REVIEW

Timing of Pubertal Milestones in Low- and Middle-Income Countries: A Systematic Review and Meta-Analysis

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ABSTRACT

Despite increasing global attention to adolescent health in low- and middle-income countries (LMICs), limited literature exists on the timing of pubertal development in these settings. This study aimed to determine the age at menarche (AAM) and age of puberty onset [female Tanner Stage Breast 2 (B2) and male Tanner Stage Genital 2 (G2)] among healthy adolescents living in LMICs. It also aimed to explore the impact of nutritional status on pubertal timing in this population. MEDLINE, Embase, Cochrane CENTRAL, Web of Science, Scopus, and grey literature databases were searched. Observational studies and control arms of randomized controlled trials (RCTs) with healthy participants from LMICs born in or after 1998 were included. Pooled estimates with 95% CIs were calculated by random-effects meta-analyses using the DerSimonian and Laird inverse variance method for each pubertal milestone and by BMI category subgroups. Twenty-seven studies were included in the meta-analysis, representing 90,188 adolescents (78.3% female). Pooled mean estimates for AAM for normal, thin, and overweight BMI groupings were 12.3 y (95% CI: 12.1, 12.5), 12.4 y (95% CI: 12.2, 12.6), and 12.1 y (95% CI: 11.7, 12.5), respectively. For Tanner Stage B2, pooled mean age estimates for normal, thin, and overweight BMI groupings were 10.4 y (95% CI: 9.2, 11.6), 10.2 y (95% CI: 9.3, 11.4), and 8.4 y (95% CI: 6.8, 10.0), respectively. Finally, for Tanner Stage G2, pooled mean estimates for normal, thin, and overweight BMI groupings were 11.0 y (95% CI: 10.3, 11.7), 11.3 y (95% CI: 9.8, 12.9), and 10.3 y (95% CI: 10.0, 10.6), respectively. Data on the timing of pubertal milestones has traditionally come from high-income settings. In this systematic review of contemporary data from adolescents in LMICs, AAM, as well as age at pubertal onset, were similar to those reported from high-income settings. *Adv Nutr* 2020;11:951–959.

Keywords: timing of puberty, low- and middle-income countries, BMI, systematic review, meta-analysis

Introduction

Adolescence is a critical developmental stage that encompasses profound physical, psychosocial, and cognitive changes (1). The most salient experiences for adolescents are the timing of attainment of pubertal milestones and the tempo of puberty (the amount of time it takes from puberty onset to full reproductive function) (2). Pubertal development in biological males and females typically occurs in the same pattern, although there is variability with regard to the age of onset, sequence, and tempo (2). Clinically, these patterns are captured using Tanner Staging, also referred to as sexual maturity rating (SMR). This method is the current global gold-standard for assessing a child's progression through puberty, whether typical or pathological.

The vast majority of literature reporting data on pubertal development is drawn from populations living in high-income countries (HICs), with relatively fewer studies publishing information from low- and middle-income countries (LMICs). Among adolescent males living in HICs, pubertal onset is usually between the ages of 9–14 y and is heralded by an increase in testicular volume (3). This typically occurs ~6 mo prior to penile growth and pubic hair

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Abbreviations used: AAM, age at menarche; B2, female Tanner Stage Breast 2; G2, male Tanner Stage Genital 2; HICs, high-income countries; LMICs, low- and middle-income countries; RCT, randomized controlled trial.

growth, events then followed by spermarche (signified by the appearance of sperm in the urine and nocturnal sperm emissions) and attainment of peak linear growth velocity (3). Females living in high-income settings typically undergo pubertal development between the ages of 8 and 13 y (3). These events commonly progress as follows: breast budding (thelarche) and development, followed by pubic and axillary hair development, then the linear growth spurt, and finally menarche, or the onset of menses, which usually occurs 2–2.5 y after the first pubertal changes (3). Pubertal timing is both influenced by, and may influence, a number of other factors related to an individual's health status. Determining population norms for this key developmental phenomenon provides a valuable tool for the appraisal of the health status of adolescents, both at the individual and population level.

Over the last 20 y, several large studies of populations in HICs have reported pubertal onset in both males and females to be earlier than historical norms (3). The timing of pubertal events has also been acknowledged to be more nuanced than was previously reported; for example, there is an emerging awareness of ethnoracial disparities in pubertal timing (3–6) and an expanding literature on the importance of nutritional status for pubertal timing. BMI has been demonstrated to be the strongest predictor of earlier age at initial breast development among females (7). Although there is a large body of literature on pubertal development and nutritional status of female adolescents in HICs, there is a dearth of literature capturing similar data among adolescents living in LMICs, and the relation between BMI and pubertal onset in male populations still remains unclear (3). Most recently, Deardorff and colleagues stressed the importance of puberty research in understudied populations including diverse ethnic groups, boys, and sexual minority youth (8).

The primary objective of this systematic review and meta-analysis was to identify the timing (age of attainment) of pubertal milestones among adolescents living in LMICs. The secondary objective of the review was to explore the relation between pubertal timing and nutritional status in this population. The results of this study will contribute to a growing body of literature on pubertal development in adolescence and will serve as a point of reference for further scientific investigation and clinical application.

Methods

We identified studies that described age at menarche (AAM) and/or Tanner Stages 2–5 among adolescents living in LMICs, as classified by the World Bank. Publications were obtained through a comprehensive search of MEDLINE, Embase, The Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, and Scopus. Additionally, a grey literature search was conducted to identify nonpeer reviewed reports on pubertal growth and development in LMICs. An initial search of the publications was undertaken followed by a textual analysis of words contained in the titles and abstracts, and of the index terms used to describe the articles. Identified keywords were used to finalize search terms, and a second search was undertaken across all included databases until 18 March, 2018 (**Supplemental Table 1**). Finally, relevant publications were amalgamated in Endnote citation manager and then imported to Covidence online systematic review software (9) for further review. The protocol is registered as PROSPERO CRD42018097102.

Study selection and data collection

Using Covidence, 4 reviewers (JM, KS, SC, AV) screened titles, abstracts, and full texts for eligibility in duplicate according to the Prisma flow chart (**Figure 1**). Data extraction was then performed in duplicate by 3 reviewers (JM, KS, MW). The extraction sheets were pilot tested with a small sample of articles ($n = 5$), and modifications were made to optimize data captured with a standardized approach to extraction. The data extraction forms were then completed and manually compared by 3 reviewers for discrepancies. Conflicts at all stages were vetted by a third reviewer or as a team.

Data extracted included: author, publication year, study design, sample size, type of recruitment (prospective or retrospective), study population characteristics, BMI, puberty assessment method, age determination method, and age at each Tanner Stage (2–5) for breast, genitals, male pubic hair, and female pubic hair including SD or CIs. In studies not reporting the BMI categories, mean age, weight, and height were used to determine BMI-for-age z-score categories according to the WHO Growth Reference for Children and Adolescents (10). For AAM and Tanner Stage, the method of assessment was distilled into categories of "questionnaire," "self-assessment using illustrative pictures," "inspection and Orchidometer," "inspection and palpation," or "not reported." The person reported to assess pubertal milestones was categorized as "physician," "researcher," "self-assessment," or "not stated." For details regarding age determination, study information was sorted into categories of "not reported," "date of birth," "school record," and "related to historical events."

Inclusion and exclusion criteria

This review included studies describing healthy (i.e. free from known diseases or conditions that affect pubertal timing) adolescent girls and boys living in LMICs who were born in or after 1998. The cut-off date of 1998 was chosen for 2 main reasons; *1*) to capture contemporary data and *2*) to allow for study populations to potentially benefit from any impact of the Millennium Development Goals during childhood. This review considered observational studies and the control arm of randomized controlled trials (RCTs). Studies were excluded according to the following criteria: experimental or interventional methodology and those not written in English due to limited capacity within the study for a translator. For studies that did not report required data (i.e. stratification of BMI categories, SDs or CIs for mean age), the studies' corresponding authors were contacted twice to request the missing data. This correspondence did not result in any additional information.

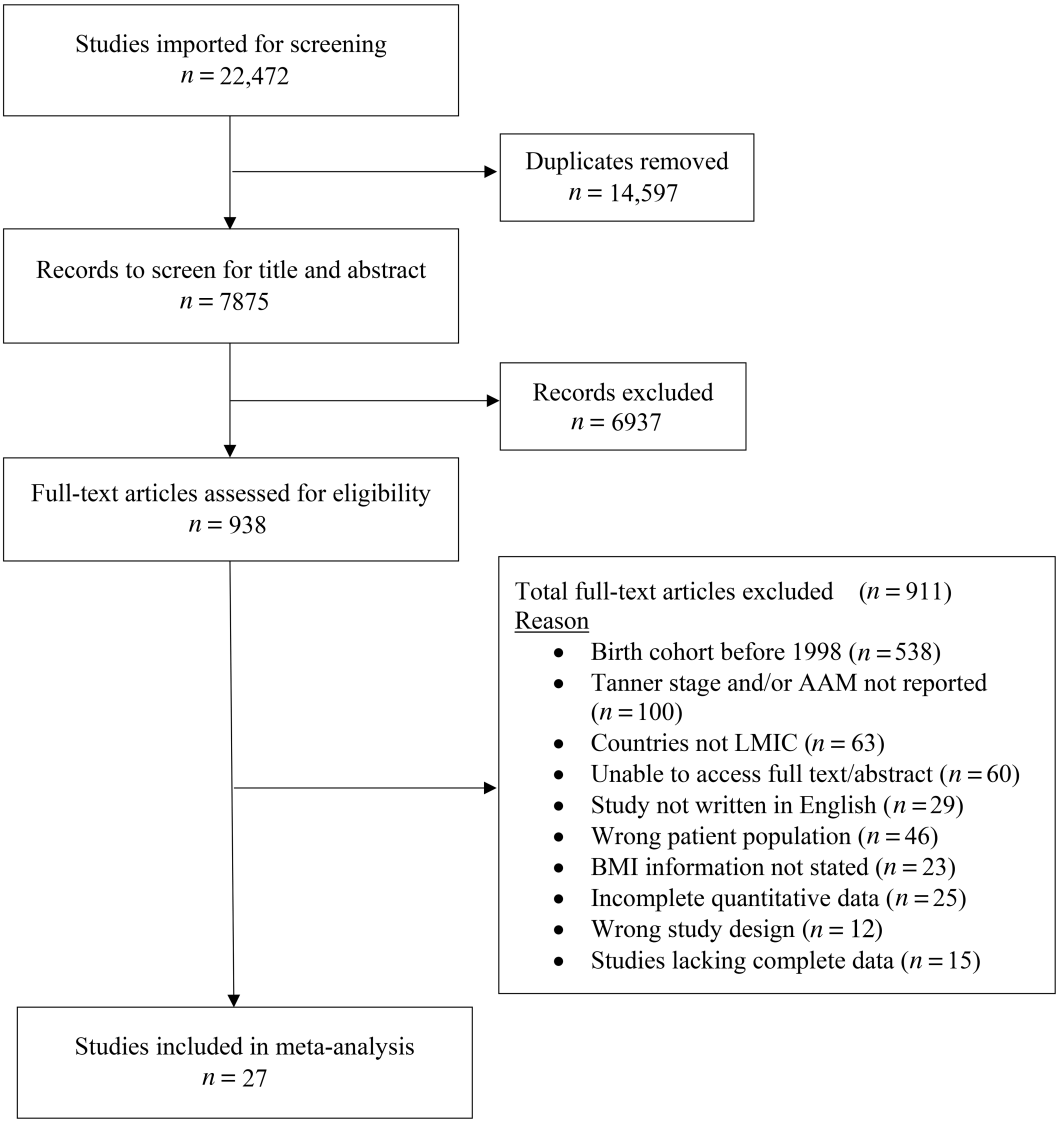

FIGURE 1 PRISMA study selection diagram. The PRISMA flow diagram illustrates the flow of the number of articles identified, included, and excluded through the different phases of the systematic review.

Assessment of methodological quality

All included selected studies were assessed by 2 independent reviewers to ensure methodological validity, using the Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross-Sectional Studies (11). This tool was adapted and modified to fit the needs of the reviewers. Discrepancies were discussed by the 2 reviewers and/or a third reviewer. No studies were excluded due to methodological quality (**Supplemental Table 2**).

Statistical analysis

Pooled age estimates with 95% CI were calculated by *meta-analyses* using DerSimonian and Laird inverse variance methods for each pubertal Tanner Stage and AAM. The analysis was stratified by BMI status to compare the pooled age estimates of studies reporting overweight/obesity and thinness/severe thinness to those of normal BMI. To increase the robustness of the data, we combined BMI categories for forest plots and the meta-analysis (severe thinness and thinness; overweight and obesity) for comparison with the normal BMI data. As several studies reported AAM, we were able to stratify the studies by WHO region to test for regional differences for studies reporting normal BMI. We determined pooled age estimates to be significantly different if the 95% CIs did not overlap. I^2 was also calculated to evaluate the percentage of variance in the meta-analysis that was attributable to study heterogeneity amongst normal, thin, and overweight BMI subgroups. A random-effects model was used to accommodate any inherent methodological heterogeneity in all calculations. All analyses were performed using RevMan version 5.3 (The Cochrane Collaboration) (12).

TABLE 1 Characteristics of studies included in the meta-analysis

Author, publication year	Country	Study period	WHO region	Sample size	Puberty milestones		Puberty assessment method
					Female	Male	
Ahmed et al. 2016 (13)	Pakistan	2014	Eastern Mediterranean Region	275	AAM	—	Self-assessed
Aribo et al. 2015 (14)	Nigeria	2012	African Region	1200	AAM	—	Self-assessed
Barros et al. 2018 (15)	Brazil	2013–14	Region of the Americas	37,390	AAM	—	Self-assessed
Castilho et al. 2015 (16)	Brazil	2012	Region of the Americas	303	AAM	—	Self-assessed
Chen et al. 2017 (17)	China	2014	Western Pacific Region	15,937	Breast, pubic hair	Genitals, pubic hair	Physical exam
Choudhary et al. 2015 (18)	India	2014	South-East Asia Region	240	AAM	—	Self-assessed
Feibelmann et al. 2015 (19)	Brazil	2012–13	Region of the Americas	536	Breast	—	Self-assessed
Hozoori et al. 2017 (20)	Iran	2016–17	Eastern Mediterranean Region	370	AAM	—	Self-assessed
Iloh et al. 2017 (21)	Nigeria	2014–15	African Region	231	AAM, breast, pubic hair	—	Self-reported; physical exam
Jmal et al. 2010 (22)	Tunisia	NR	Eastern Mediterranean Region	247	Breast	Genitals	Physical exam
Khadgawat et al. 2016 (23)	India	2013	South-East Asia Region	1539	AAM, breast	—	Self-assessed; physical exam
Kheirollahi et al. 2017 (24)	Iran	NR	Eastern Mediterranean Region	152	AAM	—	Self-assessed
Liu et al. 2017 (25)	China	2015	Western Pacific Region	5800	AAM	—	Self-assessed
Maher et al. 2013 (26)	Egypt	NR	Eastern Mediterranean Region	80	Pubic hair	Genitals	NR
Mascarenhas et al. 2015 (27)	Brazil	2010–12	Region of the Americas	328	—	Pubic hair	Self-assessed
Medeiros et al. 2014 (28)	Brazil	NR	Region of the Americas	148	—	Pubic hair	Physical exam
Mosallanejad et al., 2017 (29)	Iran	2013	Eastern Mediterranean Region	70	—	Genitals	Physical exam
Noipayak et al. 2016 (30)	Thailand	2013	South-East Asia Region	537	AAM	—	Self-assessed
Odongkara et al. 2014 (31)	Uganda	NR	African Region	271	AAM	—	Self-assessed
Rabiepoor et al. 2017 (32)	Iran	NR	Eastern Mediterranean Region	350	AAM	—	Self-assessed
Rahmawati et al. 2017 (33)	Indonesia	2015	South-East Asia Region	401	AAM	—	Self-assessed
Rebacz-Maron et al. 2015 (34)	Tanzania	NR	African Region	71	AAM	—	Self-assessed
Saffari et al. 2012 (35)	Iran	2009–10	Eastern Mediterranean Region	2638	Breast, pubic hair	—	Physical exam
Surana et al. 2017 (36)	India	2013	South-East Asia Region	515	—	Pubic hair	Physical exam
Ugege et al. 2017 (37)	Nigeria	2014–15	African Region	1008	AAM, breast	—	Self-assessed; physical exam
Xing et al. 2017 (38)	China	2015	Western Pacific Region	1505	AAM	—	Self-assessed
Yesil et al. 2013 (39)	Turkey	NR	European Region	1617	Breast	Genitals	Self-assessed

AAM, age at menarche; NR, not reported.

TABLE 2 Summary of included studies in the meta-analysis

Outcome categories	Number of studies	
	n	%
World Bank Income Groups		
Low-income	2	7
Lower-middle income	10	37
Upper-middle income	15	56
World Bank Regions		
African Region	5	19
Eastern Mediterranean Region	8	29
European Region	1	4
Region of the Americas	5	19
South-East Asia Region	5	19
Western Pacific Region	3	10
Size of the population assessed		
Urban	19	70
Rural	1	4
Mixed	1	4
Urban and rural subgroups in same paper	3	11
Unknown	3	11
Genders included in papers		
Female only	19	70
Male only	4	15
Female and male	4	15
Method of age determination		
Not stated	24	89
Known date of birth	2	7
School records	1	4
Pubertal milestones assessed		
AAM	14	52
Tanner Stages	10	37
AAM and Tanner Stages	3	11

AAM, age at menarche.

Results

A total of 27 studies were included in this meta-analysis representing 90,188 adolescents (78.3% female) (**Table 1**). Twenty-five studies were cross-sectional, 1 was a prospective cohort, and 1 was a random cluster sampling study. Over half of the included studies were from upper-middle-income countries, 37% were from lower-middle-income countries, and 7% were from low-income countries (**Table 2**). Six World Bank Regions were represented including the Eastern Mediterranean Region (29%), Region of the Americas (19%), South-East Asia Region (19%), African Region (19%), Western Pacific Region (10%), and the European Region (4%). The majority of the studies were conducted in urban settings (70%) and 3 papers (11%) stratified their participants into rural and urban subgroups (Table 2). Three studies from China included 39,179 participants and 5 studies from Brazil included 38,705 participants representing 86% of all participants in this review (**Supplemental Table 3**).

Nineteen studies collected pubertal milestone timing data from females only, 4 studies from males only, and 4 from both male and female cohorts. Specific pubertal milestones assessed in included studies are reported in Table 2. As exact birth dates are not known in many LMICs because many births are not registered, the method for participant age determination was examined in each included study. The majority of studies (89%) did not identify how the participant's age was known. However, 2 papers reported known dates of birth as the basis of age, and 1 paper used school records to determine each participant's age.

Pooled estimate for the attainment of mean age of AAM was 12.3 y (95% CI: 12.13, 12.47). As expected, for breast, genital, and pubic hair Tanner Stages, the timing for each subsequent stage had a higher pooled age estimate (**Figure 2**). Seventeen of the 27 papers reported BMI values for the participants. The method for determining BMI *z*-scores by citation and the number of studies reporting BMI subgroups is outlined in **Supplemental Tables 4** and **5**. The timing of onset of adrenarche (pubic hair Tanner Stage 2) or thelarche (Breast 2 or Genital 2) seemed to be delayed by thinness or severe thinness, although these differences were not significant (Figure 2). Thelarche in overweight/obesity in girls occurred at a younger mean age but this was not significant. Conversely, overweight/obesity in boys seemed to delay adrenarche, however, this was also not significant. Forest plots for mean age values and pooled age estimates of pubertal milestones, stratified by BMI categories, of the included studies can be found in **Supplemental Figures 1–16**.

Regionally, the African Region had a significantly later pooled AAM estimated age of 13.82 y (95% CI: 13.08, 14.55) when compared with the Western Pacific Region at 11.83 y (95% CI: 11.24, 12.43), Eastern Mediterranean Region at 12.21 y (95% CI: 11.67, 12.53), and South-East Asia Region at 12.34 y (95% CI: 12.0, 12.67) (**Supplemental Figure 17**). Regional pooled age estimates for other pubertal milestones were not calculated due to a paucity of data.

Pubertal milestone assessment methodology

Pubertal milestones were reported based on different assessment methodology (**Table 3**). AAM was always self-assessed by the participants ($n = 17$). Tanner Stages (breast, genitals, pubic hair) were either via self-assessment ($n = 3$) or assessed by a clinician ($n = 9$). Clinicians assessed Tanner Stages by inspection ($n = 1$), inspection and palpation ($n = 2$), physical exam ($n = 3$), inspection and Orchidometer ($n = 1$), inspection, palpation, and Orchidometer ($n = 1$), and method not stated ($n = 1$).

Discussion

This is the first meta-analysis of the age of pubertal milestones among girls and boys living in LMICs. In our study, the pooled age estimate for mean AAM was 12.3 y (95% CI: 12.13, 12.47). Regional differences were also observed among normal BMI girls for AAM, with the African Region having a significantly later AAM. Puberty onset is defined as Tanner Stage B2 and G2 for girls and boys, respectively. The pooled estimates for the attainment of mean Tanner Stage B2 was age 10.4 y (95% CI: 9.23, 11.58). The pooled estimates for the attainment of mean Tanner Stage G2 was age 11.01 y (95% CI: 10.34, 11.96). An additional key feature of puberty is the pubertal growth spurt. For this review, data on height was extracted from included studies with the intention of stratifying the pooled age by height. However, only 1 of the

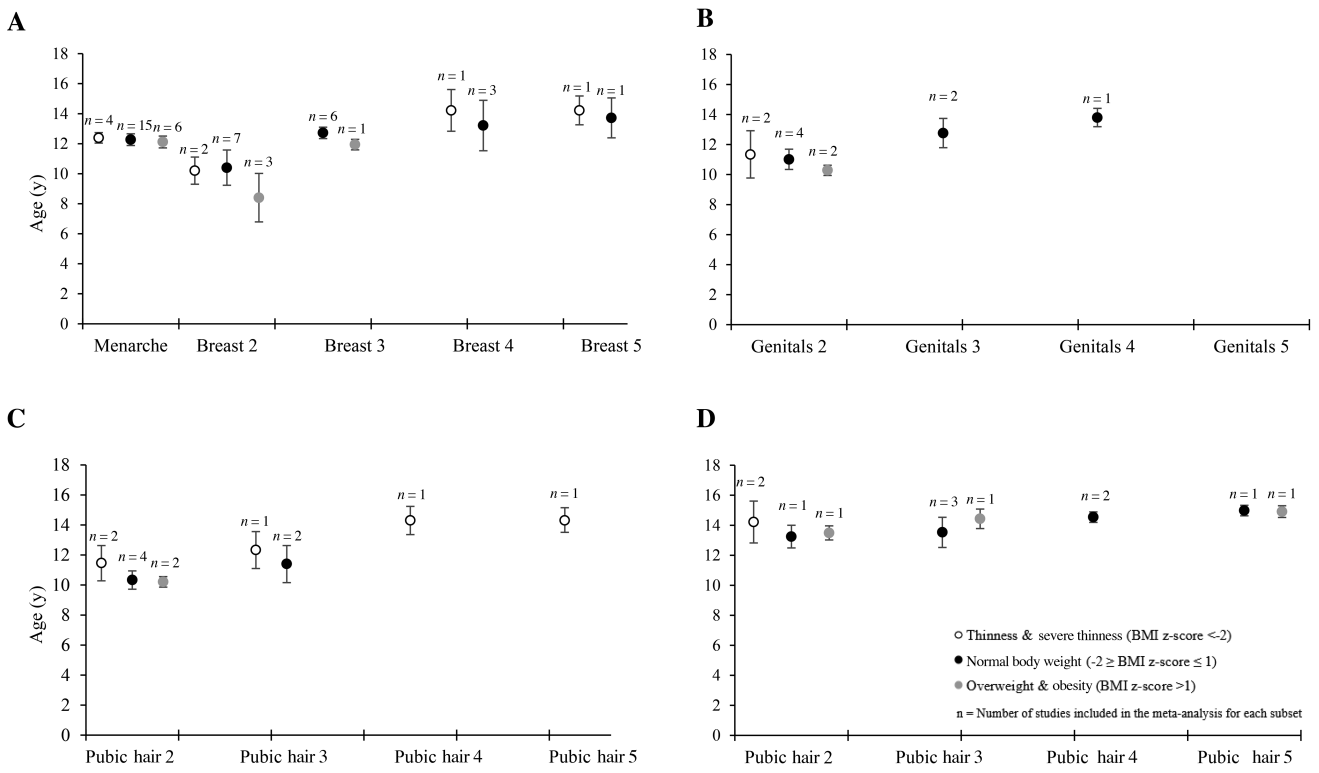

FIGURE 2 Pooled age estimates for pubertal milestones by sex. Values on the *x*-axis represent Tanner Stage, values on the *y*-axis represent age in years. Error bars represent 95% CIs. Figure 2A represents menarche and breast development; Figure 2B represents male genital development; Figure 2C represents female pubic hair development; and Figure 2D represents male pubic hair development.

included studies contained height data, thus no meaningful analysis of the timing of this event could be conducted.

Pooled age estimates in this current review align with findings from HIC settings; however, it should be noted that for girls living in HICs, the most recent review available was published >15 y ago (40). Trends in age at menarche over the past century have been well-studied, with the most recent published analysis of global secular trends demonstrating an earlier age at menarche (41). Whether this secular trend towards earlier pubertal onset has continued since the publication of that article remains unknown. Additionally, AAM and puberty onset in girls is known to vary amongst races and countries (40), which is supported by the significantly later AAM we observed in the African Region. More recently, a review on the timing of puberty in boys noted a lack of data and was therefore unable to determine any secular trends (42). In contrast to these previous reviews, the majority of articles included in the current study were published after 2010.

Contemporaneous to studies documenting a secular trend towards earlier AAM is an emerging literature documenting a trend towards increased rates of obesity in adolescence. This is of relevance given the known relation between obesity and pubertal timing (43). Obesity has been shown to promote earlier onset of Tanner Stage B2 in females but has not been shown to affect AAM (44). Consistent with data from HICs, the findings of this meta-analysis suggest a potential relation between overweight/obesity and earlier onset of female puberty, though this relation was not statistically significant. The effect of obesity on male pubertal timing has been largely underreported in the literature, which was consistent with the findings of this meta-analysis (45).

Strengths and limitations

This meta-analysis highlights AAM and pubertal milestone timing across 27 studies in 13 countries, representing a broad range of WHO regions and World Bank income groups. The pooled age estimates represent over 90,000 individuals. This study included only data drawn from individuals living within a narrow time band (born in or after 1998). This eliminated any potential influence of secular trends in pubertal timings, as well as the impact of varying socioeconomic and political landscapes over time within given countries.

Limitations in this meta-analysis are consistent with the body of literature in this sphere, including a larger focus on female pubertal timing than male, and within females, a predominant focus on AAM. With respect to challenges in assessing pubertal timing in LMICs, there is greater potential for the unreliable determination of age compared with HICs as, in many settings, individuals may not have formal documentation to validate reported age.

TABLE 3 Pubertal stage assessment methodology

Person who performed the pubertal stage assessment	Assessment methodology	Number of studies[1]
Self-assessed		
	Menarche	17
	Tool with Tanner Stage: image alone	2
	Tool with Tanner Stage: image + description	1
Clinician/researcher		
	Physician specialty	
	Pediatric specialist	3
	General practitioner	1
	Not reported	1
	Researcher[2]	2
	Trained professional[2]	2
Not reported	Tanner Stage: method not reported	1

[1] Three articles assessed both age at menarche and Tanner Stages, therefore, the number of studies total $n = 30$, which is greater than the total number of papers included in this review ($n = 27$).
[2] As reported in the study article.

We have endeavored to provide as much detail as is available from the source literature on the methods of pubertal stage assessment in this meta-analysis. The variability in pubertal assessment methodologies across studies, however, may have introduced an error in the age estimates. Generally, the gold standard for the staging of secondary sexual characteristics is a physical exam by a trained healthcare professional. The practicality of a physical exam in diverse LMIC settings may be limited as it can be resource-intensive, invasive, and/or culturally inappropriate. An alternative to the gold standard is an assessment of secondary sexual characteristics by self-report, which can be based on illustrative pictures, line drawings, photographs, or descriptions. In the context of the literature on puberty, the accuracy of self-assessment has not been systematically reviewed.

With respect to reporting AAM, self-report can be considered the gold standard. Of note, there was a high reliance on self-report, specifically AAM, in the source studies for this meta-analysis. Literature to date suggests that self-reported AAM is a reliable marker of pubertal stage (46).

A limitation in study design is also evident in the meta-analysis. Most studies were cross-sectional, not longitudinal, in nature, so the precise timing of pubertal milestones could not be captured. Finally, we were not able to include several studies in the meta-analysis because the reported data was incomplete and we did not get a response from letters to the authors.

Recommendations for future research

Due to the paucity of data on boys and within rural settings in this systematic review, we re-emphasize previous calls to action for puberty research in boys and among those living in rural settings, as both groups continue to be chronically understudied (8). Future meta-analyses would benefit from studies providing greater detail in reporting of pubertal milestones globally, such as consistency in approach to pubertal assessment and age determination. Authors may also consider reporting results stratified by BMI, which was not consistently available. Documented adolescent nutritional status in relation to pubertal timing would ensure appropriate interpretation of growth parameters.

Given that this review found that girls in LMICs are of full reproductive ability aged ∼12 y, implications for broader policy and/or program interventions must be considered. Firstly, increased access to early, comprehensive sexual education curricula and discussions around healthy pubertal development is critical. Furthermore, early adolescents should be included in and have access to all programs targeting sexual and reproductive health. A recent systematic review found that early menarche is also associated with early marriage (47). This can lead to first pregnancy at a young age, which may predispose to long-lasting, negative consequences. Nutrition is compromised in the adolescent due to the physiological demands of pregnancy, resulting in reduced and/or stunted growth of the adolescent, and thus possible fetal growth restrictions and stunting syndrome sequelae (48), among other negative potential obstetric and fetal outcomes.

This meta-analysis on recent pubertal milestone timing in LMICs provides a baseline for future monitoring of secular trends in historically understudied populations. Discerning the direction of these trends can assist in optimizing future interventions and/or resource allocation.

Acknowledgments

The authors responsibilities' were as follows—SC: conceptualized the systematic review; AV and SC: designed the systematic review; JM, KS, AV, and SC: carried out the search and study selection; JM, KS, and MW: performed the data extraction; SC: laid out the analysis plan; MW: conducted the analysis; JM, SC, KS, MW, and AV: drafted the initial manuscript; AV, SC, and ZB: provided critical feedback on the analysis and contributed to the writing process; and all authors: read and approved the final manuscript.

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