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ORIGINAL ARTICLE

Applicability of the Greulich and Pyle bone age standards to Taiwanese children: A Taipei experience

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Abstract

Background: The Greulich and Pyle (GP) method is one of the most common radiographic techniques for bone age (BA) assessment. The applicability of this method to ethnic populations outside of the United States has been investigated in several recent studies worldwide. Currently, limited data are available on the accuracy of the GP method for the Taiwanese population. The purpose of this study was to determine whether the GP standards are applicable to contemporary Taipei children.

Methods: Clinical data from October 1, 2010, to March 31, 2020, were retrospectively collected from a general hospital in Taipei. BA was determined by a senior pediatrician and was reviewed by a senior pediatric radiologist according to the GP standards. Comparison of BA and chronological age (CA) was performed in children with body weight and height in the 15th to the 85th percentiles of normal children. Ethnic variations in the maturation process in the ulnar bone were investigated. All data were statistically analyzed.

Results: In total, 2465 medical records were collected. After excluding those with diseases and unqualified data, 654 records of boys and 809 of girls were analyzed. In boys, the mean BA was significantly delayed between 6 and 9 years of age compared with the CA. In girls, the mean BA was generally advanced between 7 and 15 years of age. Ulnar bone maturation tended to be delayed in young boys.

Conclusion: A significant discrepancy between CA and BA was observed in our population. Delayed ulnar bone maturation in young boys was confirmed. Children in Taipei exhibit a different maturation pattern than children on whom the GP standards were based.

Keywords: Child; Female; Radiologists

1. INTRODUCTION

Bone age (BA) is the age expressed in years that corresponds to the level of maturation of human bones. It is a common index used in pediatric radiology and endocrinology departments worldwide for the evaluation of skeletal maturity for medical and nonmedical purposes. Although several methods have been studied to more accurately define BA, evaluation of hand and wrist radiographs is still the most common method.[1] In clinical practice, a BA assessment allows for the evaluation of developmental status, the evaluation of sexual maturity, and the prediction of ultimate height for children. BA assessment also plays a decisive role in the diagnosis and monitoring of treatment for growth disorders and endocrinological abnormalities in children by revealing significant discrepancies between BA and chronological age (CA).[2]

The Greulich and Pyle (GP) method[3] and the Tanner–Whitehouse 3 (TW3) method[4] are two main methods used for BA assessment. The GP method is the most common method in Taiwan. It is based on matching the child's left hand radiograph to standard templates provided by the GP atlas. The original reference population was North American Caucasian from 1938. The TW3 method is based on a stage assessment and scoring of skeletal maturity for each individual left hand wrist bone. The reference population for the TW3 method was European and American Caucasian children in the 1980s and 1990s.

Since the establishment of the GP atlas, many studies have been conducted in different parts of the world to determine whether the GP method is applicable to their population.[5–9] Evidence suggests that the skeletal maturation rate may vary between different ethnic and socioeconomic groups of children.[10] A systematic review and meta-analysis study revealed that the GP standard is imprecise and should be used with caution when applied to male children of Asian descent and female children of African descent.[11] Two studies have examined the reliability of the GP method for Taiwanese children. One study from Hualien County in Eastern Taiwan reported a BA delay before puberty followed by an increase during puberty.[12] Another study from Southern Taiwan using BoneXpert automatic software[13]

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reported that BA was delayed from age 3 to 11 and advanced from age 12 to 17 in boys; in girls, BA was delayed from age 4 to 8 and advanced from age 9 to 17.[14] The difference in results between these two studies implies that ethnic differences exist among Taiwanese children. To our knowledge, no study has examined the applicability of the GP method for populations from Northern Taiwan.

The primary purpose of this study was to test whether contemporary Taipei children mature differently than the GP reference population. Our null hypothesis was that the CA would match the BA. In our previous clinical experience, the maturation rate of the ulnar bone was quite different from that found in the GP atlas. The secondary purpose of our study was to examine possible ethnic variations in the rate of ulnar bone development in Taipei children.

2. METHODS

2.1. Data sources

In this retrospective study, we collected the medical records of Taiwanese children and adolescents who visited our pediatric outpatient clinic seeking height evaluation and final height prediction from October 1, 2010, to March 31, 2020. The investigation protocol was approved by the Institutional Review Board of Clinical Investigations.

Participants in this study received a physical examination by a pediatric endocrinologist to determine their general health and their Tanner stage of sexual development. The Tanner grading system is based on the pattern of development of pubic hair in all children, of breast development in girls, and of penile and testicular size in boys.[15,16] Premature thelarche was defined as isolated breast development before the age of 8 years.[17] Height and weight measurements were obtained for all children. Body mass index (BMI) was calculated as described in a pediatric textbook.[18] Candidates were excluded if they were diagnosed with any genetic or endocrine disease. Children with height and weight within the 15th to 85th percentiles for the mean age–adjusted normal values of Taiwanese children were selected for data analysis (Fig. 1).[19]

BA assessment was based on roentgenograms of the left hand and wrist using the GP method.[3] BA analysis was performed by a senior pediatric endocrinologist and reviewed by a senior pediatric radiologist. Radiographs from a total of 1463 children (809 for girls and 654 for boys) were analyzed twice. The mean value of two independent evaluations on a single film was taken as the BA value.

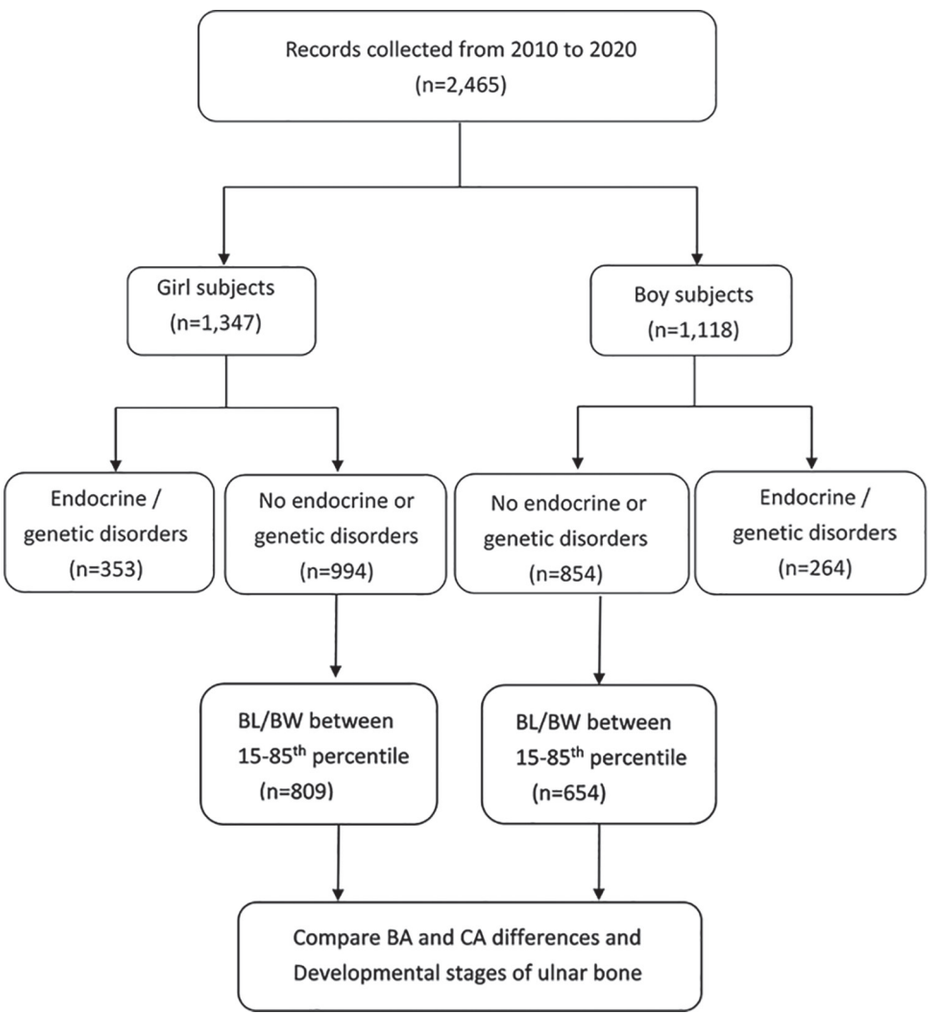

Fig. 1 Algorithm of the patient selection process. BA = bone age; CA = chronological age.

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2.2. Data analysis

The concordance between the readings of the two raters was evaluated by computing the intraobserver and interobserver correlation coefficients with a subgroup of 200 x-ray films.[16] The correlation coefficient for the intraobserver comparison was 0.993 and that for the interobserver comparison was 0.992.

A difference score was calculated for each radiograph by subtracting the CA from the mean BA provided by the two readings. A positive value indicated an advanced BA, whereas a negative value indicated a delayed BA. The difference scores were then analyzed according to sex. Moreover, they were substratified according to age groups. In each age group, a paired *t* test was used to compare the BA and CA to verify the null hypothesis.

The relative maturation process of the ulnar bone was evaluated using the TW3 staging system.[4] In the TW3 system, successive changes in the shape and density markings of each bone are divided into several discrete stages. The development of the ulnar bone is divided into eight stages. Stage A represents the absence of a visible calcified epiphysis. From B to H, each stage is defined and illustrated with drawings and radiographs. The ulnar bone maturation rate in the GP standard atlas is based on the same principle. For women, 25 GP standard atlases, for newborn to 16-year-old girls, were chosen for evaluation. Stage B of the ulnar bone is missing in these 25 atlases. The first sign of the appearance of ulnar epiphysis is seen in standard number 15, at age 6 years and 10 months, which is in stage C. The mean age of each stage was calculated according to the available age data. For boys, 29 GP standards were chosen for newborn to 18-year-old boys. Stage B of the ulnar bone is also missing in these 29 atlases. The first sign of the appearance of ulnar epiphysis is seen in standard number 15 at age 6 years. The mean age of each stage was calculated for stages A to H. To test the hypothesis that Taiwanese children exhibit no ulnar bone developmental delay, the mean BA for each stage of our participants was compared with the mean age for each stage of the GP standards.

2.3. Statistical analysis

SPSS, version 20 (SPSS Inc., Chicago, IL, USA), was used to analyze all data. Descriptive statistics, namely the means and SDs of CA, BA, and BA – CA, were evaluated. The difference between BA and CA was analyzed using the paired *t* test. The ulnar bone data comparing both boys and girls were calculated using the Student *t* test. Data are expressed as mean ± SD. Statistical significance was defined as $p < 0.05$.

3. RESULTS

The ages and anthropometric characteristics of the study groups are summarized in Table 1. By design, the average value for the height and weight was between the 15th and 85th percentiles for all ages. The mean BMI was within the 15th and 85th percentiles for most age groups of boys except the 17-year-old group. The mean BMI was close to the 85th percentile for most age groups of girls (from 6 to 16 years of age).

To study the differences in the maturation rate between our population and the reference population of GP standards, we subtracted the CA from the BA as determined using the GP method. In Table 1, the differences between the BA and CA are listed in the BA– CA column. A significant difference was observed between BA and CA both in boys and girls. For boys, the GP BA tended to underestimate CA from age 6 to 9 years. For girls, the GP BA tended to overestimate CA at almost all ages (7-15 years). Box plots of BAs in different age groups are displayed in Fig. 2A, B. The zero baseline represents no difference between the mean designated BA and the mean CA for that age group.

In Table 2, the distribution of the means and SDs of the estimated GP BAs at different maturation stages of ulnar bone are presented, and the means and SDs of the GP standard atlases at each developmental stage are also presented

Table 1

Anthropometrics characteristics, BAs, CAs, difference scores (BA – CA), and *p* values of the BA and CA comparison in different age groups

Sex	Age group, y	n	Weight, kg	Height, cm	BMI	BA, y	CA, y	BA – CA, y	*p*
M	5-5.9	27	18.8±1.7	111.8±3.4	15.0±0.8	5.1±0.8	5.6±0.2	–0.5±0.9	0.182
	6-6.9	41	20.4±3.0	115.9±3.2	15.1±1.6	5.5±0.7	6.5±0.3	–1.0±0.7	<0.001
	7-7.9	39	23.1±2.3	121.5±4.0	15.6±1.0	6.4±1.3	7.4±0.3	–1.1±1.1	0.001
	8-8.9	41	26.2±2.4	127.2±2.8	16.2±1.2	7.7±1.3	8.4±0.3	–0.7±1.5	0.034
	9-9.9	48	31.0±5.1	132.2±3.8	17.7±2.3	9.3±1.4	9.5±0.3	–0.1±1.4	0.650
	10-10.9	78	32.6±4.0	138.7±4.4	16.9±1.7	10.5±1.1	10.5±0.3	0.2±1.0	0.912
	11-11.9	125	35.8±5.9	143.7±4.5	17.3±2.4	11.5±1.2	11.4±0.3	0.0±1.2	0.902
	12-12.9	92	40.1±5.7	150.5±5.7	17.7±1.9	12.6±1.0	12.5±0.3	0.1±1.0	0.230
	13-13.9	70	45.3±5.6	158.0±5.9	18.1±1.8	13.6±0.8	13.5±0.3	0.1±0.8	0.195
	14-14.9	51	50.2±5.4	162.6±2.9	19.0±1.9	14.8±1.3	14.5±0.3	0.3±1.2	0.232
	15-15.9	27	53.5±5.5	168.1±3.0	19.0±2.0	16.2±1.6	15.6±0.3	0.6±1.6	0.211
	16-16.9	15	58.5±5.3	168.4±3.1	20.6±1.9	16.5±1.3	16.4±0.3	0.1±1.4	0.704
F	4-4.9	18	17.6±1.6	106.0±3.7	15.9±0.9	4.6±1.2	4. 5±0.3	0.1±1.2	0.805
	5-5.9	33	20.2±3.8	112.2±4.6	16.6±1.9	5.5±0.5	5.5±0.3	0.0±0.6	0.905
	6-6.9	52	22.6±4.7	119.7±3.0	17.1±3.4	6.7±0.4	6.5±0.2	0.2±0.5	0.273
	7-7.9	99	23.9±3.0	123.8±3.9	17.8±2.6	7.9±0.8	7.6±0.3	0.3±0.7	0.010
	8-8.9	136	26.5±4.1	129.6±3.5	18.2±3.7	9.0±0.8	8.6±0.3	0.5±0.8	<0.001
	9-9.9	151	29.3±5.6	134.9±4.9	19.0±4.1	10.0±1.1	9.5±0.3	0.4±1.1	<0.001
	10-10.9	126	32.7±6.2	140.4±4.9	20.3±4.6	11.2±0.9	10.5±0.3	0.7±0.9	<0.001
	11-11.9	87	37.7±6.5	146.7±4.1	20.6±4.2	12.2±0.9	11.5±0.3	0.7±0.8	<0.001
	12-12.9	49	41.2±6.1	152.1±3.9	21.6±5.4	13.3±0.9	12.4±0.3	0.8±0.8	<0.001
	13-13.9	38	45.1±7.0	153.8±3.4	22.3±5.3	14.4±0.8	13.4±0.3	1.0±0.7	<0.001
	14-14.9	20	47.0±5.0	154.3±2.0	22.3±4.7	15.1±0.4	14.4±0.3	0.8±0.3	<0.001

BA = bone age; BMI = body mass index; CA = chronological age; F = female; M = male.

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for comparison. Graphs of the mean estimated GP BAs of our participants and the mean GP standards are displayed in Fig. 3A, B. Compared with the GP standard atlas, ulnar bone development tended to be delayed during the early years of life for men (up to age 9). No difference between the estimated BA and GP standard atlas was observed for women. The maturation rate of the female ulnar bone was significantly faster than that of boys.

4. DISCUSSION

4.1. Major findings

The present study was conducted to determine whether the GP atlas standards are still adequate for assessing BA in Taiwanese children born after 2000. Our results indicated that significant differences exist between Taiwanese children and the reference population of GP standards. The maturation rate of the ulnar bone in young boys also differed from the standards.

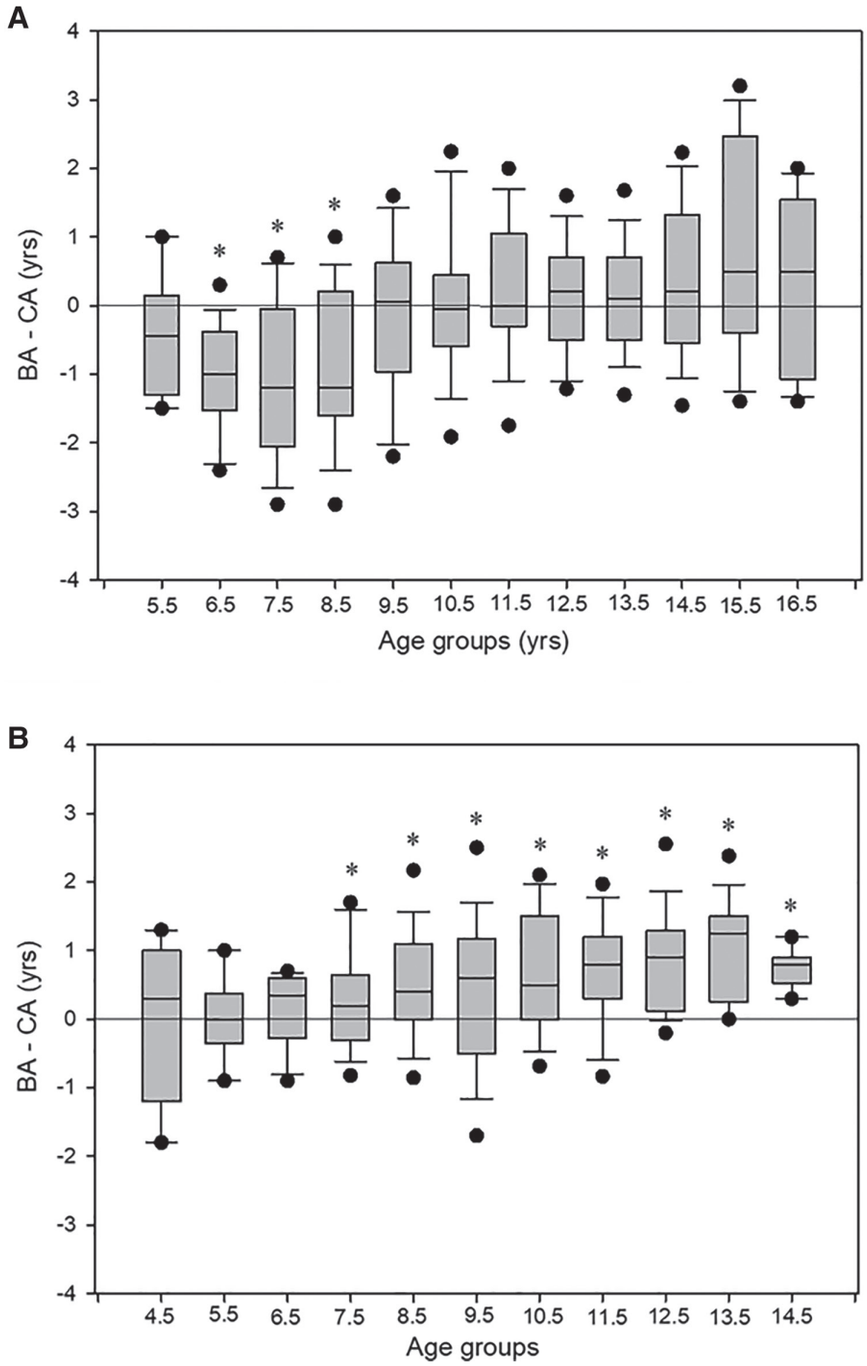

Fig. 2 Box plots of the distribution of difference scores at each age group: (A) boys and (B) girls. At each age group, the range of difference scores from the 5th to 95th percentiles are shown. BA = bone age; CA = chronological age. *Bone age and chronological age comparison; $p < 0.05$.

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Table 2

Descriptive statistics of the estimated BA and standard BA of the GP atlas at different ulnar bone maturation stages

	M: BA, y		F: BA, y			M: GP standard, y		F: GP standard, y	
TW3 stage	n	Mean ± SD	n	Mean ± SD	*p*	n	Mean ± SD	n	Mean ± SD
A	96	5.0 ± 1.6	62	4.9 ± 1.6	<0.001	14	2.2 ± 1.6	14	2.2 ± 1.8
B	31	7.4 ± 1.3	10	6.7 ± 0.8	0.046	0	…	0	…
C	13	7.9 ± 1.2	30	7.3 ± 0.8	0.020	1	6.0 ± 0.0	1	6.9 ± 0.0
D	39	8.8 ± 1.0	85	8.0 ± 0.9	<0.001	2	7.5 ± 0.7	1	7.9 ± 0.0
E	87	10.3 ± 1.1	90	8.7 ± 1.0	<0.001	2	9.5 ± 0.7	1	8.9 ± 0.0
F	159	11.8 ± 1.2	250	10.6 ± 1.2	<0.001	3	11.7 ± 0.8	2	10.5 ± 0.7
G	181	13.7 ± 0.9	223	12.4 ± 1.1	<0.001	2	13.5 ± 0.7	2	12.8 ± 0.8
H	48	16.1 ± 1.1	59	14.7 ± 0.9	<0.001	5	16.3 ± 1.2	4	15.0 ± 1.0

The *p* values of the paired *t* test between the estimated BAs of boys and girls are displayed.
BA = bone age; F = female; GP = Greulich and Pyle; M = male; TW3 = Tanner–Whitehouse 3.

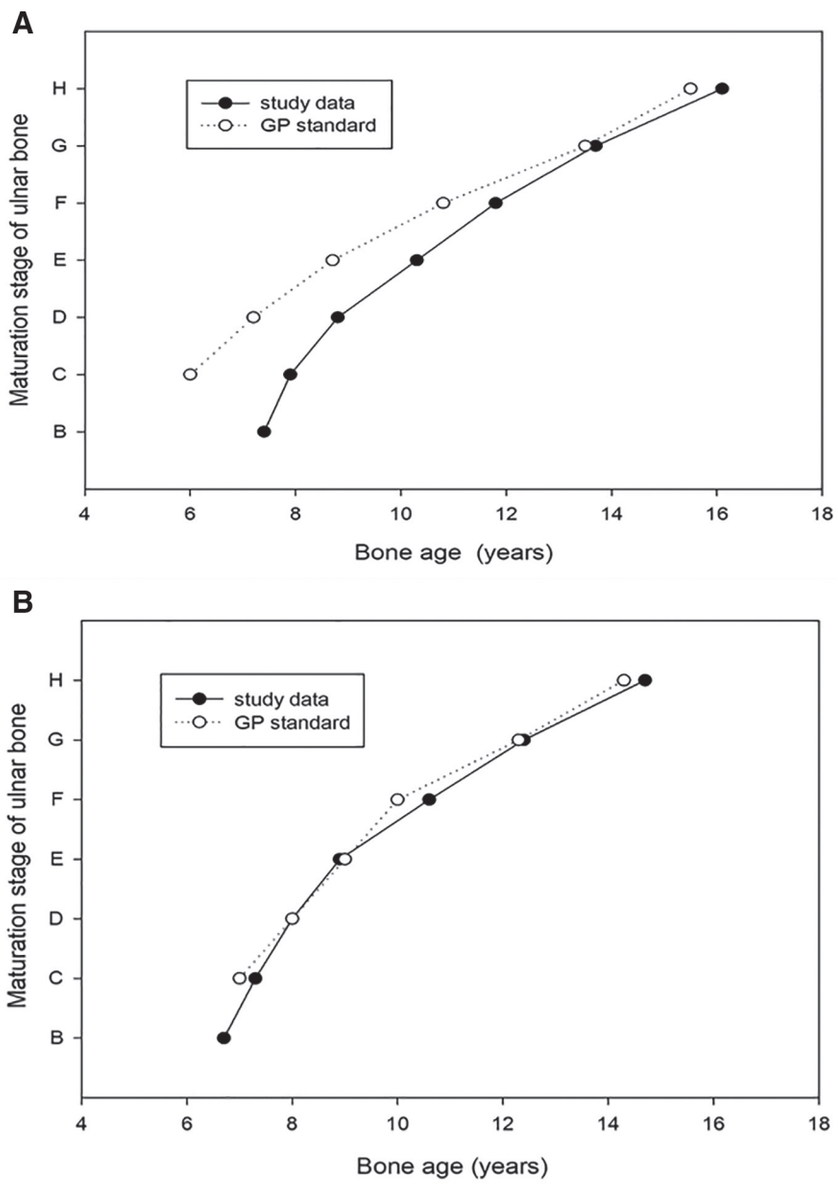

Fig. 3 Comparison between the mean estimated bone age and mean standard bone age of the Greulich and Pyle (GP) atlas at different ulnar bone maturation stages: (A) boys and (B) girls.

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In boys, the maturation pattern exhibited in our study was similar to previous reports of Taiwanese, Chinese, and other Asian populations, namely delayed in early childhood and advanced in adolescence.[10,12,20,21] In girls, the maturation occurred considerably earlier than in previous reports on Taiwanese and Chinese children, namely advanced by approximately 0.5 to 1 year from 7 to 15 years of age.[12,20,21] A study by Himes suggested that skeletal maturation increases by approximately 0.22 to 0.66 years per decade.[22] In Chow et al,[16] the decline rate of menarche timing was approximately 0.43 years per decade over the past 30 years. Our current finding about the skeletal maturation rate is comparable to the finding about menarche timing. Because bone maturation spans the entire growth period, it can be used in both sexes and may be a more accurate indicator of maturation rate.

To overcome ethnic and secular differences in skeletal maturation, standards have been developed for different populations, and the development and use of ethnicity-specific standards have been recommended.[23–27] In China, two Chinese BA reference standards were established to compare the maturation rates between populations.[28,29] One is the CHN method[28] and the other is the China-05 method.[29] Both methods were established based on the data of healthy children from five different cities in mainland China. In both cases, a scale was developed to convert the skeletal maturity score to skeletal age for Chinese children based on the TW3 method, and standard atlases were established for clinicians. When we compared the rate of ulnar bone development with these Chinese atlases, we found that our findings in Taiwanese boys matched the Chinese standards. For example, when the CA is 6 years, the standard GP atlas of boys (standard 15) ulnar bone maturation rate is in stage C, whereas in the present study and both Chinese atlases, the maturation rate of boys remains in stage A. This finding indicates that an ethnic discrepancy occurs not only in the overall rate of skeletal maturation but also in the individual bones of the hand and wrist.

4.2. Strengths and limitations of this study

The accuracy of BA determination is highly subjective and depends on the experience of the clinician. In one study, the reliability of the BA estimation was higher in experienced clinicians compared with inexperienced clinicians.[30] In this study, a single senior pediatric endocrinologist who regularly performed this technique evaluated the BA for all participants. Each x-ray film was assessed twice, and the mean value was taken as the BA value. On reevaluation by an independent pediatric radiologist of a subgroup of radiographs that contained 100 films for girls and 100 films for boys, a high interpersonal correlation was observed. We presumed that this review with a subset analysis for interrater reliability was sufficient and have confidence that the accuracy is high.

This study has several limitations. First, participants were selected from a pediatric endocrine clinic. Selection bias might have resulted from the purpose of the patients who came for medical consultation. However, due to the low birth rate in Taiwan,[31] many parents are concerned about the growth and development of their children even in the absence of worrisome symptoms. Most of the children who came to take hand and wrist radiographs were seeking their final height prediction. We selected children without genetic or endocrine disorders (including premature thelarche) and those with their age-adjusted height and weight within the 15th to 85th percentiles of the national standard growth chart. Therefore, the influence of this bias should be minimized. Second, the case number of boys and girls in age groups at both ends of age was limited. With an increase in the number of participants the absolute differences between BA and CA may have likely varied. However, we believe that the overall trend would remain the same. Third, the BMI for girls is generally high. Overweight is a well-known factor correlated with advanced BA.[32] The prevalence of obesity in Taiwan and China has increased rapidly in recent years.[33,34] Whether the high prevalence of overweight in girls observed in our study population is a general phenomenon in the Taipei population remains unknown. It is possible that parents whose daughters were overweight were most likely to take them to the clinic for final height predictions. Other studies have shown environmental factors such as phthalates and soy milk affect bone maturation[35,36]; therefore, we need more research to explain this advanced BA phenomenon.

4.3. Clinical implications

The GP method is simple and fast, requiring roughly 1.4 minutes for the evaluation;[37,38] this is why it is preferred by 76% of pediatric endocrinologists and radiologists.[37] In Taiwan, our impression is that more than 90% of pediatric endocrinologists still use the GP method. In the present study, we determined that GP standards are imprecise for Northern Taiwanese children born after the year 2000. This result represents a cautionary note for patients planning medical or surgical treatment for abnormal bone growth. The development of a hand atlas for different ethnic populations would enhance our ability to determine the skeletal maturation of subjects with greater accuracy, reliability, and consistency.

Other studies have expressed the opinion that the GP atlas is still very useful.[39,40] The World Health Organization working group developed its international growth charts based on the rationale that children grow similarly across major regions of the world when their basic needs are met. It recommended an approach that describes how children should grow when they are healthy and well provided for (the standard) rather than describing how children grow in their current environment (the reference).[41] Therefore, Hochberg suggested that all physicians use a unified international standard of bone maturity to compare the health, nutrition, and quality of life of all children, regardless of their race, nationality, or ethnicity.[40]

To overcome ethnic and racial differences, standards have been developed for the Chinese population in China.[21] Chinese children of the same age from different cities exhibited a fairly large gap in maturity. The authors surmised that this was because the cities were not only far apart but also varied in socioeconomic status. Shanghai was the most advanced in BA for children and Dalian the most delayed. As a result, the authors faced the same problem of whether to establish a city-specific reference curve. Ultimately, they decided not to because it would be impractical and result in confusion for children who move from one city to another. Instead, they pooled the data from all children to establish a national standard.

Conducting a large-scale prospective study of normal healthy Taiwanese children to establish a BA population reference in Taiwan poses difficulties due to radiograph exposure. For current clinical practice, although revising the method for assessing skeletal maturation is necessary, we believe that the GP method is still a sound choice for daily clinical work because of its quick and ease of use. Further studies are needed to investigate whether the Chinese skeletal standards are applicable to the Taiwanese population, both in terms of the overall skeletal maturation process and the individual bone maturation rate.

In conclusion, our study demonstrated that the GP method is imprecise and should be used with caution in the Taiwanese population. Boys between the CA of 6 to 9 years are most likely to demonstrate a 0.5- to 1-year delay in BA. Girls between the CA of 7 to 15 years tend to demonstrate a 0.5- to 1-year advance in BA. In young boys, the ulnar bone may be omitted during the GP atlas comparison. Until a new ethnicity-specific standard is

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created, clinicians in Taiwan should be aware of the limitations of the GP method presented in this study.

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