

## Chapter 2

# Etiology and Epidemiology

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In the present chapter, which is dedicated to the provision of examples of the different strategies to investigate for the role of etiological/risk factors and to report data for epidemiological purposes, the main focus is put on two aspects that represent the fil rouge of the various investigations here described. The first issue is related with the epidemiology of the temporomandibular disorders (TMDs), the description of which must forcedly take into account for the psychosocial features of the disease, as suggested by the biopsychosocial model of orofacial pain. The need to describe and report as many details as possible on the so-called axis II impairment is well-exampled in the large-sample study commented in the section on how to report epidemiology data. The second issue, which is strictly related to the other, is related with the shift from past beliefs of an importance of dental occlusion in the etiology and bruxism to the current concepts providing that a triangle of factors, viz., bruxism, pain, and psychosocial factors, may explain most part of the pathogenesis of TMDs. Three example investigations are provided on the topic of the etiology of bruxism and TMDs, all authored by two of this book's editors. The materials and methods as well as the results sections will be edited with respect to the original publication, especially by providing specific comments on the different clinical and statistical strategies underlying the study rationale. Taken together, the information contained in this chapter succeeds to reach the twofold aim of providing suggestions for clinical purposes (i.e., presentation of the current concepts on TMD epidemiology and etiology) as well as for statistical uses (i.e., discussion of the various models that need to be adopted for some different research situations and/or to test different hypotheses).

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## 2.1 The Need to Get Deeper Into Etiology and Define Epidemiology

In an ideal condition, a correct diagnosis and an effective treatment for a disease should be based on the knowledge about the etiology and pathophysiology of the disease. A known pathophysiology provides the identification of an etiologic agent and the description of the pathogenetic mechanism leading to the onset of the disease and to its natural course. A thorough knowledge of all these aspects is of basic importance to allow a sensible diagnosis and treatment planning.

In the case of TMDs, most part of the past century was dominated by the so-called occlusal etiology paradigm, which met consensus by the majority of clinicians and researchers. In accordance with such an occlusal paradigm, the diagnosis was focused on the assessment of dental occlusion and the treatment was based on irreversible changes of dental occlusion itself. Successively, in the last decades of the past century, several authors raised concerns about the conceptual validity of the occlusal etiology theory and, conversely, an increasing number of papers showed that patients with pain in the facial area shared many characteristics with patients affected by other chronic pain diseases in terms of psychological distress, social impairment, and reduced quality of life. These observations, along with the evolution of concepts about pain perception and modulation, put the basis for the first multidimensional pain model for TMD patients (Rollmann and Gillespie 2000; Suvinen et al. 2005).

The next step provided that the biological disorder was seen within the frame of illness experience (i.e., reactions to the physical disorders), thus leading to the biopsychosocial model for TMD and its derived terminology and classification (Dworkin and Leresche 1992). The biopsychosocial model for TMD, which is still considered the best-fitting model for TMD assessment, has to be taken into full account when reporting findings of any kind of investigations in the field of TMD and orofacial pain.

Based on these premises, examples of how to report data on TMD epidemiology will be provided in the remaining sections of this chapter as well as examples of different study design to get deeper into the etiology of TMD to add data to the multifactorial model of TMD and orofacial pain.

## 2.2 How to Report Data on Epidemiology

Clinicians and researchers approaching to medical data gathering/presenting and to manuscript writing must start with a clear definition of their objectives. The following is an example introduction for an epidemiology-based research, featuring two main characteristics:

1. A logical presentation of the study aims and rationale, viz., the need to get deeper into the epidemiology of this specific disease, along with hints to the currently available literature
2. A brief description of the instrument(s) used to perform the investigation, to be presented in greater detail later in the successive sections.

### ***2.2.1 Statement of the Problem***

As in all other fields of pain medicine, there is a strong need to define treatment-seeking populations in terms of their different patterns of signs and symptoms distribution, viz., the relative percentage of patients receiving the different TMD diagnoses, in order to gather as many data as possible on TMD epidemiology. To pursue the goal of an objective and standardized assessment of TMD patients, the Research Diagnostic Criteria for Temporomandibular Disorders (RDC/TMD) were proposed as guidelines for cross-center comparison of findings (Dworkin and Leresche 1992). Such a classification system is bi-axial, with an axis I evaluating the physical diagnoses and an axis II assessing the psychosocial issues, both providing specific and detailed diagnostic criteria. Despite their wide diffusion with multi-language translation and ongoing validation of revised diagnostic algorithms (Schifmann et al. 2010), a recent meta-analysis of the literature pointed out that only a few research groups actually described findings in their clinics' TMD patients populations by relying on the RDC/TMD (Manfredini et al. 2011c). From those studies, it emerged that myofascial pain was the most common diagnosis that combined muscle and joint disorders affect about half of the patients, and that different age peaks characterize subjects with disc displacement disorders with respect to those with inflammatory degenerative disorders (List et al. 1996; Winocur et al. 2009; Manfredini et al. 2010). Also, it emerged that the majority of TMD patients has psychosocial symptoms (i.e., psychological/psychiatric disorders related with a certain level of social impairment) belonging to the psychosocial sphere, as identified by the RDC/TMD axis II evaluating depression, somatization, and chronic pain-related impairment (Manfredini et al. 2011a).

Based on those premises, it seems to emerge that gathering more data on TMD patients populations is a compelling need to get deeper into the knowledge of disease epidemiology and to increase the external validity of the findings described so far, especially in the light of recent observations that a very low number of papers reported on both axis I and axis II findings (Palla 2011).

In consideration of the above need, the following strategy is provided as an example to describe the frequency of physical and psychosocial diagnoses in a sample of patients attending a TMD clinic (Manfredini et al. 2012a). The following sections on the description of the study design and report of main findings are thus based on an edited, arranged, and commented version of the manuscript "Manfredini et al. (2012a)".

### ***2.2.2 Description of Study Sample and Design***

When reporting epidemiological data, and more in general in all investigations involving populations of human subjects, it is always fundamental to present as much information as possible on the study population, in order to allow readers appraising the repeatability of the investigation and having a first glance at the representativeness of the study population. For instance, a sentence such as "Data were

collected from 520 consecutive patients seeking treatment for TMD at the TMD Clinic, School of Dental Medicine, University of Pavia, during the period from January 1st 2006 to June 31st 2010.” may be sufficiently exhaustive to introduce the study sample.

Then, details on the study design must be provided, with focus on the assessment procedures and the criteria for including/excluding subjects within the study population. Appropriate references must be provided for all procedures adopted in the investigation. In the case of an RDC/TMD-based epidemiological study, it should be specified that history taking and clinical examination were performed according to the RDC/TMD guidelines, and that, for instance, the standard, internationally accepted Italian version of the RDC/TMD instrument available since 2002 on the RDC/TMD consortium website was used by the authors to ease patients’ comprehension. Criteria for exclusion are usually based on an age under 18 (due to the characteristics of the RDC/TMD, the reliability of which has been tested on adult populations), a concurrent diagnosis of other orofacial pain disorders, and presence of polyarthritis and/or other rheumatic disease. The focus on any specific diagnostic axis, viz., RDC/TMD axis I and/or II, should be mentioned. An important aspect of this kind of study design is that an epidemiological investigation should be based on widely adopted classification systems, thus avoiding any possible arbitrary authors’ evaluation, which could reduce the internal and external validity of findings.

Once this premise was added to the study design, it often needs to provide some further details on the instruments adopted, since editors of peer-reviewed journals often ask for some additional specifications that allow readers to catch the main features of the diagnostic classification without referring to the original manuscript. So, it is important to give some information on the internal validity of the investigation, for instance by stating that all patients were simultaneously assessed by the same two examiners, who collected all RDC/TMD data and assigned axis I diagnoses by consensus. In the case of RDC/TMD, patients were given one or more of the following axis I group diagnoses: muscle disorders (group I), disc displacement (group II), and arthralgia, osteoarthritis, and osteoarthrosis (group III). As for axis II assessment, levels of depression and somatization were evaluated by the use of dedicated Symptoms Checklist-90 (SCL-90) items, while the Graded Chronic Pain Scale (GCPS) was used to rate pain-related impairment. Details on the diagnostic and scoring criteria were described in the original 1992 RDC/TMD publication (Dworkin and Leresche 1992).

A brief paragraph should then be dedicated to the ethical committee’s approval and patients’ consensus to take part to the study. Journals editors are facing an increasing demand for legal issues to be careful of, and sentences like “The investigation was based on routine clinical assessments and diagnostic activities of the TMD Clinic, with waiver from the local ethic committee. All patients gave their written informed consent to the clinical diagnostic procedures undertaken during the investigation and to the use of the so-gathered data for statistical purposes.” are to be included in the materials and methods.

The final part of the study design section should present a description of the statistical/analytical approaches to data assessment and description. It is important

that the statistical analyses are presented in details as for their need to answer any specific research questions. The order in which the statistical analyses are performed should be then followed exactly also in the results section of a manuscript, when the main findings of the investigation should be discussed on the basis of the same logical sequence. Of course, this general rule is much simpler in epidemiological studies than in other study designs. Indeed, for example, in the case of RDC/TMD findings in a population of TMD patients, most parts of the analyses are descriptive, and should be based on the report of the prevalence of the different RDC/TMD axis I diagnoses as well as the axis II psychosocial scores. Recent papers provided examples of how to stratify findings per age, to compare the age distribution of axis I and II diagnoses (Manfredini et al. 2012a). Then, ANOVA could be performed to test for the existence of differences in the mean age of diagnostic groups, with significance level set at  $p < 0.05$ . Importantly, if possible, the software with which all the statistical procedure were calculated should be indicated.

### 2.2.3 Description of Main Findings

In an epidemiological investigation on TMD patients, the main findings are basically represented by all kinds of possible information on the different diagnostic patterns and age distribution of the study subjects. The core results should be preceded by a specification of the number of patients who were excluded even if being potentially eligible for the study and the reasons for their exclusion. In the example of the above investigation (Manfredini et al. 2012a), all patients who were part of that consecutive sample but not satisfy the inclusion criteria should be listed in sentences as much detailed as possible, such as “ $N=x$  patients were excluded from data analysis because of the following reasons:  $N=x$  subjects received diagnoses of other orofacial pain disorders (i.e., atypical odontalgia),  $N=x$  subjects had a concurrent diagnosis of fibromyalgia or other rheumatic disorders, and  $N=x$  were aged under 18”.

Then, the study findings should be reported in details, according to a structured sequence that may help readers following the strategy of reasoning adopted by the authors and catching the main messages (Table 2.1):

1. Number of patients satisfying inclusion criteria, for whom data are presented, with information on the sex distribution and mean age.
2. Frequency of each RDC/TMD axis I diagnostic subgroup, viz., group I disorders (muscle disorders), group II disorders (disc displacements), and group III disorders (arthralgia, osteoarthritis, and osteoarthritis) in the study population. Of course, a table showing the distribution of specific RDC/TMD diagnoses should be fundamental to present the results in an intuitive way, especially to grasp data on the monolateral or bilateral disorders, which are seldom discussed in the TMD literature even if being fundamental issues in the clinical setting.
3. Frequency of axis I group diagnoses, alone or combined: muscle disorders alone, disc displacement disorders alone, arthralgia/arthritis/arthritis, different combinations of group diagnoses.

**Table 2.1** Example of a table showing the frequency of the different RDC/TMD axis I diagnoses in a sample of TMD patient population attending the University of Pavia (*N*=462 patients) Based on an edited version of the manuscript “Manfredini et al. (2012a)”

RDC/TMD axis I group diagnoses		Patients ( <i>N</i> )	% frequency
I a—myofascial pain		169	36.5
I b—myofascial pain with limited opening		92	19.9
II a—disc displacement with reduction	R or L	102	22.0
	R and L	39	8.4
II b—disc displacement without reduction with limited opening	R or L	31	6.7
	R and L	7	1.5
II c—disc displacement without reduction without limited opening	R or L	9	1.9
	R and L	7	1.5
III a—arthralgia	R or L	123	26.6
	R and L	40	8.6
III b or III c—osteoarthritis/arthritis	R or L	72	15.6
	R and L	31	6.7

*R* right joint, *L* left joint

- 4. Mean age of the patients receiving the different combinations of single and combined TMD diagnoses, with the aim to detect peculiar age patterns in diagnosis distribution (e.g., degenerative joint disorders are supposed to be more frequent in the older age groups). Also, for instance, some additional strategies to ascertain the age-related pattern of axis I diagnoses distribution could be performed, such as dividing the sample in various groups on the basis of percentile-derived intervals within the variable “age” and assessing the prevalence of different diagnoses in each age group.
- 5. Frequency and age distribution of the different axis II psychosocial disorders, viz., moderate or severe depression levels, moderate or severe somatization, different levels of pain-related impairment based on the Graded Chronic Pain Scale.

**2.3 How to Test an Association Between Two Variables**

**2.3.1 Statement of the Problem**

One of the main objectives of epidemiology is to define the etiological and risk factors for disease. In the field of TMD and orofacial pain, most studies on the etiology focused on the role of dental occlusion and bruxism. In particular, bruxism is commonly considered a major risk factor for TMD, but there are still many unsolved issues concerning the diagnosis of both disorders and their relationship (Svensson et al. 2008; Manfredini & Lobbezoo, 2010a). When introducing the issue of bruxism and TMD it should be pointed out since the early statements that the de-

sign of scientifically sound studies is complicated by difficulties in diagnosing clinical bruxism, as well as by the unclear relationship between instrumentally detected bruxism on the one hand and clinically diagnosed or self-perceived bruxism on the other hand. These difficulties also affect investigations on bruxism etiology and treatment, and a recent systematic review of the literature pointed out that inconsistent findings on the bruxism–TMD relationship may depend upon the adoption of non-homogeneous diagnostic techniques among studies (Manfredini and Lobbezoo 2010b). Works on self-reported or clinical bruxism diagnosis commonly showed a positive association with TMD pain, while, on the contrary, such positive association was not always confirmed with studies using instrumental bruxism detection, viz., by means of polysomnography (PSG) and/or electromyography (EMG). Also, the studies on the bruxism–TMD relationship rarely relied on standardized TMD diagnoses.

Based on those controversies, a possible strategy to ease the comparison of findings is to adopt standardized and reproducible diagnostic procedures for both TMD and bruxism. Thus, as in the case of epidemiological investigations, such purpose could be achieved with the diffusion of information gained over the years with the RDC/TMD, which, as stated above, provides diagnostic guidelines for TMDs as well as an anamnestic investigation of awake and sleep bruxism (Dworkin and Leresche 1992). Until recent years, no studies addressed the issues of the prevalence of TMD and bruxism by relying on the RDC/TMD for diagnosing both disorders, and a multicenter study was thus performed at two highly specialized centers for the treatment of bruxism, TMD, and orofacial pain (Manfredini et al. 2012c), with the aims: (1) to report the frequency of TMD diagnoses and prevalence of self-reported awake and sleep bruxism in patient populations recruited at two highly specialized clinics; and (2) to describe the possible differences between findings of the two centers as a basis to suggest recommendations for future improvements in diagnostic homogeneity and accuracy. The following sections on the description of the study design and report of main findings in the case of an investigation assessing the association between two variables are thus based on an edited, arranged, and commented version of the manuscript “Manfredini et al. (2012c)”.

### ***2.3.2 Description of Study Sample and Design***

As in the case of epidemiological studies and also in all example investigations described throughout the book, as much information as possible on the study design should be provided. For instance, it is important to describe if the study is prospective/longitudinal or retrospective. The latter design allows drawing no conclusions on the cause–effect relationship between the variables under investigation, but is the most diffuse strategy to gather data on large samples for obvious reasons of study feasibility. In the case of a multicenter study, all details of the clinical records of the samples of patients and their recruitment modalities should be reported. The importance of reporting data in accordance to the RDC/TMD guidelines and the version(s) used has been discussed in details in the above example of epidemiological study.

Importantly, in the case of bruxism–TMD investigations, the RDC/TMD’s standardized history taking should be used to record data on self-reported awake and sleep bruxism, on the basis of the patients’ answers to questions 15c (“Do you clench or grind your teeth during sleep?”) and 15d (“Do you clench or grind your teeth while awake?”). For a detailed description of the diagnostic criteria, it is always important to refer to the original RDC/TMD publication (Dworkin and Leresche 1992) and to the successive studies (Truelove et al. 2010), some of which have raised concerns that have been taken into consideration when revising the current RDC/TMD guidelines (Steenks and de Wijer 2009; Anderson et al. 2010; Lobbezoo et al. 2010).

In the case of retrospective studies, the strategies for gathering patients’ databases must be reported also in terms of the time span during which the patient populations were recruited. This issue assumes importance and must be discussed in detail in some particular conditions when the time spans for collecting data on the various populations are different across the centers involved in the multicenter investigation. In the example paper reporting a multicenter study on the bruxism–TMD relationship (Manfredini et al. 2012c), patients attending the TMD Clinic of the University of Padova, Italy, were recruited during the period from January 1, 2009 to June 31, 2009, while those attending the Orofacial Pain Clinic of the University of Tel Aviv, Israel, were recruited more than 5 years before, during the period from January 1, 2001 to December 31, 2004. Despite both centers being served as reference clinics for patients’ referral from vast areas around their location, and investigators responsible for the RDC/TMD assessments have been involved in previous publications on RDC/TMD-related epidemiological and diagnostic issues (Manfredini and Guarda-Nardini 2008; Winocur et al. 2009), the risk for non-homogeneity of data between the two centers should be taken into proper account and discussed thoroughly. In both clinics, several examiners were involved in the diagnostic process, data gathering, and treatment planning, but the final supervision for each single patient’s RDC/TMD diagnosis belonged to the clinicians who were responsible for the projects, as to increase the internal validity of findings. In any case, it is fundamental that findings of the various centers are also presented separately.

From a statistical viewpoint, such kind of investigation is constituted by two strategies:

1. Descriptive reports of the prevalence of each of the single and multiple RDC/TMD axis I diagnoses for TMDs as well as the frequency of positive answers to the questions on self-reported bruxism.
2. Comparison between the two centers of the frequency of the different combinations of clinical TMD diagnoses (no diagnoses; myofascial pain; disc displacement; inflammatory–degenerative joint disorders; myofascial pain and disc displacement; myofascial pain and inflammatory–degenerative joint disorders; disc displacement and inflammatory–degenerative joint disorders; myofascial pain, disc displacement, and inflammatory–degenerative joint disorders) and anamnestic bruxism reports (no reported bruxism; reported awake clenching/grinding; reported sleep clenching/grinding; reported awake and sleep clenching/grinding).

**Table 2.2** Example of a cross-tabulation of RDC/TMD diagnosis and self-reported bruxism diagnosis in a sample of TMD patients recruited at the University of Padova, Italy ( $N=219$ ). Values are expressed in percentage and refer to the total of the patients receiving each specific diagnosis. Based on an edited version of the manuscript “Manfredini et al. (2012c)”

	No SR bruxism	Awake	Asleep	Awake and asleep
No TMD	80	0	0	20
Myofascial pain alone	38.1	23.8	9.5	28.5
Disc displacement alone	60	20	0	20
Inflammatory–degenerative disorders alone	62.5	9.5	12.3	15.7
Myofascial pain + disc displacement	33.3	0	33.3	33.3
Myofascial pain + inflammatory–degenerative disorders	48.3	13.5	16.7	21.5
Disc displacement + inflammatory–degenerative disorders	66.6	2.7	13.8	21.9
Myofascial pain + disc displacement + inflammatory–degenerative disorders	52.1	13	13	21.9

*MP* myofascial pain, *DD* disc displacement, *IDD* inflammatory–degenerative disorders, *SR* self-report

### 2.3.3 Description of Main Findings

Since the strategies for reporting epidemiological findings have been already discussed, focus in the below lines will be on the cross-centers comparison and the bruxism–TMD association. The above multicenter investigation showed significant differences, which were shown between the two clinic samples as for the frequency of TMD diagnoses, with myofascial pain alone being the most prevalent diagnosis in the Tel Aviv sample and myofascial pain combined with inflammatory–degenerative disorders in Padova. A chi-square test showed that the distribution of the different RDC/TMD diagnoses was significantly different between the two centers, and the authors are always recommended to present the level of significance (e.g., chi-square,  $p < 0.001$ ) in the text and tables. If possible, gender-related diagnoses’ distribution should also be presented.

The same information must be provided on bruxism items, with the percentage of positive endorsement to the RDC/TMD questions 15c (“sleep clenching/grinding”) and/or 15d (“awake clenching/grinding”). Again, the frequency of answers should be recorded separately between the two centers (e.g., percentage of subjects answering “yes” to at least one of the two bruxism items in the Tel Aviv and in the Padova sample), with an appropriate statistical comparison (e.g., chi-square test is enough for such comparison in the majority of situations).

Importantly, the prevalence of self-reported bruxism in the different TMD diagnostic groups, which represents the main target of the study, should be reported for all the patient populations. In the example multicenter investigation, in the Tel Aviv population patients with myofascial pain alone tended to report bruxism more frequently than patients receiving other diagnoses, while in the Padova sample the prevalence of self-reported bruxism was similar among the different TMD diagnostic groups (Table 2.2).

## 2.4 How to Assess the Amount of Variance for Disease Explained by an Etiological Model

The above bruxism–TMD investigation provided an example of a single variable association/correlation analysis (i.e., the presence of a variable (bruxism) is used to predict the presence of the other variable (TMD)), which is a statistical approach that is not suitable to depict the multifactorial biological models at best. More complex examples of studies investigating the role of etiological/risk factors for disease are based on analyses in which more than one variable are used as predictors of the outcome variable, viz., the presence of disease. Such an approach provided that the role of each single predictor is influenced by the concurrent presence/absence of the other predictors, and it is called multiple variable analysis. Historically, the most interesting multiple variable studies in the field of TMD and orofacial pain came from investigations assessing the role of dental occlusion features as risk factors for bruxism and TMD.

To introduce the issue, it must be recognized that the etiology of bruxism, as it happens with TMD, is one of the most debated issues in dentistry. Past theories on the purported role of dental occlusion abnormalities in the etiology of bruxism have never been proven, and they have progressively lost importance in favor of theories supporting the role of other factors of central origin (e.g., psychosocial, neurobiological, and genetic factors) (Lavigne et al. 2008). In general, the recent literature suggests a shift from occlusal to psychological-based hypotheses and from peripheral to central regulation hypotheses (Lobbezoo and Naeije 2001; Lobbezoo et al. 2012). Notwithstanding that, the hypothesis that certain occlusal features may be related with bruxism onset has not been completely abandoned and is occasionally revisited (Sugimoto et al. 2011).

Actually, for a causal relationship between occlusion and bruxism being present, a compelling prerequisite is that the two variables are associated, viz., the prevalence of the disorder should be significantly higher in subjects presenting a certain risk factor (Hill 1965; Manfredini and Lobbezoo 2010a). Only then, hypothesis-driven studies to test the existence of a causal link may be performed on a rational basis. Past works on the issue showed that an association between bruxism and occlusal features of the natural dentition could be ruled out (Lobbezoo et al. 2001; Manfredini et al. 2004) and, in general, comprehensive reviews on the argument suggested that bruxism and the bite are likely unrelated (Lobbezoo et al. 2012). Nonetheless, the quality of the available literature on the argument is not optimal, and it might be interesting to get deeper into the issue by the adoption of the above-introduced multiple variable analyses of the various occlusal risk factors, which is more apt to depict biological models.

Within these premises, some characteristics of a recent investigation aiming to estimate the contribution of various occlusal features of the natural dentition to identify self-reported bruxers with respect to non-bruxers can be used as example to guide readers through the multiple variable assessment of risk for disease (Manfredini et al. 2012b). The following sections on the description of the study design and report of main findings in the case of an investigation assessing the association between two variables in a multifactorial model are thus based on an edited, arranged, and commented version of the manuscript “Manfredini et al. (2012b).”

Statistical Approaches to Orofacial Pain and  
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