Pubertal voice break: Temporal relation of secondary sexual characteristics in healthy boys

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Background

Despite the fact that the attainment of voice break is frequently used in population-based studies as proxy for male puberty (1), the temporal relation between timing of male pubertal milestones and timing of voice-break in combination with sex-hormones measurements are poorly studied. Further, the association between BMI and timing of puberty in boys, particularly in obese boys, remains debated. We here report the timing as well as temporal relation of pubertal events in a mixed cross-sectional and longitudinal cohort of healthy boys including analysis of age-specific BMI and reproductive hormones.

Materials & Methods

730 healthy Danish boys from the COPENHAGEN Puberty Study [cross-sectional: n = 637; longitudinal: n = 93, median (range) number of examinations (every 6 months): 10 (2-13)] underwent blood sampling including measurement of reproductive hormones as well as clinical examinations of secondary sexual characteristics. (Mean) age-specific BMI (BMI z-scores, zBMI) was calculated using the WHO reference. Longitudinal samples were analyzed using the mean age between pre- and post-event visit, while mixed cross-sectional and longitudinal were analysed using probit analysis (SAS lifereg) integrating censored data.

Results

Voice break occurs in late puberty (Table 1) at a median of 2 years after testicular enlargement (at least one testis ≥4 mL) (Table 2). At voice break mean, bi-testicular volume was 24mL and total Testosterone 10.9 nmol/L (Table 2). In the mixed cross-sectional and longitudinal part, we observed significant associations of BMI z-score (zBMI) with age at pubertal events (all $p < 0.001$) (Table 1 & Figure 1). The association point to a linear relationship between zBMI and age at event across the entire zBMI spectrum (Figure 1) with effect sizes ranging from -0.3 to -0.4 years per zBMI (Table 1).

Conclusion

We provide a comprehensive temporal analysis of pubertal events, particularly attainment of voice break, and reproductive hormone dynamics. Covering the full spectrum of BMI, we observed a linear association of pubertal events with zBMI.

Table 1 - Timing of puberty events and association with BMI

Pubertal events	Timing of events				Association with BMI (Cross-sectional & longitudinal)	
	Longitudinal only	Age at event in yrs (range/SD)[a]	Cross-sectional & longitudinal	Age at event (95% Confidence Limits) in yrs[b]	effect size in yrs (SE) per zBMI	p value$_{zBMI}$
Clinical signs						
Testicular enlargement[c]	62	11.6 (9.9 - 13.8)	714 / 730	11.6 (11.5 - 11.8)	-0.36 (0.06)	<0.001
Activation of sweat glands	73	11.8 (8.5 - 14.3)	726 / 730	12.4 (12.1 - 12.6)	-0.47 (0.09)	<0.001
Pubic hair growth	63	12.0 (9.6 - 13.8)	713 / 730	12.2 (12.1 - 12.4)	-0.45 (0.08)	<0.001
Axillary hair growth	57	13.1 (11.5 - 15.4)	727 / 730	13.6 (13.5 - 13.8)	-0.36 (0.08)	<0.001
Voice break	55	13.5 (11.9 - 15.5)	648 / 730	13.6 (13.5 - 13.8)	-0.33 (0.08)	<0.001
Peak height velocity	93	13.7 (0.94)	-	-	-	-
Hormones						
Total testosterone above LOD[d]	63	11.5 (10.0 - 13.8)	662 / 730	11.7 (11.6 - 11.9)	-0.30 (0.06)	<0.001

[a]reported as median (range) based on interval between events except "peak height velocity": mean (SD) (based on SITAR (2))

[b]reported as mean/intercept (95% Confidence Limits) based on censored data using SAS proc lifereg

[c]Testicular volume ≥4 mL (at least one testis)

[d]Limit of Detection (LOD) Total testosterone: 0.23 nmol/L

Figure 1 - Timing of pubertal events across the BMI spectrum (zBMI percentiles) (mixed cross-sectional and longitudinal samples)

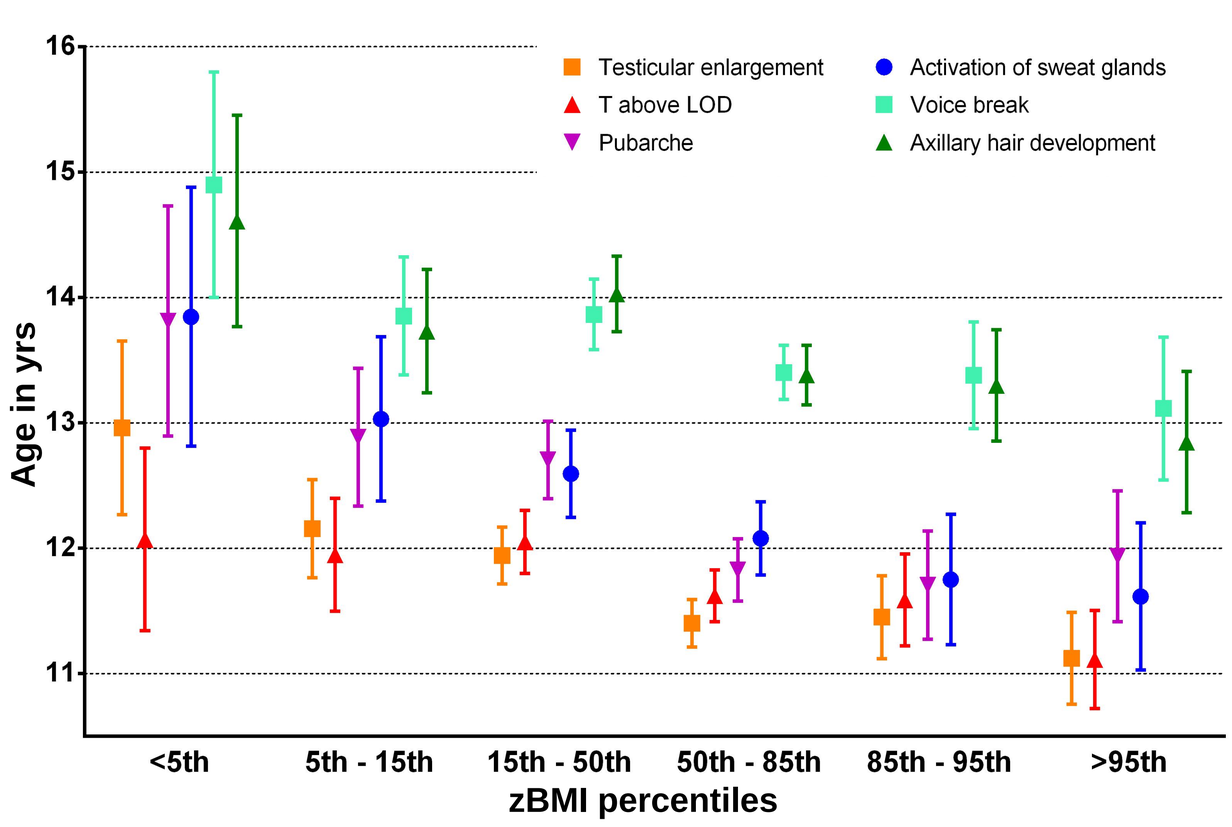

Table 2 - Intervals and values at voice break

Pubertal events	Longitudinal only	Median (range)[a]	Cross-sectional & longitudinal	Value (95% Confidence Limits)
Intervals				
Testicular enlargement[b] to Voice break	46	2.0 (0.0 - 4.0) yrs	-	-
Testosterone over LOD[c] to Voice break	47	1.9 (0.0 - 4.0) yrs	-	-
Values at Voice break				
Bi-testicular volume at Voice break	47	24 (6 - 44) mL	612 / 730	24 (23 - 25) mL
Total testosterone at Voice break	40	12.0 (0.3 - 25.7) nmol/L	561 / 730	10.9 (10.0 - 11.7) nmol/L

[a]reported as median (range) in yrs and median (range) in volume/concentration (for pre/post-values between attainment of Voice break)

[b]Testicular volume ≥4 mL (at least one testis)

[c]Limit of Detection (LOD): Total testosterone: 0.23 nmol/L

References

(1) Shared genetic aetiology of puberty timing between sexes and with health-related outcomes. *Day* et al. 2015. Nature Communications

(2) SITAR--a useful instrument for growth curve analysis. *Cole* at al. 2010. Int J Epidemiol.

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