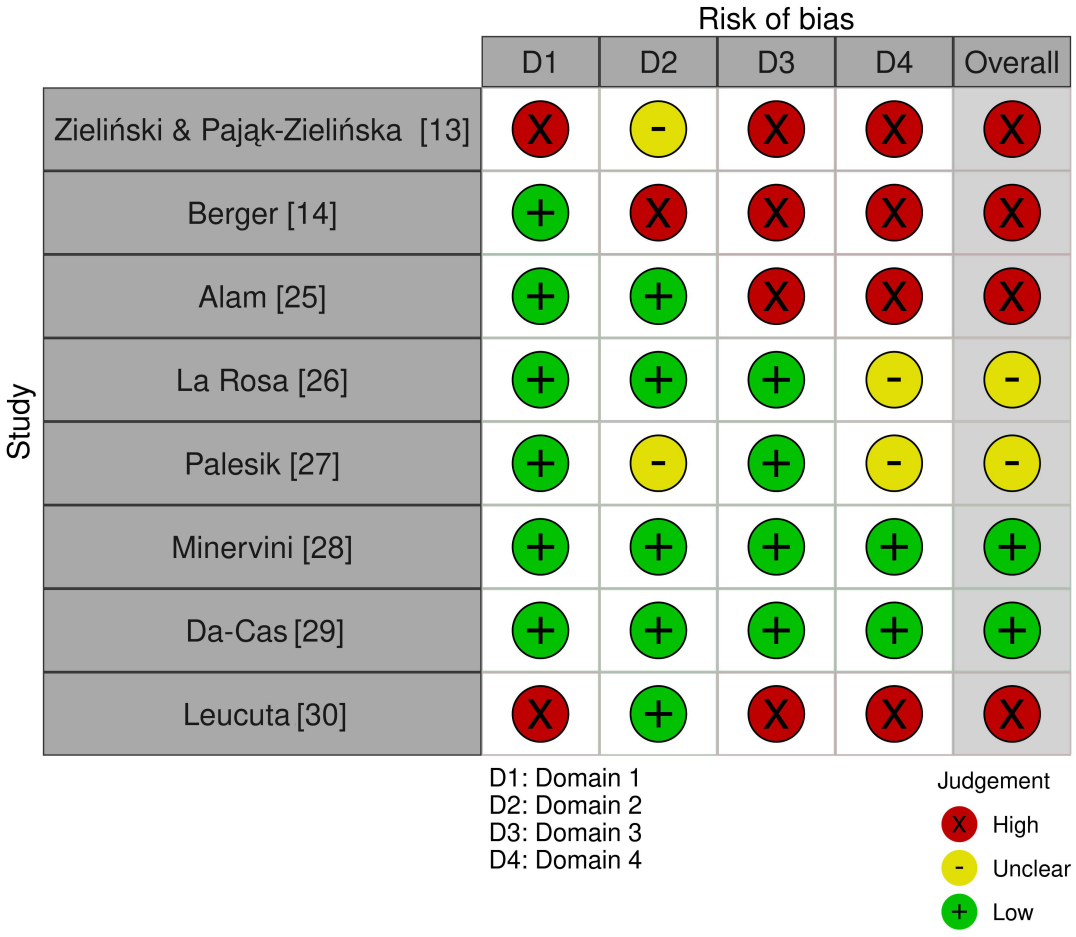
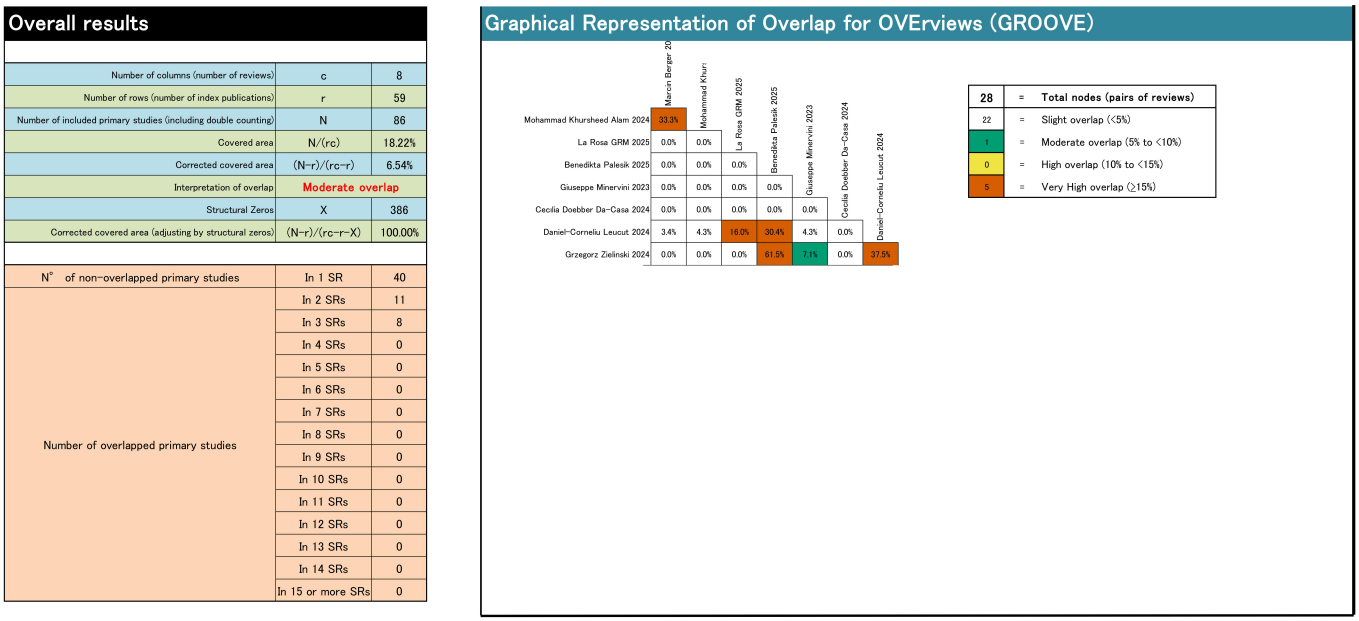


FIGURE 2. ROBIS traffic light assessment of included systematic reviews.

TABLE 1. Risk of bias assessment of the included systematic reviews using ROBIS.

Systematic Review	Domain 1 Eligibility Criteria	Domain 2 Identification & Selection	Domain 3 Data Collection & Appraisal	Domain 4 Synthesis & Findings	Overall ROBIS Judgment	Key Justification
Zieliński & Pająk-Zielińska [13]	High concern	Moderate concern	High concern	High concern	High risk of bias	Eligibility criteria allowed inclusion of narrative reviews and expert opinions, appraisal relied on a non-validated questionnaire adapted from Berger *et al.* [14], and synthesis combined heterogeneous study designs without formal handling of bias or certainty. Conclusions appropriately acknowledge insufficient evidence but are based on methodologically weak synthesis.
Berger *et al.* [14]	Low concern	High concern	High concern	High concern	High risk of bias	Restricted database search, language limitation, absence of validated risk-of-bias tool, and narrative synthesis with potential selective emphasis.
Alam *et al.* [25]	Low concern	Low concern	High concern	High concern	High risk of bias	Inappropriate use of RoB-2 for observational studies, very small evidence base, and conclusions exceeding certainty of available data.
La Rosa *et al.* [26]	Low concern	Low concern	Low concern	Moderate concern	Moderate risk of bias	Protocol registered and appropriate appraisal performed; however, substantial heterogeneity and narrative synthesis limit certainty.
Palesik *et al.* [27]	Low concern	Moderate concern	Low concern	Moderate concern	Moderate risk of bias	Restriction to open-access studies, mixed observational designs, and moderate quality of included studies constrain inference.
Minervini *et al.* [28]	Low concern	Low concern	Low concern	Low concern	Low risk of bias	Clearly defined PECO framework, appropriate meta-analytic methods, transparent exclusions, and balanced conclusions.
Da-Cas *et al.* [29]	Low concern	Low concern	Low concern	Low concern	Low risk of bias	Comprehensive search including grey literature, duplicate processes, appropriate appraisal, and cautious interpretation supported by GRADE.
Leucuța *et al.* [30]	High concern	Low concern	High concern	High concern	High risk of bias	Broad and heterogeneous eligibility criteria, unclear appraisal strategy, and narrative synthesis across mechanistic and clinical evidence.

ROBIS: Risk of Bias in Systematic Reviews; GRADE: Grading of Recommendations, Assessment, Development, and Evaluations; PECO: Population, Exposure, Comparator and Outcomes; RoB: Risk of Bias.



Overall results

Number of columns (number of reviews)	c	8
Number of rows (number of index publications)	r	59
Number of included primary studies (including double counting)	N	86
Covered area	N/(rc)	18.22%
Corrected covered area	(N−r)/(rc−r)	6.54%
Interpretation of overlap	Moderate overlap	
Structural Zeros	X	386
Corrected covered area (adjusting by structural zeros)	(N−r)/(rc−r−X)	100.00%
N° of non-overlapped primary studies	In 1 SR	40
Number of overlapped primary studies	In 2 SRs	11
	In 3 SRs	8
	In 4 SRs	0
	In 5 SRs	0
	In 6 SRs	0
	In 7 SRs	0
	In 8 SRs	0
	In 9 SRs	0
	In 10 SRs	0
	In 11 SRs	0
	In 12 SRs	0
	In 13 SRs	0
	In 14 SRs	0
	In 15 or more SRs	0

FIGURE 3. Graphical representation of overlap for overviews (GROOVE). SR: Systematic Review.

3.5 Estrogen levels and TMD

The review by Berger *et al.* [14] reported that seven out of the nine included primary studies observed a relationship between estrogen levels and TMD. However, the results across the studies were divergent and occasionally contradictory, prompting the authors to suggest the possibility of estrogen having a dual or bidirectional action on TMD pathways. Similarly, Zieliński and Pająk-Zielińska [13] found that estrogen levels were consistently associated with pain modulation within the TMJ and the orofacial region, yet concluded that there was insufficient evidence to confirm an effect of estrogen on the occurrence or incidence of TMD.

The review by Alam *et al.* [25] specifically evaluated estrogen replacement therapy (ERT) and found no conclusive evidence that ERT increases TMD risk. The authors suggested that ERT is unlikely to have a clinically significant impact on TMD, but highlighted the limited number of available studies and recommended further investigation [25].

3.6 Genetic factors (ER polymorphisms)

Two reviews evaluated ER polymorphisms and reached similar conclusions [26, 30]. ERα and ERβ polymorphisms may be associated with TMD risk, particularly in women. However, findings across studies remain inconsistent, and population-level variability appears substantial. Both reviews emphasize the need for larger, well-designed genetic studies [26, 30].

3.7 Low estrogen states and joint degeneration/pain

One systematic review focused on idiopathic condylar resorption (ICR). The evidence indicated that reduced estrogen may promote inflammatory activity in TMJ. While some studies suggested a link between low estrogen and an increased ICR occurrence, the review was unable to confirm a direct correlation [27]. The strongest relationship was found between reduced estrogen levels and chronic TMJ pain rather than structural degeneration [27].

3.8 High estrogen states (pregnancy)

A meta-analysis by Minervini *et al.* [28] found that pregnancy was not a risk factor or a protective factor for TMD. Across the included studies, pregnant women did not experience TMD more or less frequently than non-pregnant controls. The authors emphasized the need for larger prospective data [28].

3.9 Multifactorial influences involving estrogen

Another review identified multiple psychosocial, hormonal, and functional factors associated with TMD onset [29]. Estrogen was one piece of a multifactorial puzzle that also included depression and anxiety, stress and sleep quality, comorbid pain conditions, orofacial anomalies, and in-utero hormonal exposure (high estrogen, low testosterone). The authors concluded that TMD are multifactorial and, while estrogen appears to be a relevant factor, standardized methodologies are needed [29].

3.10 Quantitative heterogeneity matrix

The heterogeneity matrix demonstrated that variability extended beyond study design alone and involved substantial differences in diagnostic frameworks, endocrine assessment, exposure definitions, and outcome reporting. These factors collectively limited direct comparability between studies and reduced the feasibility of quantitative pooling (Table 3).

TABLE 2. Data extraction and study characteristics of the included reviews.

Study Reference	Number of databases searched	Number of primary studies	Study designs included	Risk of bias of primary studies as reported by review authors	Population type	Intervention/Exposure type	Outcome	Results
Zieliński G *et al.* [13]	3	12	Primary studies investigating estrogen and TMD	Not reported	Women of various ages suffering from TMD	Endogenous estrogen levels, estrogen supplementation, hormone replacement therapy	Severity and occurrence of TMD symptoms	Estrogen appears associated with pain modulation in the temporomandibular joint and orofacial region; however, evidence remains insufficient to confirm a causal relationship.
Marcin Berger [14]	3	9	Not reported	Not reported	Not reported	Estrogen levels	Association between estrogen and TMD	The relationship between estrogen levels and TMD was found in seven out of nine reviewed papers. Results of reviewed studies were divergent and sometimes contradictory.
Alam *et al.* [25]	7	3	Randomized controlled trials and case–control studies	Overall low risk of bias	Female participants irrespective of age	Estrogen replacement therapy (ERT) and hormone replacement therapy (HRT)	Risk or Incidence of TMD	One study demonstrated a dose–response relationship between estrogen therapy and TMD risk; however, overall evidence remained inconclusive.
La Rosa *et al.* [26]	3	8	Cross-sectional, case-control, and cohort studies	Overall unclear risk of bias	Participants diagnosed with TMD without age or sex restrictions	Estrogen receptor alpha (ERα) and beta (ERβ) polymorphisms	Association between estrogen receptor polymorphisms and TMD	Specific ESR1 and ESR2 polymorphisms show potential associations with the risk and severity of TMD, although findings vary across populations.
Palesik B *et al.* [27]	3	9	Prospective studies, retrospective studies, and randomized clinical trials	NOS and AXIS tools used; overall moderate risk of bias	Adults diagnosed with TMD/idiopathic condylar resorption	Estradiol levels	Occurrence, severity, and progression of TMD/idiopathic condylar resorption	Reduced estrogen levels may contribute to temporomandibular joint inflammation and idiopathic condylar resorption; however, a definitive correlation was not established.

TABLE 2. Continued.

Study Reference	Number of databases searched	Number of primary studies	Study designs included	Risk of bias of primary studies as reported by review authors	Population type	Intervention/Exposure type	Outcome	Results
Giuseppe Minervini [28]	3	3	Cross-sectional studies	Overall high risk of bias	Female participants	Pregnancy-related hormonal changes	TMD diagnosis	Pregnancy did not appear to act as either a risk factor or a protective factor for TMD.
Da-Cas *et al*. [29]	9	21	Cohort studies	13 studies showed low risk of bias; 7 studies showed moderate risk of bias; 1 study showed high risk of bias. Overall—unclear	Adults ≥18 years without baseline TMD	Hormonal and biopsychosocial risk factors	Development of TMD assessed using RDC/TMD	Female sex, psychological stressors, comorbidities, and hormonal influences including high estrogen exposure were associated with increased TMD risk.
Leucuța DC *et al*. [30]	4	22	Case–control, randomized controlled, and observational studies	Overall high risk of bias	Human participants	Estrogen receptor polymorphisms	Role of estrogen receptors in TMJ inflammation and dysfunction	Polymorphism in the alpha estrogen receptor appears to be significantly more prevalent in women with temporomandibular dysfunction, suggesting a genetic predisposition.

TMD: temporomandibular disorders; TMJ: temporomandibular joint; ESR: Estrogen Receptor; NOS: Newcastle-Ottawa Scale; AXIS: Appraisal tool for Cross-Sectional Studies; RDC: Research Diagnostic Criteria.

TABLE 3. Quantitative heterogeneity matrix.

S No.	Heterogeneity Domain	Number of Reviews Affected (n = 8)	Percentage (%)	Practical Impact on Evidence Synthesis
1.	Variable diagnostic criteria (RDC/TMD, DC/TMD, clinical diagnosis, self-report)	7	87.5%	Increased diagnostic inconsistency and limited comparability across studies
2.	Non-standardized hormone assessment methods	6	75.0%	Reduced comparability of estrogen exposure measurements
3.	Mixed estrogen exposure categories (pregnancy, HRT, menopause, endogenous estrogen, polymorphisms)	7	87.5%	Different biological pathways and mechanisms evaluated
4.	Predominantly observational study designs	8	100%	Limited causal inference
5.	Narrative synthesis without meta-analysis	5	62.5%	Reduced statistical precision and inability to estimate pooled effects
6.	Inadequate adjustment for psychosocial confounders	5	62.5%	Increased uncertainty regarding independent hormonal effects
7.	Heterogeneous outcome measures	7	87.5%	Prevented standardized outcome comparison
8.	Small or restricted evidence base	4	50.0%	Increased imprecision and reduced generalizability
9.	Mixed mechanistic and clinical evidence within reviews	3	37.5%	Limited direct clinical interpretability
10.	Variable menopausal or reproductive status reporting	6	75.0%	Reduced ability to stratify hormonal influences accurately

RDC/TMD: Research Diagnostic Criteria for Temporomandibular Disorders; DC/TMD: Diagnostic Criteria for Temporomandibular Disorders; HRT: hormone replacement therapy.

3.11 Vote counting by direction of effect

Vote counting demonstrated that evidence supporting estrogen-associated pain modulation was relatively more consistent across reviews compared with evidence relating estrogen to disease occurrence, structural degeneration, or progression. Findings regarding genetic polymorphisms and low-estrogen states remained inconsistent and population-dependent. Overall, the direction-of-effect analysis supports the interpretation that estrogen more consistently influences nociceptive and inflammatory pathways than structural TMJ pathology itself (Table 4).

3.12 GRADE assessment

The qualitative certainty assessment (GRADE) demonstrated variable confidence across estrogen-related outcomes in TMJ diseases (Fig. 4 and Table 5). Evidence for the association between estrogen and TMJ pain modulation was rated as moderate certainty due to relatively consistent findings and biologically plausible mechanisms, although downgraded for reliance on heterogeneous observational studies.

Evidence linking estrogen to TMD prevalence, estrogen receptor polymorphisms, low-estrogen states with idiopathic condylar resorption, and pregnancy-related hormonal influences was rated as low certainty because of inconsistent findings, methodological heterogeneity, small sample sizes, and predominantly cross-sectional study designs.

Evidence supporting estrogen as a direct etiological factor in structural TMJ degeneration or disease progression was considered very low certainty owing to substantial heterogeneity, limited longitudinal evidence, indirect mechanistic inference, and moderate-to-high risk of bias across included reviews.

3.13 Knowledge gap map

The knowledge gap heat map demonstrates an obvious imbalance in the existing literature on estrogen-related factors in TMD (Fig. 5). Research activity appears to be concentrated in areas such as endogenous estrogen levels and circulating estradiol, where relatively stronger evidence and a greater volume of studies are available. These findings suggest that systemic hormonal influences have been more frequently investigated in relation to TMJ pathophysiology. Conversely, other domains such as pregnancy-associated hormonal changes and hormone replacement therapy, have comparatively fewer studies and weaker evidence. This uneven distribution of research indicates that several clinically relevant hormonal contexts remain insufficiently explored. In particular, mechanistic studies addressing hormonal transitions and receptor-mediated pathways within the TMJ environment are limited, highlighting important opportunities for future research to better clarify the role of estrogen in TMD.

TABLE 4. Vote counting by direction of effect.

S No.	Outcome Domain	Positive Association Reported	No Association/Inconclusive	Contradictory Findings
1.	Estrogen and TMJ pain modulation	6 reviews	1 review	1 review
2.	Estrogen and TMD occurrence/prevalence	3 reviews	4 reviews	1 review
3.	Estrogen receptor polymorphisms and TMD risk	3 reviews	1 review	2 reviews
4.	Low estrogen states and condylar degeneration/ICR	2 reviews	2 reviews	1 review
5.	Pregnancy and TMD	0 reviews	1 review	0 reviews
6.	Estrogen and structural TMJ degeneration/progression	2 reviews	3 reviews	2 reviews

TMD: temporomandibular disorders; TMJ: temporomandibular joint; ICR: idiopathic condylar resorption.

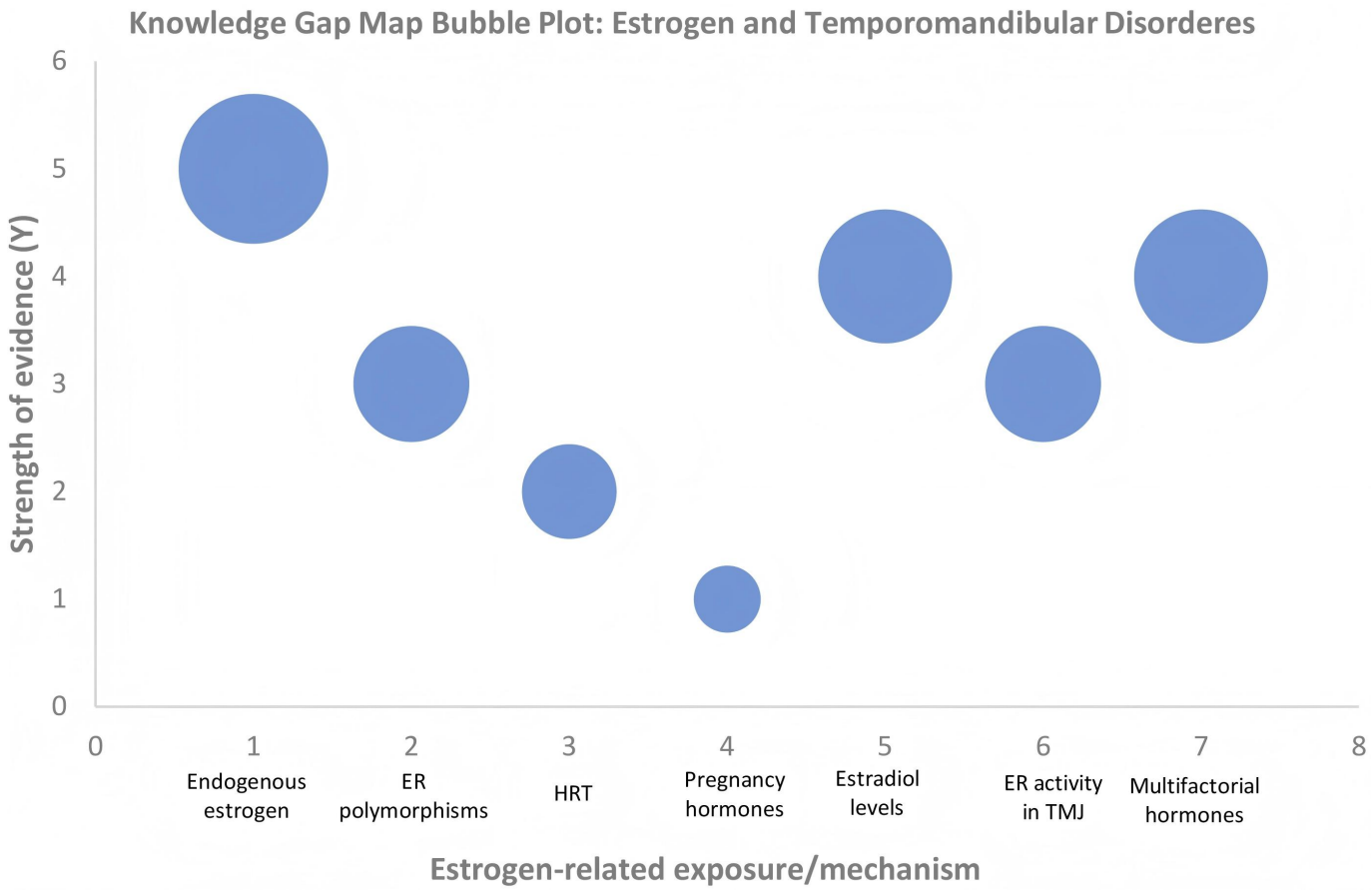


FIGURE 4. GRADE certainty bubble plot. ER: estrogen receptor; HRT: hormone replacement therapy; TMJ: temporomandibular joint.

4. Discussion

TMD demonstrate a well-documented epidemiological predilection for females. Population-based and clinical studies consistently report that women are affected by TMD approximately 1.5 to 2 times more frequently than men, with peak prevalence occurring during reproductive and peri-menopausal years [3]. This pronounced sex difference suggests that biological mechanisms, particularly hormonal influences, play a significant role in the pathophysiology of TMD, beyond mechanical or behavioral factors alone. Understanding this epidemiological pattern is essential for contextualizing the observed variability in clinical presentation, pain severity, and treatment response among affected individuals.

This umbrella review synthesized evidence from eight systematic reviews examining the role of estrogen in TMD. The use of CCA alongside GROOVE supported methodological rigor by identifying overlap among included reviews. The findings highlight that estrogen is more consistently associated with pain modulation and inflammatory processes within the TMJ; however, its contribution to the onset, severity, or structural progression of TMD remains inconsistent.

TABLE 5. GRADE certainty assessment.

S No.	Outcome	Risk of Bias	Inconsistency	Indirectness	Imprecision	Heterogeneity	Publication Bias	Overall Certainty
1.	Estrogen and TMJ pain modulation	Serious concern due to inclusion of reviews with methodological limitations and mixed ROBIS ratings	Moderate inconsistency across included reviews	No serious indirectness	Serious imprecision due to variability in outcome reporting	Moderate heterogeneity in study populations and assessment methods	No major publication bias identified	Moderate
2.	Estrogen and TMD occur-rence/prevalence	Very serious ROBIS concerns in several reviews	Considerable inconsistency in reported associations	Some indirect evidence	Very serious imprecision due to heterogeneous methodologies	High heterogeneity across populations and diagnostic criteria	Possible publication bias	Low
3.	Estrogen receptor polymorphisms and TMD risk/severity	Serious ROBIS concerns	Moderate inconsistency in genetic association findings	Some indirectness from varied populations	Serious imprecision due to limited sample sizes	Moderate heterogeneity	Possible publication bias	Low
4.	Low estrogen states and condylar degeneration/ICR	Very serious ROBIS concerns in included evidence	Some inconsistency between studies	Some indirectness from observational evidence	Serious imprecision	High heterogeneity in diagnostic and outcome measures	Possible publication bias	Low
5.	Pregnancy and TMD	Serious ROBIS concerns	Moderate inconsistency	Some indirectness	Very serious imprecision due to limited studies	Moderate heterogeneity	Possible publication bias	Low
6.	Estrogen and structural TMJ degenera-tion/progression	Very serious ROBIS concerns	Very serious inconsistency	Serious indirectness	Very serious imprecision	Very high heterogeneity	Strong suspicion of publication bias	Very low

ROBIS: risk of bias in systematic reviews; TMD: temporomandibular disorders; ICR: idiopathic condylar resorption; TMJ: temporomandibular joint.

GRADE CERTAINTY HEAT MAP

Overall Certainty of Evidence for Estrogen-Related Outcomes in Temporomandibular Disorders

Evidence Domain	Risk of Bias (ROBIS)	Inconsistency	Indirectness	Imprecision	Heterogeneity	Publication Bias	Overall Certainty of Evidence (GRADE)
Estrogen and TMJ pain modulation	↓	↓	–	↓	↓	–	MODERATE ●●●○○
Estrogen and TMD occurrence / prevalence	↓↓	↓↓	↓	↓↓	↓↓	↓	LOW ●●○○○
Estrogen receptor polymorphisms and TMD risk or severity	↓	↓	↓	↓	↓	↓	LOW ●●○○○
Low estrogen states and condylar degeneration / idiopathic condylar resorption	↓↓	↓	↓	↓	↓↓	↓	LOW ●●○○○
Pregnancy and TMD	↓	↓	↓	↓↓	↓	↓	LOW ●●○○○
Estrogen and structural TMJ degeneration / progression	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	VERY LOW ●○○○○

CERTAINTY LEVEL (GRADE)			DOMAIN RATINGS		INTERPRETATION
	MODERATE	●●●○○	–	No concern	Certainty of evidence was assessed qualitatively using GRADE principles, considering risk of bias, inconsistency, indirectness, imprecision, heterogeneity, and publication bias across the included systematic reviews.
	LOW	●●○○○	↓	Serious concern	
	VERY LOW	●○○○○	↓ ↓	Very serious concern	

FIGURE 5. Knowledge gap map heat map: estrogen and TMD. TMD: temporomandibular disorders; TMJ: temporomandibular joint.

Estrogen may contribute to degenerative joint diseases by altering the extracellular matrix composition in TMJ fibrocartilage, with collagen and elastin constituting a major part of the structure in TMJ disc. The direct influence of sex hormones on changes in collagen and elastin synthesis is well established [31]. The ERα and ERβ are found in the dorsal root ganglion (DRG) and the trigeminal nerve nucleus [32]. The interaction between estrogen and pain pathways is complex and multifaceted. Under normal physiological conditions, estrogen generally reduces pain, whereas in inflammatory pain, its effects vary according to the specific nature of the inflammatory response [33].

Hormones exert a broad influence on musculoskeletal tissues, including cartilage, bone, synovium, and neural structures, involved in pain processing. Estrogen modulates inflammatory mediators, extracellular matrix turnover, and nociceptive signalling. In the TMJ, ERs expressed in cartilage, ligaments, and sensory pathways may alter joint homeostasis and pain sensitivity, potentially predisposing susceptible individuals to chronic TMD symptoms [11, 12]. Similar hormone-mediated mechanisms have been described in other synovial joints, supporting the concept that TMD share pathophysiological features with generalized joint disorders rather than representing an isolated condition.

The included reviews consistently suggest that estrogen is more strongly associated with pain modulation than with the development of TMD itself. The ER-mediated actions have been shown to upregulate N-methyl-D-aspartic acid receptor activity in the DRG, thereby triggering the release of pronociceptive neuropeptides, including substance P, calcitonin gene-related peptide (CGRP), and brain-derived neurotrophic factor (BDNF). This mechanism may contribute to gender differences in temporal summation and the development of central sensitization [34].

Genetic susceptibility appears to modify the relationship between estrogen signaling and TMD [35]. Quinelato *et al.* [35] identified alterations in the Estrogen Receptor-1 (ESR1) and Estrogen-Related Receptor-β (ESRRB) genes as increasing the risk of developing TMD associated with chronic joint pain. This suggests a genetic predisposition that may interact with hormonal changes.

A recurring theme across the reviews is the multifactorial nature of TMD. Psychological factors (*e.g.*, anxiety, stress, and depression), sleep disturbances, comorbid pain syndromes, and anatomical or functional contributors often co-exist alongside hormonal influences [29, 36, 37]. Several reviews emphasized that estrogen interacts with these factors rather than acting independently.

The menopausal transition represents a critical period for TMJ health. Reduced estrogen levels during menopause are associated with decreased bone mineral density, impaired cartilage metabolism, and increased inflammatory activity, all of which may contribute to joint degeneration and heightened pain sensitivity [11, 16, 17, 33]. Estrogen deficiency has been linked to altered remodelling of the mandibular condyle and reduced adaptive capacity of fibrocartilaginous tissues, potentially increasing susceptibility to degenerative changes and persistent TMD symptoms [8, 10, 15, 17]. These findings align with broader musculoskeletal research demonstrating accelerated bone loss and joint vulnerability in postmenopausal women [5, 11].

Management of TMD in women should adopt a comprehensive and individualized approach. Conservative therapies, such as occlusal splint therapy, physiotherapy, and patient

education, are widely recommended as first-line treatments and are effective in reducing pain and improving function [37]. Evidence focusing on female populations suggests that conservative management strategies can achieve meaningful symptom relief without exposing patients to systemic hormonal manipulation [38].

Psychosocial factors, such as stress, anxiety, and central sensitization, are frequently reported in female patients with TMD and may amplify pain perception [29, 36, 37]. Biofeedback therapy, relaxation techniques, and cognitive-behavioral approaches may serve as useful adjuncts within a biopsychosocial framework by targeting stress-related pain amplification [39].

Beyond treatment considerations, improving diagnostic accuracy represents a critical step toward optimizing outcomes in women with TMD. The use of standardized diagnostic criteria, such as DC/TMD, enables more precise phenotyping of joint-related and muscle-related disorders and facilitates the identification of contributing psychosocial and systemic factors [40]. Incorporating hormonal status, menopausal stage, and comorbid pain conditions into clinical assessment may further enhance diagnostic precision and guide personalized management strategies [41]. Early recognition of at-risk individuals, combined with conservative and multidisciplinary interventions, represents a practical solution to mitigating chronicity and improving quality of life in women affected by TMD [37].

The interpretation of the findings of this umbrella review is limited by several methodological constraints within the included systematic reviews and their primary studies. Two reviews relied primarily on narrative synthesis rather than quantitative meta-analysis, reducing the ability to derive precise and statistically robust estimates [13, 26]. In addition, substantial heterogeneity in study designs, exposure definitions, and outcome measures limited meaningful comparison across studies [27]. Such heterogeneity reduces comparability across studies and may partially explain the inconsistency in findings, particularly regarding the role of estrogen in disease onset and structural progression.

The CCA indicated a moderate degree of overlap (6.54%) among the included systematic reviews. While not excessive, this suggests that certain primary studies may have been represented in multiple reviews and could have disproportionately influenced the synthesis. This may have contributed to the apparent consistency of findings related to estrogen-mediated pain mechanisms. Although the use of CCA and GROOVE helped account for overlap, the potential for redundancy should be considered when interpreting the results. The use of vote-counting provided a structured overview of the direction of evidence, this approach has recognized methodological limitations, including inability to account for effect size magnitude, study precision, or quantitative weighting of evidence quality. Therefore, the findings should be interpreted alongside the ROBIS and GRADE assessments used in this umbrella review.

An additional limitation relates to the restriction of included studies to English-language publications. Relevant studies published in other languages may have been overlooked, particularly in a globally studied field such as hormone-related TMD, potentially limiting the comprehensiveness of the evidence. Consequently, the results of this review should be interpreted with caution, and future umbrella reviews should consider incorporating multilingual search strategies or translation approaches to enhance inclusivity and reduce bias.

Diagnostic criteria for TMDs were inconsistent, with variable use of RDC/TMD, DC/TMD, or non-standardized clinical diagnoses, increasing the risk of misclassification [13]. The interpretation of the available evidence is limited by substantial biological and methodological heterogeneity across studies, which may include differences in study populations, hormonal status, diagnostic approaches, and outcome assessment [13].

Several primary reviews combined mechanistic, animal, and clinical evidence within a single synthesis, complicating interpretation of direct clinical relevance [27, 28]. The predominance of female-only samples limited generalizability to male populations, and inconsistent reporting of estrogen exposure prevented assessment of dose–response relationships [28]. Only a minority of reviews applied GRADE or similar certainty-of-evidence frameworks [27, 28, 30]. Consequently, the overall strength of evidence is moderated by the variable methodological quality and moderate to high risk of bias identified using the ROBIS tool. Systemic inflammatory conditions may further confound interpretation, as altered serological profiles and temporomandibular involvement have been reported in patients with rheumatoid arthritis [42].

Another limitation of this umbrella review is the inconsistent differentiation between muscular TMD and arthrogenous TMD within the included systematic reviews. Several reviews used broad TMD classifications without separately reporting joint-related subgroups, limiting the ability to isolate estrogen-associated effects specific to TMJ pathology or arthrogenous conditions. Consequently, interpretation of TMJ-specific mechanisms was partially constrained by the level of subgroup detail available in the original evidence base.

Overall, these limitations prevent definitive conclusions from being drawn about the role of estrogen in the development and progression of TMD. However, evidence for its involvement in pain modulation appears more consistent, although it should be interpreted with caution. Taken together, the synthesis of available evidence reveals a critical knowledge gap in understanding the role of estrogen in determining TMD onset and structural progression. Although epidemiological patterns and mechanistic data suggest biological plausibility, current clinical evidence remains insufficient to establish a consistent, causal, or temporally defined relationship. This gap is not due to a complete absence of research, but rather to the fragmentation of evidence across heterogeneous study designs, inconsistent diagnostic frameworks, imprecise hormonal assessments, and limited longitudinal investigations.

Future research should prioritize longitudinal evaluation of specific hormonal exposures within clearly defined patient subgroups, including cyclical endogenous estrogen fluctuations in reproductive-age women, estrogen deficiency in peri-menopausal and postmenopausal populations, pregnancy-related hormonal transitions, and exogenous hormonal exposure through oral contraceptives and hormone replacement therapy. Recent evidence published after the search period of the present review further supports the need for such investigation. A 2026 systematic review by Mazareanu *et al.* [43] reported associations between hormonal contraceptive use, menopausal status, and TMD

risk or symptom severity, while evidence regarding menstrual cycle variation, pregnancy, and ER polymorphisms remained limited or of lower certainty. These findings are broadly consistent with the present review and further emphasize the heterogeneity and uncertainty surrounding the relationship between estrogen status and TMD [43]. Greater focus is also needed on ER-mediated mechanisms and genetic susceptibility pathways. Standardization of future studies using validated DC/TMD, uniform endocrine assessment protocols, and consistent outcome measures—including validated pain scales, functional mandibular assessment, imaging-based structural evaluation, and psychosocial profiling—will be essential to improve comparability and clarify estrogen's role within the multifactorial pathophysiology of TMD.

5. Conclusions

This umbrella review synthesizes evidence from eight systematic reviews examining the relationship between estrogen and TMD. The findings suggest that estrogen plays an important role in modulating TMJ-related pain and supports its involvement in nociceptive and inflammatory mechanisms. However, the current body of evidence does not provide consistent or conclusive support for estrogen as a determinant of TMD onset, prevalence, severity, or structural progression. The overall certainty of the evidence is limited by methodological heterogeneity, inconsistent diagnostic frameworks, cross-sectional study designs, and imprecise hormonal assessments. The conclusions of this umbrella review were primarily informed by findings from reviews with lower ROBIS risk-of-bias ratings.

Taken together, these findings highlight a significant knowledge gap in clarifying whether estrogen functions as an etiological driver of TMD or primarily as a modulator of pain within a multifactorial biopsychosocial model. Well-designed longitudinal and mechanistic studies using standardized diagnostic criteria and hormonal assessment protocols are needed to clarify estrogen's role in TMD pathophysiology.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

AUTHOR CONTRIBUTIONS

SB, ASR and ET—designed the research study; analyzed the data; wrote the manuscript. SB and ASR—performed the collection and assembly of data. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

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CONFLICT OF INTEREST

The authors declare no potential conflicts of interest with respect to the authorship and/or publication of this article.

SUPPLEMENTARY MATERIAL

Supplementary material associated with this article can be found, in the online version, at https://files.jofph.com/files/article/212074726112406732 8/attachment/Supplementary%20material.pdf.

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