Published in final edited form as:

Res Child Adolesc Psychopathol. 2023 June ; 51(6): 819–832. doi:10.1007/s10802-023-01030-7.

Aging and Pubertal Development Differentially Predict Symptoms of ADHD, Depression, and Impairment in Children and Adolescents: An Eight-Year Longitudinal Study

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Abstract

Activational effects of the reproductive neuroendocrine system may explain why some youths with ADHD are at greater risk for exacerbated ADHD symptoms (hyperactivity, inattention, impulsivity) during adolescence. For youths diagnosed with ADHD, first signs of ADHD symptoms become noticeable by multiple reporters (e.g., teachers, parents) when children enter schools, typically around kindergarten. The current study examined possible sex differences in ADHD, impairment, and comorbidity due to pubertal effects, as the role of pubertal development in ADHD is understudied. ADHD symptoms, depressive symptoms, impairment, and pubertal stage were assessed annually by multiple reporters in a well-characterized community sample of 849 children over-recruited for ADHD over eight years. Ages ranged from 7 to 13 years (38.16% female) at wave 1. Multilevel models indicated that males had higher levels of hyperactivity, impulsivity, and inattention than females, but that females had higher levels of impairment than males. Inattention symptoms did not show marked maturation changes. Hyperactivity and impulsivity declined as youth aged and impairment increased as youth aged. Lastly, depressive

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Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10802-023-01030-7.

Compliance with Ethical Standards

Ethical Standards and Informed Consent The authors complied with APA ethical standards in the treatment of their participants and ethics approval was obtained from the Institutional Review Board at Oregon Health & Science University. A parent/legal guardian provided written informed consent and children provided written assent.

The authors have no relevant financial or non-financial interests to disclose.

[1]For simplicity, we designate "males" as youth who were assigned male at birth and are presumed to have testicular maturation throughout puberty, whereas we designate "females" as youth who were assigned female at birth and are presumed to have ovarian maturation throughout puberty. Although, there are many instances in which this presumption is erroneous (e.g., intersex youth; trans* youth; youth with delayed or precocious puberty).

symptoms largely increased as youth aged and were higher amongst youth at later pubertal stages. Put together, aging and pubertal development are associated with improved ADHD symptoms but not for youth with high impairment. Findings from this study contributes to understanding the role that aging, pubertal status, and pubertal development plays in ADHD, impairment, and comorbidity in children and adolescents.

Keywords

ADHD; Depression; Impairment; Puberty; Aging

Attention-deficit/hyperactivity disorder (ADHD) is a neurodevelopmental disorder with a prevalence rate of roughly 5% in youth ages 6 to 18 years across the world (Polanczyk et al., 2015). ADHD symptoms are typically noticed by caregivers/teachers when children enter primary/elementary school and behaviors diverge from those common to same-age peers. As children with ADHD mature, hyperactive symptoms generally decline (Nigg, 2013), while inattentive symptoms show stability (Banaschewski et al., 2018). Given childhood ADHD's association with increased impairment and major depressive disorder beginning in adolescence and continuing into young adulthood (Biederman et al., 2008), exploration of ADHD symptom trajectory and co-occurrence with depressive symptoms during adolescence deserves more attention. The present study's central aim is to investigate the trajectory of ADHD symptoms as well as co-occurring impairment and depressive symptoms in children from 7 to 18 years of age. We leverage eight waves of longitudinal data between childhood and adolescence to parse how aging and pubertal development differentially impact symptom trajectories.

ADHD, Impairment, and Depressive Symptom Trajectories from Childhood to Adolescence

The prevalence of ADHD diagnosis and the manifestation of its symptoms shows a developmental trajectory. ADHD diagnosis and its hyperactive-impulsive symptoms increase between preschool to reach a peak around school entry (Lahey et al., 2005) with hyperactivity-impulsivity being a particularly common manifestation of ADHD in males[1] (vs. females; Martel et al., 2009). Symptoms particularly of inattention and impairment are most noticeable starting around school entry and are more stable throughout development and into young adulthood (reviewed by Faraone et al., 2006). Impairment associated with ADHD seems to become particularly pronounced in females during adolescence (Chronis-Tuscano et al. 2010). However, adolescence remains a relatively understudied developmental period in relation to the trajectory of ADHD symptoms and their associated impairment.

Depressive disorder has typical onset during adolescence and affects approximately 13% of the U.S. population (National Survey on Drug Use and Health, 2017). Children and adolescents diagnosed with ADHD are more likely to have a depression diagnosis compared

to typically developing youth, and these problems seem to increase during adolescence (Chronis-Tuscano et al., 2010). Yet, it is unclear why depression is so often comorbid with ADHD during adolescence (Brunsvold et al., 2008), although one potential mechanism linking ADHD and depression is emotion regulation ability, or more specifically poor frustration tolerance (Seymour & Miller, 2017; Seymour et al., 2014).

Organizational-Activational Hypothesis and ADHD

Organizational and activational effects of the reproductive neuroendocrine system may provide insight into how this system interplays with ADHD and depressive symptoms across development. Early organization of sex development *in utero* through the first years of life sets the stage for secondary sex development during puberty (Schulz et al., 2009). During puberty, hormones activate growth of secondary sex characteristics (e.g., gonads, genitalia), sexually dimorphic systems (e.g., brain), and behaviors/symptoms (e.g., ADHD, depression). Puberty thus represents a sensitive developmental period when youth become increasingly vulnerable to emotional and behavioral dysregulation and psychiatric conditions (Cole et al., 2021). Youth with ADHD may be especially vulnerable to depression as they undergo physical and neurobiological changes related to activational effects of puberty and pubertal hormones that modulate neural networks implicating cognitive functioning (Roy et al., 2017) and reward neurocircuitry (Martel et al., 2009). Onset of mood symptoms in adolescence is also impacted by neurobiological sensitivity to cyclical ovarian hormone fluctuations in many individuals (Dubol et al., 2020), with cyclical changes in estradiol and testosterone predicting daily severity of ADHD symptoms among females with high trait impulsivity (Roberts et al., 2018).

Models Must Account for the Complexity of Neurodevelopment and Maturational Development

At its core, the organizational-activational hypothesis of hormonal influence posits that as youth traverse adolescence and across the process of pubertal maturation, hormonal changes affect risk in complex ways. At a cross-sectional level, age and pubertal stage are highly interrelated and statistical modeling of stage-for-age generates an index where youth are at a greater (or lower) stage compared to same-aged peers. It is impossible for cross-sectional studies to disentangle between-individual development, such as age and pubertal stage, from within-individual developmental processes, such as aging and pubertal maturation. Longitudinal investigation of symptomatology observed as youth mature from childhood to adolescence is required to advance understanding of how risk for psychopathology changes as youth mature. In addition to aging, pubertal development co-occurs at transitional ages marking the end of childhood and entry into adolescence, and pubertal stage-for-age varies across youth. Therefore, longitudinal models are needed that account for both within- and between-individual processes using statistical modeling approaches, such as multilevel models, that account for collinearity— high correlation between aging and pubertal development— while disentangling unique influence of these developmental variables on ADHD and depression symptomatology. The present study is

the first study to directly examine pubertal effects on ADHD symptoms, impairment, and comorbidity in a longitudinal community sample over-recruited for ADHD.

Current Study

The present study examined the impact of aging and pubertal development on ADHD, depressive symptoms, and impairment across eight years of development in a community sample of youth. First, we examined the impact of pubertal changes (or development) on ADHD symptoms, impairment, and depressive symptoms, respectively. Next, we examined sex differences in ADHD and depressive symptoms as youth aged. Finally, we evaluated whether effects differed in those with and without ADHD or based on ADHD-depression comorbidity. Given that the sample's age range spans from childhood to adolescence, it was expected that severity of ADHD and depressive symptoms would change over time. Specifically, we hypothesized that depressive symptoms would increase for both males and females with a larger increase for females. Inattention was expected to stay stable. Hyperactivity and impulsivity were expected to decrease, primarily for males. Lastly, we hypothesized that as youth mature in pubertal stage, ADHD-related impairment and depressive symptoms would increase in females but not in males.

Method

Study Overview

Participants were drawn from the Oregon ADHD Cohort, a well-characterized child cohort with a planned missingness design; the community-based recruitment, enrollment, and multi-informant assessment procedures for ADHD diagnosis have been detailed elsewhere (Musser et al., 2016; Karalunas et al., 2017). Ethics approval was obtained from the Institutional Review Board at Oregon Health & Science University. A parent/legal guardian provided written informed consent and children provided written assent. Data for the current study was drawn from 849 children at Year 1 (aged 7–13 years) through 305 children at Year 8 (14–18 years). Participants self-reported their sex assigned at birth and in this manuscript we utilize the terms male and female due to the hormonal, biological basis of our project, however, these limited terms may not accurately describe the gender identity of all participants (Hartung & Lefler, 2019; Heidari et al., 2016) nor does the sex assigned at birth always reflect biological sex at genetic, organic, hormonal, structural, neural and/or phenotypic levels.

Diagnostic Assignment

All materials were scored and presented to a clinical diagnostic team comprising board certified child psychiatrist with over 25 years of experience and a licensed child neuropsychologist with over 10 years of experience. Blind to one another's ratings, they formed a diagnostic opinion based on all available information. Their agreement rate for all diagnoses discussed in this paper was satisfactory (ADHD, kappa = 0.88; ADHD subtype, $k > 0.80$, all other disorders with at least 5% base rate, $k > 0.68$). Disagreements were conferenced and consensus reached. Cases where consensus was not achieved for ADHD diagnosis were excluded.

Using a best estimate procedure, DSM-IV diagnoses were made independently by each clinician. To count symptoms, the clinicians used the following rule: If both parent and teacher ratings exceeded a t-score of 60 on at least one ADHD scale and both rated at least 3 symptoms as “often” or “very often” on the ADHD rating scale (or for parents, were counted present on the KSADS), the “or” algorithm could be employed. When either informant fell below this mark, and clinicians judged that this was not explained by successful medication treatment during the school day, then the case was rejected as failing to meet the DSM requirement of substantial symptoms present in more than one setting. In addition, it was required that all other DSM criteria were met, including (a) impairment (determined through clinical interview and questionnaires), (b) onset prior to age 7 (current at the time we began enrollment), (c) sustained impairing symptoms > 1 year, and (d) symptoms of ADHD were not better accounted for by comorbid conditions, trauma history, or other confounds. 60% of participants met criteria for clinical ADHD at wave 1. Of the 340 participants who did not meet criteria for ADHD, 65% had 0 symptoms of ADHD on the KSADS and 35% had subthreshold symptoms of ADHD (see Supplemental Fig. 1).

Longitudinal Retention

Resource limitations mandated a planning missing design from among those youth such that the target *N* was 535 at Year 3 (in actuality, there were 530 children in Year 3). Those selected for follow up were chosen because their ADHD (321 participants) and non-ADHD (209 participants) status was clear and unambiguous. Those not followed included those with parent-teacher disagreement or sufficient comorbidity to reduce confidence that they were clear cases or non-cases by our criteria.

Measures

ADHD Symptoms and Overall Impairment—The Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS; Puig-Antich & Ryan 1986) is a semi-structured clinical interview used to measure current and past symptoms of mood, anxiety, psychotic, and disruptive behavior disorders in children ages 6 to 18 years old. The KSADS was administered to parents and diagnoses were based on the clinician’s overview of the interview responses, rather than relying solely on parent responses. The KSADS ADHD section has high internal consistency with a Cronbach’s alpha of 0.85 (Jans et al., 2009).

The KSADS data can be translated to DSM diagnostic criteria and was used in this study to determine the number of ADHD symptoms (for descriptive statistics see Table 1). Range of scores for each symptom type is as follows: 0–9 for inattention, 0–6 for hyperactivity, 0–3 for impulsivity. Hyperactive and impulsive symptoms were examined separately to determine if hormonal effects might differentially impact hyperactivity and impulsivity (Parke et al., 2015). Across all waves, Cronbach’s alphas ranged from 0.89 to 0.94 for inattention, 0.56–0.88 for hyperactivity, and 0.49–0.80 for impulsivity.

The Global Assessment Scale of Functioning (GAF; Endicott et al., 1976) was used by the researchers to evaluate overall levels of impairment, based on parent responses from the KSADS interview. The GAF has excellent interrater reliability with intraclass correlation coefficients (ICC) of 0.86 (Hilsenroth et al., 2000).

Depressive Symptoms—The Children's Depression Inventory (CDI; Kovacs 1985, 1992) is a well-validated measure of depressive symptoms with high levels of internal consistency (Cronbach's alphas = 0.80–0.94), test-retest reliability (reliability coefficient = 0.38–0.87), and good predictive, convergent, and construct validity (Craighead et al., 1998; Saylor et al., 1984). Participants responded to 27 items on a 0 (absent) to 2 (severe) scale regarding their symptoms in the last two weeks (see Table 1 for descriptives). Total raw scores were used in analyses in order to directly examine the effects of sex and age on depressive symptoms, rather than control for these differences using T-scores.

Pubertal Development

Pubertal Development Scale.: The parent- and self-report forms of the Pubertal Developmental Scale (PDS; Petersen et al., 1988) were administered. The PDS includes five items that ask about growth in height, body hair, and skin changes. The PDS also asks about breast development and menarche in females and deepening of voice and growth of hair on face for males. Participants rated each item on a 1 (barely started) to 4 (seems complete) scale. The PDS has demonstrated good internal consistency with Cronbach's alpha ranging between 0.91 and 0.96 and high test-retest reliability (ICC = 0.81–0.92; Koopman-Verhoeff et al., 2020). Distribution of time-fixed variables sex, pubertal stage, and age are shown in Table 2.

Although both parents and youth completed the PDS, only the parent data was used as the youth report appeared less reliable, especially at younger ages. For example, 4% of participants appeared to reverse pubertal stage from year to year. The number of physical maturation characteristic reversals in the parent data were much fewer and may be accounted for by marking skin changes as absent as acne clears up later in puberty (Clawson et al., 2020). Children with ADHD may struggle with self-reports and recall (Sibley et al., 2017), which may extend to reports on their development.

Pubertal Stage.: The PDS was converted into pubertal stages mapping onto adrenarcheal- and gonadarcheal-driven physical maturation and then a composite pubertal stage score was calculated using the Shirtcliff et al., 2009 syntax. Pubertal stage scores range from 1 to 5. Stages 1–2 indicate puberty has barely begun and likely still in adrenarche or just beginning gonadarche. Stage 3 indicates that participants have begun gonadarche, and physical maturation is more visible. Stage 4 indicates that participants have peaked in maturation, and for females, likely reached menarche (first menstrual cycle; Eckert-Lind et al., 2020). Lastly, stage 5 indicates that the participant has reached full pubertal maturation when gonadarche is complete or the slowing of visible physical changes (Ge et al., 2001a, b). Table 1 shows means and standard deviations of pubertal stages at each wave.

Statistical Analyses

Multilevel structural equation modeling (MSEM) was conducted using Mplus Version 7.4 (Muthen & Muthen, 2015). MSEM models tested between-individual differences and within-individual changes in symptoms as youth aged and developed pubertally. Repeated measurements (Level 1) were nested within participants (Level 2). Within-individual effects were modeled at Level 1; between-individual effects were modeled at Level 2. Between-

individual age and pubertal status were captured at first observation. Females were coded as 0, and males were coded as 1. Each model predicted symptoms at current assessment from: (1) between-individual ***age*** at first observation (sample-standardized so that higher numbers indicate youth was older than the sample average at first observation), (2) within-individual ***aging*** (years elapsed since first observation), (3) between-individual ***pubertal status*** at first observation (sample-standardized so that higher numbers indicate youth were more developed than the sample average at first observation), and (4) within-individual ***pubertal changes*** (development gain relative to first observation). The cross-level interaction between ***age*** and ***aging*** tests whether the slope for aging is different if youth started the study while relatively younger or older; in other words, the impact of aging may be different if youth were younger or older at study onset, capturing a non-linear effect of aging. Similarly, the cross-level interaction between ***pubertal status*** and ***pubertal changes*** tests whether the impact of pubertal development was different if youth entered the study less developed or more developed.

Interactions of within-individual aging and sex, and interactions of within-individual pubertal changes with sex, were included in MSEM models to test whether the effects of aging or development over time are different for females than for males. First, we tested the main effect of sex in the full samples as a between-individual predictor at the intercept and slopes-as-outcome (e.g., aging, development, pubertal tempo) prediction of symptoms. Then, we grouped MSEM models by ADHD status to compare effect estimates of youths who met vs. those who did not meet clinical threshold for an ADHD diagnosis. Next, we grouped MSEM models by sex to examine effect estimates separately for females and for males. Respectively, univariate MSEM models tested inattention, hyperactivity, impulsivity, impairment, depression, and comorbidity (between depression and ADHD symptoms) as outcomes. Given that clinical outcomes often show positive skew which can lead to violation of the assumption that residuals are normally distributed, we examined the normality of within-person residuals from all multilevel models. Although the residuals were positively skewed, multilevel modeling is relatively robust to non-normal residuals (Maas & Hox, 2004).

Results

Table 3a presents full sample results of MSEM models predicting each symptom type of inattention, hyperactivity, and impulsivity, and Table 3b presents full sample MSEM models results for impairment and depressive symptoms as outcome. We differentiate between between- and within-person predictors. Below, we interpret the significant results and then summarize the results for each symptom type. Analyses using parent-, teacher-, and self-report on the ADHD Rating Scale-IV were conducted separately to determine if informant type influenced results. However, these analyses had similar results as the KSADS and, due to space limitations, are included in the supplemental materials. All of the following analyses, subsequent discussion, tables, and figures refer to ADHD symptom types derived from the KSADS.

What is the Trajectory of ADHD and Depressive Symptoms as Youth Age and does Pubertal Development have an Effect on Symptom Trajectories?

Inattention—In the full sample, there was significant variability in the intercept, u0j = 9.74, SE = 0.37, demonstrating that level of inattention at first observation varied across individuals. Males had higher inattention than females, B = 1.35, SE = 0.26. The amount of pubertal development overall did not predict inattention, but there was significant variability in the slope for development, u2j = 0.29, SE = 0.14, indicating that as youth matured pubertally, some showed more inattention symptoms (i.e., positive slope for development) whereas other youth showed fewer symptoms as they matured (i.e., negative slope for development). Significant negative covariance between the intercept and development slope, COV= −0.63, SE = 0.24, indicated that youth with more inattention symptoms at baseline showed a diminishing impact of pubertal development on inattention symptoms across subsequent waves (i.e., negative development slope).

Hyperactivity—There was substantial variability in the intercept, u0j = 3.07, SE = 0.17 for hyperactivity symptoms. Youth who were older at the start of the study showed fewer hyperactivity symptoms than younger youth, B= −0.20, SE = 0.06, and hyperactivity symptoms declined as youth aged (i.e., a negative aging slope, B= −0.13, SE = 0.50). Significant variability in the aging slope, u1j = 0.04, SE = 0.02, indicated that the decline in hyperactivity symptoms longitudinally as youth aged was steeper for some youth than others. Youth with higher hyperactivity symptoms at the first observation showed steeper declines in hyperactivity symptoms as they aged (i.e., a more negative slope of aging on symptoms, COV= −0.25, SE = 0.06). Males had more hyperactivity symptoms than females, B = 0.78, SE = 0.15, and a significant interaction between sex and aging, B= −0.18, SE = 0.06, indicated the decrease in hyperactivity symptoms as years passed was highly significant for males (aging: −0.32, SE = 0.04, $p < 0.001$) and less so for females though still significant (aging: −0.09, SE = 0.05, $p = 0.036$; see Fig. 1).

Regarding puberty, youth expressed fewer hyperactivity symptoms as they developed, B=−0.17, SE = 0.08, and sex also interacted with pubertal development, B = 0.24, SE = 0.11. Specifically, females showed significant decreases in hyperactivity as they developed across puberty (estimate for development: −0.19, SE = 0.08, $p = 0.013$), whereas puberty did not significantly impact hyperactivity for males (estimate for development: 0.10, SE = 0.08, $p = 0.209$; see Fig. 2). *Put another way, the longitudinal decline in hyperactivity symptoms appears linked more closely with development for females and with aging for males.*

Impulsivity—At the intercept, impulsivity symptoms had significant variability, such that some youth had higher symptoms than others, u0j = 0.82, SE = 0.06. Males had higher impulsivity than females, B = 0.37, SE = 0.08. There was an age*aging interaction, B= −0.02, SE = 0.01, illustrated in Fig. 3. There was a smaller decrease in impulsivity as youth aged when they entered the study at younger ages (estimate for aging at −1SD below the mean of baseline age: −0.03, SE = 0.04, $p = 0.36$), whereas the decrease in impulsivity as youth aged was substantial for youth who entered the study at older ages (estimate for aging at + 1SD above the mean of baseline age: −0.09, SE = 0.04, $p = 0.018$).

Depression—Depressive symptoms varied across individuals at first observation, u0j = 21.13, SE = 2.39. Depression was higher in those who were at later pubertal stages than those who were at earlier pubertal stages at their study entry, B = 1.02, SE = 0.35. Probing the development*sex interaction, B= −1.12, SE = 0.49, post-hoc analysis found as within-person pubertal stage increased, depression in females also increased (estimate for development: 0.85, SE = 0.48, $p = 0.075$), while depression in males remained stable (estimate for development: −0.04, SE = 0.27, $p = 0.876$; see Fig. 4). A significant random slope for development, u2j = 2.82, SE = 0.85, indicated that the impact of changes in pubertal development on depressive symptoms differed across participants due to unmeasured/unmodeled individual difference (between-person) factors. Supplemental Table 5 presents multilevel model results predicting depressive symptoms levels grouped by sex and by ADHD status.

Impairment—In the full sample, impairment varied substantially across individuals as revealed by significant variability in the intercept, u0j = 77.90, SE = 6.03. Females experienced greater impairment than males, B= −4.64, SE = 0.88. Youth who were less pubertally advanced at study entry showed more impairment than youth at later stages at study entry, B= −1.58, SE = 0.62. An effect of aging, B = 0.78, SE = 0.37, indicated that impairment increased as youth became older. Helping to rectify the observation that less advanced youth were more impaired yet impairment *increased* as youth aged, the rise in impairment as youth aged was larger for some youth than others as revealed by significant variability in the slope for aging, u1j = 1.42, SE = 0.54, and a significant correlation between initial level of impairment status and slope for aging, COV= −4.40, SE = 1.82, showed that *youth who were more impaired at baseline showed a smaller rise in impairment as they aged.*

Is there Variation in ADHD and Depressive Symptom Trajectories and the Effect of Pubertal Development on Symptom Trajectories when Grouped by Males and Females?

Inattention—Supplemental Table 1 shows the full within-sex models for inattention symptoms. A significant effect of aging, B= −0.24, SE = 0.07, indicated that inattention symptoms declined as males aged. There was also a cross-level age*aging interaction, B= −0.08, SE = 0.03; aging-related reductions in inattention were stronger for males who entered the study at older ages (estimate for aging at + 1SD above baseline age: −0.37, SE = 0.11, $p = 0.001$), than for males who entered the study at younger ages (estimate for aging at −1SD below baseline age: −0.12, SE = 0.06, $p = 0.032$). Significant negative covariance between the intercept and development slope, COV= −0.78, SE = 0.30, indicated that males with more inattention symptoms at baseline showed a diminishing impact of pubertal development across subsequent waves on inattention symptoms (i.e., negative slope for development). There were no systematic maturation effects on inattention for females.

Hyperactivity—Supplemental Table 2 shows within-sex models. Hyperactivity symptoms were lower in males who were older at first observation, B= −0.26, SE = 0.08, and there was a negative within-person effect of aging in males, B= −0.32, SE = 0.04; as more time passed after the first observation, hyperactivity symptoms declined. A significant random slope for aging indicated that the impact of aging on hyperactivity was variable across males, with

some having steeper effects of aging on hyperactivity than others, ulj = 0.05, SE = 0.02. A negative covariance between aging and the hyperactivity intercept, COV= −0.26, SE = 0.08, indicated that males with higher hyperactivity symptoms at the start of the study showed sharper drops in hyperactivity symptoms as they aged.

Hyperactivity symptoms decreased in females as they grew older or more pubertally developed (within-person effects). A negative covariance between aging and hyperactivity intercept, COV= −0.25, SE = 0.07, indicates that girls with more hyperactivity showed sharper drops in symptoms as they aged.

Impulsivity—When separated by sex, males displayed fewer impulsivity symptoms as they aged, B= −0.12, SE = 0.03, and this effect of aging was moderated by an age*aging interaction, B= −0.02. Specifically, males who were older at the start of the study showed stronger longitudinal aging-related reductions in impulsivity (estimate for aging at + 1SD above the mean of baseline age: −0.16, SE = 0.04, p < 0.001) compared to males who were younger at study start (estimate for aging at −1SD below the mean of baseline age: −0.08, SE = 0.03, $p = 0.001$). See Supplemental Table 3 for full results.

Depression—When grouped by sex, males had higher depressive symptoms at baseline, B = 7.58, SE = 0.29, than females, B = 6.94, SE = 0.38, with significant variability in baseline depressive symptoms across males, u0j = 21.18, SE = 2.6, and females, u0j = 19.88, SE = 4.48.

Males who were younger at study entry experienced a decrease in depressive symptoms as they aged, whereas males who were older at study entry experienced increased depression symptoms as they grew older, B = 0.21, SE = 0.06. Probing the interaction revealed aging-related increases in depression for those who were younger at study entry (estimate for aging at −1SD above the mean of baseline age: −0.38, SE = 0.12, $p = 0.001$), but not for those who were older at study entry (estimate for aging at + 1 SD below the mean of baseline age: 0.25, SE = 0.18, $p = 0.168$). A significant random slope for development, u2j = 1.97, SE = 0.95, indicated that the change in depressive symptoms across development in males differed across participants due to unmeasured/unmodeled individual difference factors. A significant correlation between intercept and slope for aging indicated that males with greater higher depressive symptoms at baseline showed larger declines in depression as they aged, COV= −1.90, SE = 0.84.

At study entry, depressive symptoms in females were higher for those at later pubertal stages than those at earlier pubertal stages, B = 1.15, SE = 0.48. Females who were younger at study entry had smaller decreases in depressive symptoms as they aged than older females at study entry, B = 0.34, SE = 0.11. Probing the interaction revealed significant aging-related increases in depressive symptoms for females who were older than the sample average at study entry (estimate for aging at + 1SD above the mean of baseline age: 0.80, SE = 0.35, $p = 0.023$), but not for females who were younger than the sample average at study entry (estimate for aging at −1SD below the mean of baseline age: −0.25, SE = 0.0.23, $p = 0.28$).

Impairment—Females who entered the study younger at baseline had greater increases in impairment as they aged than females who entered the study older, B= −0.36, SE = 0.18 (see Fig. 5). Probing the significant age*aging interaction revealed that the increase in impairment as females grew older was substantial for those who were younger when they entering the study (estimate for aging at −1SD above the mean of baseline age: 1.12, SE = 0.39, $p = 0.004$), but the effect of aging diminished for females entering the study at older ages (estimate for aging at + 1SD below the mean of baseline age: 0.05, SE = 0.59, $p = 0.937$). In males, impairment increased as males grew older, B = 1.41, SE = 0.25. Supplemental Table 4 presents MSEM model results predicting impairment levels grouped by sex and by ADHD status.

Discussion

ADHD symptoms show diverse longitudinal trajectories with maturational influences across adolescence varying across symptom domains. Inattention symptoms did not show marked maturation changes. For youth with the most inattention, symptoms may seem relatively intractable, and the mere passage of time (aging) does not lead to symptom improvements. For hyperactivity, the longitudinal decrease in symptoms is linked with systematic maturational processes related to age and development, and youth with the most symptoms showed the most marked decreases. Similarly, impulsivity symptoms declined as youth grew older with the largest drop in impulsivity amongst older youth. Overall impairment increased as youth aged, with males displaying higher levels of impairment. Lastly, depressive symptoms largely increase as youth age and amongst youth with later pubertal stages.

The study replicated well-established differences in maturational patterns when males and females were examined separately, indicating a male preponderance for ADHD symptoms; yet this did not mean that adolescent females were unaffected and, even within males, developmental trajectories continued to shift across adolescence. For females, depression increased and inattention remained stable while males showed improvement in ADHD symptoms across adolescence. Impairment trajectories were similar between males and females; however females consistently showed higher levels of impairment than males. Pubertal effects on depression in females but not males may explain why females with ADHD exhibit higher levels of impairment during adolescence and are at increased risk for suicide attempts (Chronis-Tuscano et al., 2010). Further research is needed to explore sex- and gender-based diagnostic biases, yet these results are consistent with the idea that females need to display additional behavioral and emotional problems in order to receive a diagnosis of ADHD than males (Mowlem et al., 2019). Advances in pubertal stage may increase transdiagnostic suicide risk via adverse changes in concentration, decision-making ability, and depressed mood in susceptible females (Owens & Eisenlohr-Moul, 2018). These changes may be uniquely impactful in adolescent females due to comparison effects with peers, increased interpersonal risk because of bodily changes, and the effects of circulating hormones on mood among those with neurobiological hormone sensitivity (Eisenlohr-Moul, 2019; Spear, 2009). Such risk may particularly affect broader transdiagnostic markers because of the pervasive nature of the changes occurring during this sensitive developmental period, consistent with activational effects (Martel et al., 2009; Schulz et al., 2009). Pubertal

hormonal effects are important transdiagnostic mechanisms that may help explain common environmental stressor effects across diagnostic categories.

Such sex differences in developmental trajectories of symptoms may be influenced by rapid cyclical changes in estrogen and progesterone influencing mood among hormone-sensitive individuals (e.g., symptoms of premenstrual dysphoric disorder or cyclical exacerbation of ADHD; Roberts et al., 2018). Findings are consistent with process models of effects across the menstrual cycle, which postulate that some individuals experience increases in approach and impulsivity behaviors mid-cycle with fluctuating estrogen and increases in depression and other affective symptoms in the luteal and perimenstrual phases, in the context of fluctuating progesterone and its metabolites (Peters, Eisenlohr-Moul, & Martel, in prep). Novel hormone fluctuations, social comparison effects, noticeable bodily changes, and changes in peer and romantic relationships may make certain youth more vulnerable to both inattention and depression, which may especially be true for females with ADHD. This may in turn make them vulnerable to negative social interactions and evaluations along with the “double hit” of hormonal effects at this time (Spear, 2009). Higher levels of impairment associated with ADHD beginning around puberty may negatively impact their social relationships and lead to depression. Further, such effects are likely exacerbated by known developmental delays in neurodevelopment, particularly delayed maturation of the prefrontal cortex in ADHD (Nigg & Casey, 2005).

In contrast, hyperactivity particularly decreased across puberty, particularly in females, suggesting pubertal effects may actually be protective for hyperactivity manifestation and the control of hyperactivity during adolescence. This is consistent with general developmental patterns in ADHD and may also be affected by social pressures for females during this time period. There were no pubertal effects on impulsivity, surprisingly, possibly due to the limited item content coverage of impulsivity in ADHD criteria. Pubertal effects on impulsivity might have been found on a broader measure of impulsivity than used herein. In addition, pubertal effects did not appear to affect comorbidity patterns, suggesting the effects were mainly driven by effects on individual disorder, particularly those exerting more general, or transdiagnostic risk.

There are at least three important takeaway messages from this study that can broadly impact the field of developmental psychopathology. First, developmental effects, or the trajectories, of ADHD symptoms were unique to each symptom type. While ADHD symptoms can be grouped into a diagnosis, treatment efforts may need to focus on the particular symptoms that are most vexing for individual youth. Mechanisms of change differ across symptoms, gender, and developmental stage as well as symptom severity. Second, although maturation did appear to modestly influence the symptom trajectories in some cases, there was also strong evidence for symptom persistence. Of particular concern is that impairment didn’t decline substantively, so even when most youth seemed to outgrow a symptom, as many did with hyperactivity, overall impairment remained stubbornly intractable. As maturation unfolds across adolescence, youth may still need help traversing this vulnerable stage, and such efforts are likely to be most impactful at the symptom level. Third, the best predictor for understanding ADHD and impairment was the individual child. Robust between-individual differences revealed from large intraclass

correlations (ICCs) indicate a stability in rank-order effects where the most impaired youth maintained their rank across waves. Yet, symptoms did change and often the largest changes in symptomatology were nonsystematic. While many youth "grew out" of ADHD, the mere passage of time or maturation through puberty did not resolve symptoms, and it was common for youth to show worsening of symptoms with maturation. Therefore, our study suggests that a closer examination of the specific maturational influences on ADHD points to the broad impact of a person- stage- and age-specific understanding of ADHD and its comorbidities.

The longitudinal nature of data collection and sophisticated statistical modeling allowed this study to parse the influences of different types of maturation captured by age and aging, pubertal stage and development. These models were statistically challenging to interpret, yet such complexity was needed to parse apart overlapping developmental processes. These were conservative models given the high ICC that indicated ample symptom stability and that stage- versus age-related maturation are highly interrelated processes.

Aging and possible maturation effects also seemed to predict changes in symptoms, which is something that needs more attention in future work. Broadly construed, age-related changes appeared to be most robust. Conceptually and statistically, pubertal maturation effects were "over and above" age as a measure of development. During the window of time in which pubertal changes unfold, these maturational changes are impactful for shaping the developmental trajectory for depressive symptoms in addition to the simple passage of time. In addition, specific links between puberty and circulating hormone effects, such as estrogen, progesterone, and testosterone need attention in future work.

Limitations

Although the current study had a number of strengths including thorough diagnostic characterization and use of multiple informants, as well as longitudinal data, it also had limitations. First, although missingness across waves was planned due to funding limitations, there was attrition over time. Those who participated at later waves did not differ significantly from those at earlier waves in sex, however, the proportion of individuals diagnosed with ADHD did significantly differ from wave 1 to wave 8. This may be due to the genetic nature of ADHD where individuals with ADHD are more likely to have parents that also have ADHD. Parents with ADHD may have been more likely to withdraw from the study due to symptoms characteristic of the disorder (i.e., difficulty completing tasks, difficulty with organization, forgetfulness) which may have negatively impacted the generalizability of study findings particularly at later waves. Relatedly, ADHD diagnosis was determined based on study entry assessment and was not adjusted for following years. This was intentional to keep the current study's results more translatable, as typically youth are not re-evaluated annually. However, lack of annual re-evaluation of diagnosis may have influenced the accuracy of analyses included in the supplemental section that grouped participants by ADHD diagnosis or lack thereof.

Secondly, a few factors limited the current study's ability to specifically analyze pubertal hormonal effects on symptoms. There was some disagreement between parents and teenage ratings on pubertal development, as might be expected given known problems with use of

self-report in individuals with ADHD (Sibley et al., 2017). Further, the current study relied on parent ratings of pubertal stage and did not evaluate actual biological levels of circulating hormones. In addition, there are known hormonal effects on state changes in ADHD effects (Roberts et al., 2018), and longitudinal annual assessment of ADHD precludes examination of those effects, which is another important direction for future work. Future research should specifically measure circulating hormone levels across pubertal stages, with special attention to monthly circulating hormone levels seen in females in later puberty in order to more accurately analyze pubertal hormone effects.

Finally, there were many possible ways that ADHD could have been included in the study (i.e., continuous or dichotomized diagnosis, symptom counts, severity scores, different informant reports, different measures) and the selection of symptom counts based on the KSADS in the present study limits the predictive power of the results to that measure. However, this method was chosen for select reasons. Research suggests that ADHD is best described as a continuum (Haslam et al., 2006; Levy et al., 1997) and as such main analyses were conducted using ADHD symptoms as dimensions; however, analyses separating participants by ADHD diagnosis were included as a secondary check in the supplemental materials. Additional analyses described in the supplemental materials utilized symptom severity scores from the ADHD Rating Scale in order to explore if severity scores rather than symptom counts would significantly influence results. Future research should carefully consider how ADHD symptoms are operationalized and analyzed.

Conclusion

The utility of multilevel structural equation modeling to conduct longitudinal analysis over an eight-year period showed that aging and pubertal development differentially explained variances in ADHD symptomatology, impairment, and depressive symptom trajectories. Within- and between-individual variability in impairment and symptoms, in addition, provided further insight into whether aging and pubertal development influenced changes in symptoms ascribed to individual development and/or their gender and ADHD status. This paper showed that aging and pubertal development exhibited some protective effects on ADHD symptoms, and that those with impairment and vulnerability to depression may instead experience increased difficulties related to aging and pubertal effects. Such results suggest the importance of increased attention to age maturation and pubertal effects in understanding ADHD associations with impairment and depression during this sensitive developmental period.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors thank all participants for making this work possible. This study’s design, hypotheses, and analysis plan were preregistered; see https://osf.io/vtxej. The datasets generated and analyzed for the current study are not publicly available but are available from the corresponding author on reasonable request.

This research was supported by R01-MH119119, R01-MH122446, RF1-MH120843, T32 NIAAA AA027488, T32 NICHD HD007489, and T32 NINDS T32NS115656. Infrastructure support was provided by NICHD P50HD105353, P50HD105328-01, and U54HD090256.

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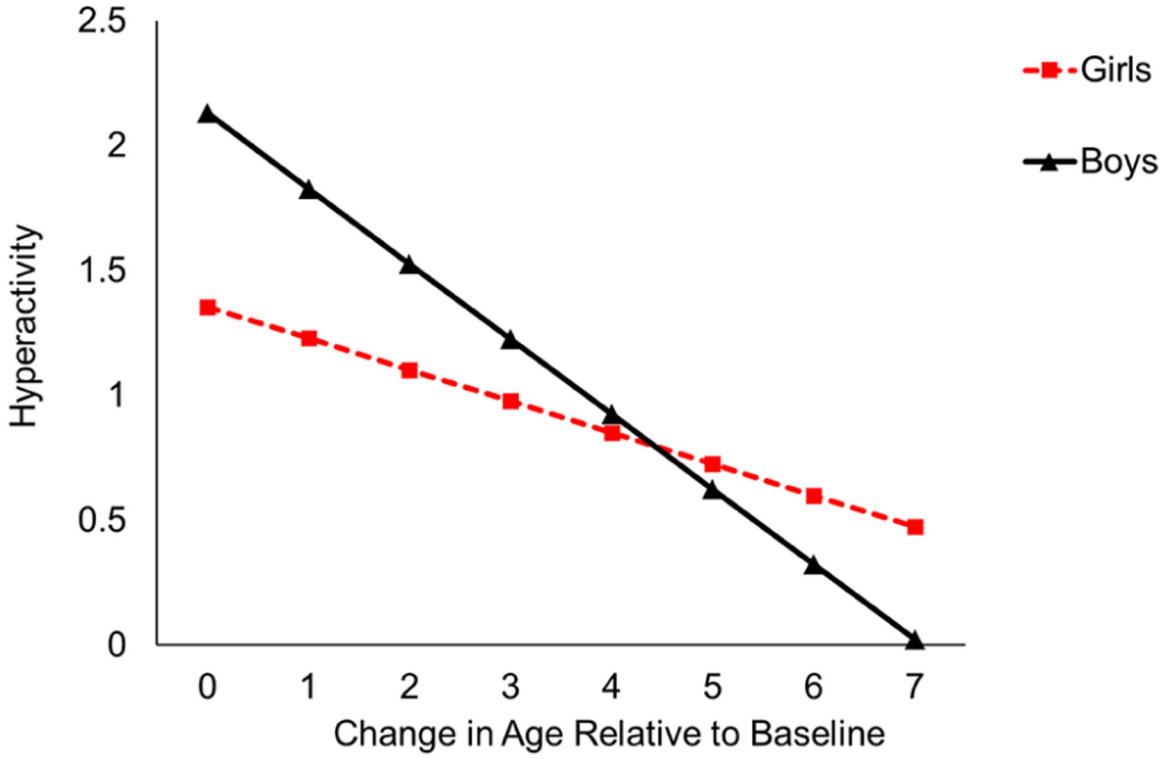

Fig. 1.

The Effect of Aging on Hyperactivity Moderated by Sex

Note: "Change in age relative to baseline" could also be conceptualized as "effect of aging longitudinally relative to baseline."

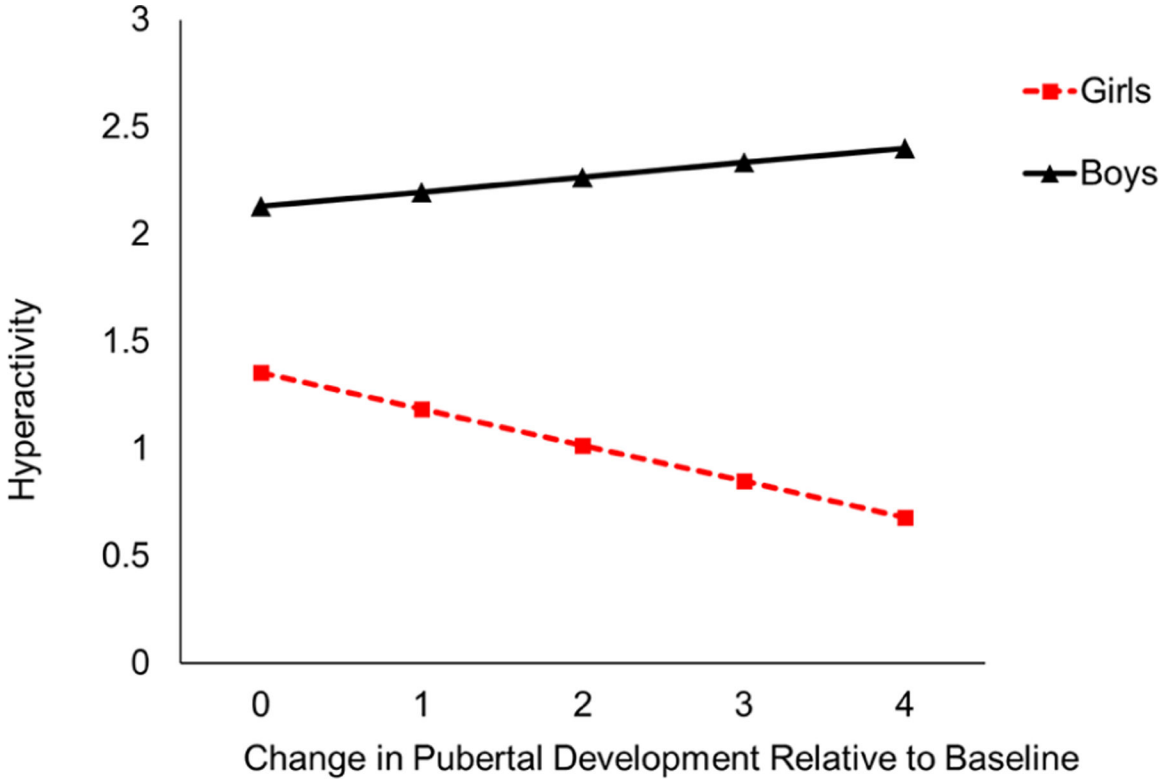

Fig. 2.
The Effect of Pubertal Development on Hyperactivity Moderated by Sex

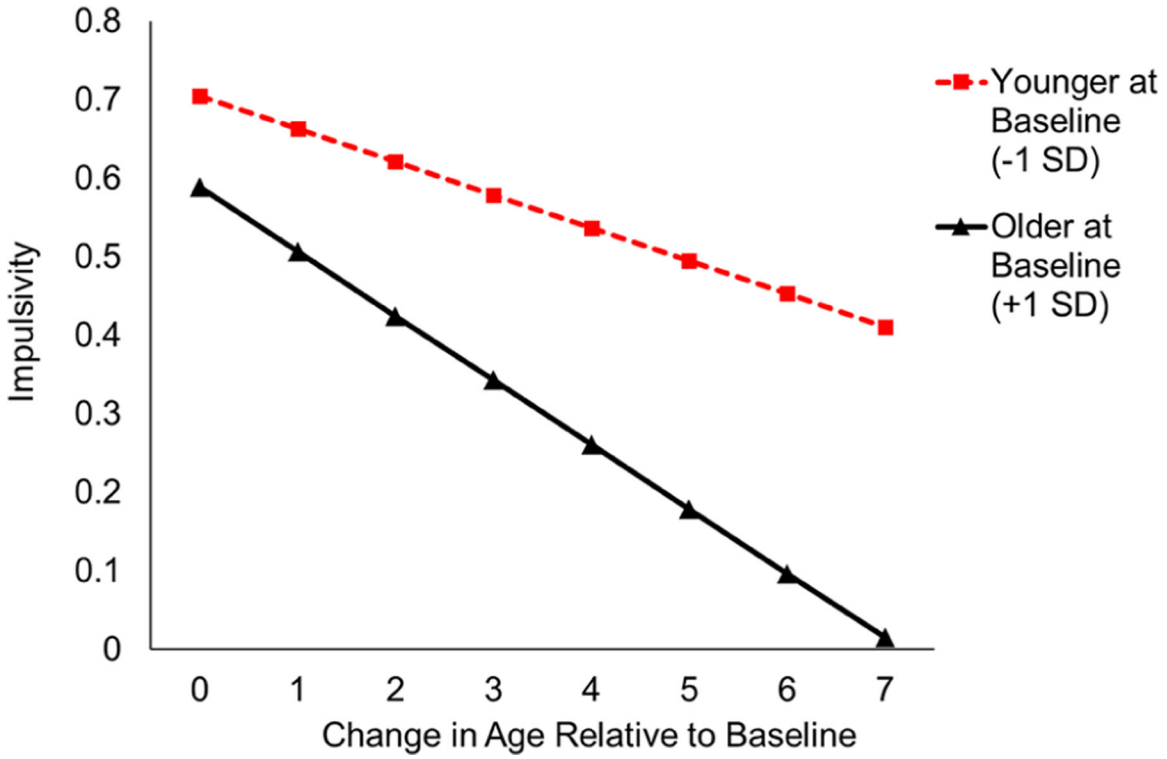

Fig. 3.

The Effect of Aging on Impulsivity Moderated by Age at Baseline

Note: "Change in age relative to baseline" could also be conceptualized as "effect of aging longitudinally relative to baseline."

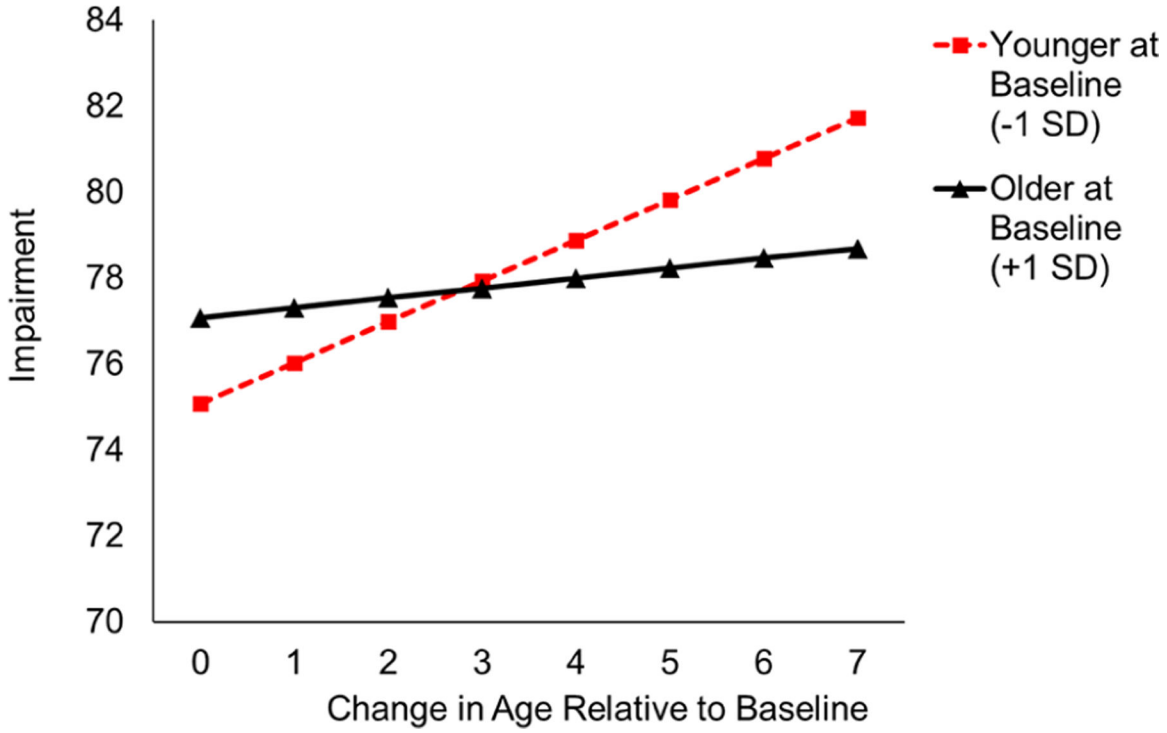

Fig. 4.

The Effect of Aging on Impairment Moderated by Age at Baseline for Females

Note: "Change in age relative to baseline" could also be conceptualized as "effect of aging longitudinally relative to baseline."

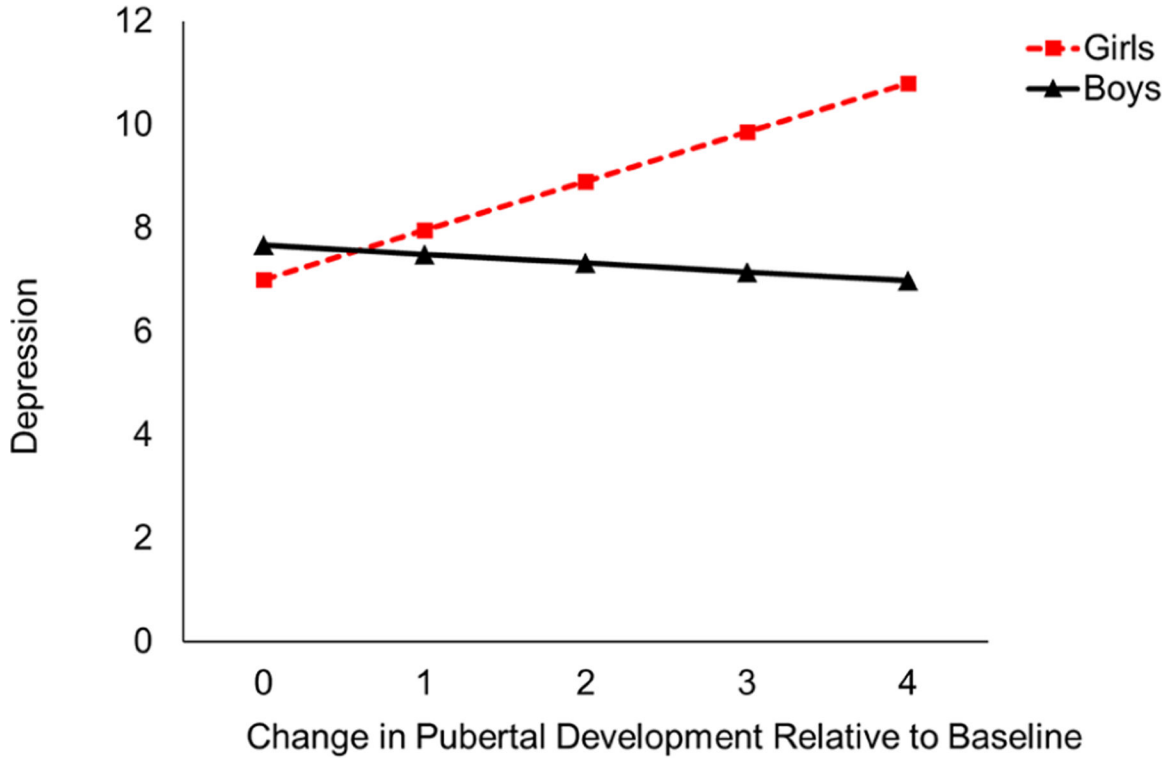

Fig. 5.
The Effect of Pubertal Development on Depression Moderated by Sex

Table 1

Descriptive Statistics Across Waves 1 Through 8

	Wave 1		**Wave 2**		**Wave 3**		**Wave 4**		**Wave 5**		**Wave 6**		**Wave 7**		**Wave 8**	
Males																
Total N	525		337		334		226		229		249		224		177	
% with ADHD	68.38		67.06		67.37		66.37		63.32		61.04		61.16		59.32	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Age	9.68	1.54	10.44	1.50	11.50	1.53	12.53	1.50	13.73	1.49	14.32	1.42	15.12	1.35	15.59	0.88
Pubertal Stage	1.41	0.60	1.49	0.73	1.86	0.99	2.02	1.21	2.89	1.30	3.34	1.24	3.81	1.04	4.18	0.83
Inattention	4.51	3.39	4.34	3.61	3.82	3.46	5.06	3.47	4.17	3.39	2.86	3.23	2.14	3.16	1.13	2.80
Hyperactivity	2.28	2.07	2.00	2.09	1.47	1.84	2.06	1.44	1.26	1.70	0.99	1.62	0.64	1.50	0.25	0.71
Impulsivity	1.05	1.19	1.03	1.17	0.74	1.05	0.94	0.93	0.61	0.94	0.53	0.95	0.21	0.58	0.25	0.71
Depression	8.20	6.35	7.54	6.72	5.86	5.61	7.25	6.40	6.66	5.74	6.93	6.35	6.75	6.19	6.90	6.71
Impairment	71.99	12.78	72.70	12.00	74.55	11.76	74.95	12.01	74.96	12.87	77.32	11.61	79.04	12.62	79.30	14.86
Females																
Total N	324		195		196		137		121		150		137		128	
% with ADHD	46.30		51.28		48.98		47.45		47.93		42.67		40.88		38.28	
	M	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Age	9.62	1.58	10.28	1.50	11.31	1.44	12.34	1.49	13.38	1.47	14.02	1.24	14.98	1.19	15.67	0.98
Pubertal Stage	1.94	0.95	1.92	0.94	2.40	1.05	3.13	1.39	3.57	1.10	4.03	0.79	4.41	0.65	4.64	0.55
Inattention	3.31	3.60	2.85	3.29	2.57	3.07	3.11	3.82	3.63	3.50	1.92	2.74	2.33	2.25	2.23	3.22
Hyperactivity	1.40	1.92	1.17	1.85	0.94	1.57	1.33	1.66	0.83	1.43	0.44	0.97	0.67	1.63	0.54	1.05
Impulsivity	0.69	1.04	0.63	1.05	0.47	0.85	0.78	1.20	0.46	0.96	0.36	0.74	0.50	0.84	0.15	0.38
Depression	7.28	6.63	7.66	6.96	6.62	6.45	8.81	8.62	10.11	9.28	9.84	8.51	9.72	9.11	8.62	7.03
Impairment	76.63	11.95	77.50	11.69	77.76	10.89	79.31	12.69	78.31	11.79	79.11	13.16	78.75	9.83	80.49	11.49

Note. Inattention, hyperactivity, and impulsivity symptom counts were determined using the KSADS data. Depression refers to total raw scores on the CDI. Impairment was determined utilizing the GAF based on parent responses from the KSADS.

Table 2

Distribution of Time-Fixed Variables

Variable	*n*	%
Sex		
Male	525	61.84
Female	324	38.16
Pubertal Stage at Wave 1		
1	491	57.83
2	113	13.31
3	65	7.66
4	9	1.06
5	1	0.00
Missing	170	20.00
Age at Wave 1		
7	113	13.31
8	238	28.03
9	179	21.08
10	124	14.61
11	113	13.31
12	65	7.66
13	17	2.00

Table 3a

Models Predicting ADHD Symptoms

Parameter	Inattention		Hyperactivity		Impulsivity	
	Estimate	*SE*	*Estimate*	*SE*	*Estimate*	*SE*
Intercept	**3.14*****	0.21	**1.36*****	0.11	**0.65*****	0.06
Between-Person Predictors						
Male Sex	**1.35*****	0.26	**0.78*****	0.15	**0.37*****	0.08
Baseline Age	−0.02	0.10	**−0.20*****	0.06	−0.06	0.03
Baseline Pubertal Stage	0.19	0.20	0.01	0.11	0.06	0.06
Within-Person Predictors						
Aging	−0.17	0.10	**−0.13****	0.50	−0.06	0.03
Development	−0.03	0.18	**−0.17***	0.08	−0.05	0.06
Cross-Level Interactions						
Aging x Age	−0.05	0.03	−0.02	0.02	**−0.02***	0.01
Aging x Sex	−0.05	0.11	**−0.18****	0.06	−0.05	0.04
Development x Pubertal Stage	−0.04	0.12	0.12	0.06	0.01	0.05
Development x Sex	0.09	0.22	**0.24***	0.11	0.06	0.07
Variance Components						
Residual (eij)	**2.28*****	0.19	**0.88*****	0.07	**0.43*****	0.04
Random Intercept (u0j)	**9.74*****	0.37	**3.07*****	0.17	**0.82*****	0.06
Random Slope for Aging (u1j)	0.06	0.05	**0.04****	0.02	0.01	0.01
Random Slope for Development (u2j)	**0.29***	0.14	0.04	0.04	0.02	0.02
Cov Rand Int w/Rand Slope for Aging	−0.10	0.13	**−0.25*****	0.06	−0.04	0.02
Cov Rand Int w/Rand Slope for Development	**−0.63****	0.24	−0.17	0.10	−0.07	0.04

Note.

* $p \leq 0.05$,

** $p \leq 0.01$,

*** $p \leq 0.001$.

Age = Between-person age at first pubertal observation, grand mean centered. Stage = Between-person pubertal stage at first pubertal observation, centered at Tanner stage 1. Aging = Within-person change in age over time. Development = Within-person change in pubertal stage over time

Table 3b

Models Predicting Impairment and Depression

Parameter	Impairment		Depression	
	Estimate	***SE***	***Estimate***	***SE***
Intercept	**76.06*****	0.66	**7.00*****	0.37
Between-Person Predictors				
Male Sex	**−4.64*****	0.88	0.66	0.48
Baseline Age	0.55	0.34	**−0.44***	0.19
Baseline Pubertal Stage	**−1.58***	0.62	**1.02****	0.35
Within-Person Predictors				
Aging	**0.78***	0.37	0.17	0.23
Development	−0.34	0.69	**0.95***	0.46
Cross-Level Interactions				
Aging x Age	0.00	0.09	**0.25*****	0.05
Aging x Sex	0.60	0.42	−0.17	0.24
Development x Pubertal Stage	−0.07	0.53	−0.11	0.29
Development x Sex	−0.25	0.78	**−1.12***	0.49
Variance Components				
Residual (eij)	**67.57*****	3.34	**21.15*****	1.74
Random Intercept (u0j)	**77.90*****	6.03	**21.13*****	2.39
Random Slope for Aging (u1j)	**1.42****	0.54	0.23	0.25
Random Slope for Development (u2j)	0.22	1.83	**2.82*****	0.85
Cov Rand Int w. Rand slope Aging	**−4.40***	1.82	−1.37	0.75
Cov Rand Int w/Rand slope Development	3.52	3.56	0.41	1.45

Note.

* $p \leq 0.05$,

** $p \leq 0.01$,

*** $p \leq 0.001$.

Age = Between-person age at first pubertal observation, grand mean centered. Stage = Between-person pubertal stage at first pubertal observation, centered at Tanner Stage 1. Aging = Within-person change in age over time. Development = Within-person change in pubertal stage over time