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Are third molars associated with orofacial pain? Findings from the SHIP study

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Abstract

Objectives: To examine the association between third molars and orofacial pain. We hypothesized that impacted third molars are a cause of orofacial pain.

Methods: Magnetic resonance images of 1808 participants from two population-based cohorts from Northeastern Germany were analysed to define the status of third molars according to the Pell and Gregory classification. A self-reported questionnaire and a clinical dental examination were used to detect chronic and acute complaints of orofacial pain, masticatory muscle pain, migraine and other types of headache. Logistic regression models were used to analyse the associations between third molar status and orofacial pain.

Results: Individuals with impacted third molars in the maxilla had a higher chance of chronic orofacial pain than those with erupted third molars (odds ratio 2.19; 95% CI 1.19-4.02). No such association was detected for third molars in the lower jaw. Third molars were not associated with masticatory muscle pain, migraine or other types of headache.

Conclusions: Impacted maxillary third molars might be a cause of chronic orofacial pain. Thus, physicians should consider the eruption/impaction status of third molars in their decision-making process when treating patients who complain of orofacial pain.

KEYWORDS

epidemiologic studies, magnetic resonance imaging, orofacial pain, third molar, whole-body imaging

1 | INTRODUCTION

Pain is a crucial reaction against chemical, physical or harmful stimuli. Some severe cases require a thorough examination, adequate imaging and may even call for a multidisciplinary approach.[1] There are several ways to categorize pain, such as by cause (eg cancer pain), location (eg orofacial pain) or affected anatomical system (eg neuropathic pain). The intensity and nature of pain can be used to differentiate between acute and chronic pain. The International Association for the Study of Pain (IASP) and the World Health Organization (WHO) created a Task Force to complement the current version of the International Classification of Diseases (ICD 11) in respect of chronic pain. It defined chronic headache and orofacial pain as 'Pains that occur on at least 50% of the days during at least 3 months'.[2] Orofacial pain is defined as pain of the hard and soft tissues around the eyes or ears, as well as pain within the oral cavity.[3] It is a broad term that encompasses multiple subsets such as masticatory musculoskeletal pain, pain related to temporomandibular joint disorders, neuropathic pain, neurovascular pain, intra-oral and dental diseases,[4] which justifies the rapidly growing role of dentists in treating orofacial pain. Orofacial pain is relatively common, affecting up to 45% of the adult population, but barely half of those seek treatment.[5-7] It can arise from different tissues and aetiologies; masticatory muscle pain and temporomandibular joint disorders (TMD) are examples of pain originating from soft and hard tissues, respectively. Previously published studies focused on orofacial pain related to those conditions with considerable variation of reported numbers,[8,9] which were often justified by the different coping abilities and treatment seeking behaviour among populations.[10,11] Additionally, there are numerous dental diseases that can cause orofacial pain which can originate from the teeth, the surrounding periodontium, oral mucosa and other structures of the oral cavity.[12]

It has long been speculated that third molars contribute to headache disorders and orofacial pain.[13] They are the most frequently impacted teeth, and many are associated with cystic changes (up to 50% in some studies), periodontal damage (impacted third molars increased the risk more than 4-fold) and caries of the distal surface of second molars (up to 12%).[14-16] There are conflicting estimates of the frequency of neoplastic lesions associated with third molars,[17-19] thus casting doubts on claims of necessity to remove third molars to prevent pathological changes.[20,21] This has led to opposing opinions among oral surgeons and general dentists on the indications for third molar removal when presented with periapical radiographs of the same patient.[22] Although this topic has been extensively discussed in the literature and summarized as well-established guidelines,[23] the need for third molar removal is still debated. The International Classification of Headache Disorders viewed partially impacted third molars as among the most common causes of orofacial pain.[13] A 2016 Cochrane review which investigated the need for removal of asymptomatic impacted third molars found no evidence to support it and called for longer-term studies to clarify this matter.[24] The review defined third molars to be asymptomatic when signs of diseases affecting the tooth and nearby structures, such as root resorption and periodontitis, were absent, and there was no mention of a possible association with orofacial pain. Dogan et al[25] examined radiographs from 832 military recruits finding partially erupted third molars to be the most symptomatic. An investigation of orofacial pain and a history of third molar removal suggested that a history of third molar extraction is associated with orofacial pain.[26] There is little in the literature revealed on the association of impacted or erupted third molars with orofacial pain. Previous studies have restricted their assessment to local symptoms specifically caused by partially impacted third molars. Anatomical proximity means that pain caused by TMD can also mislead clinicians, and this was not accounted for in previous studies. Furthermore, recruiting patients from healthcare facilities compromises the generalizability of study findings.

Despite advances in understanding pain mechanisms and referral, the association between third molars and orofacial pain remains largely overlooked with knowledge based on limited data. Responding to these shortcomings, the present study aims to shed more light upon this association in a large representative sample of the population. We employed state-of-the-art MRI assessments to examine the status of third molars, and we assessed pain complaints through self-reported questionnaires augmented with oral clinical examinations to identify potential causes of orofacial pain. We hypothesized that individuals with impacted third molars have higher rates of orofacial pain.

2 | METHODS

We included participants from the Study of Health in Pomerania (SHIP), a cross-sectional population-based study assessing the prevalence and incidence of common population-relevant diseases and their risk factors in Northeastern Germany.[27] SHIP participants were randomly selected using public registries. Baseline examinations (SHIP-0) were conducted between 1997 and 2001, at which 4308 individuals participated. Follow-up examinations were undertaken at 5 years (SHIP-1; 2002-2006; 3300 follow-up participants, follow-up response 83.6%) and 11 years (SHIP-2; 2008-2012; 2333 follow-up participants, follow-up response 62.9%) after baseline.[27] In 2008, a new cohort (SHIP-Trend; 2008-2012) with 4420 participants was established in the same geographic region. Participants in both cohorts underwent a medical examination, an oral health examination, a health-related interview and a self-administered health- and risk factor-related questionnaire. Out of 6753 participants from both SHIP-2 and SHIP-trend, a total of 2522 participants (37.3%) agreed to undergo an additional whole-body MRI examination. Of those 2522 participants, 40 were excluded due to artefacts affecting the head region, resulting in MRI data on third molars from 2482 participants (98.4%). Excluded from this study were those taking NSAIDs (n = 212), opioids (n = 18) or analgesics (n = 108). Furthermore, to avoid confusion with signs of TMD, participants describing pain upon palpation of the lateral condyles, in dorso-cranial direction or upon palpation of the masticatory muscles were also excluded (n = 336) resulting in a study sample of 1808 participants (71.7%).

Magnetic resonance imaging scans used a 1.5T system (Magnetom Avanto; Siemens Medical Solutions). The complete whole-body MRI

protocol has been described previously.[28] For the evaluation of third molars, transversal T1-weighted turbo spin echo images (TE: 11 ms, TR: 587 ms, slice thickness: 4 mm, matrix: 256 × 256) and sagittal T1-weighted turbo spin echo images (TE: 120 ms, TR: 6760 ms, slice thickness: 4 mm, matrix: 448 × 448) were used. Additionally, coronal T2-weighted fat suppressed images (TR 4891 ms, TE 670 ms, inversion time 160 ms, slice thickness 5 mm) were available for further analysis of third molars. MR images were transferred to a working station (iMac 27″; Apple) where an open-source DICOM viewer (OsiriX v.3.8.1; Pixmeo) was used to load and analyse the MRI images (Figure S1).

Magnetic resonance imaging data were visually scrutinized by two trained dentists with a predefined Kappa algorithm used to measure inter-observer agreement; this was 98.5% for the impaction of third molars. Inter-observer agreement for third molars in the maxilla was a little higher (κ: .90-.94) than in the mandible (κ: .81-.83). Third molars were identified on the images and categorized according to Pell and Gregory[29] as missing, erupted or impacted. A third molar was considered erupted if its occlusal plane was above the cervical line of the adjacent second molar. Third molars with an occlusal plane below the cervical line of the second molar were considered impacted.[14]

Study and examination protocols were approved by the ethics committee at the University Medicine Greifswald (15.05.2008, BB 39/08). All participants signed an informed consent form, and investigations were undertaken in accordance with the Declaration of Helsinki.

Data on chronic orofacial pain were collected using a self-assessment questionnaire. Participants answered the question: 'Have you experienced any facial pain, masticatory muscle pain, pain in the temporomandibular joint or around the ears in the last 6 months?' They were further asked whether they had had migraine or other types of headache. Additionally, the masseter and temporalis muscles were palpated under pressure of about 1 kg/cm^2 bilaterally during an oral clinical examination, allowing an objective evaluation of acute masticatory muscle pain. We determined TMD pain using lateral and dorso-cranial palpation of the condyles. The lateral palpation of the TMJ was conducted with lateral pressure of about 2 kg/cm,^{2} while the mouth was slightly open. The dorso-cranial condyle compression occurred with the participant's mandible in the relaxed position. Participants were asked to describe their perception as 'painless', 'uncomfortable' or 'painful'. To distinguish pain and discomfort, each outcome (TMD pain and muscle pain) was defined as present if there was at least 1 site with pain upon palpation. The category 'uncomfortable' was not excluded but coded as 'painless'. This examination was part of the oral examination of the SHIP study and was performed by 8 trained, calibrated and certified dentists.[30] Examiners' training took place before the study started and twice a year during data acquisition. Inter-examiner variability for TMD signs was measured in 5 calibrated sessions using a total of 22 volunteers (7 of them with functional complaints). Kappa values for detecting tenderness upon palpation of the masticatory muscles and the temporomandibular joint ranged from 0.53 to 0.63. Training of the dentists and consensus discussions occurred before the start of the examinations and were repeated for calibration twice a year during the period of data collection.[31]

2.1 | Oral clinical examination

Coronal caries status was recorded as overt carious defects, fillings, secondary caries or missing teeth recorded at surface level (occlusal, mesial, distal, vestibular and oral) on a half-mouth basis excluding third molars. Coronal caries was identified visually using a periodontal probe according to the WHO criteria, but excluding third molars.[32] Using this information, the DFS scores were calculated. Periodontal examinations used a half-mouth approach on the left or right side (SHIP-2: alternatingly assigned; SHIP-Trend: randomly assigned), excluding third molars. Oral examinations used a half-mouth approach due to limited examination time per participant. Probing depth (PD) and clinical attachment loss (CAL) were measured with a periodontal probe (SHIP-2: PCP11, SHIP-Trend-0: PCP15; Hu-Friedy) at four sites per tooth (distobuccal, mesiobuccal, midbuccal and midpalatal/midlingual). Demographic data (ie gender and level of education), preferred chewing side and having a medical diagnosis of migraine, were reported through a computer-assisted interview.

2.2 | Statistical analysis

Stratified by third molar status, categorical data were described as absolute numbers and percentages and continuous data as median, 25th and 75th percentile. Associations between third molar status and orofacial pain were analysed using cross-tabulation logistic regression models, adjusted for age, gender, educational status and preferred chewing side. 'Erupted third molars' were used as the reference category for odds ratios. In all analyses, a P value <.05 was considered as statistically significant. All analyses were carried out with Stata 15.1 (Stata Corporation).

3 | RESULTS

Younger participants had more impacted third molars than their older peers (Table 1). A total of 16% of all participants had at least one impacted third molar (n = 299), and 37.2% (n = 672) had no third molars at the time of examination. Higher impaction rates of third molars were observed in males than females for upper and lower jaw. In contrast, females had more missing third molars than males.

We detected an association between impacted third molars in the maxilla and orofacial pain (odds ratio 2.19; 95% confidence interval 1.19-4.02) (Figure S2, Table 2), whereas there was no such association for impacted third molars in the mandible (odds ratio 1.33; 95% confidence interval 0.74-2.37) (Figure S3). This association was more evident in the right upper jaw and independent of the age, gender, level of education and preferred chewing side. On the other hand, no significant associations of third molar status with migraine or other types of headache were found. There were no significant interactions of age or gender with impacted or missing third molars

TABLE 1 Third molar status by sociodemographic and clinical characteristics

	N	Third molar status		
		Missing (n = 672)	Erupted (n = 836)	Impacted (n = 299)
Median age (25th, 75th percentile)	1808	61 (51; 69)	51 (42; 60)	47 (38; 61)
Sex	1808			
Male		326 (48.5%)	423 (50.5%)	187 (62.5%)
Female		346 (51.5%)	414 (49.5%)	112 (37.5%)
Education	1805			
Less than 10 y		187 (27.8%)	103 (12.3%)	35 (11.7%)
10 y		319 (47.5%)	509 (61.0%)	156 (52.2%)
More than 10 y		165 (24.6%)	223 (26.7%)	108 (36.1%)
Preferred chewing side	1802			
None		336 (50.0%)	420 (50.4%)	171 (57.8%)
Left		123 (18.3%)	125 (15.0%)	42 (14.2%)
Right		213 (31.7%)	289 (34.7%)	83 (28.0%)
Orofacial pain	1808			
No		628 (93.5%)	776 (92.7%)	273 (91.3%)
Yes		44 (6.6%)	61 (7.3%)	26 (8.7%)
Migraine	1825			
No		617 (91.8%)	749 (89.6%)	277 (92.6%)
Yes		55 (8.2%)	87 (10.4%)	22 (7.4%)
Headache	1568			
No		210 (37.1%)	248 (34.1%)	84 (32.7%)
Yes		356 (62.9%)	480 (65.9%)	173 (67.3%)
Periodontitis	1572			
None or mild		198 (39.8%)	340 (43.1%)	138 (48.4%)
Moderate		199 (40.0%)	297 (37.6%)	102 (35.8%)
Severe		100 (20.1%)	153 (19.4%)	45 (15.8%)
Dental caries	1721			
Mean DFS		17 (9; 25)	19 (12; 25)	15 (9; 24)

on orofacial pain. We included caries and periodontal diseases as confounders in our analysis and found no differences.

4 | DISCUSSION

We investigated third molar status in a population-based sample and found a relatively strong association between impacted maxillary third molars and orofacial pain. Interestingly, impacted third molars had no association with migraine or other types of headache. Although orofacial pain and its multifactorial causes and pathways have been extensively discussed in the literature, we found no previous studies that looked into this particular association.

Capitalizing on the large sample size and the representative character of this study, this is the first study to evaluate the association between third molars and orofacial pain using a combination of MRI diagnostics, questionnaires and clinical examinations. Our study sample was not recruited from a healthcare facility but rather randomly drawn from public registries, and the findings are likely to be generalized. Studies based on patients do not represent the situation in the general population. High levels of quality assurance and the strict adherence to standardization of the examination methods and data management are other advantages. Third molar status is most frequently analysed through two-dimensional X-ray images, whereby participants are exposed to radiation. Using MRI images, we were able to analyse third molars without additional radiation exposure. Additionally, we excluded participants suffering pain upon two palpation methods of the temporomandibular joint (TMJ) and masticatory muscles. This aimed to limit the possible overlapping with pain caused by TMJ disorders. Pain information was collected based on a combination of subjective and objective data, improving data validity significantly.

Unfortunately, by the time of data collection, it was not possible to know whether third molars were missing due to previous

extractions or congenital absence. Moreover, partially erupted and impacted third molars were rather difficult to distinguish and thus might have biased our findings. The reason for pain medication intake by our participants is unknown. This called for the exclusion of participants taking NSAIDs, opioids or analgesics.

Woolf et al[33] described four types of mechanism-based pain: nociceptive, inflammatory, neuropathic and functional pain. This classification simplified the complexity of different mechanisms behind pain sensation and suggests a number of interpretations of our findings. According to the International Association for the Study of Pain (IASP), 'nociceptive pain arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors'.[34] Pain signals are transmitted through Aδ fibre and C-fibre. Aδ fibres are myelinated, fast-conducting and mostly found in superficial organs, whereas C-fibres are unmyelinated, slow-conducting and located in deeper organs such as the joints, muscles and bone.[35] Activation of Aδ fibres results in sharp well localized pain, such as that accompanying a partially erupted tooth. C-fibres, on the other hand, are responsible for prolonged dull painful sensations that are characterized usually by poor localization, a common feature among patients complaining of orofacial pain.

Third molar agenesis has been long studied, with some genetic loci speculated to play a role.[36] Many theories have been provided to explain the increasing rate of third molar agenesis and impaction through evolution, but this state is still controversial.[37,38] Regardless of the reason for impaction, an impacted third molar could be regarded as a potentially harmful stimulus and cause nociceptive pain. We believe that our observed association of orofacial pain with missing third molars can be explained by post-traumatic neuropathy secondary to the surgical removal of said teeth. Chronic pain following common surgical procedures is known in the medical field but remains neglected in dentistry.[39] Despite the fact that we were unable to differentiate between congenitally missing third molars and surgically removed ones, the reported low prevalence of third molars agenesis among various populations favours our proposed explanation.

Inflammatory pain, on the other hand, is caused by the chemical inflammation mediators produced locally by damaged tissues or released by inflammation cells migrating through the blood stream. Impacted third molars are often accompanied by cystic changes. Previous studies sponsored by the American Association of Oral and Maxillofacial surgeons proposed that even asymptomatic impacted third molars might pose high risks for adjacent second molars through the localized progression of periodontal disease and caries; this in turn may provoke a chronic inflammatory pain response.[40,41] However, in a previous study, we investigated the systemic effect of third molars on serum levels of inflammatory parameters and found no association.[42] Nevertheless, local inflammation due to either cystic changes around third molars or periodontal disease (even under its subclinical threshold) might amplify existing nociceptive pain.

Moreover, the cortical bone in the maxilla tends to be thinner than that of the mandible (The thickest cortical bone can be found in the mandible in the premolar and molar regions). This gives the maxilla its porous, flexible and highly vascular nature, in contrast to the dense compact mandibular bone.[43] Lower bone density has been reported in the tuberosity region, corresponding to the position of upper third molars. A higher vascularization rate reflects higher levels of nerve growth factor and the local cytokines that have been reported to be essential to the development of pain hypersensitivity.[44] Anatomically, the mandible represents the lower movable part of the face and articulates with the skull only through the temporomandibular joint, serving as the attachment point for various masticatory muscles. On the other hand, the maxillae form

TABLE 2 Association of third molar status with pain

	N (%)	Odds ratio (95% CI)	*P* > |z|
Orofacial pain	121 (7.7%)		
Molar 18			
Missing	87 (8.4%)	1.80 (1.10, 2.96)	0.020
Impacted	12 (11.3%)	2.41 (1.14, 5.09)	0.021
Molar 28			
Missing	89 (8.4%)	1.83 (1.10, 3.03)	.020
Impacted	11 (9.9%)	2.11 (0.98, 4.56)	.057
Molar 38			
Missing	67 (7.6%)	1.07 (0.71, 1.63)	.742
Impacted	14 (11.3%)	1.82 (0.94, 3.50)	.074
Molar 48			
Missing	68 (7.9%)	1.05 (0.70, 1.56)	.822
Impacted	7 (5.7%)	0.77 (0.33, 1.76)	.528
Maxilla			
Missing	74 (8.5%)	1.74 (1.10, 2.75)	.018
Impacted	18 (10.7%)	2.19 (1.16, 4.04)	.015
Mandible			
Missing	49 (7.5%)	0.99 (0.66, 1.49)	.975
Impacted	16 (8.7%)	1.25 (0.69, 2.27)	.460
Migraine	148 (9.4%)		
Maxilla			
Missing	85 (9.8%)	1.23 (0.83, 1.84)	.302
Impacted	15 (8.9%)	1.10 (0.58, 2.08)	.767
Mandible			
Missing	63 (9.6%)	1.00 (0.69, 1.45)	.986
Impacted	13 (7.0%)	0.79 (0.42, 1.51)	.479
Headache	912 (67.1%)		
Maxilla			
Missing	489 (65.3%)	1.09 (0.83, 1.44)	.524
Impacted	103 (72.0%)	1.34 (0.86, 2.10)	.200
Mandible			
Missing	378 (66.9%)	1.22 (0.94, 1.59)	.136
Impacted	116 (71.2%)	1.34 (0.89, 2.03)	.163

Note: Results are derived from logistic regression models adjusted for age, gender, educational status, preferred chewing side, periodontitis and caries with erupted third molars as reference category.

the dominant portion of the face and are connected with a number of skull bones. The difference between the maxilla and the mandible in our findings may be attributed to those anatomical characteristics. We detected a slight difference between the right and left side of the maxilla but this is unlikely to be important. We believe that complex associations among the previously mentioned mechanism-based pains, and the anatomical considerations of the upper and lower jaw are the underlying causes of orofacial pain from impacted maxillary third molars.

When examining the causes of orofacial pain, physicians should keep pain referral in mind through the diagnosis procedure. The complexity of the underlying anatomical structures and unpredictable pain referral mechanisms means that accurate diagnosis and proper management of orofacial pain disorders are a difficult challenge. A key point in orofacial pain diagnosis is to inspect and rule out all possible underlying causes which may have referred the pain to sites distant from the origin.[45] The actual source of orofacial pain might be distant from the location described by patients. The intensity, duration and nature of pain should help differentiate pain origin as part of the initial diagnosis. Pain caused by TMD is very likely to overlap and be confused with third molar complaints. DeAngelis et al[46] examined patients referred for third molar removal and suggested, on the contrary, that signs of TMD are common in patients referring for third molar removal. The guidelines of the American Academy of Orofacial Pain for assessment, diagnosis and management of orofacial pain and diagnostic criteria for temporomandibular disorders (DC/TMD) remain the gold standard for physicians differentiating both aetiologies.

The failure to diagnose and manage orofacial pain may lead to the development of chronic orofacial pain which in turn have a huge impact on patients' quality of life. Orofacial pain can prevent patients from performing their daily tasks and activities and led in some severe cases to depression.[47,48] Besides, the high percentage of patients not seeking professional treatment reported by many studies amount to unnecessary financial burden for healthcare providers and the economic system due to lost working days.[49,50] Patients are usually unsure where to start their treatment, which emphasizes again the importance of multidisciplinary work and the essential need of a dental consult to rule out causes of orofacial pain of dental origin in general and impacted third molars in particular.

We have highlighted a number of explanations for orofacial pain caused by third molars and thus will be valuable for practitioners in their decision-making on third molar removal. Dentists should be more involved in managing orofacial pain because they are well acquainted with the various underlying structures of the orofacial region, bearing in mind possible consequences of removing third molars or choosing to opt for active surveillance. Risk-benefit evaluation and possible complications associated with surgery should not be underestimated. An individual assessment for each patient with a pain complaint is essential for optimal care. Longitudinal studies focusing on orofacial pain and third molar occurrence are needed to confirm the associations reported here.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

AUTHOR CONTRIBUTIONS

MM, AD, OB, H-RM, HV and SK have made substantial contributions to conception and design of the study. MM, TI, PS, TK, RB and SK have been involved in data collection and data analysis. All authors have been involved in data interpretation, drafting the manuscript and revising it critically and have given final approval of the version to be published in this journal and agreed to be accountable for all aspects of the present work'.

COMPLIANCE WITH ETHICAL STANDARDS

Informed consent

Informed consent was obtained from all individual participants included in the study. This study was approved by the ethical committee of the University Medicine Greifswald (15.05.2008, BB 39/08). This research was conducted in full accordance with ethical principles, including the World Medical Association Declaration of Helsinki.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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