KU LEUVEN

FACULTEIT GENEESKUNDE
BIOMEDISCHE WETENSCHAPPEN

Het eruptiepotentieel van wijsheidstanden voorspeld op basis van tandinclinatie in een vroeg ontwikkelingsstadium

The eruption potential of wisdom teeth predicted by tooth inclination in a premature development stage

Masterproef voorgedragen tot het behalen van de graad van Master in de biomedische wetenschappen door

Anna OCKERMAN

Promotor: Prof. dr. Reinhilde JACOBS
Co-promotor: Prof. Dr. Constantinus POLITIS
Begeleidster: drs. Myrthel VRANCKX
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Preface

This master thesis has been written within the context of fullfilling the master of clinical biomedical sciences at the University of KU Leuven and concerns an extensive study about the wisdom teeth. The present project, formerly known as the M3 study, was undertaken by the Oral and Maxillofacial Surgery - Imaging & Pathology (OMFS-IMPATH) research group of KU Leuven in collaboration with the departments of Oral and Maxillofacial Surgery of the University Hospital Sint-Rafaël Leuven and of the Mariaziekenhuis Overpelt. The study was conducted in view of drafting directives for wisdom teeth management in Belgium.

During the past year I learned a lot, in the scientific field and personally. Conducting this research and writing this thesis was a long-term, but satisfying work, which I was able to tackle with the help of some people I would like to thank. First of all, I thank promotor Prof Dr Reinhilde Jacobs, coordinator of the OMFS-IMPATH research group, for her enthousiasm and for having faith in my capacities and welcoming me in the team. I like to acknowledge co-promotor Prof Dr Constantinus Politis, head of the departement of Oral and Maxillofacial Surgery of the University Hospitals Leuven, who made it possible to conduct this research within the oral and maxillofacial clinic. Therewithal, I am grateful for the cooperation of doctors, doctors in training, nursing staff and secretaries of the University Hospital Sint-Rafaël and the Mariaziekenhuis. Further, I would like to render thanks to Martine Van Vlierberghe and Anne Proost, two private orthodontists that granted me permission to access their patients' files and patients' radiographic records and to Wim Coucke for helping me with the statistical part of this work. I also thank my parents for their interest and encouragement and Dr Eman Shaheen, Dr Bruno Collaert and Prof Dr Anton Roebroek for being part of my examination jury. Lastly, I certainly want to express my graditude to Myrthel Vranckx, PhD researcher of the M3 study. She was always there for me and stepped into the breach when needed, which was a massive help. With her, I thank all the team members of OMFS-IMPATH for the lovely atmosphere at work, as well as Elke Claerhout and Evelien Embrechts, fellow students working on different aspects of the M3 study, for their never-ending support. Myrthel, Elke and Evelien made this a year never to forget.

Anna Ockerman
May 2017, Leuven

List of contents

List of abbreviations

AAOMS	American Association of Oral and Maxillofacial Surgeons
APHA	American Public Health Association
AO	Alveolar osteitis
CBCT	Cone bean computed tomography
IAN	Inferior alveolar nerve
LN	Lingual nerve
M1	First molar
M2	Second molar
M3	Third molar, wisdom teeth
M1/M2	Angle between the first and second molar
M1/M3	Angle between the first and third molar
M2/M3	Angle between the second and third molar
NICE	National Institute for Health and Care Excellence
NHS	National Health Service
OMFS	Oral and maxillofacial surgery
OMFS-IMPATH	Oral and Maxillofacial Surgery - Imaging & Pathology
TMJ	Temporomandibular joint
UK	United Kingdom
V1	Ophthalmic nerve
V2	Maxillary nerve
V3	Mandibular nerve

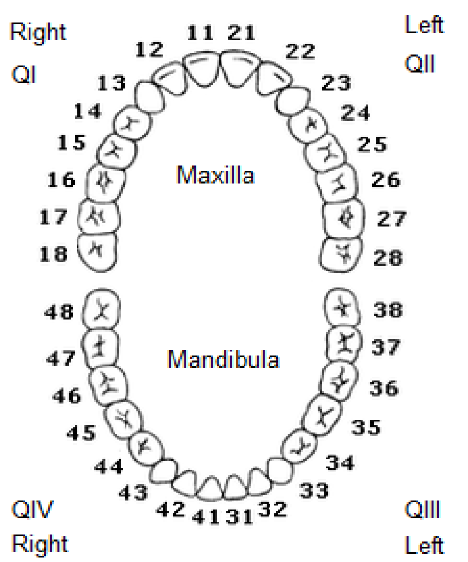
Abstract

The eruption of wisdom teeth is often hindered, resulting in impacted third molars associated with complications. In addition, the risk of a relation between third molar roots and the inferior alveolar nerve, conjointly the risk of nerve damage after third molar surgery, progressively increases with age. Therefore, experts often recommend removal of wisdom teeth at a young age. However, wisdom tooth extraction is not risk-free so that prophylactic extraction remains under discussion. In this light, two studies were constructed to investigate the eruption potential of mandibular wisdom teeth and to gather information about indications and complications of wisdom tooth extraction. A longitudinal radiographic study demonstrated that many wisdom teeth never erupt to a clinical functional position. An initial third molar angulation greater than 25 degrees relative to the second molar was found to be unfavorable for third molar eruption. Moreover, a statistical significant formula predicting third molar eruption based on mandibular molar angulations could be defined. This model needs further refinement before clinical applicability. Accordingly, a prospective epidemiological study revealed a shift from a high rate of non-acute indications, mainly impaction, to a high rate of acute indications, such as caries and pain, for third molar extraction with increasing age. Further, more postoperative neurosensory disturbances were noted in older patients. These findings complemented the results of the radiographic study, but no significant results were obtained so far. In the future, we continue our search for clinical predictive factors of third molar eruption to optimize the management of wisdom tooth treatment.

1 Literature study

1.1 Anatomy of the teeth

Humans develop two sets of teeth during their life. The first set consists of 20 primary or deciduous teeth: 10 in the maxilla (upper jaw) and 10 in the mandible (lower jaw). This set is exchanged by 32 secondary or permanent teeth during development: 16 in the maxilla and 16 in de mandible. By consensus, human dentition is divided into quadrants I to IV, each comprising eight teeth: two incisors, one canine, two premolars and three molars, and is numbered with a two-digit code (Figure 1).



Quadrant I: Two incisors: 11, 12 One canine: 13 Two premolars: 14, 15 Three molars: 16, 17, 18	**Quadrant II:** Two incisors: 21, 22 One canine: 23 Two premolars: 24, 25 Three molars: 26, 27, 28
Quadrant IV: Two incisors: 41, 42 One canine: 43 Two premolars: 44, 45 Three molars: 46, 47, 48	**Quadrant III:** Two incisors: 31, 32 One canine: 33 Two premolars: 34, 35 Three molars: 36, 37, 38

Figure 1: Quadrants of the human dentition and numbering of the permanent teeth (Figure adapted from the Nambia Dental Association.)

A tooth is divided in a crown, the visual part of a tooth, and a root, that anchors a tooth in the jaw bone. Incisors and canines have one root and molars have multiple roots. The four main dental tissues are enamel, dentin, cementum and pulp (Figure 2). The first three tissues are mineralized tissues, the last one is a connective tissue. *Enamel* forms the outer layer of the tooth crown and is the most mineralised. The underlying, more porous *dentine* is secreted by odontoblasts and supports the enamel. The *pulp* (cavity) is the central part of the tooth and is filled with soft connective tissue containing nerve and blood vessels, which enter the tooth from the apex of the root(s). Lastly, a specialized bone-like connective layer, excreted by cementoblasts, covers the root(s): the *cementum*. Periodontal ligaments, attached to the cementum, provide stability and secure the tooth in the jaw bone.

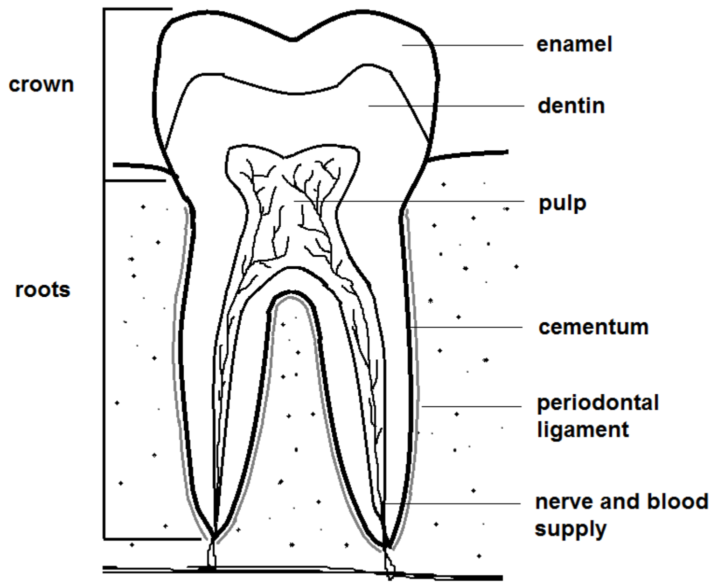


Figure 2: Anatomy of a molar

1.2 Tooth development

Primary and permanent teeth both develop from an ectodermal epithelial layer lining the primitive oral cavity: the dental lamina, which appears around 6 weeks of gestation. The specific time sequence of development is not consistent for all tooth buds, but several general development stages can be distinguished, which are communal for all teeth (1,2):

- Bud stage: During the 7th-9th week of foetal development, the first *dental or tooth buds* form along the dental lamina. These buds are nodules of more active epithelium. Each bud (10 in each jaw) grows down into the underlying mesenchyme and forms the origin of deciduous teeth (1,2).
- Cap stage: The tooth buds change into caplike structures when they are invaded by mesenchyme cells, forming a hillock-shaped *dental papilla*. At the same time, mesenchyme cells surrounding these structures condense and form a *dental sac* (1,2).
- Bell stage: The dental lamina gets more bel-shaped during development and differentiates in two layers: an inner layer, aligning the concavity of the cap, and an outer layer, aligning the convexity of the cap. The cells of the inner layer differentiate into *ameloblasts*, which later stimulate the adjacent mesenchyme cells to form *odontoblasts*. These two types of cells produce enamel and dentine respectively. The

dental lamina is transformed to the *enamel organ*. The enamel organ, together with the dental papilla and dental sac are the three formative tissues of a tooth.

After a while, the roots of the tooth begin to develop; the remaining inner and outer enamel epithelium cells proliferate and form *epithelial root sheaths.* At the same time, the inner cells of the dental sac will form *cementoblasts*, which secrete the *cementum* that covers the root's dentin. The outer cells of the dental sac will form the *periodontal ligament*, which secures the tooth in the bone (1,2).

1.3 Wisdom teeth

The wisdom tooth, third molar or M3 is the posterior molar of the permanent teeth. Normally, the human dentition comprises four wisdom teeth: teeth 18, 28, 38 and 48 in quadrant I, II, III and IV respectively (Figure 1). However almost 23% of the population shows agenesis of one or more third molars (3). The general estimate on agenesis ranges between 5.32% and 56% and differs per geographic region though (3). Having a surnumerary molar (an additional molar tooth in a quadrant) is possible as well, but very rare without any associated syndrome (less than 2%) (4).

As for the anatomical position of the M3s, maxillary third molars are located at the distal ends of the maxilla corpus and mandibular third molars at the distal ends of the mandible corpus. Mandibular third molar roots are in proximity to the mandibular canal (Figure 3). This canal contains the inferior alveolar nerve (IAN), some arteries and veins and is also called the 'inferior alveolar canal'. The IAN is originated from the cranial nerve V or the trigeminal nerve. The trigeminal nerve supplies sensations to the face, mucous membranes, and other head structures and has three major branches: the ophthalmic nerve (V1), the maxillary nerve (V2), and the mandibular nerve (V3). The mandibular nerve is divided in several branches including the buccal nerve, the lingual nerve (LN) and the IAN, which are sensory to buccal mucosa, anterior two-thirds of the tongue and the mandibular teeth and gum respectively. Complementary, the mylohyoid motor nerve is a branch of the IAN, innervating the mylohyoid muscle. The mental nerve is the terminal branch of the IAN and is sensory to the lower third of the face, namely the skin and mucous membranes of the lower lip, skin of the chin, and the gingiva of the lower teeth.

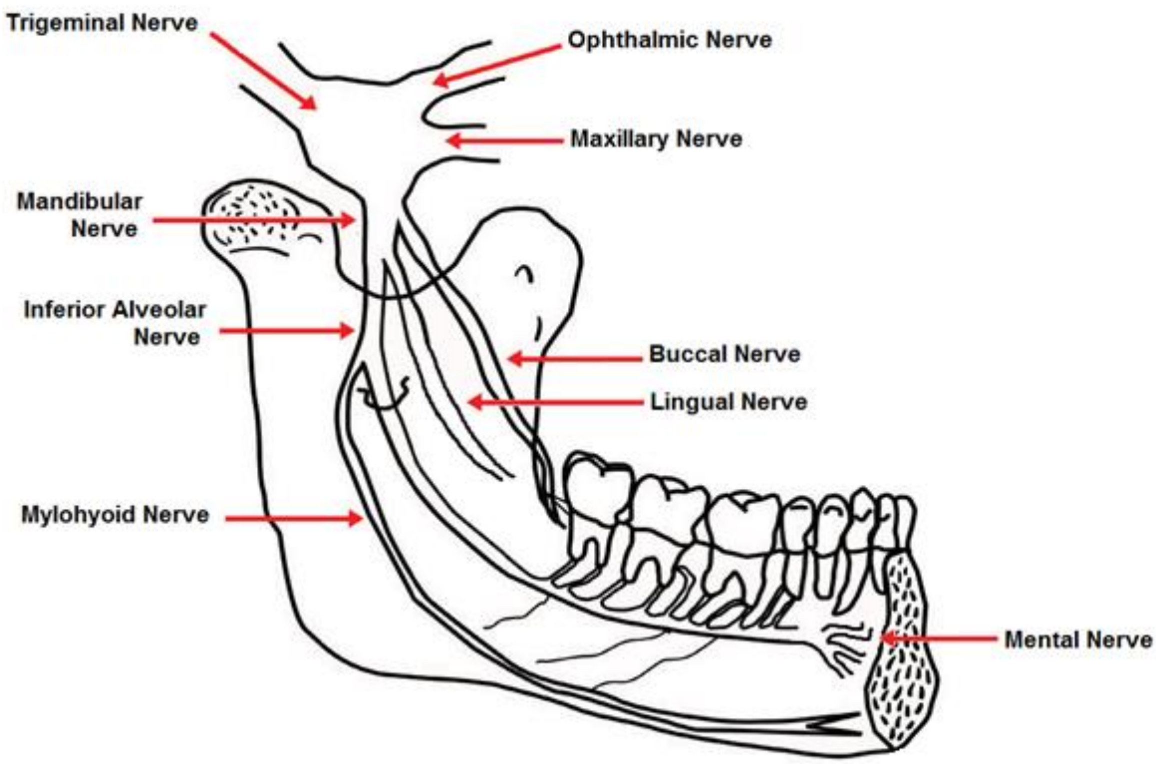


Figure 3: The mandibular nerve branch of the trigeminal nerve (Figure adapted from Desantis J, 1996.) (5)

Concerning the third molars' eruption, they are the last teeth of the permanent dentition to erupt and do so usually during adolescence and young adulthood, when people presumably get wiser. Hence the name 'wisdom' teeth. The third molar's eruption is often disrupted due to a lack of space in the jaw bones distally to the second molar (M2) (6). Subsequently, the third molar often gets impacted. Wisdom teeth can cause many complications, whether they are fully erupted, partially erupted or impacted. Therefore, they commonly are extracted. Bear in mind that this surgical operation can result in clinical problems as well. A surgeon could evoke inferior alveolar nerve damage, for instance, in case the roots of the wisdom teeth are close to the mandibular canal (7).

1.3.1 Eruption and impaction of wisdom teeth

Wisdom teeth show a great variety in time of development, anatomy (size, shape and root formation) and path of eruption among different age categories, populations and genders (8). Racial variance, genetic inheritance, nature of diet, mesiodistal crown diameter and degree of use of the masticatory apparatus are factors contributing to the timing of eruption of these teeth (8). The average age for third molars to erupt is between 17 and 21 years (9).

Nevertheless, wisdom teeth are likely to erupt inadequately: they get (partially) impacted. An impacted tooth is a tooth that fails to erupt into its natural functional position because it is hindered from eruption by adjacent teeth, dense bone, or an overgrowth of soft tissue (2). Impacted third molars can be classified into three groups based on the nature of the overlying tissue: soft tissue impaction (M3 is covered by soft tissue only), partial bony impaction (M3 is partial encased by bone) and fully bony impaction (M3 is fully encased by bone) (10). Mandibular third molars are the teeth found to be the most impacted of the wisdom teeth (11,12). In consequence, mandibular third molars have been the subject of most research concerning impacted wisdom teeth and will be treated in greater extent in this exposition compared to maxillary third molars.

1.3.2 Causes of impaction

Causes of mandibular third molar impaction could be inadequate retromolar space to erupt or an unfavourable path of eruption, as with deficient uprighting of the M3 during adolescence (related to an extensive inclination rate of the M3). Accordingly, an intrinsic large eruption space or increased eruption space as a result of premolar extraction followed by mesial third molar movement, reduce the risk of third molar impaction (13–15). Withal, *Richardson* ME. reported that people with impacted wisdom teeth differ in certain features from people with erupted wisdom teeth: they have the tendency to have shorter mandibles, less mandible growth, larger third molars with higher angulation rates and to develop an overbite (skeletal class II malocclusion). Howbeit, not all of these findings were statistically significant and the existence of predictive parameters for third molar eruption remains questionable (14).

There is no consistent estimate for the worldwide frequency of wisdom teeth impaction, and many studies may over- or underestimate the population rates due to sample differences, risk of bias, applying other methods of assessment and various definitions of impaction (12). We also have to take heterogeneity among populations into account when assessing M3 impaction. A systematic review and meta-analysis, carried out in 2015, reported a world-wide third molar impaction rate of 24.40% (16). No differences between sexes and a slight difference in frequency among geographic regions were assessed (16). The equality between sexes is under discussion, as multiple studies do report an increased prevalence in the female gender (17,18). Note that estimates of M3 impaction around the world are important in order to determine the possible causes of impaction and for clinical decision making concerning treatment protocols (16).

1.3.3 Complications of retained and impacted wisdom teeth

Several pathologic conditions can arise from wisdom teeth, whether fully erupted or not. Pericoronitis is the most acute inflammatory disease associated with retained, partially erupted wisdom teeth. As a result of enclosed food residues and oral bacteria in the operculum (this is the oral tissue covering the third molar) localized infection can emerge (2). Probing is a method used in clinical practice to determine whether the M3 communicates with the oral cavity. If probing depth is greater than 4 mm it is associated with pericoronitis and high levels of periodontal pathogens, possibly progressing into periodontal disease (19,20). Most of the time, this is an indication for M3 extraction.

Another adverse reaction is dental caries: an infectious process induced by bacteria leading to irreversible demineralization of tooth elements. Striking up to 33% of young adults and even more adults above the age of 25 with (partially) erupted wisdom teeth, dental caries are a major problem (2,21,22). Caries are the result of a microbiological shift, leading to a cariogenic environment in the mouth cavity, affecting all exposed teeth. Subsequently, previous caries experience is a good predictor for future caries development (23). Supplementary, the criterion ‘caries experience at baseline in more anterior teeth’ appears to have a negative predictive value for caries experience in third molars later in life (23), meaning that M3s are unlikely to develop caries if there are no caries detected in more anterior teeth. Notice that M3 caries are difficult to treat due to the M3’s anatomical position. Further, pathogens can also lead to periodontal diseases such as gingivitis or periodontitis, affecting one or more periodontal structures. Since (partially or fully) erupted wisdom teeth are often difficult to (keep) clean, bacteria can easily accumulate in this area and give rise to these conditions (2).

Alongside complications of (partially) erupted wisdom teeth, non-erupted third molars can yield problems as well. Root resorption of second molars, for instance, could be caused by pressure exerted by an impacted tooth (24). More severe, but rare complications associated with impacted M3s are odontogenic cysts and tumours and mandible fractures (2). Lastly, some allege that anterior dental crowding before and after orthodontic treatment can be caused by retained wisdom teeth. When there is an actual risk for crowding, one can opt to remove the asymptomatic wisdom teeth prophylactically, but a lot of contradictory literature exists about the cause-effect of impacted M3s as to crowding. Consequently, many orthodontists and oral and maxillofacial surgeons possess different opinions regarding this matter (2).

1.4 Panoramic radiographic imaging

As mentioned previously, wisdom teeth can be the cause of several pathologic conditions, which each wishes to avoid. Therefore, the prediction of eruption and impaction of these teeth, alongside with preoperative risk assessment, is of great importance for prevention of complications, the maintenance of dentition and dental treatment planning (8,19). Panoramic radiographic photography (X-rays) is reasonably accurate in assessing third molar features as level of eruption, root development and morphology, angulation of the tooth and relationship to the mandible, adjacent teeth and the mandibular canal or IAN (8,10,25). Hence, panoramic radiographic imaging – adjuvant to clinical investigation – can be helpful for wisdom teeth assessment and surgical operation planning (26). To that end, radiographic imaging can be used to stage or classify third molars or to evaluate particular parameters.

1.4.1 Classification

Several methods for staging developing third molars based on panoramic radiographs are formulated over time. A good intra- and inter-examiner agreement of such methods is important to assure the reproducibility of the stage assessment. *Demirjian et al.*'s method for mandibular third molar staging appears to be the best method as regards to this intra- and inter-examiner agreement (Figure 4) (27,28).

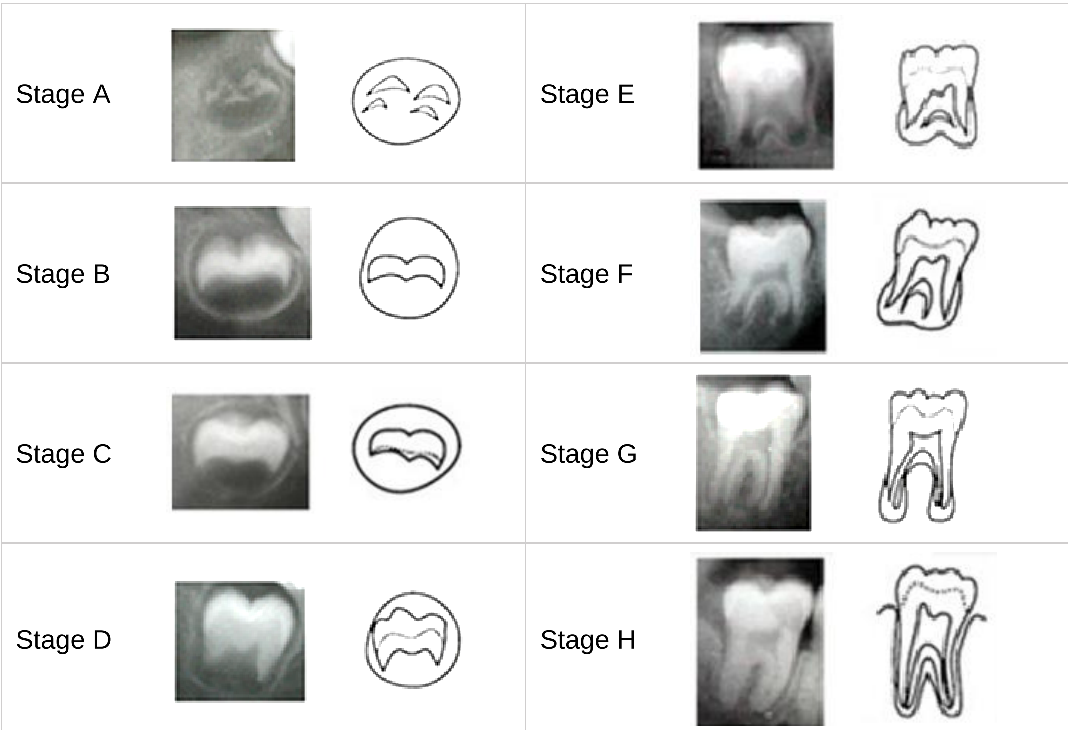


Figure 4: *Demirjian's* staging (Figure adapted from Demirjian A, 1973.) (29)

This method divides third molars in eight development stages based on tooth mineralization, starting from initial tooth calcification to root completion (29). These stages can be used for evaluating third molar parameters as root development or root/crown ratio, for predicting the third molar's eruption status, for surgical decisions about the timing of extraction and surgical difficulty, or for age estimation (28). This latter is useful for medicolegal and other purposes, but is behind the extent of this literature and will not be discussed.

A second subdivision, based on impaction status, can be made according to criteria established by *Pell and Gregory* (Figure 5). These state that impacted third molars can be divided into groups according to the relative depth of the third molar in the bone (positions) and according to the relation of the tooth to the mandibular ramus and the second molar (classes) (10,11,30,31).

Position A M3's occlusal plane is at the same level as the adjacent tooth; the M3 is not covered by bone.	**Position B** M3's occlusal plane is between the occlusal plane and the cervical line of the adjacent tooth; the M3 is partially covered by bone.	**Position C** M3's occlusal plane is apical to the cervical line of the adjacent tooth; the M3 is completely covered by bone.
Class I M3 is situated anterior to the border of the ramus.	**Class II** M3's crown is partially covered by the anterior border of the ramus.	**Class III** M3's crown is fully covered by the anterior border of the ramus.

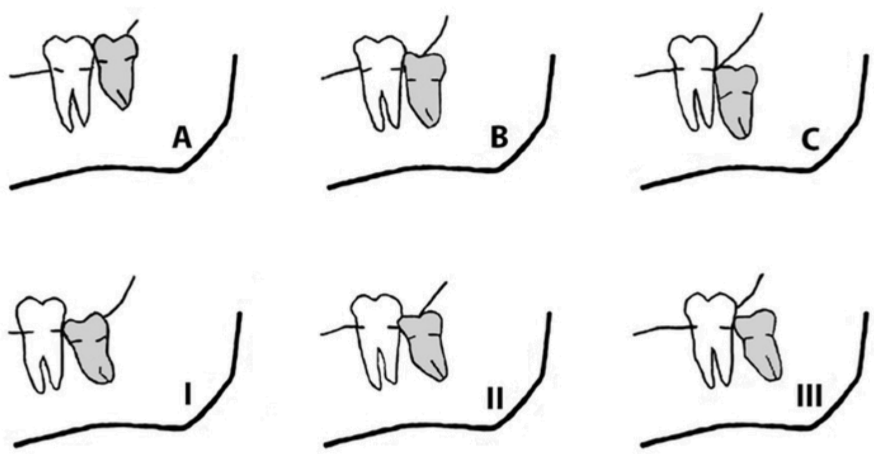


Figure 5: *Pell and Gregory*'s classification (Pell G and Gregory B, 1993.) (32)

Thirdly, impacted third molars can be divided via *Winter*'s classification (Figure 6), based on the inclination of the impacted third molar to the longitudinal axes of the second molar, into: vertical (a), horizontal (b), distoangular (c), mesioangular (d), transvers (e) and invers (f) (11,31,33). Mesioangular orientated impaction in the mandible is observed as being most frequent (11,16).

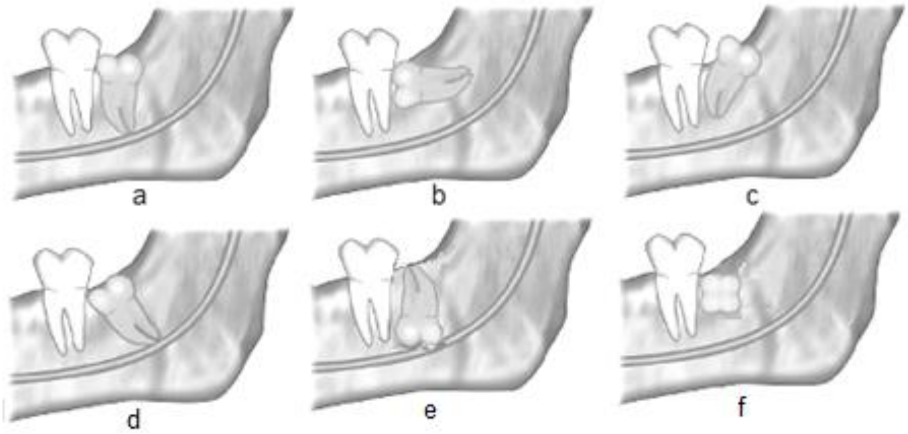


Figure 6: ***Winter*****'s classification** (Figure adapted from Borle R. 2014.) (34)

Lastly, *Whaites*' system (Figure 7) is a method that classifies the mandibular third molar according to the relationship between the molar roots and the inferior alveolar nerve. *Whaites*' system includes five categories: normal relationship (the white lines of the mandibular canal are evident across the roots) (a), loss of white lines (b), narrowing of the white lines (c), alteration in direction of the mandibular canal at root apex (d), radiolucent band across the roots (e) (33,35).

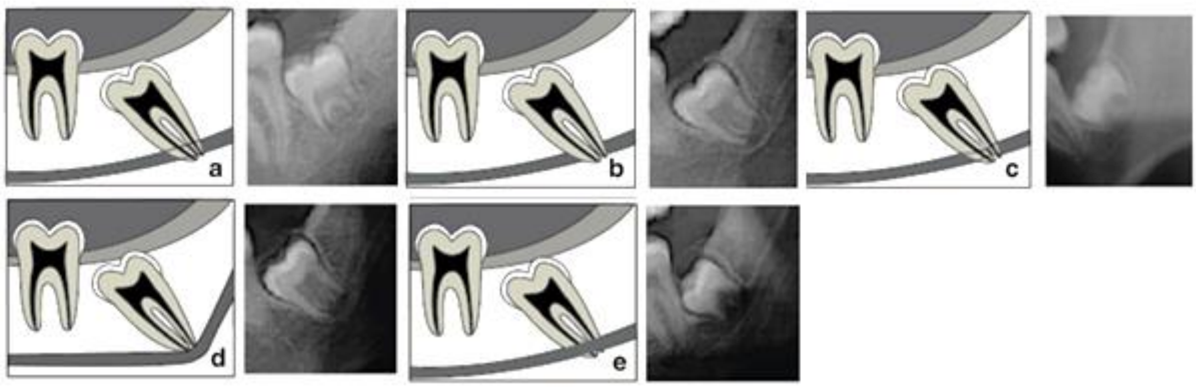


Figure 7: ***Whaites'*** **classification** (Figure adapted from Miclotte A, 2014.) (33)

This classification system shows similarities with the seven radiographic markers described by *Rood and Shehab* (Figure 8) for predicting the possibility of a root-IAN relation. Four of these markers are related to the root: darkening of the root (A), deflection of the root (B), narrowing of the root (C) and having a bifid root apex (D). Three markers are related to the mandibular canal: interruption of the white line of the mandibular canal (E), diversion of the canal (F) and narrowing of the canal (G) (36).

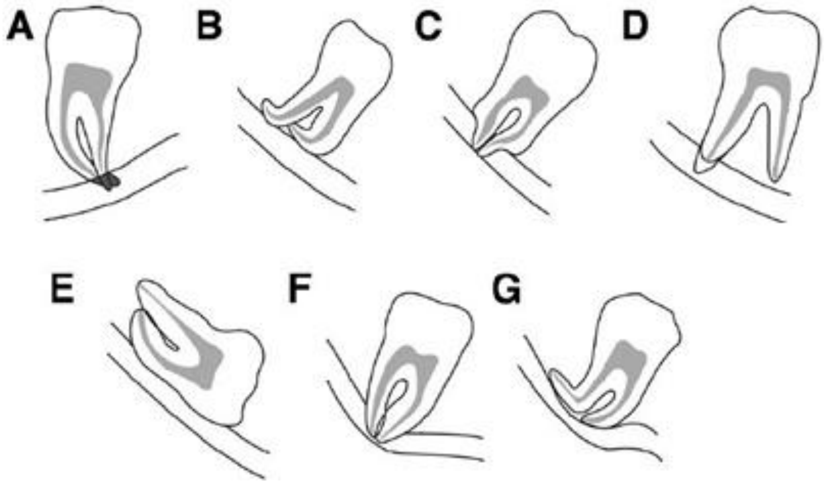


Figure 8: ***Rood and Shebab*****'s seven radiographic markers of a root-nerve relation** (Figure adapted from from Rood B and Shebab P, 1990.) (36,37)

1.4.2 Preoperative assessment

Multiple aspects can be derived from panoramic radiographs when it comes to the evaluation of wisdom teeth. 'Retromolar space', 'position of the M3' and 'relation between the M3 and the mandibular canal' are three broadly examined parameters concerning third molar eruption, risks and preoperative assessment. Based on these radiographic findings, future impaction and risk of complications can be predicted and a decision about removal can be made at an early patient's age.

Concerning retromolar space, research has pointed out that the retromolar space is significantly smaller in people with impacted wisdom teeth than in people with erupted teeth (8). On the other hand, the presence of space does not mean automatically that the third molar will erupt, as there are many other factors influencing the eruption potential, e.g. orientation and depth of impaction of a third molar. (8,14,38).

A second parameter that aids in the prediction of M3 eruption, impaction and morbidity after surgical M3 extraction is the position of the third molar, represented by the M3 angulation and type and depth of impaction. As unsatisfactory uprighting is a common cause of impaction (13), many studies about M3 angulation and its predictive value for eruption and surgical difficulty have been performed. An important finding is that the risk of impaction increases with increasing M3 angulation, measured as the angle between the M3's occlusal surface and the occlusal plane (13). On the contrary, a decrease in angulation does not necessarily imply that the M3 sooner or later will erupt (39). In addition, different angular M3 positions give rise to different risks for the development of clinical problems (39). Likewise, the type of impaction, linked with the M3's angulation, affects postoperative morbidity.

Horizontal and distoangular orientations are associated with more complications, compared to other impaction types and fully impacted third molars increase the risk of postoperative general infection (40–42). In addition, the depth of impaction could be predictive for IAN injury, as the risk of root-nerve relation increases with increased depth of impaction (37,43).

Thirdly, determining the relationship between the mandibular third molar (roots) and the mandibular canal contributes to proper preoperative assessment of third molar extraction and estimating the hazard for IAN injury (25). As mentioned, risk of IAN injury highly increases when there is an actual contact between these two (30). The risk of a contact can be assessed by evaluating the presence of (one of the) markers of *Rood and Shehab*. Three of these radiographic signs appear to be the most significant markers for the prediction of the root-nerve relationship: 'darkening of the root or increased radiolucency', 'interruption of the radiopaque borders of the mandibular canal' and 'diversion of the mandibular canal' (25,30,36).

Nonetheless, as panoramic radiography is only two-dimensional, it is more reliable for excluding the relationship between the nerve and the molar roots than for confirming it, meaning that the absence of these radiographic signs indicates a minimum risk of nerve damage (7,25,37). Hence, additional cone beam computed tomography (CBCT) imaging, which has a three-dimensional view and is extremely accurate, is indicated in cases in which the radiographic marker(s) predict a risk of nerve relation (30). Nevertheless, CBCT is usually not used in first line preoperative assessment because this type of imaging is more expensive and disposes a higher radiation dose than panoramic radiography (7,30). Besides, preoperative assessment based on CBCT imaging compared to panoramic imaging does not show a statistically significant reduction in postoperative complications (44).

1.5 Surgical extraction of wisdom teeth

Considering the multitude of complications associated with retained or impacted wisdom teeth, it is not much of a surprise that extraction of third molars is the most commonly performed procedure by oral and maxillofacial surgeons (9). Regarding the removal of disease-free and asymptomatic wisdom teeth, no treatment consensus exists among experts. Some claim that prophylactic removal would expose the patient to unnecessary surgical risks, postoperative discomforts (as pain or swelling) and adverse (personal and societal) economic consequences (45). On the other hand, wisdom teeth are frequently a source of trouble at both young and old age, so that some surgeons argue in favour of prophylactic removal. They wish to avoid complications secondary to M3 impaction and retention and to avoid morbidities associated with extraction in elderly patients (46).

1.5.1 Indications and contra-indications

There are several pathological indications supporting the removal of wisdom teeth, such as pericoronitis, caries, odontogenic cysts, odontogenic tumours, periodontal disease and bone destroying disease (45). Third molars should also be removed when they cause considerable pain, prevent the eruption of second molars or affect the health of adjacent teeth (e.g. root resorption) (45). In addition, third molars are extracted if they obstruct or affect orthodontic treatment, in preparation for orthognathic surgery or if they will predictably cause problems with overlying dental prostheses or dentures (45). Whether or not to extract wisdom teeth in order to prevent late lower incisor crowding is an ongoing discussion. Disagreement arises with regard to the effect of the specific position of a wisdom tooth on crowding and thus if such wisdom teeth should be prophylactically removed (19).

1.5.2 Complications

According to Bui et al., the overall complication rate of third molar extraction variates between 4,6% and 30% (18). Pain, swelling and trismus are to be expected with this kind of surgery, therefore they are not considered as complications (9). The most common complications of M3 extraction reported in literature are localized alveolar osteitis (AO) or dry socket, infection, bleeding and (temporary) paraesthesia (9,18). These four complications are rather minor and found to be more common with mandibular than maxillary third molar extraction (9). Dry socket is characterized by a dull, throbbing pain around the area of the tooth socket that persists several days after the surgical removal of a tooth and is often accompanied by halitosis (9,40). Injury to the temporomandibular joint (TMJ) could also appear after M3 removal and can result in a cluster of pain symptoms in the jaw, temples, jaw joints and jaw muscles (47). However, no prevailed evidence for a causal relationship between these two can be found in literature (9). Other, more rare, but severe complications of third molar extraction are damage to the trigeminal nerve (more specific, the IAN branch or LN branch) and mandibular fractures (9,19). Trigeminal nerve injury can be temporarily, meaning that the patient regains normal functioning and feeling a few weeks after surgery. In other cases, the trigeminal nerve injury can be permanent, so that the patient continues to experience neurosensory discomforts throughout his or her whole life. A significant part of patients stroke by trigeminal nerve injury present with neuropathic pain, others with paraesthesia and anaesthesia. Such injuries may lead to functional and psychological difficulties, such as trouble with eating, drinking or speaking, disturbance of social interactions and interference with normal daily life (48,49).

1.5.3 Risk factors and factors predicting postoperative complications

Besides tooth related factors as third molar eruption level, position and location relative to the IAN, some patient-related factors contribute to the complication risk following surgical extraction of the wisdom teeth (45). Several studies show that the risk for postoperative complications elevates with increased age (18,41,49,50). This should surely be taken into account when making a decision about M3 extraction and when drafting an M3 management protocol. Some age-related changes could be at the base of a high operative difficulty, such as increased bone density, decreased bone elasticity and the presence of other comorbidities (49,51). Additionally, an age-related increase in recovery time is reported (45). Note that the age-related risk factors for postoperative complications can be attributed to an age-related increase of health risk factors rather than age per se (19,49). Anywise, these findings affirm that M3s are best removed at a younger age. Alongside age, there are other individual factors influencing the risk of complications after surgery, namely: race, gender, medical history, oral hygiene, smoking habit and the use of oral contraceptive (40,45). Furthermore, operative factors as the surgeon's experience, surgical time and technique, anaesthetic technique and perioperative antibiotics are also related to the occurrence of postoperative complications (9,40,45). Two frequent findings are that an extended operation time and the exposition of the mandibular nerve during operation are associated with a higher rate of postoperative complications (41,42).

It would be of interest to draft a system based on anatomical and radiologic features that categorizes wisdom teeth into groups predicting the need and difficulty degree of extraction, and the rate of postoperative complications. Such subdivision would help surgeons in assessing the risks of a presumptive intervention and choosing the best surgical method.

1.6 Management of wisdom tooth extraction

A difficult question that occupies many oral and maxillofacial surgeons is how to manage third molars best. When to surgically remove them? When to retain them? Is a routinely follow-up designated? High quality prospective, epidemiological research concerning the clinical practice of wisdom tooth management can solve these questions.

1.6.1 Wisdom teeth divided by symptom and disease status

Third molars can be divided in four categories (Table I) based on the presence (+) or absence (-) of symptoms (S), reported by the patient, and disease (D), clinically or radiographically determined (12,20,52,53). A clinician needs to establish the cause of present symptoms, because it is possible that the patient reports symptoms in the area of the wisdom teeth that do not originate from the third molars directly. Pain in the posterior part of the mandible, for instance, could originate from masseter muscle pain or inflammatory side effects of teething (20). Evidence of disease is more straightforward; it can be checked clinically by inspecting hygiene, presence of caries, adjacent tissue and probing depths of the M3s and by means of radiographic imaging (12). When clinical signs of disease are present, radiography is used to confirm this status (20). Radiolucent lesions linked to the M3s are suggestive for disease, such as caries. Further, damage to adjacent molars, such as root resorption, can be denoted on the radiographic images (20). It is very important to keep in mind that absence of symptoms does not necessarily imply absence of disease.

Table I: Classification of wisdom teeth based on symptoms and disease status (12)

Symptoms attributed to M3s	Clinical or radiographic evidence of disease	
	D +	**D -**
S +	Group A	Group B
S -	Group C	Group D

Depending on these four categories, management decisions regarding third molars can be made. When disease is present (group A and C), decision making is an easy task: treat the disease. When disease is absent, but symptoms are present (group B), management gets more challenging. It is crucial to detect what is causing the symptoms and to adjust the treatment to the diagnosis. When disease as well as symptoms are absent (group D: asymptomatic and disease-free M3s), management decisions are controversial (20,53). No scientific evidence justifying prophylactic removal is present, nor for retention of third molars (20,52–54). Therefore, the risks and benefits of various treatment options should be closely reviewed and outweighed. If wisdom teeth are retained, active surveillance and routinely follow-up visits are recommended in order to avoid undesirable events related to retention. Additionally, studies have pointed out that retained M3s frequently and unpredictably change periodontal status, position and eruption status, to such degree that the hazard for complications and extraction also alters (20). Howbeit, the need of future extraction cannot be predicted (55).

It turns out that patients with asymptomatic and disease-free M3s, prefer extraction when presented with both treatment options (extract or retain M3s) (54). We need to consider factors associated with patients' treatment preference and surgeons' recommendation, though (54). If maxillofacial surgeons have to decide, the perceived risk of eventual clinical manifestations of retained wisdom teeth influence their choice (46). Plus, each clinician may apply other methods or use other information for identifying the complication risk, which gives rise to different management decisions (46).

1.6.2 Socioeconomic aspects

Patients, clinicians and the government do not show unanimity regarding third molar management. This reflects a bias of self-interest and makes it difficult to agree when it comes to deciding what is best practice as to wisdom teeth. Often, money is an incentive in the decision making process. However, the cost difference between retention and removal is unknown. On the one hand, the costs of active surveillance and treatment of retained M3s have to be taken into account. On the other hand, the costs of surgery, treatment of potential complications and additional costs of missing work or school are important to consider (20).

1.6.3 Guidelines

No worldwide agreement exists regarding prophylactic removal of wisdom teeth. The American Association of Oral and Maxillofacial Surgeons (AAOMS) and Academy of Paediatric Dentistry recognize the benefit of prophylactic removal in order to avoid future disease and complications, whereas the American Public Health Association (APHA) and the UK National Health Service (NHS) advocate against it (53). The United Kingdom (UK) currently employs the recommendations regarding third molar management issued by the National Institute for Health and Care Excellence (NICE) (53), which state that the surgical removal of impacted M3s should be limited to patients with evidence of pathology (51,56). The aim of the NICE guidance is to discontinue the prophylactic removal of pathology-free impacted third molars in the NHS (56). Nevertheless, the implementation of this guideline in the UK did not lead to a decrease of third molar removal. In fact the indications of extraction have altered with the changing mean age at M3 extraction of the patients. Nowadays, the mean reason for removal in the UK is predominantly periodontal pathology, rather than impaction (53,57). The Finnish Current Care Guidelines for the third molar, updated in 2014, are similar to the NICE guidelines, apart from the recommendations for preventive removal (53,58). According to the Finnish guidelines, elective early removal of mandibular third molars is justified in order to prevent caries, pericoronitis, inferior alveolar nerve injury and bone defects (58). The Finnish guidelines mention age limitations for prophylactic removal:

depending on the extraction indication, the maximum age of patients at removal should be 19 to 25 years old (58).

In short, different M3 management recommendations are applied throughout the world. The overall consensus of these recommendations is that third molars should be removed when there is evidence of disease and that retained wisdom teeth should be submitted to a life-time follow-up (53).

2 Aims and Objectives

Wisdom tooth treatment and extraction concerns us all, directly via personal health or indirectly via expenditure of health budgets. Hence, a general agreement on wisdom tooth management would benefit the whole society. Pathological wisdom teeth should surely be removed, but whether or not to extract asymptomatic and disease-free wisdom teeth remains controversial. A lot of research has been performed in order to provide evidence-based recommendations to facilitate the decision making process concerning wisdom teeth. In spite of that, no worldwide consensus on (prophylactic) removal has been attained. In this light, this thesis aids at improving knowledge about indications and complications of wisdom tooth extraction and is divided in two main parts.

A first part is an interim analysis of a large epidemiological prospective cohort study, the M3 study, which focuses on indications and postoperative complications of third molar removal. It will provide a clear view on current practice of wisdom tooth extraction in Belgium. Via this research, the effect of age on indications and complications of surgical removal of wisdom teeth can be examined. Additionally, the study helps in identifying which patients are prone to third molar pathology and postoperative complications. Eventually, the aim of the M3 study is to confirm two hypotheses. The first hypothesis is that surgical removal of symptomatic third molars at a later development stage is more often associated with complications and morbidity, compared to prophylactic removal in an early tooth development stage. The second hypothesis is that risks for complications increase with patients' age.

A second part is a radiographic longitudinal study of an extensive sample of young orthodontic patients. The study aim is to predict mandibular third molar eruption and the risk of a root-nerve relation, based on the third molar's development stage, eruption status, angulation and radiographic markers of a root-nerve relation, which can guide surgeons in the decision making process of third molar treatment. The hypothesis is that highly inclinated third molars never erupt to a functional position and that more mature wisdom teeth have a higher risk to develop a nerve relation. Hence, these wisdom teeth can be better removed prophylactically at an early development stage.

3 Patients and methods

3.1 An epidemiological, prospective cohort study to detect the indications and complications of wisdom tooth extractions

3.1.1 Study design and variables

The M3 study is a prospective, epidemiological cohort study, set up by the Oral and Maxillofacial Surgery - Imaging & Pathology (OMFS-IMPATH) research group (KU Leuven). The Commission for Medical Ethics of the University Hospitals of Leuven approved the study in September 2015 (B322201525552). The consecutive study sample consisted of patients who visited the outpatient department of Oral and Maxillofacial Surgery (OMFS) of the University Hospital Sint-Rafaël (Leuven, Belgium) and of the Mariaziekenhuis (Overpelt, Belgium) between September 2015 and February 2017. The patients consulted these departments for sake of evaluation and surgical extraction of one or more wisdom teeth. Patients with a minimum age of 12 years were included. No restriction for the maximum age was applied. Patients that had any other type of dental treatment combined with the third molar surgery were excluded. A written informed consent was recorded from each patient before his or her participation.

Questionnaires filled out by study participants and surgeons, and data from the patient's medical files, were used to gather pre-, peri- and postoperative information (Figure 9). The first questionnaire was completed at the pre-operative consultation or just before surgery and aimed at gathering demographic and health condition data of the patient. At home, the patient completed a second and third questionnaire, via internet or per letter, three and ten days after the operation. These surveys provided postoperative information like recovery status (pain, trismus, etc.) and the ability to resume work and daily activities. The questionnaires were considered as non-invasive and imply a minimum burden for the patients. Conjointly, the surgical information was gathered in two ways. A one-off questionnaire was taken from each surgeon to determine his or her individual operation technique. Secondly, the surgeon filled out a questionnaire during surgery to record operative information (such as surgery time, surgical technique and nerve damage risk).

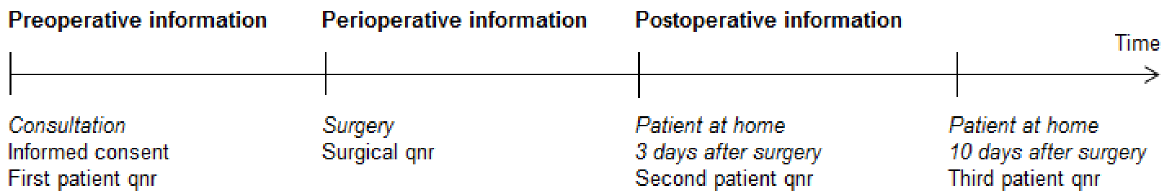


Figure 9: Time line of the M3 study. The abbreviation 'qnr' means questionnaire.

3.1.2 Statistics

Only descriptive statistics were done and tables and graphs were drafted by use of Excel 2016. The entire study population, divided in two or more age categories, was included.

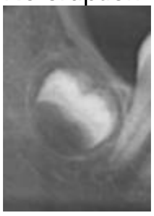
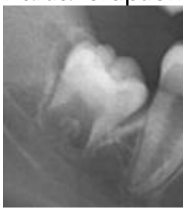
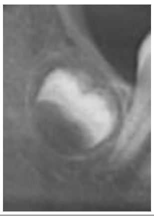
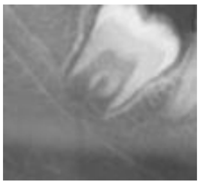
3.2 Radiographic study to evaluate the eruption potential of mandibular third molars

3.2.1 Study design and variables

A retrospective, radiographic, longitudinal study was carried out upon panoramic radiograph records of 1087 subjects. The sample could be split up in 483, 454 and 150 orthodontic patients who attended the Department of Orthodontics at the University Hospitals Leuven (Belgium), a private orthodontic practice in Zwijnaarde (Belgium) and a private orthodontic practice in Hasselt (Belgium), respectively. Subjects between the age of 10 and 25 years old were included, as this is the age interval wherein third molar development and eruption occur. Patients' demographic data were obtained from clinical records. Two radiographs per subject, with the best quality and a minimum time interval of one year, were selected. The final sample was thus composed out of 2174 panoramic radiographs. The radiographs were generated by use of one of the following digital panoramic X-ray machines: a Veraview (Morita, Kyoto, Japan), a Cranex Tome (Soredex, Tuusula, Finland), a ProMax (Planmeca, Helsinki, Finland) or a PaX-i (Vatech, Fort Lee, America). Patients with a full mandibular dentition and fully erupted teeth, except from the wisdom teeth, were included. Patients still having primary teeth, with dental agenesis, extractions or surnumerary elements in the mandible were excluded. Likewise, patients having odontomas, patients with craniofacial or syndromic anomalies affecting the mandible or patients that underwent orthognathic surgery were eliminated.

Various parameters were evaluated on the panoramic radiographs (Table II).

Table II: Evaluated parameters on the panoramic radiographs

Parameters	Evaluation		
Eruption level	Score 1: No eruption 	Score 2: Partial eruption 	Score 3: Full eruption 
Development stage or Root/crown ratio	Score 0: No roots 	Score 1: Beginning of root formation 	Score 2: Advanced root formation 
Root-nerve relation	Score 1: No relation 	Score 2: Risk of relation 	

A first one was the eruption level of the third molar (or the position of the third molar relative to the mandibular corpus). The wisdom teeth were classified in three groups. A wisdom tooth was not erupted (score 1) when the most superior part of the M3 was covered by bone or tissue. A wisdom tooth was considered as partially erupted when the most superior part of the M3 was between the occlusal plane and the cervical line of the M2 (score 2). When the occlusal plane of the M3 was at the same level as the occlusal plane of the M2, the wisdom tooth was fully erupted (score 3). Secondly, the third molar's development stage (root/crown ratio) was recorded based on *Demirjian*'s classification system (29). Third molars were divided into three groups. A first group contained all teeth that did neither show root formation, nor the start of bifurcation (score 0). Wisdom teeth with developing roots or with starting bifurcation, were addressed to a second group (score 1). Wisdom teeth with more developed or fully developed roots (length of the roots equal or greater than the crown height) were categorized in a third group (score 2). A third parameter was the possibility of a relation between the mandibular third molar roots and the mandibular canal. A subdivision was made based on *Whaites*' radiographic markers for a possible root-nerve relation (33,35). The teeth were scored as 'no relation with the mandibular canal' (score 1) or 'risk of relation with the mandibular canal' (score 2). The latter meant that one of following criteria was present on the radiograph: loss of the borders of the mandibular canal (white lines), narrowing of the white lines, alteration in direction of the mandibular canal at root apex and a radiolucent band across the roots.

Lastly, the angulation of the third, second and first molars, absolute to the horizontal axis and relative to each other, were computed by use of the program GIMP 2.0 Ink image manipulation. The angulations absolute to the horizontal axis were measured as the intersection between a molar's longitudinal axis and the horizontal axis. By consensus, the longitudinal axis of a molar was drawn using two predetermined auxiliary points: the most apical point of the pulp cavity (point 1) and the midpoint of the line connecting the most mesial and the distal contact points of the crown (point 2) (Figure 10). In case of undeveloped roots and thus undeveloped pulp cavity, the longitudinal axis was drawn perpendicularly through the midpoint of the line connecting the most mesial and the distal contact point of the crown (Figure 10).

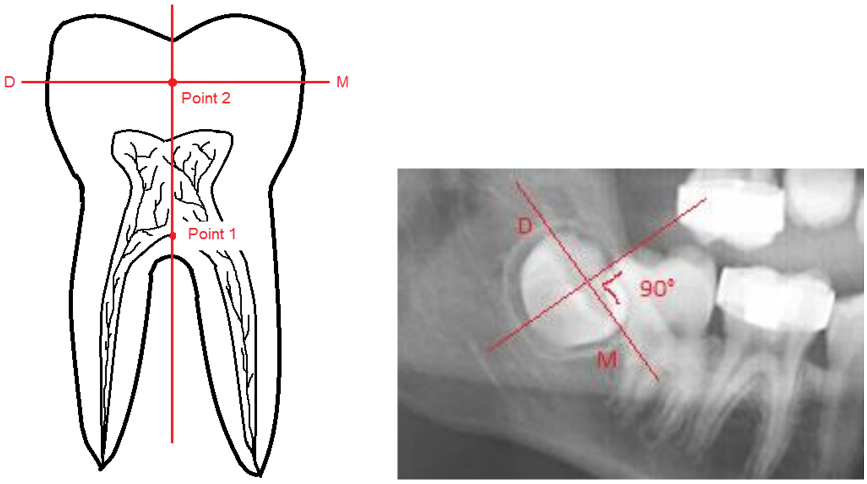


Figure 10: Longitudinal axis of a molar. At the left a molar with roots and at the right a molar without roots. "M" is the most mesial contact point of the crown and "D" is the most distal contact point of the crown.

The angle between two molars was equated as the intersection between the long axis of the one molar and the long axis of the other molar (Figure 11). Three angulations per jaw quadrant were calculated: between the second and third molar (M2/M3), between the first and third molar (M1/M3) and between the first and second molar (M1/M2). A mesioangular orientated molar and a distoangular orientated molar, relative to a vertical orientated molar, were noted as a positive and a negative angle respectively (Figure 12). The radiographs were scored in digital JPEG-format or as analogous files by use of a light source in a dark room. Two observers scored all the panoramic radiographs.

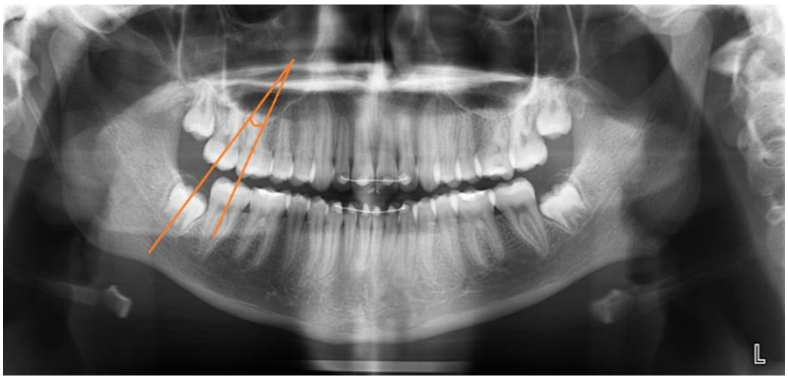


Figure 11: Measurement of the angulation between a third molar and a second molar

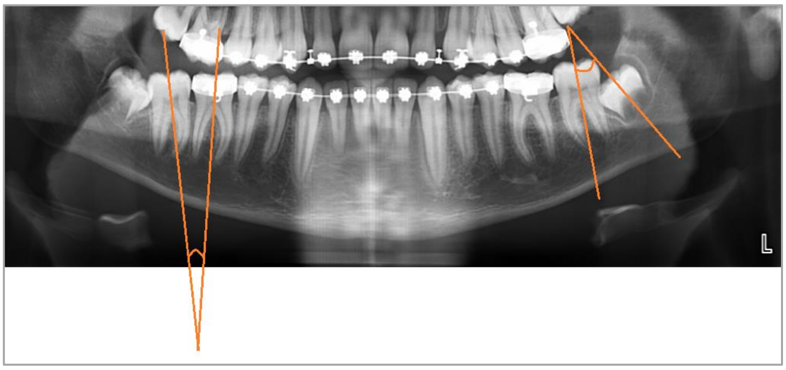


Figure 12: A negative and positive angle between mandibular molars. At the left a negative angle between a second and first molar and at the right a positive angle between a third and a second molar were observed.

3.2.2 Statistics

Descriptive and analytical statistics were performed. Graphs and tables were drafted for the descriptive statistics by use of the program Excel 2016. Analytical statistics were done by use of the program SPSS. A p-value less than 0.05 was considered significant. For assessing the intra- and interrater reliability of the evaluated radiographic parameters, two tests were performed. The Fleiss' kappa test was used to assess the reliability of observations of the categorical variables 'eruption level', 'root/crown ratio' and 'root-nerve relation'. The intraclass correlation coefficient (ICC) test was used to assess the reliability of observations of the angulation measurements, which are continuous variables. For the intrarater reliability each observer rescored 10% of its own work. For the interrater reliability, each observer rescored 10% of the other observer's work.

A generalized linear mixed model (GLMM) with probability of third molar eruption as binary data (no eruption and partial or full eruption) was fit using a logit link, in order to find the combination of angulations (M1/M2, M2/M3 or M1/M3) that had the best relation with the probability of the third molar eruption. The general form of the GLMM was:

$$y = intercept + a * (angulation1) + b * (angulation2) \text{ with } p = \frac{e^{\alpha}}{1+e^{\alpha}}$$

where *y* was the probability of third molar eruption, *a* was the coefficient of angulation 1 (which could be M1/M2, M2/M3 or M1/M3) and *b* was the coefficient of angulation 2 (which could be M1/M2, M2/M3 or M1/M3). *p* was the chance of M3 eruption, *e* was the base of the natural logarithm and *α* was the linear combination of the variables and their coefficients. Angulation 1 and 2 together gave the most accurate prediction of third molar eruption and whether these angulations were M1/M2, M2/M3 or M1/M3 was dependent of the stepwise regression method for drafting the GLMM. These analyses were done for wisdom teeth that were initially not erupted (evaluated on the first radiograph). Separate analyses were done for wisdom teeth without roots and for wisdom teeth with initiating root formation. Too little data were available of wisdom teeth with advanced root formation for a reliable analysis. It was possible that the reason of non-eruption on the second radiograph was due to the short time span between two radiographic images of a subject, so that eruption simply did not take place yet. As a result, the chance of eruption could have been underestimated. Therefore, the same analyses were done on a subset of the study sample: all the radiographic images with more than three years in between them, which will be referred to as 'subset sample >3 years'. This reduced the sample size from 4052 observations for 'the whole sample' (the number of teeth that were not erupted on the first radiographic image of the subjects (2026), multiplied by two, as two images per subject were evaluated) to 1190 observations for the 'subset sample >3 years'.

Secondly, the risk of nerve relation over time was evaluated over multiple age categories. These categories were based on the subject's age at the moment of the first panoramic radiograph: 10-11 years, 11-12 years, 13-14 years, etc. A GLMM was made with the initial age categories and the M2/M3 angulation.

Lastly, the third molars' mean change in angulation over time, based on the initial M3 angulation (M2/M3), was examined by means of a linear mixed model with the initial third molar angulation as explanatory variable, the mean change in angulation over time as dependent variable and the patient as random factor. The linearity of the model was visually assessed by comparing the regression line with a locally weighted scatterplot smoothing (LOWESS) curve and a normal quantile plot of the residual values. Once more, these analyses were done for wisdom teeth with no roots and for wisdom teeth with initiating root formation, but not for wisdom teeth with advanced root formation because of the lack of sufficient data.

4 Results

4.1 An epidemiological, prospective cohort study to detect the indications and complications of wisdom tooth extractions

The descriptive statistics of the results of the M3 study are restricted to the aspects that are related to the second part of this thesis (the radiographic longitudinal study, which will be described later on). These aspects are the indications of mandibular wisdom tooth extraction and the occurrence of nerve damage symptoms after surgery.

4.1.1 Age and gender distribution

The final sample included 1840 patients, of which 875 (48%) were men and 965 (52%) were women. The youngest patient was 13 years old and the eldest was 83. The mean age of the overall population was 25.3 (±11.1) years old. Most wisdom teeth were removed in patients between the age of 18 and 21. Above 40 years of age, the numbers were considerably lower (Figure 13).

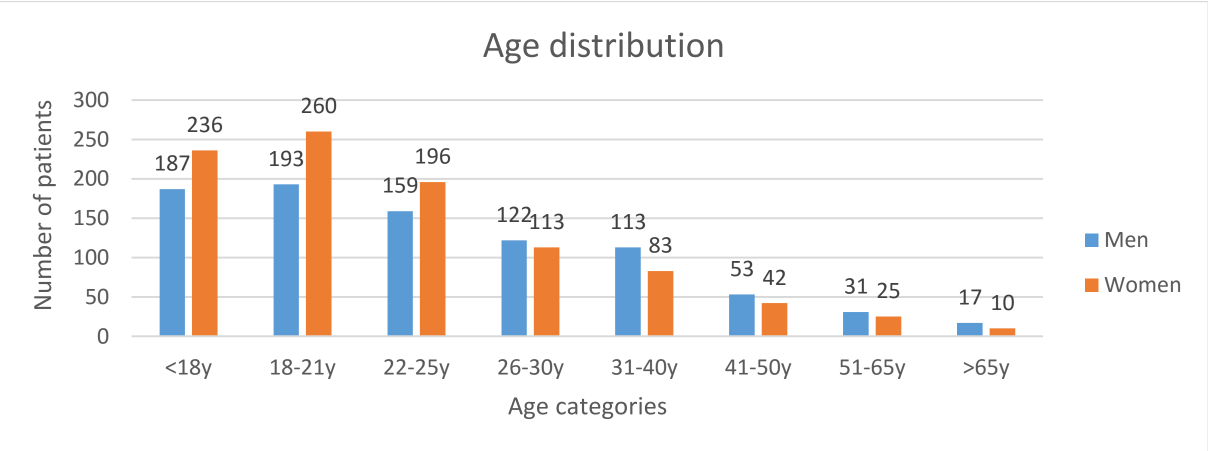
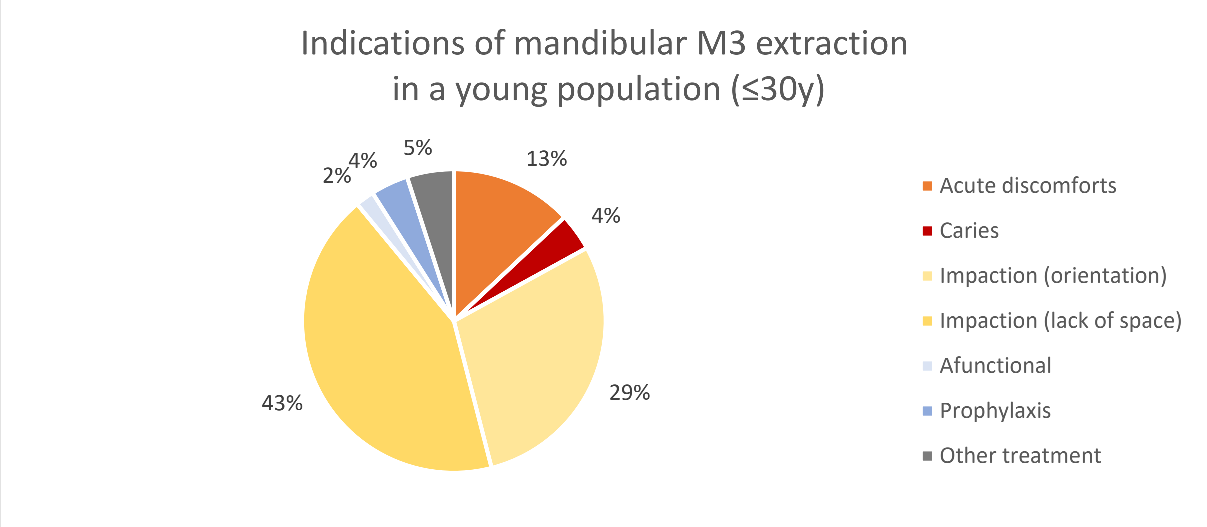


Figure 13: Age distribution per gender of the M3 study. The age distribution of men and women followed a similar course.

4.1.2 Indications for mandibular third molar extraction

During 1995 surgeries, 2764 mandibular third molars and 2691 maxillary third molars were extracted. The indications for mandibular third molar extraction were described for two subpopulations: a young population aged under 30 (1466 patients) and an older population aged over 30 (374 patients) (Figure 14).



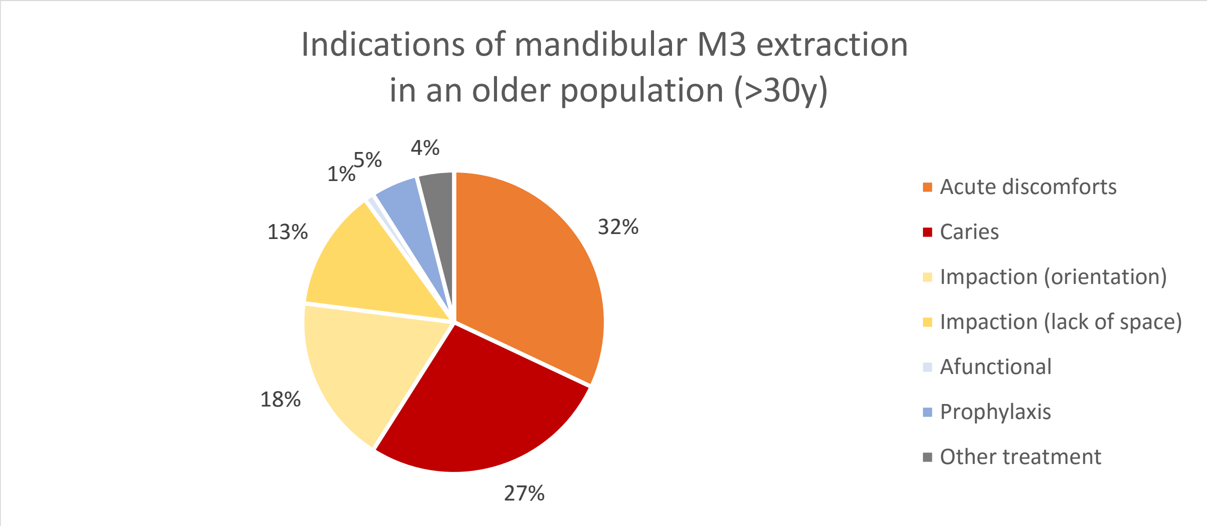


Figure 14: Indications for mandibular third molar extraction in two subpopulations. Impaction was the main extraction indication for the young population (≤30 years) and acute discomfort was the main extraction indication for the older population (>30 years).

In general, a shift from non-acute indications to acute indications as main reason for extraction with increasing age was denoted. Many more third molars in the younger population were removed because they were impacted (non-acute) compared to the older population: 72% (1377 of the 1466 patients) versus 31% (99 of the 374 patients). The 'impaction indication' was split up in impaction due to the M3's angulation and impaction due to a lack of space in the jawbone. In contrary to non-acute indications, the percentage of acute indications was strikingly higher for the older population than the young one. In the older population, the 'acute discomforts' and 'caries' categories accounted for 32% (99/374) and 27% (83/374) of the extraction indications, whereas these only accounted for 13% (258/1466) and 4% (81/1466) of the indications for the young population. The 'acute discomfort' category included pain, cysts, fractured teeth, root residues, inflammation, etc. Lastly, the categories 'afunctional', 'prophylaxis' and 'other treatment' accounted for approximately 10% of the indications in both the young (246/1466) and older age (32/374) population. Afunctional wisdom teeth were teeth that had no antagonist or showed mal-occlusion. Teeth removed prophylactically could be for the sake of avoiding inflammation and caries. ‘Other treatments’ that required wisdom tooth extraction included orthodontic treatment and preparation of orthognathic surgery, prosthesis or implants.

Concerning the eruption of wisdom teeth, we have to keep in mind that orthodontic treatment influences the size of the retromolar space and with this the eruption potential of third molars. Erupted third molars are vulnerable to caries and infection, while non-erupted molars are not. In this way, undergoing orthodontic treatment could have influenced the indication of extraction. About 61% of the young patients included in this study were orthodontically treated in the past, compared to 31% of the older patients (Table III).

Table III: Orthodontic treatment of the study population

Population	Yes		No		Unknown		Total	
Young population (≤30 years)	893	61%	553	38%	20	1%	1466	100%
Older population (>30years)	115	31%	254	68%	5	1%	374	100%
Total population	1008	55%	807	44%	25	1%	1840	100%

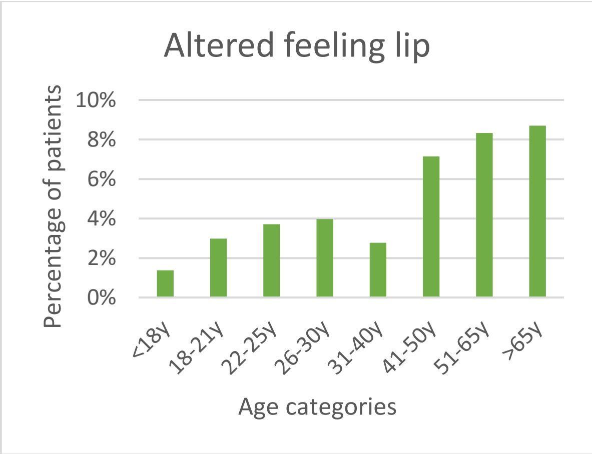
4.1.3 Nerve damage complications

In total, postoperative information of 1403 patients was gathered. 46 cases of IAN disturbances and 58 cases of LN disturbances were reported (Table IV). These symptoms are an indication of possible IAN or LN damage.

Table IV: Frequency of patients reporting an altered feeling in lip and tongue

Frequency altered feeling lip	Men		Women		Total	
No altered feeling	603	94%	706	93%	1309	93%
Altered feeling	17	3%	29	4%	**46**	**3%**
Unknown	22	3%	26	3%	48	3%
Frequency altered feeling tongue	**Men**		**Women**		**Total**	
No altered feeling	586	91%	688	90%	1274	91%
Altered feeling	23	4%	35	5%	**58**	**4%**
Unknown	33	5%	38	5%	71	5%

More older patients suffered from postoperative neurosensory disturbances. An evident increase of patients reporting an altered feeling in lip or tongue was observed with increasing age of the patient (Figure 15).



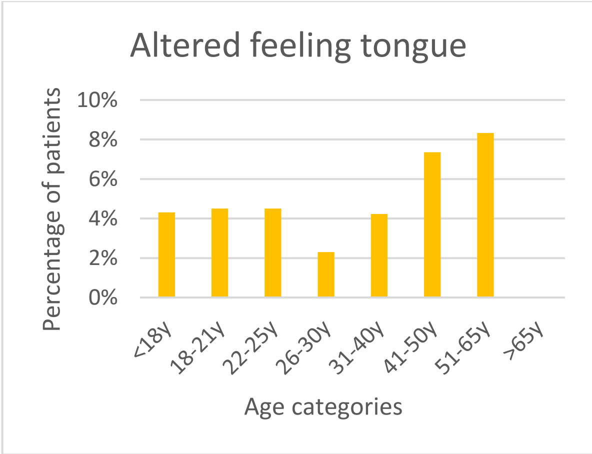


Figure 15: Patients reporting an altered feeling in lip and tongue per age category. More patients in the higher age categories reported symptoms of nerve damage.

4.2 Radiographic study to evaluate the eruption potential of mandibular third molars

4.2.1 Age and gender distribution

The final study sample consisted of 1087 patients of which 475 (44%) were men and 612 (56%) were women. For descriptive analysis of age distribution, root/crown ratio, eruption level and nerve relation each radiograph was considered as a single case; a snapshot of a subject with a specific age and with a specific scoring of the parameters. The description of the sample was thus based on 2174 cases, or 4348 wisdom teeth. The average age of the subjects was 14 years old. The minimal age and maximal age of the subjects was 10 years and 23 years old, respectively. The age distribution for men and women had a similar course (Figure 16).

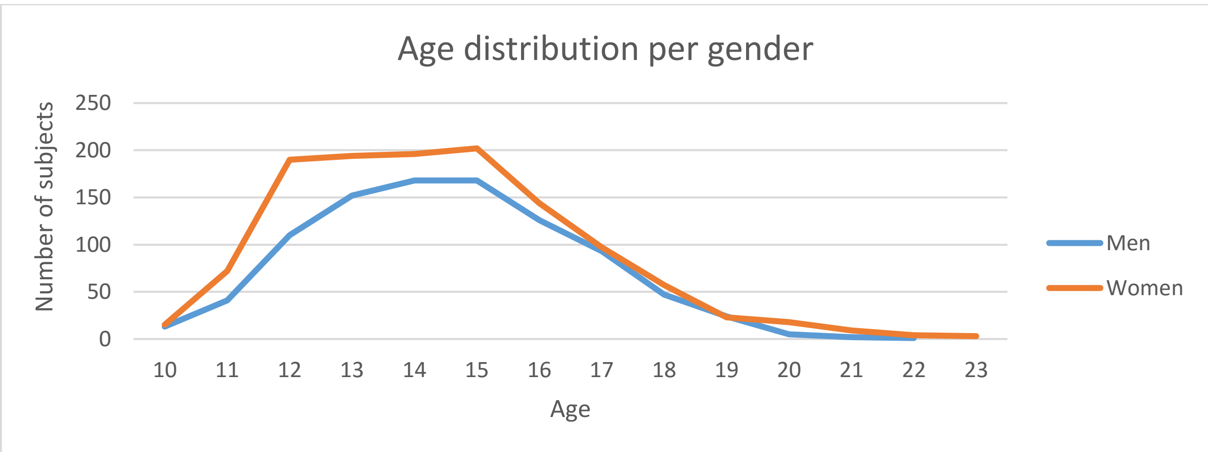


Figure 16: Age distribution per gender. The age distribution of men and women followed a similar course.

Subjects were divided into three age categories for the descriptive statistics: 10 to 14, 14 to 18 and 18 to 25 years old. These categories included 1981, 104 and 89 cases respectively (Table V). The categorization was based on the estimation of the average age of M3 development and eruption. Between the age of 10 and 14, it is expected that the M3 follicle is formed, but root formation, nor bifurcation process have begun. Between the age of 14 and 18, the M3 root development begins and the M3 starts to erupt. Lastly, advanced root formation and the chance of the M3 being partially or fully erupted is thought to be the highest between the age of 18 and 25. The bulk of the sample comprised the youngest age category (10-14 years old), conformable with the termination of the teeth exchange from primary to deciduous teeth and the beginning of orthodontics (and the sample was taken from the patient files from orthodontists). Subsequently, most of the third molars of the study sample were still in an early developmental stage.

Table V: Sample distribution of the radiographs per age category

Age category (years)	Men		Women		Total	
Age category 10-14	871	40%	1110	51%	1981	91%
Age category 14-18	47	2%	57	3%	104	5%
Age category 18-25	32	1%	57	3%	89	4%
Total	**950**	**43%**	**1224**	**57%**	**2174**	**100%**

4.2.2 Development stage

Both mandibular third molars (38 and 48) were analyzed together for the parameters 'root/crown ratio', 'eruption level' and 'nerve relation' because generally the process of wisdom teeth development and eruption happens simultaneously in both mandibular jaw sites. This means that 4348 teeth (2174 radiographs with two wisdom teeth per image) were investigated. If gender differences for a certain parameter were remarkably, the percentages were given for men and women separately. If not, they were given as a total percentage (men and women together).

The M3's development, evaluated by means of the 'root/crown ratio' parameter, was divided into three stages: 'no roots', 'start of root formation' and 'advanced root formation'. The third molar's development was investigated per age category, per gender (Figure 17). Most of the third molars for men and women of the youngest age category (10-14 years old) had no root formation (yet): 2519 of the 3962 teeth. Approximately one fourth of the wisdom teeth for both genders within this age group (965/3962 teeth) showed start of root formation and only 15% (259/1742) of men and 10% (219/220) of women had third molars with advanced root formation. Regarding age category 14-18 years old, few third molars were in the least developed stage: 19/208. Some gender differences were noticed as to initiating and advanced root formation within this age group. 35 wisdom teeth (37%) of men showed initiated root formation and 54 third molars (57%) advanced root formation, on a total of 94 teeth. For women, the distribution was almost equal: 49 wisdom teeth (43%) showed start of root formation and 51 wisdom teeth (45%) advanced root formation, on a total of 114 teeth. In the age category from 18 to 25, almost all third molars had advanced root formation: 146 of the 178 teeth. Men within this oldest age category had more M3s in this development stage, compared to women: 58/64 (91%) vs 88/114 (77%). In general, we saw a logical trend: the older a subject was, the more the wisdom teeth were developed.

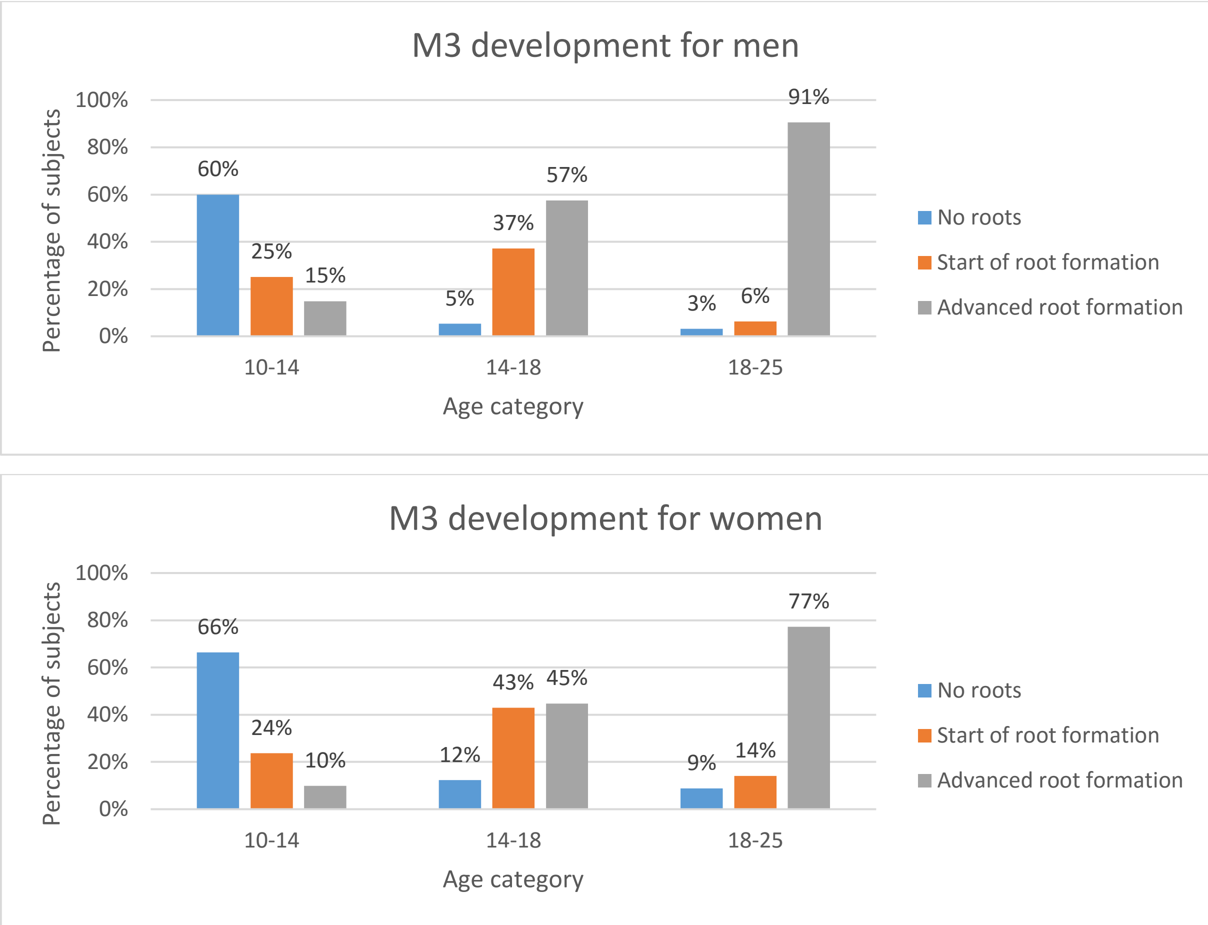


Figure 17: M3 development stage per gender. Wisdom teeth were more developed with increasing age.

4.2.3 Eruption level

The M3's eruption level was divided in three groups: 'no eruption', 'partial eruption' and 'full eruption'. While analysing third molar eruption per age category, we observed the following (Figure 18). Regarding men and women within the youngest age category, circa 76% (2918 of the 3962 teeth) had non-erupted third molars, one fourth (1017 of the 3962 teeth) had partially erupted third molars and practically none (27 of the 3962 teeth) had fully erupted third molars. These findings met our expectations. For the 14-18 category, most third molars (139/208) were partially erupted. Remarkably more men than women within this age group had partially erupted wisdom teeth: 67/94 (71%) M3s of men vs 72/114 (63%) M3s of women. Only 10 of the 208 wisdom teeth within this age category were fully erupted. Third molars are expected to erupt between the age of 17 and 21. Hence, if the eruption of these teeth was not hindered, we should have seen many fully erupted wisdom teeth in the age category of 18-25 years old. However, most wisdom teeth of this age group (men and women together) were partially erupted, namely 129 of 178 wisdom teeth, and only 18 (10%) of 178 third molars were fully erupted. Further, while studying gender differences, we noticed that a higher percentage of men (19% or 12/64 teeth) than women (5% or 6/114) of this age group had fully erupted wisdom teeth.

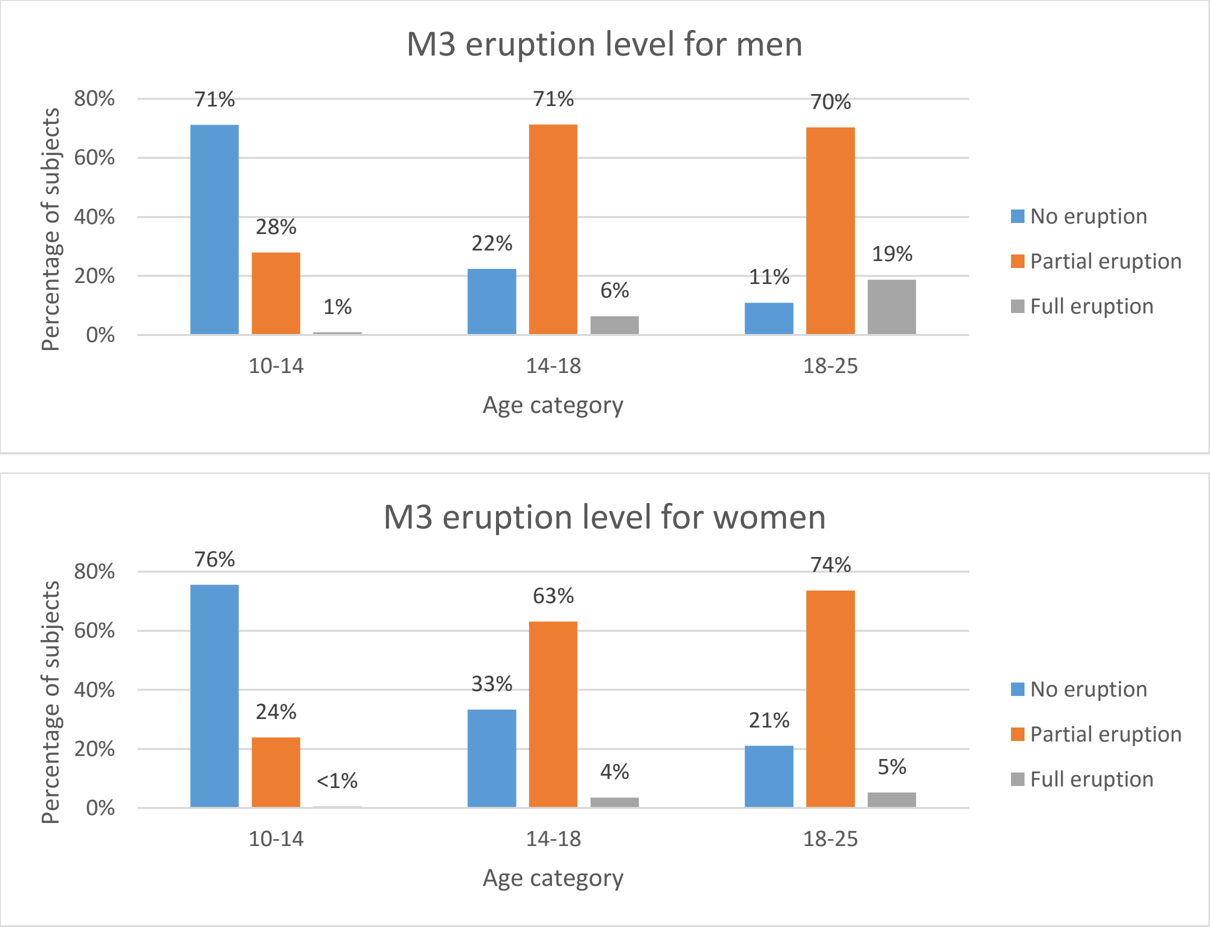
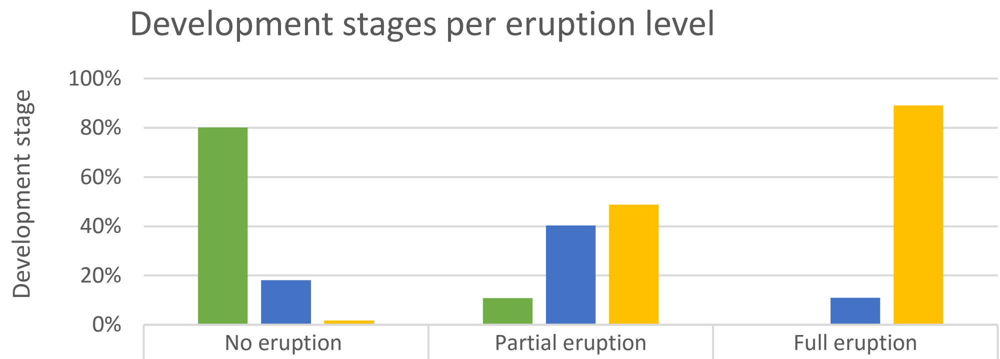


Figure 18: M3 eruption level per gender. Most wisdom teeth were not erupted between the age of 10 and 14 and partially erupted between the age of 14 and 25. Full eruption was often hindered.

If we looked at the M3's eruption level for each development stage, we saw that 2411 (80%) of the 3008 non-erupted third molars showed no root formation. As to the partially erupted third molars, 519 (40%) of the 1285 teeth showed start of root formation and 627 of the 1285 wisdom teeth (49%) showed advanced root formation. Regarding the fully erupted ones, 49 of the 55 M3s (about 89%) displayed advanced root formation (Figure 19). These findings support the joint evolution of the development and the eruption of wisdom teeth.



	No eruption	Partial eruption	Full eruption
No roots	80%	11%	0%
Start of root formation	18%	40%	11%
Advanced root formation	2%	49%	89%

Eruption level

Figure 19: Development stages per eruption level. In general, the more the wisdom teeth were developed, the more the teeth were erupted.

Concerning the probability of third molar eruption, predictive models were designed for third molars without roots and third molars with initiating root formation. Significant results were obtained ($p<0.05$). As to the analysis of the whole sample of initially non-erupted wisdom teeth and their follow-up images (2026 teeth), the M2/M3 and M1/M3 angulations were significantly linked (not necessarily separately) to the M3's eruption level of third molars without roots (1879 teeth) (Table VI and Figure 20). The greater these angulations, the lower the chance of M3 eruption. The M2/M3 and M1/M2 angulations together appeared to be predictive for M3 eruption. The M2/M3 angulation was the main contributor to the predictive model, because it had the smallest p-value (<0.0001). The M1/M2 angulation improved the eruption prediction, although its p-value was not significant.

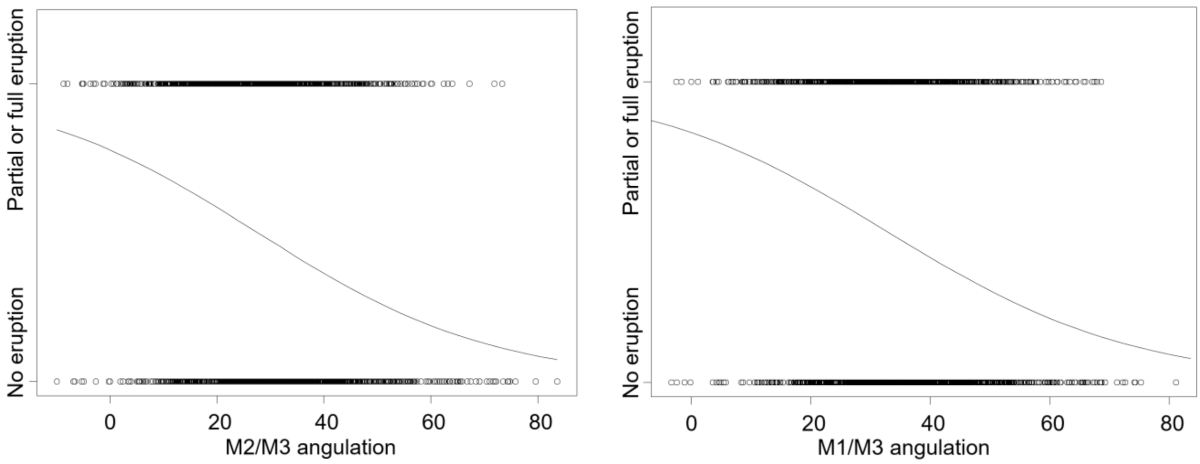


Figure 20: Relation between molar angulations and the M3 eruption level based on data of the whole sample. At the left the M2/M3 angulation and the right the M1/M3 angulation. These two molar angulations were significantly linked to the third molar eruption level.

Table VI: Outcome of GLMM predicting M3 eruption based on the whole sample

Angulation	P-value
M2/M3	<0.0001
M1/M3	<0.0001
M1/M2	0.3940

Variable	Coefficient	P-value
Intercept	1.5283	<0.0001
M2/M3	-0.0503	<0.0001
M1/M2	-0.0255	0.0768

Other results were obtained for the analysis of the subset sample of radiographs with a time interval of more than 3 years (subset sample >3 years, including 595 teeth) (Table VII). Only the M1/M3 angulation was significantly linked to the M3 eruption level (Figure 21). The M3 eruption could best be predicted by the combination of the M1/M3 and M1/M2 angulations, with the former as main contributor to the predictive model. The p-values for the analysis of the subset sample >3 years were all higher than the ones from the analysis of the whole study sample.

Table VII: Outcome of GLMM predicting M3 eruption based on a subset sample >3 years

Angulation	P-value
M2/M3	0.0845
M1/M3	0.0284
M1/M2	0.7961

Variable	Coefficient	P-value
Intercept	3.7732	<0.0001
M1/M3	-0.0343	0.0284
M1/M2	-0.0069	0.7742

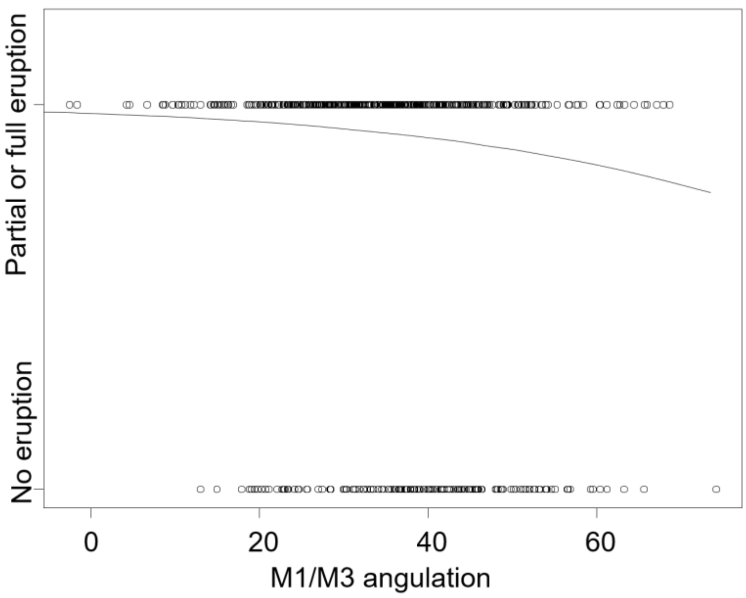


Figure 21: Relation between a molar angulation and the M3 eruption level based on data of the subset sample >3 years. Only the M1/M3 angulation was significantly linked to the third molar eruption level.

For third molars with initiating root formation (139 teeth), no significant correlations between the molar angulations and the M3 eruption could be noted and only the M1/M2 angulation was predictive for M3 eruption, but the p-value of this angulation was not significant. This was true for the whole sample. For the subset sample >3 years too little data to carry out a reliable analysis were available.

4.2.4 Nerve relation

When analysing the possibility of a relation between the third molar (roots) and the IAN, a clear shift from no relation to risk of relation for little developed to more developed wisdom teeth was determined. Practically no third molars without roots (2318 of the 2550 teeth) had a nerve relation, while 675 of the 1069 M3s (63%) with initiating root formation and 484 of 729 M3s (66%) with advanced root formation showed a risk of nerve relation (Figure 22).

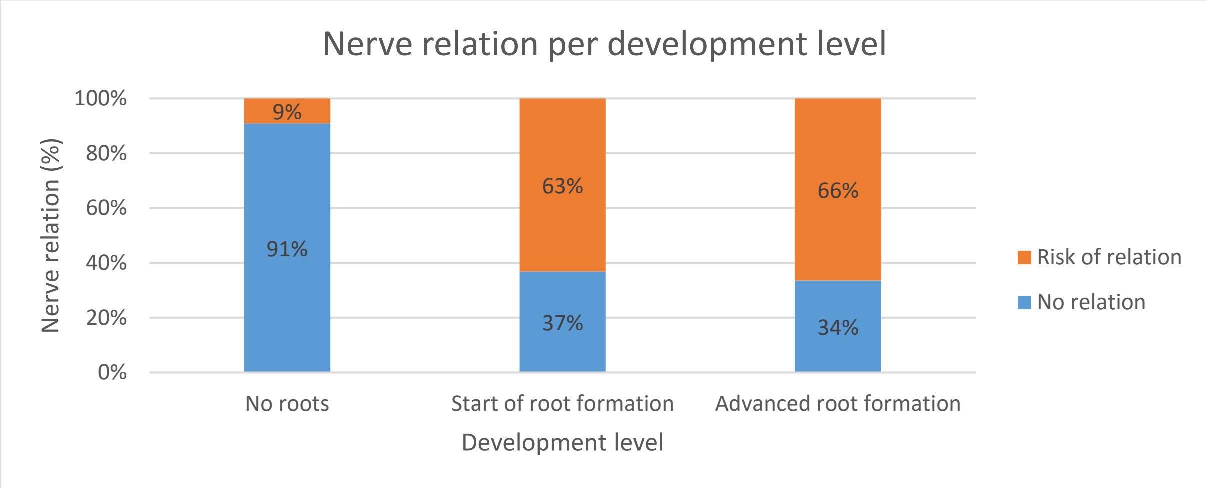


Figure 22: Nerve relation per development level. The risk of a nerve relation was much higher for wisdom teeth with initiating and advanced root formation than for wisdom teeth without roots.

The higher risk of nerve relation for starting root formation and advanced root formation was as expected, because developing roots of third molars reach out to the mandibular canal, so that the risk of nerve relation increases. For this reason, it was interesting to analyze the nerve relation of wisdom teeth within this two development stages for each eruption level. In the group of advanced root formation, we denoted a clear trend. Non-erupted third molars had the highest risk of nerve relation (42/53 or 79%), successively followed by the partially erupted ones (413/627 or 66%) and the fully erupted ones (29/49 or 59%) (Figure 23). Similarly, partially erupted wisdom teeth from the group with starting root formation had a higher risk of nerve relation than the fully erupted ones of that same group: 353/519 (68%) vs 2/6 (33%) respectively. We have to consider the very low number of fully erupted M3s though (Figure 25). Further, non-erupted wisdom teeth had a lower risk of nerve relation than the partially erupted ones in this group: 320/544 (59%) vs 353/519 (68%) (Figure 24). Lastly, the difference in risk of nerve relation between the fully erupted M3s and the partially erupted ones is more distinct for the group with starting root formation (Figure 24) than for the group with advanced root formation (Figure 23).

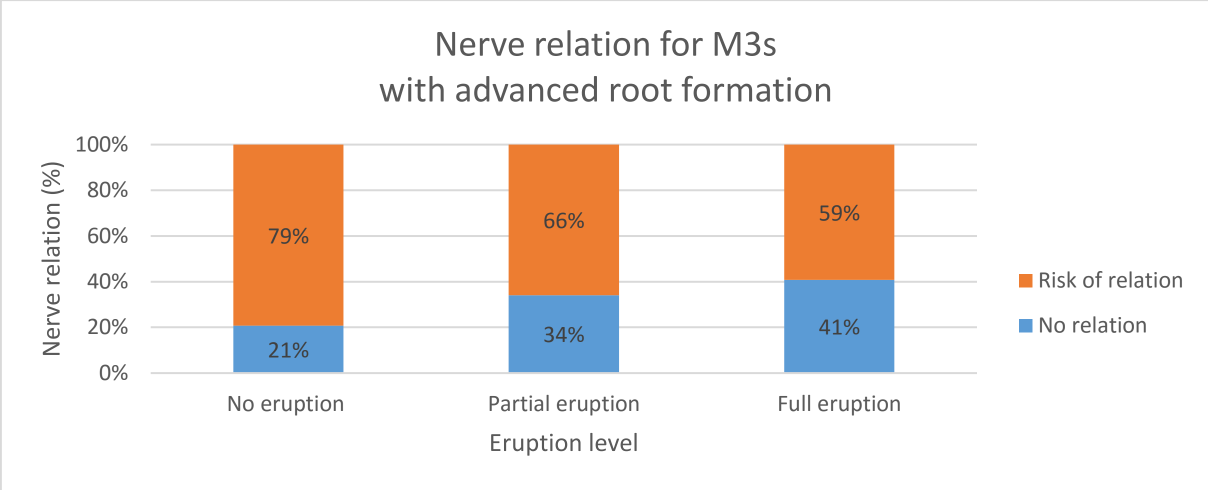


Figure 23: Nerve relation per eruption level for M3s with advanced root formation. The more the wisdom teeth were erupted, the lower the risk of nerve relation.

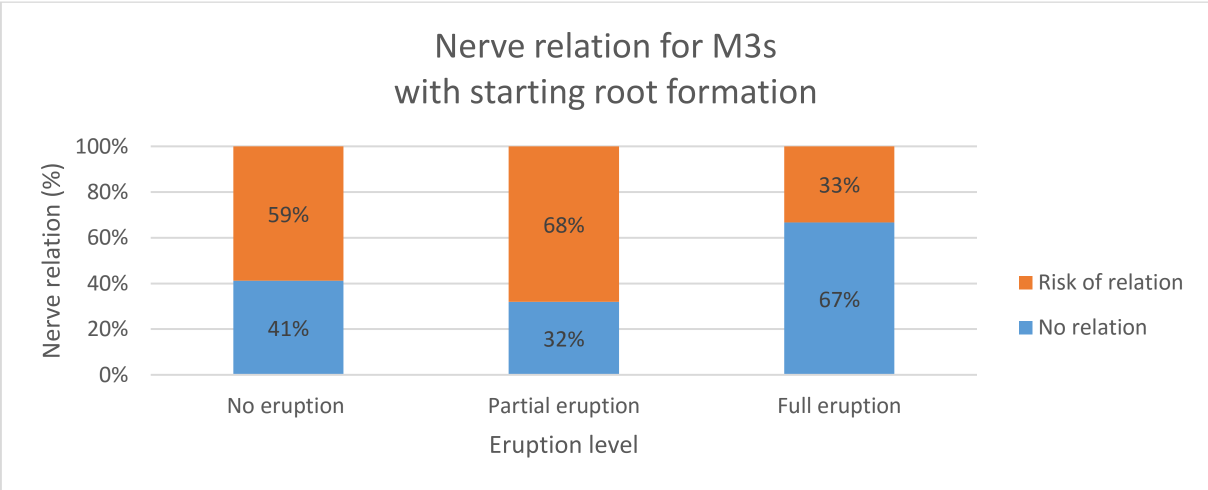


Figure 24: Nerve relation per eruption level for M3s with start of root formation. Within this group, the risk of nerve relation was the highest for partially erupted wisdom teeth.

Figure 25: Nerve relation of mandibular wisdom teeth with starting root formation. Third molar 48 is fully erupted and has no nerve relation, while third molar 38 is partially erupted and has a risk of nerve relation.

The future risk of nerve relation for multiple age categories was evaluated via analytical statistics. In general, the older a subject, the higher the risk of a nerve relation, independent of the third molar angulation. A significant association between the future risk of nerve relation and the initial age categories 10-11, 11-12, 12-13 and 13-14 years old was detected. No significant associations between age categories above 14 years old and the risk of nerve relation were observed. Further, a significant association between the future risk of nerve relation and the M2/M3 angulation of 11 to 13 years old children was discovered (Table VIII and Figure 26).

Table VIII: Overview of the GLMM predicting a third molar's risk of nerve relation per age category.

Age (years)	Number of teeth	Intercept	Coefficient age	Coefficient M2/M3 angulation	P-value age	P-value M2/M3 angulation
10-11	282	-5.9709	0.4193	0.0018	<0.0001	0.9630
11-12	826	-5.6188	0.4048	-0.0141	<0.0001	0.0240
12-13	1291	-4.0714	0.2887	-0.0138	<0.0001	0.0057
13-14	1420	-1.7989	0.1245	-0.0081	0.0060	0.1217
14-15	1468	-1.2267	0.0970	-0.0119	0.0934	0.0654
15-16	1280	-2.3211	0.1659	-0.0146	0.0746	0.1240
16-17	920	-2.3730	0.1599	-0.0110	0.4476	0.5033
17-18	588	-10.1119	0.7424	-0.1169	0.4932	0.3726

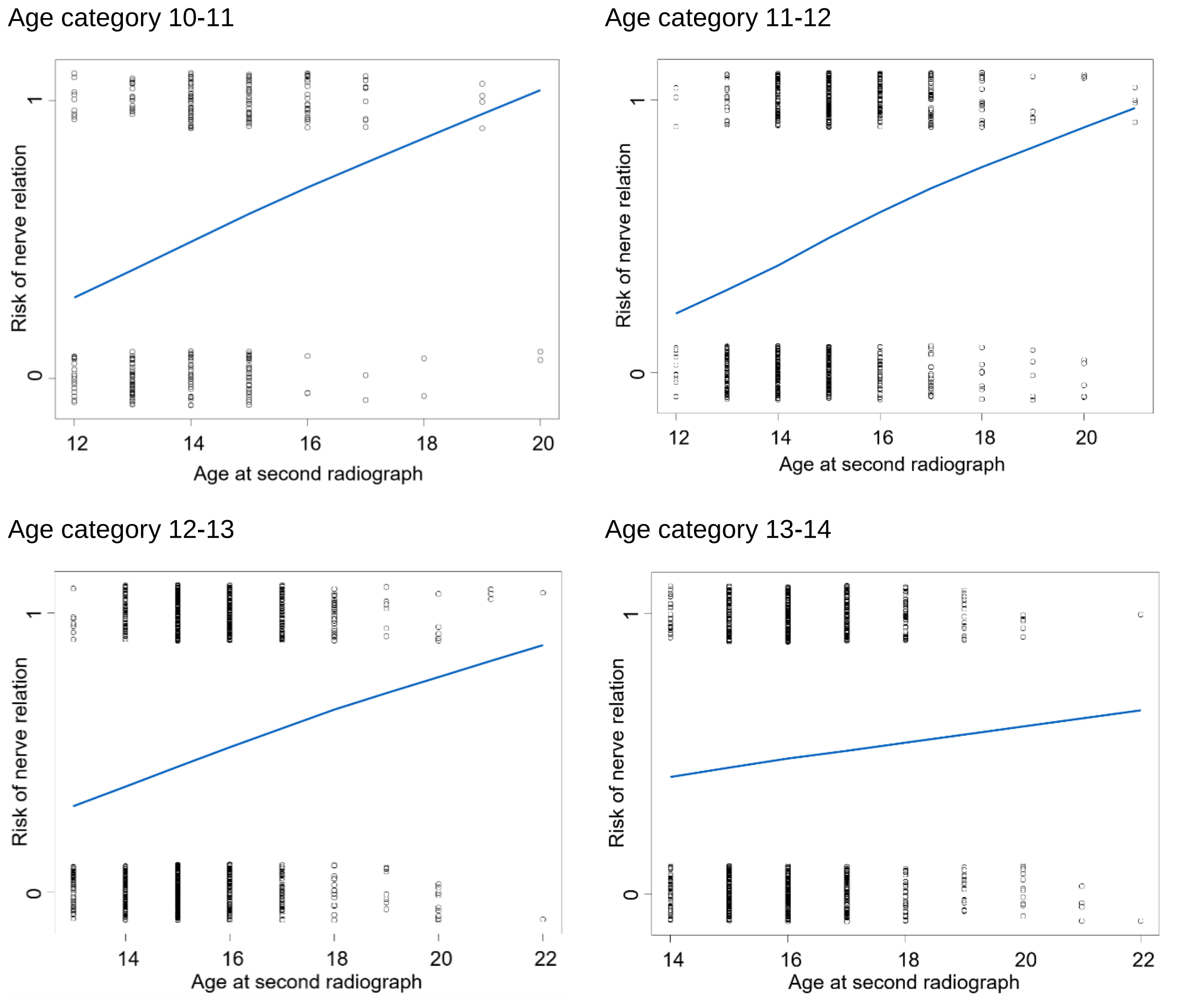


Figure 26: The future risk of nerve relation. Data are shown for age categories 10-11, 11-12, 12-13 and 13-14 years. In the y-axis the risk of nerve relation where no nerve relation is “0” and risk of nerve relation is “1”.

4.2.5 Third molar angulation

A linear regression model delineating the mean change in third molar angulation per year, based on a third molar's initial angle (relative to the second molar), showed a significant correlation between these two variables ($p<0.05$). The greater the initial angle, the higher the mean annual change in angulation. This was true for the models of wisdom teeth without roots (2550 teeth) and wisdom teeth with initiating root formation (1069 teeth) (Table IX). This indicated that the angulation of a third molar was not static. For third molars without roots, third molars with an initial angle of 25.42 (±0.89) degrees were least likely to change their angulation over time (Figure 27). Third molars with a greater angle than 25.42 (±0.89) had the tendency to enlarge their angulation over time and third molars with a smaller angle had the tendency to reduce their angulation over time. For third molars with initiating root formation, this initial angle was 27.82 (±3.25) degrees (Figure 28). A high variability of the data, visualized by the graphs, was detected (Figure 27 and Figure 28).

Table IX: Outcome of linear regression of the mean change in M3 angulation. Data are shown for third molars without roots (left) and third molars with initiating root formation (right).

Regression parameter	Value	P-value
Intercept	-4.9781	<0.0001
Initial M2/M3 angulation	0.1958	<0.0001

Regression parameter	Value	P-value
Intercept	-5.3052	<0.0001
Initial M2/M3 angulation	0.1907	<0.0001

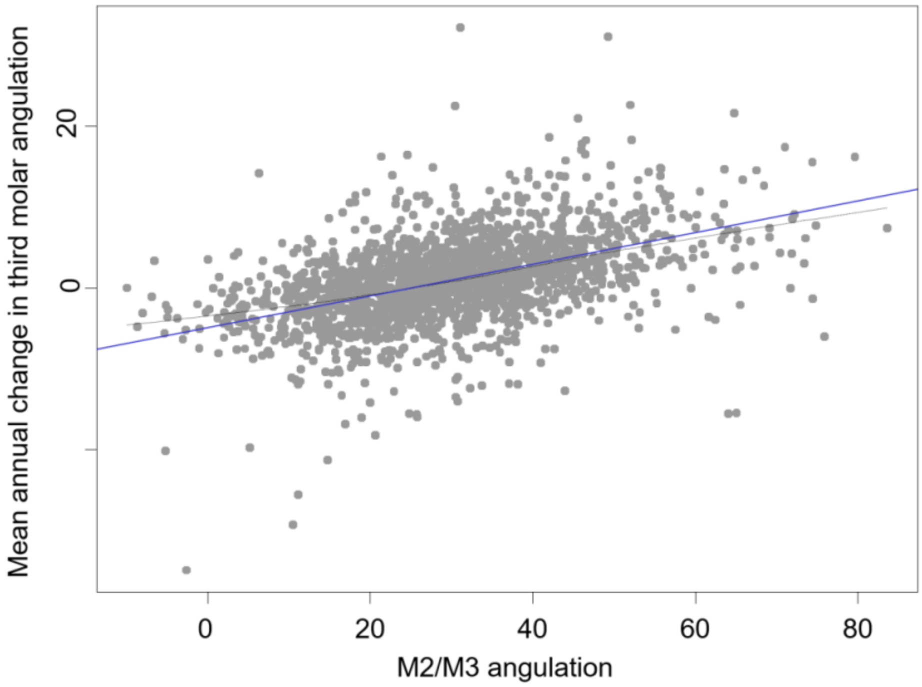


Figure 27: Mean annual change in third molar angulation of third molars without roots. With the LOWESS line in grey and the progression line in blue. Close proximity of these two lines implies a reliable regression.

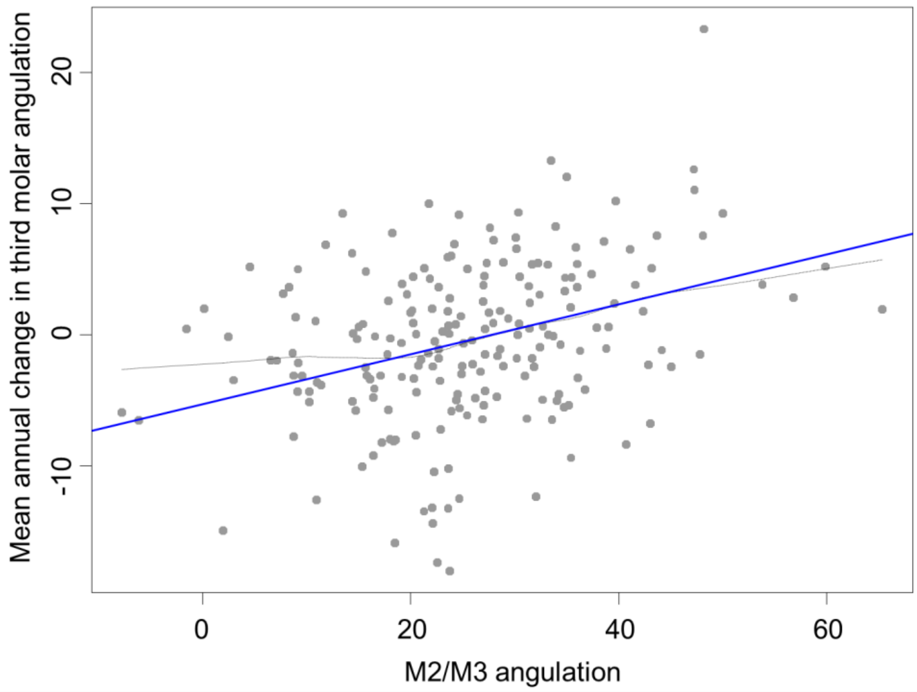


Figure 28: Mean annual change in third molar angulation of third molars with initiating root formation. With the LOWESS line in grey and the progression line in blue. Close proximity of these two lines implies a reliable regression.

Lastly, inter- and intrarater reliability was checked for the evaluated radiographic parameters. These were all between 0.76 and 1 and were satisfactory as reliability scores equal to or higher than 0.75 are considered acceptable (Table X).

Table X: Intra- and interrater reliability rates

Variable	Intrarater reliability first observer	Intrarater reliability second observer	Interrater reliability
Eruption level 38	0.8907	0.8998	0.8930
Eruption level 48	0.7948	1.0000	0.8398
Nerve relation 38	0.7619	0.8869	0.7856
Nerve relation 48	0.8684	0.8869	0.8723
Root/crown ratio 38	0.7963	0.8472	0.8085
Root/crown ratio 48	0.8974	0.8451	0.8869
Angulation of 36	0.9322	0.9573	0.9413
Angulation of 37	0.9667	0.9441	0.9604
Angulation of 38	0.9417	0.9411	0.9426
Angulation of 46	0.9439	0.9255	0.9399
Angulation of 47	0.9208	0.9689	0.9322
Angulation of 48	0.9464	0.9533	0.9492

5 Discussion and conclusion

5.1 An epidemiological, prospective cohort study to detect the indications and complications of wisdom tooth extractions

Third molars are frequently extracted as they are associated with many complications, but whether they should be removed prophylactically remains under discussion (2). The M3 study is designed to uncover the indications and postoperative complications of third molar removal. Only results concerning indications of mandibular third molar extraction and symptoms of nerve damage will be discussed as these are related to the second part of this thesis.

5.1.1 Age and gender distribution

Most subjects were female and between the age of 15 and 30 at time of M3 surgery. Considerably less older patients had to undergo surgery. Other studies with a similar set-up reported a comparable age and gender distribution (59,60). The peak of younger patients could be due to changing practice in dental care. Older patients were not as frequently submitted to a follow-up with a dentist or orthodontist in the past as younger patients are today. As a result, they were not referred to maxillofacial surgeons for check-up of their wisdom teeth, whereas younger patients are nowadays. Thence the uneven distribution. The high number of young patients having their wisdom teeth removed, together with the high number of non-acute indications (and thus rather prophylactic extractions) for these patients, could testify that oral and maxillofacial health care workers uphold a precautious approach to wisdom teeth management. However, this may be true for the two health care centers contributing to this study, but we cannot generalize to whole Belgium.

5.1.2 Indications for mandibular third molar extraction

The shift from a high rate of non-acute indications for mandibular third molar extraction for younger patients (aged under 30) to a high rate of acute indications for older patients (aged over 30) illustrated that retained third molars frequently cause problems at older age. Wisdom teeth are more likely to erupt with increasing age of patients and acquire pathologic features such as caries and periodontal disease (61). These findings were in line with the study results concerning indications for M3 surgery of *Renton T.* (2012), reviewing the retention of third molars in the United Kingdom after publication of the NICE guidelines (51). Besides, third molar caries are difficult to treat and extraction of affected teeth is often the best treatment option. Moreover, numbers of the OMFS department of Sint-Rafaël Hospital Leuven have demonstrated that more than a third of all patients older than 30 years who came for advice on tooth extraction in 2016 had to undergo wisdom tooth extraction (whether or not in combination with treatment or extraction of other teeth) because of complaints or pathologies. Keeping the higher burden of M3 surgery for older patients in mind (41), these data discourage a 'wait and see' approach for asymptomatic and disease-free wisdom teeth, that are likely to develop pathology or give problems, of patients at younger age. It is thus of interest to determine factors that can accurately identify these patients. A remark on the number of patients with retained wisdom teeth is that we have no idea about the number of (relatively) older people without any complaints about their third molars, because they do not visit an OMFS department. Oral and maxillofacial surgeons should not expose patients to risks associated with removal of the wisdom teeth without certainty that prophylactic extraction is beneficial compared to retaining the teeth. Anyway, the question of extraction or no extraction of the wisdom teeth is of no importance for these people because they are not seen by oral and maxillofacial surgeons.

Note that the indication of extraction could have been influenced by orthodontic treatment, because orthodontics influence the eruption potential of third molars (33). As almost double as much young patients than older patients were treated orthodontically, the impact of orthodontics on the M3 extraction indication could differ between these two age categories. We believe that different types of orthodontic treatment influence the eruption potential of wisdom teeth to different extent. The type of orthodontic treatment was not noted during the M3 study though. This has to be subjected to future research.

5.1.3 Nerve damage after mandibular third molar extraction

The overall reporting of nerve damage symptoms was low, but it is remarkable that the majority of these reports was denoted in the older age categories. As follows, the risk of nerve injury increases with increasing age, which is confirmed by numerous studies (37,49,62). The positive correlation could be due to a higher operative difficulty associated with complete root formation, changes in bone density, the need of more bone removal during M3 surgery and due to reduced wound healing capacity associated with decreased vascularization. Although nerve injury complications are rare, they cannot be ignored considering the life-interfering difficulties associated with such injuries.

5.1.4 Strengths and limitations

The large sample size and equal gender distribution of the study sample were surely strengths of the present study. Thanks to the low number of exclusion criteria, a broad range of patients were included, which makes an extrapolation of the study results to the whole population reliable. On the other hand, this study had some limitations. Firstly, the considerably higher number of younger patients than older patients. This can be explained by the exclusion criteria. Older patients may undergo simultaneous extractions of other teeth beside the third molars and were therefore excluded from the study. In the interest of comparing the younger and older patients, each group should contain preferably more or less the same number of subjects. A step from this, a selection bias could not be avoided, as the composition of the study sample was dependent on patients visiting the OMFS department of the University Hospital Sint-Rafaël and of the Mariaziekenhuis. This meant that patients that were not referred by primary caregivers were lacking, although they could have been in need for third molar extraction according to the surgeons that cooperated to this study. A last study limitation was the fact that the exact date of completion of the postoperative questionnaires (filled out at home by the patients) could not be controlled.

5.1.5 Conclusion

In conclusion, the descriptive statistics revealed a clear shift from non-acute to acute indications for third molar extraction with increasing age and more postoperative neurosensory disturbances in older patients. For this reason, a surgeon can recommend to extract third molars at an early age to avoid acute third molar complications and to avoid the risk of nerve damage after third molar surgery. However, these findings could not yet be statistically proven. Hence, data expansion is required to obtain sufficient evidence to support the M3 study hypothesis. Currently, the M3 study is expanding to other Belgian hospitals, which will allow us to draw a final conclusion.

5.2 Radiographic study to evaluate the eruption potential of mandibular third molars

Third molar eruption has changed over time and nowadays third molars are commonly impacted (6,16,38). Taking the results of the present studies about a mandibular third molar's risk of impaction, risk of nerve relation and extraction indications into account, it is of interest to specify parameters predicting the eruption of mandibular molars at a young age. In this way, the question if the M3 will erupt to a clinical functional position can be answered and the surgeon's decision about removing the third molar, whether or not prophylactically, can be justified.

5.2.1 Age and gender distribution

The higher percentage of women than men in the study could be due to gender differences in the anatomy of the jaw. The average female jaw is smaller than the male jaw, so that it could be that women are more prone to acquiring teeth malposition or malocclusion (due to a lack of space) and the need of orthodontic treatment (63,64). The study sample was randomly taken from the patient files of orthodontists. Ergo, the majority of the sample was female. Per contra, a study investigating the need for orthodontic treatment in children showed that malocclusion between boys and girls was the same (65).

5.2.2 Mandibular third molar development and eruption

As expected, third molars were more developed with increasing age. The higher number of men with third molars showing advanced root formation in the 14-18 and the 18-25 age categories, compared to women, suggested a faster M3 development for men. This was in accordance with a study of the KU Leuven about dental age estimation (with an adequate sample size of 1175 radiographic images) and a study comparing the third molars development over nine country specific populations, among which Belgium (66,67). It is important to keep in mind that the degree of difference in third molar development between genders is dependent on age (67). On the contrary, some research indicated the opposite, but the opposing reviewed studies had smaller sample sizes (523 and 714 images) than the present study (28,68).

Conformable with the faster M3 development of men, M3 eruption was higher in men as to women. In terms of percentages, more males than females had partially erupted wisdom teeth between the age of 14 and 18 and fully erupted wisdom teeth between the age of 18 and 25. Again, the jaw anatomy might have had something to do with this. Men develop bigger jaws, which means more retromolar space for the third molars to erupt (63). This is a possible reason why males are less susceptible to have partially or non-erupted, impacted third molars than females (69,70). Secondary, a striking observation concerning the eruption level was the low number of fully erupted teeth in the oldest age category (from 18 to 25 years of age). This indicated that the eruption of wisdom teeth was strongly impeded. In most cases, this was due to the third molar's mesioangular or, less frequently, distoangular angulation. In other cases, the teeth were orientated vertically, but impacted because of a lack of space in the dental arch. The finding that many teeth were impacted is supported by the high current number of impacted wisdom teeth over various populations (5,16). We concluded that, in general, the eruption of wisdom teeth to a functional position in the mouth was impeded.

The present study examined the eruption potential of wisdom teeth in an early development stage and tried to define models predicting the M3 eruption. The combination of which molar angulations were most predictive for M3 eruption differed when analysing follow-up data of all initially non-erupted wisdom teeth ('the whole sample') versus follow-up radiographs with a time span of more than three years pertaining to the first radiograph ('the subset sample >3 years'). The eruption potential in this former sample could be underestimated because some wisdom teeth simply did not yet had the time to erupt considering the inclusion of radiographs with short time span. Therefore, the model for predicting M3 eruption based on the subset sample >3 years seemed more reliable. According to this model, third molar eruption could be accurately predicted by the combination of the M1/M3 angulation and the M1/M2 angulation.

5.2.3 The possibility of a nerve relation

The risk of nerve relation is associated with the third molar's development stage, eruption level and the impaction status. These three factors allow us to estimate the proximity of the third molar roots to the mandibular canal.

Firstly, concerning the development stage; the older a person, the more developed the M3 roots, the closer the roots reached to the mandibular canal and the higher the risk of a nerve relation. Correspondingly, the nerve relation risk for fully erupted wisdom teeth was smaller for wisdom teeth with shorter roots than for wisdom teeth with longer roots. Secondly, regarding the eruption level, a fully erupted wisdom tooth with mature roots had a lower risk of nerve relation than a non-erupted one with mature roots. This makes sense; the mature roots of impacted non-erupted wisdom teeth are closer to the IAN than the mature roots of erupted wisdom teeth. The finding was in accordance with a research studying the radiographic proximity of the mandibular third molar to the inferior alveolar canal (71). Nevertheless, wisdom teeth with starting root formation that were partially erupted had a higher risk of nerve relation than the non-erupted ones with starting root formation. This was possibly due to the broad range of teeth categorized as 'wisdom teeth with starting root formation'. The category included wisdom teeth with initiating root bifurcation and teeth with root lengths just shorter than the crown length. (This was a result of the criteria used in this study to divide third molars according to their root/crown ratio). Considering the relation between development stage and eruption level, it was possible that, within the same category of 'starting root formation', partially erupted teeth were slightly more developed than non-erupted teeth, resulting in a higher incidence of a possible nerve relation for these teeth than for the non-erupted third molars. In any way, the predictability of a root-nerve relation is a complex matter and we cannot draw conclusions based on the development stage and eruption level alone. We have to take other parameters, as the third molar's angulation, into account. Thirdly, we reasoned that the risk of nerve relation was higher for impacted wisdom teeth than for non-impacted teeth, because the chance of impacted teeth being close to the IAN is higher compared to non-impacted teeth. A study of *Kim J.* has confirmed this presumption (37). Additionally, studies have shown that depth and type of impaction, along with the angulation of the wisdom teeth, are significantly associated with nerve damage after third molar surgery (37,40,49).

Further, it is of interest to be able to predict the risk of nerve relation based on someone's age. Analytical statistical tests performed during the present study, revealed some significant associations between age, third molar angulation and nerve relation risk. The main findings were that the age of 10 to 14 years was significantly linked to the risk of nerve relation and that the future risk of nerve relation could be accurately predicted by the M2/M3 angulation at 11 to 13 years of age. The non-significant p-values for the relation between age categories above 14 years old and the risk of nerve relation could be due to a lack of data, high variability or because there was no relation between these two. To boot, the risk of nerve relation, and with this the risk of nerve damage during third molar surgery, increases with age (37,49,62). The finding that a risk of nerve relation could be predicted at a young age, could have implications for daily practice. A surgeon could decide to extract a third molar with a high risk for future nerve relation to avoid nerve damage complications.

5.2.4 Mandibular third molar angulation

Impacted teeth that remain static are rare (38,72). At the same time, accurate models to predict the change in third molar angulation and position are not available (38). Such a model would be useful to predict the third molar's eruption and to estimate the timing and difficulty of wisdom tooth extraction. Furthermore, defining a critical angle indicating a highly unlikely functional M3 eruption would be of great interest for surgeons, making decisions about extraction.

The present study demonstrated that, on average, premature third molars (without roots) with an initial angle greater than 25.42 degrees (relative to the second molar) and third molars with initiating root formation with an initial angle greater than 27.82 degrees tended to increase their angulation over time, which was unfavorable for eruption. Be that as it may, the variability of the angulation measurements was not negligible. *N. Hattab* reported that third molars initially inclinated at 35 degrees or more (relative to the second molar) will not become upright (39). Nevertheless, the conclusion of *Hattab's* research was that positional changes and eruption of M3s are unpredictable. The small sample size (only 36 subjects) and low study power of this research have to be considered though. A more recent study (2016) reported that three variables are reliable to predict the M3's eruption: the angle between the long axis of the mandibular third and of the second molar (β angle), the angle between the third molar's long axis and the gonial-symphyseal plane (α angle) and the lower eruption space measurements. According to this research, these three variables should always be taken into account together for making a prediction about M3 eruption (73). For this reason, this method is time-consuming and perhaps inconvenient for daily dental practice. The present study tried to predict third molar eruption based on the angulations between the three mandibular molars. The prediction models were promising, but need refinement, so that they become clinical applicable. In future continuation of this study, the chance of M3 eruption over a specific time period for each initial third molar angulation will be assessed. The intention is to define the chance of third molar eruption in the following way: "for a third molar angulation of 20 degrees, the chance of eruption after one year is 25% and after five years 60%" (this is a fictive example). Note that besides the third molar's angulation, a small retromolar eruption space and a large third molar crown width contribute to a higher impaction risk (8,13). Anyhow, extensive initial mesioangular M3 inclination, a minimal M3 uprighting and a small eruption space decrease the likelihood of third molar eruption.

While analysing third molar angulation and eruption, an important factor to keep in mind is that all study subjects of the present study underwent orthodontic treatment. A previous study on the association between orthodontic treatment and the third molar's position and eruption demonstrated that orthodontic patients were likelier to develop partially erupted wisdom teeth, while non-orthodontically treated patients were likelier to develop impacted wisdom teeth, impossible to erupt (74). The magnitude of this influence is thought to be dependent of the specific type of orthodontic treatment. Orthodontics for aligning the teeth versus use of growth activators for the jaw or extra-oral corrections will have a different impact on the M3 eruption. However, the type of orthodontic treatment was not noted during this study, so that no conclusions could be drawn. This will be assessed in a next phase of the present study.

5.2.5 Strengths and limitations

The present study had strengths and limitations. The large sample size was certainly a study strength. Further, patients from three different orthodontists were included, which contributed to a heterogeneous sample, good for extrapolation to the broader population. Besides the large sample size, the longitudinal nature of this study resulted in a high study power. Longitudinal studies are trustworthy for detecting patterns over time and effective for evaluation of developmental trends, such as third molar development and eruption. Another strength was the high intra- and interreliability of the observers for the various parameters scored and evaluated on the radiographic images. This was a result of the training the two observers (that evaluated the parameters on the radiographs) received of experts in the field of orthodontics and radiology regarding the radiographic parameters.

To continue, this study had also a few limitations. Firstly, the parameter ‘eruption level’ is susceptible for misinterpretation. The eruption level of a third molar must not be confused with the impaction status. The eruption level is about a third molar’s position relative to the mandibular corpus and the impaction status is about a tooth’s position relative to the mandibular corpus, mandibular ramus and the second molar. The level of eruption is a snapshot of the position of a third molar, whereas the impaction status informs us about the eruption potential over time. Secondly, only the angulations of the mandibular molars gave information about the exact anatomical M3 position. It would be of interest to assay additional mathematical measurements to be more precise about the third molar’s position. Further, the time span between two radiographs per subject differed from one year to nine years, which made statistics hard to perform. It was thus possible that the third molar was not erupted yet, did not show a risk of nerve relation yet or had a small change in its angulation on the second radiographic image (relative to the first radiograph) of a subject purely because of the lack of time. As a result, the eruption potential, risk of nerve relation and change in angulation could have been underestimated in this study. Lastly, a big part of the 2147 radiological images evaluated for this study were analogous. The assessment of the radiologic parameters was more time consuming on the analogue files than on the digital files. The analogous nature of these files is also a burden for future research (such as determining the type of orthodontics) on this data.

5.2.6 Conclusion

The findings of this radiographic study clearly showed that third molars changed their angulation over time and that many wisdom teeth were susceptible to impaction. This study aids in the development of a clinical prediction model for third molar eruption. On average, a premature third molar with an initial angulation greater than 25.42 degrees tended to incline even more, which was unfavorable for the third molar’s eruption potential. Additionally, a significant association between mandibular third molar angulations and the third molar eruption was noted. A model accurately predicting third molar eruption depending on the angulations between the mandibular molars could be defined. However, the current model needs refinement to become clinically applicable. Further, the risk of a relation between the third molar roots and the inferior alveolar nerve increased with the third molar’s development and the patient’s age. The nerve relation risk was significantly linked to the age categories of 10 to 14 years old. Moreover, the angulation between the third and second molar at the age of 11 to 13 significantly predicted the future risk of nerve relation. These findings can have implications for the daily dental practice regarding third molar extraction management. Conclusively, a highly inclinated third molar probably never erupts to a clinical functional position and the risk of nerve relation increases with age. A surgeon could opt to remove highly inclinated third molars or molars with a high risk of developing a nerve relation to avoid impaction and partial eruption, which are associated with tooth pathologies, and to avoid nerve damage complications. In the future, we continue our search for a clinical predictive model of wisdom tooth eruption and nerve relation risk to optimize the management of third molar treatment.

6 Extensive Dutch summary

6.1 Literatuurstudie

De wijsheidstand of derde molaar (M3) is de meest distale tand van de tandenboog die als laatste tand doorbreekt in de mond, gewoonlijk tussen 17 en 21 jaar. De eruptie gebeurt echter niet altijd naar behoren, hoofdzakelijk vanwege plaatsgebrek (6). Bijgevolg blijft de tand ingesloten of geïmpacteerd. De retromolaire ruimte blijkt dan ook opvallend kleiner te zijn bij individuen met geïmpacteerde derde molaren ten opzichte van individuen met correct doorgebroken wijsheidstanden (8). Zowel geïmpacteerde als geërupteerde derde molaren kunnen aanleiding geven tot problemen zoals cariës, pericoronitis, beschadiging of wortelresorptie van buurelementen of (zeldzaam) tot odontogene cystevorming of tumorvorming (2). Derhalve wordt er vaak beslist om de wijsheidstanden, al dan niet profylactisch, te verwijderen. Wat betreft de timing van wijsheidstandextractie, dient men rekening te houden met de ontwikkeling van de tandwortels en de progressieve toename van de botdensiteit met stijgende leeftijd. De ingreep verloopt op oudere leeftijd aldus moeilijker en geeft frequenter aanleiding tot postoperatieve ongemakken en complicaties (18). Vandaar dat men ze liever op jonge(re) leeftijd verwijdert. Deze ingreep is echter niet risicoloos en complicaties zoals pijn, zwelling, bloeding, alveolaire osteitis en trismus kunnen optreden (9). Een zeldzame, maar ernstige verwikkeling is de beschadiging van de trigeminuszenuw, met name de tongzenuwtak of de inferieure alveolaire zenuwtak (die een deel van de tong, de lip en de kin bezenuwt) (62). Hierdoor kan de patiënt neuropathische pijn, paresthesie of anesthesie ervaren, tijdelijk dan wel permanent.

Panoramische radiografische beeldvorming is nuttig bij de beoordeling van derde molaren en het opstellen van een behandelplan voor deze tanden. Verschillende parameters zoals de anatomische positie, het ontwikkelingsstadium en de mogelijkheid van een wortel-zenuw-relatie kunnen behoorlijk accuraat geëvalueerd worden op radiografische beelden (10,25). Een belangrijke bevinding is dat het impactierisico van de wijsheidstanden stijgt met toenemende M3-angulatie (gemeten als de hoek tussen het occlusievlak van de wijsheidstand en het horizontale occlusievlak) (13). Verder blijkt dat de aard van impactie de postoperatieve morbiditeit beïnvloedt: een horizontale en distoangulaire, en dieper geïmpacteerde tanden worden geassocieerd met meer complicaties (40). Daarnaast zijn er radiografische factoren die duiden op een mogelijke relatie tussen de M3-wortels en de *nervus alveolaris inferior*, namelijk: onderbreking van de witte lijnen van het mandibulaire kanaal, versmalling van de witte lijnen van het kanaal, afwijking van het kanaal in de buurt van de wortelapex en een radiolucente band over de M3-wortels (36). Aldus kan men deze beeldvorming aanwenden bij het beslissingsproces over de M3-behandeling en -extractie op jonge leeftijd.

De vraag luidt hoe men het beleid van wijsheidstanden het best benadert. De algemene optiek is dat pathologische wijsheidstanden verwijderd dienen te worden en geretineerde wijsheidstanden levenslang opgevolgd dienen te worden (53). Over de profylactische extractie van deze tanden heerst wereldwijd grote onenigheid.

6.2 Doelstellingen

De behandeling en verwijdering van wijsheidstanden heeft betrekking op de hele maatschappij; rechtstreeks via ieders gezondheidsstatus en onrechtstreeks via de uitgave van gezondheidszorgbudgetten. Het is dus van algemeen belang om een éénduidig beleid rond wijsheidstandextractie op te stellen. Binnen dat kader, draagt deze thesis bij tot een betere kennis van indicaties en complicaties van wijsheidstandextracties. De thesis kan worden opgesplitst in twee delen.

Het eerste deel is een tussentijdse analyse van een epidemiologische studie, informeel gekend als de ‘M3-studie’, waarmee men de huidige praktijk rond wijsheidstandextractie in België in kaart wil brengen. Men hoopt met deze omvangrijke studie op termijn twee belangrijke punten aan te tonen. De eerste hypothese is dat de verwijdering van symptomatische derde molaren verband houdt met meer complicaties, morbiditeit, alsook moeilijkheidsgraad en tijdsduur van de operatie, ten opzichte van profylactische verwijdering. En de twee hypothese is dat complicaties toenemen met de leeftijd van de patiënt. Eenmaal dit is aangetoond, kan men argumenteren dat profylactische verwijdering van de wijsheidstand op jonge(re) leeftijd gerechtvaardigd is.

Het tweede thesisdeel is een radiografische, longitudinale studie van panoramische radiografische beelden van orthodontisch behandelde patiënten. Aan de hand van enkele parameters op deze beelden, kan men de ontwikkeling, de eruptie, de angulatie en de wortel-zenuw-relatie van wijsheidstanden binnen een jonge populatie evalueren. Vervolgens poogt men om, op basis van deze parameters, de mogelijkheid tot en wijze van eruptie van wijsheidstanden te voorspellen. Dergelijke voorspellingen zouden chirurgen kunnen leiden in de besluitvorming omtrent de behandeling van wijsheidstanden.

6.3 Onderzoek en besluit

6.3.1 Een epidemiologische, prospectieve cohortstudie om indicaties en complicaties van wijsheidstandextractie na te gaan

Patiënten met een minimumleeftijd van 12 jaar die één of meerdere wijsheidstanden lieten verwijderen, werden geïncludeerd in deze studie. Patiënten die tijdens de ingreep eender welke andere tandheelkundige behandeling ondergingen, werden geëxcludeerd. Demografische gegevens, pre-, per- en postoperatieve informatie werd verzameld aan de hand van vragenlijsten en medische patiëntendossiers.

Wat betreft de resultaten van de M3-studie, zullen enkel diegene met betrekking tot het tweede deel van deze thesis (de radiografische studie, zie verder) besproken worden. De finale studiepopulatie bestond uit 1840 patiënten, waarvan 875 (48%) mannen en 965 (52%) vrouwen. De meeste patiënten hadden een leeftijd tussen 18 en 21 jaar op het moment van de operatie. Voor analyse van de extractie-indicaties, werd de populatie onderverdeeld in een jonge leeftijdscategorie (≤30 jaar) en een oudere leeftijdscategorie (>30 jaar). Men kon een opvallende evolutie van niet-acute indicaties (hoofdzakelijk impactie) voor de jongste categorie naar acute indicaties (klachten en cariës) voor de oudere categorie bemerken. Dat gaf aan dat geretineerde wijsheidstanden op oudere leeftijd problemen kunnen geven. Deze resultaten pleiten tegen een afwachtende houding aangaande asymptomatische en ziektevrije wijsheidstanden die een hoog risico inhouden op toekomstige problemen. Inzake postoperatieve complicaties, meldde drie à vier percent van de studiepopulatie een veranderd gevoel in de lip of tong, dewelke gerelateerd zijn aan zenuwschade. Hoewel deze percentages verwaarloosbaar lijken, kunnen we ze niet links laten liggen, vermits zulke letsels belemmerende gevolgen hebben voor het dagelijkse leven van de getroffen patiënten. Opvallend meer oudere patiënten hadden last van zulke symptomen. Deze leeftijdsgerelateerde trend was in overeenstemming met verschillende studies en kan te wijten zijn aan de hogere operatieve moeilijkheidsgraad ten gevolge van meer ontwikkelde wijsheidstanden, veranderingen in botdensiteit, ankylose en een gedaalde capaciteit tot wondheling met toenemende leeftijd (41)(62).

Hoe dan ook toonden de resultaten van de M3-studie aan dat wijsheidstanden voornamelijk verwijderd werden omwille van impactie bij jonge patiënten en omwille van acute complicaties of klachten bij oudere patiënten en dat oudere patiënten meer symptomen van zenuwschade meldden. Op basis van deze bevindingen zou men kunnen staven dat profylactische verwijdering op jonge leeftijd van wijsheidstanden die waarschijnlijk complicaties zullen geven op oudere leeftijd aangewezen is. De studiepopulatie is echter nog niet groot genoeg om statistisch significante resultaten te verkrijgen.

6.3.2 Een radiografische studie voor het bepalen van het eruptiepotentieel van mandibulaire wijsheidstanden

Deze retrospectieve radiologische studie werd uitgevoerd op panoramische, radiografische beelden van orthodontisch behandelde patiënten, binnen de leeftijdscategorie van 10 tot 25 jaar. Patiënten met craniofaciale of syndromale afwijkingen in de onderkaak, die orthognatische chirurgie ondergingen of die een odontoom hadden, werden geëxcludeerd. Twee beelden per patiënt, met de hoogste kwaliteit en met de grootste tijdspanne tussenin, werden geïncludeerd. De mandibulaire tandenboog moest compleet zijn en alle tanden moesten volledig geërupteerd zijn, op de wijsheidstanden na. Op de beelden werden vier parameters van de wijsheidstand beoordeeld: het ontwikkelingsstadium, het eruptieniveau, de angulatie en het risico op een wortel-zenuw-relatie.

De uiteindelijke steekproef bestond uit 1087 patiënten, waarvan 475 mannen en 612 vrouwen, goed voor 2174 beelden. Men stelde vast dat, wat deze studiepopulatie betreft, de maturatie van de wijsheidstand vroeger plaatsvond bij mannen dan bij vrouwen. Deze bevinding wordt zowel bevestigd als tegengesproken door voorgaande studies. Ze was in elk geval in overeenstemming met een onderzoek die de wijsheidstandontwikkeling over negen specifieke populaties, waaronder België, bestudeerde en met een onderzoek van de KU Leuven over leeftijdsschatting op basis van derde molaren (66,67). Verder was het opvallend dat er weinig tanden volledig doorgebroken waren, zelfs niet op de leeftijd dat men volledige eruptie verwachte (leeftijdscategorie 18-25 jaar). Dat wees op een gehinderde M3-eruptie, wat ondersteund wordt door actuele cijfers over het hoge aantal geïmpacteerde derde molaren (16). Daarnaast constateerde men dat oudere patiënten, met meer ontwikkelde wijsheidstanden, een hoger risico hadden op een relatie tussen de wijsheidstandwortels en de *nervus alveolaris inferior* en bijgevolg ook een hogere kans hadden op zenuwschade na extractie. Dat strookte met eerder onderzoek naar risicofactoren van zenuwschade en met de resultaten van de M3-studie omtrent symptomen van zenuwcomplicaties (37,49,62). Het risico op zenuwrelatie was ook afhankelijk van het eruptieniveau en de impactiestatus van de wijsheidstand. Onderzoek toonde tevens aan dat het type en de graad van impactie geassocieerd zijn met het risico op zenuwschade (40,49).

Voorts werd ook de M3-angulatie bestudeerd. Op heden bestaat er geen model dat de verandering in angulatie en positie van de derde molaar voorspellen. Een recente studie (2016) gaf wel aan dat er drie metingen zijn die wijsheidstanderuptie accuraat kunnen voorspellen. Deze metingen dient men steeds samen te beschouwen en hebben betrekking op de ligging van de wijsheidstand in de mandibula (73). De huidige studie toonde een significante correlatie aan tussen de wijsheidstanderuptie en de hoeken tussen de mandibulaire molaren. Over het algemeen gold dat hoe groter de hoek tussen de derde en tweede molaar, hoe lager de kans op M3-eruptie. Wat betreft premature wijsheidstanden zonder wortels, bleek dat de combinatie van de hoeken tussen de derde en tweede molaar en tussen de derde en eerste molaar predictief zijn voor de M3-eruptie. Met betrekking tot de kans op M3-eruptie moet men rekening houden met de variatie op de tijdsspanne tussen twee panoramische beelden per patiënt. Het kon immers dat de wijsheidstand nog niet doorgebroken was op het tweede beeld, waardoor de kans op eruptie onderschat werd op basis van deze studiedata. De studieanalyse toonde ook aan dat, gemiddeld, een initiële hoek van een wijsheidstand groter dan 25,42 graden (ten opzichte van de tweede molaar) de neiging had om nog groter te worden, wat de kans op M3-eruptie verkleinde. Dit gold voor premature wijsheidstanden zonder wortels. Voor wijsheidstanden die reeds wortelvorming vertoonden, was die hoek net iets groter: 27,82 graden. Een sterke initiële mesioangulaire inclinatie en een minimale oprichting van de wijsheidstand verkleinen in ieder geval de waarschijnlijkheid van een toekomstige functionele eruptie. Tot slot dient men rekening te houden met de orthodontische behandeling die alle patiënten van de studiepopulatie ondergingen bij het bestuderen van de wijsheidstanderuptie. Zoals aangetoond in een voorgaande studie, speelt die in op het eruptiepotentieel van wijsheidstanden: de kans dat orthodontisch behandelde patiënten partieel doorgebroken wijsheidstanden ontwikkelen, die mogelijks leiden tot klinische morbiditeit, is hoger dan voor niet-orhodontisch behandelde patiënten (74). Men gaat ervan uit dat de invloed op de eruptie afhankelijk is van het type van orthodontie, dewelke echter niet werd geregistreerd in deze studie. Die invloed zal worden nagegaan in een volgende fase van het onderzoek.

Deze huidige studie werd opgezet met het oog op het opstellen van een model dat de eruptiekans van een wijsheidstand in een vroeg ontwikkelingsstadium voorspelt. Verder werd ook het risico op een relatie tussen de wijsheidstandwortels en de inferieure alveolaire zenuw onderzocht. De studieresultaten toonden aan dat de hoeken tussen de mandibulaire molaren significant gelinkt waren aan wijsheidstanderuptie en dat het risico op een relatie met de zenuw steeg met de leeftijd. Premature wijsheidstanden met een grotere hoek dan 25,42 graden ten opzichte van de tweede molaar hadden de neiging verder te inclineren, wat ongunstig was voor hun eruptiepotentieel. Ter conclusie kan men zeggen dat een zwaar gekantelde wijsheidstand hoogstwaarschijnlijk nooit zal doorbreken in de mond tot een klinisch functionele positie. Men zou dus kunnen aanraden om zulke wijsheidstanden profylactisch te verwijderen om complicaties gelinkt aan impactie, partiële eruptie en zenuwrelatie te vermijden. We zetten dit radiografisch onderzoek in de toekomst verder op zoek naar een klinisch bruikbaar model ter voorspelling voor wijsheidstanderuptie en risico op een zenuwrelatie om het management rond wijsheidstanden te optimaliseren.

List of tables

List of figures

References

1. Schoenwolf GC, Bleyl SB, Brauer PR, Francis-West PH. Larsen's Human Embryology. 5 ed. Philadelphia: Elsevier Inc.; 2009.

2. McCoy JM. Complications of Retention: Pathology Associated with Retained Third Molars. Atlas Oral Maxillofac Surg Clin North Am. 2012;20(2):177–95.

3. Carter K, Worthington S. Morphologic and Demographic Predictors of Third Molar Agenesis: A Systematic Review and Meta-analysis. J Dent Res. 2015;94(7):886–94.

4. Reddy GSP, Reddy G V, Krishna IV, Regonda SK. Nonsyndromic bilateral multiple impacted supernumerary mandibular third molars: a rare and unusual case report. Case Rep Dent. 2013;2013:1-4.

5. Desantis J, Liebow C, Four common mandibular nerve anomalies. J Am Dent Assoc. 1996;127(7):1081–6.

6. Breik O, Grubor D. The incidence of mandibular third molar impactions in different skeletal face types. Aust Dent J. 2008;53(4):320–4.

7. Palma-Carrió C, García-Mira B, Larrazabal-Morón C, Peñarrocha-Diago M. Radiographic signs associated with inferior alveolar nerve damage following lower third molar extraction. Med Oral Patol Oral Cir Bucal. 2010;15(6):886-90.

8. Hattab FN, Abu Alhaija ESJ. Radiographic evaluation of mandibular third molar eruption space. Oral Surgery, Oral Med Oral Pathol Oral Radiol Endodontology. 1999;88(3):285–91.

9. Bouloux GF, Steed MB, Perciaccante VJ. Complications of Third Molar Surgery. Oral Maxillofac Surg Clin North Am. 2007;19(1):117–28.

10. Santosh P. Impacted Mandibular Third Molars: Review of Literature and a Proposal of a Combined Clinical and Radiological Classification. Ann Med Health Sci Res. 2015,5(4):229–34.

11. Hashemipour MA, Tahmasbi-Arashlow M, Fahimi-Hanzaei F. Incidence of impacted mandibular and maxillary third molars: A radiographic study in a southeast iran population. Med Oral Patol Oral Cir Bucal. 2013;18(1):140–5.

12. Dodson TB. How many patients have third molars and how many have one or more asymptomatic, disease-free third molars? J Oral Maxillofac Surg. 2012;70(91):S4–7.

13. Behbehani F, Årtun J, Thalib L. Prediction of mandibular third-molar impaction in adolescent orthodontic patients. Am J Orthod Dentofac Orthop. 2006;130(1):47–55.

14. Richardson ME. The etiology and prediction of mandibular third molar impaction. Angle Orthodontist. 1977;47(3):165–72.

15. Kim TW, Årtun J, Behbehani F, Artese F. Prevalence of third molar impaction in orthodontic patients treated nonextraction and with extraction of 4 premolars. Am J Orthod Dentofac Orthop. 2003;123(2):138–45.

16. Carter K, Worthington S. Predictors of Third Molar Impaction: A Systematic Review and Meta-analysis. J Dent Res. 2015;95(3):267-76.

17. Quek SL, Tay CK, Tay KH, Toh SL, Lim KC. Pattern of third molar impaction in a Singapore Chinese population: a retrospective radiographic survey. Int J Oral Maxillofac Surg. 2003;32(5):548–52.

18. Bui CH, Seldin EB, Dodson TB. Types, Frequencies, and Risk Factors for Complications after Third Molar Extraction. J Oral Maxillofac Surg. 2003;61(12):1379–89.

19. Kandasamy S, Rinchuse DJ, Rinchuse DJ. The wisdom behind third molar extractions. Aust Dent J. 2009;54(4):284–92.

20. Dodson TB. The Management of the Asymptomatic, Disease-Free Wisdom Tooth: Removal Versus Retention. Atlas Oral Maxillofac Surg Clin North Am. 2012;20(2):169–76.

21. Divaris K, Fisher EL, Shugars DA, White RP. Risk factors for third molar occlusal caries: A longitudinal clinical investigation. J Oral Maxillofac Surg. 2012;70(8):1771–80.

22. Fisher EL, Moss KL, Offenbacher S, Beck JD, White RP. Third Molar Caries Experience in Middle-Aged and Older Americans: A Prevalence Study. J Oral Maxillofac Surg. 2010;68(3):634–40.

23. Shugars DA, Elter JR, Jacks MT, White RP, Phillips C, Haug RH, et al. Incidence of occlusal dental caries in asymptomatic third molars. J Oral Maxillofac Surg. 2005;63(3):341–6.

24. Oenning ACC, Neves FS, Alencar PNB, Prado RF, Groppo FC, Haiter-Neto F. External root resorption of the second molar associated with third molar impaction: Comparison of panoramic radiography and cone beam computed tomography. J Oral Maxillofac Surg. 2014;72(8):1444–55.

25. Atieh MA. Diagnostic Accuracy of Panoramic Radiography in Determining Relationship Between Inferior Alveolar Nerve and Mandibular Third Molar. J Oral Maxillofac Surg. 2010;68(1):74–82.

26. Juodzbalys G, Daugela P. Mandibular third molar impaction: review of literature and a proposal of a classification. J oral Maxillofac Res [Internet]. 2013 [cited 2017 May 24]; 4(2):1–11. Available from: Pubmed Central

27. Dhanjal KS, Bhardwaj MK, Liversidge HM. Reproducibility of radiographic stage assessment of third molars. Forensic Sci Int. 2006;159(1):74–7.

28. Zandi M, Shokri A, Malekzadeh H, Amini P, Shafiey P. Evaluation of third molar development and its relation to chronological age: a panoramic radiographic study. Oral Maxillofac Surg. 2014;19(2):183–9.

29. Demirjian A, Goldstein H, Tanner M, A new dental age estimation system. Hum Biol. 1973;45(2):211-27.

30. Monaco G, Montevecchi M, Bonetti GA, Gatto MRA, Checchi L. Reliability of panoramic radiography in evaluating the topographic relationship between the mandibular canal and impacted third molars. J Am Dent Assoc. 2004;135(3):312–8.

31. Balaji S. Textbook of Oral & Maxillofacial Surgery [Internet]. 2 ed. India: Elsevier India Inc.; 2009. [cited 2017 May 24]. Available from: Google Books

32. Pell GJ, Gregory BT. Impacted mandibular third molars: Classification and modified technique for removal. Dental Digest. 1933:39(9):330-8.

33. Miclotte A, Van Hevele J, Roels A, Elaut JJJ, Willems G, Politis C, et al. Position of lower wisdom teeth and their relation to the alveolar nerve in orthodontic patients treated with and without extraction of premolars: a longitudinal study. Clin Oral Investig. 2014;18(7):1731–9.

34. Borle R. Textbook of Oral and Maxillofacial Surgery [Internet]. 1 ed. Kundi: Jaypee Brothers Medical Publishers; 2014.

35. Whaites E, Drage N. Essentials of dental radiography and radiology. 5 ed. Edinburgh: Churchill Livingstone; 2008.

36. Rood JP, Shehab BA. The radiological prediction of inferior alveolar nerve injury during third molar surgery. Br J Oral Maxillofac Surg. 1990;28(1):20–5.

37. Kim JW, Cha IH, Kim SJ, Kim MR. Which risk factors are associated with neurosensory deficits of inferior alveolar nerve after mandibular third molar extraction? J Oral Maxillofac Surg. 2012;70(11):2508–14.

38. Phillips C, White RP. How predictable is the position of third molars over time? J Oral Maxillofac Surg. 2012;70(9) Suppl 1:S11–4.

39. Hattab FN. Positional changes and eruption of impacted mandibular third molars in young adults. A radiographic 4-year follow-up study. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 1997;84(6):604–8.

40. Khan A, Khitab U, Khan MT. Impacted Mandibular Third Molars : Pattern of presentation and postoperative complications. Pakistan Oral Dent J. 2010;30(2):307–12.

41. Bello SA, Adeyemo WL, Bamgbose BO, Obi EV, Adeyinka AA. Effect of age, impaction types and operative time on inflammatory tissue reactions following lower third molar surgery. Head Face Med. 2011;7(1):1-8.

42. Benediktsdóttir IS, Wenzel A, Petersen JK, Hintze H. Mandibular third molar removal: Risk indicators for extended operation time, postoperative pain, and complications. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2004;97(4):438–46.

43. Blondeau F, Daniel NG. Extraction of Impacted Mandibular Third Molars: Postoperative Complications and Their Risk Factors. J Can Dent Assoc. 2007;73(4):325a-e.

44. Guerrero ME, Botetano R, Beltran J, Horner K, Jacobs R. Can preoperative imaging help to predict postoperative outcome after wisdom tooth removal? A randomized controlled trial using panoramic radiography versus cone-beam CT. Clin Oral Investig. 2014;18(1):335–42.

45. Marciani RD. Third Molar Removal: An Overview of Indications, Imaging, Evaluation, and Assessment of Risk. Oral Maxillofac Surg Clin North Am. 2007;19(1):1–13.

46. Almendros-Marqués N, Alaejos-Algarra E, Quinteros-Borgarello M, Berini-Aytés L, Gay-Escoda C. Factors influencing the prophylactic removal of asymptomatic impacted lower third molars. Int J Oral Maxillofac Surg. 2008;37(1):29–35.

47. Huang GJ, Cunha-Cruz J, Rothen M, Spiekerman C, Drangsholt M, Anderson L, et al. A prospective study of clinical outcomes related to third molar removal or retention. Am J Public Health 2014;104(4): 728–34.

48. Renton T, Yilmaz Z, Gaballah K. Evaluation of trigeminal nerve injuries in relation to third molar surgery in a prospective patient cohort. Recommendations for prevention. Int J Oral Maxillofac Surg. 2012;41(12):1509–18.

49. Nguyen E, Grubor D, Chandu A. Risk factors for permanent injury of inferior alveolar and lingual nerves during third molar surgery. J Oral Maxillofac Surg. 2014;72(12):2394–401.

50. Kaminishi RM, Lam PS, Kaminishi KS, Marshall MW, Hochwald DA. A 10-year comparative study of the incidence of third molar removal in the aging population. J Oral Maxillofac Surg. 2006;64(2):173–4.

51. Renton T, Al-Haboubi M, Pau A, Shepherd J, Gallagher JE, Dodson TB. What has been the United Kingdom’s experience with retention of third molars? J Oral Maxillofac Surg. 2012;70(9) Suppl 1:S48–57.

52. Steed MB. The indications for third-molar extractions. J Am Dent Assoc. 2014;145(6):570–3.

53. Rafetto LK. Managing Impacted Third Molars. Oral Maxillofac Surg Clin North Am. 2015;27(3):363–71.

54. Kinard BE, Dodson TB. Most patients with asymptomatic, disease-free third molars elect extraction over retention as their preferred treatment. J Oral Maxillofac Surg. 2010;68(12):2935–42.

55. Bouloux GF, Busaidy KF, Beirne OR, Chuang SK, Dodson TB. What is the risk of future extraction of asymptomatic third molars? A systematic review. J Oral Maxillofac Surg. 2015;73(5):806–11.

56. National Institute for Health and Care Excellence. Guidance on the extraction of wisdom teeth [Internet]. Manchester: National Institute for Health and Care Excellence; 2000 [cited 2017 May 24]. Available from: https://www.nice.org.uk/guidance/ta1

57. McArdle LW, Renton T. The effects of NICE guidelines on the management of third molar teeth. Br Dent J. 2012;213(5):E8.

58. Ventä I. Current Care Guidelines for Third Molar Teeth. J Oral Maxillofac Surg. 2015;73(5):804–5.

59. Patel S, Mansuri S, Shaikh F, Shah T. Impacted Mandibular Third Molars: A Retrospective Study of 1198 Cases to Assess Indications for Surgical Removal, and Correlation with Age, Sex and Type of Impaction - A Single Institutional Experience. J Maxillofac Oral Surg. 2017;16(1):79–84.

60. Al-Khateeb TH, Bataineh AB. Pathology Associated With Impacted Mandibular Third Molars in a Group of Jordanians. J Oral Maxillofac Surg. 2006;64(11):1598–602.

61. Garaas R, Moss KL, Fisher EL, Wilson G, Offenbacher S, Beck JD, et al. Prevalence of visible third molars with caries experience or periodontal pathology in middle-aged and older Americans. J Oral Maxillofac Surg. 2011;69(2):463–70.

62. Gülicher D, Gerlach KL. Sensory impairment of the lingual and inferior alveolar nerves following removal of impacted mandibular third molars. Int J Oral Maxillofac Surg. 2001;30(4):306–12.

63. Steele DG, Bramblett CA. The anatomy and biology of the human skeleton. 8 ed. United States of America: Texas A&M University Press; 1988.

64. Ferro R, Besostri A, Olivieri A, Stellini E. Prevalence of occlusal traits and orthodontic treatment need in 14 year-old adolescents in Northeast Italy. Eur Arch Paediatr Dent. 2016;17(1):36–42.

65. Wheeler TT, Mcgorray SP, Yurkiewicz L, Keeling SD, King GJ. Orthodontic treatment demand and need in third and fourth grade schoolchildren. Am J Orthod Dentofacial Orthop. 1994;106(1):22–33.

66. Mesotten K, Gunst K, Carbonez A, Willems G. Dental age estimation and third molars: a preliminary study. Forensic Sci Int. 2002;129(2):110–5.

67. Thevissen PW, Fieuws S, Willems G. Human third molars development: Comparison of 9 country specific populations. Forensic Sci Int. 2010;201(1):102–5.

68. Yusmiaidil M, Mohd P, Cauwels R, Martens L. Stages in third molar development and eruption to estimate the 18-year threshold Malay juvenile. Arch Oral Biol. 2015;60(10):1571–6.

69. Sivaramakrishnan SM, Ramani P. Study on the Prevalence of Eruption Status of Third Molars in South Indian Population. Biol Med. 2015;7(4): 1-4.

70. Eshghpour M, Nezadi A, Moradi A, Shamsabadi RM, Rezaei NM, Nejat A. Pattern of mandibular third molar impaction : A cross-sectional study in northeast of Iran. Niger J Clin Pract. 2014;17(6):673-7.

71. Miloro M, Dabell J. Radiographic proximity of the mandibular third molar to the inferior alveolar canal. Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2005;100(5):545-9.

72. Nance PE, White RP, Blakey GH, Haug RH. Change in Third Molar Angulation and Position in Young Adults and Follow-Up Periodontal Pathology. J Oral Maxillofac Surg. 2006;64(3):424-428.

73. Kaur R, Kumar AC, Garg R, Sharma S, Rastogi T, Gupta VV. Early prediction of mandibular third molar eruption/impaction using linear and angular measurements on digital panoramic radiography: A radiographic study. Indian J Dent. 2016;7(2):66–9.

74. Miclotte A, Franco A, Guerrero ME, Willems G, Jacobs R. The association between orthodontic treatment and third molar position, inferior alveolar nerve involvement, and prediction of wisdom tooth eruption. Surg Radiol Anat. 2015;37(4):333–9.