# A literature review on the causal relationship between Occlusal Factors (OF) and Temporomandibular Disorders (TMD) VI: final conclusions

## Una revisión de la literatura sobre la relación causal entre los factores oclusales (FO) y los desórdenes temporomandibulares (DTM). VI: conclusiones

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***ABSTRACT***

***Introduction:*** *this is the sixth and last article of this extensive and complete literature review whose purpose was to evaluate the possible causal relationship between occlusal factors (OFs) and temporomandibular disorders (TMDs).* ***Methods:*** *the analysis included only the analytical epidemiologic studies —out of all the articles found —, and they were analyzed using the epidemiologic criteria commonly used to establish causality (cause/effect).* ***Results:*** *the findings suggest that, although the first criterion —strength of the associations between OFs and TMDs— existed, other criteria such as consistency with other studies, temporal sequence of events, dose-response relationship and biologic plausibility cannot be supported with the currently available scientific information. Therefore, if there is a causal relationship, it is a weak one.* ***Conclusion:*** *the scientific information available today provides weak and confusing evidence regarding the causal relationship between OFs and TMDs. More and better studies are needed, with improved research method that allow controlling confounding variables. This will pave the way for clearer and more concrete results that will also help to make more solid interpretations and conclusions about the possible causal relationship between OFs and TMDs.*

***Keywords:*** *occlusion, temporomandibular disorders, etiology, dental occlusion, occlusal factors, temporomandibular joint, occlusal adjustment, orthodontic treatment, causality.*

***RESUMEN***

***Introducción****: este es el sexto y último artículo de esta extensa y completa revisión de la literatura, que tenía como propósito evaluar la posible relación causal entre los factores oclusales (FO) y los desórdenes temporomandibulares (DTM).* ***Métodos:*** *de todos los artículos encontrados se incluyeron en el análisis solamente los estudios epidemiológicos de tipo analítico y se los analizó usando los criterios epidemiológicos comúnmente usados para establecer causalidad (causa/efecto).* ***Resultados:*** *los resultados mostraron que, aunque el primer criterio de fortaleza en las asociaciones entre los FO y los DTM existía, otros criterios como el de consistencia de las asociaciones, secuencia temporal de los eventos, la relación de dosis y respuesta, y la credibilidad biológica no se pueden sostener con la información científica disponible en la actualidad. Por lo tanto, se observa que, si existe alguna relación de causalidad, esta es débil.* ***Conclusión:*** *con la información científica disponible en la actualidad, la relación de causalidad entre los FO y los DTM es débil y confusa. Se necesitan más investigaciones con mejores diseños, que controlen las variables de confusión. Esto permitiría obtener resultados más claros y concretos, que ayuden a hacer una interpretación y conclusión más sólida en la posible relación de causalidad entre los FO y los DTM.*

***Palabras clave:*** *oclusión, desórdenes temporomandibulares, etiología, oclusión dental, factores oclusales, articulación temporomandibular, ajuste oclusal, tratamiento de ortodoncia, casualidad, absorción.*

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## INTRODUCTION

Historically, the relationship between occlusal factors (OFs) and temporomandibular disorders (TMDs) has been a clinical event long known by dentists. However, despite many years of research, the possible causal or etiological relationship between OFs and TMDs is not clear and remains a controversial topic in the dentistry profession. Since establishing a causal relationship (cause/effect) is not a simple, obvious neither direct task, and can only be achieved by having into account all and the best possible scientific evidence currently available, in this literature review about OFs and TDMs,[1-5] the studies were presented and analyzed in the context of scientific evidence. This review started by analyzing descriptive studies[1] (transversal studies and case series), then analytical studies were reviewed:[2] case and control studies (CCS), longitudinal studies (LS), and clinical studies (including randomized clinical trials, RCTs) in which experimental occlusal interferences (EOI) were used.[3] Finally, using the same methodology, the roles of occlusal adjustment (OA) by selective grinding[4] and of orthodontic treatment[5] (OT)were analyzed as preventive or therapeutic means for TMD management or as an etiologic factor in the case of OT. The sixth and last article of this review will present and analyze all the literature available, with the criteria commonly used to establish causality in the epidemiology field,[6-8] aiming to reach a well-balanced and clear conclusion about the possible causal relationships between OFs and TMDs.

## METHODS

The previous publications made in this series[1-5] are the main support of the reports presented and analyzed in this article. Nevertheless, to keep the information updated, the literature from the last five years has been reviewed again with the same methodology used in the preceding publications.[1-5] This literature update was performed using different sources of information:

**1.** The standard medical information Medline database, specifically the MedlineOVID library (from 2004 to 2009). The abstracts of the articles in English and whose titles suggested the study of the relationship between occlusal factors, occlusal interferences (OIs), EOI, OA were reviewed. The keywords used to perform the search were the different OFs and relevant terms under the heading occlusion/malocclusion, as well as OI, OA, and occlusal therapy (OT), which were cross-referenced with relevant terms under the heading of TMD and temporomandibular joint dysfunction (TMJ).

**2.** The bibliography of the articles initially found in the MedlineOVID database search.

**3.** The bibliography of different books in the domain of TMD, TMJ dysfunction, and dental occlusion.

**4.** The bibliography of different literature reviews about the topic under study, found in the MedlineOVID database.

In order to narrow and reinforce this review, studies with less strength in the hierarchy of scientific evidence (descriptive studies) were excluded, and the analysis only included analytical epidemiological studies (CCS, LS, and RCT) that allowed obtaining their corresponding measures of association —odds ratio (OR) and relative risk (RR) — either because the articles themselves provided them or because their data allowed doing the calculations. These measures of association will be discussed later.

## Epidemiological concepts used to evaluate causality

In order to adequately evaluate the possible causal relationships between dental occlusion, OF and TMDs, the criteria used in epidemiology to establish causality as recommended by Hennekens (1987)[6] were adopted. These parameters are displayed in Table 1, and even though they will be briefly described, additional complementary references should be reviewed.[6-8]

**Table 1.** Epidemiological criteria used to evaluate causality

| |
|---|
| 1. Strength of the association. |
| 2. Consistency of the association observed. |
| 3. Temporal sequence of events. |
| 4. Dose-response relationship. |
| Biological plausibility. |

**Source:** by the authors

**1. Strength of the association.** The magnitude of the association observed is useful to determine the probability of the exposure factor alone affecting or increasing the risk of developing the disease. Larger the association strength, greater the probability of the exposure factor having actual participation in the development of the disease and minor the probability of the relation being caused by unsuspected or uncontrolled confounding variables. Therefore, greater the possibility of establishing causality. The measures of association used with more frequency are odds ratio (OR) and relative risk (RR).[6-8] Simply put, when one of these indicators shows a value of 10, it is twice as strong than the value of 5. The value of 1 is considered neutral and it indicates that the exposure factor does not increase nor decrease the probability of developing the disease. A value of < 1 indicates that the factor under evaluation protects from the disease, or better, decreases the risk of developing it. Arbitrarily, values between > 0,5 and < 2 are not considered of great strength and therefore are considered marginal or weak values of association. OR is usually calculated using CCS and RR is usually calculated using LS. RCTs are a form of LS in which research variables are controlled and in epidemiology they are the type closest to a lab experiment, hence being the best experimental evidence. The association of causality produced by this type of studies strengthens the causal relationship between the exposure factor and the disease. Measures of association similar to RRs can also be obtained from these studies to demonstrate the degree of relationship between the exposure factor and the disease.

**2. Consistency of the association observed, in relation to other studies.** When studies are conducted or repeated in other laboratories or clinics at a different time, using alternative methodologies in a variety of cultural and geographical settings, this guarantees that the phenomenon is not specific to the researchers or their environment, and thus the validity of the research hypothesis or the clinical causality premise might be more easily accepted. This is of the upmost importance because epidemiology is an inexact science in which it is impossible to control variables just as it is done in a laboratory. Therefore, replicability of the studies is probably the strongest evidence to support a causal relationship in a clear and evident way. We will consider consistency to occur when at least two studies produce similar data or with the same tendency. Nevertheless, it should be taken into account that, although certain association values may eventually reappear, and therefore be considered consistent, such values should ideally come from different research groups, conducted in different settings, and with different methodologies. When a single research group reaches the same findings, the principle of consistency is at risk and the causal relationship is not supported as strongly.

**3. Temporal sequence of events.** For an exposure factor to cause a disease, it should necessarily occur before —and not after— the development of the disease. Although it is not usually easy to establish the existence of an appropriate temporal sequence of events, it is obvious that the conclusion of causality improves when the exposure factor precedes the disease in a period that fits the known or supposed biological mechanism. Although strong and consistent associations may occur, the only way of accepting that OFs cause TMDs is by clearly showing that any of the studied OFs (in this case the exposure or risk factor) precedes the emergence of TMDs (in this case the disease). This suggests that, in terms of establishing causality, RR are more important than OR. The latter is calculated using CCS, which are static studies over time in which the risk factors and the disease itself are not monitored. Therefore, it can't be easily established whether the exposure factor preceded the disease or if, on the contrary, the exposure factor is a consequence of the disease. On the other hand, RR is calculated using LS, in which the risk factors and the disease itself are monitored, and therefore one can know without doubt which one happened first. As previously mentioned, although CCS allow establishing associations between the exposure or risk factors and the disease, they do not allow clarifying which one goes first, as both factors are studied at a static point of time. Therefore, LSs and RCTs are the only type of studies that allow ensuring that exposure factor precedes disease development.

**4. Dose-response relationship.** Establishing a relationship between intensity, quantity, frequency, and duration of the exposure factor and the risk of developing the disease would strengthen the causal relationship. Nevertheless, it should be noted that the dose-response relationship usually is not a one-to-one correlation. Moreover, the absence of a dose-response relationship does not imply the absence of causality. Therefore, the presence or absence of a dose-response relationship should be evaluated considering other alternative explanations and considering the previously analyzed criteria.

**5. Biological plausibility.** A causal relationship becomes stronger in the presence of a known or supposed biological mechanism by which the exposure factor may reasonably alter the risk of developing the disease. Biological plausibility at any given moment depends on the current state of the art; therefore, the lack of knowledge about a biological mechanism to explain the statistic association that implies the presence of causality does not necessarily mean that causality does not exist.

## RESULTS

54 analytical studies were found and used to obtain OR (Table 2)[9-46] and RR (Table 3)[47-63] as measures of association. These studies were arranged and displayed in tables describing the following information: Methodological aspects, specific factors considered as exposure factors [morphologic (static) and functional (dynamic) OFs], diseases [myalgia, myofascial pain (MPS), disc displacement (DD), arthritic disorders (ADs), or signs and symptoms (SS) of TMD (TMDSS)], and the number of participants in each study with or without the disease or diagnosis that exhibited the exposure factor (Tables 2 and 3). These values allowed calculating the association values, which were also presented.

Furthermore, the values of the statistical associations reported in each publication were included. Finally, this information was also rearranged and presented separately for each OF, in relation to different TMD conditions. The overall average (OA) of the values of association was also calculated (Table 4). Although arbitrary, this overall average helps to estimate or demonstrate a tendency of the global strength of each OF in relation to the TMDSS or to TMD diagnostic sub-groups. In order to simplify the information, certain conditions showing similar characteristics or closely related were also grouped. Degenerative articular diseases, such as osteoarthrosis, osteoarthritis, and polyarthritis, were included as part of the AD group. Articles reporting information on premature contacts (PC) were analyzed along with the ones containing information on displacement in centric (DC) because clinically DC cannot occur without the existence of at least one PC. Similarly, reports containing information about occlusal stability or posterior support were grouped, because clinically both present a smaller quantity of teeth in contact.

**Table 2.** Values of the measures of association

| OR calculated using Case and Control Studies | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Main author and year (reference number)** | **Comments on the methodology to control bias and confounding variables** | **Number of symptomatic patients (patients with exposure factor)** | **Number of asymptomatic patients (exposure factor checkups)** | **Exposure factor** | **Disease** | **OR** | **Statistic association** |
| Geering, 1974[9] | NR | 139 (135) | 112 (89) | Interferences and DC | General diagnosis with TMDSS | 8.72 | P < 0,001 |
| Pullinger & col., 1988[10] | NR | | 71 (1) | Occlusal Stability | General diagnosis with TMDSS | 1.70 | P < 0,025 |

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|---|---|---|---|---|---|---|---|
| Seligman Pullinger, 1989[11] | NR | 35 (9) | 188 (33) | Class II Division I | DDwR | 1.60 | P < 0,01 |
| | | 40 (18) | 88 (24) | DC | Osteoarthritis | 2.20 | P < 0,05 |
| | | 40 (17) | 88 (24) | DC | Myalgia | 1.90 | P < 0,025 |
| | Small samples in the subgroups put statistic association at risk | 40 (12) | 222 (71) | Crossbite | DDwR | 2.00 | NS |
| | | 62 (14) | 222 (4) | Open bite | Osteoarthritis | 15.90 | P < 0,001 |
| | | 80 (8) | 222 (4) | Open bite | Myalgia | 6.00 | P < 0,025 |
| Dworkin & col., 1990[12] | Examiners training | 214 (27) | 124 (16) | Class II | General diagnosis with TMDSS | 1.00 | NS |
| | Population sample randomly chosen | 482 (25) | 210 (28) | Anterior crossbite | | 0.35 | P < 0,01 |
| Pullinger & Seligman, 1991[13] | NR | 68 (26) | 90 (13) | Class II. Division I | Osteoarthritis | 3.60 | NR |
| Steele & col., 1991[14] | Randomly chosen controls, matched by age and sex | 72 (30) | 37 (10) | DC > 1 | General diagnosis with TMDSS and migraine | 1.90 | NS |
| | "Blind" examiners | 72 (12) | 37 (9) | NWI | | 0.60 | NS |
| | | 72 (10) | 37 (10) | Protrusive interferences | | 0.40 | NS |
| Cacchiotti, 1991[15] | NR | 41 (8) | 40 (8) | Anterior guidance | General diagnosis with TMDSS | 1.60 | NS |
| | | 41(31) | 40 (31) | Group function | | 0.50 | NS |
| | | 41 (24) | 40 (24) | NWI | | 1.10 | NS |
| | | 41 (7) | 40 (7) | Crossbite | | 0.27 | NS |
| Kononen & col.,1992[16] | Randomly chosen samples | 183 (54) | 61 (15) | Lateral DC | Polyarthritis | 1.20 | P < 0,01 |
| | | 183 (48) | 61 (4) | NWI | | 5.00 | P < 0,05 |
| Pullinger & col., 1993 and Seligman & col., 1996[17, 18] | NR | 75 (8) | 132 (2) | Anterior open bite | Osteoarthritis/ DD | 7.39 | P < 0,01 |
| | | 85 (19) | 132 (2) | | Osteoarthritis | 7.72 | P < 0,01 |
| | | 124 (12) | 132 (2) | | Myalgia | 7.55 | P < 0.01 |
| | | 47 (7) | 132 (4) | Unilateral posterior crossbite | DDwR | 3.33 | P < 0,01 |
| | | 26 (6) | 132 (4) | | DDwoR | 2.64 | P < 0,05 |
| | | 51 (6) | 132 (4) | | Osteoarthritis/ DD | 1.96 | P < 0,05 |
| Tsolka & col., 1994[19] | NR | 35 (26) | 26 (16) | Cuspid protection | General diagnosis with TMDSS | 1.80 | NS |
| | | 35 (9) | 26 (10) | Group function | | 0.50 | |
| | | 35 (16) | 26 (13) | Premature contacts | | 0.80 | |
| | | 35 (24) | 26 (13) | Balance interference | | 2.18 | |
| Tsolka & col., 1995[20] | NR | 64 (26) | 28 (5) | Class II | General diagnosis with TMDSS | 3.10 | P = 0,049 |
| Raustia & col., 1995[21] | Randomly chosen control group (dentistry students) | 21 (9) | 28 (7) | DC > 2 mm | General diagnosis with TMDSS | 0.25 | P < 0,01 |
| Kahn & col., 1998[22] | Non-"blind" examiner No examiner reliability | 22 (7) | 46 (2) | OJ > 4 mm | DD at the TMJ | 9.70 | P = 0,049 |
| | | 24 (7) | 43 (11) | OB > 4 mm | | 1.40 | NS |
| | | 37 (7) | 46 (2) | OJ > 4 mm | Pain at the TMJ | 5.30 | P = 0,037 |
| | | 33 (7) | 43 (11) | OB > 4 mm | | 0.90 | NS |
| | | 195 (50) | 46 (2) | OJ > 4 mm | Pain and DD at the TMJ | 7.70 | P = 0,001 |
| | | 181 (49) | 43 (11) | OB > 4 mm | | 1.14 | NS |
| Kahn & col., 1998[22] | No examiner reliability | 25 (5) | 54 (10) | Class II | DD at the TMJ | 1.00 | NS |
| | | 27 (18) | 55 (37) | Group function | | 1.00 | NS |
| | | 13 (8) | 32 (20) | NWI | | 1.00 | NS |
| | | 42 (9) | 54 (10) | Class II | Pain at the TMJ | 1.20 | NS |
| | | 42 (22) | 55 (37) | Group function | | 0,50 | NS |
| | | 32 (7) | 32 (20) | NWI | | 0.17 | P = 0,01 |
| | | 184 (52) | 46 (2) | Class II | Pain and DD at the TMJ | 1.70 | P = 0,047 |
| | | 221 (123) | 43 (11) | Group function | | 0.60 | P = 0,02 |
| | | 157 (44) | 32 (20) | NWI | | 0.20 | P = 0,001 |
| | NR | NR | NR | Crossbite | DD | 10.29 | P < 0,019 |
| | | | | Open bite | Osteoarthros | 17.84 | P < 0,41 |

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|---|---|---|---|---|---|---|---|
| Pullinger & Seligman, 2000[24] | | | | DC | Primary osteoarthrosis | 4.45 | P < 0,007 |
| | | | | Loss of posterior teeth | Osteoarthros | 1.18 | P < 0,001 |
| | | | | Class II Division I | Osteoarthros | 1.23 | P < 0,016 |
| Seligman & Pullinger, 2000[25] | NR | 124 (NR) | 47 (NR) | Crossbite | Internal - capsule disorders | 11.67 | P < 0,01 |
| | | | | Anterior attrition | | 6.57 | P < 0,001 |
| | | | | DC < 2 mm | | 1.02 | P < 0,008 |
| List & col., 2001[26] | "Blind" calibrated examiner | 63 (7) | 64 (9) | DC > 2 mm | General diagnosis with TMDSS | 0.76 | NS |
| | | 63 (8) | 64 (4) | OJ | | 2.18 | |
| | | 63 (12) | 64 (15) | NWI | | 0.76 | |
| | | 63 (5) | 64 (4) | Interdig. < 15 teeth | | 1.75 | |
| | | 63 (6) | 64 (1) | Open bite | | 6.60 | |
| Macfarlane & col., 2001[27] | NR | 67 (23) | 108 (36) | Loss of > 5 teeth | General diagnosis with TMDSS | 1.00 | NS |
| Yamakawa & col., 2002[28] | NR | 142 (8) | 143 (4) | Teeth loss | Rheumatoid arthritis | 2.00 | P < 0,01 |
| Tallents & col., 2002[29] | No examiner reliability | 33 (4) | 48 (2) | Lack of > 2 posterior teeth | DD at theTMJ | 1.00 | NS |
| | | | | | Pain at the TMJ | 3.17 | NS |
| | | | | | Pain and DD at the TMJ | 4.80 | P < 0,03 |
| John & col., 2002[30] | "Blind" examiner | 154 (NR) | 120 (NR) | Levels of dental attrition | General diagnosis with TMDSS | 0.74 | NS |
| | Reliability of the attrition detection method | | | 1 | | | |
| | | | | 2 | | 1.10 | |
| | | | | 3 | | 0.50 | |
| | | | | 4 | | 0.56 | |
| Fujii, 2002[31] | NR | 79 (21) | 60 (14) | Canine guidance | TMD/muscular and TMJ pain | 1.10 | NS |
| | | 79 (36) | 60 (7) | No canine contact with the working side (WI) | | 6.00 | P < 0,0002 |
| | | 79 (47) | 60 (43) | NW contacts | | 0.50 | P < 0,05 |
| | | 79 (42) | 60 (30) | Premature contact | | 1.10 | NS |
| Landi & col., 2004[32] | NR | 81 (28) | 48 (8) | DC > 2 mm | MPS | 2.64 | P < 0,028 |
| | | 81 (45) | 48 (16) | NWI | | 2.50 | P < 0,015 |
| | | 81 (33) | 48 (10) | WI | | 2.60 | P < 0,020 |
| | | 81 (6) | 48 (3) | Midline discrepancies | | 1.20 | NS |
| | | 81 (17) | 48 (14) | OJ | | 0.60 | NS |
| | | 81 (20) | 48 (12) | OB | | 1.00 | NS |
| | | 81 (3) | 48 (2) | Open bite | | 0.80 | NS |
| Selaimen & col., 2007[33] | Age, sex, language, chemical dependency, trauma records, neurological disorders, and psychological conditions were monitored. | 72 (NR) | 30 (NR) | Class II | MPS | 8.00 | P < 0,0004 |
| | Education level, job, salary, race, marital status, number of children, physical activity, and consumption of coffee, cigars, and alcohol. | | | Lack of canine guidance | | 3.90 | P < 0,002 |
| Takayama & col., 2008[34] | NR | 504 (427) | 970 (578) | Lack of occlusal support | General diagnosis with TMDSS | 1.50 | P < 0,01 |

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|---|---|---|---|---|---|---|---|
| Kirveskari & col., 1989[35] | Double blind RCT | 34 (18) | 63 (33) | Preventive OA | General diagnosis with TMDSS | 1.02 | NR |
| Vallon & Col., 1991[36] | Blind RCT | 12 (3) | 38 (22) | Therapeutic OA (2 weeks later) | TMD symptoms | 0.24 | P < 0,21 |
| Vallon & col., 1995[37] | Blind RCT | 4 (1) | 36 (19) | Therapeutic OA (3 months later) | TMD symptoms | 2.68 | P < 0,05 |
| | Loss of participants in both groups | | | Class II Division I | | 0.60 | NS |
| Pullinger & col., 1988[38] | NR | 152 (79) | 331 (132) | OT | TMDSS in women | OR: 1.6 | P < 0,025 |
| Egermark & Thilander, 1992[39] | NR | 83 (20) | 148 (44) | OT | Frequent subjective symptoms | 0.43 | NR |
| | | | | | TMJ noises | 0.38 | P < 0,001 |
| Katzberg & col., 1996[40] | NR | 102 (31) | 76 (23) | OT | DD | 1.00 | NS |
| Tallents & col., 1996[41] | NR | 263 (67) | 82 (24) | OT | DD | 0.83 | NS |
| Huang & col., 2002[42] | Trained and calibrated examiners | 97 (23) | 195 (45) | OT | Myofascial pain | 1.00 | NS |
| | | 20 (3) | 195 (45) | | Arthritis | 0.60 | |
| | | 157 (38) | 195 (45) | | MPS /Arthritis | 1.00 | |
| | | 274 (64) | 195 (45) | | General diagnosis with TMDSS | 1.00 | |
| Macfarlane & col., 2001[27] | NR | 130 (29) | 195 (51) | OT | General diagnosis with TMDSS | 0.88 | NS |
| Velly & col., 2002[43] | NR | NR | NR | OT | DD | OR: 3.10 | P < 0,05 |
| Velly & col., 2002[44] | NR | 162 (NR) | 100 (NR) | OT | General diagnosis with TMDSS | OR: 2.00 | P < 0,05 |
| Mohlin & col., 2004[45] | Calibrated and "blind" examiners | 62 (34) | 72 (39) | OT | General diagnosis with TMDSS | OR: 1.00 | NS |
| Macfarlane & col., 2009[46] | NR | 32 (18) | 305 (132) | OT | General diagnosis with TMDSS | OR: 1.60 | NS |

OJ, overjet; OB, overbite; DC, displacement in centric; PC, premature contacts; NWI, non-working interference (balancing); WI, working interference, OT, orthodontic treatment; OA, occlusal adjustment; MPS, myofascial pain syndrome; ID, internal disorders; DD, disc displacement; DDwR, disc displacement with reduction; DDwoR, disc displacement without reduction; JN, joint noise; TMD, temporomandibular disorder; TMJ, temporomandibular joint; TMDSS, TMD signs and symptoms; OR, odds ratio; RR, relative risk; RCT, randomized clinical trial; NR, not reported.

**Table 3.** Measures of association values

| RR calculated using longitudinal studies | | | | | | | |
|---|---|---|---|---|---|---|---|
| **Main author and year** | **Comments on the methodology to control bias and confounding variables** | **Number of subjects with exposure factor (subjects with the condition)** | **Number of subjects without exposure factor (subjects without the condition)** | **Exposure or risk factor** | **Condition** | **Strength of the association** | **Statistic association** |
| Egermark-Eriksson, 1990[47] | NR | 46 (13) | 103 (18) | Crossbite | TMDSS | RR = 1.60 | P < 0.050 |
| Carlsson & col., 2002[48] and Magnusson & col., 2005[49] | NR | NR | NR | Tooth wear | JN at the TMJ | RR = 4.30 | P < 0.014 |
| | | | | Class II Division I | TMD signs | RR = 12.50 | P < 0.025 |
| | | | | Crossbite | TMJ pain and noises | NR | P < 0.010 |
| | | | | Lateral forced bite between retruded and intercuspal position | TMD symptoms | NR | P < 0.050 |
| Magnusson & Enbom, 1984[50] | Double "blind" RCT | 12 (10) | 12 (3) | NWI (2 weeks) | TMD symptoms | 3.30 | P < 0.005 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Le Bell & col., 2002[51] | Double "blind" RCT | 10 (6) | 11 (4) | PC (2 weeks) | TMD symptoms | 1.65 | NS |
| | | 10 (10) | 11 (4) | | TMD signs | 2.75 | P < 0.008 |
| Le Bell & col., 2006[52] | Double "blind" RCT | 10 (6) | 11 (4) | PC (2 weeks) | TMD symptoms | 1.65 | P < 0.001 |
| | | 10 (10) | 11 (4) | | TMD signs | 2.75 | P < 0.001 |
| Kirveskari & col., 1989[53] | Double "blind" RCT | 30 (13) | 32 (22) | Preventive OA | TMD symptoms | 0.60 | P < 0.001 |
| Karjalainen & col., 1997[54] | "Blind" RCT with calibrated examiners | 60 (1) | 54 (3) | Preventive OA | Mandibular pain | 0.30 | NS |
| | | 53 (6) | 47 (6) | | TMJ noises | 0.89 | NS |
| Kirveskari & col., 1998[55] | Double "blind" RCT | 60 (1) | 67 (9) | Preventive OA | Need of TMD treatment | 0.12 | P = 0.019 |
| Tsolka & col., 1992[56] | Double "blind" RCT | 16 (5) | 17 (3) | Therapeutic OA | Mandibular pain | 0.56 (1.77) | NS |
| | | 9 (2) | 8 (1) | | Facial pain | 0.56 (1.77) | NS |
| Karjalainen & col., 1999[57] | Double "blind" RCT | 14 (1) | 11 (5) | Therapeutic OA | Cephalalgias | 0.58 | P < 0.001 |
| | | 20 (9) | 20 (15) | | Cervical pain | 0.60 | P < 0.005 |
| Egermark & Thilander, 1992[39] | NR | 83 (20) | 148 (44) | OT | TMJ noises | 0.85 | P < 0.050 |
| Henrikson & col., 2000[58] Henrikson & Nilner 2000[59], 2003[60] | Calibrated and "blind" examiners | 55 (8) | 51 (4) | OT | JN at the TMJ | 1.00 | NS |
| | | 36 (5) | 36 (8) | | Tenderness to muscle palpation | 1.24 | NS |
| | | 12 (1) | 8 (4) | | Subjective TMD symptoms | 0.16 | P = 0.006 |
| | | 65 (2) | 58 (3) | | Need of TMD treatment | 0.60 | NR |
| Slade & col., 2008[61] | Trained examiners with high reliability | 99 (12) | 75 (3) | OT | General diagnosis with TMDSS | 3.30 | NS |
| | Genetic aspects were monitored | | | | | | |

OJ, overjet; OB, overbite; DC, displacement in centric; PC, premature contacts; NWI, non-working interference (balancing); WI, working interference, OT, orthodontic treatment; OA, occlusal adjustment; MPS, myofascial pain syndrome; ID, internal disorders; DD, disc displacement; DDwR, disc displacement with reduction; DDwoR, disc displacement without reduction; JN, joint noise; TMD, temporomandibular disorder; TMJ, temporomandibular joint; TMDSS, TMD signs and symptoms; OR, odds ratio; RR, relative risk; RCT, randomized clinical trial; NR, not reported.

**Table 4.** ORs and RRs of the OFs in relation to TMD diagnosis

| Occlusal factor | First author and year (reference number) | OR/RR | Diagnosis | Overall Average (OA) of OR/OO |
|---|---|---|---|---|
| Class II | Seligman, 1989[11] | 1.60 | DDwR | 2.80 |
| | Dworkin ,1992[12] | 1.00 | TMDSS | |
| | Pullinger, 1991[13] | 3.60 | AD | |
| | Tsolka, 1995[20] | 3.10 | TMDSS | |
| | Kahn, 1999[23] | 1.00 | Painless DD | |
| | | 1.20 | TMJ pain | |
| | | 1.70 | TMJ pain and DD | |
| | Selaimen, 2007[33] | 8.00 | MPS | |
| OJ > 4 mm | Kahn, 1998[22] | 9.70 | Painless DD | 5.00 |
| | | 5.30 | TMJ pain | |
| | | 7.70 | Painful DD | |
| | List, 2001[26] | 2.18 | TMDSS | |
| | Landi, 2004[32] | 0.60 | MPS | |
| OV > 4 mm (deep bite) | Kahn, 1998[23] | 1.40 | Painless DD | 3.40 |
| | | 0.90 | TMJ pain at the TMJ | |
| | | 1.14 | Painful DD | |
| | Landi, 2004[32] | 0.60 | MPS | |
| | Carlsson, 2002[48] | 12.50 | TMDSS | |
| Open bite | Seligman, 1989[11] | 6.00 | Myalgia | 7.60 |
| | | 15.90 | AD | |
| | Pullinger, 1993[17] | 7.55 | Myalgia | |
| | Seligman, 1996[18] | 7.72 | AD | |
| | Pullinger, 2000[24] | 17.80 | ID | |
| | List, 2001[26] | 6.60 | TMDSS | |
| | Landi, 2004[32] | 0.80 | MPS | |
| Crossbite | Seligman, 1989[11] | 2.00 | DDwR and pain | 3.80 |
| | Dworkin,1992[12] | 0.35 | TMDSS | |

| | | | | |
|---|---|---|---|---|
| | Cacchiotti, 1991[15] | 0.27 | TMDSS | |
| | Pullinger, 1993[17] | 3.33 | DDwR and pain | |
| | Seligman, 1996[18] | 2.64 | DDwoR | |
| | Pullinger, 2000[24] | 10.30 | Painful DD | |
| | Seligman, 2000[25] | 11.67 | ID | |
| | Egermark,1990[47] | 1.60 | TMDSS | |
| Lack of occlusal stability (posterior support problems and interdigitation | Pullinger, 1984[10] | 1.70 | TMDSS | 2.20 |
| | Pullinger, 2000[24] | 1.20 | AD | |
| | List, 2001[26] | 1.75 | TMDSS | |
| | Macfarlane, 2001[27] | 1.00 | TMDSS | |
| | Yamakawa, 2002[28] | 2.00 | AD | |
| | Tallents, 2002[29] | 1.00 | Painless DD | |
| | | 3.17 | TMJ pain | |
| | | 4.80 | TMJ pain and DD | |
| | Takayama, 2008[34] | 1.50 | TMDSS | |
| Midline discrepancies | Pullinger, 2000[24] | 1.20 | AD | 1.20 |
| | Landi, 2004[32] | 1.20 | MPS | |
| Premature contacts and displacement in centric > 2 mm | Seligman, 1989[11] | 1.90 | Myalgia | 2.00 |
| | | 2.20 | AD | |
| | Steele, 1991[14] | 1.90 | TMDSS | |
| | Tsolka, 1994[19] | 0.80 | TMDSS | |
| | Kononen, 1992[16] | 1.20 | AD | |
| | Raustia, 1995[21] | 0.25 | TMDSS | |
| | Pullinger, 2000[24] | 4.45 | AD | |
| | Seligman, 2000[25] | 1.02 | ID | |
| | List, 2001[26] | 0.76 | TMDSS | |
| | Fujii, 2002[31] | 1.10 | TMDSS | |
| | Landi, 2004[32] | 2.64 | MPS | |
| | Le Bell, 2002[51] | 2.20 | TMDSS | |
| | 2006[52] | | | |
| NWI | 1991[15] | 0.60 | TMDSS | 2.20 |
| | Cacchiotti, 1991[15] | 1.10 | TMDSS | |
| | Kononen, 1992[16] | 5.00 | AD | |
| | Tsolka, 1994[19] | 2.18 | TMDSS | |
| | Kahn, 1999[23] | 1.00 | Painless DD | |
| | | 0.50 | TMJ pain | |
| | | 0.60 | TMJ pain and DD | |
| | List, 2001[26] | 0.76 | TMDSS | |
| | Fujii, 2002[31] | 0.50 | TMDSS | |
| | Landi, 2004[32] | 2.50 | MPS | |
| | Magnusson, 1984[50] | 3.30 | TMDSS | |
| | Geerring, 1974[9](mixed premature) | 8.72 | TMDSS | |
| WI | Landi, 2004[32] | 2.60 | MPS | 4.30 |
| | Fujii, 2002[31] | 6.00 | TMDSS | |
| Anterior or canine guidance | Cacchiotti, 1991[15] | 1.60 | TMDSS | 1.20 |
| | Tsolka, 1994[19] | 1.80 | TMDSS | |
| | Fujii, 2002[31] | 1.10 | TMDSS | |
| | Selaimen, 2007[33] | 0.26 | MPS | |
| Group function | Cacchiotti, 1991[15] | 0.50 | TMDSS | 0.62 |
| | | 0.50 | TMDSS | |
| | | 1.00 | Painless DD | |
| | Tsolka, 1994[19] | 0.50 | TMJ pain | |
| | Khan, 1999[23] | 0.60 | TMJ pain and DD | |
| Dental attrition | Seligman, 2000[25] | 6.57 | ID | 1.90 |
| | | 4.30 | JN | |
| | Carlsson, 2002[48] | 0.74; 1.10 | TMDSS | |
| | John, 2002[30] | 0.5; 0.56 | | |
| Preventive OA | Kirveskari, 1989[35] | 1.02 | TMDSS | 0.74 |
| | Kirveskari, 1989[53] | 0.60 | TMDSS | |
| Therapeutic OA | Karjalainen, 1997[54] | 0.30 | TMDSS | |
| | Kirveskari, 1998[55] | 0.124 | TMDSS | |
| (2 weeks) | Vallon, 1991[36] | 0.24 | TMDSS | |
| (3 months) | Vallon, 1991[37] | 2.68 | TMDSS | |
| | Vallon, 1995[37] | 0.60 | TMDSS | |
| (6 months) | Tsolka, 1992[56] | 0.56 | TMDSS | |
| | Karppinen, 1999[57] | 0.58 | TMDSS | |
| OT | Pullinger, 1998[38] | 1.60 | TMDSS | 1.20 |

| | | | | |
|---|---|---|---|---|
| | Egermark, 1992[39] | 0.43 | TMDSS | |
| | Katzberg, 1996[40] | 1.00 | Painless DD | |
| | Tallents, 1996[41] | 0.83 | Painless DD | |
| | Huang, 2002[42] | 1.00 | MPS | |
| | | 0.60 | AD | |
| | | 1.00 | MPS and arthritis | |
| | Macfarlane, 2001[27] | 0.88 | TMDSS | |
| | Velly, 2002[43] | 3.10 | TMDSS | |
| | Velly, 2002[44] | 2.00 | Painful DD | |
| | Mohlin, 2004[45] | 1.00 | Painful DD | |
| | Macfarlane, 2009[46] | 1.00 | TMDSS | |
| | Henrikson, 2000[58, 59] | 0.16 | TMDSS | |
| | Henrikson, 2003[60] | 0.60 | TMDSS | |
| | Slade, 2008[61] | 3.30 | TMDSS | |

## Analysis of the epidemiological concepts used to evaluate causality

**1. Strength of the association.** As shown in Table 4, the only factor that presented an almost neutral overall average (OA) in the morphologic OFs was midline discrepancies (OA = 1.2). Nevertheless, many of these OFs presented strong values, such as overjet (OJ) > 4 mm (OA = 5.0), open bite (OA = 7.6), crossbite (OA = 3.8), and overbite (VO) > 4 mm (OA = 3.4), while others presented weaker values, such as Class II (OA = 2.8) and lack of occlusal stability (OA = 2.0). In functional OFs, the DC and PC showed a marginal association (OA = 2.0); however, this value seemed to be more related to the presence of TMDSS, as slightly higher values are observed when considering the average OR or /RR of muscular disorders (2.3)[11, 32] or ADs (2.8)[11, 24]. A similar situation occurred with non-working interferences (NWI): although their overall association average wasn´t strong (OA = 1.6), their relationship to MPS (OA = 2.5)[32] and ADs (5.0)[16] was reported to be higher. On the other hand, working interferences (WI) presented a strong association value (OA = 4.3), but this value was calculated using only two reports which also analyzed two different conditions of TMD (MPS and TMDSS).[31, 32] The anterior and canine guidance presented an almost neutral association average value (OA = 1.2), while the group function displayed an association value OA that, although marginal, was inverse (protective) to the presence of TMDSS (OA = 0.62). Occlusal adjustment and occlusal treatment relationship with TMDs has marginal values of association (OA = 0.74 and OA = 1.2, respectively).

**2. Consistency of the association observed, in relation to other studies.** Although different measure of association values showed several OFs associated to TMDs, results were consistent only in a few cases (Table 4). In many cases the data were generated by the same group of researchers, without records from other researchers or research projects. In several instances, if the values came from different research projects, the reported association values were contradictory. Class II was associated to TMDSS (OR: 3.1)[20] and to ADs of TMJ (OR: 3.6);[13] nevertheless, another report revealed no association with TMDSS (OR: 1.0) and no further information regarding ADs was found. Although open bite was consistently associated to ADs of TMJ (OR: 15.9; 7.7;17.8)[11, 18, 24] and to myalgia (OR: 6.0; 7.55),[11, 17] this information was reported

by the same group of researchers. This group also reported association between crossbite and the different types of DD (OR: 2.0; 3.33; 2.64; 10.3; 11.67).[11, 17, 18, 24, 25] As regards to TMDSS and this OF, two studies reported inverse association values (OR: 0.35; 0.27),[12, 15]. while another one showed a marginal association value (OR: 1.6)[47] that apparently remained after a 30-year follow-up.[49] However, the association value could not be calculated nor was it reported by the researchers. Lack of occlusal stability (problems of intercuspation or posterior support) was consistently related to marginal association values, as well as to TMDSS (OR: 1,7; 1,75; 1,0; 1,5)[10, 26, 27, 34] and ADs (OR: 1.2; 2.0).[24, 28] On the other hand, DC > 2 mm and PC were consistently associated, although with marginal values, to TMDSS (OR: 1.9; 0.8; 0.25; 0.76; 1.1. RR: 2.2)[14, 19, 21, 26, 31, 51, 52] and ADs (OR: 2.2; 1.2; 1.02).[11, 16, 25] NWIs were inconsistently associated to TMDSS: while some studies showed a strong association (OR: 2.18; 3.3; 8.72),[9, 19, 49] other studies showed inverse (protective) association (OR: 0.6; 0.76; 0.5).[14, 26, 31] Canine and anterior guidance were consistently shown to have marginal association values and TMDSS presence (OR: 1.6;1.8; 1.1);[15, 19, 31] whereas group function was consistently presented as a factor of inverse (protective) association for TMDSS (OR: 0.5; 0.5).[15, 19] When the occlusal adjustment values were analyzed, it could be observed that overall many of the values reported were consistently presented to have an inverse association (protective action) with TMDSS (OR: 0.24; 0.12, RR: 0.6; 0.3; 0.124; 0.56; 0.58; 0.60),[35, 37] although it should also be noted that in a couple of exceptional cases a relation of association with stronger values (OR: 1.02; 2.68) was shown.[35, 37] Finally, OT was consistently related to marginal association values (OR: 1.6; 0,88; 1,0)[38, 27, 46] and inverse (protective) association with TMDSS (OR: 0,43; 0,16).[39, 58, 59] Despite this fact, two of the studies presented OT as a risk factor for TMDSS (OR: 3,2; 3,3).[43, 61] Regarding DDs, several reports consistently showed OT to have a neutral association (OR: 1,0; 0,83; 1,0),[40, 41, 45] while one study presented it as a risk factor with a not very strong—almost marginal—association value (OR: 2,0).[44]

**3. Temporal sequence of events.** A long-term longitudinal study [47, 48, 49] included crossbite, deep bite (OB > 4 mm) and forced dental displacement in centric as OFs associated and preceding the emergence of TMDSS. Similarly, the same study associated tooth wear with the emergence of joint sounds (JS).[48, 49] NWIs, PC and CD have also been associated as previous to the emergence of TMDSS and RCTs in the short term.[50, 51, 52] On the other hand, some RCTs have demonstrated that removing these interferences in a preventive manner reduces the necessity of treatment and the emergence of TMDSS.[53, 55] However, this was not the case in other strong associations such as open bite, OJ > 4 mm, and DC > 2 mm with ADs, in which OFs appeared to be a consequence (they appeared after the disease) and not the cause of the disease.[13, 17]

**4. Dose-response relationship.** In general, reports specifically addressing this topic were not found. Lobbezoo et al. (2008)[30] analyzed different levels of attrition; nevertheless, they did

report association with the severity, frequency, or duration of TMDSS. None of the articles evaluated in this literature review presented a gradient relationship in terms of increase or worsening of either the TMDSS or the diagnostic sub-groups in relation to the increase, size or worsening of OF.

**5. Biological plausibility.** In spite of the various associations reported by different authors, their biological mechanisms are not fully understood.[64-67] De Boever (1994)[67] summarized the diverse etiological and physiopathological mechanisms in five general groups: mechanic displacement, neuromuscular, muscular, psychophysiological, and psychological theory. It is important to point out that all of these theories have limitations in the light of scientific evidence; therefore, the discussion on TMD etiology is not over yet, and several hypothesis stand.[64-67] A single-cause relationship between OFs and TMDs is increasingly more difficult to consider because a great number of factors besides the OFs are also associated to TMDs (sleep disorders, depression, anxiety, among others), especially when the TMD becomes a chronic disorder.[64-67] Although the etiology of acute joint or muscle pain is usually clear and is explained by history of trauma in the orofacial region or by inflammatory processes of the TMJ, in many other TMDs these mechanical factors are frequently not found. In turn, other authors, aiming not to omit any factor, have suggested the multifactorial theory, and although almost everything is multifactorial in biology and shows the complexity of the mechanisms associated to TMDs, this does not necessarily facilitate achieving a deeper understanding of the biological mechanism.[67-68] As the previously described theories have failed to explain TMD etiology, other authors have suggested that their etiology is idiopathic (diseases with an unknown origin or whose cause is unknown).[69-71] Currently, there is not an accepted biological mechanism and the scientific tendency is to search for the biological mechanism in possible disorders of the central and peripheral nervous system that would make patients more prone to TMDS development.[72-74] Genetic aspects associated to this possible predisposition to produce pain have been reported in the last decade.[75-78]

## DISCUSSION

Epidemiological concepts to establish causality are used and applied in research in order to make the best possible clinical recommendations or to carry out public health actions. A classic example is the change of policies regarding smoking areas in order to decrease the passive smoking risk, as well as the clinical recommendation, aimed at the general public, about the importance of quitting smoking. All this happened after many years of research that verified the causal association between the habit of smoking and the development of many diseases (cancer, cardiovascular diseases). Epidemiology is a field full of uncertainties, where the available evidence is rarely enough to unmistakably establish the presence of a cause-effect relationship. This is especially true in the case of chronic diseases, which usually lack strong

epidemiological bases to establish a cause-effect relationship; therefore, on many occasions, depending on the risk or the associated consequences, it is wiser to act under the premise that the relationship exists instead of waiting for new evidence. Indeed, it usually takes many years to have enough evidence leading to decision making based on judgments free from reasonable doubt of a cause-effect relationship. In their book, Lilienfeld and Stolley (1994)[8] wrote: "In practice, a relationship is considered causal provided that the evidence indicates that the factors make part of the set of circumstances that increase the possibility of developing the disease, and that decreasing one or more of these factors also decreases the frequency of the disease". They also wrote: "The etiological factor doesn't have to be the only cause of the disease, and it could have effects in other diseases".[8] These might be the same reasons why currently the cause-effect relationship between OFs and TMDs is still controversial and continues to be studied and analyzed. The complete and extensive review presented in this series of publications[1-5] is a call to awareness about the fact that establishing causality in epidemiology is not an exact activity and it depends on the evaluation of all available evidence according to the criteria for establishing causality (Table 1). Although none of these criteria alone may validate causality, greater the number of criteria, greater the possibility of a valid causal relationship.

When evaluating the strength of association between OFs and TMDs, the relationship is clear for some of the OFs [open bite (OA = 8,2); OJ > 4 mm (OA = 5,0); OB > 4 mm (OA = 4,6); crossbite (OA = 3,87)]; marginal for some others [dental attrition (OA = 2,3) occlusal stability (OA = 2,0) NWI (OA = 1,9), premature contacts/DC (OA = 1,7); Class II (OA = 1,67); lack of canine guidance (OA = 1,3); midline discrepancies (OA = 1,2)]; and even inverse (protective) for other few cases such as the presence of group function (OA = 0,62). Occlusal adjustment presented marginal values with a preventive tendency against TMDSS (OA = 0,74), while OT presented a comparable situation but with a slight tendency to be a risk factor (OA = 1,2). However, several other factors weaken the possible causal relationship between OFs and TMDs. It should be noted that, in spite of displaying these associations, not all of the OFs are associated in the same way, with the same disorders or the same strength. Similarly, when evaluating the consistency of the findings from different research studies, it is observed that a clear tendency is not necessarily present in the directionality of the association and, in some cases, totally opposed values are displayed. A common situation opposed to supporting the consistency criterion is that many of the reported association values were consistent within the same group of researchers and have not been replicated by other research groups. In California (USA), Pullinger et al proved[10] a strong relationship between open bite and myalgia (OR: 6,0), while in Italy, Landi et al proved[32] the opposite association in relation to another muscular disorder, MPS (OR: 0,8). The preventive effect of occlusal adjustment has been proved only by the Finn group of Kirveskari et al,[53, 54, 55] but no other groups have shown comparable results. However, the findings reported by Kirveskari et al[55] should not be disregarded, as they

premature contacts and NWI) by means of occlusal adjustment with selective grinding did not only have a preventive effect against the occurrence of TMDSS, but it also decreased the need of treatment. Likewise, there is one single research study, carried out by the same group, which reported the therapeutic effect of occlusal adjustment in other orofacial pain conditions commonly connected to TMDs (cephalalgia and cervical pain)[57] A similar situation occurs with the reports about occlusal conditions being treated with OT, which has been shown to reduce the need of TMD treatment.[59, 60]

However, the strength of this association is not high, nor has it been replicated by other studies allowing the concept of consistency to be supported. Moreover, many of these associations were generated by CCS studies, which do not allow confidently establishing the temporal sequence of events. As previously mentioned, this can only be achieved by means of studies (LS and RCT) that allow monitoring the behavior of the risk factors and the disease over time. The only long-term longitudinal study with a 30-year follow-up maintained the association between deep bite, crossbite, DC and TMDSS occurrence.[48, 49] The same study also proved the association between tooth wear and joint sounds (JS) in the TMJ.[38] Similarly, in a short-term (two weeks) RCT, premature contacts and the NWI remained as a risk factor for TMDSS occurrence.[50-52] Nevertheless, none of the previously mentioned studies reported some kind of association between OFs and the development of a TMD-specific diagnostic subgroup, nor the development of a condition similar to that of patients who consult specialized clinics for treatment of TMDs and orofacial pain,. Perhaps, on the contrary, those SS were more similar to TMDSS found among the general population. Regarding dose-response relation, the information provided by the articles evaluated in this review cannot support this concept. Intensity, frequency and duration of the OFs have not been associated with TMDs' worsening or accentuation. For example, none of the EOI3 research studies reported a stronger association to SS appearance or worsening due to a greater size of the interference. Association between the "size" of the OF and the TMD severity was not reported either. For example, crossbite has been associated to TMDSS, but it has not been proved whether the severity level is correlated to the SS quantity, or if these SS are more frequent, constant or intense in presence of a more pronounced crossbite. On the other hand, open bite is associated to arthritic disorders (ADs) and, if the severity of ADs was defined in terms of joint tissue destruction, it could be assumed that the severity of open bite is higher when osteoarthrosis, osteoarthritis, or polyarthritis of the TMJ are more severe. Nevertheless, this causal association lacks support because the temporal sequence of events differs (open bite is caused or happens after the AD), and ADs' biological mechanism does not lead to believe that open bite increases the risk of developing the disease. Finally, in the biological mechanisms of the masticatory system, it is reasonable to believe that sudden changes in the OFs may produce or explain the presence of acute TMDSS (of temporal occurrence), such as mandibular pain.[3, 79] However, in chronic TDM conditions, relying on the primary participation of OFs in the development of these disorders is difficult to support.[72-74] In a recent study

Aggarwal et al[80] showed that, even though an independent relationship existed between mechanical factors (reported dental grinding, facial trauma, uncomfortable bite, lack of teeth) and chronic facial pain, this relationship was altered by psychological factors which functioned as confounding variables. Besides, these mechanical factors were also common in other idiopathic conditions of chronic pain.[80] Apparently, these idiopathic conditions of chronic pain, including TMDs, coexist in the same patients and share a similar biological mechanism.[81, 82] Finally, it noteworthy that the only longitudinal study in which OT was reported as a risk factor for TMD was the one that considered genetic aspects as predisposition to generate pain.[61] This is highly important because, although the general tendency of the analyzed epidemiological reports is to favor the idea that the relationship between OFs and TMDs is inexistent, these other (genetic) factors may be the ones actually acting as confounding variables thus leading to confusing, unclear results that interfere with the establishment of the real association between OFs and TMDs.[75-78] All of these factors (either genetic or psychosocial) should be considered and monitored in future studies aiming to evaluate causal relationships between OFs and TMDs.

## CONCLUSIONS

The role of OFs in TMD etiology is undoubtedly controversial. Therefore, the possible relationship between OFs and TMDs is not easy to analyze or interpret. The purpose of this extensive literature review was to evaluate in a detailed and complete manner the possible causal relationship between OFs and TMDs.

In order to ensure a well-balanced and clear conclusion about this possible relationship, the main epidemiological principles for the evaluation of causality were used. When the strength of association between OFs and TMDs was evaluated, it was evident that several OFs had strong association values, which made them risk factors for TMD development. It should be noted that, in spite of these associations, not all of the OFs are associated in the same way, with the same disorders or the same strength. Similarly, when evaluating the consistency of the research findings, it is observed that a clear tendency is not necessarily present in the directionality of the association and, in some cases, the values are completely opposed. Another common situation, contrary to the criterion of consistency, is also observed: many of the reported association values were consistent in the same group of researchers and have not been repeated by other research groups. Moreover, many of these association values were generated by CCS studies, which do not allow confidently establishing the temporal sequence of events. Although some LSs and RCTs still reported association between some OF and TMDSS apparition, none of the previously mentioned studies reported any kind of association between OFs and the development of a TMD-specific diagnostic sub-group, nor the development of a condition similar to that of patients who consult specialized clinics for treatment of TMDs and orofacial pain. Perhaps, on the contrary, those SS were more similar

to the TMDSS found among the general population. Regarding the dose-response relation, the information provided by the articles evaluated in this review cannot be supported either because the OFs' intensity, frequency, and duration were not associated with worsening or accentuating TMDs. Finally, in the biological mechanisms of the masticatory system, it is reasonable to believe that mechanical changes (direct or indirect trauma, or sudden changes in the OFs) may produce or explain acute TMDSS (of temporal occurrence), such as mandibular pain. Nevertheless, the idea of OFs being the main participants in chronic TMD development is something difficult to support, and it appears to have a more modest peripheral participation in a multifactorial set of causes.

Therefore, with the scientific information currently available, the causal relationship between OFs and TMDs is weak and confusing, and several recommendations may be made:

**1.** Future research projects should try to emphasize more on the analysis of associations between OFs and TMD diagnostic sub-groups (instead of merely considering the presence or absence of TMDSS), considering other factors such as chronicity and treatment need, and considering other comorbid factors that may appear as confounding variables (systemic, genetic or bio-psycho-social aspects such as depression, anxiety, or sleep disorders, among others).

**2.** More multi-centric LSs and RCTs are needed in order to produce association values that may also be supported by the concepts of consistency and temporal sequence of events.

**3.** The studies must be carried out using standardized clinical evaluation and diagnosis methods in order to establish the health/disease state, so that comparisons among different studies are easier to make.

**4.** Researchers must consider producing association values or displaying data in an organized manner, following the principles of evidence-based practice so that the values are easily and clearly calculated.

**5.** Because the causal relationship between OFs (including occlusal adjustment and OT) and TMDs is weak and confusing, caution should be exercised. One should adhere to the principle of being simple and conservative when establishing a therapeutic strategy and should avoid treatments leading to irreversible occlusal changes and only supported by the belief that it will produce a decisive impact in the patients' TMDSS.

**6.** The fact that after experiencing occlusal changes, TMDSS appear in some patients while others do not display them may be due to individual genetic predisposition instead of the mechanical effect that such occlusal changes entail. It will be likely necessary in the future to perform blood tests in order to make a gene mapping and thus establish the patients' individual risk of developing TMDSS.

## CONFLICT OF INTEREST

The authors state that they have no conflict of interest.

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