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

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Corresponding Author:	Verena Toedtling, BDS MSc MFDS RCSEd MOralSurg RCSEng FHEA University of Manchester and Manchester University Dental Hospital Manchester, UNITED KINGDOM
First Author:	Verena Toedtling, BDS MSc MFDS RCSEd MOralSurg RCSEng FHEA
Order of Authors:	Verena Toedtling, BDS MSc MFDS RCSEd MOralSurg RCSEng FHEA
	Hugh Devlin, BDS, MSc, PhD
	Martin Tickle, BDS, MSc, FDS RCS, DDPH RCS, DPH RSC, PhD, FFPH
	Lucy O'Malley, BA, MA, PhD
Manuscript Region of Origin:	UNITED KINGDOM
Abstract:	<p>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.</p> <p>Material and 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.</p> <p>Results: The search yielded 81 records and after application of inclusion and exclusion criteria, 11 prevalence studies were analyzed 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.</p> <p>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.</p>

Prevalence of distal surface caries in the second molar among referrals for assessment of third molars: a systematic review and meta-analysis

Abstract

We conducted a systematic review of epidemiological studies to assess the prevalence of distal surface caries (DSC) in second molars adjacent to third molars. We searched the Cochrane Library, Lilacs, Embase, and Medline through Ovid® (Wolters Kluwer) to retrieve English and non-English papers from inception to June 2016, and supplemented this with a search of the references and by tracking citations. Three reviewers contributed: one reviewed all the papers, and the other two divided the rest between them. They extracted data, completed structured quality assessments with a validated risk of bias tool for observational studies, and categorised the summary scores. The search yielded 81 records and 11 studies were analysed. The considerable methodological diversity meant that five were not eligible for inclusion in the quantitative synthesis. A meta-analysis of six studies on the prevalence of DSC and a subgroup analysis of three on various third-molar angulations were indicated. The overall pooled prevalence estimate calculated with a random-effects model was 23% (95% CI 2% to 44%) among patients. Prevalence subtotals were 20% (95% CI 5% to 36%) for prospective, and 15% (95% CI 5% to 36%) for retrospective studies among teeth. A subgroup analysis of three studies with 1296 patients (1666 molars) yielded a prevalence of DSC of 36% (95% CI 5% to 67%) for mesial impactions and 22% (95% CI 1% to 42%) for horizontal impactions. DSC was present in 3% of distally-inclined impactions, (95% CI 1% to 5%)

and in 7% (95% CI 1% to 13%) of vertical third molars. The studies varied. The risk of bias was low in one and moderate in two. European studies suggested that DSC may be present in about one in four referrals for the assessment of third molars, and that the risk is considerably higher in those with convergent third molar impactions.

Keywords: Third molar, caries, distal surface caries, second molar, prevalence, epidemiology

Introduction

The retention of lower third molars has been associated with the development of distal caries in the second molar (in the surface of the tooth immediately adjacent to the impacted wisdom tooth).^{1,2} Distal surface caries (DSC) in a second molar that is associated with a retained third molar is also known as distal caries or distal cervical caries, and has been defined as caries that affect the crown, cervical area (amelocemental junction), root, and proximal surfaces of the distal aspect of the second molar.^{3,4}

Currently, the exact prevalence is unknown and, to the best of our knowledge, the quality of the evidence that supports existing data has not been investigated systematically.⁵ DSC leads to poor outcomes for second molars, and some authors have expressed concern that the retention of third molars can be more harmful than their prophylactic extraction.⁶

Ventä et al⁷ showed that removal of the third molar is eventually required in most patients.

Prevalence is one of the most commonly reported epidemiological measures, and it quantifies the burden of a health outcome or disease in a population at a single time point. However, although studies report the prevalence of DSC in second molars, estimates are not consistent, and vary widely from 0%⁸ to 51%.⁹ Direct comparison is difficult because denominators are differently defined, and a systematic analysis of international prevalence is warranted.

In England and Wales, the National Institute for Health and Care Excellence (NICE)¹⁰ guidelines on third molars have changed since 2000, leading to a suspected increase in the prevalence of DSC. A deliberate strategy of no intervention aims to retain impacted third molars in a pathologically prone state for longer, but predominantly mesioangular and horizontally-inclined mandibular teeth form an inaccessible area distal to the second molar where plaque collects, and long-term retention is thought to raise the susceptibility to DSC considerably. Retention may therefore contribute to the formation of DSC and 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 the prevalence of DSC among the patients referred to departments of oral and maxillofacial surgery. The main aim of this study therefore, was to review published papers on the prevalence of DSC in second molars that are associated with impacted third molars. Our primary objectives were to quantify its prevalence and to assess the associated risk of bias by systematic review with meta-analysis. The secondary objective was to find out whether this estimate varied according to population (patients attending general practice

or hospital), geographical location, demographics, the time at which the study was conducted, characteristics of third molars, and general dental health. The review was conducted according to Meta- analyses of Observational Studies in Epidemiology (MOOSE) standards.¹⁶

Material and methods

We aimed to include prospective and retrospective studies that assessed the prevalence of DSC in second molars adjacent to third molars. Full-text studies that reported its incidence in people aged 16 years and over who had had clinical and radiographic examinations, were included. The primary outcome was the development of DSC in the second molar, identified by clinical and radiographic examination. Data were also collected on demographics, type of population (care settings), continent of origin, and year of publication, as well as angulation of the third molar, and general dental health (decayed, missing, filled tooth (DMFT) scores). Prevalence was defined as the number of people or molars with DSC, divided by the number of people or molars studied.¹⁷

Studies that provided information on different or unspecified patterns of caries, or those that merely described loss of adjacent molars, disease, or patterns of resorption in the second molar (without reference to the distal surface of the crown, cervical area, or root), were excluded. Those that included patients with their primary dentition, or those that provided the incidence without a description of the method used, were also excluded.

We did a comprehensive search of published papers on the prevalence of DSC. The keywords with “wildcards” and medical subject headings were used in different combinations: “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, and Medline through the Ovid® (Wolters Kluwer) search platform), and Lilacs.

After the electronic searches and initial selection, we did a supplementary hand search of all the studies identified, tracking citations and checking the references. We also checked those of national guidelines on third molars. There were no restrictions on language or date of publication. All the references identified were compiled into a reference manager (EndNote™ X7, Clarivate Analytics). The titles and abstracts of all the articles identified through the electronic searches were screened by three contributors, and all the papers were reviewed by two. One reviewed them all, the other two divided the rest between them.

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 the authors substantially contributed to and revised the work

for intellectual content and accuracy, and ensured the integrity of the research and that all inquiries were appropriately investigated and answered.

Studies that were not in the English language were translated and assessed. The data were extracted independently using a specifically-designed data extraction form. Any differences were resolved by consultation with all the authors until mutual agreement was reached, and the study characteristics were tabulated in Word (Windows software). One author of an original report was contacted by email for more data on the care setting.¹⁸

Structured quality assessments were done according to the method designed and validated specifically for prevalence studies by Hoy et al (Table 1).¹⁹ This has two responses to each question: a high and a low risk of bias, which has resulted in high inter-rater agreement.¹⁹ It comprises 10 questions/item assessed (internal/external validity, no response and measurement biases, and bias related to the analysis of data) to provide an overall judgment of the risk (low, moderate, or high).

After consideration of specific key domains, the reviewers produced an overall summary score for each study to complement the individual scores for risk of bias. High risk was a high-risk score in item 2 or 7; moderate risk was a high-risk score in item 3 or 9; and low risk was a low-risk score in items 2, 3, 7, and 9.

For synthesis and assessment of heterogeneity, the data were imported into Metaprop version 14 (StataCorp software) to calculate appropriate pooled prevalence estimates;

95% CI, and subtotal estimates for subgroups according to study characteristics and various angulations of third molar, in line with the secondary objectives of the review.

The I^2 metrics and p values were used to quantify heterogeneity across the studies.

Tau² was used to estimate variance between studies, and z values to test for overall effect.

The random effects model was used because of the differences in the studies, and the decision was based on statistical and clinical judgement.

Ethics approval was not necessary, as the study was a review of published papers.

Results

The electronic searches initially yielded 81 records and the hand searches one. Two studies were excluded because only the abstracts were available. Table 2 shows those excluded,^{11,20-29} and Figure 1, the selection process.³⁰ The corresponding author of one of the published abstracts was contacted but did not reply. One study was only available electronically, and one, which had been withdrawn for unknown reasons, was consequently excluded. A total of 11 studies were included,^{4,9,13-15,18,31-35} and prevalence subtotals of three prospective,^{4,9,13} and three retrospective studies,^{18,31,33} are presented.

The meta-analysis comprised three studies,^{4,9,13} which also provided the information and data for subgroup analysis of different angulations of third molars and DSC. Descriptive information and characteristics of the studies are shown in Table 3.

Results of narrative review

Studies from nine countries (11 452 second molars) showed a prevalence of DSC that ranged from 4.5% - 52%. Two were multicentre studies (three and seven sites).^{9,13} The population was assessed at a single time in each one, and in four^{4,9,13,35} both the outcome assessment and data collection were done at a single time point. Seven studies^{14,15,18,31-34} assessed this time point retrospectively through clinical notes and records.

Our secondary objective was to find out whether the estimate varied by factors such as population (general practice or hospital care), geographical location, demographics, time at which the study was conducted, general dental health, and characteristics of the third molars. All studies were conducted in hospitals. Six studies were from Asia,^{15,18,31-35} three from Europe,^{4,9,13} and two from South America.^{14,34} The earliest included, by Knutsson et al, was published in 1996.¹³ Since 2013, the prevalence of DSC reported in 10 further studies has been higher than that reported in 1996.

The studies reported the number and percentage of affected teeth or patients, or both, the corresponding sample size, and the diagnostic criteria/criterion used to detect DSC. Six studies used dental panoramic tomograms (DPT) as well as clinical examination,^{4,9,13,18,31,33} and two of them also used preoperative or intraoperative examination after wisdom teeth had been removed.^{13,33} In the remaining studies the methods varied, and caries were detected on radiographs (two studies used DPT,^{32,34} one used periapical radiographs (PA)¹⁴ and one a combination of DPT and periapical radiographs).³⁵ One used 3-dimensional scans and cone-beam computed tomography (CT).¹⁵

The overall age range was 14 – 89 years. The mean age, which was reported in seven studies,^{4,13-15,18,32,33} ranged from 24 - 29 years. One study reported a median age of 28 years,⁹ and another a mode of 27 years.⁴ Three included a small number of patients under the age of 16.^{9,13,33} The impact of this was taken into account and was integrated in the assessment of risk of bias (Table 3).

Eight studies reported the number of male and female participants^{4,13-15,32,33-35} and all of them reported more women than men. A ratio of roughly 40:60 was common. Only two studies provided the DMFT index and DMFT range,⁴ which varied widely (0-27⁹ and 0-28,⁴ respectively). Characteristics such as sex, DMFT index, and age, were either not fully reported or reported in a way that made direct comparison and analysis of specific subgroups impossible.

Our narrative review provided an insight. Synthesised data across studies, however, are largely subjective, and dissimilar estimates are likely to reflect a high degree of heterogeneity among the different groups. A meta-analysis can summarise the evidence objectively, and to facilitate this we excluded studies with dissimilar outcome measures. Five were excluded because they did not report clinical examination and DPT.^{14,15,32,34,35}

Meta-analysis and subgroup analyses

Our meta-analysis included three studies^{4,9,13} all of which provided samples for subgroup

analyses. The prevalence subtotal among teeth was 20% (95% CI 5% to 36%) $z = 2.57$ ($p = 0.01$) in prospective,^{4,9,13} and 15% (95% CI 6% to 23%) $z = 3.36$ ($p = 0.01$) in retrospective studies (Fig. 2).^{18,31,33}

The pooled estimate according to the prospective studies,^{4,9,13} and the prevalence among patients, are presented in Figure 3. The heterogeneity across and between groups, as well as the significance within the subgroup, were: $I^2=98.88\%$, $\text{Tau}^2 = 0.03$, $z=2.16$, and $p=0.03$. In the subgroup analyses^{4,9,13} the subtotals of the prevalence of DSC among third molars that were inclined mesially (36%, 95%CI 5% to 67%) and horizontally (22%, 95%CI 1% to 42%) ($z=2.03$, $p=0.04$) were significantly higher than those that were inclined distally (3%, 95% CI 1% to 5%) ($z=3.20$, $p=0.01$) or vertically (7%, 95%CI 1% to 13%) ($z=2.38$, $p=0.04$) (Fig. 4). The test of heterogeneity between subgroups was $I^2 = 96.55\%$.

DSC has been reported in three continents: Asia, Europe, and South America. Studies based in Europe suggest that up to 20% of third molar referrals and 23% of the patients referred for assessment have DSC in the second molar. Its prevalence in mesial and horizontal angulations was significantly higher than it was in distal and vertical angulations. Wide confidence intervals, however, suggest a lack of precision and the need for further studies, or inherent variation because of differences in the denominator populations.

Discussion

Previous studies have suggested that the retention of third molars can result in harm to

the second molar, but the precise variables that increase the risk of DSC have not been adequately described. Our epidemiological data help us understand the extent of the problem, and our meta-analysis gives an insight into the epidemiology of DSC in the second molars of patients referred to hospital for assessments of third molars. All the studies were conducted in hospitals so there is no general population-based prevalence, which is an important limitation. However, our results show that DSC is a global phenomenon that is measured with an assortment of radiographic methods.

The meta-analysis showed a 23% pooled prevalence of DSC among patients (DSC therefore affects about one in four of those referred). The confidence intervals, however, were wide (44% to 2%), which suggests a lack of precision. We also detected considerable heterogeneity and suggest that this may be caused by several factors that are linked to differences in practice. To remove the uncertainty of the precision of the combined prevalence estimate, we did a random effects analysis. A subtotal of DSC among molars showed a prevalence of 20% in prospective, and 15% in retrospective, studies.

Testing for significance showed that the null hypothesis could be rejected, and we could accept that the prevalence of DSC was significantly higher in mesial (36%) and horizontal (22%) impactions than it was in vertical (7%) and distal (3%) impactions.

This overall rate is a product of current and previous clinical practice (removal of symptomatic and asymptomatic, or disease-free third molars) and therefore reflects both

approaches to the management of retained teeth. Knuttson et al¹³ reported the prevalence of DSC when third molars were removed prophylactically, whereas both the UK-based studies (Allen et al,⁹ and Toedtling et al⁴) reported it when national guidelines stated that third molars should be removed only when associated with disease. This may explain the large difference in prevalence, and it supports current thinking on the retention of third molars and the harm this can cause.

The limitations of the meta-analysis include the considerable heterogeneity and, overall, the moderate quality of the studies. As described previously, the study sample comprised patients treated in hospital, so is not representative of the general population. Differences in the structure of publicly funded healthcare systems and insurance-based remuneration systems in different parts of the world, as well as variations in education and availability of resources, such as clinical guidance, may also have influenced our estimates. The remuneration systems in industrialised countries with national health services or insurance schemes, which range from fee-for-service to capitation payments, produce different incentives that influence attitudes to the retention and removal of third molars,³⁶ and rates of third molar agenesis and impaction differ.³⁷ The need and demand for their removal, which is thought to be associated with a lower prevalence of DSC, therefore varies widely.

The diagnostic criteria for DSC also varied, and some studies reported clinical examinations, which were correlated with a variety of radiographic images at various stages before and after the removal of third molars.

The European Commission radiation protection guidelines state that DPT is the radiographic investigation of choice for the assessment of third molars and, in most cases, this was used,³⁸ but as panoramic radiographs have poor sensitivity for the diagnosis of caries,³⁸ the prevalence of caries and progression may be underestimated.

Possible sources of bias in the meta-analysis were assessed with the risk of bias tool published by Hoy et al (Table 4).¹⁹ We classified items 1, 4, 5, 6, 8, and 10 as less pertinent, items 3 and 9 as valuable, and items 2 and 7 as pertinent domains. Our reasoning was that all those in the less pertinent domain were already part of our exclusion criteria or had no direct application, whereas studies with a risk of bias in items in the valuable domain had direct implications for the analyses, and had the potential to introduce selection bias or reduce internal validity, which could overestimate or underestimate the results. Items in the pertinent domain were marked as most important and were therefore given the greatest weight. Studies with a 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 could be extrapolated. We did not analyse the subgroups (DMFT, sex, and age) further, together or separately, because they were too small and too variable, and did not seem to reflect the purpose of the study.

We planned to assess possible publication bias with a funnel plot, but the number of studies was too low. We were also unable to do a sensitivity analysis, as only a small number of studies met our inclusion criteria. Despite this, we think that our selection

process was rigorous. We addressed specific sources of bias and excluded studies of low quality and high risk of bias, so our results give the best possible estimates of the prevalence of DSC.

Indications for the removal of impacted wisdom teeth have been controversial for many years, and NICE has provided guidance specifically for England and Wales.¹⁰ Several international guidance documents refer to the NICE first technology appraisal (TA1) recommendations (with an explanation of formal alignment),³⁹⁻⁴² but as NICE clearly stated that there was no research evidence to support them,^{10,11} these documents also have a limited evidence base. Understandably, some nations (including the US) have challenged the NICE recommendations, and they have not been universally adopted.⁴³⁻⁴⁷

At present the cause of DSC remains unknown, but significant associations have been shown with mesially and horizontally impacted third molars.^{4,9} Our subgroup analyses showed that when these were combined, the prevalence of DSC was almost six times higher than it was among a combination of distally and vertically inclined third molars. These findings agree with previous research and with the clinical suspicion and observation of practitioners over many years.⁶

Given the possible risks and costs of both DSC and prophylactic removal, international guidelines must be based on the results of high quality trials in different populations. Ultimately, to improve estimates of the prevalence of DSC and to find answers to our secondary objectives, larger well-reported observational studies are needed, but research

funding might be better spent on interventional studies that show how best to manage impacted third molars and their consequences.

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Conflict of interest

We have no conflicts of interest.

Ethics statement/confirmation of patient permission

Ethics approval not required as this manuscript is a systematic review of published papers. Patients' permission N/A

Note to author

Please check that references 23 and 47 are correct

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Figure legends

- Fig. 1. PRISMA (Preferred Reporting Items for Systematic Review and Meta-analyses) flow diagram of the selection process.³⁰
- Fig. 2. Analyses of prevalence of distal surface caries (DSC) among molars in prospective and retrospective studies of patients who had clinical and

radiological (DPT) examinations, and were referred from general practice to hospital care.

Fig. 3. Meta-analysis for prevalence of distal surface caries (DSC) among patients in prospective studies of patients who had clinical and radiological (DPT) examinations, and were referred from general practice to hospital care.

Fig. 4. Subgroup analysis for distal surface caries (DSC) among molars in various third molar angulations

Table 1.
Adapted tool for assessment of risk of bias in prevalence studies.¹⁹

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?			
10. (Assesses bias related to the analysis)			
11. Were the numerators(s) and denominator(s) for the parameter of interest appropriate?			
Summary assessment			
12. Summary item on the overall risk of bias	Low risk	Moderate risk	High risk

Table 2.
Characteristics of excluded studies.

First author, year, and reference	Reason for rejection
Shugars 2004 ²⁰	Assessed caries in the second molar but not specifically those affecting the distal aspect
Shugars 2005 ²¹	Assessed caries in the second molar but not specifically those affecting the distal aspect
Garaas 2012 ²²	Assessed caries in the second molar but not specifically those affecting the distal aspect
Fisher 2012 ²³	Assessed caries in the second molar but not specifically those affecting the distal aspect
Bozzatello 2006 ²⁴	Assessed caries in the second molar but not specifically those affecting the distal aspect
Alves 2014 ²⁵	Assesses association between stage of eruption and occlusal caries in second molars among 12-year-old schoolchildren
Ajrish 2015 ²⁶	Assessed caries in the second molar but not specifically those affecting the distal aspect
Oderinu 2012 ²⁷	Withdrawn study
McArdle 2006 ²⁸	Case series of DSC
Nunn 2013 ¹²	DSC incidence study
Huang 2014 ²⁹	DSC incidence study

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

First author, year, and reference	Country/ Location	Continent	Care setting	Study design (single time point)	Age (years) Mean Range Median Mode	No. of molars and patients % male/female	DMFT Mean Range Median	Diagnostic criteria (method of diagnosis)	Prevalence of DSC No. of molars No. of patients % % angulation	Risk of bias
Knutsson 1996 ¹³	Sweden	Europe	Hospital multi-centre (7)	Prospective	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 2003 ³¹	China Hong Kong	Asia	Hospital	Retrospective	- 17-89 - 20-29	3178 molars - -	-	CE DPT	234 molars - 7.37% -	Low
Polat 2008 ³²	Turkey Cumhuriyet	Asia	Hospital	Retrospective	25.91 18-60 - -	3050 molars 1914 patients 43.3 M/56.7 F	-	DPT	383 molars 241 patients 12.6% -	High
Chang 2009 ³³	Korea	Asia	Hospital	Retrospective	28.3 14-75 - -	883 molars 786 patients 39.3 M/60.7F	-	CE DPT CE (intra-op)	152 molars 135 patients 17.2% -	Moderate
Allen 2009 ⁹	United Kingdom Surrey	Europe	Hospital multi-centre (3)	Prospective	- 14-88 28 -	776 molars 420 patients -	- 0-27 5	CE DPT	150 molars 113 patients 19.3% Mesial 74.7 Horizontal 8.7 Distal 3.3 Vertical 13.3	Moderate
Ozeç 2009 ¹⁸	Turkey	Asia	-	Retrospective	25.2 18-49 - -	585 molars 485 patients -	-	CE DPT	117 molars 97 patients 20% -	High
Falci 2012 ¹⁴	Brazil Mucuri	South America	Hospital	Retrospective	24.17 16-57	246 molars -	-	PA	33 molars -	Moderate

					-	28 M/72 F			13.4%	
Silva 2015 ³⁴	Brazil	South America	Hospital	Retrospective	-	157 molars	-	DPT	40 molars	Moderate
					18-35+	120 patients			30.6 patients	
					-	36.3 M/63.7 F			25.5%	
Kang 2016 ¹⁵	China Shanghai	Asia	Hospital	Retrospective	29	500 molars	-	CBCT	260 molars	Moderate
					16 – 59	469 patients			244 patients	
					-	43.6 M/ 56.4 F			52%	
Yadav 2016 ³⁵	India Delhi	Asia	Hospital	Prospective	-	1187 molars	-	DPT/PA	132 molars	High
					18-55	-			-	
					-	45.9 M / 54.1 F			11.12%	
					-				-	
Toedtling 2016 ⁴	United Kingdom Manchester	Europe	Hospital	Prospective	29	224 molars	6	CE	85 molars	Low
					16-60	210 patients	0-28	DPT	80 patients	
					-	45.5 M/54.5 F			38%	
					27				Mesial 70.6	
									Horizontal 15.2	
									Distal 2.4	
									Vertical 11.8	

CE- preoperative clinical examination, CE (intra-op)- intra-operative clinical examination, DPT- dental panoramic tomogram, PA-periapical radiograph, CBCT – Cone-beam computed tomography

Table 4.

Risk of bias of individual studies.

Studies	Risk of bias tool items*										
	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
Polat 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
Ozeç 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

Figure 1. PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) flow diagram of the study selection process
Source: PRISMA-P¹⁰ (2005)

Figure 2

Figure 3

The University of Manchester

Dr Verena Toedtling
PhD Student and Specialist Oral Surgeon
The University of Manchester
Division of Dentistry
School of Medical Sciences
Biology Medicine and Health
JR Moore Building
Oxford Road
Manchester
M13 9PL
Tel: +44 (0)161 275 4383
E-mail vtoedtling@hotmail.co.uk

30th July 2018

Dear Mr Mitchell,

We wish to submit an original research article entitled “Prevalence of distal surface caries in the second molar amongst third molar assessment referrals: A systematic review and meta-analysis” for consideration by the British Journal of Oral & Maxillofacial Surgery.

We confirm that this work is original and has not been published elsewhere, nor is it currently under consideration or accepted for publication elsewhere.

In this paper, we reviewed the literature on prevalence of distal surface caries (DSC) in the second molars adjacent to a third molar. This research is significant because third molar retention may be a contributing factor to DSC and patients suffer more harm as a result.

We believe that this manuscript is appropriate for publication by the British Journal of Oral & Maxillofacial Surgery because it provides novel information concerning the indications for extraction of third molars and this topic is likely to encourage discussion amongst oral and maxillofacial surgeons, general dental practitioners, scientists and researchers who read your journal.

Please address all correspondence concerning this manuscript to me.

Thank you for your consideration of our manuscript. We appreciate your time and look forward to your response.

Yours sincerely,

A handwritten signature in black ink, reading "Verena Toedtling". The signature is written in a cursive style with a large, stylized 'V' and 'T'. It is enclosed within a thin black rectangular border.

Dr Verena Toedtling

PhD Student and Specialist Oral Surgeon
BDS MSc (OMFS) PGCert (DPH) MFDS RCSEd MOralSurg RCSEng FHEA

BRITISH JOURNAL OF ORAL & MAXILLOFACIAL SURGERY Author contribution

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

Please provide details in the table below of each author(s) contribution to the submitted manuscript

AUTHORS	Conception and design of study/review	Acquisition of data: laboratory or clinical/literature search	Analysis and interpretation of data collected	Drafting of article and/or critical revision	Final approval and guarantor of manuscript
Dr Verena Toedtling	Contributed	Contributed	Contributed	Contributed	Contributed
Professor Hugh Devlin	Contributed	Contributed	Contributed	Contributed	Contributed
Professor Martin Tickle	Contributed	Contributed	Contributed	Contributed	Contributed
Dr Lucy O’Malley	Contributed	Contributed	Contributed	Contributed	Contributed

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

V Toedtling¹ BDS, MSc (OMFS), PGCert (DPH), MFDS RCSEd, MOralSurg
RCSEng, FHEA

H Devlin² BSc, BDS, MSc, PhD

M Tickle³ BDS, MSc, FDS RCS, DDPH RCS, DPH RSC, PhD, FFPH

L O'Malley⁴ BA, MA, PhD

Corresponding author:

¹ PhD Student and Specialist Oral Surgeon, Faculty of Biology, Medicine and Health,
Division of Dentistry, University of Manchester, JR Moore Building, Oxford Road,
Manchester, M13 9PL, UK phone: +44(0)161 275 4383 fax: +44(0)161 275 6636
email: vtoedtling@hotmail.co.uk

² Professor of Restorative Dentistry, Faculty of Biology, Medicine and Health,
Division of Dentistry, University of Manchester, JR Moore Building, Oxford Road,
Manchester, M13 9PL, UK

³ Professor of Dental Public Health and Primary Care University of Manchester, JR
Moore Building, Oxford Road, Manchester, M13 9PL, UK

⁴Lecturer in Oral Health Research, Faculty of Biology, Medicine and Health,
Division of Dentistry, University of Manchester, JR Moore Building, Oxford Road,
Manchester, M13 9PL, UK

Key words: Third molar; Caries; Distal surface caries; Second molar; Prevalence;
Epidemiology

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

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.

Keywords: Third molar, caries, distal surface caries, second molar, prevalence

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,⁷ (1993) has shown that removal of the third molar is ultimately required in the majority of patients.

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 Excellence¹⁰ 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,¹⁶ (2000).

MATERIALS 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 [REDACTED] (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.

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

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.

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 study¹³, 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 years⁴. 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).

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 0-27⁹ and 0-28⁴. 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).

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; $I^2 = 98.88\%$, $\text{Tau}^2 = 0.03$, $z = 2.16$, $p = 0.03$. 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 $I^2 = 96.55\%$.

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, 1996¹³ reported on DSC prevalence when prophylactic third molar removal was performed whereas both UK based studies, Allen et al, 2009⁹ and Toedtling et al, 2016⁴ 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' behaviour³⁶ 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 etiology 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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Captions to Tables

- Table 1.** Adapted tool for risk of bias assessment in prevalence studies by Hoy et al,¹⁹ (2012)
- Table 2.** Characteristics of excluded studies
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Caption to figures

- Figure 1.** PRISMA (Preferred Reporting Items for Systematic Review and Meta-analysis) flow diagram of the study selection process Source: PRISMA – P³⁰ (2005)
- 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.
- 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

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			

Table 2. Characteristics of excluded studies

<i>Investigator</i>	<i>Reason for rejection</i>
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

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 % Male/Female	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)	prospective	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	retrospective	- 17-89 - 20-29	3178 Molars - -	-	CE DPT	234 Molars - 7.37% -	Low
Polat et al, ³² 2008	Turkey Cumhuriyet	Asia	HC	retrospective	25.91 18-60 - -	3050 Molars 1914 Patients 43.3 M/56.7 F	-	DPT	383 Molars 241 Patients 12.6% -	High
Chang et al, ³³ 2009	Korea	Asia	HC	retrospective	28.3 14-75 - -	883 Molars 786 Patients 39.3 M/60.7F	-	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)	prospective	- 14-88 28 -	776 Molars 420 Patients -	- 0-27 5	CE DPT	150 Molars 113 Patients 19.3% mesial 74.7 horizontal 8.7 distal 3.3 vertical 13.3	Moderate
O'zec et al, ¹⁸ 2009	Turkey	Asia	-	retrospective	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	retrospective	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	retrospective	- 18-35+ - -	157 Molars 120 Patients 36.3 M/63.7 F	-	DPT	40 Molars 30.6 Patients 25.5% -	Moderate
Kang et al, ¹⁵ 2015	China Shanghai	Asia	HC	retrospective	29 16 – 59 - -	500 Molars 469 Patients 43.6 M/ 56.4 F	-	CBCT	260 Molars 244 Patients 52%	Moderate
Yadav et al, ³⁵ 2016	India Delhi	Asia	HC	prospective	- 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	prospective	29 16-60 - 27	224 Molars 210 Patients 45.5 M/54.5 F	6 0-28	CE DPT	85 molars 80 patients 38% mesial 70.6 horizontal 15.2 distal 2.4 vertical 11.8	Low

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

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

CONFIRMATION OF AUTHORSHIP

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

REFERENCE NO:

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