ABSTRACT: Several works showed a decreased role for occlusion in the etiology of temporomandibular disorders (TMD). Nonetheless, it may be hypothesized that occlusion acts as a modulator through which bruxism activities may cause damage to the stomatognathic structures. To test this hypothesis, a logistic regression model was created with the inclusion of clinically diagnosed bruxism and eight occlusal features as potential predictors for temporomandibular joint (TMJ) pain in a sample of 276 consecutive TMD patients. The final logit showed that the percentage of the total log likelihood for TMJ pain explained by the significant factors was small and amounted to 13.2%, with unacceptable levels of sensitivity (16.4%). The parameters overbite $\geq$ 4 mm combined with clinically diagnosed bruxism [OR (odds ratio) 4.62], overjet $\geq$ 5 mm (OR 2.83), and asymmetrical molar relationship combined with clinically diagnosed bruxism (OR 2.77) were those with the highest odds for disease, even though none of those values was significant with respect to confidence intervals. Thus, the hypothesis under evaluation has to be rejected. It is possible that future studies with a higher discriminatory power for the different bruxism activities might be indicated to get deeper into the analysis of the potential mechanisms through which occlusion may play a role, even if small, in the etiology of the different TMD.

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Temporomandibular disorders (TMD) have a multifactorial etiology, and there are many studies in the literature identifying several local and systemic risk factors for the disease.

In recent years, many studies have shown that the role of occlusal factors is less important than was believed in the past, and case-control studies have identified logistic regression models, suggesting that occlusal variables account for only about 27% of the total amount of variance for temporomandibular joint (TMJ) disorders and up to 10% for masticatory muscle disorders.

Nonetheless, there is still some disagreement among researchers, since some authors suggest that occlusal abnormalities may be important in patients with a previous TMD history or in subjects who have an occlusal hypersensitivity.

One plausible hypothesis to explain the reluctance of some clinicians to accept the diminished role of occlusion in TMD patients may be the actual absence of a concrete alternative pathophysiological model of disease that fits with the actual clinical and research knowledge.
The inclusion of bruxism assessment in an integrated model with the analysis of occlusal parameters may be helpful to more fully understand the issue and be more in accordance with the hypothesis that the role of occlusion in TMD patients might be mediated by bruxism activity on some peculiar occlusal patterns.

The aim of this study was twofold: 1. to quantify the relative risk of clinically diagnosed bruxism and multiple occlusal variables, alone and combined with each other, for painful disorders of the temporomandibular joint; 2. to estimate the contribution of clinically diagnosed bruxism and occlusion to differentiate patients with TMJ pain from those without TMJ pain.

Materials and Methods

Study Design

A sample of consecutive patients referred to the TMD Clinic, Department of Maxillofacial Surgery, University of Padova, Italy during the period from January 2007 to September 2008 was considered for inclusion in the study.

Criteria for inclusion in the study were the following: age between 25 and 45 years; absence of fibromyalgia, as diagnosed in accordance with the American College of Rheumatology criteria; absence of rheumatoid arthritis or other rheumatic disorders, as diagnosed in accordance with the American Rheumatism Association criteria; no history of drugs or alcohol abuse; and an absence of any mental or psychiatric disorders.

Two-hundred-seventy-six (N=276) patients (193 females; 83 males; mean age 32.2±5.7, range 25-44) were selected for the study, based upon fulfillment of the criteria for inclusion, and underwent the following assessments.

A clinical assessment for TMD was performed in accordance with the Research Diagnostic Criteria for TMD (RDC/TMD) guidelines by one of two trained operators with expertise in TMD clinical assessment and research methodology.

The following occlusal features were also accurately recorded for each patient, in accordance with a protocol adopted by a main investigator in a previous study: retruded contact position (RCP) to maximum intercuspation (MI) slide length (normal value <2 mm), calculated in the three spatial axes after manual mandibular distraction; vertical overlap, viz, overbite (0 mm < normal value <4 mm); horizontal overlap, viz, overjet (0 mm < normal value <5 mm); posterior reverse articulation, viz, posterior cross-bite; anterior open occlusal relationship, viz, anterior open bite; mediotrusive and laterotrusive interferences within the first millimeters of the lateral excursions identified by 40 mm thick articulating paper (Baush Dental KG, Köln Germany); and symmetrical molar relationships between the two dental arches.

The patients were clinically assessed for the presence of bruxism, in accordance with a set of clinically-oriented criteria that were used for the validation of polysomnographic criteria for sleep bruxism diagnosis and that were already adopted in the clinical setting for research purposes. Such criteria provided that diagnosis of bruxism was made when the patient exhibited, at least five nights a week, grinding bruxism sounds during sleep during the last six months, as reported by his/her bed partner, and at least one of the following adjunctive criteria: observation of tooth wear or shiny spots on restorations; report of morning masticatory muscle fatigue or pain; and masseteric hypertrophy upon digital palpation.

Patients were divided into two groups on the basis of the presence of a painful disorder of the TMJ, namely, RDC/TMD Axis I Group IIIa diagnosis of arthralgia and/or RDC/TMD Axis I Group IIIb diagnosis of osteoarthritis. RDC/TMD Axis I Group IIIa diagnosis of arthralgia was made when pain was elicited in one or both joint sites (lateral pole and/or posterior attachment) during palpation and in combination with one or more of the following self-reports of pain: pain in the region of the joint; pain in the joint during maximum unassisted opening; pain in the joint during assisted opening; and pain in the joint during lateral excursion. For a diagnosis of simple arthralgia, coarse crepitus had to be absent. RDC/TMD Axis I Group IIIb diagnosis of osteoarthritis was diagnosed by the presence of arthralgia as defined in IIIa in combination with either coarse crepitus in the joint or radiological signs of arthrosis.

A logistical regression model was created to estimate the contribution of clinically diagnosed bruxism and occlusal features to differentiate patients with TMJ pain from those without TMJ pain.

Statistical Analysis

A stepwise multiple logistical regression model was used to identify the significant associations between the potential predictors and TMJ pain. Selection was made among the potential predictors (slide ≥2 mm; crossbite; overbite ≥ 4 mm; anterior open bite; overjet ≥ 5 mm; mediotrusive interferences; laterotrusive interferences; symmetrical molar relationship; clinically diagnosed bruxism) of TMJ pain using a stepwise selection method. Significance needed for removal was set at P ≥ 0.10 and significance for reentry at P ≤ 0.05.

Hosmer and Lemeshow Goodness-of-Fit test was performed at each step to test the null hypothesis that there was no difference between the observed and the model-
predicted value of the dependent variable.\textsuperscript{18} If the $P$ value is less than .05, the null hypothesis that there is no difference between the observed and predicted values of the fitted model must be rejected, indicating poor fit of the model; therefore, the $P$ value of the Hosmer and Lemeshow Goodness-of-Fit test statistic should be greater than .05. This does not mean that the model necessarily explains the variance in the dependent variable, only that however much or little it explained was significant.

At each step, a model chi-square test was also performed. A model chi-square is a likelihood ratio test, which reflects the difference between the error of not knowing the independent variables, and the error when the independent variables are included in the model. When $P \leq .05$, the null hypothesis that knowing the independent variables makes no difference in predicting the dependent variable in logistic regression can be rejected. Therefore, the model chi-square should be significant at the .05 level or better.

The odds ratio (OR) for TMJ pain was simultaneously assessed for each predictor. The odds ratio describes the risk that a subject with a particular predictor variable will belong to the TMJ pain group, while simultaneously controlling for all the other variables.

Nagelkerke’s R-square ($R^2$) was obtained as an estimation of the total log likelihood explained by a summation of the significant occlusal factors. The log likelihood in a logistical regression model is the analog of the variance in a linear regression model and represents the amount that the independent variables (occlusal factors, clinically diagnosed bruxism) can differentiate the dependent variable (TMJ pain versus absence of TMJ pain).

$R^2$ represents a numerical expression of the dependent variable’s (presence/absence of TMJ pain) variance, accounted for by the model constituted by the significant occlusal variables. If $R^2$ is greater than 0.75, the fitted model is considered capable of predicting the presence of disease at a very good level. The model’s ability to predict disease is considered good if $R^2$ is between 0.50 and 0.75, fair if $R^2$ is between 0.25 and 0.50, and poor for a $R^2$ of 0.25 or less.\textsuperscript{19} Therefore, in the last situation the fitted model should predict disease at an unacceptable level.

The accuracy of the final logistical regression model to predict patients with TMJ pain (sensitivity) or without TMJ pain (specificity) was determined from a 2x2 classification table and from a classification plot. The cutoff value that provided the highest value for both sensitivity and specificity was selected.

Furthermore, to illustrate the relative limitations of univariate analysis, the $P$ values, sensitivity, specificity, and odds ratios derived from the multiple logistical regression were compared with single factor (univariate) analysis, conducted by means of a chi-square test.

All data were analyzed using statistical software (Statistical Package for the Social Sciences, SPSS 14.0, SPSS Inc, Chicago, IL).

Results

The prevalence of all the potential predictors included in the multivariate model in patients with or without TMJ pain is reported in Table 1.

Among the potential predictors included in the initial model for logistic regression analysis (Table 2), those remaining in the final model were: overjet $\geq 5$ mm, overbite $\geq 4$ mm, laterotrusive interferences, asymmetrical molar relationship, and the combined effect of bruxism with overbite $\geq 4$ mm, asymmetrical molar relationship and laterotrusive interferences (Table 3).

The odds ratio for TMJ pain ranged between 0.23 for overbite $\geq 4$ mm to 4.62 for overbite $\geq 4$ mm combined with clinically diagnosed bruxism.

Hosmer and Lemeshow Goodness-of-Fit test was not significant, indicating that no inconsistency could be detected between the sample and the model being considered as having generated the sample.

Also, the final model chi-square was significant at $P<.05$, indicating that the error in predicting the dependent variable (presence of TMJ pain) is significantly lower when the independent variables (predictors included in the final regression model) are included in the model.

The percentage of the total log likelihood for TMJ pain explained by the significant factors was small and amounted to 13.2% (Nagelkerke’s $R^2= 0.132$).

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
Predictors & No & Yes \\
\hline
Clinically diagnosed bruxism & 88/80 & 72/38 \\
RCP-MI slide $\geq 2$ mm & 71/95 & 57/53 \\
Mediotrusive interferences & 75/91 & 57/53 \\
Laterotrusive interferences & 45/121 & 35/75 \\
Overjet $\geq 5$ mm & 14/152 & 20/90 \\
Overbite $\geq 4$ mm & 39/127 & 19/91 \\
Open bite & 9/157 & 10/100 \\
Crossbite & 40/126 & 31/79 \\
Symmetrical relationship & 131/35 & 78/32 \\
Molar & & \\
\hline
\end{tabular}
\caption{Descriptive Table of All Potential Predictors In the Multivariate Model By Presence of TMJ Pain}
\end{table}
<table>
<thead>
<tr>
<th>Multivariate model</th>
<th></th>
<th>Odds ratio</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Accuracy</th>
<th>Total $R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCD/TMD Arthralgia (IIa) and/or Osteoarthritis (IIb)</td>
<td></td>
<td></td>
<td>34.5%</td>
<td>84.9%</td>
<td>64.9%</td>
<td>16.9%</td>
</tr>
<tr>
<td>Overbite $\geq 4$ mm (bruxism)</td>
<td>.021</td>
<td>7.34</td>
<td>(1.35-39.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overjet $\geq 5$ mm</td>
<td>.020</td>
<td>4.43</td>
<td>(1.26-15.55)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymmetrical molar relationship* (bruxism)</td>
<td>.050</td>
<td>3.38</td>
<td>(0.96-11.95)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laterotrusive interferences</td>
<td>.041</td>
<td>2.73</td>
<td>(1.04-7.13)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymmetrical molar relationship</td>
<td>.021</td>
<td>0.30</td>
<td>(0.11-0.83)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laterotrusive interferences* (bruxism)</td>
<td>.016</td>
<td>0.22</td>
<td>(0.06-0.75)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overbite $\geq 4$ mm</td>
<td>.025</td>
<td>0.18</td>
<td>(0.04-0.80)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mediotrusive interferences* (bruxism)</td>
<td>.083</td>
<td>29.7</td>
<td>(0.87-10.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mediotrusive interferences</td>
<td>.295</td>
<td>0.59</td>
<td>(0.22-1.57)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overjet $\geq 5$ mm* (bruxism)</td>
<td>.259</td>
<td>0.39</td>
<td>(0.07-2.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinically diagnosed bruxism</td>
<td>.329</td>
<td>0.49</td>
<td>(0.12-2.02)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crossbite* bruxism</td>
<td>.209</td>
<td>0.44</td>
<td>(0.12-1.57)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCP-MI slide $\geq 2$ mm* bruxism</td>
<td>.306</td>
<td>1.79</td>
<td>(0.58-5.53)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open bite* bruxism</td>
<td>.449</td>
<td>2.29</td>
<td>(0.27-19.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCP-MI slide $\geq 2$ mm</td>
<td>.854</td>
<td>0.92</td>
<td>(0.37-2.23)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crossbite</td>
<td>.269</td>
<td>1.79</td>
<td>(0.63-5.02)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Open bite</td>
<td>.914</td>
<td>0.91</td>
<td>(0.19-4.40)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI: confidence level
The final model, including the significant predictors, showed a specificity of 94.0% and a sensitivity of 16.4% to predict TMJ pain (accuracy = 63.0%).

Univariate analysis (chi-square test) revealed a significant association between the presence of TMJ and clinically diagnosed bruxism ($P = .025$), and overjet $\geq 5$ mm ($P = .016$, Table 4).

Despite the fact that clinically diagnosed bruxism showed a significant association with TMJ pain in univariate analysis, multifactorial analysis did not show that factor as significant, suggesting that it is not fundamental to increase accuracy of the final logit, and it is of some importance if combined with some occlusal factors.

As regards single factor analysis of the other occlusal features, the presence of TMJ pain was not significantly associated with crossbite ($P = .447$), open bite ($P = .238$), overbite $\geq 4$ mm ($P = .214$), slide RCP-MI $\geq 2$ mm ($P = .140$), mediotrusive interferences ($P = .280$), laterotrusive interferences ($P = .398$), and symmetrical molar relationship ($P = .129$).

The odds ratio for TMJ pain at univariate analysis was assessed for each occlusal variable. A two to one odds ratio, that might be considered a threshold to detect a clinically important risk factor for disease, was achieved only for the presence of overjet $\geq 5$ mm (OR 2.41), even it was not significant when considering 95% confidence intervals.

The accuracy to predict the presence or absence of TMJ pain was assessed for each factor. For the two significant factors, namely, clinically diagnosed bruxism and overjet $\geq 5$ mm, specificity was 48.2% and 91.5%, sensitivity was 65.4% and 18.2%, and accuracy 56.1% and 62.3%.

### Discussion

Over the last decade, many claims were made to indicate that an approach to the study of risk factors for a disease in biological models cannot be based on simple statistical models, such as univariate analysis. In the case
of TMD, which has a multifactorial etiopathogenesis,\textsuperscript{20} multiple logistic regression analysis was introduced for the study of potential risk factors.\textsuperscript{6}

Literature data showed that such an analysis was performed to assess the odds for disease for risk factors identified through the patients’ clinical history,\textsuperscript{5,21} as well as through the clinical assessment of morphological, viz, occlusal, features.\textsuperscript{7,8,22}

In particular, models created through logistical regression contributed much to a better understanding the role of dental occlusion in TMD patients, showing that occlusal features demonstrated a maximum of 27.1\% of the log likelihood for TMJ disorders, such as osteoarthritis and disk displacement,\textsuperscript{7} and 10.8\% of the log likelihood for muscle disorders, such as myofascial pain with or without limited opening.\textsuperscript{8}

Since multifactorial models have improved accuracy in detecting the presence of disease, this study was an attempt to combine the assessment of occlusal factors with that of clinically diagnosed bruxism in the detection of risk factors associated with painful disorders of the temporomandibular joint.

The work hypothesis was that the minimum amount of importance of occlusal factors may be increased by the presence of a concurrent bruxing behavior.

From a clinical viewpoint, this hypothesis may find biological plausibility in the current concepts on joint overload, which provides that prolonged forces exerted on the articular structures, such as those associated with bruxism activity, may damage joint tissues at the molecular level\textsuperscript{23} and then exhibit in joint effusion and pain.\textsuperscript{24-27}

It may be hypothesized that bruxism activity per-

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Association Between the Presence of TMJ Pain and Predictors Revealed By Univariate Analysis (Chi-Square Test)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Univariate model</strong></td>
<td><strong>Odds ratio (95% CI)</strong></td>
</tr>
<tr>
<td>Clinically diagnosed bruxism</td>
<td>.025</td>
</tr>
<tr>
<td>RCP-MI slide ≥2 mm</td>
<td>.140</td>
</tr>
<tr>
<td>Mediotrusive interferences</td>
<td>.280</td>
</tr>
<tr>
<td>Laterotrusive interferences</td>
<td>.398</td>
</tr>
<tr>
<td>Overjet ≥5 mm</td>
<td>.016</td>
</tr>
<tr>
<td>Overjet ≥4 mm</td>
<td>.214</td>
</tr>
<tr>
<td>Open bite</td>
<td>.238</td>
</tr>
<tr>
<td>Crossbite</td>
<td>.447</td>
</tr>
<tr>
<td>Symmetrical molar relationship</td>
<td>.129</td>
</tr>
</tbody>
</table>

CI: confidence level
formed over unfavorable occlusal patterns may lead to TMJ pain. If this was the case, the percentage of the total amount of the log likelihood for disease explained by the model comprising both occlusal factors and bruxism should be higher than that described by models including only occlusal features.

In the present investigation, 276 TMD patients underwent a clinical assessment of bruxism and occlusal features to test the hypothesis that those factors may allow identification of patients with RDC/TMD axis I diagnosis of arthralgia and/or osteoarthritis. Predictors that remained in the final multiple logistical regression equation were overjet $\geq 5$ mm, overbite $\geq 4$ mm, laterotrusive interferences, asymmetrical molar relationship, and the combined effect of bruxism with overbite $\geq 4$ mm, asymmetrical molar relationship and laterotrusive interferences. The highest odds ratios for TMJ pain were respectively $4.62$ for overbite $\geq 4$ mm combined with clinically diagnosed bruxism, $2.83$ for overjet $\geq 5$ mm, and $2.77$ for asymmetrical molar relationship combined with clinically diagnosed bruxism, even though none of those values is significant with respect to confidence intervals. 

Unfortunately, the final multifactorial model did not show a marked increase in accuracy ($63.0\%$) with respect to that shown by single factor analysis (diagnostic accuracy of significant factors, viz, clinically diagnosed bruxism and overjet $\geq 5$ mm, was $56.1\%$ and $62.3\%$ respectively. Consequently, the final model, including significant predictors, explained only $13.2\%$ of the log likelihood for temporomandibular joint pain.

Thus, the inclusion of bruxism assessment in a multifactorial model along with occlusal factors did not increase the predictability of TMJ pain with respect to the low predictability shown by the assessment of occlusal features alone.

A comparison of findings from this investigation with results from other studies is difficult, because very few studies performed a combined analysis of occlusion and bruxism in TMD patients, and none adopted standardized clinical criteria for the diagnosis of both TMD and bruxism. The majority of works on this issue are largescale epidemiological investigations, which provide an interview-based, self-report or nonstandardized diagnosis of bruxism.$^{28-30}$ Moreover, data emerging from univariate analysis, which are of poor clinical significance due to the low statistical power of such analysis, are hardly comparable to other studies because of the different criteria adopted for TMD diagnosis. In general, single-factor analysis showed moderate levels of association with several occlusal variables, and in particular with mediotrusive interferences and slide RCP-MI,$^{11}$ which are not among the most significant factors in this study. In the present investigation, a significant association with TMJ pain has been detected only for a large overjet and clinically diagnosed bruxism, and a moderate level of accuracy was shown for open bite. Such findings, even though they have a low statistical power, may provide further support of the fact that the importance of gross occlusal abnormalities in the pathophysiology of TMD cannot be underestimated.$^{12}$

More importantly, to our knowledge, this is the first investigation, which addresses the issue of the identification of occlusal risk factors for TMD by adopting a standardized assessment for both bruxism and TMD and by using multiple logistic regression analysis.

Despite these potential strengths, this investigation fell short in the attempt to describe a convincing model for the presence of temporomandibular joint pain based on the combination of occlusal assessment and clinical diagnosis of bruxism.

From a clinical standpoint, these findings lend support to the currently available literature on the TMD-occlusion relationship, which has progressively dismantled the old belief that occlusal abnormalities are the main etiological factor for TMD. Nonetheless, the low influence of bruxism in modifying the predictive value of the logistical regression model was quite unexpected, since it means that the clinical relationship that bruxism has with TMJ pain is independent of the occlusal pattern of the patient who exhibits bruxing behavior.

Such finding is quite surprising if one considers that occlusion is the battleground where muscle forces are exerted during bruxism activity, thus potentially influencing the transmission of those forces to the temporomandibular joints.

As pointed out in some systematic reviews of the literature, the bruxism-TMD relationship is yet to be clarified$^{31,33}$ and may have been biased so far by the absence of a clear-cut discrimination between clenching and grinding, which are actually two distinct entities at the etiological level.$^{34,36}$

Univariate analysis in this study showed that bruxism, as clinically diagnosed, is associated with TMJ pain, but this finding added nothing to the amount of literature on this complex issue, due to the well-known low statistical robustness of such analysis.

Thus, methodological shortcomings affecting the majority of studies on the relationship between bruxism and TMD might have influenced this study’s findings as well, due to the undiscriminated inclusion of both jaw clenching and teeth grinding habits within the parameter labeled as clinically diagnosed bruxism. Otherwise, uncertainties about this issue will be solved as soon as a reliable measure of bruxism, with a good discriminatory
power between the different activities is available.

These potential shortcomings may have been responsible for the low increase in the predictive value of the logistical regression model, including occlusal features and bruxism with respect to previous models based on occlusal features alone.

Moreover, it is possible that the inclusion of an age and gender-matched control group of healthy subjects may allow for a description of more satisfactory models with respect to this study’s selection of a single wide group of TMD patients among which those with TMJ pain had to be identified. All these aspects need to be re-examined with attention in the design phases of future studies. Also, future studies with a higher discriminatory power for different bruxism activities might be indicated to get a better understanding of the analysis of the potential mechanisms through which occlusion may play a role, even if small, in the etiology of the different TMD.

Conclusions

Within all the limitations of this study, the following suggestions can be drawn:

1. The occlusal features and the presence of bruxism, as assessed in this investigation, account for a small part (13.2%) of the log likelihood for RDC/TMD axis I group IIIa diagnosis of temporomandibular joint arthralgia or RDC/TMD axis I group IIIb diagnosis of temporomandibular joint osteoarthropathy.
2. The parameters of overbite ≥ 4 mm combined with clinically diagnosed bruxism (OR 4.62), overjet ≥ 5 mm (OR 2.83), and asymmetrical molar relationship combined with clinically diagnosed bruxism (OR 2.77) were those with the highest odds for disease, even though none of those values is significant with respect to confidence intervals.

References

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