The bumpy road to adulthood; pubertal development in autism spectrum conditions and its relation to mental health

Short title: Pubertal development in relation to mental health in autism

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Data availability statement

The data that support the findings of this study will be made openly available in open science framework at [http://doi.org/\[doi\]](http://doi.org/[doi]), reference number [reference number].

Ethics approval statement

The study is in accordance with the 1964 Helsinki declaration and its later amendments and approved by the appropriate institutional research ethics committee (2013-PN-2861 and 2015-BC-4576).

Patient consent statement

All participants and their parents gave informed consent

Abstract

Background: Adolescence is a period of social, psychological, and physiological change, including the onset of puberty. Differential pubertal onset has been linked to a myriad of problems, including mental health problems. In autism spectrum conditions (ASC) deviating pubertal development has been reported. Therefore, it is of the utmost importance to examine the effect that pubertal timing has in ASC teens.

Methods: 68 individuals ($n_{ASC} = 34$, n_{COM} (comparisons) = 34) aged 12 to 16 years were administered test concerning pubertal development and mental health (i.e., sensory sensitivity, autistic traits, depression, anxiety, and externalizing problems). We examined whether there was evidence for deviating pubertal development in ASC, and whether this asynchronicity was linked to mental health problems.

Results: Our statistical (Frequentist and Bayesian) analyses revealed earlier onset and slower development of pubertal development in ASC and we did not find any sex differences. This maturation disparity was linked to higher mental health problems in ASC, but not in COM. No sex differences in the relation with mental health outcomes was found.

Conclusions: We found evidence for a slower development of “true” puberty in those with ASC compared to those without. Moreover, we show that disparities in pubertal development are related to mental health in ASC, suggesting a greater impact on mental health in autistic than in non-autistic teens. Longitudinal studies are necessary to elucidate important developmental trajectories in puberty in neurodiverse populations.

Keywords: autism spectrum conditions; puberty, pubertal development, mental health, sex differences

Key points

- Timing of pubertal development can have a great impact on youths' mental health
- There are reasons to assume that there are sex differences in the relation between mental health and pubertal development
- Adolescence with autism spectrum conditions (ASC) show earlier onset and slower development of gonadal pubertal development in ASC, but we did not find any sex differences
- Disparities in pubertal development are related to mental health in ASC, but not in comparisons
- Asynchronous pubertal development has a greater impact on mental health in autistic than in non-autistic teens

Adolescence is a period of social, psychological, and physiological change (Spear, 2000). One of these changes, the onset of puberty, is a major developmental milestone in the lives of children. For those that have more difficulties dealing with change, as is often described in autism spectrum conditions (ASC), this change can have a major impact. Moreover, differential pubertal onset has been reported in ASC (Corbett et al., 2020; Ingudomnukul et al., 2007; Knickmeyer et al., 2006; Pohl et al., 2014; Tordjman et al., 1997). This differential pubertal onset has been linked to a myriad of problems, such as depression and suicidal ideation (Copeland et al., 2019; Ho et al., 2021). Therefore, it is of the utmost importance to examine the effect that pubertal timing has in ASC.

Two biological processes underly pubertal development, adrenarche and gonadarche (or “true puberty”) (Buck Louis et al., 2008; Reiter et al., 1977). First, around the age of eight adrenarche occurs, which is the development of adrenal androgens in both girls and boys. Adrenarche is responsible for pubic hair development, and changes in body odor. Gonadarche is initiated by the hypothalamic-pituitary-gonadal (HPG) axis and leads to rising levels of estradiol and progesterone in girls and testosterone in boys, leading to breast growth and menstruation in girls and phallic growth and voice changes in boys. Typically, gonadarche occurs one year earlier in girls than in boys (Dorn et al., 2006). The onset, and speed of pubertal development can be tracked by rating these secondary sex characteristics.

Timing of pubertal onset is important because it conveys a risk for later physical (Fuhrman et al., 2021), mental (Copeland et al., 2019; Deardorff et al., 2021; Lynch et al., 2021), and social problems (Mensah et al., 2013). Numerous factors can influence the onset of puberty. Known factors are racial background, socio economic status, and body mass index (Braithwaite et al., 2009; Herting et al., 2021). There are signs that ASC also influences pubertal timing. Autistic girls appear to have a younger age of menarche (i.e., first menstruation; Corbett et al., 2020). Moreover, a large retrospective study showed that autistic women were more likely to belong to the “steroidopathic” group, which was characterized by an early growth spurt, and precocious puberty and menarche (Pohl et al., 2014). There are however, also reports of late menarche in ASC (Knickmeyer et al., 2006) or delayed puberty (Ingudomnukul et al., 2007). In autistic boys these results have been less clear cut, while one study reported precocious puberty in autistic boys (Tordjman et al., 1997), another did not (May et al., 2017). Moreover, a large Australian community sample did not find any differences in pubertal development between autistic and non- autistic adolescents (May et al., 2017). Nevertheless, there are clear suggestions that pubertal development is different in autistic children, with more evidence for deviating patterns in girls than in boys.

Precocious puberty has been linked to an increased risk for psychopathology (Lynch et al., 2021). Most focus in research has been on internalizing symptoms. Early pubertal timing and testosterone levels appear related to depressive symptoms (Copeland et al., 2019; Galvao et al., 2014) and anxiety in girls (Deardorff et al., 2021). In boys both pubertal timing, but also pubertal tempo were related to depressive symptoms, while in girls only pubertal timing predicted depressive symptoms (Mendle et al., 2010). However, a different study showed that differential pubertal timing lowered the risk of depressive symptoms in boys, while it was a risk factor in girls (Stumper et al., 2020). Moreover, there is evidence showing that externalizing symptoms are specifically associated with early puberty in boys, but not girls (Mensah et al., 2013). However, these sex specific patterns are not reported in all studies (Hamlat et al., 2019). Nonetheless, there are some indications that there are sex specific associations between internalizing and externalizing symptoms and deviating pubertal timing.

As there are indications of early pubertal timing in ASCs (Corbett et al., 2020; Pohl et al., 2014), and elevated rates of comorbidities (Simonoff et al., 2008) are reported in those with ASCs, a thorough investigation on pubertal development and its associated psychological problems in ASC is warranted. While this is an important topic, there is currently little research into this area. A case reports notes the regression of therapeutic effect after the onset of puberty in a girl with ASC (Ayres & Mailloux, 1983), and another study on five autistic individuals reported a worsening of problems at the start of puberty (Gillberg & Schaumann, 1982). There are reports that sensory sensitivity is increased in autistic women during menstruation (Steward et al., 2018) and menopause (Moseley et al., 2020a, 2020b). Moreover, our recent work shows that menopausal complaints are associated to increased autistic characteristics in autistic women (Groenman et al., 2021). Although these findings are not directly related to puberty, both these periods are associated with large hormonal variations, and could hint toward increased symptoms during pubertal development. Likewise, a recent review poses that exposure to sex hormones, as occurs in puberty, causes a period of neural plasticity in which the brain is increasingly sensitive to social stressors that amplify emotional dysregulation and impulse control (Ho et al., 2021). In autistic adolescents these social and daily life stressors might be more prevalent (Maïano et al., 2016) and impactful (Corbett, Muscatello, & Baldinger, 2019), and in combination with early pubertal onset that posits a risk in itself, could increase the impact that puberty has on mental health in these individuals.

Therefore, we aim to investigate whether pubertal development occurs at different ages in autistic and non-autistic girls and boys, and whether this pattern is sex

specific. We hypothesize that we will find differences in pubertal development and menarche between autistic and non-autistic girls, and we will explore the pubertal development in boys. Moreover, we will explore the association between mental health (including autistic characteristics, sensory sensitivity, depressive symptoms and anxiety, and externalizing problems) and deviating (earlier or later) pubertal development for boys and girls, and non-autistic and autistic individuals separately. We expect that girl's mental health will be more highly associated by pubertal development than boys, and that autistic girls and boys mental health is more affected by pubertal development than non-autistic individuals.

Methods

Participants

In total, 68 individuals ($n_{ASC} = 34$, $n_{COM} = 34$) between the ages of 12 and 16 were included between 2013 and 2015. Autistic participants were recruited via Dutch mental health organizations and the Dutch association of Autism website (NVA) and comparison participants were recruited through the social networks of the psychologists and students who tested the participants. For the ASC group the exclusion criteria were: i) scores below the autism cutoff on the *Developmental, Dimensional and Diagnostic interview* (3Di-sv; Slappendel et al., 2016) and below the autism cut off (51 for girls; 60 for boys) on the Dutch *Social Responsiveness Scale* (SRS; Roeyers, Thys, Druart, Schryver, & Schittekkade, 201), ii) a history of neurological disorders, iii) an estimated IQ < 80 based on two subtests (Block Design and Vocabulary) of the Dutch Wechsler Intelligence Scale for Children-II (WISC-III-NL; Kort et al., 2005). Exclusion criteria were for comparison (COM) subjects were i) a score above the autism cutoff on the SRS, ii) history of psychiatric disorders (including ASC) according to DSM-IV or DSM-5 criteria (APA, 2000; APA, 2013), iii) an estimated IQ < 80, iv) use of psychotropic medication, v) ASC in close relatives (i.e., parents and siblings), vi) a history of neurologic disorders. Autistic and non-autistic individuals were matched on sex.

Materials

Pubertal development scale (PDS; self-report) (Petersen et al., 1988) was used to assess pubertal development. In girls, growth in height, body hair, skin changes, breast development, and menstruation was assessed. In boys, growth in height, body hair, skin changes, deepening of voice, and facial hair was assessed. Adolescents scored these features on a 4-point scale ranging from 1 (not started) to 4 (completed). Average scores will be

calculated for adrenal (pubic/body hair and skin changes), and gonadal associated (girls: growth spurt, breast development, and menarche, boys: growth spurt, deepening of voice, and facial hair growth) processes (Shirtcliff et al., 2009). In case of missing items, we calculated the averages based on the available information. Furthermore, we will examine age at menarche for girls.

Autism Quotient (AQ; self-report & parent-report)(Baron-Cohen et al., 2001; Hoekstra et al., 2008) is a 50-item questionnaire that assesses autistic traits. Total scores of adolescent reports will be used as an indication of autistic traits, with higher scores reflecting higher autistic traits. For this outcome, we will also use parental report of their child's autistic traits.

The *Sensory sensitivity questionnaire* (SSQ; self report) (Minshew & Hobson, 2008) is a 13-item questionnaire in which the adolescents themselves are asked to rate their own subjective sensory experiences. Items can be rated yes/no. Here the total number of yes-scores is used as an indication of sensory sensitivity. A higher score reflects more sensory sensitivities.

Childrens depression inventory (CDI; self-report)(Kovacs, 1992; Timbremont et al., 2002) is a 27-item self-report questionnaire that can be used as a screening tool for cognitive, behavioral, and affective signs of depression in children. Items are scored on a 3-point scale. For the current research the total sum score will be used as an indication of depressive symptoms, with higher scores reflecting more depressive symptoms.

The *SCARED-71* (self-report) (Bodden et al., 2009) is a 71-item questionnaire assessing the degree of anxiety symptoms (Birmaher et al., 1997). Parents indicate on a 3-pointscale from 0 (almost never) to 2 (often) how often they believe each symptom is experienced by their child. The total score was used as measure of anxiety, with a higher score indicating a higher degree of anxiety.

The Strength and difficulties questionnaire (SDQ; self-report)(Goodman, 2001) is a questionnaire to measure the social and emotional health in youth. Youth indicate on a 3-point scale whether an item applies to them. For the current study the SDQ was used as an indication of externalizing problems by combining the hyperactivity/attention problems and behavioral problems subscales.

Procedure

The study is in accordance with the 1964 Helsinki declaration and its later amendments and approved by the appropriate institutional research ethics committee (2013-PN-2861 and 2015-BC-4576). It is part of an overarching study focusing on executive functioning in

autistic teens. Therefore, the measurements of this study are a subset of the instruments used for the larger project. Teens received a small gift for participating, and their travel expenses were covered to a maximum of €10,-.

Analyses plan

All analyses were performed in R (RStudio Team, 2015).

We compared whether our groups differed on age, and mental health outcomes using t-tests. Possible group differences in sex and education of father were assessed using a Chi-squared test.

To assess whether pubertal development differed between autistic and non-autistic individuals an ANOVA with and age*group interaction and adrenal/gonadal pubertal development as dependent variable will be conducted. Furthermore, we will run separate analyses for boys and girls, as girls develop earlier on average than boys. In girls we will also examine possible differences between ASC and COM in age at menarche.

Moreover, we will explore whether deviating pubertal development (either adrenal or gonadal) was associated with increased levels of mental health problems (autistic symptoms, sensory sensitivity, depressive symptoms and anxiety, and externalizing problems), using two approaches. First, as a reflection of deviating pubertal development, we calculated the predicted values of pubertal development based on the values COM group by running a regression with age and sex as predictors and pubertal development as outcomes. Next, we used these estimates to calculate a predicted value in both the ASC and COM group and subtracted actual development from this value, negative values reflect late pubertal development compared to peers, and positive values reflect early development compared to peers. First, we built a model where deviating pubertal development predicted mental health. Next, the interaction between deviating pubertal development*sex was added to the model to examine a possible differential effect of pubertal development in girls and boys. Second, we investigated whether asynchrony (those with either early [deviating score $>.5$] or late [deviating score $<-.5$] development) was related to psychiatric complaints. We used a t-test to assess whether the asynchrony group deviated on all mental health outcomes, again separately for ASC and COM.

Moreover, we will rerun group-based analyses with Bayesian statistics using the BayesFactor package (Morey et al., 2018), to assess the strength of our conclusions. BF_{10} expresses the probability of the data given H_1 relative to H_0 , BF_{01} expresses the probability

of the data given H_0 relative to H_1 (please note that $BF_{01} = 1/BF_{10}$). Bayes factors larger than 3 can be interpreted as substantial or stronger evidence for H_1 (Lee & Wagenmakers, 2014). We will draw conclusions based on the combined results of both frequentist and Bayesian analyses.

As SES (highest education of father) is known to influence pubertal development (i.e., lower SES is associated with a greater risk for early development) (Braithwaite et al., 2009), all analyses will be rerun using SES as covariate.

Results

Participants

Groups were matched on age and sex. Further, groups did not differ in father's education or IQ (also see Table 1). Groups did differ in all psychological outcomes.

[INSERT TABLE 1 HERE]

H1: Differential pattern of pubertal development

Frequentist and Bayesian analyses show that the speed and timing of adrenal pubertal development did not differ between autistic and non-autistic participants (group*age; Table 2). Moreover, Bayesian analyses showed that there was more evidence for equal adrenal development in autistic compared to non-autistic girls. We do not find evidence for, or against, an earlier age of menses in autistic girls compared to non-autistic girls ($F(1,23)=.219$, $p=.15$, $BF_{10}=.81$, also see Figure 1A-C).

Frequentist analyses revealed that gonadal development in ASC seemed slower when compared to COM (Table 2, Figure 1D). This is confirmed by Bayesian statistics. Frequentist statistics do not show significant results in boys and girls separately, but Bayes factors suggest that our data is more likely to occur under the alternative hypothesis, i.e., earlier but slower gonadal pubertal development in autistic boys and girls (also see Table 2 and Figure 1E-F).

[INSERT FIGURE 1 & TABLE 2 HERE]

Deviating pubertal development and its relation to mental health

As all reports of mental health problems differed (see Table 1) in ASC and COM we ran analyses separately for both groups.

Deviating pubertal development (both adrenal and gonadal) was related to depressive symptoms and externalizing problems in autistic adolescents, but not in non-autistic adolescents. Specifically, pubertal development that was more advanced than their -non-autistic peers was associated with greater mental health problems. This pattern was not sex specific. Moreover, no other mental health problems were related to pubertal development (also see Table 3, Figures 2 and 3). Correction for SES did not change the results (see Appendix 1).

[INSERT FIGURE 2 & TABLE 3 HERE]

Synchronicity

There was no difference in the percentage of individuals that fell in the asynchrone adrenal development group (ASC= 64.7%, COM= 44% $\chi^2 = 2.91$, $p = .09$, $BF_{10} = 1.79$), or the asynchrone gonadal development group (ASC= 50%, COM= 19.4%, $\chi^2 = 3.01$, $p = .08$, $BF_{10} = 1.85$). There was no difference in mental health outcomes between the asynchrone ASC and synchrone ASC group on any mental health outcomes, although Bayes statistics did not point to either H0 or H1. In COM frequentist analyses pointed to fewer externalizing problems in the asynchrone group compared to the synchrone group (also see Appendix 2), but Bayes factors did not confirm this. In COM Bayes statistics showed that there was more evidence for H0 (no difference between groups) in comparisons on anxiety and autistic traits as reported by parents. We next compared delayed (behind on peers), or advanced (ahead of peers) developers to those synchronous developers on mental health outcomes and found that in those with advanced adrenal development sensory sensitivity and externalizing problems were increased compared to synchronous developers in ASC but not COM. Advanced adrenal developers show higher levels of depression and externalizing problems compared to synchronous developers in ASC but not COM (see Appendix 3 for full results).

[INSERT FIGURE 3 HERE]

Discussion

Pubertal development is a major process in an adolescent's life. While it is known that timing, and speed of pubertal development can influence the individual tremendously, little is known about pubertal development and its effects in ASC. Therefore, we aimed to investigate whether pubertal development occurs at different ages in autistic and non-autistic girls and boys, and whether this pattern is sex specific. In contrast to our hypothesis, we did not find an

earlier age of menarche in autistic girls compared to non-autistic girls. We did however find earlier but slower gonadal pubertal development in autistic boys and girls compared to non-autistic participants. Furthermore, we found that late pubertal development was related to increased mental health problems in autistic adolescents, but not in non-autistic adolescents. This shows that maturation disparity, and particularly advanced pubertal development, is related to mental health in ASC.

Our results point to both earlier onset, and slower development of “true” puberty in ASC. If this is the case, this could indicate that previous results of both early (advanced) (Pohl et al., 2014; Tordjman et al., 1997), and late (delayed) pubertal development (Ingudomnukul et al., 2007) in ASC might not be contradictory to each other, but rather reflect a slower pubertal development, with an earlier onset in ASC. However, as our data was cross-sectional this could also reflect two different subgroups of individuals, one with slow development and one with advanced pubertal development, but without a difference in the speed of development. While this pattern was not ASC specific, our results indeed point to an advanced and a delayed developing group. While our results are indicative a slower rate of development in ASC, we cannot make any inferences about the individual speed of development. For this, longitudinal studies are necessary, starting at an early age before the onset of pubertal. Moreover, although our results are likely suggestive of an earlier pubertal development in ASC, but in contrast with previous research (Corbett et al., 2020; Pohl et al., 2014), this was not reflected in an earlier age of menarche in autistic girls, possibly due to our relatively small sample.

Further to note is that while we found a different development of gonadal pubertal development, we did not find a difference between autistic and non-autistic adolescents related to adrenal pubertal development. Our Bayesian statistics even point to a similar development in autistic girls compared to non-autistic girls; at age 14 adrenal pubertal development is similar in autistic compared to non-autistic adolescents. Our sample with a mean age of 14.16 might not have been optimal to detect differences as adrenarche often occurs around 8 years of age (Buck Louis et al., 2008; Reiter et al., 1977), and differences might occur early in development. Timing in the measurements of pubertal development is of the utmost importance (Ge et al., 2003), and future longitudinal research from childhood to adolescence.

Maturation disparity, both in adrenal and gonadal development was related to depressive symptoms and externalizing problems in autistic youth, but not in non-autistic youth. Autistic youth that showed advanced development compared to their peers showed

more depressive symptoms and externalizing problems. We found both individuals that matured faster than their peers, but also individuals that matured slower. Exploratory analyses showed that asynchronicity (either advanced or delayed development) in itself was not significantly related to mental health problems. However, when we subdivided these groups in delayed and advanced developers, we found higher mental health problems (externalizing problems, depression, and sensory sensitivity) in the advanced developers, but not in the delayed developers, compared to the synchronous developers in ASC, but not in COM. While our sample of advanced developers was small, this could indicate that fast pubertal tempo might be experienced as traumatic in those sensitive to change, as is found in ASC, and less so in COM. Longitudinal follow-up is necessary to elucidate if this is the origin of psychiatric comorbidities in ASC, or whether these effects are transient.

Again here the timing of measurement may be important, for example in the Pittsburgh Girl Study (a longitudinal study into the development of girls), it was shown that early in development (age 10) a fast pubertal tempo was related to depressive symptoms, while from age 10-13 a slow pubertal tempo was related to depressive symptoms (Keenan et al., 2014). This in combination with the results from our analyses on continuous disparity, could suggest that advanced development has a larger effect in ASC. This is particularly important, as we also show evidence that deviating pubertal development occurs more often in autistic youth. Possibly, as suggested by Ho and colleagues (Ho et al., 2021), exposure to hormones, in a period of high neural plasticity such as in puberty, leaves an individual more susceptible to the effects of daily life stressors. Future studies should look at pubertal development in relation to daily life stressors to assess whether this can prove detrimental in the development of mental health problems in autistic individuals.

We are the first to assess the effects of pubertal development in ASC on mental health. However, our findings should also be seen in the light of some limitations. First, the PDS does not evaluate pubertal stage directly, and should therefore be seen as a subjective report of pubertal development (Cheng et al., 2021). It could be that autistic youth are more aware of the changes in their bodies than non-autistic youth, which could have led to a bias in the reporting of pubertal development. Nevertheless, previous research suggest that the agreement between physical examination of pubertal stage, and self-report is similar, but low, in ASC and COM (Corbett, Muscatello, Tanguturi, et al., 2019). A strong argument for using self-report scales, is that physical examination can be experienced as invasive. Second, our sample was relatively small. Although our conclusions are based on Bayesian (i.e., not dependent on power as well as frequentist statistics), this should be kept in mind when

interpreting our results. Lastly, as the sample is slightly later in their development compared to previous studies, and the timing of measurement is very important for the outcomes, it could be that by our timing for measurement we missed important development marks. Future studies should focus on including measurements at multiple time points from an earlier age, to fully capture the entire trajectory of pubertal development and its relation to mental health indices.

In conclusion, we found evidence for a slower development of “true” puberty in those with ASC compared to those without. Moreover, we show that disparities in pubertal development are related to mental health in autistic teens specifically, suggesting a greater impact on mental health in autistic teens than in non-autistic teens. Longitudinal studies are necessary to elucidate important developmental trajectories in puberty in neurodiversity.

References

- Ayres, A. J., & Mailloux, Z. K. (1983). Possible pubertal effect on therapeutic gains in an autistic girl. *The American Journal of Occupational Therapy: Official Publication of the American Occupational Therapy Association*, 37(8), 535–540.
<https://doi.org/10.5014/ajot.37.8.535>
- Baron-Cohen, Wheelwright, S., Skinner, R., Martin, J., & Clubley, E. (2001). The autism-spectrum quotient (AQ): Evidence from Asperger syndrome/high-functioning autism, males and females, scientists and mathematicians. *Journal of Autism and Developmental Disorders*, 31(1), 5–17. PubMed.
<https://doi.org/10.1023/a:1005653411471>
- Birmaher, B., Khetarpal, S., Brent, D., Cully, M., Balach, L., Kaufman, J., & Neer, S. M. (1997). The Screen for Child Anxiety Related Emotional Disorders (SCARED): Scale construction and psychometric characteristics. *Journal of the American Academy of Child and Adolescent Psychiatry*, 36(4), 545–553. <https://doi.org/10.1097/00004583-199704000-00018>
- Bodden, D. H. M., Bögels, S. M., & Muris, P. (2009). The diagnostic utility of the Screen for Child Anxiety Related Emotional Disorders-71 (SCARED-71). *Behaviour Research and Therapy*, 47(5), 418–425. <https://doi.org/10.1016/j.brat.2009.01.015>
- Braithwaite, D., Moore, D. H., Lustig, R. H., Epel, E. S., Ong, K. K., Rehkopf, D. H., Wang, M. C., Miller, S. M., & Hiatt, R. A. (2009). Socioeconomic status in relation to early menarche among black and white girls. *Cancer Causes & Control: CCC*, 20(5), 713–720. <https://doi.org/10.1007/s10552-008-9284-9>
- Buck Louis, G. M., Gray, L. E., Marcus, M., Ojeda, S. R., Pescovitz, O. H., Witchel, S. F., Sippell, W., Abbott, D. H., Soto, A., Tyl, R. W., Bourguignon, J.-P., Skakkebaek, N. E., Swan, S. H., Golub, M. S., Wabitsch, M., Toppari, J., & Euling, S. Y. (2008).

- Environmental Factors and Puberty Timing: Expert Panel Research Needs. *Pediatrics*, 121(Supplement 3), S192–S207. <https://doi.org/10.1542/peds.1813E>
- Cheng, T. W., Magis-Weinberg, L., Guazzelli Williamson, V., Ladouceur, C. D., Whittle, S. L., Herting, M. M., Uban, K. A., Byrne, M. L., Barendse, M. E. A., Shirtcliff, E. A., & Pfeifer, J. H. (2021). A Researcher's Guide to the Measurement and Modeling of Puberty in the ABCD Study® at Baseline. *Frontiers in Endocrinology*, 12, 608575. <https://doi.org/10.3389/fendo.2021.608575>
- Copeland, W. E., Worthman, C., Shanahan, L., Costello, E. J., & Angold, A. (2019). Early Pubertal Timing and Testosterone Associated With Higher Levels of Adolescent Depression in Girls. *Journal of the American Academy of Child and Adolescent Psychiatry*, 58(12), 1197–1206. <https://doi.org/10.1016/j.jaac.2019.02.007>
- Corbett, B. A., Muscatello, R. A., & Baldinger, C. (2019). Comparing Stress and Arousal Systems in Response to Different Social Contexts in Children with ASD. *Biological Psychology*, 140, 119–130. <https://doi.org/10.1016/j.biopsycho.2018.12.010>
- Corbett, B. A., Muscatello, R. A., Tanguturi, Y., McGinn, E., & Ioannou, S. (2019). Pubertal Development Measurement in Children With and Without Autism Spectrum Disorder: A Comparison Between Physical Exam, Parent- and Self-Report. *Journal of Autism and Developmental Disorders*, 49(12), 4807–4819. <https://doi.org/10.1007/s10803-019-04192-w>
- Corbett, B. A., Vandekar, S., Muscatello, R. A., & Tanguturi, Y. (2020). Pubertal Timing During Early Adolescence: Advanced Pubertal Onset in Females with Autism Spectrum Disorder. *Autism Research: Official Journal of the International Society for Autism Research*, 13(12), 2202–2215. <https://doi.org/10.1002/aur.2406>
- Deardorff, J., Marceau, K., Johnson, M., Reeves, J. W., Biro, F. M., Kubo, A., Greenspan, L. C., Laurent, C. A., Windham, G. C., Pinney, S. M., Kushi, L. H., & Hiatt, R. A.

- (2021). Girls' Pubertal Timing and Tempo and Mental Health: A Longitudinal Examination in an Ethnically Diverse Sample. *The Journal of Adolescent Health: Official Publication of the Society for Adolescent Medicine*, 68(6), 1197–1203. <https://doi.org/10.1016/j.jadohealth.2021.01.020>
- Dorn, L. D., Dahl, R. E., Woodward, H. R., & Biro, F. (2006). Defining the Boundaries of Early Adolescence: A User's Guide to Assessing Pubertal Status and Pubertal Timing in Research With Adolescents. *Applied Developmental Science*, 10(1), 30–56. https://doi.org/10.1207/s1532480xads1001_3
- Fuhrman, B. J., Moore, S. C., Byrne, C., Makhoul, I., Kitahara, C. M., Berrington de González, A., Linet, M. S., Weiderpass, E., Adami, H.-O., Freedman, N. D., Liao, L. M., Matthews, C. E., Stolzenberg-Solomon, R. Z., Gaudet, M. M., Patel, A. V., Lee, I.-M., Buring, J. E., Wolk, A., Larsson, S. C., ... Hoover, R. N. (2021). Association of the Age at Menarche with Site-Specific Cancer Risks in Pooled Data from Nine Cohorts. *Cancer Research*, 81(8), 2246–2255. <https://doi.org/10.1158/0008-5472.CAN-19-3093>
- Galvao, T. F., Silva, M. T., Zimmermann, I. R., Souza, K. M., Martins, S. S., & Pereira, M. G. (2014). Pubertal timing in girls and depression: A systematic review. *Journal of Affective Disorders*, 155, 13–19. <https://doi.org/10.1016/j.jad.2013.10.034>
- Ge, X., Kim, I. J., Brody, G. H., Conger, R. D., Simons, R. L., Gibbons, F. X., & Cutrona, C. E. (2003). It's about timing and change: Pubertal transition effects on symptoms of major depression among African American youths. *Developmental Psychology*, 39(3), 430–439. <https://doi.org/10.1037/0012-1649.39.3.430>
- Gillberg, C., & Schaumann, H. (1982). Infantile autism and puberty. *Journal of Autism and Developmental Disorders*, 11(4), 365–371. <https://doi.org/10.1007/BF01531612>

- Goodman, R. (2001). Psychometric properties of the strengths and difficulties questionnaire. *Journal of the American Academy of Child and Adolescent Psychiatry*, 40(11), 1337–1345. <https://doi.org/10.1097/00004583-200111000-00015>
- Groenman, A., Torenvliet, C., Radhoe, T., Rentergem, J. A. van, & Geurts, H. (2021). *Menstruation and Menopause in autistic adults: Periods of importance?* PsyArXiv. <https://doi.org/10.31234/osf.io/kn8xe>
- Hamlat, E. J., Snyder, H. R., Young, J. F., & Hankin, B. L. (2019). Pubertal Timing as a Transdiagnostic Risk for Psychopathology in Youth. *Clinical Psychological Science*, 7(3), 411–429. <https://doi.org/10.1177/2167702618810518>
- Herting, M. M., Uban, K. A., Gonzalez, M. R., Baker, F. C., Kan, E. C., Thompson, W. K., Granger, D. A., Albaugh, M. D., Anokhin, A. P., Bagot, K. S., Banich, M. T., Barch, D. M., Baskin-Sommers, A., Breslin, F. J., Casey, B. J., Chaarani, B., Chang, L., Clark, D. B., Cloak, C. C., ... Sowell, E. R. (2021). Correspondence Between Perceived Pubertal Development and Hormone Levels in 9-10 Year-Olds From the Adolescent Brain Cognitive Development Study. *Frontiers in Endocrinology*, 11. <https://doi.org/10.3389/fendo.2020.549928>
- Ho, T. C., Gifuni, A. J., & Gotlib, I. H. (2021). Psychobiological risk factors for suicidal thoughts and behaviors in adolescence: A consideration of the role of puberty. *Molecular Psychiatry*, 1–18. <https://doi.org/10.1038/s41380-021-01171-5>
- Hoekstra, R. A., Bartels, M., Cath, D. C., & Boomsma, D. I. (2008). Factor structure, reliability and criterion validity of the Autism-Spectrum Quotient (AQ): A study in Dutch population and patient groups. *Journal of Autism and Developmental Disorders*, 38(8), 1555–1566.

- Ingudomnukul, E., Baron-Cohen, S., Wheelwright, S., & Knickmeyer, R. (2007). Elevated rates of testosterone-related disorders in women with autism spectrum conditions. *Hormones and Behavior*, 51(5), 597–604. <https://doi.org/10.1016/j.yhbeh.2007.02.001>
- Keenan, K., Culbert, K. M., Grimm, K. J., Hipwell, A. E., & Stepp, S. D. (2014). Timing and tempo: Exploring the complex association between pubertal development and depression in African American and European American girls. *Journal of Abnormal Psychology*, 123(4), 725–736. <https://doi.org/10.1037/a0038003>
- Knickmeyer, R. C., Wheelwright, S., Hoekstra, R., & Baron-Cohen, S. (2006). Age of menarche in females with autism spectrum conditions. *Developmental Medicine and Child Neurology*, 48(12), 1007–1008. <https://doi.org/10.1017/S0012162206222229>
- Kovacs, M. (1992). *Children's Depression Inventory (CDI)*. New York: Multi-health Systems, Inc.
- Lee, M. D., & Wagenmakers, E.-J. (2014). *Bayesian Cognitive Modeling: A Practical Course*. Cambridge University Press.
- Lynch, S. J., Sunderland, M., Newton, N. C., & Chapman, C. (2021). A systematic review of transdiagnostic risk and protective factors for general and specific psychopathology in young people. *Clinical Psychology Review*, 87, 102036. <https://doi.org/10.1016/j.cpr.2021.102036>
- Maïano, C., Normand, C. L., Salvas, M.-C., Moullec, G., & Aimé, A. (2016). Prevalence of School Bullying Among Youth with Autism Spectrum Disorders: A Systematic Review and Meta-Analysis. *Autism Research: Official Journal of the International Society for Autism Research*, 9(6), 601–615. <https://doi.org/10.1002/aur.1568>
- May, T., Pang, K. C., O'Connell, M. A., & Williams, K. (2017). Typical Pubertal Timing in an Australian Population of Girls and Boys with Autism Spectrum Disorder. *Journal*

of Autism and Developmental Disorders, 47(12), 3983–3993.

<https://doi.org/10.1007/s10803-017-3281-3>

Mendle, J., Harden, K. P., Brooks-Gunn, J., & Graber, J. A. (2010). Development's tortoise and hare: Pubertal timing, pubertal tempo, and depressive symptoms in boys and girls. *Developmental Psychology*, 46(5), 1341–1353. <https://doi.org/10.1037/a0020205>

Mensah, F. K., Bayer, J. K., Wake, M., Carlin, J. B., Allen, N. B., & Patton, G. C. (2013). Early puberty and childhood social and behavioral adjustment. *The Journal of Adolescent Health: Official Publication of the Society for Adolescent Medicine*, 53(1), 118–124. <https://doi.org/10.1016/j.jadohealth.2012.12.018>

Minshew, N. J., & Hobson, J. A. (2008). Sensory sensitivities and performance on sensory perceptual tasks in high-functioning individuals with autism. *Journal of Autism and Developmental Disorders*, 38(8), 1485–1498. <https://doi.org/10.1007/s10803-007-0528-4>

Morey, R. D., Rouder, J. N., Jamil, T., Urbanek, S., Forner, K., & Ly, A. (2018). *BayesFactor: Computation of Bayes Factors for Common Designs* (0.9.12-4.2) [Computer software]. <https://CRAN.R-project.org/package=BayesFactor>

Moseley, R. L., Druce, T., & Turner-Cobb, J. M. (2020a). Autism research is 'all about the blokes and the kids': Autistic women breaking the silence on menopause. *British Journal of Health Psychology*, n/a(n/a). <https://doi.org/10.1111/bjhp.12477>

Moseley, R. L., Druce, T., & Turner-Cobb, J. M. (2020b). 'When my autism broke': A qualitative study spotlighting autistic voices on menopause. *Autism*, 24(6), 1423–1437. <https://doi.org/10.1177/1362361319901184>

Petersen, A. C., Crockett, L., Richards, M., & Boxer, A. (1988). A self-report measure of pubertal status: Reliability, validity, and initial norms. *Journal of Youth and Adolescence*, 17(2), 117–133. <https://doi.org/10.1007/BF01537962>

- Pohl, A., Cassidy, S., Auyeung, B., & Baron-Cohen, S. (2014). Uncovering steroidopathy in women with autism: A latent class analysis. *Molecular Autism*, 5(1), 27.
<https://doi.org/10.1186/2040-2392-5-27>
- Reiter, E. O., Fuldauer, V. G., & Root, A. W. (1977). Secretion of the adrenal androgen, dehydroepiandrosterone sulfate, during normal infancy, childhood, and adolescence, in sick infants, and in children with endocrinologic abnormalities. *The Journal of Pediatrics*, 90(5), 766–770. [https://doi.org/10.1016/s0022-3476\(77\)81244-4](https://doi.org/10.1016/s0022-3476(77)81244-4)
- RStudio Team. (2015). *RStudio: Integrated Development Environment for R*.
<http://www.rstudio.com/>
- Shirtcliff, E. A., Dahl, R. E., & Pollak, S. D. (2009). Pubertal development: Correspondence between hormonal and physical development. *Child Development*, 80(2), 327–337.
<https://doi.org/10.1111/j.1467-8624.2009.01263.x>
- Simonoff, E., Pickles, A., Charman, T., Chandler, S., Loucas, T., & Baird, G. (2008). Psychiatric Disorders in Children With Autism Spectrum Disorders: Prevalence, Comorbidity, and Associated Factors in a Population-Derived Sample. *Journal of the American Academy of Child & Adolescent Psychiatry*, 47(8), 921–929.
<https://doi.org/10.1097/CHI.0b013e318179964f>
- Spear, L. P. (2000). The adolescent brain and age-related behavioral manifestations. *Neuroscience and Biobehavioral Reviews*, 24(4), 417–463.
[https://doi.org/10.1016/s0149-7634\(00\)00014-2](https://doi.org/10.1016/s0149-7634(00)00014-2)
- Steward, R., Crane, L., Mairi Roy, E., Remington, A., & Pellicano, E. (2018). “Life is Much More Difficult to Manage During Periods”: Autistic Experiences of Menstruation. *Journal of Autism and Developmental Disorders*, 48(12), 4287–4292.
<https://doi.org/10.1007/s10803-018-3664-0>

Stumper, A., Graham, A. A., Abramson, L. Y., & Alloy, L. B. (2020). Pubertal Synchrony and Depressive Symptoms: Differences by Race and Sex. *Journal of Youth and Adolescence*, 49(11), 2275–2284. <https://doi.org/10.1007/s10964-020-01314-x>

Timbremont, B., Braet, C., & Roelofs, J. (2002). Children's depression inventory: Nederlandstalige versie [Children's Depression Inventory: Dutch version]. In *Lisse: Swets & Zeitlinger*.

Tordjman, S., Ferrari, P., Sulmont, V., Duyme, M., & Roubertoux, P. (1997). Androgenic Activity in Autism. *American Journal of Psychiatry*, 154(11), 1626-a. <https://doi.org/10.1176/ajp.154.11.1626-a>

Table 1. Participants' characteristics

	ASC (n=34)		Com (n=34)		p-value
	M(SD)		M(SD)		
Age	14.14 (1.42)	11.91-16.69	14.2 (1.44)	11.79-16.83	0.864
IQ	104.41 (15.85)	81-138	110.65 (14.08)	81-145	0.091
SRS	96.76 (24.9)	49-166	15.5 (7.26)	1-33	<.001
Sex n (%) girl	16 (47%)	-	16 (47%)	-	1.00 ^c
Education father ^a n	0/4/17/7/6	-	1/2/10/14/7	-	.2 ^c
PDS- adrenal	2.65 (0.83)	1.5-4	2.5 (0.69)	1.5-3.5	0.429
PDS-gonadal	2.6 (0.94)	1-4	2.7 (1.07)	1-4	0.695
Age menarche ^b	11.7 (1.5)	9-14	12.4(.87)	11-14	.17
SDQ	7.26 (3.96)	0-16	5.01 (3.19)	0-12.5	0.012
externalizing					
SCARED	41.24 (23.1)	9-88	20.24 (11.87)	3-56	<.001
Autistic traits-self	126.97 (16.67)	76-157	95.03 (13.44)	69-121	<.001
Autistic traits-parents	145 (15.2)	121-182	84.6 (9.02)	70-104	<.001
SSQ	4.58 (2.39)	0-9	1.47 (1.48)	0-5	<.001
CDI	12.62 (7.14)	1-29	5.79 (5.69)	0-28	<.001

Note. AQ= autism quotient, ASC= Autism Spectrum Condition, CDI= child depression inventory, COM= Comparison, IQ=intelligence quotient, PDS= pubertal development scale, SDQ= strengths and difficulties questionnaires, SRS = social responsiveness questionnaire, SSQ= sensory sensitivity scale. ^aeducation was rated on a 5-points scale ranging from 1 (primary education) to 5 (university level education). ^b (n=25, 12 ASC, 13 COM). ^c Restuls of Chi squared test.

Table 2. Differential pattern of pubertal development

	Group*age		Group*age- girls		Group*age- boys	
	F, p	BF ₁₀	F, p	BF ₁₀	F, p	BF ₁₀
Adrenal	1.27, .263	.83	.371, .713	.26	1.294, .21	.68
Gonadal	5.37, .02	998.93	0.29, 0.59	46.94	3.27, .079	137.75

Note. BF₁₀ expresses the probability of the data given H1 relative to H0, BF₁₀ larger than 3 can be interpreted as substantial or stronger evidence for H1, BF₀₁ smaller than .333 can be seen as substantial or stronger evidence for H0

Table 3: Relation between deviating pubertal development and psychological symptoms

ASC	Adrenal		Gonadal		Adrenal*sex		Gonadal*sex	
	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>
Sensory sensitivity (S)	0.33	.03	.14	.07	.35	-.04	.14	.11
Autistic traits (S)	.13	.08	.83	.00	.59	.07	.88	.07
Autistic traits (P)	.35	.02	.45	.02	.94	-.06	.81	.00
Depression (S)	.002	.26	.03	.14	.89	.22	.24	.12
Anxiety (S)	.30	.03	.16	.06	.80	-.06	.59	.01
Externalizing (P)	.04	.13	.01	.18	.44	.06	.29	.18
COM	Adrenal		Gonadal		Adrenal*sex		Gonadal*sex	
	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>r</i>
Sensory sensitivity (S)	.52	.01	.16	.06	.89	-.08	.93	-.03
Autistic traits (S)	.45	.02	.42	.02	.61	-.07	.82	-.08
Autistic traits (P)	.94	.00	.54	.01	.94	-.1	.93	-.09
Depression (S)	.31	.03	.30	.03	.15	.01	.42	-.04
Anxiety (S)	.82	.00	.78	.00	.21	-.04	.07	.02
Externalizing (P)	.40	.02	.89	.00	.64	-.07	.89	-.10

Note. ASC= Autism Spectrum Condition, COM= Comparison, P= parent-report S= self- report

Figure 1. Speed of pubertal development of autistic (Autism in yellow) and non-autistic (Comparison in blue) boys and girls

Note. * indicates an effect of group.

Figure 2. Relationship between deviating adrenal pubertal development and mental health in autistic (Autism in yellow (and non-autistic (Comparison in blue) boys and girls

Figure 3. Relationship between deviating gonadal pubertal development and mental health in autistic (autism in yellow (and non-autistic (Comparison in blue) boys and girls

Note. * indicates an effect of group.