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Contemporary Dental Age Estimation Models in Children and Sub-adults

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"Age assessment is no determination but only just an educated guess"

– London Boroughs of Hillingdon and Croydon, 2003:1

List of Publications

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- **M.Y.P.M. Yusof**, R. Cauwels, E. Deschepper, L. Martens. *Application of third molar development and eruption models in estimating dental age in Malay sub-adults.* J Forensic Leg Med. 2015 May;32:40-44.
- **M.Y.P.M. Yusof**, P.W. Thevissen, S. Fieuws, G. Willems. *Dental age estimation in Malay children based on all permanent teeth types.* Int J Legal Med. 2014 Mar;128(2):329-33.
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- **M.Y.P.M. Yusof**, R. Cauwels, L. Martens. *Age Assessment Policies and Procedures for Undocumented Minors in Malaysia*
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Yusmi Aidil Putera

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List of Abbreviations

48_{mr}	Lower right third molar mesial root
AGFAD	Study Group on Forensic Age Diagnostics
C	Canine
CA	Chronological age
DA	Dental age
I_1	Central incisor
I_2	Lateral incisor
Li_1	Lower primary central incisor
Li_2	Lower primary lateral incisor
LL	Lower left
LR	Lower right
M_1	First molar
M_2	Second molar
MAE	Mean absolute error
Mand	Mandibular
MandPT	Mandibulary permanent teeth
Max	Maxilla
MaxI	Maxillary incisors
ME	Mean error
MLR	Multiple linear regression
MM2H	Malaysia my second home
NR	Not relevant
OLS	Ordinary least square
PCR	Principal Component regression
Pm_1	First premolar
Pm_2	Second premolar

PMandM	Permanent mandibular molar
PT	Permanent teeth without third molar
RMSE	Root mean square error
SMD	Standardized mean difference
SrT	Single-rooted teeth
TM	Third molar
TMD	Third molar development
TME	Third molar eruption
Ui$_1$	Upper primary central incisor
Ui$_2$	Upper primary lateral incisor
UL	Upper left
UNHCR	United Nations High Commissioner for Refugees
UR	Upper right
USCRI	United States Committee for Refugees and Immigrants
VIF	Variance inflation factor

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Chapter 1

Introduction

Part of this chapter has been based on:

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Introduction

The use of teeth to estimate age has always been an open secret in scientific community especially within forensic applications. Dental age assessments aid in accurately estimating the age of subjects with unknown birth records. This process is particularly indispensable during investigation involving penal legislation. One of the main reasons necessitating this procedure is to rule out minors from the age of majority where mandatory sentencing is compulsory. Due to the atrocious impact should one be wrongfully convicted, the authorities are facing a great pressure and need for much more accurate age estimation models.

Dental age estimations have generally been carried out by evaluating the applicability of certain methods based on a previously established database as a standard reference dataset of comparison. In 1973, Demirjian and his co-workers garnered what is considered to be the most reliable dataset at the time, a sample of French-Canadian subjects. The method derived from this dataset has subsequently been tested on various population groups by several investigators for its universal applicability, often with consistent overestimation of the dental age. Numerous studies on population-specific are verified [Bagherpour et al., 2010; Cruz-Landeira et al., 2010; Nik-Hussein et al., 2011] and there are efforts from various institutions to develop a data bank that gathers as much as dental age information from different countries. However, it must be borne in mind that not every country-specific population consists of mono-ethnic population. Countries with multi-ethnic population may show high diversity in terms of skeletal pattern and dental maturity.

In past years, there was a growing interest among researchers to validate the applicability of certain methods on specific populations. Although validation study is one of the important part to assess accuracy, most studies only concluded that the method used was accurate or inaccurate and therefore merely appropriate or inappropriate to be used for the selected populations. Recently, the forensic community witnesses another milestone in its development. The shifting from traditional research practice en route for more comprehensive research and accuracy is seen through the development of various dental age prediction models based on the modifications of previously published methods in children (Table 1.1), sub-adults (Table 1.2). The modified methods were depicted following their respective precursors (bold text) in both tables. The shades difference denotes different methods. Comprehensive studies involving contemporary and elegant statistical approaches are observed through combination of several identified predictors. For example, a study utilizing the combination of third molar and skeletal developments as predictors has been developed by Thevissen and his team [Thevissen et al., 2012].

Table 1.1 Examples of original and modified radiographic-based dental age estimation methods in children

Children	Addition/Statistics	Score(s)
Schour and Massler, 1941	**Atlas**	**NR**
Ubelaker, 1978	Atlas	NR
Kahl and Schwarze, 1988	Atlas	NR
Ubelaker, 1989	Atlas	NR
Moorrees et al., 1963	**Atlas**	**NR**
Gustafson and Koch, 1974	**Atlas**	**NR**
Al-Qahtani et al., 2009	**Atlas**	**NR**
Nolla, 1960	**Norms of maturation**	**10 stages based on 7/14 permanent teeth**
Bolanos et al., 2000	Regression analyses	Permanent teeth stages on 21,46,43and 21,47,46
Moorrees et al., 1963	**Atlas**	**13 SrT stages and 14 PMandM stages (2 MaxI**

		and 8MandPT)
Liversidge, 2009	Probit regression	Permanent teeth development
Fanning, 1961	**Norms of formation and root resorption**	**9 stages primary root resorption**
O'Meara and Knott, 1967	**Primary teeth root resoprtion**	**3-stage primary incisors (Ui$_1$, Ui$_2$, Li$_1$, Li$_2$)**
Demirjian et al., 1973	**7-tooth system (LL of M$_2$, M$_1$, Pm$_2$, Pm$_1$, C, I$_2$, I$_1$)**	**8 stages (Stage A-H)**
Levesque et al., 1981	Quantile regression analysis	8 stages (Stage A-H)
Willems et al., 2001	Weighted ANOVA	9 stages (Stage A-H, 0)
Chaillet et al. 2004a-c, 2005	Polynomial regression	9 stages (Stage A-H, 0)
TeMoananui et al., 2008	Quantile regression analysis	8 stages (Stage A-H)
Roberts et al., 2008	Meta-analysis	8 stages (Stage A-H)
Willems et al., 2010	Weighted ANOVA	8 stages (Stage A-H), non-gender specific
Blenkin and Evans, 2010	Regression analyses	8 stages (Stage A-H), Simple Maturity Score
Demirjian and Goldstein, 1976^s	**4-tooth system (M$_2$, M$_1$, Pm$_2$, Pm$_1$ and M$_2$, Pm$_2$, Pm$_1$, I$_1$)**	**8 stages (Stage A-H)**
Ubelaker, 1989	**Atlas**	**NR**
Blenkin and Taylor, 2012	Atlas	NR
Roberts et al., 2008	**Meta-analysis**	**8 stages (Stage A-H)**
Mitchell et al., 2009	Meta-analysis	8 stages (Stage A-H)

SrT single-rooted teeth, *PMandM* permanent mandibular molar, *MaxI* maxillary incisors, *MandPT* mandibular permanent teeth, *Ui*$_1$ upper primary central incisor, *Ui*$_2$ upper primary lateral incisor, *Li*$_1$ lower primary central incisor, *Li*$_2$ lower primary lateral incisor, *LL* lower left, *M*$_2$ second permanent molar, *M*$_1$ first permanent molar, *Pm*$_2$ second permanent premolar, *Pm*$_1$ first permanent premolar, *C* permanent canine, I_2 second permanent incisor, I_1 first permanent incisor

Table 1.2 Examples of original and modified radiographic-based dental age estimation methods in sub-adults

Sub-adults	Addition/Statistics	Predictor(s)
Gleiser and Hunt, 1955	**10 stages (5 crown stages, 5 root stages)**	**NR**
Haaviko, 1970	12 stages (6 crown stages, 6 root stages)	NR
Kohler et al., 1994	10 stages (3 crown stages, 7 root stages)	NR
Garn et al., 1958	**9 stages (4 crown stages, 5 root stages)**	**NR**
Moorrees et al., 1963	**13 SrT stages and 14 PMandM stages**	**NR**
Shackelford et al., 2012	Graphical scores converted to digitized values	NR
Demirjian et al., 1973	**8 stages (Stage A-H)**	**NR**
Levesque et al., 1981	8 stages (Stage A-H)	NR
Mincer et al., 1993	Regression analyses	Third molars of UR, UL, LL and LR
Solari and Abramovitch, 2002	10 stages (Stage A-H, F1, G1)	NR
Orhan et al., 2006	10 stages (Stage A-H, 0 and 1)	NR
Cameriere et al., 2008	Logistic regression	Third molar developmental stages
Knell et al., 2009	Logistic regression	Third molar developmental stages
Lee et al., 2009	Regression analyses	Third molar developmental stages
Cantekin et al., 2012	Regression analyses	Third molar developmental stages
Johan et al., 2012	Regression analyses	Demirjian et al., 1973 and gender
Jafari et al., 2012	Generalized Estimating Equation	Third molar location (Max and Mand) and Gender
Corradi et al.,	Naïve Bayes	Third molar developmental

2013a		stages
Levesque et al., 1981	**8 stages (Stage A-H)**	**NR**
Orhan et al., 2006	Regression analyses	Third molar developmental stages
Sisman et al., 2007	Regression analyses	Third molar developmental stages
Bai et al., 2008	Regression analyses	Third molar developmental stages
Rai et al., 2009	Regression analyses	Third molar developmental stages
Acharya, 2011	Regression analysis, Logistic regresssion, Bayesian	Third molar developmental stages
Engström et al., 1983	**5 stages (Stage A-E)**	**NR**
Nortje, 1983	8 stages (Stage 1-8) and changed to 5 stages	**NR**
Harris and Nortje, 1984	5 stages (Stage 1-5), suggesting measurement of 48_{mr}	NR
Kullmann et al., 1992	7 stages (Stage 1-7)	**NR**
Kohler et al., 1994	**10 stages (3 crown stages, 7 root stages)**	**NR**
Mesotten et al., 2002	Regression analysis of two third molars present	Third molar developmental stages of UR, UL, LL and LR
Mesotten et al., 2003	Regression analysis of single third molar present	Third molar developmental stages of UR, UL, LL and LR
Guns et al., 2002	Continuation of Mesotten et al., 2002 with larger samples	Third molar developmental stages of UR, UL, LL and LR
Thevissen et al., 2010	Bayesian approach	Third molar developmental stages
Bagherpour et al., 2012	Regression analyses	Third molar developmental stages
Ramanan et al., 2012	Regression analyses	Kohler et al., 1994 and Willems et al., 2001
Thevissen et al., 2012	Regression analyses	Kohler et al., 1994 and Kvaal et al., 1995
Franco et al., 2013	Regression analyses	Kohler et al., 1994 and Willems et al., 2001
Yusof et al., 2014	Regression analyses	Kohler et al., 1994 and Willems et al., 2002
Altalie et al.,	Regression analyses	Kohler et al., 1994 and

2014		Willems et al., 2003
Mohd Yusof et al., 2015a-b	Regression analyses	Kohler et al., 1994 and Olze et al., 2007
Kvaal et al., 1995	**Regression analyses**	**Gender, width and length of pulp ratio**
Orhan et al., 2006	**Regression analyses**	**Third molar developmental stages**
de Oliveira et al., 2012	Exponential function	Third molar developmental stages
Olze et al., 2007	**4 stages of radiographic third molar eruption**	**NR**
Mohd Yusof et al., 2015a-b	Regression analyses	Kohler et al., 1994 and Olze et al., 2007
Corradi et al., 2013a	**Naïve Bayes**	**Third molar developmental stages**
Corradi et al., 2013b	Modified Naïve Bayes	Third molar developmental stages

NR not relevant, *Max* maxilla, *Mand* mandibular, 48_{mr} lower right third molar mesial root, *UR* upper right, *UL* upper left, *LL* lower left, *LR* lower right

The incorporation of wrist age with third molar in regression model also has been performed by a German study [Gelbrich et al., 2015]. These studies are compelling however less practical as justification to acquire two separate radiographs on a single event cannot be met. The opposition from various local and international legislations on non-treatment use of the radiographic imaging also seems unfavorable for the use of age assessment methods especially in living individuals [Aynsley-Green et al., 2012; Cole, 2015]. Therefore, this study is undertaken largely to address the issue while developing models utilizing predictors that can be instrumental to increase accuracy within a single radiograph.

1.1 Dental panoramic radiographs

The advantage of dental panoramic radiograph is that it allows comprehensive imaging of all the teeth and their stage of development, also the simplicity of this imaging technique ensures acceptance by even young children.

Furthermore, radiation exposure is relatively low compared to other imaging procedures. The effective dose for dental panoramic radiographs is between 6.24-7.02 μSv [Shin et al., 2014]. These values is considered negligible and in fact lower than the average person in the U.S. who receives an effective dose of about 3 mSv per year from naturally occurring radioactive materials and cosmic radiation from outer space. Effective dose for chest plain radiograph is 6 mSv [Wall and Hart, 1997]. In perspective, dental panoramic radiograph is a thousand times less radiation exposure risk as compared to the plain chest radiograph. Magnification of panoramic imaging has been widely discussed in the literature. Langland and co-workers reported a uniform magnification of 19% for panoramic radiographs which is a function of the distance between the focus and the object [Langland et al., 1989].

Similarly, a 3–10% enlargement on the left side of the mandible has been reported on panoramic radiographs [Sapoka and Demirjian, 1971]. A justification for using panoramic radiographs is that the distortions and variations in magnification do not affect the assessment because the rating of developing teeth is based on the shape criteria and relative values and not on absolute length measurements [Sapoka and Demirjian, 1971].

1.1.1 Demirjian's dental maturity stages

The number of dental maturity stages varies between 4 and 24 depending on the system. The classification system developed by Demirjian and his co-workers starts with radiographic appearance of calcification of the crown (Stage A) up to the time of root completion (Stage H) as exhibited in Figure 1.1. The reliability of scoring a tooth developmental stage was a compromise between a small number of stages that are easy to identify and a large number of stages that are less reliable. Various methods of tooth development stages have been reviewed and Demirjian's method of tooth development stages has achieved the highest values for both observer agreement and for correlation between the stages.

1.1.2 Willems's dental maturity scores

In 2001, Willems and his team [Willems et al., 2001] attempted to validate the use of Demirjian method on a large sample of Belgian Caucasian population (*n* = 2,523). As expected from previous literature, the Willems study confirmed a significant overestimation of the dental age when using Demirjian method. A weighted ANOVA was performed in order to adapt the scoring system for this Belgian population and new maturity scores tables were developed. The predicted dental age can be directly obtained by adding all seven scores (based on 7 permanent teeth developmental stages) which was expressed in years.

1.1.3 Gleiser and Hunt modified by Kohler's third molar maturity stages

A serial or longitudinal study of the calcification, eruption and decay of the right permanent mandibular first molar has been initiated by Gleiser and Hunt [Gleiser and Hunt, 1955]. In their early study, radiographic images of this tooth were arbitrarily divided into 15 stages of calcification. It was later that Kohler [Kohler et al., 1994] modified and re-evaluated the selection criteria by using a 10 stage developmental scoring method. Each of the 10 stages relates to a particular developmental phase as illustrated by Figure 1.2. All of the third molars present on the radiograph were given a score corresponding to the stage of root development. In the case of a different developmental stage of the multiple roots of one-third molar, the least developed root was evaluated and scored.

1.1.4 Olze's third molar eruption stages

Olze [Olze et al., 2007b] developed third molar eruption stages based on a sample of German population (Figure 1.3). The eruption stages are described as follows:

Stage A: Occlusal plane covered with alveolar bone.

Stage B: Alveolar eruption; complete resorption of alveolar bone over occlusal plane.

Stage C: Gingival emergence; penetration of gingiva by at least one dental cusp.

Stage D: Complete emergence in occlusal plane.

Figure 1.1 Stages of permanent teeth development according to Demirjian et al., 1973 (Reproduced with permission from publisher)

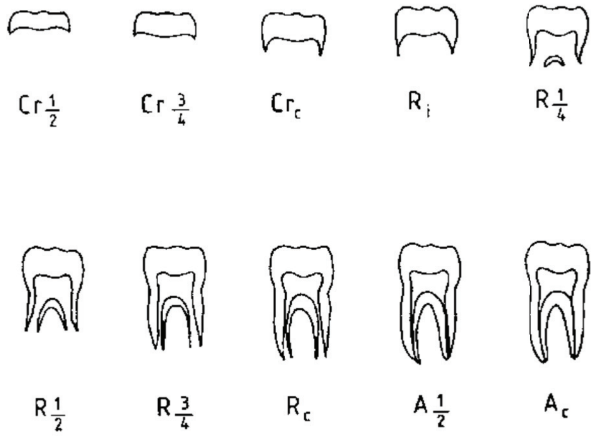

Figure 1.2 Stages of third molar development according to Gleiser and Hunt, 1955 modified by Kohler et al., 1994 (Reproduced with permission from publisher)

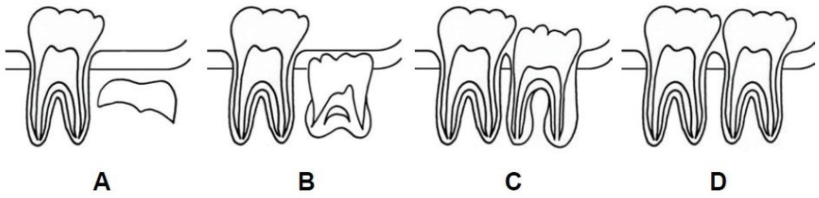

Figure 1.3 Stages of third molar eruption according to Olze et al., 2007 (Reproduced with permission from publisher)

1.2 Age assessment policies in Malaysia

Since 1970s Malaysia has provided a certain level of discretionary protection to some categories of displaced persons, primarily persons fleeing from the ravages of war in Vietnam and soon in 1990s, the Bosnians who escaping the ethnic cleansing imposed by Balkan wars. The main recognized groups of refugees in Malaysia are Acehnese, Rohingya, Burmese (the Chin, Shan, Kareni, Arakan, Kachin and Mon) and Nepali. At the end of 2011 Malaysia had allowed a total inflow of 217,618 refugees and people of concern[1]. Of this numbers, several large communities such as 57,000 to 70,500 of Filipinos from Mindanao and the Rohingyas from the Arakan region in Myanmar to settle in Sabah (west Malaysia) and peninsular Malaysia, respectively (Figure 1.4). By estimation, since 2004 there is about more than 10,000 resettlements from the Rohingya community and the figure remains increasing over the recent years [Kassim, 2004].

Presently, the alien population is a heterogeneous group comprising legally recruited foreign workers, students, permanent residents, refugees, Malaysia My Second Home (MM2H) participants and irregular migrants whose number cannot be ascertained. The latter group plays an important part in this study.

In June 2008, UNHCR Kuala Lumpur estimated their number at around 39,700 in the Peninsular, in addition to approximately 57,194 refugees in Sabah (a total of about 96,894). However, the USCRI World Refugee Survey gave a much higher figure for December 2007 i.e. 164,400 and that the ratio of refugees to the total population in Malaysia is 1: 165. There may be discrepancies in the figures given but the fact remains that there are a substantial number of refugees in the country. Malaysia is fast becoming a popular destination for asylum seekers as indicated by the number of refugee applications worldwide in 2007. Within that year, 75,000 new applications for refugee status were received

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[1] UNHCR global trends 2011

by UNHCR. Of these 13,800, the second largest number of applicants was received in Malaysia[2].

It must be emphasized that refugees in Malaysia are found only in Sabah (the west Malaysia) and the Peninsular (Figure 1.4). Of the many types of refugees found in Malaysia, Sabah is host to Filipino refugees only. The rest of the refugees and asylum seekers are found in the Peninsular. The Filipino refugees, who in the 1970s and 1980s were recognized by UNHCR, are now excluded from UNHCR Kuala Lumpur Factsheet on Refugees. They are presently categorized by the world body merely as “people of concern” whose needs are less urgent than newly arrived asylum seekers.

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[2] UNHCR Refugee Factsheet 2008: 14

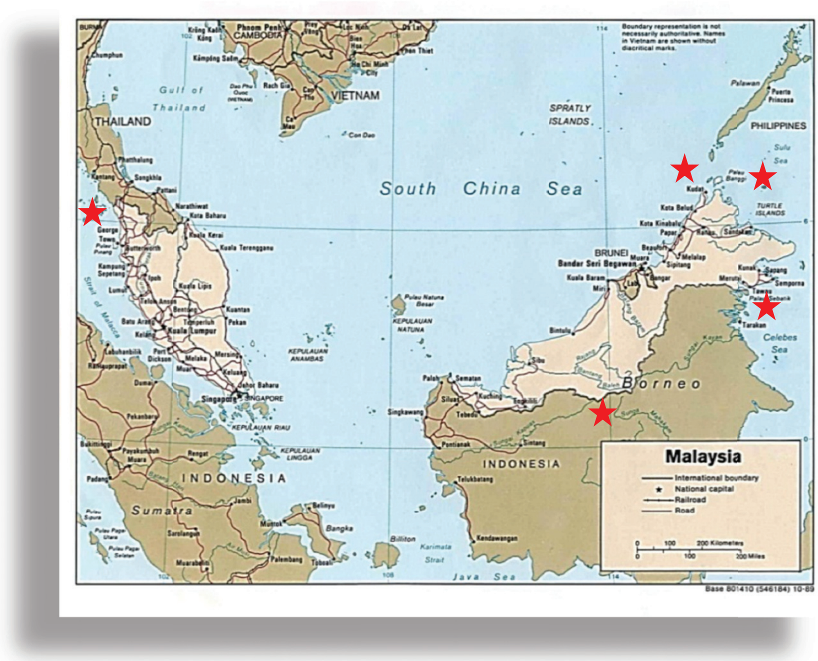

Figure 1.4 Map of Malaysia (red stars denote the hot spots of cross-borders movement)

Malaysia is not a party to many of the key international human rights instruments. Malaysia is neither a party to the 1951 Convention relating to the Status of Refugees nor to the 1967 Protocol relating to the Status of Refugees. As a result, by law, Malaysia does not provide any specific formal protection to people who have fled their own country due to a fear of persecution on convention grounds. However, Malaysia has, on humanitarian grounds, given temporary shelter to them until they can be repatriated to their homeland or sent to a third country for resettlement. By doing so, Malaysia observes the principle of *non-refoulement* in conformity with customary international laws [Fradot, 2007].

Malaysian law distinguishes only two main categories of migrants, namely, documented or 'legal' migrants and undocumented or 'illegal' migrants [Kaur and Metcalfe, 2007]. The first category includes people who enter (and are allowed to stay) in Malaysia and who hold passports, visas, work permits and other valid documents, as required by the immigration legislation. The largest group included here comprises contract migrant workers in possession of a work permit and the necessary documents issued by the Malaysian authorities. The second category includes all people who enter Malaysia without documents or who subsequently become undocumented after arrival.

The usage and governance of foreign labour is regulated by three key legislative instruments: the Immigration Act; the Employment Act 1955/1998; and the Penal Code. The Immigration Department oversees, and the Immigration Act 1959/1963 provides the basis for, immigration regulations and procedures in the country. The Department comes under the authority of the Ministry of Home Affairs. Following the establishment of an official foreign labour recruitment policy in the 1980s, the Home Ministry (through the Immigration Department) formulated new structures to control the entry of people and establish forms of permission to enter and stay in the country through the issuance of visit passes for temporary employment or work permits. Work permits for this category of (unskilled) migrant workers are governed by strict criteria to restrict and regulate the migrant workers' entry, residence and employment.

The Immigration Act was further amended in 1997 and 2002, leading to the establishment of harsh penalties for immigration violations. The Act allows the indefinite detention of illegal migrants pending deportation. Thus undocumented persons in Malaysia, irrespective of whether they are alleged illegal migrant workers or asylum seekers, can face up to a five-year jail sentence, a MYR10,000 (US$2,600) fine and six strokes of the cane under the Immigration Act [Kaur, 2006].

Although, the current policy is neither favorable to the asylum seekers nor the irregular migrants, the incoming flow of these groups is not decreasing. The latter group is particularly of concern due to intricacy of attaining their exact numbers. As their number is difficult to establish considering the lack in border surveillance controls especially within the west coast of west Malaysia region and the tri-border area that comprise the territory and territorial seas of three littoral states (the Philippines, Malaysia and Indonesia) [Rabasa and Chalk, 2012], only individuals who has been apprehended committing crimes will be identified as undocumented immigrants. Since the Vietnamese refugee crisis in 1975, Malaysia has co-operated with UNHCR allowing it to be the primary responsible agency for refugees and asylum seekers. Within its capacity, UNHCR provides for all activities related to registering, documenting, and determining the status of asylum seekers. It also pursues long term solutions and provides humanitarian support through some programs with its non-governmental organization partners[3]. In 1997, the UNHCR established guidelines on policies and procedures on dealing with unaccompanied children seeking asylum[4]:

“If an age assessment of the child’s age is necessary, the following considerations should be noted:

- Such an assessment should take into account not only the physical appearance of the child but also his/her psychological maturity.

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[3] Amnesty International June 2010. Index: ASA 28/010/2010
[4] UNHCR, 1997:5

- When scientific procedures are used in order to determine the age of the child, margins of error should be allowed. Such methods must be safe and respect human dignity.
- **The child should be given the benefit of the doubt if the exact age is uncertain.**"

Due to an increase prevalence of criminals by undocumented and disputed age of perpetuators, the needs for a validated and scientific methods of age estimation is significantly required to discern the minors from general population. The court appearance by medical examiners, forensic odontologists and other related personnel are vital for a thorough rationalization and justification as regard to age assessment. Therefore, to be well-versed with only scientific methods is no longer an acceptable practice. One must be able to endow a sound knowledge of local and international policies as well as the guidelines proposed for the refugees and immigrants.

1.2.1 Age of concern

In 2002, Malaysia amended the Education Act 1966[5] to make 6 years of primary education compulsory for all children of Malaysian citizens who are of ages 6-12 years. According to the Islamic Family Law (Federal Territories)[6] the minimum age for marriage is eighteen for man and sixteen for woman. No marriage deemed to be solemnized under these ages except where the Sharia Judge has granted his permission in writing in certain circumstances. In Malaysia, the legal age of majority is recognized as above eighteen years of age as stated in the Age of Majority Act 1971[7].The minority of all males and

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[5] Laws of Malaysia, Education Act 1966 Act 550

[6] Laws of Malaysia, Islamic Family Law (Federal Territories) Act 1984, Section 8 Act 303

[7] Laws of Malaysia, Age of Majority Act 1971, Act 21

females at the age of eighteen years and every such male and female attaining that age shall be of the age of majority.

According to Child Act 2001[8], the capital punishment may not be applied to children in Malaysia. However, in lieu of this punishment, the constitution allows the court to order a person convicted of an offence to be detained in a prison during the pleasure of the *Yang di-Pertuan Agong*[9]. Practically, the death penalty has not been used for minors in several years.

Life imprisonment is an alternative sentence for all crimes where the death penalty cannot be applied against children. In principle, children under 14 years of age cannot be sentenced to life imprisonment. However, this clause is voided if they are associated with people who possess firearms or explosives, which are linked to terrorist acts.

It is illegal for children under the age of 14 to work, but they are permitted to contribute to family business. It is also legal for children to work in entertainment (acting in public view movies or films), for the government, in schools, or as apprentices. In all cases, a child may not work more than six hours per day, more than six days per week, or during the night.

1.2.2 Ethical concern

The "nonclinical" use of ionizing radiations on subjects in the growth phase has always been an interesting subject to debate on. The "clinical" use of X-rays includes the purpose of preventing, diagnosing, or treating or rehabilitating a disease or an injury or its symptoms. In Malaysia, the medical exposure to the public is subjected to acts and regulations that have been set forth by the

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[8] Laws of Malaysia, Act 611 Child Act 2001 section 97 on Death (Powers of the court for children at the
conclusion of the trial)

[9] The states ruler; Malaysia is a constitutional monarchy with an elected monarch as head of state

International Commission on Radiological Protection (ICRP) and the International Atomic Energy Agency (IAEA). The basic safety standard is gazette as Act 304[10] where various regulations are enforced to ensure the protection of people from exposure to ionizing radiation. Currently, the enforcement agencies that deal with this matter are Atomic Energy Licensing Board (AELB) for non-medical applications and Malaysian Ministry of Health for medical applications. In 1971, the government of Malaysia adopted a definition of medical law through a Medical and Dental Act 1971[11]: "The medical and dental act encompasses all the professional action, e.g. scientific, teaching, training and educational, registration, clinical and technical steps, performed to promote health, prevent diseases, and provide diagnostic or therapeutic care to patients. The act must at all times be performed by a licensed medical doctor/physician/dentist or under his/her direct supervision and/or prescription". According to Malaysian Radiological Society (Guidelines for Clinical Practice in Radiology) and Malaysian Dental Council (Guidelines on Radiation Safety in Dentistry), a radiographic examination should only be for the purpose of obtaining diagnostic information about the patient's condition. In addition, routine or screening examination without prior clinical assessment should not be prescribed. Although the guidelines did not specifically discussed the use of X-rays for legal or administrative purposes and whether or not it can be considered as a "treatment" or a diagnosis, the use of radiographic procedures are still widely performed in various states of the country. Dental panoramic radiographs are the most commonly requested and utilized for age assessment in public dental clinics.

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[10] Laws of Malaysia, Atomic Energy Licensing Act 1984, Act 304

[11] Laws of Malaysia, Act 50 Medical Act 1971; This act is amended in 2012 as Act A1443 Medical (Amendment) Act
2012. Dental Act 1971 is amended in 2012

In Belgium, the age estimation protocol for unaccompanied fugitives called the Triple Test was developed at the Katholieke Universiteit Leuven. Among others, the protocol outlined three major procedures to arrive at final age assessment report involving clinical assessments and radiographic acquisitions. According to Belgian law[12], the Guardianship Service[13] may order a medical test to verify whether or not the person is younger than 18 years old.

Essentially, the World Health Organization (WHO) definition of "health" [World Health Organization, 1946] is empirical and should always be incorporated within the purview of age estimation context.

"Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity."

The age estimation could be considered in this perspective, considering, for instance, the execution of age estimation for adoption purposes; for an appropriate school placement or for asylum requests (after which, the minor could not be expelled and could be introduced in a social context appropriate to its age). The question is still not resolved, and already in 1996, the Royal College of Radiologists in London [Council of Europe, 2011] stated that it was "unjustified to undertake a radiograph examination for age estimation purposes. It is not acceptable to expose children to ionizing radiation for an examination which has no therapeutic benefit and is purely for administrative purposes." Likewise, many clinicians, radiologists, and pediatricians highlighted the ethical issue connected to exposing growing individuals to the risk (exposure to ionizing radiation) solely for administrative/legal purposes. The Royal College of Radiologists in 2007 reiterated that there was little evidence on the reliability

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[12] Belgian Laws, Guardianship Act Article 7

[13] Part of the Federal Public Service for Justice with mission to ensure judicial protection of all unescorted minors (asylum seeker or not) staying or arriving in Belgium

of age estimation through wrist and hand X-ray and dental panoramic radiographs, asserting that "from a patient safety viewpoint, we could never recommend irradiating for nonmedical purposes. No level of radiation is safe" [Husband J, 2007]. At the moment, the position of the UK Border Agency about age estimation is: "The use of X-rays to assess the age of children is not admissible. Doctors must not be asked to use radiological date when giving age assessments" [United Kingdom Border Agency, 2013]. Furthermore, a pilot project started in March 2012 in the United Kingdom, which included the execution of dental radiographs of all asylum seekers in order to assess their age was immediately stopped because of the lack of the ethics committee approval[14].

The Royal Australian and New Zealand College of Radiologists (RANZCR) declared that "any possibility of taking an X-ray of a person's body part as a prescribed procedure for age determination" was unlawful, affirming that the radiation risk in dental age estimation was greater than the benefit [Senate Committees Parliament of Australia, 2013]. The Senate Committees of the Parliament of Australia has pointed out a different orientation, admitting the possibility of ordering X-ray exams for age estimation: "Australian courts should have access to all relevant evidence in determining the age of a defendant, including X-ray age assessments where necessary". The Commonwealth joint submission also suggested that there could be increased use of dental x-rays for age assessment in the future:

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[14] The trial has been put on hold after it emerged that government should have sought ethical approval for the scheme,
which qualifies as health "research". Children may be unable to give informed consent to take part and it could put
them at risk of unnecessary exposure to medical radiation.
https://www.crin.org/en/library/news-archive/united-kingdom-border-agency-suspends-asylum-x-ray-pilot

"In addition to introducing a suite of improved age assessment measures in mid-2011, including offering voluntary dental x-rays and interviews, the Commonwealth is also considering adding dental x-rays as a prescribed procedure in the Crimes Regulations. This would allow investigating officials to seek an order from a court to conduct a dental x-ray and subject them to the same procedural safeguards as wrist x-rays[15]."

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[15] House of Representatives Committees Parliament of Australia Submission 20 p19

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Chapter 2

Research Aims & Methodology

2.1 Aims

From the introduction, it became clear that the use of radiation for administrative purposes such as age assessment may not be easily welcomed. Although the acceptability of such practice varies from one country to another, the justification to perform multiple radiographic examinations on an individual is still considered by many to be unethical. Therefore, in view of this shortcoming, the current thesis attempts to provide the alternative standards in advancing dental age assessments. The overall objectives of the thesis are to validate the different methods of dental age estimations and evaluate the use of different statistics and predictors influencing accuracy of dental age assessment models in children and sub-adults based on a single radiograph.

The aims of the present study are threefold:

1. To investigate the performance of dental age estimation models through different statistical methods (Chapters 3, 4 & 5).
2. To evaluate the accuracy of dental age prediction models when another predictor[16] is added to its equation (Chapters 4 & 6).
3. To assess the stage(s) in third molar development and eruption that involves in discriminating the minors from the age of majority (≥18 years old) (Chapter 5).

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[16] In children, the predictor TMD is added to PT prediction model while in sub-adults, the predictor TME is added to TMD prediction model

2.2 Methodology

A sample of 1,403 digital panoramic radiographs was retrospectively collected (691 males, 712 females). The general inclusion criteria included the following:

- individuals with Malaysian nationality
- residing in the same geographic area and from equal Malay ethnic origin
- good image quality
- healthy individuals with no medical evidence or pathology affecting tooth development

The Malaysian nationality was checked by controlling the citizenship status in the presented Malaysian national registration identity card. The individuals were classified from Malay origin if their paternal and maternal names indicated the same ethnic origin. The selected radiographs were constantly cross-checked with patient's own assessment reports to exclude individuals with systemic diseases. The collected sample consisted of 702 children (4– 14.99 years) and 701 sub-adults (15–23.99 years).

The sampling was performed at the Oral & Maxillofacial Radiology units in the Faculty of Dentistry of University Teknologi MARA (UiTM) and University of Malaya (UM), Malaysia from the year 2006 to July 2013. Protocols to collect radiographs for human subjects were approved by the Ethics Committee for Research Involving Human Subjects of both universities (UiTM, UM). In addition, ethics approval to perform this study has also been obtained from the Commission for Medical Ethics Ghent University Hospital (EC UZG 2013/146).

Given the objectives of Chapters 4, 5 and 6, several specific inclusion criteria on panoramic radiographs had been imposed to fulfill these investigations:

- sub-adult individuals had at least one third molar present (Chapter 4)

- sub-adults had all four third molars present (Chapters 5 and 6)
- the available retro-molar space more than 1.1 Ganss ratio (Chapter 6)

The third molar exhibited with horizontal or vertical impaction and angulation between long axis of third molar and long axis of second molar is > 10° were considered the exclusion criteria for this investigation. The available mandibular retro-molar space was measured in addition to third molar crown width. The available retro-molar space was defined as the distance between the distal border of the second molar and the anterior border of the ramus measured on the occlusal plane, in proportion to the width of the third molar crown (Figure 2.1). The ratio of retro-molar space to crown width was calculated according to the method described by Olive and Basford [Olive and Basford, 1981] and later modified by Ganss [Ganss et al., 1993].

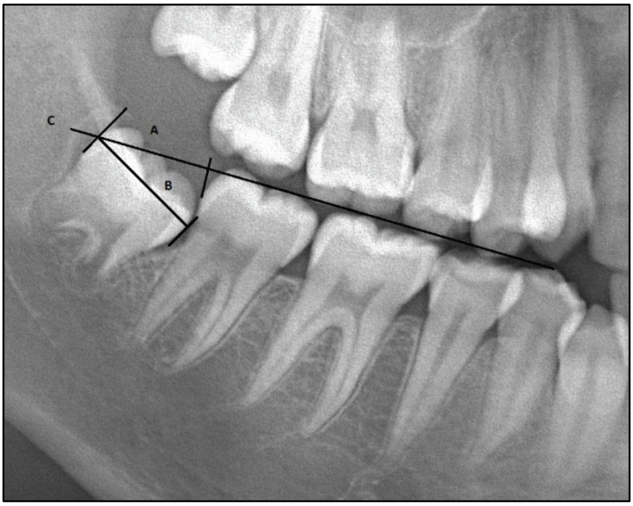

Figure 2.1 A sectioned panoramic radiograph. Distance between distal border of second molar crown and anterior border of ramus measured on occlusal plane (*A*) in proportion to width of third molar crown (*B*) for upper and lower third molars as well, *C* = occlusal plane.

The images were stored without compression as jpeg files of 2.5 MB and dimension of 2,440×1,280 pixels. To avoid bias, prior to data scoring, all images were relabeled randomly in numeric order and all related information was made anonymous. Assessments were performed using Adobe Photoshop® CS2 version 9.0 software, (Adobe Systems Incorporated, San-Jose CA, USA), enabling image enlargement and improvement of the image quality during data collection.

The development of seven permanent left mandibular teeth in children were staged according to the Demirjian technique [Demirjian et al., 1973] and all third molars available in the sample were staged according the Gleiser and Hunt technique [Gleiser and Hunt, 1955] modified by Kohler [Kohler et al., 1994]. Third molar eruption was staged based on Olze classification criteria [Olze et al., 2007a]. After 1 month, 100 randomly selected radiographs were staged by the first (MYPMY) and a second observer (RC). Kappa statistics were used to evaluate the intra- and inter-observer reliability.

Subsequent to age (categories) and gender stratification, the children sample was randomly divided in a training dataset and a test dataset. Two Malay-specific prediction models utilizing the Willems and Kohler methods were fitted on the subjects in the training datasets based on lower left permanent teeth and third molar developments, respectively (Figure 2.2). The test datasets were used to verify the constructed Malay-specific prediction model and the original Willems model. To compare the age prediction performances, the error of the age prediction was defined as the difference between the chronological age and the estimated age (chronological age - estimated age). For calibration purposes, the error was expressed as mean error (ME), to quantify the direction of the error (overestimation or underestimation); mean absolute error (MAE), to quantify the magnitude of the error; and the root mean square error (RMSE), to enable to quantify the variance in errors (giving large errors more weight).

Note that the RMSE will be larger or equal than the MAE. In circumstances where the RMSE equals the MAE, then all errors are of the same magnitude.

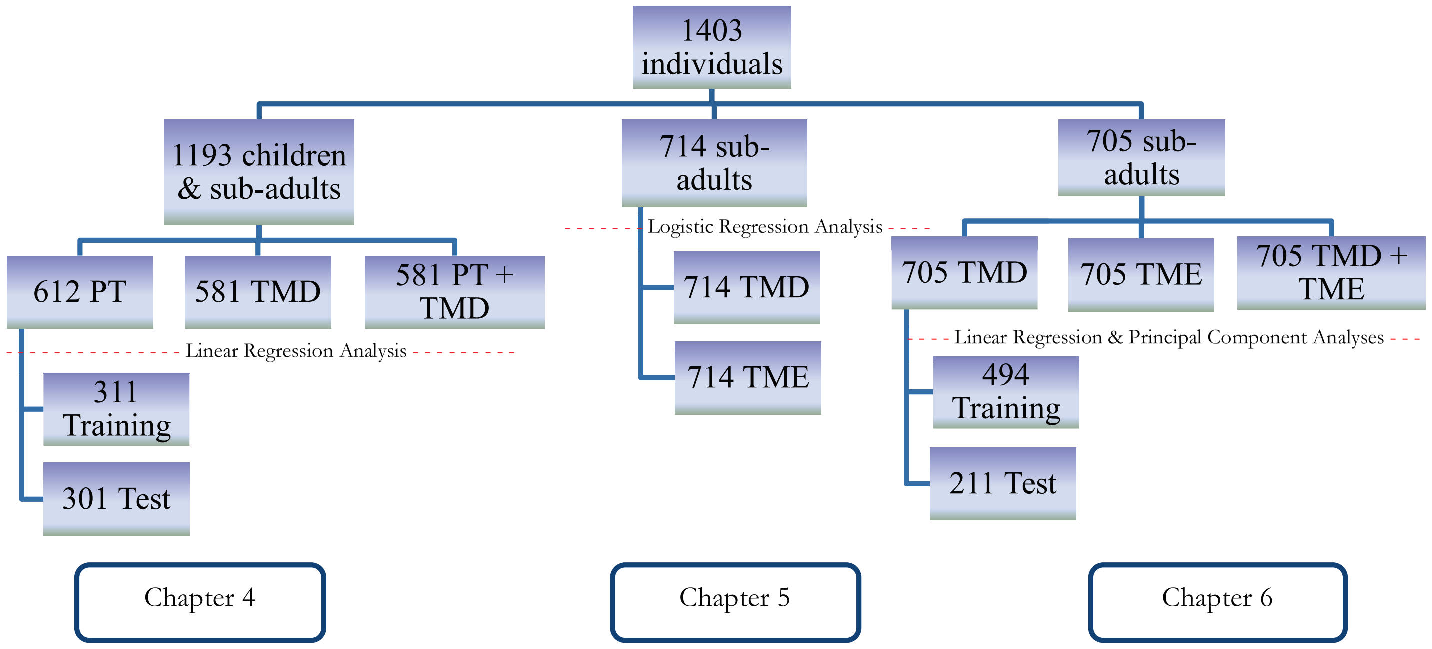

Figure 2.2 Overview of sample selection for dental age estimation models

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Chapter 3

Performance of Willems Dental Age Estimation Method

This chapter has been based on:

M.Y.P.M. Yusof, I. Wan Mokhtar, S. Rajasekharan, R. Overholser, L. Martens. *Performance of Willems Dental Age Estimation Method in Children: A Systematic Review and Meta-analysis.*

Submitted to Forensic Science International

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Abstract

Through numerous validation and method comparison studies on different populations, the Willem's method exhibited a superior accuracy. This article aims to systematically examine how accurate the application of Willems dental age method on children of different age groups and its performance based on various populations and regions. A strategic literature search of PubMed , MEDLINE, Web of Science, Embase and hand searching were used to identify the studies published up to September 2014 that estimated the dental age using the Willem's method (modified Demirjian), with a populations, intervention, comparisons and outcomes (PICO) search strategy using MeSH keywords, focusing on the question: How much Willem's method deviates from the chronological age in estimating age in children? Of 116 titles retrieved based on the standardized search strategy, only 19 articles fulfilled the inclusion criteria. The pooled estimates were separately kept as underestimation (*n*=7) and overestimation (*n*=12) of chronological age for both genders according to primary studies. On absolute values, females (underestimated by 0.13; 95% CI: 0.09-0.18 and overestimated by 0.27; 95% CI: 0.17-0.36) exhibited better accuracy than males (underestimated by 0.28; 95% CI: 0.14-0.42 and overestimated by 0.33; 95% CI: 0.22-0.44). For comparison purposes, the overall pooled estimate overestimated the age by 0.10 (95% CI: -0.06-0.26) and 0.09 (95% CI: -0.09-0.19) for males and females, respectively. There was no significant difference between the young and older child in subgroup analysis. The mean age between different regions exhibited no statistically significant. The use of Willem's method is appropriate to estimate age in children considering its accuracy on different populations, investigators and age groups.

Chapter 3 | Performance of Willem's Method

Introduction

Age assessment has become a mandatory procedure in where chronological age cannot be determined. The situation becomes apparent during the court of law ruling to decide whether or not an undocumented individual is reached the certain age of interest and more importantly to ascertain the individual from the age of majority. Improper handling of registration may lead to wrongly registered and documented age thus places a great weight on accuracy of the select age assessment methods. The use of Willem's method has been increasing over the years largely due to its easy to use technique as well as better accuracy compared to its prototype, Demirjian [Demirjian et al., 1973]. According to Liversidge [Liversidge, 2008b], the Willem's method was the best as regards to average difference and median absolute difference between the dental age and chronological age. Several studies have been performed to estimate the age of majority threshold as well as other specific age categories by assessing third molar [Mohd Yusof et al., 2015a; Mohd Yusof et al., 2015b], permanent teeth excluding third molar, deciduous teeth [Fulton and Liversidge, 2015] and the combination of both third molar and the rest of permanent teeth [Altalie et al., 2014; Franco et al., 2013; Ramanan et al., 2012; Yusof et al., 2014]. Dental age in children proves to be more favorable than chronological age during various conditions such as orthodontic treatment planning, certain forensic applications as well as other clinical situations. Subjects with pre-term or improper handling during registration may lead to wrongly registered and documented age. Although the decision to use specific dental age estimation methods is an arbitrary matter, one cannot refute the fact that the select method must be backed up by an informed knowledge on the method of choice. Validated accuracy (relevance of method) in dental age estimation is necessary to ensure reliable and reproducible results in forensic odontology. Therefore, this study aims to examine the accuracy of Willem's dental age application on children of different age groups and its performance based on various populations and regions.

Methods

This systematic review was performed according to criteria set forward by PRISMA statement [Moher et al., 2009]. The research question for this study is "How much Willem's method deviates from the chronological age in estimating age in children?" The research question was formulated based on PICO strategy [Akobeng, 2005].

Selection of studies

Articles published in English and other languages between January 2001 and September 2014 were searched. The selection of papers suitable for inclusion in the review was independently carried out by two authors (MYPMY and IWM). The finding discrepancies during selection process were settled through discussion.

Inclusion criteria

Original research papers that used Willem's data set for age estimation on healthy subjects, either for validating its applicability or for creating an adopted data set, were included in the study. Studies expressing the results in mean differences alone were included as it was intended to analyze the exact degree of variation between the estimated dental age (DA) and the chronological age (CA).

Exclusion criteria

As this study is performed to generalize the results in mean difference, the studies expressing age estimation results in median or in percentages were excluded. In addition, studies conducted on subjects who were physically or medically compromised and those with developmental anomalies were excluded. In order to be able to perform robust analysis on the generalized applicability of the data set, studies performed on only a fewer teeth and those exclusively on third molars were also excluded. It should be noted that the original system of assessment proposed by the authors excluded third molars.

Electronic searches

PubMed, Embase, MEDLINE and COCHRANE databases were searched for the terms 'Willems' OR 'modified Demirjian' AND 'dental age'. The search for the studies was confined on the date of publication from January 2001 to September 2014.

Hand searching

The following journals were hand searched with similar search terms to locate any relevant articles: Forensic Science International, Journal of Forensic Sciences, Journal of Forensic Odontostomatology,
International Journal of Legal Medicine, Journal of Forensic and Legal Medicine, International Journal of Paediatric Dentistry and Archives of Oral Biology. The journals were shortlisted on the basis of the number of studies published relevant to 'dental age estimation in children'. The reference lists of the selected articles were further scrutinized to identify additional studies.

Data analysis and statistical methods

After the identification of articles in the databases, the articles were imported into EndNote X6 software (Thompson Reuters, Philadelphia, PA, USA) to remove duplicates. Meta-analyses were carried out by using RStudio version 0.97.551 - © 2009-2012 RStudio, Inc. software. The *metafor* function package was used to develop graphics and quantitative measurement in this analysis. Random effect model was chosen prior to commencement of the study and test of heterogeneity was performed to confirm the common effects. Statistical heterogeneity between studies was assessed with the chi-square test and the I^2

statistic [Higgins and Thompson, 2002]. The statistical significant *p* values for this Q statistics were set at $p<0.10$. Potential causes of heterogeneity were further explored by sensitivity and subgroup analyses. The weighted mean difference was calculated with 95% confidence interval. The larger sample sizes (*n*) received more weight than the smaller samples. To prevent misleading interpretation, bias directions from original studies were standardized by the difference of estimated dental age to chronological age (DA-CA). Based on the standardization in current study, all positive values represented overestimation while negative values exemplified underestimation of the real age. All *p* values reported are two-tailed and statistical significant was set at 0.05.

Funnel plot was used to assess publication bias. Sub-group analyses that included the age interval between 4 to 14.9 years old and examiners from different geographical backgrounds were pre-specified to explain the possible sources of heterogeneity within the studies for each gender. In addition, two age groups of younger (4-8 years) and older (9-14 years) children representing pre-pubertal and post-pubertal groups respectively were also included in the sub-group analyses. The sensitivity analyses were accomplished according to the Handbook of Systematic Reviews of Interventions of Cochrane software (version 5.0.2; The Cochrane Collaboration).

Results

Results of the literature search

The comprehensive process of the study collection is shown in Figure 3.1. In total, 116 records have been initially identified through various database searches. After the removal of duplicates, 70 were screened by the titles and abstracts. At this stage, 45 records were excluded due to different methods (*n*=24), the use of third molars (*n*=17) and deciduous teeth (*n*=2), and foreign language articles (*n*=3).

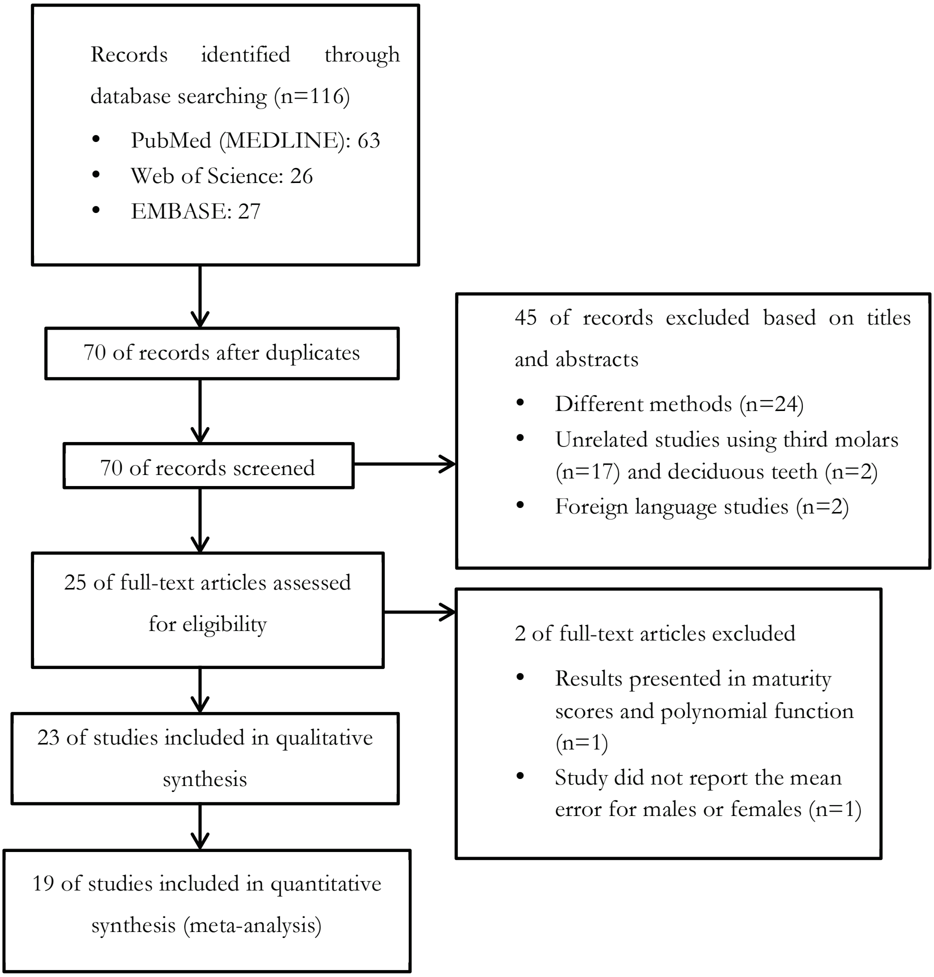


Figure 3.1 Flowchart on literature search and study selection process

Of the 25 studies retained for detailed review, 2 were not included; 1 study presented results in maturity scores and polynomial functions [Chaillet et al., 2004] and 1 study did not report the mean error for males and females [Liversidge et al., 2010].

Study characteristics

Summary of the study characteristics involved in meta-analysis is presented in Table 3.1. A total of 13,915 (6746 males and 7169 females) individuals were included in the 19 eligible studies. The age of these individuals ranged from 3 to 16.9 years old. On study level prior to bias direction adjustment, 12 studies calculated age mean difference as DA-CA and 7 studies as CA-DA.

Accuracy of Willem's method on under- and overestimated age groups

As shown in Figures 3.2 and 3.3, the accuracy of Willem's method was significantly impaired on both ends of bias direction for males (underestimated by 0.28; 95% CI: 0.14-0.42 and overestimated by 0.33; 95% CI: 0.23-0.43) and females (underestimated by 0.13; 95% CI: 0.09-0.18 and overestimated by 0.25; 95% CI: 0.15-0.34) on absolute values. However, as depicted in Figure 3.4a, not all studies remained underestimated or overestimated across age interval. Furthermore, the significant between-study heterogeneity was observed in all estimations with I^2 ranges from 70.1 to 97.1% for both genders ($p<0.0001$).

Subgroup and sensitivity analyses

The subgroup analysis was conducted to explore the accuracy of Willem's method for each age interval in the under- and overestimated age groups. The age range for subgroup analysis was confined from 4 to 14.9 years old. Mean differences for age interval prior to 4 and beyond 14.9 years were omitted from the analysis due to low number of within-study subjects [Altalie et al., 2014] or the authors did not disclose the data in the articles [Altalie et al., 2014; El-Bakary et al., 2010; Franco et al., 2013; Galic et al., 2011; Grover et al., 2012; Kumaresan et al., 2014; Lee et al., 2011; Maber et al., 2006; Mohammed et al., 2014; Pinchi et al., 2012; Ramanan et al., 2012]. Among them, three had provided data for current analysis [Altalie et al., 2014; Franco et al., 2013; Ramanan et al., 2012]. Since the direction of bias is stated in every report, the absolute values were used to elucidate the magnitude in mean difference. Subgroup analysis indicated that the underestimation in male pooled mean difference varies from 0.15 to 0.84 and 0.24 to 0.56 in the overestimated group (Figure 3.2). The test of heterogeneity exhibited no statistical significant ($p>0.10$) for all age groups except 7 and 14 years (underestimation) and 4, 6,7, 12-14 years (overestimation). The magnitude of pooled mean difference for underestimation (0.08-0.71) and overestimation (0.19-0.38) groups in female children was also presented in Figure 3.3.

The pooled mean difference between younger (4-8 years) and older (9-14 years) children exhibited no statistical difference in both underestimation and overestimation groups for each gender and age groups (Figure 3.4b). The test of heterogeneity revealed substantial homogeneity within the subgroups across age groups and regions ($p>0.10$) except for younger children in male underestimation group (Table 3.2). The accuracy of pooled mean difference was affected in all subgroups as displayed in Table 3.2 ($p\text{-value}^2<0.05$). In general, females showed better accuracy than males with absolute pooled mean difference ranged from 0.13 (95% CI = 0.01, 0.26) to 0.30 (95% CI = 0.12, 0.48) and 0.20 (95% CI = 0.01, 0.38) to 0.42 (95% CI = 0.31, 0.52), respectively (Figure 3.5), sparing the South American subgroup ($n = 1$).

Table 3.1 Demographic data of the included studies

Studies	Year	Population	Male				Female				Age range (years)	Direction of bias
			N	MD	SD	Outcome	N	MD	SD	Outcome		
Yusof et al.	2014	Malay	345	-0.58	1.33	OE	357	-0.32	1.43	OE	4 to 14.9	CA-DA
Ye et al.	2014	Chinese	410	0.36	1.19	UE	531	-0.02	1.18	OE	7 to 14.9	CA-DA
Mohammed et al.	2014	South Indian	166	-0.69	2.14	UE	166	-0.08	1.34	UE	6 to 15.9	DA-CA
Medina et al.	2014	Venezuelan	117	0.29	0.96	OE	121	0.01	0.96	OE	5 to 13.9	DA-CA
Kumaresan et al.	2014	Malaysian*	179	0.55	1.4	OE	247	0.53	1.2	OE	5 to 15.9	DA-CA
Ambarkova et al.	2014	Macedonian	481	0.52	0.87	OE	485	0.33	0.83	OE	6 to 13.9	DA-CA
Altalie et al.	2014	Emirati	481	-0.08	0.83	OE	474	0.12	0.78	UE	4 to 15.9	CA-DA
Urzel and Bruzek	2013	French	357	0.14	0.16	OE	386	-0.09	0.2	UE	4 to 15.9	DA-CA
Franco et al.	2013	Brazilian	417	-0.38	0.94	UE	521	-0.17	0.88	UE	5 to 15.9	DA-CA
Djukic et al.	2013	Serbian	322	-0.16	1.01	OE	364	-0.12	1.1	OE	4 to 15.9	CA-DA
Ramanan et al.	2012	Japanese	530	0.06	0.97	UE	519	0.08	1.1	UE	15 to 14.9	CA-DA
Pinchi et al.	2012	Italian	244	-0.28	1.23	UE	257	0.44	1.28	OE	11 to 15.9	DA-CA
Grover et al.	2012	North Indian	102	0.36	0.41	UE	113	0.24	0.43	UE	6 to 15.9	CA-DA
Nik-Hussein et al.	2011	Malaysian*	504	0.3	1.3	OE	487	-0.05	1.1	UE	5 to 14.9	DA-CA
Lee et al.	2011	South Korean	754	-0.15	0.58	OE	729	-0.19	0.72	OE	3 to 16.9	CA-DA
Galic et al.	2011	Bosnian-Herzegovinan	498	0.42	0.77	OE	591	0.25	0.89	OE	6 to 13.9	DA-CA
El-Bakary et al.	2010	Egyptian	134	0.29	0.48	OE	152	0.14	0.74	OE	5 to 16.9	DA-CA
Mani et al.	2008	Malay	214	0.55	0.99	OE	214	0.41	1.08	OE	7 to 15.9	DA-CA
Maber et al.	2006	Bangladeshi & British Caucasian*	491	-0.05	0.81	UE	455	-0.2	0.89	UE	3 to 16.9	DA-CA

MD, Mean difference; SD, Standard deviation; OE, Overestimation; UE, Underestimation; CA, Chronological age; DA, Dental age

*Mixed population

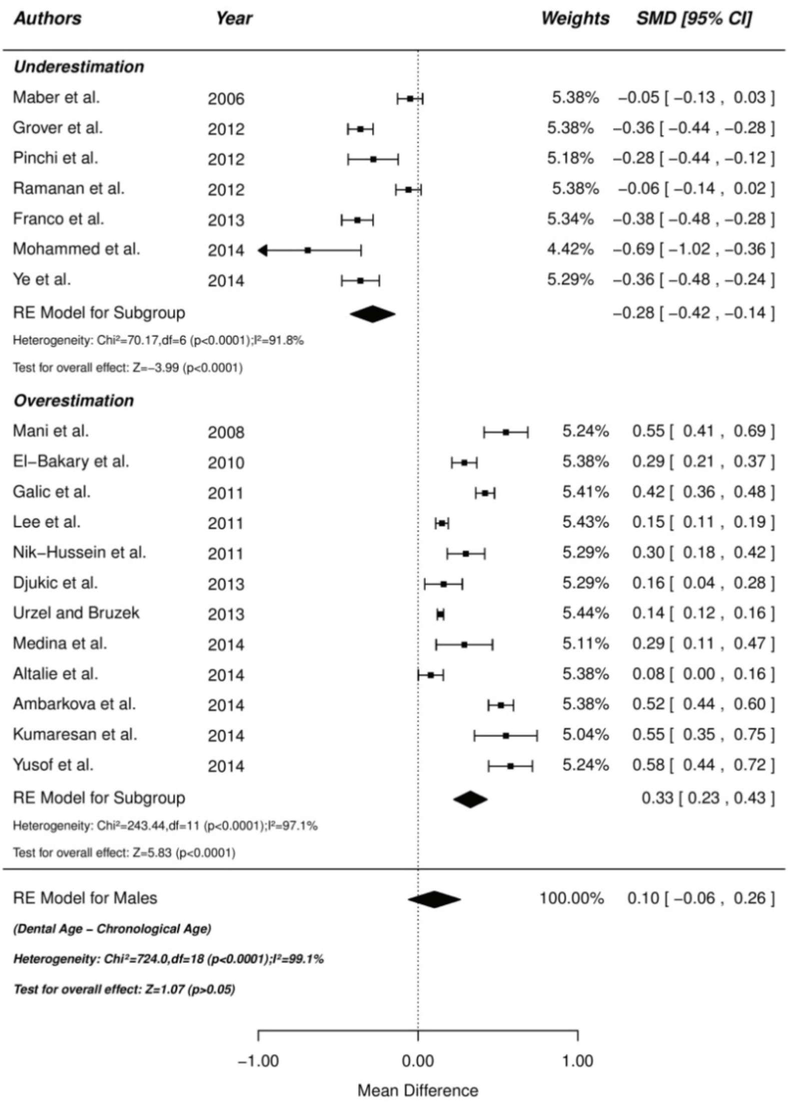


Figure 3.2 Forest plot of mean difference for male children subjected to Willem's dental age estimation method, comparing the underestimated and overestimated groups of individuals. Weights were assigned by RStudio version 0.97.551 using the number of subjects and SD. SMD, standardized mean difference; RE, random effects.

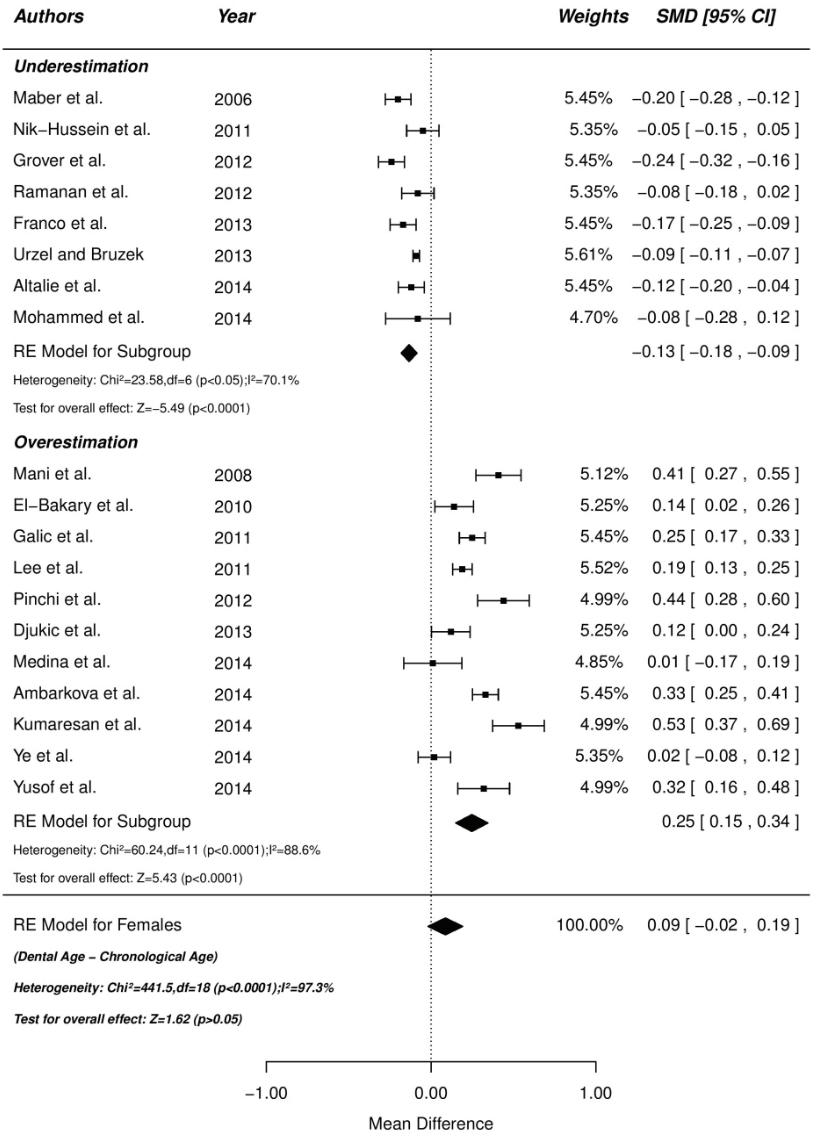


Figure 3.3 Forest plot of mean difference for female children subjected to Willem's dental age estimation method, comparing the underestimated and overestimated groups of individuals. Weights were assigned by RStudio version

0.97.551 using the number of subjects and SD. SMD, standardized mean difference; RE, random effects.

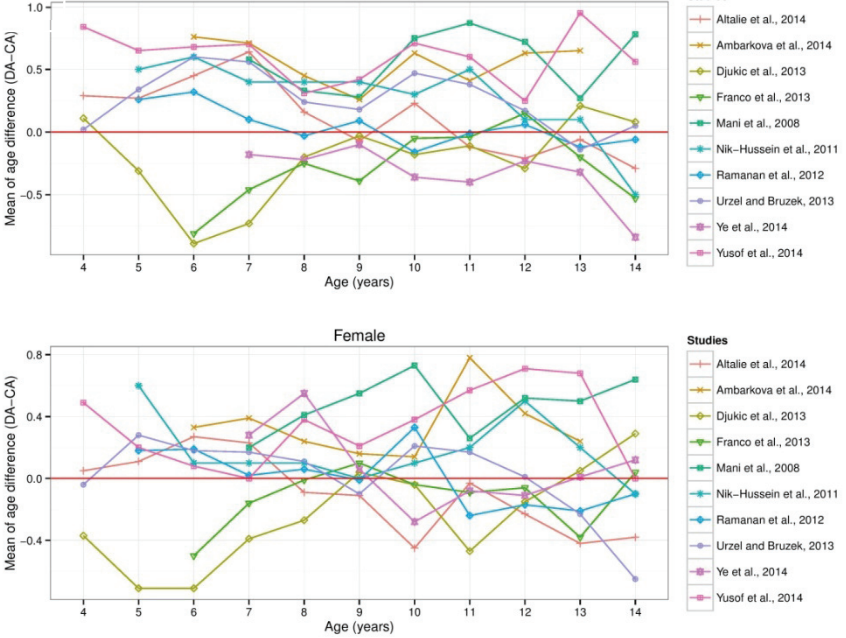
Discussion

The current study collected eighteen studies that utilizing Willem's method on various specific-populations skimmed through a series of systematic review process [Altalie et al., 2014; Ambarkova et al., 2014; Djukic et al., 2013; El-Bakary et al., 2010; Franco et al., 2013; Galic et al., 2011; Grover et al., 2012; Kumaresan et al., 2014; Lee et al., 2011; Maber et al., 2006; Mani et al., 2008; Mohammed et al., 2014; Nik-Hussein et al., 2011; Pinchi et al., 2012; Ramanan et al., 2012; Urzel and Bruzek, 2013; Ye et al., 2014; Yusof et al., 2014]. Out of this, ten studies have been selected to undergo meta-analysis based on the sufficiency of data supplied in respective literatures [Altalie et al., 2014; Ambarkova et al., 2014; Djukic et al., 2013; Franco et al., 2013; Mani et al., 2008; Nik-Hussein et al., 2011; Ramanan et al., 2012; Urzel and Bruzek, 2013; Ye et al., 2014; Yusof et al., 2014].

Accuracy and bias

In general, accuracy is defined as the closeness of a measurement to the true value. When the term is applied to sets of measurements of the same standard, it involves a component of random error and a component of systematic error. In this case, trueness is the closeness of the mean of a set of measurement results to the actual (true) value [ISO5725-1, 1994]. A primary finding on the accuracy of Willem's method revealed that the overestimation and underestimation of dental age varied from 0.01 to 0.69 years for both genders based on study distributions (Figures 3.2 and 3.3). In perspectives, Willem's method accurately estimated age for less than one year with majority of studies reported less than six months on error rate. Interestingly, individuals within the age range of 8 to 9 years old exhibited the least deviation in mean age difference. However, little advantage can be drawn to this age group due to its impracticability as per forensic application.

a



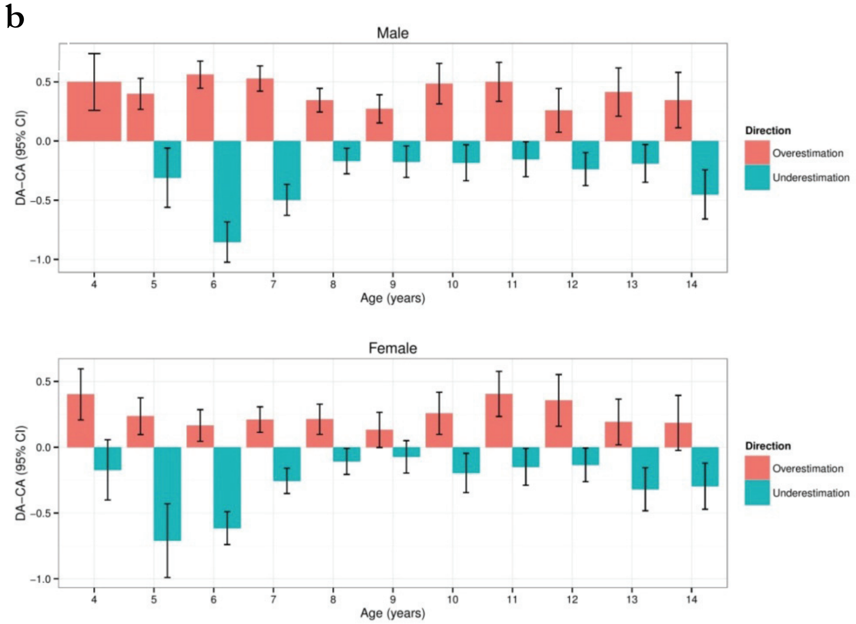


Figure 3.4 Distribution of mean error comparing performance of Willem's method by primary study (**a**) and age group (**b**)

The mean error difference as shown in Willems's method performs better than the two previous meta-analysis studies conducted on Demirjian's method [Jayaraman et al., 2013; Yan et al., 2013] where the mean absolute error ranged from 0.02 to 2.03 [Yan et al., 2013] and 0.04 to 3.0 [Jayaraman et al., 2013] for all genders in primary studies. Although this finding is expected, there is a major flaw in interpreting quantitative analysis of systematic review that needs to be addressed. This especially pertains to age estimation study. As a result of the independent investigation in primary studies, the validation of certain methods in dental age estimation may give rise to either the age is being underestimated or overestimated. Therefore, to be able to generate a meaningful generalization out of the pooled estimate, it is important to make a distinct segregation for underestimation and overestimation groups. The investigators should not particularly dwell too much on the overall mean difference as portrayed at the bottom of the forest plot. The reason is that the overall mean difference tends to shift to the middle due to the averaging effect of the mean values from both ends (underestimation and overestimation). This leads to the danger of reporting the false value of the mean difference. In addition, the test of heterogeneity as exemplified in I^2 will be so high indicating the common effect is not homogenous and warranting the use of meta-analysis may be possibly inappropriate.

Table 3.2 Subgroup analyses of under- and overestimation for children stratified by prior study characteristics

	Males									
Variables	Underestimation mean (95% CI)	No. of studies	Test of heterogeneity		*p*-value[2]	Overestimation mean (95% CI)	No. of studies	Test of heterogeneity		*p*-value[2]
			I^2 (%)	*p*-value[1]				I^2 (%)	*p*-value[1]	
Age group										
4-8 years	-0.29 (-0.51,-0.06)	4	67.7	0.02	0.01	0.42 (0.31,0.52)	8	38.7	0.12	<0.01
9-14 years	-0.20 (-0.31,-0.08)	7	0	0.82	<0.01	0.29 (0.18,0.40)	9	20.2	0.27	<0.01
Regions										
Asia	-0.35 (-0.64,-0.06)	4	97.5	< 0.01	0.02	0.34 (0.22,0.47)	7	89.6	<0.01	<0.01
Europe	-0.21 (-0.32,-0.09)	2	34.9	0.22	<0.01	0.36 (0.13,0.58)	3	98.1	<0.01	<0.01
America (South)	-0.38 (-0.47,-0.29)	1	-	-	<0.01	0.29 (0.12,0.46)	1	-	-	<0.01

	Females									
Age group										
4-8 years	-0.14 (-0.25,-0.03)	4	7.25	0.21	0.01	0.22 (0.14,0.30)	8	0	0.72	<0.01
9-14 years	-0.18 (-0.28,-0.08)	7	0	0.66	<0.01	0.20 (0.10,0.30)	9	5.98	0.45	<0.01
Regions										
Asia	-0.13 (-0.24,-0.03)	5	80.0	<0.01	0.01	0.26 (0.11,0.38)	6	91.2	<0.01	<0.01
Europe	-0.09 (-0.11,-0.07)	2	0	0.61	<0.01	0.32 (0.23,0.41)	3	66.6	0.06	<0.01
America (South)	-0.17 (-0.25,-0.09)	1	-	-	<0.01	0.01 (-0.16,0.18)	1	-	-	0.92

[1] *p*-value of heterogeneity: heterogeneity was assessed by using Cochran's test, where $p < 0.1$ and $I^2 > 50\%$ were considered to indicate significant heterogeneity across studies.

[2] *p*-value for meta-analysis. $P < 0.05$ was considered to indicate a significant effect of subgroup variables on the accuracy of Willem's dental age estimation by using a random-effects model.

Dental age estimation methods

After the modification of Demirjian's work [Demirjian et al., 1973] by Willem's team in 2001 [Willems et al., 2001], the first comparison study on different dental age estimation methods that included Willems was initiated by Maber in 2006 [Maber et al., 2006]. This followed by series of other study replicating the use of multiple methods on specific populations [Galic et al., 2011; Grover et al., 2012; Kumaresan et al., 2014; Lee et al., 2011; Pinchi et al., 2012]. According to these studies, Willem's method exhibited superiority among other methods used in children. Methods by Demirijian [Demirjian et al., 1973] was the most frequently compared to Willems followed by Demirjian (based on seven and four teeth) [Demirjian and Goldstein, 1976], Cameriere [Cameriere et al., 2006], Haavikko [Haavikko, 1974], Chaillet [Chaillet et al., 2005], Nolla [Nolla, 1960], and Willems II (based on non-gender specific) [Willems et al., 2010]. Two studies on Bosnian-Herzegovinan [Galic et al., 2011] and Malaysian population [Kumaresan et al., 2014] were the only studies that exhibited the superiority of Cameriere [Cameriere et al., 2006] over Willems [Willems et al., 2001]. Pinchi [Pinchi et al., 2012] on their 14-year threshold study based on four dental age estimation methods (Cameriere included) stated that Willem's method was still the most accurate method despite its tendency to overestimate the real age. However, the comparison between these studies is difficult as Galic [Galic et al., 2011] had limited the age range up to 13 years old while Kumaresan [Kumaresan et al., 2014] did not provide data on age group. Liversidge claimed that the method by Willems was the best as regards to average difference and median absolute difference between the dental age and chronological age [Liversidge, 2008b].

Reliability and inter-operator agreement

Performance of dental age estimation is highly correlated with the method used in its assessment. Although the method of choice in estimating dental age is a matter of personal preference and varies from one examiner to another, the use of population-specific reference data does not necessarily improve estimates of dental age [Liversidge, 2015]. However, the statement triggers a potential exploration. Does performance of different examiners from different background influences the precision of dental age estimation if measured on the same method? Good intra and inter-observer agreement may answer the question in a straight forward manner. Kappa statistics for example is a measure of the agreement difference, standardized to lie on a -1 to 1 scale, where 1 is perfect agreement, 0 is exactly what would be expected by chance, and negative values indicate agreement less than chance, i.e., potential systematic disagreement between the observers [Viera and Garrett, 2005]. In addition, the maturity events/indicators should be universal, conservative and reliable [Cameron, 2002].

Recent studies done in Leuven, Belgium on different population-specific reference data representing Emiratis, Brazilians, Malays and Japanese [Altalie et al., 2014; Franco et al., 2013; Ramanan et al., 2012; Yusof et al., 2014] show important example of this scenario. All four studies exhibited substantial inter-observer agreement ranging from 63% to 91% with small differences in dental age estimation between them. While the inter-observer agreements hold constantly high across other studies, are they really an indicator to universality? Independent observers are usually procured by convenience and therefore provide bias on the measurement of inter-agreement due to the fact that the observers/examiners are from the same institution of knowledge. In this context, the observers may receive training or calibration prior to the start of the study which may confine to the standard body of knowledge possessed between the inter-observers. Therefore, comparatively, the inter-observer agreement values from one institution to another may differ substantially.

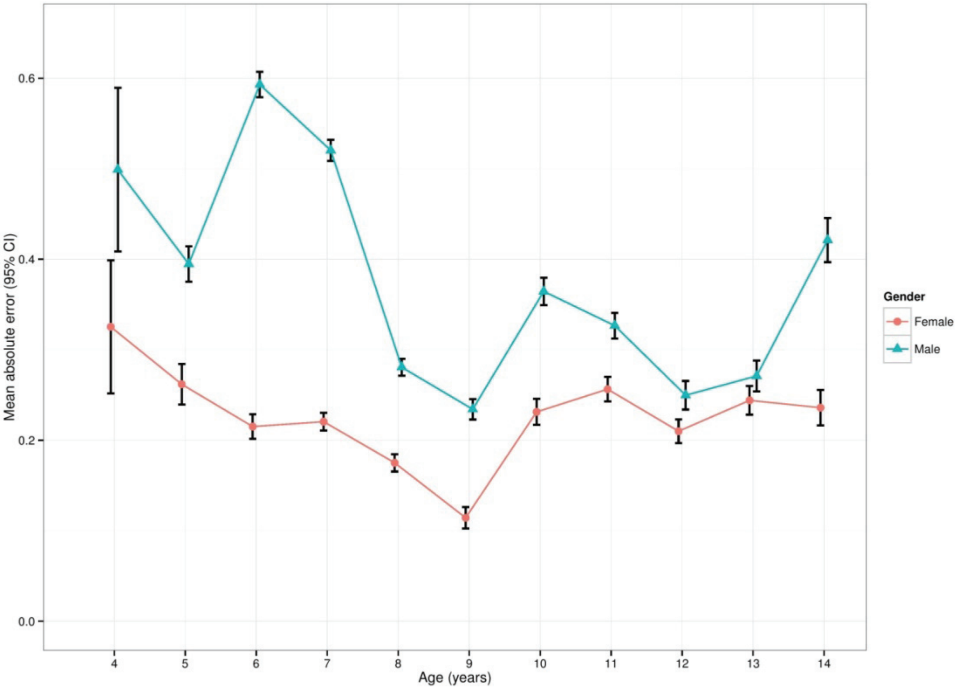


Figure 3.5 Mean absolute error based on gender and specific age categories

The current study exhibited the mean difference between regions were the same (*p*>0.05) supporting the earlier statement that population-specific reference data has little effect on accuracy of dental age estimation. The lack of validation studies on Willem's method that provided sufficient data however, lead to statistical power deficiency in this study.

By virtue of this shortcoming, the present study warrants potential future works to investigate the use of observer's agreement to reflect reliability. De Angelis et al. [De Angelis et al., 2014] explained the vast difference in inter-observer agreement between 'expert' and 'non-expert' examiners based on the third molar four-stage Olze's classification [Olze et al., 2007b]. Although the idea behind this study is interesting to contemplate, the finding is susceptible to challenge and cannot be generalized due to the small size of sample.

Conclusion

The Willem's method accurately estimated age for less than one year with majority of studies reported less than six months. The age estimation difference ranges from 0.01 years to 0.69 years for both genders. By analyzing the results from different countries, the mean difference between regions were the same indicating that population-specific reference data has little effect on accuracy of dental age estimation. The use of Willem's method is appropriate to estimate age in children considering its accuracy on different populations, investigators and age groups.

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Chapter 4

Adaptation of Willem's Model as Co-predictor

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Chapter 4 | Adaptation of Willem's Model

Abstract

The applicability of the Willems et al., 2001 model was verified on a collected sample of Malay (Malaysian nationality) children. This sample was split in a reference sample to develop a Malay-specific prediction model based on the Willems method and in a test sample to validate this new developed model. Next, the incorporation of third molars into this model was analyzed. Panoramic radiographs (*n* = 1,403) of Malay children aged between 4 and 14.99 years (*n* = 702) and sub-adults aged between 15 and 23.99 years (*n* = 701) were collected. The left mandibular seven permanent teeth of the children were scored based on the staging technique described by Demirjian et al., 1973 and converted to age using the Willems method. Third molar development of all individuals was staged based on the technique described by Gleiser and Hunt, 1955 modified by Kohler et al., 1994. Differences between dental age and chronological age were calculated and expressed in mean error (ME), mean absolute error (MAE), and root mean square error (RMSE). The Willems model verified on the collected Malay children overestimated chronological age with a ME around 0.45 year. Small differences in ME, MAE, and RMSE between the verified Malay-specific prediction model and the Willems et al. model were observed. An overall neglected decrease in RMSE was detected adding third molar stages to the developed permanent teeth model.

Chapter 4 | Adaptation of Willem's Model

Introduction

The most accurate dental age estimation methods in children (4 to 14.9 years) are based on the radiologically observed tooth development of the permanent teeth (except third molars) [Maber et al., 2006]. This radiologically observed dental development can be staged using the technique of Demirjian [Demirjian et al., 1973]. The same author developed an age estimation method based on the observed developmental stages of the lower left permanent teeth excluding the third molars. This method was modified by Willems [Willems et al., 2001] using a weighted ANOVA on a reference sample of Belgian children ($n = 2116$). The Willem's method was found to provide most accurate age predictions in children [Maber et al., 2006; Mani et al., 2008; Nik-Hussein et al., 2011].

In Malaysia, the flood of irregular migrants from the neighboring countries is high. With the increase in border surveillance, irregular migrants are predominantly those who enter the country lawfully under different visa conditions, but over-stayed. For instance, about half of the Indonesians who entered Malaysia under a tourist visa between 1996 and February 2003 failed to return home upon the expiry of their visa [Kassim, 2004]. When it comes to offenses and punishments, most irregular migrants have no valid age documentation or falsified documents, implicating that age estimations play an important role in pertinent to conviction and juvenile rehabilitation. Therefore, age estimations in particular age groups are of interest. Children below 12 years for example, are not liable for certain major offenses such as aggravated assault, murder, and robbery. And a child cannot be employed below 14 years. The status of majority for both sexes and the legal permissible age for marriage in females is set at 18 years. Legally, males can marry at the age of 21. According to Malaysian law Section 2 of the Malaysian Child Act 2001 and Section 82 of the Penal Code, a person under the age of 18 years old is considered as child and has not attained the age of criminal responsibility.

The aims of this study were as follows: firstly, to verify the Willems et al., 2001 age estimation model on a sample of Malay children; secondly, to develop and verify a Malay-specific age prediction model based on the Willem's age estimation method; thirdly, to evaluate the age prediction accuracy adding third molar information in the Willem's model.

Materials and methods

A sample of 1,403 digital panoramic radiographs from individuals with Malaysian nationality (691 males, 712 females) residing in the same geographic area and from equal Malay ethnic origin was retrospectively collected. The Malaysian nationality was checked by controlling the citizenship status in the presented Malaysian national registration identity card. The individuals were classified from Malay origin if their paternal and maternal names indicated the same ethnic origin. The collected sample consisted of 702 children (4– 14.99 years) and 701 sub-adults (15–23.99 years) (Table 4.1).

Table 4.1 Age and gender distribution of sampled Malay children and sub-adults

Age group	Male	Female	Total	Age group	Male	Female	Total
	Children				Sub-adults		
4-4.9	16	16	32	15-15.9	39	34	73
5-5.9	47	49	96	16-16.9	32	33	65
6-6.9	55	43	98	17-17.9	29	42	71
7-7.9	44	44	88	18-18.9	31	45	76
8-8.9	25	35	60	19-19.9	42	48	90
9-9.9	30	34	64	20-20.9	56	44	100
10-10.9	32	36	68	21-21.9	41	37	78
11-11.9	27	21	48	22-22.9	56	36	92
12-12.9	17	22	39	23-23.9	20	36	56
13-13.9	26	32	58				
14-14.9	26	25	51				
Total	345	357	702		346	355	701

Age group in years

The sampling was performed at the Faculty of Dentistry of University Teknologi MARA (UiTM) and University of Malaya (UM), Malaysia from the year 2006 to July 2011. The selection criteria were good image quality and no medical evidence or pathology affecting tooth development visible on the panoramic radiographs. All included sub-adult individuals had at least one third molar present. Protocols to collect radiographs for human subjects were approved by the Ethics Committee for Research Involving Human Subjects of both universities (UiTM, UM). The images were stored without compression as jpeg files of 2.5 MB and dimension of 2440 × 1280 pixels. To avoid bias, prior to data scoring, all images were relabeled randomly in numeric order and all related information was made anonymous. Assessments were performed using Adobe Photoshop® CS2 version 9.0 software, (Adobe Systems Incorporated, San-Jose CA, USA), enabling image enlargement and improvement of the image quality during data collection.

The seven permanent left mandibular teeth (PT) of the children were staged using the Demirjian technique [Demirjian et al., 1973] and all third molars available (TM) in the sample were staged according the Gleiser and Hunt technique [Gleiser and Hunt, 1955] modified by Kohler [Kohler et al., 1994]. After 1 month, 100 randomly selected radiographs were staged by the first and a second observer. Kappa statistics were used to evaluate the intra- and inter-observer reliability. The Willem's model, developed on a reference sample of Belgian children [Willems et al., 2001], was verified on the collected Malay children sample.

Next, the children sample was randomly, but stratified on age (categories) and gender, divided in a training dataset and a test dataset. A Malay-specific prediction model, utilizing the Willem's method, was fitted on the subjects in the training dataset. The test dataset was used to verify the constructed Malay-specific prediction model and the original Willem's model. To compare the age prediction performances, the error of the age prediction was defined as the difference between the chronological age and the estimated age (chronological age - estimated age). For calibration purposes, the error was expressed as mean error (ME), to quantify the direction of the error (overestimation or underestimation); mean absolute error (MAE), to quantify the magnitude of the error; and the root mean square error (RMSE), to enable to quantify the variance in errors (giving large errors more weight). Note that the RMSE will be larger or equal than the MAE. In circumstances where the RMSE equals the MAE, then all errors are of the same magnitude.

Table 4.2 Mean error, mean absolute error, and root mean square error verifying the Willem's method on the collected Malay children

Sex	ME	SD	MAE	SD	RMSE	95 % CI
F	-0.32	1.43	1.09	0.97	1.46	1.35-1.58
M	-0.58	1.33	1.13	0.92	1.45	1.34–1.57
M + F	-0.45	1.39	1.11	0.95	1.46	1.38–1.54

All reported values are expressed in years

M male, *F* female, *ME* mean error, *SD* standard deviation, *MAE* mean absolute error, *RMSE* root mean square error, *95 % CI* 95 % confidence interval

To detect the age prediction accuracy of TM development information added to PT development information, three linear regression models, with the scored stages as predictor and age as response, were developed. The first provided predictions based only on the observed PT stages, the second only on the TM stages, and the third was a multiple regression model combining the PT and TM stages. This analysis was based on subjects with no missing PT and no missing TM stages. From each model, the RMSE was calculated for comparison. For all analyses, SAS software, version 9.2 of the SAS System for Windows was used.

Result

The intra-observer analysis for PT and TM revealed a weighted kappa coefficient of 0.98 and 0.78, respectively. The weighted kappa coefficient for the inter-observer analysis was of 0.73 for PT and 0.67 for TM. The Willem's model verified on the collected Malay children overestimated chronological age with a ME of 0.45 year considering girls and boys together (Table 4.2).

Small differences in ME, MAE, and RMSE between the verified Malay-specific model and the Willems et al. model were detected: 0.29, 0.03, and 0.08 year in females and 0.70, −0.01, and 0.07 years in males, respectively (Table 4.3). All these differences were not significant ($p = 0.05$) except for the ME difference in males. Starting at the age of 5 years, gender-specific, the RMSE values from the verified Malay-specific and the Willems et al. model were listed per age category of 1 year (Table 4. 4).

Table 4.3 Mean error, MAE, and RMSE verifying the Willems and the Malay-specific model

Sex	Model	N	ME	SD	MAE	SD	RMSE	95 % CI
F	Willems et al. model	149	-0.33	1.33	1.04	0.9	1.37	1.21;1.53
	Malay model	149	-0.04	1.45	1.07	0.98	1.45	1.28;1.61
M	Willems et al. model	150	-0.6	1.3	1.09	0.93	1.43	1.27;1.59
	Malay model	150	0.1	1.51	1.08	1.06	1.5	1.33;1.68

F female, M male, ME mean error, SD standard deviation, MAE mean absolute error, RMSE root mean square error, CI confidence interval

Table 4.4 Root mean square error calculated from the verified Willems and the Malay- specific model per age category of 1 year

RMSE	Female			Male		
Age group	N	Willem's model	Malay model	N	Willem's model	Malay model
5-5.9	20	1.53 (1.02; 2.03)	2.21 (1.48; 2.94)	20	1.78 (1.21; 2.35)	2.41 (1.61; 3.20)
6-6.9	19	1.09 (0.72; 1.47)	1.53 (1.01; 2.06)	26	1.08 (0.77; 1.39)	1.00 (0.72; 1.29)
7-7.9	17	1.15 (0.73; 1.57)	0.91 (0.58; 1.23)	18	1.14 (0.74; 1.54)	0.95 (0.62; 1.29)
8-8.9	14	1.06 (0.63; 1.49)	1.17 (0.70; 1.65)	12	0.94 (0.52; 1.35)	1.04 (0.57; 1.49)
9-9.9	14	0.87 (0.51; 1.22)	1.00 (0.59; 1.40)	14	0.81 (0.48; 1.14)	1.13 (0.67; 1.59)
10-10.9	16	1.77 (1.11; 2.43)	1.56 (0.98; 2.14)	15	1.62 (0.99; 2.25)	1.28 (0.78; 1.78)
11-11.9	10	1.14 (0.57; 1.70)	1.28 (0.64; 1.92)	13	1.62 (0.93; 2.30)	0.93 (0.54; 1.33)
12-12.9	10	1.74 (0.87; 2.61)	0.81 (0.41; 1.21)	8	2.24 (0.95; 3.53)	1.78 (0.75; 2.81)
13-13.9	15	1.85 (1.13; 2.57)	1.37 (0.84; 1.90)	12	1.89 (1.05; 2.73)	1.46 (0.81; 2.10)
14-14.9	6	1.16 (0.34; 1.98)	1.23 (0.36; 2.09)	6	0.99 (0.29; 1.70)	1.42 (0.42; 2.42)

Between parenthesis 95% confidence intervals of RMSE, age groups in years, RMSE root mean square error

The regression models using only PT, only TM, and PT combined with TM were evaluated on the group of subjects having PT and TM stages. An overall trivial, statistically not significant, decrease in RMSE of 0.007 year (2.5 days) in females and 0.027 year (9.8 days) in males was detected adding TM stages to the PT model. The results varied over age. A decrease of the variance in error was only observed in the age category between 14 and 16 years in females (−0.34 year) and in males (−0.60 year). The model combining PT and TM stages provided decreasing RMSE values compared to the TM model, but the obtained combined RMSE values remained higher than the RMSE values of the PT model (Table 4.5).

Table 4.5 Gender-specific root mean squared errors for the permanent teeth model, the third molar model and the combined model

	RMSE PT	RMSE TM	RMSE PT + TM	p value TM	p value PT
Males	1.236 (1.09; 1.38)	2.033 (1.80; 2.27)	1.209 (1.07; 1.35)	0.0474	<.0001
Females	1.198 (1.06; 1.34)	1.981 (1.75; 2.21)	1.191 (1.05; 1.33)	0.2892	<.0001

Between brackets 95 % confidence intervals, RMSE values in years

RMSE root mean squared error, PT permanent teeth model, TM third molars model, p value TM test if there is additional information in the TM scores = p value from a likelihood ratio test comparing the model with only PT scores and the model with PT and TM scores, p value PT test if there is additional information in the TM scores = p value from a likelihood ratio test comparing the model with only TM scores and the model with PT and TM scores

Discussion

The land of peninsular Malaysia is enriched with a multiracial population of mixed ethnicity. In the Malaysian population, three major ethnic groups are present, with Malays in the biggest portion (around 50 %) followed by Chinese (around 25 %) and Indian (around 7 %). The remaining ethnics constitute minor ethnic groups and foreigners [Nik-Hussein et al., 2011]. Therefore, care was taken to derive the studied sample, specifically from the Malay ethnic population.

In the present study, it was observed that Malay children were overestimated; verifying the Willem's model (developed on a reference sample of Belgian children) on the collected Malay children sample, because negative results were obtained subtracting predicted age from the chronological age. Indeed, the calculated ME indicated a mean overestimation of male ages with 0.58 year (212 days) and female ages with 0.32 year (117 days) (Table 4.2). Nik-Hussein [Nik-Hussein et al., 2011] and Mani [Mani et al., 2008] reported dental age assessments in Malaysian children comparing the Demirjian [Demirjian et al., 1973] and the Willems [Willems et al., 2001] method. In both studies, the ages were overestimated applying the Willems method with 0.55 and 0.30 year in males and 0.41 and 0.05 year in females for the Nik-Hussein and Mani study, respectively. The finding by Mani [Mani et al., 2008] showed best resemblance with the current study and included likely Malay subjects. However, this finding does not allow concluding that the origin of the included subjects was the cause of the difference in age prediction error between these studies. Therefore, further research on samples from the involved populations, collected on identical basis (e.g., number of subjects, distribution in age and gender), is necessary.

The verified Malay-specific model and the Willem's model revealed age estimation results with equal magnitude and variance in error. These findings reflect not only the usefulness of the Belgian population as reference but also the difference (if any) in size of the training set (*n* = 311) and the set of subjects used by Willems (*n* = 2,116) to develop the prediction model. The obtained results were not constant over the different age categories of 1 year. To determine the variance in age estimation outcome in the particular age groups of interest in Malay, the RMSE were reported per age category of 1 year (Table 4.4).

The RMSE decreased in the age category from 14.00 to 15.99 years, in females with 0.34 and in males with 0.60 year, adding age-related dental development information of TM to the available PT information. This gain in explained variance in age prediction can be explained by the fact that in the considered age category multiple PT are already fully matured, consequently providing no more tooth developmental age information. In this period, TM is fully developing and their added age-related tooth developmental information improves the accuracy of the age predictions. In the context of the particular age groups of interest in Malaysia, it should be considered, evaluating the age of 14 year (child employment), to use the model combining PT and TM stages. The combined PT and TM model provides in all age categories decreased RMSE values compared to the RMSE values obtained from the model based on only TM. Because the magnitude of this decrease is not high enough to obtain smaller RMSE values than obtained from the model based on only PT information, the age estimation model expected to provide the best age prediction accuracy in children remains the model including only PT stages.

Conclusion

Although the Willem's model verified on Malay children overestimates chronological age, no indication were found to develop a Malay-specific prediction mod-el based on a large Malay reference sample. Adding age-related third molar development information to age-related permanent teeth information is only ameliorating the age prediction accuracy in the age group of children between 14 and 16 years.

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Chapter 5

Stages in Third Molar Development and Eruption to Estimate 18-year Threshold

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Chapter 5 | Stages in Third Molar Development and Eruption

Abstract

Age 18 is considered as the age of majority by most countries. To reach certain age of interest, the use of both third molar development (TMD) and eruption (TME) staging scores are beneficial without the need of multiple imaging modalities. This study aimed to assess the chronological course of third molars development and eruption in a Malay sub-adult population and evaluate the prediction when specific stage(s) of TMD and TME has been attained pertinent to the age group of interest (<18-year or ≥18-year). A sample of 714 digital panoramic radiographs stratified according to age between 14.1 and 23.9 years was retrospectively collected. The techniques described by Gleiser and Hunt (modified by Kohler) and Olze were employed to stage the TMD and TME, respectively. A binary logistic regression was performed to predict the 18-year threshold with staging score as predictors. Stages 4 to 6 (TMD) and A-B (TME) in males and stages 4 (TMD) and A (TME) in females were found to be in concordance discriminating the <18-year group. In both genders, the stages 9 to 10 (TMD) and D (TME) were accountable to be used as reference stages to estimate whether the subject was likely to be ≥18-year, with 94.74-100% and 85.88-96.38% of correct predictions, respectively. Stage 4 (TMD) and A (TME) can also be used to identify juvenile (<18-year) with high degree of correct prediction, 100%. The juvenility of an individual is easily identified by attaining specific staging scores of both third molar variables (TMD and TME) without complex calculations.

Introduction

The age of majority is the threshold of adulthood as conceptualised in law. It is the chronological moment when a child legally ceases to be considered a minor and assumes control over their possessions, actions and decisions, thereby terminating the legal control and legal responsibilities of their parents or guardians over and for them. The age of majority is a legally fixed age, concept or statutory principle, which may differ depending on the jurisdiction, and may not necessarily correspond to the actual mental or physical maturity of an individual [Steinberg, 2013].

In Malaysia, the legal age of majority is recognised as 18 years of age as stated in the Age of Majority Act 1971: "The minority of all males and females at the age of eighteen years and every such male and female attaining that age shall be of the age of majority" [1971]. The age of criminal responsibility in most countries is also established at 18 years, and the law's view of the criminal chastisements changes at this age. However, given the lighter sentences faced by juveniles compared to adults, the current legal system is challenged by individuals who claim to be minors to escape harsher punishments. To increase the accuracy of age estimation in a criminal proceeding in determining whether an individual is of criminally responsible age and whether adult criminal law is applicable, multiple methods of age assessment are recommended taking the ethical and medico-legal aspects into account. The use of regression models such as multiple linear [Mohd Yusof et al., 2015a; Thevissen et al., 2010], logistics [Acharya et al., 2014; Guo et al., 2014], Bayesian [Thevissen et al., 2010] and principal component analysis [Mohd Yusof et al., 2015a] has been performed to address the issue. This is in line with the updated recommendation by the members of the Study Group on Forensic Age Diagnostics [Schmeling et al., 2008]. Therefore, the third molar provides a useful tool to assess individual's chronological age based on the dental developmental age boundary. Plus, by using two staging criteria, third molar development (TMD) and eruption (TME), with the same radiograph, the exposure to radiation of living individuals can then be lessened. The use of TMD and TME as individual methods to estimate age has been well documented and there is a relatively high success rate in estimating age groups for children and sub-adults in different populations [Altalie et al., 2014; Franco et al., 2013; Guo et al., 2014; Olze et al., 2008a; Olze et al., 2008b; Olze et al., 2007b; Ramanan et al., 2012; Yusof et al., 2014].

The aims of this study are firstly, to assess the individual stages of TMD and TME in determining the chronological age of Malay sub-adults. Secondly, to evaluate the prediction of age using both third molar variables stages to discriminate the 18-year threshold.

Materials and methods

Patient selection

Digital panoramic images of 714 Malay individuals (341 males and 373 females) with known chronological age and gender were retrospectively collected for this study in the Oral & Maxillofacial Radiology unit in the Faculty of Dentistry of University Teknologi MARA (UiTM), Malaysia. The individuals were classified as Malaysian citizens and ethnically Malays based on retrieval of their identity cards. The ages of the sub-adults in this collected sample ranged from 14.1 to 23.8 years (Table 1). The youngest and oldest subjects were born in 1997 and 1988, respectively. The majority of individuals came as outpatients. Several selection criteria, such as good image quality and the visible absence of medical evidence or pathology affecting tooth development on the panoramic images, were imposed to prevent any confounders to the data.

Table 5.1 Age and sample distribution of Malay sub-adults

Age group	Males	Females	Total
14-14.9	21	20	41
15-15.9	37	39	76
16-16.9	36	34	70
17-17.9	29	41	70
18-18.9	30	41	71
19-19.9	38	46	84
20-20.9	43	44	87
21-21.9	36	32	68
22-22.9	46	42	88
23-23.9	25	34	59
Total	341	373	714

Age groups in years

Third molar scoring

Initially, TMD and TME were scored according to the Gleiser and Hunt technique [Gleiser and Hunt, 1955] as modified by Kohler et al. [Kohler et al., 1994] and the Olze technique [Olze et al., 2007a], respectively. The former technique was devised from chronological descriptions of ten developmental stages of third molar maturity using crown and root formation (Table 5.2). The latter technique was formulated from four-stage TMEs (Table 5.3). After three weeks, 100 randomised panoramic images were scored by a second examiner (RW) and re-scored by the primary examiner (MYPMY). The panoramic images were kept without compression as JPEG files of size 2.5 Mb and dimension 2400 × 1280 pixels. Precautions to avoid bias included randomly re-labelling all images and all related information was made anonymous prior to data scoring. Images were assessed using Adobe®Photoshop® CS2 version 9.0 software (Adobe Systems Incorporated, San Jose, CA, USA), which allowed image to be enhanced and image quality to be improved during data collection. Ethics approval to perform this study has been obtained by the Commission for Medical Ethics Ghent University Hospital (EC UZG 2013/146).

Table 5.2 Third molar developmental stages describing the crown and root formation

Stage	Score	Description
Crown formation		
1	1	Crown 1/2 calcified
2	2	Crown 3/4 calcified
3	3	Crown completely calcified
Root formation		
4	4	Beginning of root formation
5	5	Root 1/4 calcified
6	6	Root 1/2 calcified
7	7	Root 3/4 calcified
8	8	Nearly completed root formation, root canals terminally divergent
9	9	Completed root formation, root canals terminally parallel
10	10	Completed root formation, root canals terminally convergent

Table reprinted with permission of Elsevier [Gleiser and Hunt, 1955]

Table 5.3 Third molar eruptional stages describing the crown and its surrounding relationship

Stage	Score	Description
A	1	Occlusal plane covered with alveolar bone
B	2	Alveolar eruption; complete resorption of alveolar bone over occlusal plane
C	3	Gingival emergence; penetration of gingiva by at least one dental cusp
D	4	Complete emergence in occlusal plane

Table reprinted with permission of Elsevier [Olze et al., 2007a]

Statistical analysis

Inter-observer and intra-observer reliability was measured using kappa statistics. Correlations between developmental and eruptional scores for third molars were calculated using the Spearman correlation test. The course of third molar variables pertinent to age is presented with descriptive statistics. Weighted means were calculated to represent an overall mean of all third molars for each stage. The sizes of the sample (n) were used as weights. Binary logistic regression analysis was applied to obtain a predicted probability between 0 and 1 (0–100%). The predicted probability (p) can be derived from the logit using the function $p = 1 / (1 + e^{-L})$, where L is the logit of the logistic regression formula (i.e., $L = \beta_0 + \beta_1 X_1 + \beta_2 X_2$). The binary responses for the logistic regression are <18 years and ≥18 years while the predictors are third molar staging scores (kept as a factor). The cut-off was arbitrarily chosen as 0.80 (80%), so a subject with a probability >0.80 (>80–100%) would be discriminated as <18 years or ≥18 years using the stages. All tests were performed using RStudio version 0.97.551 (© 2009–2012 RStudio, Inc.) and evaluated on a 0.05 significance level.

Results

The intra-observer and inter-observer analysis for third molar scoring yielded weighted kappa coefficients of 0.92 and 0.87, respectively. Significant Spearman correlation coefficients and high values for both TMD and TME scores reflected a strong dependency on each predictor. Both genders had more than a 90% correlation coefficient for all teeth with no indication of discrepancies for upper and lower or left and right third molars (Figure 5.1).

The age distribution for TMD based on Gleiser and Hunt's staging criteria (as modified by Kohler) is shown in Table 5.4 for different stages and teeth. Figure 5.2 demonstrates that there are relatively higher weighted means for females for stages 5, 6, 7 and 10 ($p < 0.001$).

For males, stages A and B in Olze's TME staging system are in concordance with stages 4 to 7 in Gleiser and Hunt's TMD staging criteria (as modified by Kohler), being stage markers for <18 years. The same pattern is also observed in females except only stages 4 to 6 in TMD are included. The weighted means for these stages range from 15.22 to 17.66 years for males and 15.39 to 16.75 years for females.

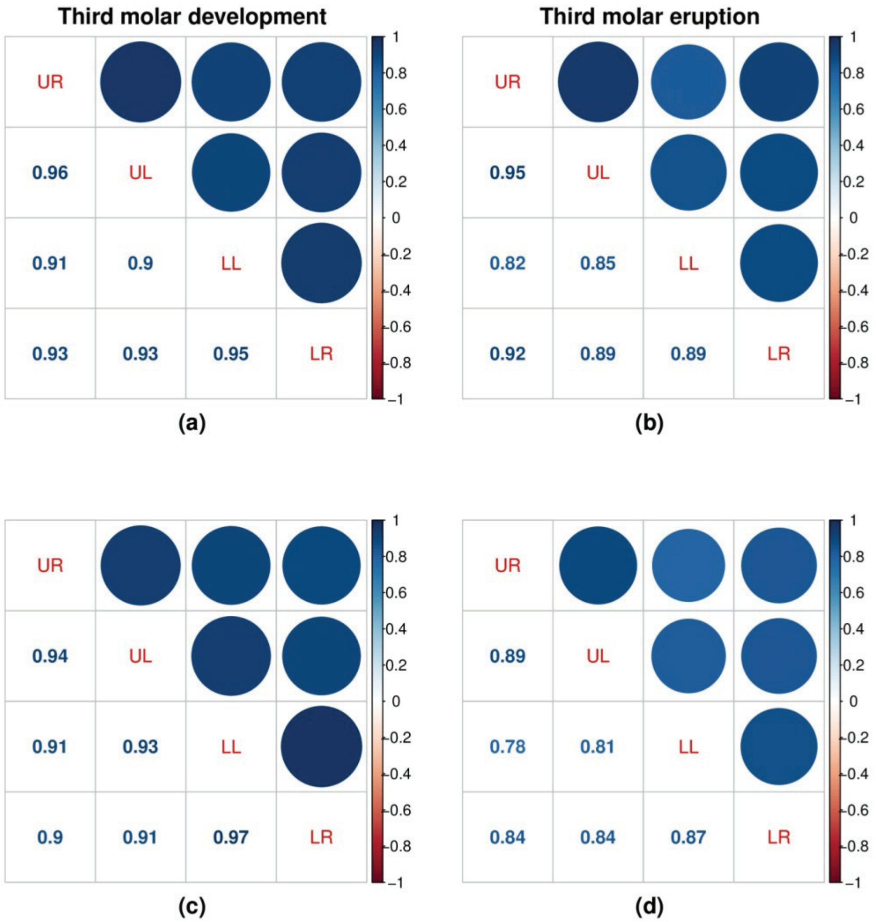

Figure 5.1 Spearman correlations between third molars based on developmental scores in males (a) and females (c) and eruptional scores in males (b) and females (d), *UR* upper right, *UL* upper left, *LL* lower left, *LR* lower right

Table 5.5 shows the details of each stage according to age means, standard deviations and third molar locations based on Olze's TME staging classification. The weighted means of stage A for both males and females are 15.22 and 15.39 years. Stage B varies from 16.20 to 16.99 years. Stages C and D exhibit a range of 18.06 to 20.77 years in males and 18.92 to 20.57 years in females, respectively. The weighted means for females are statistically higher than for males for stages B (95% CI 15.97–16.44 for males and 95% CI 17.03–17.55 for females; $p < 0.001$) and C (95% CI 17.70–18.42 for males and 95% CI 18.53–19.31 for females; $p < 0.001$) as shown by the error plot (Figure 5.2).

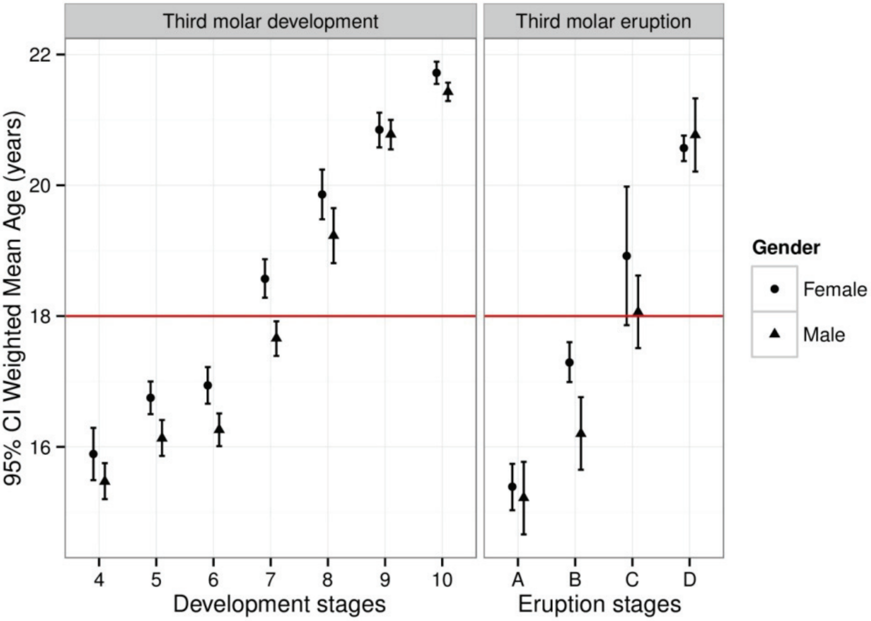

Figure 5.2 95% Confidence interval of weighted mean age according to third molar development and eruption stages in males and females

The means of the chronological ages increased with increasing stage for both TMD and TME, demonstrating that there was good agreement between the stages and the chronological ages of the subjects. In binary logistic regression analysis, stages 9 to 10 (TMD) and stage D (TME) can be used as reference stages to estimate whether a subject is likely to be equal to or over age 18, with 85.88–96.38% (Table 5.6) and 94.74–100% (Table 5.7) correct predictions, respectively, for both genders.

Stages 4 (TMD) and A (TME) can also be used to identify juvenility (<18 years) with a high degree of correct predictions, 100%.

Table 5.4 Age distribution by stage and tooth for third molar development

Stage	Tooth	Male			Female		
		N	Mean	SD	N	Mean	SD
4	18	13	15.22	0.78	5	16.16	0.84
	28	15	15.41	0.93	4	15.66	0.55
	38	10	15.67	1.10	7	16.03	1.53
	48	14	15.64	1.15	11	15.76	0.95
5	18	20	16.32	1.42	47	16.47	1.38
	28	21	16.65	1.92	45	16.83	1.75
	38	23	15.86	1.00	43	16.82	1.68
	48	21	15.74	0.86	42	16.91	1.88
6	18	32	16.45	1.40	45	17.07	1.81
	28	29	16.38	1.54	46	17.11	2.07
	38	29	16.07	1.21	42	16.82	1.82
	48	22	16.08	1.13	33	16.67	1.58
7	18	48	17.56	1.84	41	18.82	2.08
	28	47	17.55	1.72	49	18.62	1.98
	38	48	17.90	2.04	35	18.79	2.26
	48	48	17.62	1.81	48	18.16	1.56
8	18	16	19.42	1.60	27	19.58	1.75
	28	17	19.35	1.91	19	19.42	1.45

	38	19	19.29	1.70	29	19.73	2.02
	48	20	18.92	1.91	29	20.54	2.35
9	18	44	20.98	1.42	33	20.89	1.69
	28	40	20.76	1.52	38	21.07	1.78
	38	46	20.73	1.44	51	20.85	1.72
	48	43	20.63	1.51	41	20.60	1.66
10	18	95	21.40	1.41	80	21.82	1.41
	28	99	21.42	1.40	76	21.76	1.46
	38	93	21.44	1.41	70	21.56	1.56
	48	100	21.46	1.34	75	21.72	1.50

Table 5.5 Age distribution by stage and tooth for third molar eruption

Stage	Tooth	Male			Female		
		N	Mean	SD	N	Mean	SD
A	18	12	14.98	0.55	2	15.43	1.70
	28	11	14.96	0.57	3	15.61	1.24
	38	11	15.34	0.85	3	15.42	1.19
	48	8	15.75	0.93	3	15.10	0.70
B	18	51	16.48	1.78	89	17.21	2.32
	28	52	16.37	1.72	88	17.37	2.51
	38	46	16.20	1.96	77	17.50	2.39
	48	43	15.68	1.12	61	17.03	2.23
C	18	48	18.36	2.34	52	19.12	2.45
	28	42	18.48	2.38	60	19.38	2.42
	38	24	17.94	2.02	23	18.37	2.52
	48	20	16.62	1.12	23	17.82	2.49
D	18	138	20.89	1.64	108	20.66	1.93
	28	152	20.69	1.82	108	20.65	1.96
	38	93	20.75	1.82	85	20.52	2.27
	48	99	20.75	1.74	99	20.41	2.14

Discussion

Age estimation is particularly important in Malaysia as a result of a major influx of immigrants. The use of more than one method to estimate dental age is essential to allow courts to rule with adequate certainty on whether a subject has reached majority or is a juvenile. Various methods are used to determine TMD and TME when assessing chronological age in specific populations. The staging technique by Demirjian et al. [Demirjian et al., 1973] has been commonly used to stage TMD as well as the technique described by Gleiser and Hunt [Gleiser and Hunt, 1955] as modified by Kohler [Kohler et al., 1994]. Traditionally, the evaluation of TME is done clinically by observing the rate of visible eruption intra-orally. However, as this technique is prone to variation and inaccuracy among different populations, a technique utilising four levels of radiographic TME was proposed by Olze et al. [Olze et al., 2005].

Table 5.6 Correct prediction percentage by stage and tooth for third molar eruption

Stages	Tooth	Male		Female	
		Age predicted correctly (%)			
		<18	≥18	<18	≥18
A	18	100	0	100	0
	28	100	0	100	0
	38	100	0	100	0
	48	100	0	100	0
B	18	86.27	13.72	70.79	29.21
	28	88.46	11.54	67.05	32.95
	38	89.13	10.87	63.64	36.36
	48	95.35	4.65	76.77	23.23
C	18	54.17	45.83	36.54	63.46
	28	52.38	47.62	31.67	68.33
	38	58.33	41.67	47.83	52.17
	48	90.00	10.00	65.22	34.78

D	18	3.62	96.38	12.04	87.96
	28	7.89	92.10	12.04	87.96
	38	6.45	93.55	14.12	85.88
	48	6.06	93.94	12.12	87.88

The difference in means for third molars in all quadrants is not significant and therefore a weighted mean was constructed for each stage. It is important to note that the weighted mean in this study is not proposed as a new method to estimate dental age but rather to make a simple mathematical inference of several age means. For each stage except stage D, the older age means exhibited by females may be explained by the early maturation due to the early puberty phase in females. The trends are similar for both TMD and TME. Stages C and D, however, showed a mild to high degree of variability, suggesting the transitional interval between the two stages may be prolonged. This could be due to a local factor, such as poor spacing in the retro-molar region. Stage C (gingival emergence, that is the penetration of the gingiva by at least one dental cusp) especially, will be adversely affected by overestimation if this is not rectified.

Table 5.7 Correct prediction percentage by stage and tooth for third molar development

Stages	Tooth	Male		Female	
		Age predicted correctly (%)			
		<18	≥18	<18	≥18
4	18	100	0	100	0
	28	100	0	100	0
	38	100	0	100	0
	48	100	0	100	0
5	18	85.11	14.89	85.00	15.00
	28	77.78	22.22	80.96	19.04
	38	76.74	23.26	100	0
	48	73.81	26.19	100	0
6	18	64.44	35.56	87.50	12.50
	28	65.22	34.78	89.66	10.34
	38	76.19	23.81	89.66	10.34
	48	78.79	21.21	95.45	4.55
7	18	36.59	63.41	66.67	33.33
	28	40.82	59.18	63.83	36.17
	38	45.71	54.29	62.50	37.50
	48	47.92	52.08	64.58	35.42
8	18	22.22	77.78	12.50	87.50
	28	21.05	78.95	23.53	76.47
	38	20.69	79.31	15.79	84.21
	48	17.24	82.76	25.00	75.00
9	18	3.030	96.97	0	100
	28	5.260	94.74	0	100
	38	3.920	96.08	0	100
	48	2.440	97.56	0	100
10	18	0	100	0	100
	28	0	100	0	100
	38	0	100	0	100
	48	0	100	0	100

Olze [Olze et al., 2007b] outlined several qualitative exclusion criteria for impacted and unclear direction of the third molar as recommended by Archer [Archer, 1955] and Wolf and Haunfelder [Wolf and Haunfelder, 1960]. However, due to reproducibility issues and the need for several quality measurements, a latent guideline has been discussed among authors in this study to establish quantitative exclusion criteria not only to account for any potential disturbances that could inhibit the normal eruption of the third molar but also to standardise the criteria to control the quality in estimating dental age. A recommendation by Mohd Yusof [Mohd Yusof et al., 2015a] to measure the impaction degree and the retro-molar space to crown width ratio was seemed appropriate and therefore is proposed to be applied in future study during the subjects selection process especially in TME analysis.

Pertinent to this study, only stages 4 to 7 for TMD and stages A to B for TME for males are the stages below the 18-year threshold (Figure 5.2). However, these stages were calculated as the weighted means for all third molars for each stage and therefore they have to be observed simultaneously with the correct prediction table. Juveniles can be discriminated from those over the age of majority if they are at stage A and stage 4 for TME and TMD, respectively, with 100% correct predictions. In other words, a subject is likely to be classified as being below the 18-year threshold if the development of the third molar has not reached stage 5 (TMD) with evidence of a calcified cleft or a calcified quarter root (Table 5.2). Stage C (TME) gained more scores on lower right third molar (tooth 48) for male individuals age less than 18 years old. Therefore, higher prediction (90%) was observed as compared to other third molar position on the same stage. A detail re-visit to the dataset has been performed to rule out any systematic deletion of missing data. The inspection revealed that the missing data was spread at random and had taken almost a third of the overall dataset on tooth 48. Although the finding did not warrant any procedural faults, the prediction value was too high to ignore. This result may implicate on one hand, the vast variation in tooth 48 as compared to the other third molars in term of eruption pattern. On the other hand, tooth 48 in general may be more susceptible to crowding due to the lack of retro-molar space leading to longer interval switch between stages as discussed earlier in the discussion. For these reasons, the authors recommend the use of prediction values of other third molar positions on the same stage as reference.

In other population-specific studies, people at stage A in Canadian, Chinese and Black African populations [Guo et al., 2014; Olze et al., 2007b; Schmeling et al., 2010] had weighted age means <18 years, ranging from 12.09 to 15.06 years. German and Japanese people [Olze et al., 2008a; Olze et al., 2008b] experience earlier eruption for the same stage, since the weighted means for both genders are between 16.14 and 19.71 years. Clearly, the latter populations have earlier eruption as seen radiographically. Interestingly, although Chinese population [Guo et al., 2014] has age means well below 18 years for stage A, predictions were not correct for this particular stage. Almost 100% of people at stage A in the Chinese population study were correctly predicted as being in the age group ≥16 years. In contrast, in the current study, 0% of people at stage A were predicted to be in the age group ≥18 years.

For TMD, there is little in the literature describing data on stages pertinent to age, especially for the Gleiser and Hunt technique (as modified by Kohler). Studies on TMD usually relate to the technique by Demirjian [Qing et al., 2014; Sasso et al., 2015], although Demirjian in his original study [Demirjian et al., 1973] did not propose that this technique be used only with the third molar but with all seven permanent teeth. Nevertheless, the difficulty in making comparisons across different populations is apparent. To the author's knowledge, among the studies on staging the third molar using the Gleiser and Hunt technique (as modified by Kohler) [Acharya et al., 2014; Altalie et al., 2014; Bagherpour et al., 2012; Ramanan et al., 2012; Thevissen et al., 2012], only a study with a Polish population [Van Vlierberghe et al., 2010] supplied the full range of data pertinent to mean age and its correlated stages. TMD in Polish people is comparatively similar to that in the population in the current study in terms of mean age. Stage 4 for males was at a mean of 16.12 years while for females there was a long tail with a large standard deviation for the 18-year threshold despite the low mean.

Conclusion

An individual is highly likely to be <18 years when there is still no sign of a calcified cleft, which is stage 5 (TMD) and stage B (TME), with a high probability (100% for males and females). However, a validation study on specific population level is needed to confirm this validity. As the legal requirements necessitate a probability limitation on certainty, the use of more than one criterion, as in this study, is therefore recommended.

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Chapter 6

Application of Third Molar Development and Eruption Models to Assess Prediction Accuracy

This chapter has been based on:

M.Y.P.M. Yusof, R. Cauwels, E. Deschepper, L. Martens. *Application of Third Molar Development and Eruption Models in Estimating Dental Age in Malay Sub-adults*. J Forensic Leg Med. 2015 May; 32:40-44.

Oral presentation at the 23rd International Association of Legal Medicine (IALM) Conference, Dubai, 2015

Abstract

The third molar development (TMD) has been widely utilized as one of the radiographic method for dental age estimation. By using the same radiograph of the same individual, third molar eruption (TME) information can be incorporated to the TMD regression model. This study aims to evaluate the performance of dental age estimation in individual method models and the combined model (TMD and TME) based on the classic regressions of multiple linear and principal component analysis. A sample of 705 digital panoramic radiographs of Malay sub-adults aged between 14.1 and 23.8 years was collected. The techniques described by Gleiser and Hunt (modified by Kohler) and Olze were employed to stage the TMD and TME, respectively. The data was divided to develop three respective models based on the two regressions of multiple linear and principal component analysis. The trained models were then validated on the test sample and the accuracy of age prediction was compared between each model. The coefficient of determination (R^2) and root mean square error (RMSE) were calculated. In both genders, adjusted R^2 yielded an increment in the linear regressions of combined model as compared to the individual models. The overall decrease in RMSE was detected in combined model as compared to TMD (0.03-0.06) and TME (0.2-0.8). In principal component regression, low value of adjusted R^2 and high RMSE except in male were exhibited in combined model. Dental age estimation is better predicted using combined model in multiple linear regression models.

Chapter 6 | Third Molar Development & Eruption Models

Introduction

The study on third molar developmental (TMD) stages and eruption (TME) as regard to age estimation has been extensively documented and published. While most authors agree to adopt developmental stages as a method of choice in dealing with third molars to estimate dental age, the eruptional study receives a far less overwhelming fate. The TMD model is considered more robust especially in estimating dental age for inter-ethnic variation. The eruption or emergence of third molar on the other hand, has been claimed to be most susceptible to skeletal pattern as well as local factors that includes poor spacing in the retro-molar area, between the distal of the second molar, and the anterior border of the ascending ramus of the mandible [Björk et al., 1956; Silling, 1973]. However, by carefully limiting the factors that may disrupt the TME process, the eruptional staging may offer a great potential to achieve more precision in dental age estimation.

On the legal perspective, the age of criminal responsibility in most countries is 18 years and therefore third molar provides a legal platform to assess the person's chronological age based on the dental developmental age boundary. However, due to its high variability, estimation error may occur to some extent according to the technique used [Lewis and Senn, 2010]. To reduce this setback, several studies have proposed a combination of variables added into existing third molar regression model. Although no significant results were obtained, adding the information on all seven permanent mandibular teeth to the third molar model has clearly giving low estimation error especially on specific age categories level [Altalie et al., 2014; Franco et al., 2013; Ramanan et al., 2012; Yusof et al., 2014]. In order to increase the accuracy of age estimation in criminal proceeding for determining whether an individual is of criminally responsible age or whether adult criminal law is applicable, an updated recommendation has been adopted by the members of Study Group on Forensic Age Diagnostics[Schmeling et al., 2008].

The aim of this study is twofold. Firstly, to develop dental age estimation models based on the information of only TMD, only TME and combination of both information; secondly, to validate the performance of all three models as well as the model developed by Gunst and his team [Gunst et al., 2003] and thus to evaluate the prediction accuracy on all different models.

Materials and methods

Digital panoramic radiographs of 705 Malay individuals (336 males and 369 females) with known chronological age and gender were retrospectively selected for this study. The individuals were classified as Malaysian citizen and Malay based on the identity cards and data record retrieval, respectively. The age of sub-adults for this collected sample ranged from 14.1 to 23.8 years old (Table 6.1). The sampling was performed at the radiology unit in Faculty of Dentistry of University Teknologi MARA (UiTM) Malaysia from the year 2007 through July 2013. Although the majority of individuals came as outpatients, several selection criteria such as good image quality and no medical evidence or pathology affecting tooth development on the panoramic radiographs had been imposed to prevent any confounding to the data. In addition, a criterion to prevent the local factors that may influence the eruption of third molar has been established in this study. The third molar exhibited with horizontal or vertical impaction and angulation between long axis of third molar and long axis of second molar is > 10° were considered the exclusion criteria for this study. A specific criterion was applied to the mandibular third molar. The available mandibular retro-molar space was measured in addition to third molar crown width. The available retro-molar space was defined as the distance between the distal border of the second molar and the anterior border of the ramus measured on the occlusal plane, in proportion to the width of the third molar crown. The ratio of retro-molar space to crown width was calculated according to the method described by Olive and Basford [Olive and Basford, 1981] and later modified by Ganss et al [Ganss et al., 1993]. Should the ratio was found to be less than 1.1, the subject would be excluded.

The third molar development and eruption were scored according to the Gleiser and Hunt technique [Gleiser and Hunt, 1955] modified by Kohler [Kohler et al., 1994] and Olze technique [Olze et al., 2007b], respectively. The former technique devised ten developmental stages based on third molar maturity and the latter technique formulated on four third molar eruptional stages. After three weeks, one-hundred randomized panoramic radiographs were extracted and scored by second examiner and re-scored by primary examiner for kappa inter-observer and intra-observer reliability. The non-scores were treated as missing values.

Table 6.1 Age and sample distribution of Malay sub-adults

Age group	Males	Females	Total
14-14.9	21	20	41
15-15.9	37	39	76
16-16.9	31	34	65
17-17.9	29	41	70
18-18.9	30	41	71
19-19.9	38	46	84
20-20.9	43	40	83
21-21.9	36	32	68
22-22.9	46	42	88
23-23.9	25	34	59
Total	336	369	705

Age groups in years

The accumulation of individual dataset was then split into two groups. A dental age estimation model was developed on the training dataset and performance for this model was tested on the test dataset. The former utilized 70% of accumulated dataset for model development and the remaining 30% were used for testing. Males and females were treated in different models.

The panoramic images were kept without compression as JPEG file of 2.5Mb and dimension of 2,400 x 1,280 pixels. Precautions measure to avoid bias has been taken by randomly re-label all images and all related information was made anonymous prior to data scoring. Image assessments were performed using Adobe®Photoshop® CS2 version 9.0 software (Adobe Systems Incorporated, San-Jose CA, USA), enabling image enhancement and improvement of the image quality during data collection. Ethics approval to collect radiographs for human subjects has been obtained by the Ethics Committee for Research Involving Human Subjects of UiTM.

Table 6.2 Indicators of collinearity between third molars based on developmental and eruptional scores

	Developmental scores											
	Males						*Females*					
	UR-UL	UR-LL	UR-LR	UL-LL	UL-LR	LL-LR	UR-UL	UR-LL	UR-LR	UL-LL	UL-LR	LL-LR
Spearman's *r*	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9	0.9
VIF	21	8.5	9.0	7.1	8.6	13	12	7.4	6.2	8.1	6.4	20
	Eruptional scores											
Spearman's *r*	0.9	0.8	0.9	0.9	0.9	0.9	0.9	0.8	0.8	0.8	0.8	0.9
VIF	16	3.5	5.7	3.8	4.7	6.0	4.9	2.6	3.2	2.9	3.1	4.0

VIF variance inflation factor, *UR* upper right, *UL* upper left, *LL* lower left, *LR* lower right

Spearman's r $p<0.0001$

Statistical analysis

The missing data rate was relatively low (12.4%) and the 'completer' or 'complete' case analysis approach to manage missing data was used. Multiple linear regression (MLR) analysis based on the method of least squares was performed to evaluate the relationship between chronological age as response and all four permanent third molar based on its developmental stages [Gunst et al., 2003] and eruptional stages [Schmeling et al., 2010] as predictors. The first part of the study dealt with two important statistics that were employed to develop the TMD, TME, and combine model; selection of variables and multicollinearity. In order to ensure the most reliable prediction, the selection of variables in stepwise regression analysis was carried out by calculating the Mallows' Cp statistic, which is a measure of the bias of the prediction equation [Mallows, 1973]. This method provides a single combination of variables for each equation. The model size and fitting criteria are fixed since the optimum Cp value must be close to the number of variables involved in the model. Regression coefficients and their standard deviations were calculated. As for multicollinearity, the principal collinearity diagnostics for dependency measurement includes: the variance inflation factor (VIF), condition index and variance decomposition proportions. If none of the VIFs are greater than 10, collinearity is not a problem. Multicollinearity is a concern when the VIF exceeds 10. The condition index and variance proportions were used to identify which variables were involved. Principal component regression (PCR) was carried out to establish orthogonal predictors (uncorrelated components) and thus removing the problem of multicollinearity. The minimum eigenvalue to retain the number of components was set at 1 based on Kaiser criterion [Kaiser, 1960]. The conventional multiple linear regression and PCR models developed from the training dataset were compared to each other to assess prediction accuracy. The second part quantified the performance of the trained prediction model by root mean square error (RMSE) in test dataset. The error of age prediction was defined as the difference between chronological age and estimated age (chronological age – estimated age). All *p* values reported are two-tailed. Statistical significant was set at 0.05 and analyses were conducted using

RStudio version 0.97.551 - © 2009-2012 RStudio, Inc. software. The *prcomp* function was used to develop PCR in RStudio.

Results

The intra-observer and inter-observer analysis on third molar scoring yield a weighted kappa coefficient of 0.92 and 0.87, respectively.

Significant Spearman correlation coefficients and their high values in both TMD and TME scores reflected strong dependency on each predictor. Both gender showed more than 90% correlation coefficient on all teeth with no significant difference between TMD and TME scores in all sides of jaw, respectively. All upper third molar except female eruptional scores exhibited VIFs having the value of more than ten suggesting serious multicollinearity (Table 6.2).

Table 6.3 shows the principal component analysis of the eight variables with three different models. The eight variables were standardized from their original values. One principal component with corresponding eigenvalue of 1 or greater for each model was obtained.

Table 6.3 Principal component loadings of the eight standardized variables

	Males			*Females*		
	TMD	TME	Combine	TMD	TME	Combine
	PC1	PC1	PC1	PC1	PC1	PC1
UR	0.502		0.359	0.498		0.360
UL	0.500		0.357	0.499		0.361
LL	0.497		0.355	0.503		0.365
LR	0.499		0.357	0.499		0.360
UR*		0.504	0.350		0.499	0.342
UL*		0.503	0.346		0.504	0.338
LL*		0.489	0.344		0.493	0.347
LR*		0.502	0.355		0.502	0.350
Eigenvalue	3.843	3.689	7.169	3.815	3.502	6.885
Percentage of explained variance, %	0.960	0.922	0.896	0.953	0.875	0.860
Cumulative percentage of explained variance, %	0.960	0.922	0.896	0.953	0.875	0.860

TMD third molar development model, TME third molar eruption model, PC1 principal component 1, UR,UL,LL,LR upper right, upper left, lower left, lower right based on third molar development scores, UR*,UL*,LL*,LR* based on third molar eruption scores

The first principal component for model TMD, TME and combination contained 96%, 92% and 89% information of the eight variables in males and contained 95%, 87% and 86% information of the eight variables in females, respectively. In addition, the loadings had positive signs on all correlations giving an overall measure and similar magnitude of each variable on principal component across different models.

In males, small coefficient of determination (R^2) difference between the TMD and combined model was observed with 76% and 78% variance explained by the respective MLR models. On the other hand, TME received relatively low adjusted R^2 and the performance of this model on test dataset was no better than TMD and combined model with average RMSE of 2.0 years compared to 1.6 and 1.5 years for both genders, respectively (Figure 6.1). The combined model yielded the following MLR formula:

$$\text{Age} = 9.6143+0.3700\text{UL}+0.4987\text{LR}+1.8005\mathit{ur}-1.1022\mathit{ul}$$

Equation 6.1

$$\text{Age} = 9.0252+0.838\text{UR}+0.5461\text{LR}-0.8163\mathit{ur}+0.5584\mathit{ul}$$

Equation 6.2

where UL is upper left third molar, LR is lower right third molar and UR is upper right third molar based on developmental scores. The *ur* is upper right third molar and *ul* is upper left third molar based on eruptional scores. Equation 6.1 and Equation 6.2 refer to formula for male and female children, respectively.

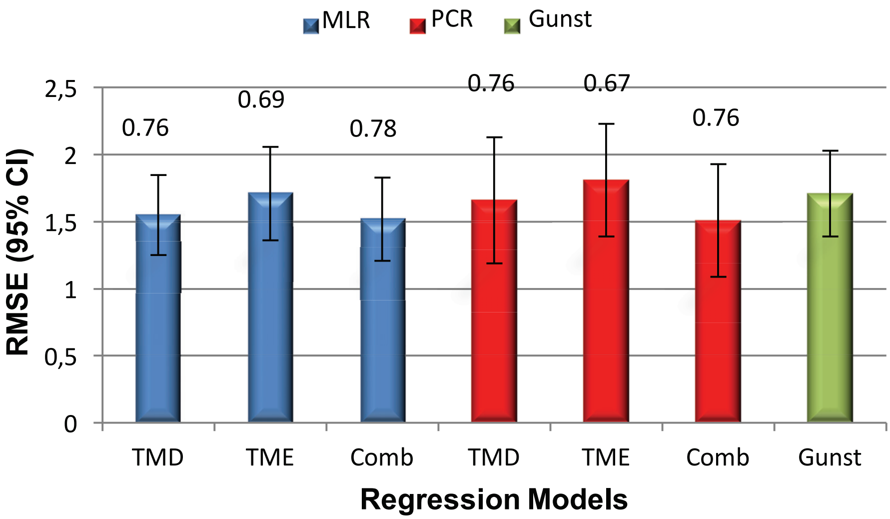

Figure 6.1 Regression estimates for males based on all third molar present. Values above the error bars denote the adjusted coefficient of determination (R^2), *RMSE* root mean square error, 95% CI confidence interval, *TMD* third molar development model, *TME* third molar eruption model, *Comb* combined model, *MLR* multiple linear regression, *PCR* principal component regression, *Gunst* Gunst et al. (2003).

In PCR, all models revealed comparable values of adjusted R^2 as in MLR. However, their performance on test dataset was rather poor especially in TME where the average RMSE was 2.1 years. The difference in RMSE across all models followed a similar pattern as MLR models. The only exception was that the addition of TME information to TMD model did not decrease the RMSE. No significant difference between age predicted by Gunst et al [Gunst et al., 2003] and other models except in females (Figure 6.2).

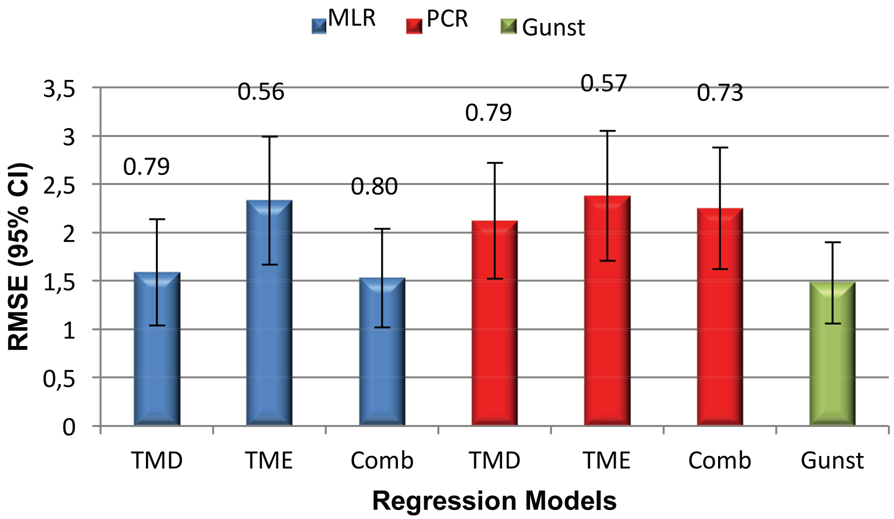

Figure 6.2 Regression estimates for females based on all third molar present. Values above the error bars denote the adjusted coefficient of determination (R^2), *RMSE* root mean square error, 95% CI confidence interval, *TMD* third molar development model, *TME* third molar eruption model, *Comb* combined model, *MLR* multiple linear regression, *PCR* principal component regression, *Gunst* Gunst et al. (2003).

Discussion

The missing values in this study were spread at random and thus treated by row deletion. As the data derived from the non-missing third molar (all four third molar are present), the score '0' was not implemented for scoring. Care should be taken especially during scoring of TMD stages to refrain from scoring 0 for any missing third molar. In fact, the missing third molar(s) should be exclusively treated as different domains and have to be classified according to quadrants so that each of them can be designed for a specific situation. Zero value may cause a disguise in correlation test when testing for multicollinearity.

Hence, in the present study a strong correlation that leads to multicollinearity was treated with principal component analysis and later regressed for multiple linear regressions. Strong multicollinearity especially in third molar on the same arch concurred with several other studies [Gunst et al., 2003; Mesotten et al., 2002].

Although PCR was proposed to address multicollinearity issue in this study, negligible effects has been observed as regard to the prediction accuracy. In fact, PCR does not outperform MLR as regard to prediction performance on out-of-sample data. Note that, based on principal component analysis that was carried out earlier, only the first principal component (PC) was selected for each model. The succeeding PCs were not selected due to their low eigenvalues (<0.7). As a result, the orthogonality between the PCs could not be demonstrated. Due to the fact that PC is a weighted average of the underlying variables, the PCR that was then carried out in this study is as well based on the principle of weighted average. Interestingly, the weighted average calculated in PCR is fairly resembling the weighted mean of the mean ages of the tooth development stages proposed by Roberts et al [Roberts et al., 2008]. Weights are chosen so as to maximize the explained proportion of the variance in the original set of variables (Table 6.3). The loading values in principal component for each model suggested that every variable contributing about the same magnitude of correlation coefficient. In other words, the loading value could be perceived as R^2 counting for percentage explained by model or in this case by axis of principal component.

Ultimately, the question on how to remove muticollinearity in highly correlated variables in dental age estimation model remained unanswered. The attempt to utilize PCR apparently revealed inconclusive evidence. Furthermore, the mathematical complexity behind PCR may be found to be a challenge as the age estimate calculation is not as direct as MLR model. In addition, the PCR model requires users to set the staging scores data in standardized form (normalized). The present study however, was not intended to verify the use of PCR in combating multicollinearity per se but rather to locally assess the potential damage presented by having plenty of highly correlated variables in the models. Although multicollinearity was evident in this study, the RMSE was not reducing in PCR hence suggesting its harmfulness was not affecting the model performance. Thevissen [Thevissen et al., 2010] dealt with multicollinearity by considering stages as repeated responses instead of predictors in Bayesian approach. The current study on the other hand, utilized age as response and third molar stages as predictors in both MLR and PCR models. Note that the data derived from this study excluded any missing third molars and thus limiting its applicability to be used for missing third molar subjects. Future studies to build individual model based on specific location of missing third molars are therefore recommended.

Few studies arbitrarily removed one of the two highly correlated variables in regression especially on the same arch [Gunst et al., 2003; Mesotten et al., 2002] largely due to insignificant left-right asymmetry. However, this is not the case when all variables are highly correlated to each other. In the present study, the highly correlated variables are in fact equally correlated to the principal component which revealed two important consequences. First, the inclusion of more than one variable in MLR may well be perceived as redundant and carries risks of multicollinearity. Although low to moderate multicollinearity may not be problematic, when the values are extreme (around 0.95), type II error rates are substantial and generally perceived as unacceptably high [Grewal et al., 2004]. Second, the scores from individuals may be weightedly-averaged and compared to population study. Apparently, although the latter seems to be the best remedy to overcome multicollinearity, it does not reflect well in the current study.

The high value in RMSE and low coefficient of determination R^2 for TME models in all categories (genders, MLR and PCR) indicate poor age predicting performance for this specific domain. This also suggests that third molar eruption is not a good alternative as a sole predictor to perform dental age estimation for sub-adults age 14 to 24 years despite strict selection criteria on TME prior to sampling. Although both genders shows RMSE reduction in the combined model, a conclusive proof to use a combined model over only TMD model may not be fully translated to practice due to its trivial value (0.03 year). In other words, the value difference between the two models is too small that it may be considered as clinically negligible. However, the combined model is still to be preferred due to the likelihood that the estimated age of an individual may be lessened and thus giving rise to the advantage of being a juvenile, the benefit of the doubt. In addition, the assessment of both TMD and TME can be performed simultaneously and generally does not require additional imaging acquisition and therefore, giving less radiation exposure. In the case of unobtainable population reference, the formula from Gunst et al [Gunst et al., 2003] may be used. Registration of subject with missing third molar using formula from this study should be avoided to ensure accuracy and therefore remains as a limitation to the current study.

Conclusion

MLR has proven to perform better than regressional PCA despite the arising multicollinearity issue. Adding age-related TME information to the TMD regression provides better dental age prediction than on only TME model. The TMD model alone offers better accuracy than TME. However, the use of combined model or in fact any of the individual models should be supported by prior validation study on specific population level. Therefore, the authors recommend a proper validation and test surveys using the criteria set forth by the present study to estimate dental age in sub-adults.

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Chapter 7

General Discussion

General Discussion

The accuracy of age estimation methods has always been a topic of interest among forensic odontologists, oral biologists and clinicians. Dental age estimation methods have come a long way since Demirjian established a system of dental age assessment in 1973. The method that developed from the French-Canadian population has been widely used and became a fundamental reference in the recent development of contemporary methods. As most studies designed to estimate dental age retrospectively, the use of extensive statistical approaches and techniques is inevitable to reduce the gap between the predicted dental age and chronological age. In addition, through these statistical techniques, various prediction models have been constructed combining different variables as predictors to estimate dental age. With a sample of 1,403 digital panoramic radiographs, this dissertation presents results of the dental age prediction models based on Malay population and acts as a pioneer project to develop age assessment policies and guidelines in Malaysia.

This thesis described age estimation models in three different parts. Part one explained the current trend and approach of age assessments in particular dental age estimation. The age assessment policies and procedures as regard to international guidelines such as UNHCR, USCRI and local legislations through various acts and laws were profoundly discussed in this part (Chapter 1). Part two dealt with dental age estimation models in children where the use of the Willems method (a modification of Demirjian et al., 1971) was heavily utilized (Chapters 3 and 4). Part three scrutinized the use of third molar as co-predictors to develop dental age estimation models in sub-adults. Methods from Gleiser and Hunt, 1955 modified by Kohler et al., 1994 and Olze et al., 2007 were arbitrarily chosen (Chapters 5 and 6) in this section.

Aspects of this retrospective study that were further scrutinized included the accuracy of the Willems method on different populations (Chapter 3), the use of multiple linear (Chapter 4), logistics (Chapter 5) and principle component (Chapter 6) regressions in prediction models, the combination of permanent teeth and third molar development (Chapter 4), and the combination of third molar eruption and third molar development (Chapters 5 and 6).

7.1 Statistical models

In children, Willems method is considered by many as one of the most accurate method. Statistically developed by weighted ANOVA, this method was also a modification from the original study of Demirjian. Methods by Demirijian [Demirjian et al., 1973] was the most frequently compared to Willems followed by Demirjian (based on seven and four teeth) [Demirjian and Goldstein, 1976], Cameriere [Cameriere et al., 2006], Haavikko [Haavikko, 1974], Chaillet [Chaillet et al., 2005], Nolla [Nolla, 1960], and Willems II (based on non-gender specific) [Willems et al., 2010]. Two studies on Bosnian-Herzegovinan [Galic et al., 2011] and Malaysian population [Kumaresan et al., 2014] were the only studies that exhibited the superiority of Cameriere [Cameriere et al., 2006] over Willems [Willems et al., 2001]. Pinchi [Pinchi et al., 2012] on their 14-year threshold study based on four dental age estimation methods (Cameriere included) stated that Willems method was still the most accurate method despite its tendency to overestimate the real age. However, the comparison between these studies is difficult as Galic [Galic et al., 2011] limited the age range up to 13 years old while Kumaresan [Kumaresan et al., 2014] did not provide data on age group. It was claimed that the method by Willems was the best as regards to average difference and median absolute difference between the dental age and chronological age [Liversidge, 2008a].

Based on 19 primary studies, the systematic review and meta-analysis on Willems method in this study exhibited just how accurate this method was when the primary studies were segregated into underestimation and overestimation groups. On absolute values, both groups yielded mean error that less than 0.5. In perspective, Willems method is able to estimate age with great accuracy within the error margin of up to 6 months.

Nevertheless, the current study did not intended to go into detail discussing the validation as done in primary studies. This is partly on one hand due to the overwhelming amount of literatures demonstrating the use of specific dental age estimation methods on population level. On the other hand, as it is widely known that validation is only part of equation to develop a prediction model. In many situations the reference data has to adapt according to the method by the original model. For example, in Chapter 4 of the current work, the flow of the validation and adaptation process was explained by means of mean errors, mean absolute errors and root means square errors (Figure 7.1). The validated Malay-specific model and the Willems model revealed age estimation results with equal magnitude and variance in error. These findings reflected not only the usefulness of the Belgian population as reference but also the difference (if any) in size of the training set (*n* = 311) and the set of subjects used by Willems (*n* = 2116) to develop the prediction model. In other words, the finding did not warned the necessity to collect more data to develop an own specific model.

"The validated Malay-specific model and the Willems model revealed age estimation results with equal magnitude and variance in error. These findings reflected not only the usefulness of the Belgian population as reference but also the difference (if any) in size of the training set (n=311) and the set of subjects used by Willems (n=2,116) to develop the prediction model"

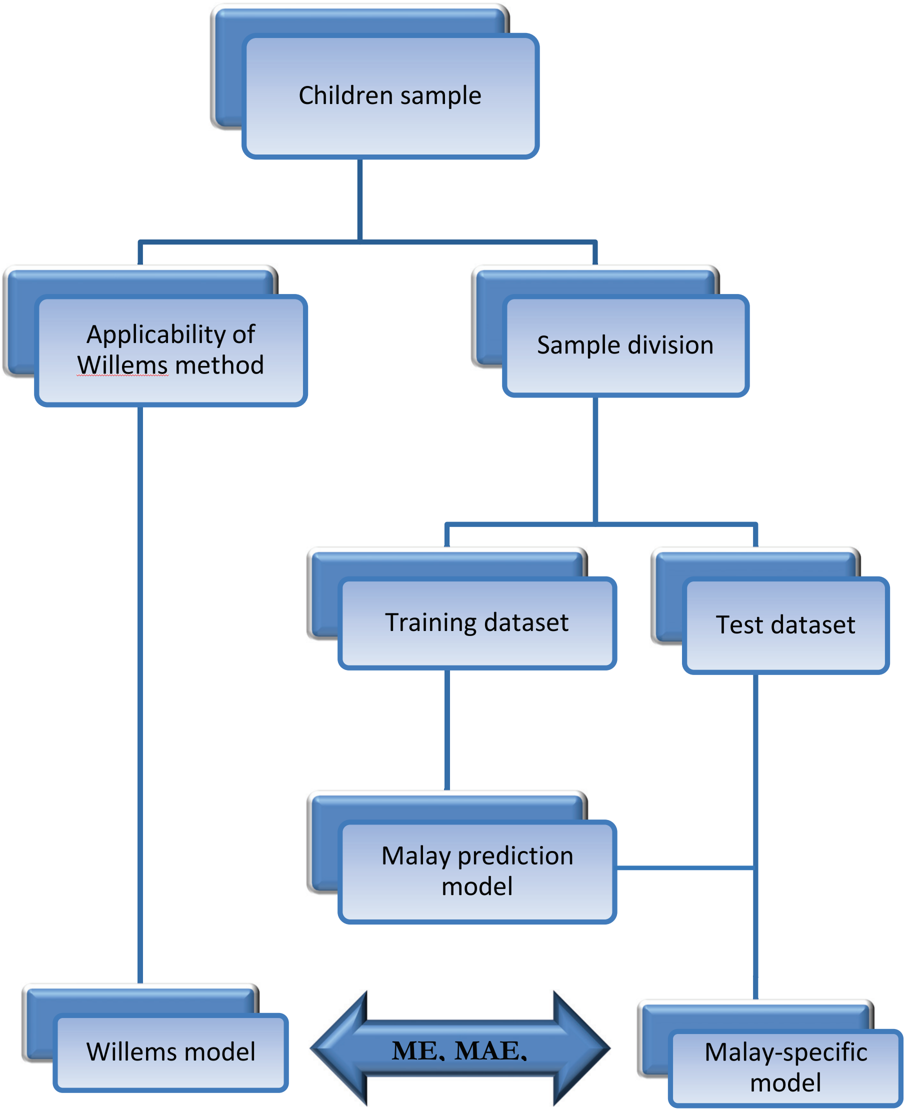

Figure 7.1 The flow of validation and adaptation process in the development of dental age estimation model

7.1.1 The linear regression

In data analysis, linear regression is used when there is as need to model the values of a dependent variable according with the values of at least two independent variables, also called “predictors”, using the equation of a straight line. The main requirement that must be fulfilled by all the variables involved in the model is that these variables must have at least the scale type – but the model behaves best when all the variables are quantitative [Draper et al., 1998]. The linear regression model assumes that there is a linear relationship between the dependent variable and each predictor, described in the following formula:

$y_i = b_0 + b_1x_{i1} + ... + b_px_{ip} + e_i$,

where:

y_i - is the value of the i-th case of the dependent scale variable

p - is the number of predictors

b_j - is the value of the j-th coefficient, $j \in \{0, 1, ..., p\}$

x_{ij} - is the value of the i-th case of the j-th predictor

e_i - is the error in the observed value for the i-th case

Notice that the formula deals with an equation of first degree, with p variables; b_0 is the intercept or the model-predicted value of the dependent variable when the value of every predictor is equal to 0 (the point where the line intersects the Oy axes, in a representation using a Cartesian coordinates system). The error term e_i must fulfill also the following conditions:

- Its distribution is normal, with a mean of 0;

- Its variance is constant across cases and independent of the variables in the model;

- Its value for a given case is independent of the values of the variables in the model and of its values term for other cases.

Lucy [Lucy et al., 1996] have described a number of disadvantages that traditional regression analysis has. Most important of these, probably, is that regression analysis assumes the independent variable as being on a continuous scale and is therefore unsuitable for ordinal variables, such as Demirjian's grading of tooth development (regressing ordinal variables can lead to a loss of information which obscures the real probability distribution of the predicted age). While the application of regression analysis to ordinal data may not be appropriate and has been criticized [Lucy et al., 1996], its continued use and recommendation [Chaillet and Demirjian, 2004] were among the reasons for considering it in the present study.

7.1.2 The logistic regression

Logistic regression analysis is suitable for assessing ordinal variables; moreover, it produces probabilities that can be used to predict group membership (< or ≥18 years, i.e. majority or minority status, juvenile or adult in Chapter 5). In current work, the stages 9 to 10 (TMD) and stage D (TME) can be used as reference stages to estimate whether a subject is likely to be equal to or over age 18, with 85.88–96.38% and 94.74–100% correct predictions, respectively, for both genders.

Stages 4 (TMD) and A (TME) predicted a 100% correct prediction in discriminating juvenility minors from the age of majority.

7.1.3 Principal components regression

Principal components regression is a method for combating multicollinearity and results in estimation and prediction better than ordinary least squares when used successfully (Draper and Smith 1981, Myers 1986). Its goal is to reduce the dimensionability of the original data set. A small of uncorrelated variables is much easier to understand and use in further analyses than a larger set of correlated variables.

Since the multicollinearity was suspected from the variables in this study, statistical tests have been performed according to Fekedulegn [Fekedulegn et al., 2002] to rectify this problem. In theory, when the independent variables exhibit multicollinearity (in this case the TMD and TME staging scores), estimation of the coefficients using ordinary least square (OLS) may result in regression coefficients much larger than the physical or practical situation would deem reasonable (Draper and Smith 1981); coefficients that wildly fluctuate in sign and magnitude due to a small change in the dependent or independent variables; and coefficients with inflated standard errors that are consequently non-significant. More importantly, OLS inflates the percentage of variation in estimated age accounted for by TMD and TME staging scores (R^2). Therefore, using ordinary regression procedures under high levels of correlation among the variables affects the four characteristics of the model that are of major interest to forensic odontologists: magnitude, sign, and standard error of the coefficients as well as R^2. However, as the results shown in Chapter 6, the use of principal component regression did not aid in better accuracy of dental age prediction models.

7.2 Combination of predictors

Various potential predictors have been discussed prior to the start of the current work. To reduce the burden of excessive acquisition of radiographic modalities, only predictors that can be explained within a single panoramic radiograph were scrutinized for further in-depth investigation. Permanent teeth staging development, third molar development and third molar eruption were chosen in this study.

7.2.1 Permanent teeth and third molar developments

The permanent teeth prediction model was developed according to the Willems method based on the Belgian population [Willems et al., 2001]. The incorporation of third molar development to this model was based on staging by Gleiser and Hunt [Gleiser and Hunt, 1955] modified by Kohler [Kohler et al., 1994]. The RMSE decreased in the age category from 14 to 16 years, in females with 0.34 and in males with 0.60 year, adding age-related dental development information of third molar to the available permanent teeth information (Table 7.1). This gain in explained variance in age prediction can be explained by the fact that in the considered age category multiple permanent teeth are already fully matured, consequently providing no more tooth developmental age information. In this period, third molar is fully developing and their added age-related tooth developmental information improves the accuracy of the age predictions. In the context of the particular age groups of interest in Malaysia, it should be considered, evaluating the age of 14 year (child employment), to use the model combining permanent teeth and third molar stages. The combined permanent teeth and third molar model provides in all age categories decreased RMSE values compared to the RMSE values obtained from the model based on only third molar. Because the magnitude of this decrease is not high enough to obtain smaller RMSE values than obtained from the model based on only third molar information, the age estimation model expected to provide the best age prediction accuracy in children remains the model including only permanent teeth stages.

"In the context of the particular age groups of interest in Malaysia, it should be considered, evaluating the age of 14 year (child employment), to use the model combining permanent teeth and third molar stages"

7.2.2 Third molar development and third molar eruption

Small coefficient of determination (R^2) difference between the TMD and combined model was observed with 1 to 2% variance explained by the regression models. On the other hand, TME received relatively low adjusted R^2 and the performance of this model on test dataset was no better than TMD and combined model with average RMSE of 2.0 years compared to 1.6 and 1.5 years for both genders, respectively (Figures 6.1and 6.2). The combined model yielded from the multiple linear regression formula is as in Box 7.1.

Box 7.1

EQUATIONS FOR DENTAL AGE ESTIMATION

Equation 1 Age estimation in males using scores from TMD and TME

$$Age = 9.6143+0.3700UL+0.4987LR+1.8005ur-1.1022ul$$

Equation 2 Age estimation in females using scores from TMD and TME

$$Age = 9.0252+0.838UR+0.5461LR-0.8163ur+0.5584ul$$

UL upper left third molar, LR lower right third molar and UR upper right third molar based on developmental scores. *ur* upper right third molar and *ul* upper left third molar based on eruptional scores

Table 7.1 RMSE specific within age categories

	Male			Female		
Age category	RMSE PT	RMSE TM	RMSE PT+TM	RMSE PT	RMSE TM	RMSE PT+TM
<8 years	1.19 (1.00;1.39)	1.49 (1.24;1.73)	1.04 (0.87;1.21)	1.34 (1.10;1.57)	1.85 (1.53;2.17)	1.27 (1.05;1.49)
8-10 years	0.90 (0.65;1.15)	1.44 (1.05;1.83)	0.92 (0.67;1.18)	0.92 (0.68;1.18)	1.39 (1.02;1.77)	0.76 (0.55;0.96)
10-12 years	1.29 (0.93;1.64)	2.63 (1.91;3.35)	1.26 (0.91;1.60)	1.07 (0.77;1.36)	2.13 (1.54;2.73)	1.17 (0.84;1.49)
12-14 years	1.59 (1.07;2.11)	3.42 (2.26;4.58)	1.96 (1.30;2.62)	1.13 (0.79;1.47)	2.81 (1.95;3.66)	1.47 (1.02;1.91)
14-16 years	1.53 (0.66;2.40)	1.60 (0.69;2.51)	1.19 (0.51;1.87)	1.50 (0.56;2.44)	1.14 (0.43;1.85)	0.90 (0.34;1.46)
> 16 years	1.00	1.00	1.00	1.00	1.00	1.00

Between parenthesis 95% confidence intervals of RMSE

RMSE root mean square error, *PT* permanent teeth, *TM* third molar

A definite proof to use a combined model over only TMD model may not be fully translated into practice due to its trivial value of difference (0.03 year). In other words, the value difference between the two models is too small that it may be considered as clinically negligible. However, the combined model is still to be preferred due to the likelihood that the estimated age of an individual may be lessened and thus giving rise to the advantage of being a juvenile, the benefit of the doubt.

To control for the TME variation a quantitative measure has been proposed in this study as described in Chapter 6. Among others, the measurement demonstrated the use of the retro-molar space to crown width ratio as an exclusion criteria in third molar selection. The ratio of retro-molar space to crown width was calculated according to the method described by Olive and Basford [Olive and Basford, 1981] and later modified by Ganss et al [Ganss et al., 1993]. Should the ratio found to be less than 1.1, the subject would be excluded. However, bear in mind that although TME variation may be controlled, this proposed criteria has its trade off. Not all individuals are suitable to be used for the prediction model developed in this dataset (exclusion of individuals with less than 1.1 Ganss ratio). And that may seem as a disadvantage for this model. Those who have at least one impacted third molar will directly be considered unsuitable in this age prediction model. In this case, the model can be applied to almost 70% of Malay population as study from Kanneppady [Kanneppady et al., 2013] revealed that on ethnic-specific level, 30.6% Malays presented with at least one impacted third molar. On a global population-specific level, this model is useful

"However, bear in mind that although TME variation may be controlled, this proposed criteria has its trade off. Not all individuals are suitable to be used for the prediction model developed in this dataset"

to more than 30% of American [Morris and Jerman, 1971] and Singaporean Chinese [Quek et al., 2003] populations. Furthermore, as the dataset was also derived from individuals who had all third molars present, this model could not cater for people with any kinds of missing third molar. The reason for the exclusive inclusion of all third molars was simply that the staging could not be scored as '0' or no known value ('NA'). Firstly, the '0' value did not convey a valuable information pertaining the dental age in third molar staging system. As the scores were used as predictors in the prediction model, the score '0' was seemed rather illogical and unsound to the equation. Secondly, it also implicated no sense of third molar positioning as the missing may came from any of its four positions. During data collection process, third molar segregation according to its missing position(s) had been attempted. However, small number of individuals within certain groups especially for missing in single third molar inhibited the progress to obtain significant results in the analysis. Thus, it is recommended in this study to collect enough datasets from particular groups to develop specific prediction models for any missing third molars.

The current study provides age interval of the individuals by implying the error rate at the scientifically accepted threshold of 95% for determining statistical significance. On legal perspective, actions should be taken to serve the "best interest" of the patient during the medical diagnostic procedures and treatments (beneficence). Age misclassification is not only harmful for the individual, but the whole group into which someone is wrongly appointed is affected. During the status determining procedures, most individuals or applicants are living together. As such no benefit is given to a wrongly classified child that has to live together with adults, or to wrongly classify mature people who want to receive protection and will be treated as children. One of the major ethical issues must be to avoid misclassification – this applies both when children are estimated to be adults and when adults are estimate still to be children. There needs to be a constant awareness that children should be protected from exploitation, human trafficking and other related offences where children are especially vulnerable.

The age estimation has to include the uncertainty of the prediction. The lowest bound of the predicted age should give the optimal benefit of the doubt to the examined applicant. The uncertainty of the prediction gives the parameters in which the final decision can be made. Consequently, another benefit for the applicant may be the radiological findings, and diagnoses which are made available to the applicant, allowing medical treatment to be initiated.

Justice is served to all parties involved if proof of the age of the individuals can be attained. Thus, the individual has nothing to fear if she/he has indeed an age of minority. The proof allows the authorities to provide a legally correct decision. Legally correct decisions do not require the basic information of the estimated age of the applicant, but the ability to discriminate between minors or the age of majority (child or adult). The threshold is legally regulated on the national level and in some instances is also gender specific. In certain countries, other age thresholds may be of importance for additional decision making. Classification of the applicant above or under a set age threshold is commonly used. The current study has set an 18-year threshold to discern the children from the age of majority. However, the level of likelihood that has to be reached during this classification needs to be properly addressed. Setting this level is nonetheless more of a legal decision than an ethical issue. The range of percentage between 50% and higher is the scientific requirement for certainty. For instance, Figure 7.2 illustrates the percentiles for each stage in third molar development and eruption as a function of age in males (a) and females (b). The percentiles elucidate the 25% to 95% possibility of stages attaining the 18-year threshold.

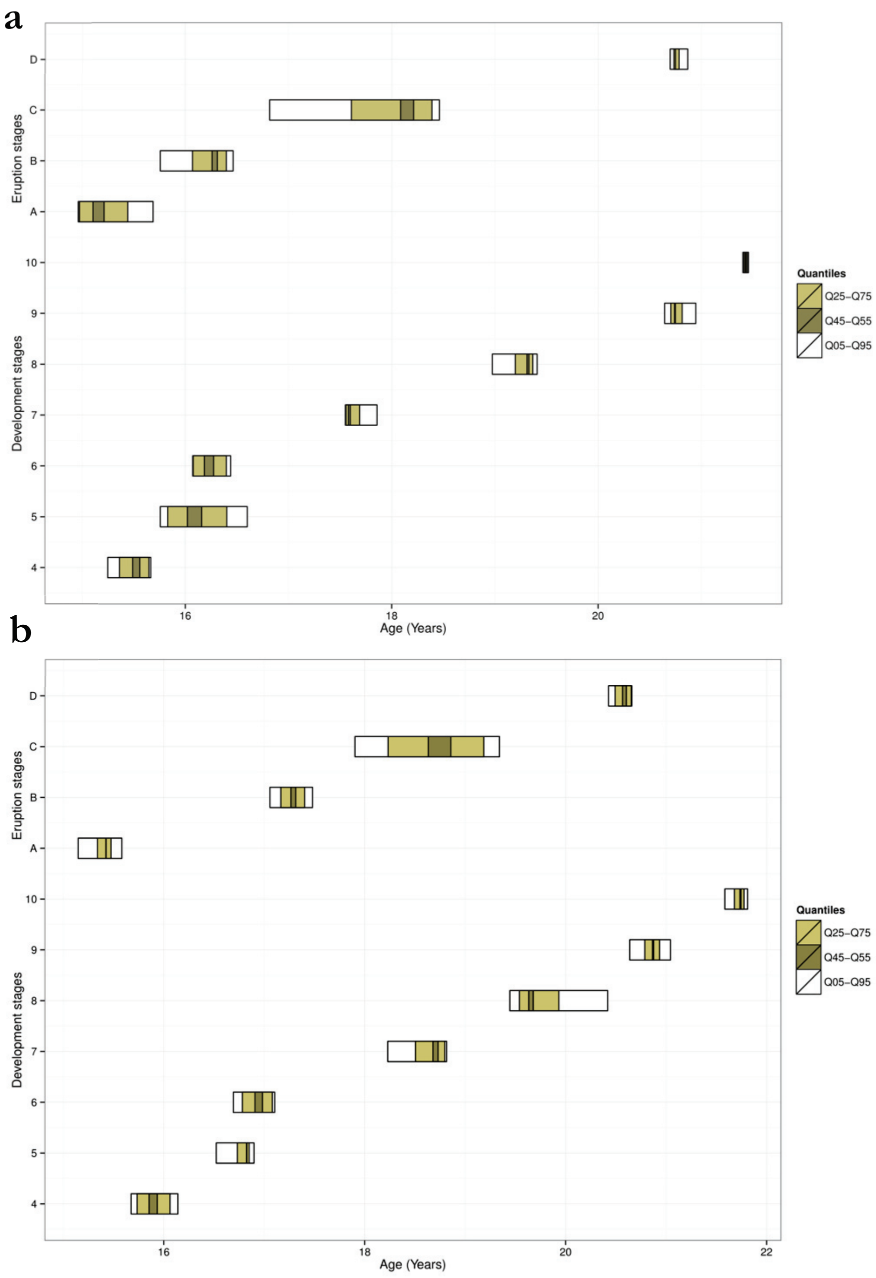

Figure 7.2 Percentiles of the staging scores as a function of the age for males (a) and females (b)

Chapter 8

Conclusions, Limitations and Future Research

8.1 Conclusions

With regards to the aims stated previously, the following conclusions can be made.

1. Despite statistical issues such as multicollinearity and the use of ordinal variables in linear regression as rectified in this study utilizing principal component analysis and transformation of ordinal variables to the scale-type variables, respectively, the prediction model using the traditional multiple linear regressions exhibited excellent superiority in accuracy compared to principal component regression. The logistic regression worked well with ordinal variables.
2. The addition of predictors (third molar development and third molar eruption stages) to the respective regressions equation showed trivial increment of accuracy. The prediction model of combined permanent teeth and third molar development is more accurate to estimate age for children suspected of being less than 15 years old.
3. Using the logistic regression with <18 and ≥18 years old as binary outcomes, specific stages in third molar development and eruption were obtained with high degree of correct prediction. Stage 4 (TMD) and A (TME) can be used to discern juvenile (<18-year) from the age of majority.

8.2 Limitations and directions for future research

The risk of radiation exposure imposed by the use of dental panoramic radiographs is considered relatively negligible. Although the dose of exposure is unlikely to cause any deterministic effects such as skin erythema and radiation sickness, there is a risk of stochastic effects where the occurrence follows a linear no-threshold hypothesis. This means that although there is no threshold level for these effects, the risk of an effect occurring increases linearly as the dose increases. Exploration works on non-ionizing radiation modalities such as ultrasonographic instruments and magnetic resonance imaging (MRI) may provide an excellent alternative to the current method although the latter may come in more substantial costs.

The digital dental panoramic radiographs in this study were collected retrospectively and due to its cross sectional design, firm conclusions about the directions of causality implied in the model especially in the meta-analysis of Chapter 3 cannot be drawn. The cause for over- and underestimation of chronological age within the primary studies can only be rendered by inter-population difference. Thus, the relationships among variables must be interpreted with caution. For future research, longitudinal data can be used to draw the true causal inferences. This is especially important to assess different age categories as per forensic interest such as 18-years threshold.

Another limitation in this study is the use of prediction models in the form of regression analysis which cannot be applied to every individual. Due to restriction of the dataset used to develop prediction models, individuals must be screened for any missing of third molars. In this case, all third molars that meet the requirement for scoring must be present. Therefore, in order to be able to estimate the age of individual with missing third molar, selection of a specific dataset according to the particular location and missing combination of third molars needs to be performed. It is imperative to note that prior to the use of any models in this study, the model validation must first be performed. This includes validation studies within specific populations and the risk groups such as malnutrition and growth retardation.

The scoring for every teeth of their developmental and eruptional stage is subjective in nature and often requires prior knowledge and experience by the evaluators. Scoring several different methods such as in this study may also entail some amount of time and delay the process of reporting. Thus, the development of automated inspection system in the form of computer-aided dental age scoring system based on different methods may be able to curb these drawbacks.

Summary

In the first part of this work, **Chapter 1** portrayed the current trends and approaches of age assessment in particular on dental age estimation. Willems method, a modification from Demirjian et al., 1973, Kohler method (modification from Gleiser and Hunt, 1955), and Olze method pertinent to children and sub-adults dental age estimation were introduced. The age assessment policies and procedures as regard to international guidelines such as UNHCR, USCRI and local legislations through various acts and laws were profoundly discussed in this section.

The aim of this thesis was to validate the different methods of dental age estimations and evaluate the use of different statistical methods and predictors influencing accuracy of dental age assessment models in children and sub-adults based on a single radiograph. Hypotheses derived from each objective in this study were presented in **Chapter 2**.

Chapter 3 examined in detail the accuracy of the Willems method in children. Through numerous validation studies on different populations, this chapter systematically examined the applicability of Willems dental age method on different age groups and its performance based on various populations and regions. On absolute values, females (underestimated by 0.13; 95% CI: 0.09-0.18 and overestimated by 0.27; 95% CI: 0.17-0.36) exhibited better accuracy than males (underestimated by 0.28; 95% CI: 0.14-0.42 and overestimated by 0.33; 95% CI: 0.22-0.44). The overall pooled estimate overestimated age by 0.10 (95% CI: -0.06-0.26) and 0.09 (95% CI: -0.09-0.19) for males and females, respectively. These values are lower than the Demirjian et al. 1973. There was no significant difference between the young (4-8 years old) and older child (9-14 years old) in subgroup analysis. The mean age between different regions also exhibited no statistically significant.

In this combo of validation, adaptation and combined predictors, the Willems model which was originally developed from a large sample of Belgian children was once again being the center of attention. Based on the Willems method in this **Chapter 4**, the collected Malay children was verified and overestimated chronological age by 0.45 year. Small differences in mean error, mean absolute error and RMSE between the verified Malay-specific prediction model and the Willems et al. model (Belgian children) were observed indicating that developing a Malay-specific prediction model based on a large Malay reference sample is not entirely necessary. An overall trivial decrease in root mean square error (RMSE) was detected adding third molar stages to the developed permanent teeth model making the use of combine model more preferable especially within the age group of children between 14 to 16 years old.

The focus in **Chapter 5** was on age 18 as it is considered as the age of majority by most countries. Both third molar development (TMD) and eruption (TME) staging scores were used as predictors in binary logistic regression analysis. The binary outcomes were determined as <18-year and ≥18-year. Stages 4 to 6 (TMD) and A-B (TME) in males and stages 4 (TMD) and A (TME) in females were found to be in concordance discriminating the <18-year group (100% of correct prediction). In other words, a subject is likely to be classified as being below the 18-year threshold if the development of the third molar has not yet reached the stage 5 (TMD) or the evidence of a calcified cleft or a calcified quarter root as seen in radiographs. In both genders, the stages 9 to 10 (TMD) and D (TME) were accountable to be used as reference stages to estimate whether the subject was likely to be ≥18-year, with 94.74-100% and 85.88-96.38% of correct predictions, respectively.

Chapter 6 aimed to evaluate the performance of dental age estimation in individual method models and the combined model (TMD and TME) based on the classic regressions of multiple linear and principal component analysis. A sample of 705 digital panoramic radiographs of Malay sub-adults aged between 14.1 and 23.8 years was collected. The techniques described by Gleiser & Hunt (modified by Kohler) and Olze were employed to stage the TMD and TME, respectively. The data was divided to develop three respective models (two individual models and one combined model) based on the two regressions of multiple linear and principal component analysis. The trained models were then validated on the test sample and the accuracy of age prediction was compared between each model. The coefficient of determination (R^2) and RMSE were calculated. In both genders, adjusted R^2 yielded an increment in the linear regressions of combined model as compared to the individual models. The overall decrease in RMSE was detected in combined model as compared to TMD (0.03-0.06) and TME (0.2-0.8). In principal component regression, low value of adjusted R^2 and high RMSE except in male were exhibited in combined model. Dental age estimation is better predicted using combined model in multiple linear regression models.

Chapter 7 discussed the overall results of this research project in a more general context. Dental age estimation models based on its applicability in children and sub-adults were developed. The advantages and limitations for every model were explained in detail.

Chapter 8 outlined the conclusion and several limitations in this study. Further works to address the limitations were also explained in this chapter.

Samenvatting

In **Hoofdstuk 1** worden de huidige trends en benaderingen in het kader van leeftijdsbepaling, en in het bijzonder de dentale leeftijdsbepaling, beschreven. Meer bepaald, de Willems methode, een gewijzigde methode van Demirjian et al., 1973, de Kohler methode (wijziging van Gleiser en Hunt, 1955) en de Olze methode, allen relevant voor leeftijdsbepaling bij kinderen en jongvolwassenen worden toegelicht. Bovendien worden in het eerste deel beleidsmaatregelen en procedures voor leeftijdsbepaling, verwijzend naar internationale richtlijnen zoals de UNHCR, USCRI en lokale wetgeving, aan de hand van feiten en wetten grondig besproken.

Het doel van dit proefschrift was om de verschillende methoden van tandheelkundige leeftijdsbepalingen te valideren en het evalueren van verschillende statististische methoden en voorspellers die, op basis van één enkele röntgenfoto, de nauwkeurigheid van dentale leeftijdsbepalingsmodellen bij kinderen en jongvolwassenen beïnvloeden. Hypothesen afgeleid van elke doelstelling in deze studie worden weergegeven in **Hoofdstuk 2**.

Hoofdstuk 3 onderzocht in detail de nauwkeurigheid van de Willems methode bij kinderen. Aan de hand van meerdere validiteitsstudies op verschillende bevolkingsgroepen werd in dit hoofdstuk systematisch de toepasbaarheid ervan onderzocht op basis van verschillende bevolkingsgroepen en regio's. In absolute waarden vertoonden de leeftijdsbepalingen bij meisjes (onderschatting 0,13; 95% CI: 0,09-0,18 en overschatting 0,27; 95% CI: 0,17-0,36) een betere nauwkeurigheid dan bij jongens (onderschatting 0,28; 95% CI: 0,14-0,42 en overschatting 0,33; 95% CI: 0,22-0,44). De verzamelde resultaten van leeftijdsoverschatting bij beide geslachten, jongens en meisjes, zijn respectievelijk 0,10 (95% CI: -0.06-0.26) en 0,09 (95% CI: -0.09-0.19). Deze resultaten liggen beduidend lager dan bij Demirjian et al. 1973. De gemiddelde leeftijdsbepaling in de subgroep analyse tussen de jonge (4-8 jaar) en oudere kinderen (9-14 jaar) toonde geen significant verschil. Ook tussen de verschillende regio's werd eveneens geen significant verschil gemeten.

In de gehele context van van validiteit, adaptatie en gecombineerde voorspellers kreeg het Willems model, dat oorspronkelijk ontwikkeld werd uit een ruime onderzoeksgroep van Belgische kinderen terug de nodige aandacht. In **Hoofdstuk 4** werd, gebaseerd op deze methode, een leeftijdsoverschatting van 0.45 jaar gemeten bij de onderzoeksgroep Maleier kinderen. Het specifieke voorspellingsmodel bij de Maleier kinderen en het origineel Willems model (Belgische kinderen) toonde slechts kleine verschillen in the 'mean error', 'mean absolute error' en 'root mean square error (RMSE)'. Dit toont aan dat de ontwikkeling van een Maleier-specifiek voorspellingsmodel op een grote Maleier studiegroep niet nodig is. Wanneer ontwikkelingsstadia van derde molaren werd toegevoegd aan het model werd een verwaarloosbare daling van de RMSE gemeten. Daaruit werd besloten dat het gebruik van dit gecombineerde model bijzondere voorkeur biedt in de leeftijdsgroep tussen 14 en 16 jaar oud.

In **Hoofdstuk 5** ligt de nadruk op de 18 jarige leeftijd. Dit is in de meeste landen de leeftijd waarbij men als meerderjarig beschouwd wordt. Zowel derde molaar ontwikkelingsstadia (TMD) als doorbraakstadia (TME) scores worden gebruikt als voorspellers in de binaire logistische regressie analyse. De binaire resultaten worden bepaald als <18 jaar en ≥18 jaar. Stadia 4 tot en met 6 (TMD) en A-B (TME) bij mannen en stadia 4 (TMD) en A (TME) bij vrouwen bleken in overeenstemming met de < 18 jaar groep (100%). Met andere woorden, een patiënt zal waarschijnlijk jonger dan 18 jaar bevonden worden wanneer de ontwikkeling van de derde molaar stadium 5 (TMD) niet bereikt heeft, noch verkalkte bifurcatie noch verkalkte 1/4de van de wortel in een monoradiculair bereikt heeft op radiografie.

In beide geslachten kunnen de stadia 9 tot 10 (TMD) en D (TME) met respectievelijk 94,74-100% en 85,88-96,38% hoge graad van correctheid aantonen dat de leeftijd ≥18-jaar waarschijnlijk bereikt werd.

Hoofdstuk 6 heeft als doel om op basis van de klassieke regressie van 'multiple linear analysis' en 'principal component analysis', de dentale leeftijdsbepaling te beoordelen, gemeten aan de hand van individuele modellen en het gecombineerde model (TMD en TME). Een reeks van 705 digitale orthopantomogrammen van Maleier jongvolwassenen tussen de leeftijd van 14,1 en 23,8 jaar werden verzameld. De technieken beschreven door Gleiser & Hunt (gewijzigd door Kohler) en Olze, werden gebruikt om respectievelijk de TMD en TME stadia te bepalen. De gegevens werden verdeeld over de drie modellen (2 individuele en 1 gecombineerd model) gebaseerd op twee 'regressions of multiple linear' en 'principal component analysis'. De modellen werden vervolgens gevalideerd op de steekproef en de accuraatheid van de resultaten werden tussen de modellen onderling vergeleken. Hiertoe werd de determinatiecoëfficient (R^2) en RMSE berekend. Voor beide geslachten toonde de 'Adjusted R^2' een toename in de lineaire regressie van het gecombineerd model in vergelijking met de individuele modellen. De algemene daling RMSE werd gedetecteerd bij het gecombineerde model vergeleken met TMD (0,03-0,06) en TME (0,2-0,8). In het gecombineerde model gaf de 'principal component regression analysis' lage 'adjusted R^2' waarden en hoge RMSE met uitzondering voor het mannelijke geslacht. Het voorspellen van de dentale leeftijdsbepaling is accurater in de meervoudige lineaire regressie analyse in het gecombineerde model.

In **Hoofdstuk 7** worden alle resultaten van dit onderzoeksproject in een meer algemene context gezet. Tandheelkundige leeftijdsbepalingsmodellen gebaseerd op de toepasbaarheid bij kinderen en jongvolwassenen werden ontwikkeld. De voordelen en beperkingen voor elk model worden in detail toegelicht.

Hoofdstuk 8 beschrijft de conclusie alsook een aantal beperkingen van deze studie. Er wordt tevens gewaarschuwd voor een veralgemeende toepassing van het model op een individu zonder voorafgaandelijk de nodige validiteit en risicobepaling te hebben uitgevoerd.

Curriculum Vitae

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Articles in Academic Journals

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Seminars/Workshops

- Graphics in R, Hasselt University (Flanders Training Network for Methodology and Statistics, FLAMES), Diepenbeek, Belgium, *27-29 May 2015*
- Big Data, FLAMES Annual Meeting 2015, Ghent University, Ghent, Belgium, 13 May 2015
- Applications of 2D and 3D Geometric Morphometrics in Forensic Comparisons, Washington State Convention Center, American Academy of Forensic Sciences, Seattle, WA, United States of America, *18 February 2014*
- Oral Pathology in Children, Holiday Inn Hotel Diegem, Brussels, Belgium, *27 April 2013*
- Forensic Human Identification (DipFHID), Charterhouse Square, Academy of Forensic Medical Sciences, London, UK, *18–22 March 2013*
- Course in Forensic Anthropology, Leuven, Belgium, *25 April 2012*
- Seminar on Use of Cone Beam CT for Dentomaxillofacial Diagnostics, Leuven Centre for Irish Studies (LCIS), Leuven, Belgium, *31 May – 1 June 2012*

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