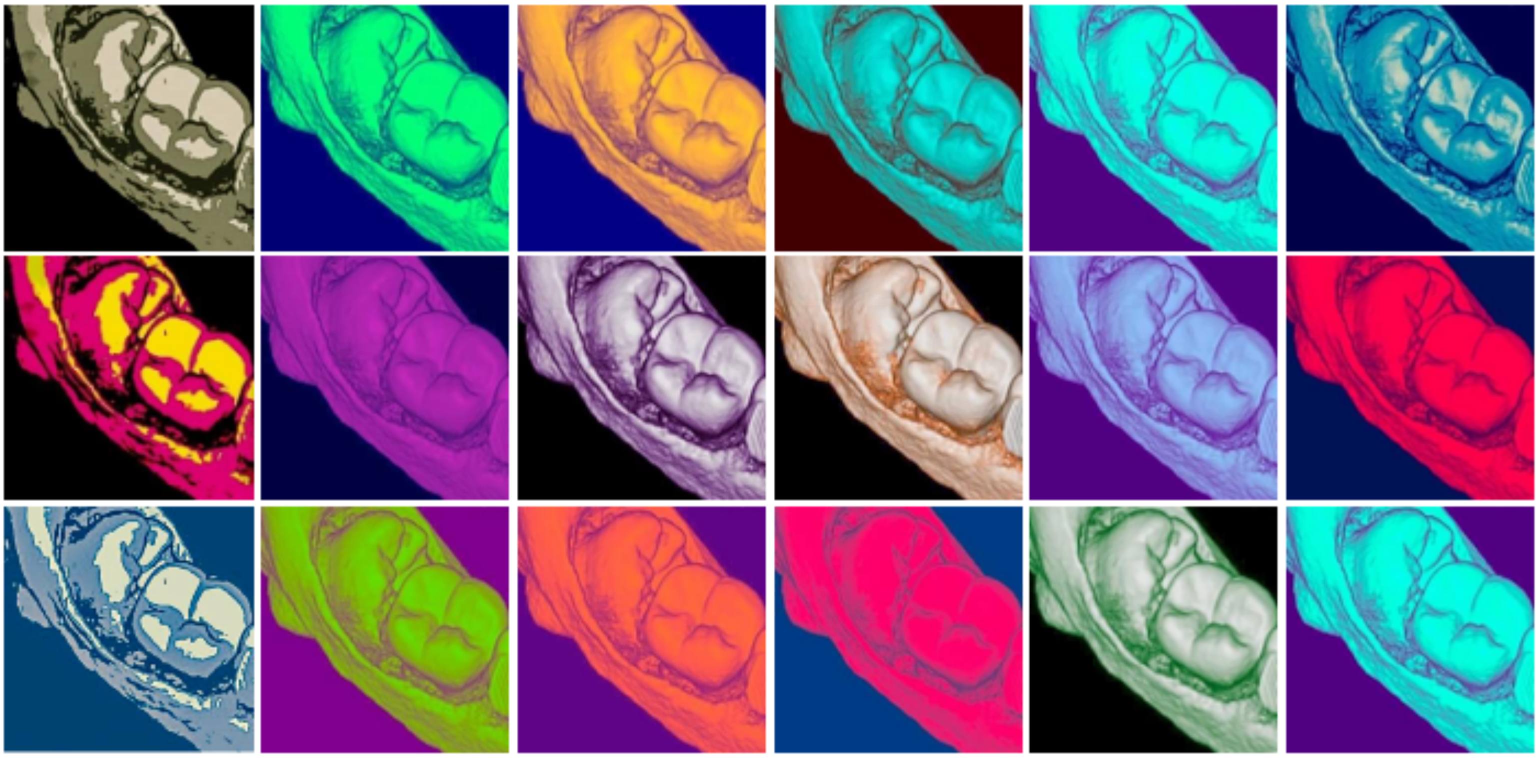
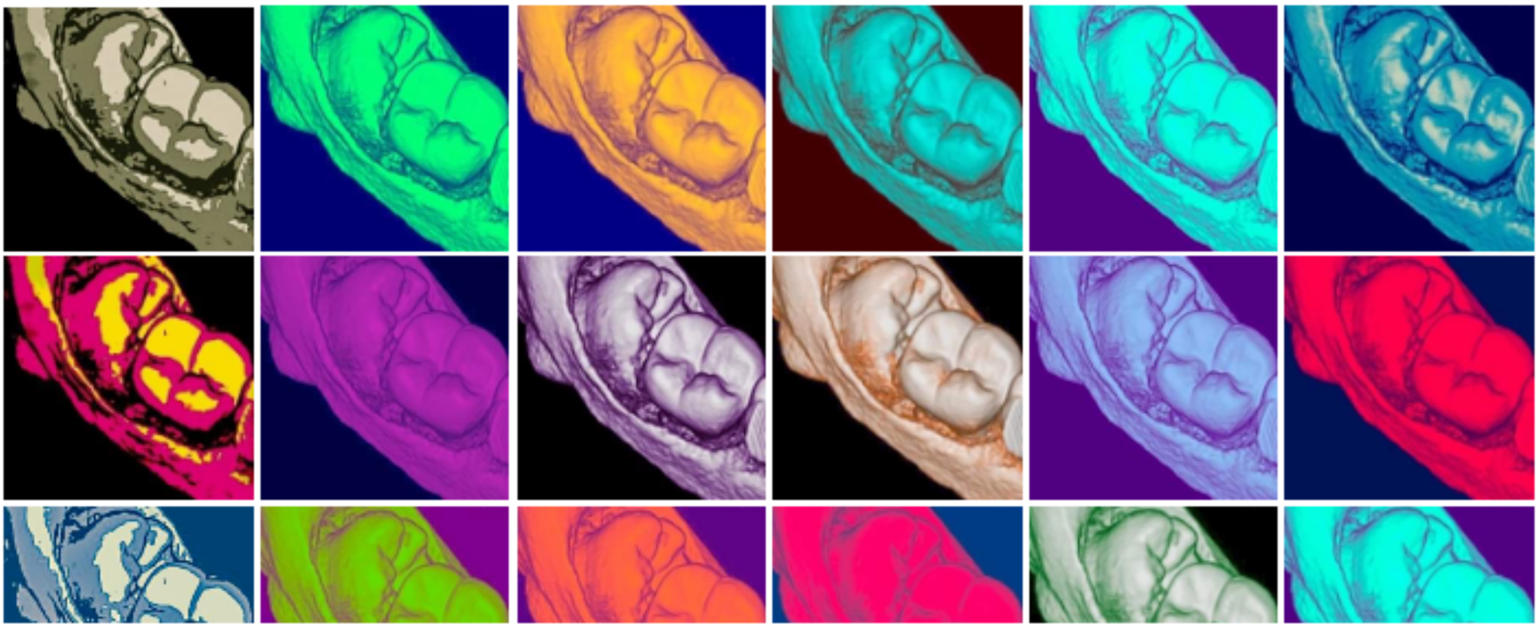


Second molar distal surface caries in the context of mandibular third molar absence and impactions

Verena Tödtling



The research described in this thesis was conducted at the department of Oral and Maxillofacial Surgery department, University of Manchester, UK and Oral and Maxillofacial unit in Amsterdam and the combined faculty of the Vrije Universiteit Amsterdam and Academic Centre for Dentistry Amsterdam (ACTA), University of Amsterdam, (the Netherlands).

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VRIJE UNIVERSITEIT

SECOND MOLAR DISTAL SURFACE CARIES IN THE CONTEXT OF MANDIBULAR THIRD MOLAR ABSENCE AND IMPACTIONS

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad Doctor of Philosophy aan
de Vrije Universiteit Amsterdam,
op gezag van de rector magnificus
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ten overstaan van de promotiecommissie
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door

Verena Tödtling

geboren te Weiz, Oostenrijk

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Contents

Chapter 1

General Introduction

General paper

Historical aspects about third molar removal vs. retention and distal surface caries in the second molar adjacent to impacted third molars

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British Dental Journal 2023

Toedtling V, Forouzanfar T, Brand HS (2023) Historical aspects about third molar removal vs. retention and distal surface caries in the second molar adjacent to impacted third molars. *BDJ 234 (4):268-273*

Key points of paper

- Considers the global controversy about asymptomatic third-molar management, chiefly related to distal surface caries in the adjacent second molar;

- Highlights the influences of third-molar management in the UK

- Emphasises the growing concern related to the increasing prevalence of distal surface caries in the lower second molar that is adjacent to an impacted mandibular third molar.

ABSTRACT

This paper provides an insight into the historical recommendations regarding removal of mandibular third molars, as set out by the Royal College of Surgeons of England and the National Institutes of Health (NIH) in the US, as well as regional guidance from the National Institute for Health and Care Excellence (NICE) and the controversy that surrounds surgical removal of third molars. The influences of third-molar management as it developed in the UK, the historical economic evaluations and the available evidence base on third-molar removal vs. retention are described. This article seeks to address the growing concerns regarding the increasing frequency of distal surface caries (DSC) in mandibular second molar teeth when the decay is associated with asymptomatic, partially erupted, mandibular third molars, especially when they are mesially or horizontally impacted. Lastly, we illustrate radiographs of patients affected by DSC and how guidance that has been issued by a guideline institution regarding third-molar surgery, even though it is based on insufficient evidence, is perceived as a strictly compulsory clinical strategy and has been used in clinical practice in the UK for more than 20 years.

In 1943, Broadbent reported that impaction of third molars occurred when full tooth emergence was prevented. He suggested that this was caused by a lack of space in the retromolar area, the presence of obstructions, or when tooth development had occurred in atypical positions within the jawbone. He reported that these factors alone or in combination might result in partial or, less frequently, no eruption of third molars. Consequently, third molars were classified as vestigial molars as they had lost most or all of their ancestral function [1,2]. Begg, in 1954, claimed that this was the result of environmental factors such as changes in the diet of the human race over thousands of years, with a shift to softer food than that eaten by the first humans. It is thought that this dietary change affected the mesial drift of the dentition and resulted in a decrease in approximal attrition [3]. These evolutionary changes in the inherited trait have been encoded and are linked to the paired box 9 (PAX9) gene complex [4]. They have resulted either in alterations of the skull's anatomical characteristics, which have led in successive generations to impactions and partial eruptions, or in deletion of anatomical structures, which has led to agenesis of one or more third molars [5]. Andresson *et al.* (2010) reported a prevalence of 25% of agenesis in the third molar region in their study of a Swedish population. A few years later, Cater and Worthington (2016) performed a systematic review and meta-analysis to assess worldwide rates of third-molar impaction and reported its prevalence across different morphological and demographic subgroups. They concluded that the average global impaction rate of third molars was 24.4% [6,7], but that the effect sizes were highly heterogeneous. Subgroup analyses showed that there were differences in geographic regions, that impaction occurred more frequently in the mandible in comparison to the maxilla, and that the most frequently observed orientation of impaction was mesioangular. This orientation comprised 42% of impactions; vertical and distal angulations comprised 26% and 12% respectively; and horizontal angulation was reported as 11%. Atypical or aberrant positions in which impacted teeth were angled in buccolingual directions were seen much less frequently [8,9].

Pathogenic consequences of third-molar retention

The literature suggests that these anomalous angulations lead third molars and their surrounding hard and soft tissues to become more liable to developing of a range of diseases and pathological conditions. Some of these conditions can be acute in nature and present suddenly with rapid onset of symptoms, while others may run a chronic course and develop over many years, which therefore leads to late presentation of these conditions in patients [9]. For example, retained third molars are at increased risk of periodontal disease, resorption and caries, which may develop over many years and cause irreversible damage, not only to the third-molar teeth but also to their adjacent structures [10,11].

Fejerskov and Kidd (2008) highlighted that partially erupted teeth did not participate in mastication and, for this reason, offered more favourable locations for bacterial accumulation than did fully erupted teeth [12]. Furthermore, Chu *et al*. (2003) claimed that mesioangularly and horizontally impacted teeth had their occlusal surfaces against the distal surfaces of the second molars, which formed a risk factor for plaque stagnation [13]. (see Figure 1). In 1989, Newburn reported that fissure areas of the posterior teeth were the most common sites of decay and that there was a relationship between the depths of the fissures and caries susceptibility, because food debris and micro-organisms accumulated in the embrasure and fissures. The food debris and micro-organisms could not be cleaned reliably from these locations by normal brushing, and therefore caries developed. Consequently, Newburn concluded that tooth morphology was an important risk factor for caries development [14].

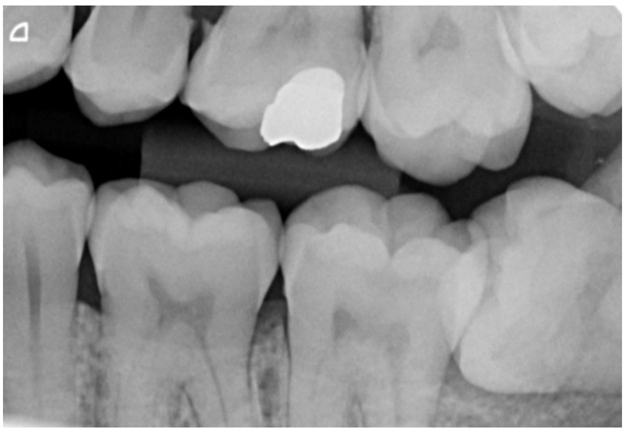

Figure 1. Impacted third molar with occlusal surface against the distal surface of the second molar

Statement of problem

Caries is one of the most common reasons for mandibular third-molar removal [15], but there is also an emerging incidence of DSC in the second molar that is adjacent to an impacted third molar [16-20]. Figure 2 illustrates this specific caries pattern.

McArdle and Renton (2006) suggested that the prevalence of second molar caries was the reason for 5% of mandibular third-molar removals in the population of England and Wales [21]. However, data from different authors suggest that the prevalence is much higher. Van der Linden *et al.* (1995) reported caries in 42.7% of adjacent molars (1,227 of 2,872 teeth) in their study population [22]. Knutsson *et al.* (1996) reported a caries frequency of 31% with impactions, which was most common in patients between 20 and 29 years, followed by the 30 to 39-year-old group [23]. In summary, a growing number of international clinical studies have described a rising DSC prevalence across the globe that ranges from 5% to 51% in several populations in different care settings [24-28]. Nevertheless, so far, no formal causal link has been established, and fear of second molar caries is not currently a justification for prophylactic removal of third molars in the UK [29].

Figure 2. Dental caries on the distal aspect of the mandibular second molar that is adjacent to a mesioangularly impacted third molar.

Third-molar management in the UK: consequences of non-intervention strategy

In 1979, a consensus conference of the US NIH regarding third molars received major media attention and, as a result, influenced the surgical practice of third-molar removal in the UK. It reported that impaction or malposition of third molars in itself was not a pathological condition. The conclusion was that impaction was an abnormality in development that merely predisposed a patient to pathological changes, and therefore that prophylactic removal should not be performed [30]. This view was and remains widely accepted in the UK and led to the abolition of prophylactic removal of impacted third molars. However, in the US, where this view originated, it has met considerable opposition, because surgical removal of impacted third molars is perceived as interceptive and not as prophylactic [31]. The American Association of Oral and Maxillofacial Surgeons has a clear recommendation that treatment should be provided before the pathology adversely affects the patient's oral and/or systemic health, and that the aim should be to limit surgical side effects and to provide an environment for optimal healing [32].

Prophylactic removal of impacted third molars began in the UK during the 1970s. Third-molar surgery became one of the most commonly performed surgical procedures within the National Health Service (NHS). The associated UK healthcare costs were considerable [33,34]. In the 1990s the annual cost of third-molar surgery was estimated to be more than £30 million. In response to such financial statistics, guidelines were developed by the Faculty of Dental Surgery of the Royal College of Surgeons of England (RCSEng) in 1997, which were published as *Current clinical practice and parameters of care: the management of patients with third molar (syn: wisdom) teeth*. These guidelines were based on evidence collected from research that had been conducted in the UK, Canada and Scandinavia. Reference was also made to the practice in the US, and numerous similarities in care with regard to indications of the need for third-molar removal existed at that point in time [35]. Prior to 1997, surgical practice in the UK and US included both the removal of impacted third molars that had caused pathological changes and the prophylactic removal of pathology-free, impacted third molars to prevent future problems [30].

It is estimated that the implementation of the RCSEng 1997 guideline resulted in a 22% reduction in the annual cost of third-molar surgery (compared with 1994/95 NHS data), which amounted to almost £7 million annually. However, approximately one in five third-molar removals were still considered unnecessary. The awareness of this substantial expenditure, together with a general economic downturn in the UK, stimulated research into healthcare resources and cost-effectiveness [36]. Worall *et al*. (1998) found that, during this period, at least 20-30% of third-molar removals were purely prophylactic; yet a study by Pratt *et al.* (1998) estimated this figure to be as low as 2.4% [37]. Nevertheless, the government set up and urged the formation of professional advisory groups in England and Scotland, which issued two independent leadership documents that were designed to restrict the removal of third molars to specific therapeutic indications. In England and Wales, the National Institute for Health and Care Excellence (NICE) published *Technology appraisal guidance number 1 (TA1)* [38], *guidance on the extraction of wisdom teeth* and the Scottish Intercollegiate Guidelines Network (SIGN) published *Management of unerupted and impacted third molar teeth* [39]. Both sets of guidelines came into force around 2000 and replaced the less strict RCSEng document [35]. Although both UK-based documents referred to this 1997 RCSEng publication, they listed different therapeutic indications for third-molar removal. The SIGN guidelines were much more inclusive and encouraged clinicians to take into account each patient's medical history, their ability to access care and the treatment setting. In comparison, the NICE guidelines limited the indications of the need for third-molar removal to: one severe episode of pericoronitis; recurrent episodes of pericoronitis; unrestorable third molar (caries and fracture); internal/external resorption of third and/or second molar; non-treatable pulpal and/or periapical pathology; cyst/tumour formation; cellulitis or abscess formation; osteomyelitis; orthognathic surgery; reconstructive jaw surgery; and a third molar that was involved in tumour resection. These limitations on the removal of third molars were estimated to result in an additional cost reduction of approximately £5 million to the NHS annually [40].

The introduction of this changed guidance was justified in terms firstly of the avoidance of surgery and secondly in the reduction of expenditure and of the associated surgical and anaesthetic risks, in particular the risks of injuries that could affect the lingual and inferior alveolar nerves [38,39]. The cost savings that were associated with these changes in third-molar surgery might be attributable to the reduction in rates of prophylactic removal of third molars; however, a review of the use of general anaesthesia (GA) led to tightened regulations regarding the prescription of GA at about the same time, and this would also have led to significant cost reductions to the NHS [41-43]. Data on oral surgery procedures taken from the Dental Practice Board and the Department of Health's hospital episode statistics in the UK, which were reported by Dhariwal *et al*. (2002), revealed that the use of GA fell by 77% from 260,763 procedures in oral surgery in 1998 to 59,004 such procedures in 2000. GA seems to have been the principal method of anaesthesia for third-molar surgery [40,44]. The NHS welcomed the reductions in the occurrence of GA-related complications and in associated costs.

In 2000, however, the National Centre of Health Technology concluded in its review of third-molar-related complications that the likelihood that third molars would cause problems in the future was high and that, by comparison, the incidence of complications after operating on them was relatively low. Also, Bienstock *et al*. reported in 2011 that most postoperative morbidities in oral surgery were related to mandibular third molars, although as with any surgical procedure, various short- and long-term complications as well as adverse effects might occur. The researchers reported that the overall complication rate, which included minor complaints, varied between 4.6% and 36% and included pain, trismus, swelling, secondary haemorrhage and disruption of regular activities in daily life [45]. The frequency of development of postoperative infection varied between 0.5% and 2.8%, and the incidence of alveolitis between 0.1% and 14.9%. In a Finnish population, long-term complications of oral surgery, such as damage to adjacent teeth and mandibular fractures (one per 22,000 operations), were found to be uncommon [45,46]. The incidence of temporary impairment of the lingual and inferior alveolar nerves has been estimated to range from 0.5% to 20%, although permanent iatrogenic injury is reported to be much less frequent at 0.01% to 1% in low-risk cases and 2% in high-risk cases [47].

The NICE rules and guidelines regarding surgery on third molars have been adopted by national guideline organisations and centres of expertise in several countries. Examples of derived guidelines are those of the Ministry of Health in Malaysia (2005) and the Health Partners Dental Group in the US. This illustrates that NICE's view and its very strict indications for the removal of third molars have a worldwide impact [48,49].

Methods used for economic evaluations

At approximately the same time as the NICE guidelines were introduced, Edwards and co-workers investigated the most effective and cost-effective strategies for the management of trouble-free, mandibular third molars [50]. The authors assessed the effects of removal or retention of asymptomatic, disease-free, mandibular third molars at the University of Wales Dental Hospital. A decision-tree model was constructed with the use of probability data and possible outcomes of retention or removal of these teeth. The authors concluded that mandibular third-molar retention was less expensive for the NHS than removal (£170 vs £226, respectively). Taking into account both the cost and effects, the authors found that retention of the lower third molars was generally more effective than removal, but that if pericoronitis, caries or other issues developed it became more cost-effective to remove an impacted lower third molar [50]. A small number of economic evaluations have been performed. These evaluations found that, at a population level, the watch-and-wait policy was less cost-effective than prophylactic removal. Furthermore, none of these studies took into account any long-term, societal perspective, costs related to the consequences of third-molar retention such as development of DSC, or the consequent removal. The latter outcome has been researched by Ventä *et al*. (2011), who showed that 70% of third molars had been removed once people had reached 38 years of age [51].

Since 2000, the NICE guidance on third-molar removal has been widely criticised for its non-intervention strategy as an increasing number of studies have reported the consequences of long-term third-molar retention, such as caries development [20,22,52]. The process of this development usually affects the second molar and has been associated strongly with the presence of impacted mandibular third molars, especially for mesio-angular impactions [24]. Knutsson *et al*. (1996) noted that horizontally and mesioangularly positioned third molars had more effects on adjacent second molars because impacted teeth in these positions impinged on the distal surface of the second molar [32,24]. In many cases, the development of caries in the second molars remains unnoticed for a long time, partly due to the difficulty in detecting caries via visual examination (Figure 3), and partly because there is a lack of detailed recommendations or guidance for dentists regarding screening for this issue [17]. Various cariology studies have shown that third-molar removal is required ultimately in the majority of these cases, with additional dental restorations of the adjacent second mandibular molars. In some cases, the adjacent second molars have to be removed too (Figure 4) due to lack of restorability (Figure 5).

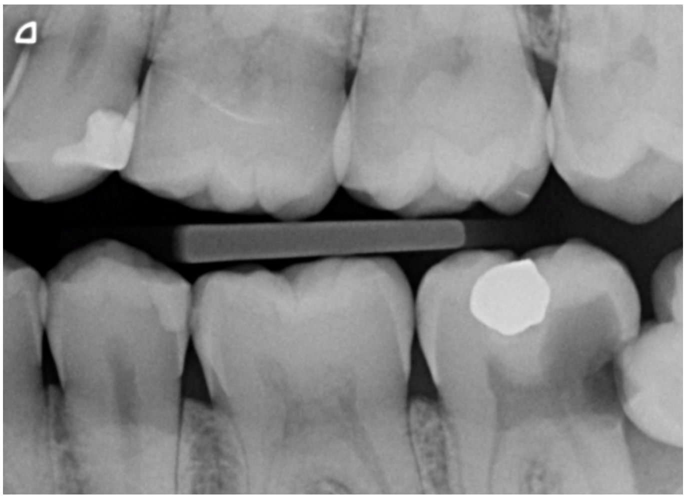

Figure 3. Example illustrates late diagnosis of DSC.

Figure 4. This example shows how restoration of the distal surface of the second molar may not be possible with the third molar in situ.

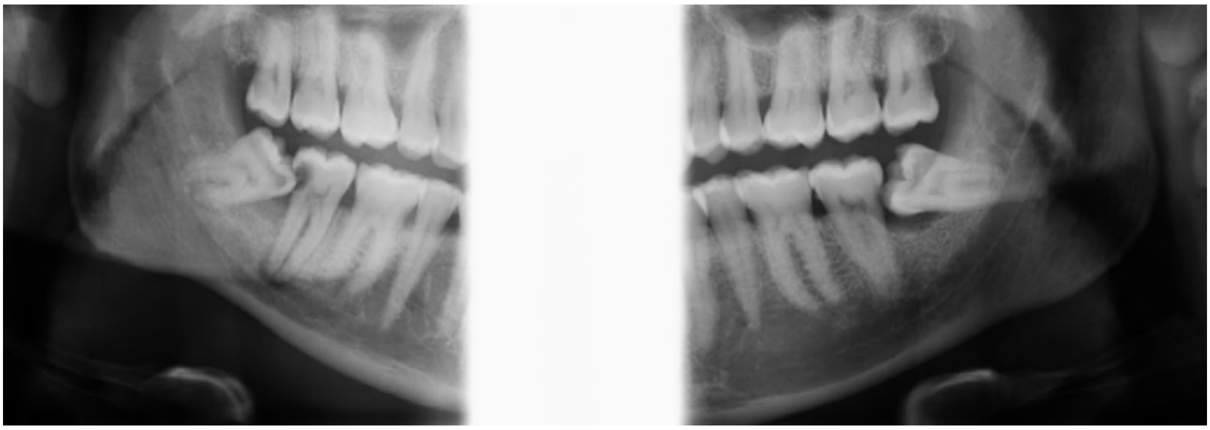

Figure 5. Dental panoramic radiograph of mandibular mesioangularly impacted third molars in a patient at low risk of caries but who exhibits bilateral DSC in the adjacent second molars.

Surgical removal vs. retention of third molar: evidence base

At present, robust scientific evidence to support the removal or retention of third molars is scarce throughout the world. Originally, a Cochrane review by Mettes *et al.* in 2012 assessed the available evidence and concluded that there was insufficient evidence against routine prophylactic removal of asymptomatic third molars, or that watchful monitoring of asymptomatic third molars might be a more prudent strategy [53]. However, there was also no evidence to suggest that watchful monitoring provided a better outcome. Therefore, one could debate the interpretation and exactitude of this conclusion, which has been quoted many times throughout the literature and has been used as a basis for numerous international third-molar strategies and guideline documents [54-58].

The SIGN guideline on third-molar management has been considered for review several times since it was published in 1999; on each occasion, insufficient research evidence to justify the guideline was identified. Therefore, SIGN removed the guideline from its programme in February 2015. SIGN stated that, without a full review of the evidence, it was not possible to be certain that the guideline: (1) remained relevant to the NHS in Scotland; (2) made recommendations that were based on the most up-to-date evidence for best practice; (3) recommended safe practice; or (4) complied with current making and clear communication of risk and benefits for both third molar removal as well as retention [59].

Nevertheless, further high-quality research is needed to underpin the third molar removal indications. It has been reported that one clinical trial was initiated in Denmark and another in the US many years ago, with the intention of long-term follow-up [33]. However, to our knowledge, the results have not been disseminated. It is unclear whether these trials are still continuing or whether their results will ever become available. Performance of well-designed randomised controlled trials that would compare the effects of prophylactic removal of asymptomatic third molars with those of retention and long-term follow-up would be very challenging. Such trials are unlikely to be feasible given the enormous costs; therefore, non-randomised studies such as those of practice-based cohorts are considered to offer the next best but achievable evidence regarding long-term outcomes such as caries [60,61].

Conclusion

There is considerable suspicion that the strict NICE guidance regarding third-molar removal contributes to the high incidence of DSC that clinicians see currently [62], because it promotes third-molar retention and restricts the removal of decay-related third molars to situations in which caries renders the tooth unrestorable. The existing NICE guidance was based on evidence from an assessment report that was published by Song *et al.* in 1999 and which refers to research evidence that was gathered almost four decades ago. It must be highlighted that this research was conducted during a period when large numbers of third molars were removed prophylactically. Tellingly, the assessment report documented a very low rate of DSC in mandibular second molars of 1% to 4.5% [33]; currently, when few third molars are removed prophylactically, the literature states that this range is 15% to 51% [34,63].

Outline of the thesis

The thesis is laid out in 9 chapters and aimed to provide answers to the current knowledge gabs in prevalence and incidence of DSC in different patient populations. We also assess the current evidence base of third molar removal vs retention with a Cochrane systematic review. Additionally, this research further acquired new understanding of the caries process by profiling the microbiome of distal surfaces adjacent to various third molar impactions and identified are the risk factors associated with DSC. Finally, socioeconomic aspects in relation to DSC are assessed and shortcomings of clinical guidance are discussed.

In **chapter 2** an evaluation of the evidence base of effects/consequences of prophylactic or interceptive removal compared with retention (conservative management/non-intervention) of asymptomatic disease-free impacted third molar in adolescents and adults is made by conducting a Cochrane systematic review.

C**hapter 3** addresses the prevalence of DSC in the second molar among referrals for third molar assessment is described and discussed by conducting a systematic review with meta-analysis.

C**hapter 4** describes the incidence of DSC in an additional systematic review by assessing longitudinal studies.

In **chapter 5** further insight is obtained from the microbiome of impacted third molars by analysing the associated plaque stagnation of the neighbouring mandibular second molars.

Chapter 6 provides insight into the rate and risk factors of DSC in patients who attend routine dental check-ups in Manchester, UK population during an era when National Institute for Health Care and Excellence (NICE) third molar surgery guidelines were followed.

In **chapters 7** the prevalence and risk factors of DSC were assessed in UK population and are compared with a sample population from Romania. In addition to this the implications and limitation of clinical guidelines are discussed.

In **Chapter 8** the results of the studies in this thesis are recapitulated and how they relate to wider research and future perspective are discussed. Conclusively, **Chapter 9** provides a summary of all research findings.

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Chapter 2

Cochrane Systematic Review

Surgical removal versus retention for the management of asymptomatic disease-free impacted wisdom teeth

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I am an author of both Cochrane reviews; 2016 and 2020

ABSTRACT

Background: Prophylactic removal of asymptomatic disease-free impacted wisdom teeth is the surgical removal of wisdom teeth in the absence of symptoms and with no evidence of local disease. Impacted wisdom teeth may be associated with pathological changes, such as pericoronitis, root resorption, gum and alveolar bone disease (periodontitis), caries and the development of cysts and tumours. When surgical removal is performed in older people, the risk of postoperative complications, pain and discomfort is increased. Other reasons to justify prophylactic removal of asymptomatic disease-free impacted third molars have included preventing late lower incisor crowding, preventing damage to adjacent structures such as the second molar or the inferior alveolar nerve, in preparation for orthognathic surgery, in preparation for radiotherapy or during procedures to treat people with trauma to the affected area. Removal of asymptomatic disease-free wisdom teeth is a common procedure, and researchers must determine whether evidence supports this practice. This review is an update of a review originally published in 2005 and previously updated in 2012 and 2016

Objectives: To evaluate the effects of removal compared with retention (conservative management) of asymptomatic disease-free impacted wisdom teeth in adolescents and adults.

Search methods: Cochrane Oral Health's Information Specialist searched the following databases: Cochrane Oral Health's Trials Register (to 10 May 2019), the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library, 2019, Issue 4), MEDLINE Ovid (1946 to 10 May 2019), and Embase Ovid (1980 to 10 May 2019). The US National Institutes of Health Trials Registry (ClinicalTrials.gov) and the World Health Organization International Clinical Trials Registry Platform were searched for ongoing trials. No restrictions were placed on the language or date of publication when searching the electronic databases.

Selection criteria: We included randomised controlled trials (RCTs), with no restriction on length of follow-up, comparing removal (or absence) with retention (or presence) of asymptomatic disease-free impacted wisdom teeth in adolescents or

adults. We also considered quasi-RCTs and prospective cohort studies for inclusion if investigators measured outcomes with follow-up of five years or longer.

Data collection and analysis: Eight review authors screened search results and assessed the eligibility of studies for inclusion according to the review inclusion criteria. Eight review authors independently and in duplicate conducted the risk of bias assessments. When information was unclear, we contacted the study authors for additional information.

Main results: This review update includes the same two studies that were identified in our previous version of the review: one RCT with a parallel-group design, which was conducted in a dental hospital setting in the United Kingdom, and one prospective cohort study, which was conducted in the private sector in the USA.

Primary outcome: No eligible studies in this review reported the effects of removal compared with retention of asymptomatic disease-free impacted wisdom teeth on health-related quality of life

Secondary outcomes: We found only low- to very low-certainty evidence of the effects of removal compared with retention of asymptomatic disease-free impacted wisdom teeth for a limited number of secondary outcome measures.

One prospective cohort study, reporting data from a subgroup of 416 healthy male participants, aged 24 to 84 years, compared the effects of the absence (previous removal or agenesis) against the presence of asymptomatic disease-free impacted wisdom teeth on periodontitis and caries associated with the distal aspect of the adjacent second molar during a follow-up period of three to over 25 years. Very low-certainty evidence suggests that the presence of asymptomatic disease-free impacted wisdom teeth may be associated with increased risk of periodontitis affecting the adjacent second molar in the long term. In the same study, which is at serious risk of bias, there is insufficient evidence to demonstrate a difference in caries risk associated with the presence or absence of impacted wisdom teeth. One RCT with 164 randomised and 77 analysed adolescent participants compared the effect of extraction with retention of asymptomatic disease-free impacted wisdom teeth on dimensional changes in the dental arch after five years. Participants (55% female) had previously undergone orthodontic treatment and had 'crowded' wisdom teeth. No evidence from this study, which was at high risk of bias, was found to suggest that removal of asymptomatic disease-free impacted wisdom teeth has a clinically significant effect on dimensional changes in the dental arch. The included studies did not measure any of our other secondary outcomes: costs, other adverse events associated with retention of asymptomatic disease-free impacted wisdom teeth (pericoronitis, root resorption, cyst formation, tumour formation, inflammation/infection) and adverse effects associated with their removal (alveolar osteitis/postoperative infection, nerve injury, damage to adjacent teeth during surgery, bleeding, osteonecrosis related to medication/radiotherapy, inflammation/infection).

Authors' conclusions: Insufficient evidence is available to determine whether asymptomatic disease-free impacted wisdom teeth should be removed or retained. Although retention of asymptomatic disease-free impacted wisdom teeth may be associated with increased risk of periodontitis affecting adjacent second molars in the long term, the evidence is very low certainty. Well-designed RCTs investigating long-term and rare effects of retention and removal of asymptomatic disease-free impacted wisdom teeth, in a representative group of individuals, are unlikely to be feasible. In their continuing absence, high quality, long-term prospective cohort studies may provide valuable evidence in the future. Given the current lack of available evidence, patient values should be considered and clinical expertise used to guide shared decision-making with people who have asymptomatic disease-free impacted wisdom teeth. If the decision is made to retain these teeth, clinical assessment at regular intervals to prevent undesirable outcomes is advisable.

Plain language summary - Surgical removal versus retention for the management of asymptomatic disease-free impacted wisdom teeth

Review question

We carried out this review, through Cochrane Oral Health, to find out whether impacted wisdom teeth in teenagers or adults should be removed if they are not causing any problems or they should be left alone and checked at regular intervals. This is an update of a review first published in 2012 and first updated in 2016.

Background

Wisdom teeth (also known as third molars) generally erupt between the ages of 17 and 26 years. They are the last teeth to come in, and normally erupt into a position closely behind the last standing teeth (second molars). Space for wisdom teeth can be limited and so they often fail to erupt or erupt only partially, because of impaction of the wisdom teeth against the teeth directly in front. In most cases, this occurs when second molars are blocking the path of eruption of third molar teeth and act as a physical barrier, preventing complete eruption. An impacted wisdom tooth is called 'asymptomatic' and 'disease-free' if there are no signs or symptoms of disease affecting the wisdom tooth or nearby structures.

Impacted wisdom teeth can cause swelling and ulceration of the gums around the wisdom teeth, damage to the roots of second molars, decay in second molars, gum and bone disease around second molars and development of cysts or tumours. It is generally agreed that removing wisdom teeth is appropriate if signs or symptoms of disease related to the wisdom teeth are present, but there is less agreement about how asymptomatic disease-free impacted wisdom teeth should be managed.

Study characteristics

The Cochrane Oral Health Information Specialist searched the medical literature up to 10 May 2019. We found two studies, one where the participants had been randomly chosen to have their wisdom teeth removed or not (a randomised controlled trial or RCT), and one where the study authors examined people who have opted themselves to either retain or remove their wisdom teeth (a prospective cohort study). The studies involved 493 people. The RCT was conducted at a dental hospital in the UK and included 77 adolescent male and female participants who had completed treatment with braces. The cohort study was conducted at a private dental clinic in the USA and involved 416 men aged 24 to 84 years who volunteered to take part.

Key results

The available evidence is insufficient to tell us whether or not asymptomatic disease-free impacted wisdom teeth should be removed. The included studies did not measure health-related quality of life, costs or side effects of taking teeth out. One study (the cohort study), which was at serious risk of bias, found that keeping asymptomatic disease-free impacted wisdom teeth in the mouth may increase the risk of gum infection (periodontitis) affecting the adjacent second molar in the long term, but this evidence was very uncertain. In the same study, the evidence was insufficient to draw any conclusions about the effect on the risk of caries in the adjacent second molar. The other study (the RCT) was also at high risk of bias. It measured crowding of the teeth in the mouth, and found that this may not be significantly affected by whether impacted wisdom teeth are kept in the mouth or removed.

Quality of the evidence

We assessed the evidence provided by the two studies to be low to very low certainty, so we cannot rely on these findings. High-quality research is urgently needed to support clinical practice in this area.

Conclusion

There is a lack of scientific evidence on which dental health professionals and policy makers can base treatment decisions for asymptomatic disease-free impacted wisdom teeth. Dental professionals will therefore be guided by clinical expertise and local or national clinical guidance, taking patient preferences into account. Where asymptomatic disease-free impacted wisdom teeth are not removed, monitoring by a dental health professional at regular intervals will help identify and address any problems that may develop.

Background

Description of the condition

Wisdom teeth, or third molars, generally erupt between the ages of 17 and 26 years [1, 2]. More than other teeth, wisdom teeth can fail to erupt or can erupt only partially, with a worldwide impaction prevalence of 24% [3]. Impaction occurs when complete eruption into a normal functional position is prevented and completion of root growth is fully established. This can be due to lack of space (in the mouth), obstruction by another tooth or development in an abnormal position [1]. A tooth that is completely impacted can be entirely covered by soft tissue, covered partially by bone and soft tissue or completely covered by bone. Partial eruption occurs when the tooth is visible in the dental arch but has not erupted into a normal functional position [4]. Impacted wisdom teeth have been associated with pathological changes such as pericoronitis, root resorption, periodontal disease, caries and development of cysts or tumours. An impacted wisdom tooth is called 'trouble-free' if the patient does not experience signs or symptoms of associated pain or discomfort [5]. and when the wisdom tooth is not associated with any signs of pathology. Other terms used in the literature include 'disease-free' and 'asymptomatic' [6].

The prevalence of asymptomatic disease-free impacted third molars varies widely and is influenced by age, sex and ethnicity [7]. Impaction of wisdom teeth in the lower jaw is more common than in the upper jaw [3, 8]. Most of the difficulties that follow surgical removal, such as postoperative morbidity, pain, discomfort and restricted activity, are related to lower wisdom teeth [9].

When an impacted wisdom tooth causes pathological changes or pain, the tooth is no longer trouble-free. General agreement indicates that a wisdom tooth should be removed if pathology or symptoms are present. However, the management of asymptomatic disease-free wisdom teeth remains globally controversial [10].

Description of the intervention

Prophylactic removal of asymptomatic disease-free impacted wisdom teeth is defined as the surgical removal of wisdom teeth in the absence of symptoms and with no evidence of local disease. Many dentists and their patients believe that removal of asymptomatic disease-free wisdom teeth is justified to avoid the possible future complications associated with these teeth. When surgical removal is performed on older patients, the risk of postoperative complications is increased [11, 12, 13]. Furthermore, the healing of the periodontal tissues is better in younger people [14]. (An impacted wisdom tooth almost never has a functional role in the mouth and might increase risk of caries, periodontal disease and external root resorption associated with the adjacent second molar [15, 16]. Another argument often given for the removal of asymptomatic wisdom teeth is to prevent late lower incisor crowding.

Removal of impacted wisdom teeth is a common surgical procedure with significant associated costs [17]. Short-term adverse effects of the removal of wisdom teeth include temporary nerve damage, alveolar osteitis (dry socket), infection, secondary haemorrhage, pain, swelling and trismus (restricted mouth opening). Long-term adverse effects of third molar surgery are uncommon but can include permanent nerve damage (in up to 0.5% of cases) [11].

Retention of impacted wisdom teeth is defined as monitoring the status of wisdom teeth. To avoid adverse effects and the costs of removing wisdom teeth, some advocate retention of asymptomatic disease-free impacted wisdom teeth [18]. This approach requires individuals to have regular dental reviews or 'check-ups', so that the status of the wisdom teeth can be monitored.

How the intervention might work

In many countries, prophylactic removal of asymptomatic disease-free wisdom teeth, whether impacted or fully erupted, was long considered as 'appropriate care' [13, 19]. Removal of wisdom teeth that may remain disease-free indefinitely is costly [17] and can produce an unnecessary burden on healthcare resources [18]. However, concerns include the possibility that retained wisdom teeth will increase the risk of pathology to surrounding structures in the long term, and that their removal at an older age may cause more frequent and severe complications [20, 17].

Why it is important to do this review

Cochrane Oral Health undertook an extensive prioritisation exercise in 2014 to identify a core portfolio of titles [21]. This review was identified as a priority title by the oral and maxillofacial surgery expert panel (Cochrane OHG priority review portfolio). In addition, the review has a very high Altimetric score, which is a weighted measure to represent coverage of the article in the media.

Wisdom tooth impaction is a common phenomenon [3]. Economic and personal costs are associated with removal of asymptomatic disease-free impacted wisdom teeth. Large variations have been noted in the management of asymptomatic disease-free impacted wisdom teeth [22], but clinicians' decisions should be based on an evidence-based approach that encompasses the best available research evidence, their own clinical expertise, local and national guidance, and patient values and preferences [23].

Objectives

To evaluate the effects of removal compared with retention (conservative management) of asymptomatic disease-free impacted wisdom teeth in adolescents and adults.

Methods

Criteria for considering studies for this review

Types of studies

We considered randomised controlled trials (RCTs) for inclusion for all outcomes, with no restriction on their length of follow-up.

To assess long-term outcomes, we also considered quasi-RCTs and prospective cohort studies for inclusion only if outcomes were measured with follow-up of at least five years. We considered these non-randomised studies (NRSs) for inclusion in this review update, as long-term outcomes of retention/removal of asymptomatic disease-free impacted wisdom teeth are extremely unlikely to be studied in randomised trials.

Types of participants

Individuals (males and females of all ages) with asymptomatic disease-free impacted (maxillary or mandibular) wisdom teeth. An impacted tooth is defined as a tooth that has not erupted into a normal functional position. The tooth may be partially or completely covered by soft tissue and/or bone and might be visible, partially visible or invisible in the mouth.

Types of interventions

Studies comparing removal (or absence) with retention (or presence) of asymptomatic impacted wisdom teeth. The control group (retention or presence of asymptomatic disease-free impacted wisdom teeth) was likely to have continued to receive routine oral examinations and may have undergone wisdom tooth removal if symptoms or disease became evident.

Types of outcome measures

1) **Primary outcome**

Health-related quality of life measures associated with retention or removal of wisdom teeth (desirable and undesirable effects).

2) **Secondary outcomes**

Outcomes associated with retention of wisdom teeth (undesirable effects)

- Pericoronitis, infection and osteomyelitis
- Periodontitis (increased probing depths or alveolar bone loss affecting wisdom teeth or adjacent second molars)

- Caries (tooth decay affecting wisdom teeth or adjacent second molars (distal aspect)
- Root resorption affecting wisdom teeth or adjacent second molars
- Dimensional changes in the dental arch (crowding)
- Cyst formation
- Tumour formation
- Inflammation/infection

Outcomes associated with removal of wisdom teeth (undesirable effects)

- Alveolar osteitis, postoperative infection and osteomyelitis
- Nerve injury (lingual nerve and inferior alveolar nerve)
- Damage to adjacent teeth during surgery
- Bleeding
- Osteonecrosis related to medication/radiotherapy
- Inflammation/infection

Costs

- Days off work/study
- Direct costs associated with retention or removal of wisdom teeth and treatment of associated symptoms or complications

Search methods for identification of studies

Electronic searches

Cochrane Oral Health's Information Specialist conducted systematic searches in the following databases for randomised controlled trials and controlled clinical trials without language or publication status restrictions:

- Cochrane Oral Health's Trials Register (searched 10 May 2019) (Appendix 1);
- Cochrane Central Register of Controlled Trials (CENTRAL; 2019, Issue 4) in the Cochrane Library (searched 10 May 2019) (Appendix 2);
- MEDLINE Ovid (1946 to 10 May 2019) (Appendix 3);
- Embase Ovid (1980 to 10 May 2019) (Appendix 4).

Subject strategies were modelled on the search strategy designed for MEDLINE Ovid.

Searching other resources

We searched the following trials registries:

- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (http://clinicaltrials.gov/; searched 10 May 2019) (Appendix 5);
- World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch; searched 10 May 2019) (Appendix 6).

We did not perform a separate search for adverse effects of interventions; we considered these in included studies only.

We searched the reference lists of included studies and relevant systematic reviews for further studies.

We checked that none of the included studies in this review were retracted due to error or fraud.

Data collection and analysis

1) Selection of studies

Eight review authors (Hossein Ghaeminia (HG), Marloes Nienhuijs (MN), Verena Toedling (VT), John Perry (JP), Marcia Tummers (MT), Theo Hoppenreijs (TH), Wil van der Sanden (WvdS) and Dirk Mettes (DM)), in duplicate, independently and not blinded, assessed the titles, keywords, abstracts and/or methods sections of studies identified by the search strategy. The search was designed to be sensitive and include controlled clinical trials; these were filtered out early in the selection process if they were not randomised. We obtained relevant articles identified by reference searching as well as full-text articles selected by the review authors. We read in full the articles on which review authors disagreed and made the decision to include or exclude upon discussion.

Eligibility criteria were:

- studies comparing the removal (or absence) with retention (or presence) of (maxillary or mandibular) asymptomatic disease-free impacted wisdom teeth;
- studies providing data on at least one of the selected primary or secondary outcomes;
- studies reporting quantitative outcomes; and
- studies with a suitably matched control or comparison group.

2) Data extraction and management

Five review authors (HG, JP, VT, MT and DM) extracted relevant data from the included studies independently and in duplicate. We recorded the following types of data: study design, risk of bias, studied outcome measures, year of publication, duration of follow-up, sample size, number and characteristics of participants in each group and reported results. We assessed the comparability of participant characteristics at baseline, how researchers dealt with confounding, eligibility criteria and the methodology used in measuring outcomes. We discussed the results until we reached agreement. In cases of uncertainty, we contacted study authors for clarification. Should uncertainty persist, we did not use the data.

3) Assessment of risk of bias in included studies

All review authors assessed risk of bias of included studies independently and in duplicate. We resolved disagreements by discussion.

A. Randomised controlled trials (RCTs)

We used the tool of The Cochrane Collaboration for assessing risk of bias along with a 'risk of bias' table to assess each study, as outlined in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* version 5.1.0 [24].

We assessed several domains as having 'low risk' of bias, 'high risk' of bias or 'unclear risk' of bias, including:

- random sequence generation (selection bias);
- allocation concealment (selection bias);
- blinding of outcome assessment (detection bias);
- incomplete outcome data (attrition bias);
- selective outcome reporting (reporting bias); and
- other bias.

We further assessed the randomisation procedure, sample size calculation, definitions of eligibility criteria, definitions of success criteria and comparability of control and treatment groups at the start of the trial. We contacted study authors to seek clarification when data were uncertain. We reported these assessments for each individual study in the 'Risk of bias' table and under Characteristics of included studies.

We performed an overall assessment of risk of bias for primary and secondary outcomes (across domains) across RCTs [24]. Within a study, we assigned a summary assessment of low risk of bias when risk of bias was low for all key domains, unclear risk of bias when risk of bias was unclear for one or more key domains and high risk of bias when risk of bias was high for one or more key domains. Across studies, we rated a summary assessment as having low risk of bias when we derived most information from studies at low risk of bias, unclear risk of bias when we obtained most information from studies at low or unclear risk of bias and high risk of bias when we gathered most information from studies with risk of bias high enough to affect interpretation of results.

B. Non-randomised studies (NRSs)

We used the Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI) when assessing risk of bias of NRSs [25].

We assessed various domains for each primary or secondary outcome as 'low risk' of bias, 'moderate' risk of bias, 'serious' risk of bias, 'critical' risk of bias or 'no information', including:

- bias due to confounding;
- bias in selection of participants into the study;
- bias in measurement of interventions;
- bias due to departure from intended interventions;
- bias due to missing data;
- bias in measurement of outcomes; and
- bias in selection of the reported result.

Control for confounding

We prespecified age, oral and general health status as critically important confounding domains.

We assessed which of these confounding domains had an impact on the specific outcome, and whether they were balanced at baseline or at outcome assessment in studies where participants were allocated to groups on the basis of their outcome. We also assessed whether the confounding domains were balanced between groups or at the design stage through matching when participants were allocated to groups or through statistical adjustments at the analysis stage.

Oral health status included the frequency of routine dental check-ups, the DMFS/T (Decayed Missing Filled Surfaces/Teeth) index, frequency of oral hygiene and carbohydrate intake from which at least one of these variables required to be balanced or adjusted for. No critically important co-interventions were expected to influence the long-term outcomes.

We undertook risk of bias assessment for each primary and secondary outcome (across domains) within each non-randomised stud [25]. Within a study for each outcome, we assigned low risk of bias when risk of bias for all key domains was low, moderate risk of bias when risk of bias for one or more key domains was moderate, serious risk of bias when risk of bias for one or more domains was serious, critical risk of bias when risk of bias for one or more key domains was critical and 'no information' when no clear indication suggested that the outcome was at serious or critical risk of bias and information was insufficient in one or more key domains of bias. We considered certain risks of bias to be additive, so that certain risks of bias in multiple domains led to an overall judgement of greater risk of bias.

Measures of treatment effect

For RCTs and prospective studies with dichotomous outcomes, we expressed the estimates of treatment effects of an intervention as risk ratios (RRs) (outcome present or absent) together with 95% confidence intervals (CIs). For continuous outcomes, we used mean differences (MDs) and standard deviations (SDs).

Unit of analysis issues

We assessed the carry-over effect for all split-mouth studies. If a split-mouth design was deemed inappropriate for investigating the outcome or outcomes assessed in a particular study, we excluded the study. If we had included split-mouth studies, we intended to approximate a paired analysis, as recommended by the *Cochrane Handbook for Systematic Reviews of Interventions* [24]. In the case of an ideal study (i.e. one that reported means and SDs for both groups, and MDs and SDs/standard errors (SEs) between two groups), we intended to calculate intragroup correlation co-efficient (ICCs); if we identified more than one ideal study, we intended to calculate the mean ICC, which we would have adopted in calculating the MD and SD/SE for other, similar split-mouth studies. If no ideal study was identified, then we assumed that the ICC was 0.5.

For clustered data, in trials where the unit of analysis was the tooth, and the number of teeth included in the trial was not more than twice the number of participants, we treated the data as if the unit of analysis was the individual. We recognised that the 95% confidence intervals produced would appear narrower (i.e. the estimate would seem to be more precise) than they should have been, and we therefore interpreted these accordingly.

Dealing with missing data

We assessed incomplete data during the risk of bias assessment. If data were absent, we recorded the presence of reporting bias. We captured missing data on the data extraction form and reported them in the risk of bias tables. We contacted study authors to try to acquire missing data for inclusion.

Assessment of heterogeneity

We would have carried out assessment of heterogeneity in quantifying inconsistency across studies by using the I^2 statistic, as described in Section 9.5.2 of the *Cochrane Handbook for Systematic Reviews of Interventions*.

Assessment of reporting biases

We assessed reporting bias as between-study publication bias or within-study reporting bias. We assessed within-study reporting bias by comparing outcomes reported in the published report against the study protocol, whenever this could be obtained. If we could not obtain the protocol, we compared outcomes listed in the methods section with those whose results were reported. If non-significant results were mentioned but were not reported adequately, we considered that bias was likely to occur in a meta-analysis, and we sought further information from the authors of study reports. Otherwise, we noted this meta-analysis as having high risk of bias. If information was insufficient to judge the risk of bias, we noted this meta-analysis as having unclear risk of bias. If any meta-analysis had included a sufficient number of trials (more than 10), we would have assessed publication bias according to the recommendations on testing for funnel plot asymmetry, as described in Section 10.4 of the *Cochrane Handbook for Systematic Reviews of Interventions* [24]. If asymmetry had been identified, we would have examined possible causes or assessed the asymmetry by using a table to list the outcomes reported by each study included in the review, to identify whether any studies did not report outcomes that had been reported by most studies.

Data synthesis

For RCTs, we planned to conduct a meta-analysis if sufficient studies reported the same outcome measure. We planned to combine risk ratios and calculate 95% confidence intervals for dichotomous data, and to combine mean differences with 95% confidence intervals for continuous data. We planned to use the fixed-effect model unless more than three studies were included in each meta-analysis, or if clinical heterogeneity among studies existed, in which case we would have used the random-effects model.

Given that data from NRSs are prone to bias and are often heterogeneous, we would have carried out separate meta-analyses for NRSs and presented results according to different study designs and outcomes. For NRSs, we would not have performed a meta-analysis in cases of severe methodological and clinical heterogeneity, or when we found too few NRSs. In this instance, we would group the studies by outcome and present results as a narrative summary in the text, as well as in tables and in the form of a forest plot without an overall summary statistic. We would not have included in any analyses data from NRSs with a critical risk of bias.

Subgroup analysis and investigation of heterogeneity

Owing to lack of data, we did not perform a subgroup analysis. If sufficient data had been present, we would have performed a subgroup analysis for participant age (younger than 18 years, 18 to 25 years, 26 to 30 years, over 30 years).

Sensitivity analysis

For any pooled analyses, we planned to undertake sensitivity analyses to examine the effects of randomisation, allocation concealment and blinded outcome assessment on overall estimates of effect.

For meta-analyses of NRSs, we planned to undertake sensitivity analyses after removing NRSs that had not adequately adjusted for significant differences in confounding domains.

Presentation of main results

We prepared a 'Summary of findings' (SoF) (Table 1.) for the primary and secondary outcomes of this review using GRADE (Grading of Recommendation, Assessment, Development and Evaluation Working Group) profiler software. We assessed the overall quality of the evidence, using GRADE criteria, as high, moderate, low or very low (Higgins 2011). GRADE guidance states that RCTs are considered to present high quality evidence and are downgraded as necessary on the basis of overall risk of bias of included studies, directness of the evidence, consistency of the results, precision of the estimates, risk of publication bias and magnitude of effect. Sound observational studies are considered to present low quality evidence but can be upgraded if a large effect size is reported with no obvious bias to explain that effect.

Table 1. Summary of findings

Extraction (absence) compared with retention (presence) for managing asymptomatic disease-free impacted wisdom teeth						
Population: adolescents or adults with asymptomatic disease-free impacted wisdom teeth **Setting:** clinics in university or primary care (UK and USA) **Intervention:** extraction (absence) of wisdom teeth **Comparison:** retention (presence) of wisdom teeth						
Outcomes	**Assumed risk** Retention (presence)	**Corresponding risk** **Extraction (absence)**	**Relative effect (95% CI)**	**Number of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
Health-related quality of life	Our primary outcome was not assessed in the included studies.					
Undesirable outcomes associated with retention (bony impaction): **Periodontitis** Distal alveolar bone loss second molar Assessed by clinical and radiographic examination at follow-up ranging from 3 to 25 years	Not estimable[a]		0.32 (0.19 to 0.54)	416 (1 observational study)	⊕⊕⊖⊖ very low [b,c,d]	For soft tissue impaction, the RR was 0.11 (95% CI 0.06 to 0.22) Also measured by distal probing depth > 4 mm second molar: for bony impaction, the RR was 0.63 (95% CI 0.37 to 1.04); for soft tissue impaction, the RR was 0.15 (95% CI 0.07 to 0.34)
Undesirable outcomes associated with retention (bony impaction): **Caries** affecting the 2nd molar Assessed by clinical and radiographic examination at	Not estimable[a]		RR 0.69 (0.27 to 1.82)	416 (1 observational study)	⊕⊖⊖⊖ **very low** [b,c,d,e]	For soft tissue impaction, RR was 1.20 (95% CI 0.17 to 9.10)

follow-up ranging from 3 to 25 years						
Undesirable outcomes associated with retention: **Dimensional changes in the dental arch** Assessed using digitised study models at follow-up of 66 months Little's index of irregularity	Mean Little's index of irregularity was 1.1 mm	Mean Little's index of irregularity in the intervention group was 0.30 mm lower (1.30 lower to 0.70 higher)	-	77 (1 RCT)	⊕⊕⊖⊖ **low** [f,g]	Also measured by: • Intercanine width: mean decrease in Intercanine width in control group was 0.38 mm. Mean decrease in Intercanine width in intervention group was 0.01 mm lower (0.37 lower to 0.35 higher); and • Arch length: mean decrease in arch length in control group was 2.13 mm. Mean decrease in arch length in intervention group was 1.03 mm lower (0.56 lower to 1.5 lower)
Undesirable outcomes associated with removal	Not measured					
Costs	Not measured					
*The basis for the **assumed risk** (e.g. median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **RR:** risk ratio						
GRADE Working Group grades of evidence **High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect. **Moderate certainty:** we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. **Low certainty:** our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect. **Very low certainty:** we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.						

[a]Results were presented at tooth level, not at participant level. However, adjusted RRs were presented at participant level

[b]Observational study downgraded one level for serious risk of bias due to confounding and missing data

[c]Only male participants were included, which does not reflect the overall population. No direct causal effect of gender and second molar pathology is expected. Therefore, not downgraded for applicability

[d]Participants enrolled in the study and returning for follow-up are likely to be more health aware than their age-matched peers in the community, and to practise better health behaviours. This would suggest more motivated participants in this study compared with the overall population. The presented significant effect may be greater in the overall population; however, we have not upgraded the quality of evidence for plausible confounding

[e]Owing to the wide CI, this outcome was downgraded one level for imprecision

[f]RCT downgraded one level for risk of bias owing to 'some limitations' for multiple criteria (allocation concealment and incomplete outcome data), sufficient to lower confidence in the estimate of effect

[g]Owing to the small number of participants and the high rate of loss to follow-up, the quality of evidence was downgraded one level for imprecision.

Results

Description of studies

Results of the search

After performing the search up to 10 May 2019, we retrieved a total of 4677 references; this resulted in 3254 records after de-duplication. We found no additional studies or ongoing studies after searching the trial registers. After screening the titles and abstracts of these references, we found no new studies and we included only the two studies from our previous review. See Figure 1 for a study flow diagram of the search update.

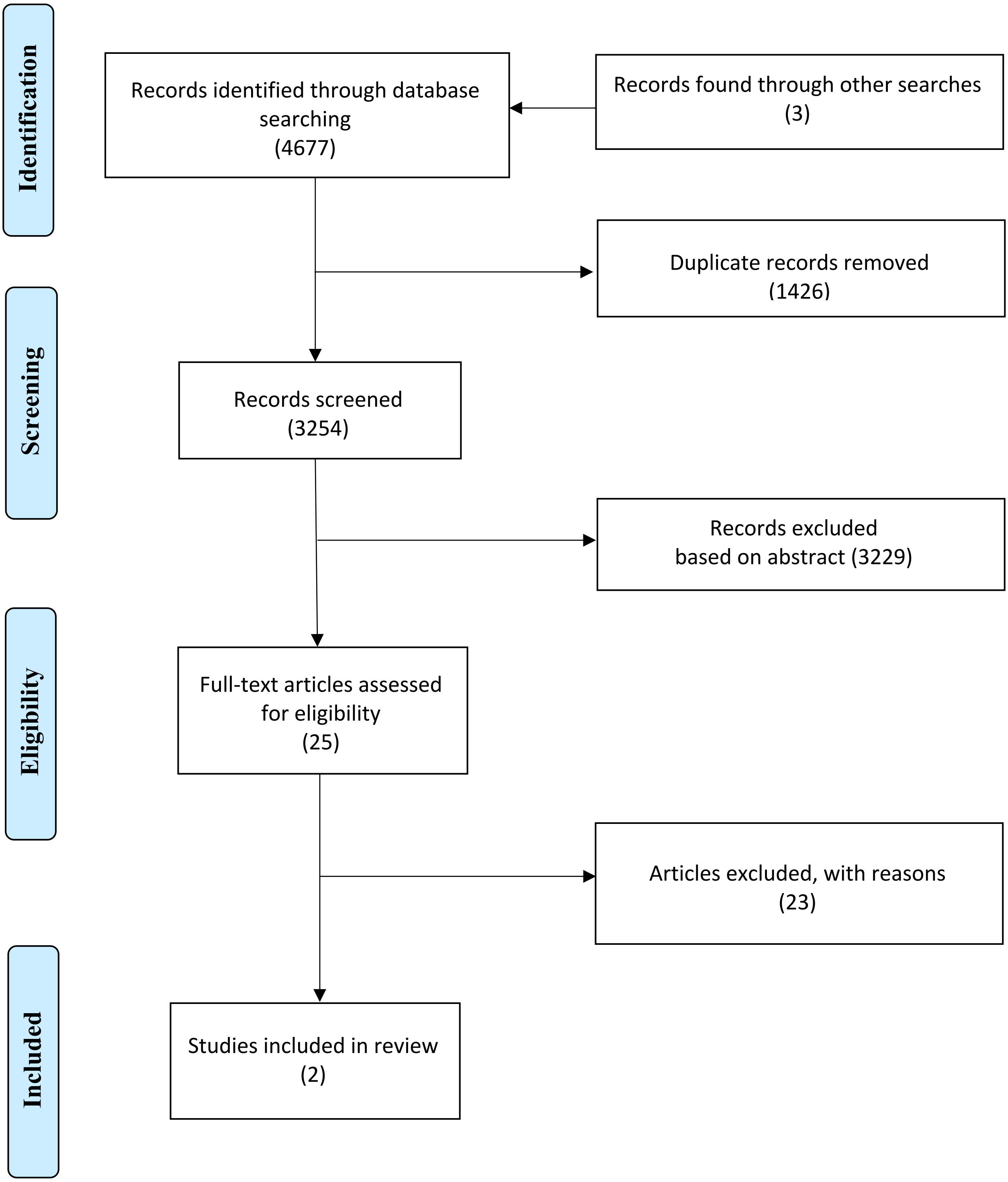

Figure 1. Study selection flow diagram

Included studies

The 2012 version of this review included one RCT [26] which compared surgical removal with retention of asymptomatic disease-free impacted wisdom teeth in adolescent participants who had previously undergone orthodontic treatment. We assessed this study including 164 participants to be at overall high risk of bias. In the previous review update (2016), we added one prospective cohort study and included a total of two studies with 1395 participants (493 analysed participants). We have provided summary details in the Characteristics of included studies Table 2 and Table 3.) No additional studies have been added to this current review update.

Characteristics of study settings

We included in this review two studies involving data from 493 analysed participants: one RCT with a parallel-group design conducted in a dental hospital setting in the United Kingdom [26], and one prospective cohort study conducted in the private sector in the USA [27].

Characteristics of participants

The RCT recruited 164 adolescents (55% female) who had previously undergone orthodontic treatment and had 'crowded' wisdom teeth, in which the long axis and the presumed path of eruption of the wisdom teeth was through the adjacent second molar [26].

The prospective cohort study recruited 1231 healthy male volunteers, aged 24 to 84 years, who had both first and second molars present in at least one quadrant at baseline and had undergone at least one follow-up examination (at three years) [27]. Wisdom teeth at baseline were categorised as absent (previous removal or agenesis), erupted, ‘soft tissue’ impacted or ‘bony’ impacted.

Characteristics of interventions

The RCT compared surgical removal with retention of asymptomatic disease-free impacted wisdom teeth [26]. The prospective cohort study compared absence (previous removal or agenesis) with erupted and unerupted asymptomatic disease-free impacted wisdom teeth [27]. The latter was split into soft and hard tissue impaction.

Characteristics of outcome measures

The RCT measured the secondary outcome - dimensional changes in the dental arch - at baseline and five years later [26]. Study authors assessed three measures of dimensional change in the dental arch (Little's irregularity index, intercanine width and arch length) using digitised study models.

The prospective cohort study measured secondary outcomes - periodontitis and caries associated with the distal aspect of the adjacent second molar - during a follow-up period of 3 to 25+ years [27]. Probing depths of greater than 4 mm associated with the distal surface of the adjacent second molar were assessed clinically, and a trained, calibrated periodontist assessed alveolar bone loss and caries associated with the distal aspect of the adjacent second molar, both clinically and radiographically (Table 3. And Table 4.)

Table 2. Characteristics of included study - **Harradine 1998**

Study characteristics	
Methods	Randomised controlled trial, parallel-group design, 2 treatment groups Location: Bristol, UK Single centre Research aim: to investigate prospectively the effects of early extraction of third molars on late lower incisor crowding
Participants	Inclusion criteria: individuals who had previously undergone orthodontic treatment but were no longer wearing orthodontic appliances or retainers. Orthodontic treatment comprised active treatment in the upper arch with only removable appliances or a single-arch fixed appliance, with no treatment or premolar extractions carried out in the lower arch. Individuals with crowded molars (third molars whose long axis and, therefore, presumed path of eruption was through the adjacent second molar) Exclusion criteria: residual premolar extraction space Number randomised: 164 individuals (55% were female) Number evaluated after 5 years: 77 individuals completed the trial (58% were female) Age of entry to the trial (mean ± standard deviation (SD)): 14 years 10 months ± 16.2 months Baseline characteristics: reported for overall group sample, not per study group
Interventions	Group I: extraction of third molars (N = 44 evaluated) Group II: retention of third molars (N = 33 evaluated)
Outcomes	Outcome measures • Little's irregularity index (LII). Mean differences ± SD for change • Intercanine width (ICW). Mean differences ± SD for change • Arch length (AL). Mean differences ± SD for change Length of follow-up: 5 years, mean length of follow-up was 66 ± 12.6 months For the upper arch, investigators found no statistical differences between the 2 groups for the 3 outcome variables

Notes	Sample size calculation: not described Analysis (linear modelling) of measurements of casts demonstrated no systematic differences between individuals who completed the trial and those lost to follow-up Baseline characteristics per study group for comparability at entry would have been appropriate	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation	Low risk	Quote: "...a list of randomly generated numbers was used to allocate..."
Allocation concealment	High risk	Quote: "...a list of randomly generated numbers was used to allocate..." Comment: The method of concealment is not fully described; it is likely that selection bias could affect the outcome of the study
Blinding of outcome assessment	Low risk	Quote: "the third molar status was unknown to the digitizer in order to eliminate sub-conscious bias"
Incomplete outcome data	High risk	Quote: "...no systematic differences existed between those patients who entered the trial and completed, and those who entered and did not complete" Comment: 53% attrition overall, evaluation of 44 and 33 participants in extraction and non-extraction groups (54% and 40%, respectively) and reasons for non-completion are given as "loss of contact with occupiers of their previous address". No data are available on the gender balance of those who completed compared with those who did not, for each treatment group. Trial authors report only the results of modelling of 44 non-responders. This trial would seem to be at high risk of attrition bias
Selective reporting	Unclear risk	Comment: The only outcomes reported in the paper are orthodontic indices. No adverse effects of treatments or symptoms are reported
Other sources of bias	Low risk	Comment: More specific characteristics per study group for comparability at entry would have been appropriate

Table 3. Characteristics of included study - **Nunn 2013**

Study characteristics	
Methods	Prospective cohort study, part of Longitudinal Veterans Affairs Normative Aging Study, beginning in 1961 (Kapur 1972) Location: United States (greater Boston area) Research aim: to examine the association of third molar status with prevalent and incident caries and periodontal outcomes in adjacent second molars
Participants	Healthy male patients who had both first and second molars present in at least 1 quadrant at baseline and had at least 1 follow-up. Examinations were performed every 3 years with duration to > 25 years Number of participants: 416 (804 third molars) from 1231 enrolled patients met the inclusion criteria Age of entry to the trial (mean ± standard deviation (SD)): 45.8 years 9 months ± 7.4 years Baseline characteristics: Analyses were adjusted for baseline age, smoking status, education and baseline second molar measures
Interventions	Retention of asymptomatic wisdom teeth compared with absence of wisdom teeth (previous extraction or agenesis at baseline)
Outcomes	Second molar pathology • Caries • Distal probing depth > 4 mm • Distal alveolar bone loss These outcomes were measured every 3 years Clinical outcomes (caries and probing depths > 4 mm) measured by a trained, calibrated periodontist. Radiological outcome (alveolar bone loss and caries) measured by board-certified oral and maxillofacial surgeon and a board-certified oral and maxillofacial radiologist. Alveolar bone loss was measured with a Schei ruler
Notes	Risk of bias is assessed to be serious for this study.

Excluded studies

We have provided summary details in the Characteristics of excluded studies in table 4. After screening the full text of the identified NRSs, we excluded 23 studies because:

- Three studies had follow-up less than five years [28, 29, 30]
- Six studies used an inappropriate study design [32-38]
- Seven studies did not have a suitably matched control or comparison group [15, 40-45]
- Six studies included an inappropriate study population [38, 46-50]

Table 4. Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Ades 1990	Retrospective design
Blakey 2009	Short follow-up (< 5 years), not impacted third molars
Coleman 2011	Short follow-up (< 5 years)
Dicus 2010	Comparison of 2 different cohorts
Dicus-Brookes 2013	Only symptomatic third molars included
Fisher 2012	No comparison between retention and extraction or absence and presence of third molars
Fisher 2013	No comparison between retention and extraction or absence and presence of third molars. Short follow-up (< 5 years)
Garaas 2012	No comparison between retention and extraction or absence and presence of third molars
Golden 2015	No comparison between retention and extraction or absence and presence of third molars
Haug 2005	No comparison between retention and extraction or absence and presence of third molars
Huang 2014	Short follow-up (< 5 years)
Lindqvist 1982	Split-mouth study, which is an inappropriate design for evaluation of crowding of teeth
Moss 2007	Cross-sectional design
Moss 2007a	Cross-sectional design
Moss 2009	Only obstetric patients with periodontal disease were included
Moss 2013	Only obstetric patients with periodontal disease were included
Moss 2013a	Only obstetric patients with periodontal disease were included
Nemcovsky 1997	Removal of second molars (not third molars)
Offenbacher 2012	Cross-sectional design
Rahman 2009	Cross-sectional design
Venta 1993	Data were not presented at patient level, but at sextant level. Participants who had wisdom teeth removed during the study were excluded from analyses. The senior study author was contacted successfully, but the complete dataset was not available

Study	Reason for exclusion
Venta 1993a	Retrospective design
Venta 2015	No comparison between retention and extraction or absence and presence of third molars

Risk of bias in included studies

We have reported risk of bias separately for the RCT (Table 2.) and the prospective cohort study (Table 5.).

The RCT had adequate sequence generation [26]. Study authors did not explicitly describe the method of allocation concealment, and this gave rise to high risk of selection bias. It was impossible for participants and operators to be blinded to the intervention, but the outcome assessor was blinded. We assessed risk of performance and detection bias to be low. Fifty-three per cent of the original participants (N = 87) were lost to follow-up at five years. More participants were lost from the retention group (49/82 = 60%) than from the removal group (38/82 = 46%), and study authors were unable to contact these participants. study authors provided no data on the gender balance between groups of those who completed the study compared with those who did not. We assessed this trial to be at high risk of attrition bias, which could have affected overall results. We assessed risk of bias due to selective reporting as unclear. We could identify no other major potential sources of bias. We considered this RCT to be at high risk of bias overall.

We assessed the prospective cohort study to be at serious risk of bias owing to confounding and missing data [27]. Study authors adjusted analyses for baseline age, smoking status, education and baseline second molar measures but did not measure oral health status. These factors may contribute to the development of second molar pathology; therefore, this study is at serious risk of bias owing to confounding. In the first Dental Longitudinal Study, beginning in 1969, 1231 volunteers were enrolled [51]. Eventually only 416 met the inclusion criteria and were analysed. Data regarding the excluded participants are missing. Participants with pathology associated with their wisdom teeth are likely to have had them removed before the study was initiated; therefore, this study is at serious risk of bias owing to missing data. We assessed this study to be at low risk of bias in measurement of interventions and outcomes. We assessed risk of bias due to selection of participants into the study, departures from intended interventions and selection of reported results as moderate. We considered this prospective cohort study overall to be at serious risk of bias for all assessed outcomes. See Table 3.

Table 5. Risk of bias assessed using ACROBAT-NRSI for Nunn 2013

Bias	Authors' judgement	Support for judgement
Confounding	Serious risk	Analyses were adjusted for baseline age, smoking status, education and baseline second molar measures. However, oral health status such as oral hygiene and frequency of dental checkups was not measured. These factors may contribute to the development of second molar pathology. However, "participants enrolled in the study returning for follow-ups are likely to be more health aware than their age-matched peers in the community and practice better health behaviors". This would suggest more motivated participants in this study compared with the overall population. Therefore, the predicted direction of bias due to oral health status confounding favours retention (presence), and it is likely that the effect estimate would be even higher if was adjusted
Selection of participants into the study	Moderate risk	Only male volunteers were included. However, gender is not expected to contribute to the development of second molar pathology. Some participants lost third molars before the start of follow-up – in the target randomised trial for this study, participants would be followed from the time the third molars were removed. As third molars were removed before the start of follow-up, a potentially important amount of follow-up time is missing
Measurement of interventions	Low risk	Intervention status was well defined and was based solely on information collected at the time of intervention
Departure from intended interventions	Moderate risk	Switching of participants from retention to removal was likely, but this switching occurs as part of the natural course of events

Missing data	Serious risk	1231 volunteers enrolled in the Dental Longitudinal Study beginning in 1969 (Kapur et al. 1972), but only 416 analysed. This first study could not be obtained. Those with problems from third molars were likely to have them removed before the study was initiated; therefore, this study has serious risk of bias due to missing data
Measurement of outcomes	Moderate risk	Caries, probing depths and alveolar bone loss were assessed clinically and on radiographs adequately. Blinding was not possible, but we do not expect that non-blinding would have influenced the results
Selection of reported results	Moderate risk	There is no evidence to suggest that multiple outcome measurements and/or multiple analyses were conducted for each outcome. Only participants with both first and second molars in at least 1 quadrant were included in the study, rather than the whole subset of 1231 volunteers in the Dental Longitudinal Study. No a priori measurement or analysis plan was included

Effects of interventions

Primary outcome - health-related quality of life

Neither of the two included studies investigated health-related quality of life measures associated with retention or removal of asymptomatic disease-free impacted wisdom teeth.

Secondary outcomes - outcomes associated with retention of wisdom teeth (undesirable effects)

Periodontitis (increased probing depths or alveolar bone loss affecting wisdom teeth or adjacent second molars)

The prospective cohort study with 416 analysed participants (with 804 wisdom teeth) reported relative risks for probing depths greater than 4 mm and alveolar bone loss associated with the distal of the adjacent second molar in the absence compared with the presence of asymptomatic disease-free impacted wisdom teeth [27]. 'Soft tissue' and 'bony' impactions were calculated at the participant level.

In the absence of wisdom teeth, the risk of probing depths greater than 4 mm associated with the distal of the adjacent second molar was significantly less than if soft tissue impacted wisdom teeth were present (RR 0.15, 95% CI 0.07 to 0.34) (very low-certainty evidence). There was no statistically significant difference in the risk of probing depths greater than 4 mm associated with the distal of the adjacent second molar in the absence compared with the presence of bony impacted wisdom teeth (RR 0.63, 95% CI 0.37 to 1.04) (very low-certainty evidence).

In the absence of wisdom teeth, the risk of alveolar bone loss associated with the distal of the adjacent second molar was significantly less than if soft tissue (RR 0.11, 95% CI 0.06 to 0.22) or bony impacted wisdom teeth (RR 0.32, 95% CI 0.19 to 0.54) were present (very low-certainty evidence).

Caries (tooth decay affecting wisdom teeth or adjacent second molars (distal-cervical)

The prospective cohort study with 416 analysed participants (804 wisdom teeth) reported relative risks for caries associated with the distal of the adjacent second molar in the absence compared with retention of asymptomatic disease-free impacted wisdom teeth [27]. 'Soft tissue' and 'bony' impactions were calculated at the participant level.

The evidence was very uncertain for the prevalence of distal caries associated with the adjacent second molar in the absence compared with the presence of bony impacted wisdom teeth (RR 0.69, 95% CI 0.27 to 1.82) and soft tissue impacted wisdom teeth (RR 1.20, 95% CI 0.17 to 9.10) (very low-certainty evidence).

Dimensional changes in the dental arch (crowding)

The RCT with 77 analysed participants reported mean differences with 95% confidence intervals for dimensional changes in the dental arch for surgical removal compared with retention of asymptomatic disease-free impacted wisdom teeth (Harradine 1998). There were no statistically significant differences between groups for the outcomes of Little's irregularity index (MD -0.3 mm, 95% CI -1.3 to 0.7) and intercanine width (MD -0.01 mm, 95% CI -0.37 to 0.35) (low-certainty evidence). There was a small but statistically significant difference between groups in arch length (MD -1.03 mm, 95% CI -0.56 to -1.50, P value = 0.0001), but this difference is unlikely to be clinically significant (low-certainty evidence). These findings appear to be inconsistent with each other but may be explained, as the study authors' note, by persistent residual premolar extraction space in some participants at study entry.

Other outcomes associated with retention

No included studies reported pericoronitis, root resorption, cyst formation, tumour formation or inflammation/infection.

Outcomes associated with removal of wisdom teeth (undesirable effects)

No included studies measured outcomes or adverse events associated with removal of asymptomatic disease-free impacted wisdom teeth (alveolar osteitis/postoperative infection, nerve injury, damage to adjacent teeth during surgery, bleeding, osteonecrosis related to medication/radiotherapy, inflammation/infection).

Costs

The included studies did not measure days off work/study or direct costs associated with retention or removal of wisdom teeth and treatment of associated symptoms or complications.

Discussion

Summary of main results

No eligible studies in this review reported the effects of removal compared with retention of asymptomatic disease-free impacted wisdom teeth for the primary outcome measure: health-related quality of life.

Studies have provided only low- or very low-certainty evidence of the effects of removal compared with retention of asymptomatic disease-free impacted wisdom teeth for a limited number of secondary outcome measures. Very low-certainty evidence from one prospective cohort study suggests that the presence of asymptomatic disease-free impacted wisdom teeth may be associated with increased risk of periodontitis associated with the adjacent second molar in the long term. The same study provided insufficient evidence about the risk of caries affecting the adjacent second molar. Low-certainty evidence from a single randomised controlled trial (RCT) included in this review found no evidence to suggest that removal of asymptomatic disease-free impacted wisdom teeth has a clinically significant effect on dimensional changes in the dental arch.

No included studies have reported other outcomes or adverse events associated with removal (alveolar osteitis/postoperative infection, nerve injury, damage to adjacent teeth during surgery, bleeding, osteonecrosis related to medication/radiotherapy, inflammation/infection) or retention (pericoronitis, root resorption, cyst formation, tumour formation, inflammation/infection) of asymptomatic disease-free impacted wisdom teeth.

Overall completeness and applicability of evidence

Substantial differences are evident between participants in the two included studies, and these participants are not representative of the general population with asymptomatic disease-free impacted wisdom teeth.

The included RCT focused only on adolescent patients who had completed orthodontic treatment. Loss to follow-up was a major obstacle in obtaining data about the effects of extraction of asymptomatic disease-free impacted wisdom teeth, as participants are likely to be recruited towards the end of their high school years and are difficult to follow up as they move to higher education, go travelling or change locations when seeking employment.

The prospective cohort study included only male participants aged 24 to 84 years from a single geographic area who were self-selected volunteers. Participants enrolled in the study who returned for follow-up are likely to be more health aware than their age-matched peers in the community and to practise better health behaviours. This would suggest that participants in this study were more motivated than the overall population. Retained wisdom teeth in this group of participants were associated with increased risk of periodontal disease affecting the adjacent second molar. Risk of damage to the second molar might be even greater in populations with poor oral health. If wisdom teeth or adjacent second molars need to be removed at an older age owing to disease, the personal and financial costs may be greater than at a young age. However, included studies have provided no information on quality-of-life measures and costs.

Included studies have provided no information regarding other adverse effects of removal (alveolar osteitis/postoperative infection, nerve injury, damage to adjacent teeth during surgery, bleeding, osteonecrosis related to medication/radiotherapy, inflammation/infection) or retention (pericoronitis, root resorption, cyst formation, tumour formation, inflammation/infection) of asymptomatic disease-free impacted wisdom teeth.

We chose the primary outcome of health-related quality of life to capture the benefits and harms associated with removal and retention of asymptomatic disease-free impacted wisdom teeth. We chose this outcome measure because of the difficulties of comparing various outcomes (e.g. rate of complications after surgical removal, incidence of pathological change in cases of retention, rate of complications due to delayed surgical removal) [52]. Unfortunately, the included studies did not assess this primary outcome. The Oral Health Impact Profile is a valid and reliable measure of oral health-related quality of life in general dental practice and is responsive to impacted third molar clinical change [53]. It is suitable for measuring the effects of removal or retention of asymptomatic disease-free impacted wisdom teeth on oral health-related quality of life in future studies.

Quality of the evidence

The single RCT included in this review provided low-certainty evidence of the effects of surgical removal of asymptomatic disease-free impacted wisdom teeth on dimensional changes in the dental arch at five years' follow-up. We considered this trial to be at high risk of bias overall owing to limitations of allocation concealment and incomplete outcome data sufficient to lower confidence in the estimate of effect. In addition, the small number of participants and the high rate of loss of participants to follow-up led to imprecision in the estimate of effect.

As RCTs investigating longer-term and rare effects of removal or retention of asymptomatic disease-free impacted wisdom teeth are unlikely to be feasible, we considered non-randomised studies (NRSs) for inclusion in this review update. A high quality prospective cohort study might be a more suitable design for evaluating the outcomes of retained wisdom teeth. However, NRSs are likely to be at higher risk of bias compared with RCTs. With the introduction of the Cochrane Risk of Bias Tool for NRSs (ACROBAT-NRS) [25] it is possible to assess the risk of bias in NRSs more systematically. (The tool was updated in 2016 and is now called ROBINS-I).

We assessed the included prospective cohort study, [27], to be at serious risk of bias because of confounding. Study authors adjusted the analyses for baseline age, smoking status, education and baseline second molar measures but did not measure oral health status. Oral health status may contribute to the development of pathology associated with wisdom teeth and adjacent second molars. A recent study that measured the frequency of dental check-ups reported no effects of wisdom tooth removal on the incidence of pathology associated with the second molar [30]. However, this study provided only two years of follow-up and was not eligible for inclusion in this review. As pathology may develop in a wisdom tooth or in the adjacent second molar over the whole of a person's lifetime, studies with long-term follow-up are needed.

The evidence available from the two studies included in this review provides only low- to very low-certainty evidence, so we cannot rely on these findings to guide clinical practice.

Agreements and disagreements with other studies or reviews

Despite the lack of evidence, clinical practice guidelines (CPGs) on the management of impacted wisdom teeth have been available for 20 years. The Scottish Intercollegiate Guideline Network published a CPG for the management of unerupted and impacted wisdom teeth in 1999 [54], though this was withdrawn in 2015 due to lack of evidence. The National Institute for Health and Care Excellence in the UK published a CPG for removal of wisdom teeth in 2000 [18]. NICE concluded that in light of the costs and risks associated with removal, no valid evidence supports the prophylactic removal of asymptomatic disease-free wisdom teeth. It has been debated whether this is an appropriate strategy for all patients with impacted wisdom teeth [17, 20]. Well-designed RCTs investigating the long-term and rare effects of retention and removal of asymptomatic disease-free impacted wisdom teeth, in a representative group of individuals, are unlikely to be feasible. The Finnish Current Care Guidelines 2014 and Dutch Clinical Care Guidelines 2020 focused on a more individualised approach, based on the risk of developing pathology of the wisdom teeth in the future, and the risk of complications following removal of the wisdom teeth. Both CPGs conclude that the prophylactic removal of asymptomatic disease-free wisdom teeth is indicated in selected cases based on a patient-tailored risk assessment.

Disagreement regarding the removal of asymptomatic disease-free impacted wisdom teeth is ongoing [30], and the key question remains: why should impacted wisdom teeth be removed in the absence of symptoms or pathological conditions? Unfortunately, reliable estimates of the onset of pathology related to retained impacted wisdom teeth are unavailable [31], in large part because of the widespread practice of routine removal over past decades. Recently, an assessment of the prevalence of distal surface caries (DSC) in the second molar adjacent to third molars in a systematic review and meta-analysis revealed that European studies suggest that DSC may be present in about 25% of third molar assessment referrals and that the risk is considerably higher in those with convergent third molar impactions [55].

Cross-sectional studies performed in elderly individuals in the USA [56] and Finland [57] have reported that most wisdom teeth are removed over a lifetime, and that up to 80% of surviving wisdom teeth have associated pathology such as caries or periodontitis in patients over the age of 74 years. The incidence of severe pathology associated with wisdom teeth, such as cysts and tumours, is low (< 2%). Evidence from these cross-sectional studies is very unreliable, and studies assessing the outcomes of retained wisdom teeth are rare because of problems associated with a complex long-term prospective study design [58]. Actuarial lifetime tables have shed some light on the natural history of asymptomatic impacted lower wisdom teeth, but longer follow-up periods are required [59].

In the late 1990s, the American Association of Oral and Maxillofacial Surgeons acknowledged the absence of evidence to guide clinical decision-making for the management of asymptomatic disease-free impacted wisdom teeth, and allocated a significant amount of money for a multi-centre study [10]. More than 70 papers have been published as a result of this study, including a large cohort study that documents the incidence of adverse effects following more than 8000 third molar extractions in participants of 25 years of age or older [43]. Large studies have documented the incidence of complications associated with retention of asymptomatic disease-free wisdom teeth. Most of these studies did not focus on asymptomatic disease-free impacted wisdom teeth but investigated the occurrence of pathology associated with 'visible teeth'. This resulted in serious risk of selection bias in all of these studies; therefore, we did not include them in this review. The American Association of Oral and Maxillofacial Surgeons "leans more towards the removal of asymptomatic disease-free third molars on the basis they are associated with increased periodontal probing depths and are therefore a potential source of chronic inflammation" [10]. However, it should be questioned whether only pocket depths are indicative of periodontal pathology. A 4-mm pocket depth in the second molar may be influenced by the eruption status of the third molar, without inflammation or other pathology. The prospective cohort study included in this review found increased risk of second molar periodontal pathology adjacent to impacted third molars when distal alveolar bone loss was assessed radiographically in addition to distal probing depths [27].

The decision about whether to recommend removal or retention of asymptomatic disease-free wisdom teeth may be influenced by cost (whether publicly funded, covered through insurance or borne by the patient) and by professional liability. Patient values and preferences should play a more prominent role in deciding whether asymptomatic disease-free impacted wisdom teeth should be removed.

Authors' conclusions

Implications for practice

Insufficient evidence is available to support the surgical removal or retention of asymptomatic disease-free impacted wisdom teeth. Although some evidence suggests that retaining asymptomatic disease-free impacted wisdom teeth may increase the risk of periodontitis associated with adjacent second molars in the long term, we assessed this evidence has having very low certainty. Given the lack of evidence from scientific studies, patient values should be considered and clinical expertise and local and national guidance used to guide shared decision-making with people who have asymptomatic disease-free impacted wisdom teeth. If the decision is made to retain asymptomatic disease-free impacted wisdom teeth, clinical assessment at regular intervals to prevent undesirable outcomes is advisable.

Implications for research

Long-term, well-designed prospective studies comparing removal or retention of asymptomatic disease-free impacted wisdom teeth are urgently needed. Well-designed RCTs investigating the long-term and rare effects of retention and removal of asymptomatic disease-free impacted wisdom teeth, in a representative group of individuals, are unlikely to be feasible. If randomisation is not possible, studies should register important baseline data such as age and general and oral health status, including the frequency of dental check-ups, the DMFS/T (Decayed Missing Filled Surfaces/Teeth) index or frequency of oral hygiene. These confounding domains should be balanced at baseline or adjusted for with appropriate analyses.

There is a need for research investigating the primary outcome in this review, oral health-related quality of life, in the context of managing impacted wisdom teeth [60]. Future review updates may focus on a different primary outcome measure to accommodate for this current lack of evidence.

The secondary outcomes described in this review are also of great importance for decision-making in the management of asymptomatic disease-free impacted wisdom teeth and should be measured in future studies. Because pathology may develop in a wisdom tooth or in the adjacent second molar over the whole of a person’s lifetime, studies with long-term follow-up (at least five years) are needed. This is very challenging, as young participants are difficult to contact when they move to higher education, travel or change locations while seeking employment.

What's new

Date	Event	Description
28 February 2020	New citation required but conclusions have not changed	No change to conclusions as no new studies were added. Minor change to author order.
24 February 2020	New search has been performed	We ran a new search but did not identify any additional studies for inclusion.

History - Protocol first published: Issue 1, 2002, Review first published: Issue 2, 2005

Date	Event	Description
26 June 2016	New citation required and conclusions have changed	We added 1 new longitudinal study in this review update Conclusions have changed. In the original review, we concluded that "watchful monitoring of asymptomatic impacted wisdom teeth may be a more prudent strategy". However, the available evidence is very low quality and there are insufficient data on which to base clinical decisions about the management of asymptomatic disease-free impacted wisdom teeth Search strategy changed: trials investigating short- and long-term risks and complications of retention/removal of asymptomatic disease-free impacted wisdom teeth are unlikely to be feasible.
9 June 2015	New search has been performed	We included non-randomised studies (NRSs) in this review update if they assessed long-term outcomes, i.e. over 5 years. The introduction of a new Cochrane Risk of Bias Tool for NRSs means we can now assess the risk of bias in NRSs more systematically
14 May 2012	New search has been performed	New search was conducted. Title was changed to "Surgical removal versus retention for the management of asymptomatic impacted wisdom teeth"
14 May 2012	New citation required and conclusions have changed	As the result of changes in methodology, we have deleted 1 previously included study. We have revised the review conclusions because evidence is insufficient to determine effects of prophylactic extraction of asymptomatic wisdom teeth

Contributions of authors

For this update:

- Literature search update and study selection: Hossein Ghaeminia, John Perry, Marloes Nienhuijs, Verena Toedtling, Marcia Tummers, Theo Hoppenreijs, Wil van der Sanden, Dirk Mettes;
- Risk of bias and quality assessment: Hossein Ghaeminia, John Perry, Marcia Tummers, Marloes Nienhuijs, Verena Toedtling, Theo Hoppenreijs, Wil van der Sanden, Dirk Mettes; and
- Editing of the review: Hossein Ghaeminia, John Perry, Marcia Tummers, Marloes Nienhuijs, Verena Toedtling, Theo Hoppenreijs, Wil van der Sanden, Dirk Mettes.

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Declarations of interest

The participating review authors declare that they have no financial conflicts of interest, nor do they have any associations with industry regarding the topic of this review.

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Differences between protocol and review

- Title - we added 'disease-free'.
- Types of participants. In the original protocol, the intention was to include only studies on adult participants (over 17 years of age). However, review authors identified no suitable trials. It was therefore decided to expand the remit to include studies on adolescent participants. The change in the age of participants is not expected to have any clinical implications because little clinical difference has been noted between adolescents (14 to 17 years of age) and young adults (18 to 25 years of age).
- Types of studies. Long-term outcomes of retention/removal of asymptomatic disease-free impacted wisdom teeth are extremely unlikely to be studied in randomised controlled trials (RCTs). Therefore, we considered non-randomised studies (NRSs) for inclusion in this review update, if outcomes were measured with follow-up of at least five years.
- Types of interventions. Presence and absence of wisdom teeth were added to investigate the long-term outcomes of retention or removal of wisdom teeth. This enabled us to study the effects of absence or presence of wisdom teeth on adjacent structures such as the second molar.
- Types of outcomes. More than 15 years after the initial protocol, many publications have addressed periodontitis as a possible undesirable effect of

retention of wisdom teeth. Furthermore, attention to medication/radiotherapy-related osteonecrosis of the jaw associated with surgical extractions is increasing. Therefore, we added these secondary outcomes to the methods. We expanded other outcomes.

- Because we considered NRSs for inclusion in the review update, we used the Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (ACROBAT-NRSI) for the risk of bias assessment of NRSs [25].
- As we were including NRSs, we executed the search without an RCT study design filter, and the results of the full search are reported in Appendix 1-6.

Appendices

Appendix 1. Cochrane Oral Health's Trials Register search strategy

Cochrane Oral Health's Trials Register is available via the Cochrane Register of Studies. For information on how the register is compiled, see https://oralhealth.cochrane.org/trials.

From June 2015, searches of the Cochrane Oral Health Trials Register were conducted using the Cochrane Register of Studies and the search strategy below:

1 (("third molar*" or "wisdom tooth" or "wisdom teeth" or "3rd molar*" or third-molar):ti,ab) AND (INREGISTER)
2 (retain* or retention or present* or presence):ti,ab
3 ((extract* or remov* or absent* or missing or absence):ti,ab) AND (INREGISTER)
4 #2 and #3
5 (asymptom*:ti,ab) AND (INREGISTER)
6 ((symptomless or symptom-free or "symptom free"):ti,ab) AND (INREGISTER)
7 (("trouble free" or trouble-free):ti,ab) AND (INREGISTER)
8 (#5 or #6 or #7) AND (INREGISTER)
9 #4 or #8
10 (#1 and #4 and #9) AND (INREGISTER)

Previous searches of this database were conducted using the Procite software and the search strategy below:

(("third molar*" OR "molar third" OR "wisdom teeth" or "wisdom tooth" OR "third-molar*" or "3rd molar*") AND (impact* or unerupt*) AND ("Tooth extraction" or extract* or remov* or asymptom* or "trouble free" or trouble-free or "symptom free"))

Appendix 2. Cochrane Central Register of Controlled Trials (CENTRAL) search strategy

#1 [mh ^"molar, third"]
#2 ("third molar*" or "wisdom teeth" or "wisdom tooth" or "3rd molar*" or third-molar*)
#3 #1 or #2
#4 [mh ^"Tooth extraction"]
#5 (extract* or remov* or absent* or missing or absence)
#6 #4 or #5
#7 (retain* or retention or present* or presence)
#8 #6 and #7
#9 asymptom*
#10 (symptomless or symptom-free or "symptom free")
#11 (trouble-free or "trouble free")
#12 {or #9-#11}
#13 #8 or #12
#14 #3 and #13

Appendix 3. MEDLINE Ovid search strategy

1. Molar, Third/
2. ("third molar*" or "wisdom tooth" or "wisdom teeth" or "3rd molar*" or third-molar).mp.
3. 1 or 2
4. Tooth extraction/
5. (extract$ or remov$ or absent$ or missing or absence).mp.

6. 4 or 5

7. (retain$ or retention or present$ or presence).mp.

8. 6 and 7

9. asymptom$.mp.

10. (Symptomless or symptom-free or "symptom free").mp.

11. (trouble-free or "trouble free").mp.

12. or/9-11

13. 8 or 12

14. 3 and 13

Appendix 4. Embase Ovid search strategy

1. Molar tooth/

2. ("third molar$" or "wisdom tooth" or "wisdom teeth" or "3rd molar$" or third-molar$).mp.

3. 1 or 2

4. Tooth extraction/

5. (extract$ or remov$ or absent$ or missing or absence).mp.

6. 4 or 5

7. (retain$ or retention or presence).mp.

8. ((present or presence) adj3 (tooth or teeth or molar)).mp.

9. 7 or 8

10. 6 and 9

11. asymptom$.mp.

12. (Symptomless or symptom-free or "symptom free").mp.

13. (trouble-free or "trouble free").mp.

14. or/11-13

15. 10 or 14

16. 3 and 15

Appendix 5. US National Institutes of Health Ongoing Trials Register (ClinicalTrials.gov) search strategy

asymptomatic and third and molar

asymptomatic and wisdom and tooth

asymptomatic and wisdom and teeth

Appendix 6. World Health Organization International Clinical Trials Registry Platform search strategy

asymptomatic and third molar

asymptomatic and wisdom tooth

asymptomatic and wisdom teeth

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Chapter 3

Systematic Review

Prevalence of distal surface caries in the second molar amongst third molar assessment referrals: A systematic review and meta-analysis

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ABSTRACT

Purpose: We conducted a systematic review of epidemiological studies to assess the prevalence of distal surface caries (DSC) in the second molar adjacent to a third molar.

Methods: A literature search using the Cochrane Library, Lilacs, Embase and Medline via Ovid retrieved English and non-English articles from inception to June 2016. The electronic searches were supplemented with reference searching and citation tracking. Reviewers independently and in duplicate performed data extraction, completed structured quality assessments with a validated risk of bias tool for observational studies and categorized the summary scores.

Results: The search yielded 81 records and after application of inclusion and exclusion criteria, 11 prevalence studies were analysed in the systematic review. Due to considerable methodological diversity, five studies were not eligible for inclusion in the quantitative synthesis. A meta-analysis of 6 DSC prevalence studies and a subgroup analysis of 3 studies concerning various third molar angulations were indicated. The overall pooled prevalence estimate was calculated with a random-effects model and was 23% (95% CI, 2% to 44%) on a patient level. Prevalence subtotals were 20% (95% CI, 5% to 36%) for prospective and 15% (95% CI, 5% to 36%) for retrospective studies on a molar level in a population referred to hospital care. A subgroup analysis of three studies with 1296 patients (1666 molars) yielded DSC prevalence rates among mesial impactions of 36% (95% CI, 5% to 67%) and 22% with horizontal impactions (95% CI, 1% to 42%). Among, distally inclined impactions 3% of teeth had DSC (95% CI, 1% to 5%) and 7% of vertical third molars had DSC (95% CI, 1% to 13%). The included studies showed variation across studies, one study was assessed to be at low risk of bias and two studies at moderate risk of bias.

Conclusions: European based studies suggest that about 1 in every 4 patients referred to hospital care for a third molar assessment may be affected by DSC and that convergent third molar impactions pose a significantly greater risk to this emerging presentation of caries.

Introduction

Retention of lower third molars has been associated with the development of distal caries in the second molar, the tooth surface immediately adjacent to the impacted wisdom tooth [1, 2]. Second molar distal surface caries (DSC) associated with a retained third molar is also known as distal caries or distal-cervical caries and has been defined as a caries process affecting the crown, cervical area (amelocemental junction), root and approximal surfaces of the distal aspect of a second molar [3, 4]. Currently the exact prevalence of this condition is unknown and the quality of evidence supporting existing prevalence data has not been previously investigated in a systematic approach [5]. Nevertheless, it is well recognized that DSC leads to poor outcomes of second molars and some commentators have expressed concern that patients suffer more harm as a result of third molar retention rather than prophylactic extraction of impacted third molars [6]. Indeed, third molar research by Ventä et al, (1993) has shown that removal of the third molar is ultimately required in the majority of patients [7].

Prevalence is one of the most commonly reported epidemiological measures and quantifies the burden of a health outcome or disease in a population at a single time point. Although prevalence of DSC in second molars has been reported in some cariology studies, there is no consistent estimate for the frequency of DSC as prevalence reported in the literature varies widely, ranging from 0% [8] to 51% [9]. A major problem of prevalence studies of this condition is that the denominator populations are differently defined, making a direct comparison very difficult thus justifying a systematic analysis of international DSC prevalence. Also, in England and Wales the third molar guidelines from the National Institute for Clinical Excellence [10]. have changed since 2000, leading to a suspected increase in DSC prevalence. A deliberate non-intervention strategy aims to retain impacted third molar in a pathologically prone state for longer. Predominantly mesio-angular and horizontally inclined third molars in the mandible form an inaccessible plaque stagnation area distally to the second molar and long-term retention is thought to significantly raise the susceptibility to DSC. This is clinically important because retention of impacted third molars may be a contributory factor to DSC and therefore will have a deleterious effect on second molars [1-5].

In the last decade, several observational studies [4, 8, 9, 11-15] have suggested an increase in DSC among patients referred to oral and maxillofacial surgery departments. The overarching aim of this study is to review the literature on prevalence of DSC in second molars when associated with an impacted third molar with the primary objective to quantify the prevalence of DSC and assess the associated risk of bias inherent in the studies using a systematic review methodology with meta-analysis. The secondary objective is to determine whether this estimate varies by factors such as population (patients attending general practice or hospital care), geographical location, demographic factors, time of study conduct, third molar characteristics as well as general dental health. This systematic review was conducted in accordance with MOOSE standards, that is the reporting of Meta- analyses of Observational Studies in Epidemiology by Stroup et al, in 2000 [16].

Material and Methods

The investigators performed a systematic review and aimed to include; prospective as well as retrospective studies designs assessing the prevalence rate of DSC in the second molar adjacent to third molars. Studies reporting the occurrence rate of distal surface caries in the second molar in populations ≥ 16 years of age who underwent a clinical and radiographic examination were included. The primary outcome was development of DSC in the second molar, identified by clinical and radiographic examination. Other variables for which data were collected were: demographics, type of population (care settings), continent of origin and time periods (publication of article) as well as third molar characteristics (angulation) and general dental health (DMFT index - Decayed Missing Filled Tooth scores). Prevalence was defined as the number of people or molars with DSC divided by the number of people or molars studied [17].

Excluded were all cariology studies that provided information of different or unspecific caries patterns, as were studies that merely described tooth material loss of adjacent molars, pathoses or resorption patterns in the second molar without reference to the distal surface of the crown, cervical area or root. In addition to this, population and subjects in the primary dentition and studies or surveys that provided the incidence without description of the methodology were excluded. Included were full text articles only.

A comprehensive literature search was conducted on the international prevalence of DSC. The succeeding keywords with wildcards and Medical Subject Headings terms were used in different combinations for our search: “molar”; “wisdom tooth”; “3rd molar”; third-molar”; “wisdom adj3 t**th”; “distal surface caries"; “distal”; “adj3 caries”; “cervical caries"; "distocervical caries"; "disto-cervical caries"; “second molar*”; “or 2nd molar*”; “second-molar*”; “adjacent molar*”; “approximal caries"; "interproximal caries"; “caries adj3 second”; ”root surface"; "decay"; “not secondary”; “incidence”; “prevalence”; “frequency”; “population”; and “proportion”. The following databases were searched from inception to June 2016: Cochrane Library, (Embase, Medline via Ovid search platform) and Lilacs. After electronic searches and the initial selection process, a supplementary hand search was conducted by tracking citations and checking the references of all identified studies as well as national third molar guideline and guidance documents. No restrictions for language or publication date were used. All references identified were compiled into a referencing manager (EndNote X7). The titles and abstracts of all articles identified through the electronic searches were screened by three contributors in duplicate and independently using the inclusion and exclusion criteria. Any disagreements were resolved by consultation until mutual agreement was reached. The University of Manchester (UK) provided the statistical analysis and the authors interpreted the results. All authors substantially contributed and revised the work for intellectual content, accuracy and ensured integrity of the research and that all inquiries were appropriately investigated and answered.

Three reviewers independently and in duplicate reviewed the included studies. Non-English articles were translated and assessed. The data from the included studies were extracted independently using a specifically designed data extraction form. Any differences were resolved by consultation with all authors until mutual agreement was reached and the study characteristics were tabulated in Word (Windows software). One author of the original report without sufficient data on the care setting was contacted by email [18].

Structured quality assessments were performed by three reviewers independently and in duplicate according to published methods designed and validated specifically for prevalence studies by Hoy et al, [19] (2012) (Table 1). This tool has two response options; namely, high and low risk of bias to each question and this has proven to result in a high inter-rater agreement [19]. This risk of bias tool comprises 10 questions/items assessing; (internal/external validity, nonresponse and measurement biases, and bias related to the data analysis) that provides an opportunity to give an overall judgment of the risk of bias of the included studies, which can be categorized as low, moderate, or high. The reviewers agreed that it would be appropriate to produce an overall summary score for each study. This was formed by giving consideration to specific key domains and was intended to complement the individual risk of bias scores. A prioritisation process was employed towards individual items within the risk assessment tool. The following criteria were used to judge the risk of bias from the quality assessment tool: criteria for judgment of high risk of bias was high risk score in items 2 or 7. Criteria for judgment of moderate risk of bias was high risk score in items 3 or 9. Criteria for judgment of low risk of bias was low risk score in items 2, 3, 7 and 9.

Table 1. Adapted tool for risk of bias assessment in prevalence studies by Hoy et al, [19] (2012)

Item	Low risk	High risk
External validity		
1) Was the study's target population a close representation of the national population in relation to relevant variables?		
2) Was the sampling frame true or a close representation of the target population?		
3) Was some form of random selection used to select the sample, OR was a census undertaken?		
4) Was the likelihood of nonresponse bias minimal?		
Internal validity		
5) Were data collected directly from the subject (as opposed to a proxy)?		
6) Was an acceptable case definition used in the study?		
7) Was the study instrument that measured the parameter of interest shown to have validity and reliability?		
8) Was the same mode of data collection used for all subjects?		
9) Was the length of the shortest prevalence period for the parameter of interest appropriate?		
(Assesses bias related to the analysis)		
10) Were the numerators(s) and denominator(s) for the parameter of interest appropriate?		

Summary assessment	Low risk	Moderate risk	High risk
11) Summary item on the overall risk of bias			

For data synthesis and heterogeneity assessment the data were imported into Version 14; Metaprop (STATA software) to calculate the pooled prevalence estimates were appropriate; 95% confidence intervals (CIs) and subtotal estimates for subgroups according to study characteristics and various angulations of the third molar, in line with the secondary objectives of the review.

The I^2 metrics and P values were used to quantify the heterogeneity across studies, Tau^2 was used to estimate between-study variance and Z values were used to test for overall effect. The random effects model was used due to between-study differences. This decision was based on statistical and clinical judgment.

Ethical approval was not necessary as this study is a review of published literature.

Results

The search initially yielded 81 records from the electronic searches and 1 from the hand searches, 2 studies were excluded because only abstracts were available. The corresponding author of one published abstract was contacted but no response was received. One study was not in print but the electronic version was available. One study was withdrawn for unknown reasons and was consequently excluded. After application of the eligibility criteria 11 articles remained. In studies that reported multiple samples, only those that met our inclusion criteria were used. Table 2 shows the excluded studies and Figure 1 illustrates the selection process [30].

Table 2. Characteristics of excluded studies

Investigator	*Reason for rejection*
Shugars et al,[20] 2004	Study assessed caries in the second molar but not specifically caries affecting the distal aspect
Shugars et al,[21] 2005	Study assessed caries in the second molar but not specifically caries affecting the distal aspect
Garaas et al,[22] 2012	Assessed caries in the second molar but not specifically caries affecting the distal aspect
Fisher et al,[23] 2012	Assessed caries in the second molar but not specifically caries affecting the distal aspect
Bozzello et al,[24] 2006	Assessed caries in the second molar but not specifically caries affecting the distal aspect
Alves et al,[25] 2014	Study assesses association between eruption stage and occlusal caries in second molars among 12-year-old schoolchildren
Ajrish et al,[26] 2015	Assessed caries in the second molar but not specifically caries affecting the distal aspect
Oderinu et al,[27] 2012	Withdrawn study
McArdle et al,[28] 2005	Case series of DSC
Nunn et al,[11] 2013	DSC incidence study
Huang et al,[29] 2014	DSC incidence study

This systematic review included 11 prevalence studies [4, 9, 13-15, 18, 31-35] Prevalence subtotals of 3 prospective [4, 9, 13] and 3 retrospective studies [18, 31, 33] are presented. The meta-analysis [4, 9, 13] is comprised of 3 studies which also provided the information and data for a subgroup analysis [4, 9, 13] of different angulation of third molars and distal surface caries. Descriptive information and characteristics of the 11 prevalence studies [4, 9, 13-15, 18, 31-35] are shown in Table 3.

Table 3. Descriptive information and characteristics of included prevalence studies (Cross-sectional studies)

First author publication year	**Country Location**	**Continent**	**Care setting**	**Study design (Single time point)**	**Age (y) Mean Range Median Mode**	**(n) Molars (n) Patients % M/F**	**DMFT Mean Range Median**	**Diagnostic criteria (method of diagnosis)**	**Prevalence of DSC (n) Molar level (n) Subject level % % Angulation**	**Risk of bias**
Knutsson et al,[13] 1996	Sweden	Europe	HC multi-center (7)	prospect	28 15-80 - -	666 Molars 666 Patients 47 M/ 53 F	-	CE DPT CE (intra-op)	29 Molars 29 Patients 4.35% mesial 55 horizontal 17.2 distal 13.8 vertical 13.8	Moderate
Chu et al,[31] 2003	China Hong Kong	Asia	HC	retrospect	- 17-89 - 20-29	3178 Molars - -	-	CE DPT	234 Molars - 7.37% -	Low
Polat et al,[32] 2008	Turkey Cumhuriyet	Asia	HC	retrospect	25.91 18-60 - -	3050 Molars 1914 Patients 43M/57 F	-	DPT	383 Molars 241 Patients 12.6% -	High
Chang et al,[33] 2009	Korea	Asia	HC	retrospect	28.3 14-75 - -	883 Molars 786 Patients 40 M/60F	-	CE DPT CE (intra-op)	152 Molars 135 Patients 17.2% -	Moderate
Allen et al,[9] 2009	United Kingdom Surrey	Europe	HC multi-center (3)	prospect	- 14-88 28 -	776 Molars 420 Patients -	- 0-27 5	CE DPT	150 Molars 113 Patients 19.3% mesial 74.7	Moderate

									horizontal 8.7 distal 3.3 vertical 13.3	
O'zec et al,[18] 2009	Turkey	Asia	-	retrospect	25.2 18-49 - -	585 Molars 485 Patients -	-	CE DPT	117 Molars 97 Patients 20% -	High
Falci et al,[14] 2012	Brazil Mucuri	South America	HC	retrospect	24.17 16-57 - -	246 Molars - 28 M/72 F	-	PA	33 Molars - 13.4% -	Moderate
Silva et al,[34] 2015	Brazil	South America	HC	retrospect	- 18-35+ - -	157 Molars 120 Patients 36 M/67 F	-	DPT	40 Molars 30.6 Patients 25.5% -	Moderate
Kang et al,[15] 2015	China Shanghai	Asia	HC	retrospect	29 16 – 59 - -	500 Molars 469 Patients 46M/ 54 F	-	CBCT	260 Molars 244 Patients 52%	Moderate
Yadav et al,[35] 2016	India Delhi	Asia	HC	prospect	- 18-55 - -	1187 Molars - 45.9 M / 54.1 F	-	DPT/PA	132 Molars - 11.12% -	High
Toedtling et al,[4] 2016	United Kingdom Manchester	Europe	HC	prospect	29 16-60 - 27	224 Molars 210 Patients 46M/54 F	6 0-28	CE DPT	85 molars 80 patients 38% mesial 70.6 horizontal 15.2 distal 2.4 vertical 11.8	Low

M/F – Male/Female, HC- Hospital care, CE- pre-operative clinical examination, CE (intra-op)- intra-operative clinical examination, DPT- Dental Panoramic Tomogram, PA- Periapical radiograph, CBCT - Cone Beam Computer Tomography

Narrative review results

Articles from 9 countries investigated 11,452 second molars and showed a prevalence of DSC ranging from 4.5% - 52%. Two studies were multicentre studies, with 3 and 7 sites respectively [9, 13]. The population assessment was at a single time in each study. In 4 studies [4, 9, 13, 35] both outcome assessment and data collection were performed at a single time point. In 7 studies [14, 15, 18, 31-34] this time point was assessed retrospectively via clinical notes and records.

Our secondary objective was to determine whether this estimate varies by factors such as population (general practice or hospital care), geographical location, demographic factors, time of study conduct, and general dental health as well as third molar characteristics. All studies were conducted in hospital care settings. Six studies were carried out in Asia [15, 18, 31-35], 3 studies in Europe [4, 9, 13] and 2 in South America [14, 34]. The earliest prevalence study [13], which also meets our inclusion criteria, was published in 1996. From 2013, 10 further studies have published prevalence data on DSC, all with a prevalence value higher than the Swedish pioneer study that was conducted in 1995.

The studies report the number and percentage of the affected participants at tooth and/or subject level, the corresponding sample size and the diagnostic criteria/criterion that measured distal surface caries. Six studies used dental panoramic tomograms (DPT) as well as clinical examination to measure the prevalence of DSC [4, 9, 13, 18, 31, 33]. Two of these 6 studies also performed an additional pre- or intra-operative examination after wisdom tooth removal [13, 33].

However, the diagnosis varied in the remaining studies and caries detection was performed on radiographs; 2 studies used extra-oral radiographs namely DPTs, [32, 34] 1 study used periapicals (PA) [14] and 1 used a combination of DPT and PAs [35] One study performed 3-dimensional scans and assessed DSC via cone beam computed tomography (CBCT) scans [15].

The overall age range was 14 – 89 years and the mean age was reported by 7 studies [4, 13-15, 18, 32, 33] and ranged from 24 - 29 years. One study reported the median age of the population to be 28 years [9], and another study reported the mode to be 27 years [4]. Three studies included a small number of patients younger than 16 years [9, 13, 33]. The impact of this was taken into account and was integrated in the risk of bias assessment. Among the 11 prevalence studies, 3 were at high risk of bias [18, 32, 35], 2 of low risk [4,31] and 6 were assessed to be at moderate risk [9, 13-15, 33, 34] (Table 4).

Table 4. Risk of bias table of individual studies

	ROB Tool Items*										
Studies	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Knutsson[13]	L	L	L	L	L	L	L	L	H	L	M
Chu[31]	H	L	L	L	L	L	L	L	L	L	L
Polate[32]	L	H	H	L	L	L	L	L	L	L	H
Chang[33]	H	L	L	L	L	L	L	L	H	L	M
Allen[9]	H	L	L	L	L	L	L	L	H	L	M
Ozec[18]	H	H	H	L	L	L	L	L	L	L	H
Falci[14]	H	L	H	L	L	L	L	H	L	L	M
Silva[34]	H	L	L	L	L	L	L	L	H	L	M
Kang[15]	H	L	H	L	L	L	L	L	H	L	M
Yadav[35]	H	L	H	L	L	L	H	L	L	L	H
Toedtling[4]	H	L	L	L	L	L	L	L	L	L	L

L – low risk, M- moderate risk, H – high risk, *2 and 7 – Pertinent items, 3 and 9 – Valuable items

Eight studies reported the number of male/female participants [4, 13-15, 32, 33-35] and all of these studies reported a greater involvement of females. A ratio of approximately 40/60 was frequently observed. Only 2 studies provided the DMFT index and DMFT range [4, 9] of the study population and the ranges were similarly wide, at 0-27 [9] and 0-28 [4]. Characteristics, such as gender, DMFT index as well as age, were either not fully reported in all studies or were reported in a way that direct comparison was not achievable, making a specific subgroup analysis of these characteristics not possible.

Our narrative review provided insight but synthesized data across studies are largely subjective in nature. These dissimilar estimates are also likely to reflect a high degree of heterogeneity among study populations. A meta-analysis by contrast can summarize the body of evidence on prevalence of DSC in a more objective way and to facilitate this we excluded studies in our meta-analysis with dissimilar outcome measures. We explicitly included studies that examined patients clinically for DSC in addition to the standard radiological examination for wisdom tooth assessment which is a DPT. After application of our selection criteria, five studies [14, 15, 32, 34, 35] were excluded.

Meta-analysis and sub-group analyses

Our meta-analysis included 3 studies [4, 9, 13] all of which provided samples for subgroup analyses. The prevalence subtotal of DSC on a molar level in our analysis was 20% (95% CI, 5% to 36%) $z = 2.57$, $p = 0.01$ in prospective studies [4, 9, 13] and 15% (95% CI, 6% to 23%) $z = 3.36$, $p = 0.01$ in retrospective studies [18, 31, 33] (Figure 2).

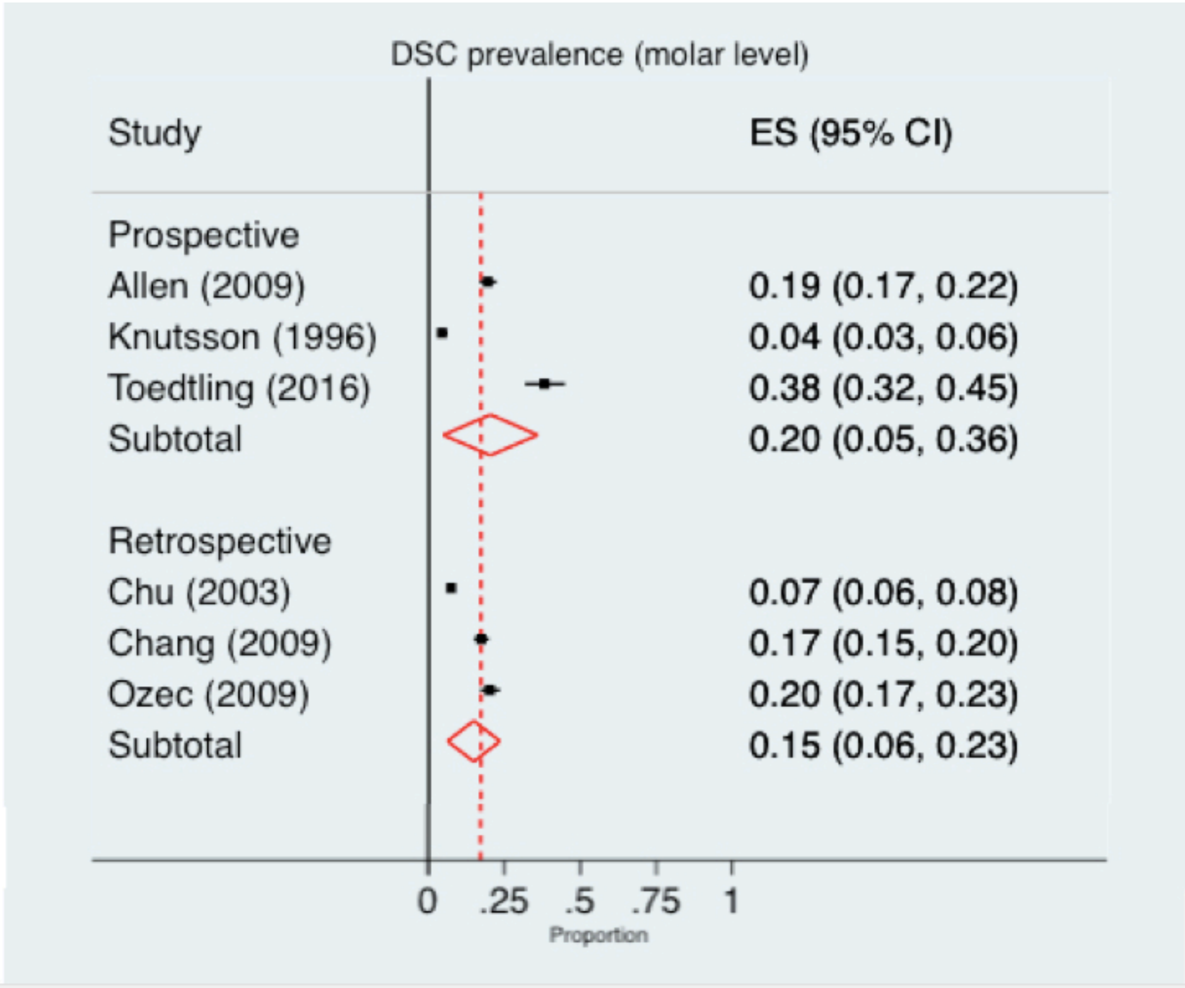

Figure 2. Analyses for DSC prevalence on a molar level in studies with prospective and retrospective study directionality of populations that received clinical and radiological (DPT) examinations and were referred from general practice to hospital care settings.

The pooled estimate according to the prospective study [4, 9, 13] design and prevalence on a patient level is presented in Figure 3 and was 23% (95% CI, 2% to 44%) and the heterogeneity across and between groups as well as the significance information of the subgroup was as follows; I^2 = 98.88%, Tau^2 = 0.03, z = 2.16, p = 0.03.In the subgroup analyses [4, 9, 13] we present subtotals of DSC prevalence among mesially (36%; 95% CI, 5% to 67%) z = 2.26, p = 0.02 and horizontally (22%; 95% CI, 1% to 42%) z = 2.03, p = 0.04 inclined third molars which were significantly higher than that of distally (3%; 95% CI, 1% to 5%) z = 3.20, p = 0.01 and vertically inclined third molars (7%; 95% CI, 1% to 13%) z = 2.38, p = 0.04 (Figure 4). The test of heterogeneity between subgroups was identified as I^2 = 96.55%.

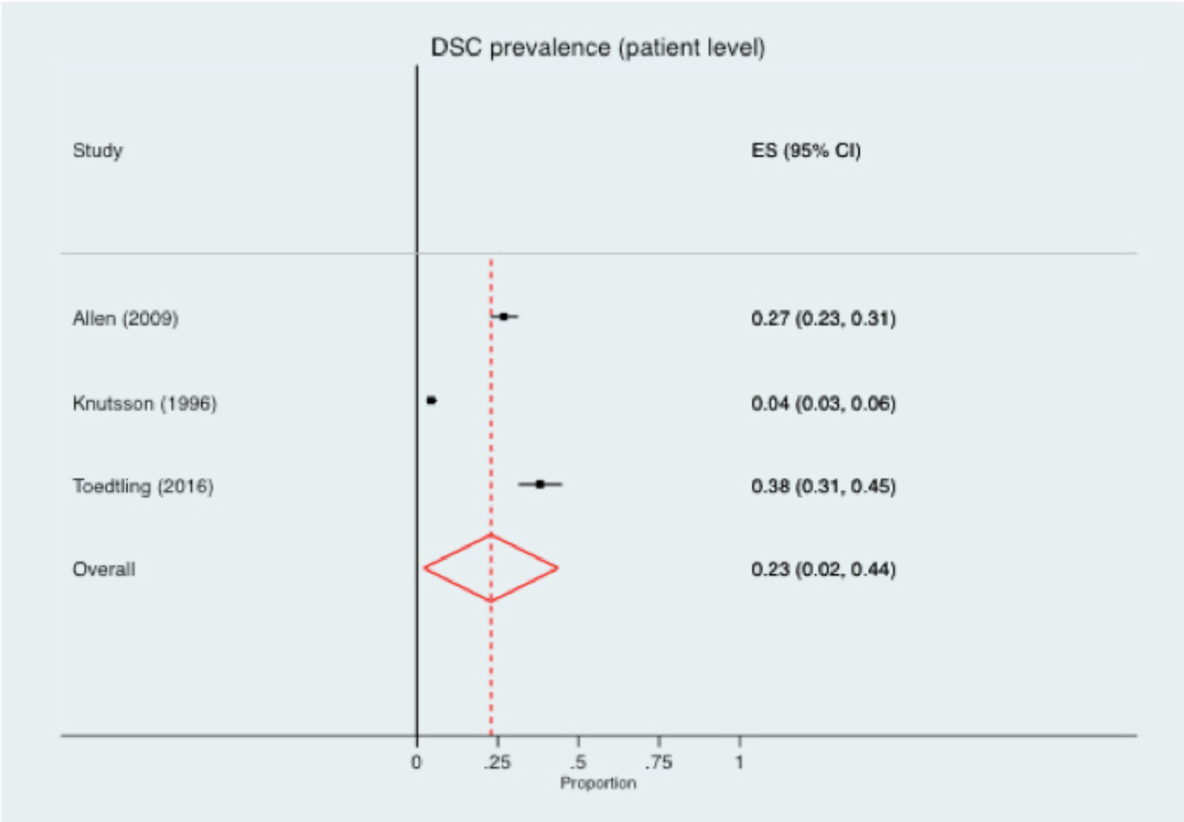

Figure 3. Meta-analysis for DSC prevalence on a patient level in studies with Prospective study directionality of populations that received clinical and radiological (DPT) examinations and were referred from general practice to hospital care settings.

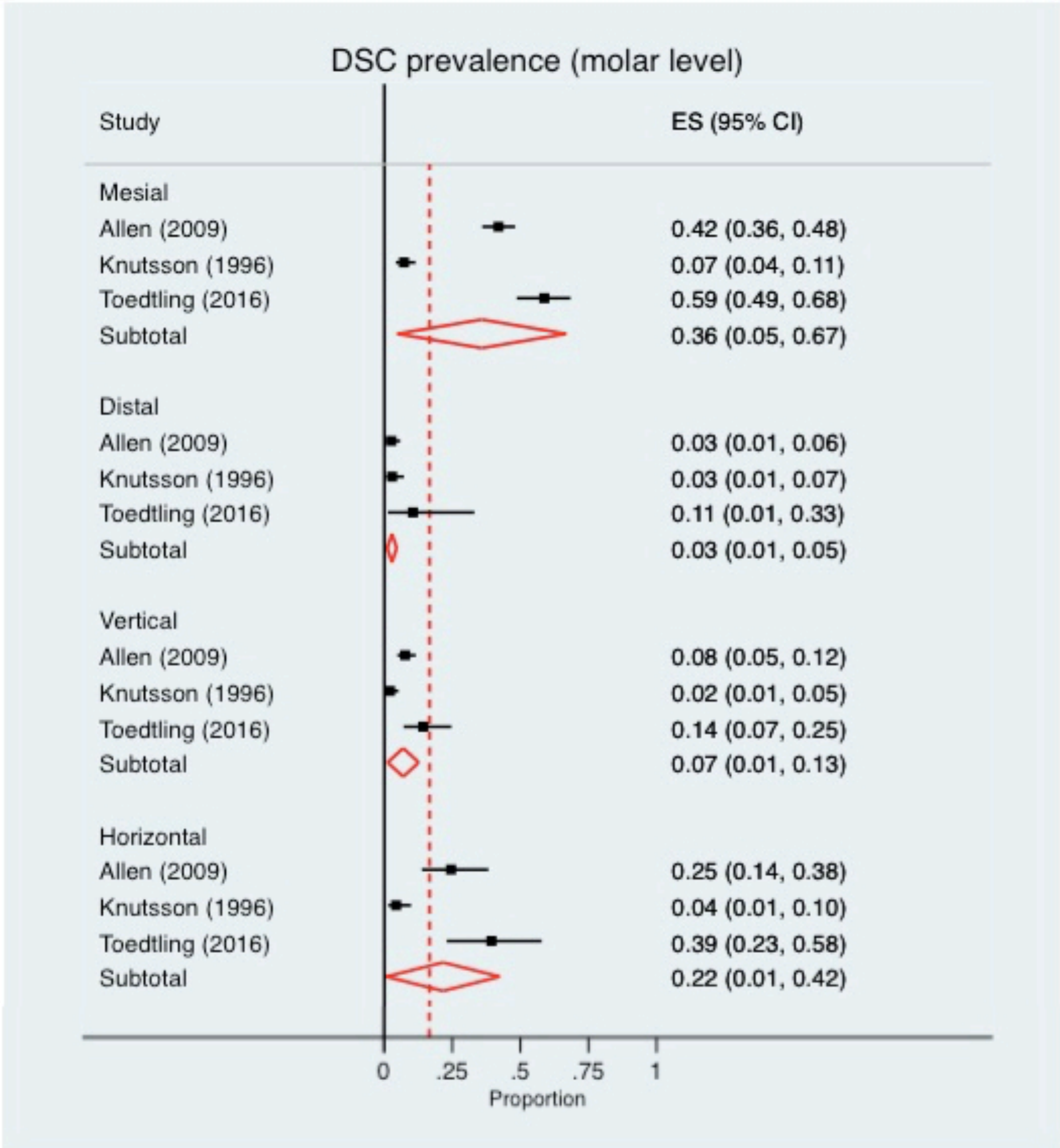

Figure 4. Subgroup analysis for DSC on a molar level in various third molar angulations

DSC is a globally emerging caries pattern that has been reported in three continents namely, Asia, Europe and South America. Our analysis showed that European- based studies suggest that up to (20%) of third molar assessment referrals and 23% of patients who are referred from general practice to hospital sectors for a third molar assessment are affected by DSC in the second molar. Moreover, DSC prevalence values for mesial and horizontal angulations were significantly higher than that for distal and vertical third molar angulations. However wide CIs were noticeable which suggests either that lack of precision is a problem indicating that further studies are needed or this could be a result of inherent variation due to differences in denominator populations.

Discussion

The purpose of this research was to assess the prevalence of DSC in second molars associated with retained third molars by conducting a systematic review with meta-analysis of observational studies. Prior to this review the literature suggested that third molar retention results in harm to the second molar but the precise variables, which cause an increase in risk of DSC, have not been adequately described. We believe that the provision of this epidemiological data is a necessary first step in understanding the extent of the problem and this meta-analysis provides insight into the epidemiological footprint of DSC in the second molars of patients referred to hospital services for third molar assessments. All included studies were performed in a hospital setting thus this analysis does not provide a general population based prevalence of DSC but merely the prevalence of DSC amongst third molars and patients referred for an assessment, which is an important limitation of this review. However, our narrative results showed that DSC is a global phenomenon that has been measured with an assortment of radiographic investigations. Meta- and subgroup analyses were performed of those studies with similar and comparable characteristics. We excluded all studies from our analyses that did not perform a clinical examination in conjunction with a standardized DPT for third molar assessment. The meta-analysis showed that the prevalence of DSC was pooled at 23% in the 3 prospective studies on a patient level. This revealed that DSC affects about 1 in every 4 referred patients. However, it is worthwhile pointing out that the confidence intervals were wide and have an upper limit of 44% and lower limit of 2%, which suggests imprecision. In addition to this we detected considerable heterogeneity and suggest that this is caused by a number of factors which are linked to differences in practice of third molar removal across various countries by different hospitals teams with different clinical approaches. To take the uncertainty of the precision of the combined prevalence estimate into consideration a random-effects analysis was performed.

A subtotal of DSC on a molar level is also presented and shows a DSC prevalence of 20% in prospective studies and 15% in retrospective studies respectively.

Additionally, we found that significance testing shows that the null hypothesis can be rejected and we can accept that there is a significantly higher prevalence rate of DSC in mesial (36%) and horizontal (22%) impactions compared to vertical (7%) and distal (3%) impactions.

Nevertheless, this overall prevalence rate is a product of current and past clinical practice namely, symptomatic and asymptomatic or pathology free removal of third molars and thus reflects both approaches to management of retained third molars. Specifically, the study by Knuttson et al, 1996 [13] reported on DSC prevalence when prophylactic third molar removal was performed whereas both UK based studies, Allen et al, 2009 [9] and Toedtling et al, 2016 [4] reported a DSC prevalence when national guidelines dictated that third molar removal was performed only on wisdom teeth with associated pathology. This may also provide an explanation for the large difference in DSC prevalence and supports current thinking on third molar retention and harm.

The limitations of this meta-analysis includes considerable heterogeneity and overall a medium quality of the included studies. As described previously, the study sample is comprised of patients that attended hospital care settings and therefore is not representative of the general population. Likewise, there are also notable background differences in the structure of global publicly funded healthcare systems and insurance-based remuneration systems. Variations in educational structures and availability of resources, such as clinical guidance or guidelines, may have also influenced our DSC prevalence estimates. Industrialized countries with national health services or insurance schemes have different remuneration systems ranging from fee-for-service to a capitation pay approach. Different remuneration systems produce different incentives which influence clinicians' behaviour [36] with regard to third molar retention and removal. Similarly, the base populations in terms of third molar agenesis and impaction rates differ between diverse global populations [37]. Therefore the need and demand for the supply of third molar removal, a factor that is thought to be associated with a reduced DSC prevalence, is subject to large variation around the globe.

Moreover, there was a level of inconsistency, in the diagnostic criteria for DSC. Some studies reported clinical examinations at various stages of pre- and post- third molar removal and these clinical findings were correlated with a variety of radiographic images. Most commonly, dental panoramic tomograms, were used, as these are the radiographic investigation of choice for third molar assessments according to the European Commission Radiation Protection guidelines (2004) [38] thus were selected as inclusion criteria for our meta-analysis. However, there are problems of poor sensitivity associated with diagnosing caries using panoramic radiographs [38]. This may actually under-estimate the prevalence figures for caries diagnosis and lesion progression.

Possible sources of bias in the meta-analysis were assessed according to our prioritization process of a risk of bias tool published by Hoy et al, [19] (2012). We classified items (1), (4), (5), (6), (8) and (10) as less pertinent domain, items (3) and (9) as valuable domain and items (2) and (7) as pertinent domain. Our reasoning was that all items in the less pertinent domain were either already part of our study's exclusion criteria or had no direct application. Whereas, studies with risk of bias in the items in the valuable domain have direct implications for the analyses and the potential to introduce selection bias or reduce the internal validity, thus we could over- or underestimate the results. Items in the pertinent domain were signposted as most important: these items therefore received the greatest weighting. Studies at risk of bias in this domain could affect the external validity and reliability of the meta-analysis and reduce the extent to which the results can be extrapolated.

With regard to subgroup analyses, pooled prevalence estimates for DMFT, gender and age were not obtained due to significant population diversity, insufficient information and because not all studies reported the same summary statistics. Although each study reported a completely reasonable approach, yet a combination was not indicated and was thought to be primarily due to differences in investigator focus and study perspective. With respect to possible publication bias, we planned a statistical assessment with a funnel plot; however, the number of included studies was too low to permit this test. Also, a sensitivity analysis is generally of benefit but was not possible as only a small number of studies fitted our inclusion criteria. Nonetheless, we believe that our selection process was rigorous, we addressed specific sources of bias and excluded low quality and high risk of bias studies, therefore, we feel that this study represents the best estimates of DSC prevalence possible with the available data.

Indications for the removal of impacted wisdom teeth have been a global controversy for many years and NICE provided guidance on wisdom tooth surgery specifically for England and Wales [10]. Internationally, clinical practice in many countries has been strongly influenced by the evidence that supported the recommendations provided by NICE's (first ever technology appraisal) TA1. The proof of this is documented in international guideline and guidance documents as reference is made to the TA1 with an explanation of formal alignment [39-42], which means that their standards are based on very limited evidence. NICE clearly states that they had 'no' research evidence to support their recommendations [10, 11]. It seems that the status afforded to NICE (on their wisdom tooth guidance) by international guideline makers is extremely high but based on weak evidence. Understandably, the recommendations by NICE guidance has been challenged in some nations including the US and as a result has not been universally adopted [43-47].

At present the aetiology of DSC is still unknown; however, statistically significant associations have been demonstrated with mesial and horizontally impacted third molars [4, 9]. These subgroup analyses, based on this sample and integrated approach provided a conclusion that mesial and horizontal inclined third molars, when combined, show an almost six times greater prevalence of DSC than distal and vertical inclinations combined. These findings are consistent with previous research on third molars as well as clinical suspicion and observations over many years by practitioners [6]. However, given the possible risk and costs of both DSC and prophylactic removal we need to conduct high quality trials in different populations to inform international guidelines.

Conclusion

The present systematic review has revealed that DSC in the mandibular second molar is a common and globally emerging oral condition. It affects an increasing number of patients and its distinct caries pattern has become a common observation in hospital care settings. Identified are some of the clinical determinants for DSC and third molar angulations; especially, mesial and horizontal impactions appear to be significant risk factors. Ultimately, to increase the precision of DSC prevalence and to find answers to all our secondary objectives, larger well-reported observational studies need to be conducted but research dollars would perhaps be spent better by funding interventional studies which decide on how to manage impacted third molars and their consequences.

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Conflict of Interest

None of the authors have any conflict of interest

Ethics statement/confirmation of patient permission

Ethics approval not required as this manuscript is a systematic review of already published literature. Patient permission N/A

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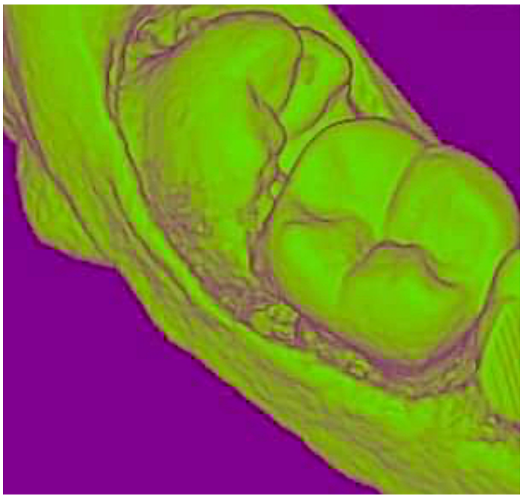

Chapter 4

Systematic Review

A systematic review of second molar distal surface caries incidence in the context of third molar absence and emergence

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ABSTRACT

Objective: The aim of this systematic review was to gain a greater insight into the incidence rates of distal surface caries (DSC) on second permanent molars.

Data-sources: A literature search using the Cochrane Library, Lilacs, Embase and Medline via Ovid retrieved English and non-English language articles from inception to June 2016. The electronic searches were supplemented with reference searching and citation tracking. Reviewers independently and in duplicate performed data extraction and completed structured quality assessments using a validated risk of bias tool for observational studies and categorized the summary scores.

Data-selection: The search yielded 81 records and after application of inclusion and exclusion criteria, 2 incidence studies were included in this systematic review.

Data-extraction: The DSC incidence was reported in 1 study as relative risk (RR = 2.53; 95% CI, 1.55 to 4.14) adjacent to erupted, (RR = 0.83; 95% CI, 0.11 to 6.04) soft tissue impacted and (RR = 1.44; 95% CI, 0.55 to 3.72) bony impacted third molars in comparison to when the third molar was absent with a 25-year follow-up. The second study reported a DSC incidence of 100 surface-years (1% of all sites) with an 18-month follow-up period.

Conclusions: Both cohort studies indicated that DSC incidence was higher when third molars were erupted in the intermediate term, but greater over the long term for an aging male population. However, further high quality research is required to improve the accuracy of these findings.

Key words: Wisdom teeth; Third molar; Caries; Distal surface caries; Second molar; Incidence; Epidemiology

Introduction

Distal surface caries (DSC) in the second molar is a phenomenon that is associated with impacted third molars [1]. Whilst the aetiology of dental caries is well understood and extensively documented, the cause of DSC is believed to have an additional dimension; therefore, reliable data on its incidence would be particularly interesting and may inform the mechanism and natural history of the disease's progression. Second molar DSC associated with a retained third molar is also known widely as distal caries and is defined as a carious process affecting any portion of the distal aspect of a second molar including the distal-cervical region [2]. Distal-cervical caries (DCC) is thought to be specific to the mesio-angular and horizontally impacted mandibular third molar [3]. This review concerns the entire distal surface of the second molar because in the authors' opinion the exact location of where a carious lesion originates is frequently undeterminable from radiographic or oral examinations, especially on late presentation, and precise development of the carious lesions are usually unreported in the patients' records.

Incidence in epidemiological terms is a measure of the probability of occurrence of a given condition in a population within a specified period of time. Although sometimes loosely expressed as the "number of new cases" during a given time period, it is more appropriate for it to be defined as a proportion or a rate with a denominator within a defined time period. Currently, the precise international incidence of DSC is undetermined and the quality of evidence supporting the incidence data has not been formerly combined and assessed in a systematic approach [4]. Frequency statistics also play a role in health care planning and epidemiological research as they provide fundamental knowledge for decision-making and assess the burden of DSC within a population.

In the last decade several authors of scientific papers suggested an increase in the emergence of DSC among patients in various populations [5-7]. The overarching aim of this study is to review the literature on DSC incidence in second molars when associated with a third molar, with the primary objective to quantify the incidence specifically of DSC and assess the associated risk of bias inherent in the studies using a systematic review methodology. The secondary objective is to determine whether variations in incidence by time, place, population (primary or secondary care settings) and gender can provide clues to possible environmental risk factors for the disease.

Material and Methods

The investigators performed a systematic review and aimed to include experimental and prospective as well as retrospective observational study designs, assessing the incidence of DSC in the second molar adjacent to third molars. Studies reporting the occurrence rate of distal surface caries in the second molar in populations of 16 years of age or over who underwent a clinical and radiographic examination were included. The primary outcome was development of DSC in the second molar, identified by clinical or radiographic examination. Other variables for which data were planned to be collected were: demographics, type of population (care settings), continent of origin and time periods as well as third molar characteristics.

Incidence was defined as the number of new cases that have occurred in a distinct period of time. This has been calculated by using the following equation: number of people/molars that developed DSC in a specific time period divided by the number of people/molars at risk of developing DSC at the start of the time period [8].

Data-sources

A comprehensive literature search was conducted on the international incidence of DSC**.** A librarian from the University of Manchester reviewed the search strategy proposed by the authors. The succeeding keywords with wildcards and Medical Subject Headings terms were used in different combinations for our search: “molar”; “wisdom tooth”; “3rd molar”; third-molar”; “wisdom adj3 t**th”; “distal surface caries"; “distal”; “adj3 caries”; “cervical caries"; "distocervical caries"; "disto-cervical caries"; “second molar*”; “or 2nd molar*”; “second-molar*”; “adjacent molar*”; “approximal caries"; "interproximal caries"; “caries adj3 second”; ”root surface"; "decay"; “not secondary”; “incidence”; “prevalence”; “frequency”; “population”; and “proportion”. The following databases were searched from inception to June 2016: Cochrane Library, (Embase, Medline via Ovid search platform) and Lilacs which covers Latin American literature. After electronic searches and the initial selection process, a supplementary hand search was conducted by tracking citations and checking the references of all identified studies as well as relevant clinical guidance documents. No restrictions regarding language or publication date were used. All references identified were compiled into a referencing manager (EndNote X7). The titles and abstracts of all articles identified through the electronic searches were screened by 3 reviewers in duplicate and independently using the inclusion and exclusion criteria.

Excluded were all cariology studies that provided information of different or unspecific decay patterns, as were studies that merely described tooth material loss of adjacent molars, pathologies or resorption patterns in the second molar without reference to the distal surface of the crown, including the cervical area or root. In addition to this, population and subjects in the primary dentition and articles or surveys that provided the incidence without description of the methodology were excluded, as were cross-sectional studies that reported on DSC prevalence (Table 1).

Non-English articles were translated and assessed. The data from the included studies were extracted and any differences were resolved by consultation with all authors until mutual agreement was reached and the study characteristics were tabulated in Word (Windows software).

Structured quality assessments were performed according to published methods designed and validated by Hoy *et al.* [9] (2012).

Data-selection

The search initially yielded 81 records (Figure 1) from the electronic searches and no further articles could be identified from the hand searches. Nineteen duplicates were removed and 40 abstracts were read and subsequently excluded. A total of 20 studies were fully assessed and excluded with stated reasons [10-29], of which 1 study was withdrawn [23] and was consequently also excluded. However, after application of the eligibility criteria 2 articles remained. Of the studies, that reported multiple second molar pathologies, only those that met our inclusion criteria were assessed [30, 31]. Table 1 illustrates the excluded studies and Figure 1 demonstrates the selection process.

Table 1 Characteristics of excluded studies

Investigator	***Reason for rejection***
Knutsson *et al.*[10], (1996)	Prevalence study
Chu *et al.*[11], (2003)	Prevalence study
Shugars *et al.*[12], (2004)	Study assessed caries in the second molar but not specifically caries affecting the distal aspect
McArdle *et al.*[13], (2005)	Case series of DSC
Shugars *et al.*[14], (2005)	Study assessed caries in the second molar but not specifically caries affecting the distal aspect
Bozatello *et al.*[15], (2006)	Assessed caries in the second molar but not specifically caries affecting the distal aspect
Polat *et al.*[16], (2008)	Prevalence study
Allen *et al.*[17], (2009)	Prevalence study
Chang *et al.*[18], (2009)	Prevalence study
O'zec *et al.*[19], (2009)	Prevalence study
Falci *et al.*[20], (2012)	Prevalence study
Fisher *et al.*[21], (2012)	Assessed caries in the second molar but not specifically caries affecting the distal aspect
Garaas *et al.*[22], (2012)	Assessed caries in the second molar but not specifically caries affecting the distal aspect
Oderinu *et al.*[23], (2012)	Withdrawn study
Ajrish *et al.*[24], (2015)	Assessed incidence caries in the second molar but not specifically caries affecting the distal aspect
Alves *et al.*[25], (2014)	Study assesses association between eruption stage and occlusal caries in second molars among 12-year old schoolchildren
Kang *et al.*[26], (2015)	Prevalence study
Silva *et al.*[27], (2015)	Prevalence study
Toedtling *et al.*[28], (2016)	Prevalence study
Yadav *et al.*[29], (2016)	Prevalence study

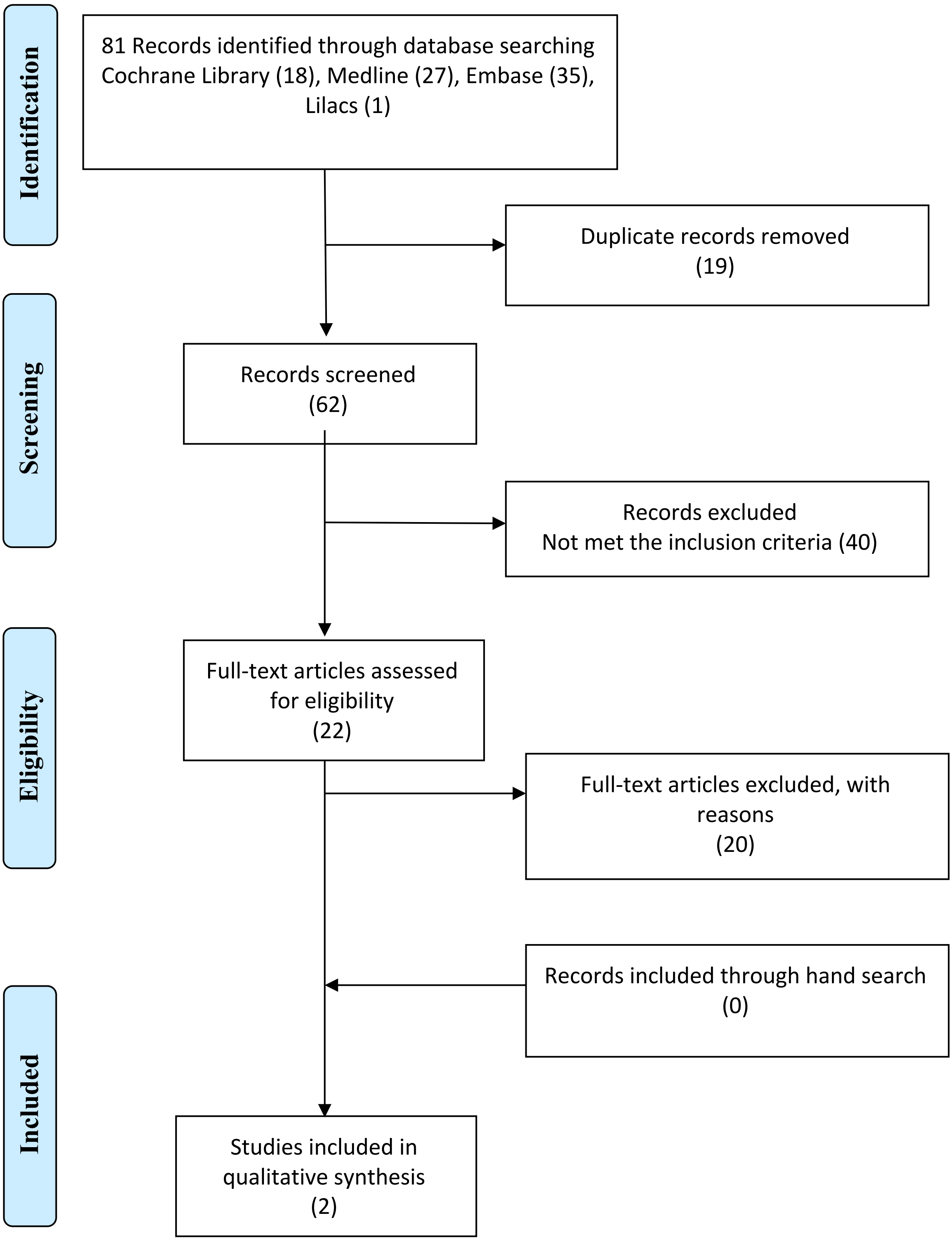

Figure 1 PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) flow diagram of the study selection process. Source: PRISMA-P[32] (2005)

Data-extraction

The incidence analysis included 2 studies [30, 31] (Table 2), both of which took place in a general practice setting and were conducted in North America. Whilst the study by Huang *et al*. [30] 2014 was initiated in Greater Boston with a sample size of 416, the other study by Nunn *et al.* [31] 2013 was conducted in the Pacific Northwest with 218 patients. Both were prospective cohort studies, investigating DSC in the second molar adjacent to absent verses retained third molars. The selected study populations appeared very heterogeneous in the study by Nunn *et al.* as only male volunteers with an age range of 25 to 84 years were enrolled with asymptomatic third molars, and the study by Huang *et al*. assessed a very young population cohort aged 16 to 22 years with symptomatic and asymptomatic third molars. However, both studied populations mainly had private dental care insurance and assessed patients longitudinally, reporting on the natural history of DSC in the intermediate and long term. Nunn *et al.'s* follow up was 25 years and Huang *et al.'s* participants were followed up for 18 months. The diagnostic criteria included a clinical examination and a combination of dental panoramic tomograms (DPT) and full mouth periapical radiographs (PA) in Nunn *et al.'s* study and although the Huang *et al.*'s study lacked detail on the diagnostic criteria used, the methodology was described in a companion article clarifying that radiographs were used but specific views were not described [3].

Table 2 Descriptive information and characteristics of included incidence studies (Cohort studies)

First author Year	Country Location	Continent	Care setting	Study direction	Population selection criteria	Absent or Removed	Erupted, Unerupted, Impacted or Retained	Dx Criteria	Incidence of DSC	Incidence period	Risk of bias
Huang *et al.*[30], (2014)	USA N/W Pacific	North America	GP	prospect	218 patients aged 16-22, majority with private dental insurance Inclusion: Symptomatic and asymptomatic third molars, one third molar present and never undergone third molar removal	1 case (removal group) 0.2 surfaces per 100 susceptible second molar distal surfaces Person-Years (95% CI) 0.0–1.4 Total Person-Years 528	4 cases (retention group) 0.6 surfaces per 100 susceptible second molar distal surfaces Person-Years (95% CI) 0.2–1.5 Total Person-Years 678	CE RA	Cross-sectional analysis: 6% Longitudinal analysis: (Incidence of DSC per 100 surface-years) <1% of all sites	18 month follow up	High
Nunn *et al.*[31], (2013)	USA Greater Boston	North America	GP	prospect	416 male volunteers (804 molars) Veterans Affairs Dental study aged 25-84 with private dental care insurance Inclusion: Asymptomatic third molars, first and second molars present in at least 1 quadrant and at least 1 follow up exam	Absent (Mn 207 + Mx 253) 460 tooth level	Present (Mn 165 + Mx 179) 344 tooth level	CE DPT and full mouth PAs	Cross-sectional analysis: OR = 1.73 Longitudinal analysis: RR = 2.53 (95% CI 1.55, 4.14)	Study began 1969 25 years	High

GP- General Practice, RA- Radiographic examination (imaging not specified), CE- Clinical examination, DPT- Dental Panoramic Tomogram, PAs- Periapical radiographs Mx – Maxilla, Mn - Mandibular

Both studies reported the affected participants at subject level and the corresponding sample size. The DSC incidence was reported as relative risk in the Veterans Affairs Dental Study initiated in 1969 by Nunn *et al*. (risk ratio – probability of DSC occurring) (RR = 2.53; 95% CI, 1.55 to 4.14) adjacent to erupted, (RR = 0.83; 95% CI, 0.11 to 6.04) soft tissue impacted and (RR = 1.44; 95% CI, 0.55 to 3.72) soft bony impacted third molars when 416 patients with 804 molars were identified and examined every 3 years clinically and radiologically for 25 years, in comparison to the Huang *et al.'s* study in which incidence was reported per 100 surface-years (1% of all sites). Four hundred participants were enrolled for 18 months, 182 participants were lost and 218 (55%) underwent the final exam. DSC occurred at an annual rate of 0.2 surfaces per 100 susceptible second molar distal surfaces, which occurred in 1 case when third molars were removed and 4 cases when third molars were retained. Indeed, it is worthwhile acknowledging that the Huang *et al.'s* cohort study had a follow up of around 18 months. At the beginning of the two studies, 6% of participants [30]. had DSC in Huang *et al.'s* study and the longitudinal study by Nunn *et al*. reported a DSC odds ratio of 1.73 at the cross-sectional analysis [31].

Both cohorts were assessed as high risk of bias according to Hoy *et al.*'s [9] (2012) quality assessment tool (Table 3) and our summary assessment. Due to the clinical and methodological diversity, a pooled overall meta-analysis of new DSC cases could not be performed because both studies had very different methods and data interpretation. The lack of comparable incidence studies and research in this field means that fewer inferences can be made about time trends, geographic and population differences as well as third molar characteristics and demographics. Nevertheless, our narrative analysis provides some insight into the subject and allowed as to interpret data across studies, provide conclusions and present recommendations for further research.

Table 3 Risk of bias table of individual cohort studies

	ROB Tool Items										
Studies	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**
Huang *et al.*[30], (2014)	H	L	L	H	L	L	H	H	H	L	H
Nunn *et al.*[31], (2013)	H	H	H	H	L	L	L	L	L	L	H

L – low risk, H – high risk

Discussion

The purpose of this research was to assess the incidence of DSC in second permanent molars by conducting a systematic review. The literature suggests that third molar retention results in harm to the adjacent second molar [33], but currently neither the precise mechanisms leading to DSC nor the incidence is known or has been described in a systematic integral approach. We believe that the provision of this epidemiological data is a necessary first step to gain an understanding of the extent of the problem. Moreover, our objective was to review and analyze the literature on incidence with a secondary objective to determine whether this estimate varies by factors such as population, geographical location, demographic factors, era, third molar characteristics as well as general dental health.

This systematic review provides insight into the longitudinal epidemiology of DSC in the second molars of an insured population in primary care in North America. Both cohort studies reported a greater risk of DSC incidence in the second molar in the presence of an adjacent third molar, in contrast to when the third molar was absent or removed. However, the incidence was reported in fewer than 1% of sites in a young adult to adolescent cohort, which was followed up for 18 months and affected 1 case in the removal group and 4 cases in the retention group. Nonetheless, a larger longitudinal study reported a relative risk ratio of 2.53 (95% CI, 1.55 to 4.14) which means that those who had an erupted third molar were at 153% greater risk of acquiring DSC in comparison to patients with absent third molars. No further detail was provided whether this category exclusively included third molars that had erupted into a normal functional position or erupted third molars that had developed in an abnormal position or angulation. More detail was provided on soft tissue impacted third

molars (which included all soft tissue impacted third molars and partial bone impacted third molars). The latter was defined as those molars with radiographic evidence of less than two-thirds bony coverage of the coronal aspect of the third molar). Soft tissue impacted 3rd molars had a caries risk ratio of 0.83 (95% CI, 0.11 to 6.04) and bony impacted third molars (which included third molars with radiographic evidence of at least two-thirds of the bony coverage of the coronal aspect) had a risk ratio of 1.44 (95% CI, 0.55 to 3.72) DSC in comparison to patients with absent third molars. The later two categories were considered together as unerupted third molars in the paper by Nunn however, the relative risk of caries was reported for each subcategory.
The classification system used for impaction lacks clarity in the Nunn study. It is subjective as it uses a two-thirds crown coverage threshold for bony coverage but the true radiographic coverage of bone may be difficult to determine in the absence of 3D imaging. Therefore, any classification system used that tries to distinguish between true soft and hard tissue impactions can be unreliable. Additionally, both categories are highly likely to include unerutped or partially emerged third molars.

The Huang study reported the incidence of DSC in the second molar as extremely low in a young population with a relatively short follow-up period independent of whether third molars are present or removed, and Nunn's study suggests that retention of third molars is associated with an increased risk of second molar DSC in middle-aged and older male patients with erupted third molars when followed up for 25 years.

To our knowledge, this is the first systematic review to be published on the incidence of DSC in the second molar adjacent to a third molar, and in light of this no comparisons could be made with other systematic reviews in this field. The cohort studies aimed to investigate associations between various risk factors and the outcome of interest (DSC), and the study design is further strengthened by the fact that it tells the story of the sequence of events leading up to a defined clinical problem. In addition, systematic reviews have specific advantages because they follow an explicit method, highlighting biases to signpost validity, reliability and generalizability. Further, the incidence rates were derived from cohort studies with intermediate and long-term clinical observation periods. Nonetheless, this systematic review has several important limitations including considerable diversity amongst the study population characteristics. The study designs included in the review were assessed to be at high risk of bias - therefore the incidence rates should be viewed with some caution. As described previously, the study sample of the study by Nunn *et al*. was composed of only male patients and the other study included participants with an uncharacteristic age for the occurrence of DSC. This is likely to underestimate the incidence of DSC, as DSC is thought to peak around the third decade of life [13, 5], and woman present more commonly than men [17]. Both studies were conducted in primary care settings, but in the light of the likely underestimation of DSC it may not be representative of the general population. The majority of patients were privately insured which would mean this data cannot readily be extrapolated to patients in the US without insurance or those treated around the globe in publicly funded health care systems, or to nations where clinical third molar guidance or guidelines that recommend different indications for third molar removal. Similarly**,** the need and supply for third molar removal will be distinctly different in states like the US in comparison to countries that have an unmet need [34]. There was also a level of inconsistency, in the diagnostic criteria for DSC. One study reported clinical examinations at various stages and these clinical findings were correlated with radiographic images, while the other study reported non-specified radiographic views. The problem is that poor sensitivity is associated with the diagnosis of dental caries when non-standardized radiographs are used and this may considerably underrate the incidence figures of DSC and lesion progression [35].

Since the patient's baseline third molar status could be viewed as a cross-sectional snapshot and DSC prevalence in these study populations were reported as 6% [30] and an odds ratio of 1.73 (95% CI, 1.23 to 2.43) [31] respectively. In both cohort studies, the prevalence values are greater in relation to the reported DSC incidence rates and this shows that there is a larger proportion of existing DSC cases in comparison to the number of new cases. This implies that DSC is a chronic condition and an associated long-term consequence of third molar retention. These findings are consistent with previous research on DSC in second molars associated with retained third molars as well as clinical suspicion by practitioners over many years [5,6,36]. Although at present the precise aetiology of DSC is still unknown, strong associations have been established. These suggest, that the retention of third molars especially when impacted over a long period of time is a risk factor for DSC and is likely to result in harm to the second molar. None of the papers included data on the type of angulation or what effect the angulation of the third molar has on the caries incidence rate of DSC in second molar teeth.

In the presence of an adjacent third molar, plaque may be can be undisturbed in the approximal area, which is often inaccessible to cleaning devices. This is especially so in convergent (mesial and horizontal) third molar angulations and impactions below the contact point. This is when the mesial cusp of the impacted third molar contacts inferiorly to the amelocemental junction or the most bulbous part of the adjacent second molar crown.

Systematic reviews can only report what is present in the literature. The value of a systematic review is to provide a high-quality summary of current knowledge, in this case, on the incidence of distal surface caries in the second molar on what the peer-reviewed literature tells. Ultimately, the value of this paper is to highlight this emerging issue, point out that published research conducted on this topic is very limited thereby highlighting an urgent need for well-funded high quality studies

Additionally, this review provides the opportunity to highlight important shortcomings of current studies such as the inclusion of a very young cohort of patients. Furthermore, the paper provides assistance for researchers in the filed in that a published, well-conducted systematic review is fundamental for future grant application and can aid and inform the design of future studies.

Conclusion

This review highlights the difficulty in performing high quality incidence studies of DSC associated with impacted third molars and has shown that few high quality studies exist. The limited literature suggests that incidence of DSC in second molars is higher in the presence of a third molar and DSC has become a frequent indication for third molar removal. Ultimately to better determine the incidence of DSC in second molars further longitudinal observational studies in a variety of populations, with well described clinical and socio-demographic characteristics of the population lengthy follow-up times and an indications of participants' caries risk will lead to a better understanding of incidence and the factors which increase the risk of DSC.

Declaration of Interests

The authors have no competing interest to declare

All authors have viewed and agreed to the submission

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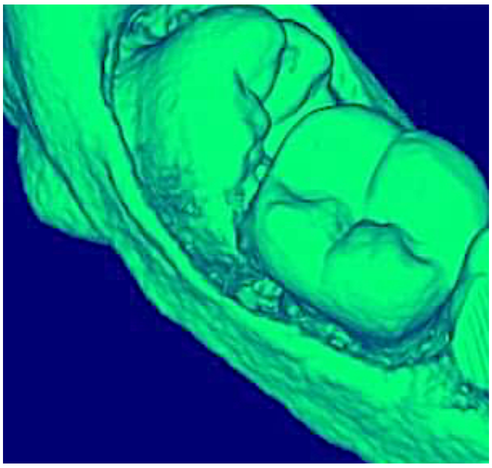
Chapter 5



Original Research – Laboratory

Distinct Microbiome Profiles in Convergent Wisdom Tooth Impactions

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Chapter of thesis is a modified version of the publication

ABSTRACT

Aims: Long-term retention of impacted third molars (wisdom teeth) is associated with plaque stagnation and the development of caries on the distal surfaces of the neighbouring mandibular second molar. Whilst caries and tooth loss are common outcomes of impaction, there is not currently enough evidence to advise pre-emptive removal of asymptomatic wisdom teeth. Emerging evidence suggests that convergently growing impactions are more associated with caries. We have therefore investigated the composition of dental plaque on the distal surface of the mandibular second molar.

Methods and Results: Using short read sequencing of the bacterial 16S rRNA gene, we compared the microbiome of these surfaces at four impaction angulations: two convergent (horizontal and mesial) and two divergent (distal and vertical) angulations, and where the wisdom tooth is missing. Analysis of alpha and beta diversity showed that horizontal angulations had distinct, lower community diversity than mesial impactions. Amplicon Sequence Variants (ASVs) associated with *Veillonella* were significantly more abundant at angulations with convergent directions of growth. Within convergent groups, *Veillonella* ASVs were also found to be more abundant in horizontal impactions. Using machine learning, distinct microbiome profiles, which included a high abundance of *Veillonella*-associated ASVs, were used to inform the prediction of original angulations for a small set of samples, with the two convergent impactions estimated with the greatest accuracy.

Conclusions: We found distinct differences in diversity between caries-associated convergent (horizontal and mesial) impacted wisdom teeth, as well as greater abundances of *Veillonella* ASVs at horizontal impactions. High levels of *Veillonella* ASVs detected in convergent impactions could indicate that its presence, alongside *Streptococcus*, increases cariogenic risk.

Significance and impact of study: Distal surface caries is more prevalent in convergent impactions, and *Veillonella* is found at higher abundance in caries-active patients. Here, detection of *Veillonella* at increased abundance in convergent impactions, and distinctive profiles at horizontal impactions, may partly elucidate associations of convergent angles with distal surface caries.

Introduction

Tooth decay (caries) is caused by the fermentation of carbohydrates by microorganisms in dental plaque. *Streptococcus mutans, Streptococcus sobrinus,* and *Lactobacillus* spp., for example, produce fermentation acids which de-mineralize calcium phosphate in tooth enamel [1-4]. Without intervention, this process can lead to cavitation and tooth loss [5].

Distinct microbiota compositions have been associated with active caries. For example, studies comparing children with and without active caries have reported increases in the proportion of bacterial species including *Streptococcus* spp., *Veillonella* spp., *Actinomyces* spp., *Bifidobacterium* spp., *Lactobacillus* spp., *Propionibacterium* spp. and *Atopobium* spp [6, 7]. Moreover, in adults with deep caries lesions, microbiomes are dominated by *S. mutans* and *Lactobacillus* spp., but also include *Prevotella, Selenomonas, Dialister*, *Fusobacterium*, *Bifidobacterium* and *Pseudoramibacter* [8, 9]. As caries progresses, the overall species diversity of the microbial community has also been observed to decrease [10].

When the eruption of an emerging wisdom tooth (third molar) becomes inhibited, impaction occurs. The type of impaction is classified by the angle at which the wisdom tooth emerges. As displayed in Figure 1, there are four predominant angulations at which wisdom teeth become impacted. These angulations include horizontal (where the third molar lies horizontally, growing towards the adjacent second molar), distal (the third molar is angled towards the back of the mouth), mesial (tooth is angled towards the front of the mouth), and vertical (near-vertical orientation). However, these angulations can be grouped by their growth in relation to the second molar, “convergent” impactions see third molars erupting and making contact with the second molar (mesial and horizontal), and “divergent” angulations see third molars erupting in a direction away from the second molar (distal and vertical).

Wisdom tooth impaction can lead to the development of distal surface caries (DSC) on the adjacent second molar [11]. Whilst this association is well documented, current UK clinical guidelines for the management of wisdom teeth advise against the prophylactic removal of healthy impacted teeth [12], and a recent Cochrane review suggests there is insufficient evidence to guide whether or not asymptomatic impacted wisdom teeth should be removed [13]. Emerging evidence suggests, however, that wisdom teeth impaction at particular angles are more associated with caries than others. A recent systematic review found that one in four referrals for the assessment of third molars presented with DSC, and those with convergent (horizontal and mesial) impactions were at greater risk [14].

Recently published data indicate that partially impacted third molars with convergent angulations are associated with higher caries risk [15-19]. Where teeth converge, difficulty in maintaining dental hygiene in this area could cause the formation and stagnation of plaque. Ultimately, this could be aetiologically involved in DSC on the second molar [12]. A resultant deficient gingival collar between the teeth may thereafter expose the root of the second molar to the oral environment. If the progression of plaque formation leading to tooth decay continues, intervention (usually in the form of wisdom tooth removal) must be employed. If this intervention is conducted early, this can allow reversal of the cariogenic process, preventing or reversing decay of the second molar. But it is not uncommon for this intervention to be employed past the point of reversal, and require the removal of both teeth [20, 21].

Whilst plaque stagnation in convergent angulations might drive DSC, the microbiome at each of these sites has remained uncharacterised. Evidence such as early colonisation by caries-associated species could clarify why convergent angulations are more likely to lead to DSC. Accordingly, the following study aimed to investigate and characterize, by 16S rRNA sequencing, the oral microbiome at each angulation of impaction. Through advanced understanding of the microbiome’s role in this process, the aetiology of distal surface caries in wisdom tooth impaction could be elucidated. By doing so, better-informed decisions on treatment of DSC, including updated recommendations on prophylactic removal of wisdom teeth, might be enabled.

Material and Methods

Patient recruitment and sampling

Patients referred to the oral surgery department at Manchester Dental hospital for wisdom tooth assessment were recruited to the study. Patient recruitment and sampling was conducted under NHS approved ethics, IRAS ID: 265014. All participants conformed to the following inclusion criteria: aged 18 years or over, good-fair oral and general health (discerned by the dental practitioner collecting samples), non-smokers, with 20 or more natural teeth and a gingival index score of ≤1 [22]. Patients were excluded if they had partial or full dentures, were pregnant or lactating, had any metabolic or systemic diseases (including cardiovascular or renal diseases and diabetes), were currently taking antibiotics, or had any mouth piercings. To measure oral health behaviour, patients were asked to self-report the frequency of toothbrushing per day, as well as the number of visits to an oral hygienist per year.

Fifty patients were recruited in total, ten with each angulation of impacted wisdom tooth (shown in Figure 1) (horizontal, distal, mesial and vertical), and ten with either no wisdom tooth or deeply un-erupted (missing). DNA was collected by swabbing the tooth surface at the base of the second molar, on the side adjacent to the lower third molar. Regions of contact between molars, particularly at convergent angles, presented difficulty in accessing plaque. Narrow, sterile swabs were used to ameliorate this. The sample site (left or right side) was determined randomly.

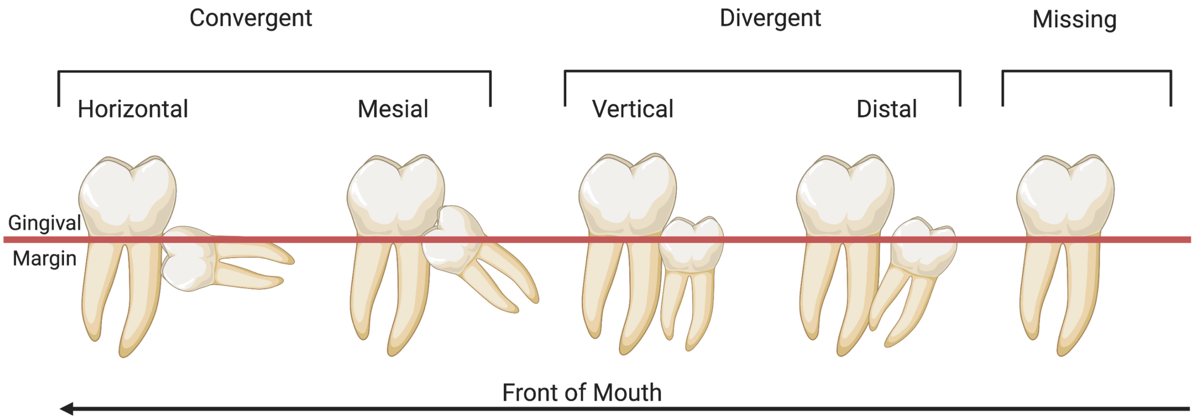


Figure 1. Schematic diagram of four main angulations of wisdom tooth (right tooth) impactions relative to the mandibular second molar (left).

MiSeq analysis of microbiome samples

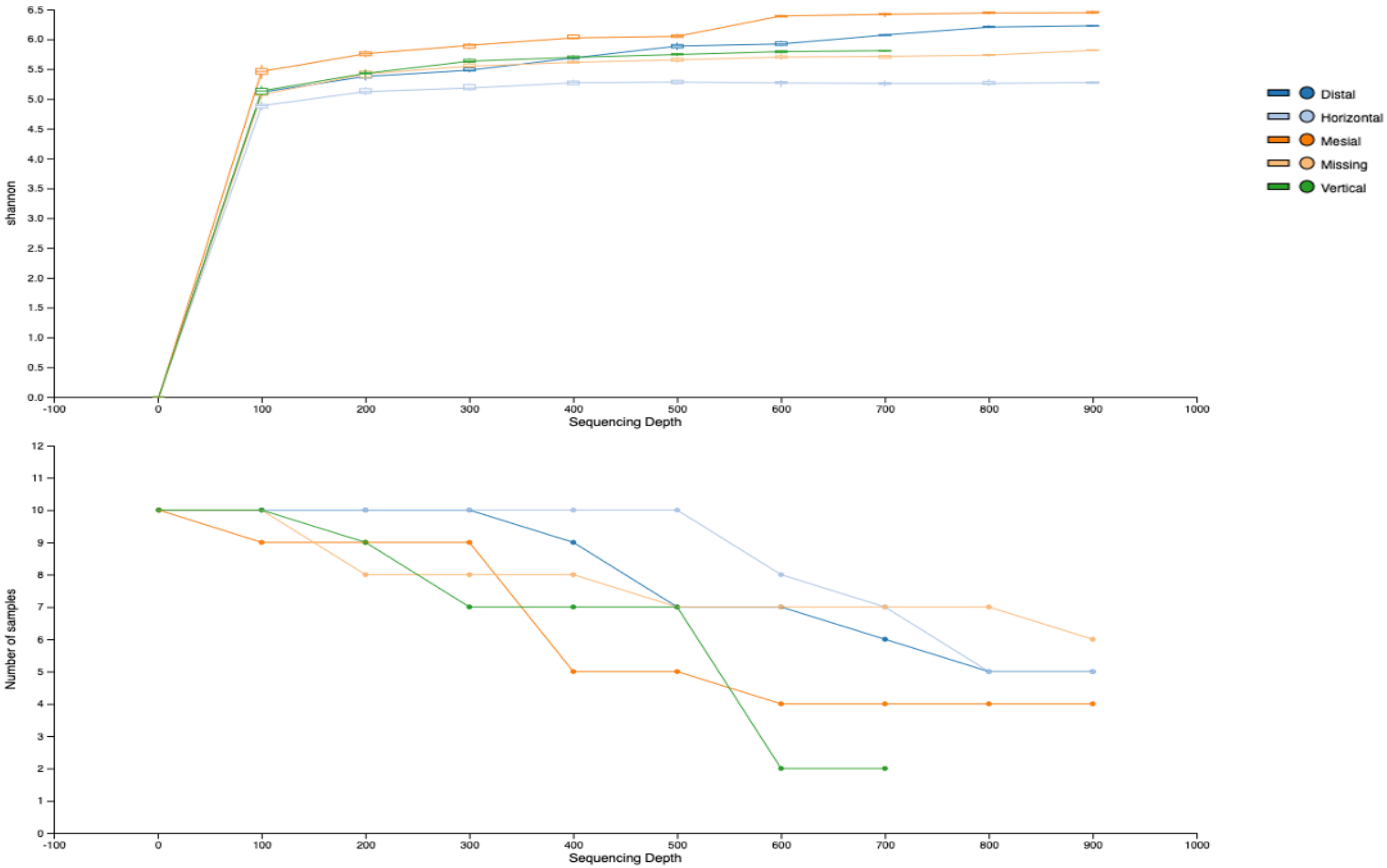
Bacterial DNA was extracted from the samples using the Qiagen Power Soil Kit and associated protocol. Bacterial DNA was then sent to the Centre for Genomic Research, The University of Liverpool for sequencing on the Illumina MiSeq platform. Primers used were 515F (5'-TGCCAGCMGCCGCGGTAA-3') and R806 (5'-GGACTACHVGGGTWTCTAAT-3'), previously designed by [23] to target amplification of the highly variable V4 region of the 16S small-subunit ribosomal gene.

Raw sequence data generated by the Illumina MiSeq runs were checked for the presence of Illumina adapter sequences using Cutadapt version 1.2.1 [24] with any reads matching the adapter sequence for 3bp or more trimmed. Reads were further trimmed using Sickle version 1.200 [25] with a minimum quality score of 20. Reads shorter than 20bp after trimming were also removed. Trimmed reads were then processed using Quantitative Insights Into Microbial Ecology (QIIME) v2.2020.2 [26].

Following demultiplexing there was a total of 18,442,719 sequences within the samples, with a mean sequence number of 368,854, a minimum of 197,746 and maximum of 738,534 per sample (Supplementary Table 1). Trimmed sequences were quality filtered by implementing the approach described by [27], and denoised using the Deblur [28] workflow, truncating the reads at a sequence position of 265, chosen based on median quality scores. After quality filtering and denoising with Deblur 1,704 Amplicon Sequence Variants (ASVs) were found within the samples with a mean frequency per sample of 867 (Supplementary Table 1). Following consultation of alpha rarefaction plots (Supplementary Figure 1), alpha and beta diversity metrics were calculated on a table rarefied to equal read depths (sampling depth of 525). The small sampling depth threshold was selected to be as high as possible without reducing power by removing large amounts of samples.

Table 1. Kruskal-Wallis (Non-Parametric) test results of metrics estimating alpha diversity and richness (number of ASVs). Results of each test showing significant differences in diversity are in bold and marked with an asterisk ($p<0.05$).

	Shannon			Pielou's Evenness		
Groups Compared	Mean rank diff.	Summary	Adjusted P Value	Mean rank diff.	Summary	Adjusted P Value
Horizontal (n=10) vs. Mesial (n=5)	**-18.6**	*	**0.013**	**-18.9**	*	**0.011**
Horizontal (n=10) vs. Vertical (n=7)	-9.257	ns	0.75	-11.99	ns	0.21
Horizontal (n=10) vs. Distal (n=7)	-10.83	ns	0.37	-12.27	ns	0.18
Horizontal (n=10) vs. Missing (n=7)	-7.257	ns	>0.99	-9.557	ns	0.66
Mesial (n=5) vs. Vertical (n=7)	9.343	ns	>0.99	6.914	ns	>0.99
Mesial (n=5) vs. Distal (n=7)	7.771	ns	>0.99	6.629	ns	>0.99
Mesial (n=5) vs. Missing (n=7)	11.34	ns	0.66	9.343	ns	>0.99
Vertical (n=7) vs. Distal (n=7)	-1.571	ns	>0.99	-0.287	ns	>0.99
Vertical (n=7) vs. Missing (n=7)	2	ns	>0.99	2.429	ns	>0.99
Distal (n=7) vs. Missing (n=7)	3.571	ns	>0.99	2.714	ns	>0.99



Supplementary Figure 1. The effect of rarefaction at ASV (feature) counts (sequencing depth) on alpha diversity, measured by Shannon's Diversity Index (top), and the total number of samples at or above this ASV count threshold (bottom). Sequencing depth above 500 begins to drastically reduce the number of samples included in the analysis without a large response in diversity. Beyond a sequencing depth of 700, no samples from the "Vertical" group remain.

Supplementary Table 1. Per Sample Sequence Count (post-demultiplexing) and ASV (feature) Count (post-denoising via Deblur) for each sample included in this study.

Sample Number	Sequence Count	ASV (Feature) Count
1	355258	910
2	343744	1026
3	416967	761
4	501727	1417
5	738534	1602
6	474465	1234
7	570111	1891
8	390969	533
9	465893	945
10	492163	1379
11	492806	2448
12	460993	949
13	377387	2605
14	354113	713
15	377379	648
16	364026	698
17	459688	1902
18	405235	1520
19	427663	900
20	296192	2481
21	383976	1274
22	344276	451
23	264183	360
24	443179	941
25	371210	552
26	198275	74
27	271963	217
28	308252	366
29	366714	797
30	280744	543
31	465417	1032
32	249988	297
33	280730	385
34	456904	1301
35	338674	870
36	234654	175
37	286547	388
38	297232	449
39	286802	359
40	246250	175
41	290271	545
42	357291	589
43	425973	900
44	314376	708
45	358842	737
46	294184	447
47	325082	528
48	197746	193
49	413982	599
50	323689	525

Samples which did not meet this ASV count were removed from alpha and beta diversity analysis, leaving 10 horizontal, 7 distal, 5 missing, 5 mesial, and 7 vertical impaction samples. Remaining samples were used to calculate community richness (alpha diversity) via Shannon's Richness (quantitative), Observed ASVs (qualitative), Faith's Phylogenetic Diversity (a qualitative measure which incorporates phylogenetic relationships) and Pielou's Evenness (quantitative measure of community evenness) metrics. Beta diversity (community dissimilarity) measurements included Jaccard (qualitative), Bray-Curtis (quantitative), unweighted UniFrac (qualitative incorporating phylogenetic relationships), and weighted UniFrac (quantitative incorporating phylogenetic relationships). Alpha diversity measurements were imported into Prism 8 Version 8.3.0 for plotting. Beta diversity distance metrics were fed to principal coordinate analysis for the investigation of clustering based on metadata. Results were imported into RStudio (Rstudio Team, 2020) via the QIIME2R package [29] and plotted using ggplot2 [30]. The statistical significance of differences in alpha-diversity metrics between angulations and direction groups (convergent, divergent, and missing) was tested using Kruskal-Wallis tests both between all groups and pairwise. The clustering of beta diversity metrics between these groups was tested via PERMANOVA (999 permutations) within QIIME2 [31].

A taxonomic classifier optimized for the same V4 region of the 16S rRNA gene from the Greengenes database (v13_6) was trained using the q2-feature-classifier and the reference taxonomy was assigned to the ASVs (features) with a 97% confidence threshold. Stacked taxonomic bar plots were produced using the ggplot2 package [32]. To determine statistically significant variations in ASVs between angles of impaction, differential abundance testing was conducted using the DESeq2 R package [33]. Differential abundance testing was performed on un-rarefied data after adding a pseudocount of 1. Dispersions were estimated using a parametric fit type and p values attained by the Wald test were corrected for multiple testing using the Benjamini and Hochberg method, with an adjusted *P* value (p adj.) of ≤ 0.05 accepted as significantly different.

The Random Forest classifier implemented in the sample-classifier QIIME2 plugin [34] was used to predict the sample angulation group. The number of trees to grow for estimation was set to 10,000. The test was performed on three data splits; the first (default) used 80% of the data to 'train' the classifier and tested the classifier's prediction ability on the remaining 20% of the data, this was repeated on 70:30 and 60:40 data splits (Supplementary Table 4). The results of the training:test split with the highest overall accuracy is reported here and used to produce heatmaps of most important ASVs. ASV importance scores were assigned using "impurity-based feature importance" by the scikit-learn learning estimator (RandomForestClassifier) [35]

Supplementary Table 4. Accuracy results for random forest classifiers tested on the relative abundance of ASVs at different wisdom tooth angulations. Values in the matrix are ratios of correct estimates for test samples. Three random forests were performed on different splits of “training” and “test” data, with an 80% training, 20% test split showing the highest overall accuracy compared to 70%/30% and 60%/40% splits.

Training 80:20 Test

	Distal	Horizontal	Mesial	Missing	Vertical	Overall Accuracy
Distal	0.00	0.00	0.50	0.50	0.00	
Horizontal	0.00	1.00	0.00	0.00	0.00	
Mesial	0.00	0.00	0.50	0.00	0.50	
Missing	0.00	0.50	0.00	0.50	0.00	
Vertical	0.00	0.00	0.50	0.00	0.50	
Overall Accuracy						0.50
Baseline Accuracy						0.20
Accuracy Ratio						**2.50**

Training 70:30 Test

	Distal	Horizontal	Mesial	Missing	Vertical	Overall Accuracy
Distal	0.00	0.00	0.33	0.67	0.00	
Horizontal	0.00	0.67	0.00	0.33	0.00	
Mesial	0.67	0.00	0.00	0.00	0.33	
Missing	0.00	0.33	0.33	0.33	0.00	
Vertical	0.00	0.00	0.33	0.33	0.33	
Overall Accuracy						0.27
Baseline Accuracy						0.20
Accuracy Ratio						**1.33**

Training 60:40 Test

	Distal	Horizontal	Mesial	Missing	Vertical	Overall Accuracy
Distal	0.00	0.00	0.25	0.75	0.00	
Horizontal	0.25	0.50	0.00	0.25	0.00	
Mesial	0.25	0.00	0.00	0.50	0.25	
Missing	0.00	0.25	0.00	0.75	0.00	
Vertical	0.00	0.00	0.25	0.25	0.50	
Overall Accuracy						0.35
Baseline Accuracy						0.20
Accuracy Ratio						**1.75**

Results

Oral health behaviour

Frequency of daily toothbrushes and annual hygienist visits were self-reported by all study subjects. No difference was found, by Kruskal-Wallis test, in frequency of toothbrushing between convergent, divergent or missing groups (H_2 = 0.51, p=0.77), or between individual angulation groups (i.e. "horizontal", "mesial", "vertical", "distal" and "missing" groups), (H_4 = 2.3, p=0.67). Similarly, no difference was found in the number of annual dental hygienist visits between impaction groups (H_2 = 1.9, p=0.39) or individual angulation groups (H_4 = 3.2, p=0.53).

Alpha diversity

Alpha diversity was quantified by the total number of observed ASVs and by Shannon's diversity, Faith's phylogenetic diversity and Pielou's evenness diversity indices. Figure 2 shows the results of alpha diversity measurements for samples taken from each angulation of wisdom tooth. When samples were grouped into "convergent", "divergent" and "missing" impactions, overall Kruskal-Wallis testing revealed no significant differences using Shannon's (H_2= 1.0, p=0.61), observed ASVs (H_2 = 0.043, p=0.98), Faith's (H_2 = 0.25, p=0.88) or Pielou's (H_2= 2.2, p=0.33) diversity metrics.

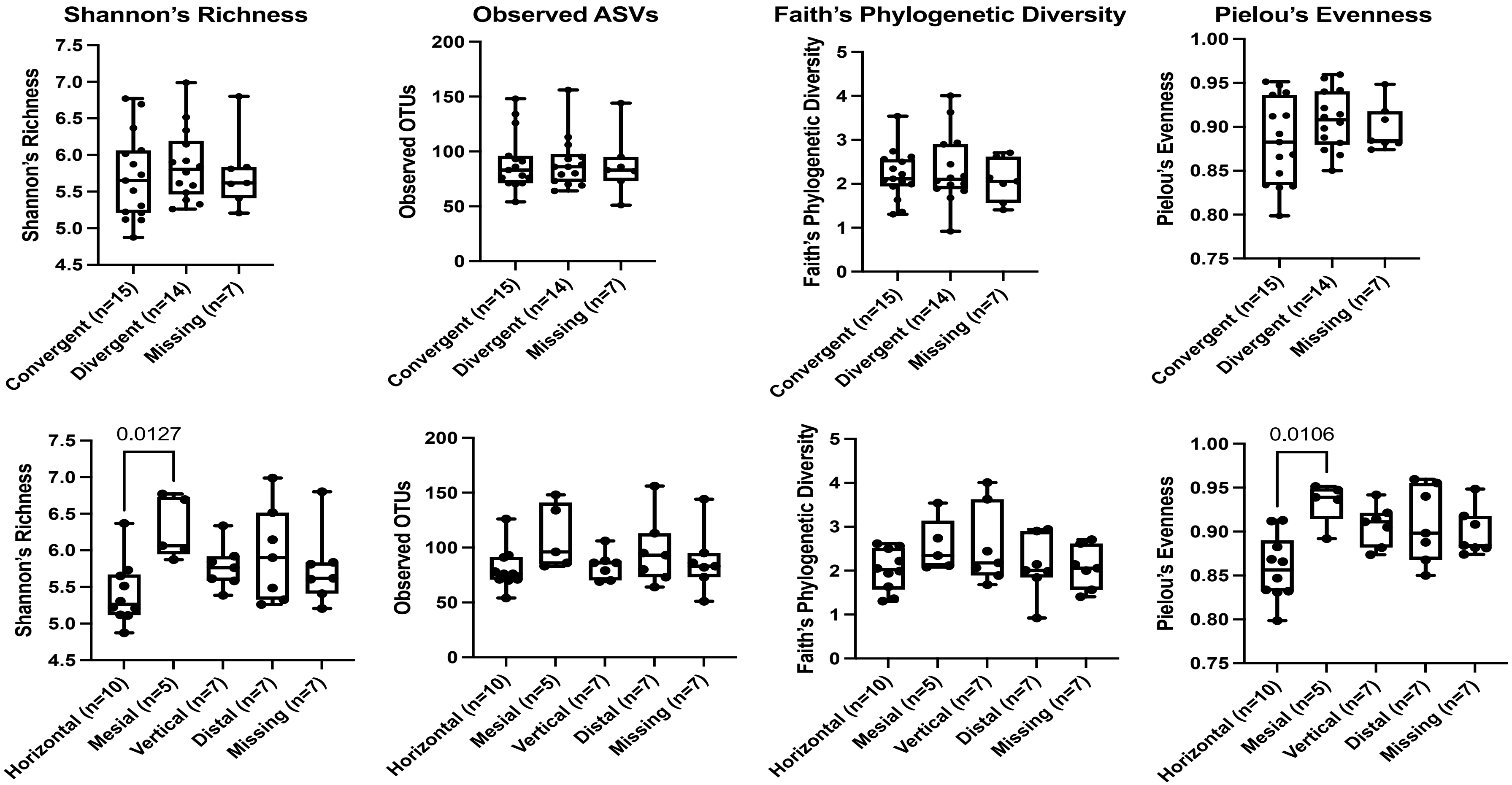


Figure 2. Alpha Diversity of Wisdom Tooth Samples. Alpha diversity, measured by Shannon's Richness, Observed ASVs, Faith's Phylogenetic Diversity and Pielou's Evenness species (left). Whiskers show data range, interquartile range is shown by boxes and median in signified by line. Significant differences (p adj. < 0.05) calculated by pairwise Kruskal-Wallis testing (Dunn's Multiple comparisons test) are indicated by value above bars.

Kruskal-Wallis testing was repeated comparing individual angulation groups. No significant differences were found via observed (H_4= 5.7, p=0.22) or Faith's (H_4=3.9, p=0.42) indices. However, significant differences in alpha diversity were found using Shannon's (H_4=11, p=0.022) and Pielou's (H H_4=13, p=0.012) metrics. Post-hoc testing was performed on the significant Kruskal-Wallis results using Dunn's multiple comparisons test (Table 1). For each of these pairwise comparisons, the only significant difference in mean alpha diversity was found between the two convergent impactions, with decreased diversity shown in the horizontal group versus mesial impactions (Shannon's p.adj =0.013, Pielou's p.adj =0.011). No other differences between impaction groups were significantly different.

Beta-diversity (Principal Coordinates Analysis)

Beta-diversity was calculated using principal coordinates analysis (PCoA) with four metrics: Jaccard, Bray-Curtis, Unweighted UniFrac, and Weighted UniFrac. Visually, there was no obvious clustering of samples based upon angulation (shown by different colours) or directional groups (shown by shapes) (Figure 3). For directional groups, this was confirmed statistically using permutational multivariate ANOVA (PERMANOVA) tests (999 permutations) which found no significant difference in beta diversity between convergent, divergent, or missing wisdom teeth using any of the four metrics (Bray-Curtis p = 0.23, Unweighted UniFrac p = 0.34, Weighted UniFrac p = 0.34, Jaccard p = 0.30).

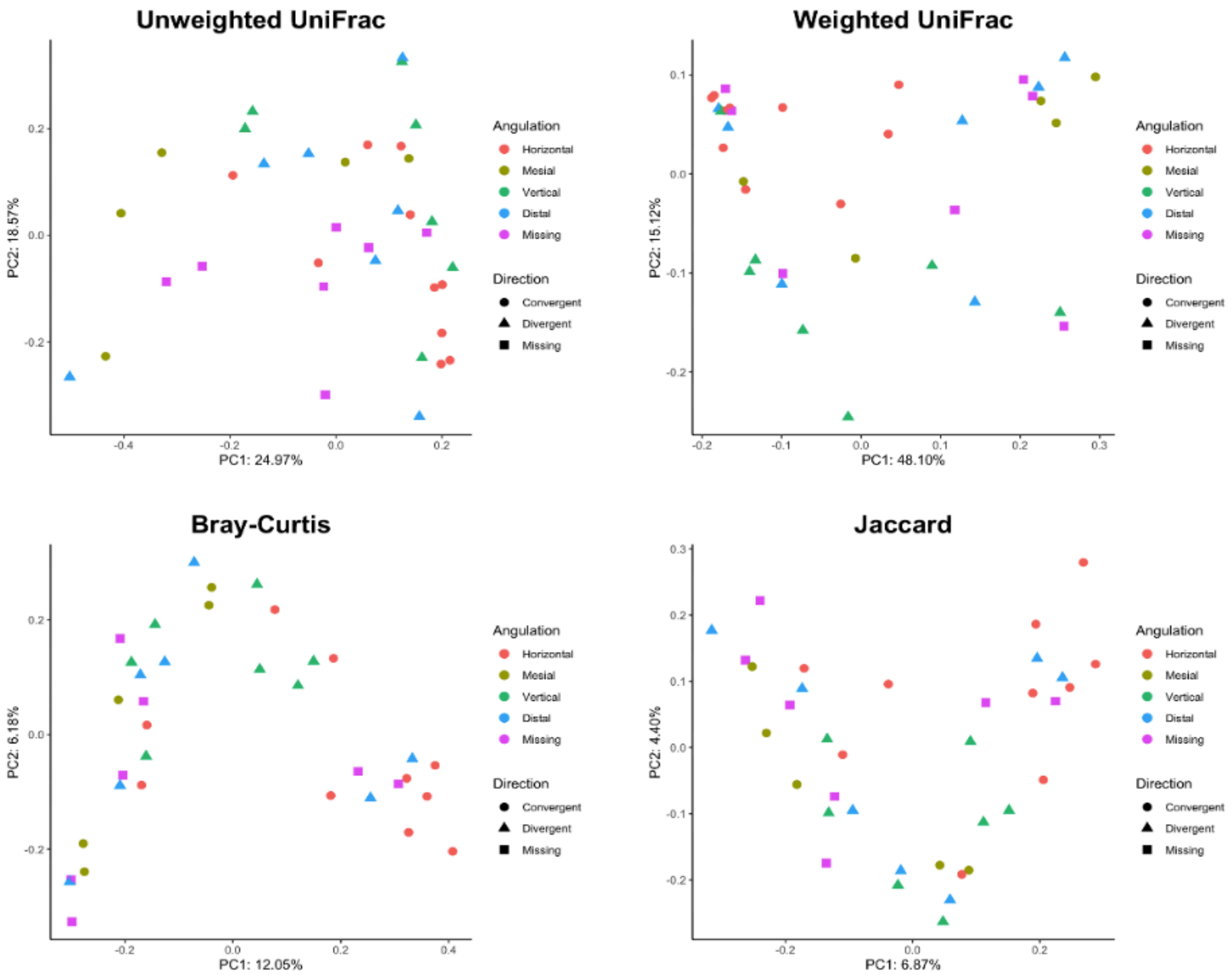


Figure 3. Beta Diversity Analysis of Wisdom Tooth Samples. Beta diversity Principal Coordinates Analysis (PCoA) plot based on Bray-Curtis, Jaccard, weighed and unweighted UniFrac. Angulation of impacted wisdom tooth is indicated by colour, directional group is shown by shape (legend, right).

However, statistical comparisons using permutational multivariate ANOVA (PERMANOVA) tests (999 permutations) found overall differences between angulations using weighted UniFrac (p=0.023), Jaccard (p=0.021) and Bray-Curtis (p=0.006) (Table 2). Angulations were not found to have significantly different beta diversity according to the unweighted UniFrac metric (p=0.088). Pairwise analysis (Table 3) of the significant overall tests revealed that horizontal and mesial angulations had significantly different beta diversity (Bray-Curtis p.adj = 0.040, Unweighted UniFrac p.adj = 0.040, Weighted UniFrac p.adj = 0.007). Furthermore, horizontal impactions also had significantly different beta diversity compared to vertical impactions using the Bray-Curtis metric (p.adj = 0.040).

Table 2. Results of overall PERMANOVA for four diversity metrics comparing beta diversity of wisdom tooth angulations in individual and grouped forms. Significant differences between groups are in bold and marked with an asterisk (p<0.05).

Groups Compared	*Diversity Metric*	*Pseudo-F*	*Summary*	*p-value*
Horizontal (n=10) vs Mesial (n=5) vs Vertical (n=7) vs Distal (n=7) vs Missing (n=7)	Unweighted UniFrac	1.4	ns	0.088
	Weighted UniFrac	**2.1**	*	**0.023**
	Jaccard	**1.1**	*	**0.021**
	Bray-Curtis	**1.3**	**	**0.006**
Convergent (n=15) vs Divergent (n=14) vs Missing (n=7)	Unweighted UniFrac	0.78	ns	0.728
	Weighted UniFrac	1.1	ns	0.342
	Jaccard	1.0	ns	0.295
	Bray-Curtis	1.1	ns	0.229

Table 3. Pairwise beta diversity values obtained following significant overall PERMANOVA results. Pairwise differences are considered significant at adjusted p value (q value), p adj. <0.05.

		Bray			*Unweighted UniFrac*			*Weighted UniFrac*		
Groups Compared	Sample size	pseudo-F	p-value	q-value	pseudo-F	p-value	q-value	pseudo-F	p-value	q-value
Distal vs Horizontal	17	1.5	0.040	0.100	1.3	0.201	0.500	2.8	0.108	0.043
Distal vs Mesial	12	0.97	0.556	0.618	0.9	0.441	0.529	0.59	0.707	0.636
Distal vs Missing	14	0.80	0.945	0.945	0.65	0.810	0.810	0.27	0.911	0.911
Distal vs Vertical	14	1.0	0.336	0.480	0.94	0.476	0.529	1.49	0.293	0.205
Horizontal vs Mesial	15	2.0	0.008	**0.040***	3.1	0.004	**0.040***	5.5	0.070	**0.007***
Horizontal vs Missing	17	1.6	0.031	0.100	1.2	0.250	0.500	3.5	0.108	0.034
Horizontal vs Vertical	17	1.6	0.008	**0.040***	1.0	0.358	0.529	3.6	0.070	0.014
Mesial vs Missing	12	0.99	0.485	0.606	1.0	0.376	0.529	1.1	0.390	0.312
Mesial vs Vertical	12	1.1	0.184	0.367	2.2	0.041	0.205	2.3	0.128	0.064
Missing vs Vertical	14	1.1	0.220	0.367	1.8	0.066	0.220	1.6	0.292	0.175

Relative abundance of genera

The mean composition of samples taken from different wisdom tooth angulations reveals distinct microbiome profiles (Figures 4a and 4b). Visually, the samples are dominated by the genus *Veillonella*, particularly in horizontal impactions. *Selenomonas* also appears to dominate in mesial, distal, and vertical impactions; however, the proportion is lower in horizontal impactions and where the wisdom tooth was missing. Moreover, large proportions of *Escherichia* are seen in distal, horizontal, mesial, and “missing” impactions, but not in vertical.

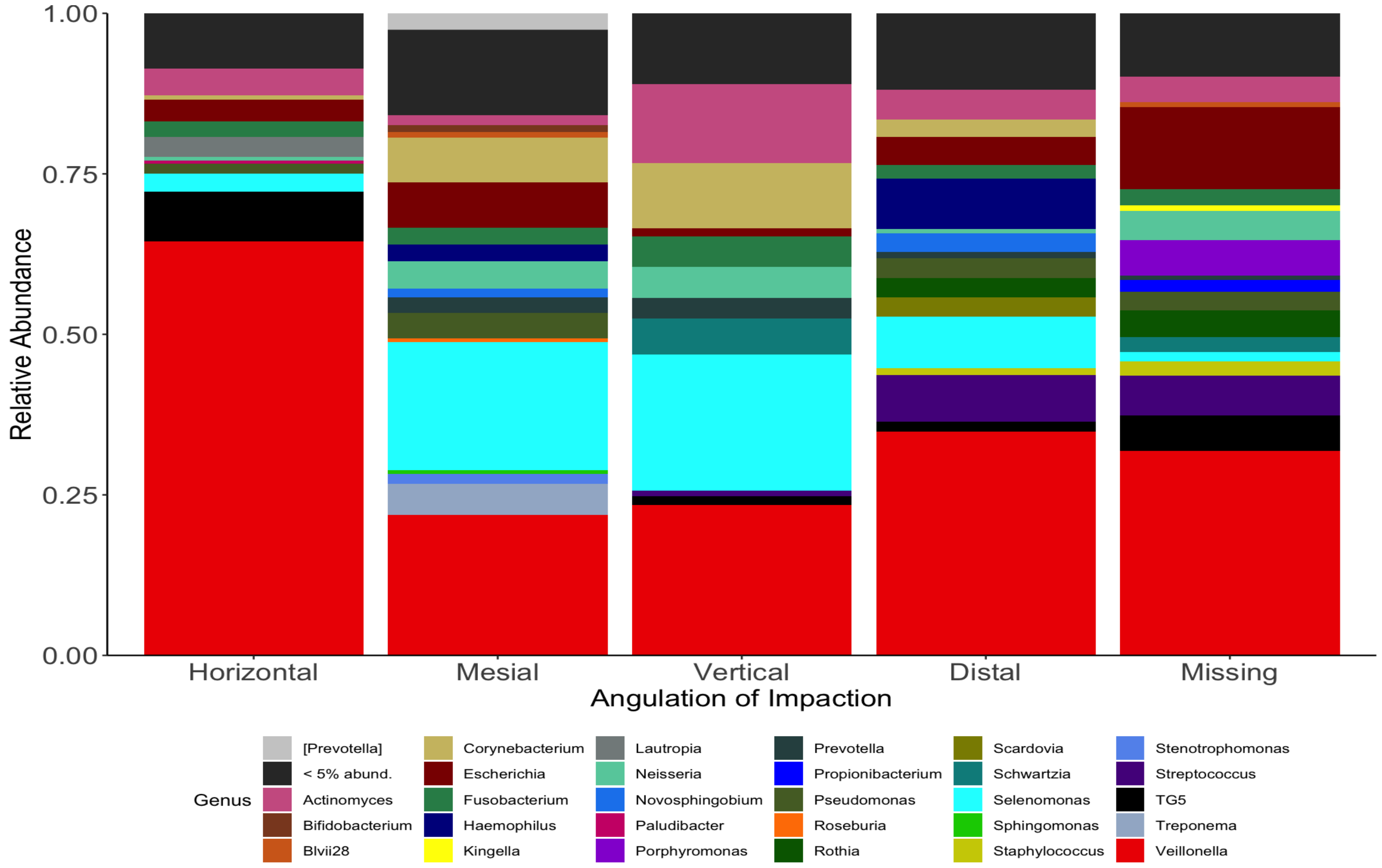


Figure 4a. Mean Oral Microbiome of Impacted Wisdom Teeth at Different Angulations. The stacked bar chart shows the mean proportion of genera (relative abundance) at each angulation. Colours represent different genera (legend, below). Genera found at below 5% relative abundance in any one sample are grouped together.

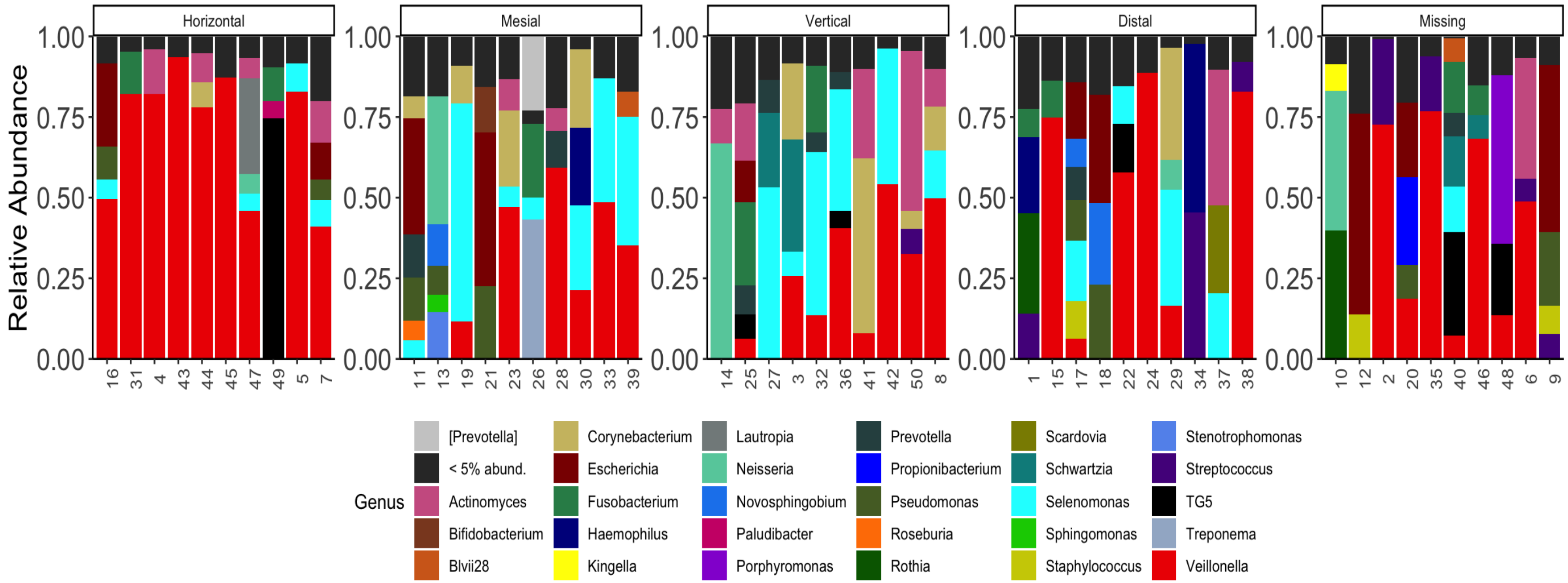


Figure 4b. The Oral Microbiome Profile of Each Sample in Study. Stacked bar chart shows the proportion of genera (relative abundance) in each sample (10 of each angulation). Samples are grouped in the angulation of wisdom tooth from which they were taken.

Observing the microbiome profiles individually reaffirms the domination by *Veillonella* in samples from horizontal impactions, with the exception of sample 49 (Figure 4b). Excluding the horizontal impaction, there is limited consistency between samples of the same angulation. This overt domination by *Veillonella* is not mirrored in the mesial convergent impaction. *Veillonella* is one of the most prominent genera in just 6 out of 10 samples from mesial impactions. Four samples from the distal angulation have high proportions of *Veillonella*, with no clear, consistent domination by any other genus in the remaining six samples.

Differential abundance testing

Figure 5 summarizes the results of differential abundance testing, with full taxonomy of significant ASVs found in Supplementary Table 2. Significant compositional variations in ASVs were investigated in DESeq2. Twelve ASVs belonging to *Veillonella dispar* were found to have significantly lower relative abundance in divergent impactions vs convergent impactions, with one ASV found to be significantly higher. Two ASVs belonging to *Veillonella* were also significantly lower in the divergent group, although these could not be assigned to the species level.

Supplementary Table 2. Deseq2 Results showing all ASVs with significant differential abundance in convergent wisdom teeth (vs divergent wisdom teeth) (p adj. <0.05). Columns include taxonomy at different levels, where assigned, (Order, Family, Genus and Species), the baseMean (average of normalized count values divided by size factors from all samples), the log2Fold-Change (effect size estimate), the lfcSE (standard error estimate of the log2Fold-change), the test statistic (stat), the unadjusted significance value (pvalue) and the False Discovery Rate (FDR) adjusted p value (padj). ASVs also found to be differentially abundant in comparison of mesial and horizontal impactions are underlined in bold.

ASV ID	***Order***	***Family***	***Genus***	***Species***	***baseMean***	***log2FoldChange***	***lfcSE***	***stat***	***P value***	***padj***
e709a247274042490632cbcb6307ca9c	Actinomycetales	Corynebacteriaceae	Corynebacterium	NA	2.021	1.459	0.507	2.879	0.004	0.046
ef2bc141dd8ae29fc98f0a11c9ab0fc1	Enterobacteriales	Enterobacteriaceae	Escherichia	coli	2.344	-1.743	0.544	-3.203	0.001	0.028
91034d8dc0c56b40847da9b38cff098c	Pasteurellales	Pasteurellaceae	Haemophilus	parainfluenzae	2.398	1.695	0.564	3.004	0.003	0.036
fed3491860751fa62fbfad2fd9342e7c	Clostridiales	Veillonellaceae	Selenomonas	noxia	2.854	-1.931	0.575	-3.359	0.001	0.028
9b5763d1a70ffdd6459b43d6c0a2f6ea	Clostridiales	Veillonellaceae	Veillonella	dispar	45.254	-2.225	0.684	-3.255	0.001	0.028
ae7d2b84a912c3f0de74fc13e87774a7	Clostridiales	Veillonellaceae	Veillonella	dispar	2.802	-2.069	0.570	-3.633	0.000	0.015
62b30462f092791697593492acce602a	Clostridiales	Veillonellaceae	Veillonella	dispar	6.389	-2.732	0.628	-4.348	0.000	0.003
fa104e77a935caf2e7695cd6700e39ee	Clostridiales	Veillonellaceae	Veillonella	dispar	3.743	-2.410	0.575	-4.192	0.000	0.003

<u>e8f223a366559c530cab467958c474b2</u>	Clostridiales	Veillonellaceae	Veillonella	dispar	3.098	-1.847	0.573	-3.226	0.001	0.028
37751d0afe5a105169964bdd0a88ae03	Clostridiales	Veillonellaceae	Veillonella	dispar	2.048	-1.485	0.483	-3.077	0.002	0.032
15a21b07a36b82aaaebb46ba11c60009	Clostridiales	Veillonellaceae	Veillonella	dispar	2.452	-1.564	0.549	-2.850	0.004	0.048
2bd550f69838c8c817c1e80002abd853	Clostridiales	Veillonellaceae	Veillonella	dispar	2.156	-1.584	0.550	-2.881	0.004	0.046
3f0564f5338b167529ad89d05f4846ed	Clostridiales	Veillonellaceae	Veillonella	dispar	2.885	2.122	0.590	3.595	0.000	0.015
<u>248150527f0f11d0b94bae55c9bf6ea0</u>	Clostridiales	Veillonellaceae	Veillonella	dispar	2.183	-1.609	0.513	-3.134	0.002	0.030
b04997d5bfdf9af5eade7acf45422f8b	Clostridiales	Veillonellaceae	Veillonella	dispar	2.533	-1.887	0.569	-3.316	0.001	0.028
c054a5357726e9d3b14122ed006fdd7d	Clostridiales	Veillonellaceae	Veillonella	NA	2.425	-1.627	0.521	-3.123	0.002	0.030
d10849c0d5e27db3160208de07bf147d	Clostridiales	Veillonellaceae	Veillonella	NA	2.156	-1.584	0.529	-2.994	0.003	0.036

ASVs belonging to *Corynebacterium* and *Haemophilus parainfluenzae* were found to be higher in the divergent group, with *Escherichia coli* and *Selenomonas noxia* lower.

The differential abundance of ASVs in convergent (mesial and horizontal) groups was also compared (Supplementary Table 3). This analysis found 14 *Veillonella* ASVs (12 *V. dispar*) were higher in the horizontal group than the mesial group, as well as one ASV belonging to *Selenomonas noxia* and one belonging to the genus *Actinomyces*.

Supplementary Table 3. Deseq2 Results showing all ASVs with significant differential abundance in mesial wisdom teeth (vs horizontal wisdom teeth) (p adj. <0.05). Columns include taxonomy at different levels, where assigned, (Order, Family, Genus and Species), the baseMean (average of normalized count values divided by size factors from all samples), the log2Fold-Change (effect size estimate), the lfcSE (standard error estimate of the log2Fold-change), the test statistic (stat), the unadjusted significance value (pvalue) and the False Discovery Rate (FDR) adjusted p value (padj). ASVs also found to be differentially abundant in convergent vs divergent impactions are underlined in bold.

ASV ID	*Order*	*Family*	*Genus*	*Species*	*baseMean*	*log2FoldChange*	*lfcSE*	*stat*	*pvalue*	*padj*
af224593479000a79529bc46171a2016	Actinomycetales	Actinomycetaceae	Actinomyces	NA	4.276	-2.792	0.827	-3.378	0.001	0.019
f80c2719c07a07e8c29baf0f7c8f5ff1	Clostridiales	Veillonellaceae	Selenomonas	noxia	4.819	-2.987	0.838	-3.563	0.000	0.014
9b5763d1a70ffdd6459b43d6c0a2f6ea	Clostridiales	Veillonellaceae	Veillonella	dispar	74.652	-3.676	0.833	-4.414	0.000	0.001
af53482213331da9fdec961badae7f67	Clostridiales	Veillonellaceae	Veillonella	dispar	7.570	-2.765	0.829	-3.336	0.001	0.020
5d0607e9756bd800f6cfffbac3008136	Clostridiales	Veillonellaceae	Veillonella	dispar	20.539	-3.543	0.812	-4.362	0.000	0.001
0df86d242400e5b207109877d7a0517f	Clostridiales	Veillonellaceae	Veillonella	dispar	15.033	-4.034	0.854	-4.724	0.000	0.001
475487bff88ea4abcc2575d6bd163170	Clostridiales	Veillonellaceae	Veillonella	dispar	9.174	-3.998	0.884	-4.523	0.000	0.001
2bacc6baa52be5841d589878e5ce9ef3	Clostridiales	Veillonellaceae	Veillonella	dispar	5.179	-2.805	0.829	-3.382	0.001	0.019
ae7d2b84a912c3f0de74fc13e87774a7	Clostridiales	Veillonellaceae	Veillonella	dispar	4.536	-2.887	0.834	-3.460	0.001	0.018
e8f223a366559c530cab467958c474b2	Clostridiales	Veillonellaceae	Veillonella	dispar	4.859	-2.698	0.852	-3.167	0.002	0.032
dd1eafd27b4019145769070bc6bfbd11	Clostridiales	Veillonellaceae	Veillonella	dispar	3.963	-2.663	0.844	-3.156	0.002	0.032
248150527f0f11d0b94bae55c9bf6ea0	Clostridiales	Veillonellaceae	Veillonella	dispar	3.311	-2.357	0.757	-3.115	0.002	0.034
09db0acc84881088880aa5da7c71ec72	Clostridiales	Veillonellaceae	Veillonella	dispar	6.221	-3.242	0.861	-3.767	0.000	0.007
eb23c532507bfcf103c3c02d4669ef78	Clostridiales	Veillonellaceae	Veillonella	dispar	3.408	-2.408	0.811	-2.969	0.003	0.049
a959f136d78dfd17b3ccbd7b45708d9e	Clostridiales	Veillonellaceae	Veillonella	NA	7.129	-3.324	0.874	-3.804	0.000	0.007
ae739f39086a80500c6a950233b150c6	Clostridiales	Veillonellaceae	Veillonella	NA	5.355	-2.600	0.844	-3.081	0.002	0.036

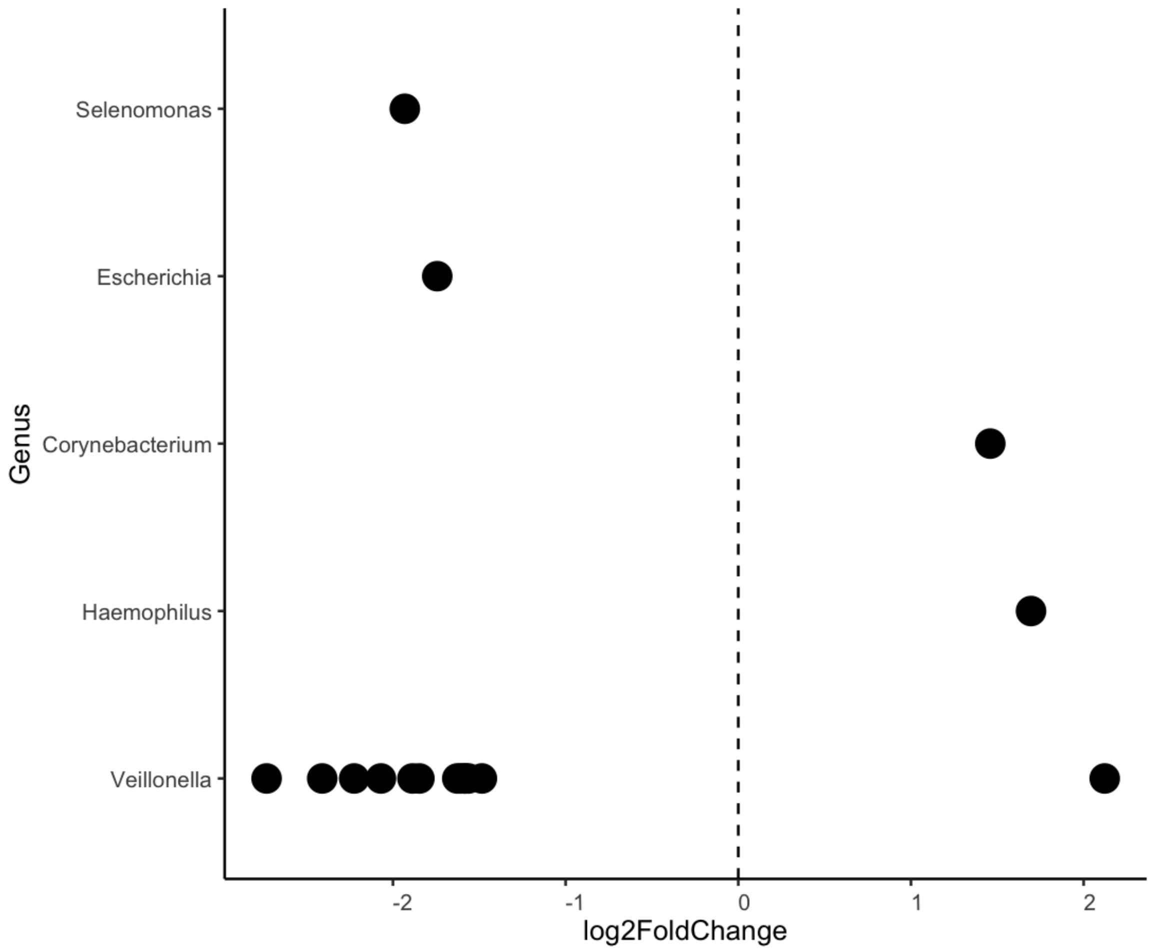


Figure 5. Differential Abundance Analysis of ASVs detected from divergent impacted wisdom teeth (vs convergent impacted wisdom teeth), relative to the second molar. Differential abundance analysis identified that 3 ASVs (above the line) were increased and 14 ASVs (below the line) were decreased in divergent impactions compared to convergent impactions (p adj. <0.05).

Random forest classifying

For supervised learning analysis, a random forest classifier was used to predict the angulation of samples based on microbiome composition using 3 different data splits, with a split of 80% for training and 20% for testing showing the greatest overall prediction accuracy (Supplementary Table 2). The classifier showed an overall accuracy of 60%, 3 times higher than the baseline accuracy of 20%. Comparing the "true label" vs "predicted label" (Figure 6a), the two convergent groups (horizontal and mesial) showed the highest probability to correctly predict the angulation of all four convergent test samples. The prediction level for the divergent groups (distal and vertical) showed higher uncertainty (accuracy 0.0 and 0.5, respectively), as did the missing impaction group (accuracy 0.5).

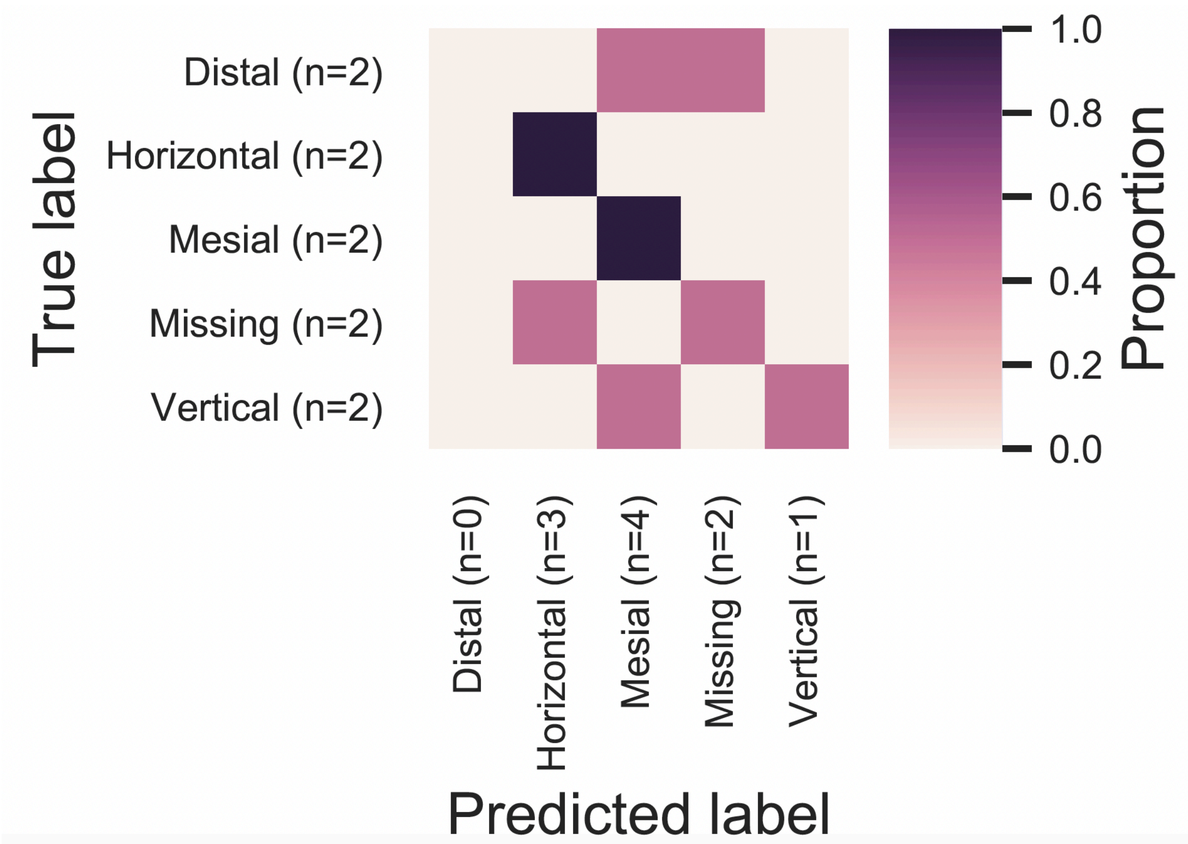


Figure 6a. Performance of machine learning analysis trained on 80% of the ASV relative abundance data and tested on the remaining 20% (n=2) of the angulation groups (chosen at random). True labels of the test group are shown on the Y axis, the labels predicted by the machine learning analysis are shown on the x axis. The proportion of correctly estimated true labels is indicated by colour (key, right).

A heat map (Figure 6b) was used to evaluate which microbiome components contributed the most to correct predictions of angulation. This heatmap contains the top 30 most abundant ASVs in each sample which remained after recursive ASV elimination. Figure 6b illustrates the importance of the high relative abundance of ASVs associated with *Veillonella* in distinguishing between microbiome profiles of angulation groups, for example, showing a high abundance of several ASVs belonging to *Veillonella dispar* in the horizontal impaction. Likewise, a higher relative abundance of ASVs associated with *Streptococcus* and *Actinomyces* distinguish the mesial impaction from other groups

Figure 6b. Abundance heat map showing most predictive ASVs, i.e., the 30 ASVs with the greatest abundance remaining after recursive feature elimination for optimal model accuracy. Scale is given as log10 frequency $log10(x)$ where x is the number of times the ASV was detected.

Discussion

Caries is a disease caused by microbial activity, and caries-active patients have significantly distinct microbiome compositions and diversity [6-9]. Combined with evidence that particular angulations of wisdom tooth impaction increase caries risk [15-19], the role of the microbiome at convergently growing wisdom tooth angulations is implied.

The aetiology of distal surface caries is driven by microbial activity [1-4]. Wisdom tooth impaction is known to increase distal surface caries risk [6-9] and some angulations of impaction generate more risk than others [14-19]. Variations in oral hygiene behaviour are associated with plaque formation and stagnation, however, our analysis showed no difference in the self-reported frequency of toothbrushing or the number of annual hygienist visits between patients in each angulation group of this study.

In this investigation of wisdom tooth impaction, the primary aim was to profile and compare the microbiomes at four angulations (distal, mesial, horizontal, and vertical), as well as where the wisdom tooth was not present or had been extracted (missing). In later analyses, the four angles were grouped by the direction of growth relative to the second molar. This allowed comparison of convergent (horizontal and mesial), with divergent (distal and vertical) angulations. This was of particular interest because the stagnation of plaque and inaccessibility for cleaning in convergent impactions has been hypothesised as the cause for distal surface caries [12].

Diversity metrics identify differences within convergent impaction groups

The first measure employed to compare the microbiome at the four angulations, and where the wisdom tooth was missing, was a comparison of the alpha diversity of each sample. For two out of four diversity measurements, significant differences in alpha diversity were found between samples taken from each angulation. This showed the horizontal angulation to have a lower alpha diversity than mesial (Shannon's Richness and Pielou's evenness). Species diversity is positively correlated with the heterogeneity of the environment [36]. Therefore, significantly lower alpha diversity associated with horizontal impaction may suggest that, if stagnation of plaque does occur, it may result in a less heterogenous environment. Less diverse communities are more susceptible to invasion by foreign species due to a lower coverage of ecological niches [37]. Hence, less diverse horizontal impactions may be more prone to invasion by pathogenic species. When grouped with other convergent impaction angulations, no significant differences were found in alpha diversity versus divergent impactions.

Regarding beta diversity, pairwise PERMANOVA testing indicated no significant clustering of data due to the overall direction of growth (convergent, divergent, or missing) by any metric. However, analysed by individual angulations, Bray-Curtis, Jaccard and weighted UniFrac metrics all found significantly different clustering for the horizontal impaction versus the mesial group. Furthermore, Bray-Curtis detected significant differences in beta diversity between the horizontal and vertical impactions. Similar to the results of alpha diversity, this could imply plaque stagnation at the horizontal impaction is driving differences in community diversity and richness. Taken together, alpha and beta diversity analyses both highlight significant differences between two "convergent" impactions, implying that the angle of impaction to the mandible second molar is a greater driver of environmental diversity than the overall (convergent/divergent) general direction of growth.

Horizontal impactions drive higher *Veillonella* abundance in convergent group

The microbiome of each angulation group was dominated by the genus *Veillonella* (Figures 4a and b). Differential abundance testing showed that several ASVs assigned to this genus were significantly higher in the convergent (caries associated) impaction group versus non-convergent impaction groups. This included 12 associated with *Veillonella,* as well as *Escherichia* and *Selenomonas*, the latter has previously been found at high abundances in adults with advanced caries in adults by [9]. One ASV belonging to *Veillonella* was found to be higher in divergent impactions. Whilst beyond the scope of this study, the potential importance of functional differences at strain level should be investigated. Transcriptome analysis has shown that the functional metabolism of *Veillonella* strains differ in terms of histidine biosynthesis and potassium uptake systems, which may favour growth in acidic and carious environments respectively [38]. Therefore, similar strain-level analyses might improve understanding of functional differences in the cariogenic-associated convergent impactions.

Veillonella was particularly prevalent in the horizontal impaction, and further differential abundance testing confirmed that 14 ASVs belonging to *Veillonella* (12 *V. dispar*) were higher in the horizontal impaction than the mesial convergent impaction. Four of these ASVs found to be higher in horizontal (versus mesial) impactions matched those at greater abundance in the convergent group, suggesting that the greater relative abundance seen in convergent impactions is driven by horizontal impactions.

Machine learning uses *Veillonella* ASVs to distinguish the convergent groups

Machine learning showed that it was possible to correctly predict the angulation from which samples were derived with high accuracy relative to the baseline (3x greater). This accuracy was highest for the two convergent (horizontal and mesial) groups. Here, ASVs assigned to the genus *Veillonella* (predominantly *V. dispar*) were shown to be highly informative to a classifier that correctly predicted the angulation of horizontal samples based on microbial composition. The domination of horizontal impactions by *Veillonella* is particularly relevant since species of *Veillonella* dominate progressing incipient carious lesions [39] and significant increases in abundance of this genus has been found in caries active children [6, 7]. Hence, this result may imply a role for *Veillonella* in the development of wisdom tooth-associated decay.

Co-action of *Veillonella* might have importance in caries aetiology

Previously, *Streptococcus* has been found at higher relative abundances in caries-active children [6-7]. In particular, *Streptococcus mutans* has a wealth of epidemiological evidence linking the genus to caries [40]. Alongside *S. sobrinus*, *S. mutans* produce lactic acid, driving caries [40]. Yet here the convergent impactions were not found to host ASVs assigned to the genus *Streptococcus* at greater relative abundance via differential abundance analysis. One ASV belonging to *Streptococcus* did appear in high abundance in horizontal impactions (Figure 6b), with two other *Streptococcus* ASVs high at distal angulations. *Streptococcus* is a common and diverse genus within the oral cavity, with member species ranging from commensals to pathogens. A limitation of the present study is that in such cases, where taxonomy is unable to be resolved to species, a high relative abundance of a genus *Streptoccocus* is difficult to interpret as either beneficial or detrimental to the microbiome and host.

However, due to its greater cariogenic potential, the combination of *Streptococcus* and *Veillonella* might demand greater attention. Whilst analysis of convergent (vs divergent) angulations showed that ASVs belonging to *Veillonella*, but not *Streptoccocus*, were differentially abundant (Figure 5), random forest analysis highlighted nearly as many *Streptococcus* ASVs (5) as *Veillonella* (7) were important in distinguishing between angulations (Figure 6). It has been demonstrated *in vitro* that *Veillonella* and *S. mutans* together results in greater acid production and demineralization than *S. mutans* alone [41]. Moreover, *Veillonella* might act as a lactic acid sink, causing greater glycolysis in *S. salivarius* with increased acid production, again, the end result [42]. Whilst it is difficult to conceptualise the highly numerous and complex processes between the oral microbiota, considering interactions between constituents in this way may produce more favourable outcomes in terms of understanding the microbiome differences driving increased caries at convergent sites. Hence, future studies which supplement the key differences in microbiome profiles generated by sequencing with functional explanations are recommended to improve understanding.

Summary

This study aimed to profile and compare the oral microbiome at the four main wisdom tooth impaction angulations. In doing so, we found no distinct differences in either alpha or beta diversity between caries-associated convergent impacted wisdom teeth groups and instances where the wisdom tooth was missing. Since the “missing” group should be the easiest in which to maintain dental hygiene, and the least associated with plaque stagnation, this result suggests these factors do not influence diversity. Given convergent angulations are often grouped together in their association with distal-surface carries, our additional finding of alpha and beta diversity differences between convergent impactions (horizontal and mesial) highlights that key microbial community differences exist between different convergent angulations [17, 43, 44]. Since species diversity correlates with environmental heterogeneity, it highlights the importance of understanding whether more subtle environmental change at horizontal, rather than mesial, convergent impactions might have a greater influence on cariogenesis. Whilst all groups were dominated by the genus *Veillonella*, this was particularly profound in convergent impactions, which had 13 *Veillonella* ASVs present at greater abundance. Within-convergent impaction analysis showed that 14 ASVs belonging to *Veillonella* were in higher abundance in horizontal versus mesial impactions. This implies that much of the overall differences in the convergent (vs divergent) analysis was driven by the horizontal impaction alone. Furthermore, the composition of ASVs associated with *Veillonella* was shown to be highly informative in machine learning, being particularly important in distinguishing the microbial communities associated with the two convergent impactions. For *Veillonella*, past studies of function and metabolic interactions with other genera in the oral cavity have demonstrated that its presence alongside *Streptococcus* species may increase cariogenic risk. Detection of *Veillonella* at increased abundance in convergent (particularly horizontal) impactions may, therefore, partly elucidate the association between convergent angles of impaction between molars and distal surface.

Conflict of interest statement

The authors declare no competing interest.

Acknowledgments

Figure 1 for this paper was created with BioRender.com

Statement of ethical approval

Recruitment and sampling was conducted under NHS approved ethics (IRAS ID: 265014).

Data availability statement

Upon acceptance of the manuscript the 16S rRNA amplicon data will be uploaded to the National Centre for Biotechnology Information Short Reads Archive (NCBI SRA) and accession number provided.

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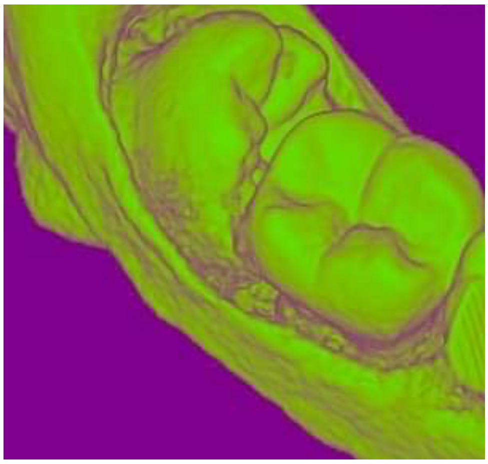

Chapter 6

Original Research – Imaging Study

Parameters associated with radiographic distal surface caries in the mandibular second molar adjacent to an impacted third molar

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ABSTRACT

Background: To determine the risk factors for the development of radiographic distal surface caries (DSC) in patients who attend routine dental check-ups during an era of National Institute for Health Care Excellence third molar surgery guidelines.

Methods: Radiographs taken during routine dental examinations involving 1012 patients from Manchester, UK were accessed. Clinical parameters, oral health, patient demographics, and socioeconomic factors were assessed. Risk factors were identified by multivariate logistic regression analysis.

Results: The prevalence of DSC was 63.9% and rDSC was distributed homogenously across all five socioeconomic groups ($p = 0.425$). Risk factors associated with DSC ($p < 0.001$) were identified as partially erupted mesio-angularly impacted mandibular third molars, third molars with compromised molar to molar contact points, loss of lamina dura of ≥ 2 mm, male gender, increasing age, and a higher modified Decayed Missing Filled Tooth score.

Conclusion: DSC was significantly associated with the angulation of third molars, the compromised contact position of the adjacent third molar, the periodontal status of the distal aspect of the second molar and the cumulative history of oral health in a population governed by specific third molar guidelines. An active approach to third molar surgical management could reduce DSC and serve this population, irrespective of patients' socioeconomic or deprivation status.

Introduction

In the UK, clinical guidelines state that impacted lower third molars should be left in situ unless strict criteria are met. Reasons for removal, as stated in the National Institute for Health Care Excellence (NICE) guidance 2000, are repeated episodes of pericoronitis, unrestorable caries, non-treatable pulpal or periapical pathology, abscess, osteomyelitis, internal or external resorption, fracture, tooth impeding surgery, reconstructive jaw surgery, tooth involved in tumour resection, cellulitis or disease of the follicle including cysts/tumours [1]. However, clinicians and recent studies draw attention to an increasing prevalence of caries that develop in the distal aspect of the lower second molar teeth as a result of the persistence of food and debris stagnation and inaccessibility to cleaning devices leading to mature dental plaque between both teeth. An in-depth analysis of the literature found a significant prevalence of distal surface caries (DSC) in mandibular second molars. However, the prevalence was usually assessed in referred hospital patients and does not relate to the risk in the general dental population [2]. We foresee a difference in the prevalence of DSC between UK hospital referred populations and patients who are routinely assessed and, as a consequence, a difference in the pattern of dental disease associated with impacted mandibular third molars and its risk factors. We also hypothesised that patients in the general population with impacted third molars have a greater dental caries experience in the adjacent second mandibular molar when they belong to areas of lower socioeconomic status. Therefore, this retrospective observational study aimed to determine the prevalence of distal surface caries detected on radiographs (rDSC) in a non-third molar assessment-based population guided by strict third molar removal indications. The study sought to correlate this with potential risk factors such as the orientation and contact point localisation of the adjacent third molar, periodontal support of the second molar, patient demographics, past dental disease experience and socioeconomic status.

Materials and methods

The investigator (VT) designed and implemented a retrospective cross-sectional study which was submitted via the Integrated Research Application System (IRAS) (ref: 265014). Ethical approval was obtained from the Health Research Authority (HRA), Health and Care Research Wales (HCRW) (ref: 20WM/0008), West Midlands - Solihull Research Ethics Committee and the Confidentially Advisory Group (CAG) London Committee (ref: 20/CAG/0050). The study was conducted in full conformance with all the relevant legal requirements and the principles of the Declaration of Helsinki, Good Clinical Practice (GCP) and the UK Policy Framework for Health and Social Care Research 2017.

The sample size for this study was calculated by power calculation (G*Power 3.1.5, Heinrich-Heine-Universität Düsseldorf), which allowed for a CI of 95% with a 5% margin of error (standard power level of 80% and alpha level of 80%, $p = 0.05$). A sample size of 969 was calculated and 1012 patients were assessed. The retrospective study samples were derived from populations of patients who presented to the Manchester University NHS Foundation Trust, University Dental Hospital, UK and who attended routine examinations and had bitewings and periapical radiographs taken. In addition, the investigator had access to a panoramic radiograph of some of the included patients. All patients had been managed and treated in the past by the local dental team and the target population of this study included adults who attended a dental appointment for caries screening within a national healthcare-based setting. The investigator of the centre accessed the previously taken radiographs electronically via a Picture Archiving and Communication System (PACS). This medical imaging technology was used to perform a re-evaluation of specific patient characteristics. Included were radiographs taken after 31st January 2012 of patients ≥ 25 years of age with impacted and partially erupted mandibular third molars adjacent to a second mandibular molar. Fully erupted and functional third molars were excluded from the study. We only included excellent quality images (Grade 1). Images with artefacts such as severe cervical burnout and positioning errors or otherwise obscured areas of interest were excluded. We also excluded second molars with full coverage crowns or which were extensively restored or with severe decay or retained roots. However, when both the right and left sides of the same patient met the inclusion criteria, only one image was randomly selected by tossing a coin. All images with a head outcome were included in the study. This resulted in a final study population of 1012 patients.

In this study, partial eruption or partial emergence of the mandibular third molar was determined by assessing the third molar position in relation to the adjacent second molar and the anatomical landmarks. The third molars were deemed to be partially erupted when one of the third molar cusps was positioned above the external oblique ridge or the occlusal plane level of the neighbouring second molar. In cases where these anatomical landmarks could not be assessed on the radiograph, the Cementoenamel Junction (CEJ) of the adjacent mandibular second molar in relation to the marginal ridge position of the adjacent third molar was also used to obtain information on the eruption status of mandibular third molars and its depth of impaction. This assessment method is a modified description of the Pell & Gregory classification and class I B, class II B, class III A and B from the original Pell & Gregory categorisation were included [3]. This was applied to all third molar angulation types (mesial, distal, vertical, horizontal and transverse). Figure 1 illustrates an impacted and partially erupted mandibular third molar on a bitewing radiograph contacting the second mandibular molar below the CEJ. Figure 2 shows a section of a panoramic radiograph of a mandibular third molar that was deemed partially erupted. The external oblique ridge or bony anterior border of the ramus that appears radiopaque and is located on the outer aspect of the mandible which runs from the ramus to the first molar is indicated with a white dashed line.

The primary outcome of interest was caries on the distal aspect of the mandibular second molar (DSC). A caries lesion was determined to be present when a radiolucency with irregular morphology and margins could be detected in enamel and/or dentine or cementum. The secondary outcomes of interest included variables such as patient demographics, socioeconomic status and oral health status. The study investigator of the centre collected the following information: patient ID, age (in years) and gender. They also collected the following radiographic characteristics: side of the mandible (right or left), angulation type of the third molar according to Winter's classification, periodontal status assessed by recording the vertical lamina dura (LD) loss in millimetres distally to the second mandibular molar, and the mesial-buccal cusp relationship of the third molar with the CEJ of the adjacent second molar (molar-to-molar contact point: above, below, at or no contact with the CEJ of the adjacent second

molar). These data were recorded on standardised Excel spreadsheets. We also adapted the traditional Decayed, Missing, Filled Tooth (DMFT) index for use in this study according to the radiographic appearance of the total number of decayed, missing and filled teeth on radiographs. This is a modified version (mDMFT-R) of the original DMFT index. The formula we developed to calculate the mDMFT-R score was: DMFT count x 100 / tooth count (tooth crowns fully visible on the radiograph). To assess the socioeconomic status of the patients from Manchester, the postcode of their home address was entered into an online conversion tool and was adapted to the Index of Multiple Deprivation (IMD) score which has five categories. The ranges of IMD scores from least to most derived were: Category 1, ≤ 8.49; Category 2, 8.5 - 13.79; Category 3, 13.8 - 21.35; Category 4, 21.36 - 34.17; Category 5, ≥ 34.18 [4].
A pre-data collection test was performed to provide feedback on the protocol. Calibration meetings were held via Zoom, and assessments of standards and data collection methods and approaches were standardised. A pilot study was performed before the full study to assess the work and data collection flow. The radiographs were initially viewed and assessed for mandibular second molar characteristics, such as the presence of DSC and LD loss of ≥ 2 mm, by one observer. Subsequently, the entire data set was reassessed by a second observer and any disagreements were resolved by consensus. To analyse the intra-observer agreement, 102 randomly selected cases (10% of the whole study population) were reassessed by the two observers after at least six weeks.

The statistical analysis was performed using IBM SPSS Statistics Version 26.0 for MAC (Release 26.0.0.0, 64-bit edition). The intra-observer and inter-observer agreement on the radiographic finding of DSC and loss of LD was analysed using the Cohen's K test (an agreement of 0.75 to 1.00 was considered excellent, 0.60 to 0.74 good, 0.40 to 0.59 moderate, and less than 0.40 poor). The associations between DSC in the second mandibular molar and radiographic, demographic, socioeconomic and oral health variables were analysed using Pearson's chi-square test and the t-test was used to compare the means of the two groups. Additionally, a multivariate logistic regression model was used to further evaluate predictive values for the risk factors of the prevalence of DSC. The significance level was set at $p < 0.05$.

Results

On PACS, 8304 patients were viewed and 1012 (12.18%) patients were included. The level of agreement between the two observers for DSC and loss of LD was excellent ($\kappa = 0.776$, $p < 0.0001$). The intra-observer reliability of both observers was also excellent (κ of observer A = 0.812, κ of observer B = 0.797; $p < 0.0001$). Six hundred forty-seven of the included 1012 patients were affected, resulting in a prevalence of DSC of 63.9%. Fifty-three percent (n = 532) of third molars were located on the left side of the mandible and 57% (n = 578) of the affected patients were male. The percentages in each age (years) category were as follows: 25-30 (39.4%, n = 402), 31-35 (20.3%, n = 205), 36-40 (11.4%, n = 115), 41-50 (16.4%, n = 166), 51-60 (8.2%, n = 83) and ≥ 61 (4.1%, n = 41). The orientations of the third molars were: mesial (59.2%, n = 599), horizontal (20.3%, n = 203), vertical (9.7%, n = 98), distal (10.8%, n = 109) and transverse (0.3%, n = 3). The molar-to-molar contact points of the mesial-buccal cusp position of the third molar in relation to the CEJ of the second molar were: above (2.6%, n = 26), at (10.9%, n = 110), below (84.6%, n = 846) and no contact (3.0%, n = 30). In this patient sample, 13.6% (n = 138) had < 2 mm loss of LD and 86.4% (n = 874) had ≥ 2 mm loss of LD on the distal aspect of the second molar. The IMD quintile scores were (from 1 least deprived to 5 most deprived): 1 (11.3%, n = 114), 2 (12.7%, n = 129), 3 (16.4%, n = 166), 4 (21.1%, n = 214), 5 (36.1%, n =365) and missing score (2.4%, n = 24). The mDMFT-R (%) group scores were as follows: 0 (7.2%, n = 73), 1-15 (7.9%, n = 80), 16-30 (17.2%, n = 178), 31-45 (17.7%, n = 179), 46-60 (16.6%, n = 167), 61-75 (17.1%, n = 173) and ≥ 76 (16.4%, n = 166).

The presence of DSC in the second molar and its association with various patient demographics, radiographic characteristics and socioeconomic and oral health status are shown in Table 1. Pearson's chi-square independence test indicated that the variables were significantly associated with the occurrence of DSC in second mandibular molars, with the exceptions of the side of the mandible and socioeconomic status. Among the different groups of angulations of mandibular third molars, mesially inclined were related to the highest prevalence of DSC in the second mandibular molar (78.3%), followed by horizontally inclined third molars (55.7%). DSC was less frequently observed in patients in which the molar-to-molar contact was above the CEJ (24.6%), compared to those patients in which the contacts were made at or below the CEJ (27.3% and 70.8% respectively). There was a statistically significant increase in DSC with increasing age ($p < 0.001$). rDSC was also significantly more frequently observed in patients with loss of LD of ≥ 2 mm (71.4%) and increasing mDMFT-R percentages. Male patients were significantly more frequently affected by DSC (68.2%) than female patients (58.3%). Further analysis showed that when comparing male (n = 394) and female (n = 253) patients with DSC they had identical mean ages (38 years) and loss of LD ≥ 2 mm (96.6%), equal mean IMD quintile groups (Category 4), and very similar mean mDMFT-R scores (51.6% and 52.1% respectively). The most common cusp position was below the CEJ (92.9% and 92.1% respectively) and the most frequent third molar orientation was mesially angulated (71.6% and 73.9% respectively). Both gender groups were not significantly different from each other.

Table 1. Prevalence of DSC in mandibular second molars adjacent to impacted third molars and its relation to clinical, demographic, socioeconomic and oral health characteristics.

Characteristic	Total	Presence of DSC		*p*-value
	n = 1012 (%)	Yes (%)	No (%)	
Side of mandible				0.883
Right	480 (47.4)	308 (64.2)	172 (35.8)	
Left	532 (52.6)	339 (63.7)	193 (36.3)	
Gender				0.001*
Female	434 (42.9)	253 (58.3)	181 (41.7)	
Male	578 (57.1)	394 (68.2)	184 (31.8)	
Mean age (years) ± SD	36.6±11.1	38.1±11.9	33.9±8.9	< 0.001*
Age (years)				< 0.001*
25-30	402 (39.4)	236 (58.7)	166 (41.3)	
31-35	205 (20.3)	105 (51.2)	100 (48.8)	
36-40	115 (11.4)	80 (69.6)	35 (30.4)	
41-50	166 (16.4)	126 (75.9)	40 (24.1)	
51-60	83 (8.2)	64 (77.1)	19 (22.9)	
≥ 61	41 (4.1)	36 (87.8)	5 (12.2)	
Orientation of third molar impaction				< 0.001*
Mesial	599 (59.2)	469 (78.3)	130 (21.7)	
Horizontal	203 (20.1)	113 (55.7)	90 (44.3)	
Vertical	98 (9.7)	38 (38.8)	60 (61.2)	
Distal	109 (10.8)	25 (22.9)	84 (77.1)	
Transverse	3 (0.3)	2 (66.7)	1 (33.3)	
Contact point localisation: MB cusp position				< 0.001*
Above	26 (2.6)	9 (24.6)	17 (65.4)	
At	110 (10.9)	30 (27.3)	80 (72.7)	
Below	846 (83.6)	599 (70.8)	247 (29.2)	
No contact	30 (3.0)	9 (30)	21 (70)	
Loss of lamina dura				< 0.001*
< 2 mm	138 (13.6)	23 (16.7)	115 (83.3)	
≥ 2 mm	874 (86.4)	624 (71.4)	250 (28.6)	
Mean quintile group IMD score ± SD	3.6±1.4	3.7±1.4	3.5±1.4	0.280
Quintile group IMD score				0.425
1 (least deprived)	114 (11.3)	68 (59.6)	46 (40.4)	
2	129 (12.7)	81 (62.8)	48 (37.2)	
3	166 (16.4)	98 (59.0)	68 (41.0)	
4	214 (21.1)	142 (66.4)	72 (33.6)	
5 (most deprived)	365 (36.1)	244 (66.8)	121 (33.2)	
Missing	24 (2.4)	14 (58.3)	10 (41.7)	
Mean mDMFT-R (%) ± SD	47.5±28.2	51.8±27.7	39.9±27.6	< 0.001*
mDMFT-R (%)				< 0.001*
0	73 (7.2)	22 (30.1)	51 (69.9)	
1-15	80 (7.9)	40 (50.0)	40 (50.0)	
16-30	174 (17.2)	111 (63.8)	63 (36.2)	
31-45	179 (17.7)	118 (65.9)	61 (43.1)	
46-60	167 (16.6)	115 (68.9)	52 (31.1)	
61-75	173 (17.1)	107 (61.8)	66 (38.2)	
≥ 76	166 (16.4)	134 (80.7)	32 (19.3)	

MB cusp, Mesial-Buccal cusp; IMD, Index of Multiple Deprivation; mDMFT-R (modified decayed, missing, filled, tooth index applied to radiographs). * Statistically significant ($p < 0.05$). Pearson's chi-square independence test performed between categorical variables and the t-test to test between means of two groups.

The multivariate logistic regression analysis (Table 2) revealed the following risk factors for developing DSC: third molars with mesial angulation (OR = 3.62, $p \leq 0.001$), loss of LD of ≥ 2 mm (OR = 6.55, $p \leq 0.001$), molar-to-molar contact points below the CEJ (OR = 4.21, $p = 0.002$), male gender (OR = 1.51, $p = 0.010$) and patients with ages between 41 and 50 years (OR = 2.20, $p = 0.002$). Also, all mDMFT-R scores had a statistically significantly greater odd of DSC in comparison to the reference mDMFT-R score (OR = 2.57 – 6.10; $p = 0.015$ – $p < 0.001$).

Table 2. Multivariate logistic regression model for DSC

	OR	95% CI of OR		*p-value*	Coefficient
		Lower	Upper		
Gender					
Female	1				
Male	1.51	1.11	2.10	0.010*	0.42
Age (years)				< 0.001*	
25-30	1				
31-35	0.55	0.37	0.83	0.004*	- 0.59
36-40	1.51	0.89	2.55	0.124	0.41
41-50	2.20	1.34	3.62	0.002*	0.79
51-60	1.66	0.86	3.20	0.132	0.51
≥ 61	2.85	0.96	8.44	0.060	1.05
Orientation of 3rd molar impaction				< 0.001*	
Vertical	1				
Distal	0.63	0.30	1.32	0.221	- 0.46
Horizontal	1.36	0.71	2.59	0.352	0.31
Mesial	3.62	1.98	6.59	< 0.001*	1.29
Transverse	6.36	0.36	111.74	0.206	1.85
Contact point localisation: MB cusp				0.021*	
position	1				
No contact	5.36	1.30	22.16	0.020*	1.68
Above	3.67	1.21	11.13	0.021*	1.30
At	4.21	1.67	10.59	0.002*	1.44
Below					
Loss of lamina dura					
< 2 mm	1				
≥ 2 mm	6.55	3.71	11.60	< 0.001*	1.88
mDMFT-R (%)				< 0.001*	
0	1				
1-15	2.57	1.20	5.51	< 0.015*	0.95
16-30	3.72	1.91	7.25	0.001*	1.32
31-45	3.37	1.74	6.55	0.001*	1.22
46-60	3.77	1.93	7.40	0.001*	1.33
61-75	2.49	1.27	4.87	0.008*	0.91
≥ 75	6.10	2.93	12.70	0.001*	1.81

1 Reference group; OR, Odds Ratio; CI, Confidence Interval. * Statistically significant ($p < 0.05$) by multivariate logistic regression analysis.

Discussion

The literature suggested that third molar retention over the long-term results in oral detriment and that impacted third molars cause plaque retention leading to caries on the distal aspect of the second molar [5]. However, the cariogenic risk factors of DSC are still currently unknown. Our study assessed the prevalence of DSC in the second mandibular molar and IMD status of patients who had intra-oral radiographs taken as part of routine dental check-ups, during a period when the NICE third molar surgery guidelines were issued and strictly followed in the UK. Strict adherence to the guidelines was ensured by regular trust wide audits of patients records of reasons for third molar removal as well as trust referral policy on third molar removal which were in place. Outcomes of the assessments and audits were regularly presented during four annually timetabled trust clinical effectiveness meeting days and the data were subsequently submitted to insurance providers with the aim to show evidence of compliance thus reduce the insurance fee for the hospital. In our study, we aimed to determine the risk factors for the development of DSC in this patient population during this era.

The present study found a higher prevalence proportion of DSC (63.9%) than previous studies which reported a rate of up to 52% [6]. A systematic review with a meta-analysis of previous studies on patients who underwent preoperative assessment for the removal of third molars reported a prevalence of one in five patients [2]. Another study investigated the prevalence of non-third molar assessed populations and reported a prevalence of 31.6% by examining CBCT scans [7]. Other studies reported distal caries on panoramic radiographs, which ranged from 4.35 to 38% [8, 9]. The lower prevalence in these previous studies may be because most studies solely used panoramic radiographs to detect DSC, and extra-oral radiographs are much less sensitive in caries detection than intra-oral radiographs [10]. The high rate of DSC in the present study might also be related to the strict inclusion criteria used. It is well documented that third molar crown completion and eruption are usually around 12-16 and 16-21 years old respectively. However, there is wide individual variation in eruption times and root formation of the third mandibular molar is usually completed around 18-25 years old, limiting positional changes of the third molar [11, 12]. Research suggests that interproximal caries take around two to three years to develop [13] and there is some evidence that DSC peaks around 32 years of age in a population referred for third molar assessment [14]. We included female and male patients aged ≥ 25 years of age to ensure that third molar root formation was completed. In contrast, in previous studies, populations as young as 16-22 years of age were assessed for DSC and, consequently, DSC may have been more difficult to detect [15]. A further reason why the present study found a higher DSC prevalence could be that we only included partially erupted and superficial impaction third molars as we aimed to assess this specific clinical relationship. This set a baseline that the third molar was in communication with the oral cavity and differentiated partially erupted and impacted third molars from unerupted impacted and functional third molars, as second molars adjacent to both unerupted and functional third molars have a reduced risk of DSC [16]. However, since the eruption of a tooth is a clinical parameter, the partial eruption of the mandibular third molar in the present study was radiographically determined by meticulously assessing its position in relation to the adjacent second molar and anatomical landmarks. However, the most likely explanation for the high prevalence of DSC in the present study is that the data were collected after the introduction of the NICE third molar clinical guidelines in England, United Kingdom (UK) in 2000. This ensured that all radiographs included in the present study were taken when strict third molar removal criteria were in force and clinical audits were performed regularly to ensure compliance of clinicians to these guidelines. Whilst UK-based clinicians strictly adhered to the NICE guidelines and only removed symptomatic third molars or when specific pathology was present, many international clinicians do not face such restrictive guidelines but can discuss the risk of third molar retention with their patients and offer a patient-tailored-approach [17-23]. As a result, clinicians outside the UK might be more likely to remove third molars, with a subsequent lower rate of DSC.

One main characteristic associated with DSC is the angulation of the adjacent third molar. The literature repeatedly describes a strong association with mesially impacted third molars adjacent to impacted third molars [24 -26]. This is in line with the present study where multivariate logistic regression analysis (Table 2) revealed that third molars with mesial angulation have a significantly greater probability of rDSC in the second molar (OR = 3.62, $p \leq 0.001$). Another anatomical variation that is significantly associated with DSC is the molar-to-molar contact points region and contacts below the CEJ are at 4.21 times greater risk of DSC compared to third molars with no contact with the adjacent molar. There has been much speculation about the molar-to-molar contact point but very few studies have examined this explicitly [7, 27]. The American

Association of Oral and Maxillofacial Surgeons (AAOMS) states in their white paper that when third molars are impacted and have an uncharacteristic molar-to-molar contact limiting the third molar's functional ability, the third molar is classified as pathological, and this justified early surgical removal in the US [28]. Our regression analysis showed that all atypical contact points between mandibular second and third molars are associated with rDSC although molar-to-molar below the contact points are most strongly linked to rDSC (p = 0.002). We believe that DSC localisation can be categorised into the following groups: DSC above the usual molar-to-molar contact is a form of smooth surface caries, DSC at the usual molar-to-molar contact is a form of interproximal caries and DSC below the usual molar-to-molar contact is a type of root surface caries. No direct contact between molars may be compared to a situation where a third molar is absent. In this study, the various types contribute to the overall prevalence of DSC (63.9%): 0.6%, above, smooth surface; 3%, at, interproximal; 59.3%, below, root surface; and 3%, no contact, absent third molar. This indicated that in the vast majority of patients, rDSC affects the root surface of the second molar next to mesially and horizontally angulated third molars.

We radiographically examined the loss of LD to assess the loss of periodontium. An intact LD is considered a sign of a healthy periodontium [29]. Few studies have previously studied the relationship between these two parameters and according to our knowledge, this is the first study investigating the relationship between the two measurements using linear regression analysis of DSC. We found that third molars with radiographic evidence of loss of LD ≥ 2 mm on the distal aspect of the second molar were 6.55 times more likely to be associated with DSC compared to the third molar with loss of LD < 2 mm. This finding was highly statistically significant and was the variable in the multivariate log regression analysis with the highest odd ratio and a positive coefficient (1.88). Consequently, we believe that vertical loss of LD of ≥ 2 mm is a significant precursory state and predictor for the projection of rDSC on the root aspect. From our observations, we also found that rDSC takes place on the root aspect after the occurrence of LD loss, allowing access to the exposed root surface of the distal aspect of the second molar. Thus, we propose that loss of LD ≥ 2 mm is an

important precursor that may be used to predict DSC risk in susceptible patients, especially those with other risk factors.
The literature suggested that DSC peaks during the early fourth decade of life in a third molar assessed population. However, we found in a population who attended for dental check-up that the DSC group had a mean age of 38 years while the rDSC free group was on average four years younger. Further analysis showed that the average age of patients with DSC and mesially and horizontally angulated third molars was lower compared to DSC patients with distal, vertical and transverse third molars. This suggests that mesial and horizontal third molar angulations may have greater cariogenic potential. Therefore, it would be interesting to compare the microbiological profile of dental plaque and the relative abundance of each microbe from the distal surface of the second mandibular molar adjacent to different third molar angulations.

In 2019, McArdle and McDonald reported lower DMFT scores of patients with DSC than those of a surveyed population [30]. In the present study, the mean modified mDMFT-R was used, which was significantly higher in patients with DSC in comparison to DSC-free patients. Nonetheless, the clinical relevance of this observation seems limited. Firstly, the relatively small difference in mDMFT-R (<12%) would be difficult to clinically differentiate and secondly, the patients with DSC were on average four years older, and caries experience and resultant DMFT score increase with age. In the present study, male patients had a 1.51 times greater probability of suffering from DSC in comparison to female patients. When we performed a further analysis, we could not find a significant difference in the sample characteristics of both genders that could explain the observed DSC risk. However, it has been documented in the literature that men visit dentists less frequently compared to women. Men seek oral treatment more often for acute dental problems rather than chronic conditions and less frequently for disease prevention [31]. It has also been documented that women exhibit more positive attitudes about dental visits, greater oral health literacy and better oral health behaviours [32]. Thus, women may be more likely to have their third molar-related pathoses treated, with eventual third molar removal surgery and consequently are at reduced risk of DSC. Interestingly, the prevalence of DSC within the investigated patient population showed that DSC was equally distributed across all IMD groups, therefore affecting the least deprived almost as frequently as the most deprived patients. Since there is a well documented strong association of socioeconomic status with general health and oral health, including caries and periodontal disease [33] a similar increase in DSC in more deprived categories was expected. The lack of a relation between DSC and socioeconomic status in the present study can be explained by the strict clinical third molar removal NICE guidelines, which are applied regardless of a person's socioeconomic status. The present study has a number of potential limitations. First, no attempt was made to assess the severity of the lesions. Future research on this topic should include the depth of caries lesions and explore whether both enamel and dentine are involved. In addition, our study could have been improved by clinical verification as both clinical and radiographic examinations should be performed for increased accuracy of diagnosis. On the other hand, the advantages of the present study are the large sample size and the use of a multivariate analysis. This permits analysis of more than one independent variable that influences the outcome variable, leading to more accurate results.

Conclusion

DSC in the second mandibular molar adjacent to a partially erupted and impacted third molar is a common clinical condition with a high prevalence in all socioeconomic groups in a population bound by specific third molar removal indications and guidelines. Long-term retention of third molars as well as clinical characteristics such as mesial impaction, compromised contact points and loss of LD of ≥ 2 mm are associated with increased risk of DSC and almost exclusively affect the root aspect of the second molar. Future studies in well-selected study populations of nations with preventative third molar removal could provide evidence of whether preventative third molar removal has the potential to prevent DSC in second mandibular molars adjacent to impacted and partially erupted third molars. Loss of LD ≥ 2 mm on the distal aspect of the second molar in the presence of an impacted and partially erupted mandibular third molar may present a newly described risk indicator for DSC.

List of abbreviations

American Academy of Periodontology (AAP)

American Association of Oral and Maxillofacial Surgeons (AAOMS)

Cementoenamel Junction (CEJ)

Confidentially Advisory Group (CAG)

Decayed, Missing, Filled Tooth (DMFT)

Distal Surface Caries (DSC)

Good Clinical Practice (GCP)

Health Research Authority (HRA), Health and Care Research Wales (HCRW)

Index of Multiple Deprivation (IMD)

Integrated Research Application System (IRAS)

Lamina Dura (LD)

modified Decayed, Missing, Filled Tooth index on Radiographs (mDMFT-R)

National Institute for Health Care Excellence (NICE)

Picture Archiving and Communication System (PACS)

United Kingdom (UK)

Ethical approval and consent to participate

Ethical approval was obtained from Health Research Authority (HRA), Health and Care Research Wales (HCRW) [ref: 20WM/0008], West Midlands – Solihull Research Ethics Committee.

The need for written informed consent to participate was waived by the Confidentially Advisory Group (CAG), ethics committee [ref: 20/CAG/0050], due to the retrospective nature of the study. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent for publications

Not applicable

Availability of data and materials

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Competing interests

The authors declare that they have no conflict of interests, including financial interests.

Funding information

Nil

Authors' contributions

VT, TF and H.S B contributed to the design and implementation of the research, to the analysis of the results and to the writing of the manuscript. All authors discussed the results and commented on the manuscript.

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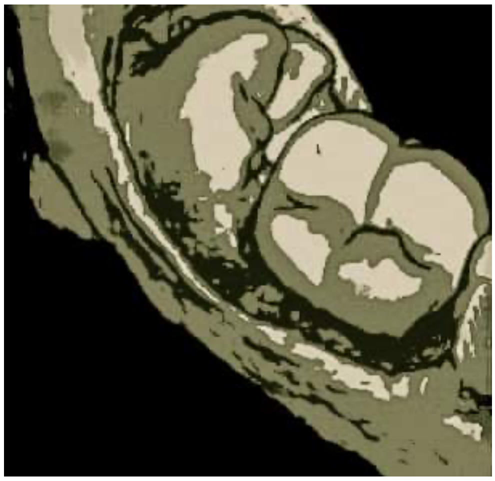
Chapter 7



Original Research – Multi-centre Study

Prevalence of distal surface caries (DSC) in the mandibular second molar in populations with different third molar management strategies: A multi-centre study

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Pending publication

ABSTRACT

***Objective*:** The objective of this study was to determine the prevalence of distal surface caries (DSC) during examination of patients at routine dental check-ups, and to compare the prevalence between two populations with different third molar management strategies: Manchester, UK and Bucharest, Romania.

Materials and Methods: Radiographs that had been taken during routine dental examinations that had involved 1012 and 251 patients from the populations of Manchester and Bucharest respectively were evaluated. These parameters were assessed: the state of the distal surface in the second mandibular molar, loss of periodontal support, third-molar impaction type, contact point localisation, gender, age and cumulative history of dental health.

Results: The overall prevalence of DSC in the second mandibular molar was 63.9% and 19.9% in the Manchester and Bucharest populations respectively. Although the study groups were derived from different populations, common DSC risk factors were identified. Mesially impacted mandibular third molars with contact points below the cementoenamel junction adjacent to second molars, loss of lamina dura of ≥2mm, being of male gender and increased percentages of decayed, missing or filled teeth were found to be risk factors for the development of DSC in both populations and were statistically significant in the Manchester sample ($p < 0.001$).

Conclusion: The UK population, which is governed by strict guidelines that limit the removal of third molars, had a much higher DSC prevalence than the Romanian group and the DSC was cumulative with increasing age. In contrast, third molar removal with opportunity for preventative removal had been practised among the Romanian group, which presented with increased DSC prevalence in younger age groups.

Clinical Relevance: An increased DSC prevalence among elderly patients compared with the young is a characteristic of third-molar retention in a population.

Keywords: Surgery, Dental Disease, Public Health, Prevention, Distal Surface Caries, Third Molar, Third-molar Guidelines, Preventative Removal, Interceptive Treatment, Third-molar Retention

Introduction

The worldwide reported prevalence of third-molar impaction across different morphological and demographic subgroups is 24.4% [1]. Impaction occurs more frequently in the mandible in comparison to the maxilla, and mesioangular impaction is overall the most frequently seen orientation (42%). The vertical and distal angulations comprise 26% and 12% of the impaction respectively, and horizontal angulation was reported to be the least common impaction type (11%). In the literature, many mesial and horizontal angulations have been associated with caries on the distal aspect of the adjacent second molar. An in-depth analysis of prevalence studies found significant prevalence: one in four patients who had been referred for assessment of a third molar showed evidence of distal surface caries (DSC) in mandibular second molars. Moreover, the types of third-molar impaction that are most often linked to the development of DSC are mesial and horizontal [2]. Clinical scientists have suggested that prophylactic or interceptive removal of the impacted third molar is the remedy for this problem, but global debates regarding the appropriateness of such treatment have been ongoing for many years [3, 4]. Currently, there are two chief management strategies: one involves the retention of the third molar unless symptoms or signs of pathology such as DSC develop, and the other involves removal of the third molar prior to the development of signs or pathoses. We believe that a comparison of study populations in nations in which opportunity for preventative third-molar removal surgery is practised with those in which retention of third molars is advocated can provide evidence of whether preventative third-molar removal may prevent DSC in second mandibular molars that are adjacent to impacted or partially erupted mandibular third molars.

Therefore, the purpose of this collaborative study between the University of Bucharest in Romania and the University of Manchester in the UK was to investigate the prevalence of DSC in mandibular second molars that were adjacent to impacted mandibular third molars through examination of radiographs of patients who had attended dental hospitals or clinics for routine dental examinations. In addition to this, the third molar removal strategy in Romania is to remove impacted third molars which are symptomatic or show evidence of pathology as well as prophylactic removal. This is a more flexible approach than that taken in the UK and leads to more prompt removal of impacted third-molar teeth with an emphasis on the prevention of third-molar-related pathoses. On the other hand, the UK guidelines, which are issued by the National Institute for Health and Care Excellence (NICE), contain a very limited number of indications for third-molar removal [3]. We, therefore, foresaw a difference in the prevalence of DSC between the Romanian population (third molar removal including preventative approach and care) and that of the UK (non-intervention strategy) and, as a consequence, a difference in the pattern of dental disease and its risk factors that were associated with impacted mandibular third molars. We also hypothesised that patients with impacted third molars who lived in areas of greater socioeconomic need would show a greater amount of dental caries in the adjacent second mandibular molar than those who lived in less deprived areas.

The aim of this retrospective, observational study was to determine the prevalence of DSC in a population that had received an element of preventative care compared with a population that had been subject to a non-intervention strategy. The prevalence findings would then be correlated with the orientation and contact point localisation of the adjacent third molar, periodontal support of the second molar, patient demographics and a summary measure of past dental disease experience and socioeconomic status.

Materials and methods

Sample selection

The study conformed to all the relevant legal requirements and the principles of the Declaration of Helsinki, good clinical practice and the UK policy framework for health and social care research (2017). The investigators designed and implemented a retrospective, cross-sectional study, which was submitted via the integrated research application system (ref: 265014) and was given ethical approval by the UK's Health Research Authority (HRA), Health and Care Research Wales (ref: 20WM/0008) and the West Midlands – Solihull research ethics committee. Approval was also gained from the London committee of the HRA's confidentiality advisory group (ref: 20/CAG/0050). Ethical approval and equivalent study permission were also obtained from the scientific research ethics commission of Carol Davila University of Medicine and Pharmacy of the University of Medicine and Pharmacy Bucharest, Romania (Code PO-35-F-03, Nr. 8823/01.04.2022).

The retrospective study samples were derived from populations of patients who had presented to dental hospitals in two different countries of Europe. The UK sample comprised patients from the Manchester University NHS Foundation Trust, University Dental Hospital, Manchester, UK, who had attended for routine examinations and who had undergone bitewing and periapical radiography. The investigators also had access to panoramic radiographs for some of the included patients. The Romanian sample comprised patients from the University of Medicine and Pharmacy at Carol Davila Bucharest Dental Hospital, Bucharest, Romania. They were self-referred and attended almost exclusively for private dental check-ups. For these patients, a combination of bitewing and periapical radiographs was available. Several panoramic radiographs had also been taken; these formed a classic part of the local oral assessment and dental check-up.

All the patients had previously been managed and treated by local dental teams. The target populations of this study were adults who had attended dental appointments for caries screening within insurance or national-health-care-based settings. The investigators at the two centres accessed and assessed the previously taken radiographs electronically via the use of the picture archiving and communication system (PACS) and re-evaluated specific characteristics. The radiographs that were investigated had been taken after 31 January 2012, of patients ≥25 years of age, who had impacted or partially erupted mandibular third molars adjacent to second mandibular molars. Fully erupted and functional third molars were excluded from the study. Only excellent and good quality (grade 1) images were considered. Images with artefacts such as severe cervical burn-out and positioning errors, or other issues that obscured the area of interest, were excluded. Images that showed second molars with full coverage crowns or extensively restored second molars were excluded, as were those that showed severely decayed second molars. In cases in which both the right and left sides of the mouth of the same patient met the inclusion criteria, only one image was randomly selected through the tossing of a coin. All images with a head outcome were included in the study. The application of these inclusion and exclusion criteria resulted in a final study population of 1012 patients in Manchester and 251 patients in Bucharest.

Radiographic assessment

In this study, partial eruption or partial emergence of the mandibular third molar was determined by assessment of the position of the third molar in relation to that of the adjacent second molar. Figure 1 illustrates an impacted and partially erupted mandibular third molar on a bitewing radiograph, while Figure 2 shows a panoramic radiograph of a mandibular third molar that was deemed to be partially erupted. Partial emergence was judged from the third-molar cusp levels; the third molars were deemed to be partially erupted when one of the cusps was positioned above the external oblique ridge or above the occlusal plane level. However, in cases in which these anatomical landmarks could not be assessed on the radiograph, the cementoenamel junction (CEJ) of the adjacent mandibular second molar in relation to the marginal ridge position of the adjacent third molar was used to obtain information regarding the depth of the mandibular third molar and its eruption status. This assessment method is a modification of the Pell and Gregory classification [5] and classes IB, IIB, IIIA and IIIB of the original Pell and Gregory categorisation were included. This assessment was applied to all third-molar angulations (mesial, distal, vertical, horizontal and transverse).

Figure 1. Left bitewing radiograph of an impacted and partially erupted mandibular third molar

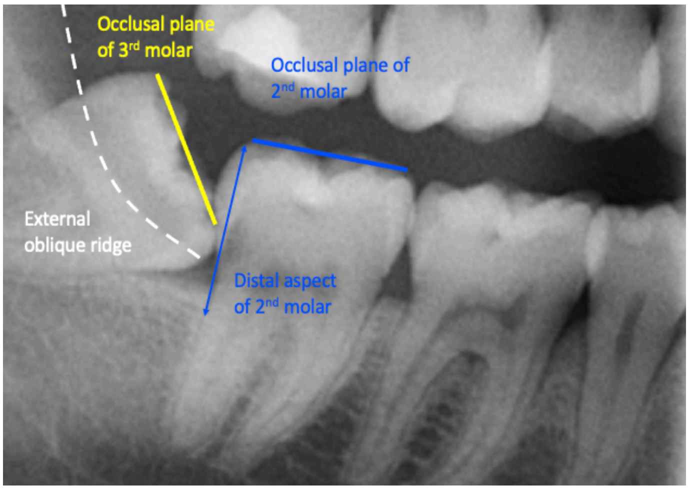

Figure 2. The various anatomical points required for the assessment of third-molar partial emergence/eruption, indicated on a panoramic radiograph

The primary outcome of interest was caries on the distal aspect of the mandibular second molar (DSC). A caries lesion was determined to be present when radiolucency with irregular morphology and margins could be detected in enamel and/or dentine or cementum. The secondary outcomes of interest included variables such as patient demographics and oral health status. The study investigators at both centres collected the following information: patient age (in years) and gender, with the following radiographic characteristics: side of the mandible (right or left); angulation type of the third molar according to Winter's classification; periodontal status as assessed by recording the vertical lamina dura (LD) loss in millimetres distally to the second mandibular molar; and the mesial-buccal cusp relationship of the third molar with the adjacent second molar. This data was recorded on a standard Excel spreadsheet. We also adapted the traditional decayed, missing or filled teeth (DMFT) index for use in this study according to the appearance of the total number of such teeth on the radiographs. This was a modified version of the DMFT (mDMFT-R). The formula used to calculate the mDMFT-R score was: DMFT count x 100 / tooth count (tooth crowns fully visible on radiograph).

The radiographs were viewed and assessed by one investigator in each centre to avoid inter-examiner bias. In addition, a test was performed before the data collection, which was used to provide feedback on the protocol and as an aid in the exchange of ideas and comments. Calibration meetings were held via Zoom and discussions of standards, data collection methods and approaches were assessed in order to standardise them. A pilot was performed prior to the start of the study to assess the work and data collection flow in the different centres. The entire data set of the mandibular second molar characteristics, such as the presence of DSC and LD loss of ≥2mm, was reassessed by a second observer in each centre and any disagreements were resolved by consensus. To analyse the intra-observer agreement, 10% of the cases were randomly selected (102 from Manchester and 26 from Bucharest) and these were reassessed and re-recorded after at least six weeks.

Statistical analysis

The statistical analysis was performed through the use of the IBM SPSS Statistics software, version 26.0, for MAC (release 26.0.0.0, 64-bit edition). The intra- and inter-observer agreement regarding the measurement of the radiographic findings of DSC and loss of attachment was analysed through use of the Cohen's *K* test. Agreement of 0.75 to 1.00 was considered excellent; 0.60 to 0.74, good; 0.40 to 0.59, moderate; and less than 0.40, poor). The association between the presence of DSC in the second mandibular molar and radiographic, demographic and oral health variables was analysed through the application of Pearson's chi-square independence test. A t-test was used to compare the means of the two groups. All significance levels were set at a *p*-value of <0.05.

Results

A total of 8304 radiographs from Manchester patients were viewed on PACS and 1012 patients (12.18%) were included in the study. The level of agreement between the two observers of DSC and loss of LD was excellent (κ = 0.776; p <0.001). The intra-observer reliability of both observers was also excellent (κ of observer A = 0.812; κ of observer B = 0.797; p <0.001). A total of 820 radiographs taken of patients in Bucharest were viewed on PACS and 251 patients (30.61%) were included. The level of agreement between the two observers of DSC and loss of LD was excellent (κ = 0.752; p <0.001), and the intra-observer reliability of both observers was also excellent (κ of observer A = 0.877; κ of observer B = 0.759; p <0.001).

Table 1 provides a summary of the study variables for the entire sample from both research centres. In the Manchester sample, 647 of the 1012 patients were affected, resulting in a DSC prevalence of 63.9%. Most of the affected third molars were located on the left side of the mandible (52.6%, n = 532). The female:male gender ratio was 1:1.3 and the mean age was 37 years. Most of the third molars were mesially impacted (59.2%, n = 599); the second most frequent angle of impaction was horizontal (20.1%, n = 203). The vast majority of the third molars had a molar-to-molar contact point in the mesial-buccal (MB) cusp position below the third molar in relation to the CEJ of the second molar (83.6%, n = 846). In this sample, 86.4% of patients (n = 874) had ≥2mm loss of LD on the distal aspect of the second molar. The mean mDMFT-R of the entire Manchester sample was 48%.

In the Bucharest sample, 50 of the studied 251 patients were affected, resulting in a significantly lower prevalence of DSC (19.9%) compared with the Manchester population. Most of the affected third molars were located on the left side of the mandible (52.6%, n = 132). The female:male ratio was 1:1.3 and the mean age was

38 years. The most common form of impaction of the third molars was mesial (42.6%, n = 107) and the second most frequent direction of impaction was vertical (42.2%, n = 106). The vast majority of the third molars had a molar-to-molar contact point in the MB cusp position below the third molar in relation to the CEJ of the second molar (79.3%, n = 199). In this sample, 84.9% of patients (n = 213) had ≥2mm loss of LD on the distal aspect of the second molar. The mean mDMFT-R of the entire Bucharest sample (28%) was significantly lower than that of the Manchester sample.

Table 2 lists the clinical, demographic and oral health characteristics of patients from Manchester who had DSC in mandibular second molars that were adjacent to impacted third molars. Application of the Pearson chi-square independence test indicated that all variables, with the exception of the side of the mandible on which the teeth were situated, were associated significantly with the occurrence of DSC in second mandibular molars. Among the different types of angulation of lower third molars, mesial inclination was related to the highest prevalence of DSC in the second mandibular molar (78.3%), followed by horizontal inclination (55.7%). DSC was observed less in patients in whom the contact point was above the third mandibular molar, compared with those patients in whom the contact point was at or below the CEJ of the second molar. Significantly more male patients were affected by DSC (68.2%) than female patients (58.3%) and there was a statistically significant increase ($p < 0.001$) in amounts of DSC with increasing age. DSC was significantly more frequently observed in patients with loss of LD of ≥2mm (71.4%) and the occurrence of DSC was related to increasing mDMFT-R percentages.

Table 3 shows the clinical, demographic and oral health characteristics of patients from Bucharest who had DSC in mandibular second molars that were adjacent to impacted third molars. In this study group, the prevalence of DSC was not related to the side of the mandible in which the second molar was situated. Among the different types of angulation of lower third molars, mesial impactions showed the highest prevalence of DSC in the second mandibular molar (24.3%), closely followed by distal (23.3%). DSC was almost equally observed in the patients in whom the contact point was below (20.1%) or at (19.2%) the cusp position of the third mandibular molars.

More male patients (22.4%) were affected than female (16.7%), and DSC prevalence was found to fall with increasing age. DSC was observed more frequently in patients with a loss of LD of ≥2mm (21.1%) and was related to increasing mDMFT-R percentages. With the exception of mDMFT-R, none of the relationships reached statistical significance.

Table 1. Summary of study variables for the sample from both research centres

Population Third molar strategy Characteristics	Manchester (n = 1012) Retention *n* (% of total)	Bucharest (n = 251) Preventative removal *n* (% of total)	*p-value*
Prevalence of DSC	647 (63.9)	50 (19.9)	<0.001*
Side of mandible			0.995
Right	480 (47.4)	119 (47.4)	
Left	532 (52.6)	132 (52.6)	
Gender			0.851
Female	434 (42.9)	108 (43.0)	
Male	578 (57.1)	143 (57.0)	
Age (years)			
Mean age (years) ± standard deviation	36.6 ± 11.1	37.5 ± 9.9	0.241
(SD)	402 (39.4)	59 (23.5)	
25-30	205 (20.3)	81 (32.3)	
31-35	115 (11.4)	47 (18.7)	
36-40	166 (16.4)	40 (15.9)	
41-50	83 (8.2)	15 (6.0)	
51-60	41 (4.1)	9 (3.6)	
≥61			
Orientation of third-molar impaction			<0.001*
Mesial	599 (59.2)	107 (42.6)	
Horizontal	203 (20.1)	8 (3.2)	
Vertical	98 (9.7)	106 (42.2)	
Distal	109 (10.8)	30 (12.0)	
Transverse	3 (0.3)	0 (0)	
Contact point localisation: MB cusp			0.538
position	26 (2.6)	0 (0)	
Above	110 (10.9)	52 (20.7)	
At	846 (83.6)	199 (79.3)	
Below	30 (3.0)	0 (0)	
No contact			
Loss of LD			0.538
<2mm	138 (13.6)	38 (15.1)	
≥2mm	874 (86.4)	213 (84.9)	
Mean mDMFT-R (%) ± SD	47.5 ± 28.2	28.4 ± 21.7	<0.0001*
0	73 (7.2)	6 (2.4)	
1-15	80 (7.9)	66 (26.3)	
16-30	174 (17.2)	78 (31.1)	
31-45	179 (17.7)	69 (27.5)	
46-60	167 (16.6)	16 (6.4)	
61-75	173 (17.1)	13 (5.2)	
≥76	166 (16.4)	3 (1.1)	

*Statistically significant ($p < 0.05$) Pearson's chi-square independence test between categorical variables and the *t*-test or analysis of variance (ANOVA) between different means.

Table 2. Prevalence of DSC in mandibular second molars adjacent to impacted third molars and its relation to clinical, demographic and oral health characteristics in patients from Manchester, UK with third molar retention strategy

Characteristics	Total (*n* = 1012) *n* (%)	Presence of DSC		*p*-value
		Yes (%)	No (%)	
Side of mandible				0.883
Right	480 (47.4)	308 (64.2)	172 (35.8)	
Left	532 (52.6)	339 (63.7)	193 (36.3)	
Gender				0.001*
Female	434 (42.9)	253 (58.3)	181 (41.7)	
Male	578 (57.1)	394 (68.2)	184 (31.8)	
Age (years)				<0.001*
Mean age (years) ± SD	36.6±11.1	38.1±11.9	33.9±8.9	<0.001*
25-30	402 (39.4)	236 (58.7)	166 (41.3)	
31-35	205 (20.3)	105 (51.2)	100 (48.8)	
36-40	115 (11.4)	80 (69.6)	35 (30.4)	
41-50	166 (16.4)	126 (75.9)	40 (24.1)	
51-60	83 (8.2)	64 (77.1)	19 (22.9)	
≥ 61	41 (4.1)	36 (87.8)	5 (12.2)	
Orientation of third-molar impaction				<0.001*
Mesial	599 (59.2)	469 (78.3)	130 (21.7)	
Horizontal	203 (20.1)	113 (55.7)	90 (44.3)	
Vertical	98 (9.7)	38 (38.8)	60 (61.2)	
Distal	109 (10.8)	25 (22.9)	84 (77.1)	
Transverse	3 (0.3)	2 (66.7)	1 (33.3)	
Contact point localisation: MB cusp position				<0.001*
Above	26 (2.6)	9 (24.6)	17 (65.4)	
At	110 (10.9)	30 (27.3)	80 (72.7)	
Below	846 (83.6)	599 (70.8)	247 (29.2)	
No contact	30 (3.0)	9 (30.0)	21 (70.0)	
Loss of LD				<0.001*
<2mm	138 (13.6)	23 (16.7)	115 (83.3)	
≥2mm	874 (86.4)	624 (71.4)	250 (28.6)	
mDMFT-R (%)				< 0.001*
Mean mDMFT-R (%) ± SD	47.5±28.2	51.8±27.7	39.9±27.6	< 0.001*
0	73 (7.2)	22 (30.1)	51 (69.9)	
1-15	80 (7.9)	40 (50.0)	40 (50.0)	
16-30	174 (17.2)	111 (63.8)	63 (36.2)	
31-45	179 (17.7)	118 (65.9)	61 (43.1)	
46-60	167 (16.6)	115 (68.9)	52 (31.1)	
61-75	173 (17.1)	107 (61.8)	66 (38.2)	
≥76	166 (16.4)	134 (80.7)	32 (19.3)	

MB cusp, mesial-buccal cusp; LD, lamina dura; mDMFT-R, modified decayed, missing or filled teeth index applied to radiographs. *Statistically significant (p <0.05) Pearson's chi-square independence test between categorical variables.

Table 3. Prevalence of DSC in mandibular second molars adjacent to impacted third molars and its relation to clinical, demographic and oral health characteristics in patients in Bucharest, Romania with third molar preventative removal strategy

Characteristics	Total (*n* = 251) n (%)	Presence of DSC		*p-value*
		Yes (%)	No (%)	
Side of mandible				0.136
Right	119 (47.4)	19 (16.0)	100 (84.0)	
Left	132 (52.6)	31 (23.5)	101 (76.5)	
Gender				0.262
Female	108 (43.0)	18 (16.7)	90 (83.3)	
Male	143 (57.0)	32 (22.4)	111 (77.6)	
Age (years)				0.773
Mean age (years) ± SD	37.5 ± 9.9	36.4 ± 9.8	38.1 ± 9.2	0.250
25-30	59 (23.5)	14 (22.7)	45 (76.3)	
31-35	81 (32.3)	17 (21.0)	64 (79.0)	
36-40	47 (18.7)	8 (17.0)	39 (82.0)	
41-50	40 (15.9)	8 (20.0)	32 (80.0)	
51-60	15 (6.0)	1 (6.7)	14 (93.3)	
≥ 61	9 (3.6)	2 (22.2)	7 (77.8)	
Orientation of third-molar impaction				0.344
Mesial	107 (42.6)	26 (24.3)	81 (75.7)	
Horizontal	8 (3.2)	1 (12.5)	7 (87.5)	
Vertical	106 (42.2)	16 (15.1)	90 (84.9)	
Distal	30 (12.0)	7 (23.3)	23 (76.7)	
Transverse	0 (0)	0 (0)	0 (0)	
Contact point localisation: MB cusp position				0.889
Above	0 (0)	0 (0)	0 (0)	
At	52 (20.7)	10 (19.2)	42 (80.8)	
Below	199 (79.3)	40 (20.1)	159 (79.9)	
No contact	0 (0)	0 (0)	0 (0)	
Loss of LD				0.257
<2mm	38 (15.1)	5 (13.2)	33 (86.8)	
≥2mm	213 (48.9)	45 (21.1)	168 (78.9)	
mDMFT-R (%)				0.103
Mean mDMFT-R (%) ± SD	28.4 ± 21.7	36.3 ± 33.4	26.3 ± 17.2	0.0034*
0	6 (2.4)	0 (0)	6 (100)	
1-15	66 (26.3)	11 (16.7)	55 (83.3)	
16-30	78 (31.1)	11 (14.1)	67 (85.9)	
31-45	69 (27.5)	18 (26.1)	51 (73.9)	
46-60	16 (6.4)	4 (25.0)	12 (75.0)	
61-75	13 (5.2)	4 (30.8)	9 (69.2)	
≥76	3 (1.1)	2 (66.7)	1 (33.3)	

MB cusp, mesial-buccal cusp; LD, lamina dura; mDMFT-R, modified decayed, missing or filled teeth index applied to radiographs. *Statistically significant ($p < 0.05$) Pearson's chi-square independence test between categorical variables.

Discussion

Should asymptomatic, disease-free, impacted third molars be removed prophylactically before they cause local disease? A Cochrane systematic review of observational studies was performed in 2020 with the aim to provide answers to this globally debated research question [6]. DSC was one of the assessed long-term outcomes in this systematic review. However, the review could include only a small number of relevant studies and could not identify clear evidence for or against the removal of third molars to prevent DSC. The aim of the present retrospective, cross-sectional, observational study was to compare the prevalence of DSC in a population to which a non-intervention strategy with regard to third-molar surgery had been applied, with the DSC prevalence in a population that had the possibility to been treated preventatively. Data was collected regarding patients who had undergone radiography as part of a routine dental check-up in two European countries. Various clinical characteristics such as orientation and contact point localisation of the third molar, periodontal support of the adjacent second molar, patient demographics and a summary measure of past dental disease experience were compared. We hypothesised that DSC would be more prevalent in nations in which third molars were retained and that epidemiological prevalence data for diverse populations would aid in the understanding of risk factors for the development of DSC and would identify differences between groups of patients exposed to different third-molar surgery strategies.

The two populations investigated did not differ statistically with regard to the side of the mandible on which the impacted molar was discovered, gender, age, contact point location or loss of LD. This multicentre study showed that dentists in both centres detected a prevalence of DSC in the second molar adjacent to impacted or partially erupted mandibular third molars among populations that accessed general dental care. We found that the prevalence in the Manchester population was significantly higher than in Bucharest (64% versus 20%). The lower prevalence in the Bucharest sample might partly be related to the fact that most patients had a panoramic radiograph taken as part of their routine dental assessment, while the Manchester data was composed mainly of consecutive intra-oral radiographs from an archive. Intra-oral radiographs show much greater sensitivity in the detection of caries in comparison with extra-oral radiographs [7], suggesting that DSC could be observed more clearly in the Manchester data than in the Bucharest images. As previously mentioned, fewer mesial and horizontally impacted third molars were observed in the Bucharest sample. Both impactions have been identified as those most frequently associated with DSC in the literature when third molars are retained [8]. This could be another reason why lower DSC prevalence rates were found in the Bucharest population. Furthermore, the patients from Bucharest had a lower average mDMFT-R percentage score, which indicated that this sample had, on average, better dental health than the Manchester sample. However, we believe that these reasons do not explain entirely the 3.2-fold higher DSC prevalence in the Manchester study sample. While UK dentists adhere strictly to NICE guidelines, clinicians in Romania discuss the risks as well as financial consequences of third-molar retention with patients, which results in proactive third-molar removal. Therefore, the high rate of DSC occurrence in the Manchester population could in part be related to the long-term retention of third molars due to strict removal guidance [9], although a causal link has not been established.

With regard to the groups of patients in Manchester and Bucharest who exhibited DSC, one main risk factor that was associated with the disease was the angulation of the adjacent third molar. The literature describes a strong association between DSC development and mesially impacted third molars adjacent to mandibular second molars [10]. This description is in line with the findings of the present study, which in both populations showed that third molars with mesial angulation were associated with the greatest prevalence of DSC in the second molar. However, in the Bucharest population, the second most frequent third-molar angulation associated with DSC was vertical impaction. This finding is not in line with the Manchester results, nor with those of other studies [11,12]. The second most frequent angulation that is associated with DSC has been reported to be the horizontal, which was the least frequent angulation associated with DSC in the Bucharest sample and is indeed in general a very rare type of third-molar angulation [1]. We speculate that the reason for this could be related to preventative third-molar removal among the Bucharest subjects, which would have affected the distribution of cases. Shepherd and Brickley (1994) stated that impacted third molars that caused most pathological risk were of vertical type and that they presented most frequently for removal. This assessment was made during an era when prophylactic third-molar removal was routinely performed in the UK [13].

Another anatomical variation that was associated with the occurrence of DSC in our study in both populations was the region of molar-to-molar contact points and contacts below the CEJ. These were associated with a greater risk of DSC compared with third molars with no contact, or those that were at or above the CEJ of the adjacent second molar. Ozec et al. [14] reported that third molars with inclinations of 31-90 degrees, which encompasses horizontally and most mesially inclined third molars, were more likely to cause DSC in the second molar. They assessed the CEJ distance, which is the distance between the mesial CEJ of the third molar and the distal CEJ of the second molar (an arbitrary line through the embrasure). They showed that the more the third molar was tilted mesially, the more the CEJ of the third molar moved distally, and subsequently the CEJ distance and associated embrasure would become larger. Some previous studies have revealed a linear correlation between third-molar mesial angulation and CEJ distance, and it has been reported that DSC prevalence was increased in the presence of third molars that showed contact points at or below the second mandibular molar CEJ [15]. We also found that third molars with radiographic evidence of loss of LD ≥2mm on the distal aspect of the second molar were much more likely to be associated with DSC than third molars with loss of LD <2mm. Consequently, we believe that vertical loss of LD of ≥2mm indicates mild loss of attachment and development of periodontal disease, a precursor for DSC. This was evident in both populations. We are not aware of other studies that have assessed LD as an indicator of DSC development, so we suggest that this parameter should be included in future studies on DSC.

Both sample populations had similar mean ages (approx. 37 years), but in the Manchester population there was almost a five-year difference between the average age of those with DSC (38.1 years) and those without (33.9 years) whilst in the Bucharest population the difference was less marked: DSC group 36.4 years, DSC-free group 38.1 years. Also, in the Manchester patients, the DSC prevalence markedly increased with age, but it decreased overall with age in the Bucharest sample. This would mean that as the Bucharest patients grew older, their level of DSC decreased. Such a finding would be unusual for caries as it is a cumulative disease over a person's lifetime that requires the presence of substrate, bacteria and time. However, preventative removal of third molars could give rise to this finding.

Relatively small but statistically significant differences were observed regarding the orientation of the third-molar impaction and mDMFT-R percentage scores. Overall, the Bucharest sample population contained fewer patients with mesial and horizontal impactions and a greater percentage of vertical impactions. In addition, the mean mDMFT-R percentage was almost 20% less in the Bucharest sample than in the Manchester sample population. This suggests that the Bucharest sample had statistically significant better dental health than the Manchester sample. Clinically this would translate as the Bucharest patients having on average approximately 1.5 fewer DMFT. McArdle and McDonald (2019) reported lower DMFT scores among patients with DSC when compared with those of a regularly surveyed general population [8]. In the present study, the mean modified mDMFT-R was used, which was statistically significantly higher in patients with DSC in comparison with DSC-free patients in the Manchester sample and statistically significantly lower in the Bucharest DSC population than in the Manchester DSC population. Nonetheless, the clinical relevance of this observation seems limited, firstly because the difference in mDMFT-R was small (20%) and it was unclear how this would be clinically differentiated, and secondly because the patients with DSC in Manchester were on average four years older than those without, and caries experience and resultant DMFT scores increase with age.

Previous studies have suggested that the prevalence of DSC in the second molars of men is higher than that in women [15]. The present study also showed that gender influenced the prevalence of DSC in the second molars, as in both population samples, there was a greater prevalence of DSC among male patients. The literature consistently documents that female patients exhibit better oral health behaviours and higher levels of oral hygiene than men [16,17].

The results of the present study confirmed our hypothesis in part, as DSC was found to be significantly more prevalent in patients who had been subject to the non-intervention strategy in Manchester than those who had access and were give the possibility to have preventative care in Bucharest. However, other factors may have contributed to the differences between the populations. Remuneration systems for dental care, health care or social factors may have affected the DSC prevalence. The socioeconomic status of individual patients could not be compared between Manchester and Bucharest. Therefore, future research on this topic should include an assessment of the socioeconomic background, and explore whether there is a correlation or association with DSC development.

Whilst it may be valid to assume that a radiolucent area on the distal aspect of the second molars next to an impacted tooth is due to caries, a limitation of the present study was that there was no clinical or histological verification of caries, and potential radiological artefacts such as burn-out and March band effect, or even root resorption, could not be excluded in all cases [18]. Therefore, future studies should also include clinical verification of the accuracy of diagnosis. On the other hand, the advantages of the present study were the large sample size and the multicentre assessment. Even though this study was retrospective in nature, we designed it in such a way that dental health and oral hygiene data drawn from it could be assessed, as these factors are important in caries prevalence. This multicentre study provides insight into the epidemiology of DSC in the second molars of populations that access general dental care in the UK and Romania and contributes to future research in this field.

Conclusion

The population that was governed by strict restrictive guidelines regarding third-molar removal had a much greater DSC prevalence in comparison with a population that could undergo preventative third-molar removal. In the former population, DSC was cumulative with increasing age, which was not found in the latter population. Although the epidemiological data on DSC is limited, these results support the assumption that retention of third molars is associated with an increased risk of second molar pathology such as DSC. Ultimately, to better determine the impact of third-molar guidelines on DSC occurrence, future studies of populations with similar socioeconomic status in nations that practise preventative or interceptive third-molar removal are warranted. Such studies should include the collection of clinical data such as lesion colour, texture, plaque index, probing depths, bacterial composition and extent of caries in addition to the radiographic data, in order to provide evidence of whether preventative third-molar removal may prevent the development of DSC in second mandibular molars adjacent to impacted or partially erupted third molars.

Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Competing interests

The authors declare that they have no conflict of interests this in includes no financial interests.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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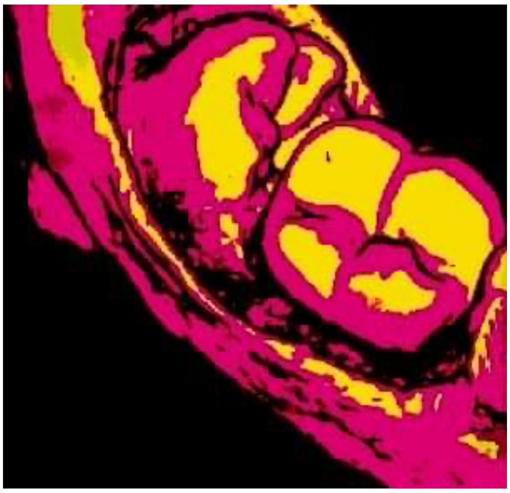

Chapter 8

Research/Evidence base on DSC

General discussion and future prospective

Verena Toedtling
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General discussion

This thesis concludes with a general discussion on how our findings have influenced and improved current thinking on DSC, how it may shape new guidance documents and how artificial intelligence may contribute to treatment plans tailored to the individual patient.

Oral health and oral disease in the population

Three billion five hundred thousand people worldwide have oral diseases and disorders [1]. Untreatable dental caries and periodontal disease in the permanent dentition are the most common global health conditions according to the Global Burden of Disease Study 2019 [2]. Often these conditions are painful which can negatively affect the capacity to eat, speak, smile, impact the psychosocial wellbeing and how people live, work and age. Many social interactions we perform are taken for granted and depend on good oral health and oral diseases can severely impact the quality of life and affect people throughout their lifetime [3]. These effects have not only been measured and confirmed via surveys with various scales but are also well understood and documented. It is understood that those with an unhealthy mouth and few teeth are also forecasted to live shorter lives [4].

Conventionally, the social gradient in health is a phrase used to describe the phenomenon whereby people who are less advantaged in terms of socioeconomic status have worse health and shorter lives than those who are more advantaged. Self-evaluated health status as well as quality of life and symptoms are also worse in subjects in lower status employment [5]. This is also true for oral conditions; people in higher social classes have more and healthier teeth. There is a clear socioeconomic gradient in the proportion of adults who have 21 or more natural teeth ranging from 91% of adults from managerial and professional occupation households to 79% of adults from routine and manual occupation households [6].

There is a very strong and consistent association between socioeconomic status (income, occupation and educational level) and the prevalence and severity of general as well as oral diseases [7]. This association exists from early childhood to older age and across populations in high-, middle- and low-income countries. It is well known that oral health inequalities and oral diseases disproportionally affect the poor and socially disadvantaged members of society and that most low- and middle-income countries are unable to provide services to prevent and treat oral health conditions such as caries [1].

Caries is a cumulative disease with lifetime consequences and a lifetime cost. The prevalence and impact on society as well as the expense resulting from treating caries is significant [8]. Although the latest Adult Dental Health Survey (ADHS) described an overall reduction in dental caries prevalence across the UK population, in 1998 from 54% to 31% in 2009, this survey also described that root surface caries was increasing and becoming a growing problem for a subgroup of the population [6].

Distal surface caries (DSC) in the second molar adjacent to third molar as we have established in **chapter 6** presents not exclusively but mostly frequently as root surface caries. DSC has a specific clinical presentation and many clinicians acknowledged that DSC associated with impacted and partially erupted mandibular third molars has become an issue of concern [9]. In addition to this, DSC in the second molar has been reported to be on the rise and is also known as distal caries or distal-cervical caries [10,11]. Our meta-analysis of DSC prevalence in **chapter 3** revealed that the overall pooled prevalence estimate was calculated with a random-effects model and was 23% (95% CI, 2% to 44%) on a patient level. Prevalence subtotals were 20% (95% CI, 5% to 36%) for prospective and 15% (95% CI, 5% to 36%) for retrospective studies on a molar level in a population referred to hospital care [12]. The literature also suggests that DSC prevalence is higher in the presence of a third molar and DSC has become a familiar diagnosis and reason for subsequent third molar removal [13].

Figure 1. Radiographic and clinical representation of DSC affecting the root aspect of the lower right second molar (rotated to face the distal surface) after removal of both lower right second and third molar. The caries process is undermining the enamel and spreads along the cementum preceded by loss of periodontal attachment and alveolar bone resorption.

We also investigated the historic aspect of third molar surgery in **Chapter 1** and laid out the influences of third molar management such as health economic evaluations to gain an insight into the rationale behind the current third molar guidelines by NICE and why such strict third molar indications have been put in place. We have discussed the guidance document and concluded that there is insufficient evidence available to support the NICE third molar removal indications with regards to DSC. Specifically, the existing NICE guidance was based on evidence from an assessment report that was published by Song *et al.* in 1999 [14]. Which refers to research evidence that was gathered almost four decades ago. We have also highlighted that this research was conducted during a period when large numbers of third molars were removed prophylactically. Significantly, the assessment report documented a very low rate of DSC in mandibular second molars of 1% to 4.5%; currently, when few third molars are removed prophylactically, the literature states that this range is 15% to 51% [15]. We also found that DSC affects a significant number of patients who attend for routine dental check-up and have the distal surface of the second mandibular molar assessed with a bite wing radiograph **(Chapter 6)**. Our systematic review of DSC incidence studies in **chapter 4** concluded that the DSC incidence was higher when third molars were present and this summary finding is currently the best available review of the incidence of DSC [16]. This indicates that it is not just considerable suspicion that the strict NICE guidance regarding third-molar removal contributes to the high incidence of DSC that clinicians currently see, because it promotes third-molar retention and restricts the removal of decay-related third molars to situations in which caries renders the tooth unrestorable [17].

Latest research/evidence base on DSC and impact

At present, robust evidence in third molar research across the globe remains sparse. A Cochrane review update by Mettes *et al.,* in 2012 analysed the available evidence and could still not identify a randomised controlled trial (RCT) that assessed DSC [18]. Apparently, there have been few reasons for research on DSC. However, two clinical trials reportedly were initiated in Denmark and the US many years ago with the intention to provide data on DSC. However, results have not yet been shared and it seems highly unlikely that these trials are still continuing [19]. Nonetheless, a further Cochrane review by Ghaeminia *et al.,* 2016 **(Chapter 2)** was indicated and we included observational studies and non-randomised studies. The introduction of the Cochrane risk of bias tool for non-randomised studies of interventions (ACROBAT-NRSI) made it possible to assess the risk of bias more systematically in epidemiological studies [20]. We identified one longitudinal cohort study by Nunn *et al.,* (2013) in the systematic review, involving 416 subjects (804 third molars) who received their medical and dental care in the private sector and underwent comprehensive oral and radiological examinations approximately every 3 years. They were followed up for a maximum of 25 years [21]. We found that the lowest prevalence and incidence of second molar pathology (caries and periodontitis) occurred when the adjacent third molar was absent. Interestingly, the presence of a third molar that was partially erupted and impacted had a 4.88-fold greater risk of second molar pathology. Although the study with this finding is currently the most respected in the field of DSC, this research was assessed to be at risk of bias due to confounding factors. Importantly we therefore concluded in **chapter 2** that there were insufficient data to advocate prophylactic removal of the third molar in order to prevent DSC at this current time. We noted that asymptomatic and disease free impacted third molars are associated with an increased risk of DSC in the second molars but the evidence is weak and this is the best available evidence at this moment in time. However, the Cochrane systematic review in **chapter 2** did show evidence that the presence of an asymptomatic disease free impacted third molar may be associated with increased risk of periodontitis affecting the adjacent second molar over the long term [22]. The relationship between the occurrence of localised periodontitis on the distal aspect of the second molar in relation to DSC has also become more apparent during this PhD research.

Although there is a lack of conclusive research data on DSC specifically. It is important that the recommendations from this systematic review highlight and underpin evidence-based practice to the clinician. Sacket and colleagues in 1996 have highlighted evidence-based decisions making in health care and described it as a combination of three main components; research evidence, clinical expertise and consideration of the individual patient's values, situation and preferences [23]. With regards to DSC, and in the continuing absence of high-quality research evidence, patient values should be considered and clinical expertise used to guide shared decision making with patients [22]. This was much emphasized in the latest Cochrane review **(Chapter 2)** and this has now been taken into consideration partly by NICE [24]. Regrettably they did not retract their guidelines after reviewing them, but instead have added some form of flexibility to their guidance online. In addition to this the Dental Facility of the Royal College of Surgeons of England introduced a new mandibular third molar guideline called '*Parameters of care for patients undergoing mandibular third molar surgery 2020'*, which has recently been published by the Faculty of Dental Surgery Clinical Standards Committee (Royal College of Surgeons of England) and referred to our Cochrane review and conclusion. The new guidelines by the RCSEng include how to manage a high risk mandibular third molar, the current status of patients' social wellbeing and their involvement in the decision-making [25].

What's new on DSC?

In this thesis we describe further evidence gained by a systematic review which concluded that European based studies suggest that about 1 in every 4 patients referred to hospital care for a third molar assessment may be affected by DSC and that convergent third molar impactions show a significantly greater risk [12]. In **chapter 4** we performed a further systematic review and concluded that two cohort studies indicated that DSC incidence was higher when third molars were erupted and the incidence is higher in an aging population [16]. **Chapter 5** assesses how long-term retention of impacted third molars is associated with plaque stagnation and development of DSC. We found a great abundance of *Veillonella* associated with convergent specifically horizontal third molar impactions and this could indicate that its presence alongside *Streptococcus*, is associated with an increased risk of DSC. **Chapter 7** determines the prevalence of DSC in two different populations: one with prevention strategy and the other with third molar removal strategy. The prevalence of DSC was almost 64% in the UK with retention strategy and 20% in Romania with preventive and early removal strategy. Generally, the DSC prevalence was greater with increasing age in the UK in comparison to the Romanian population sample which was treated with preventative third molar removal which presented with increased DSC in younger age groups. This finding suggests that an increasing DSC prevalence in older patients is a trait of the use of a third molar long term retention strategy within a population and a new finding that hasn't previously been described. In addition to this, the following risk factors were identified and described in **chapter 6**; mesio-angular impacted mandibular third molars with compromised molar to molar contact point most frequently below the emelocemental junction (ECJ), loss of lamina dura (LD) of ≥ 2mm on the distal aspect, male gender, increasing age and higher modified decayed, missing, filled tooth (mDMFT-R) percentage scores assessed on radiographs.

Moreover, Broadbent and Thomson in 2005 suggest that the decayed, missing, and filled teeth (DMFT) index is one of the most common methods in oral epidemiology for assessing dental caries prevalence. It can be used to measure dental treatment needs among populations but may also serve as a socioeconomic indicator [26]. The literature reports that patients with DSC have a 50% lower mean DMFT score in comparison to similar age groups in the general population as assessed by the latest ADHS in 2009 [27]. This proposes that the susceptibility to DSC in second molar teeth is linked to a lower susceptibility to dental caries in general. McArdle and Renton in 2012 reported that DMFT scores of patients with DSC are usually lower than that for a similar age group in a London population [28]. In addition to this a Manchester team also showed that the DMFT score was higher in patients without DSC [29].

Similarly, in **chapter 6** we describe, by using the mDMFT-R index, that DSC is although slightly higher in patients with DSC but these patients were also on average 4 year older. However, caries is a cumulative disease and is expected to increases with age and patients with high DMFT sores are largely in socioeconomically deprived groups. However, our findings suggest too that patient with DSC may have similar or better dental health. These research findings imply that DSC is at odds with the population perception of dental caries in general as caries is usually much more prevalent in lower-economic classes [30]. **Chapter 6** also provides insight into the risk factors of DSC in patients who attended for routine dental check-ups in the UK via multivariate logistic regression analysis. We assessed that the overall prevalence of DSC as 63.9% in the Manchester population with homogeneously prevalence across all socioeconomic groups. Since there is a well-documented strong association of socioeconomic status with general health and oral health, including caries and periodontal disease a similar increase in DSC in more deprived socioeconomic categories was expected. The lack of relation between DSC and socioeconomic status in the present study can be explained by the strict clinical NICE third molar removal guidelines, which are applied regardless of a person's socioeconomic or oral health status. [24].

Although recurrently available results on delaying and preventing preventative practice on third molar removal still have not demonstrated a causal relationship between DSC and third molar retention, there are nevertheless remarkable indications from our research that interceptive or prophylactic third molar removal most likely plays an important role in avoiding DSC and improving the outcome of mandibular second molars adjacent to impacted third molars. In the past decade, more attention has been given to DSC and further studies have been performed. Guidelines have been introduced or changes to existing ones have been made [16,31,32]. Whether this has an impact on the DCS prevalence and incidence or improves the outcomes of second molars still has to be confirmed and proofed. The fact that clinicians in the UK are recommended to strictly adhere to guidelines on third molar removal in order to rationalise health care, while clinicians in others countries have more clinical freedom might provide information. However, it will remain a challenge as it is difficult to extrapolate epidemiological data from the entire population in different areas of the UK or the rest of the world.

Therefore, additional studies with well-designed research methods are still needed to further assess the extent of DSC and the problem it poses in the UK population and beyond. With the current data and approach, it is not possible to conclude suggest whether DSC is a national dental public health concern. Nevertheless, there is some evidence that DSC is becoming more prevalent following delayed extraction of these teeth. Oral surgeons, dental public health consultants, restorative dentists, general dental practitioners and patient lead focus groups, need to be involved in the development of modified guidelines, and views of patients are required. With regards to NICE (the National Institute for Health and Care Excellence) new guidelines on the prophylactic removal of third molars are eagerly anticipated but seems to be deprioritized. However, the increasing prevalence of DSC results in costs, suffering of patients, and may have an impact on economic performance and productivity of the workforce.

Assessing, screening, teaching and training

On reflection, another contributing factor of DSC is related to how this caries pattern is assessed and screened for. DSC may be a continuum of periodontal disease as suggested by our profiling of the microbiome. The development of periodontal pockets and bone loss provides microbes such as *Veillonella* access to the distal aspect of the second molar. Current screening methods, and tools such as basic periodontal examinations (BPE) and bitewing radiographs, frequently exclude the third molar in the analyses and caries risk assessments do not recognize impacted or partially erupted third molar as a caries risk factor [33]. Therefore, it should not be a surprise that DSC is difficult to identify, and there is often less suspicion in patients of socioeconomically advantaged groups that typically have fewer risk factors for caries in general (such frequency of sugar intake, better oral hygiene, education and access to health care and health education and screening). Clinicians and dental students should be trained to recognise this insidious caries pattern. Additionally, DSC should be included in the undergraduate curriculum and in cariology lectures to optimized recognition of DSC and the structures of the posterior mandible. Finally, the NICE third molar guidance as they currently stand seems to indirectly discriminate against patients with better dental health/higher socioeconomic status, as they need to suffer DSC in the second molar first in order to fulfill the requirement for third molar removal before they can request clinical action.

Future perspectives

A) Research study and approach

Despite the results of the studies presented in this thesis, further high-quality research still is required to improve the accuracy of these findings. Well-designed randomised controlled clinical trials investigating the long-term effects of asymptomatic third molar retention vs removal, in a representative sample, are still highly desirable.

Ultimately, to better determine the impact of third molar guidelines on DSC future studies of populations with similar socio-economic need of nations with preventative or interceptive third molar removal are warranted. In addition to the radiographic data, such studies should include clinical parameters on lesion colour, texture, plaque index scores, full mouth periodontal probing depths and bacterial composition of dental plaque. It would also be beneficial to assess the extent of caries by proving additional evidence whether preventative third molar removal has the potential to prevent DSC in second mandibular molars adjacent to impacted and partially erupted third molars. In addition, one should realize that the socioeconomic status of the individual patients within nations might differ considerably. Therefore, future research on this topic should include an assessment of the socioeconomic background of the individual patient, and explore whether there is a statistically significant correlation or association with DSC.

Whilst it may be valid to assume that a radiolucent area on the distal aspect of the second molars next to an impacted tooth is due to caries, a limitation of the present study is that there was no clinical or histological verification of the caries. Potential radiological artifacts such as burn out and March band effect or even root resorption could not be completely excluded in all cases [34,35]. Therefore, future studies should also include clinical verification of the radiographically based diagnosis of DSC. Other improvements of the study design would be to involve general dentists of the patients. This would enable evaluation of dental health and oral hygiene, as these factors are important in caries prevalence, but would also provide insight in the epidemiology of DSC in the second molars of populations that access general dental care.

The results and outcomes from a well-designed RCT will not only provide better understanding of DSC risk factors and proof of a causal relationship, but also facilitate the development of treatment strategies, advancing oral and maxillofacial surgery as a discipline and most importantly, contributing to better oral health globally for millions of patients.

B) Individualised guidelines

Development of future guidelines should adopt individualised care, and an individualised approach should be recommended at all stages of diagnosis, investigation and management. The Cochran review which is part of this thesis was used as evidence building block to contribute to the new third molar guidelines by the RCS England [22,25,]. However, despite the fact that the new RCSEng third molar guidelines make a good attempt to address DSC, but they do not replace the NICE guidelines and don’t have the same mandate. Whilst the RCSEng third molar guidelines provide flexibility for patients and clinicians in the selection of third molar management they do not provide further evidence or add to the existing body of evidence. This could lead to confusion amongst clinicians, which is a limitation of the new guidelines.

C) Artificial intelligence

Artificial intelligence (AI) may be incorporated in advanced diagnostics as a tool to differentiate between patients high at risk to DSC and low risk patients. An AI system is only feasible if accurate, with standardised methods for objectifying clinical symptoms, tooth position, and clinical outcomes collected for every patient [36]. The training of the algorithm relies heavily on the quality and quantity of the data input to ensure the diagnosis and output decision of DSC is accurate [37].

Dentists may employ AI systems as an additional tool to improve the precision of DSC diagnosis, treatment planning, and treatment result prediction via machined learning algorithms. Such deep-learning technologies can provide diagnostic assistance to dental professionals as they mimic human cognition and are capable of learning, thinking and making decision or taking actions [38]. AI enhances the precision of the diagnosis [39]. However, AI is unlikely to completely replace radiologists and dental surgeons for the diagnosis and clinical decisions of DSC.

Conclusion

Our research has shown that DSC occurs most frequently on the root aspect and is associated with localized loss of periodontal support and bone resorption on the distal aspect of the second molar adjacent to a partially erupted and impacted mandibular third molar. DSC is the ramification of loss of periodontal tissue which may be induced by a change in microbiome composition of the distal aspect of the second molar. Making it possible for *Veillonella spp.* to reside and strive in abundance who have the ability to cause root caries and periodontal destruction. As result of the inaccessibility and inability to regularly disturb the biofilm on the distal aspect of the second molars, these well documented periodontal pathogens overpopulate and overgrow in such a favorable environment. Firstly, this can lead to site specific periodontal disease and caries process. As a result, there will be loss of periodontal attachment and cementum exposure. This is associated with the potential to develop root caries on the distal aspect of the second molar next to an impacted third molar tooth. However, whilst there is currently insufficient evidence that impacted third molar retention will cause DSC via the conventional cariogenic process. However, the Cochrane review of 2020 showed evidence that the presence of an asymptomatic disease free impacted third molar is associated with increased occurrence of periodontitis affecting the periodontium of the adjacent second molar over the long term.

Therefore, a better term may be **DSC in the second mandibular molar secondary to localised periodontitis.** Any RCTs that are planned should plan to investigate and prove the causal relationship of both effects, namely loss of periodontal support and root surface caries on the distal aspect of the second molar. The research questions may be broken down into *'Does retention vs. removal of the third molar cause localised loss of periodontal support on the distal aspect of the second molar?'* and investigation should assess the causes of periodontal disease as part of DSC. '*Does third molar retention vs removal cause a change in the microbiome on the distal aspect of the second molar?*' and investigation should be into potential causes of caries processes and caries causing organism. As the DSC process may be driven by different organism or interactions, or bacterial communities depending on the angulation and depth position of the third molar which seems to have an impact on the microbial profile of the distal aspect of the adjacent second molar.

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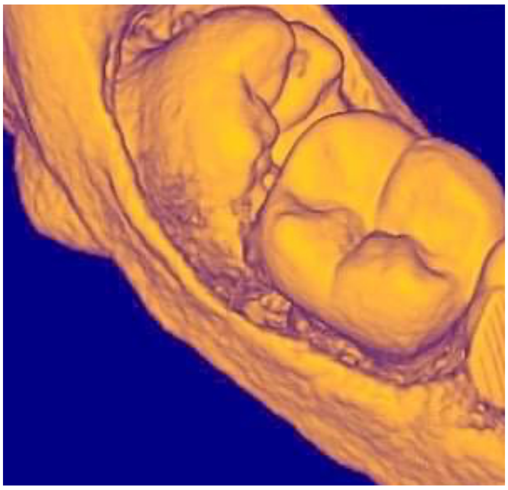

Chapter 9
Addendum

Summary: English, Dutch & German

New understanding and further insight into Distal Surface Caries (DSC) in the second mandibular molar neighbouring an impacted and partially erupted third molar

Verena Toedtling

Tim Forouzanfar

Henk S. Brand

Summary in English

Summary of new understanding and further insights into Distal Surface Caries (DSC)

The objective of this thesis was to explore DSC in the mandibular second molar adjacent to an impacted third molar; 1) assess and up-date the currently available evidence of third molar removal vs retention; 2) define the incidence and prevalence of DSC in different populations; 3) acquire an understanding of the caries process by studying the microbiome and risk factors associated with DSC and 4) improve outcomes of second mandibular molars by identifying potential limitations of the NICE third molar surgery guidance and ultimately improve patient care for the population, regardless of patients' socio-economic or deprivation status within society.

Chapter 1 provides an insight into the historic aspect of third molar removal indications set out initially by the Royal College of Surgeons of England, National Institute of Health US and by the UK-founded NICE guidance, and highlights the controversy that surrounds third molar removal surgery. We lay out the influences of third molar management in the UK and include insight into the historic economic evaluations assessment as well as the available evidence on third molar removal vs retention. We address the growing concerns relating the increasing frequency of DSC in mandibular second molars associated with asymptomatic partially erupted third molars, especially when these are mesially or horizontally impacted. Lastly, we discuss how DSC impacts patients and how established guidance on third molar surgery by a national institution are perceived as strictly compulsory clinical strategies, despite insufficient evidence, and have been used in clinical practice in the UK for more than 20 years.

In **chapter 2** we compared the scientific evidence of effects/consequences of removal of third molars with retention (conservative management) of asymptomatic disease-free impacted third molars in adolescents and adults by conducting a Cochrane systematic review. In our selection criteria we included randomised controlled trials (RCTs), with no restriction on length of follow-up, comparing removal (or absence) with retention (or presence) of asymptomatic disease-free impacted third molars in

adolescents' and adults. We also considered quasi-RCTs and prospective cohort studies for inclusion if investigators measured outcomes with a follow-up of five years or longer. The data collection and analysis of eligible studies was performed and a risk of bias assessment was conducted. We found only studies with low to very low-certainty evidence of the effects of removal compared with retention of asymptomatic disease-free impacted third molars on periodontitis and caries associated with the distal aspect (DSC) of the adjacent second molar. The evidence suggests that the presence of asymptomatic disease-free impacted third molars teeth may be associated with increased risk of periodontitis affecting the adjacent second molar in the long term. However, there is insufficient evidence to demonstrate a difference in DSC risk associated with the presence or absence of impacted third molars. We concluded that there is currently insufficient evidence available to determine whether asymptomatic disease-free impacted third molars should be removed or not. Although retention of asymptomatic disease-free impacted third molars may be associated with increased risk of periodontitis affecting adjacent second molars in the long term, the available evidence is of very low certainty. When the decision is made to retain these disease-free impacted third molars clinical assessment at regular intervals to monitor the development of undesirable outcomes is advisable.

In **chapter 3** we conducted an additional systematic review of epidemiological studies to assess the prevalence of distal surface caries (DSC) in the second molar adjacent to a third molar. Electronic searches were supplemented with reference searching and citation tracking. Reviewers independently and in duplicate performed data extraction, completed structured quality assessments with a validated risk of bias tool for observational studies and categorized the summary scores. The search yielded 81 records and after application of inclusion and exclusion criteria, 11 prevalence studies were analysed in the systematic review. Due to considerable methodological diversity, five studies were not eligible for inclusion in the quantitative synthesis. A meta-analysis of the remaining 6 DSC prevalence studies and a subgroup analysis of 3 studies concerning various third molar angulations were indicated. The overall pooled prevalence estimate was calculated with a random-effects model and was 23% (95% CI, 2% to 44%) on a patient level. Prevalence subtotals were 20% (95% CI, 5% to

36%) for prospective and 15% (95% CI, 5% to 36%) for retrospective studies on a molar level in a population referred to hospital care. A subgroup analysis of three studies with 1296 patients (1666 molars) yielded DSC prevalence rates among mesial impactions of 36% (95% CI, 5% to 67%) and 22% with horizontal impactions (95% CI, 1% to 42%). Among distally inclined impacted third molars 3% had DSC (95% CI, 1% to 5%) and 7% of vertical third molars had DSC (95% CI, 1% to 13%). The included studies showed variation in bias across studies, one study was assessed to be at low risk of bias and two studies at moderate risk of bias. We concluded that European based studies suggest that about 1 in every 4 patients referred to hospital care for a third molar assessment may be affected by DSC and that convergent third molar impactions pose a significantly greater risk to this presentation of caries.

In **chapter 4** a further systematic review was conducted to gain a greater insight into the incidence rates of DSC on second permanent molars. The literature was assessed diligently and in line with systematic review guidelines and a validated risk of bias assessment tool for observational studies. The search yielded 81 records and after application of inclusion and exclusion criteria, 2 incidence studies were included in this systematic review. The DSC incidence was reported in 1 study with a 25-year follow-up as relative risk adjacent to erupted (RR = 2.53; 95% CI, 1.55 to 4.14), soft tissue impacted (RR = 0.83; 95% CI, 0.11 to 6.04) and bony impacted third molars (RR = 1.44; 95% CI, 0.55 to 3.72) in comparison to when the third molar was absent. The second study reported a DSC incidence of 100 surface-years (1% of all sites) with an 18-month follow-up period. We concluded that both cohort studies indicated that DSC incidence was higher when third molars were erupted in the intermediate term, and also higher in an aging male population over the long term.

Chapter 5 assesses how long-term retention of impacted third molars is associated with plaque stagnation and the development of DSC of the neighbouring mandibular second molar. Whilst caries and tooth loss are common outcomes of impaction, there is currently not enough evidence to advise pre-emptive removal of asymptomatic impacted third molars. Emerging evidence suggests that convergently (mesial and horizontal) impactions are more associated with DSC. We have therefore investigated the composition of dental plaque on the distal surface of the mandibular second molar.

Using short read sequencing of the bacterial 16S rRNA gene, we compared the microbiome of these surfaces at four impaction angulations: two convergent (horizontal and mesial) and two divergent (distal and vertical) angulations, and where the third molar is missing. Analysis of alpha and beta diversity showed that horizontal angulations had distinct, lower community diversity than mesial impactions. Amplicon Sequence Variants (ASVs) associated with *Veillonella* were significantly more abundant at angulations with convergent directions of growth. Within convergent groups, *Veillonella* ASVs were also found to be more abundant in horizontal impactions. Using machine learning, distinct microbiome profiles, which included a high abundance of *Veillonella*-associated ASVs, were used to inform the prediction of original angulations for a small set of samples, with the two convergent impactions estimated with the greatest accuracy. We found distinct differences in diversity between DSC-associated convergent (horizontal and mesial) impacted third molars, as well as greater abundances of *Veillonella* ASVs at horizontal impactions. High levels of *Veillonella* ASVs detected in convergent impactions could indicate that its presence, alongside *Streptococcus*, is associated with an increased risk of caries. DSC is more prevalent in convergent impactions, *Veillonella* is found in general at higher abundance in caries-active patients. Detection of *Veillonella* at increased abundance in convergent impactions, and distinctive profiles at horizontal impactions, may partly elucidate associations of convergent angles with DSC.

Chapter 6 provides insight into the risk factors for the development of DSC in patients who attend routine dental check-ups in Manchester, UK population during an era when NICE (National Institute for Health Care Excellence) third molar surgery guidelines were followed. Radiographs taken during routine dental examinations involving 1012 patients from the Manchester population were accessed and clinical parameters; oral health, patient demographic, and socio-economic factors were assessed. Risk factors were identified by multivariate logistic regression analysis. The overall prevalence of DSC was 63.9%. DSC was distributed homogenously across all five socio-economic groups ($p = 0.425$). Partially erupted mesio-angularly impacted mandibular third molars and third molars with compromised molar-to-molar contact points, loss of lamina dura (LD) of ≥ 2mm, male gender, increasing age and a higher modified decayed, missing, filled tooth (mDMFT-R) score were identified as risk factors associated with the prevalence of DSC ($p < 0.001$). We concluded that loss of LD ≥ 2 mm on the distal aspect of the second molar may present a newly described risk indicator for DSC. As the presence of DSC is significantly associated with the angulation, compromised molar-to-molar cusp-contact position of the adjacent third molar, the periodontal status of the distal aspect of the second molar and the cumulative history of oral health in a population governed by specific third molar guidelines with an active approach to third molar surgical management, our findings are clinically relevant as they could reduce the prevalence of DSC in the surveyed population, irrespective of patients' socio-economic or deprivation status within society.

In **Chapter 7** we determine the prevalence of Distal Surface Caries (DSC) when examining patients for routine dental check-ups and compare the prevalence in Manchester, UK with the population in Bucharest, Romania. Radiographs taken during routine dental examinations involving 1012 and 251 patients from the Manchester and Bucharest population respectively were evaluated. The state of distal surface in the second mandibular molar, loss of periodontal support, third molar impaction type, contact point localisation, gender, age and cumulative history of dental health were assessed. The overall prevalence of DSC in the second mandibular molar was 63.9% and 19.9% in the Manchester and Bucharest population respectively. Although both samples derived from different populations, common DSC risk factors were identified. Mesially impacted mandibular third molars with contact point below the cementoenamel junction adjacent to second molars, loss of lamina dura of ≥ 2mm, male gender and an increased mDMFT-R percentages are DSC risk factors in both populations and were statistically significant in the Manchester sample ($p < 0.001$). The UK population which is governed by very strict third molar guidelines with limited indications for removal had a much higher DSC prevalence and DSC was cumulative with increasing age in comparison to the Romanian population sample in which patients are treated with preventative third molar removal which presented with increased DSC prevalence in younger age groups. The clinical relevance of this is that an increasing DSC prevalence in elderly patients is a characteristic of third molar retention in a population.

In **Chapter 8** presents the results of the different studies described in this thesis and how they relate to wider research and future perspectives are discussed. Although considerable effort has been put into assessing the prevalence and incidence of DSC thus evaluating the extent of the problem, current available evidence of delayed and preventative third molar removal research however, still has not demonstrated a causal relation with DSC and third molar retention. Nevertheless, there are remarkable indications from our research findings that suggest that interceptive or prophylactic third molar removal most likely plays an important role in preventing and improving the outcome of second molars adjacent to impacted third molars. Based on knowledge of the composition of the microbiome and associated risk factors, DSC can be anticipated and timely action can be taken, including proactive removal of mandibular third molars.

Despite the results of the studies presented in the thesis, further high-quality research is required to improve the accuracy of these findings. Well-designed randomised controlled clinical trials investigating the long-term effects of asymptomatic third molar retention vs removal, in a representative sample, are still desirable. In the continuing absence of such clinical trials, high quality, long term prospective cohort studies may also provide valuable evidence. However, given the current lack of available evidence, an individual approach of asymptomatic and disease-free impacted mandibular third molar is recommended, which should be based on the clinical characteristics of the patient, the clinical expertise of the practitioner and shared decision making between patients and their clinicians.

Samenvatting in het Nederlands

Inzichten in cariës van het distale vlak van de tweede ondermolaar grenzend aan een geïmpacteerde, gedeeltelijk geërupteerde derde molaar

Het doel van dit proefschrift was om cariës van het distale vlak van de tweede ondermolaar grenzend aan een geïmpacteerde derde molaar (in het Engels: Distal Surface Cariës = DSC) te onderzoeken; 1) het momenteel beschikbare wetenschappelijke bewijs van verwijdering van de derde molaar versus behouden te beoordelen en te actualiseren; 2) de incidentie en prevalentie van DSC in verschillende populaties te bepalen; 3) het cariësproces beter te begrijpen door het microbioom en risicofactoren voor DSC te bestuderen en 4) de klinische prognose van tweede ondermolaren te verbeteren door mogelijke beperkingen van de NICE richtlijn voor chirurgische verwijdering van derde molaar te identificeren met als uiteindelijk doel de patiëntenzorg voor de bevolking te verbeteren, ongeacht de socio-economische of achterstandsstatus van patiënten binnen de samenleving.

Hoofdstuk 1 geeft inzicht in de historische aspecten van de indicaties voor het verwijderen van derde molaren, zoals deze in eerste instantie zijn opgesteld door het Royal College of Surgeons in Engeland, het National Institute of Health in de Verenigde Staten en de in het Verenigd Koninkrijk opgerichte NICE-richtlijn, en belicht de controverse die er bestaat rond het verwijderen van derde molaren. We schetsen de invloeden in het Verenigd Koninkrijk op het beleid van het verwijderen van derde molaren en geven inzicht in de historische economische evaluaties en het beschikbare bewijs over het verwijderen van derde molaren versus behoud. We gaan in op de groeiende bezorgdheid over de toegenomen incidentie van DSC in tweede ondermolaren dat geassocieerd is met asymptomatische gedeeltelijk geërupteerde derde molaren, vooral wanneer deze mesiaal of horizontaal zijn geïmpacteerd. Tenslotte bespreken we hoe DSC de patiënten beïnvloedt en hoe richtlijnen van een nationale instelling met betrekking tot chirurgie van derde molaren ondanks onvoldoende bewijs worden gezien als strikt verplichte klinische strategieën, en al meer dan 20 jaar in de klinische praktijk in het Verenigd Koninkrijk worden toegepast.

In **hoofdstuk 2** vergeleken we door het uitvoeren van een Cochrane systematische review het wetenschappelijk bewijs van de effecten/gevolgen van verwijdering van derde molaren van asymptomatische gezonde geïmpacteerde derde molaren met behoud (conservatief management) bij adolescenten en volwassenen. In onze selectiecriteria namen wij gerandomiseerde gecontroleerde onderzoeken (Randomised Clinical Trials, RCT's) op, zonder beperking van de duur van de follow-up, waarin verwijdering (of afwezigheid) werd vergeleken met behoud (of aanwezigheid) van asymptomatische gezonde geïmpacteerde derde molaren bij adolescenten en volwassenen. Wij hebben ook quasi-RCT's en prospectieve cohortstudies in aanmerking genomen indien de onderzoekers de uitkomsten hadden gemeten met een follow-up van vijf jaar of langer. De gegevens van in aanmerking komende studies werden geanalyseerd en de studies werden beoordeeld op het risico op bias. Wij vonden alleen studies met een lage tot zeer lage kwaliteit over de effecten van verwijdering in vergelijking met behoud van asymptomatische gezonde geïmpacteerde derde molaren op parodontitis en op cariës van het distale vlak (DSC) van de aangrenzende tweede ondermolaar. Er bleken aanwijzingen dat de aanwezigheid van asymptomatische gezonde geïmpacteerde derde molaren op de lange termijn geassocieerd kan zijn met een verhoogd risico op parodontitis van de aangrenzende tweede molaar. Er was echter onvoldoende bewijs om een verschil in DSC risico tussen de aan- of afwezigheid van geïmpacteerde derde molaren aan te tonen. Wij concluderen dat er momenteel onvoldoende wetenschappelijk bewijs beschikbaar is om te bepalen of asymptomatische gezonde geïmpacteerde derde molaren al dan niet verwijderd moeten worden. Hoewel het behouden van asymptomatische gezonde geïmpacteerde derde molaren geassocieerd kan zijn met een verhoogd risico op parodontitis van de aangrenzende tweede molaren op de lange termijn, is het beschikbare bewijs van zeer lage kwaliteit. Wanneer besloten wordt om deze gezonde geïmpacteerde derde molaren te behouden, is klinische beoordeling met regelmatige tussenpozen aan te bevelen om de eventuele ontwikkeling van ongewenste effecten te kunnen vaststellen.

In **hoofdstuk 3** hebben wij een aanvullend systematische review van epidemiologische studies uitgevoerd om de prevalentie van cariës op het distale vlak

(DSC) in de tweede ondermolaar grenzend aan een derde molaar te bepalen. Elektronische zoekacties werden aangevuld met het doorzoeken van referentielisten en het volgen van de citatiegeschiedenis van publicaties. Twee beoordelaars voerden onafhankelijk van elkaar de data-extractie uit, voltooiden gestructureerde kwaliteitsbeoordelingen met een gevalideerde tool voor observationele studies en categoriseerden de samenvattende scores. De zoekactie leverde 81 records op en na toepassing van in- en exclusiecriteria werden 11 prevalentiestudies geanalyseerd in een systematisch review. Vanwege de aanzienlijke methodologische diversiteit kwamen vijf studies niet in aanmerking voor inclusie in de kwantitatieve synthese. Een meta-analyse van de resterende 6 studies naar de prevalentie van DSC en een subgroep-analyse van 3 studies met betrekking tot verschillende angulaties van derde molaren werden uitgevoerd. De totale gepoolde prevalentieschatting werd berekend met een random-effect model en was 23% (95% CI, 2% tot 44%) op patiëntniveau. Subtotalen van prevalenties op molaarniveau in een populatie verwezen naar een ziekenhuis waren 20% (95% CI, 5% tot 36%) voor prospectieve en 15% (95% CI, 5% tot 36%) voor retrospectieve studies. Een subgroep analyse van drie studies met 1296 patiënten (1666 molaren) leverde voor mesiale impactie een DSC prevalentie percentage op van 36% (95% CI, 5% tot 67%) en 22% bij horizontale impactie (95% CI, 1% tot 42%). Bij distaal geïnclineerde plaatste geïmpacteerde derde molaren was 3% DSC (95% CI, 1% tot 5%) en 7% van de verticale derde molaren had DSC (95% CI, 1% tot 13%). De geïncludeerde studies vertoonden een aanzienlijke variatie in bias tussen de studies: één studie werd beoordeeld als laag risico op bias en twee studies met een matig risico op bias. Wij concluderen dat Europese studies suggereren dat ongeveer 1 op de 4 patiënten die naar het ziekenhuis worden verwezen voor het beoordelen van een derde molaar DSC kan hebben en dat convergente derde molaar impacties een significant groter risico vormen voor deze vorm van cariës.

In **hoofdstuk 4** is een aanvullende systematisch review uitgevoerd om meer inzicht te krijgen in de incidentie van DSC op tweede blijvende ondermolaren. De literatuur is zorgvuldig, en in overeenstemming de richtlijnen voor een systematisch review, onderzocht en het risico op bias met een gevalideerde tool voor observationele studies beoordeeld. De search leverde 81 records op, en na toepassing van in- en exclusiecriteria werden 2 incidentiestudies in dit systematisch review geïncludeerd. De DSC incidentie werd in 1 studie met een follow-up van 25 jaar gerapporteerd als relatief risico grenzend aan geërupteerde geïmpacteerde (RR = 2,53; 95% CI, 1,55 tot 4,14), in weke delen geïmpacteerde (RR = 0,83; 95% CI, 0,11 tot 6,04) en in bot geïmpacteerde derde molaren (RR = 1,44; 95% CI, 0,55 tot 3,72) vergeleken met de afwezigheid van de derde molaar. De tweede studie rapporteerde een DSC-incidentie van 100 tandoppervlakten (1% van alle tandoppervlakten) met een follow-up periode van 18 maanden. Wij concludeerden dat beide cohortstudies aangaven dat de incidentie van DSC hoger was wanneer de derde molaren op de middellange termijn waren geërupteerd, en op de lange termijn ook hoger in een verouderende mannelijke populatie.

In hoofdstuk 5 wordt onderzocht hoe langdurig behoud van geïmpacteerde derde molaren samenhangt met plaque stagnatie en de ontwikkeling van DSC van de aangrenzende tweede ondermolaar. Hoewel cariës en verlies van gebitselementen veel voorkomende gevolgen van impactie zijn, is er momenteel onvoldoende bewijs om preventieve verwijdering van asymptomatische geïmpacteerde derde molaren te adviseren. Er zijn nieuwe aanwijzingen dat convergente (mesiale en horizontale) impacties vaker geassocieerd zijn met DSC. Wij hebben daarom de samenstelling van tandplaque op het distale vlak van de tweede ondermolaar onderzocht. Met behulp van short read sequencing van het bacteriële 16S rRNA-gen hebben wij het microbioom van deze oppervlakken vergeleken bij vier impactiehoeken: twee convergente (horizontaal en mesiaal) en twee divergente (distaal en verticaal) hoeken, en daar waar de derde molaar ontbreekt. Analyse van alfa en beta diversiteit toonde aan dat horizontale angulaties een duidelijke, lagere diversiteit qua microbiële gemeenschappen hadden dan mesiale impacties. Amplicon sequentievarianten (ASV's) geassocieerd met *Veillonella* waren significant talrijker bij angulaties met convergente richting. Binnen de convergerende groepen bleken *Veillonella* ASVs ook overvloediger aanwezig te zijn bij horizontale impacties. Met behulp van machine learning werden verschillende microbioom profielen, waaronder profielen met een overvloedige aanwezigheid van *Veillonella*-geassocieerde ASV's, gebruikt in een kleine set samples de oorspronkelijke angulatie te voorspellen, waarbij de twee convergente impacties het meest accuraat werden voorspeld. We vonden duidelijke verschillen in diversiteit tussen DSC-geassocieerd met convergente (horizontale en mesiale) geïmpacteerde derde molaren, als ook een grotere overvloed aan *Veillonella* ASVs bij horizontale impacties. Het hoge gehalte aan *Veillonella* ASV's bij convergente impacties zou erop kunnen wijzen dat de aanwezigheid van deze bacterie, naast *Streptococcus*, geassocieerd is met een verhoogd risico op cariës. DSC komt meer voor in convergente impacties, *Veillonella* wordt in het algemeen in hogere aantallen gevonden bij cariës-actieve patiënten. De verhoogde aanwezigheid van *Veillonella* bij convergente impacties, en kenmerkende profielen bij horizontale impacties, zouden de associatie van convergente angulaties met DSC deels kunnen verklaren.

Hoofdstuk 6 geeft inzicht in de risicofactoren voor het ontwikkelen van DSC bij patiënten in Manchester (Verenigd Koninkrijk) die routinematig de tandarts voor een controle bezoeken, in een tijdperk waarin de NICE (National Institute for Health Care Excellence) richtlijnen voor derde molaar chirurgie werden gevolgd. Röntgenfoto's die tijdens routine tandartsbezoeken werden gemaakt bij 1012 patiënten van de bevolking in Manchester werden bestudeerd en klinische parameters, mondgezondheid, demografische en socio-economische factoren werden beoordeeld. Risicofactoren werden geïdentificeerd met multivariate logistische regressieanalyse. De totale prevalentie van DSC was 63,9%. DSC was homogeen verdeeld over alle vijf socio-economische groepen ($p = 0,425$). Partieel geërupteerde mesio-angulair geïmpacteerde derde ondermolaren en derde molaren met molaar-molaar contactpunten, verlies van lamina dura (LD) van ≥ 2mm, mannelijk geslacht, toenemende leeftijd en een hogere gemodificeerde DMFT-score (mDMFT-R) werden geïdentificeerd als significante risicofactoren geassocieerd met DSC ($p < 0,001$). Wij concludeerden dat verlies van LD ≥ 2 mm van het distale vlak van de tweede ondermolaar een nieuw beschreven risico-indicator voor DSC kan vormen. Aangezien de aanwezigheid van DSC significant geassocieerd is met de angulatie, molaar-molaar contact met een knobbel van de aangrenzende derde molaar, de parodontale status van het distale vlak van de tweede ondermolaar en de algemene cumulatieve mondgezondheid in een bevolking die behandeld wordt volgens specifieke richtlijnen voor chirurgische behandeling van derde molaren, zijn onze bevindingen klinisch relevant omdat ze de prevalentie van DSC in de onderzochte populatie zouden kunnen verminderen, ongeacht de sociaaleconomische of achterstandssituatie van patiënten binnen deze samenleving.

In **hoofdstuk 7** vergelijken we de prevalentie van DSC van patiënten tijdens voor routinematige tandheelkundige controles in Manchester (VK) met een populatie in Boekarest, Roemenië. Röntgenfoto's gemaakt tijdens routinematig tandheelkundig onderzoek van 1012 en 251 patiënten uit respectievelijk Manchester en Boekarest werden geëvalueerd. De toestand van het distale vlak van de tweede ondermolaar, het verlies van parodontale aanhechting, het type impactie van de derde molaar, de lokalisatie van het contactpunt, het geslacht, de leeftijd en de cumulatieve mondgezondheid werden beoordeeld. De totale prevalentie van DSC in de tweede ondermolaar was 63,9% en 19,9% in respectievelijk de populatie in Manchester en Boekarest. Hoewel beide steekproeven afkomstig waren van verschillende populaties, werden gemeenschappelijke DSC risicofactoren geïdentificeerd. Mesiaal geïmpacteerde derde ondermolaren met een contactpunt onder de cement-glazuur grens tegen de aangrenzende tweede molaar, een verlies van lamina dura van ≥ 2mm, mannelijk geslacht en een verhoogd mDMFT-R percentage bleken in beide populaties risicofactoren voor DSC en waren in de Manchester onderzoeksgroep statistisch significant ($p < 0.001$). De Britse populatie, waarvoor specifieke richtlijnen met indicaties voor verwijdering van derde molaren gelden, had een veel hogere DSC-prevalentie die toe namen met de leeftijd in vergelijking met de Roemeense bevolkingsgroep waarbij patiënten met preventieve verwijdering van derde molaren worden behandeld, die een verhoogde DSC-prevalentie in jongere leeftijdsgroepen vertoonde. Een toenemende DSC-prevalentie bij oudere patiënten is dus een kenmerk van het behoud van de derde molaar in een populatie.

In **hoofdstuk 8** worden de resultaten van de verschillende in dit proefschrift beschreven studies besproken, hoe deze zich verhouden tot ander onderzoek en worden toekomstperspectieven geschetst. Hoewel er veel moeite is gedaan om de prevalentie en incidentie van DSC in kaart te brengen en zo de omvang van het probleem te evalueren, heeft het huidige beschikbare bewijs naar behoud en preventieve verwijdering van derde molaren echter nog steeds geen causaal verband aangetoond tussen DSC en behoud van een derde molaar. Niettemin zijn er opmerkelijke aanwijzingen in onze onderzoeksbevindingen die suggereren dat interceptieve of profylactische verwijdering van derde molaren hoogstwaarschijnlijk een belangrijke rol speelt bij het voorkomen van DSC in tweede ondermolaren die grenzen aan geïmpacteerde derde molaren. Op basis van kennis over de samenstelling van het microbioom en andere geassocieerde risicofactoren zou op het ontstaan van DSC kunnen worden geanticipeerd en tijdig actie worden ondernomen, waaronder proactieve verwijdering van derde ondermolaren.

Ondanks de resultaten van de in het proefschrift gepresenteerde studies, is verder hoogwaardig onderzoek nodig om de betrouwbaarheid van deze bevindingen te verbeteren. Goed opgezette gerandomiseerde gecontroleerde klinische trials (RCT's), waarbij de lange termijn effecten van het behoud van asymptomatische derde molaren wordt vergeleken met verwijdering, in een representatieve steekproef, zijn nog steeds wenselijk. Bij gebrek aan dergelijke klinische studies, kunnen kwalitatief hoogstaande prospectieve cohortstudies op lange termijn ook waardevol bewijs leveren. Gezien het huidige gebrek aan beschikbaar bewijsmateriaal wordt echter een individuele benadering van asymptomatische en gezonde geïmpacteerde derde ondermolaren aanbevolen, die gebaseerd moet zijn op de klinische kenmerken van de patiënt, de klinische expertise van de behandelaar en gezamenlijke besluitvorming door patiënten en hun behandelaars.

Zusammenfassung auf Deutsch

Zusammenfassung des neuen Verständnisses und der weiteren Erkenntnisse über die Distale Aspekt Karies (Zusammenfassung zu neuen Erkenntnissen über Distale Aspekt Karies /distale Kontaktkaries)

Ziel dieser Arbeit war es, die distale Kontaktkaries (in English: Distal Surface Caries = DSC) im zweiten Molaren des Unterkiefers, der an einen impaktierten dritten Molaren angrenzt, wie folgt zu erforschen.

1.) Die derzeit verfügbaren Erkenntnisse über die Entfernung bzw. den Erhalt des dritten Molaren wurden bewertet und aktualisiert.
2.) Die Inzidenz und Prävalenz der DSC in verschiedenen Bevölkerungsgruppen wurde definiert.
3.) Erlangung der Nachvollziehbarkeit des Kariesprozesses, indem das Mikrobiom und die mit DSC verbundenen Risikofaktoren untersucht wurden.
4.) Die Ergebnisse bei zweiten Unterkiefermolaren zu verbessern, indem potenzielle Einschränkungen der NICE-Leitlinien für die Chirurgie der dritten Molaren identifiziert wurden, um schließlich die Patientenversorgung für die Bevölkerung zu verbessern, unabhängig vom sozioökonomischen Status des Patienten innerhalb der Gesellschaft.

Kapitel 1 gibt einen Einblick in den historischen Aspekt der Indikationen für die Entfernung dritter Molaren, die ursprünglich vom Royal College of Surgeons of England, dem National Institute of Health US und der im Vereinigten Königreich gegründeten NICE-Leitlinie festgelegt wurden, und zeigt die Kontroverse auf, die die Chirurgie zur Entfernung dritter Molaren umgibt. Wir legen die Einflüsse auf die Behandlung von dritten Molaren im Vereinigten Königreich dar und geben einen Einblick in die historisch wirtschaftlichen Bewertungen sowie in die verfügbare Evidenz zur Entfernung von dritten Molaren im Vergleich zur Retention. Wir befassen uns mit den wachsenden Bedenken hinsichtlich der zunehmenden Häufigkeit von DSC bei zweiten Molaren im Unterkiefer in Verbindung mit asymptomatischen, teilweise durchgebrochenen dritten Molaren, insbesondere wenn diese mesial oder horizontal impaktiert sind. Schließlich erörtern wir, wie sich die DSC auf die Patienten auswirkt und wie die etablierten Leitlinien für die Chirurgie der dritten Molaren von einer nationalen Institution trotz unzureichender Evidenz als strikt obligatorische klinische Strategie angesehen werden, und in der klinischen Praxis im Vereinigten Königreich seit mehr als 20 Jahren angewandt werden.

In **Kapitel 2** haben wir die wissenschaftliche Evidenz zu den Auswirkungen/Folgen der Entfernung dritter Molaren mit der Retention (konservatives Management) asymptomatischer krankheitsfreier impaktierter dritter Molaren bei Jugendlichen und Erwachsenen verglichen, indem wir eine systematische Cochrane-Review durchgeführt haben. In unsere Auswahlkriterien schlossen wir randomisierte kontrollierte Studien (RCTs) ohne Einschränkung der Nachbeobachtungszeit ein, in denen die Entfernung (oder das Fehlen) mit der Retention (oder dem Vorhandensein) asymptomatischer krankheitsfreier impaktierter dritter Molaren bei Jugendlichen und Erwachsenen verglichen wurden.
Wenn die Forschungsergebnisse mit einer Nachbeobachtungszeit von fünf Jahren oder länger gemessen wurden, haben wir ebenso Quasi-RCTs und prospektive Kohortenstudien einbezogen.
Die Datenerfassung und -analyse der in Frage kommenden Studien wurde durchgeführt, und es wurde eine Bewertung des Verzerrungsrisiko vorgenommen. Wir fanden lediglich Studien mit sehr geringer Aussagekraft in Bezug auf die Auswirkungen der Entfernung, im Vergleich zum Verbleib asymptomatischer krankheitsfreier impaktierter dritter Molaren auf Parodontitis und Karies im Zusammenhang mit dem distalen Kontakt (DSC) des benachbarten zweiten Molaren. Es gibt Hinweise darauf, dass das Vorhandensein asymptomatischer, krankheitsfreier impaktierter dritter Molaren langfristig mit einem erhöhten Parodontitisrisiko für den benachbarten zweiten Molaren verbunden sein könnte. Es gibt jedoch keine ausreichende Evidenz, um einen Unterschied im DSC-Risiko in Verbindung mit dem Vorhandensein oder Nichtvorhandensein von impaktierten dritten Molaren

nachzuweisen. Wir kamen zu dem Schluss, dass es derzeit keine ausreichenden Belege dafür gibt, ob asymptomatische, krankheitsfreie impaktierte dritte Molaren entfernt werden sollten oder nicht. Obwohl der Verbleib asymptomatischer, krankheitsfreier impaktierter dritter Molaren langfristig mit einem erhöhten Parodontitisrisiko für die benachbarten zweiten Molaren verbunden sein könnte, ist die verfügbare Evidenz von sehr geringer Sicherheit. Wenn die Entscheidung getroffen wird, diese krankheitsfreien impaktierten dritten Molaren zu behalten, ist eine klinische Untersuchung in regelmäßigen Abständen ratsam, um die Entwicklung unerwünschter Ergebnisse zu überwachen.

In **Kapitel 3** führten wir eine zusätzliche systematische Überprüfung epidemiologischer Studien durch, um die Prävalenz der distalen Kontaktkaries (DSC) im zweiten Molaren, der an einen dritten Molaren angrenzt, zu bewerten. Das Ergebnis der Studie stützt sich auf elektronische Suchergebnisse und wurde mit Referenzregister und einer Auflistung von Zitaten ergänzt. Die Gutachter führten unabhängig voneinander und in zweifacher Ausfertigung eine Datenextraktion durch, bewerteten die Qualität der Studien mit einem validierten Instrument zur Beurteilung des Verzerrungsrisikos für Beobachtungsstudien, und kategorisierten die zusammenfassenden Ergebnisse. Die Suche ergab 81 Datensätze, und nach Anwendung der Ein- und Ausschlusskriterien wurden 11 Prävalenzstudien im Rahmen der systematischen Überprüfung analysiert. Aufgrund der großen methodischen Vielfalt kamen fünf Studien nicht für die quantitative Synthese in Frage.
Eine Meta-Analyse der verbleibenden 6 DSC-Prävalenzstudien und eine Subgruppenanalyse von 3 Studien zu verschiedenen Winkeln der dritten Molaren wurden durchgeführt.
Die gepolte Gesamtprävalenzschätzung wurde mit einem Modell im Zufallsprinzip berechnet und betrug 23 % (95 % CI, 2 % bis 44 %) auf Patientenebene. Die Zwischensummen der Prävalenz betrugen 20 % (95 % KI, 5 % bis 36 %) für prospektive und 15 % (95 % CI, 5 % bis 36 %) für retrospektive Studien auf Molaren-Ebene in einer Population, die an ein Krankenhaus überwiesen wurde. Eine Subgruppenanalyse von drei Studien mit 1296 Patienten (1666 Molaren) ergab DSC-

Prävalenzraten bei mesialen Impaktierungen von 36 % (95 % CI, 5 % bis 67 %) und 22 % bei horizontalen Impaktierungen (95 % CI, 1 % bis 42 %). Bei distal geneigten impaktierten dritten Molaren wiesen 3 % (95 % CI, 1 % bis 5 %) und 7 % der vertikalen dritten Molaren eine DSC auf (95 % CI, 1 % bis 13 %). Die eingeschlossenen Studien wiesen unterschiedliche Verzerrungen auf, wobei eine Studie als geringes und zwei Studien als mittleres Verzerrungsrisiko eingestuft wurden. Wir kamen zu dem Schluss, dass europäische Studien darauf hindeuten, dass etwa einer von vier Patienten, die zur Untersuchung der dritten Molaren in ein Krankenhaus überwiesen werden, von DSC betroffen sein könnte und dass konvergente Einschläge der dritten Molaren ein deutlich höheres Risiko für diese Kariesform darstellen.

In **Kapitel 4** wurde eine weitere systematische Übersichtsarbeit durchgeführt, um einen besseren Einblick in die Inzidenzraten von DSC an zweiten bleibenden Molaren zu erhalten. Die Literatur wurde sorgfältig und im Einklang mit den Leitlinien für systematische Überprüfungen und einem validierten Instrument zur Bewertung des Verzerrungsrisikos für Beobachtungsstudien ausgewertet. Die Suche ergab 81 Datensätze, und nach Anwendung der Ein- und Ausschlusskriterien wurden 2 Inzidenzstudien in diese systematische Überprüfung aufgenommen. Die DSC-Inzidenz wurde in einer Studie mit 25-jähriger Nachbeobachtungszeit als relatives Risiko neben durchgebrochenen (RR = 2,53; 95 % CI, 1,55 bis 4,14), weichgewebig impaktierten (RR = 0,83; 95 % CI, 0,11 bis 6,04) und knöchern impaktierten dritten Molaren (RR = 1,44; 95 % CI, 0,55 bis 3,72) im Vergleich zum Fehlen des dritten Molars angegeben.
Die zweite Studie berichtete über eine DSC-Inzidenz von 100 Oberflächenjahren (1 % aller Stellen) mit einer 18-monatigen Nachbeobachtungszeit. Wir kamen zu dem Schluss, dass beide Kohortenstudien darauf hindeuten, dass die DSC-Inzidenz höher ist, wenn die dritten Molaren mittelfristig durchbrechen, und auch langfristig in einer alternden männlichen Bevölkerung höher ist.

In **Kapitel 5** wird untersucht, wie die langfristige Retention impaktierter dritter Molaren mit der Plaquestagnation und der Entwicklung von DSC am benachbarten zweiten Unterkiefermolaren zusammenhängt. Karies und Zahnverlust sind zwar häufige

Folgen von Impaktierungen, doch gibt es derzeit nicht genügend Beweise, um eine präventive Entfernung asymptomatischer impaktierter dritter Molaren zu empfehlen. Neue Erkenntnisse deuten darauf hin, dass konvergente (mesiale und horizontale) Impaktierungen eher mit DSC assoziiert sind. Wir haben daher die Zusammensetzung von Zahnbelag auf der distalen Oberfläche des zweiten Unterkiefermolaren untersucht. Mithilfe der Short-Read-Sequenzierung des bakteriellen 16S rRNA-Gens haben wir das Mikrobiom dieser Oberflächen bei vier Impaktionswinkeln verglichen: zwei konvergente (horizontale und mesiale) und zwei divergente (distale und vertikale) Winkel, und bei denen der dritte Molar fehlt. Die Analyse der Alpha- und Beta-Diversität zeigte, dass horizontale, eine deutlich geringere Gemeinschaftsdiversität aufwiesen als mesiale Winkel. Die mit Veillonella assoziierten Amplikon-Sequenzvarianten (ASVs) waren in Winkeln mit konvergenten Wachstumsrichtungen deutlich häufiger anzutreffen. Innerhalb konvergenter Gruppen wurden Veillonella-ASVs auch in horizontalen Einschlägen häufiger gefunden. Mithilfe von maschinellem Lernen wurden eindeutige Mikrobiomprofile, die eine hohe Abundanz von Veillonella-assoziierten ASVs enthielten, zur Vorhersage der ursprünglichen Winkelungen für eine kleine Gruppe von Proben verwendet, wobei die beiden konvergenten Einschläge mit der größten Genauigkeit geschätzt wurden. Wir fanden deutliche Unterschiede in der Diversität zwischen DSC-assoziierten konvergenten (horizontalen und mesialen) impaktierten dritten Molaren sowie größere Abundanzen von Veillonella ASVs bei horizontalen Impaktierungen. Der hohe Anteil von Veillonella ASVs bei konvergenten Impaktierungen könnte darauf hindeuten, dass ihr Vorhandensein neben Streptokokken mit einem erhöhten Kariesrisiko verbunden ist. DSC ist bei konvergenten Winkelungen häufiger anzutreffen, während Veillonella im Allgemeinen bei kariesaktiven Patienten in größerer Menge vorkommt. Der Nachweis von Veillonella in erhöhter Abundanz bei konvergenten Impaktierungen und ausgeprägten Profilen bei horizontalen Impaktierungen könnte die Assoziation von konvergenten Winkeln mit DSC teilweise erklären.

Kapitel 6 gibt einen Einblick in die Risikofaktoren für die Entwicklung von DSC bei Patienten, die an zahnärztlichen Routineuntersuchungen in Manchester, Großbritannien, teilnehmen, und zwar in einer Zeit, in der die Richtlinien des NICE

(National Institute for Health Care Excellence) für die Chirurgie des dritten Molaren befolgt wurden. Es wurde auf Röntgenbilder zugegriffen, die bei zahnärztlichen Routineuntersuchungen von 1012 Patienten aus der Bevölkerung von Manchester gemacht wurden, und es wurden klinische Parameter, Mundgesundheit, demografische und sozioökonomische Faktoren der Patienten bewertet. Die Risikofaktoren wurden durch eine multivariate logistische Regressionsanalyse ermittelt. Die Gesamtprävalenz der DSC lag bei 63,9 %. Die DSC war homogen über alle fünf sozioökonomischen Gruppen verteilt ($p = 0,425$). Partiell eruptierte, mesio-angulär impaktierte dritte Unterkiefermolaren und dritte Molaren mit kompromittierten Molaren-zu-Molaren-Kontaktpunkten, ein Verlust der Lamina dura (LD) von ≥ 2 mm, männliches Geschlecht, zunehmendes Alter und ein höherer modifizierter Wert für kariöse, fehlende, gefüllte Zähne (mDMFT-R) wurden als Risikofaktoren identifiziert, die mit der Prävalenz von DSC assoziiert sind ($p < 0,001$). Wir kamen zu dem Schluss, dass der Verlust von LD ≥ 2 mm auf der distalen Seite des zweiten Molaren einen neu beschriebenen Risikoindikator für DSC darstellen könnte. Da das Vorhandensein von DSC signifikant mit der Angulation, der beeinträchtigten Molar-zu-Molar-Kontaktposition des benachbarten dritten Molars, dem parodontalen Status des distalen Aspekts des zweiten Molars und der kumulativen Mundgesundheitsanamnese in einer Population verbunden ist, für die spezifische Leitlinien für dritte Molaren mit einem aktiven Ansatz für die chirurgische Behandlung dritter Molaren gelten, sind unsere Ergebnisse klinisch relevant, da sie die Prävalenz von DSC in der untersuchten Population verringern könnten, unabhängig vom sozioökonomischen Status oder der Deprivation der Patienten innerhalb der Gesellschaft.

In **Kapitel 7** bestimmen wir die Prävalenz von Distal Surface Caries (DSC) bei der Untersuchung von Patienten im Rahmen zahnärztlicher Routineuntersuchungen und vergleichen die Prävalenz in Manchester, UK, mit der Bevölkerung in Bukarest, Rumänien. Ausgewertet wurden Röntgenbilder, die bei zahnärztlichen Routineuntersuchungen von 1012 bzw. 251 Patienten aus der Bevölkerung von Manchester und Bukarest angefertigt wurden. Bewertet wurden der Zustand der distalen Oberfläche des zweiten Unterkiefermolars, der Verlust der parodontalen

Abstützung, die Art der Impaktion des dritten Molars, die Lokalisierung des Kontaktpunkts, das Geschlecht, das Alter und die kumulative Zahngesundheitsgeschichte. Die Gesamtprävalenz von DSC im zweiten Unterkiefermolaren betrug 63,9 % in der Manchester- und 19,9 % in der Bukarester Bevölkerung. Obwohl beide Stichproben aus unterschiedlichen Populationen stammten, wurden gemeinsame DSC-Risikofaktoren identifiziert. Mesial impaktierte dritte Unterkiefermolaren mit einem Kontaktpunkt unterhalb der Schmelz-Zement-Grenze neben den zweiten Molaren, ein Verlust der Lamina dura von ≥ 2 mm, männliches Geschlecht und ein erhöhter mDMFT-R-Prozentsatz sind in beiden Populationen DSC-Risikofaktoren und waren in der Manchester-Stichprobe statistisch signifikant ($p < 0{,}001$). In der britischen Bevölkerung, für die spezifische Richtlinien und Indikationen für die Entfernung dritter Molaren gelten, war die DSC-Prävalenz wesentlich höher, und die DSC kumulierte mit zunehmendem Alter im Vergleich zur rumänischen Bevölkerungsstichprobe, die eine erhöhte DSC-Prävalenz in jüngeren Altersgruppen aufwies und Patienten mit der präventiven Entfernung dritter Molaren behandelte. Somit ist eine zunehmende DSC-Prävalenz bei älteren Patienten ein Merkmal der Retention dritter Molaren in der Bevölkerung.

In **Kapitel 8** werden die Ergebnisse der verschiedenen Studien, die in dieser Arbeit beschrieben werden vorgestellt, und es wird erörtert, wie sie sich auf die weitere Forschung beziehen und welche Perspektiven es gibt. Obwohl beträchtliche Anstrengungen unternommen wurden, um die Prävalenz und Inzidenz von DSC zu ermitteln und damit das Ausmaß des Problems zu bewerten, konnte in der aktuellen Forschung zur verzögerten und präventiven Entfernung von dritten Molaren noch kein kausaler Zusammenhang mit DSC und der Retention von dritten Molaren nachgewiesen werden. Nichtsdestotrotz gibt es bemerkenswerte Hinweise aus unseren Forschungsergebnissen, die darauf hindeuten, dass die interzeptive oder prophylaktische Entfernung dritter Molaren höchstwahrscheinlich eine wichtige Rolle bei der Vorbeugung und Verbesserung des Ergebnisses von zweiten Molaren neben impaktierten dritten Molaren spielt. Auf der Grundlage des Wissens über die Zusammensetzung des Mikrobioms und der damit verbundenen Risikofaktoren kann die DSC antizipiert werden, und es können rechtzeitig Maßnahmen ergriffen werden, einschließlich der proaktiven Entfernung von dritten Unterkiefermolaren.

Trotz der Ergebnisse der in dieser Arbeit vorgestellten Studien sind weitere hochwertige Forschungsarbeiten erforderlich, um die Genauigkeit dieser Erkenntnisse zu verbessern. Gut konzipierte, randomisierte, kontrollierte klinische Studien, in denen die langfristigen Auswirkungen des Verbleibs asymptomatischer dritter Molaren im Vergleich zur Entfernung in einer repräsentativen Stichprobe untersucht werden, sind weiterhin wünschenswert. Da solche klinischen Studien nach wie vor fehlen, können auch qualitativ hochwertige, langfristig prospektive Kohortenstudien wertvolle Erkenntnisse liefern. In Anbetracht des derzeitigen Mangels an Evidenz wird jedoch ein individueller Ansatz für asymptomatische und krankheitsfreie impaktierte dritte Unterkiefermolaren empfohlen, der auf den klinischen Merkmalen des Patienten, dem klinischen Fachwissen des Behandlers und einer gemeinsamen Entscheidungsfindung zwischen Patienten und ihren Ärzten beruhen sollte.

Curriculum Vitae

Dr Verena Toedtling BDS MSc (OMFS) PGCert (DPH) MFDS RCSEd MOralSurg RCSEng FHEA FICOI

PERSONAL STATEMENT

I have a well-rounded background in dentistry as I have gained experiences in many clinical specialties and clinical settings within primary and secondary care. However, my specialist training gave me the opportunity to become an expert in oral surgery and provided me with great insight into oral and maxillofacial surgery. My clinical skills are built upon an extensive integrated experience in all aspects of oral surgery and advanced implantology/grafting which permits me to perform a wide range of surgical procedures.

I am a self-motivated, enthusiastic and hardworking individual with a strong track record of academic progression and success which is coupled by a high degree of clinical ability. In addition to this, I am a responsible, dedicated and a valuable team member, with an aptitude to achieve high standards of performance. I always take a professional approach to my work and I have the ability to work very effectively within a team. I have excellent organisational skills and I am an effective communicator with very good interpersonal skills.

Major achievements

- An assortment of experiences and key qualifications that underpin my clinical ability and surgical skills.
- Several awards for my clinical work and care improvements which I showcased and disseminated in form of posters & presentations and that significantly improving patient satisfaction and care delivery.
- Research experience with SDCEP (Scottish Dental Clinical Effectiveness Programme), Cochrane Oral Health Group and NICE (National Institute of Clinical and Care Excellence) leading to guideline development and nationally and internationally relevant publications.
- Nominated for the University of Manchester Teaching Award ‘Best Personal/Advisor of the Year’.

EDUCATION & QUALIFICATIONS

Doctor of Philosophy - Oral and Maxillofacial Surgery 2023

Academic Centre for Dentistry Amsterdam (ACTA), Faculty of Dentistry, University of Amsterdam and VU University Amsterdam

- Third molar research and Distal Surface Caries in the adjacent second molar

- **Alan Hilton Medal – Section of Odontology, Manchester Medical Society.** *“Incidence and prevalence of distal surface caries adjacent to a third molar. A systematic review and meta-analysis”, prize and token awarded Feb 2017,* University of Manchester/University Hospital NHS Foundation Trust.

Fellow of the International Congress of Oral Implantologists **2019**
Awarded at the New York University College of Dentistry

Postgraduate Certificate in Dental Public Health **2018**
The University of Manchester, Faculty of Biology, Medicine & Health

- **Course modules:**
    - Research Methods, Biostatistics, Health Economics & Epidemiology

Master of Science - Oral & Maxillofacial Surgery **2015**
The University of Manchester - Graduated with Distinction

- Specialist clinical component:
    - Oral and Maxillofacial Surgery, incl. Implantology and Grafting
- Research training & academic component:
    - Dissertation title: Development of a Risk-based Oral Health Need Assessment (ROHNA) tool to improve the outcome of second molars adjacent to asymptomatic partially erupted mandibular third molars

Specialist Oral Surgeon **2015**
Diploma & Membership in Oral Surgery
Faculty of Dental Surgery - Royal College of Surgeons of England

- Certificate of Completion of Specialist Training (CCT)
- Entered GDC Oral Surgery Specialist List in 2015

Fellow of the Higher Education Academy **2013**
The University of Manchester, New Academics Programme
Portfolio showcased as example of excellence

- Focus: Leadership, Research & Teaching

Diploma & Membership of the Faculty of Dental Surgery **2010**
Royal College of Surgeons of Edinburgh, Scotland

- RCSEd Member

Bachelor of Dental Surgery **2007**

University of Dundee, Scotland - Graduated with Distinction & award of B.D.S with Commendation

- **Norman Duthie Medal** – "*Best clinical and academic performance in complete Prosthodontics",* awarded June 2007, (University of Dundee, Scotland)

- **William Mackenzie Prize** – "*Comparative study based on the differences in dental curricula"*, Best study carried out during the elective period, awarded June 2007, (University of Dundee, Scotland)

PROFESSIONAL MEMBERSHIPS

- Faculty of Dental Surgery, Royal College of Surgeons of Edinburgh (78870)
- Faculty of Dental Surgery, Royal College of Surgeons of England (9046427)
- Fellow of the Higher Education Academy
- Royal Odonto-Chirurgical Society of Scotland
- UK Educational Committee - Association of British Academic Oral & Maxillofacial Surgeons

- British Association of Oral Surgeons (635)
- European Association of Osseointegration
- Association of Dental Implantology
- Scottish Dental Clinical Effectiveness Programme
- Dental Sedation Teachers Group
- Committee Member of the Manchester Medical Society - Section of Odontology

APPOINTMENTS

Visiting Specialist Oral Surgeon in Private Practice UK **24/10/2017 – present**

Working in an assortment of private referral clinics/practices and providing all aspects of oral surgery including dental implantology (immediate placement and loading including full arch reconstructions with conventional and zygomatic implants) as well as soft and hard tissue grafting under local anaesthesia and intravenous sedation.

I have completed extensive post-graduate studies and advanced course in bone (horizontal and vertical defects) and soft tissue regeneration including platelet-rich-fibrin (PRF), various sinus augmentation & elevation techniques, periodontal plastic surgery, full arch (all-on-3, all-on-4) and extra maxillary implant courses including zygomatic & pterygoid implants. I have trained across the UK, Europe, Brazil, US and in South Africa. I have set up many implantology clinics across the UK and some in very remote locations in Scotland. I also mentor general dental practitioner in implant dentistry and provide oral surgery services to isolated populations.

Specialty Doctor in Oral Surgery **01/09/2017 – 31/11/2017**
Central Manchester University Hospital & NHS Foundation Trust
Led various clinical teams in oral surgery including general anaesthesia and consultation lists/clinics –Deputising for Consultant Oral Surgeons and Associate Specialist.

Academic Clinical Lecturer & Specialist Oral Surgeon **01/07/2015 – 31/08/2017**
The University of Manchester – Faculty of Biology, Medicine and Health
NHS University Dental Hospital of Manchester

- **Clinical: Central Manchester University Hospital & NHS Foundation Trust**
  Based at the University Dental Hospital of Manchester and the Manchester Royal Infirmary

  Clinical: Duties built upon my wide integrated experiences in all aspects of Oral Surgery (diagnostic and surgical) & advanced implantology/grafting and permitted the acquisition of extended competencies.

  Management: Criminal Injuries and compensation reports for insurance companies, health service administration & management, service improvement on provision of informed consent and clinical effectiveness role.

- **Academic: The University of Manchester, School of Biology, Medicine and Health, Division of Dentistry**

Teaching: Core academic with leadership role (Academic BDS Year 3 Lead), co-ordination and delivery of undergraduate (BDS & BSc) and Lecture of postgraduate (MSc) programme in Oral & Maxillofacial Surgery.

Research field: Third Molar Surgery

Clinical Lecturer & Honorary Specialist Registrar in Oral Surgery **2012 – 30/6/2015**
The University of Manchester
NHS University Dental Hospital of Manchester

- **Clinical: Specialist Oral Surgery Clinical Training**
  NHS Higher Specialist Training Programme:
  Specialist training number - NWN/066/003/A

Central Manchester University Hospital & NHS Foundation Trust
(Rotations: University Dental Hospital of Manchester, Manchester Royal Infirmary, Manchester Eye Hospital, Manchester Children's Hospital and Trafford Royal Infirmary)

Specialist Advisory Committee approved post with educational monitoring, clinical/academic portfolio and annual review of competence progression by Health Education North West. Clinical duties and training included a wide integrated experience in all aspects of Oral Surgery including Implantology (full arch and zygomatic implants) and (extra and intra-oral) grafting techniques.

Management of health care delivery:
1. NHS management, administration & use of resources, implementation of IV sedation service
2. Evidence-based practice, clinical guidelines and monitoring of outcomes
3. Medico-legal responsibilities and ethics

- **Academic: The University of Manchester, School of Dentistry**
  Deputy for Examination and Assessment, management & delivery of undergraduate and taught postgraduate programme in Oral Surgery & Maxillofacial Surgery. Leader of various oral surgery clinical teams and a member of multidisciplinary teams / representing oral surgery in joint (oral surgery/restorative) implant and hypodontia clinics. Oral surgery audit deputy / Evaluation of care to improve patient services. Faculty teaching peer reviewer, enquire based learning tutor as well as an academic advisor and mentor. Representative of Manchester Oral Health Group at the National Institute for Health and Care Excellence / Research into the development of national health service wisdom tooth removal indications and guidelines.

Career Development Posts

- **Dental Foundation Trainee** **01/08/2011 - 05/02/2012**
  Edinburgh Dental Institute
  Rotation: Restorative Dentistry & Periodontology/Oral Medicine & Surgery

  Working in Restorative Dentistry and Oral Medicine has further developed my diagnostic skills, this has allowed me to enhance my ability to investigate and provide treatment plans for a wide range of patients with diseases of their teeth and periodontium and the rehabilitation of the dentition to their functional and aesthetic requirements. I feel that this post has broadened my knowledge and combined the theoretical and practical aspects of restorative care.

- **Dental Foundation Trainee** **1/08/2010 - 31/07/2011**
  University of Dundee, Dental Hospital & School
  Rotation: Oral Surgery/Special Care Dentistry & Prosthodontics

Special care dentistry provided an excellent insight into the practice of treating patients with complex medical histories, physical/mental disabilities and those with dental anxieties/phobias. It helped me to develop a more holistic outlook of patient care by acknowledging my patients limitations whilst providing restorative/prosthodontic care under conscious sedation. The oral surgery rotation allowed me to develop further my operative skills in dental alveolar surgery and encouraged the application of an evidence-based approach. I worked in a variety of teams that and I feel that this honed my verbal communication as well as interpersonal skills.

- **Oral-Maxillofacial Surgery Foundation Trainee** **01/08/2008 - 31/07/2010**
  Aberdeen Royal Infirmary
  OMFS/On Call, 1:5/Weekend Locum Cover

  Working in the OMFS unit has provided me with good knowledge of healthcare in a general hospital whilst strengthening my ability to work under pressure and think on my feet to solve problems. My on call commitment came with large responsibilities for trauma, oncology and in-patients with acute infections on the ward including HDU/ITU as well as out-patient clinics. I enjoyed being a valued member of a multidisciplinary team and provided care in a variety of clinical settings: LA/IV sedation & GA.

  Rotation: OMFS/Paediatric Dentistry & Special Care Dentistry

  The community rotation of this post exposed me to a dynamic training environment, making me a more pro-active and flexible individual. I have gained experiences in health promotion, disease prevention, provide care as a visiting dental surgeon in patients own homes, attended schools/nursing homes and specialist clinics/attachments offering care for the homeless. Participating in G-Dens, a busy out-of-hour emergency dental service gave me additional experiences in pain management whilst working under pressure.

- **Vocational Dental Practitioner, Edinburgh GDS** **01/08/2007 - 31/07/2008**
  Primary Dental Care – all aspects of general dentistry
  Employment in a demanding NHS surgery shaped my time-keeping and organisational skills. This post reinforced my core dental knowledge and allowed me to relate well to my peers. Training and guiding an inexperienced dental nurse enabled me to learn to motivate others and strengthened my leadership skills.
  - Performer number: 4130-0

- **Undergraduate Elective, Scotland/Austria** **July/August 2006**
  A burning interest in oral surgery and endodontics shaped my elective plans and allowed me to gain experiences in a wide range of surgical procedures (Edinburgh Dental Specialists, University of Graz & Dundee). Besides my clinical passion for oral surgery, I also developed an interest in the provision of dental education and this drove my decision to carry out a comparative study based on the differences in dental curricula.

INTERESTS

In my spare time, I like to keep fit. I am an enthusiastic swimmer, cyclist and play tennis. I have completed several long distance sportives for charities. In addition to this I have an active social life and I like travelling. My latest interests include running, flying and scuba diving.

Authors contributions

Chapter 1 - *Historical aspects about third molar removal vs. retention and distal surface caries in the second molar adjacent to impacted third molars*

Verena Toedtling, Tim Forouzanfar, Henk S. Brand

Published in British Dental Journal 2023
Conceived and designed the study: VT, TF, HSB
Performed the study: VT, TF, HSB
Analysed the data: VT, TF, HSB
Drafted the manuscript: VT, HSB
Critically revised the manuscript: VT, TF, HSB

Chapter 2 - *Surgical removal versus retention for the management of asymptomatic disease-free impacted wisdom teeth*

Hossein Ghaeminia, Marloes EL Nienhuijs, Verena Toedtling, John Perry, Marcia Tummers, Theo J M Hoppenreijs, Wil JM van der Sanden, Theodorus (Dirk) G Mettes

Published in Cochrane Database of Systematic Reviews 2016 and 2020
Conceived and designed the study: HG, MELN, VT, JP, MT, TJMH, WKMS, TGM
Performed the study: HG, MELN, VT, JP, MT, TJMH, WKMS, TGM
Analysed the data: HG, MELN, VT, JP, MT, TJMH, WKMS, TGM
Drafted the manuscript: HG, MELN, VT, JP, MT, TJMH, WKMS, TGM
Critically revised the manuscript: HG, MELN, VT, JP, MT, TJMH, WKMS, TGM

Chapter 3 - *Prevalence of distal surface caries in the second molar amongst third molar assessment referrals: A systematic review and meta-analysis*

Verena Toedtling, Hugh Devlin, Martin Tickle, Lucy O'Malley

Published in British Journal of Oral and Maxillofacial Surgery 2019
Conceived and designed the study: VT, HD
Performed the study: VT, HD, MT, LO
Analysed the data: VT, HD, MT
Drafted the manuscript: VT, HD
Critically revised the manuscript: VT, HD, MT, LO

Chapter 4 - *A systematic review of second molar distal surface caries incidence in the context of third molar absence and emergence*

Verena Toedtling, Hugh Devlin, Lucy O'Malley, Martin Tickle

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Conceived and designed the study: VT, HD
Performed the study: VT, HD, MT, LO
Analysed the data: VT, HD, MT
Drafted the manuscript: VT, HD
Critically revised the manuscript: VT, HD, MT, LO

Chapter 5 - *Distinct Microbiome of Convergent Wisdom Tooth Impactions*

Verena Toedtling, Paul M Campbell, Gavin J Humphrey, Christopher G Knight, Hugh Devlin, Andrew J McBain

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Conceived and designed the study: VT, HD
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Performed the clinical study and laboratory experiments: VT
Analysed the data: PMC, VT, GJH, CGK, HD, AB
Drafted the manuscript: PMC, VT, GJH, CGK, HD, AB
Critically revised the manuscript: VT, PMC, GJH, CGK, HD, AB

Chapter 6 – *Parameters associated with radiographic distal surface caries in the mandibular second molar adjacent to an impacted third molar*

Verena Toedtling, Tim Forouzanfar, Henk S. Brand

Published in BioMed Central (BMC) Oral Health 2022
Conceived and designed the study: VT, TF, HSB
Ethics application and approval: VT
Performed the study: VT, TF, HSB
Analysed the data: VT, TF, HSB
Drafted the manuscript: VT, TF, HSB
Critically revised the manuscript: VT, TF, HSB

Chapter 7 - *Prevalence of distal surface caries (DSC) in the mandibular second molar in populations with different third molar management strategies: A multi-centre study*

Verena Toedtling, Tim Forouzanfar, Elena-Cristina Marco, Narcis Marcov, Dana Bodnar, Henk S. Brand

Submission pending
Conceived and designed the study: VT, TF, ECM, NM, DB, HSB
Ethics application and approval for each institution: VT, TF, ECM, NM, DB, HSB
Performed the study: VT, TF, ECM, NM, DB, HSB
Analysed the data: VT, TF, ECM, NM, DB, HSB
Drafted the manuscript: VT, TF, HSB
Critically revised the manuscript: VT, TF, ECM, NM, DB, HSB

Chapter 8 – *General Discussion*
Verena Toedtling, Tim Forouzanfar, Henk S. Brand

Chapter 9 – Summary
Verena Toedtling, Tim Forouzanfar, Henk S. Brand

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To whom it may benefit: Sometimes, life isn't fair and each and every one of us come face-to-face with harsh situations and naked truths. These moments demand every ounce of our courage and strength to keep us going. However, when life's terms are truly understood and you are able to see that every adversity creates opportunity which is there for you to take but you need to allow yourself to see it first. However, to do this during hardship takes strength but it guarantees recovery and peace and prepares you for any future struggle life might bring. What matters is to learn to get past it and not to be consumed because the truth is struggles and difficulties will always exist.

Finally, a little note to myself. **Verena**, you did it! You have achieved what you set out to do and you have proved it to yourself. Be proud of yourself and be immensely pleased that you didn't settle for compromises but stayed intensely focused on your ambitions and goals. Smile, close your eyes, breathe in and dance.

"Tell me, what is it you plan to do with your one wild and precious life?"

- Mary Oliver -