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The Evolution of Third Molar Agenesis and Impaction

A dissertation presented

by

Katherine Elizabeth Carter

to

The Department of Human Evolutionary Biology

in partial fulfillment of the requirements

for the degree of

Doctor of Philosophy

in the subject of

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The Evolution of Third Molar Agenesis and Impaction

Abstract

Up to 70% of modern humans experience problems with their third molars, whether it is failure of proper eruption (impaction) or not erupting at all (agenesis). Thus, it is a commonly used example for explaining why humans are still evolving and the relevance of evolutionary medicine. Agenesis dates back to at least early *Homo erectus*, and is seen with greater frequency during the evolution of later *Homo*. However, there are currently few data that support any of the three hypotheses (agenesis as selection against impaction, developmental delay, and the probable mutation effect) proposed to explain the evolution of agenesis and impaction. Furthermore, while most researchers associate changes in the physical properties of food with an increased frequency of third molar pathologies, it is unclear whether these changes took place during the advent of agriculture, the beginning of industrialization or both. Considerable variation exists among modern human populations in the rate of agenesis and impaction, but there are inconsistencies in reports of how modern variation partitions among sex, population, and morphological traits. Thus, this study first aims to explain modern variance in agenesis and impaction, then to use morphological data to assess how the third molar pathologies of four different populations from Serbia, Egypt, Japan and SE USA changed with the adoption of agriculture

and the beginnings of industry. This will lead to an understanding of the evolution of third molar agenesis and impaction that will help understand the evolutionary origins of an important condition affecting modern humans.

First, we aimed to consolidate all available data on worldwide third molar agenesis frequencies, with a particular emphasis on exploring the factors leading authors to find contradictory results for the demographic and morphological predictors of this anomaly. A total of 12,376 studies were originally identified, then narrowed down to 1,312 for title/abstract screening. Based on our inclusion and exclusion criteria, we selected 92 studies, containing 100 effect sizes and 63,314 subjects, for systematic review and meta-regression. The worldwide rate of agenesis was found to be 22.63% (95% CI: 20.64%-24.76%), though the estimates ranged from 5.32% to 56.0%. Our subgroup analyses revealed that females are 14% more likely to have agenesis of one or more third molars than males and that maxillary agenesis was 36% more likely than mandibular agenesis in both sexes. Further, we found that having agenesis of one or two molars was most common, while agenesis of three molars was least common. Finally, we found large differences among agenesis frequency depending on geographic region. This information is expected to be of use not only to clinicians and patients but also to policy makers, given the implications for third molar extraction protocols.

Next, we performed a meta-analysis to synthesize the abundant existing literature on third molar impaction frequencies worldwide. A total of 7,936 records were originally identified, then narrowed down to 864 for title/abstract screening. Based on our inclusion and exclusion criteria, we selected 49 studies,

containing 83,484 subjects, for systematic review and meta-regression. The worldwide rate of impaction was found to be 24.40% (95%CI: 18.97%-30.80%), though the estimates ranged from 3.08% to 68.60%. Our subgroup analyses revealed that mandibular impaction was 57.58% more likely than maxillary impaction, while we did not detect any difference in impaction frequency between males and females. In addition, we found that mesioangular impaction was most common, followed by vertical impaction, with distoangular and horizontal impaction less frequent. Further, we found that having impaction of one or two third molars was most common, while impaction of three or four third molars was least common. Finally, we found small differences among impaction frequency depending on geographic region. Given the rich debate surrounding third molar treatment policy, understanding demographic and morphological differences in impaction rates is an important first step in assessing appropriate treatment protocols.

Finally, we applied the results of these analyses to explore the evolutionary origins of third molar agenesis and impaction. Humans are unique in having high frequencies of pathological third molars, including impacted molars that fail to erupt and agenesis, or missing, molars. Many researchers attribute an increased prevalence of third molar agenesis and impaction to highly processed modern diets. Three competing hypotheses exist to explain the evolution of third molar agenesis: 1) agenesis as the result of selection against impaction, 2) agenesis as developmental delay, and 3) the probable mutation effect. These hypotheses, however, remain untested. Here we test these hypotheses using data from four populations sampled before, during and after the transitions to agriculture and two

populations before, during, and after the transition to industry. We found the selection against impaction hypothesis contributed to the rise in third molar agenesis at the end of the industrial transition, but impaction remained at such low frequencies during the agricultural transition that this mechanism is unlikely to have been a causative force. Furthermore, we found a negative relationship between dental arch space and third molar agenesis in the industrial transition, but a positive relationship between these two variables in the agricultural transition. Overall, these data suggest that two different mechanisms influenced the prevalence of human third molar agenesis: one operating since the time of *Homo erectus* and one with much more recent origins.

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Introduction

Third molars, commonly known as wisdom teeth, are highly polymorphic within modern humans, with roughly one-quarter of humans across the globe born without one or more of these teeth (Carter and Worthington, 2015) and one-quarter of humans having one or more of these teeth impacted (present but failing to properly erupt into occlusion; Carter and Worthington, 2016). In other individuals, the third molars may be present, but reduced in size or morphological complexity (Bermudez de Castro, 1989; Gomez-Robles et al., 2015). Treatment of impacted wisdom teeth, while commonplace, remains contentious, as it is often prophylactic. An abundance of studies exist delineating the side effects and best surgical practices to treat impaction (e.g., Marciani, 2012; Venta 2012). However, the ultimate causes of third molar agenesis and impaction, including how these two pathologies relate, remains unknown.

While third molar loss is seen in multiple mammalian orders, humans and domestic animals are the only mammals to consistently have impacted third molars. Among extant primates, *Homo*, Callitrichini, and the platyrrhine *Xenothrix* are the only known taxa to show high rates of M3 agenesis. Third molar agenesis is first seen in the hominin fossil record at 1.5 Ma with *H. erectus.* Most notably KNM WT-15000 has no mandibular M3 formation (Brown et al., 1993), and adult fossils from Lantian and Chenciao locality 63709 also show evidence of agenesis (Aigner and Laughlin, 1973; Wu and Xianglong, 1996). While other individual cases of agenesis are detected throughout the rest of human evolution (e.g., Curnoe et al., 2012 ; Lukacs and Pal., 2013; Sawyer et al., 2015), it is currently unknown how the prevalence of M3 agenesis in humans changed over time. Impaction is more difficult to detect in the fossil record; there are few- if any –definitive

cases of impaction predating the origin of *H. sapiens* (Neiburger, 1975; Wolpoff, 1979; Skinner and Sperber, 1982; Frayer and Russell, 1987; Gibson and Calcagno, 1993, 1995; Neiburger, 1995).

The main purpose of this dissertation is to analyze both the proximate and ultimate causes of M3 agenesis and impaction. Below are the five main research questions this thesis is structured around, with some background on what is currently known and why the topic is interesting.

What predicts third molar agenesis and impaction in modern populations?

Third molars, particularly in the mandible, are the most metrically and non-metrically (e.g., crown surface features) variable tooth in the human dentition (Turner, 1987; Kondo, 2005). The last tooth to mineralize and erupt, third molar development begins with crypt formation from 3-8 years of age (Massler et al., 1941; Orhan et al., 2007). Mineralization, however, is highly variable within a population, with a range of 6-14 years (Garn et al., 1962; Moorees et al., 1963; Haavikko, 1970; Fanning, 1971; Anderson et al., 1976; Levesque et al., 1981; Nystrom et al., 2007). While population differences exist in the age of onset for mandibular M3 mineralization (Liversidge, 2008), M3 agenesis, or failure for the third molar to form, is definitively detectable by age 11 in even the slowest developing individuals (Banks, 1934; Garn and Lewis, 1962; Richardson, 1980). Third molar impaction, however, is harder to definitively confirm before age 20, and can change substantively in some individuals long after this time (Kruger et al., 2001; Venta et al., 2001).

Given the human health implications, there is no shortage of literature on modern third molar pathologies. A google scholar search for "third molar" AND "agenesis" produces 2,240 papers and a similar search for impaction produces 5,560 results. However, these results are frequently highly contradictory. Females are typically reported to have greater frequencies of M3 agenesis (Richardson, 1980; Afify and Zawawi; 2012; Bansai, 2012), though some studies found no sex differences (Lynham et al., 1990; Celikoglu et al., 2010; Kazanci et al., 2010), and other studies report male M3 agenesis rates as higher than female (Upadhyaya, 2012; Ren, 2014). Similarly, while some researchers report a high frequency of bilateral symmetry in M3 tooth agenesis (Bailit, 1975), others suggest over half of missing teeth occur unilaterally (Lundstrom, 1960). Reports of morphological and developmental correlates also vary widely. While some researchers report correlations between reduced molar size (Brook, 1968) or simplicity (Keene 1965, 1968; Davis, 1968), others have found no relationship (Garn et al., 1966; Turner, 1987). Within a small population of Norwegian children, a high frequency of M3 agenesis correlated with reduced prognathism, and maxillary length (Wisth et al., 1974a; Roald et al., 1982), but no correlation was found between agenesis and maxillary breadth (Wisth et al., 1974b). Population differences in third molar agenesis are well-established, with the frequency highest in Sinodonts (East Asians and Native Americans; 44%), South East Asians (20.9%) and Europeans (14.5%; Turner, 1987; Irish, 1997). Third molar agenesis is least common in Sub-Saharan African (0.5%) and Australian (1.8%) populations. Differences in the frequency of agenesis among populations are at a magnitude similar to that of reported differences in both metric and non-metric traits (Hanihara and Ishida, 2005; Matsumura,

2007), but it is unknown whether the frequencies correspond with genetic distance across populations.

Previous work on the frequency and distribution of third molar impaction has yielded even more contradictory results. Population estimates range from 16.7%-68.6% (Daichi and Howell, 1961; Morris and Jerman 1971; Hattib and Alhaija, 1999; Quek et al., 2003), with some studies reporting higher frequency in maxillary molars (e.g., Daichi and Howell, 1961: maxillary molar impaction 29.9%, mandibular molar impaction 17.5%), while others report higher frequency in mandibular molars (e.g., Hashempiour et al., 2013 maxillary: 35.6%, mandibular 64.4%). Most studies report that impaction does not vary by sex (Dachi and Howell, 1961; Brown et al., 1982; Haidar and Shalhoub, 1986; Hattab et al., 1995; Kaya et al., 2010), though some have observed much higher prevalence in females (Hugoson and Kugelberg, 1988; Quek et al., 2003; Celikoglu et al., 2010; Hashempiour et al., 2013). Similarly, while some reports suggest differences among populations (e.g., Daichi and Howell, 1961, Kaya et al., 2010) others suggest that there are few inter-population differences (Celikoglu et al., 2010).

Many researchers have sought to test whether individual morphological features indicative of small jaws correspond to impaction. The degree of mandibular impaction correlates with mandibular length, the angle of the mandibular base, or the angle of molar eruption in almost 90% of cases, but these factors have not been evaluated in unison (Bjork et al., 1956). Correlations were also found between impaction and the bicondylar breadth, second molar size (Olive and Basford, 1981), height and width of the retro-molar space (Ganss et al., 1993; Hattab and Alhaija, 1999; Behbehani et al., 2006), mesio-distal molar size, vertical height of the anterior ramus, length of the posterior basal corpus, number of

third molar roots, and vertical height of the posterior border of the ramus (Kaya et al., 2010). These studies suggest that small jaws are linked to impaction. However, a study of micrognathic and macrognathic patients found impacted teeth equally in both groups (Manuela et al., 2009), suggesting soft tissue structures and growth patterns may be equally important for predicting impaction in teeth.

The emerging picture on the state of third molar agenesis and impaction studies suggests that despite many years of work, there is little consensus on the morphological, developmental and demographic factors contributing to the expression of third molar pathologies. Many of these problems are likely resolvable with the application of proper analytic techniques. To fully understand multi-factoral contributions to the expression of complex traits, multiple regression models are most appropriate, while most studies rely on chi-squared tests.

Do any of the three hypotheses previously proposed to explain the origin of agenesis fit the data?

While many peer-reviewed and popular science articles have proposed evolutionary hypotheses to explain the prevalence of M3 agenesis, impaction, and reduction, there is currently no study that directly tests the predictions of these hypotheses across multiple populations. Thus, one of my aims in this project is to address this issue by testing predictions from three evolutionary hypotheses in six populations across two time transitions: the introduction of agriculture and industrialization. The first and second of these hypotheses represent "conventional wisdom" about the evolution of M3 agenesis and impaction, which have never been tested using archaeological data. While the "Probable

Mutation Effect Hypothesis" is attributable to Brace (1964), the "Selection Against Impaction Hypothesis" is attributable in parts to a wide range of authors (Robinson, 1954; Lavelle and Moore, 1973), but has most recently been championed by Alan Mann. The "Developmental Hypothesis" follows from Brothwell et al. (1963) and Bermudez de Castro (1989) as well as modern dental literature. Below, I briefly explain each hypothesis followed by a discussion of the evidence that supports and contradicts each theory.

Selection against impaction: While third molar agenesis has existed at low frequency in hominins for almost 2 million years, some modern human populations experience agenesis at rates exceeding 50% of the population (Daito, 1992; Bolanos, 2003; Arany, 2004; Goren et al., 2005; Lee, 2009; Upadhyaya, 2012; Rey, 2014). Impaction, similarly, may exist in low frequencies in some late-Pleistocene humans, but is evident in over 50% of many worldwide populations (Breik and Grubor, 2008). Under the "Selection against Impaction" hypothesis, large-scale impaction developed because changes in tool uses and food processing led to reduction in jaw size and no space for the third molar (e.g., Wu and Xianglong, 1996; Swee et al., 2013). Selection for M3 agenesis occurs because of the pathologies associated with impaction when adequate dental care is not available (e.g., Dixon et al., 1997). As agenesis existed in low background frequencies across most Pleistocene human populations, the trait increased in frequency as those lacking third molars had more reproductive success.

Evidence exists that both supports and challenges this hypothesis. For example, there is little doubt that, despite different domesticated crops and differences in processing techniques, post-agricultural diets require less masticatory processing (Gilbert and Mielke, 1985; Larsen, 1995). Experimental studies documenting the effects of soft or liquid diets

on craniofacial growth suggest that soft foods change breadth and depth measurements in the mandible (Ito et al., 1988; Lieberman et al., 2004), though these differences are not always significant (e.g., Ozaki et al., 2007). Evidence that variation in size and shape of the mandible correlates much more highly with diet than the rest of the cranium suggests that changes in diet may bring about changes in the mandible (von Cramon-Taubadel, 2012), and recent reduction in mandible size has been particularly noted in corpus breadth and retromolar space, where third molars would likely erupt (Franciscus and Trinkaus, 1995).

Connecting changes in mandible size and shape to increases in M3 impaction and agenesis, however, has proven more difficult. One prediction of the selection against impaction hypothesis is that populations with the smallest jaws (controlling for tooth size) would have the highest rates of agenesis, as they would be most affected by impaction. However, previous studies have shown no correlation between jaw size and frequency of M3 agenesis, even when tooth size is taken into account (Bermudez de Catro, 1989). Furthermore, the evidence remains mixed about the effect of agriculture on mandibular morphology. In the Levant, the transition to farming brought about changes in the buccolingual dental dimensions and in mandibular ramus breadth and anterior height, but not in overall mandibular size (Pinhasi et al., 2008).

Probable Mutation Effect: Another hypothesis, the Probable Mutation Effect, posits wear and dental reduction as the selective mechanism for M3 agenesis. Brace (1963, 1964) suggested that human dental reduction occurred because relaxed selective pressure for proper occlusion and occlusal crown area led to a build-up of mutations within different human populations, eventually leading to the independent acquisition of third molar agenesis. Tooth reduction is known across the evolution of *H. sapiens* (Brace and Mahler,

1971; Brace et al., 1987), and between the Neolithic and contemporary people across populations in Australia (Brace and Hinton, 1981), Africa (Calcagno, 1986), North America (Nelson, 1938; Moorrees and Reed, 1954; Hill, 2004) and South America (Kieser et al., 1985). In the Ohio River Valley, dental reduction has been found to correlate with dietary abrasiveness (but not dietary hardness) suggesting a role for changing physical properties of food (Hill, 2004). However, a comparison across Industrial and archaeological populations worldwide revealed no significant or consistent pattern of dental reduction (Garn et al., 1969; y'Edynak, 1989; Jacobs, 1994). Furthermore, a comparison of post-agricultural tooth wear rates and agenesis rates across populations suggest that populations with some of the highest rates of wear (e.g. Native American populations; Kaifu, 2000; Kaifu, 2006; Ritter et al., 2009) also have the highest rates of agenesis (Lahr, 1995; Hillson, 1996) while populations with low wear rates have low rates of agenesis (Irish, 1998), contradictory to the predictions of the Probable Mutation Effect. Finally, despite remaining a prominent explanation for reduction and agenesis, this theory has come under intense scrutiny for what many suggest an increased understanding of genetics and developmental processes has now shown as flawed evolutionary thinking (e.g., Holloway, 1966; Calcagno and Gibson, 1988; Weiss, 2010).

Developmental Delay: A third hypothesis, the developmental delay hypothesis posits that slowed somatic growth caused by poor nutrition is one of the best predictors of M3 agenesis. The onset of agriculture also correlates with the onset of various pathologies associated with the over reliance on a few plants and poor nutritional values of some domesticated crops (e.g., maize; Larsen, 1995). These changes are reflected in human morphology as a decrease in overall stature (Piontek et al., 2001), an increase in dental

caries (Turner, 1979; Cohen and Armelagos, 1984; Milner, 1984; Larsen, 1995) and a greater frequency of enamel defects (Rose et al., 1978; Cohen and Armelagos, 1984), though variation exists among populations in the magnitude of changes (e.g., Lukacs, 1990; Lubell et al., 1994; Sobolik, 1994). The rate of skeletal growth also declined in early agricultural populations, especially during the juvenile stage (Papathanasiou et al., 2009; Mummert et al., 2011). Though dental eruption is typically compared to skeletal development to determine delays, as eruption is less susceptible to environmental influence (Lewis and Garn, 1960), dental eruption is also delayed in malnourished modern populations (Hiernaux, 1968; Enwonwu, 1973; Suri et al., 2004).

Thus, another possibility is that third molar agenesis increased in agricultural populations not from changes in jaw morphology but rather from delays in later ontogenetic growth (Bermudez de Castro, 1989). Third molar agenesis correlates with the timing of eruption of the 2nd molar (Garn et al., 1962) and the timing of the mineralization of the 2nd premolar (Wisth et al., 1974a), as individuals with late-developing teeth are more likely to develop agenesis. Thus, developmental delays related to the shift to agriculture may be the causal mechanism, instead of changes in jaw growth patterns or in wear rates. This would explain both why there is no correlation between jaw length and frequency of third molar agenesis between populations, and why third molar agenesis appears much earlier than the shift to agriculture in the fossil and archaeological record. The first known case of third molar agenesis in hominins occurred in the *Homo erectus* species KNM WT15000, which may have had a slightly longer period of development than older fossil hominins (Dean et al., 2001). It would also be congruent with

recent work suggesting minimal correlation between available space in the jaw and the successive timing of molar formation (Boughner and Dean, 2003).

Furthermore, though teeth are thought to be relatively robust to environmental perturbation (Kiontke and Fitch, 2010), tooth size can be affected by differences in the quality of the environment in early life. Nutrition can also positively impact tooth size, such as in a secular study of Chinese family data (Harris et al., 2001) and across the Fels Longitudinal Study (Garn et al, 1968) where molar and premolar sizes increased in children with better nutrition. In Japan, the incidence of third molar agenesis has declined slightly over multiple generations born in the 20th century (Nakahara et al., 1997; Kajii et al., 2001). While the mandible is highly evolvable and responsive to dietary functional demands when compared to the rest of the cranium, the teeth are typically thought to be less mutable and more slowly evolving (Zelditch and Carmicheal, 1989; von Cramon-Taubadel, 2011). Thus, even if agriculture were found to cause a significant reduction in jaw metrics, it is unlikely that the teeth would be able to adapt as quickly. Dis-integration between the jaws and the teeth has been cited as the cause of human-wide malocclusions, and may also explain the rise of impaction within human populations.

These evolutionary hypotheses have been applied to explain differences in modern human variation in M3 agenesis, either suggesting that the type of food eaten or different selective regimes led to large differences among modern populations (Rose et al., 1978). However, when these hypotheses have been applied to non-metric traits, such as odontomes (pearl-like deposits of enamel atop occlusal crowns), there was no functional or selective evidence found (Scott and Alexandersen, 1992). Thus, variation in the modern

human dentition, including M3 agenesis, could also be explainable through genetic drift, which is the null hypothesis.

Are agenesis and impaction related pathologies?

This question is highly related to the previous research question. Both agenesis and impaction tend to predominantly affect the third molar and tend to have increased in frequency in modern times. However, while impaction is established late in adolescence, agenesis can be determined by age 11 (Banks, 1934; Garn and Lewis, 1962). Some mechanisms to explain third molar agenesis, such as selection against impaction, presume an underlying relationship between the two pathologies, while others (particularly the probable mutation effect) do not presume a relationship. Thus, by testing hypotheses for the origin of M3 agenesis, I hope to be able to understand whether agenesis and impaction are related.

How did changes in the human diet change the frequencies of these pathologies?

Two major transitions in human evolutionary history, the adoption of agriculture and the beginnings of industrialization, brought about widespread changes in nutrition, demography, and mobility (Rindos and Dunnell, 1984; Larsen, 2002). While there is evidence to suggest these transitions impacted human health both positively (Larsen, 1995; Cohen, 1995) and negatively (Armelagos et al., 1991; Popkin, 1999, 2003; Cordain, 2005; Larsen, 2006), it is rarely possible to directly test the effects of evolutionary shifts on human anatomy and physiology. Teeth, given their high preservation rate and resilience to remodeling and taphonomy, represent an ideal anatomical system for evaluating the patterns of anatomical change over time. While changes in dental pathology during these

time periods are well known (Scott, 1979; Larsen, 1995; Kaifu, 2000), understanding how agriculture and industry contributed to modern third molar pathologies will help us gain insight into changes in developmental processes and the modern selective regime.

How can understanding the evolutionary origins of impaction and agenesis shed light on modern tooth extraction?

The high frequencies of third molar impaction and agenesis across modern human populations also have health implications. Impacted third molars are often removed, but as impaction may not develop until age 25 or 30, treatment is prophylactic more than 50% of the time. This is unique among medical procedures, especially as it is applied equally across all population demographics (e.g., there is no special screening in place to determine whether someone is at risk for developing impaction). Impaction costs billions of dollars in palliative dental care annually (Anderson et al., 1976; Nystrom et al., 2007). While a growing number of oral biologists suggest that third-molar removal is often unnecessary, un-extracted impacted molars can cause caries, inflammation, malocclusion, follicular cysts, and ameloblastomas (Suri et al., 2004). Currently, it is unclear how to predict whether third molars require extraction, or what suite of features predispose an individual to impaction, and one purpose of this thesis is to establish ways to predict this.

From a broader perspective, dentistry has yet to embrace the evolutionary medicine revolution that has shifted treatment regimes to reflect the ultimate, not just the proximate causes of pathology. There are likely evolutionary explanations to explain the increase in frequency of third molar pathologies, and understanding the ultimate mechanisms leading

to this common problem may aid in a more widespread adoption of evolutionary thinking among dentists.

Conclusion

To answer these questions, I collected and analyzed data for three related projects, published in the following three chapters. The first is a meta-analysis of the predictors of M3 agenesis in modern populations, the second is a meta-analysis of the predictors of M3 impaction in modern populations, and the third is an archaeological analysis that examines how third molar pathologies changed over the agricultural and industrial transitions.

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Chapter 2: Morphological and Demographic Predictors of Third Molar Agenesis: A Systematic Review and Meta-analysis.

ABSTRACT

We aimed to consolidate all available data on worldwide third molar agenesis frequencies, with a particular emphasis on exploring the factors leading authors to find contradictory results for the demographic and morphological predictors of this anomaly. A total of 12,376 studies were originally identified, then narrowed down to 1,312 for title/abstract screening. Based on our inclusion and exclusion criteria, we selected 92 studies, containing 100 effect sizes and 63,314 subjects, for systematic review and meta-regression. The worldwide rate of agenesis was found to be 22.63% (95% CI: 20.64%-24.76%), though the estimates ranged from 5.32% to 56.0%. Our subgroup analyses revealed that females are 14% more likely to have agenesis of one or more third molars than males and that maxillary agenesis was 36% more likely than mandibular agenesis in both sexes. Further, we found that having agenesis of one or two molars was most common, while agenesis of three molars was least common. Finally, we found large differences among agenesis frequency depending on geographic region. This information is expected to be of use not only to clinicians and patients but also to policy makers, given the implications for third molar extraction protocols.

INTRODUCTION

In this study, we characterize the prevalence and predictors of third molar (M3) agenesis across different modern populations of humans, using systematic review and meta-analysis. Up to 50% of modern humans experience problems with their third molars, whether it is failure of proper eruption (impaction) or absence of calcification (agenesis)

(Ricketts, 1972; Kruger, 2001). Side effects of third molar pathology range from caries, inflammation and malocclusion to follicular cysts and ameloblastomas (Suri et al., 2004). Understanding diversity in the prevalence of third molar pathologies informs dentist's decision making and patient's health outcomes following treatment (Flick, 1999; Steed, 2014). While agenesis does not directly cause pathology, it can present as a symptom of a larger oral problem (Celikoglu et al., 2010). Thus, the morphological, demographic and developmental predictors of third molar agenesis are a frequent topic of study among dentists. Agenesis has long been shown to have a genetic component (Garn and Lewis, 1962; Vastardis, 2000), but can also develop as the result of developmental pathology (Shapira, 2000), delayed growth (Bermudez de Castro, 1989) and arguably the amount of space available in the jaw (e.g., Kajii et al., 2014). As the third molar is the last tooth to develop and erupt, it has been thought to be most sensitive to environmental perturbation (Shapira et al., 2000), thus potentially helping to inform clinicians of early life history.

The literature on factors relating to M3 agenesis is rich but also highly contradictory, which can make defining best practice for the pathology difficult. Females are typically reported to have greater frequencies of agenesis (e.g., Bansal, 2012), though other studies have found no sex differences (e.g., Celikoglu et al., 2010), and some studies report male agenesis rates as higher than female (e.g., Upadhyaya, 2012). Similarly, while some researchers report a greater than 50% frequency of bilateral symmetry in M3 agenesis (Bailit, 1975), others suggest over half of missing teeth occur unilaterally (Lundstrom, 1960). Reports of morphological and developmental correlates, including third molar impaction, also vary widely. While some researchers report correlations

between reduced molar size (Brook, 1984) or morphological simplicity (Keene, 1965; Davies, 1968) and agenesis, others have found no relationship (Garn et al., 1966; Turner, 1987). Within a small population of Norwegian children, a high frequency of M3 agenesis correlated with reduced prognathism and maxillary length (Roald et al., 1982), but no correlation has been found between agenesis and maxillary breadth (Wisth et al., 1974). Explaining the differing patterns from the breadth of studies available is crucial to understanding the development and manifestation of third molar agenesis in humans.

One hypothesis for why studies reach different conclusions about the prevalence of M3 agenesis is that this pathology developed independently in different populations. Population differences in third molar agenesis are well-established, with the prevalence highest in Sinodonts (East Asians and Native Americans; 44%), South East Asians (20.9%) and Europeans (14.5%; Turner, 1987; Irish, 1997). Agenesis is least common in Sub-Saharan African (0.5%) and Australian aboriginal (1.8%) populations (Irish, 1997). It is thus possible that the variation in M3 agenesis frequency among these populations may develop from different underlying causes. Understanding this would greatly aid our knowledge of personalized dentistry and probable treatment outcomes of related pathologies (Kruger et al., 2001). However, in order to further this hypothesis, an analysis to explain the differences in results among previous studies must be conducted. We conducted a systematic review and meta-analysis of 92 previously-published papers to study the demographic and morphological predictors of M3 agenesis.

MATERIALS AND METHODS

Data sources and search criteria

The guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement were followed where relevant (Moher et al., 2009). To reduce selection bias we sought to identify, appraise, and synthesize all relevant studies (Uman, 2011). In June 2014, one of us (KC) used online publication search engines (Pubmed, Google Scholar, and Thomson Reuters ISI Web of Science) to extensively search the literature using keyword combinations (full electronic search strategy provided in Figure 1). No limits were placed on language or year of publication. KC then conducted further manual searches of the literature using the bibliographies of papers found in the online search.

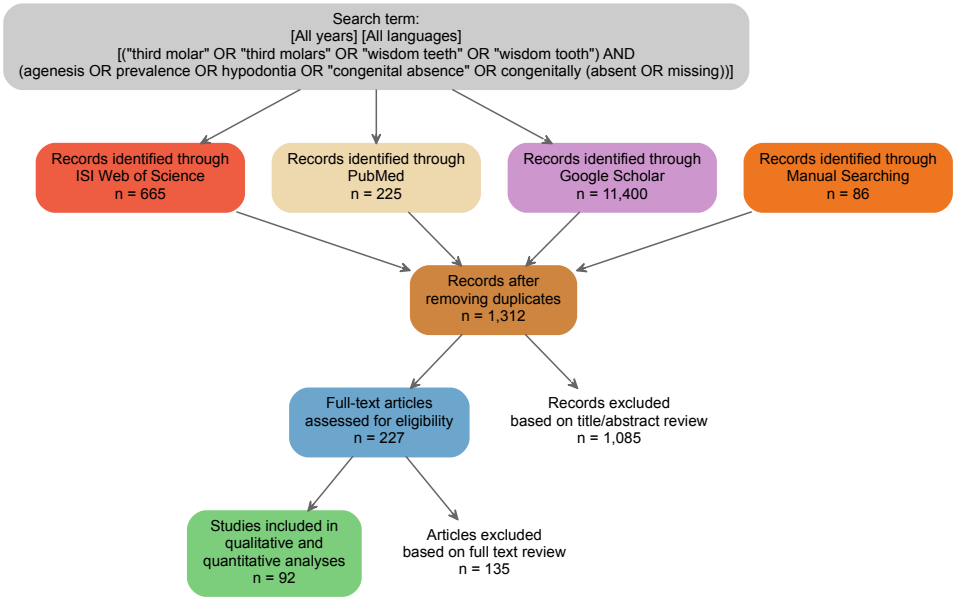


Figure 1: Flowchart illustrating the search strategy and article selection process.

Inclusion and exclusion criteria

The eligibility criteria for inclusion were:

- Presence of an English abstract and/or summary and/or manuscript, or presence of one of the above in a language known to one of the authors.
- Diagnosis of M3 agenesis based on radiographic examination.
- Minimum age of subjects at least 11 years.
- Reporting of M3 agenesis frequency as the number of individuals with at least one missing third molar.

The exclusion criteria were:

- A second study using the same subjects.
- A second effect size estimate relying on the same subjects within a single study.
- Studies that included individuals with prior extraction of any permanent tooth in effect size estimates.
- Reporting of M3 agenesis frequency conflated with frequencies of agenesis in other teeth (possibly including other molars).
- Reporting of M3 agenesis frequency only as the number of teeth affected, rather than the number of individuals.
- Reporting of M3 agenesis frequency only as a percentage, without information about sample size.
- Reporting of M3 absence frequency, but failure to distinguish molar agenesis from lack of eruption.
- Study limited to patient group with craniofacial syndromes or developmental disorders.

Outcome measures and explanatory variables

The outcome measures of interest in this systematic review were the proportion of individuals with agenesis of at least one third molar, and the odds-ratio (OR) of M3 agenesis rate for females versus males and maxilla versus mandible. Proportions were logit-transformed for analysis and subsequently back-transformed for each figure. Maxillary and mandibular agenesis rates were calculated as the sum of bilateral and unilateral agenesis. The data needed for analysis were retrieved from tables, figures, or text; sometimes calculations were required.

An important assumption of meta-analysis is that study outcomes are independent. This assumption can be violated in two ways. First, if multiple effect sizes rely on the same individuals. Second, if two or more effect sizes are derived from the same study or research group (Stevens and Taylor, 2009). We dealt with the first issue, dependence at the sampling level (pseudoreplication), by excluding any effect sizes that used the same individuals. The second violation, dependence at the hierarchical level, was a potential problem, as eight of the studies we sampled reported effect sizes for two different populations. We addressed this issue by including study-level random-effects in analyses that included these studies (Konstantopoulos, 2011).

Predictors of M3 agenesis rate included: 1) study sample size, 2) study sample type, 3) study minimum subject age, 4) study publication year, 5) study population's continent of origin, and, 6) number of missing third molars. The variable 'study sample type' described the different kinds of samples used by researchers (e.g., orthodontic patients, university students, military personnel etc.).

Consideration of bias

Our final selection of studies exhibits great variation in sample size, ranging from n=50 to n=4000. Larger studies may contain sampling issues that impact the frequency of agenesis, as reporting this frequency is often only one aim of the study. However, studies with smaller sample sizes, particularly those reporting low frequencies of agenesis, are less likely to be accepted for publication (Dickersin, 2005; Rothstein et al., 2005). Thus, the influence of sample size on M3 agenesis frequency must be assessed as part of the analysis.

Data analysis

Included studies, together with their outcome and explanatory variables are presented the Appendix. Both random- and mixed-effects generalized linear models were used to estimate effect sizes and their 95% confidence intervals (CIs). Random-effects modeling was chosen, rather than its fixed-effects counterpart, so that the results of the analysis could be generalized to the population of studies from which we sampled (Normand, 1999). For analyzing proportions of individual groups we used mixed-effects logistic regression models with a binomial-normal data distribution (Hamza et al., 2008). For two-group analyses (i.e., outcomes partitioned by sex or jaw) we used a two-by-two contingency table format, and the corresponding model was a mixed-effects conditional logistic regression model with a non-central hypergeometric distribution for the data (Stijnen et al., 2010).

Heterogeneity (among-study variance in effect size additional to that attributable to sampling error) was estimated using the I^2 index, which describes the percentage of total variation in effect size estimates that is due to heterogeneity (Higgins and Thompson, 2002; Higgins et al., 2003). We used a likelihood ratio test (LRT) to assess whether

heterogeneity was significantly larger than zero. To investigate heterogeneity in effect-size estimates we conducted meta-regression analyses using a total of six moderator variables. We assessed whether heterogeneity could be explained by either bias (artifactual variation in study design etc.) or diversity (biological variation in participants and outcomes etc.).

Estimated effect sizes and their 95% CIs for individual studies were visualized using forest plots. Summary estimates for the entire sample represent inverse-variance weighted averages and 95% CIs. Publication bias was assessed via funnel plots. Multiple comparisons of mean agenesis frequency have *p*-values adjusted using the sequential Bonferroni method (Holm, 1979). All analyses were conducted using the 'metafor' package v. 1.9-3 (Viechtbauer, 2010) in the R statistical language v. 3.1.1 (R Core Team, 2014).

RESULTS

Study selection

In an attempt to accurately assess the rate of agenesis in the third molar, the last tooth to erupt and calcify during development, we only included studies that sampled individuals of age 11 years and over. Liversidge (2008) demonstrated that by 11 years of age the third molar has begun calcifying across several populations (White and Bangladeshi children from London and black African and Cape coloured children from South Africa). We also sought to eliminate studies that used populations previously shown to have abnormally high rates of agenesis, such as those with craniofacial disorders (Shapira et al., 2000). In total, 12,376 records were identified using our search criteria. Duplicates were removed, leaving 1,312 records for title/abstract screening. After initial screening, 227 full-text articles were assessed for eligibility. Of these, 39 were excluded because they used a study

population with expected high rates of pathology and 28 were excluded because they did not incorporate radiography to confirm presence of M3 agenesis. A further 51 were excluded because the data presented in the text could not be reliably extracted as individual-level prevalence of agenesis (e.g., the studies reported total number of molars missing or reported a sub-sample of data that was not discussed within the text). Finally, 17 studies were excluded for using data previously reported in other studies. Our systematic review yielded 92 studies reporting a total of 100 effect sizes for frequency of M3 agenesis (Figure 1). Of these 92 studies, 32 were foreign language publications with English abstracts and/or summaries. The total number of subjects across all studies was 63,314, of which 14,516 exhibited agenesis of at least one third molar. In addition, effect sizes for the relative prevalence of female versus male (n=66 studies), and maxillary versus mandibular (n=15 studies) M3 agenesis were recorded for a subset of these studies.

Publication bias

One assumption of meta-analysis is that all outcomes are equally likely to be reported in publications. In other words, publications that find evidence for small and/or statistically non-significant effect sizes are as likely to be published as those finding large, statistically significant effect sizes (Møller and Jennions, 2001). As evidence suggests that results from the former type of study often go unreported (Rothstein et al., 2005), an important step in meta-analysis is to determine how missing data affects results.

We evaluated publication bias by assessing the asymmetry of effect sizes in funnel plots (Sterne et al., 2005). Using the trim and fill method (Duval, 2005), which estimates the number of studies missing from a meta-analysis due to suppression of extreme results on one side of a funnel plot, we found that the estimated number of missing studies with

small effect sizes was 0 for all models. We also assessed effect size asymmetry using a version of Egger's regression test, designed for random- and mixed-effects models (Sterne and Egger, 2005). For all five models, we did not detect a relationship between observed outcomes and the standard error of the estimate (p>0.05), indicating no support for funnel plot asymmetry, or potentially, publication bias. (Appendix Figure 1).

Random-effects analysis

We estimated the (logit-transformed) proportion of individuals with one or more missing M3s using a random effects logistic regression model. Across all 100 effect sizes, the mean rate of M3 agenesis was 22.63% (95%CI: 20.64%-24.76%; Figure 2). There was, however, considerable variation in agenesis frequency among outcomes. The standard deviation of effect sizes was 9.97%, while the estimates ranged from 5.32% in a Ugandan population (Chagula, 1960) to 56.0% in a South Indian cohort (Ren and Kumar, 2014; Figure 2). We therefore sought to characterize how much of this variability was due to heterogeneity, rather than sampling error. An I^2 index estimate of 97.14% ($LRT_{[99]}$=4227, p<0 .0001) indicates that most among-study variation was attributable to heterogeneity (Appendix Table 1). This suggests that omitted study-level predictors may explain some of the variation in M3 agenesis frequency.

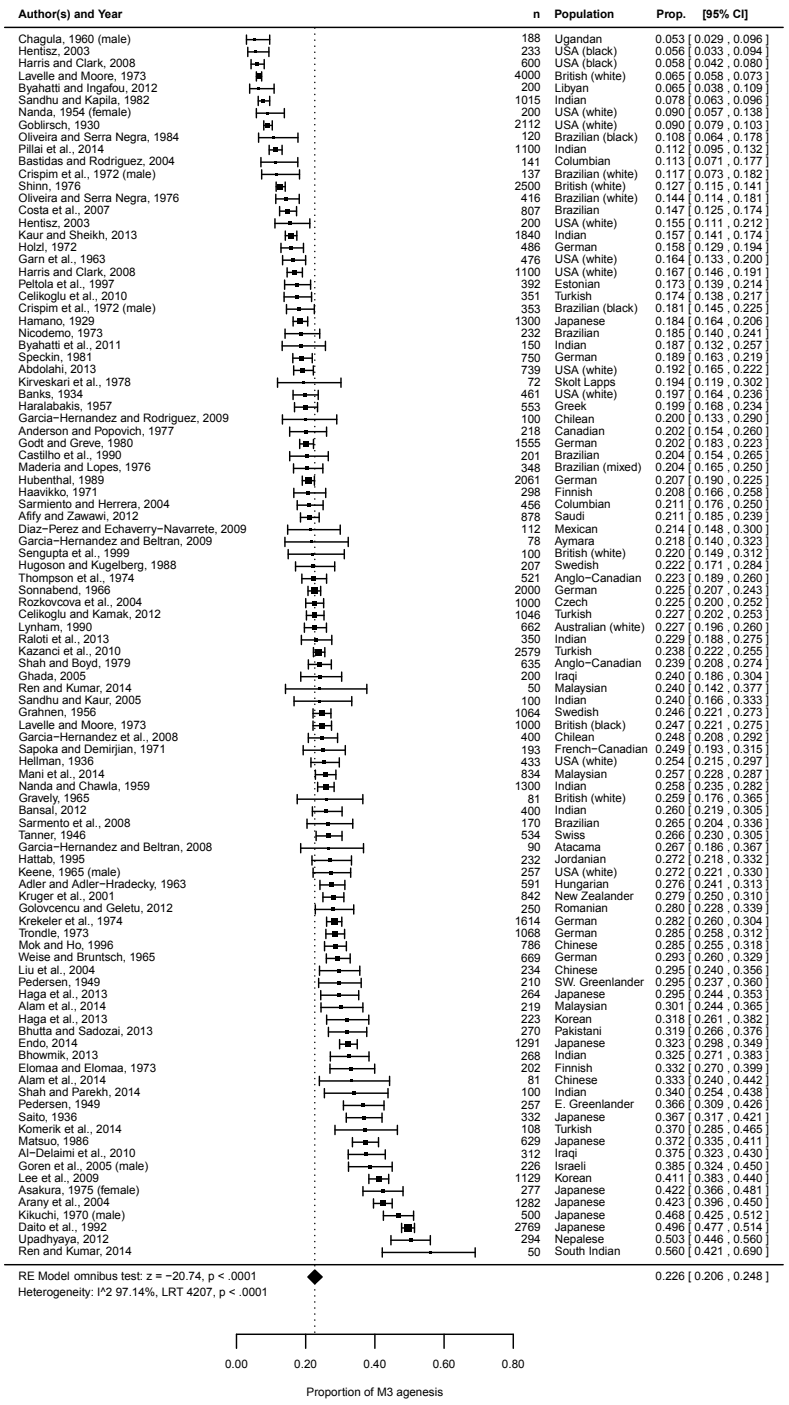


Figure 2: Forest plot of the proportion of individuals with agenesis of at least one third molar (92 studies; 100 effect sizes). The vertical dotted line indicates the (inverse-variance weighted) average proportion while the width of the black filled diamond denotes its 95%CI. Solid squares for individual studies are scaled by the influence that study has on the average proportion, while error bars are 95% CIs. Sample provenience and size are given for each study. Analysis was performed on logit-transformed proportions, but means and 95%CIs are back-transformed for easier interpretation.

Mixed-effects (moderator) analysis

We tested whether this high level of heterogeneity could be partially explained by six moderator variables, using mixed-effects logistic regression models. Four of the six moderators were potential sources of bias: neither 'study sample size' ($F_{[1, 98]}$=2.45, p=0.12), 'study sample type' ($F_{[8, 91]}$=1.44, p=0.19), 'study minimum subject age' ($F_{[1, 98]}$=0.47, p=0.50), nor 'study publication year' ($F_{[1, 98]}$=1.81, p=0.18) were found to be associated with frequency of M3 agenesis. The two remaining moderators were, however, found to explain substantial amounts of diversity in M3 agenesis rate.

Geographic provenience ('continent of origin') explained some of the heterogeneity in agenesis frequency (F-test for difference in mean agenesis frequency across all regions, $F_{[6, 93]}$=7.61, p< 0.0001). Such regional differences in M3 agenesis frequency have long been known in the archaeological record (Scott and Turner, 1988). We found that Asian populations (n=30, mean=29.71%, 95%CI: 26.1%-33.5%) had the highest rates of agenesis while African populations (n=2, mean=5.74%, 95%CI: 2.7%-11.8%) had the lowest rates (Figure 3). The African rate of M3 agenesis was significantly smaller than all other geographic regions (z>=3.08, p<=0.027), though it should be cautioned that this continent was severely undersampled. Furthermore, European (n=24, mean=21.60%, 95%CI: 18.4%-25.1%), S. American (n=15, mean=18.19%, 95%CI: 14.6%-22.4%), and N. American (n=18, mean=17.88%, 95%CI: 14.7%-21.5%) populations all expressed substantially lower frequencies of M3 agenesis than Asians (Appendix 1 Table 2).

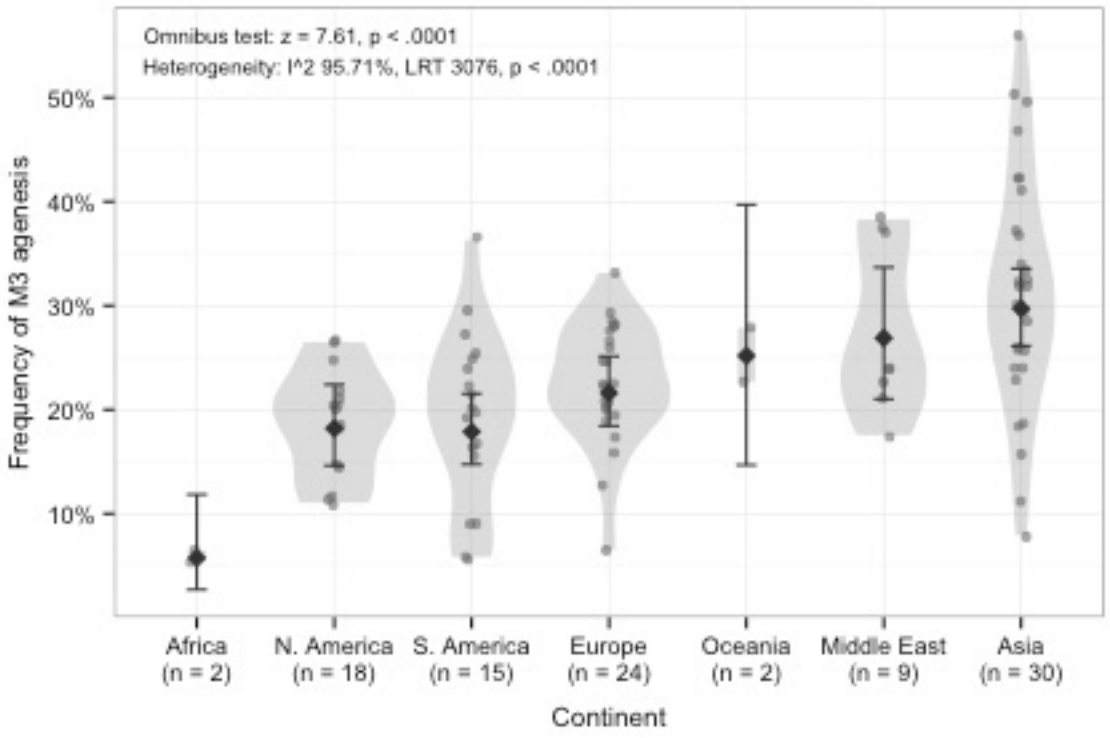


Figure 3: Bean plot of the proportion of individuals with agenesis of at least one third molar, partitioned by geographic provenience (92 studies, 100 effect sizes). Solid diamonds and error bars denote the (inverse-variance weighted) means and 95%CIs of proportions for each region. Dark-grey circles are individual studies, while light-grey polygons are kernel density estimates of the distribution of proportions within each region. Analysis was performed on logit-transformed proportions, but means and 95%CIs are back-transformed for easier interpretation.

The number of missing third molars also explained some of the heterogeneity in M3 agenesis frequency. In studies that reported these frequencies (n=50), individuals were significantly more likely to have one (mean=8.44%, 95%CI: 7.4%-9.6%) or two (mean=7.79%, 95%CI: 6.8%-8.9%) third molars missing than have three (mean=2.53%, 95%CI: 2.2%-3.0%) or four (mean=3.42%, 95%CI: 2.9%-4.0%) third molars exhibit agenesis (Figure 4).

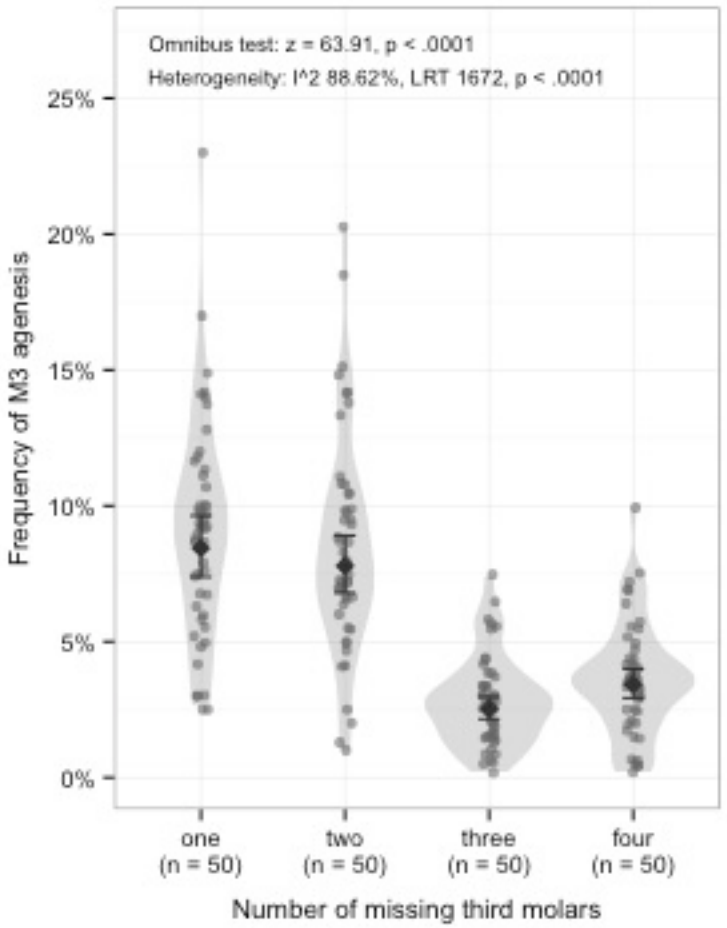


Figure 4: Bean plot of the proportion of individuals with agenesis of at least one third molar, partitioned by number of missing molars (48 studies; 50 effect sizes). Solid diamonds and error bars denote the (inverse-variance weighted) means and 95%CIs of the proportions for each region. Dark-grey circles are individual studies, while light-grey polygons are kernel density estimates of the distribution of proportions within each category. Analysis was performed on logit-transformed proportions, but means and 95%CIs are back-transformed for easier interpretation.

Sex and jaw effects of M3 agenesis

Across studies that reported effect sizes for both sexes (n=66), the odds of females exhibiting agenesis of at least one molar were 14.02% higher than males (95%CI: 5.38%-23.35%, p=0.0014; Figure 5). In studies presenting separate outcomes for both maxillary and mandibular M3 agenesis (n=15) we found the odds of agenesis of at least one M3 to be

35.97% higher for the maxilla than the mandible (95%CI: 16.53%-58.66%, *p*=0.0008; Figure 6).

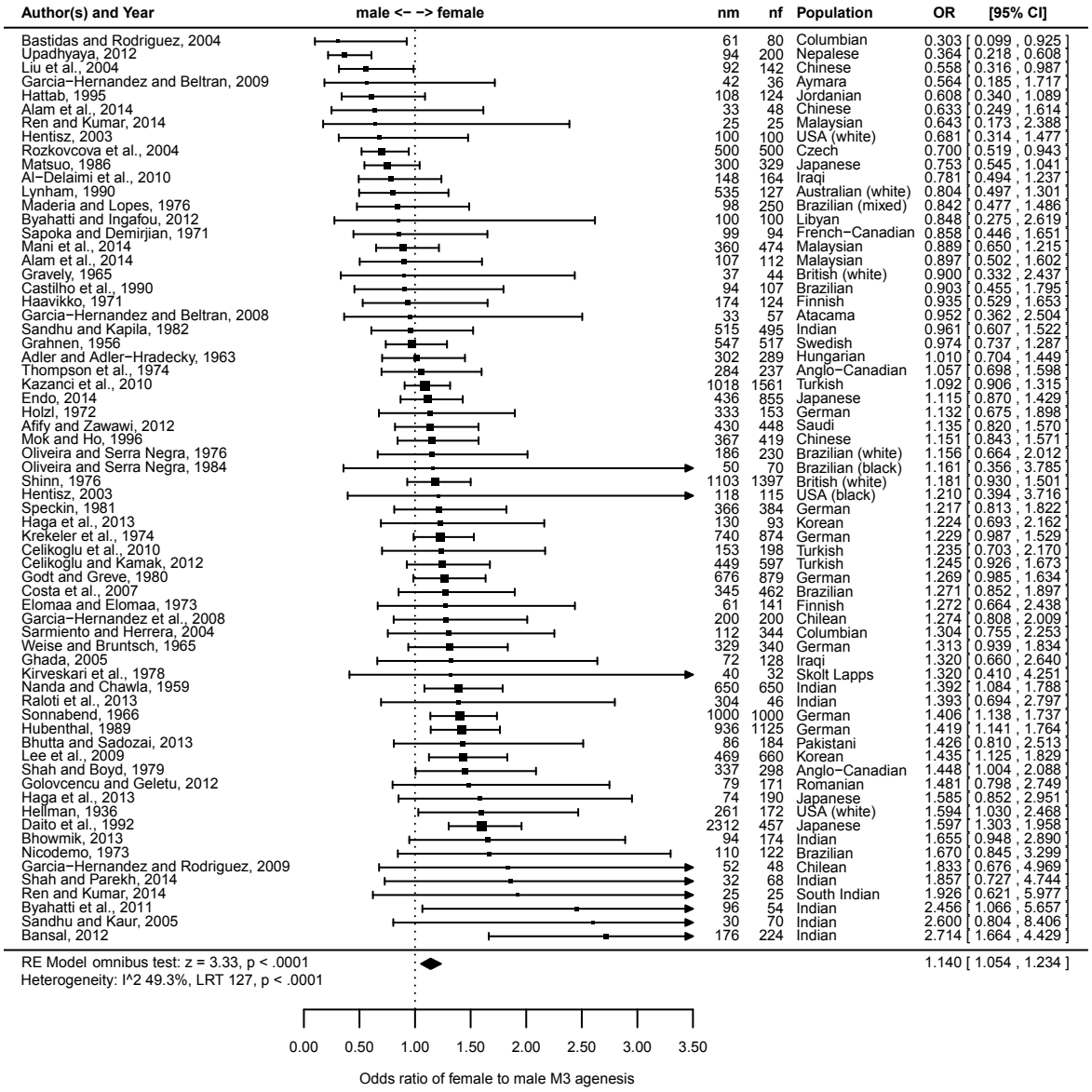


Figure 5: Forest plot of the odds ratio of agenesis of at least one third molar in females versus males (62 studies; 66 effect sizes). The vertical dotted line at 1 indicates unity in the ratio of the odds. Positive values indicate greater female odds of agenesis and negative values greater male odds. The position and width of the black filled diamond denotes the mean and 95%CI of the (inverse-variance weighted) average odds-ratio. Solid squares for individual studies are scaled by the influence that study has on the average proportion, while error bars are 95% CIs. Sample provenience and size are given for each study and sex ('nm' = male, 'nf' = female). Analysis was performed using a logit link function, but means and 95%CIs are exponentiated to odds-ratios for easier interpretation.

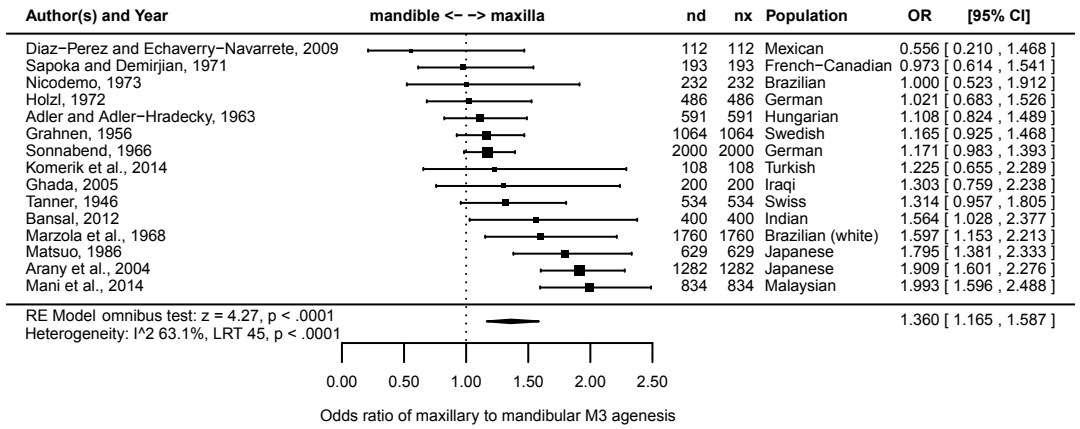


Figure 6: Forest plot of the odds ratio of agenesis of at least one third molar in the maxilla versus the mandible (15 studies and effect sizes). The vertical dotted line at 1 indicates unity in the ratio of the odds. Positive values indicate greater maxillary odds of agenesis and negative values greater mandibular odds. The position and width of the black filled diamond denotes the mean and 95%CI of the (inverse-variance weighted) average odds-ratio. Solid squares for individual studies are scaled by the influence that study has on the average proportion, while error bars are 95% CIs. Provenience and sample size are given for each study and jaw ('nd' = mandible, 'nx' = maxilla). Analysis was performed using a logit link function, but means and 95%CIs are exponentiated to odds-ratios for easier interpretation.

DISCUSSION

The prevalence of third molar agenesis, particularly whether a difference exists among sexes, between upper and lower jaws, or among the number of molars missing, has been debated in the literature for over 100 years (e.g., Sergi, 1914). The contributions of environment and genetics to third molar agenesis are not yet well understood. Some mutations have been shown to cause agenesis, but there are currently no known mutations that cause agenesis without other symptoms. While studies have long-suggested a genetic component to agenesis (Garn and Lewis, 1962; Shimizu 2013), environmental disturbances occurring before the third molar initiates have also been shown to produce this pathology (Swee, 2013). Similarly, the relationship between third molar agenesis and impaction remains unexplored. While many researchers have argued that agenesis and impaction are

caused by similar underlying phenomena (e.g., Raloti, 2013), others have found evidence to the contrary (e.g., Bermudez de Castro, 1989).

This meta-analysis was an attempt to use an extensive collection of published studies, firstly to characterize the average prevalence of M3 agenesis, then to estimate the degree of heterogeneity among study outcomes and assess if certain predictors could account for this. To our knowledge, this is the first meta-analysis on the prevalence of third molar agenesis, though similar studies have been conducted on the absence of other teeth (e.g., Mattheeuws et al., 2004; Polder et al., 2004).

Main findings

We found an average worldwide rate of third molar agenesis of 22.63% (95%CI: 20.64%-24.76%; Figure 2). This result is substantially higher than other meta-analyses of missing teeth (e.g., Mattheeuws et al., 2004; Polder et al., 2004), which should be expected given previous studies ranking agenesis in third molars as more common than in any other tooth (Garn et al., 1963; Vastardis, 2000). Frequencies of agenesis of one or more third molars ranged from 5.3% to 56.0%, across all studies. Despite this broad range, no single study appears as an outlier. Instead, as evidenced by the I^2 index of heterogeneity, our data contains much among-study variance. This is perhaps not unexpected, given the high worldwide variation in agenesis previously found in other studies (Hillson, 2006; Lukacs and Pal, 2013). However, it is important to assess whether variation among study outcomes is the result of bias (differences in methods or artifacts of study design) or biological diversity. In our study, none of the four artifactual moderators tested ('study sample size', 'study sample type', 'study minimum subject age', 'study publication year') were shown to have a significant effect on the frequency of M3 agenesis. Thus, much of the

heterogeneity seen in M3 agenesis rate can be attributed to genetic or environmental variation inherent among populations and between individuals with differing numbers of missing third molars.

Subgroup analyses

Sex

Subgroup analyses were conducted to assess the influence of sex, population, molar location and number of missing molars on prevalence of M3 agenesis. The existence of sex differences in agenesis rate has been a frequent source of debate. Although many previous studies have found either no significant difference between the rates of male and female agenesis (e.g., Alam et al., 2014) or male agenesis higher than female agenesis, our study suggests that females are on average 14% more likely to have missing third molars (Figure 5). Assessing the cause of higher rates of third molar agenesis among females is difficult. While this could possibly be explained by the smaller, more gracile jaws of females leading to agenesis, there is mixed evidence that individuals and populations with smaller jaws show higher rates of agenesis (Kajii et al., 2014; but see Wisth et al., 1974; Bermudez de Castro et al., 1989). Furthermore, many of these studies have not accounted for differences between the size of teeth between males and females, which may negate any effect from jaw size (see discussion in John, 2012). Studies of agenesis rates in other teeth have found an even higher discrepancy between males and females (e.g., female relative risk 1.37 times higher [95%CI: 1.28-1.45] in Polder et al., 2004), perhaps indicating different underlying causality between agenesis of the third molar and more generalized hypodontia.

Population

Differences in the rate of agenesis, along with other qualitative dental traits, are known to exist across populations. However, there are few studies that have systematically documented differences of third molar agenesis across many modern (i.e., non-archaeological) populations. In this study we found expected differences across modern populations in rates of agenesis, with Asian populations having the highest frequencies and African populations having the lowest frequencies (Figure 3). This suggests that the genetic mechanism or selective regime behind agenesis may differ across populations.

Molar Number

A subgroup analysis of the number of missing third molars revealed a few surprising results. We expected one missing molar to be the most common condition, followed by two, three and then four missing molars, consistent with other studies (e.g. Banks, 1934; Nanda, 1954). However, we found it was much more likely for individuals to have three or four molars missing than to have one or two molars missing (Figure 4). This can likely be explained by the high occurrence of bilateral agenesis in patients with missing third molars (much higher than occurrence of bilaterality in other teeth: Celikoglu et al., 2010; Bansal et al., 2012). While limited sample size precluded testing between unilateral and bilateral agenesis, these results provide further support for different underlying causes of third molar agenesis and generalized hypodontia.

Jaw

We found a higher rate of agenesis in maxillary (mean=18.97%) than in mandibular (mean=15.25%) third molars (OR 1.36, 95%CI: 1.17-1.59; Figure 6). All but one study found the odds ratio of maxillary to mandibular agenesis to be equal to or above 1 (i.e.,

more maxillary agenesis). The study finding a higher rate of mandibular agenesis (Diaz–Perez and Echaverry–Navarrete, 2009) had the second smallest sample size (n=112), and only 7 maxillae and 12 mandibles showed agenesis in the study. Thus, it is likely that our finding is a robust outcome.

Limitations

Although we used a rigorous search criteria, consistent with PRISMA guidelines and spanning multiple databases, it is possible that some gray literature was not included in our sample (McCauley et al., 2000; Hopewell et al., 2005). This is a particular concern for this analysis given the volume of studies published on third molar agenesis and the relative ease of conducting these studies.

Given the ethical concerns with unnecessary radiography, observational studies that rely on radiographs, such as those reporting M3 agenesis frequencies, are not based on truly random samples. Some degree of selection bias is therefore unavoidable when conducting such studies. Even 'random' samples of dental patients are subject to selection bias, as people that seek dental examination may be systematically different from those that do not. While we excluded obvious convenience samples and studies that included individuals with craniofacial syndromes, we used a few studies where details of the inclusion criteria were not fully described. It is unclear whether selection bias would systematically increase or decrease reported frequencies of M3 agenesis, or whether any effect on frequency would be more stochastic in nature.

For subgroup analysis, one major limitation of our study is the under-sampling of certain regions of the world, particularly Africa and Oceania. This may be worrying given the relatively low rates of M3 agenesis found in these populations. Without better

sampling of these regions, it is difficult to say whether the patterns of agenesis found in these study are applicable worldwide. Given the existing large sample size of third molar agenesis studies in many populations, further work should focus on characterizing the prevalence of agenesis in understudied populations.

CONCLUSION

Understanding the prevalence of M3 agenesis is the first step to understanding the relationship between congenitally absent and impacted teeth within populations, family lineages and individuals. Our systematic review and meta-analysis demonstrate that there is an average worldwide rate of M3 agenesis of 22.63% (95%CI: 20.64%-24.76%; Figure 2), but this rate differs across studies and is driven by biological variables. Subgroup analyses showed that females have a slightly higher rate of agenesis than males across all populations, and that modern population rates of agenesis vary similarly to the rates shown by archaeological studies. Third molar agenesis is much more likely in the maxilla than the mandible, and it is most common to have one or two teeth missing and least common to have three teeth missing. This information is expected to be of use not only to clinicians and patients but also to policy makers, given the implications for third molar extraction protocols.

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Chapter 3: Morphological and Demographic Predictors of Third Molar Impaction: A Systematic Review and Meta-analysis.

ABSTRACT

Our meta-analysis is an attempt to synthesize the abundant existing literature on third molar impaction frequencies worldwide. A total of 7,936 records were originally identified, then narrowed down to 864 for title/abstract screening. Based on our inclusion and exclusion criteria, we selected 49 studies, containing 83,484 subjects, for systematic review and meta-regression. The worldwide rate of impaction was found to be 24.40% (95%CI: 18.97%-30.80%), though the estimates ranged from 3.08% to 68.60%. Our subgroup analyses revealed that mandibular impaction was 57.58% more likely than maxillary impaction, while we did not detect any difference in impaction frequency between males and females. In addition, we found that mesioangular impaction was most common, followed by vertical impaction, with distoangular and horizontal impaction less frequent. Further, we found that having impaction of one or two third molars was most common, while impaction of three or four third molars was least common. Finally, we found small differences among impaction frequency depending on geographic region. Given the rich debate surrounding third molar treatment policy, understanding demographic and morphological differences in impaction rates is an important first step in assessing appropriate treatment protocols.

INTRODUCTION

In this study we aim to assess the worldwide prevalence of third molar impaction and the demographic and morphological factors that increase susceptibility to this pathology. Prophylactic treatment of third molars (M3s) remains a contentious topic

within the dental community, with some practitioners arguing that early treatment is necessary to avoid complications from later removal (Marciani 2012**)** and others arguing that treatment of asymptomatic teeth exposes patients to unnecessary risk (Venta 2012**).** As a result of this debate, the last decade has seen many changes to best practice policies across the world (e.g., NICE guidelines in the UK; Renton 2012**).** Despite a rich literature on side effects, patient complications, and best surgical practices to inform this debate, information elucidating the factors most likely to give rise to impaction remains undescribed.

At the most fundamental level, there is no consistent estimate for the worldwide frequency of M3 impaction, with current by-population estimates ranging from 3 to 57% (Olasoji and Odusanya 2000; Hashemipour et al. 2013). Many of the classic studies cited for comparative impaction frequencies (e.g., Mead 1930; Montelius 1933) used methods that may over- or under-estimate the population rates (e.g., no radiography to confirm impaction, no exclusion of juveniles, a conflation of impaction with failure of eruption), and should thus be treated with skepticism. These disparate estimates also likely reflect a high degree of heterogeneity among populations, making the characterization of factors driving variance vital for assessing individual risk of developing impaction. Currently, there are inconsistent reports on whether M3 impaction differs by sex (Hellman 1938; Shah 1978; Hattab 1995), whether prevalence is higher in the maxilla or mandible (Stermer Beyer-Olsen et al. 1989; Quek et al. 2003), how impaction rates change by age (Pogrel 2012), and which types of impaction are most frequently seen (e.g., Eliasson et al. 1989; Chu et al. 2003; Al-Anquidi et al. 2014).

Finally, understanding population variance in M3 impaction frequency may help elucidate the causes of impaction worldwide. Many non-metric traits, including third molar agenesis, vary predictably across populations (e.g., Hanihara 2008; Carter and Worthington 2015) and within families (Garn et al. 1963), leading many researchers to think they are patterned genetically. Though there is some evidence to suggest impaction has a high heritability component (Łangowska-Adamczyk and Kamanska 2001), a multitude of studies suggest that environmental factors, most notably diet, contribute much more to the trait's expression (Olasoji and Odusanya 2000; Reddy 2012). The mechanisms by which impaction develops during ontogeny also remain unclear. Most researchers agree that M3 impaction develops as a result of space constraints within the jaw, but disagree on whether the primary mechanism is corpus breadth (Krecioch 2012), ramus angle (Bishara 1999), the timing of mandibular growth relative to eruption, or a combination of these and other factors (Bjork et al. 1956; Kaya et al. 2010). With this meta-analysis we aim to gain further understanding of the causes of third molar impaction by: 1) synthesizing and evaluating previous studies of impaction, 2) characterizing the among-study variation in impaction prevalence, and 3) making comparisons between third molar impaction and agenesis prevalence.

MATERIALS AND METHODS

Data sources and search criteria

The guidelines from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement were followed where relevant (Moher et al. 2009). To reduce

selection bias we sought to identify, appraise, and synthesize all relevant studies (Uman 2011). In June 2015, one of us (KC) used online publication search engines (Google Scholar, PubMed and Thomson Reuters ISI Web of Science) to extensively search the literature using keyword combinations (full electronic search strategy provided in Figure 7). No limits were placed on language or year of publication. KC then conducted further manual searches of the literature using the bibliographies of papers found in the online search.

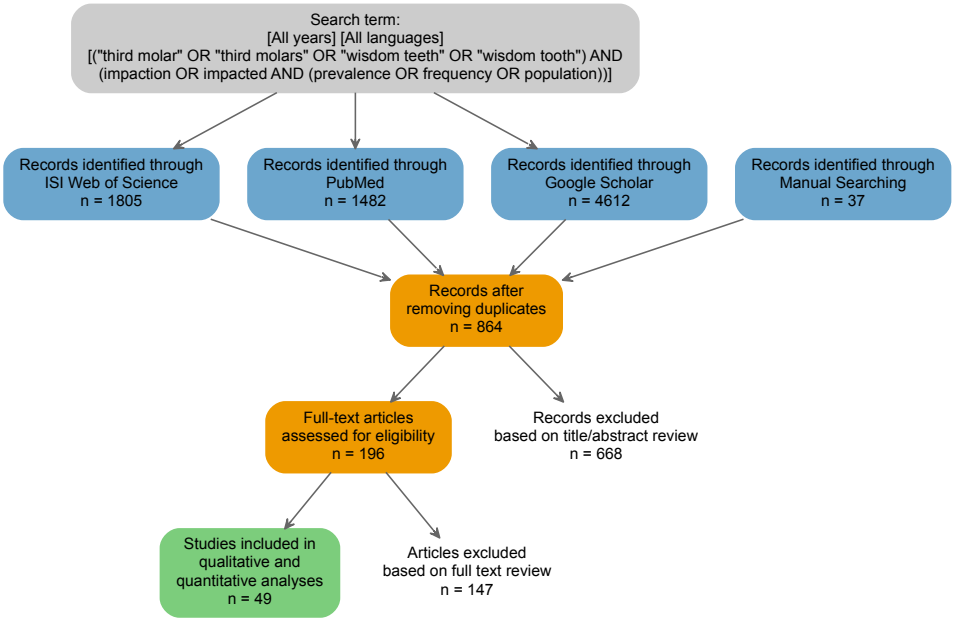


Figure 7: Flowchart illustrating the search strategy and article selection process.

Inclusion and exclusion criteria

Inclusion and exclusion criteria were compiled to insure methodological consistency across all studies being included in the meta-analysis and to address potential study-level bias.

The eligibility criteria for inclusion were:

- Presence of an English abstract and/or summary and/or manuscript, or presence of one of the above in a language known to one of the authors.
- Diagnosis of M3 impaction based on radiographic examination.
- Minimum age of subjects at least 17 years, or data presented separately for different ages.
- A stated definition of impaction that distinguished this pathology from failure to erupt.

The exclusion criteria were:

- A second study using the same subjects.
- A second effect size estimate relying on the same subjects within a single study.
- Studies that included individuals with prior extraction of any permanent tooth in effect size estimates.
- Reporting of M3 impaction frequency conflated with frequencies of impaction in other teeth.
- Reporting of M3 impaction frequency only as a percentage, without information about sample size.
- Reporting of M3 impaction frequency, but failure to distinguish molar impaction from lack of eruption.
- Study limited to patient group with craniofacial syndromes, developmental disorders, or who presented with any kind of dental pain.

- Sample obtained from patients presenting for third molar surgery (though some studies were included in some moderator analyses)

Outcome measures and explanatory variables

Outcome measures of interest included: 1) the proportion of individuals with impaction of at least one third molar, 2) the odds-ratio (OR) of M3 impaction rate for a) mandible versus maxilla and b) male versus female, and 3) the proportion of impacted third molars exhibiting various angulations of impaction. We followed Winter's (1926) classification of angle of impaction into "horizontal", "mesioangular", "vertical", and "distoangular" types. Proportions were logit-transformed for analysis and subsequently back-transformed in figures. Mandibular and maxillary impaction rates were calculated as the sum of unilateral and bilateral rates. Data were extracted from figures, tables, or text; sometimes calculations were performed.

Predictors of M3 impaction rate included: 1) study sample size, 2) study sample type, 3) study minimum subject age, 4) study publication year, 5) study population's continent of origin, 6) number of impacted third molars, and, 7) type of third molar impaction. The variable 'study sample type' described the different kinds of samples used by researchers (e.g., orthodontic patients, university students, military personnel etc.). Included studies, together with their outcome and explanatory variables are reported in the Appendix.

Consideration of bias

A fundamental assumption of meta-analysis is that studies that find evidence for small and/or statistically non-significant effect sizes are as likely to be published as those finding large, statistically significant effect sizes (Møller and Jennions 2001). However, evidence suggests that results from the former type of study often go unreported (Dickersin 2005; Rothstein et al. 2005). It is therefore important when conducting meta-analysis to determine how results are affected by data missing due to publication bias. We evaluated such publication bias in two ways: 1) using a version of Egger's regression test designed for random- and mixed-effects models (Sterne and Egger 2005), and, 2) assessing the asymmetry of effect sizes in funnel plots (Sterne et al. 2005) using the trim and fill method (Duval 2005), which estimates the number of studies missing from a meta-analysis due to suppression of extreme results on one side of a funnel plot.

One further assumption of meta-analysis is that study outcomes are independent. This assumption can be violated in two ways: 1) if multiple effect sizes rely on the same individuals; 2) if two or more effect sizes are derived from the same study or research group (Stevens and Taylor 2009). We dealt with the first issue, dependence at the sampling level (pseudoreplication), by excluding any effect sizes that used the same individuals. We addressed the second violation, dependence at the hierarchical level, by including study-level random-effects in analyses that included multiple effect sizes from a single study (Konstantopoulos 2011).

Data analysis

Random- and mixed-effects generalized linear models were used to estimate effect sizes and their 95% confidence intervals (CIs). We chose random-effects over fixed-effects so

that our results would generalize to the population of studies from which we sampled (Normand 1999). For individual group proportions we used mixed-effects logistic regression models with a binomial-normal data distribution (Hamza et al. 2008). For two-group analyses (i.e., outcomes partitioned by sex or jaw) we used a two-by-two contingency table format, and the corresponding model was a mixed-effects conditional logistic regression model with a non-central hypergeometric distribution for the data (Stijnen et al. 2010).

Heterogeneity (among-study variance in effect size additional to that attributable to sampling error) among effect sizes was estimated using the I^2 index, which describes the percentage of total variation among effect sizes that is due to heterogeneity (Higgins and Thompson 2002; Higgins et al. 2003). We used a likelihood ratio test (LRT) to assess whether the I^2 index estimate was larger than zero. To investigate possible explanators of heterogeneity in effect-size estimates we conducted meta-regression analyses using a total of six moderator variables. This involved the assessment of whether heterogeneity could be explained by either bias (artifactual variation in study design) or diversity (biological variation in participants and outcomes).

Effect sizes with 95% CIs for individual studies and omnibus estimates were visualized using forest plots. Omnibus estimates for each analysis represent inverse-variance weighted averages. Multiple comparisons of mean impaction frequency have *p*-values adjusted using the sequential Bonferroni method (Holm 1979). All analyses were conducted using the 'metafor' package v. 1.9-6 (Viechtbauer 2010) in the R statistical language v. 3.1.3 (R Core Team 2015).

RESULTS

Study selection

In an attempt to accurately assess the rate of impaction in the third molar, the last tooth to erupt and calcify during development, we only included studies that sampled individuals of age 17 years and over (Fielding et al. 1981). We also sought to eliminate studies that used populations previously shown to have abnormally high rates of impaction, such as those with craniofacial disorders (Shapira et al. 2000), though populations pooled from people presenting with impacted molars were used for comparisons between maxillary and mandible and most frequently seen form of impaction. In total, 7,936 records were identified using the search criteria across three databases and manual searching. After duplicates were removed (leaving 864 records), one author (KC) assessed the titles and abstracts for relevance. Of the 196 relevant studies, 147 were excluded. Reasons for exclusion included: no new primary data on impaction frequency reported (n=46), not excluding individuals with prior extraction (n=21), reporting impaction of third molars and other teeth together (n=16), unclear minimum age for inclusion (n=34) or minimum age below 17 (n=23), and no use of radiography to assess impaction (n=7). Our systematic review found 49 studies, which reported 53 effect sizes. There were 7 foreign language publications with English abstracts and/or summaries. Across all studies, the total number of subjects was 83,484.

Publication bias

We did not detect a relationship between observed effect sizes and their standard errors (p>0.05) for any model using Egger's regression test. In addition, using the trim and fill method we found that the estimated number of missing studies with small effect sizes was 0 for the overall random effects model and dental arch model, and 2 for the model testing sex effects. This indicates lack of support for funnel plot asymmetry and publication bias (Appendix Figure 1).

Random-effects analysis

We estimated the proportion of individuals with one or more impacted M3s using random effects logistic regression on a sample of 32 studies (33 effect sizes). The average rate of M3 impaction was 24.40% (95%CI: 18.97%-30.80%; Figure 8). Impaction frequency varied greatly among studies, with a standard deviation of 16.20%, a minimum of 3.08% in a rural Nigerian cohort (Olasoji and Odusanya 2000) and maximum of 68.60% in a Singaporean Chinese population (Quek et al. 2003). Almost all among-study variation was attributable to heterogeneity (I^2: 99.52%, $LRT_{[32]}$=5642, p<0 .0001; Appendix Table 1). This suggested that some of the variation in M3 impaction frequency may be explained by including study-level predictors in the model.

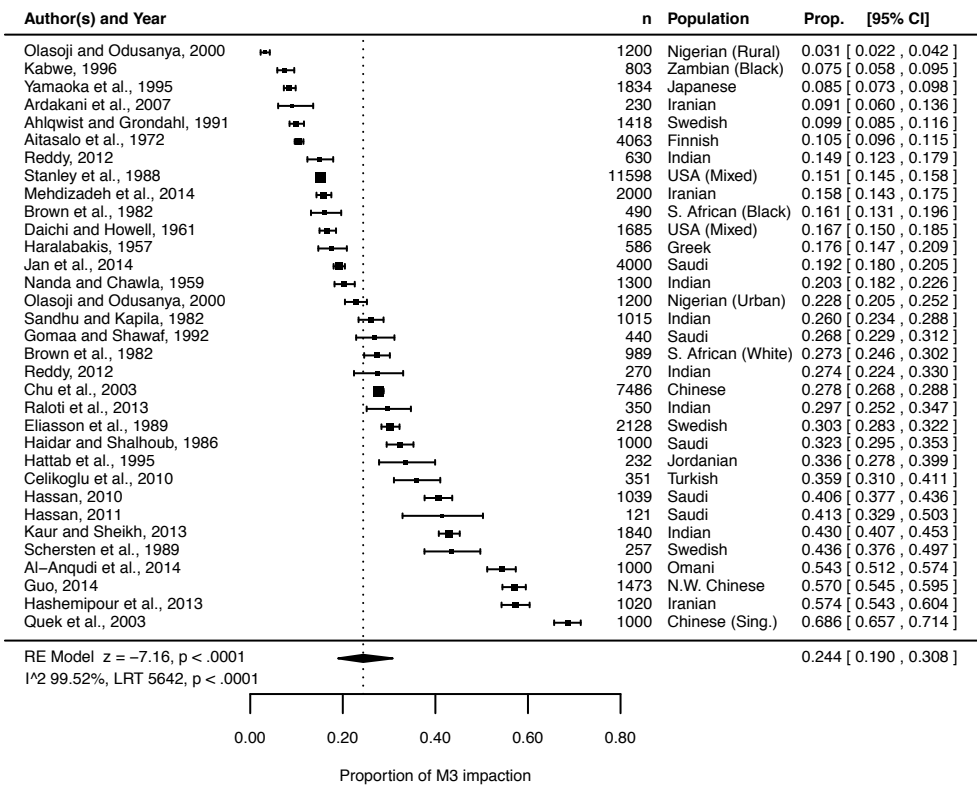


Figure 8: Forest plot of the proportion of individuals with impaction of at least one third molar (31 studies, 33 effect sizes). Vertical dotted line indicates the (inverse-variance weighted) average proportion while width of the black filled diamond denotes its 95%CI. Solid squares for individual studies are scaled by the influence that study has on the average proportion, while error bars are 95% CIs. Sample provenience and size are given for each study. Analysis was performed on logit-transformed proportions, but means and 95%CIs are back-transformed.

Mixed-effects (moderator) analysis

To determine possible explanators of this high level of heterogeneity we included six moderator variables in separate mixed-effects logistic regression models. Four of the six moderators were potential sources of bias: neither study sample size ($F_{[1, 31]}$=0.89, p=0.35), study sample type ($F_{[3, 29]}$=0.83, p=0.49), study minimum subject age ($F_{[1, 31]}$=2.03, p=0.16), nor study publication year ($F_{[1, 31]}$=3.89, p=0.058) were found to be associated with

frequency of M3 impaction. The two remaining moderators were, however, found to explain substantial amounts of diversity in M3 impaction rate.

Effect of geographic provenience on M3 impaction rate

Geographic provenience (study continent of origin) explained a small portion of the heterogeneity in M3 impaction frequency (F-test for difference in mean impaction frequency across all regions, $F_{[4, 28]}$=2.72, p=0.049). We found that Middle Eastern populations (n=10, mean=33.33%, 95%CI: 23.1%-45.4%) had the highest rates of impaction while African populations (n=5, mean=12.38%, 95%CI: 6.4%-22.5%) had the lowest rates (Figure 9). The Middle Eastern rate of M3 impaction was significantly larger than that in Africa (z=2.93, p=0.034; Appendix Table 2), though both samples were small. Asian (n=11, mean=28.33%, 95%CI: 19.6%-39.1%), European (n=5, mean=19.76%, 95%CI: 10.7%-33.6%) and North American (n=2, mean=15.88%, 95%CI: 5.7%-36.9%) populations all exhibited intermediate rates of M3 impaction.

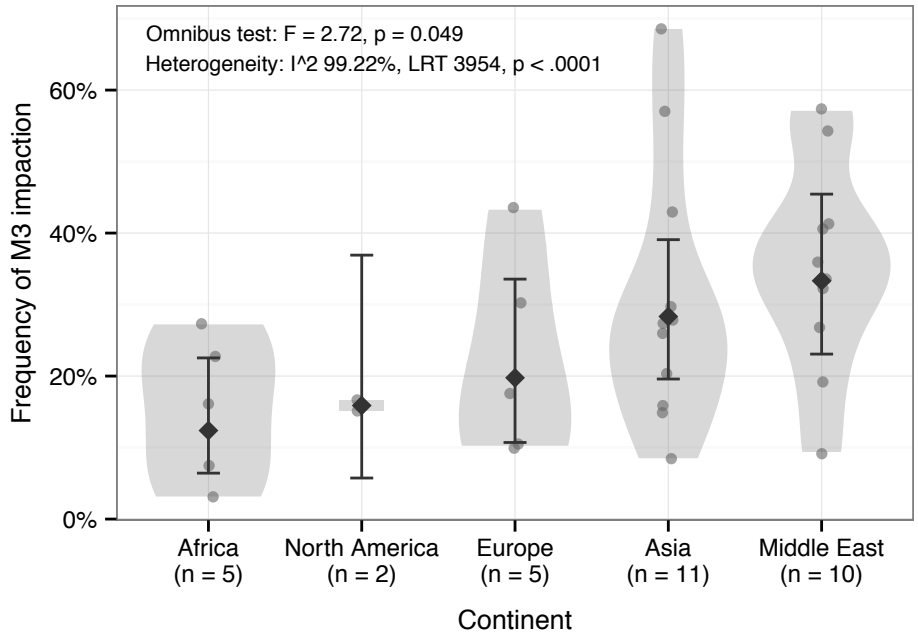


Figure 9: Bean plot of the proportion of individuals with impaction of at least one third molar, partitioned by geographic provenience (31 studies, 33 effect sizes). Solid diamonds and error bars denote the (inverse-variance weighted) means and 95%CIs of proportions for each region. Dark-grey circles are individual studies, while light-grey polygons are kernel density estimates of the distribution of proportions within each region. Analysis was performed on logit-transformed proportions, but means and 95%CIs are back-transformed.

Angle of M3 impactions

The angulation of third molar impaction accounted for some of the heterogeneity in M3 impaction frequency. In the 31 studies (32 effect sizes) that reported these frequencies, third molars were significantly more likely to exhibit mesioangular impaction (mean=41.17%, 95%CI: 33.8%-49.0%) than any other type. Vertical impaction of M3s (mean=25.55%, 95%CI: 20.0%-32.0%) occurred less often, but with significantly greater prevalence than either distoangular (mean=12.17%, 95%CI: 9.1%-16.0%) or horizontal (mean=11.06%, 95%CI: 8.3%-14.6%) impaction (Figure 10a; Appendix Table 3).

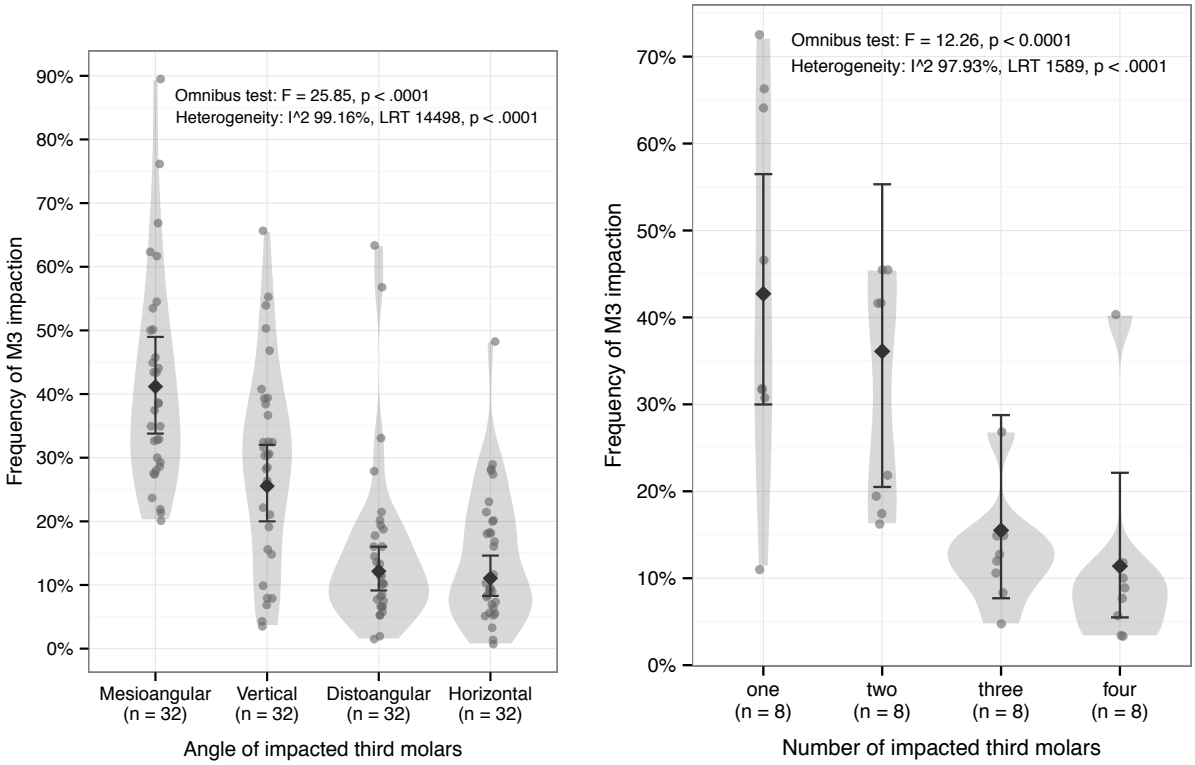


Figure 10a: Bean plot of the proportion of impacted third molars, partitioned by angulation of impaction (31 studies, 32 effect sizes). Solid diamonds and error bars denote the (inverse-variance weighted) means and 95%CIs of the proportions for each region. Dark-grey circles are individual studies, while light-grey polygons are kernel density estimates of the distribution of proportions within each category. Analysis was performed on logit-transformed proportions, but means and 95%CIs are back-transformed.

Figure 10b: Bean plot of the proportion of individuals with impaction of the third molar, partitioned by number of missing molars (8 studies). Solid diamonds and error bars denote the (inverse-variance weighted) means and 95%CIs of the proportions for each region. Dark-grey circles are individual studies, while light-grey polygons are kernel density estimates of the distribution of proportions within each category. Analysis was performed on logit-transformed proportions, but means and 95%CIs are back-transformed.

Number of M3 impactions

The number of impacted third molars also explained some of the heterogeneity in M3 impaction frequency. In studies that reported these frequencies (n=8), individuals were significantly more likely to have one (mean=42.71%, 95%CI: 30.0%-56.5%) or two (mean=29.64%, 95%CI: 19.5%-42.3%) third molars impacted than to have three (mean=12.04%, 95%CI: 7.2%-19.3%) or four (mean=8.74%, 95%CI: 5.2%-14.5%) third molars exhibit impaction (Figure 10b; Appendix Table 4).

Dental arch and sex effects of M3 impaction rate

In the 23 studies (24 effect sizes) presenting separate outcomes for both maxillary and mandibular M3 impaction we found the odds of M3 impaction to be 57.58% higher in the mandible than the maxilla (95%CI: 43.3%-68.3%, $p<0.0001$; Figure 11). Across studies that reported effect sizes for both sexes (n=14), we did not find evidence of a difference in the odds of females and males exhibiting impaction of at least one molar (mean: 18.62%, 95%CI: -4.9%-48.0%, $p=0.12$; Figure 6).

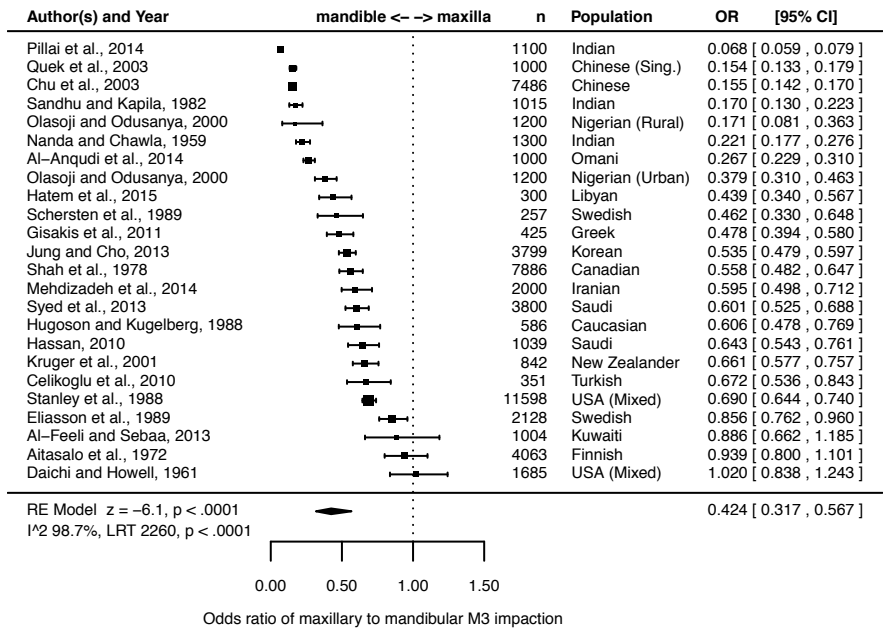


Figure 11: Forest plot of the odds ratio of impaction of at least one third molar in the maxilla versus the mandible (23 studies, 24 effect sizes). Vertical dotted line at 1 indicates unity in the ratio of the odds. Positive values indicate greater maxillary odds of impaction and negative values greater mandibular odds. The position and width of the black filled diamond denotes the mean and 95%CI of the (inverse-variance weighted) average odds-ratio. Solid squares for individual studies are scaled by the influence that study has on the average proportion, while error bars are 95% CIs. Sample provenience and size are given for each study. Analysis was performed using a logit link function, but means and 95%CIs are exponentiated to odds-ratios.

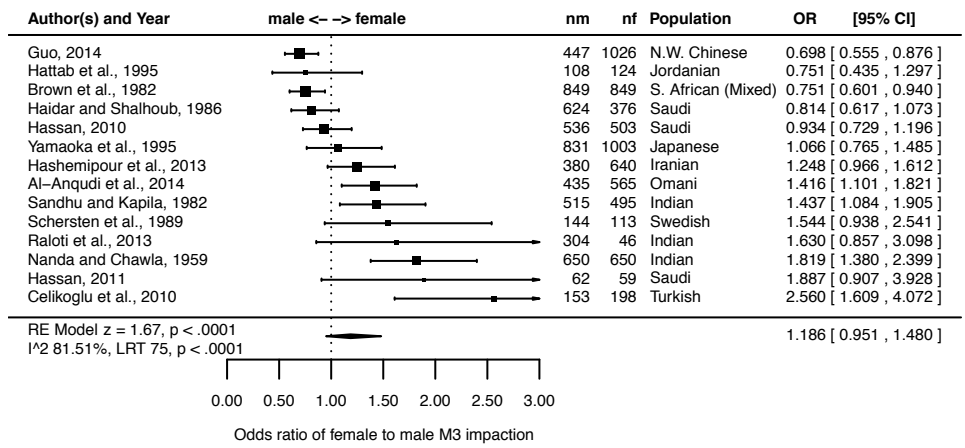


Figure 12: Forest plot of the odds ratio of impaction of at least one third molar in females versus males (14 studies). Vertical dotted line at 1 indicates unity in the ratio of the odds. Positive values indicate greater female odds of impaction and negative values greater male odds. The position and width of the black filled diamond denotes the mean and 95%CI of the (inverse-variance weighted) average odds-ratio. Solid squares for individual studies are scaled by the influence that study has on the average proportion, while error bars are 95% CIs. Sample provenience and size are given for each study and sex ('nm' = male, 'nf' = female). Analysis was performed using a logit link function, but means and 95%CIs are exponentiated to odds-ratios.

DISCUSSION

Third molar impaction is a common dental problem experienced worldwide, but currently neither the mechanisms causing this pathology nor the worldwide rate of occurrence are known. Furthermore, there are questions as to whether there are differences in impaction rate between the sexes, among populations, across different age groups, and across time. Describing the pattern of prevalence worldwide is a necessary first step for understanding the mechanisms causing impaction and the relationship between impaction and other third molar anomalies, such as agenesis.

Our goals in conducting this meta-analysis were to use the wealth of previously published studies, firstly to characterize the overall rate of M3 impaction, secondly to

explain among-study variation, and thirdly to compare our results with those predicting third molar agenesis prevalence. To our knowledge, this is the first meta-analysis on the prevalence of third molar impaction.

Main findings

We found an average worldwide rate of third molar impaction of 24.40% (95%CI: 18.97%-30.80%; Figure 2). This rate is lower than almost any other published study (e.g., ~50%, Henry and Morant 1936; 27%, Aitasalo 1972; 72%, Hugoson and Kugelberg 1988), though it is higher than the 16.7% suggested by Daichi and Howell (1961). It is also substantially lower than modern clinical writings predict for industrialized populations, or the percentage of individuals typically treated for third molar problems (**e.g. up to 53% Magraw et al., 2015).** The impaction rate is also slightly higher than our previous findings on the average worldwide rate of third molar agenesis (22.6%; Carter and Worthington 2015**)**. Frequencies of impaction of one or more third molars ranged from 3.08% to 68.60% across all studies, which, together with the high I^2 index of heterogeneity suggests that a high degree of among-study variability exists in impaction rate. Based on our assessment of moderator effects, this variability is mostly clinical rather than an artifact of studies using different methodologies. None of the four moderators that could explain statistical heterogeneity had a significant effect on the rates of M3 impaction (study sample size, study sample type, study minimum age, and study publication year). We excluded all studies with subjects below 17 years of age, given numerous studies suggesting that third molar impaction rate increases in populations until approximately age 30 (Yamaoka et al. 1995; Venta et al. 2001). While there was a slight increase in impaction rates over time

(study publication year), this trend was also non-significant. Impaction is generally thought to have risen since changes in food processing caused by industrialization (Varrela 1990), though our results suggests that M3 impaction rate has been relatively stable at least across the last three generations. Overall, we find little support for the impaction rate being close to 50% in industrialized populations or that impaction rate is significantly increasing. Given that most clinicians view wisdom teeth as "ticking time bombs" that will eventually become impacted if not removed, our analysis provides evidence that the majority of patients may not be at risk of impaction.

Subgroup analyses

Dental Arch and Molar Number

We found a higher rate of impaction in mandibular (mean=25.43%) than in maxillary (mean=14.16%) third molars (OR 0.424, 95%CI: 0.317-0.567; Figure 5). All but one study found the odds ratio of mandibular to maxillary impaction to be either below 1, or indistinguishable from 1 (i.e., more mandibular impaction). This is opposite the trend we reported for third molar agenesis, where the maxillary third molars are much more likely to be missing (Carter and Worthington 2015). Intriguingly, populations from Africa and Asia tend to show much greater variability in the rates of maxillary to mandibular

impaction than populations from North America, Europe, or the Middle East. Further research is needed to confirm the robustness of this trend.

Similarly, we found that one or two impacted third molars were more common than three or four impacted molars (Appendix Table 4). This is in agreement with many studies, though some found that four impacted molars was the most common expression pattern (e.g., Ma'aita 2000).

Angle of Impaction

Comparisons across Winter's original categories of impaction (mesioangular, distoangular, vertical, and horizontal) revealed that mesioangular impaction was significantly more prevalent than other forms of impaction. Vertical impaction was also significantly more prevalent than horizontal or distoangular impaction. This is in agreement with many previously published studies (e.g., Celikoglu 2010; Al-Anquidi et al. 2014, but see Byahatti and Ingafou 2012**),** including Winter's (1926) own work, though an overall percentage of 42% of impacted molars being mesioangularly orientated is at a slightly lower frequency than originally presented by Winter. Ontogenetically, third molars are unlikely to change in their angle of impaction (though they frequently change in their degree of impaction, a data category therefore not considered here). Therefore, knowledge of the most common angles of rotation likely to lead to impaction can aid clinicians in determining whether to adopt an early extraction protocol or wait to see if the molar will present with pathology in later adulthood.

Sex and Population

Surprisingly, neither sex nor population was found to greatly affect M3 impaction frequency. Given the relationship frequently found between jaw size and impaction frequency (Evensen and Ogaard 2007), females are thought to incur impaction with a higher rate than males. While nine of the 15 studies found female impaction rates to be higher, five studies found male rates relatively higher. Alternatively, though we did not have the sample size to test this with our own data, other studies have found that while males may have a higher prevalence of M3 impaction, females exhibit impaction in more third molars (Murtomaa et al. 2010), which may help explain some of the discrepancies.

This meta-analysis appears to be the first large cross-cultural study of third molar impaction rates using radiography, so comparisons between these results and other studies are difficult. While there were significant differences among populations in the rates of third molar impaction (Figure 3), only one pairwise comparison showed significant results (Middle East versus Africa; Appendix Table 2). Also of note is the high degree of variability in impaction rate within each geographic region studied. While this does not rule out a genetic component for impaction or factors causing impaction, it does suggest that environmental factors have a much greater role in determining the presence of M3 impaction than in many other dental non-metric traits. This is in agreement with several studies comparing rates of M3 impaction between rural and urban environments within the same geographic population (e.g., Olasoji and Odusanya 2000; Reddy 2012), most of which found much higher rates in urban environments.

Clinical procedures for third molar extraction typically involve deciding whether early intervention is necessary (e.g. Kandasamy et al., 2011). Our analysis helps highlight the demographic profile of individuals who are most at risk for impaction once they reach

adulthood. Knowing the risk factors for individuals to develop third molar impaction will aid in determining which clinical policy is best for each patient.

The relationship between third molar impaction and agenesis

One of the main purposes of this meta-analysis is to make comparisons between third molar impaction and our previous work on third molar agenesis. The mechanisms for both third molar anomalies are currently not well understood, and while many researchers suggest a similar underlying cause (Nanda, 1954; Kanazawa et al. 1987), the evidence for this is mixed at best (e.g., De Castro 1989; Rakhshan 2015). Although the overall rates of third molar impaction and agenesis are very similar, sub-group analysis reveals differences in the patterns of expression. Third molar agenesis is more common in the maxillary dentition while impaction was much more likely to be found in the mandibular dentition. While females had a higher frequency of agenesis, there was no sex difference found in impaction rate. Across populations, Africa had the lowest frequency of both impaction and agenesis. However, while there were clear significant differences among many of the populations for agenesis, there were few for impaction. The expression patterns of agenesis and impaction are similar in that having one or two molars missing or impacted is more common than three or four. Together, these patterns indicate that either third molar agenesis and impaction are two unrelated phenomenon with different developmental origins, or, given the different ontogenetic timing of the events, two related thresholds exists for determining impaction and agenesis.

Limitations

One major concern with this or any similar study is the lack of random sampling, which, while born out of the need to prevent unnecessary radiography, may still potentially create sampling bias. We were systematic in our exclusion of clear non-random samples, such as those from patients presenting with tooth pain or those with craniofacial syndromes, but used several studies where the selection criteria was not fully explained in the methods. It is plausible to think that our estimation of impaction frequency may be an overestimate, both because patients with dental problems are more likely to seek treatment, and because urban populations where impaction is higher are frequently more closely located to a dental care provider (Allison and Manski 2007). However, we feel that this study represents the best estimates of impaction possible with the available data.

For subgroup analysis of the angle of impaction, we excluded categories outside of Winter's initial classification (e.g., "buccolingual", "rotated", "transverse", "other") as there was no consistent usage or definition of these terms. Certain continents, particularly Africa, North America and Europe, were also under-sampled for this study (we note that the latter two continents had a wealth of publications that did not meet our inclusion criteria). However, given the high variability in impaction frequency found across all continents, it is likely that an increase in study number would not change our results.

CONCLUSION

Our systematic review and meta-analysis sought to assess the worldwide rate of third molar impaction and understand this prevalence across different morphological and demographic sub-groups. We demonstrated that the average worldwide rate of M3 impaction is 24.40% (95%CI: 18.97%-30.80%; Figure 2), but that effect sizes are highly

heterogeneous and driven by biological variables. Subgroup analyses showed no differences in M3 impaction rate between sexes, and only slight differences in frequency among geographic regions. Third molar impaction is much more likely in the mandible than the maxilla, and mesioangular impaction is the most frequently seen orientation. Understanding the distribution of third molar impaction frequencies is an important first step both for understanding the ultimate causes of impaction and for clinicians making decisions on treatment protocols.

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Chapter 4: Separate mechanisms drove the prevalence of wisdom tooth agenesis in archaic and modern human populations.

ABSTRACT

Humans are unique in having high frequencies of pathological third molars, including impacted molars that fail to erupt and agenesis, or missing, molars. Many researchers attribute an increased prevalence of third molar agenesis and impaction to highly processed modern diets. Three competing hypotheses exist to explain the evolution of third molar agenesis: 1) agenesis as the result of selection against impaction, 2) agenesis as developmental delay, and 3) the probable mutation effect. These hypotheses, however, remain untested. Here we test these hypotheses using data from four populations sampled before, during and after the transitions to agriculture and two populations before, during, and after the transition to industry. We found the selection against impaction hypothesis contributed to the rise in third molar agenesis at the end of the industrial transition, but impaction remained at such low frequencies during the agricultural transition that this mechanism is unlikely to have been a causative force. Furthermore, we found a negative relationship between dental arch space and third molar agenesis in the industrial transition, but a positive relationship between these two variables in the agricultural transition. Overall, these data suggest that two different mechanisms influenced the prevalence of human third molar agenesis: one operating since the time of *Homo erectus* and one with much more recent origins.

INTRODUCTION

Two major transitions in human evolutionary history, the adoption of agriculture and the beginnings of industrialization, brought about widespread changes in nutrition, demography,

and mobility. However, while there is evidence to suggest these dietary transitions had both positive and negative effects on human health (Larsen, 1995; Cohen, 2009) (Armelagos et al., 1991; Popkin, 1999, 2003; Cordain, 2005; Larsen, 2006; Lieberman, 2013), there have been few efforts to directly test the effects of evolutionary shifts on human dental anatomy. While changes in dental pathology during these time periods are well known (Scott, 1979; Larsen, 1995; Kaifu, 2000), understanding how the agricultural and industrial revolutions contributed to modern pathologies will help us gain insight into changes in developmental processes and the modern selective regime.

Third molars, commonly known as wisdom teeth, are highly polymorphic within modern humans, with roughly one-quarter of humans across the globe born without one or more of these teeth and a similar proportion of humans having one or more of these teeth impacted, here defined as present but failing to properly erupt into occlusion (Carter and Worthington, 2015, 2016). In other individuals, third molars may be present, but are often reduced in size or morphological complexity (Bermudez de Castro, 1989; Gomez-Robles et al., 2015). Before the widespread use of antibiotics and access to dental care, impacted third molars could be fatal (Dixon et al., 1997; Kunkel et al., 2007). However, prophylactic treatment of impacted wisdom teeth, while commonplace today in developed nations, is considered excessive (Anderson et al., 1976; Nystrom et al., 2007). Understanding the evolutionary origins of these pathologies in humans can assist with assessing modern risk and predicting treatment outcomes. However, while an abundance of studies exist analyzing the side effects and best surgical practices of treating impaction (Marciani, 2012; Venta 2012), the ultimate causes of third molar agenesis and impaction, including how these two pathologies relate, remains unknown.

Third molar loss is seen in multiple mammalian orders, but humans and domestic animals are the only mammals to have consistently impacted third molars. Among primates, *Homo*, Callitrichini, and the platyrrhine *Xenothrix* are the only known taxa to show high rates of M3 agenesis. Third molar agenesis is first seen in the hominin fossil record at 1.5 Ma with *H. erectus.* Most notably KNM WT-15000 has no mandibular M3 formation (Brown et al., 1993), and adult fossils from Lantian and Chenchiawo locality 63709 also show evidence of agenesis (Aigner and Laughlin, 1973; Wu and Xianglong, 1996). While other individual cases of agenesis have been detected in the hominin fossil record (e.g., Curnoe et al., 2012 ; Lukacs and Pal., 2013; Sawyer et al., 2015), it is currently unknown how the prevalence of M3 agenesis in humans changed over time. Impaction is more difficult to detect in the fossil record and there are few definitive cases of impaction predating the origin of *H. sapiens* (Neiburger, 1975; Wolpoff, 1979; Skinner and Sperber, 1982; Frayer and Russell, 1987; Gibson and Calcagno, 1993, 1995; Neiburger, 1995).

Given the apparently concurrent increase in the prevalence of third molar abnormalities with major changes in food subsistence and processing, it is reasonable to hypothesize dietary change as an underlying driving force (Brace 1963; von Cramon-Taubadel, 2011) However, no study has directly tested mechanisms that can account for changes in third molar agenesis prevalence over these transitional periods in human history. Furthermore, while many studies posit that the causative mechanism is changes in material properties of food with the adoption of agriculture (Daegling et al., 2007; Lucas 2007; Ungar, 2012), others put the origin of wide-scale third molar agenesis and impaction at the time of the Industrial Revolution (Sewo and Makinen, 1996; Peterson et al., 2005).

Currently three hypotheses have been proposed to account for third molar abnormalities: 1) selection against impaction (SAI), 2) the probable mutation effect (PME), and, 3) developmental delay (DD). However, few studies have applied empirical data to test these hypotheses and none have done so with a cross-populational sample that captures the variance in human dietary change. Under the SAI hypothesis, large-scale impaction developed because changes in tool use and food processing led to reduction in jaw size, leaving no space for the third molar (e.g., Wu and Xianglong, 1996; Swee et al., 2013). Selection for agenesis is theorized to occur because of the pathologies associated with impaction in the absence of modern dental care, especially antibiotics (e.g., Dixon et al., 1997). As agenesis existed in low frequencies in most Pleistocene human populations, the trait increased in frequency as those lacking third molars had more reproductive success. Under this hypothesis, we predict that agenesis will increase, while impaction decreases, over time during a transition. We also predict that individuals with 1 to 3 impacted M3s will be more likely to have agenesis in the other third molars. The PME hypothesis posits wear and dental reduction as the selective mechanism for M3 agenesis. Brace (1963, 1964) suggested that human dental reduction occurred because relaxed selective pressure for proper occlusion and occlusal crown area led to a build-up of mutations that interfere with normal development within different human populations, eventually leading to the independent evolution of third molar agenesis. If the PME is supported, we predict that third molar size and wear will decrease over time during a transition and that both of these variables will be correlated with an increase in agenesis. Finally, the DD hypothesis posits that a slowed rate of tooth development led to M3 agenesis becoming prevalent, drawing from evidence that the best predictors of third molar agenesis are delays in second molar

eruption and development (Brothwell et al., 1963; Bermudez de Castro, 1989). Given the poor nutritional status of many early agricultural populations (Rose et al., 1978; Cohen and Armelagos, 1984; Piontek et al., 2001) and the delays in somatic growth known to accompany nutritional distress, third molar agenesis may have arisen as a result of dietary shifts. Under the DD hypothesis, we predict an increase in dental fluctuating asymmetry (shown to be a marker of developmental stress; Bailit et al., 1970; Doyle and Johnston, 1977; Perzigian, 1977) over time during a transition and a high positive correlation between asymmetry and agenesis.

While evidence is available that either supports (e.g., Garn et al, 1968; Hill, 2004; Suri et al., 2004) or challenges (e.g., Garn et al., 1969; Bermudez de Castro, 1989; Scott and Alexandersen, 1992; Lahr, 1995; Weiss, 2010) these hypotheses and their underlying assumptions, there has never been a direct test of these hypotheses. It is also possible that genetic drift may be the mechanisms responsible for determining trait frequencies, as is assumed in many non-metric dental studies using agenesis (e.g., Irish, 2014). In this study, we use four populations during the transition to agriculture and two populations during the transition to industry to test the predictions of these three hypotheses.

MATERIALS AND METHODS

Archeological Sample

Skulls from 776 individuals from six different populations were sampled (see Table 1 and SI Materials), four during the agricultural transition and two during the industrial transition. Populations were chosen based for their geographic and subsistence variability, genetic continuity across the transitional period, and a low degree of tooth wear and

antemortem tooth loss. Sites from each population were classified into three time periods: pre-transition, during the transition, and post-transition for both agricultural and industrial populations. This allowed comparisons to be made both across populations and between different stages of the transition. Each individual was assessed for definitive characteristics of sex using pelvic and cranial features (Giles and Eliot, 1963; Meidnl, 1985; Ubelaker and Volk, 2002) and age using manubrial, cranial, and pelvic features (Gautam, 2002; Lewis, 2007, Chandrakanth, 2012). Individuals at least 11 and 17 years old were used for the M3 agenesis and impaction analyses, respectively (Banks, 1934; Garn and Lewis, 1962; Richardson, 1980; Kruger, 2001; Venta, 2001). Individuals were excluded from the study if there was evidence of dental trauma, more than five large carious lesions, or oligodontia (missing six or more permanent teeth, not including third molars). Only individuals with at least six unbroken molars and premolars on both the maxilla and mandible were included

Table 1: Sample size and sites of the populations used in this study.

Transition	Region	N	Time Period*	Sites
Agricultural	Danube Gorges	78	Pre	Padina, Vlasac
			During	Lepenski Vir, Padina, Vlasac
			Post	Ajmana, Lepenski Vir
Agricultural	Japan	114	Pre	Doigahama
			During	Kanenokuma, Koura, Nagaoka
			Post	Hirota, Koura,
Agricultural	Egypt	157	Pre	Badari, Kerma
			During	Naqada
			Post	Naqada, Tarkham
Agricultural	SE Coastal US	151	Pre	Belle Glade, Sea Islands Mound, St Simon's Island, Western Side of Pericho Island
			During	Belle Glade, Fuller Mound, Irene Mound
			Post	Airport, Fuller Mound
Industrial	Portugal	200	Pre, During, Post	Coimbra Identified Skeletons Collection
Industrial	Japan	76	Pre, During, Post	Suugenji Syokenji

***'Pre' refers to pre-agricultural/industrial populations, 'During' to populations undergoing the transition, and 'Post' to post-agricultural/industrial populations.**

Third Molar Impaction and Agenesis Assessment

Evidence of third molar agenesis and impaction, as well as the type of impaction, was recorded for all available dental quadrants. We also collected buccolingual measurements of P3-M3, mandible and maxilla measurements, qualitative third molar assessments, and measurements of wear by molar quadrant. Using these measures, we created derived variables of dental arch space, third molar crown complexity, wear rate, and fluctuating asymmetry (see SI Methods).

To confirm M3 agenesis, radiographs were taken using a SKYSEA dental portable radiography machine and Ergonom self-developing X-ray film. Each quadrant was radiographed with the occlusal plane at M2 perpendicular to the X-ray. For impacted teeth, the state of eruption (completely erupted, partially erupted, unerupted) as well as the angle of impaction (horizontal, vertical, mesioangular, distoangular, inverted, buccoangular, lingoangular) was recorded following Winter (1926) and Kruger (1984).

Data Analysis

The primary variables of interest in this study are binary, notably whether a given third molar exhibited agenesis or impaction. We therefore used several different specifications of logistic regression to model these data (see SI Methods for a detailed description). We treat archeological sites from different time periods as a longitudinal sample within a given population. Since different sources of variation lead to different estimates, and interpretations, of regression coefficients, we use panel-data estimators to focus comparisons on only the 'within' population time change variation, rather than those based on both time and cross-sectional population variation (Wooldridge, 2010).

For most analyses, the panel-data estimator consists of population-level fixed effects to control for unobserved time-invariant population-level heterogeneity, such as variables that were stable within-populations over time (Greene, 2004, Allison, 2009). For the analysis of dental arch space, however, we use 'hybrid' mixed effects logistic models. These models employ a within-between estimator, since they include within- and between-cluster terms in the model specification (Mundlak, 1978; Chamberlain, 1980; Dieleman and Templin, 2014; Bell and Jones, 2015). This alternative strategy is useful for modeling the type of dietary transition as a fixed effect, since population type and transition type cannot both be included as fixed effects due to collinearity. In these models, population is included as a random effect, while all fixed effects predictors are decomposed into between- (population mean) and within-cluster (population mean centered) terms in the model specification.

All analyses were conducted with the **R** statistical language v 3.2.1 (R Core Team, 2015), using the packages **stat, lme4, effects, lsmeans,** and **ggplot2**. Hypothesis tests involving pairwise comparisons between levels of categorical variables were adjusted for family-wise error using the sequential Bonferroni method (Holm, 1979).

RESULTS

Overall Third Molar Agenesis and Impaction Rates

The frequency of M3 agenesis ranged from 0% to 30.5% across all time periods and populations studied, with the post-agricultural population from the Danube Gorges having the lowest rate of agenesis, and the agricultural population from Japan having the highest rate. Pooled across time periods, both agricultural and industrial Japan had high rates of

M3 agenesis (18.6% and 26.3%, respectively; Figure 13a), similar to estimates of agenesis rates in modern populations (22.6%, 95% CI 20.6%, 24.8%; Carter and Worthington, 2015). We found that populations differed in average prevalence of M3 agenesis (likelihood ratio X^2_{138}, $p < 0.0001$), with pairwise differences between Japanese (26.3%, 95% CI 21.7%, 31.6%) and Portuguese (9.8%, 95% CI 7.9%, 12.0%) industrial populations ($p < 0.00001$) and between agricultural Japanese (18.6%, 95% CI 15.3%, 22.5%) and all other agricultural populations ($p < .0001$; <9.2%, 95% CI <7.2%, <11.8%). The frequency of M3 impaction showed a very different pattern, with industrial Portugal (15.4%, 95% CI 13.0%, 18.0%) and Japan (13.8%, 95% CI 10.4%, 18.2%) having a higher prevalence of impaction when pooled across all time periods, and agricultural populations having rates of impaction below 5% (Figure 13b). Industrial populations had higher ($p < 0.00001$) rates of M3 impaction (15.0%, 95% CI 13.0%, 17.2%) on average than agricultural populations (3.4%, 95% CI 2.6%, 4.2%), but these rates are below estimates of impaction frequency (24.4%, 95% CI 19.0%, 30.8%; Carter and Worthington, 2016).

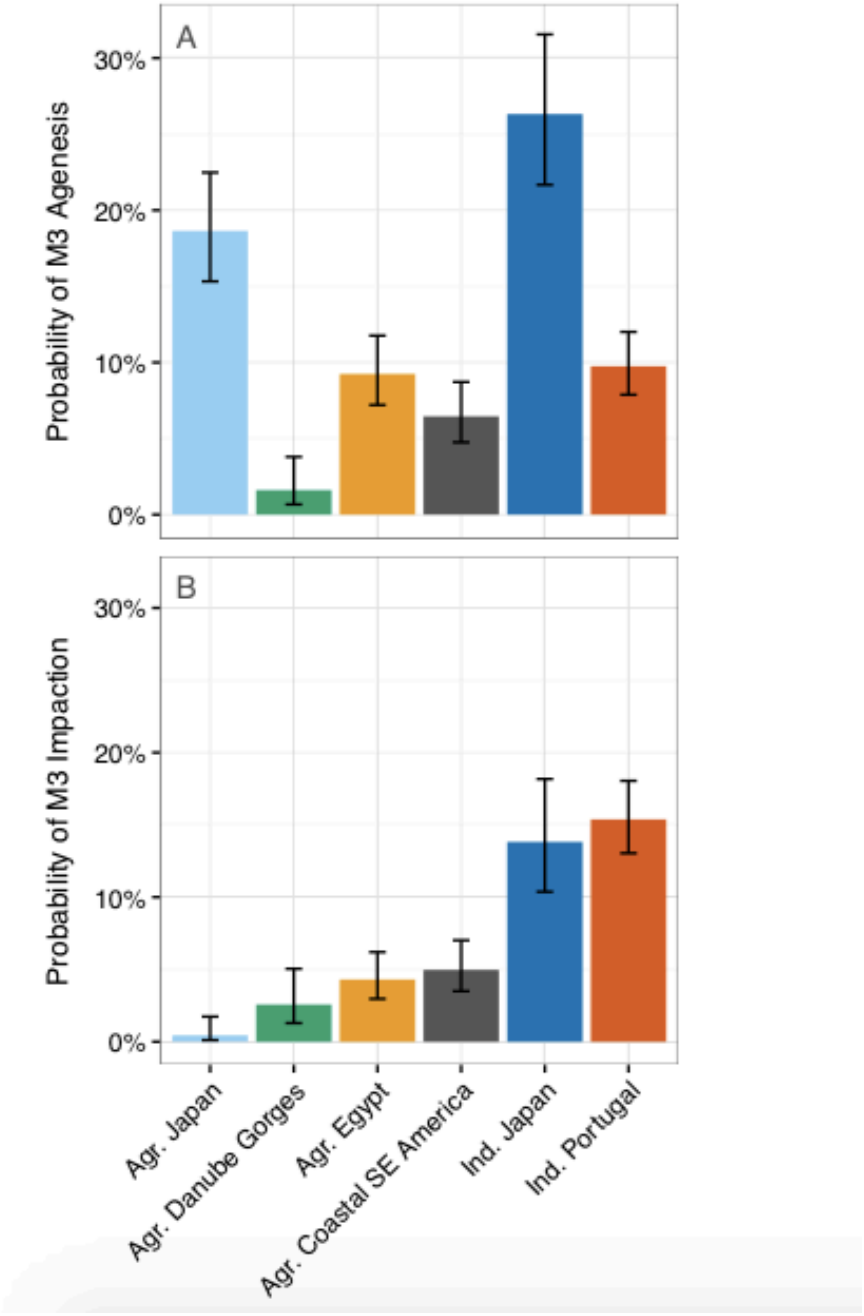


Figure 13: Probability of M3 pathology by archeological population. Bars denote predicted marginal means, while error bars are 95% CIs. A) M3 agenesis, and B) M3 impaction.

Dental Arch Space and Third Molar Agenesis and Impaction

To test the hypothesis that third molar impaction and agenesis increased over agricultural and industrial transitions because of changes in the size and shape of the dental arches, we estimated the relationship between dental arch space and probability of M3 impaction and agenesis, while controlling for average M1 breadth. For the industrial transition, we found that the probability of M3 agenesis decreased as dental arch space increased in the maxilla ($p = 0.00078$) and mandible ($p = 0.0051$; Table S1, Figure 14ab). During the agricultural transition, larger dental arch space was associated with a higher probability of M3 agenesis in the maxilla ($p = 0.038$) and mandible ($p = 0.00081$; Figure 14ab). These contrasting negative and positive relationships for the two transitions differed in both the mandible ($p < 0.000013$) and maxilla ($p = 0.00014$). We found the probability of M3 impaction, during the agricultural transition, decreased as maxillary ($p = 0.00002$) and mandibular ($p = 0.0019$) arch space increased (Figure 14cd). This negative relationship persisted during the industrial transition for the maxilla ($p < 0.00001$) and mandible ($p < 0.00001$; Figure 14cd).

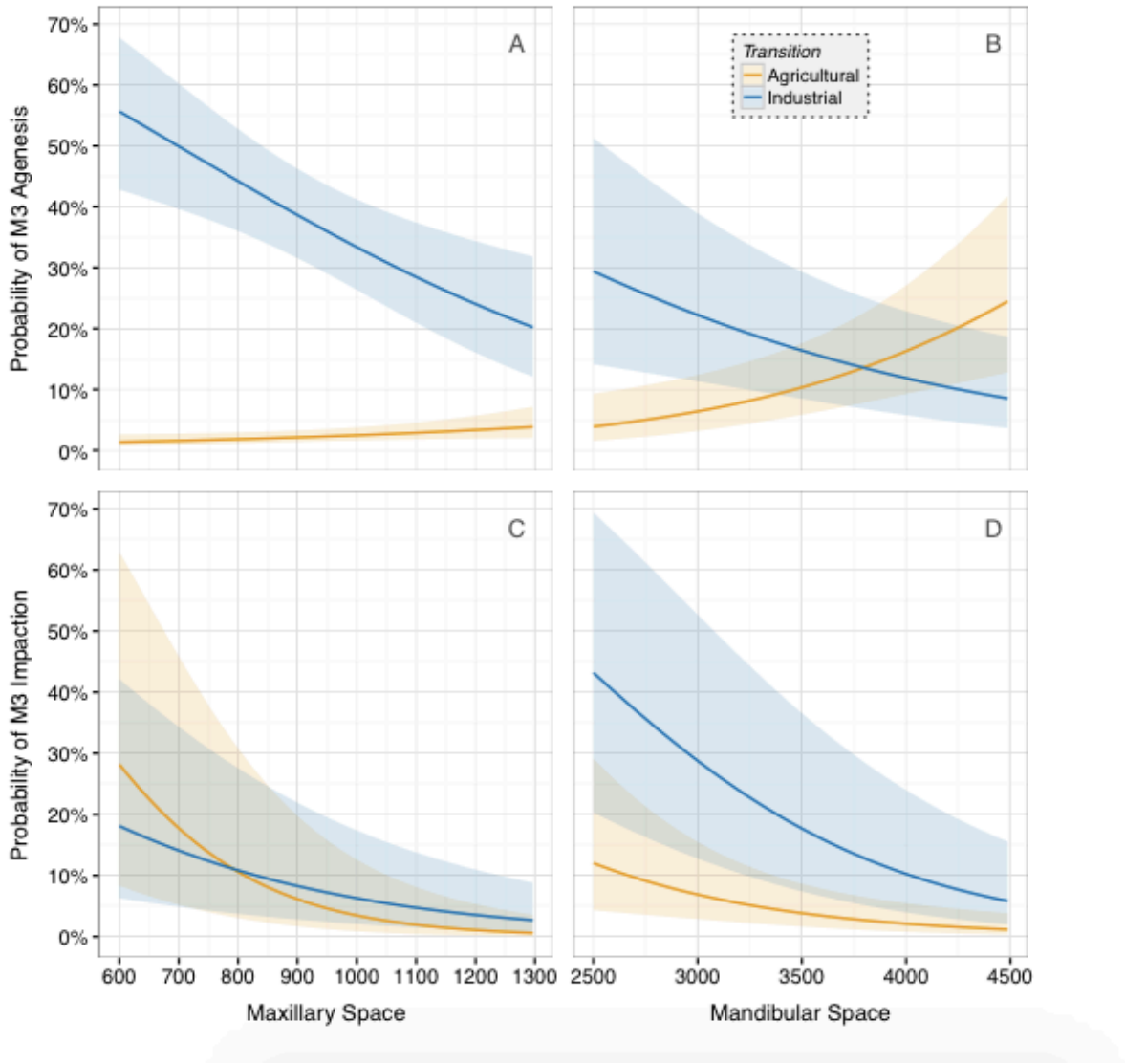


Figure 14: Probability of M3 pathology by dental arch space. Lines denote predicted marginal means, while colored polygons are 95% CIs. A) maxillary M3 agenesis, B) mandibular M3 agenesis, C) maxillary M3 impaction, and D) mandibular M3 impaction.

Selection Against Impaction

To test the SAI hypothesis that as M3 impaction frequencies increased within populations the rate of M3 agenesis also increased, we built separate logistic regression models for the agricultural and industrial transitions. These models predicted the probability of M3

agenesis from the proportion of M3 impaction (in M3s that underwent genesis), within each time period. For the agricultural transition, we did not detect a relationship ($p = 0.81$) between the proportion of M3 impaction and probability of M3 agenesis in any time period (Table S2, Figure 15a). For the industrial transition, we did not find a relationship between M3 impaction and agenesis during pre-industrial ($p = 0.87$) or industrial time periods ($p = 0.80$), but we found evidence of a positive relationship ($p < 0.0003$) for post-industrial individuals (Figure 15b). For these individuals, the probability of M3 agenesis increased sharply with the percentage of M3 impaction, from 5.4% (95% CI 3.0%, 9.7%) when there was no impaction to 38.7% (95% CI 18.9%, 63.2%) when all M3s that underwent genesis were impacted.

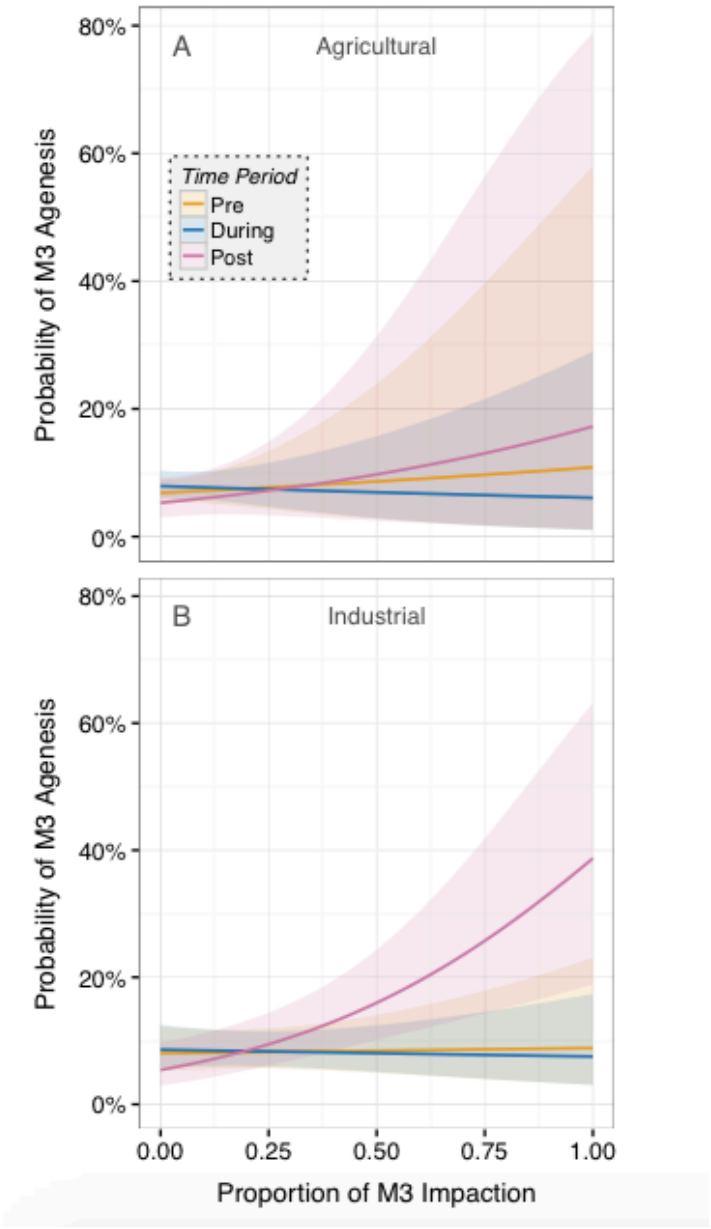


Figure 15: Probability of M3 agenesis by proportion of M3 impaction. Lines denote predicted marginal means, while colored polygons are 95% CIs. A) Agricultural transition, and B) Industrial transition.

Probable Mutation Effect

To test the PME hypothesis that as M3 wear rate decreased within populations the M3 decreased in size and complexity, leading to agenesis, we built separate logistic regression

models for each transition, which predicted the probability of M3 agenesis from the degree of M3 wear and crown complexity, within each time period. In the agricultural transition, there was no evidence of a relationship between wear and probability of M3 agenesis in the mandible ($p = 0.12$) or maxilla ($p = 0.12$). We detected a positive association between complexity and M3 agenesis in the maxilla ($p = 0.0008$), but not the mandible ($p = 0.23$; Figure S2ab). The probability of M3 agenesis increased from 1.7% (95% CI 0.9%, 3.2%) when maxillary complexity was 0, to 5.6% (95% CI 3.8%, 8.2%) when complexity was 1.5. For the industrial transition, we found a negative relationship ($p = 0.025$) between M3 wear and probability of M3 agenesis in the mandible. The probability of M3 agenesis decreased from 11.4% (95% CI 5.5%, 22.0%) when mandibular wear was -3, to 4.2% (95% CI 2.8%, 6.3%) when mandibular wear was 0. However, we found a positive association between M3 complexity and M3 agenesis ($p = 0.008$) in the mandible (Figure S2cd). The probability of M3 agenesis increased from 3.7% (95% CI 2.4%, 5.9%) when mandibular complexity was 0, to 12.8% (95% CI 6.5%, 23.6%) when mandibular complexity was 1.5. We did not find evidence of relationships between wear rate ($p = 0.51$) or complexity ($p = 0.91$) and M3 agenesis in the maxilla.

Developmental Delay

To test the DD hypothesis that slowed somatic growth caused by poor nutrition is one of the best predictors of M3 agenesis, we used fluctuating asymmetry as a correlate of nutritional status and built separate logistic regression models for each transition, which predicted the probability of M3 agenesis from the degree of fluctuating asymmetry, within each time period. For the agricultural transition, we found no evidence of a relationship

between rate of fluctuating asymmetry and probability of M3 agenesis in any time period for either the maxilla ($p = 0.33$) or mandible ($p = 0.17$; Figure S3ab). During the industrial transition, we found higher fluctuating asymmetry associated with lower probability of mandibular M3 agenesis across all time periods ($p = 0.0007$). The probability of M3 agenesis decreased from 17.0% (95% CI 13.8%, 20.8%) when mandibular fluctuating asymmetry was 0, to 5.3% (95% CI 2.9%, 9.5%) when mandibular fluctuating asymmetry was 1.5. In the maxilla, the probability of M3 agenesis increased with higher fluctuating asymmetry only within the pre-industrial period ($p = 0.002$; Figure S3cd). Within this period the probability of M3 agenesis increased from 9.1% (95% CI 5.9%, 13.9%) when maxillary fluctuating asymmetry was 0, to 33.6% (95% CI 18.7%, 52.6%) when fluctuating asymmetry was 1.5.

DISCUSSION

Although the incidence of third molar agenesis and impaction is well characterized in modern and archaeological populations, this study is the first to compare the prevalence of M3 agenesis and impaction across time and populations. We found that many of the archeological populations studied had M3 agenesis prevalence similar to modern rates, but that impaction prevalence was much lower during the transition to agriculture than during the industrial transition or today. Other studies have found a high level of impaction in populations prior to the industrial transition (e.g., Silvana et al., 1985). This may be the result of populations relying on crops with different physical properties that change the mechanical demands on mastication earlier than the populations sampled here. More

research is needed to determine when M3 impaction became more prevalent in different populations.

Modern third molar pathology has long been linked to changes in jaw size, and there are well-documented changes in jaw size across recent human history (von Cramon-Taubadel, 2011; Pinhasi et al., 2015). We found support for this relationship during the industrial transition, with both third molar impaction and agenesis frequencies increasing as jaw size decreases (controlling for tooth size). Similarly, we found that smaller jaws have a higher frequency of impaction during the agricultural transition. It was surprising, however, to find that during the agricultural transition, for both mandible and maxilla, larger jaws were associated with a higher probability of M3 agenesis. This suggests that not only is reduction in jaw size not the primary cause of M3 agenesis across the agricultural transition, but smaller jaws may actually be less likely to have agenesis, even when controlling for tooth size.

Probable Mutation Effect and Developmental Delay

We did not find any support for the PME hypothesis, which predicted that wear would increase and variability would decrease across dietary transitions. Despite the many well-regarded, thoughtful =critiques of the supposed evolutionary basis for the PME hypothesis (Calcagno and Gibson, 1988; Weiss, 2010), it remains one of the most common ideas presented to explain third molar agenesis in both popular science articles and introductory textbooks (Saniotis and Henneberg, 2013; Kaidonis et al., 2014; Martín-Albaladejo et al., 2016). Using a model that incorporated both tooth wear and crown complexity, we did not find support for the PME hypothesis. In particular, we found that individuals with complex

third molars were more likely to have M3 agenesis in the maxilla, for agricultural populations, and in the mandible, for industrial populations. Only for industrial populations in the mandible, did we find some support for the PME, with individuals exhibiting low rates of wear being more likely to have M3 agenesis. However, without evidence of third molar reduction happening in conjunction with wear, the PME hypothesis lacks corroboration.

We did not find support for the DD hypothesis during the agricultural or industrial transition. For the mandible, the prevalence of third molar agenesis declined as the rate of fluctuating asymmetry increased, contradictory to predictions from this hypothesis. We found limited support for the DD hypothesis in the maxillary dentition of the pre-industrial population. An hypothesis that can potentially explain these results is that fluctuating asymmetry, which is highly correlated with delays in somatic growth (Sciulli, 2002), but may not correlate as strongly to delays in tooth growth and eruption (e.g., Elamin and Liversidge, 2013). Developmental delay could be a mechanism that explains agenesis, if these delays in tooth eruption and growth are caused by processes other than nutritional stress (e.g., mandibular surgery at a young age (Swee et al., 2013)). However, it is unlikely that changes in human diet would have brought about this type of developmental delay, and it is therefore not surprising that the model was not supported in our analyses.

Impaction and Agenesis in the Agricultural Transition

We did not find support for any of the models tested to explain the evolution of M3 agenesis and impaction during the agricultural transition. Therefore, it is impossible to reject a hypothesis of genetic drift based on these data. However, a purely drift-based

explanation seems unlikely, given the surprising pattern of larger mandibles and maxillae having higher rates of agenesis. While this relationship is consistent with other studies of archaeological populations (Bermudez de Castro, 1989), it is inconsistent with both the PME and the SAI hypotheses. The pattern of dental arch space and agenesis frequency also differed markedly between the agricultural and industrial transitions. Therefore, it is reasonable to hypothesize that there are at least two independent mechanisms driving the evolution of agenesis in the human fossil record. Other than drift, this pattern could be driven by a trade-off between investment in jaw growth and investment in the mineralization of the third molar. Further analysis is needed to determine whether any of these hypotheses adequately explain M3 agenesis.

Notably, none of the potential predictors of M3 agenesis (e.g., wear rate, rate of fluctuating asymmetry, impaction rate) showed any evidence of change during the agricultural transition in the populations sampled. This lack of change may suggest that the mechanisms that produce third molar agenesis in early populations were not affected by dietary changes. It is also possible that many of the populations chosen for this study were already too agricultural to notice an effect across the transition, particularly in Egypt and agricultural Japan, where many tenets of the agricultural package were already well in place by the time of the earliest populations sampled (but see Starling and Stock, 2007; Temple and Larsen, 2007; Kuper and Riemer, 2013; Temple, 2015**).**

Selection Against Impaction in the Industrial Transition

Third molar impaction frequency initially is high during the early industrial periods, before sharply declining in post-industrial populations ($p = 0.03$), while agenesis initially

decreases (p = .05) then increases (p = 0.15) in post-industrial populations (Figure S4bd), suggesting that selection may have acted against impaction to produce agenesis. Furthermore, the post-industrial population showed a tight interlinkage between M3 agenesis and impaction, not seen in earlier periods. Taken together, these lines of evidence suggest that selection may be acting against third molar impaction to produce agenesis, but this mechanism appears to be active during only the industrial transition. The mechanism may also have been present in the agricultural transition, but a low incidence of M3 impaction would make this nearly impossible to detect.

Overall, the results from this study point to selection against impaction as a driving force in the evolution of third molar pathologies during the industrial transition. Experimental studies documenting the effects of soft or liquid diets on craniofacial growth suggest that soft foods change breadth and depth dimensions in the mandible (Ito et al., 1988; Lieberman et al., 2004), though these differences are not always significant (e.g., Ozaki et al., 2007). Evidence that variation in mandibular size and shape correlate much more highly than the cranium with variations in diet, suggests that changes in diet may cause change in the mandible (von Cramon-Taubadel, 2012). Recent reduction in mandible size is especially marked in corpus breadth and retromolar space, where third molars would likely erupt (Franciscus and Trinkaus, 1995). Furthermore, third molar agenesis is highly heritable (Garn, 1963; Peres et al., 2005; Saito et al., 2006), and existed at a high enough frequency (in these populations 14%; Figure S4D) before the industrial transition for selection to act upon. Although there is no evidence on the direct fitness cost of impacted third molars, many studies suggest that infection from impaction can be fatal if untreated (Calcagno and Gibson, 1988; Berge, 1996; Dixon et al., 1997; Kunkel et al., 2007).

More research is needed, however, to test better that selection is acting against impaction. Without knowing the genetic relationships among individuals, directly testing the effects of selection is challenging. Furthermore, the industrial transition involved not just shifts in diets but also increased sanitation, antibiotics, and other medical treatments (Popkin, 1999; Popkin, 2003; Cordain, 2005; Larsen, 2006; Lieberman, 2013) that can affect rates of skeletal growth (Hiernaux, 1968; Enwonwu, 1973; Suri et al., 2004). Industrialization in Japan and Portugal was very rapid, and parsing out the contributions of individual pieces of the industrial package is nearly impossible. Analyzing populations for which food processing happened before or after the adoption of other industrialization changes will shed light on how much dietary change alone can account for changes in third molar pathologies. Finally, though the industrial transition began less than 200 years ago (and is still ongoing in some parts of the world), the subsequent widespread access to dental care and antibiotics has reduced the potential costs associated with dental maladaptations, such as impaction, and it is unclear whether this result holds true with the most recent generations of humans. This relaxed selective regime may also explain the increase in the rate of impaction after 1950.

To conclude, we hypothesize that two separate mechanisms are responsible for third molar agenesis in humans. Despite the overall trend of jaw reduction and gracilization that characterized much of the evolution of *H. sapiens*, the first mechanism appears to be wholly independent of potential spatial constraints. During the past 200 years, as impaction frequencies climbed from <5% to the ~25% seen today, there is evidence that the fitness costs associated with impacted third molars were strong enough to select for third molar agenesis. This suggests that changes in the modern human diet in

the last 250 years may have had a rapid impact on the selective regime of skeletal and dental characters.

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CHAPTER 5: DISCUSSION

My goal in this thesis was to address 5 inter-related questions. Below I discuss the contributions of my project in answering each of the following questions, while also listing the limitations of the studies and avenues for future research.

1. What predicts third molar agenesis and impaction in modern populations?

I first attempted to tease apart the predictors of third molar agenesis and impaction in modern humans. I felt that understanding these predictors was important because there was conflicting evidence about which demographic and morphological features were most likely to cause impaction or agenesis. This was done in Chapters 2 and 3 through conducting meta-analyses to understand the overall effect in modern populations, and in Chapter 4 by directly analyzing the frequencies of the predictors of agenesis and impaction in my sample. Below is a summary table that details the overall results for both modern and archaeological populations.

Differences between Modern and Archaeological Data

Overall, I found very little difference between the probability of M3 agenesis in modern and archaeological populations across a range of predictors. However, there are two important results, sex bias for impaction and jaw bias for agenesis, that merit further discussion. Other contradictory results, such as impaction type, are likely due to differences in the recording data from X-rays or archaeological material. Impaction type can be determined in bitewing X-rays by examining both the protrusion of the crown from the

gum line and the occlusal fit between the M3 and other teeth, two types of data missing in skeletal material.

	M3 Agenesis		**M3 Impaction**	
	modern	archaeological	modern	archaeological
Overall Rate	22.6% (Fig 2)	11.11% (Appendix 4 Fig S1)	24.4% (Fig 8)	7.47% (Appendix 4 Fig S1)
Sex Differences	Females higher (Fig 5)	Females higher (Appendix 3 Fig S1a)	No difference (Fig 12)	Females higher (Appendix 3 Fig S1b)
Jaw Differences	Yes, Maxilla more frequent (Fig 6)	Yes, Mandible more frequent; (Appendix 3 Fig S1c)	Yes, Mandible more frequent (Fig 11)	Yes, Mandible more frequent (Appendix 3 Fig S1d)
Number of Teeth Affected	1 or 2 > 4 or 3 (Fig 4)	2 or 1 > 4 > 3 (Appendix 4 Fig S2a)	1 or 2 > 3 or 4 (Fig 10B)	1> 2> 3> 4 (Appendix 4 Fig S2b)
Type of Impaction	N/A	N/A	Mesioangular (Fig 10A)	Horizontal (Chapter 5 Fig S3)
Population Differences	Asia > Middle East > Oceania > Europe > S. America > N. America > Africa (Fig 3)	in. Japan > ag. Japan > Portugal > Egypt > SE America > Danube Gorges (Fig 13a)	Middle East > Asia > Europe > N. America > Africa (Fig 9)	Portugal > in. Japan > SE America > Egypt > Danube Gorges > ag. Japan (Fig 13b)

Table 2: Comparisons of the predictors of third molar impaction and agenesis in the analysis. The response variable is the frequency of having at least one third molar with agenesis or impaction. Modern refers to populations sampled during the meta-analyses (Chapters 2 and 3) and archaeological refers to material presented in Chapter 4.

While both the archaeological and modern studies found females had higher rates of third molar agenesis, there were slight differences found between the archaeological and modern samples in the sex ratios of third molar impaction (Appendix 3 Fig S1b vs Fig 12). The archaeological analysis suggested that females had a higher rate of impaction, while the analysis of modern populations found no significant differences. Overall, more modern studies found females to have a higher rate of impaction than males (9 out of 14 total studies). However, the meta-analysis of impaction showed a great deal of variation in sex ratio with estimates ranging from males being 1.43 times more likely to have impaction to females being 2.5 times more likely. Importantly, this variation cannot be attributed to differences in types of data collection (e.g., type of X-ray, year study was conducted) or regional differences (e.g., Saudi populations have estimated sex odds ratios of impaction that range from 0.814 to 1.887). Originally, I predicted that the result in modern populations was attributed to females having shorter jaws than males (as in Rothstein and Phan, 2001; Lesterel et al., 2004), but the archaeological analysis showed that these differences were in place without corresponding differences in dental arch space between males and female (Appendix 4, Fig S4). In modern populations where the higher rate of impaction is likely driven by the physical properties of food, it is reasonable that there would not be much sex bias between males and females. Differences found in the archaeological analysis suggests that either: a) females and males were eating diets of differing qualities (a hypothesis that has variable support; Lukacs 1996; Bonsall et al., 1997; Temple and Clark, 2007 but see Dürrwächter et al., 2006; Lukacs and Largaespada, 2006) or b) that females are genetically predisposed to have higher rates of impaction. There is some evidence to support a gender difference in diets. Caries rates are typically

higher in females, particularly in East Asian sites, but this may be caused by differences in hormones or life history (Lukacs and Largaespada, 2006). Isotopic differences in carbon and nitrogen between males and females have been found in Mesolithic Danube Gorges, but not in any Neolithic sites (Bonsall et al., 1997). There may also be a genetically-determined difference between male and female impaction rates, potentially linked to dental eruption. Females erupt teeth slightly earlier than males in modern populations (e.g., Haaviko, 1973; Alqahtani, 2010), and this slightly earlier eruption may be one possible mechanism to explain the sex difference in archaeological impaction rate. Given the results of the dental arch space analysis, this could also help explain sex differences in agenesis frequency between males and females in the agricultural transition.

Given that jaws have frequently been shown to be less integrated than the rest of the cranium (Preuschoft and Witzel 2002; von Cramon-Taubadel 2011; Klingenberg 2013; but see Bastir and Rosas, 2005), I predicted that jaws would be more prone to vary with dietary changes. This would cause impaction to be higher in the mandible, and I found this result in both the archaeological and modern populations. For agenesis, the results are more complex. In modern populations, maxillary agenesis is more common than mandibular agenesis (Fig 12), and in populations with the overall highest rates of agenesis the ratios grow as large as 2:1 in favor of the maxilla (e.g., Arany et al., 20014; Mani et al., 2014). Populations with lower frequencies of agenesis tend to have more equal ratios of maxillary to mandibular agenesis, though there are several exceptions to this trend. This initially suggested that maxillary agenesis may be driven by genetic mechanisms and is less determined by environmental factors. However, assessing the archaeological evidence

suggests that mandibular agenesis is higher particularly in agricultural populations. This instead suggests that impaction may be preferentially being selected against in the maxilla.

Perhaps the most surprising result from this part of the analysis was the similarity between agricultural and modern populations in agenesis frequency. In Japan, the modern estimates agenesis ranged from 29% to 49% while agricultural populations ranged from 28 to 52% (Figure 16). Other populations are more admixed, making it difficult to compare modern and archaeological populations. With the exception of the Danube Gorges, these populations still follow the patterns seen in modern groups, though almost all of these estimates are lower than their modern counterparts. Jomon populations, which were studied but then excluded from the archaeological analysis, have a higher rate of agenesis than other agricultural populations, but not as high as most of the Yayoi farmer populations (Appendix 4 Figure S5; see also section 4). With one population that is adequate for making comparisons, it is difficult to determine whether genetic drift or stabilizing selection fits as a mechanism, or if the results are purely happenstance. However, it does suggest that the modern pattern of agenesis may have been established much earlier. Impaction frequency, by contrast, is very different between archaeological and modern populations (Figure 16b).

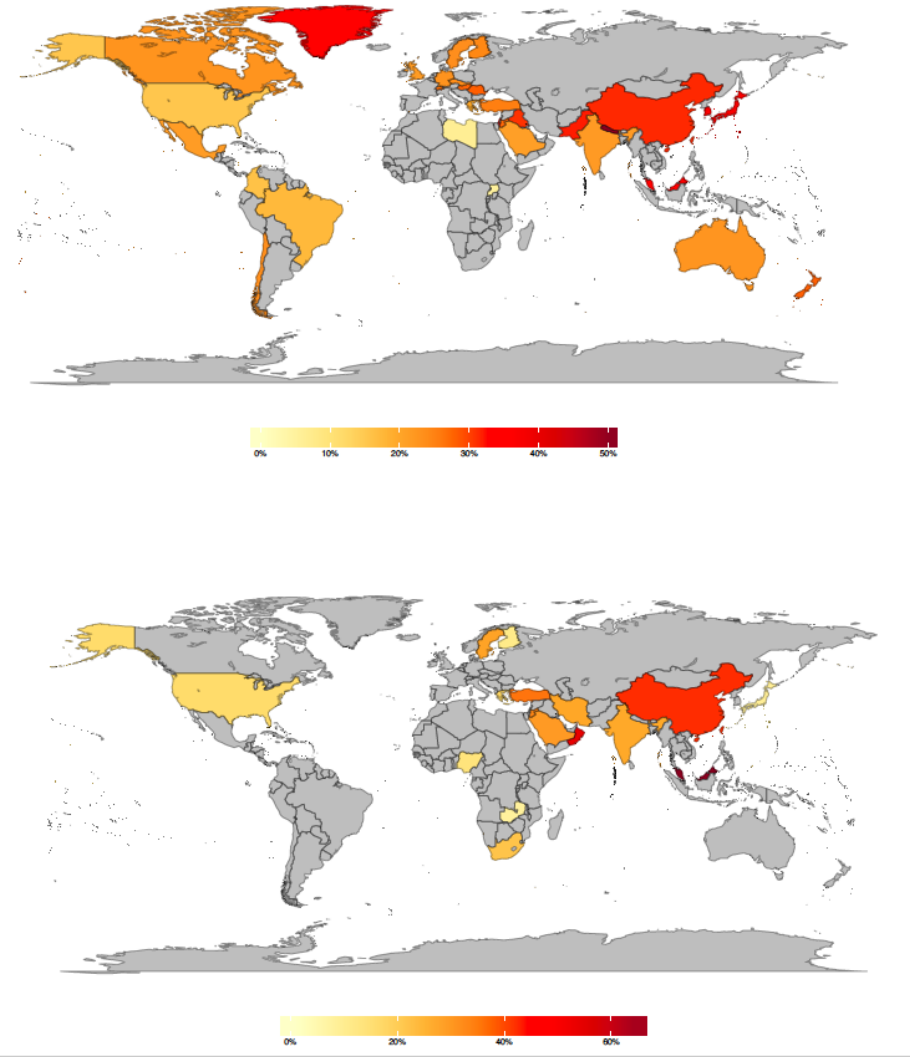


Figure 16: Chloropleth maps showing frequencies of (top) third molar agenesis and (bottom) third molar impaction in modern human populations. When multiple estimates are available for populations, the mean was taken scaled by sample sizes of the estimates.

Jaw size, tooth size and the frequency of third molar agenesis and impaction

Assessing the relationship between morphometric measurements and third molar agenesis or impaction is nuanced given that the relationship between jaw size and tooth size most likely helps determine the frequency of these third molar pathologies (though tooth size is uncorrelated with dental crowding or impaction; Howe et al., 1983). Observationally, I came across many individuals (particularly in the Yayoi) that had small jaws and large

teeth, and other individuals that had small teeth and large jaws . Therefore, for the archaeological analyses, I included M1 breadth in the model comparing dental arch space and agenesis frequency and also analyzed the relationship of these two variables separately (Figure 17). The results of the latter analysis were consistent with the predictions I expected, with small teeth being correlated with small jaws and large teeth correlated with large jaws (the individuals described above were included in the analysis, but did not mask the overall effect). While this is not a particularly interesting result in itself, it suggests that much of the relationship between jaw and tooth size is driven by scaling, as opposed to other factors.

When tooth size was included into the model predicting third molar agenesis, I found that small teeth and large jaws were correlated with an increase in agenesis in the agricultural transition, but large teeth and small jaws were correlated with agenesis in the mandible during the industrial transition (Figure 18). This was a surprising result both because of the discrepancies between the agricultural and industrial transition and the interpretation of the results for the agricultural analysis. It is clear that space constraints are not the driving force behind high rates of third molar agenesis before the industrial transition. In fact, individuals with the most available space for a third molar are those that are most likely to have agenesis. The biological implications of this are discussed at length in section 3 of this chapter.

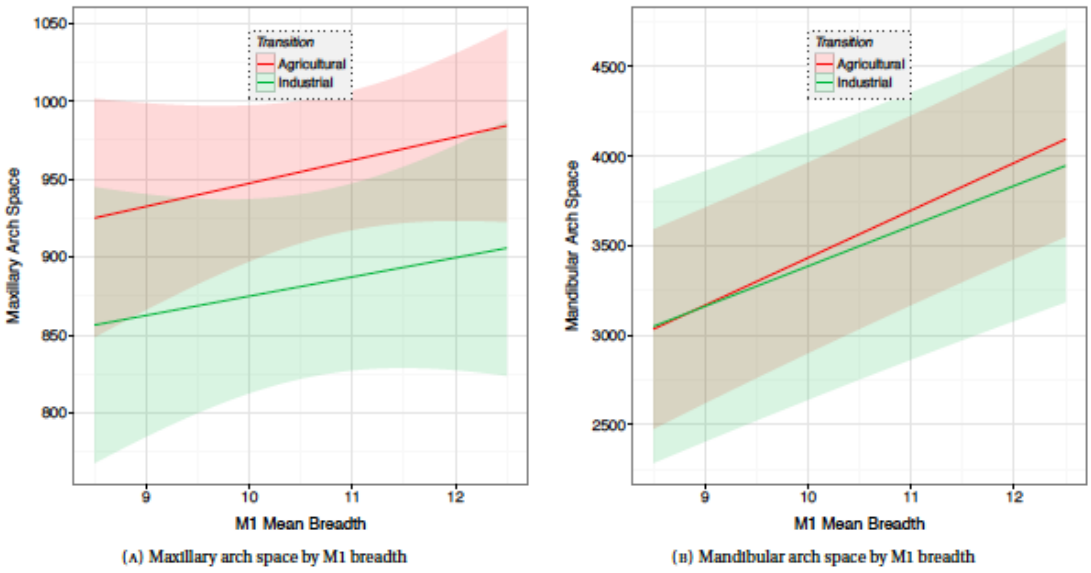


Figure 17: Comparisons between tooth size (M1 breadth) and dental arch space in the maxilla and mandible.

Limitations and future directions

Overall, I feel confident in my assessment of the predictors of third molar agenesis and impaction. Unlike most previous studies, I used large sample sizes, rigorous statistical analyses, and strict inclusion criteria, which together yielded the most accurate results possible. However, even with regards to these questions, there is more work to be done. The sample size for both the modern and archaeological populations was not sufficient to ask questions about the interactions of many of these predictors (e.g., are females from Africa more likely to be missing maxillary or mandibular molars?). Furthermore, for all three of these studies, the response variable was either "some agenesis", "some impaction" or "proportion of agenesis". It is completely possible that there may be different processes underlying (for example) agenesis of one maxillary molar compared with two mandibular molars. However, the sample size needed for 16 different response variables (yes/no for

agenesis for four teeth) and the non-independent nature of these data (requiring both correcting for multiple comparisons and using seemingly unrelated regression models) is beyond the scope of a doctoral thesis, but could be collected in a long-term team effort.

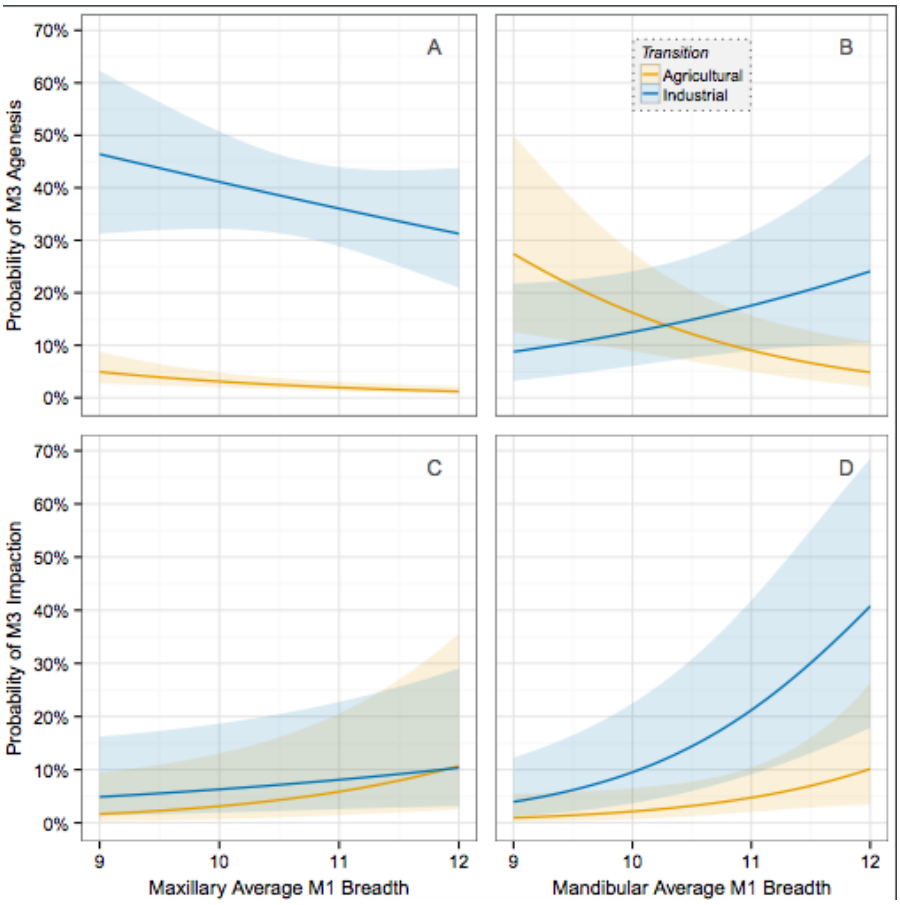


Figure 18: Comparisons of M1 breadth and agenesis frequency. This is the same model as in Chapter 4 Figure 2, but with M1 breadth graphed instead of jaw length. Both variables are included in the model in both cases.

2. Do any of the three models previously proposed to explain the origin of agenesis fit the data?

Based on the existing evidence, I originally predicted that the developmental delay model would be supported. There is copious evidence from modern dentistry that suggested that individuals were more likely to be missing third molars if the second molar was delayed in

formation or eruption (Garn and Lewis, 1962; Hentisz, 2003), and I expected this to be demonstrable in archaeological populations by analyzing the rates of fluctuating asymmetry. By contrast, I expected the probable mutation effect to have no support both because of the flawed theory underlying the hypothesis and the evidence that wear rate does not universally decrease with the adoption of agriculture (Irish 1998; Kaifu, 2000; Kaifu, 2006; Ritter et al., 2009). I also originally expected the selection against impaction model to be rejected based on the average jaw length and average rates of agenesis I plotted during pilot data collection for archaeological populations (Figure 19) and studies reporting no relationship between jaw length and agenesis (Roald, 1982; Yuksel, 1997; Tavajohi-Kermani et al., 2002; but see Wisth et al, 1974; Sarnas et al., 1983; Dermaut et al., 1986). Instead, I found a high level of support for the selection against impaction model to explain changes in the human dentition across the industrial transition (Figure 15) and no model to be supported during the agricultural transition.

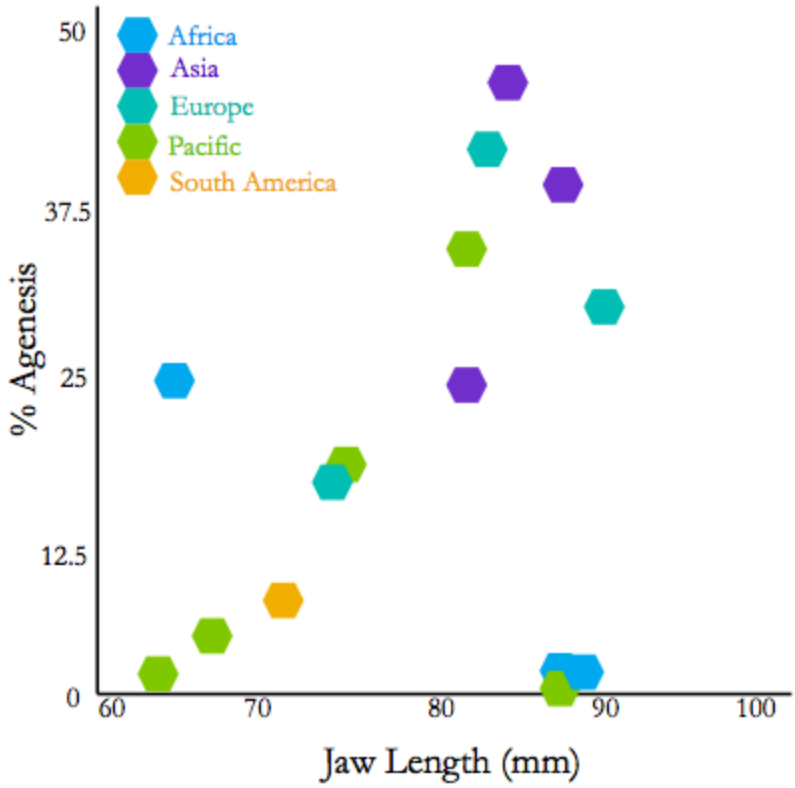


Figure 19: Jaw length data compared with agenesis frequencies for archaeological populations. This data was taken from the literature and, while potentially informative, was summed across each population and did not control for tooth size.

Despite being highly unexpected, I feel confident in the statistical and analytical underpinnings of my result, as it was done in the most conservative way possible. Unless impaction could be definitively determined in the specimen, I coded it for this analyses as "no impaction". This means that all individuals that had evidence of roots but no crown were assumed to be not impacted, and my sample represents a clear underestimate. Furthermore, this transition is supported in both Portuguese and Japanese populations, indicating that one population is not driving the output of the results. Biologically, I am more hesitant to accept the results of the study. I am surprised by the speed at which selection appeared to have happened, as normally it takes more than five generations for

the effects of differential reproductive success to manifest (Hawks et al., 2007; Bell, 2012; Gillman and Wright, 2013). However, it is plausible that if both the dietary shift related to industrialization was very rapid and the negative effects of impaction so great to impede the reproductive success of the population then this result could be obtained. While there is some evidence to support this (see Discussion in Chapter 4)**,** I would like to test this hypothesis in more populations. Therefore, determining the robusticity of these results is a high priority.

If this claim is supported, one of the broader impacts of this work is demonstrating that the Arizona State University Dental Anthropology Scoring System (ASUDAS) trait frequencies may be determined by selection, instead of just drift as previously thought (Scott and Alexandersen, 1992**)**. While analysis of ASUDAS characters works well for modern populations, recent work has attempted to use these traits to analyze relationships of early modern humans or fossil hominins (Guatelli-Steinberg and Irish, 2005; Irish et al., 2013; Xing et al., 2014; Crompton and Stringer, 2015**).** One of the underlying assumptions of this analysis has been that differences in character frequency among the traits are attributed to drift. Demonstrating that selection is acting on some of the characters casts doubt on the utility of this system to determine relationships of more distant groups, as traits under selection are more likely to undergo convergence due to similar functional demands.

During the agricultural transition, none of the hypotheses were supported. This means both a) that there was very little change in agenesis or impaction over the agricultural transition and b) that the underlying predictions of the three hypotheses were not supported during the agricultural transition. Two of the populations, Japan and Egypt,

were sampled after some initial adoption of agriculture, and this may help explain the former result (though the other two populations show little over time in these factors either). The latter result, however, is robustly supported and suggests that none of the proposed explanations actually fit the data. Given the correspondence of the archaeological and modern patterns of agenesis, genetic drift is one possibility, as discussed above. However, the unexpected relationship between dental arch space and M3 agenesis suggests that drift is not a complete explanation. Robust jaws are generally thought to be useful in processing hard or tough food, initially suggesting dietary stress as the mechanism (although most researchers have found agricultural diets had softer physical properties; Gilbert and Mielke, 1985; Larsen, 1995). However, if nutritional stress were the causative mechanism, there would have been a greater correspondence between agenesis probability and fluctuating asymmetry. As discussed in Chapter 4, there are two possible evolutionary interpretations to explain the data. First, that there was a trade-off in energy investments to grow big jaws or form the third molar. Alternatively, developmental delay could be the ultimate cause of third molar agenesis, but this developmental delay is unrelated to changes in nutritional status. Humans have a slowed life history (Dean, 2006; Smith et al., 2010) relative to even their closest relatives, and individuals with the most delayed development tend to have the greatest frequencies of agenesis. While there is a clear link between skeletal growth and nutritional status, it is unclear whether this link exists between nutrition and eruption pattern, with researchers finding evidence that both support (Hiernaux, 1968; Enwonwu, 1973; Suri et al., 2004) and contradict (Elamin and Liversidge, 2013**)** this claim. Slowing down the pace of development, which does seem to

lead to third molar agenesis in modern populations, may have allowed individuals to grow more robust jaws.

3. Are third molar agenesis and impaction related pathologies?

I predicted that third molar agenesis and impaction were independent phenomena. Specifically, I predicted that agenesis was driven by developmental delay and thus independent to changes in jaw size, while impaction was driven by changes in jaw size. This hypothesis, though supported by some data, was novel in its supposition that not all pathologies affecting the third molar have a single cause. My results support very few of these conclusions, instead suggesting that: a) frequencies of both agenesis and impaction are driven by changes in jaw size and b) agenesis and impaction are sometimes but not always, related.

In the agricultural transition, and presumably in earlier human evolution, there was no relationship found between third molar agenesis and impaction. While an increase in impaction was correlated with a decrease in jaw size, agenesis had the opposite relationship, even when controlling for tooth size (Figure 14)**.** As discussed above, I still lack the mechanism to explain the pattern of agenesis before the industrial transition, but feel confident in stating that it is independent from impaction in this case.

Third molar agenesis and impaction were related phenomena when the selective pressure against impaction was so strong as to create selection for agenesis. This likely explains my results for the industrial transition, though it may have emerged earlier in other populations. Testing a larger cross-cultural sample that extends into the mid-20th century will help determine the robustness of the results. However, the window of time between industrialization having a large effect on the rate of impaction and antibiotics and

modern medical interventions becoming widespread is at most 7 generations. Therefore, the ability to further explore this phenomenon is problematic. If pre-industrial non-pathological archaeological populations with high levels of impaction (>10%) can be identified, this may be a way to expand the study further.

Importantly, while impaction may be thought of as an "intermediate" character state between third molar presence and agenesis during the industrial transition, it is unlikely that the mechanism responsible for impaction is (usually) the same mechanism responsible for agenesis. There are likely multiple mechanisms responsible for determining both impaction and agenesis (e.g. M3 agenesis linked to down syndrome vs M3 agenesis linked with surgery numbing the inferior alveolar nerve; Swee et al., 2013; Ramiro-Verduga et al., 2015), but in general agenesis appears to be determined earlier in ontogeny and has less of an environmental component (Vastardis, 2000; Matalova et al., 2008; Panchabi, 2012). This does not preclude the possibility of some types of impaction being determined early, particularly those cases where available space is not a factor (Tsai, 2006; Sharpira et al., 2011).

Determining the predictors and evolutionary processes that explain agenesis still does not explain the mechanism by which it is produced. Developmentally, there is little evidence to suggest that teeth arrest after initial crypt formation, with almost all cases of agenesis showing no initiation (Sisman et al., 2007; Liversidge, 2008; Kazanci et al., 2010). Still, the morphological evidence suggests multiple related causes. Agenesis is most common in 1 or 2 molars, and this is true in both modern and archaeological populations. Therefore, either there may be different mechanisms which determine agenesis in different numbers of teeth, or each dental arch responds to environmental feedback to determine

whether or not a tooth will form. Other studies, however, have found that having agenesis of one third molar makes it more likely to have agenesis in other teeth (Garn and Lewis, 1962), suggesting that there may be higher level mechanisms that determine agenesis in other individuals. Since many of the patterns of agenesis are the same in the industrial, agricultural, and modern populations, it is likely that many of these mechanisms have been determining agenesis from early in human evolutionary history.

4. How did changes in the human diet change the frequencies of these pathologies?

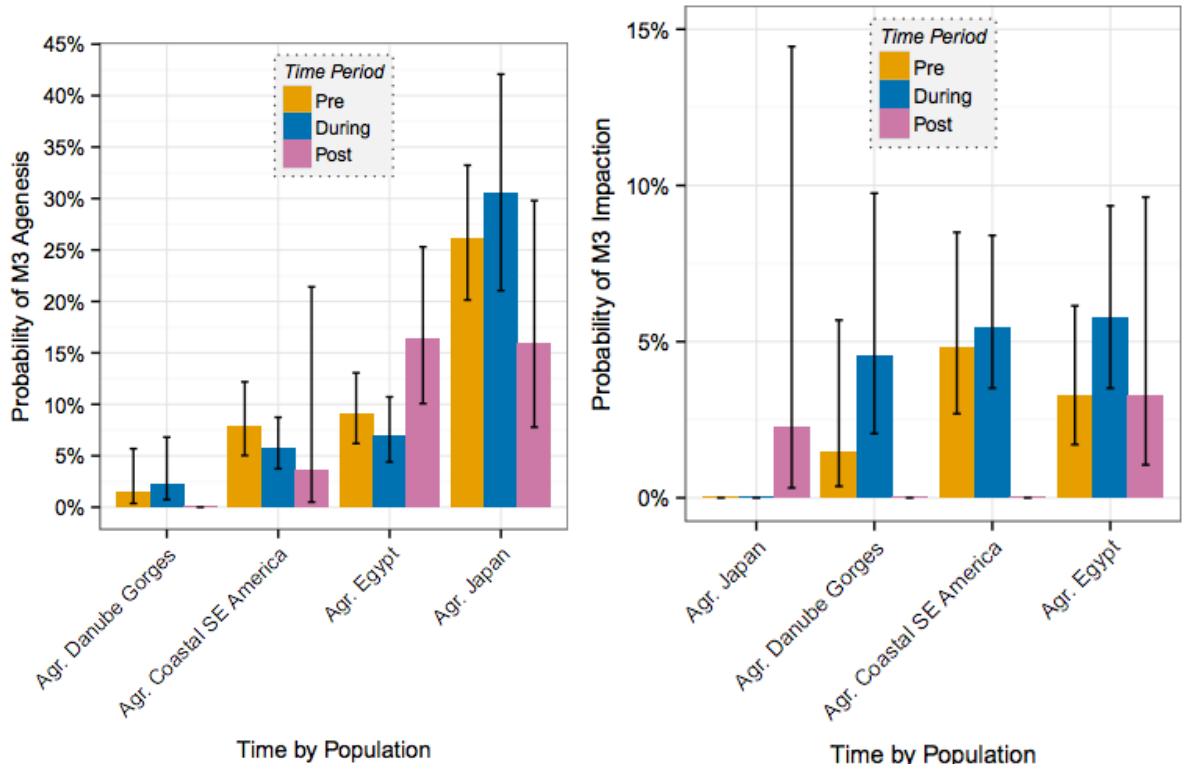


Figure 20: Comparisons of agricultural transition populations across time points.

I found some evidence for change in M3 agenesis and impaction across the industrial transition, as discussed in the previous sections. During the agricultural transition, I found very little change in the rates of agenesis. None of the time points were significantly different from other time points (Figure 20a) in the frequency of agenesis and there were no consistent trends over time**.** Impaction, by contrast, remained at a low rate until the origins of industrialization (Figure 20b) If anything, there were decreases in impaction rate at the end of the agricultural transition, but the events were so rare to not have sample sizes large enough to test this result. Though it is possible that this lack of change in agenesis reflects the biological reality, there are other sampling concerns that may also explain my results. Agenesis was at relatively low frequencies for many of the populations, and detecting changes across time for rare occurrences presents many statistical problems (Frei and Schar, 2001; King and Zeng, 2001; Hartmann 2002). I tried to correct for this before data collection started by purposely choosing populations where the rate of agenesis was high in modern samples. While this was moderately successful, it also meant sampling some sites (e.g., Kanenokuma in Japan) where the rate of agenesis was much higher than any other site in the population. There are also problems with starting the sampling after some agriculture has been detected in Egypt or Japan. The Jomon and Jebel Sahaba populations were originally considered as more appropriate pre-agricultural time points for these populations, but there are problems with validating the genetic or even cultural affinity of these groups to later samples. Doigahama, the earliest sample in the Japanese agricultural transition, likely combined agriculture foraged plants and tubers similar to the Jomon pattern (Temple and Larsen, 2007; Temple, 2015). Similarly, Badari and Naqada in Egypt are considered proto-agriculturalists (Starling and Stock, 2007; Kuper

and Riemer, 2013**).** Therefore, I made the choice to have some variance in the rate of agriculture available in the pre-agricultural sample instead of potentially comparing the effects in unrelated populations. To address this issue, many of the agricultural results presented are pooled across time points. Therefore, though this does not affect the outcome of the industrialization study or any of the positive results presented for the agricultural study, it may help explain why I received negative results for assessing the fit of the three hypotheses across time points.

Understanding the skeletal impacts on cultural change has been one of the main goals of bioarchaeology. Morphological changes that arise with the advent of farming have been well-documented (e.g., Larsen, 1995), though the methods and speed by which farming is introduced as well as the type of crops domesticated (Taylor et al., 2000; Bellwood, 2001; Eshed and Hershkovitz ,2006; Hershkovitz and Gopher, 2008). The differences between, for example emmer wheat and barley in Egypt and rice in Japan may affect morphology directly through, for example, the magnitude of change in jaw size or other physical changes and indirectly through changes to lifestyle that have an effect on health. For example, the increase in Linear Enamel Hypoplasias on early proto-agricultural populations in Egypt and suggests that the transition to agriculture had a greater negative affect on health than similar transitions in the South East USA (Starling and Stock, 2007). There is also evidence for variance in diet within the sites sampled during the transition (e.g. Doigahama vs Koura in Japan; Temple and Larsen, 2007). Therefore, the main reason that there was no clear signal in the agricultural transition may be that individual populations experienced these dietary changes differently. For this study, I purposely chose populations with disparate agricultural crops to capture this variation. However, future

studies might benefit by developing an experimental design that minimizes inter-population variance.

5. How can understanding the evolutionary origins of impaction and agenesis shed light on modern tooth extraction?

First, while evolutionary medicine has become more prominent over the past decade, evolutionary dentistry is still in its nascency. For example, it was surprising how many dental papers referenced early man evolving third molars because of their dietary needs (e.g. Bergman, 1998; Silvestri and Singh, 2003; Zou et al., 2010; Kaur et al., 2012; Siddiqui et al., 2015), misunderstanding that third molar retention is the ancestral state for hominins, hominoids, primates, and mammals. There is also an understanding of evolution as "use it or lose it" that lacks so much nuance to make the staunchest supporters of the probable mutation effect blush. While the results from the archaeological analysis are certainly complicated, "selection against impaction" being the driving force of agenesis in recent human populations is something that is both easy to understand and reflects many of the broader concepts useful for thinking in an evolutionary perspective. I plan to share my work broadly with the dental community as I think it may be a helpful example for why it is important to consider evolution, or ultimate causes, in treatment.

On a more controversial note, one of the biggest debates in dentistry is whether third molars should be removed prophylactically. Proponents for early removal point to an increase in complications with surgeries later in life (Renton et al., 2001; Phillips et al., 2010; Bello et al., 2011), while those against it stress the risk of unnecessary complications and potential for fraud (Kandasamy and Rinchuse, 2009; Siddiqui et al., 2015). Measured in compensation for hours worked, it is the most lucrative form of dental procedure for both

oral surgeons and general dentists (Gavazzi et al., 2014; Nguyen 2014), and dentists are able to charge more for procedures done earlier in life when the tooth has not left the crypt (Eklund and Pittman, 2001). Currently it is estimated that up to ⅔ of procedures carried out are superfluous, at costs of up to 3 billion dollars annually in the US alone (Friedman, 2007; Costa et al., 2013 Nguyen 2014).

Certainly, impaction is a life-threatening illness without medical intervention, and some individuals need to have their third molars removed. While arguments exist on both sides for when and how third molars should be treated, one understudied line of research is the relative impaction risk of different factions of the population. Assessing future risk for pathology and using this assessed risk to plan treatment is an established protocol for many prophylactic procedures (Priori et al., 2003; Tansley et al., 2004). It is clear from the results of the meta-analyses that, for example, an Asian female missing two maxillary third molars would be at a higher risk for developing impaction on the mandibular third molars than an African man, even if these two individuals consumed the same diet. Determining relative risk of impaction would help lower overall healthcare spending while providing targeted treatment to those most likely to develop this pathology.

Furthermore, the results of my impaction meta-analysis paper revealed what is potentially principal-agent conflict in dental publications. Those with the greatest to gain financially from certain results are also those who potentially have the greatest expertise to assess the results. In the six cases where dental researchers and practicing dentists published studies of impaction in populations from the same country, the dentists estimated the frequency of impaction to be higher than their non-practicing cohort in five

cases (Figure 21) While the sample size is small and variance in the populations may be one explanatory variable, it is one of the most interesting future directions for this project.

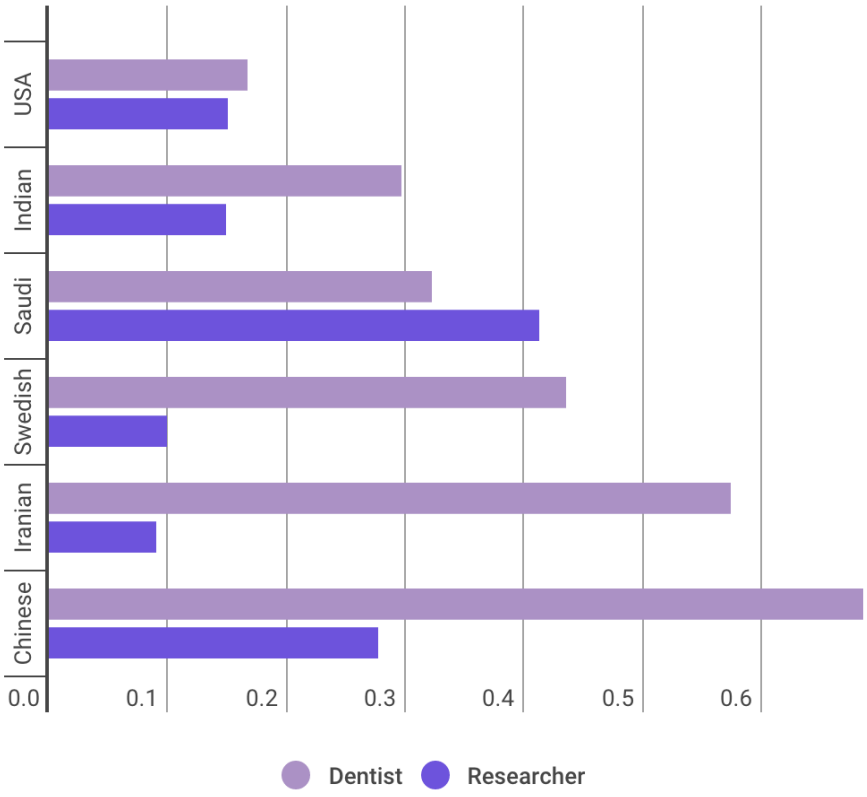


Figure 21: Comparisons of estimations of third molar impaction by profession. The methods of each paper was read to determine which author assessed impaction, then determinations were made whether this author had a private practice outside of dental school teaching.

CONCLUSIONS

1) Roughly 1 in 4 adults have agenesis of one or more third molars and 1 in 4 adults have impaction of one or more third molars.
2) Third molar agenesis is higher in females, populations from Asia and the Middle East and in the maxilla. It is most common to have 1 or 2 third molars missing.
3) Third molar impaction, by contrast, is higher in the mandible and may not differ between sexes. It is also highest in populations from the Middle East and Asia and occurs most frequently in 1 or 2 molars.
4) At least in the populations studied, impaction did not exist in high frequencies until well after agriculture had been adopted.

5) In industrial populations, selection against impaction is the model that best explains the pattern of agenesis.
6) In agricultural populations, there was very little change across time in agenesis or impaction. Furthermore, while we found a positive relationship between these two variables in the agricultural transition.
7) There are likely two different mechanisms driving the prevalence of human third molar agenesis, one at work since the time of *Homo erectus* and one with much more recent origins.
8) Using the results of this study to assess relative risks of developing impaction will decrease healthcare spending on unnecessary prophylactic procedures while targeting treatment to those most likely to develop this pathology.

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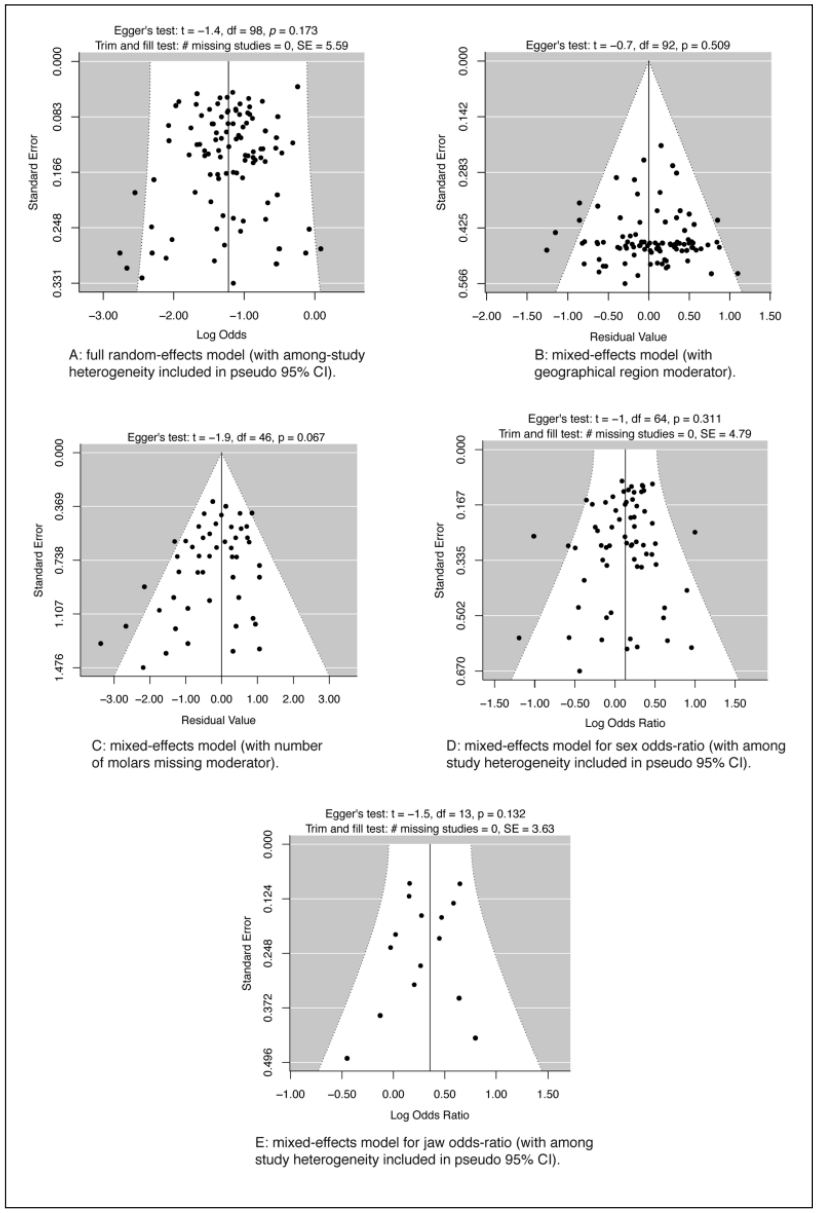
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Morphologic and Demographic Predictors of Third Molar Agenesis: A Systematic Review and Meta-analysis

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Appendix



Appendix Figure 1. Funnel plots and asymmetry tests to assess potential publication bias for the 5 models discussed in the main text.

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Appendix Table 1. Heterogeneity Estimates and Tests.

Model	n[a]	I^2, %	H^2	Tau^2	LRT [b]
All studies					
Random effects	100	97.14	34.95	0.3284	4,207.4
Continent moderator	100	95.71	23.32	0.2215	3,075.9
No. of molars missing	50	88.62	8.79	0.2233	1,671.9
Male vs. female	66	49.30	1.97	0.0404	127.2
Mandible vs. maxilla	15	63.10	2.71	0.0401	44.5

LRT, likelihood ratio test.
[a]Effect sizes.
[b]All LRT values, $P < 0.0001$.

Appendix Table 2. Pairwise Comparisons of Third Molar Agenesis Frequency in 7 Geographic Regions.

Continent	Estimate[a]	SE	z	P Value[b]
Africa				
Asia	1.94	0.41	4.75	**<0.0001**
Europe	1.51	0.41	3.68	**0.0040**
Middle East	1.80	0.43	4.18	**0.0006**
N. America	1.27	0.41	3.07	**0.0280**
Oceania	1.71	0.52	3.27	**0.0170**
S. America	1.29	0.42	3.09	**0.0280**
Asia				
Europe	–0.43	0.13	–3.20	**0.0209**
Middle East	–0.14	0.19	–0.75	1.0000
N. America	–0.66	0.15	–4.51	**0.0001**
Oceania	–0.23	0.35	–0.65	1.0000
S. America	–0.64	0.16	–4.04	**0.0010**
Europe				
Middle East	0.29	0.19	1.51	1.0000
N. America	–0.24	0.15	–1.53	1.0000
Oceania	0.20	0.35	0.57	1.0000
S. America	–0.21	0.16	–1.30	1.0000
Middle East				
N. America	–0.52	0.20	–2.61	0.1071
Oceania	–0.09	0.38	–0.23	1.0000
S. America	–0.50	0.21	–2.40	0.1798
North America				
Oceania	0.44	0.36	1.22	1.0000
S. America	0.02	0.18	0.12	1.0000
Oceania: S. America	–0.41	0.36	–1.14	1.0000

[a]Estimate of first difference on log-odds scale.
[b]Based on the sequential Bonferroni method. Values in bold are significant at the $P < 0.05$ level.

Appendix Table 3. Third Molar Agenesis Frequencies.

Study	Year	Population	Sample Type	Age, y[a]		Sex	Continent	*N*	Agenesis	
				Min	Max				*n*	%
Abdolahi	2013	USA (white)	Orthodontic patients	13	17	Pooled	N. America	739	142	19.22
Adler and Adler-Hradecky	1963	Hungarian	Orthodontic patients	18	21	Pooled	Europe	591	163	27.58
Afify and Zawawi	2012	Saudi	Dental patients	12	30	Pooled	Middle East	878	185	21.1
Alam et al.	2014	Malaysian	Orthodontic patients	12	21	Pooled	Asia	219	66	30.1
Alam et al.	2014	Chinese	Orthodontic patients	12	21	Pooled	Asia	81	27	33.3
Al-Delaimi et al.	2010	Iraqi	Dental students	18		Pooled	Middle East	312	117	37.5
Anderson and Popovich	1977	Canadian	Dental patients	16	20	Pooled	N. America	218	44	20.18
Arany et al.	2004	Japanese	Dental patients	14	24	Pooled	Asia	1,282	542	42.28
Asakura	1975	Japanese	Dental patients	16	26	Female	Asia	277	117	42.24
Banks	1934	USA (white)	Dental patients	15	22	Pooled	N. America	461	91	19.74
Bansal	2012	Indian	Orthodontic patients	13	25	Pooled	Asia	400	104	26
Bastidas and Rodriguez	2004	Columbian	Orthodontic patients	14	21	Pooled	S. America	141	16	11.35
Bhowmik et al.	2013	Indian	Orthodontic patients	14	23	Pooled	Asia	268	87	32.46
Bhutta and Sadozai	2013	Pakistani	Orthodontic patients	12	35	Pooled	Asia	270	86	31.85
Byahatti et al.	2011	Indian	Dental patients	17	30	Pooled	Asia	150	28	18.67
Byahatti and Ingafou	2012	Libyan	Dental students	17	26	Pooled	Africa	200	13	6.5
Castilho et al.	1990	Brazilian	Dental patients	12	14.9	Pooled	S. America	201	41	20.4
Celikoglu et al.	2010	Turkish	Orthodontic patients	20	26	Pooled	Middle East	351	61	17.31
Celikoglu and Kamak	2012	Turkish	Orthodontic patients	13	17	Pooled	Middle East	1,046	237	22.66
Chagula	1960	Ugandan	Museum collection	16		Male	Africa	188	10	5.32
Costa et al.	2007	Brazilian	Orthodontic patients	12		Pooled	S. America	807	119	14.75
Crispim et al.	1972	Brazilian (black)	Military personel	18	24	Male	S. America	353	64	18.13
Crispim et al.	1972	Brazilian (white)	Military personel	18	24	Male	S. America	137	16	11.7
Daito et al.	1992	Japanese	Dental students	24		Pooled	Asia	2,769	1373	49.6
Diaz-Perez and Echaverry-Navarrete	2009	Mexican	Dental patients	13	50	Pooled	N. America	112	24	21.43
Elomaa and Elomaa	1973	Finnish	Dental patients	15	22	Pooled	Europe	202	67	33.2
Endo et al.	2015	Japanese	Orthodontic patients	13	21	Pooled	Asia	1,291	417	32.3
Garcia-Hernandez and Beltran	2008	Atacama	Random sample	16	55	Pooled	S. America	90	24	26.67
Garcia-Hernandez and Beltran	2009	Aymara	Random sample	18	40	Pooled	S. America	78	17	21.79
Garcia-Hernandez et al.	2008	Chilean	Orthodontic patients	14	20.9	Pooled	S. America	400	99	24.75
Garcia-Hernandez and Rodriguez	2009	Chilean	Dental patients	14.1	26.8	Pooled	S. America	100	20	20
Garn et al.	1963	USA (white)	Orthodontic patients	14		Pooled	N. America	476	78	16.4
Ghada	2005	Iraqi	Dental patients	11	25	Pooled	Middle East	200	48	24
Goblirsch	1930	USA (white)	Dental patients	19	78	Pooled	N. America	2,112	191	9.04
Godt and Greve	1980	German	Orthodontic patients	12	16	Pooled	Europe	1,555	314	20.19
Golovcencu and Geletu	2012	Romanian	Orthodontic patients	11	25	Pooled	Europe	250	70	28
Goren et al.	2005	Israeli	Military personel	18		Male	Middle East	226	87	38.5
Grahnen	1956	Swedish	Dental students	17	43	Pooled	Europe	1,064	262	24.62
Gravely	1965	British (white)	Dental patients	14	15	Pooled	Europe	81	21	25.9
Haavikko	1971	Finnish	Students[b]	14	18	Pooled	Europe	298	62	20.81
Haga et al.	2013	Japanese	Anthropological survey	16	57	Pooled	Asia	264	78	29.55
Haga et al.	2013	Korean	Anthropological survey	20	40	Pooled	Asia	223	71	31.84
Hamano	1929	Japanese	Dental patients	16		Pooled	Asia	1,300	239	18.38
Haralabakis	1957	Greek	Dental students	19	39	Pooled	Europe	553	110	19.89

(continued)

Appendix Table 3. (continued)

Study	Year	Population	Sample Type	Age, y[a]		Sex	Continent	*N*	Agenesis	
				Min	Max				*n*	%
Harris and Clark	2008	USA (white)	Orthodontic patients	12	18	Pooled	N. America	1,100	184	16.73
Harris and Clark	2008	USA (black)	Orthodontic patients	12	18	Pooled	N. America	600	35	5.83
Hattab	1995	Jordanian	Dental students	18	23	Pooled	Middle East	232	63	27.16
Hellman	1936	USA (white)	Dental patients	18		Pooled	N. America	433	110	25.4
Hentisz	2003	USA (white)	Orthodontic patients	11	24	Pooled	N. America	200	31	15.5
Hentisz	2003	USA (black)	Orthodontic patients	11	28	Pooled	N. America	233	13	5.58
Holzl	1972	German	Students[b]	18	31	Pooled	Europe	486	77	15.84
Hubenthal	1989	German	Orthodontic patients	12	36	Pooled	Europe	2,061	427	20.7
Hugoson and Kugelberg	1988	Swedish	Anthropological survey	15	30	Pooled	Europe	207	46	22.22
Kaur and Sheikh	2013	Indian	Students[b]	18	25	Pooled	Asia	1,840	289	15.7
Kazanci et al.	2010	Turkish	Orthodontic patients	12	16	Pooled	Middle East	2,579	615	23.85
Keene	1965	USA (white)	Military personel	17	25	Male	N. America	257	70	27.24
Kikuchi	1970	Japanese	Military personel	16	25	Male	Asia	500	234	46.8
Kirveskari et al.	1978	Skolt Lapps	Anthropological survey	12	20	Pooled	Europe	72	14	19.44
Komerik et al.	2014	Turkish	Orthodontic patients	15		Pooled	Middle East	108	40	37
Krekeler et al.	1974	German	Orthodontic patients	12	33	Pooled	Europe	1,614	455	28.19
Kruger et al.	2001	New Zealander	Longitudinal study	18	18	Pooled	Oceania	842	235	27.91
Lavelle and Moore	1973	British (white)	Dental patients	18	40	Pooled	Europe	4,000	259	6.48
Lavelle and Moore	1973	British (black)	Dental patients	18	40	Pooled	Europe	1,000	247	24.7
Lee et al.	2009	Korean	Dental patients	16	24	Pooled	Asia	1,129	464	41.1
Liu et al.	2004	Chinese	Orthodontic patients	14	18	Pooled	Asia	234	69	29.49
Lynham	1990	Australian (white)	Military personel	16	26	Pooled	Oceania	662	150	22.66
Maderia and Lopes	1976	Brazilian (mixed)	Dental students	18	21	Pooled	S. America	348	71	20.4
Mani et al.	2014	Malaysian	Dental patients	12	16	Pooled	Asia	834	214	25.7
Matsuo	1986	Japanese	Students[b]	18	27	Pooled	Asia	629	234	37.2
Mok and Ho	1996	Chinese	Dental patients	12	16	Pooled	Asia	786	224	28.5
Nanda	1954	USA (white)	Orthodontic patients	18	21	Female	N. America	200	18	9
Nanda and Chawla	1959	Indian	Dental patients	17	30	Pooled	Asia	1,300	335	25.77
Nicodemo	1973	Brazilian	Students[b]	12	25	Pooled	S. America	232	43	18.53
Oliveira and Serra Negra	1976	Brazilian (white)	Students[b]	14	22	Pooled	S. America	416	60	14.42
Oliveira and Serra Negra	1984	Brazilian (black)	Students[b]	14	18	Pooled	S. America	120	13	10.83
Pedersen	1949b	S.W. Greenlander	Anthropological survey	25	50	Pooled	N. America	210	62	29.52
Pedersen	1949a	E. Greenlander	Anthropological survey	25	50	Pooled	N. America	257	94	36.6
Peltola et al.	1997	Estonian	Dental patients	14	17	Pooled	Europe	392	68	17.35
Pillai et al.	2014	Indian	Dental patients	20	35	Pooled	Asia	1,100	123	11.2
Raloti et al.	2013	Indian	Students[b]	18	30	Pooled	Asia	350	80	22.9
Ren and Kumar [AQ: 4]	2014	Malaysian	Dental patients	17	25	Pooled	Asia	50	12	24
Ren and Kumar	2014	South Indian	Dental patients	17	25	Pooled	Asia	50	28	56
Rozkovcova et al.	2004	Czech	Dental patients	12	21	Pooled	Europe	1,000	225	22.5
Saito	1936	Japanese	Dental patients	16		Pooled	Asia	332	122	36.75
Sandhu and Kapila	1982	Indian	Dental patients	17	35	Pooled	Asia	1,015	79	7.78
Sandhu and Kaur	2005	Indian	Dental students	17.5	20	Pooled	Asia	100	24	24
Sapoka and Demirjian	1971	French-Canadian	Dental patients	11	11	Pooled	N. America	193	48	24.87
Sarmento et al.	2008	Brazilian	Orthodontic patients	11	15	Pooled	S. America	170	45	26.47

(continued)

Appendix Table 3. (continued)

Study	Year	Population	Sample Type	Age, y[a]		Sex	Continent	*N*	Agenesis	
				Min	Max				*n*	%
Sarmiento and Herrera	2004	Columbian	Dental students	16	25	Pooled	S. America	456	96	21.05
Sengupta et al.	1999	British (white)	Dental patients	25		Pooled	Europe	100	22	22
Shah and Boyd	1979	Anglo-Canadian	Dental patients	20		Pooled	N. America	635	152	23.94
Shah and Parekh	2014	Indian	Dental patients	15	19	Pooled	Asia	100	34	34
Shinn	1976	British (white)	Orthodontic patients	14		Pooled	Europe	2,500	318	12.72
Sonnabend	1966	German	Orthodontic patients	15	30	Pooled	Europe	2,000	449	22.45
Speckin	1981	German	Orthodontic patients	15	26	Pooled	Europe	750	142	18.93
Tanner	1946	Swiss	Orthodontic patients	13	17	Pooled	Europe	534	142	26.59
Thompson et al.	1974	Anglo-Canadian	Dental patients	16		Pooled	N. America	521	116	22.27
Trondle	1973	German	Dental patients	12	33	Pooled	Europe	1,068	304	28.46
Upadhyaya	2012	Nepalese	Orthodontic patients	12	34	Pooled	Asia	294	148	50.34
Weise and Bruntsch	1965	German	Orthodontic patients	12	24	Pooled	Europe	669	196	29.3

[a]Blank cells indicate missing values.
[b]College, high school.

Appendix Table 4. Third Molar Agenesis Frequencies by Number of Missing Molars.

Study	Year	Population	Sample Type	Age, y[a]		Continent	No. of Third Molars Missing				
				Min	Max		0	1	2	3	4
Abdolahi	2013	USA (white)	Orthodontic patients	13	17	N. America	597	64	49	11	18
Adler and Adler-Hradecky	1963	Hungarian	Orthodontic patients	18	21	Europe	428	67	55	20	21
Al-Delaimi et al.	2010	Iraqi	Dental students	18		Middle East	195	53	43	12	9
Banks	1934	USA (white)	Dental patients	15	22	N. America	370	29	33	14	15
Bhowmik et al.	2013	Indian	Orthodontic patients	14	23	Asia	181	38	29	20	0
Byahatti et al.	2011	Indian	Dental patients	17	30	Asia	122	13	7	3	5
Byahatti and Ingafou	2012	Libyan	Dental students	17	26	Africa	187	5	2	1	5
Celikoglu et al.	2010	Turkish	Orthodontic patients	20	26	Middle East	101	14	31	4	3
Celikoglu and Kamak	2012	Turkish	Orthodontic patients	13	17	Middle East	809	96	73	26	42
Costa et al.	2007	Brazilian	Orthodontic patients	12		S. America	688	40	44	11	24
Daito et al.	1992	Japanese	Dental students	24		Asia	1391	412	512	179	275
Diaz-Perez and Echaverry-Navarrete	2009	Mexican	Dental patients	13	50	N. America	88	10	11	3	0
Endo et al.	2015	Japanese	Orthodontic patients	13	21	Asia	874	138	143	43	93
Garcia-Hernandez and Beltran	2008	Atacama	Random sample	16	55	S. America	66	9	12	0	3
Garcia-Hernandez and Beltran	2009	Aymara	Random sample	18	40	S. America	61	11	6	0	0
Garcia-Hernandez et al.	2008	Chilean	Orthodontic patients	14	20.9	S. America	301	35	39	11	14
Garcia-Hernandez and Rodriguez	2009	Chilean	Dental patients	14.1	26.8	S. America	80	10	7	3	0
Ghada	2005	Iraqi	Dental patients	11	25	Middle East	152	24	16	3	5
Godt and Greve	1980	German	Orthodontic patients	12	16	Europe	1241	123	113	20	58
Golovcencu and Geletu	2012	Romanian	Orthodontic patients	11	25	Europe	180	32	18	11	9

(continued)

Appendix Table 4. (continued)

Study	Year	Population	Sample Type	Age, y[a]		Continent	No. of Third Molars Missing				
				Min	Max		0	1	2	3	4
Grahnen	1956	Swedish	Dental students	17	43	Europe	802	105	94	26	37
Gravely	1965	British (white)	Dental patients	14	15	Europe	60	6	8	3	4
Harris and Clark	2008	USA (white)	Orthodontic patients	12	18	N. America	916	74	70	17	23
Harris and Clark	2008	USA (black)	Orthodontic patients	12	18	N. America	565	18	12	1	4
Hattab	1995	Jordanian	Dental students	18	23	Middle East	169	27	25	7	4
Hellman	1936	USA (white)	Dental patients	18		N. America	323	42	41	11	16
Hentisz	2003	USA (white)	Orthodontic patients	11	24	N. America	169	15	11	2	3
Hentisz	2003	USA (black)	Orthodontic patients	11	28	N. America	220	7	3	2	1
Holzl	1972	German	Students[b]	18	31	Europe	409	29	20	13	15
Hubenthal	1989	German	Orthodontic patients	12	36	Europe	1634	114	138	43	132
Hugoson and Kugelberg	1988	Swedish	Anthropologic survey	15	30	Europe	161	14	15	8	9
Kazanci et al.	2010	Turkish	Orthodontic patients	12	16	Middle East	1964	238	214	66	97
Kirveskari et al.	1978	Skolt Lapps	Anthropologic survey	12	20	Europe	58	3	5	3	3
Komerik et al.	2014	Turkish	Orthodontic patients	15		Middle East	68	12	16	6	6
Kruger et al.	2001	New Zealander	Longitudinal study	18	18	Oceania	607	79	73	46	37
Lee et al.	2009	Korean	Dental patients	16	24	Asia	665	155	160	64	85
Maderia and Lopes	1976	Brazilian (mixed)	Dental students	18	21	S. America	277	33	26	7	5
Mani et al.	2014	Malaysian	Dental patients	12	16	Asia	616	81	72	22	39
Matsuo	1986	Japanese	Students[b]	18	27	Asia	395	88	89	21	36
Mok and Ho	1996	Chinese	Dental patients	12	16	Asia	562	76	82	23	43
Nicodemo	1973	Brazilian	Students[b]	12	25	S. America	189	7	22	2	12
Oliveira and Serra Negra	1976	Brazilian (white)	Students[b]	14	22	S. America	356	20	17	6	17
Oliveira and Serra Negra	1984	Brazilian (black)	Students[b]	14	18	S. America	107	3	3	2	5
Pogrel	1967	British	Orthodontic patients	13	13.5	Europe	60	5	13	5	3
Sandhu and Kaur	2005	Indian	Dental students	17.5	20	Asia	96	12	6	2	4
Shah and Parekh	2014	Indian	Dental patients	15	19	Asia	66	23	6	3	2
Sonnabend	1966	German	Orthodontic patients	15	30	Europe	1551	186	131	56	76
Speckin	1981	German	Orthodontic patients	15	26	Europe	608	39	37	14	52
Tanner	1946	Swiss	Orthodontic patients	13	17	Europe	392	63	42	18	19
Weise and Bruntsch	1965	German	Orthodontic patients	12	24	Europe	473	51	70	29	46

All samples were pooled sexes.
[a]Blank cells indicate missing values.
[b]College, high school.

Appendix Table 5. Third Molar Agenesis Frequencies by Sex.

Study	Year	Population	Sample Type	Age, y[a]		Sex	Continent	*N*	Agenesis	
				Min	Max				*n*	%
Adler and Adler-Hradecky	1963	Hungarian	Orthodontic patients	18	21	Male	Europe	302	83	27.48
Adler and Adler-Hradecky	1963	Hungarian	Orthodontic patients	18	21	Female	Europe	289	80	27.68
Afify and Zawawi	2012	Saudi	Dental patients	12	30	Male	Middle East	430	86	20
Afify and Zawawi	2012	Saudi	Dental patients	12	30	Female	Middle East	448	99	22.1
Al-Delaimi et al.	2010	Iraqi	Dental students	18		Male	Middle East	148	60	40.5
Al-Delaimi et al.	2010	Iraqi	Dental students	18		Female	Middle East	164	57	34.8
Alam et al.	2014	Chinese	Orthodontic patients	12	21	Male	Asia	33	13	39.4
Alam et al.	2014	Chinese	Orthodontic patients	12	21	Female	Asia	48	14	29.2
Alam et al.	2014	Malaysian	Orthodontic patients	12	21	Male	Asia	107	33	30.8
Alam et al.	2014	Malaysian	Orthodontic patients	12	21	Female	Asia	112	32	28.6
Bansal	2012	Indian	Orthodontic patients	13	25	Male	Asia	176	28	15.91
Bansal	2012	Indian	Orthodontic patients	13	25	Female	Asia	224	76	33.93
Bastidas and Rodriguez	2004	Columbian	Orthodontic patients	14	21	Male	S. America	61	11	18.03
Bastidas and Rodriguez	2004	Columbian	Orthodontic patients	14	21	Female	S. America	80	5	6.25
Bhowmik et al.	2013	Indian	Orthodontic patients	14	23	Male	Asia	94	24	25.53
Bhowmik et al.	2013	Indian	Orthodontic patients	14	23	Female	Asia	174	63	36.21
Bhutta and Sadozai	2013	Pakistani	Orthodontic patients	12	35	Male	Asia	86	23	26.74
Bhutta and Sadozai	2013	Pakistani	Orthodontic patients	12	35	Female	Asia	184	63	34.24
Byahatti et al.	2011	Indian	Dental patients	17	30	Male	Asia	96	13	13.54
Byahatti et al.	2011	Indian	Dental patients	17	30	Female	Asia	54	15	27.78
Byahatti and Ingafou	2012	Libyan	Dental students	17	26	Male	Africa	100	7	7
Byahatti and Ingafou	2012	Libyan	Dental students	17	26	Female	Africa	100	6	6
Castilho et al.	1990	Brazilian	Dental patients	12	14.9	Male	S. America	94	20	21.28
Castilho et al.	1990	Brazilian	Dental patients	12	14.9	Female	S. America	107	21	19.63
Celikoglu et al.	2010	Turkish	Orthodontic patients	21	26	Male	Middle East	153	24	15.85
Celikoglu et al.	2010	Turkish	Orthodontic patients	22	26	Female	Middle East	198	37	18.43
Celikoglu and Kamak	2012	Turkish	Orthodontic patients	13	17	Male	Middle East	449	92	20.49
Celikoglu and Kamak	2012	Turkish	Orthodontic patients	13	17	Female	Middle East	597	145	24.29
Costa et al.	2007	Brazilian	Orthodontic patients	12		Male	S. America	345	45	13.04
Costa et al.	2007	Brazilian	Orthodontic patients	12		Female	S. America	462	74	16.02
Daito et al.	1992	Japanese	Dental students	24		Male	Asia	2,312	1103	47.7
Daito et al.	1992	Japanese	Dental students	24		Female	Asia	457	271	59.3
Elomaa and Elomaa	1973	Finnish	Dental patients	15	22	Male	Europe	61	18	29.51
Elomaa and Elomaa	1973	Finnish	Dental patients	15	22	Female	Europe	141	49	34.75
Endo et al.	2015	Japanese	Orthodontic patients	13	21	Male	Asia	436	134	30.73
Endo et al.	2015	Japanese	Orthodontic patients	13	21	Female	Asia	855	283	33.1
Garcia-Hernandez and Beltran	2008	Atacama	Random sample	18	55	Male	S. America	33	9	27.27
Garcia-Hernandez and Beltran	2008	Atacama	Random sample	16	39	Female	S. America	57	15	26.32
Garcia-Hernandez and Beltran	2009	Aymara	Random sample	18	40	Male	S. America	42	11	26.19
Garcia-Hernandez and Beltran	2009	Aymara	Random sample	18	26	Female	S. America	36	6	16.67
Garcia-Hernandez et al.	2008	Chilean	Orthodontic patients	14	20.9	Male	S. America	200	45	22.5
Garcia-Hernandez et al.	2008	Chilean	Orthodontic patients	14	20.9	Female	S. America	200	54	27
Garcia-Hernandez and Rodriguez	2009	Chilean	Dental patients	15.2	26.8	Male	S. America	52	8	15.38
Garcia-Hernandez and Rodriguez	2009	Chilean	Dental patients	14.1	26.6	Female	S. America	48	12	25
Ghada	2005	Iraqi	Dental patients	11	25	Male	Middle East	72	15	20.8
Ghada	2005	Iraqi	Dental patients	11	25	Female	Middle East	128	33	25.8
Godt and Greve	1980	German	Orthodontic patients	12	16	Male	Europe	676	122	18.05

(continued)

Appendix Table 5. (continued)

Study	Year	Population	Sample Type	Age, y[a]		Sex	Continent	*N*	Agenesis	
				Min	Max				*n*	%
Godt and Greve	1980	German	Orthodontic patients	12	16	Female	Europe	879	192	21.84
Golovcencu and Geletu	2012	Romanian	Orthodontic patients	11	25	Male	Europe	79	18	22.8
Golovcencu and Geletu	2012	Romanian	Orthodontic patients	11	25	Female	Europe	171	52	30.4
Grahnen	1956	Swedish	Dental students	17	43	Male	Europe	547	136	24.86
Grahnen	1956	Swedish	Dental students	17	43	Female	Europe	517	126	24.37
Gravely	1965	British (white)	Dental patients	14	15	Male	Europe	37	10	27
Gravely	1965	British (white)	Dental patients	14	15	Female	Europe	44	11	25
Haavikko	1971	Finnish	Students[b]	14	18	Male	Europe	174	37	21.26
Haavikko	1971	Finnish	Students[b]	14	18	Female	Europe	124	25	20.16
Haga et al.	2013	Japanese	Anthropologic survey	16	57	Male	Asia	74	17	22.97
Haga et al.	2013	Japanese	Anthropologic survey	16	57	Female	Asia	190	61	32.11
Haga et al.	2013	Korean	Anthropologic survey	20	40	Male	Asia	130	39	30
Haga et al.	2013	Korean	Anthropologic survey	20	40	Female	Asia	93	32	34.41
Hattab	1995	Jordanian	Dental students	18	23	Male	Middle East	108	35	32.41
Hattab	1995	Jordanian	Dental students	18	23	Female	Middle East	124	28	22.58
Hellman	1936	USA (white)	Dental patients	18		Male	N. America	261	57	21.84
Hellman	1936	USA (white)	Dental patients	18		Female	N. America	172	53	30.81
Hentisz	2003	USA (black)	Orthodontic patients	11	26	Male	N. America	118	6	5.08
Hentisz	2003	USA (black)	Orthodontic patients	11	28	Female	N. America	115	7	6.09
Hentisz	2003	USA (white)	Orthodontic patients	11	24	Male	N. America	100	18	18
Hentisz	2003	USA (white)	Orthodontic patients	11	21	Female	N. America	100	13	13
Holzl	1972	German	Students[b]	18	31	Male	Europe	333	51	15.32
Holzl	1972	German	Students[b]	18	31	Female	Europe	153	26	16.99
Hubenthal	1989	German	Orthodontic patients	12	36	Male	Europe	936	165	17.63
Hubenthal	1989	German	Orthodontic patients	12	36	Female	Europe	1,125	262	23.29
Kazanci et al.	2010	Turkish	Orthodontic patients	12	16	Male	Middle East	1,018	233	22.9
Kazanci et al.	2010	Turkish	Orthodontic patients	12	16	Female	Middle East	1,561	382	24.5
Kirveskari et al.	1978	Skolt Lapps	Anthropologic survey	12	20	Male	Europe	40	7	17.5
Kirveskari et al.	1978	Skolt Lapps	Anthropologic survey	12	20	Female	Europe	32	7	21.88
Krekeler et al.	1974	German	Orthodontic patients	12	33	Male	Europe	740	192	25.95
Krekeler et al.	1974	German	Orthodontic patients	12	33	Female	Europe	874	263	30.09
Lee et al.	2009	Korean	Dental patients	16	22	Male	Asia	469	169	36.03
Lee et al.	2009	Korean	Dental patients	16	24	Female	Asia	660	295	44.7
Liu et al.	2004	Chinese	Orthodontic patients	14	18	Male	Asia	92	34	36.96
Liu et al.	2004	Chinese	Orthodontic patients	14	18	Female	Asia	142	35	24.65
Lynham	1990	Australian (white)	Military personel	16	26	Male	Oceania	535	125	23.36
Lynham	1990	Australian (white)	Military personel	16	26	Female	Oceania	127	25	19.69
Maderia and Lopes	1976	Brazilian (mixed)	Dental students	18	21	Male	S. America	98	22	22.45
Maderia and Lopes	1976	Brazilian (mixed)	Dental students	18	21	Female	S. America	250	49	19.6
Mani et al.	2014	Malaysian	Dental patients	12	16	Male	Asia	360	97	26.9
Mani et al.	2014	Malaysian	Dental patients	12	16	Female	Asia	474	117	24.7
Matsuo	1986	Japanese	Students[b]	22	27	Male	Asia	300	122	40.67
Matsuo	1986	Japanese	Students[b]	18	27	Female	Asia	329	112	34.04
Mok and Ho	1996	Chinese	Dental patients	12	16	Male	Asia	367	99	26.98
Mok and Ho	1996	Chinese	Dental patients	12	16	Female	Asia	419	125	29.83
Nanda and Chawla	1959	Indian	Dental patients	17	30	Male	Asia	650	147	22.62

(continued)

Appendix Table 5. (continued)

Study	Year	Population	Sample Type	Age, y[a]		Sex	Continent	*N*	Agenesis	
				Min	Max				*n*	%
Nanda and Chawla	1959	Indian	Dental patients	17	30	Female	Asia	650	188	28.92
Nicodemo	1973	Brazilian	Students[b]	12	25	Male	S. America	110	16	14.55
Nicodemo	1973	Brazilian	Students[b]	12	25	Female	S. America	122	27	22.13
Oliveira and Serra Negra	1984	Brazilian (black)	Students[b]	14	18	Male	S. America	50	5	10
Oliveira and Serra Negra	1984	Brazilian (black)	Students[b]	14	18	Female	S. America	70	8	11.43
Oliveira and Serra Negra	1976	Brazilian (white)	Students[b]	14	22	Male	S. America	186	25	13.44
Oliveira and Serra Negra	1976	Brazilian (white)	Students[b]	14	22	Female	S. America	230	35	15.22
Raloti et al.	2013	Indian	Students[b]	18	30	Male	Asia	304	67	22
Raloti et al.	2013	Indian	Students[b]	18	30	Female	Asia	46	13	28.3
Ren and Kumar	2014	Malaysian	Dental patients	17	25	Male	Asia	25	7	28
Ren and Kumar	2014	Malaysian	Dental patients	17	25	Female	Asia	25	5	20
Ren and Kumar	2014	South Indian	Dental patients	17	25	Male	Asia	25	12	48
Ren and Kumar	2014	South Indian	Dental patients	17	25	Female	Asia	25	16	64
Rozkovcova et al.	2004	Czech	Dental patients	12	21	Male	Europe	500	128	25.6
Rozkovcova et al.	2004	Czech	Dental patients	12	21	Female	Europe	500	97	19.4
Sandhu and Kapila	1982	Indian	Dental patients	17	35	Male	Asia	515	41	7.96
Sandhu and Kapila	1982	Indian	Dental patients	17	35	Female	Asia	495	38	7.68
Sandhu and Kaur	2005	Indian	Dental students	17.5	20	Male	Asia	30	4	13.33
Sandhu and Kaur	2005	Indian	Dental students	17.5	20	Female	Asia	70	20	28.57
Sapoka and Demirjian	1971	French Canadian	Dental patients	11	11	Male	N. America	99	26	26.26
Sapoka and Demirjian	1971	French Canadian	Dental patients	11	11	Female	N. America	94	22	23.4
Sarmiento and Herrera	2004	Columbian	Dental students	16	25	Male	S. America	112	20	17.86
Sarmiento and Herrera	2004	Columbian	Dental students	16	25	Female	S. America	344	76	22.09
Shah and Boyd	1979	Anglo-Canadian	Dental patients	20		Male	N. America	337	70	20.77
Shah and Boyd	1979	Anglo-Canadian	Dental patients	20		Female	N. America	298	82	27.52
Shah and Parekh	2014	Indian	Dental patients	15	19	Male	Asia	32	8	25
Shah and Parekh	2014	Indian	Dental patients	15	19	Female	Asia	68	26	38.2
Shinn	1976	British (white)	Orthodontic patients	14		Male	Europe	1,103	129	11.7
Shinn	1976	British (white)	Orthodontic patients	14		Female	Europe	1,397	189	13.53
Sonnabend	1966	German	Orthodontic patients	15	30	Male	Europe	1,000	195	19.5
Sonnabend	1966	German	Orthodontic patients	15	30	Female	Europe	1,000	254	25.4
Speckin	1981	German	Orthodontic patients	15	26	Male	Europe	366	50	13.66
Speckin	1981	German	Orthodontic patients	15	26	Female	Europe	384	62	16.15
Thompson et al.	1974	Anglo-Canadian	Dental patients	16		Male	N. America	284	62	21.83
Thompson et al.	1974	Anglo-Canadian	Dental patients	16		Female	N. America	237	54	22.79
Upadhyaya	2012	Nepalese	Orthodontic patients	12	34	Male	Asia	94	63	67.02
Upadhyaya	2012	Nepalese	Orthodontic patients	12	34	Female	Asia	200	85	42.5
Weise and Bruntsch	1965	German	Orthodontic patients	12	24	Male	Europe	329	87	26.44
Weise and Bruntsch	1965	German	Orthodontic patients	12	24	Female	Europe	340	109	32.06

[a]Blank cells indicate missing values.
[b]College, high school.

Appendix Table 6. Third Molar Agenesis Frequencies by Jaw.

								Mandible			Maxilla	
				Age, y[a]				Agenesis			Agenesis	
Study	Year	Population	Sample Type	Min	Max	Continent	*N*	*n*	%	*N*	*n*	%
Adler and Adler-Hradecky	1963	Hungarian	Orthodontic patients	18	21	Europe	591	103	17.43	591	112	18.95
Arany et al.	2004	Japanese	Dental patients	14	24	Asia	1,282	277	21.61	1,282	442	34.48
Bansal	2012	Indian	Orthodontic patients	13	25	Asia	400	42	10.5	400	62	15.5
Diaz-Perez and Echaverry-Navarrete	2009	Mexican	Dental patients	13	50	N. America	112	12	10.71	112	7	6.25
Ghada	2005	Iraqi	Dental patients	11	25	Middle East	200	28	14	200	35	17.5
Grahnen	1956	Swedish	Dental students	17	43	Europe	1,064	161	15.13	1,064	183	17.2
Holzl	1972	German	Students[b]	18	31	Europe	486	53	10.91	486	54	11.11
Komerik et al.	2014	Turkish	Orthodontic patients	15		Middle East	108	24	22.22	108	28	25.93
Mani et al.	2014	Malaysian	Dental patients	12	16	Asia	834	168	20.14	834	279	33.45
Marzola et al.	1968	Brazilian (white)	Students[b]	14	50	S. America	1,760	62	3.52	1,760	97	5.51
Matsuo	1986	Japanese	Students[b]	18	27	Asia	629	120	19.08	629	187	29.73
Nicodemo	1973	Brazilian	Students[b]	12	25	S. America	232	20	8.62	232	20	8.62
Sapoka and Demirjian	1971	French Canadian	Dental patients	11	11	N. America	193	49	25.39	193	48	24.87
Sonnabend	1966	German	Orthodontic patients	15	30	Europe	2,000	279	13.95	2,000	319	15.95
Tanner	1946	Swiss	Orthodontic patients	13	17	Europe	534	83	15.54	534	104	19.48

All samples were pooled sexes.
[a]Blank cells indicate missing values.
[b]College, high school.

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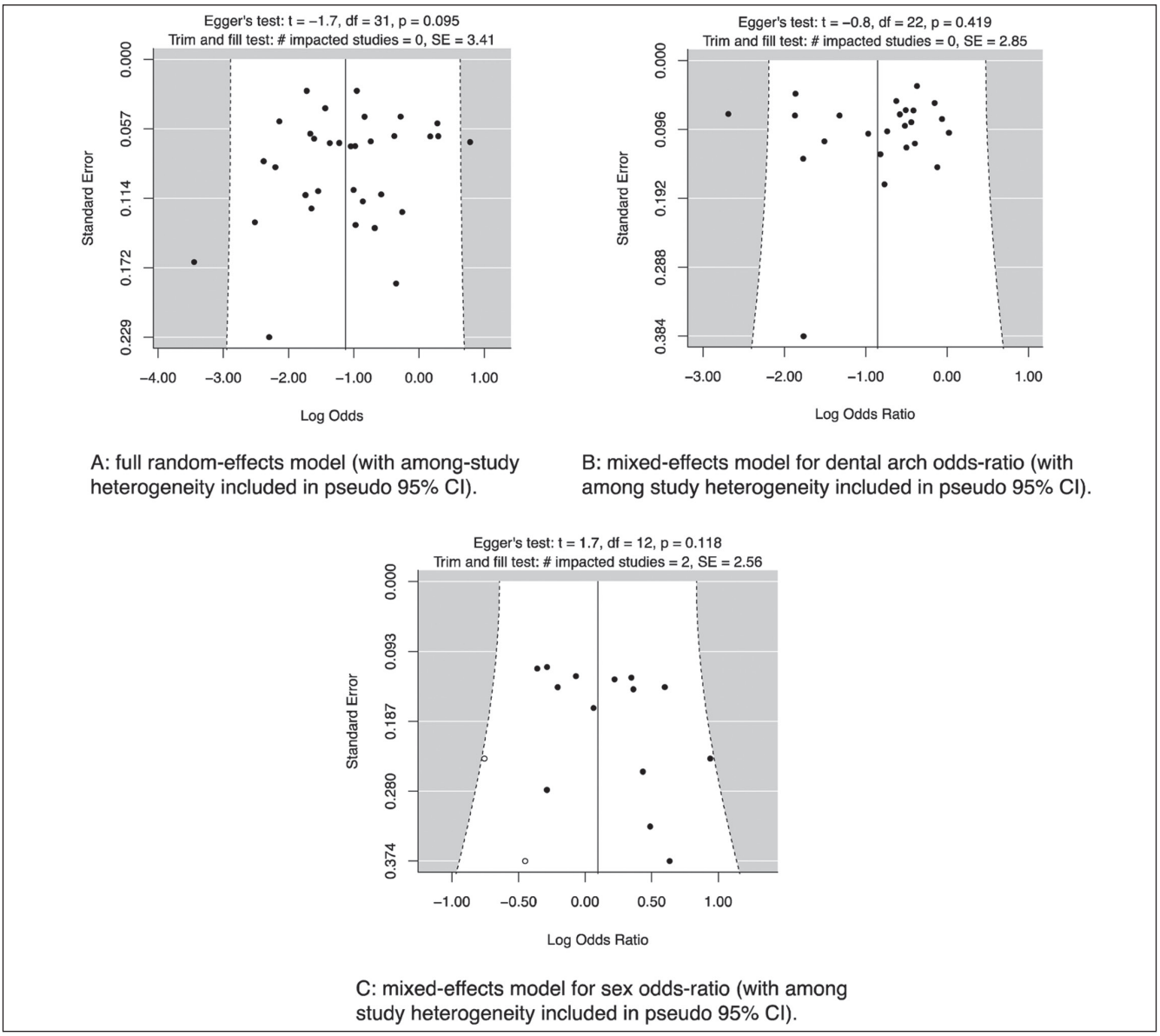
Predictors of Third Molar Impaction: A Systematic Review and Meta-analysis

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Appendix

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Appendix Figure. Funnel plots and asymmetry tests to assess potential publication bias for the nonmoderator models discussed in the main text.

Appendix Table 1. Heterogeneity Estimates and Tests.

Model	*n*	I^2, %	H^2	Likelihood Ratio Test[a]
All studies				
Random effects	33	99.52	206.39	5,642
Continent moderator	33	99.22	127.73	3,954
Angle of M3 impaction	32	99.16	119.75	14,498
Number of M3s impacted	8	97.93	48.32	1,589
Mandible vs. maxilla	24	98.70	76.73	2,260
Male vs. female	14	81.51	5.41	75

[a]For each model, $P < 0.0001$.

Appendix Table 2. Pairwise Comparisons of Third Molar Impaction Frequency in 5 Geographic Regions.

Continent	Est	SE	*z*	*P* Value[a]
Africa				
Asia	1.03	0.42	2.42	0.1384
Europe	0.55	0.50	1.12	1.0000
Middle East	1.26	0.43	2.93	**0.0344**
North America	0.29	0.66	0.44	1.0000
Asia				
Europe	–0.47	0.42	–1.12	1.0000
Middle East	0.23	0.34	0.68	1.0000
North America	–0.74	0.60	–1.23	1.0000
Europe				
Middle East	0.71	0.43	1.65	0.7990
North America	–0.27	0.65	–0.41	1.0000
North America–Middle East	–0.97	0.61	–1.61	0.7990

Est, estimate of first difference on log-odds scale; SE, standard error of the estimate.
[a]Adjusted *P* values reported with the sequential Bonferroni method. Values in bold are significant at the $P < 0.05$ level.

Appendix Table 3. Pairwise Comparisons of Third Molar Impaction Frequency by Winter's (1926) Angle of Impaction.

Angulation	Est	SE	*z*	*P* Value[a]
Mesioangular				
Vertical	–0.71	0.24	–3.15	**0.0032**
Distoangular	–1.62	0.23	–7.13	**0.0000**
Horizontal	–1.73	0.23	–7.61	**0.0000**
Vertical				
Distoangular	–0.91	0.23	–3.99	**0.0002**
Horizontal	–1.01	0.24	–4.47	**0.0000**
Horizontal–distoangular	–0.11	0.24	–0.47	0.6388

Est, estimate of first difference on log-odds scale; SE, standard error of the estimate.
[a]Adjusted *P* values reported with the sequential Bonferroni method. Values in bold are significant at the $P < 0.05$ level.

Appendix Table 4. Pairwise Comparisons of Third Molar Impaction Frequency by Number of Third Molars Impacted.

Number Impacted	Est	SE	*z*	*P* Value[a]
One				
Two	–0.57	0.38	–1.49	0.2717
Three	–1.70	0.38	–4.40	**0.0001**
Four	–2.05	0.39	–5.30	**0.0000**
Two				
Three	–1.12	0.39	–2.92	**0.0105**
Four	–1.48	0.39	–3.82	**0.0005**
Four–three	–0.36	0.39	–0.91	0.3604

Est, estimate of first difference on log-odds scale; SE, standard error of the estimate.
[a]Adjusted *P* values reported with the sequential Bonferroni method. Values in bold are significant at the $P < 0.05$ level.

Appendix Table 5. Third Molar Impaction Frequencies.

						Impacted	
Study	Year	Population[a]	Minimum Age, y	Continent	*n*	*n*	%
Ahlqwist and Grondahl	1991	Swedish[b]	38	Europe	1,418	141	9.94
Aitasalo et al.	1972	Finnish	20	Europe	4,063	427	10.51
Al-Anqudi et al.	2014	Omani	19	Middle East	1,000	543	54.30
Ardakani et al.	2007	Iranian	20	Middle East	230	21	9.13
Brown et al.	1982	So. African (black)	20	Africa	490	79	16.12
Brown et al.	1982	So. African (white)	20	Africa	989	270	27.30
Celikoglu et al.	2010	Turkish[c]	20	Middle East	351	126	35.90
Chu et al.	2003	Chinese	17	Asia	7,486	2,081	27.80
Dachi and Howell	1961	USA (mixed)	20	North America	1,685	281	16.68
Eliasson et al.	1989	Swedish	30	Europe	2,128	644	30.26
Gomaa and Al Shawaf	1992	Saudi	17	Middle East	440	118	26.82
Guo et al.	2014	NW Chinese	20	Asia	1,473	840	57.03
Haidar and Shalhoub	1986	Saudi	20	Middle East	1,000	323	32.30
Haralabakis	1957	Greek[d]	19	Europe	586	103	17.58
Hashemipour et al.	2013	Iranian	19	Middle East	1,020	585	57.35
Hassan	2011	Saudi	20	Middle East	121	50	41.32
Hassan	2010	Saudi	19	Middle East	1,039	422	40.62
Hattab et al.	1995	Jordanian	18	Middle East	232	78	33.62
Jan et al.	2014	Saudi	25	Middle East	4,000	768	19.20
Kabwe	1996	Zambian (black)	21	Africa	803	60	7.47
Kaur and Sheikh	2013	Indian[d]	18	Asia	1,840	791	42.99
Mehdizadeh et al.	2014	Iranian	20	Asia	2,000	317	15.85
Nanda and Chawla	1959	Indian[d]	17	Asia	1,300	264	20.31
Olasoji and Odusanya	2000	Nigerian (rural)	20	Africa	1,200	37	3.08
Olasoji and Odusanya	2000	Nigerian (urban)	20	Africa	1,200	273	22.75
Quek et al.	2003	Chinese (Singapore)	20	Asia	1,000	686	68.60
Raloti et al.	2013	Indian	18	Asia	350	104	29.71
Reddy	2012	Indian	22	Asia	270	74	27.41
Reddy	2012	Indian	22	Asia	630	94	14.92
Sandhu and Kapila	1982	Indian	17	Asia	1,015	264	26.01
Schersten et al.	1989	Swedish	20	Europe	257	112	43.58
Stanley et al.	1988	USA (mixed)	20	North America	11,598	1,756	15.14
Yamaoka et al.	1995	Japanese[e]	21	Asia	1,834	155	8.45

[a]All populations are dental patients of pooled sexes unless noted otherwise.
[b]Female population.
[c]Orthodontic patients.
[d]Dental students.
[e]Maxillofacial patients.

Appendix Table 6. Third Molar Impaction Frequencies by Dental Arch.

					Mandible, *n*		Maxilla, *n*	
Study	Year	Population[a]	Minimum Age, y	Continent	Impacted	Not Impacted	Impacted	Not Impacted
Aitasalo et al.	1972	Finnish	20	Europe	323	7,803	304	7,822
Al-Anqudi et al.	2014	Omani	19	Middle East	817	1,183	311	1,689
Al Feeli and Sebaa	2013	Kuwaiti	21	Middle East	101	1,907	90	1,918
Celikoglu et al.	2010	Turkish[b]	20	Middle East	252	450	192	510
Chu et al.	2003	Chinese	17	Asia	3,178	11,794	600	14,372
Dachi and Howell	1961	USA (mixed)	20	No. America	209	3,161	213	3,157
Eliasson et al.	1989	Swedish	30	Europe	734	3,522	644	3,612
Gisakis et al.	2011	Greek	18	Europe	508	342	353	497
Hassan	2010	Saudi	19	Middle East	393	1,685	271	1,807
Hatem et al.	2015	Libyan	20	Africa	472	128	371	229
Hugoson and Kugelberg	1988	Caucasian	20	Europe	200	972	130	1,042
Jung and Cho	2013	Korean	25	Asia	956	6,642	543	7,055
Kruger et al.	2001	New Zealander	18	Oceania	987	697	814	870
Mehdizadeh et al.	2014	Iranian	20	Asia	339	3,661	209	3,791
Nanda and Chawla	1959	Indian[c]	17	Asia	419	2,181	106	2,494
Olasoji and Odusanya	2000	Nigerian (rural)	20	Africa	46	2,354	8	2,392
Olasoji and Odusanya	2000	Nigerian (urban)	20	Africa	359	2,041	150	2,250
Pillai et al.	2014	Indian	20	Asia	1,750	450	460	1,740
Quek et al.	2003	Chinese (Singapore)	20	Asia	1,079	921	306	1,694
Sandhu and Kapila	1982	Indian	17	Asia	343	1,687	68	1,962
Schersten et al.	1989	Swedish	20	Europe	116	398	61	453
Shah et al.	1978	Canadian	20	No. America	505	15,267	286	15,486
Stanley et al.	1988	USA (mixed)	20	No. America	2,068	21,128	1,468	21,728
Syed et al.	2013	Saudi	18	Middle East	582	7,018	361	7,239

[a]All populations are dental patients unless noted otherwise.
[b]Orthodontic patients.
[c]Dental students.

Appendix Table 7. Third Molar Impaction Frequencies by Sex.

					Male, *n*		Female, *n*	
Study	Year	Population[a]	Minimum Age, y	Continent	Impacted	Not Impacted	Impacted	Not Impacted
Al-Anqudi et al.	2014	Omani	19	Middle East	215	220	328	237
Brown et al.	1982	So. African (mixed)	20	Africa	225	624	181	668
Celikoglu et al.	2010	Turkish[b]	20	Middle East	37	116	89	109
Guo et al.	2014	NW Chinese	20	Asia	282	165	558	468
Haidar and Shalhoub	1986	Saudi	20	Middle East	212	412	111	265
Hashemipour et al.	2013	Iranian	19	Middle East	205	175	380	260
Hassan	2010	Saudi	19	Middle East	222	314	200	303
Hassan	2011	Saudi	20	Middle East	21	41	29	30
Hattab et al.	1995	Jordanian	18	Middle East	40	68	38	86
Nanda and Chawla	1959	Indian[c]	17	Asia	101	549	163	487
Raloti et al.	2013	Indian	18	Asia	86	218	18	28
Sandhu and Kapila	1982	Indian	17	Asia	117	398	147	348
Schersten et al.	1989	Swedish	20	Europe	56	88	56	57
Yamaoka et al.	1995	Japanese[d]	21	Asia	68	763	87	916

[a]All populations are dental patients unless noted otherwise.
[b]Orthodontic patients.
[c]Dental students.
[d]Maxillofacial patients.

Appendix Table 8. Third Molar Impaction Frequencies by Angle of Impaction.

Study	Year	Population[a]	Minimum Age, y	Continent	HOR, *n*	MES, *n*	VER, *n*	DIS, *n*
Akinbami and Ifomala	2011	Nigerian[b]	17	Africa	22	33	16	5
Al-Anqudi et al.	2014	Omani	19	Middle East	11	282	247	267
Al Feeli and Sebaa	2013	Kuwaiti	21	Middle East	55	44	79	23
Byahatti and Ingafou	2012	Libyan[c]	17	Africa	25	180	420	135
Celikoglu et al.	2010	Turkish[d]	20	Middle East	36	222	135	51
Chu et al.	2003	Chinese	17	Asia	1,508	1,171	134	313
Eliasson et al.	1989	Swedish	30	Europe	339	333	312	227
Gbotolorun et al.	2007	Nigerian[b]	17	Africa	60	177	49	45
Haidar and Shalhoub	1986	Saudi	20	Middle East	60	384	632	96
Hashemipour et al.	2013	Iranian	19	Middle East	266	444	304	139
Hassan	2010	Saudi	19	Middle East	114	156	185	115
Hatem et al.	2015	Libyan	20	Africa	47	292	264	233
Hattab et al.	1995	Jordanian	18	Middle East	19	182	143	19
Hugoson and Kugelberg	1988	Caucasian	20	Europe	21	99	166	44
Jung and Cho	2013	Korean	25	Asia	396	458	456	93
Kaur and Sheikh	2013	Indian[c]	18	Asia	828	1,343	1,683	736
Kruger et al.	2001	New Zealander	18	Oceania	13	1,204	399	185
Ma'aita and Alwrikat	2000	Jordanian	17	Middle East	183	772	539	285
Mehdizadeh et al.	2014	Iranian	20	Asia	38	180	223	106
Nanda and Chawla	1959	Indian[c]	17	Asia	57	463	48	40
Nazir et al.	2014	Pakistani	20	Asia	38	126	92	70
Obiechina et al.	2001	Nigerian	21	Africa	53	151	107	19
Perumal	2013	So. African (black)[e]	17	Africa	85	247	92	733
Perumal	2013	So. African (Indian)[e]	17	Africa	111	371	91	753
Pillai et al.	2014	Indian	20	Asia	370	630	1,030	170
Quek et al.	2003	Chinese (Singapore)	20	Asia	190	642	103	106
Raloti et al.	2013	Indian	18	Asia	19	109	57	15
Ramamurthy et al.	2012	Indian	18	Asia	93	288	72	9
Sandhu and Kapila	1982	Indian	17	Asia	74	155	66	50
Schersten et al.	1989	Swedish	20	Europe	16	78	68	15
Secic et al.	2013	Bosnian[b]	19	Europe	92	206	673	54
Shokri et al.	2014	Iranian[d]	19	Middle East	22	358	14	6

DIS, distoangular; HOR, horizontal; MES, mesioangular; VER, vertical.
[a]All populations are dental patients unless noted otherwise.
[b]Oral surgery patients.
[c]Dental students.
[d]Orthodontic patients.
[e]Maxillofacial patients.

Appendix Table 9. Third Molar Impaction Frequencies by Number of Impacted Third Molars.

					Third Molars Impacted, *n*			
Study	Year	Population[a]	Minimum Age, y	Continent	1	2	3	4
Al-Anqudi et al.	2014	Omani	19	Middle East	172	226	81	64
Hashemipour et al.	2013	Iranian	19	Middle East	375	95	70	45
Hassan	2010	Saudi	19	Middle East	306	82	20	14
Ma'aita and Alwrikat	2000	Jordanian	17	Middle East	66	131	161	242
Nanda and Chawla	1959	Indian[b]	17	Asia	123	110	22	9
Pillai et al.	2014	Indian	20	Asia	350	500	140	110
Quek et al.	2003	Chinese (Singapore)	20	Asia	211	312	102	61
Sandhu and Kapila	1982	Indian	17	Asia	175	46	28	15

[a]All populations are dental patients unless noted otherwise.
[b]Dental students.

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Chapter 4: Supporting Information

Supporting materials

Osteological materials

Agricultural Danube Gorges (University of Belgrade Museum, Serbia)
Many of the agricultural transitions in Europe have recently been found to have been replacement-based, with migrating agriculturalists taking over hunter-gatherer populations [1, 2]. One exception to this model is likely the material from the Danube Gorges, where agricultural populations from Vlasac, Lepenski Vir and Padina seemed to arise from the hunter-gatherer populations living there beforehand [3, 4].

Egypt and Nubia (Duckworth Lab. Human Osteological Collection, UK)
The material from Egypt represents one of the earliest adoptions of agriculture worldwide, and is one of the few places in Africa where agriculture was adopted without simultaneous or earlier adoption of pastoralism. This material was selected for its relatively low amount of tooth wear and well-established archaeological context [5, 6].

Native American populations (Smithsonian Collection, USA)
Material from the Calusa and Timucua tribe networks were sampled for this study. While many North American native populations have large amounts of tooth wear caused by maize agriculture, these populations were late-adapters of a modified agricultural strategy, which allowed tooth metrics and wear to be easily sampled [7, 8].

Yayoi foragers (Kyushu University Collections, Japan)
Early rice cultivators, mostly from the sites of Doigahama, Kanenokuma, and Koura, were sampled for this population. While the nature of the agricultural transition in Japan, particularly the contribution of Jomon foragers to early Yayoi farmers, remains controversial [9, 10], the high degree of M3 agenesis seen in modern Japanese makes this population of great interest [11, 12].

Industrial Coimbra (University of Coimbra Museum, Portugal)
The Coimbra Identified Skeletons Collection largely contains individuals from the same gravesite, born between 1826 and 1926 (cut-off at 1890 for this study). Industrialization came to Portugal rapidly, as opposed to other parts of Europe where the transition occurred more slowly [13, 14].

Industrial Japan (National Science Museum Osteological Collection, Tsukuba)
The Japanese industrial material is from two excavated temples, Suukenji and Syogenji, dating from 1830 to 1890 [15]. These were selected for the high degree of M3 agenesis and impaction seen in modern Japan (e.g., [16]).

Supporting methods

Morphometric variables

Mitutoyo™ digital calipers were used to collect buccolingual measurements to 0.01 mm accuracy on each premolar and molar present. We used mandibular measurements (breadth at M_1 protoconid, breadth at mental foramen, breadth at mandibular notch, breadth at distal M_2, length from canine to M_2, and length from central incisor to the intersection of the corpus and ramus) and maxillary measurements (breadth of palate at palatine suture, length from palatine suture to incisive foramen, and breadth of palate at M^1 paracone), to create two derived variables:

$$s_{mx} = b_{ps} \times l_{if2ps} \tag{1a}$$

$$s_{md} = \left[\left(b_{mn} + b_{M_1p} \right) \Big/ 2 \right] \times l_{C2M_2}, \tag{1b}$$

where s_{mx} is maxillary space, b_{ps} is maxillary breadth at the palatine suture, l_{if2ps} is maxillary length from the incisive foramen to the palatine suture, s_{md} is mandibular space, b_{mn} is mandibular breadth at the mandibular notch, b_{M_1p} is mandibular breadth at the M_1 protoconid, and l_{C2M_2} is the mandibular length from canine to M_2.

We assessed the degree of fluctuating asymmetry for the subset of individuals where at least two maxillary dental antimeres and two mandibular dental antimeres existed. To correct for the presence of directional asymmetry, fluctuating asymmetry was calculated as:

$$\begin{aligned} fa = &|P3_{\mathrm{L}} - P3_{\mathrm{R}}| + |P4_{\mathrm{L}} - P4_{\mathrm{R}}| + |M1_{\mathrm{L}} - M1_{\mathrm{R}}| + |M2_{\mathrm{L}} - M2_{\mathrm{R}}| \\ &- \left| \left(P3 - M2_{\mathrm{L}} \right) - \left(P3 - M2_{\mathrm{R}} \right) \right|, \end{aligned} \tag{2}$$

where fa is fluctuating asymmetry, Pi_j and Mi_j are the i^{th} premolar and molar from the j^{th} arch side.

We calculated tooth wear for each first and second molar for the subset of individuals where age was determined skeletally (to within 5 years for under 30 yo and to within 15 years for over 30 yo). We used the Scott [17] scale of molar wear by quadrant (which uses a scale of 0–10 to assess the progression of enamel and dentine exposure at four places on the tooth) to get the most accurate quantification of molar wear across occlusal area. Individuals were excluded if both the first and second molar were rated as 10. The difference between wear in the first and second molar was calculated by quadrant to quantify the rate of wear between first and second molar eruption [18]:

$$\begin{aligned} w = \frac{\left(M2_{\mathrm{q1}} - M1_{\mathrm{q1}} \right) + \left(M2_{\mathrm{q2}} - M1_{\mathrm{q2}} \right)}{} \\ \frac{+ \left(M2_{\mathrm{q3}} - M1_{\mathrm{q3}} \right) + \left(M2_{\mathrm{q4}} - M1_{\mathrm{q4}} \right)}{4}, \end{aligned} \tag{3}$$

where w is tooth wear, and Mi_j is the i^{th} molar from the j^{th} dental quadrant.

To calculate a measure of crown complexity for third molars across quadrants, we assessed the number of cusps, cuspules, and diagnostic features (e.g., wrinkling of enamel) present. These were initially evaluated qualitatively, then converted to a quantitative scale for analysis. Within each dental arch, the level of reduction of each M3 was quantified on the scale 0–4, with 4 being equal in size to M2 and 0 being peg-shaped. Within each dental quadrant, the number of cusps (0–3) on the M3 was counted and an average calculated from the left and right sides. Within each dental arch, the values from these two scales were then averaged. This yielded a scale of 0–3.5 for maxillary and mandibular third molar complexity:

$$cpx = \frac{rs + \left[\left(cns_{\mathrm{L}} + cns_{\mathrm{R}} \right) \big/ 2 \right]}{2}, \tag{4}$$

where cpx is M3 complexity, rs is the reduction scale (0–4) and cns is the cusp number scale (0–3).

Intra-observer error study

We conducted an intra-observer error study, using 15 female individuals from 3 archeological populations (5 individuals each at the beginning, middle, and end of the data collection period). For each individual, all ratio- and interval-scale variables were measured 10 times, non-consecutively. To quantify the variation explained by measurement error (S_{e}^2), we used repeated measures analysis of variance to estimate the relative between- (S_{b}^2) and within-individual (S_{w}^2) variance for each derived variable [19]. To facilitate interpretation, we then calculated the percentage of variance explained by measurement error ($\%S_{\mathrm{e}}^2$) as the ratio of the variance of repeated measurements (S_{w}^2) to the total variance multiplied by 100:

$$\%S_{\mathrm{e}}^2 = \frac{S_{\mathrm{w}}^2}{S_{\mathrm{w}}^2 + S_{\mathrm{b}}^2} \times 100. \tag{5}$$

Logistic regression models

We employed two varieties of logistic regression model in this study: 1) models with population-level fixed effects, and 2) 'hybrid' models with population-level random effects and each right-hand side variable decomposed into within (population mean-centered) and between (population mean) terms.

The basic composition of the models was as follows. We had k observations $y_1, \ldots, y_k$, which were assumed to be independent, and the i-th observation was treated as a realization of a random variable Y_i:

$$Y_i = \begin{cases} 1 & \text{if M3}_i \text{ exhibited agenesis} \\ 0 & \text{if M3}_i \text{ was present.} \end{cases} \tag{6}$$

We assumed that Y_i had a Bernoulli distribution:

$$Y_i \sim \mathcal{B}\big(\pi_i\big), \tag{7}$$

with probability π_i. This defined the stochastic structure of the models. Further, we assumed that the logit of the underlying probability π_i was a linear function of the predictors:

$$\text{logit}\big(\pi_i\big) = \mathbf{X}\boldsymbol{\beta} + \mathbf{e}, \qquad \ln\left(\frac{Y_i}{(1 - Y_i)}\right) = \mathbf{X}\boldsymbol{\beta} + \mathbf{e}, \tag{8a}$$

or, equivelantly, that the underlying probability π_i was a function of the logistically transformed predictors:

$$\pi_i = \text{logistic}\big(\mathbf{X}\boldsymbol{\beta} + \mathbf{e}\big), \tag{8b}$$

where $\mathbf{X}$ is a design matrix that relates the predictors ($\mathbf{x}_1 \ldots \mathbf{x}_n$) to the data, $\boldsymbol{\beta}$ is a vector of regression coefficients, and $\mathbf{e}$ is a vector of residuals. We estimated additional effects to account for clustering of individual-level observations within populations and control for any unobserved time-invariant population-level heterogeneity. These effects were either fixed ($\boldsymbol{\gamma}$) or random ($\boldsymbol{\zeta}$), depending on the model. In models with population fixed effects ($\boldsymbol{\gamma}$), the 'population' term in the following regression equations was expanded into five dummy variables in the design matrix. This defined the systematic structure of the models.

Since we wished to calculate unconditional probabilities as effect sizes, we estimated fixed effects using dummy variables for each population, rather than the typical method for logistic models of maximizing the conditional likelihood. The dummy variable fixed effects estimator can produce biased estimates in logistic regression models when the number of clusters (i.e., populations) is high and the number of observations within clusters (i.e., specimens) is low [20]. However, in our study we included only six populations with a large minimum sample size of 76 specimens. Simulations demonstrate that in such situations bias is non-existent or minimal [21, 22] when using the dummy variable fixed effects estimator. As a robustness check, we also estimated each model using the conditional likelihood estimator and compared coefficient and standard error estimates with the unconditional likelihood estimates.

Selection against impaction hypothesis

$$\begin{aligned} \mathbb{P}\Big(Y_i = 1 \,\Big|\, \mathbf{X}\boldsymbol{\beta}, \boldsymbol{\gamma}, \mathbf{e}\Big) = \text{logistic}\big(&\beta_0 1 + \beta_1 \text{M3impaction}_{itp} \\ &+ \beta_2 \text{time}_{ip} \\ &+ \beta_3 \text{M3impaction} \times \text{time}_{itp} \\ &+ \gamma_1 \text{population}_{it} \\ &+ e_{itp}\big), \end{aligned} \tag{9}$$

Probable mutation effect hypothesis

$$\begin{aligned} \mathbb{P}\Big(Y_i = 1 \,\Big|\, \mathbf{X}\boldsymbol{\beta}, \boldsymbol{\gamma}, \mathbf{e}\Big) = \text{logistic}\big(&\beta_0 1 + \beta_1 \text{M3complexity}_{itp} \\ &+ \beta_2 \text{M3wear}_{itp} \\ &+ \beta_3 \text{time}_{ip} \\ &+ \beta_4 \text{M3complexity} \times \text{time}_{itp} \\ &+ \gamma_1 \text{population}_{it} \\ &+ e_{itp}\big), \end{aligned} \tag{10}$$

Developmental delay hypothesis

$$\begin{aligned} \mathbb{P}\Big(Y_i = 1 \,\Big|\, \mathbf{X}\boldsymbol{\beta}, \boldsymbol{\gamma}, \mathbf{e}\Big) = \text{logistic}\big(&\beta_0 1 + \beta_1 \text{M3flucAsym}_{itp} \\ &+ \beta_2 \text{time}_{ip} \\ &+ \beta_3 \text{M3flucAsym} \times \text{time}_{itp} \\ &+ \gamma_1 \text{population}_{it} \\ &+ e_{itp}\big), \end{aligned} \tag{11}$$

Dental arch space hypothesis

$$\begin{aligned} \mathbb{P}\Big(Y_i = 1 \,\Big|\, \mathbf{X}\boldsymbol{\beta}, \boldsymbol{\zeta}, \mathbf{e}\Big) = \text{logistic}\big(&\beta_0 1 + \beta_1 \overline{\text{archSpace}}_{itp} \\ &+ \beta_2 \Big[\text{archSpace}_{itp} - \overline{\text{archSpace}}_{it}\Big] \\ &+ \beta_3 \text{transition}_{it} \\ &+ \beta_4 \Big[\text{archSpace}_{itp} - \overline{\text{archSpace}}_{it}\Big] \\ &\quad \times \text{transition}_{it} \\ &+ \zeta_1 \text{population}_{it} \\ &+ e_{itp}\big), \end{aligned} \tag{12}$$

Supporting results

Intra-observer error study

We calculated the percentage of variance explained by measurement error ($\%S_e^2$) for all ratio- and interval-scale variables. The variables with the largest intra-observer error ('mandibular arch space' and 'M_3 complexity') had error rates of 1.47% and 1.39%, respectively. All other variables had error rates below 1.2%.

Conditional likelihood logistic regression comparison

For each logistic model, we found that coefficients $\hat{\beta}_i$ and standard errors $\sigma_{\hat{\beta}_i}$ estimated using the conditional likelihood were consistent with their unconditional likelihood counterparts (reported here) to the second decimal place. This indicates that the dummy variable fixed effects estimator was providing unbiased estimates of $\hat{\beta}_i$ and $\sigma_{\hat{\beta}_i}$.

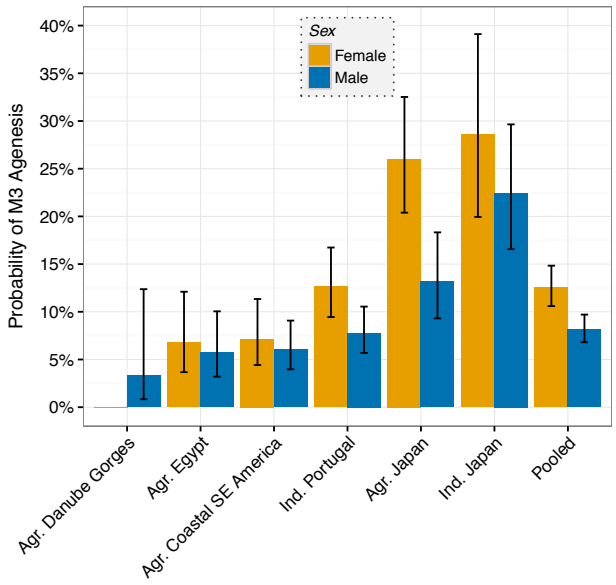
Sex differences in third molar agenesis and impaction

Based on results from modern populations, significant sex differences were expected for third molar agenesis but not impaction (Carter and Worthington, 2015, 2016). Pooled across all populations, we found that females (12.6%, 95% CI 10.6%, 14.8%) were more likely ($p < .0003$) to have M3 agenesis than males (8.1%, 95% CI 6.8%, 9.7%), though only agricultural Japan was consistent with this trend at the individual population level (Fig. S1a). For M3 impaction probability, females (6.6%, 95% CI 4.9%, 8.9%) were again consistently higher ($p < .008$) than males (4.6%, 95% CI 3.4%, 6.2%) when populations were pooled, though only agricultural Egypt was consistent with this trend at the individual population level (Fig. S1b).

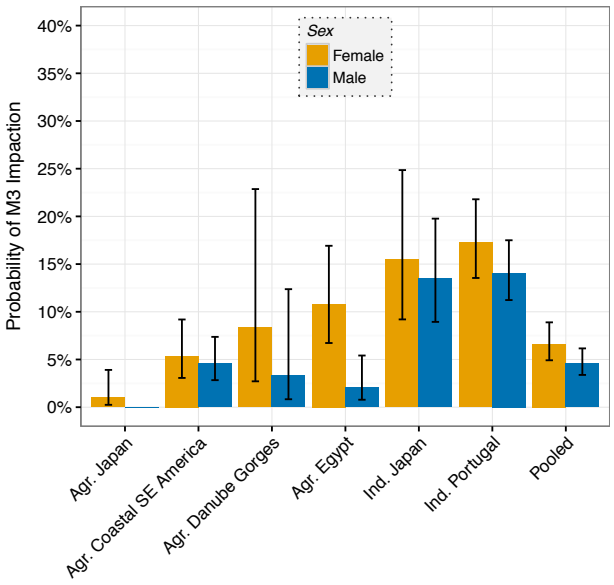
Dental arch differences in third molar agenesis and impaction

Pooled across all populations, we found that M3 agenesis was more likely ($p = .0061$) in the mandible (10.6%, 95% CI 9.0%, 12.3%) than the maxilla (7.9%, 95% CI 6.6%, 9.4%) (Fig. S1c). This contrasts with modern populations in which the opposite pattern was exhibited (Carter and Worthington, 2015). The probability of M3 impaction was also higher ($p < .00001$) in the mandible (6.6%, 95% CI 5.1%, 8.4%) than the maxilla (3.1%, 95% CI 2.3%, 4.2%) when populations were pooled (Fig. S1d). However, for impaction there were also differences in the pattern of dental arch effects across populations (LR χ^2 17.7, $p = .0033$). Modern populations also followed this pattern, with mandibles exhibiting higher probabilities for impaction.

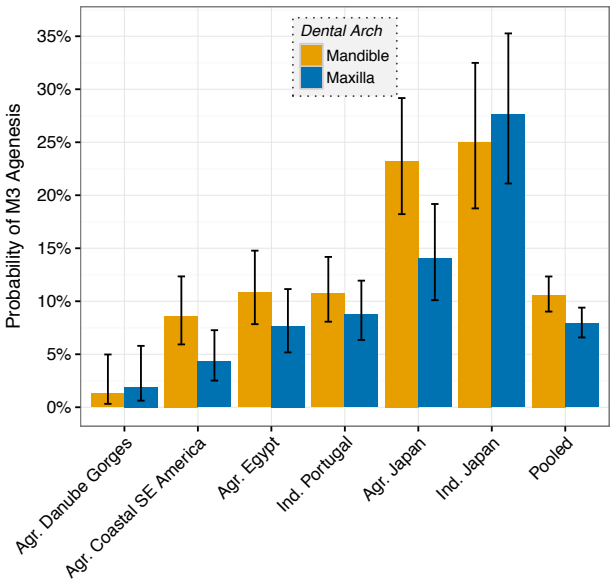
Supporting Figures



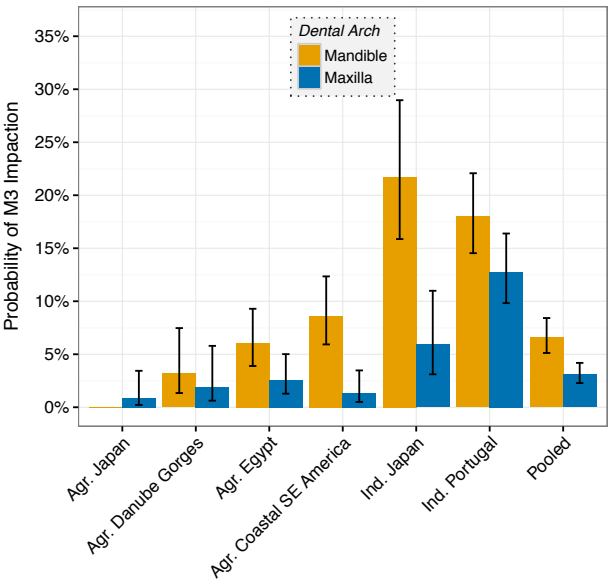
(A) M3 agenesis by sex & population



(B) M3 impaction by sex & population

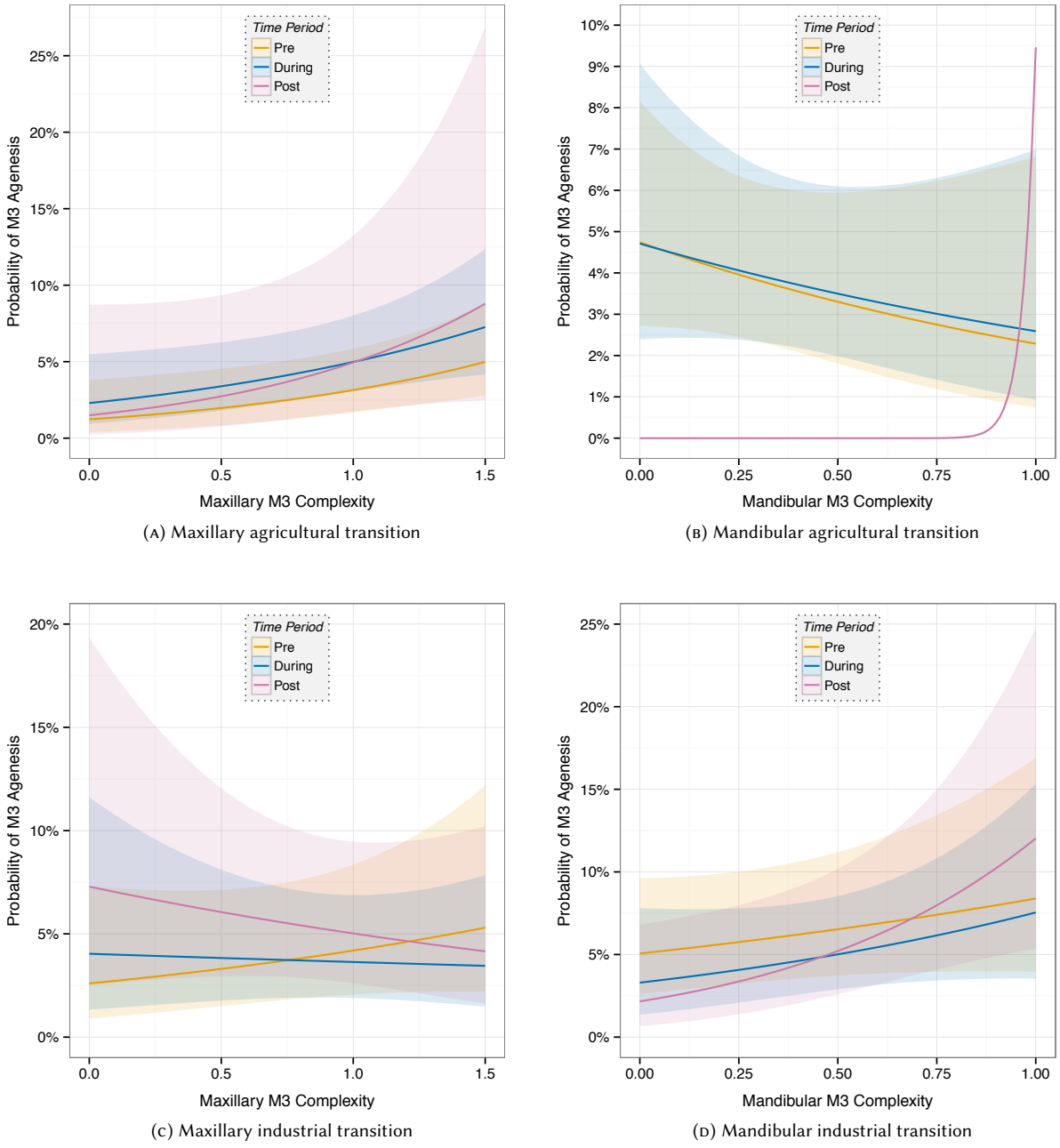


(C) M3 agenesis by dental arch & population



(D) M3 impaction by dental arch & population

FIG. S1. Probability of M3 agenesis & impaction by sex, dental arch, & population.



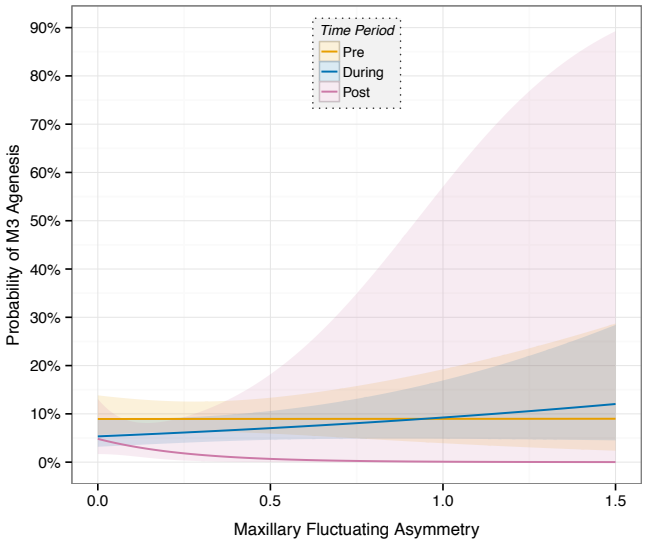
(A) Maxillary agricultural transition

(B) Mandibular agricultural transition

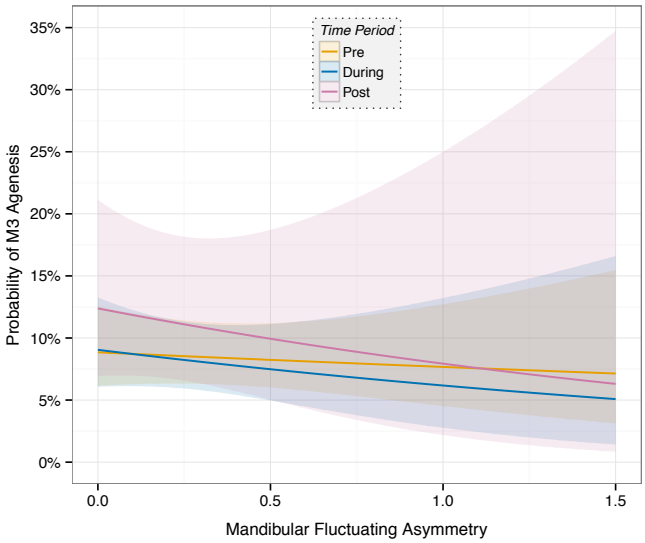
(C) Maxillary industrial transition

(D) Mandibular industrial transition

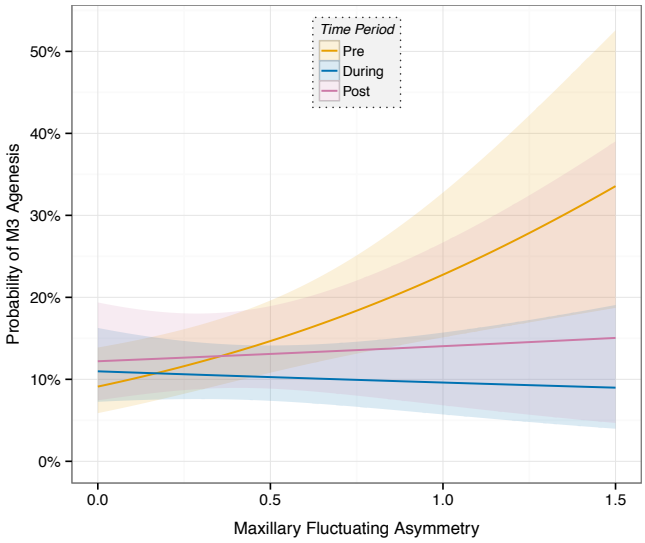
FIG. S2. Probable mutation models: Probability of M3 agenesis by M3 crown complexity and M3 wear, for agricultural & industrial transitions.



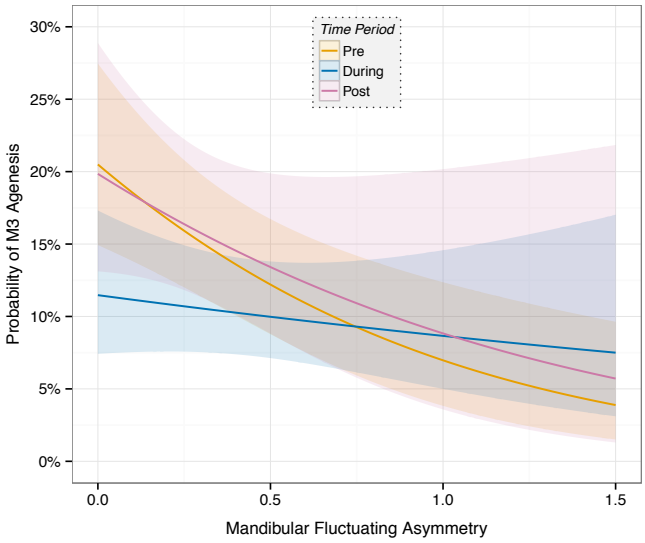
(A) Maxillary agricultural transition



(B) Mandibular agricultural transition

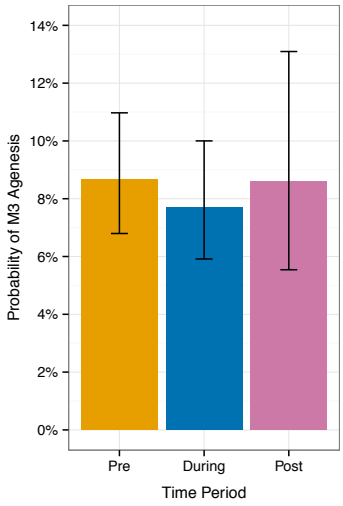


(C) Maxillary industrial transition

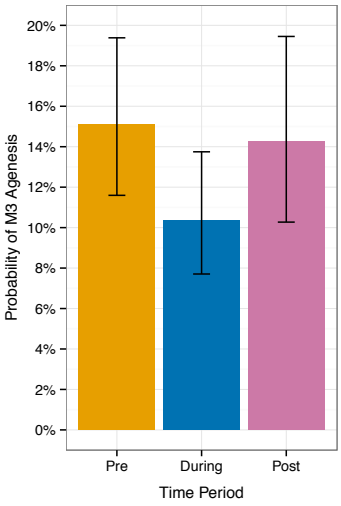


(D) Mandibular industrial transition

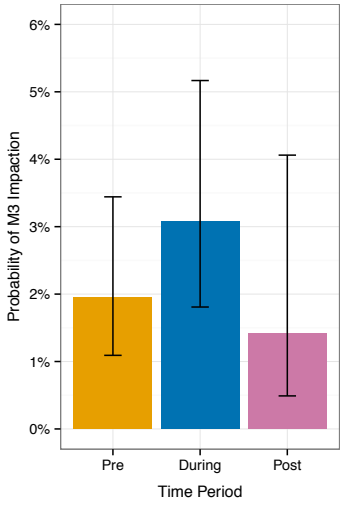
FIG. S3. Developmental delay models: Probability of M3 agenesis by M3 fluctuating asymmetry, for agricultural & industrial transitions.



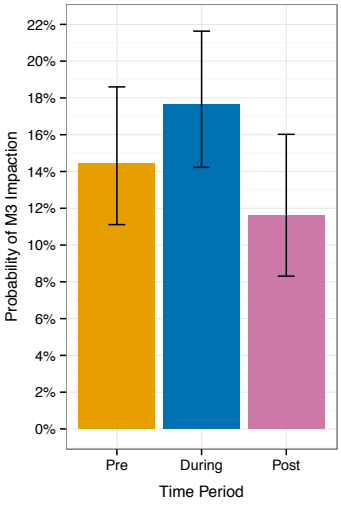
(A) Agricultural



(B) Industrial



(C) Agricultural



(D) Industrial

FIG. S4. Probability of M3 agenesis & impaction by time period, for agricultural & industrial transitions.

Supporting Tables

Table S1. Probability of Third Molar Agenesis and Impaction by Dental Arch Space

Transition		Agricultural				Industrial			
Dental Arch		Maxilla		Mandible		Maxilla		Mandible	
Space Size (mm^2)*		600	1300	2500	4500	600	1300	2500	4500
M3 Agenesis	95% UCL	2.6%	7.2%	9.3%	42.2%	67.8%	31.7%	51.3%	18.6%
	estimate	1.4%	3.9%	3.9%	24.7%	55.6%	20.1%	29.4%	8.5%
	95% LCL	0.7%	2.0%	1.6%	12.9%	42.8%	12.0%	14.1%	3.6%
M3 Impaction	95% UCL	62.9%	3.6%	29.2%	3.8%	42.1%	8.8%	69.3%	15.4%
	estimate	28.2%	0.6%	12.0%	1.2%	18.1%	2.7%	43.2%	5.7%
	95% LCL	8.3%	0.1%	4.3%	0.3%	6.3%	0.8%	20.3%	2.0%

* Minimum and maximum dental arch space areas.

Table S2. Selection Against Impaction Logistic Regression Results

			M3 Impaction Proportion*				
Transition	Time Period	Stat Type§	0	0.25	0.5	0.75	1
Agricultural	Post	95% UCL	9.18%	14.84%	31.35%	56.35%	78.83%
		Estimate	5.3%	7.21%	9.74%	13.04%	17.24%
		95% LCL	3%	3.35%	2.49%	1.71%	1.15%
	During	95% UCL	10.33%	11.55%	15.73%	21.56%	28.98%
		Estimate	7.91%	7.41%	6.94%	6.49%	6.07%
		95% LCL	6.02%	4.67%	2.89%	1.72%	1.01%
	Pre	95% UCL	9.01%	13.38%	23.94%	39.66%	57.99%
		Estimate	6.85%	7.7%	8.64%	9.68%	10.84%
		95% LCL	5.18%	4.31%	2.76%	1.72%	1.06%
Industrial	Post	95% UCL	9.65%	14.4%	24.33%	41.83%	63.17%
		Estimate	5.42%	9.45%	15.99%	25.75%	38.73%
		95% LCL	2.98%	6.09%	10.12%	14.33%	18.89%
	During	95% UCL	12.51%	11.49%	12.43%	14.54%	17.38%
		Estimate	8.6%	8.32%	8.05%	7.79%	7.53%
		95% LCL	5.83%	5.96%	5.12%	4.02%	3.05%
	Pre	95% UCL	12.25%	11.93%	14.04%	17.87%	23.04%
		Estimate	8.06%	8.25%	8.45%	8.65%	8.86%
		95% LCL	5.22%	5.64%	4.96%	3.96%	3.06%

* Proportion of third molars impacted (of those undergoing genesis).
§ Interval and point estimates.

Supporting References

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Chapter 5: Supporting Information

Supporting Figures

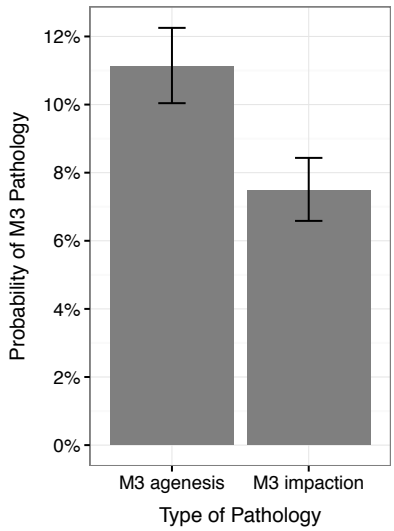
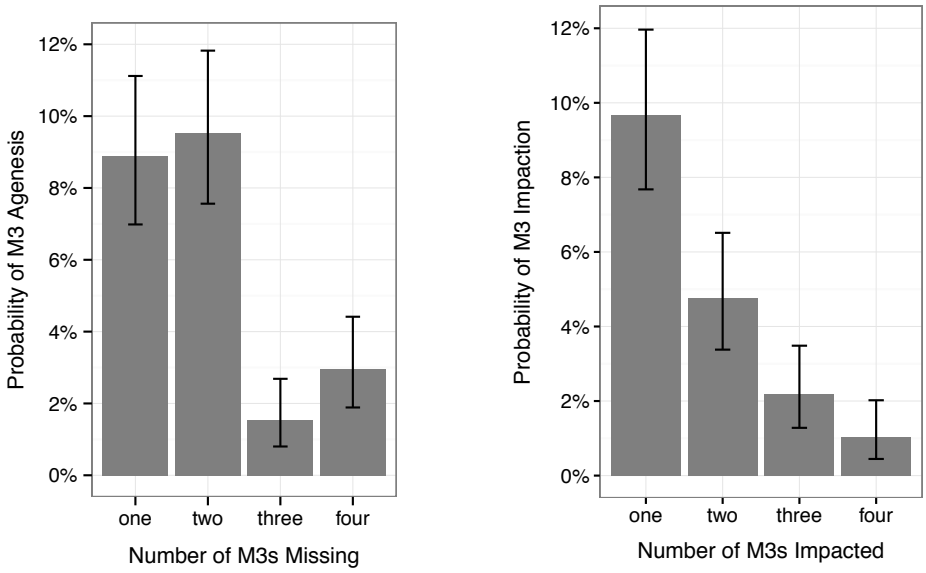


Fig. S1. Frequency of M3 pathology: M3 agenesis (11.11%, 95% CI 10.04%, 12.25%), M3 impaction (7.47%, 95% CI 6.58%, 8.43%).



(A) M3 agenesis

(B) M3 impaction

Fig. S2. Probability of M3 agenesis & impaction by number of third molars missing. (A) The probability of having one (8.9%, 95% CI 7.0%, 11.1%) or two (9.5%, 95% CI 7.6%, 11.8%) third molars missing was much higher ($p < .00001$) than that of having three (1.6%, 95% CI 0.8%, 2.7%) or four (3.0%, 95% CI 1.9%, 4.4%) missing. (B) Having one (9.7%, 95% CI 7.7%, 12.0%) third molar impacted was over twice as probable ($p < .00001$) as having two (4.8%, 95% CI 3.4%, 6.5%) impacted. The probability of having three (2.2%, 95% CI 1.3%, 3.5%) or four (1.0%, 95% CI 0.4%, 2.0%) M3s impacted was small.

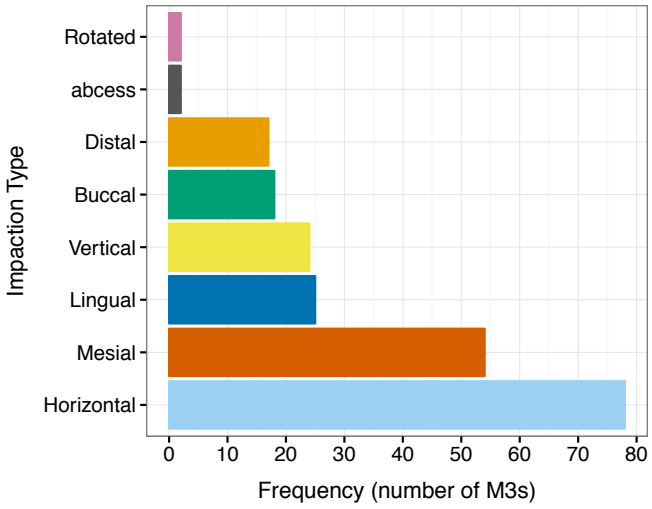
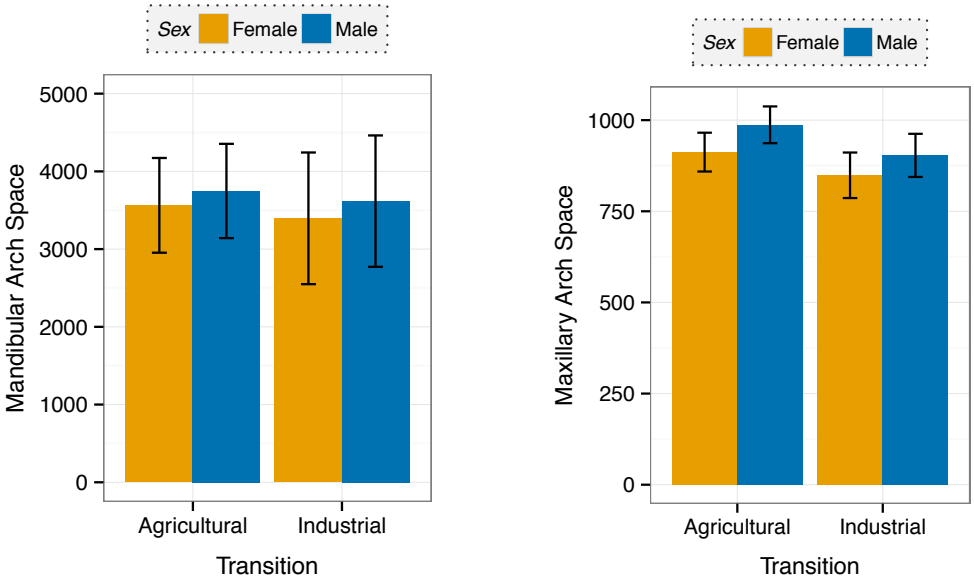


Fig. S3. Frequency of impaction by type.



(A) Mandible

(B) Maxilla

Fig. S4. Dental arch space by transition.

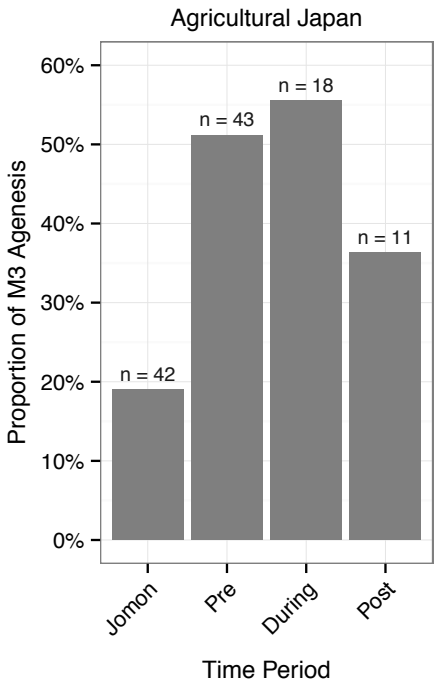


Fig. S5. Proportion of M3 agenesis by time period for agricultural Japan.