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Examination of Pubertal Timing and Tempo in Females and Males with Autism Spectrum Disorder compared to Typically Developing Youth

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Abstract

Autism spectrum disorder (ASD) is characterized by impaired social communication and poor adaptation to change; thus, pubertal development may be precarious. Pubertal timing and tempo were measured in 244 youth (7.9% Black, 83.3% White, 8.7% multiracial) with ASD (N=140) and typical development (N=104). Pubertal development was measured using Tanner Staging of Genital (G, males), Breast (B, females) and Pubic Hair (PH) in both sexes at Year 1 (10–13-years), Year 2 (11–14-years), and Year 3 (12–15 years). Nonlinear mixed effects models analysed interindividual differences in timing and tempo. For both sexes, ASD and higher BMI were associated with earlier pubertal timing. Males generally exhibited faster tempo than females. Linear regression models did not show associations between pubertal timing and internalizing symptoms at Time 3. Findings showing advanced pubertal maturation in ASD youth suggest greater risk of psychological, social, and physiological challenges.

Lay Summary

Youth with autism spectrum disorder (ASD) have difficulty in social communication and adaption to change, thus puberty may be a challenging transition. The study examined onset (timing) and progression (tempo) of puberty over three years, using physical exam, in 244 adolescents with and without ASD, enrolled at ages 10–13. ASD youth started puberty earlier, while males generally progressed at a faster pace. Further examination of puberty in ASD should identify impact on social, behavioral, and mental health outcomes.

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Keywords

autism; puberty; adolescence; female; development

Introduction

Adolescence formally refers to the developmental transition of juvenile social and cognitive processes to their adult forms and is directly associated with chronological age as well as psychological and social experience (Spear, 2000; Steinberg, 2005). It is a time when peer relationships become more salient and complex (Graber & Brooks-Gunn, 1996). It can be conceptualized across periods; namely, early adolescence (10–14 years), middle adolescence (15–17 years) and late adolescence/young adulthood (17– 24). The progression from childhood to adulthood is formed by experience-dependent brain reorganization (Andersen, 2003), rendering it a time of novel psychological opportunities as well as challenges (Dahl, 2004). Among the challenges is a significant increase in psychiatric disorders (Breslau et al., 2017), as half of people who suffer from mental illness have their onset during adolescence (Kessler et al., 2005).

Puberty: Definition and Measurement

Generally co-occurring during adolescence, puberty refers to biological maturation leading to striking developmental changes in cognitive, emotional, and physiological development (e.g., (Chrousos et al., 1998; Spear, 2000; Steinberg, 2005). The biological changes related to puberty are initiated after a period of childhood quiescence via activation of the hypothalamic-pituitary-gonadal (HPG) axis driven by gonadotropin-releasing hormone stimulating the secretion of luteinizing hormone and follicle-stimulating hormone. Subsequently, interrelated neuroendocrine processes and hormones are initiated: adrenarche (e.g., dehydroepiandrosterone; DHEAS), gonadarche (e.g., estradiol and testosterone), and rapid physical growth (Buck Louis et al., 2008; Dahl, 2004). The surge of gonadotrophins produced in and released from the anterior pituitary, increases estrogen in females (e.g., ovulation, menstruation and breast development) and testosterone in males (e.g., phallic growth, voice changes). The activation of these pubertal hormones facilitates the motivation for social and sexual relationships with peers in both sexes (Forbes & Dahl, 2010; Sisk & Foster, 2004).

Patterns in pubertal stages were first conceptualized and standardized by Marshal and Tanner for girls (Marshall & Tanner, 1969) and boys (Marshall & Tanner, 1970), separately characterizing physical development along two dimensions and five stages described below. Subsequently, Tanner growth stages have become a gold standard to characterize pubertal progression. While menses has often been used as a proxy for puberty, it occurs in the later stages of puberty (Tanner stage 4 or 5; (Marshall & Tanner, 1969) and only moderately correlates with the onset of puberty (Biro et al., 2006). The parameters used to examine physical maturation include timing (onset), stage (sequence), and tempo (pace).

There is significant interindividual variation in maturation that can be impacted by biobehavioral (e.g., body mass index), demographic (e.g., race, ethnicity), and

environmental (e.g., social economic status, family composition) factors contributing to early, normative, or delayed onset (Mendle et al., 2019). Rising rates of overweight and obesity in the general population (Hales et al., 2018) and ASD (Corbett, Muscatello, et al., 2020; Whiteley et al., 2004) has been linked to significant physical and mental health conditions (Hill et al., 2015; Phillips et al., 2014; Zuckerman et al., 2014), thus BMI must be carefully considered in research on pubertal onset and progression.

The way in which puberty is assessed (e.g., (Beltz et al., 2014; Corbett et al., 2019; Koopman-Verhoeff et al., 2020; Shirtcliff et al., 2009) or analyzed (e.g., linear vs. nonlinear methods; (Beltz et al., 2014)) can result in significant differences in findings (Biro et al., 2010; Marceau et al., 2011). Pubertal development, like many biological growth trajectories, is not linear and theorized as a sigmoid shape in which there is a definitive start and end point with significant heterogeneity in the growth trajectory (Grimm & Ram, 2009; Marceau et al., 2011). The way in which puberty is measured can influence the precise determination of onset (timing) and trajectory (tempo).

Pubertal Timing

Pubertal timing generally provides a more robust explanation for the physical and psychosocial changes that occur during adolescence than chronological age (Biro et al., 2006). While there is a broad developmental range, age of pubertal onset has been steadily dropping in the United States for females (Herman-Giddens et al., 1997), with mean onset of 9.6 and 10.2 years for Black and White girls, respectively (Biro et al., 2006). The first physical sign of puberty in girls is the development of glandular breast tissue (thelarche) with early reports suggesting a mean onset of 11.15 years (Marshall & Tanner, 1969, 1970). A recent systematic review indicates the pubertal onset for girls in the United States ranges from 8.8 to 10.3 years (Eckert-Lind et al., 2020). Boys mature somewhat later than girls. Early reports indicated a mean onset of genitalia development between 9.5 to 13.5 years (Marshall & Tanner, 1969, 1970). Currently, the mean age for genital development is 10.14, 9.14, and 10.04 years for White, African American, and Hispanic boys, respectively (Herman-Giddens et al., 2012). Earlier sexual maturity in females and males have been demonstrated worldwide (e.g., (Eckert-Lind et al., 2020; Goldstein, 2011). To date, most of the research on pubertal development has focused on timing, yet the progression over the course of puberty is also important.

Pubertal Tempo

Pubertal tempo refers to how rapidly or slowly an individual progresses from the onset of puberty until full sexual maturation. While logical to assume timing and tempo would be associated, a lack of association has been found (Huang et al., 2009) including dissociable sex-based patterns. Marceau (2011) found that timing and tempo were correlated in males, but not in females suggesting different underlying mechanisms. Other studies have shown that earlier timing in females was associated with faster tempo (Biro et al., 2001; Mendle et al., 2010) such that girls with earlier pubertal onset tend to reach menarche faster (Apter & Vihko, 1983; Pantsiotou et al., 2008). It should be noted that girls tend to progress through puberty more quickly (e.g., faster tempo) than boys (e.g., (Beltz et al., 2014)). Early

onset in combination with more rapid pubertal maturation (tempo) is predictive of poor psychological outcomes (Marceau et al., 2011).

While less studied than timing, the pace of growth from prepubertal (Tanner Stage 1) to sexual maturity (Tanner Stage 5) has important developmental implications for understanding individual differences (Marshall & Tanner, 1969, 1970). Progression from Tanner Stage 2 to 5 in female breast development ranges from 1.51 to 9 years (mean 4 years), whereas male genital development ranges from 1.86 to 4.72 years (mean 3 years). The precision of pubertal measurement is important for studying factors associated with atypical development.

Psychological Consequences of Deviations in Timing and Tempo

Differences in the timing and tempo of puberty can have significant psychological, social, and physiological consequences. Incongruence between psychological and physical maturation can increase the risk for mental health problems (Graber et al., 1997; Kaltiala-Heino et al., 2003; Waylen & Wolke, 2004). Several negative psychological outcomes have been associated with early pubertal timing in adolescent females when compared to normative or later maturing females (Mendle et al., 2007), including depression (Angold, 2003; Conley & Rudolph, 2009; Ge et al., 2001; Llewellyn et al., 2012; Rierdan & Koff, 1991), suicidality (Graber et al., 1997) and anxiety (Patton et al., 1996). However, puberty has been less well studied in many neurodevelopmental disorders.

Autism Spectrum Disorder[1]

Autism spectrum disorder (ASD) is a complex neurodevelopmental disorder characterized by impairments in reciprocal social communication and a repertoire of restricted, repetitive interests and behaviors (APA, 2013). Frequently, a male bias is reported showing a 4:1 male-to-female ratio (Maenner et al., 2020); however, other evidence suggests the ratio may be closer to 2:1 or 3:1 due to under-diagnosis (Kim et al., 2011; Loomes et al., 2017) and a unique female phenotype (Corbett, Vandekar, et al., 2020; Kreiser & White, 2014; Mandy et al., 2012; Uljarevic et al., 2020). The constellation of symptoms in ASD contributes in poor adaptation to change including developmental transitions (Taylor et al., 2017; Taylor & Seltzer, 2010); therefore, adolescence may be particularly challenging (Picci & Scherf, 2015) although research for youth with ASD is mixed. There is evidence of improvement in ASD symptom presentation (Seltzer et al., 2004), social cognition (Anderson et al., 2007; Anderson et al., 2009) and behavior regulation (Anderson et al., 2011; Brown, 1969; Eisenberg, 1956; Gillberg & Schaumann, 1981; Rutter, 1970). However, social withdrawal and psychosocial problems can intensify during adolescence (Anderson et al., 2011; Billstedt et al., 2005; Gillberg & Steffenburg, 1987) and sex-based differences can be magnified. For example, in females with ASD, the onset of menses can present significant difficulties with mood and emotion regulation but is understudied (Burke et al., 2010; Hamilton et al., 2011; Obaydi & Puri, 2008).

[1]At the time of writing this manuscript there is controversy regarding the use of terminology and whether *person-first* language in which the individual (e.g., adolescent) is referenced before the condition (e.g., autism) or whether *identity-first* language (e.g., autistic adolescent) should be used. Because such issues have not been resolved, we have opted to take a mixed terminology approach. Similarly, we will use the terms *autism*, *autism spectrum disorder* and *autistic* interchangeably.

Pubertal Measurement, Timing, Menses in ASD

There has been limited research on pubertal timing in ASD and most of it has been primarily focused on females largely because it has been easier to detect physical changes (e.g., breast development, onset of menses); yet, such studies have been lacking in methodological rigor (e.g., retrospective and online reporting, based strictly on menarche). Case reports suggest precocious puberty (onset of secondary sexual characteristics before age 8) occurs in some females with ASD (Mouridsen, 1989; Pohl et al., 2014; Yoshirmura et al., 2005), accompanied by deterioration of functioning following pubertal onset (Ayres & Mailloux, 1983; Gillberg & Schaumann, 1981). However, delayed puberty was reported in a clinically referred sample (Harper & Collins, 1979), and from retrospective self-reports (Herguner & Herguner, 2016; Knickmeyer et al., 2006; Whitehouse et al., 2011). In one study, May and colleagues (2017) found no significant differences in pubertal timing between ASD males and females compared to TD peers based on parent- and self-report measures (May et al., 2017). One study that focused on males with ASD reported precocious puberty in a small, clinically referred sample (Tordjman et al., 1997).

Although many studies examining puberty rely on parent- and self-report measures, which may not be reliable indices of precise pubertal timing (Koopman-Verhoeff et al., 2020). In a comprehensive study of early adolescents with and without ASD and their parents, pubertal level based on self- and parent-report showed only slight to fair (κ=.17-.32) and slight to moderate (κ=.21-.44) concordance, respectively when compared to Tanner staging (Corbett et al., 2019). Using such reports may be adequate for general estimates of classification (Koopman-Verhoeff et al., 2020), yet there is low agreement gold standard measures.

Recent research examining early adolescence reported earlier pubertal development in females with ASD, relative to ASD males and TD females (Corbett, Vandekar, et al., 2020). Specifically, females with ASD had significantly earlier breast development and menses by an average of 9.5 months compared to TD females. While results were compelling, the data were cross-sectional and focused strictly on pubertal timing.

The purpose of the current study was to examine interindividual differences in pubertal timing and tempo (progression) in a large sample of early-to-middle adolescents at three time points, one year apart, based on biological sex (female vs. male) and group (ASD vs. TD). The study had two primary aims and hypotheses. Aim 1 estimated interindividual differences in Male External Genitalia (G), Female Breast (B), Pubic Hair (PH) Tanner stage of timing and tempo. The first hypothesis (Hyp) 1a. was that males and females would demonstrate significant interindividual differences in pubertal timing (based on Tanner staging) (Marceau et al., 2011). Hyp 1b. was that males would exhibit later pubertal development compared to females. Aim 2 examined the relation between diagnosis and biological sex by estimating timing and tempo separately in males and females comparing ASD with TD. Based on previous findings, Hyp. 2 stated females with ASD would demonstrate earlier pubertal onset and faster tempo compared to TD females, whereas males with ASD will show comparable timing and tempo compared to TD males. An exploratory aim examined the extent to which pubertal timing predicted internalizing symptoms between the groups.

Methods

The research was carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). The Vanderbilt Institutional Review Board approved the study. Informed written consent and assent were obtained from all parents and study participants, respectively, prior to inclusion in the study.

Participants

Data were collected as part of a longitudinal study on pubertal development and stress (Corbett, 2017). The current study includes data from the first three assessments: Year 1 (Y1) enrollment when the children were between 10-years-0-months to 13-years-11-months of age, Year 2 (Y2), 11 to 14 years and Year 3 (Y3) when the children were between 12 to 15 years. The diagnostic procedures were completed in Y1; however, the physical exam and psychological measures were completed annually.

In Y1, the sample included 244 total youth, with 239 participants that completed the physical exam described below. The ASD group consisted of 140 participants (median age 11.2) including 36 females and 104 males. The TD group consisted of 104 participants (median age 11.6) including 46 females and 58 males. Of the 239 participants to complete the physical exam, one ASD male was missing measurement for G stage, and one TD female was missing measurement for PH stage, resulting in 238 non-missing measurements for GB and PH stage at Y1.

For Year 1, the racial and ethnic characterization of the sample was comprised of 7.9% Black, 83.3% White, 8.7% multiracial, and less than 1% Asian or Pacific Islander. Participants in the ASD and TD groups were recruited from a broad community sample in the southern United States covering a 200-mile radius that targeted medical and health-related services, clinics, research registries, regional autism/disability organizations, schools, and social media platforms. Inclusion for both groups required an intelligence quotient (IQ) score ≥ 70 due to task demands in the source longitudinal study. Children were excluded if taking medications that alter the Hypothalamic-Pituitary-Adrenal (HPA) axis (e.g., corticosteroids; see (Granger et al., 2009)) or HPG axis (e.g., growth hormone), or medical condition known to impact pubertal development (e.g., Cushing's Disease). Demographic information for each group is presented in Table 1.

In Y2, 174 participants were retained (ASD = 89, TD = 89). The ASD group had a median age of 12.5 years, and the TD group had a median age of 12.7 years. The overall attrition rate was 28%, which was comparable to other longitudinal studies after the initial enrollment (Negriff et al., 2015). In Y3 there were 163 participants (ASD = 83, TD = 80). The ASD group had a median age of 13.3 years, and the TD group had a median age of 13.8 years. The overall attrition rate was 33% after the initial enrollment. At Y2 and Y3, some participants were unable to complete the full physical examination due to restrictions on in-person lab visits resulting from the COVID-19 pandemic (Y2 N= 43; Y3 N= 59). For comprehensive characterization of attrition across several demographic variables and by sex and diagnosis see Supplementary Tables 1 and 2. Importantly, the significant drop in numbers between Y1 and Y2 for the ASD group was often the result of dropping out after

eligibility testing was completed such that families chose to no longer participate in the study despite receiving ASD diagnostic confirmation and documentation.

Diagnostic Procedures

The diagnosis of ASD was based on the Diagnostic and Statistical Manual-5 (APA, 2013) and confirmed by an established diagnosis by a psychologist, psychiatrist, or behavioral pediatrician with autism expertise, current clinical judgment by a study team member, and corroborated by the Autism Diagnostic Observation Schedule (ADOS-2; (Lord et al., 2012). In Y1, all participants with suspected or confirmed autism diagnosis completed a comprehensive assessment at an initial eligibility visit. Following the visit, all participants received a research letter containing the diagnostic results from the measures outlined below.

Autism Diagnostic Observation Schedule-Second Edition—Autism Diagnostic Observation Schedule-Second Edition *(ADOS*-2; (Lord et al., 2012) is a semi-structured interactive play and interview-based instrument used to support the diagnosis of ASD. The ADOS was administered by research-reliable personnel.

Social Communication Questionnaire—Social Communication Questionnaire (SCQ; (Rutter et al., 2003) is a screening instrument for symptoms of ASD. A score of 15 is suggestive of ASD. Recent research reported lower sensitivity and specificity (Barnard-Brak et al., 2016); therefore, TD children with a score ≥ 10 were excluded.

Wechsler Abbreviated Scale of Intelligence, Second Edition—Wechsler Abbreviated Scale of Intelligence, Second Edition (WASI-II, (Wechsler, 2011) is a measure of cognitive ability which was used to obtain an estimate of the youth's intellectual functioning (IQ ≥ 70 required to participate in the study).

After an initial eligibility visit, study participants with confirmed classification as ASD or TD, and meeting inclusion criteria, participated in the study visit at Y1 and annually for Y2 and Y3.

Dependent Measures

To measure pubertal development rigorously and comprehensively, the source study employed three different approaches: a physical exam, a parent-report measure, and self-report based on visual representation of Tanner stages (Marshall & Tanner, 1969, 1970). The current study used physical exam as the primary dependent variable for pubertal development, as recent research demonstrated that physical exam is the optimal approach for accurate pubertal measurement rather than parent- and self-reports (Corbett et al., 2019; Koopman-Verhoeff et al., 2020).

Physical Examination (PE).—The PE was completed at each annual visit to reliably identify pubertal development and assign Tanner stage (Marshall & Tanner, 1969, 1970). The exam ascertained two measures with 5 stages for Male External Genitalia (G1-G5 for males) and Female Breast (B1-B5 for females) (G/B stage) and Pubic hair (P1-P5 for both genders) (PH stage). The exam consisted of visual inspection and categorization of pubertal

and genital maturation. To be consistent with the original Tanner staging and to maximize participation, palpation of breasts or measurement of testes was not conducted.

Pubertal assessment consisted of a brief, standardized physical exam conducted by trained, licensed study physicians. A male physician conducted most of the exams, but a female physician provided same-gender exams as requested. The sex of the physician is usually not as important as the participant's comfort level and the competence of the physician (Dorn et al., 2006). Physicians spent approximately 5-minutes to establish rapport, explain the rationale for the exam and address any questions or concerns, which helped to normalize the experience. During the exam, the adolescent was requested to loosen clothing to fully expose breast and lower genital region, rather than disrobing, which aided in the level of comfort for the participants. A companion (e.g., parent or same-gender research member) was offered to accompany the participant in the exam room.

Physicians were blinded to parental- and self-reports. Inter-rater reliability was established between study physicians on 10 randomly selected participants. Cohen's Kappa (κ) was calculated between study physicians to assess the degree to which raters were able to identify Tanner stages for G/B and PH markers. Inter-rater reliability for markers ranged from κ= 0.62 to 0.75 (all $p < 0.001$; substantial agreement). Absolute agreement was .75. Kappa was also calculated to assess the extent to which physicians were able to reliably and independently identify when participants had initiated pubertal maturation (Stage 2) for each marker. Kappa ranged from 0.62 to 1.00 (good to very good). In cases of disagreement, physician ratings were never greater than one stage difference.

Pubertal Development Scale: Pubertal Development Scale (PDS; (Petersen et al., 1988) is a widely used parent- or self-report measure of pubertal status which has satisfactory reliability and validity as an alternative to PE. The PDS responses range from 1 (has not begun) to 4 (is complete) examining growth, skin changes, pubic hair and breast across gender, and girls were asked if they have begun menstruating. The PDS has been employed in studies in autism (Corbett et al., 2012; Corbett et al., 2010; Corbett et al., 2013). To convert the 4-point scale to the Tanner 5-scale stages, the Puberty Category Scores were calculated according to previously established criteria (Carskadon & Acebo, 1993; Crockett, 1988; Shirtcliff et al., 2009). While PE was the primary dependent variable, the PDS was collected for comparison.

The Child Behavior Checklist: The Child Behavior Checklist (CBCL; (Achenbach, 2001) is a broad-based parent report form used to provide children's competencies and behavioral/emotional problems from 6 to 18 years of age. The CBCL Anxiety and Affective (Depression) Domains from Year 3 were used in regression data analysis. However, data from all three years are provided for completeness.

Body Mass Index (BMI): BMI was calculated using the standard formula ($lb./in^2$) × 703 for use with the CDC growth charts for children and adolescents (2 through 19 years; https://www.cdc.gov/healthyweight/bmi/calculator.html). Percentiles were calculated based on sex and age.

Statistical Approach

The analytic approach used to model puberty can produce varying results especially for tempo (Beltz et al., 2014). To examine pubertal timing and tempo, it was essential to use an analytic approach that considers the interindividual heterogeneity of the child to adolescent transition while measuring *when* participants enter puberty and *how* quickly they take to reach subsequent developmental stages. A nonlinear mixed effects model (NLME) was used to estimate individual differences in G/B Tanner stage timing and tempo (Marceau et al., 2011). This model uses a sigmoid curve to estimate subject specific parameters corresponding to timing (the approximate age of Tanner Stage 3).

A nonlinear mixed effects model (NLME) was used to fit Tanner stage (G/B or PH stage) as a function of covariates using a sigmoid model (Marceau et al., 2011).

$$stage_{it} = 1 + [4 \times (1 + exp\{-(\alpha_i + \alpha_1 \times dx_i + \alpha_2 \times BMI_{it} + \alpha_3 \times sex_i) \times (age_i - [\lambda_i + \lambda_1 \times dx_i + \lambda_2 \times BMI_{it} + \lambda_3 \times sex_i])\})^{-1}] + r_{it} \quad (1)$$

where $stage_{it}$ is the Tanner stage for subject i at time point t, and dx_i denotes diagnosis. The alpha terms describe the association between each covariate and pubertal tempo and control the steepness of the sigmoid curve, whereas the lambda terms describe how each variable is associated with pubertal timing and affect the age at which a child reaches Tanner stage 3. We modeled associations between Tanner stage and diagnosis, BMI, and sex. We also allowed interindividual differences in timing by including the subject random effect λ_i. We fit the same model using the parent report to compare results to physician staging.

To test Hyp. 1a for interindividual differences in G/B and PH Tanner stage timing the variance component of the random effect term was tested using a parametric bootstrap to simulate the data under the null hypothesis, that there is no subject-specific intercept, and then fit the NLME model to each bootstrap sample. We used the distribution of 1000 bootstrap samples to compute p-values for the random effect variance component.

To test Hyp. 1b for sex differences in pubertal timing, the λ_3 parameter was tested and the effect of sex on pubertal tempo was tested using the α_3 parameter. Because estimation in NLME models can be challenging, parameter estimates were first by nonlinear least squares, and those values were used as starting values for the NLME model.

To study Hyp. 2, which compared diagnostic differences in timing/tempo within each sex, the model in equation (1) was fit in each sex, separately, without the terms including sex. Within the male and female models, the diagnosis terms were tested to investigate how timing and tempo differ between the diagnostics groups for each sex.

To examine the exploratory aim, linear regression models using the random effects extracted from the non-linear models were used to predict internalizing symptoms from Year 3. These models included age at Year 3, and Year 3 BMI as covariates.

Results

Genital/Breast (G/B) Stage

All Participants: In order to test interindividual and sex differences in pubertal timing and tempo, separate NLME models were fit with G/B stage and PH stage as the outcome. The test of the random effects term was significant in both models indicating substantial interindividual differences in pubertal timing (both bootstrap $p<0.001$). The standard deviation of the random effect term was 0.99 years, suggesting substantial variability in the age at which an individual reaches Tanner stage 3. Tests of fixed effects terms indicated that diagnosis and higher BMI were independently associated with earlier pubertal onset for G/B (Diagnosis, $t=-2.71$, $p=0.007$; BMI, $t=-3.56$, $p=0.001$, Table 2) and PH stage (Table 3) across both sexes. Therefore, Diagnosis and BMI were strong predictors of G/B stage. Specifically, ASD diagnosis is characterized by nearly 5.0 months (0.43 years) earlier G/B stage (Figure 1) and approximately 4.0 months (0.34 years) earlier PH stage. Regarding BMI, an increase in 1 BMI percentile was associated with earlier pubertal onset in G/B stage by approximately 2.96 days and 3.60 days in PH stage. There was no effect of sex on pubertal timing for G/B stage ($t=-1.04$, $p=0.298$), but there was evidence for earlier onset for females in PH stage (Table 3).

In the total sample, there was evidence for tempo differences in G/B stage associated with BMI ($t=3.33$, $p=0.001$), or sex ($t=-3.31$, $p=0.001$), but not diagnosis ($t=0.47$, $p=0.64$) (Table 2). For PH stage, there was only evidence for an effect of sex (Table 3).

Males: We fit the G/B and PH stage models separately in males and females to investigate diagnostic differences specific to each sex. Male participants with ASD showed earlier G stage by approximately 3.43 months (Table 4; Figure 2A) and earlier PH stage by 2.88 months but neither was significantly different than TD males (Table 5; Figure 3A). In addition, we found evidence that BMI was associated with earlier timing in G/B stage and PH stage (Table 4 & 5; Supplementary Figures 1 and 2).

Females: For the females, participants with ASD showed earlier B stage by approximately 8.28 months (Table 4; Figure 2B) and earlier PH stage by nearly 6.0 months (Table 5; Figure 3B). However, there was little evidence for differences in tempo for B or PH stage. An increase in 1-unit of percentile BMI was associated with earlier GB by 5.8 days and PH stage by roughly 4.6 days (Supplementary Figures 3 and 4).

PDS Algorithm

All Participants: Results for the PDS model align with the PH stage model, with strong effects for timing in diagnosis, BMI, and sex. As such, ASD is associated with earlier PDS by nearly 6.0 months (0.46 years) (Supplementary Table 3). An increase of one BMI percentile is associated with earlier PDS values by nearly 2.9 days. Female sex is associated with more advanced perceived development on the PDS by nearly 1.75 years.

Pubertal Timing and Internalizing Symptoms

The random effects terms from the nonlinear models were extracted and used as a predictor in exploratory linear models with internalizing symptoms at Year 3 (CBCL Anxiety and Affective domains) as the outcome in order to understand how timing affects internalizing symptoms in males and females separately. Age at Year 1 and Year 1 BMI were included as covariates. Models with random effects for pubertal timing for GB stage and PH stage were evaluated. Parameter estimates for GB and PH models in males and females are provided in Supplementary Tables 4 and 5.

Females: For females, pubertal timing was not significantly associated with anxiety ($p=0.25$) or affective problems ($p=0.054$) at Year 1. Similarly, models with the PH Stage timing random effect were not associated with anxiety ($p=0.27$) or affective problems ($p=0.19$). No other terms in these models were significant.

Males: For the model using the GB stage random effect, in males, only BMI at Year 1 was a significant predictor of anxiety ($p=0.016$) but not for affective problems ($p=0.19$). Pubertal timing was not predictive for both anxiety ($p=0.16$) and affective problems ($p=0.70$). In males, PH stage pubertal timing was not associated with anxiety ($p=0.16$) or affective problems ($p=0.41$). No other terms in this model were significant.

Discussion

The overarching goal of the study was to examine pubertal timing and tempo in a large, well characterized sample of youth with ASD and TD across three time-points as part of a longitudinal study. The aims examined interindividual differences based on sex (males and females), diagnosis (ASD and TD) and the relationship to physical characteristics (BMI). This was accomplished with the use of sophisticated statistical models and rigorous characterization of pubertal development.

Regarding sex-based differences, females entered puberty earlier than males, which is consistent with extensive research and established developmental norms (e.g., (Lee, 1980; Marceau et al., 2011; Susman et al., 2010). While pubertal tempo is less studied and established in the field for typically developing children, prior studies have revealed a faster tempo in males compared to females, which is predicted by BMI. However, in the current study in which we include TD and ASD children, there were no diagnostic differences based on tempo.

Nevertheless, based on the extant literature, the relation between diagnosis and biological sex was examined by estimating timing and tempo separately in males and females with ASD compared to TD males and females. For males, the results showed that males with ASD enter puberty 3.43 months earlier than TD males, though this effect for diagnosis was not statistically significant. In contrast BMI was a strong predictor of genital stage. The result is largely consistent with hypotheses and previous reports showing only females with ASD evidenced earlier puberty based on breast development (Corbett, Vandekar, et al., 2020). It may be the case that due to males in general having later development, the diagnostic distinction is not observed until the later waves of the study when the boys

were relatively older. The results are not consistent with one of the few studies exclusively looking at males with ASD, which reported earlier pubertal timing (Tordjman et al., 1997); although they are partially consistent with another study showing no onset differences for males or females with ASD compared to TD youth (May et al., 2017).

Similarly to genital stage, there were no diagnostic differences in pubic hair stage between TD and ASD males, underscoring the physiologically distinct hormonal changes that underlie genital vs. pubic hair development. Overall, while females showed earlier onset compared to males, the males progressed through puberty at an accelerated rate; therefore, the faster tempo may intensify the impact of early timing (Marceau et al., 2011). Males with ASD with atypical physical maturation may be particularly vulnerable due to incongruence between psychosocial and physical development. As predicted in the *Maturational Deviance* hypothesis, such divergence in normative development in both timing and tempo could contribute to enhanced psychological and emotional distress (Petersen & Taylor, 1980).

For females, the results corroborate previous findings of advanced pubertal onset in females with ASD (Corbett, Vandekar, et al., 2020; Mouridsen, 1989; Pohl et al., 2014; Yoshirmura et al., 2005). Breast development showed a nearly 9-month difference in onset for females on the autism spectrum compared to TD peers. In addition, PH differences emerged by the third year of data collection revealing earlier emergence of pubic hair in adolescent females with ASD by nearly 6 months. While the underlying mechanism of early entry into puberty remains unclear, prior studies have suggested that the age of onset of puberty is driven by genetic factors (Palmert & Hirschhorn, 2003). There are well-described associations of early or precocious puberty in various syndromes (e.g., Cohen syndrome, Williams syndrome, Angelman syndrome; and neurological disorders (e.g., Rett syndrome, epilepsy) (Winter et al., 2019). It is theorized that the complex genetic landscape of these disease processes plays a pivotal role in the determination of pubertal timing and may involve alterations in the finely tuned hypothalamic-pituitary-gonadal axis. For example, in Rett syndrome, a neurodevelopmental disorder that is most commonly caused by a mutation in the Methyl-CpG-binding protein 2 gene (MECP2), earlier onset of puberty has been described (Killian et al., 2014). Data from mouse models suggest that MECP2-null mice have modified gene expression in the hypothalamus (Ben-Shachar et al., 2009) and altered estrogen receptor expression (Westberry et al., 2010). Although studies are needed, differences in the HPG axis form the basis of a possible mechanistic explanation for pubertal differences in children with Rett syndrome. Findings in other neurodevelopmental disorders underscore the importance of thoroughly describing pubertal timing in the ASD population in order to more fully elucidate the role of genetic determinants of pubertal progression in all children.

The tempo or rate of change was similar in females. The disassociation between timing and tempo appears consistent with some studies (Huang et al., 2009; Marceau et al., 2011), but in contrast to others that have found inverse relationships in females (Biro et al., 2001; Mendle et al., 2010; Pantsiotou et al., 2008) or males (Marceau et al., 2011). Collectively, findings underscore the notion that distinct underlying endocrine mechanisms influence timing and tempo development for genital and breast development (e.g., gonadotropin-releasing hormone) and pubic hair (e.g., androgens) and therefore should be studied

together, when possible. In general, adrenarche precedes and is independent of gonadarche (Marceau et al., 2015; Palmert et al., 2001).

Several models have been proposed to explain how deviations in pubertal timing and/or tempo can lead to developmental psychopathology. For example, the *Maturational Deviance* hypothesis proposes that differences in normative development in timing (early, delayed) or tempo (fast, slow) lead to greater psychological distress and behavioral issues (Petersen & Taylor, 1980). On the other hand, the *Accentuation* hypothesis posits that life transitions accentuate underlying emotional and behavioral predispositions during these periods of heightened novelty and uncertainty (Caspi & Moffitt, 1991). Whether cause or effect, it seems that youth who mature early (especially with faster tempo) are at greater psychological, social and physiological risk due to their lack of preparedness for the increased demands of adolescence (Ge et al., 2002). Such discrepancy may be magnified in ASD, a condition marked by social communication difficulties and poor adaptation to change (APA, 2013). However, in the current study pubertal timing did not predict internalizing symptoms in Year 3. It is possible that we did not have the sample size to identify potential differences. Also, we used a proxy for anxiety and depression symptoms based on parent report, but we did not use clinical interviews or similar approaches to formally identify symptomology or diagnose participants.

Furthermore, pubertal onset and progression across biological sex and diagnostic groups are highly influenced by BMI, which appears stronger in females than males. Yet in relation to predicting internalizing symptoms, BMI was a strong predictor albeit in males only. Recently it was reported that children and adolescents with ASD are more overweight and obese compared to their peers (Corbett et al., 2021), a finding consistent with other previous studies (e.g., (Criado et al., 2018; Curtin et al., 2010; Healy et al., 2019; Zuckerman et al., 2014). This concerning trend is within the context of increasing numbers of youth with weight-related health concerns in the general public, which warrants clinical and research attention to identify the antecedents, predictors, and treatment targets specific to ASD.

In the current study, Tanner stages using the gold standard physical exam served as the primary dependent variable. For comparison, the often-used PDS (parent questionnaire) was assessed for comparison. Analysis of the timing and tempo of puberty according to the PDS revealed that diagnosis and BMI were strong predictors. There was also a significant effect of sex showing that females enter puberty earlier. However, the PDS estimated pubertal entry to be around 1.75 years earlier in females than males, whereas the physical exam was closer to one half year earlier. The difference of an entire year suggests that the PDS may have overestimated pubertal onset in the current sample. Given such findings, the PDS is able to broadly characterize pubertal development; however, it has been shown to be less precise than more robust measures such as physical exam (Corbett et al., 2019; Koopman-Verhoeff et al., 2020), so estimates of differences in timing or tempo may be biased.

To our knowledge, this is the first study examining pubertal tempo in youth with ASD and among only a few rigorously examining tempo in TD participants. The initial findings underscore the importance of considering timing and tempo in adolescents with and

without ASD. Insights gained from carefully exploring pubertal changes with regards to interindividual progression offers insights for psychological, social, and physiological development, especially for those experiencing atypical patterns. Youth with ASD are less socially mature than peers and often experience difficulty during the heightened social demands of adolescence; therefore, deviations in pubertal development may intensify such challenges amidst discordance between social and physical development.

Limitations and Future Directions

While there are several strengths of the study (e.g., focus on pubertal timing and tempo, comprehensive examination, well-characterized large sample), there are limitations to acknowledge. There was significant attrition from Y1 to Y3, largely between Y1 and Y2, which is a challenge with longitudinal studies. It is plausible that the inclusion of physical exam may have contributed to participant drops after initial participation. Another limitation is the annual vs. bi-annual or more frequent study visits. Due to the non-linear nature of pubertal progression, a more frequent collection of data may be optimal. The decision to include physical exams as a more precise albeit potentially invasive procedure was balanced with the idea of more frequent visits. As noted by others, there is an ongoing tension in longitudinal research between the rigor of methodology and attrition outcomes (Marceau et al., 2011). Finally, the initial wave of the study occurred when the participants were between 10 to 13 years of age; however, as previously reported (Corbett, Vandekar, et al., 2020) and shown in Figures 2 and 3, many of the females had already entered puberty; therefore, the absolute onset and progression of puberty cannot be determined. Lest children are measured before the onset of puberty and followed until full sexual maturation, children who are more developed will have less growth to acquire thereby limiting the measurement of timing and tempo (Negriff et al., 2015). Finally, an exploratory aim examined the extent to which pubertal timing predicted internalizing symptoms between the groups when the majority of the sample reached early-to-mid puberty (Y3). It is plausible that pubertal onset impacted internalizing symptoms at different developmental stages; nevertheless, comparing timing to internalizing symptoms across all years was beyond the scope of the current study. Future studies are planned to address these aforementioned concerns.

To our knowledge, this is the first study examining pubertal tempo in youth with ASD and among only a few rigorously examining timing. Findings showing advanced and faster pubertal maturation in ASD youth suggest greater risk of psychological, social, and physiological challenges due to their lack of preparedness for the increased demands of adolescence. The findings underscore the importance of considering developmental trajectories in adolescents with and without ASD and the associations with important physical (BMI) profiles. Insights gained from carefully exploring pubertal changes may offer insights for psychological, social, and physiological development especially for those experiencing atypical patterns.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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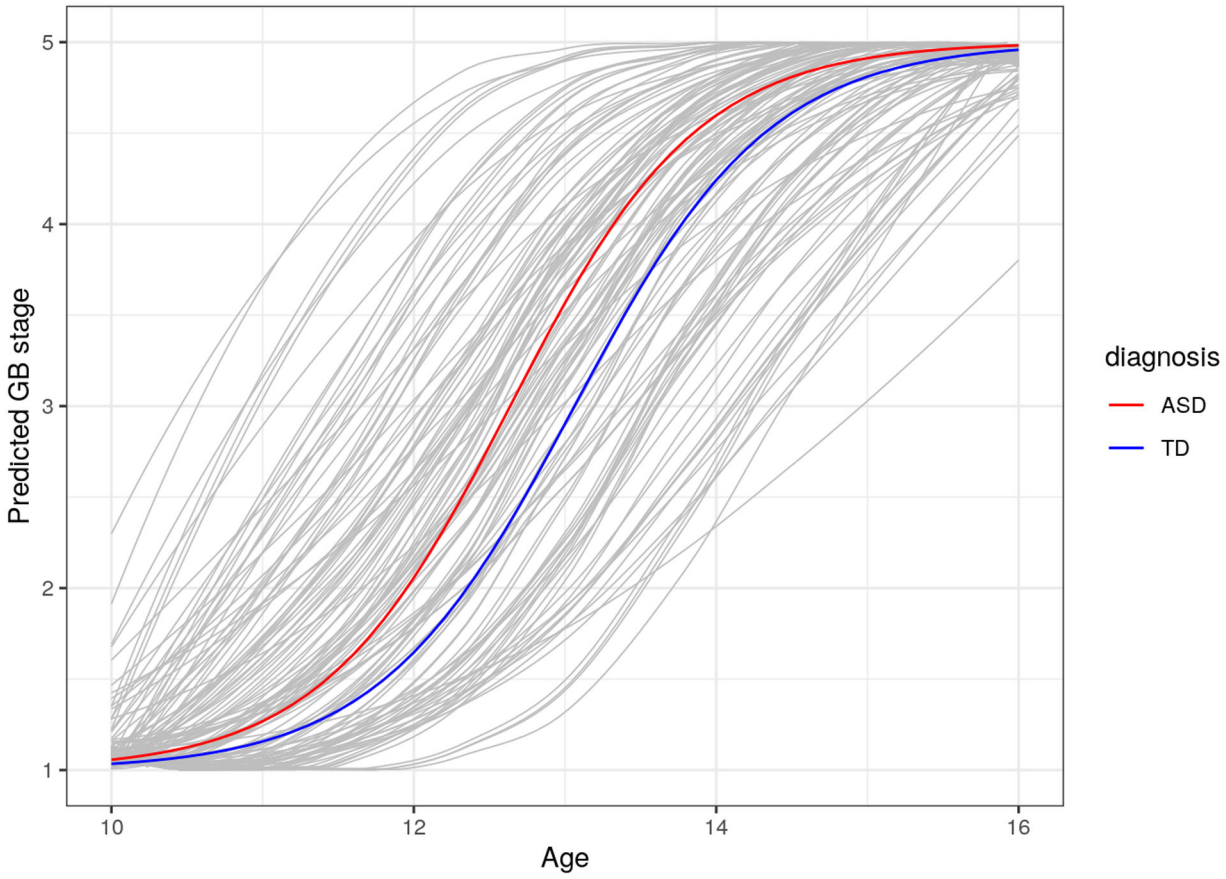

Figure 1.
Participants with ASD Show Advanced Pubertal Onset in Genital (G) and Breast (B) Development Compared to TD Youth.

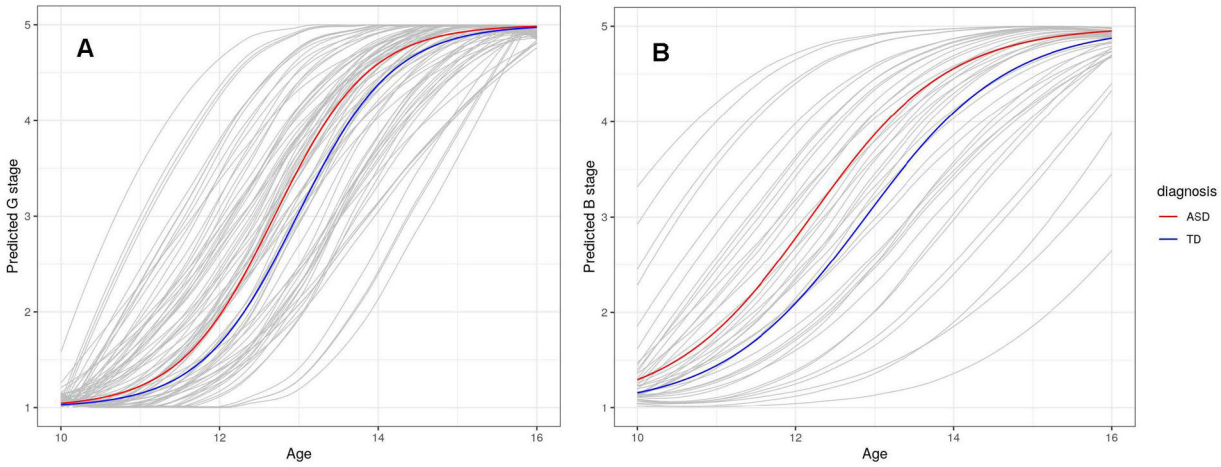

Figure 2.

(A) Males with ASD Show Advanced Genital Development Compared to Typically Developing Males. **(B)** Females with ASD show advanced Breast Development Compared to Typically Developing Females.

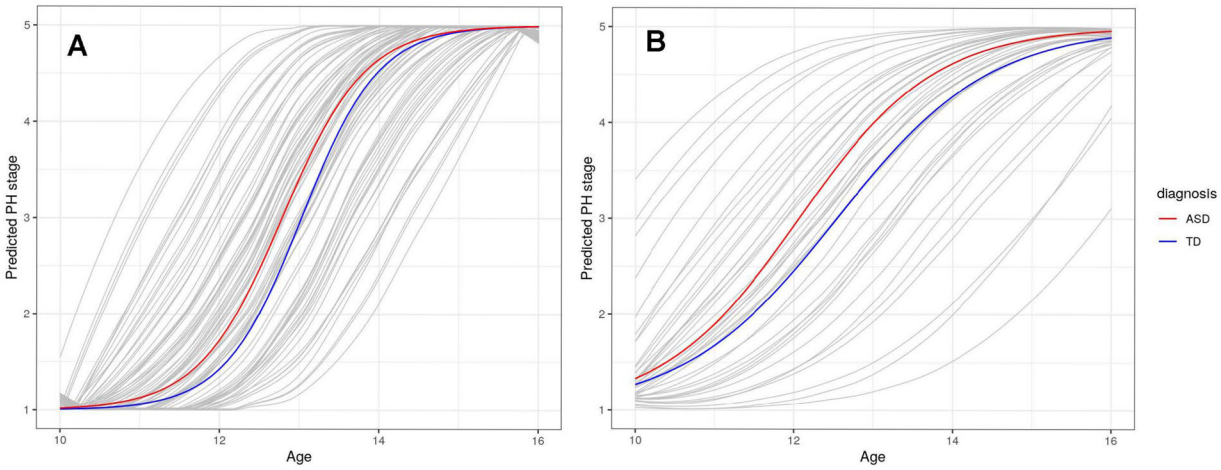

Figure 3.

(A) No Diagnostic Differences in Pubic Hair (PH) Development Between Males with ASD or Typically Development. **(B)** Females with ASD show advanced Pubic Hair (PH) Development Compared to Typically Developing Females

Table 1.

Demographic Statistics

		TD (N=104)		ASD (N=140)		Test Statistic	*p*-value
	N	**Md**	**IQR**	**Md**	**IQR**		
Age at Y1	244	11.6	(10.6, 12.6)	11.2	(10.5, 12.2)	$F_{1,242}$=2.71	0.101[3]
Percentile BMI Y1	239	53	(30, 88)	69	(39, 96)	$F_{1,237}$=6.12	0.014[3]
GB stage at Y1	238	2	(1, 3)	2	(1, 3)	$F_{1,236}$=0.04	0.835[3]
PH stage at Y1	238	2	(1, 3)	1	(1, 3)	$F_{1,236}$=0.12	0.733[3]
PDS algorithm Y1	239	2	(1, 3)	2	(1, 3)	$F_{1,237}$=0.13	0.719[3]
CBCL Affective Y1	242	52	(50, 59)	67	(60, 73)	$F_{1,240}$=114.50	<0.001[3]
CBCL Anxiety Y1	242	51	(50, 59)	70	(60, 72)	$F_{1,240}$=133.25	<0.001[3]
Age at Y2	174	12.7	(11.8, 13.8)	12.5	(11.7, 13.6)	$F_{1,172}$=1.27	0.261[3]
Percentile BMI Y2	129	50	(29, 89)	85	(58, 98)	$F_{1,127}$=15.38	<0.001[3]
GB stage at Y2	132	2	(2, 4)	3	(2, 4)	$F_{1,130}$=1.33	0.250[3]
PH stage at Y2	133	2	(2, 4)	3	(2, 4)	$F_{1,131}$=2.42	0.122[3]
PDS algorithm Y2	171	3	(2, 4)	3	(2, 4)	$F_{1,169}$=0.23	0.633[3]
CBCL Affective Y2	171	51	(50, 56)	63	(55,72)	$F_{1,169}$=55.14	<0.001[3]
CBCL Anxiety Y2	171	51	(50, 59)	66	(58, 71)	$F_{1,169}$=74.42	<0.001[3]
Age at Y3	163	13.8	(12.8, 14.8)	13.3	(12.6, 14.4)	$F_{1,161}$=3.30	0.071[3]
Percentile BMI Y3	104	51	(31, 86)	77	(42, 95)	$F_{1,102}$=4.72	0.032[3]
GB stage at Y3	103	4	(2, 5)	4	(3, 5)	$F_{1,101}$=0.00	0.984[3]
PH stage at Y3	104	4	(3, 5)	4	(3, 5)	$F_{1,102}$=0.00	0.976[3]
PDS algorithm Y3	163	3	(3, 4)	3	(3, 4)	$F_{1,161}$=0.13	0.723[3]
CBCL Affective Y3	163	51	(50, 63)	61	(51, 70)	$F_{1,161}$=19.24	<0.001[3]
CBCL Anxiety Y3	163	51	(50, 58)	62	(58, 70)	$F_{1,161}$=46.36	<0.001[3]
	N	**Proportion**		**Proportion**		**Test Statistic**	
Sex: Female	244	0.442 46/104		0.257 36/140		X^2=9.17	0.002[2]
Race	244					X^2=12.06	0.007[2]
White		0.856 (89/104)		0.814 (114/140)			
Black		0.019 (2/104)		0.121 (17/140)			
Asian/Pacific Islander		0.000 (0/104)		0.007 (1/140)			
Multiracial		0.125 (13/104)		0.057 (8/140)			

Note: N is the number of non-missing values.

[1] Kruskal-Wallis.

[2] Pearson.

[3] Wilcoxon.

TD, typical development; ASD, autism spectrum disorder; Md, median; IQR, interquartile range; BMI, body mass index; CBCL, Child Behavior Checklist; GB, genital/breast; PH, pubic hair; PDS, pubertal development scale; Y, Year.

Table 2.

Fixed Effects Parameter Estimates for GB Stage Model

	Parameter	Estimate	SE	DF	*t*-value	*p*-value
Tempo						
	Intercept	1.133	0.135	222	8.38	<0.0001
	Diagnosis	0.058	0.124	222	0.47	0.642
	BMI	0.006	0.002	222	3.33	0.001
	Sex	−0.411	0.124	222	−3.31	0.001
Timing						
	Intercept	13.591	0.188	222	72.09	<0.0001
	Diagnosis	−0.425	0.157	222	−2.71	0.007
	BMI	−0.008	0.002	222	−3.56	0.001
	Sex	−0.171	0.164	222	−1.04	0.298

Note: Tempo parameters control the rate of progression through puberty, with positive values being faster. Timing parameters control the age at which an individual reaches stage 3 in years. SE, standard error; DF, degrees of freedom; BMI, body mass index

Table 3.

Fixed Effects Parameter Estimates for the PH Stage Model

	Parameter	Estimate	SE	DF	*t*-value	*p*-value
Tempo						
	Intercept	1.867	0.166	223	11.22	<0.0001
	Diagnosis	0.080	0.123	223	0.65	0.517
	BMI	0.001	0.002	223	0.64	0.523
	Sex	−0.892	0.135	223	−6.62	<0.0001
Timing						
	Intercept	13.702	0.172	223	79.53	<0.0001
	Diagnosis	−0.335	0.145	223	−2.31	0.022
	BMI	−0.010	0.002	223	−4.71	<0.001
	Sex	−0.482	0.150	223	−3.21	0.002

Note: Tempo parameters control the rate of progression through puberty, with positive values being faster. Timing parameters control the shift of the curve along the X-axis in years. SE, standard error; DF, degrees of freedom; BMI, body mass index

Table 4.

Fixed Effects Parameter Estimates for GB Stage Model by Sex

	Parameter	Estimate	SE	DF	*t*-value	*p*-value
Males						
Tempo						
	Intercept	1.039	0.152	155	6.82	<0.0001
	Diagnosis	0.018	0.165	155	0.11	0.915
	BMI	0.009	0.003	155	3.64	0.0004
Timing						
	Intercept	13.337	0.202	155	66.03	<0.0001
	Diagnosis	−0.286	0.182	155	−1.57	0.119
	BMI	−0.006	0.002	155	−2.25	0.026
Females						
Tempo						
	Intercept	0.856	0.217	64	3.94	0.0002
	Diagnosis	0.049	0.195	64	0.25	0.804
	BMI	0.003	0.003	64	1.07	0.287
Timing						
	Intercept	14.035	0.360	64	38.94	<0.0001
	Diagnosis	−0.693	0.290	64	−2.39	0.020
	BMI	−0.016	0.005	64	−3.32	0.002

Note: Tempo parameters control the rate of progression through puberty, with positive values being faster. Timing parameters control the shift of the curve along the X-axis in years. SE, standard error; DF, degrees of freedom; BMI, body mass index

Table 5.

Fixed Effects Parameter Estimates for PH Stage Model by Sex

	Parameter	Estimate	SE	DF	*t*-value	*p*-value
Males						
Tempo						
	Intercept	1.786	0.203	157	8.78	<0.0001
	Diagnosis	−0.147	0.200	157	−0.74	0.462
	BMI	0.004	0.003	157	1.58	0.115
Timing						
	Intercept	13.566	0.182	157	74.60	<0.0001
	Diagnosis	−0.244	0.166	157	−1.47	0.143
	BMI	−0.008	0.002	157	−3.74	0.0003
Females						
Tempo						
	Intercept	1.002	0.220	63	4.55	<0.001
	Diagnosis	0.131	0.182	63	0.72	0.473
	BMI	0.0004	0.003	63	0.15	0.880
Timing						
	Intercept	13.461	0.325	63	41.39	<0.0001
	Diagnosis	−0.476	0.280	63	−1.70	0.094
	BMI	−0.013	0.004	63	−2.88	0.005

Note: Tempo parameters control the rate of progression through puberty, with positive values being faster. Timing parameters control the shift of the curve along the X-axis in years. SE, standard error; DF, degrees of freedom; BMI, body mass index