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Low BMI, but not high BMI, influences the timing of puberty in boys

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Abstract

Background: Previous studies investigating the association between weight status and onset of puberty in boys have been equivocal. It is currently unclear to what extent weight class influences puberty onset and progression.

Objectives: To explore the relationship between degree of sexual maturation and anthropometric measures in Norwegian boys.

Methods: The following endpoints were collected in a Norwegian cross-sectional study of 324 healthy boys aged 9–16: ultrasound-determined testicular volume (USTV), total serum testosterone, Tanner pubic hair stage, height, weight, waist circumference (WC), subscapular skinfolds (SSF), and body fat percentage (%BF). Testicular volume-for-age *z*-scores were used to classify "early," "average," or "late" maturing boys. Ordinal logistic regression analyses with a proportional odds model were applied to analyze the association between anthropometric variables and age-adjusted degree of pubertal development, with results expressed as age-adjusted odds ratios (AOR). Cumulative incidence curves for reaching pubertal milestones were stratified by BMI.

Results: Boys with a low BMI for age ($BMI_z < -1$) were less likely to have reached a pubertal testicular volume (USTV ≥ 2.7 mL) or a pubertal serum level of testosterone (≥0.5 nmol/L) compared to normal weight boys (AOR 0.3, $p = 0.038$, AOR 0.3, $p = 0.026$, respectively), and entered puberty on average with a delay of approximately eight months. Boys with high BMI for age ($BMI_z > 1$) exhibited a comparable timing as normal weight boys. The same was found for WC. Pubertal markers were not associated with SSF or %BF.

Conclusion: By examining the association between puberty and weight status classified as low, average, or high, we found that a low BMI or WC for age were associated with a less advanced pubertal development and delayed timing of puberty in boys. No significant association was observed for a high BMI or WC. Moreover, no significant effects of SSF or %BF were observed. A low weight status should also be considered when assessing pubertal development in boys.

KEYWORDS
associations, BMI, puberty, testicular volume, weight class

1 | INTRODUCTION

Several studies have shown secular trends toward earlier puberty onset in girls during the past decades.[1,2] Some studies suggest similar trends in boys,[3,4] but results are more equivocal.[5] The mechanism behind the onset of puberty and factors influencing this process are still not fully unraveled. Identification of modifiable causes of early puberty is however of great interest as early puberty is a known risk indicator for disease in adult men, such as type 2 diabetes, cardiovascular disease, and reproductive cancers.[6,7]

It has long been known that an adequate nutritional status is a requirement for a timely initiation of central pubertal development,[8] and the secular increase in overweight and obesity has also received special attention as a potential driving factor for the concurrent secular trend toward earlier age at pubertal onset.[9,10] Several studies have demonstrated earlier puberty in girls with a high BMI or obesity,[11–14] but findings in boys are more ambiguous. While some studies show that the BMI is negatively correlated with pubertal timing in overweight and obese boys[4,15] others demonstrate *later* pubertal development in obese boys.[16] One study showed earlier puberty in overweight boys but delayed in obese.[17]

The lack of consistent evidence regarding the effect of weight status on pubertal timing in boys might be due to difficulties obtaining reliable measures of pubertal timing or because these measures represent different benchmarks of puberty. A few studies report the testicular volume measured using a Prader orchidometer or a genital assessment using Tanner stages (Tanner G),[18] while others use proxy markers of pubertal onset and progression, such as peak height velocity[19] or age at voice breaking.[20] Attainment of a testicular volume ≥4 mL using the Prader orchidometer is the most widely used clinical marker for onset of puberty in boys, but the use of a Prader orchidometer is regarded as impractical for larger population studies.[21] At the same time, testicular ultrasound is considered to be a more precise method for volume assessment[22–25] and the implementation of an ultrasound protocol has the advantage of being a more objective measurement on a continuous scale,[26] but may suffer from the same impracticality as the Prader assessment.

The aim of the current study was to investigate the relationship between anthropometric measures and age-adjusted degree of sexual maturation in Norwegian boys. In line with the literature, we hypothesized that boys with overweight or obesity would present with a more advanced pubertal development compared to boys with an average weight. Because of previous findings in the literature, boys with a low weight status were considered as a separate group in the analysis.

2 | MATERIALS AND METHODS

2.1 | Childhood population

Participants were recruited as part of the Bergen Growth Study 2, a cross-sectional study of pubertal development and growth in Norwegian children. A total of 1329 boys between 6 and 16 years of age from six randomly selected public schools in Bergen, Norway, were invited to participate. Parental consent was obtained for the 493 (37%) boys included. The present analyses included 342 boys aged ≥9 years, to eliminate the strictly prepubertal population. One boy did not assent on the day of examination, and four boys were absent. In addition, four boys were excluded due to a condition or a disease likely to affect growth and development, and nine boys were excluded due to past or ad hoc evidence of scrotal pathology including cryptorchidism, hydrocele or microlithiasis, leaving 324 eligible boys for analysis. Evidence of scrotal pathology was coupled with personal referrals to our affiliated regional hospital for follow-up. The mean (range) age of the final sample was 12.3 (9.0–16.3) years. A parental questionnaire was obtained for 228 (70.4%) of the boys included in the analysis. The questionnaire contained items on country of origin, chronic disease, and previous genital pathology. Of the 217 (67%) with known country of origin of both parents, 165 (76.0%) had both parents from Norway, 22 (10.1%) had one or two European parents, and 30 (13.8%) had one or two non-European parents, mostly from Asia (n = 11), Africa (n = 8), or South America (n = 7). The analyses include data from all boys, regardless of their country of origin.

2.2 | Pubertal development and testicular volume

A trained pediatric radiographer performed all ultrasound examinations and anthropometric measurements. Length, depth, and width of the right testicle were measured with the boy in the supine position using a Sonosite Edge ultrasound machine with a 15–6 MHz linear probe according to a standardized protocol.[27] The testicular volume (TV) was calculated using the Lambert equation TV = length × width × depth × 0.71.[28] The intra-observer variability was 9.2% and the technical error of measurement 6.5%.[27] An empirical equation to predict the equivalent Prader orchidometer volume from ultrasound volume was previously derived as $Vol_{OM} = 1.96 \times Vol_{US}^{0.71}$, and the Prader orchidometer volume of ≥4 mL that defines puberty onset is thus equivalent to an ultrasound measured testicular volume ≥2.7 mL (USTV).[27] The boys with a testicular volume below this cutoff (USTV <2.7 mL, corresponding to Prader orchidometer volume of <4 mL) were considered as prepubertal. Further, the boys were classified as early, average, or late maturing based on their testicular volume-for-age z-score ($USTV_z$). The boys in the upper tertile (>67th percentile) were considered as early maturing, those between percentiles 33–67 as average, and boys with the smallest testicular volume for age (<33rd percentile, lower tertile) as late maturing (Figure 1).

Tanner stages of pubic hair (PH) development were visually assessed in the supine position using descriptions based on the work of Marshall and Tanner as a reference[29] (n = 321 boys). Tanner stage PH2 defined pubarche.

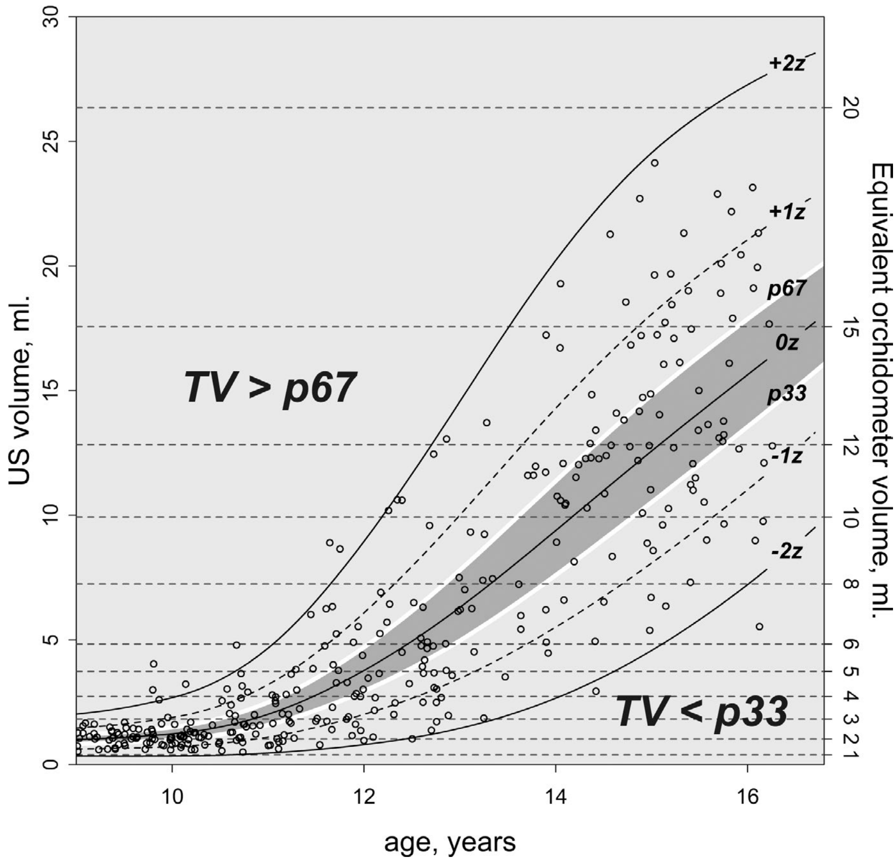

FIGURE 1 Grouping of boys as early (z-score > p67), average (p33 ≤ z-score ≤ p67), or late (z-score < p33) maturing based on testicular volume (TV) measured with ultrasound (US).[26] The equivalent orchidometer volumes on the Y2 axis are calculated from the ultrasound measurements as $Vol_{OM} = 1.96 \times Vol_{US}^{0.71}$ (see text for details)[27]

2.3 | Anthropometry

Height was measured in the standing position with a Harpenden Portable Stadiometer (Holtain Ltd Crosswell, UK) and recorded to the nearest 0.1 cm. Weight was measured in light clothing with an electronic scale (Tanita MC-780MA, Tanita Corp. of America, Inc. Illinois, USA) with a precision of 0.1 kg. Body mass index (BMI) was calculated as weight (kg) divided by the square of height (m^2). The waist circumference (WC) and subscapular skinfold (SSF) were measured according to the protocol used in the Bergen Growth Study 1.[30] Further, the percentage of body fat (%BF) was assessed with bioelectrical impedance analysis (BIA), using a Tanita MC-780MA (Tanita corp. of America, Inc. Illinois, USA). The anthropometric measurements (BMI, WC and SSF) were converted to z-scores using the Norwegian growth reference charts from 2003 to 2006[31–33] while %BF z-scores were calculated using the references by McCarthy et al[34] Boys with a BMI z-score < −1 were classified as having a "low" BMI_z, with a BMI z-score between −1 and 1 as "average," and those with a BMI z-score >1 as having a "high" BMI_z. The same cutoffs (z-scores −1 and 1) were also used for WC, SSF, and %BF (WC_z, SSF_z, and $\%BF_z$).

2.4 | Blood test

Blood samples from 299 (92.3%) boys were collected between 0800 and 1400 h and processed according to a protocol for blood sampling and analysis that was previously described.[35] Total testosterone was assayed by LC-MS/MS as described previously.[36] The analytical inter-assay coefficient of variation (CV%) was 4% in the range 1.5–37 nmol/L, and limit of detection (LOD) was 0.01 nmol/L. A concentration of 0.5 nmol/L or more was used as an alternative marker for the start of puberty. This cutoff was determined with a ROC analysis of total testosterone to predict the onset of puberty defined as USTV ≥2.7 mL in 240 prepubertal and 180 pubertal boys in the BGS2. The area under the curve (AUC) was 0.9778 (95% CI; 0.96 to 0.99), and the positive and negative predictive values were 91.3% and 97.6%, respectively.

2.5 | Statistical analysis

Continuous variables were compared between groups with a t-test and categorical variables with a chi-squared test. Multiple logistic regression with age as a covariate was used to estimate the odds ratio (OR) for having reached a pubertal level of either testicular volume (USTV ≥ 2.7 mL), pubarche (Tanner PH2), or serum testosterone (≥0.5 nmol/L) in boys with a high (>1) or low (<−1) versus average (between −1 and 1) z-score for the different anthropometric measurements separately. Proportional odds logistic regression was used to study the association between the level of maturity (early, average, or late based on the USTV z-scores) and the grouped anthropometric measurements, comparing boys with a "low" or "high" value to those with an average value for each measure separately. An OR larger than 1 means that boys in the tested group had a higher probability to be more advanced with respect to USTV for age. A non-significant score test indicated that the assumption of proportional odds was valid. Further, we present the cumulative incidence curves for the three different pubertal markers in the three different weight groups $BMI_z < -1$, $-1 \le BMI_z \ge 1$ and $BMI_z > 1$. The curves were estimated with a generalized additive model with a binary outcome and probit link function. The degree of smoothing was determined with generalized cross validation using the mgcv package in R. The mean age at reaching maturity (USTV 2.7 mL) was obtained by inverse prediction. All statistical analyses were performed using IBM SPSS statistics version 25 (IBM Corp) and R version 3.4 (R foundation for Statistical Computing).

2.6 | Ethical considerations

This study was approved by the Norwegian Regional Committee for Medical and Health Research Ethics West (REC-WEST 2015/128). Written informed consent was obtained from a parent or legal guardian of each participant in the study, as well as assent from the participants themselves. A cinema voucher was given as an incentive.

3 | RESULTS

Of the 324 boys included in the analysis, 180 boys exhibited pubertal testicular volume USTV ≥2.7 mL (equivalent to ≥4 mL by orchidometer) and 144 had a volume USTV <2.7 mL and were thus considered prepubertal. The youngest pubertal boy was 9.8 years, and the oldest prepubertal boy 13.1 years. Twenty-one boys presented with a prepubertal testicular volume, while pubic hair had already advanced to Tanner stage PH2. Only two of these had a pubertal serum testosterone level (≥0.5 nmol/L). The mean and SD of the *z*-scores for height, weight, BMI, WC, and SSF for the whole group were not significantly different from the reference population in the Bergen Growth Study 1. Further, the *z*-scores for all anthropometric measures showed no significant difference between the prepubertal and pubertal boys. Based on the IOTF criteria, 37 boys were defined as being overweight, and six as being obese. Further, 20 boys were defined as being underweight grade 1, and four as underweight grade 2. While BMI *z*-scores were not significantly different between the groups ($p = 0.310$), the proportion of boys with a high BMI for age was larger in pubertal boys (16.7% vs 11.8%) but this difference was not statistically significant ($p = 0.267$). Further, pubertal boys exhibited statistically significant lower %BF compared to the prepubertal boys ($p = 0.010$).

Multiple logistic regression analysis with age as a covariate showed that boys with a low BMI_z had a lower probability of being pubertal (USTV ≥2.7 mL; AOR 0.3; 95% CI 0.1, 0.9; $p = 0.038$) compared to boys with average BMI_z (Table 1). Boys with a high BMI_z did not have a significant higher probability of being pubertal (AOR 1.3; 95% CI 0.4, 3.9; $p = 0.691$). The same was observed for WC which showed a strong association with a low WC_z, but not with high WC_z. When these analyses were repeated for the other pubertal markers (serum testosterone ≥0.5 nmol/L and Tanner PH2), we could confirm the trend of an association with a low value for the BMI_z and WC_z but no clear association with a high BMI_z or WC_z, but it was only statistically significant for serum testosterone ≥0.5 nmol/L and not for Tanner PH2. No significant associations were found between SSF or %BF and any of the pubertal markers (Table 1).

Ordinal logistic regression showed that boys with low BMI or low WC for age had a significant lower probability of being in a higher category of testicular volume for age compared to those with average BMI_z (OR 0.3; 95% CI 0.2,0.5; $p < 0.001$) or WC_z (OR 0.2; 95%

TABLE 1 Age-adjusted logistic regression analysis of having reached pubertal status according to different anthropometric measurements and markers of puberty

		USTV ≥2.7 mL (*N* = 324)				Serum testosterone ≥0.5 nmol/L (*N* = 299)				Tanner PH2 (*N* = 321)			
		N	A-OR	95%CI	*p*-Value	N	A-OR	95%CI	*p*-Value	N	A-OR	95%CI	*p*-Value
BMI *z*-score	Low	54	0.3	0.1, 0.9	0.038	54	0.3	0.1, 0.8	0.026	54	0.4	0.1, 1.1	0.070
	High	43	1.3	0.4, 3.9	0.691	40	1.0	0.3, 3.4	0.997	42	1.1	0.4, 3.3	0.889
Waist *z*-score	Low	36	0.2	0.0, 0.6	0.008	35	0.2	0.1, 0.9	0.039	36	0.3	0.1, 1.1	0.079
	High	45	0.9	0.3, 2.9	0.918	42	1.1	0.3, 3.7	0.850	44	1.2	0.4, 3.5	0.761
SSF *z*-score	Low	50	0.6	0.2, 1.9	0.412	49	0.8	0.2, 2.7	0.731	50	0.6	0.2, 1.6	0.284
	High	61	1.4	0.6, 3.7	0.462	57	1.6	0.6, 4.4	0.377	60	1.3	0.5, 3.3	0.588
%BF *z*-score	Low	32	0.5	0.1, 2.1	0.363	28	0.8	0.2, 3.6	0.724	32	1.5	0.4, 5.8	0.555
	High	51	1.6	0.6, 4.7	0.387	47	1.6	0.5, 5.0	0.456	51	1.1	0.4, 3.2	0.811

Note: AOR: age-adjusted odds ratio; USTV ≥2.7 mL: pubertal testicular volume of 2.7 mL or more (ultrasound) or T4 mL (orchidometer); Tanner PH2: pubarche; Low *z*-score: < −1; High *z*-score: >1; BMI, body mass index; Waist, waist circumference; SSF, subscapular skinfold, %BF, body fat percentage. BMI, WC, and SSF were converted to *z*-scores using the Norwegian growth reference from 2003 to 2006[31–33] while %BF *z*-scores were calculated using the references by McCarthy et al.[34]

CI 0.1,0.4; $p < 0.001$) (Table 2). However, boys with high BMI or high WC for age did not have an increased probability of being in a higher category of testicular volume for age, as a sign of being more mature for age. We did not find any significant associations for SSF and %BF with the degree of maturation (Table 2).

The cumulative proportion of boys having attained a pubertal testicular volume in each of the three BMI_z groups separately is shown in Figure 2A. A comparison of the weight-specific curves at the levels of the 50% attainment confirms that boys with low BMI for age ($BMI_z < -1$) entered puberty with a delay of approximately eight months compared to normal weight boys, while the timing in boys with a high BMI for age ($BMI_z > 1$) was comparable. The mean age of reaching a pubertal testicular volume was 12.34, 11.66, and 11.54 years in boys with a low, average, and high BMI for age, respectively (Figure 2A). Similar trends were observed for the attainment of a serum testosterone level above the threshold associated with puberty onset (serum testosterone ≥0.5 nmol/L; Figure 2B) and for the appearance of pubic hair (Tanner PH2; Figure 2C). For both pubertal markers, there is a clear delay in boys with a low BMI_z, and a slight advancement in boys with a high BMI_z. Also, the variability was smaller in these groups which resulted in steeper curves (Figure 2B–C).

4 | DISCUSSION

In the current study, we examined the association between the timing of sexual maturation and a low or high weight status in a cross-sectional cohort of healthy boys. We found that boys with a low BMI_z and a low WC_z reached puberty almost eight months later than those with an average BMI_z or WC_z and were delayed over the whole pubertal age range as demonstrated by the smaller testicular volume by age. On the other hand, neither a high BMI nor high WC for age were associated with earlier maturity as originally anticipated. These results were confirmed for puberty onset according to the level of serum testosterone.

Our endpoints for male puberty status included measurements of testicular volume with ultrasound, a pubertal level of serum testosterone, and the development of pubic hair as described by Marshall and Tanner.[29] Indisputably, the best and most objective clinical marker of male puberty is the assessment of testicular volume.[37] The size of the testicle is traditionally assessed by Prader orchidometry, but measurements of testicular dimensions with ultrasound have been shown to be the preferred method when accuracy of testicular volume is important.[38] In addition, the ultrasound volume is a continuous variable which facilitated the development of testicular volume-for-age reference charts.[26,39] Age-adjusted testicular volume *z*-scores calculated with the Norwegian references[26] allowed us to stratify boys into tertiles of pubertal progress, with the 33rd and 67th percentiles as cutoffs for late, average, and early maturation. Sørensen and Juul previously used a similar approach based on the discrete testicular volume measured with a Prader orchidometer,[40] while Ribeiro et al. divided the boys into quartiles based on age and Tanner G stage.[41] To our knowledge, the current study is the first to compare testicular volume measured with ultrasound with anthropometric measures.

To assess the association of adiposity and body composition on the timing of puberty and degree of maturation, we stratified boys into three groups according to their BMI, WC, SSF, and %BF for age *z*-score. Boys with a *z*-score below −1 were considered as low and those with a *z*-score above 1 as high. The effect of having a low "weight status" was analyzed separately as previous studies revealed effects of low vs. average values for anthropometric variables that were independent from the high values.[14,42] For instance, Tomova et al. studied more than 4000 boys between 7 and 19 years of age.[42] They observed that boys with a low BMI (<12th percentile) were delayed

TABLE 2 Logistic regression and proportional odds logistic regression analysis of having a high (early maturing) or low (late maturing) testicular volume for age according to anthropometric measures

			USTV > p33			USTV > p67			Higher USTV tertile (proportional odds)		
		N	OR	95%CI	*p*-Value	OR	95%CI	*p*-Value	OR	95%CI	*p*-Value
BMI *z*-score	Low	54	0.3	0.2, 0.5	<0.001	0.2	0.1, 0.5	0.002	0.3	0.2, 0.5	<0.001
	High	43	1.0	0.5, 2.1	0.981	1.2	0.6, 2.3	0.627	1.1	0.6, 2.1	0.731
Waist *z*-score	Low	36	0.2	0.1, 0.4	<0.001	0.2	0.1, 0.6	0.008	0.2	0.1, 0.4	<0.001
	High	45	1.1	0.5, 2.3	0.838	1.3	0.7, 2.5	0.476	1.2	0.7, 2.2	0.538
SSF *z*-score	Low	50	0.8	0.4, 1.5	0.510	0.7	0.3, 1.3	0.250	0.8	0.4, 1.3	0.310
	High	61	1.0	0.6, 1.9	0.913	1.1	0.6, 2.0	0.720	1.1	0.6, 1.8	0.774
%BF *z*-score	Low	32	0.7	0.3, 1.5	0.308	1.0	0.4, 2.1	0.903	0.8	0.4, 1.6	0.478
	High	51	1.0	0.5, 1.9	0.955	0.9	0.5, 1.7	0.771	1.0	0.6, 1.7	0.863

Note: OR, odds ratio; USTV > 33p: this corresponds to the odds for being average or early vs. late maturing based on ultrasound measured testicular volume for age; USTV > 67p: this corresponds to the odds for being early vs. average or late maturing; for the proportional odds model, this corresponds to the odds for being in a higher category; Low *z*-score: <−1; High *z*-score: >1; BMI, body mass index; Waist, waist circumference; SSF, subscapular skinfold, %BF, body fat percentage. BMI, WC, and SSF were converted to *z*-scores using the Norwegian growth reference from 2003 to 2006[31–33] while %BF *z*-scores were calculated using the references by McCarthy et al.[34]

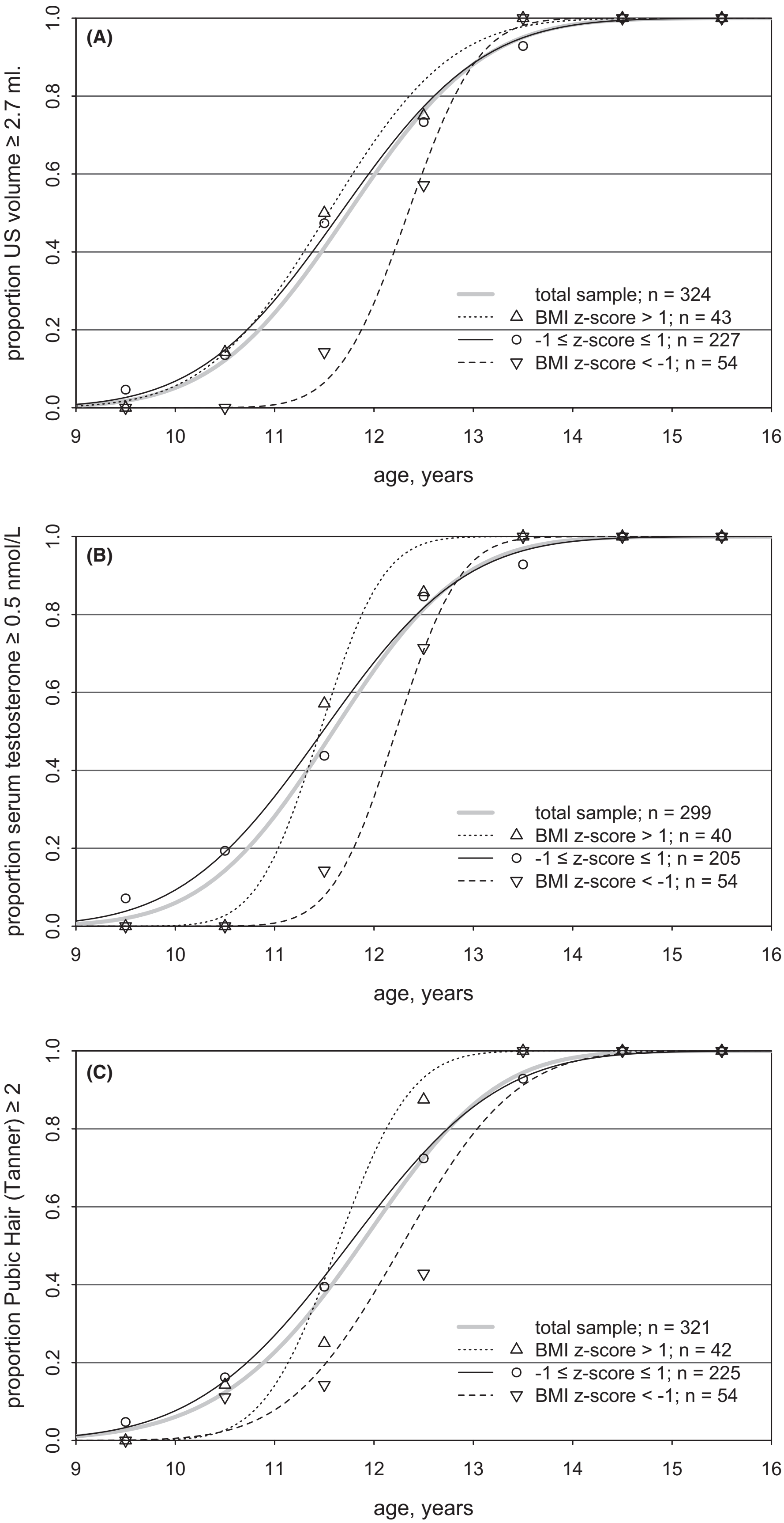

FIGURE 2 (A-C) Proportion of boys having attained (A) a pubertal testicular volume (USTV ≥2.7 mL, *n* = 324), (B) a pubertal testosterone level (≥0.5 nmol/L, *n* = 299), and (C) Tanner stage 2 for pubic hair (PH2, *n* = 321) in each of the three BMI *z*-groups in boys aged 9–16 years. A generalized additive model with probit link was used to estimate the cumulative distribution curve in each BMI group. The mean ages of reaching a pubertal marker in boys with a low, average, and high BMI for age were 12.34, 11.66, and 11.54 years for testicular volume (USTV ≥ 2.7 mL), 12.22, 11.48, and 11.46 years for serum testosterone level (≥0.5 nmol/L), and 12.28, 11.74, and 11.63 years for Tanner PH2. BMI *z*-scores were calculated using references from the Bergen Growth Study 1[31]; USTV *z*-scores were calculated using references from the Bergen Growth Study 2[26]

at every stage of pubertal development, while boys with a high BMI (>85th percentile) started puberty at an earlier age and reached the final stage of puberty ahead of their normal weight peers.[42] But most previous studies have compared pubertal development in overweight versus non-overweight subjects without considering low weight class as a separate group.[15,43]

It is well known that energy homeostasis is an important factor for the timing of puberty and that adequate nutrition is key for normal puberty.[44] The satiety hormone leptin produced in fat cells has been suggested as a possible link between weight status and pubertal timing.[45] Our finding that boys with a low BMI and WC for age were delayed is therefore not surprising and is supported by others.[42,46] The finding that boys with a high BMI_z did not significantly differ from normal weight boys and thus did not achieve pubertal milestones at an earlier age was more surprising given the numerous studies reporting an association between adiposity and earlier puberty onset.[4,15,19,20,41,47-49] However, even though we did not find an association for a high BMI_z in the present study, we cannot exclude that this is due to the limited number of boys with overweight, and even lower number with obesity.

Busch et al. recently demonstrated that boys with obesity (defined as $BMI_z > 2$) experienced earlier timing of testicular enlargement (mean age 11.3 years), as compared to control group with a $BMI_z < 2$ (mean age 11.7 years).[15] However, all boys with a BMI *z*-score of 0 to 1, 1 to 2, and 2 to 3 entered puberty at the same mean age of 11.4 years, while boys with a BMI_z 0 to −1 entered puberty at a mean age of 11.9 years and those with a BMI_z below −1 at 12.4 years. Their conclusion of an advancement in boys with obesity could thus also be interpreted as a delay in boys with a low BMI_z in line with our current findings. Another Danish study using self-reported pubertal data also concluded that overweight boys reached Tanner G2 almost three months earlier than normal weight boys,[43] but a normal weight was defined as any BMI below the 85th percentile. Further scrutiny of the tabulated results confirmed that boys with low BMI (<16 kg/m^2) appeared to reach Tanner G2 at an older age than those with a higher weight.

In the current study, WC, a proxy for abdominal fat that has shown a stronger association with cardiovascular risk than BMI,[50] followed that for BMI, in that boys with lower WC for age had lower probability of being more mature than their peers, while having a larger WC_z was not associated with earlier maturation. This contrasts with a recent study from Brazil showing that boys with early pubertal development presented higher prevalence of central adiposity, which was defined as increased WC.[51]

No significant differences were found between SSF_z and $\%BF_z$ and early or late maturing boys in the present study. SSF is a direct measure of subcutaneous (trunk) fat, and the %BF measured with BIA is generally considered to be more sensitive and specific for grading adiposity than anthropometric indices such as the BMI.[52] Vizmanos and colleagues measured skinfolds and %BF in a longitudinal study of 282 boys.[53] They found that the BMI increased with age at onset of puberty in boys, but since the amount of body fat mass was constant, it was concluded that puberty onset initiates with a characteristic accumulation of subcutaneous body fat mass that is independent of the age of puberty onset. In contrast with this, Biro et al. found that boys with more advanced maturation at age 12 had lower sum of skinfolds and that boys who arrived at any given maturation stage at a younger age had lower BMI and lower adiposity.[54]

Some limitations are worth mentioning. Because of the cross-sectional design, we can only describe the associations, but not causality between weight class and pubertal timing. Conclusions drawn from cross-sectional studies are vulnerable to potential confounding by reverse causality, that is, that children could be assigned to wrong weight classes due to early or late puberty onset, or due to differential tempo of growth.[55] Sørensen and Juul found that early pubertal timing was not associated with a degree of higher adiposity, measured with BIA, and that BMI_z tended to overestimate adiposity and more readily classified children as overweight in early versus late maturing children.[40] Considering the associations found for BMI and WC, but not for SSF and %BF, may imply that BMI is a marker of maturity more than adiposity.

The conflicting results in association studies between weight class and pubertal timing are striking; however, it is plausible that differences in methods to assess pubertal development and different definitions of obesity have contributed to a diverging range of conclusions. Moreover, the lack of longitudinal studies limits the possibility of defining the causal relationship between obesity and pubertal maturation. These inconsistencies warrant further investigations using a longitudinal design and consensus endpoints to determine puberty onset to solve the effect of adiposity on pubertal timing.

Another limitation of the current study is the potential of selection bias. Only 37% of the invited boys agreed to participate, potentially making very early or late maturing boys, less inclined to participate. In addition, non-significant findings should be interpreted cautiously as the relatively small number of boys with a high (>1) or low (<-1) *z*-score for anthropometric measurements (the expected prevalence is 16%) may have impacted the statistical power of our analysis.

A major strength of our study is the use of ultrasound, which facilitated measurements of the testicular volume on a continuous scale, without the interference of the surrounding scrotal tissue. This, in turn, enabled the calculation of age-adjusted *z*-scores for each study participant in accordance with our previously published reference chart.[26] We have previously shown that the USTV of 2.7 mL immediately precedes a drastic surge in testosterone levels[35] and our current findings for the associations between testicular volume and anthropometric measurements were corroborated by equivalent findings with regard to serum testosterone. This highlights the co-occurrence of testicular enlargement and testosterone production. Another strength is that we not only included BMI, but also WC, SSF, and %BF in addition to blood tests in a quite large cohort of healthy boys.

5 | CONCLUSION

A good understanding of the relationship between sexual maturation and weight status has many important clinical and public health implications. By using a continuous measure of testicular volume, obtained with ultrasound, we found that puberty was less advanced in boys with a low BMI or low WC for age, but not that it was more advanced in those with a high BMI or WC. Boys with a low BMI_z also entered puberty with a delay of eight months. We assume that pubertal timing is more strongly related to variables that define shape (BMI and WC) and less to variables that define body composition (SSF and %BF). While previous studies often focused on obesity as an influencing factor, we believe that both high and low weight status should be taken into consideration when assessing pubertal status in children and adolescents.

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CONFLICT OF INTEREST

The authors have no financial relationships relevant to this article to disclose.

AUTHOR CONTRIBUTIONS

Dr. Oehme coordinated and supervised data collection, carried out initial analyses and interpretation, drafted the initial manuscript, and reviewed and revised the manuscript. Dr. Roelants carried out initial analysis, substantial statistical work and critically reviewed the manuscript. Mrs. Bruserud coordinated, supervised, and collected data, and reviewed the manuscript. Dr. Madsen contributed to statistical analysis and interpretation of data and reviewed the manuscript. Prof. Bjerknes contributed to conceptualization and design of the study and reviewed the manuscript. Prof. Rosendahl contributed to the design of the study, supervision and collection of data, and revision of the manuscript. Prof. Júlíusson conceptualized and designed the study, supervised data collection, and critically reviewed the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all the aspects of the work.

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